Triorganoindium Reagents in Cross-Coupling Reactions: Transition-Metal-Free Reactions with Benzopyranyl Acetals and Tetrahydroisoquinolines and Solid-Stable Organometallics

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Abbreviations and Acronyms

In this Manuscript the most common abbreviations in Organic Chemistry have been used following the recommendations of the ACS.

COD	ciclooctadiene
d	doublet
dd	doublet of doublets
DEPT	distortionless enhancement by polarization
DMA	*N*,*N*-dimethylacetamide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPEPhos	(Oxydi-2,1-phenylene)bis(diphenylphosphine)
EI	electronic impact
ESR	electron spin resonance
FTIR	Fourier-transform infrared
m	multiplet
MS	mass spectrometry
rt	room temperature
SET	single electron transfer
TBDPS	*tert*-Butyldiphenylsilyl
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultra violet

Abstract.

This Thesis presents the development of a new transition-metal-free coupling reaction of triorganoindium reagents with chromene and isochroman acetals under $BF_3{\cdot}OEt_2$ activation. This reaction allows the synthesis of the corresponding 2-substituted 2*H*-chromenes and 1-substituted isochromans in good yields, in which aryl, heteroaryl, alkynyl, alkenyl, and alkyl groups can be transferred using only 50 mol% of the triorganoindium reagents. As an extension of this methodology, a transition-metal-free coupling reaction of triorganoindium reagents with *N*-protected tetrahydroisoquinolines (THIQs) under oxidative conditions is presented as well, where different aryl, heteroaryl, alkynyl, benzyl, and alkyl groups can be installed at the C-1 position of the THIQs, using only 50 mol% of the triorganoindium reagent. To demonstrate the synthetic utility of this reaction, it was applied to the synthesis of alkaloid Nuciferine.

This Thesis also presents the synthesis and isolation of solid, bench-stable triorganoindium reagents by coordination with 4-dimethylaminopyridine (DMAP). Different $R_3In{\cdot}$DMAP complexes bearing aryl, heteroaryl, alkynyl, and benzyl groups were prepared and then used in palladium-catalyzed cross-coupling reactions, where they reacted efficiently with diverse electrophiles including aryl, alkenyl, allyl, and benzyl bromides.

Resumen.

En esta Tesis se presenta el desarrollo de una nueva reacción de acoplamiento de reactivos triorganoíndicos con acetales de cromeno e isocramano mediante activación con $BF_3{\cdot}OEt_2$ en ausencia de metales de transición. Esta reacción permite la síntesis de los correspondientes 2*H*-cromenos-2-sustituidos e isocromanos 1-sustituidos en buenos rendimientos, en donde grupos arilo, heteroarilo, alquinilo, alquenilo y alquilo se transfieren empleando solamente un 50 mol% de los reactivos triorganoíndicos. Como extensión de esta metodología, se presenta también la reacción de acoplamiento de reactivos triorganoíndicos con tetrahidroisoquinolinas (THIQs) *N*-protegidas en condiciones oxidantes y ausencia de metales de transición, en donde grupos arilo, heteroarilo, alquinilo, bencilo, y alquilo se acoplan en la

posición C-1 de las THIQs, empleando solamente un 50 mol% del reactivo triorganoíndico. Para demostrar su utilidad sintética, esta nueva reacción se emplea en la síntesis del alcaloide Nuciferina.

En esta Tesis también se presenta la síntesis y aislamiento de reactivos triorganoíndicos sólidos y estables mediante coordinación con 4-dimetilaminopiridina (DMAP). Distintos $R_3In{\cdot}DMAP$ con grupos arilo, heteroarilo, alquinilo y bencilo se preparan y son empleados en reacciones de acoplamiento cruzado catalizadas por paladio, donde reaccionan de forma eficiente con distintos electrófilos incluyendo bromuros de arilo, alquenilo, alilo y bencilo.

Resumo.

Nesta Tese presentamos o desenvolvemento dunha nova reacción de acoplamento de reactivos triorganoínicos con acetais de cromeno e isocromano pola activación con $BF_3{\cdot}OEt_2$ en ausencia de metais de transición. Esta reacción permite a síntese dos correspondentes 2*H*-cromenos-2-sustituidos e isocromanos 1-sustituidos en bos rendementos, onde grupos arilo, heteroarilo, alquinilo, alquenilo y alquilo transfírense utilizando só un 50 mol% dos reactivos triorganoíndicos. Como extensión desta metodoloxía, presentamos tamén la reacción de reactivos triorganoíndicos con tetrahidroisoquinolinas *N*-protegidas, en condicións de oxidación e ausencia de metais de transición en que grupos arilo, heteroarilo, alquinilo, bencilo y alquilo pódense acoplar na posición C-1 das THIQs, utilizando só un 50 mol% dos reactivos triorganoíndicos. Para demostrar a súa utilidade sintética, a reacción emprégase na síntese do alcaloide Nuciferina.

Nesta Tese son sintetizados e illados reactivos triorganíndicos sólidos por coordinación con 4-dimetilaminopiridina (DMAP). Varios triorganoíndicos sólidos con grupos arilo, heteroarilo, alquinilo y bencilo prepáranse y son utilizados en reaccións de acoplamento cruzado catalizadas por paladio, reaccionando eficientemente con diferentes electrófilos incluíndo bromuros de arilo, alquenilo, alilo e bencilo.

This Thesis is aimed at expanding the synthetic utility of triorganoindium compounds in Organic Chemistry. This work involves the development of novel, more efficient synthetic methodologies to access relevant heterocyclic scaffolds using triorganoindium compounds, as well as the development and structural study of new triorganoindium reagents with improved stability.

The first chapter covers an introduction about the use of indium organometallics in Organic Chemistry, with a special focus on triorganoindium reagents. The unique features and distinctive reactivity of triorganoindium reagents in transition-metal catalyzed cross-coupling reactions is outlined in detail.

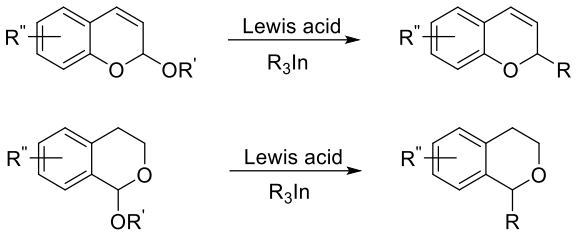
The second chapter is focused on the use of triorganoindium reagents in transition-metal-free coupling reactions with chromene acetals. First, a general introduction to transition-metal-free reactions and a review of recent, novel methodologies is presented. Then, our results on transition-metal-free reactions with triorganoindium reagents based on the use of Lewis acids for the synthesis of the oxygen-containing benzoheterocyclic substrates, chromene and isochramene, are discussed. Finally, a new transition-metal-free oxidative coupling reaction of triorganoindium reagents with *N*-protected tetrahydroisoquinolines is presented as well, including the use of this new reaction for the synthesis of natural product Nuciferine.

The third chapter is dedicated to the development and structural study of new solid, bench-stable triorganoindium reagents. As introduction, various types of stabilized organometallic nucleophiles are presented. Then, the development of bench-stable triorganoindium reagents based on the formation of Lewis acid-base adducts with nitrogen-containing donor ligands is discussed. The synthesis, structure, and stability of these new reagents is described, and their reactivity in palladium-catalyzed cross-coupling reactions is thoroughly studied. Finally, the bench-stable solid triorganoindium reagents are employed in palladium-catalyzed reactions with aryne intermediates, highlighting their performance in conditions otherwise incompatible with the classically *in situ* generated triorganoindium reagents.

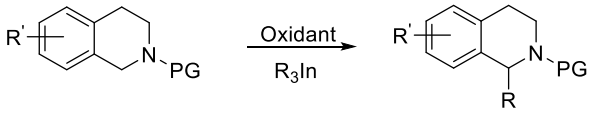
Objectives

Two major objectives have been established for this Doctoral Thesis:

1. The development of new reaction methods to access chromene, isochroman, and tetrahydroisoquinoline derivatives using triorganoindium reagents under transition-metal-free conditions. In the case of chromene and isochroman, the reactions will be based on the use of Lewis acids from the corresponding acetals.

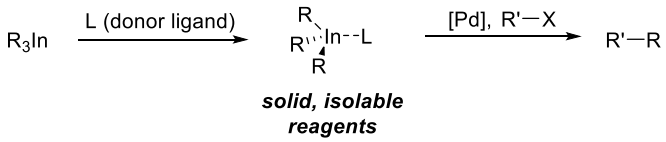


In the case of the development of a reaction of triorganoindium reagents with *N*-protected tetrahydroisoquinolines, oxidative conditions will be employed.



The scope of the reactions will be investigated and its synthetic potential demonstrated by its application to the synthesis of alkaloid Nuciferine.

2. The preparation of isolable triorganoindium complexes with improved stability based on coordination with adequate donor ligands, and the study of their reactivity in palladium-catalyzed cross-coupling reactions.



Chapter 1.

Indium Organometallics in Organic Synthesis: An Overview.

1.1 Introduction.

Indium is the chemical element with atomic number 49, located in the fourth row of group 13 of the Periodic Table. It is a silvery-white metal, highly ductile and very soft, to the point that it can be easily cut with a knife. Indium was discovered in 1863 by German chemists Reicht and Richter, who named the element after the characteristic indigo blue line observed in its spectrum.[1] Indium is a relatively scarce element, with an abundance in the Earth crust comparable to that of silver or mercury. It has an electronic configuration of $[Kr]4d^{10}5s^{2}5p^{1}$ and thus it is most commonly found as indium(III), although in some compounds it can also be found as indium(I).

Until the early 1990s, the majority of applications of indium remained within the field of semiconductors or in the preparation of special metal alloys, and organic chemists showed little interest in this metal.[2] However, in the past two decades there has been a surge in the use of indium organometallics and indium salts for a wide range of organic transformations, including addition reactions, cross-coupling reactions, or Lewis acid catalysis among others. The first application of indium in organic synthesis was reported in 1975 by Rieke and co-workers in the Reformatsky reaction between α-halo esters and carbonyl compounds.[3] In this case, an activated form of indium (known as Rieke indium), prepared by reduction of indium trichloride in the presence of elemental potassium, was deemed necessary for the reaction to proceed. More than a decade later, in 1988, Araki, Ito, and Butsugan demonstrated that it is possible to generate allylindium reagents from commercially available indium powder that react with carbonyl compounds to afford homoallyl alcohols.[4] These contributions called considerable attention and marked an ever-increasing interest from the synthetic community towards the use of indium.

1 Bailar, J. C.; Emeléus, H. J.; Nyholm, R. S.; Trotman-Dickenson, A. F. *Comprehensive Inorganic Chemistry*. Pergamon, New York, **1973**, Vol 1, p. 1065.

2 Downs, A. J. *Chemistry of Aluminium, Gallium, Indium, and Thallium*. Springer, Netherlands, **1993**, p. 89.

3 Chao, L. C.; Rieke, R. D. *J. Org. Chem.* **1975**, *40*, 2253-2255.

4 Araki, S.; Ito, H.; Butsugan, Y. *Synth. Commun.* **1988**, *18*, 453

The development of simple, practical methods for the preparation of organonindium compounds by Knochel,[5] Loh,[6] and others helped to further expand their synthetic applications. In a pioneering work in 1999, Sarandeses and Sestelo discovered the transition-metal catalyzed cross-coupling reaction of organoindium reagents.[7] Since then, a diversity of organoindium reagents have been efficiently coupled with a wide array of electrophiles using different transition metals catalysts. Organoindium compounds can be used under mild reaction conditions and show remarkable chemoselectivity and atom-efficiency. In addition, organoindium reagents are generally non-toxic in nature.

This introductory chapter offers an overview of the different applications of organoindium reagents in organic synthesis, making special emphasis in the application of triorganoindium reagents.

5 Chen, Y. H.; Sun, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 2236-2239.

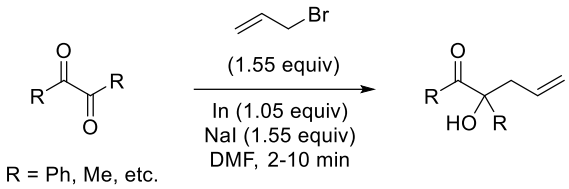
6 Shen, Z. L.; Goh, K. K.; Yang, Y. S.; Lai, Y. C.; Wong, C.H.; Cheong, H. L.; Loh, T. P. *Angew. Chem. Int. Ed.* **2011**, *50*, 511-514.

7 (*a*) Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155-4160. (*b*) Pérez, I.; Pérez Sestelo, J.; Maestro, M. A.; Mouriño, A.; Sarandeses, L. A. *J. Org. Chem.* **1998**, *63*, 10074-10076.

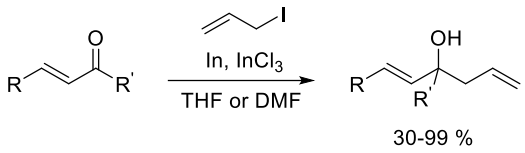
1.2 Allyl-, Propargyl- and Allenylindium Reagents.

A significant part of all organoindium chemistry involves addition reactions of allylindium reagents. As mentioned before, the disclosure of the first practical allylation protocol using commercial indium influenced much of the later research concerning organoindium reagents. Allylindium reagents may be generated by indium insertion of allyl bromide or iodide in polar organic solvents such as DMF at room temperature. The *in situ* generated allylindium reagents react towards carbonyl compounds affording homoallylic alcohols.[4] The relatively low nucleophilicity of allylindium reagents offers a unique reactivity towards carbonyl substrates and related compounds. For example, indium has been employed for the monoallylation of 1,2−diketones.[8] Upon addition of 1.05 equivalents of indium, only the monoallylated α−hydroxyalketone is observed (Scheme 1). Likewise, reaction in the presence α,β−saturated ketones results in the allyl moiety being inserted only in the ketone functionality (Scheme 2).[9]

Scheme 1. *Monoallylation of 1,2-diketones.*



Scheme 2. *Selective allylation of α,β-saturated ketones.*



Allylindium reagents are also known to react in aqueous media. In 1991, Li and Chan were the first to report the use of allylindium for the addition of aldehydes and ketones in water at room temperature.[10] In their study they noted the superior

8 Nair, V.; Jayan, C. N.; *Tetrahedron Lett.* **2000**, *41*, 1091-1094.

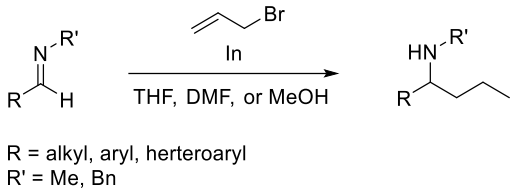
9 Kim, H. Y.; Choi, K. Y.; Pae, A. N.; Koh, H. Y.; Choi, J. H.; Cho, Y. S. *Synth Commun*. **2003**, *33*, 1899-1904.

10 Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017-7020.

performance of the indium reagent compared to zinc or tin, which in turn afforded significantly lower yields and required higher temperatures.

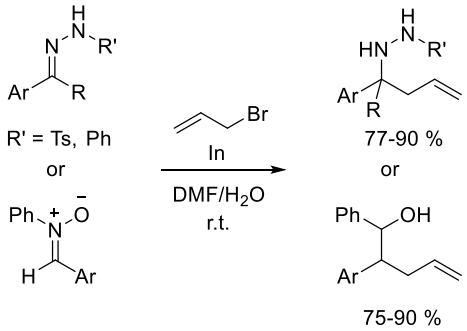
Indium-mediated allylation of imines leads to homoallylic amines, which are important synthetic intermediates for many nitrogen-containing natural products. These reactions may be carried out with aprotic solvents such as THF or DMF, or alcoholic solvents (Scheme 3). The scope for these reactions involve imines derived from aliphatic, aromatic, or heteroaromatic aldehydes.[11]

***Scheme 3**. Addition of allylindium reagent to imines.*



Water-tolerant tosylhydrazones and nitrones have proven to be reactive electrophiles towards indium-promoted allylation reaction in aqueous media. Several homoallylic tosylhydrazones and hydroxilamines can be furnished in good to excellent yields under these conditions (Scheme 4).[12] Moreover, the addition of *in situ* generated allylindium reagents to nitriles, epoxides, or aziridines has also been reported.[13]

***Scheme 4**. Addition of allylindium reagent to tosylhydrazones and nitrones.*



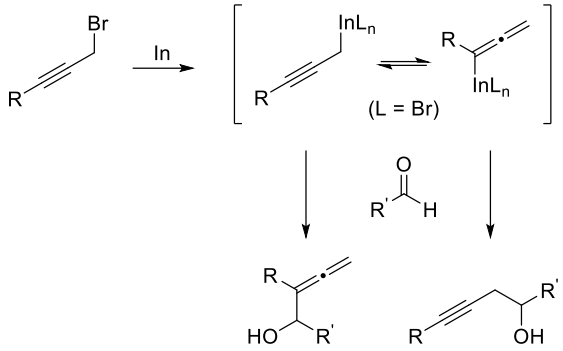
11 (*a*) Vilaivan, T.; Winotapan, C.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2001**, *42*, 9073-9076 (*b*) Beuchet, P.; Le Marrec, N.; Mosset, P. *Tetrahedron Lett.* **1992**, *33*, 5959-5960.

12 Kumar, H. M. S.; Anjaneyulu, S.; Reddy, E. J.; Yadav, J. S. *Tetrahedron Lett.* **2000**, *41*, 9311-9314.

13 (*a*) Ranu, B. C.; Das, A.; *Tetrahedron Lett.* **2004**, *45*, 6875-6877. (*b*) Yadav, J. S.; Anjaneyulu, S.; Ahmed, M. M.; Reddy, B. V. S. *Tetrathedron Lett.* **2001**, *42*, 2557-2559. (*c*) Hirashita, T.; Toumatsu, S.; Imagawa, Y.; Araki, S.; Setsune, J. *Tetrahedron Lett.* **2006**, *47*, 1613-1616.

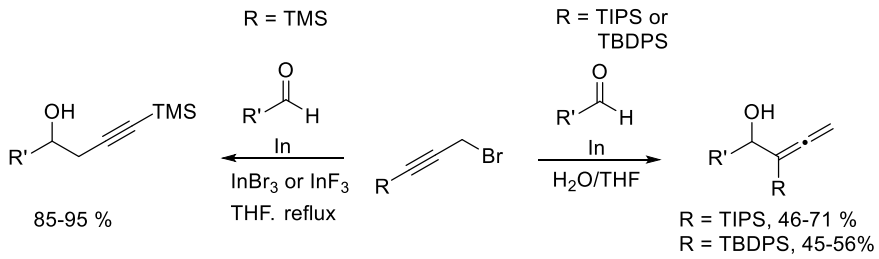
Other organoindium compounds can be used in addition reactions as well. Propargyl and allenyl indium reagents are generated from propargyl bromides and exist in equilibrium either in organic solvents or aqueous media (Scheme 5).[14] These species can be added to electrophiles like aldehydes to afford propargyl and allenyl alcohols, which in turn can be easily further functionalized.

Scheme 5. *Propargyl/allenyl indium tautomeric equilibrium and addition to aldehydes.*



In general, the regioselectivity depends largely on the substituent at the *γ* position of the propargyl halide, where bulky substituents favor the formation of the allenyl alcohol. For example, when the less bulky *γ*-TMS propargyl bromide reacts with aldehyde in the presence of indium and catalytic $InBr_3$ or InF_3 under refluxing THF, homopropargyl alcohol can be selectively formed. In contrast by carrying out the reaction in aqueous THF at room temperature with bulkier *γ*-TMS or *γ*-TBDPS propargyl bromide, allenyl alcohol is in turn predominantly obtained (Scheme 6).[15]

Scheme 6*. Regioselective synthesis of allenic and homopropargylic alcohols.*



14 Isaac, M. B.; Chan, T.-H. *J. Chem. Soc., Chem. Commun*. **1995**, 1003-1004.

15 Lin, M. J.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 13042-13043.

Intramolecular variants of these reactions have also been reported. In this sense, salicylaldehydes or benzoates containing a propargyl bromide moiety can undergo intramolecular allenylation in the presence of indium to afford the corresponding allenyl chromanes or allenyl δ-lactones respectively.[16] Aditionally, allenyl and propargyl indium reagents can react with other electrophiles apart from aldehydes, including imines, nitrones, acyl cyanides, or aryl nitriles.[17]

1.3 Triorganoindium Reagents.

Unlike other organoindium species such as allylindium reagents, triorganoindium are not nucleophilic enough to undergo addition reactions over common organic electrophiles like carbonyl compounds. However, the most important application of triorganoindium reagents is their use in transition-metal catalyzed cross-coupling reactions.[18] Precisely, their moderate reactivity has proven to be a distinctive advantage because it allows cross-coupling reactions to take place in the presence of sensitive functional groups such as ketone, ester, nitro, or even hydroxyl. In addition to this, triorganoindium reagents present a number of unique features, such as the ability to transfer the three organic groups attached to the indium metal center, their remarkable chemoselectivity, or their low toxicity in comparison to other organometallic reagents like stannanes. Because of this, over the past two decades numerous examples involving the use of triorganoindium reagents in cross-coupling with different substrates have been reported.

Tiorganoindium reagents can be readily prepared by reaction of indium(III) halides with three equivalents of organolithium or Grignard reagents in (Scheme 7).[19]

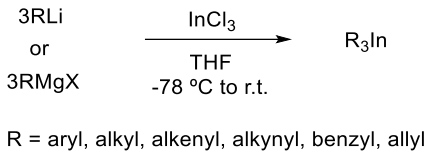
16 (*a*) Hua, X.-G.; Li, C.-J. *Main Group Met. Chem.* **1999**, *22*, 533-538. (*b*) Kang, H.-Y.; Kim, Y.-T.; Yu, Y.-K.; Cha, J.-H.; Cho, Y.-S.; Koh, H. Y. *Synlett.* **2004**, 45-48.

17 (*a*) Yoo, B.-W.; Lee, S.-J.; Choi, K.-H.; Keum, S.-R.; Ko, J.-J.; Choi, K.-I. Kim, J.-H. *Tetrahedron. Lett.* **2001**, *42*, 7287-7289. (*b*) Prajapati, D.; Laskar, D. D.; Gogoi, B. J.; Devi, G. *Tetrahedron Lett.* **2003**, *44*, 6755-6757.

18 (*a*) Zhao, K.; Shen, L.; Shen, Z.-L.; Loh, T.-P. *Chem. Soc. Rev.* **2017**, *46*, 586-602. (*b*) Shen, Z.L.; Wang, S.-Y.; Chok, Y.-K.; Xu, Y.-H.; Loh, T.-P. *Chem. Rev.* **2013**, *113*, 271-401.

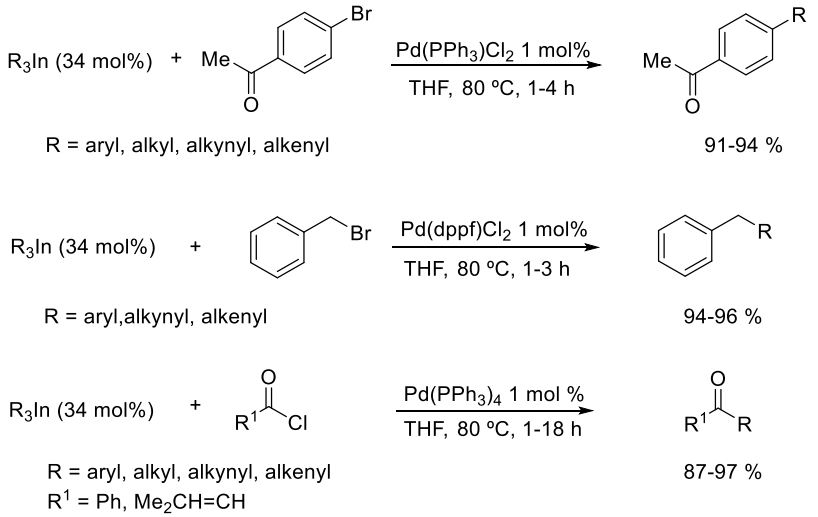
19 (*a*) Clark, H.C.; Pickard, A. L.; *J. Organomet. Chem.* **1967**, *8*, 427-434 (*b*) Hoffmann, K.; Weiss, E.*J. Organomet. Chem.* **1972**, *37*, 1-8.

***Scheme 7**. Preparation of triorganoindium reagents from indium(III) halides.*



Using this method a wide range of triorganoindium compounds can be accessed. Alkyl, vinyl, aryl, and alkynyl were the first triorganoindium reagents to be used in palladium-catalyzed cross-coupling reactions; where aryl halides, benzyl bromides, and acyl chlorides were used as electrophiles (Scheme 8).[7] The results showed that the cross-coupling products could be obtained in excellent yields and short reaction times. Remarkably, these reactions can be carried out with only 34 mol% of the triorganoindium, which demonstrated that all three organic groups were transferred during the process.

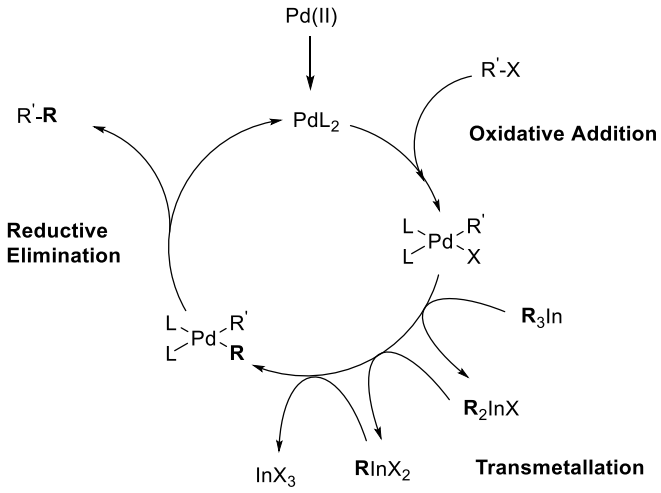
***Scheme 8**. Palladium-catalyzed cross-coupling of triorganoindium reagents with aryl halides, benzyl bromides, and acyl chlorides.*



An examination into the reaction mechanism can explain the high atom efficiency behind this process. The cross-coupling reaction involves a catalytic cycle that starts with the oxidative addition of the Pd(0) complex to the electrophilic partner, followed by transmetallation of an organic group from indium to palladium, and finally a reductive elimination step that releases the reaction product and regenerates the active catalyst (Scheme 9). The intermediate indium species R_2InX and $RInX_2$ take part in the reaction until all the organic groups have been transferred. The driving force behind this process is the significant difference in enthalpy that exists between

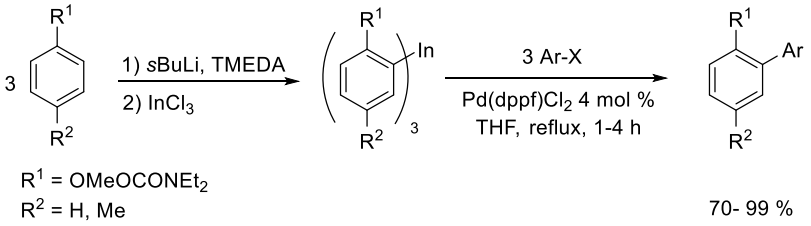
indium organometallics and the InX_3 salts that are formed once the reaction is complete.[20]

***Scheme 9**. Catalytic cycle of the Pd-catalyzed cross-coupling reaction of R_3In.*



Triorganoindium reagents can also be prepared by direct ortho-lithiation of benzene derivatives that contain directing groups, followed by transmetallation with $InCl_3$ (Scheme 10). [21] This method can be used to readily prepare biaryl compounds under Pd catalysis in the presence of aryl halides as electrophiles. The reaction proceeds with high yields with a substoichiometric quantity of InX_3.

***Scheme 10**. Pd-catalyzed synthesis of biaryls with in situ prepared R_3In by direct o-metalation.*



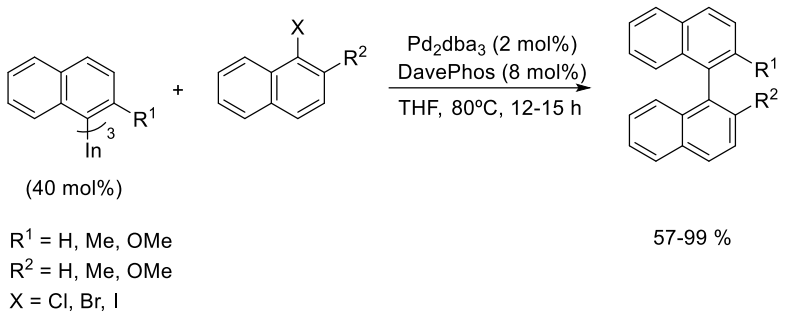
Following this procedure, 1,1'-binaphtalenes can also be efficiently prepared by palladium-catalyzed cross-coupling reactions between tri-1-naphtylindium reagents

20 (*a*) Pilcher, G.; Skinner, H. A. *The Chemistry of the Metal-Carbon Bond*; Harley, F. R.; Patai, S. Eds. Wiley: Chichester, U. K., 1992, Vol 1, Ch. 2, p 68. (*b*) O´Neil, M. E.; Wade, K. *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W.; Eds.; Pergamon: Oxford, U.K., 1982, Vol 1, Ch. 1, p. 8.

21 Pena, M. A.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Org. Chem.* **2007**, *72*, 1271-1275.

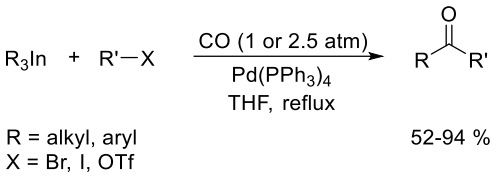
and 1-halogenonaphtalenes (Scheme 11).[22] The reactions can be carried out at 80 °C in THF with only a slight excess of the indium reagent (40 mol%) and low catalyst loadings. Moreover, when the cross-coupling reaction is performed in the presence of chiral ferrocene ligands, binaphtalenes can be obtained with good to moderate enantioselectivities.

***Scheme 11**. Synthesis of 1,1'-binaphtalenes by Pd-catalyzed cross-coupling of reaction of R_3In.*



Triorganoindium reagents can be used in the synthesis of ketones through a palladium-catalyzed carbonylative reaction with CO. The cross-coupling reactions of trialkyl and triarylindium reagents using alkyl or aryl halides as electrophiles affords the corresponding unsymmetrical ketones in good yields (Scheme 12).[23]

***Scheme 12**. Palladium-catalyzed carbonylative cross-coupling with R_3In.*



In a related work, the group of Lei described the preparation of carboxylic acid derivatives via palladium-catalyzed oxidative carbonylation reaction of trialkyl organoindium reagents in alcoholic solvents (Scheme 13).[24] In addition, oxalyl chloride can be used as the source of CO for carbonylations under palladium catalysis furnishing symmetrical ketones.[25]

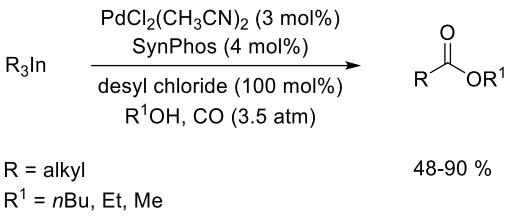
22 Mosquera, A.; Pena, M. A.; Pérez Sestelo, J.; Sarandeses, L. A. *Eur. J. Org. Chem.* **2013**, 2555-2562.

23 Pena, M. A.; Pérez Sestelo, J.; Sarandeses, L. A. *Synthesis* **2003**, *5*, 780-784.

24 Zhao, Y.; Jin, L.; Li, P.; Lei, A. *J. Am. Chem. Soc.* **2008**, *130*, 9429-9433.

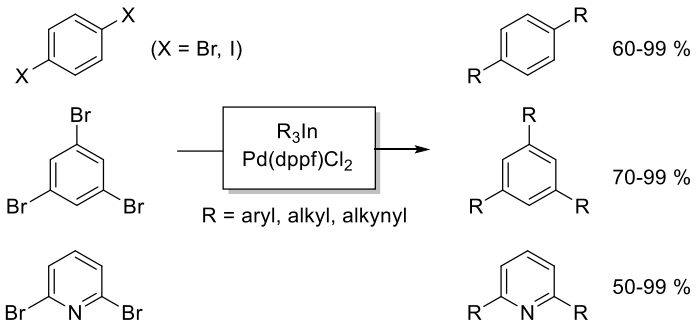
25 Rao, M. L. N.; Venkatesh, V; Dasgupta, P. *Tetrahedron Lett.* **2010**, *51*, 4975-4980.

***Scheme 13**. Synthesis of carboxylic acid derivatives by Pd-catalyzed carbonylative cross-coupling reaction of R_3In.*



Triorganoindium reagents can be used in multifold cross-coupling reactions with polyhalogenated aromatic or heteroaromatic electrophiles including 1,4-dihalobenzene, 1,3,5-tribromobenzene, or 2,6-dibromopyridine (Scheme 14).[26] These reactions allow the formation of several carbon-carbon bonds in a one-pot procedure and using a single catalyst loading.

***Scheme 14**. Multifold cross-coupling reactions with R_3In.*



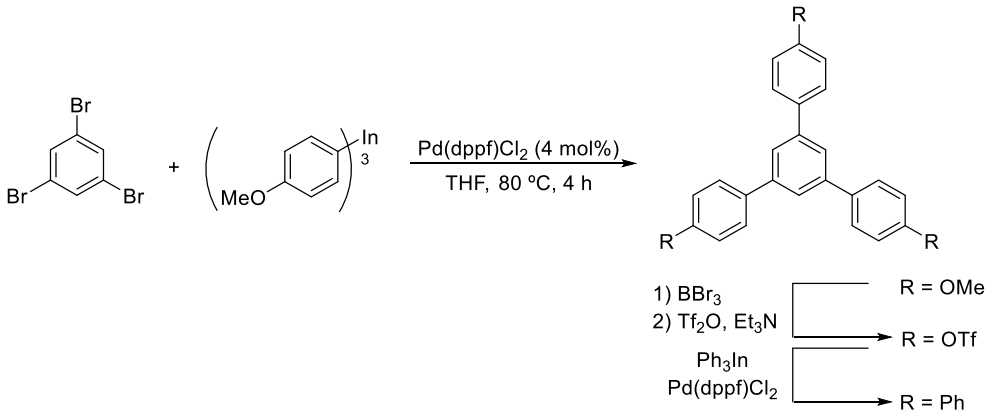
Remarkably, a four step synthesis of a polyphenylene dendrimer was achieved further demonstrating the synthetic utility of triorganoindium in multifold cross-coupling (Scheme 15).[27] This type of highly conjugated π systems have potential applications in the field of material science. The multifold cross-coupling reaction with triorganoindium reagents has been successfully applied for the synthesis of dithienosilole derivatives as well as other polyaromatic compounds with relevant physicochemical properties.[28]

26 Pena, M. A.; Pérez Sestelo, J.; Sarandeses, L. A. *Synthesis* **2005**, *3*, 485-492.

27 Pena, M. A.; Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *Chem. Commun.* **2002**, 2246-2244.

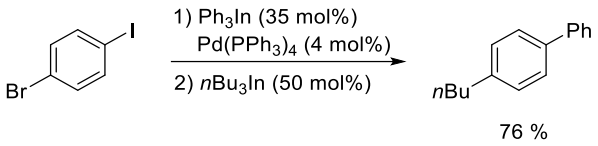
28 (*a*) Lee, W.; Kang, Y.; Lee, P. H. *J. Org. Chem. J. Org. Chem.* **2008**, *73*, 4326-4329. (*b*) Jung, H.; Hwang, H.; Park, K.-M.; Kim, J.; Kim, D-H.; Kang, Y. *Organometallics* **2010**, *29*, 2715-2732.

***Scheme 15**. Synthesis of a polyphenylene dendrimer by multifold cross-coupling with R_3In.*



Triorganonindium reagents can be chemoselectively coupled with dihalogenated aromatic electrophiles, thus enabling the formation of two different carbon-carbon bonds with a single catalyst loading in a sequential process (Scheme 16).[21]

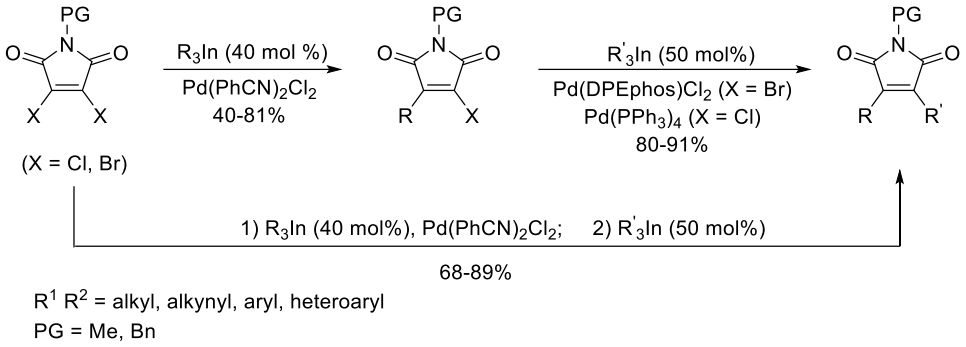
***Scheme 16**. Chemoselective sequential cross-coupling of dihalogenated electrophiles with R_3In.*



The high chemoselectivity shown by triorganoindium reagents in cross-coupling was applied to conveniently access relevant heteroaromatic scaffolds by performing sequential reactions. For example, 3,4-disubstituted maleimides, an important family of natural and synthetic products with valuable properties, can be synthesized from 3,4-dihalomaleimides using various triorganoindium reagents (Scheme 17).[29] The synthesis can be achieved either by a stepwise procedure in which the 3-halo-4-substituted maleimide is first obtained and isolated, or by sequential one-pot procedure to directly access the 3,4-disubstituted products. Interestingly, this methodology represented the first example of the synthesis of non-symmetrical 3,4-disubstituted maleimides using palladium-catalyzed cross-coupling.

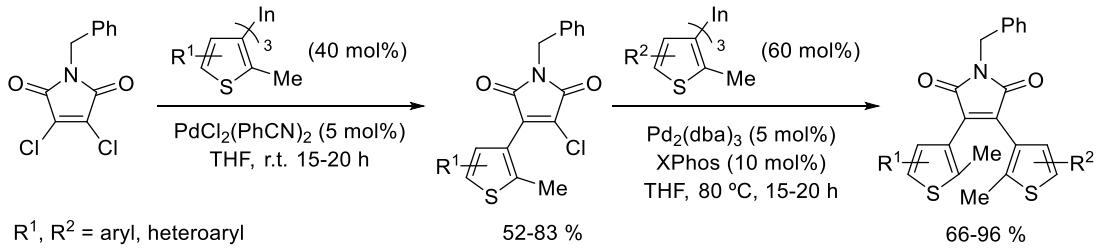
29 Bouissane, L.; Pérez Sestelo, J.; Sarandeses, L. A. *Org. Lett.* **2009**, *11*, 1285-1288.

Scheme 17. *Synthesis of 3,4-disubstituted maleimides by selective cross-coupling using triorganoindium reagents.*



In a related work, the synthesis of nonsymmetrical 1,2-dithienylethenes with a maleimide bridge was achieved based on the sequential cross-coupling of 3,4-dichloromaleimides with triorganoindium reagents under palladium catalysis (Scheme 18).[30] This methodology allowed the synthesis of a collection of novel 1,2-dithienylethenes whose photocromic properties were also studied.

Scheme 18*. Synthesis of 1,2-dithienylethenes with a maleimide bridge using R_3In.*

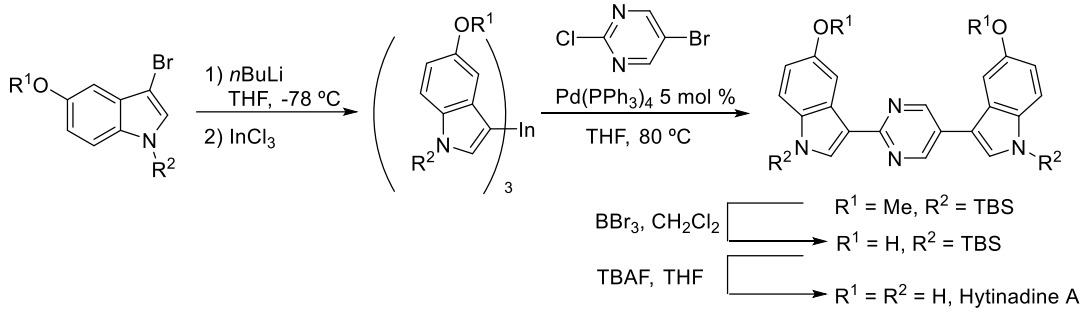


The high chemoselectivity of triorganoindium reagents has been used for the synthesis of natural products. Triorganoindium reagents can react with 2,5-dihalopyrimidines, in single, double, or sequential cross-coupling reactions. [31] This methodology was employed for the first reported synthesis of natural product Hyrtinadine A, by means of a two-fold cross-coupling reaction of 3-indolylindium reagent and 2,5-dihalopyrimidine (Scheme 19).

30 Mosquera, A.; Fernández, M. I.; Canle López, M.; Pérez Sestelo, J.; Sarandeses, L. A. *Chem. Eur. J.* **2014**, *20*, 14524-14530.

31 Mosquera, A.; Riveiros, R.; Pérez Sestelo, J.; Sarandeses, L. A. *Org. Lett.* **2008**, *10*, 3745-3748.

***Scheme 19**. Synthesis of natural product Hyrtinadine A with R_3In.*

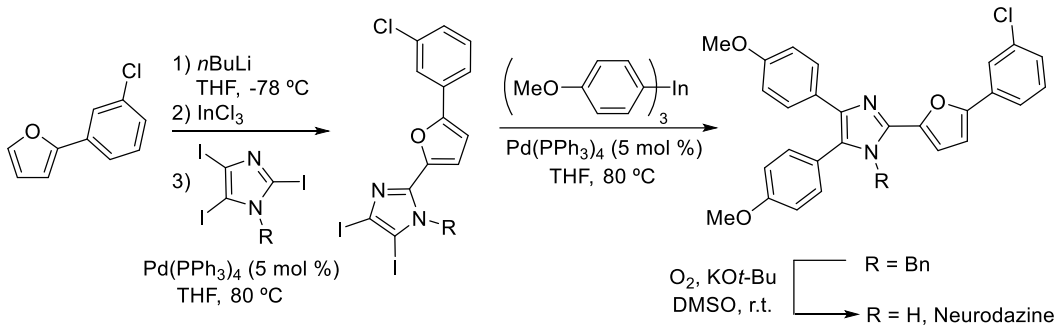


Moreover, 4,6-disubstituted pyrimidines can be accessed from 4,6-dichloropyrimidines by palladium catalyzed cross-coupling reaction with triorganoindium reagents. This strategy is an efficient alternative to the traditional approach to substituted pyrimidines by condensation or aromatic substitution reactions.[32] Similarly, triorganoindium reagents can be used for the synthesis of 2,4,5-trisubstituted imidazoles starting from *N*-benzyl-2,4,5-triiodoimidazole under palladium catalysis.[33] A variety of aromatic and heteroaromatic triorganoindium reagents can be coupled selectively in good yields. This methodology was employed to access bioactive compound Neurodazine (Scheme 20). The synthesis of Neurodazine was carried out by means of three sequential cross-coupling reactions using triorganoindium reagents; first with the selective coupling of 2-(3-chlorophenyl)furan triorganoindium reagent at the C2 position of *N*-benzyl-2,4,5-triiodoimidazole, followed by a two-fold cross-coupling reaction with 4-methoxy-phenyl triorganoindium reagent.

32 Martinez, M. M.; Pérez-Caaveiro, C.; Peña-López, M.; Sarandeses, L. A.; Pérez Sestelo, J. *Org. Biomol. Chem.* **2012**, *10*, 9045-9051.

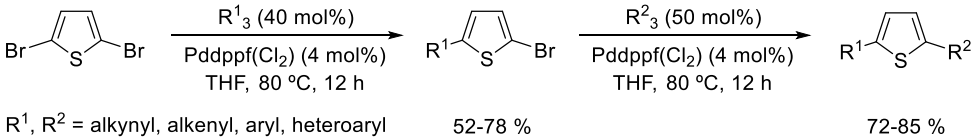
33 Pérez-Caaveiro, C.; Pérez Sestelo, J.; Martínez, M. M.; Sarandeses, L. A. *J. Org. Chem.* **2014**, *79*, 9586-9593.

***Scheme 20**. Synthesis of Neurodazine with R_3In.*



The use of triorganoindium reagents for the selective functionalization of heteroaromatic substrates via cross-coupling reactions was successfully extended to 2,5-dibromothiophenes (Scheme 21).[34] Two different groups can be sequentially coupled to the electrophile furnishing 2,5-disubstituted thiophenes, where alkynyl, alkenyl, aryl, or heteroaryl groups can be transferred in good yields.

***Scheme 21**. Sequential cross-coupling of 2,5-dibromothiophenes using R_3In.*

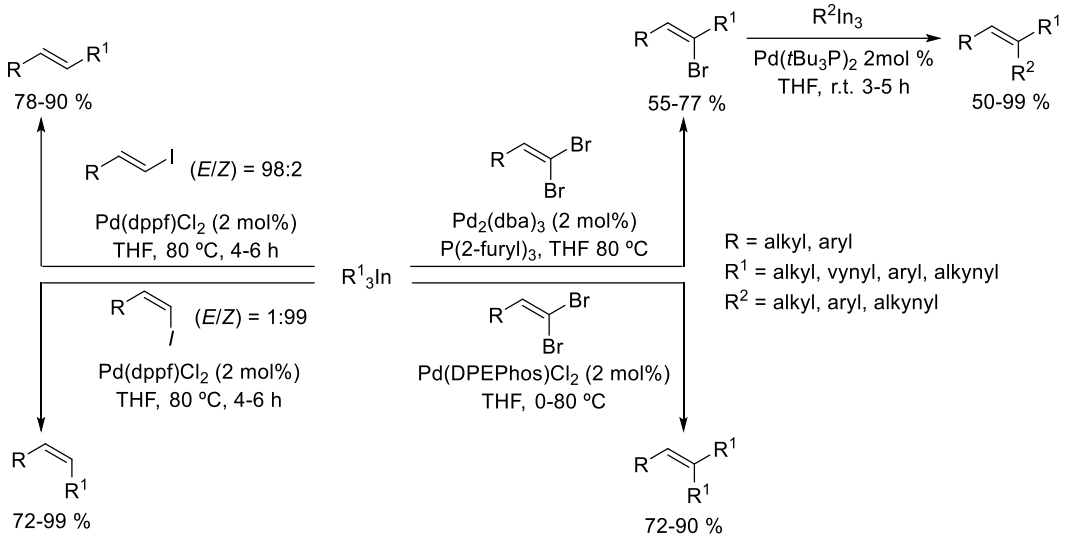


Another important application of triorganonindium reagents in palladium-catalyzed cross-coupling reactions is the regio and stereoselective reaction with stereodefined alkenes (Scheme 22).[35] Reactions can be performed on 1-haloalkenes and 1,1-dihaloalkenes resulting in the coupling of alkyl, aryl, vinyl, and alkynyl groups. The stereochemistry of the double bond is retained and reaction times are short affording the products in good to excellent yields. In the case of dihalogenated alkenes, substrates can undergo either a two-fold coupling reaction or two stereoselective sequential couplings incorporating two different organic groups.

34 Martínez, M. M.; Peña-Lopez, M.; Pérez Sestelo, J.; Sarandeses, L. A. *Org. Biomol. Chem.* **2012**, *10*, 3892-3898.

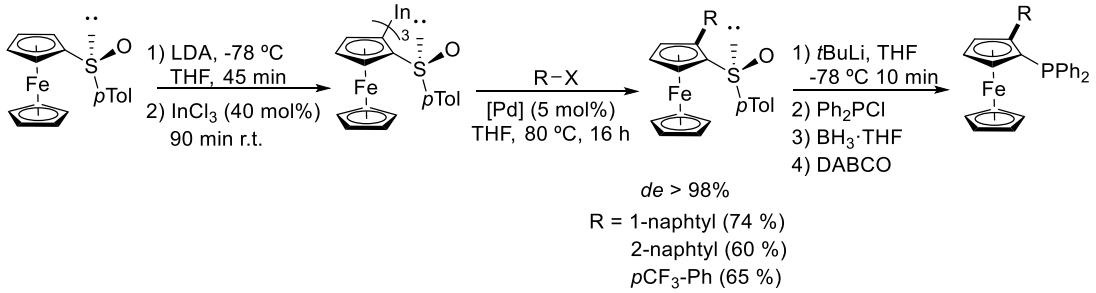
35 Riveiros, R.; Saya, L.; Pérez Sestelo, J.; Sarandeses, L. A. *Eur. J. Org. Chem.* **2008**, 1959-1966.

Scheme 22. *Stereoselective Pd-catalyzed coupling of R_3In with stereodefined alkenyl halides.*



In a more recent contribution, triferrocenylindium reagents, prepared by lithiation of ferrocene and subsequent treatment with $InCl_3$, have also shown to react efficiently under palladium catalysis to afford substituted ferrocenes (Scheme 23).[36]

Scheme 23. *Synthesis of planar chiral 2-aryl-1-diphenylphosphine ferrocenes by palladium-catayzed cross-coupling of triorganoindium reagents.*



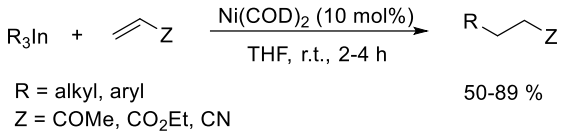
Interestingly, the use of chiral directing groups in the ferrocene molecule enables the diasteroselective lithiation and formation of triorganoindium reagents that ultimately lead to the obtention of planar-chiral phosphines.

The use of triorganoindium reagents in transition-metal catalyzed reactions is not limited to the use of palladium as catalyst. Nickel catalysis enables the 1,4-conjugate addition to α,β-unsaturated systems.[7b] The reaction proceeds with α,β-unsaturated ketones, esters, and nitriles transferring alkyl or aryl groups in good yields under

36 Mato, M.; Pérez-Caaveiro, C.; Sarandeses, L. A.; Pérez Sestelo, J. *Adv. Synth. Catal.* **2017**, *359*, 1388-1393.

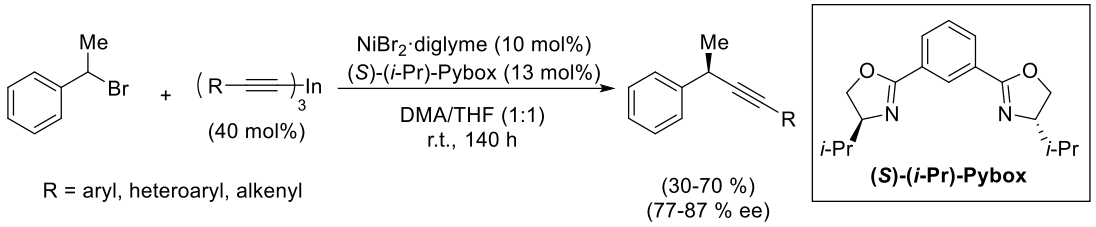
$Ni(COD)_2$ catalysis, in a selective manner, without any of the 1,2-addition product being observed (Scheme 24).

***Scheme 24**. Ni-catalyzed 1,4-conjugate addition of R_3In to α,β-unsaturated systems.*



Remarkably, it is also possible to carry out enantioselective cross-coupling reactions using triorganoindium reagents under nickel catalysis. Trialkynylindium can react with secondary benzylic bromides in an enantioconvergent cross-coupling reaction under nickel catalysis using a chiral pybox ligand (Scheme 25).[37] In this reaction, both enantiomers of the racemic starting material are preferentially transformed into one enantiomer of the product.

***Scheme 25**. Enantioconvergent Ni-catalyzed cross-coupling reaction of trialkynylindium reagents with racemic secondary benzyl bromides.*



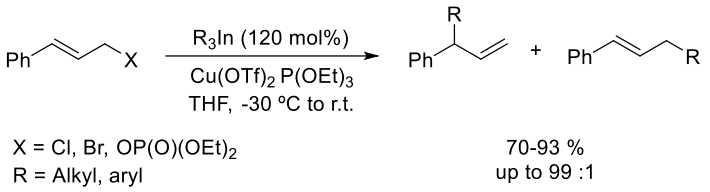
Triorganoindium reagents take part in the regioselective allylic substitution reaction of halides and phosphates under Cu(II) catalysis.[38] The reaction can be performed with trialkyl or triaryl indium reagents using triethyl phosphite as additive, although in this case only one of the three organic groups attached to indium metal is transferred in the process (Scheme 26). Posterior investigations showed that under palladium catalysis it is possible to obtain regioselectively the S_N2 product.[39]

37 Caeiro, J.; Pérez Sestelo, J.; Sarandeses, L. A. *Chem. Eur. J.* **2008**, *14*, 741-746.

38 Rodriguez, D.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Org. Chem*. **2003**, *68*, 2518-2520.

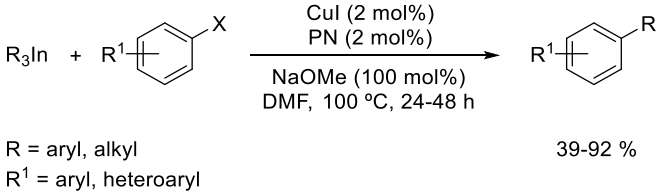
39 (*a*) Rodriguez, D.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Org. Chem*. **2004**, *69*, 8136-8139 (*b*) Baker, L.; Minehan, T.; *J. Org. Chem.* **2004**, *69*, 3957-3960.

***Scheme 26**. Copper-catalyzed allylic substitution reaction with triorganoindium reagents.*



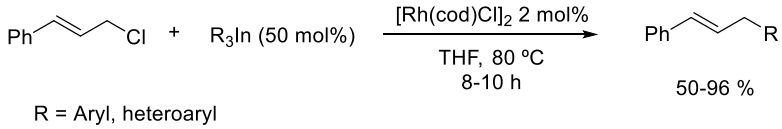
The group of Giri disclosed that copper catalysis can allow the cross-coupling of aryl triorganoindium reagents with various aryl halides.[40] The reaction proceeds smoothly in the presence of CuI and 2-(di-*tert*-butylphosphino))-*N*,*N*-dimethylaniline (PN) in DMF, affording the corresponding cross-coupling products in moderate to good yield (Scheme 27).

***Scheme 27.** CuI catalyzed cross-coupling of triorganoindium reagents with aryl halides.*



Triorganoindium reagents can also take part in allylic substitution reactions under rhodium catalysis.[41] The reaction proceeds with a variety of aryl and heteroaryl indium reagents to afford selectively the S_N2 substitution products (Scheme 28).

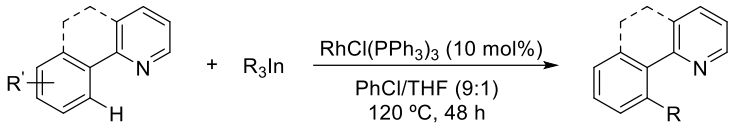
***Scheme 28**. Rhodium-catalyzed allylic substitution reaction with triorganoindium reagents.*



More recently, it was disclosed that triorganoindium reagents can take part in the rhodium catalyzed C-H activation/cross-coupling reaction of 2-arylpyridines (Scheme 29).[42] Trimethyl and triarylindium can react with a variety of 2-arylpyridines affording the corresponding ortho coupling products in good to moderate yields.

40 Thapa, S.; Gurung, S. K.; Dickie, D. A.; Giri, R. *Angew. Chem. Int. Ed.* **2014**, *53*, 11620-11624.
41 Riveiros, R.; Tato, R.; Pérez Sestelo, J.; Sarandeses, L. A.; *Eur. J. Org. Chem.* **2012**, 3018.
42 Riveiros, R.; Tato, R.; Pérez Sestelo, J.; Sarandeses, L. A.; *Molecules*, **2018**, 1582.

***Scheme 29**. R_3In in Rh-catalyzed C-H activation/cross-coupling reaction with 2-arylpyridines.*



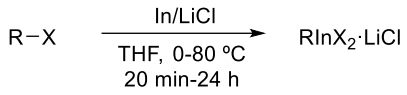
R = Me, Ar
R' = Me, H

45-93 %
14 examples

1.4 Other Indium (III) Organometallic Reagents.

Another type of indium(III) organometallic reagents capable of taking part in cross-coupling reactions are the $RInX_2$ species, developed independently by the groups of Mineham and Knochel, where R can be an aryl, heteroaryl or benzyl group.[43] These reagents are prepared by direct insertion of indium into the corresponding organic halides in the presence of LiCl (Scheme 30).

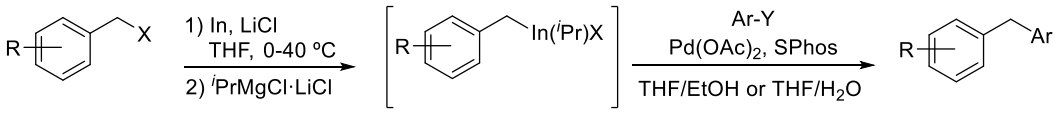
***Scheme 30**. Preparation of $RInX_2$ reagents.*



R = aryl, heteroaryl, benzyl
X = I, Br, Cl

Remarkably, these reagents can tolerate protic solvents in the reaction media. For example, it was found that the activation of benzylindium reagent with ^{i}PrMgCl·LiCl allowed the palladium-catalyzed cross-coupling reaction to proceed in the presence of ethanol or water (Scheme 31).[44]

***Scheme 31**. Pd-catalyzed cross-coupling of benzylindium in the presence of protic solvents.*



X = Cl or Br; Y = Br or I
R = CN, CO_2Et, COR, CHO, CONHR, OH

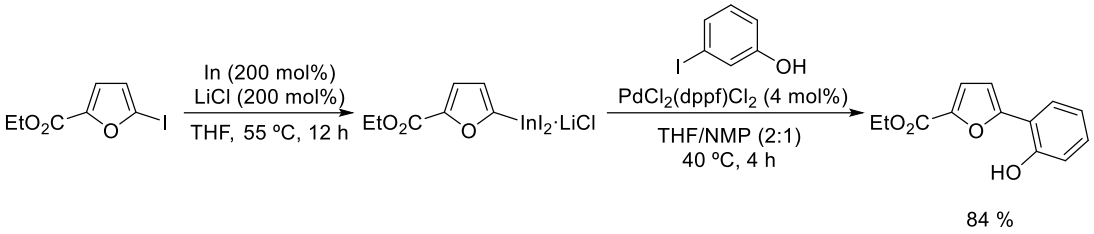
37-94 %

43 (*a*) Papoian, V.; Minehan, T. *J. Org. Chem.* **2008**, *73*, 7376-7379. (*b*) Chen, Y.-H. Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 7648-7651.

44 Chen, Y.-H.; Sun, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 2236-2239.

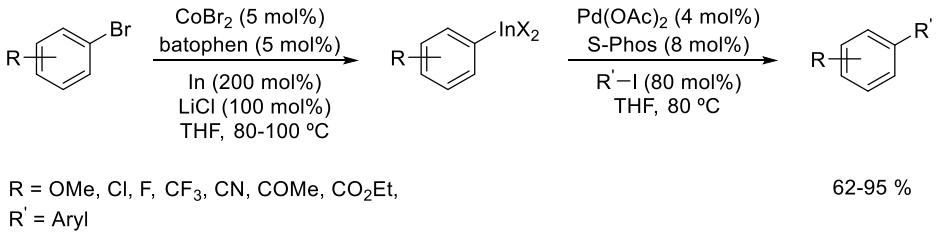
$RInX_2$ reagents also show excellent chemoselectivity as they can take part in palladium-catalyzed cross-coupling reactions in the presence of sensitive functional groups like aldehyde, ester, nitrile, or hydroxyl (Scheme 32). However, despite their notable properties in cross-coupling, $RInX_2$ reagents do not possess the potential for atom-economy that triorganoindium compounds show, as only one organic group may be transferred for each indium atom that participates in the reaction.

***Scheme 32**. Chemoselective Pd-catalyzed cross-coupling reaction of $RInX_2$ reagents.*



$RInX_2$ species can be prepared by cobalt-catalyzed indium insertion of aryl bromides in the presence of lithium chloride (Scheme 33).[45] The resulting arylindium reagents undergo efficient palladium-catalyzed cross-coupling reaction with aryl iodides. Alternatively, catalytic CuCl can be used to synthesize alkyl $RInX_2$ reagents by insertion of indium into alkyl halides.[6]

***Scheme 33**. Cobalt catalyzed preparation of $RInX_2$ reagents and subsequent Pd-catalyzed cross-coupling reaction.*



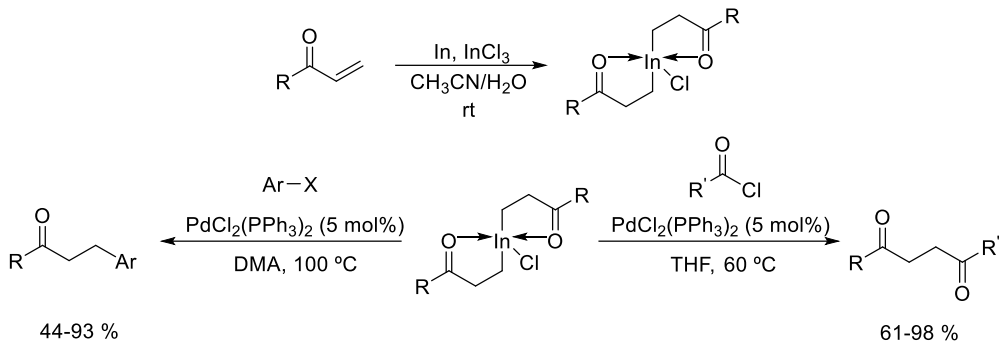
Another type of indium(III) reagents that participate in transition-metal catalyzed cross-coupling reactions are indium homoenolates, developed by the group of Loh, and which are generated from indium metal and indium halide in the presence of enones (Scheme 34).[46] Indium homoenolates can react under palladium catalysis

45 Adak, L.; Yoshikai, N. *J. Org. Chem.* **2011**, *76*, 7563-7568.

46 Shen, Z. L.; Goh, K.K.K.; Cheong, H. L.; Wong, C. H. A.; Lai, Y. C.; Yang, Y. S.; Loh, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 15852-15855.

with acyl chlorides to afford 1,4-dicarbonyl compounds, or with aryl halides to afford β-aryl ketones when the reaction is performed at higher temperature in DMA. [47]

Scheme 34*. Indium homoenolate in Pd-catalyzed cross-coupling.*



47 Shen, Z. L.; Lai, Y. C.; Wong, C. H.; Goh, K. K. K.; Yang, Y. S.; Cheong, H. L.; Loh, T. P. *Org. Lett.* **2011**, *13*, 422-425.

Chapter 2.

Transition-Metal-Free Coupling Reactions of Triorganoindium Reagents with Chromene and Isochroman Acetals and *N*-Protected Tetrahydroisoquinolines.

2.1. Transition-Metal-Free Coupling Reactions.

Transition-metal catalyzed cross-coupling reactions are one of the most versatile and reliable synthetic tools for the construction of C-C bonds in organic chemistry,[48] however, they still amount to considerable drawbacks, such as the high cost of the catalysts, which are normally based on precious metals such as gold, platinum or palladium. Other serious disadvantages include the use of complex ligands in the reactions, or the toxic nature of the metallic species involved which may limit the application in the potential synthesis of pharmaceuticals or chemicals.[49] Therefore, the development of new methods capable of achieving the same selectivity and reliability than transition-metal catalyzed reactions, while at the same time devoid of their associated drawbacks results both highly desirable and attractive.

A variety of reactions, based on different mechanistic pathways may be grouped into the category of transition-metal-free coupling reactions. These include, for example, base-promoted homolytic aromatic substitution (BHAS) reactions (Figure 1, equation 1), where aryl radicals react in the presence of a large excess of an arene at high temperature or under microwave assistance, yielding biarylated products.[50] Another important class of transition-metal-free reactions are oxidative coupling reactions, which are promoted by (at least) a stoichiometric amount of an oxidant reagent.[51] These reactions proceed through different mechanisms including single electron transfer (SET) oxidative coupling (figure 1, equation 2),[52] hydrogen transfer mechanism (figure 1, equation 3),[53] or Brönsted acid-catalyzed oxidative coupling.[54] Oxidative reactions may involve either the cross-coupling of two different organic molecules or the homocoupling reaction of the starting material. A remarkable

48 (*a*) *Cross Coupling Reactions in Organic Synthesis* Themed Issue. *Chem. Soc. Rev.* **2011**, *40*, 4877-5208. (*b*) *Metal Catalyzed Cross-Coupling Reactions and More, 3 Vol. Set*; De Meijere, A.; Bräse, S.; Oestreich, M. Eds. Wiley-VCH: Weinheim, **2014**.

49 (*a*) Garret, C. E.; Prasad, K.; *Adv. Synth. Catal.* **2004**, *346*, 889-900. (*b*) Huang, J.-P.; Chen, X.-X.; Gu, S.-X.; Zhao, L.; Chen, W.-X.; Chen, F.-E. *Org. Process. Res. Dev.* **2010**, *14*, 939-941.

50 Studer, A.; Bossart, M.; In *Radicals in Organic Synthesis*; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, **2001**; Vol. 2, pp. 62-80.

51 Klussmann, M.; Sureshkumar, D. *Synthesis* **2011**, *3*, 353-369.

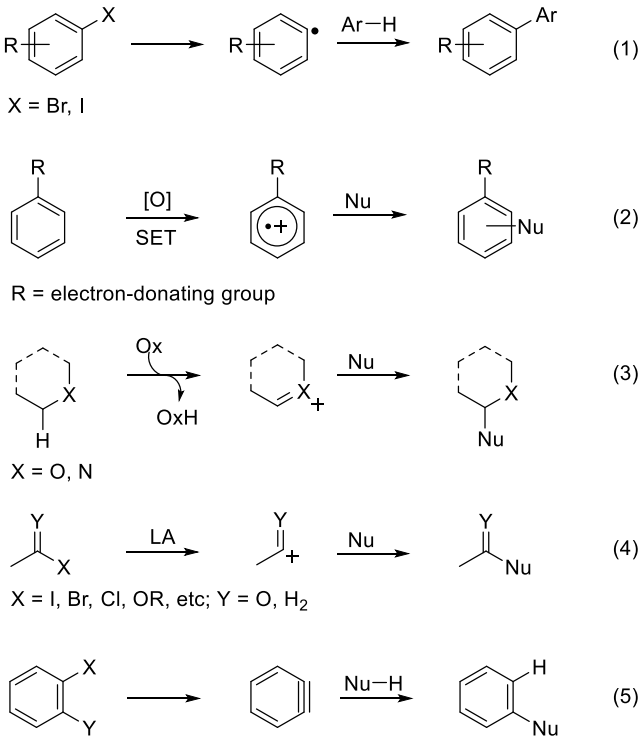
52 Kita, Y. Tohma, H.; Hatakana, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684-3691.

53 Jackman, L. M.; *Adv. Org. Chem.* **1960**, *2*, 329

54 Pinter, A.; Sud, A.; Sureshkumar, D.; Klussmann, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 5004-5007.

variant is the transition-metal free oxidative cross-dehydrogenative reaction, where new carbon-carbon bonds are formed via the coupling of sp^3 C-H bonds with other C-H bonds and thus avoiding the otherwise necessary prefunctionalization steps.[55] Lewis acids can also mediate in transition-metal free coupling reactions (Figure 1, equation 4), where alkaline, alkali, and p-block metal Lewis acid species participate in these reactions.[56] Arynes constitute important intermediaries in many carbon-carbon forming processes and they can also be regarded within the context of transition-metal-free reactions (Figure 1, equation 5).[57]

Figure 1. *Various types of transition-metal free coupling reactions.*



Homolytic aromatic substitution reactions can be regarded as one of the most straightforward methods to access biaryl structural motifs in organic chemistry.[58] In

55 (*a*) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. *Science*, **2010**, *328*, 1376-1379. (*b*) Chudasama, V.; Fitzmaurice, R. J.; Caddick, S. *Nat. Chem.* **2010**, *2*, 592-596.

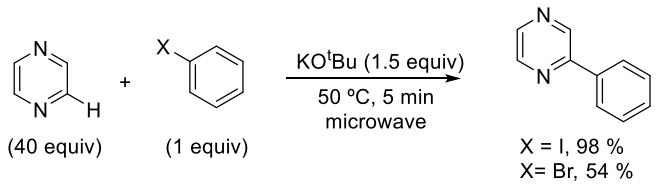
56 (*a*) Frost, C. G.; Hartley, J. P. *Mini-Rev. Org. Chem.* **2004**, *1*, 1-7. (*b*) Fugami, K.; Kosugi, M. *Top. Curr. Chem.* **2002**, *219*, 87-130. (*c*) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem Rev.* **2002**, *102*, 1359-1469.

57 (*a*) Bhunia, A.; Reddy, Y. S.; Biju, A. T.; *Chem. Soc. Rev.* **2012**, *41*, 3140-3152. (*b*) García López, J. A.; Geaney, M. F. *Chem. Soc. Rev.* **2016**, *45*, 6766-6798. (*c*) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550-3577.

58 (*a*) Rostovsev, V. V.; Snieckus, V. Macklin, T.; Waldvogel, S. V.; Mirk, D. In *Handbook of C-H Transformations: Applications in Organic Synthesis*. Dyker, G. WILEY-VCH, Weinheim, **2008**. (*b*) Harrowven, D. C.; Sutton, B. J. *Prog. Heterocycl. Chem.* **2004**, *16*, 27-

these reactions a leaving group on an aromatic ring is replaced by an attacking radical species. The whole process generally involves formation of the attacking radical species, addition to the aromatic ring, and finally elimination of the leaving group. Various substrates can be used as the source for the precursor aryl radical where the preferred choice is generally an aryl halide. The intermolecular BHAS cross-coupling of aryl halides with *N*-containing heteroarenes was reported for the first time in 2008 by the group of Itami and co-workers.[59] They found that iodobenzene could be coupled to pyrazine in the presence of potassium *tert*-butoxide under microwave activation (Scheme 35). The mechanism for this reaction involves the generation of a radical species from iodobenzene, which has a tendency to react faster with electron-deficient arenes, such as pyrazine. The base assists in the elimination of the proton once the radical attacks pyrazine.[60]

***Scheme 35**. KO^{t}Bu promoted HAS reaction of pyrazine with halobenzenes.*



The use of an organocatalyst with hydroxyl or amine moieties has enabled the BHAS cross-coupling reaction to be extended to common arenes including anisole, toluene, or fluoroarenes, among others.[61] For example, 4-bromoanisole has been shown to react in benzene in the presence of potassium *tert*-butoxide and a catalytic quantity of phenanthroline (Scheme 36).

59 Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673-4676.

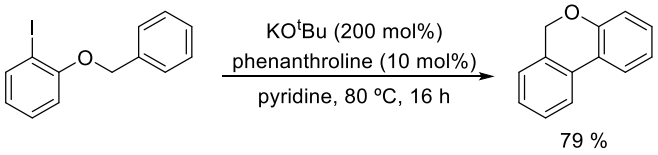
60 *Arene Chemistry: Reaction Mechanisms and Methods for Aromatic Compounds*. Rossi, R. A.; Budén, M. E.; Guastavino, J. F. John Wiley and Sons. **2016**.

61 (*a*) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S. F.; Li, B.-J.; Shi, Z.-J. *Nat. Chem.* **2010,** *2*, 1044-1049. (*b*) Liu, W.; Cao, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737-16740. (*c*) Shirakawa, E.; Itoh, K.; Higashino, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537-15539.

***Scheme 36**. Transition-metal-free coupling of 4-bromoanisole in benzene.*

Intramolecular variants of BHAS reactions have been used to the construction of polycyclic compounds, and provide an alternative not just to transition metals but also to other toxic or hazardous reagents commonly employed for the generation of aryl radicals in intramolecular reactions such as R_3SnH or AIBN. For example, 6*H*-benzo[*c*]chromene can be accessed from 1-benzyloxy-2-iodobenzene via a KO^{t}Bu promoted intramolecular reaction using phenanthroline as catalyst (Scheme 37).[62]

***Scheme 37**. Intramolecular BHAS reaction for the construction of 6H-benzo[c]chromene.*



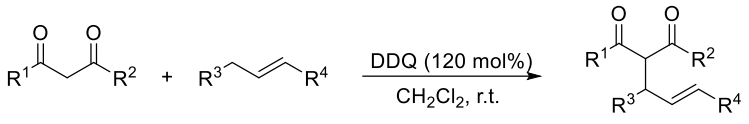
Oxidative coupling reactions are another class of versatile transition-metal-free reactions. Many oxidative coupling protocols were initially studied by employing a combination of transition metal catalysts and oxidants, but it was later found that these reactions still proceeded in the absence of the metallic species. An important oxidant widely used in several oxidative coupling reactions is 2,3-dichloro,5,6-dicyano-1,4-benzoquinone, commonly known as DDQ.[5] In DDQ-promoted cross-couplings the mechanism involves both electron and hydrogen transfer via a radical pathway. An example of this type of reaction is the coupling between allylic substrates and 1,2-dicarbonyl compounds (Scheme 38).[63] This methodology was also extended to the coupling of other nucleophiles such as aliphatic alcohols and thiols, aromatic thiols, and oximes.[64]

62 Sun, C.-L.; Gun, Y.-F.; Huang, W.-P.; Shi, Z.-J. *Chem. Commun.* **2011**, *47*, 9813-9815.

63 Cheng, D.; Bao, W. L. *Adv. Synth. Catal.* **2008**, *350*, 1263-1266.

64 (*a*) Li, Y.; Bao, W. L. *Adv. Synth. Catal.* **2009**, *351*, 865-868. (*b*) Jin, J.; Li, Y.; Wang, Z.-J.; Qian, W.-X.; Bao, W. L. *Eur. J. Org. Chem.* **2010**, 1235-1238.

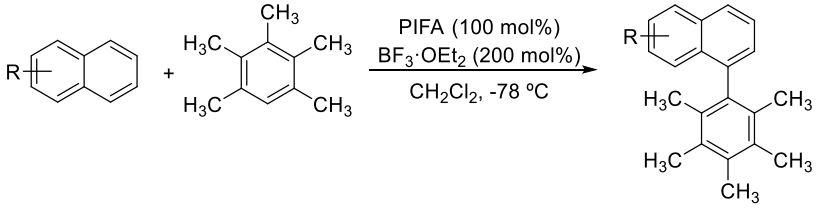
***Scheme 38**. DDQ-promoted coupling between allylic substrates and 1,2-dicarbonyls.*



R^1 = aryl, heteroaryl, alkyl
R^2 = Ph, Me, OEt
R^3 = Ph, 4-CN-Ph, 4-MeO-Ph
R^4 = Ph, 4-MeO-Ph

Hypervalent iodine reagents are another important type of oxidants, such as phenyliodine(III) diacetate (PIDA), phenyliodine(III) bis(trifluoroacetate) (PIFA), or 2-iodoxybenzoic acid (IBX). These compounds possess comparatively low toxicity, high stability, can be easily handled, and are commercially available, all of which makes them an attractive alternative from the synthetic point of view. In 1994, Kita and co-workers were the first to report a hyperiodine-induced nucleophilic substitution of *para*-substituted phenol eters.[65] UV and ESR spectroscopic studies confirmed that a radical cation generated via single electron transfer was the reactive intermediate. Since then, hypervalent iodine(III) has been used as an efficient oxidizing agent for the direct C-H functionalization of electron-rich arenes and heteroarenes under transition-metal-free conditions. For example, the coupling of pentamethylbenzene with naphthalene derivatives can be achieved using PIFA as oxidant (Scheme 39).[66]

***Scheme 39**. PIFA-promoted oxidative cross-coupling of naphthalenes and mesitylenes.*



R = Br, Ph, CO_2Me

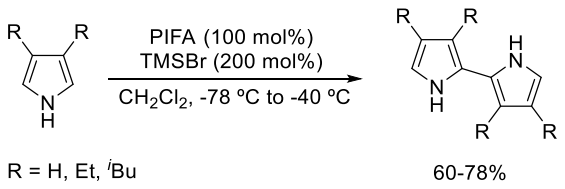
The utility of these methods is still limited by the undesired homocoupling reaction; however, this in turn has been capitalized resulting in the development of efficient reactions for the synthesis of substrates such as bipirroles or bithiophenes. For

65 Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684-3691.

66 Dohi, T.; Ito, M.; Morimoto, K.; Iwata, M.; Kita, Y. *Angew. Chem. Int. Ed.***2008**, *47*, 1301-1304.

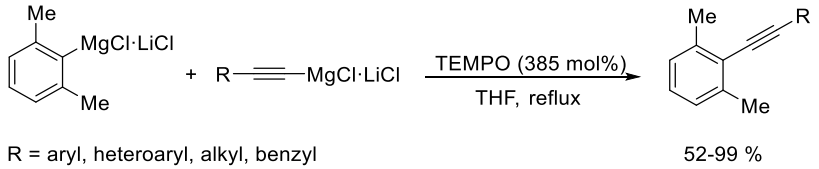
example, 3,4-disubstituted pyrroles can be subjected to direct oxidative homocoupling reaction using PIFA in the presence of TMSBr as activator (Scheme 40).

***Scheme 40**. PIFA-mediated direct oxidative coupling of 3,4-disubstituted pyrroles.*



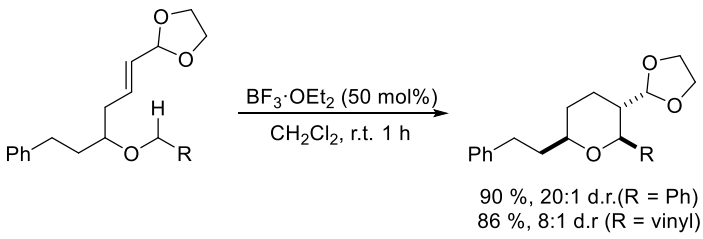
More interestingly, oxidants may enable Sonogashira-type coupling reactions in the absence of metal catalysts; in these reactions, bulky aryl Grignard reagents are cross-coupled in the presence of TEMPO while only trace amounts of the homocoupling products are observed (Scheme 41).[67]

***Scheme 41**. Sonogashira-type transition-metal-free reactions of Grignard reagents.*



Lewis acids can also enable transition-metal-free coupling reactions. A growing of synthetic methods are based on the Lewis acid-assisted functionalization of the position adjacent to heteroatoms.[68] For instance, $BF_3{\cdot}OEt_2$ mediates in the diastereoselective cyclization of alkenyl acetals via the generation of an oxocarbenium (Scheme 42)[69].

***Scheme 42**. $BF_3{\cdot}OEt_2$ mediated intramolecular cyclization reaction.*



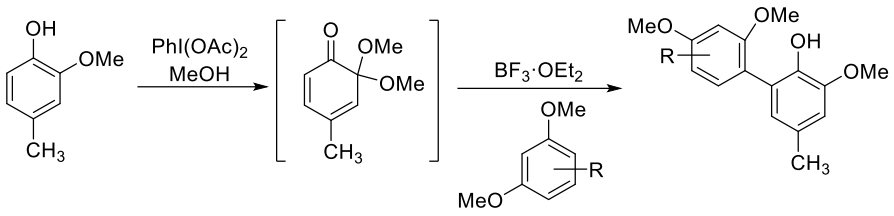
67 Maji, M. S.; Murarka, S.; Studer, A. *Org. Lett.* **2010**, *12*, 3878-3881.

68 (*a*) Shang, M.; Chan, J. Z.; Cao, M.; Chang, Y.; Wang, Q.; Cook, B.; Torker, S.; Wasa, M. *J. Am. Chem. Soc.* **2018**, *140*, 10593-10601. (*b*) Hisano, N.; Kamei, Y.; Kansaku, Y.; Yamanaka, M.; Mori, K. *Org. Lett.* **2018**, *20*, 4223-4226. (*c*) Zheng, C.; You, S.-L. *RSC Advances* **2014**, *4*, 6173-6214.

69 McQuaid, K.; Dalibor, S. *J. Am. Chem. Soc.* **2009**, *131*, 402-402.

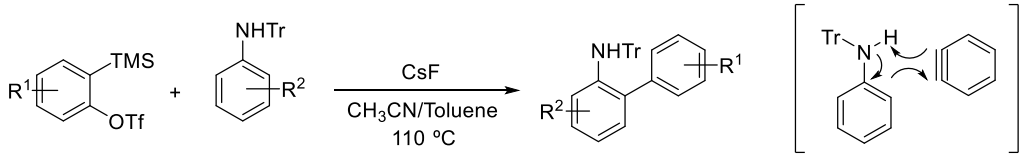
In another interesting example, $BF_3{\cdot}OEt_2$ can allow the site-selective synthesis of biaryls from 2-methoxyphenols (Scheme 43).[70] In the reaction, 2-methoxyphenols are first converted into electrophilic benzoquinone monoketals by treatment with hypervalent iodine, which are then attacked by electron-rich arenes after activation with the Lewis acid.

***Scheme 43**. Site-selective, $BF_3{\cdot}OEt_2$ mediated transition-metal-free synthesis of biaryls.*



Finally, another sustainable alternative to existing transition-metal-catalyzed protocols is the use of arynes intermediates. This type of strategy can be followed for the synthesis of biaryls as an alternative to transition-metal-metal catalyzed cross-coupling reactions. In a recent example, the C-H arylation of trityl anilines using 2-trimethylsilylphenyl triflates as precursors was disclosed. [71] The reaction is likely to involve an aryne hetero-ene mechanism (Scheme 44). The reaction displays excellent functional group compatibility and unlike other methods of arylation is devoid of strong bases, ligands or additives.

***Scheme 44**. Transition-metal-free C-H arylation of anilines using aryne precursors.*



R^1 = H, OMe, *i*Pr, Br
R^2 = H, OMe, Me, Bn, Cl, CF_3, CO_2Et

51-97 %

70 Sharma S.; Parumala, S. K. R.; Peddinti, R. K. *J Org. Chem.* **2017**, *82*, 9367-9383.

71 Pirali, T.; Zhang, F.; Miller, A. H.; Head, J. L.; MsAusland, D.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 1006-1009.

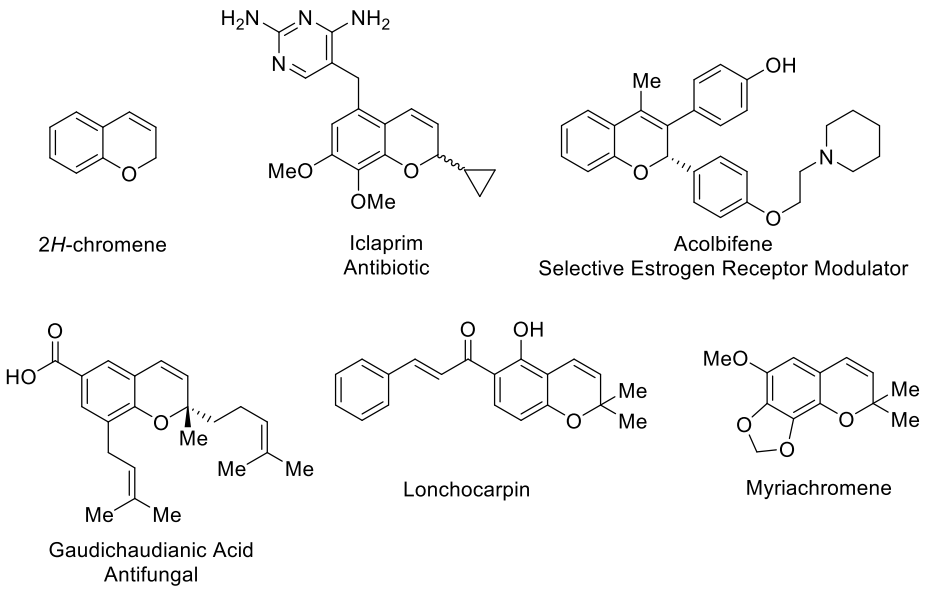
2.2 Transition-Metal-Free Coupling of Triorganoindium Reagents with 2*H*-Chromene and Isochroman Acetals.

2.2.1 Introduction.

Triorganoindium reagents react with a wide array of organic electrophiles under transition-metal catalysis featuring remarkable selectivity, versatility, and atom economy. On the other hand, the use of triorganoindium reagents in transition-metal-free protocols has stayed largely unexplored and remains a pending challenge within synthetic organic chemistry. Therefore, taking into account recent works disclosing the formation of new carbon-carbon bonds adjacent to heteroatoms under transition-metal-free conditions, we decided to investigate the reaction of triorganoindium reagents with relevant oxygenated heterocyclic scaffolds such as chromenes and isochromans.

2H-Chromenes (*2H*-1-benzopyrans) are important building blocks for the synthesis of many natural products with significant biological properties as well as pharmaceutical drugs (Figure 2).[72]

Figure 2. *Examples of relevant* 2*H-chromenes among natural products and pharmaceutical drugs.*



72 (*a*) Pratap, R.; Ram, V. J. *Chem. Rev.* **2014**, *114*, 10476-10526. (*b*) Nicolau, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939-9953.

For example, Iclaprim is an antibiotic in phase III clinical trials for the treatment of hospital-acquired pneumonia;[73] Acolbifene is a nonsteroidal selective estrogen receptor modulator that also exhibits activity against breast cancer;[74] Gaudichaudianic acid is a potent antifungal compound isolated from *P. Gaudichaudianum*;[75] lonchocarpine is a natural product isolated from *L. Sericeus* that shows effects on human platelet aggregation;[76] Myriachromene is a natural product isolated from *M. Humilis* and which shows in vitro cytoxicity against several cancer cell lines.[77]

Isochroman (3,4-dihydro-1*H*-2-benzopyran) is also a relevant structural motif present both in natural products with potential therapeutic applications as well as in drugs already approved for the treatment of various diseases (Figure 3).[78] Among the great diversity of biologically important isochromans there are drugs such as Sonepiprazole, a selective dopamine receptor antagonist used to reduce stress-induced cognitive impairment;[79] the molecule catalogued CJ-17493 and which is currently being researched by Pfizer as a neurokinin-1 receptor antagonist for the treatment of conditions such as migraine or depression;[80] Penidicitrinin B, which is a natural product isolated from *P. citrinum* that exhibits antioxidant properties;[81] Ustusorane D, an isochroman acetal isolated from the fungus *A. ustus* that displays cytotoxic activity against colon cancer cells.[82]

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73 Sorbera, L. A.; Castaner, J.; Rabasseda, X. *Drugs Future* **2004**, *29*, 220-225.

74 Gauthier, S.; Caron, B.; Cloutier, J.; Dory, Y. L.; Favre, A.; Larouche, D.; Mailhot, J.; Ouellet, C.; Schwerdtfeger, A.; Leblanc, G.; Martel, C.; Simard, J.; Mérand, Y.; Bélanger, A.; Labrie, C.; Labrie, F. *J. Med. Chem.* **1997**, *40*, 2117–2122.

75 Lago, J. H. G.; Ramos, C. S.; Casanova, D. C. C.; Morandim, A. A.; Bergamo, D. C. B.; Cavalheiro, A. J. Bolzani, V. S.; Furlan, M.; Guimaraes, E, F.; Young, M. C. M.; Kato, M. J. *J. Nat. Prod.* **2004**, *67*, 1783-1788.

76 Fontenele, J. B.; Leal, L.K. A. M.; Ferreira, M. A. D.; Silveira, E. R.; Viana G. S. B. *Pharm. Biol.* **2005**, *43*, 726-731.

77 Chen, J.-J.; Duh, C.-Y.; Chen, Y.-S. *Planta Med.* **2005**, *71*, 370-371.

78 (*a*) Yamaori, S.; Kushihara, M.; Yamamoto, I.; Watanabe, K. *Biochem. Pharmacol.* **2010**, *79*, 1691-1698. (*b*) de Groot, M.J.; Alex, A. A.; Jones, B. C.; *J. Med. Chem.* **2002**, *45*, 1983-1988.

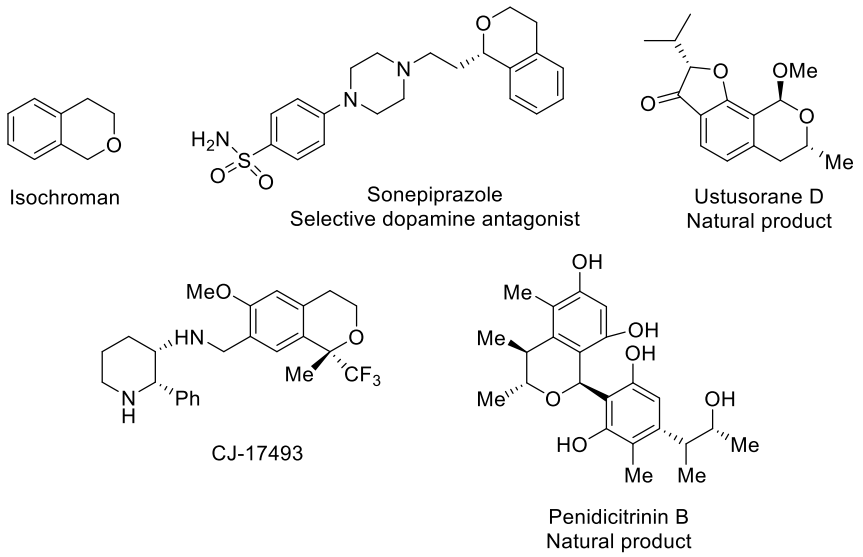
79 Smith, M. W. (and 12 authors) *J. Med. Chem.* **1996**, *39*, 2435-2437

80 Shishido, Y. (and 17 authors) *Bioorg. Med. Chem.* **2008**, *16*, 7193-7205.

81 (*a*) Clark, B. R.; Capon, R. J.; Lacey, E.; Tennant, S.; Gill, J. H. *Org. Biomol. Chem.* **2006**, *4*, 1520-1528. (*b*) Liu, H.-C.; Du, L.; Zhu, T. J.; Li, D.-H.; Geng, M.-Y.; Gu, Q.-Q. *Helv. Chim. Acta*, **2010**, 93, 2224-2230.

82 Kuramochi, K.; Tsubaki, K.; Kuriyama, I.; Yoshiyuki, M.; Yoshida, H.; Takeuchi, T.; Kamisuki, S.; Sugawara, F.; Kobayashi, F. *J. Nat. Prod.* **2013**, 76, 1737-1745.

***Figure 3**. Examples of isochromans with relevant biological properties.*



Classically, chromene and isochroman scaffolds may be accessed by condensation or annulation reaction protocols, although these approaches normally involve multiple steps or harsh reaction conditions. 1-Substitued isochromans can be prepared by oxa-Pictect-Spengler reaction between 2-phenylethan-1-ol derivatives and aldehydes or ketones using Bronsted or Lewis acids as activators (Scheme 45).[83] Similarly, the *2H*-chromene skeleton can be accessed from phenol or salicylaldehyde derivatives by oxa-Michael type annulations.[84]

***Scheme 45**. Sythesis of 1-substitued isochromans via oxa-Pictet-Spengler reaction.*

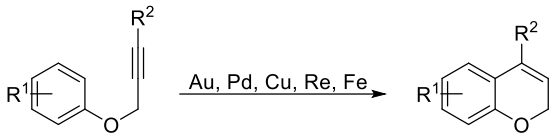
More recently, 2*H*-chromenes have been prepared via hydroarylation reaction of aryl propargyl eters under transition-metal catalysis (Scheme 46). A number of gold catalysts such as $Ph_3PAuNTf_2$, or [IPrAu(Cl)] can catalyze efficiently the reaction of

83 (*a*) Wunsch, B.; Zott, M. *Liebigs Ann. Chem.* **1992**, 39-45. (*b*) Guiso, M.; Marra, C.; Cavarischia, C. *Tetrahedron Lett.* **2001**, *42*, 6531-6534. (*c*) Guiso, M.; Bianco, A.; Marra, C.; Cavarischia, C. *Eur. J. Org. Chem.* **2003**, 3407-3411.

84 (*a*) Liu, S.-X.; Jia, C.-M.; Yao, B.-Y.; Chen, X.-L.; Zhang, Q. *Synthesis* **2016**, *48*, 407-412. (*b*) Zhang, Z.; Jakab, G.; Schreiner, P. R. *Synlett* **2011**, 1262-1264.

aryl propargyl eters to afford the corresponding *2H*-chromenes in good yields.[85] Palladium can also enable this type of reaction, where the use of chiral ligands has shown to induce high enantiomeric excesses under mild conditions.[86]

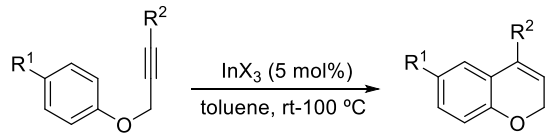
Scheme 46*. Transition-metal catalyzed hydroarylation reaction for the synthesis of 2H-chromenes.*



R^1 = H, Alkyl,aryl, F, OMe, CO_2Me, CN, NO_2
R^2 = H, Cl, Br, OMe, Aryl, Alkyl

Besides these noble metals, the use of other catalysts based on copper, rhenium or iron have also been reported.[87] Interestingly, our group recently reported the use of indium(III) halides for the synthesis of 2*H*-chromenes, affording comparable results to those obtained with transition-metal catalysts (Scheme 47).[88]

Scheme 47*. Indium(III) catalyzed hydroarylation reaction for the synthesis of 2H-chromenes.*



R^1 = OMe, Me, Br, NO_2, CN, CO_2Me X = Cl, Br, I 65-98 %
R^2 = Ph, *p*-Tol, *p*-AcPh, Me, CO_2Me, Br, I

The preparation of 2*H*-chromenes via the hydroarylation reaction of aryl propargyl eters can also be achieved under metal-free conditions, where the presence of electron-donating groups in the benzene ring increases reaction yields while electron-withdrawing groups cause the opposite effect (Scheme 48). [89]

85 (*a*) Lykakis, I. N.; Efe, C.; Gryparis, C.; Stratakis, M. *Eur. J. Org. Chem.* **2011**, 2334-2338. (*b*) Aponick A.; Biannic, B.; Jong, M. R. *Chem. Commun.* **2010**, *46*, 6849-6851. (*c*) Nevado C.; Echavarren, A. M. *Chem. Eur. J.* **2005**, *11*, 3155-3164.

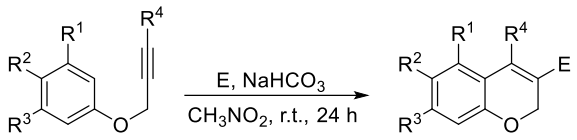
86 Zeng, B. S.; Yu, X.; Siu, P. W.; Schdeit, K. A. *Chem Sci.* **2014**, *5*, 2277-2281.

87 (*a*) Paul, N. D.; Mandal, S.; Otte, M.; Cui, X.; Zhang, X. P.; de Bruin, B. *J. Am. Chem. Soc.* **2014**, *136*, 1090-1096. (*b*) Xu, X.; Liu, J.; Liang, L.; Li, H.; Li, Y. *Adv. Synth. Catal.* **2009**, *351*, 2599-2604. (*c*) Zeng, H.; Hu, J.; Hua, R. *Tetrahedron Lett.* **2011**, *52*, 3926-3928.

88 Alonso-Marañón, L.; Martínez, M. M.; Sarandeses, L. A.; Pérez Sestelo, J. *Org. Biomol. Chem.* **2015**, *2*, 379-387.

89 Worlikar, S. A.; Kesharwani, T.; Yao, T.; Larock, L. C. *J. Org. Chem.* **2007**, *72*, 1347-1353.

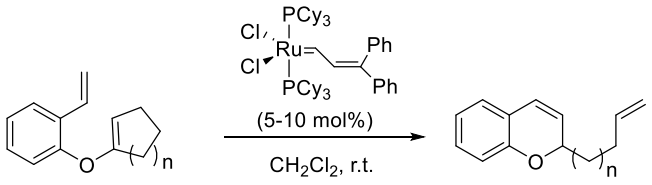
***Scheme 48**. Transition-metal free hydroarylation reaction for the synthesis of 2H-chromenes.*



R^1 = ^{t}Bu, Cl, OMe
R^2 = Me, ^{t}Bu, OMe, Cl, CHO
R^3 = ^{t}Bu, Cl, OMe
R^4 = Ph, C_6H_4Me-p,C_6H_4OMe-p, $C_6H_4NO_2$-p, C_6H_4Me-o
E = I_2, PhSeBr

Another approach towards the synthesis of 2*H*-chromenes involves the use of ring-closing metathesis of styrenyl ethers.[90] The reaction can be carried out on either terminal or disubstituted styrenyl susbtrates. In the case of the disubstituted olefines, the use of ethylene atmosphere becomes necessary. (Scheme 49)

***Scheme 49**. Synthesis of 2-susbtituted-2H-chromenes by RCM reaction.*

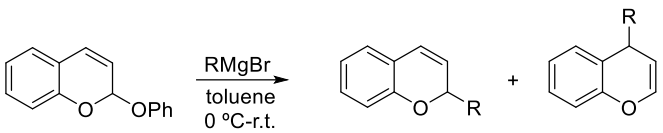


n = 1-3

n = 1-3
90-99 %

The functionalization of chromene acetals with Grignard reagents has been reported; although this approach normally affords mixtures of isomers and there is incompatibility with many functional groups. (Scheme 50).[91]

***Scheme 50**. Synthesis of 2-susbtituted-2H-chromenes by addition of Grignard reagents.*



R = alkyl, aryl, alkenyl

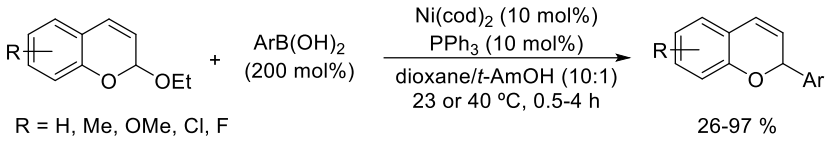
Up to 95:5 isomer ratio
18-84 % yield

90 Harrity, J. P. A.; La, D. S.; Cefalo, D. R.; Visser, M. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, 120, 2343-2351.

91 (*a*) Li, X.; Reuman, M.; Russel, R. K.; Adams, R.; Ma, R.; Branum, S.; Youells, S.; Roberts, J.; Jain, N.; Kanojia, R.; Sui, Z. *Org. Process Res. Dev.* **2007**, *11*, 414-421. (*b*) Grese, T. A.; Pennington, L. D. *Tetrahedron Lett.* **1995**, *36*, 8913-8916.

Transition-metal catalyzed cross-coupling reactions have also been employed in the synthesis of 2*H*-chromenes. A remarkable example is the nickel-catalyzed cross-coupling of chromene acetals with arylboronic acids, a reaction that takes place under mild conditions and is compatible with different functional groups (Scheme 51).[92]

Scheme 51. *Nickel-catalyzed cross-coupling of chromene acetals with arylboronic acids.*



In the last years a number of synthetic methods for the synthesis of substituted 2*H*-chromenes and isochromans have emerged based on the nucleophilic addition to *in situ* generated oxonium ions. Oxocarbenium ions play an importat role in the synthesis of natural products and bioactive drugs, and in particular, in the chemistry of carbohydrates and polycyclic ethers.[93] Furthermore, the synthesis of *α*-functionalized benzopyranes and *α*-substituted ethers can be achieved by nucleophilic addition to *in situ* generated oxonium ions, where the nucleophilic counterparts include enolates and derivatives, active methylene compounds, electron rich arenes and alkenes, or organoboron compounds.[94] For example, 2-alkenyl-2*H*-chromenes can be synthesized from the corresponding acetals using a combination of catalytic tartaric acid derivative and $Yb(OTf)_3$ (Scheme 52). [95] The oxonium ion generated in the reaction process undergoes nucleophilic addition by an alkenyl boronate affording the desired products in high enantiomeric excess.

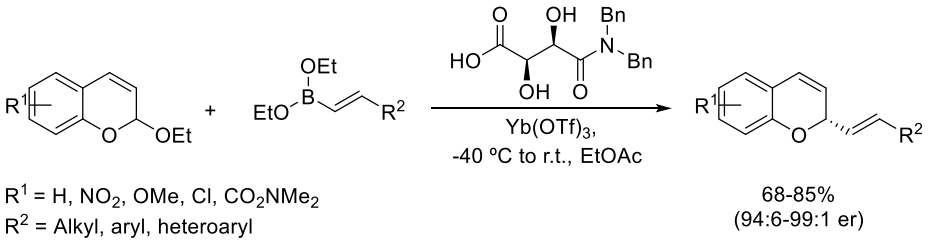
92 Graham, T. J. A.; Doyle, A. G. *Org. Lett.* **2012**, *14*, 1616-1619.

93 (*a*) Nakata, T. *Chem. Rev.* **2005**, *105*, 4314-4347. (*b*) Kang, E. J.; Lee, A. E. *Chem. Rev.* **2005**, *105*, 4348-4378.

94 (*a*) Liu, X.; Sun, B.; Xie, Z.; Qin, X.; Liu, L.; Lou, H. *J. Org. Chem.* **2013**, *78*, 3104-3112. (*b*) Xiang, M.; Meng, Q.-Y.; Li, J.-X.; Zheng, Y.-W.; Ye, C.; Li, Z.-J.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *Chem. Eur. J.* **2015**, *21*, 18080-18084. (*c*) Qian, B, Quiao, C.; Xie, Y.; Huang, H. *ChemCatChem* **2015**, *7*, 250-253. (*d*) Padhi, B.; Reddy, D. S.; Mohapatra, D. K. *Eur.J. Org. Chem.* **2015**, 542-547. (*e*) Michalska, M.; Songis, O.; Taillier, C.; Bew. S. P.; Dalla, V. *Adv. Synth. Catal.* **2014**, *356*, 2040-2050.

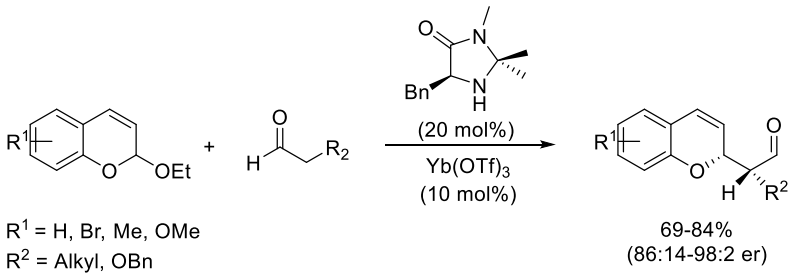
95 Moquist, P. N.; Kodama, T.; Schaus, S. E. *Angew. Chem. Int. Ed.* **2010**, *49*, 7096-7100.

***Scheme 52**. Enantioselective synthesis of 2-alkenyl-chromenes by catalytic Lewis/Brönsted acid*



In a similar reaction, aldehydes can be asymmetrically added to oxonium ions generated from 2*H*-chromene acetals by combination of $Yb(OTf)_3$ and a chiral imidazolidinone as catalyst (Scheme 53).[96] The Lewis acid is responsible for the generation of the planar oxonium species while the imidazolidinone and the aldehyde form a chiral enamine that adds selectively into one of its faces.

***Scheme 53**. Enantioselective addition of aldehydes to chromene derived oxonium ions.*

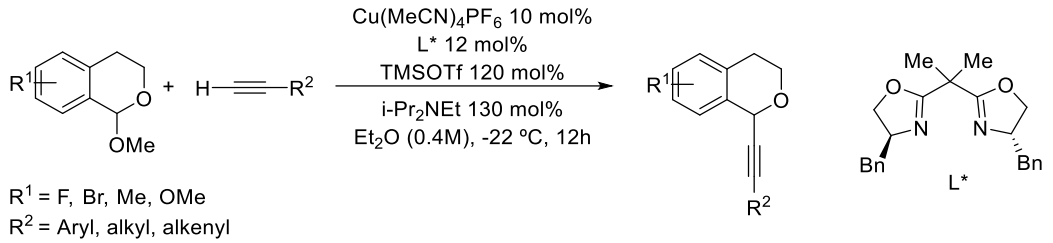


Likewise, 1-alkynyl isochromans can be prepared from the corresponding isochroman acetals using catalytic amounts of Cu and a chiral oxazoline ligand (Scheme 54).[97] High enantiomeric excesses can be reached when the reaction is performed at low temperature; stoichiometric amounts of Lewis acid generate the oxonium ion followed by addition of the alkynylcuprate follows.

96 Rueping, M.; Volla, C. M. R.; Atodiresei, I. *Org. Lett.* **2012**, *14*, 4642-4645.

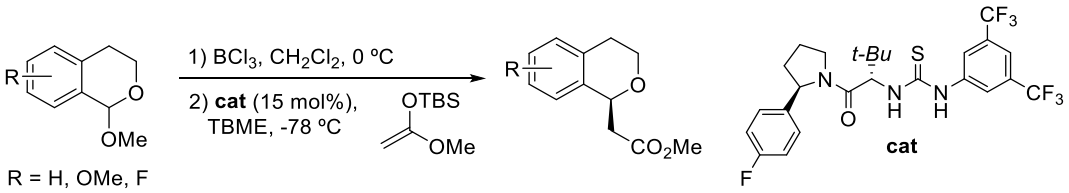
97 Maity, P.; Srinivas, H. D.; Watson, M. P. *J. Am. Chem. Soc.* **2011**, 133, 17142-17145.

***Scheme 54**. Enantioselective synthesis of 1-alkynyl isochromans.*



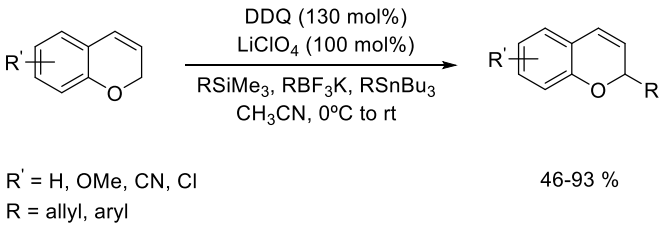
In a related work, the enantioselective addition of silyl ketene acetals to isochroman derived oxonium ions can be achieved by means of a thiourea catalyst (Scheme 55).[98] In this case, the chloride ion is the actual leaving group, generated *in situ* in the reaction media from the corresponding isochroman acetal at low temperature. The reaction proceeds with up to 90 % and tolerates different functionalities in the benzene ring of isochroman.

***Scheme 55**. Enantioselective synthesis of isochromans using chiral thiourea catalysts.*



Oxonium ions may also be generated under oxidative conditions. A diversity of 2-substituted chromenes can be synthesized by oxidative activation of the C-H bond adjacent to the oxygen atom and subsequent reaction with different nucleophiles (Scheme 56). [99]

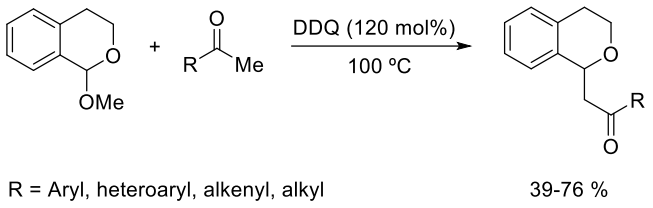
***Scheme 56**. Oxidative coupling of 2H-chromene with different nucleophiles.*



98 Reisman, S. E.; Doyle, A. G.; Jacobsen, N. E. *J. Am. Chem. Soc.* **2008**, *130*, 7198-7199.
99 Clausen, D. J.; Floreancig, P. E. *J. Org. Chem.* **2012**, *77*, 6574-6582.

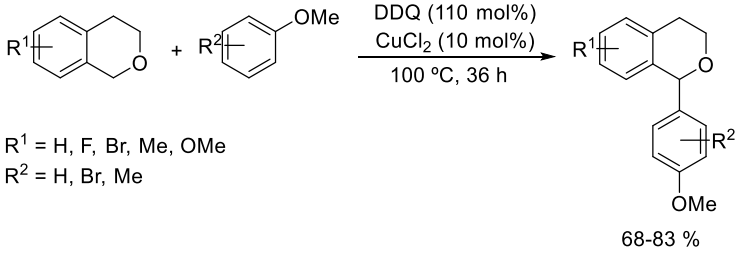
Oxidative coupling reactions with isochroman derived oxonium ions have also been reported. The oxidative coupling of isochroman acetal and ketones mediated by DDQ can be achieved under transition-metal-free conditions (Scheme 57).[100]

***Scheme 57**. Oxidative coupling reaction of isochroman acetal and simple ketones.*



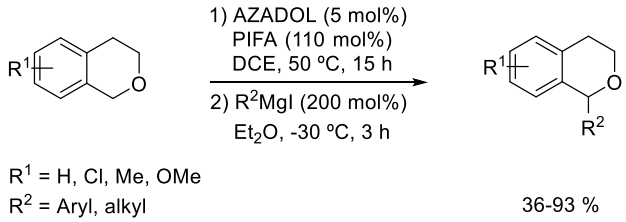
The cross-dehydrogenative coupling reaction of isochroman acetal and anisole derived nucleophiles has also been reported, although in this case the use of catalytic $CuCl_2$ in combination with the stoichiometric oxidant is deemed necessary for the reaction to proceed efficiently (Scheme 58).[101]

***Scheme 58**. Cross-dehydrogenative coupling of isochroman acetal and anisole.*



In another recently reported example of this type of reaction, isochroman undergoes oxidative coupling using hypervalent iodine (PIFA) in combination with aryl and alkyl Grignard reagents at low temperature (Scheme 59). [102]

***Scheme 59**. PIFA-mediated oxidative coupling of isochroman with Grignard reagents.*

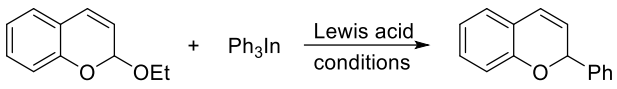


100 Zhang, Y.; Li, C.-J. *J. Am. Chem. Soc.* **2006**, *128*, 4242-4243.
101 Park, S. J.; Price, J. R.; Todd, M. H. *J. Org. Chem.* **2012**, *77*, 949-955.
102 Muramatsu, W.; Nakano, K. *Org. Lett.* **2015**, *17*, 1549-1552.

2.2.2 Results and Discussion.

Our investigation began studying the reaction of triorganoindium reagents with 2*H*-chromenes by means of Lewis acid activation. In this reaction, we envisioned that the generation of a highly electrophilic oxonium species would enable the nucleophilic addition of the triorganoindium reagents. Although the addition of different organometallic species to oxonium ions derived from 2*H*-chromene has been documented, there are no reports of such reactions involving indium organometallics. Triorganoindium reagents are well known for their versatility, functional group compatibility, and atom economy with the transference of all three organic groups attached to the indium metal center. For this purpose, triphenylindium was chosen as the organoindium reagent for the optimization of the reaction with chromene acetal **1**.

Table 1. *Screening of Lewis acids for the reaction of 2H-chromene acetal with Ph_3In.*



1 **1a**

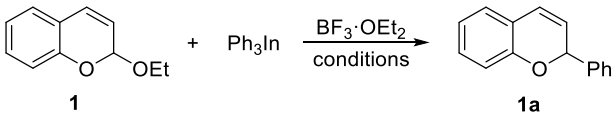
Entry	mol % Ph_3In	Lewis acid (mol%)	Reaction conditions	Yield (%)[a]
1	50	–	THF, r.t. to 80 °C, 16 h	–
2	50	TMSOTf (120)	THF, 80 °C, 16 h	–
3	50	$Cu(OTf)_2$ (120)	THF, 80 °C, 16 h	–
4	50	$Yb(OTf)_3$ (120)	THF, 80 °C, 16 h	33
5	50	$InBr_3$ (120)	THF, 80 °C, 16 h	6
6	100	$BF_3{\cdot}OEt_2$ (200)	THF, r.t, 16 h	92

[a] Isolated yield.

Initially, we tried the reaction of triphenylindium with chromene acetal **1** without Lewis acid (Table 1, entry 1); however, no reaction was observed and the starting material was fully recovered. Next, a series of Lewis acids reported in similar oxonium-mediated transformations[95-97] were tested in stoichiometric amounts at 80 °C (Table 1, entries 2-5); only in the case of $Yb(OTf)_3$, **1a** was obtained in 33 % yield. The poor performance was reasoned to the use of THF as solvent, which is generally incompatible with many Lewis acids. Since, the use of THF is recommended in the

preparation of the triorganoindium reagents,[103] the attention was shifted towards the use of $BF_3{\cdot}OEt_2$ which had been reported to enable the coupling reaction of *O*-alcoxymethyl acetals with organotrifluoroborates via an oxocarbenium ion intermediate.[104] Satisfyingly, performing the reaction in the presence of $BF_3{\cdot}OEt_2$ afforded product **1a** in an excellent 92% yield.

***Table 2**. Optimization of the reaction of chromene acetal **1a** and Ph_3In mediated by $BF_3{\cdot}OEt_2$.*



1 **1a**

Entry	mol % Ph_3In	mol % of $BF_3{\cdot}OEt_2$	Conditions	Yield (%)[a]
1	100	120	THF, r.t, 16 h	92
2	40	120	THF, r.t., 16 h	56
3	40	120	THF, 80 °C, 16 h	65
4	50	120	THF, 80 °C, 16 h	91
5	50	20	THF, 80 °C, 16 h	10

[a] Isolated yield.

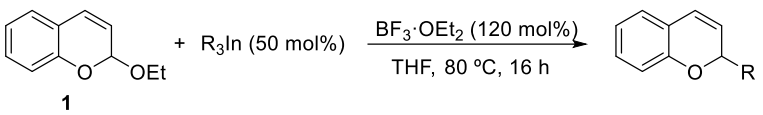
In an effort to optimize the reaction conditions, we studied the most appropriate amount of triorganoindium reagent and reaction temperature. The use of only 0.4 equivalents of Ph_3In at room temperature diminished the yield of product **1a** to be just 56 % (Table 2, entry 2), and most of the unreacted starting product **1** was recovered unchanged. Although, a slight increase in Ph_3In to 0.5 equivalents at room temperature, caused just a modest improvement in the reaction output (Table 2, entry 3). The reaction at 80 °C using only 0.5 equivalents of the triorganoindium reagent afforded **1a** in 91 % yield (Table 2, entry 4). This result implies that more than one organic group attached to indium is transferred during the reaction. The use of a catalytic amount of $BF_3{\cdot}OEt_2$ afforded only a residual yield of **1a** (Table 1, entry 5) showing that a stoichiometric amount is necessary for the reaction to proceed efficiently.

103 See the experimental section for details. For a method on the preparation of triorganoindium reagents see reference 20.

104 Vo, C.-V. T.; Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 14082-14089.

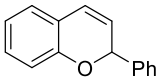
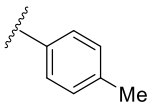
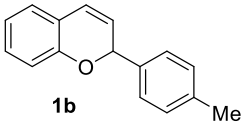
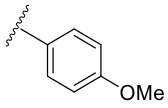
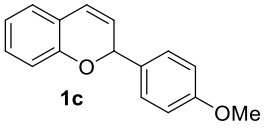
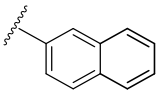
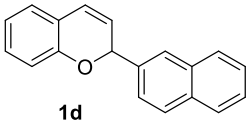
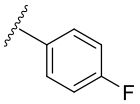
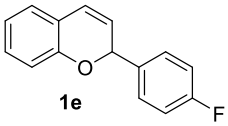
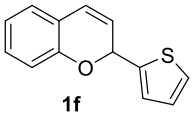
Once the optimal reaction conditions were established, we explored the versatility of the reaction using different triorganoindium reagents (Table 3).

***Table 3**. Reaction of **1** with aryl and heteroaryl triorganoindium reagents.*



1

R = aryl, heteroaryl

Entry	R	Product	Yield (%)[a]
1	Ph	 **1a**	91
2		 **1b**	88[b]
3		 **1c**	84[b]
4		 **1d**	67
5		 **1e**	85
6		 **1f**	74

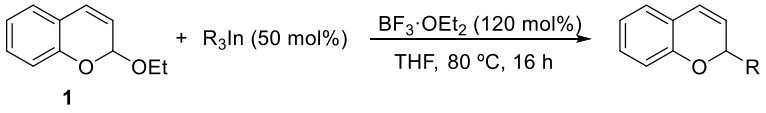
[a] Isolated yield. [b] Reactions performed at room temperature

Previous research on the cross-coupling of triorganoindium reagents under transition metal catalysis have consistently demonstrated that a wide array of these reagents bearing different aryl, heteroaryl, alkynyl, alkenyl, or alkyl groups react efficiently. In our case, the $BF_3{\cdot}OEt_2$-mediated reaction of **1** proceeded well with triaryl organoindium reagents (Table 3, entries 2-5). Remarkably, we observed that triarylindium furnished with electron-donating groups led to the coupling products **1b** and **1c** in high yields even at room temperature (Table 3, entries 2 and 3). This

increased reactivity may be attributed to the more nucleophilic character of the electron-rich arenes. The reaction also proceeded in the case of tri(naphtalen-2-yl)indium and tris-4-fluorophenylindium affording the corresponding 2-substituted-2*H*-chromenes **1d** and **1e** in good yields, although in these cases it was necessary to heat at 80 °C for the starting material to be completely consumed (Table 3, entries 4 and 5). Additionally, heteroarylindium compounds such as tris(2-thienyl)indium reacted efficiently giving compound **1f** in 74% yield (Table 3, entry 6).

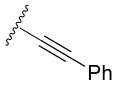
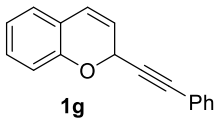
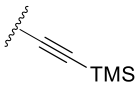
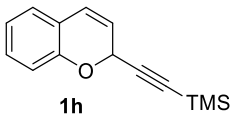
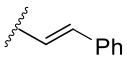
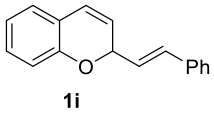
The reaction also proceeded with trialkynylindium reagents at 80 °C, providing the desired alkynyl chromenes **1g** and **1h** in good 89 and 85 % yields, respectively (Table 4 entries 1 and 2).

***Table 4**. Reaction of **1** with alkynyl and alkenyl triorganoindium reagents.*



1

R = alkynyl, benzyl

Entry	R	Product	Yield (%)[a]
1		 **1g**	89
2		 **1h**	85
3		 **1i**	92

[a] Isolated yield.

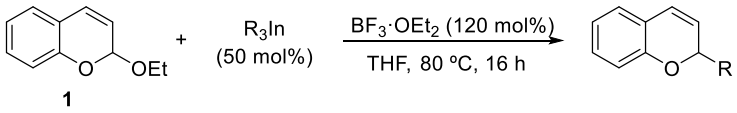
The alkynylation of acetals is an interesting approach to deliver α-carbon substituents to oxygen functionalities due to the possibility of further functionalization of the triple bond.[105] In addition, formation of 2-alkenyl chromene **1i** was achieved in an

105 (*a*) Johnson, W. S.; Elliott, R.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2904–2905. (*b*) Granja, J. R.; Castedo, L.; Mouriño, A. *J. Org. Chem.* **1993**, *58*, 124–131 (*c*) Schneider, U.; Dao, H. T.; Kobayashi, S. *Org. Lett.* **2010**, *12*, 2488–2491.

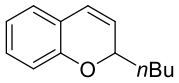
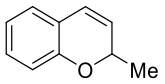
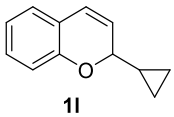
excellent 92 % yield, thus demonstrating the great versatility of triorganoindium reagents in this reaction (Table 4, entry 3).

Finally, we tested the reaction with trialkylindium reagents (Table 5). The coupling of tributylindium and trimethylindium afforded the corresponding 2-alkyl chromenes **1j** and **1k**, although in lower yields and with a loss of regioselectivity in the reaction, leading to a mixture of the C2 and C4 isomers in approximately 2:1 ratio.

***Table 5**. Reaction of **1** with alkyl triorganoindium reagents.*



R = alkyl

Entry	R	Product	Yield (%)[a]
1	*n*Bu	 **1j**	42[b]
2	Me	 **1k**	40[b]
3		 **1l**	84

[a] Reactions performed at room temperature. [b] Major regioisomer isolated; 65% overall yield, ratio C-2/C-4 = 65:35. [c] Major regioisomer isolated; 65% overall yield, ratio C-2/C-4 = 62:38.

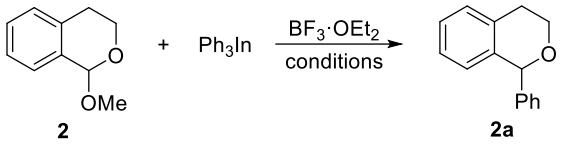
Interestingly, the reaction using tricyclopropylindium gave the 2-substituded chromene **1l** regioselectively in 84% yield, a result contrasting with the other alkylindium reagents and that demonstrates the special reactivity of cyclopropyl derivatives, notably due to bond constraints in the cyclopropane ring that cause an increased π interaction in the C-C bonds than it would normally be expected.[106]

After studying the reactivity of the acetal of 2*H*-chromene, the next step was to extend the new methodology to other relevant substrates. Isochroman, a

106 Hamilton, J. G.; Palke, W. E. *J. Am. Chem. Soc.* **1993**, *115*, 4159-4164.

benzoheterocyclic scaffold closely related to 2*H*-chromene, has the potential to give rise to the same type of electrophilic oxonium intermediate via Lewis acid activation of its corresponding acetal. To this effect, we found that the reaction of triphenylindium with the acetal of isochroman **2** afforded 1-phenylisochroman (**2a**) in an excellent 92 % yield (Table 6, entry 1). Interestingly, unlike the case of chromene acetal **1**, the reaction did not provide any of the product at room temperature, and it was necessary to heat at 80 °C (Table 6, entry 2). No reaction was observed without $BF_3{\cdot}OEt_2$ (Table 6, entry 3), while the use of a catalytic amount led only to a modest 8 % (Table 6, entry 4).

***Table 6**. Reaction of isochroman acetal **2** with Ph_3In mediated by $BF_3{\cdot}OEt_2$.*



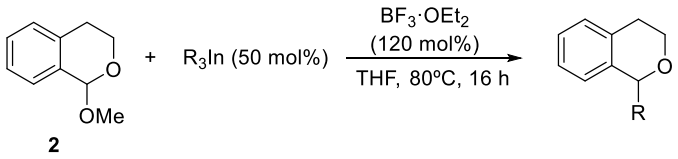
2 **2a**

Entry	mol % Ph_3In	mol % of $BF_3{\cdot}OEt_2$	Conditions	Yield (%)[a]
1	50	120	THF, 80 °C, 16 h	92
2	100	120	THF, r.t., 16 h	–
3	50	–	THF, 80 °C, 16 h	–
4	50	20	THF, 80 °C, 16 h	8

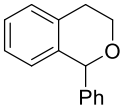
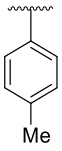
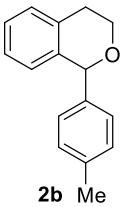
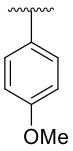
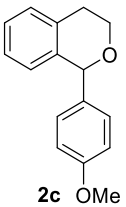
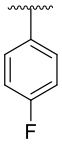
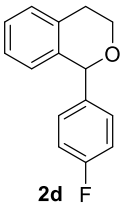
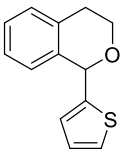
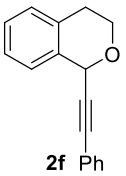
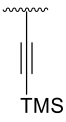
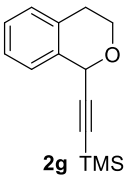
[a] Isolated yield.

We studied the scope of the reaction of isochroman acetal **2** with different types of triorganoindium reagents under $BF_3{\cdot}OEt_2$ activation (Table 7). During this research, we found that the coupling of aryl indium reagents proceeded in similar yields (Table 7, entries 2-4). Nevertheless, unlike chromene acetal **1**, it was necessary to perform the reaction at 80 °C even with the triaryl reagents bearing electron-donating groups. The reaction of isochroman acetal **2** was carried with heteroaryl triorganoindium reagents such as tris(2-thienyl)indium, affording 2-thienyl isochroman derivative **2e** in 71 % yield (Table 7, entry 5). Trialkynylindium reagents were also efficiently coupled, providing products **2f** and **2g** in 82 and 70 % yields respectively (Table 7, entries 6 and 7). Overall, these results show that isochroman acetal **2** can react with a variety of triorganoindium reagents under $BF_3{\cdot}OEt_2$ activation.

***Table 7**. Scope of the $BF_3{\cdot}OEt_2$ mediated reaction of R_3In reagents and acetal **2**.*



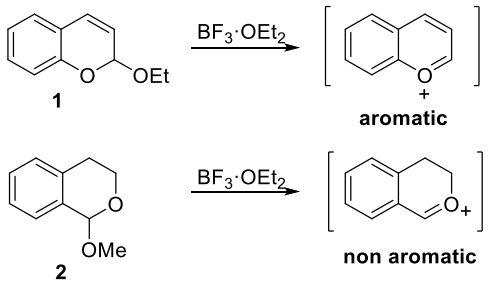
2

Entry	R	Product	Yield (%)[a]
1	Ph	 **2a**	92
2		 **2b** Me	90
3		 **2c** OMe	84
4		 **2d** F	88
5		 **2e**	71
6		 **2f** Ph	82
7		 **2g** TMS	70

[a] Isolated yield.

As with chromene acetal, the reaction takes place with substoichiometric amounts of the triorganoindium reagent, showing that more than one organic group attached to indium is transferred in the process as well. In comparisson, isochroman acetal **2** was less reactive than chromene acetal **1**, since no reaction takes place at room temperature or with alkyl and alkenyl indium reagents. The different reactivity shown between **1** and **2** can be explained by the different stability of the oxonium intermediates (Figure 4). In the case of 2*H*-chromene, the resulting oxonium cation is aromatic, while the resulting from isochroman is not. Therefore, the generation of the intermediate for **1** should be more favorable and hence the observation of reaction products at room temperature and when using less nucleophilic (slower-reacting) indium compounds.

***Figure 4**. Comparison of the proposed intermediates derived from **1**and **2**.*

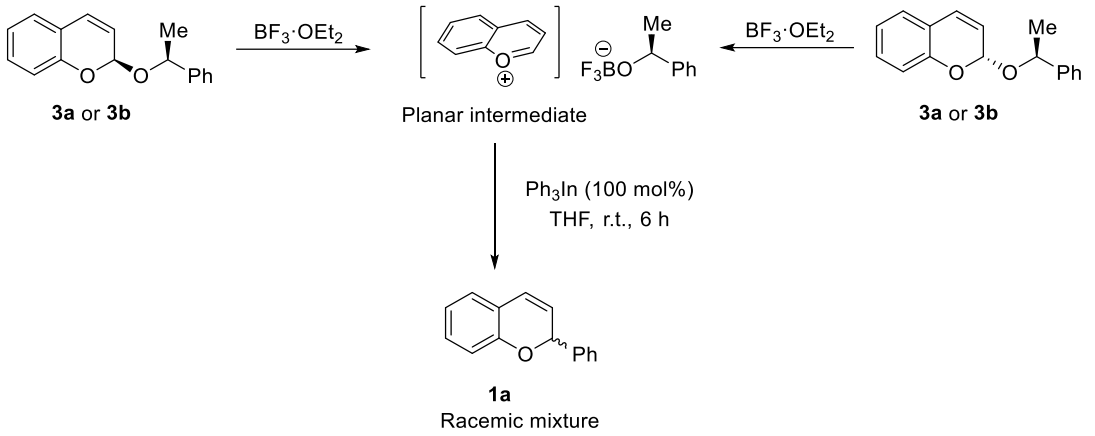


The identification of the proposed oxonium intermediate via NMR was attempted. After treatment of chromene acetal **1** with stoichiometric $BF_3{\cdot}OEt_2$, the proposed species could not be detected, perhaps due to its the short lived, highly reactive nature. Alternatively, we designed an experiment to shed some light into the reaction mechanism concerning the $BF_3{\cdot}OEt_2$ mediated reaction. We reasoned that if the reaction proceeds through a planar aromatic oxonium intermediate, then an enantiomerically pure acetal should give rise to a racemic mixture of the product upon reaction with the triorganoindium. Consequently, chiral chromene acetals **3a** and **3b** (prepared by reduction of coumarine, subsequent reaction with (*R*)-1-phenylethanol, and separation of the ensuing diastereomers through column chromatography)[107] were set to react independently with Ph_3In under $BF_3{\cdot}OEt_2$ activation (Scheme 60). In both cases, a racemic mixture of product **1a** was obtained,

107 The absolute stereochemistry of **3α** and **3β** was not determined; see experimental part for details.

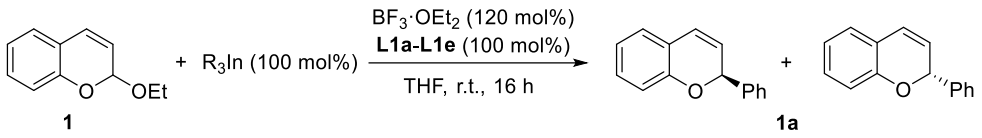
which provides strong evidence that the reaction takes place through a planar oxonium intermediate.

***Scheme 60**. Reaction of chiral chromene acetals **3a** and **3b** with Ph_3In under $BF_3{\cdot}OEt_2$ activation.*



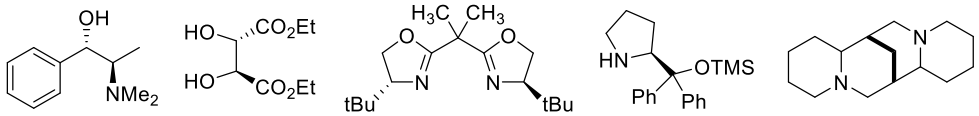
As mentioned before, many natural products and pharmaceutical drugs bearing the chromene structural motif are enantiomerically pure compounds, where only one of the enantiomers shows bioactive properties. Therefore, it would be highly desirable to develop a diastereoselective variant for the reaction with triorganoindium reagents. Hitherto, few synthetic methods achieve the enantioselective synthesis of 2-substituted-2*H*-chromenes, generally with the aid of a chiral ligand. In an attempt to induce the enantioselective addition of triorganoindium reagents to the chromene derived oxonium ion, a collection of different chiral ligands was screened. For this purpose, a stoichiometric amount of ligand was added to a solution of chromene acetal **1**, followed by sequential addition of Ph_3In, and $BF_3{\cdot}OEt_2$ at room temperature (Table 8).

***Table 8**. Screening of chiral ligands for the enantioselective reaction of Ph_3In with **1**.*



Entry	Additive	Yield (%)[a]	Enantiomeric Ratio[b]
1	**L1a**	45	50 : 50
2	**L1b**	20	45 : 55
3	**L1c**	–	–
4	**L1d**	18	50 : 50
5	**L1e**	–	–

[a] Isolated yield. [b] Determined by chiral HPLC analysis of the crude sample.



L1a **L1b** **L1c** **L1d** **L1e**

The affinity of nitrogen and oxygen donors for Group 13 metals is well known and has been used for the preparation of chiral reactions complexes that result in diastereoselective addition to different electrophiles. For instance, (1*S* 2*R*)-*N*-methylephedrine (**L1a**) has been used for the preparation of chiral aluminate complexes that result in the highly diastereoselective and enantioselective addition to unsaturated carbonyl compounds.[108] In consequence, additive **L1a** was used in combination with triphenylindium under the standard reaction conditions (Table 8, entry 1), affording product **1a** in 45 % yield, although only a racemic mixture was observed. The use of tartaric esters in combination with boron or zinc reagents for the asymmetric addition to various types of electrophiles has also been desribed,[109] which led us to probe the use of **L1b** as ligand (Table 8, entry 2). This afforded product **1a** in 20 % yield, resulting in most of the starting material being recovered unchanged, while practically no diastereoselectivity could be observed. Likewise, the use bis-

108 (*a*) Terashima, S.; Tanno, N. *Chem. Pharm. Bull.* **1983**, *31*, 837. (*b*) Williams, D. R.; Brooms, D. A.; Berliner, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 4924-4925.

109 (*a*) Sobiecka, A; Synoradzki, L.; Hajmowicz, H.; Zawada, K. *Org. Prep. Proced. Int.* **2017**, *49*, 1-27. (*b*) Ukaji Y.; Shimizu, Y.; Kenmoku, Y.; Ahmed, A.; Inomata, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 447-451. (*c*) Sui, J. T.; Vu, T.; Hernandez, A.; Congdon, J.; Singaram, B. *Tetrahedron Lett.* **2002**, 3649-3652.

oxazoline **L1c** or prolinol trimethylsilyl ether **L1d** provided no results in this sense (Table 8, entries 3 and 4). Sparteine (**L1e**), which has been extensively used for chiral lithiation as well as in combination with organozinc,[110] was also tested, but the result in this case was inhibition of the reaction (Table 8, entry 5).

Overall, the results show that a new transition-metal-free reaction of triorganoindium reagents with chromene and isochroman acetals has been established. This reaction proceeds efficiently with different types of triorganoindium reagents including aryl, heteroaryl, alkynyl, alkenyl, and alkyl to afford the corresponding 2-susbtituted 2*H*-chromenes and 1-substituted isochromans in good yields. Moreover, only 50 mol% of the triorganoindium reagent is employed in the reaction, which implies that more than one organic group is transferred in the process. Preliminary studies on the reaction mechanism suggest the formation of oxocarbenium intermediates in the presence of the Lewis acid.

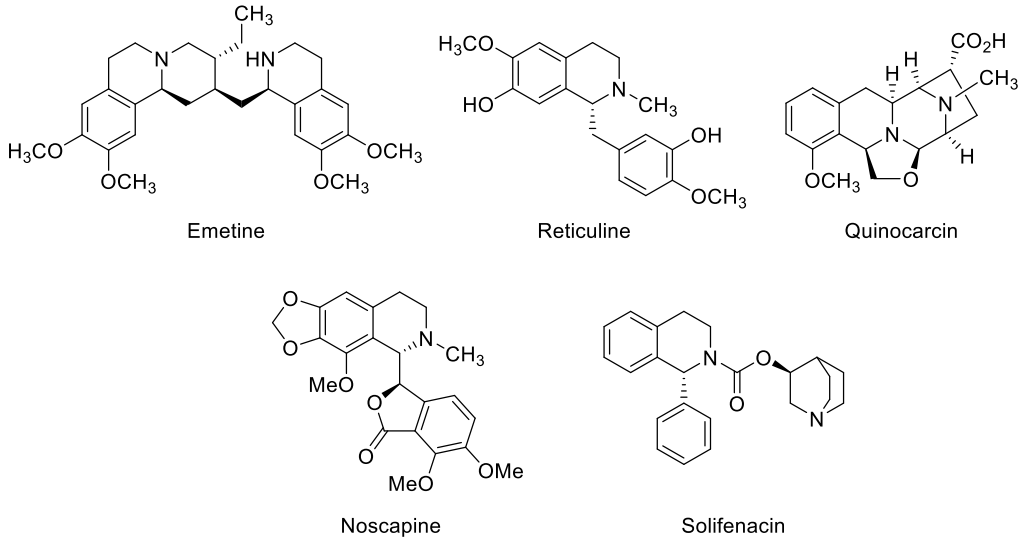
110 (*a*) Chuzel, O.; Riant, O. *Top. Organomet. Chem.* **2005**, *15*, 59. (*b*) Kloetzing, R. J.; Thaler, T.; Knochel P. *Org. Lett.* **2006**, *8*, 1125-1128. (*c*) Fujiwara, I.; Katagiri, T.; Uneyama, K. *Tetrahedron Lett.* **2003**, *44*, 6161-6163.

2.3 Transition-Metal-Free Coupling of Triorganoindium Reagents with *N*-Protected Tetrahydroisoquinolines.

2.3.1 Introduction.

After having studied the Lewis acid mediated reaction of triorganoindium reagents with isochroman and chromene acetals, we decided to extend the methodology to nitrogen containing substrates. Tetrahydroisoquinolines (THIQs) are one of the most common nitrogen-containing heterocycles that can be found among bioactive natural products and pharmaceutical drugs alike (Figure 5).[111] As example, these scaffolds serve as key intermediates in the synthesis and biosynthesis of important alkaloids such as Emetine, isolated from the roots of plants of genus *Carapichea* and which shows antiprotozoal properties,[112] or Reticuline which has powerful analgesic properties.[113] Antitumor antibiotics such as Quinocarcin, which display broad-range cytotoxicity against several types of human cancer cells, also contain the THIQ skeleton.[114]

***Figure 5**. THIQs in the structure of natural products and pharmaceutical drugs.*



111 (*a*) Herbert, R. B. in *The Chemistry and Biology of Isoquinoline Alkaloids* (Eds. Phillipson, J. D.; Roberts, M. F.; Zenk, M. H.) Springer, Verlag, Berlin, Heidelberg, New York, Tokyo, **1985**, p.213. (*b*) Jack, D.; Williams, R. *Chem Rev*. **2012**, *102*, 1669-1730.

112 Phillipson, J. D.; Wright, C. W.; *Planta Med.* **1991**, *57*, S53-S59.

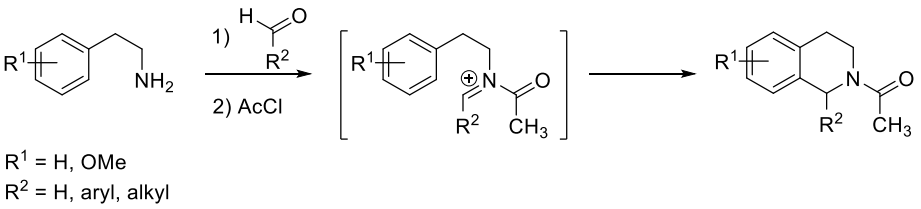
113 Custodio, D.L.; Da Veiga, V. F. *RSC Adv.* **2014**, *4*, 21864-21890.

114 Hiratsuka, T.; Koketsu, K.; Minami, A.; Kaneko, S.; Yamazaki, C.; Watanabe, K.; Oguri, H.; Oikawa, H. *Chem. Biol.* **2013**, *20*, 1523-1535.

Pharmaceuticals like antimuscarinic agent Solifenacin,[115] used in the treatment of spasmodic bladder, or Noscapine, a drug used for its antitussive properties,[116] also display the THIQ motif.

Due to the significance of this family of compounds, considerable efforts have been dedicated to the development of reliable methods to access THIQs and their derivatives. Usually, THIQs can be synthesized using the Bischler-Napieralski or Pitect-Spengler reactions.[117] The Bischler-Napieralski reaction is carried out in refluxing acidic conditions and requires the presence of dehydrating agents such as $POCl_3$ or P_2O_5. Depending on the presence or absence of electron donating groups in the phenyl ring of the phenethylamide, high temperature and long reaction times may be necessary. Recent developments into this reaction include the use microwave-assisted conditions to shorten reaction times, although there are still a number of disadvantages associated.[118] Alternatively, it is possible to acylate the intermediate iminium ion in the Pictect-Spengler reaction, thus increasing electrophilicity and enabling the cyclization to take place under milder conditions (Scheme 61).[119]

***Scheme 61**. N-acyliminium Pictect-Spengler reaction.*



In recent years, the selective functionalization at the C-1 position has emerged as an attractive alternative for the synthesis of THIQs. Among these, several protocols based on transition-metal-catalysis have been reported.[120] For example, dialkylzinc

115 Mealy, N.; Castaner, J. *Drugs Future* **1999**, *24*, 871-874.

116 Singh, H.; Singh, P.; Kumari, K; Chandra, A.; Dass, S. K.; Chandra, R. *Current drug metabolism* **2013**, *14*, 351-360.

117 (*a*) Heravi, M. M.; Khaghaninejad, S.; Nazari, N. *Adv. Heteocycl. Chem.* **2014**, *112*, 183-234. (*b*) Heravi, M. M.; Nazari, M. *Curr. Org. Chem.* **2015**, *19*, 2358-2408. (*c*) Nagubandi, S.; Fodor, G. *J. Heterocycl. Chem.* **1980**, *17*, 1457-1463.

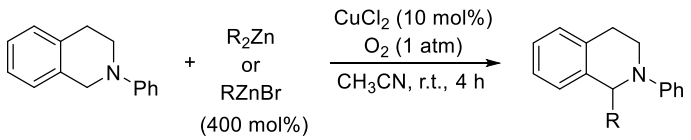
118 Awuah, E.; Capretta, A. *J. Org. Chem.* **2010**, *75*, 5627-5634.

119 Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431-1628.

120 (*a*) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312-15313. (*b*) Ghobrial, M.; Harhammer, K.; Mihovilovic, M. D.; Schnürch, M. *Chem. Commun.* **2010**, *46*, 8836-8838. (*c*) Xie, J.; Li, H.; Zhou, J.; Cheng, Y.; Zhu, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 1252-

or alkyl zinc bromide reagents have been used for the alkylation of the alpha position of THIQs under Cu cataysis (Scheme 62).[120e]

***Scheme 62**. Cu-catalyzed alkylation of THIQs using R_2Zn or RZnBr.*

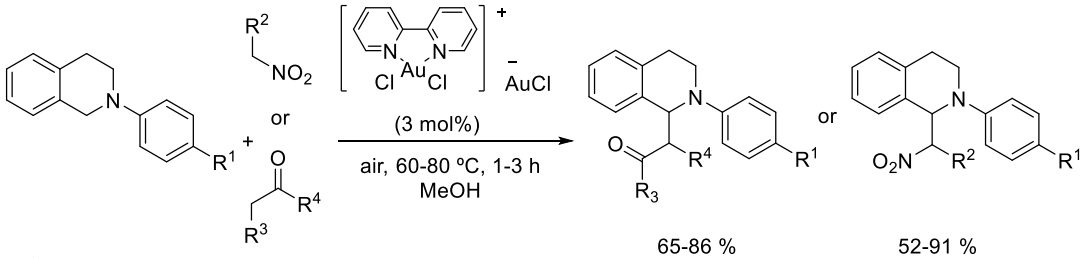


R = n-octyl, n-heptyl, cyclohexyl, ethyl, benzyl

60-85 %

Gold catalysis can also be employed for the functionalization of *N*-aryl THIQs using atmospheric air as the oxidant (Scheme 63).[120c] The reaction conditions are mild, requiring short reaction times and low catalyst loads. The process allows the coupling of THIQs with nitroalkanes and different unmodified ketones. The authors propose formation of an iminium gold hydride complex as the key intermediate species.

***Scheme 63**. Gold-catalyzed oxidative coupling of THIQs with nitroalkanes and ketones.*



65-86 %

52-91 %

R^1 = H, Me, OMe, Br, Cl
R^2 = H, Me
R^3 = H, *i*Pr; R^4 = H, Me, *n*Bu, *t*Bu, Ph

Alternatively, the *α* functionalization of THIQs can be performed in the absence of transition metals.[121] A prominent example is the use of Grignard reagents for the alpha functionalization of THIQs using stoichiometric DDQ as oxidant. (Scheme 64).[122] The same group later developed a similar synthetic methodology based on the use of

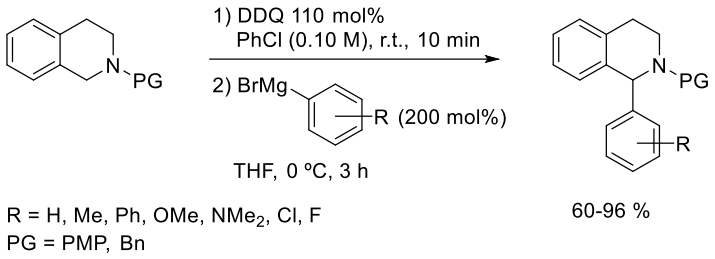
1255. (*d*) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc.* **2012**, *134*, 5317–5325. (*e*) Wang, T.; Schrempp, M.; Berndhäuser, A.; Schiemann, O.; Menche, D. *Org. Lett.* **2015**, *17*, 3982-3985.

121 (*a*) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1019-1084. (b) Rohlmann, R.; García Mancheño, O. *Synlett*, **2013**, *24*, 6-10 (*c*) Narayan, R.; Matcha, K.; Antonchick, A.; *Chem. Eur. J.* **2015**, *21*, 14678-14693.

122 Muramatsu, W.; Nakano, K.; Li, C.-J. *Org. Lett*. **2013**, *15*, 3650-3653.

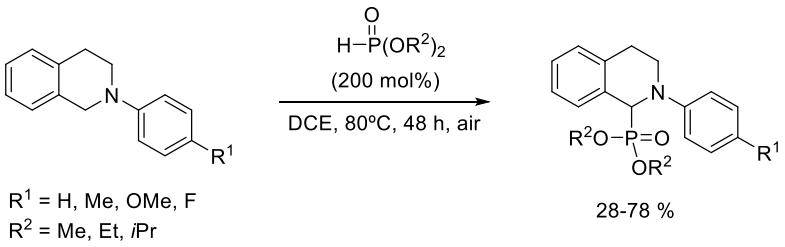
PIFA as oxidant that enabled the coupling of THIQs with a wider variety of Grignard compounds including alkyl, vinyl, and allyl reagents.[123]

Scheme 64*. DDQ-mediated α-arylation of THIQs using Grignard reagents.*



The reaction of dialkyl phosphites with *N*-aryl THIQs using atmospheric air as the source of oxidant affords the corresponding α-aminophosphates under transition-metal-free conditions (Scheme 65).[124] In this process, an iminium intermediate is proposed, where the electron density in the *N*-phenyl ring of the THIQ has a strong influence in reaction yield.

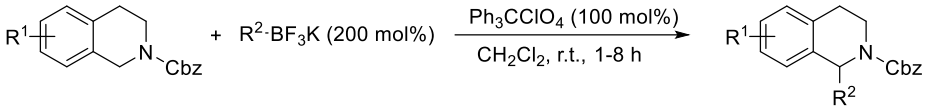
Scheme 65. *Transition-metal-free coupling of N-aryl THIQs with dialkyl phosphites.*



The group of Liu disclosed the coupling of *N*-protected tetrahydroisoquinolines with organoborane nucleophiles using trityl perchlorate as stoichiometric oxidant in the absence of transition-metals (Scheme 66).[125] The reaction proceeds efficiently affording a wide variety of 1-substituted THIQs. Later, this same group developed an asymmetric variant of the reaction involving *N*-acyl THIQs in the presence of chiral organocatalysts.[126]

123 Muramatsu, W.; Nakano, K.; Li, C.-J. *Org. Biomol. Chem.* **2014**, *12*, 2189–2192.
124 Dhineshkumar, J.; Samaddar, P.; Prabhu, K. R. *ACS Omega* **2017**, *2*, 4885–4893.
125 Xie, Z.; Liu, L.; Chen, W.; Zheng, H.; Xu, Q.; Yuan, H.; Lou, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 3904-3908.
126 Liu, X.; Sun, S.; Meng, Z.; Lou, H.; Liu, L. *Org. Lett.* **2015**, *17*, 2396–2399.

***Scheme 66**. Oxidative coupling of N-protected THIQs with organoboranes.*

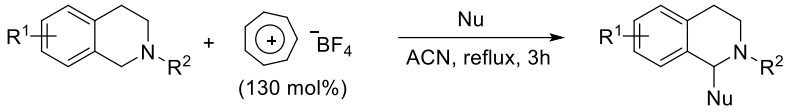


R^1 = H, Me, OMe, Br, Cl, F
R^2 = aryl, heteroaryl, alkynyl, alkenyl, benzyl

50-97 %

In a related work, tropylium tetrafluoroborate was found to promote the oxidative coupling of *N*-protected and *N*-substituted THIQs with different nucleophiles including silyl enol ethers, nitromethane, dialkyl zinc reagents or Grignard compounds, without the need of transition-metal catalysts (Scheme 67).[127]

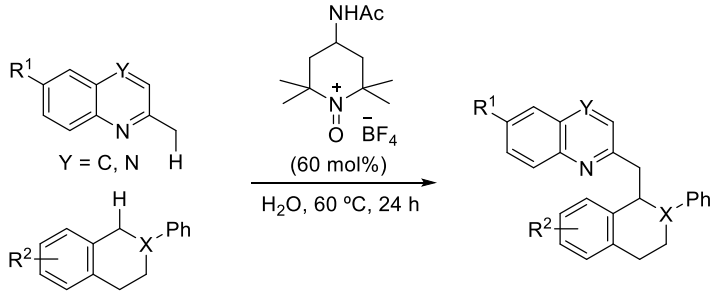
***Scheme 67**. Tropylium tetrafluoroborate mediated coupling of THIQs.*



R^1 = H, OMe
R^2 = alkyl, aryl, benzyl, CBz
Nu = silyl enol ether, $MeNO_2$, R_2Zn, RMgBr

Among the oxidative functionalization of THIQs, the cross-dehydrogenative coupling procedures are remarkable.[128] In these reactions, a new carbon-carbon bond is formed after the activation of two C-H bonds. For example, the cross-dehydrogenative coupling of *N*-aryl THIQs and 2-methylazaarenes can be achieved using oxoammonium salts as oxidants in aqueous media (Scheme 68).[129]

***Scheme 68**. Metal-free cross-dehydrogenative coupling of N-aryl THIQs.*



R^1 = H, Me, OMe, Cl, Br, NO_2
R^2 = H, OMe

47-96 %

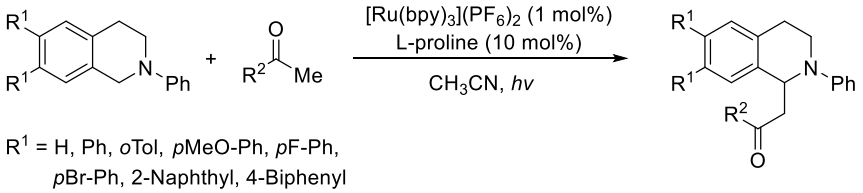
127 Oss, G.; de Vos, S. D.; Luc, K. N. H.; Harper, J. B.; Nguyen, T. V. *J. Org. Chem.* **2018**, *83*, 1000–1010.

128 (*a*) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335-344. (*b*) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74-100. (*c*) Gini, A.; Brandhofer, T.; García Mancheño, O. *Org. Biomol. Chem.* **2017**, *15*, 1294-1312. (*d*) Cheng, M.-X.; Yang, S.-D. *Synlett* **2017**, *28*, 159-174.

129 Fang, L.; Li, Z.; Jiang, Z.; Tan, Z.; Xie, Y. *Eur. J. Org. Chem.* **2016**, 3559-3567.

The functionalization at the C-1 position of THIQs can also be achieved by means of photocatalytic or electrochemical methods.[130] One example is the photoredox coupling of *N*-aryl THIQs with ketones in the presence of a metal catalyst (Scheme 69).[130a]

***Scheme 69**. Coupling of THIQs and ketones by means of metal and Lewis base dual catalysis.*



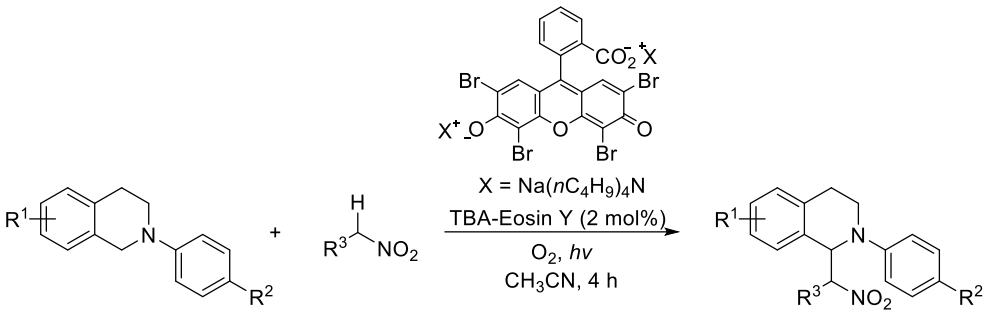
R^1 = H, Ph, *o*Tol, *p*MeO-Ph, *p*F-Ph, *p*Br-Ph, 2-Naphthyl, 4-Biphenyl

R^2 = Me, Et

59-95 %

More interestingly, the photoredox coupling of THIQs can also been carried out in the absence of transition metals, for example, nitromethane can be coupled in this manner using catalytic amounts of fluorescent dye Eosin Y in the presence of visible light and oxygen (Scheme 70).[130c]

***Scheme 70**. Transition-metal-free light-induced coupling of nitroalkanes and THIQs.*



R^1 = H, OMe

R^2 = H, Me, OMe, Br, Cl, F

R^3 = H, Me, Et

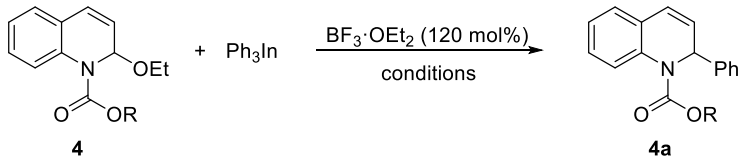
46-86 %

130 (*a*) Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360–2362. (*b*) Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852–3855. (*c*) Liu, Q.; Li, Y.-N.; Zhang, H.-H.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *Chem. Eur. J.* **2012**, *18*, 620–627. (*d*) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94–97. (*e*) Xuan, J.; Zeng, T.-T.; Feng, Z.-J.; Deng, Q.-H.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J.; Alper, H. *Angew. Chem., Int. Ed.* **2015**, *54*, 1625–1628. (*f*) Bartling, H.; Eisenhofer, A.; König, B.; Gschwind, R. M. *J. Am. Chem. Soc.* **2016**, *138*, 11860–11871.

2.3.2 Results and Discussion.

The importance of *N*-heterocyclic molecules in general, and THIQs in particular, is paramount, as they are present in countless pharmaceutical drugs, agrochemicals, and bioactive natural products. Therefore, the development of versatile transition-metal-free protocols to access these compounds becomes a priority within modern organic chemistry. In the context of our ongoing investigation, we hypothesized whether *N*,*O*-mixed acetals had the potential to undergo the same type of Lewis acid-mediated reaction than in the case of benzopyran acetals. For this purpose, *N*-carboxylate 2-methoxy quinoline **4** was selected as the substrate to test the reaction with triphenylindium through Lewis acid activation (Table 9).

***Table 9**. Reaction of quinoline N,O-acetal **4** with Ph_3In mediated by $BF_3{\cdot}OEt_2$*



4 **4a**

Entry	mol % Ph_3In	R	Conditions	Yield (%)[a]
1	50	Me	THF, 80 °C, 16 h	43
2	100	Me	THF, 80 °C, 16 h	55
3	100	Me	THF, r.t., 16 h	33
4	100	*i*Pr	THF, 80 °C, 16 h	59

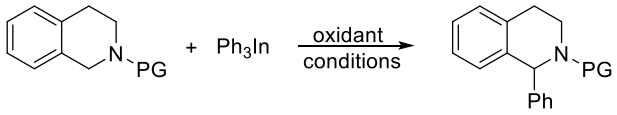
[a] Isolated yield.

During this research we found that stoichiometric amounts of $BF_3{\cdot}OEt_2$ promote the reaction of triorganoindium reagents with benzopyran acetals in THF. When triphenylindium was reacted with **4** under these conditions, 2-phenyl quinoline carboxylate **4a** was obtained in 43 % yield (Table 9, entry 1). This result contrasts with the almost quantitative yields obtained for chromene and isochroman acetals **1** and **2**. Increasing the quantity of triorganoindium reagent up to 100 mol% did not provide a significantly better result (Table 9, entry 2). A closer examination of the reaction crude revealed the presence of quinoline in all of the experiments. TLC and NMR analysis indicated quinoline was generated in the reaction media before work-up, while none of the starting material could be recovered or detected. This finding might suggest that BF_3 can act as Lewis acid activating the carbonyl group of the

carbamate and favouring its cleveage. In an attempt to minimize the side reaction a bulkier isopropyl was chosen as protecting group (Table 9, entry 4), although the yield practically did not improve and once again quinoline was detected in the crude material.

With these results in hand, we envisioned a different type of strategy for the coupling of nitrogen-containing benzoheterocyclic substrates with triorganoindium reagents through iminium intermediates. As an alternative to the use of Lewis acid activation, we proposed to generate the iminium intermediate via C-H bond activation in the position adjacent to the nitrogen atom using a suitable oxidant. In a number of recent works, the functionalization of the alpha position of tetrahydroisoquinolines (THIQs) has been achieved by means of oxidative coupling with different nucleophiles, including organometallic reagents.[120-127] For this purpose, *N*-protected THIQs were set to react with triphenylindium in the presence of various oxidants (Table 10), where reactions were performed in dichloromethane or dichloroethane using THF as co-solvent.

***Table 10**. Optimization of reaction conditions for the oxidative coupling of **5** with Ph_3In.*



Entry	Oxidant (mol%)	Ph_3In (mol%)	Protecting group	Reaction conditions	Yield (%)
1	DDQ (110)	50	Cbz	CH_2Cl_2/THF, r.t., 16 h	–
2	PIFA (110)	50	Cbz	CH_2Cl_2/THF, r.t., 16 h	–
3	Ph_3CClO_4 (110)	50	Cbz	CH_2Cl_2/THF, r.t., 16 h	56
4	Ph_3CBF_4 (110)	50	Cbz	CH_2Cl_2/THF, r.t., 16 h	58
5	Ph_3CBF_4 (110)	50	Cbz	CH_2Cl_2/THF, r.t., 72 h	44
6	Ph_3CBF_4 (110)	50	Cbz	DCE/THF, 80 °C, 16 h	52
7	Ph_3CBF_4 (110)	100	Cbz	CH_2Cl_2/THF, r.t., 16 h	66
8	Ph_3CBF_4 (150)	50	Cbz	CH_2Cl_2/THF, r.t., 16 h	51
9	Ph_3CBF_4 (110)	50	Boc	CH_2Cl_2/THF, r.t., 16 h	–
10	Ph_3CBF_4 (110)	50	Ts	CH_2Cl_2/THF, r.t., 16 h	–

[a] Isolated yield.

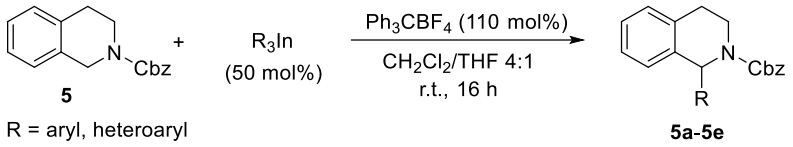
During the initial experiments, the use of DDQ or PIFA as oxidants did not afford any of the desired coupling product **5a** (Table 10, entries 1-2), however, when trityl perchlorate (Ph_3CClO_4) was employed as oxidant the reaction took place with 56 % yield of **5a** (Table 10, entry 3). Gratifyingly, the use of commercially available trityl tetrafluoroborate afforded a similar result than in the case of the perchlorate salt (Table 10, entry 4). Different reaction conditions were then screened with the aim of optimizing the yield of **5a**. The increase of reaction time did not have an effect on the reaction output (Table 11, entry 5). Heating the reaction to 80 °C did not provide a better result (Table 10, entry 6). Increasing the amount of triorganoindium reagent towards one equivalent did not improve the reaction yield (Table 10, entry 7), while the use of more oxidant did not provide a better result either (Table 10, entry 8). Finally, other protecting groups were also tested during the optimization studies (Table 10, entries 9 and 10), showing that the use of Cbz plays a critical role in the reaction.

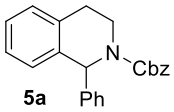
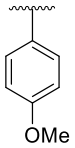
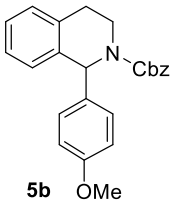
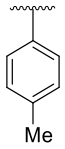
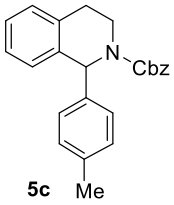
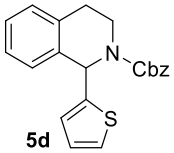
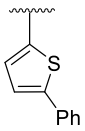
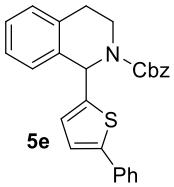
Although the yield of the reaction remained moderate, these results represent the first example of oxidative, transition-metal-free coupling of THIQs with triorganoindium reagents. Formally, the process can be regarded as a C-H activation reaction where no previous installment of a leaving group is required. In addition to this, the reaction takes place in the presence of a readily removable protecting group, which enables further functionalization of the THIQ substrates.

According to our research plan, we studied the scope of the reaction with other aryl and heteroaryl triorganoindium reagents for the oxidative coupling of **5** (Table 11). Interestingly, since we found that electron-rich triarylindium reagents afforded higher yields, using tri-tolyl and tri-p-methoxyphenyl indium reagents afforded 1-substituted THIQs **5b** and **5c** in 89 and 77 % isolated yield respectively (Table 11, entries 2 and 3). The coupling of substrate **5** with heteroaromatic triorganoindium reagents was also performed successfully. In the case of tris(2-thienyl)indium, the reaction provided product **5d** in 80 % yield (Table 11, entry 4), and the use of tris(2-phenylthiophenyl)indium led to an excellent 93 % yield of **5e** (Table 11, entry 5). This results had been obtained using just 50 mol% of the triorganoindium reagents, which

showed that more than one organic group attached to indium is capable of being transferred during the reaction.

***Table 11**. Scope of aryl and heteroaryl triorganoindium reagents for the oxidative coupling of **5**.*



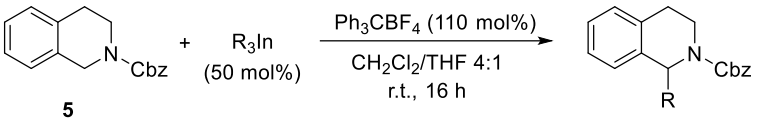
Entry	R	Product	Yield (%)[a]
1	Ph	 **5a**	58
2		 **5b**	89
3		 **5c**	77
4		 **5d**	80
5		 **5e**	93

[a] Isolated yield.

The coupling of alkynyl and benzyl triorganoindium reagents was also investigated (Table 12). Remarkably, alkynyl triorganoindium reagents were found to be transferred in good yields (Table 12, entries 1 and 2). The insertion of alkyne moieties in the C-1 position of THIQs is particularly attractive due to the possibility of further transformation of the triple bond, including potentially the construction of tricyclic

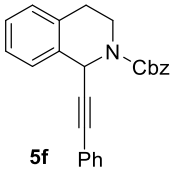
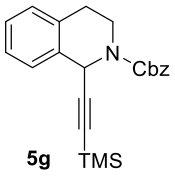
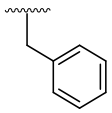
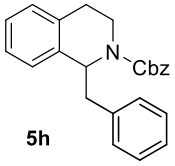
amines.[131] Finally, tribenzylindium afforded 1-benzyl THIQ **5h** in 93 % yield, demonstrating the versatility of this reaction.

***Table 12**. Alkynyl and benzyl triorganoindium reagents for the oxidative coupling of **5**.*



R = alkynyl, benzyl

5f-5h

Entry	R	Product	Yield (%)[a]
1		 **5f**	72
2		 **5g**	61
3		 **5h**	93

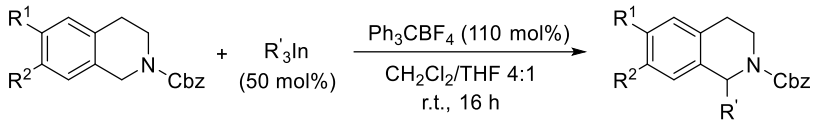
[a] Isolated yield.

We also studied the effect of substituents in the benzene ring of the THIQ. The reactivity of electron-rich 6-methoxy-THIQ **6a** was tested under the previously optimized reaction conditions and using a selection of triorganoindium reagents (Table 13). The reaction of **6** with triphenylindium afforded coupling product **7a** in a similar yield as in the case of bare THIQ **5** (Table 13, entry 1). The use of the more electron-rich tris(*p*-methoxyphenyl)indium reagent afforded the corresponding product with higher efficiency, providing **7b** in 90 % yield (Table 13, entry 2). Lastly, the reaction of **6a** with tris(2-thienyl)indium afforded the coupling product **7c** in 79 % yield (Table 13, entry 3). Overall, the reactivity of **6a** was comparable to **5**. Also as

131 Sato, Y.; Nishimata, T.; Mori, M. *J. Org. Chem.* **1994**, *59*, 6133-6135.

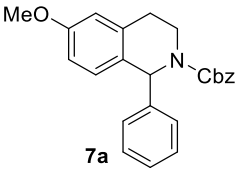
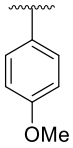
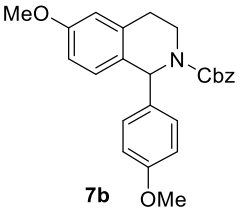
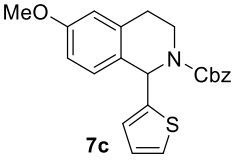
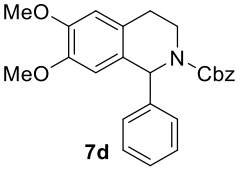
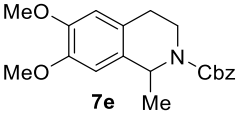
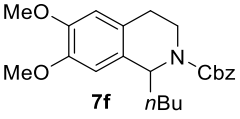
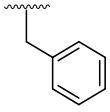
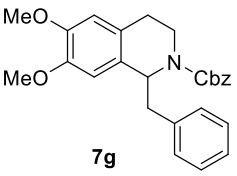
in **5**, the reaction with trimethyl or tributylindium did not provide any of the 1-alkylated products.

***Table 13**. Effect of substituents in the oxidative coupling reaction of THIQs with R_3In.*



6a, R^1 = OMe, R^2 = H
6b, R^1 = R^2 = OMe

7a-7g

Entry	THIQ	R′	Product	Yield (%)[a]
1	**6a**	Ph	 **7a**	52
2	**6a**		 **7b**	90
3	**6a**		 **7c**	79
4	**6b**	Ph	 **7d**	80
5	**6b**	Me	 **7e**	61
6	**6b**	*n*Bu	 **7f**	83
7	MeO		 **7g**	93

[a] Isolated yield.

When 6,7-dimethoxy-THIQ **6b** was set to react with triphenylindium, product **7d** was obtained in 80 % yield (Table 13, entry 4). More remarkably, we found that **6b** reacted with trialkylindium reagents to afford the corresponding methyl and butyl derived products **7e** and **7f** in 61 and 83 % yield respectively (Table 13, entries 5 and 6). The reaction of **7** with tribenzylindium afforded product **7g** in an excellent 93 % yield (Table 13, entry 7).

We also studied the reaction with less electronically rich THIQs, bearing chlorine or bromine moieties (compounds **8** and **9**); however, in these cases only trace amounts of the corresponding reaction products could be detected. These results show that the reactivity of the THIQs is influenced by the electron density of the benzene ring, where the presence of electron donating groups favors reaction performance. The enhanced reactivity of iminium or oxonium intermediates as a result of the presence of electron donating groups under oxidative conditions has been reported in other works.[132]

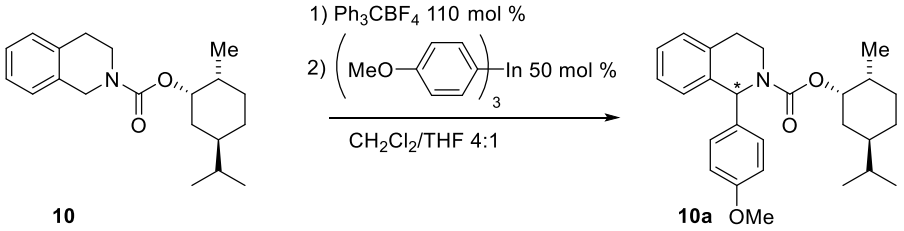
Once the reaction scope was investigated, we decided to study an enantioselective version for this reaction. The results obtained so far had shown that the oxidative coupling using triorganoindium reagents offered the possibility to access a wide variety of functionalized THIQ substrates, therefore the ability to access the enantiomerically pure version of the products would be of great additional value to this synthetic methodology. In this context, the potential application to the synthesis of naturally occurring THIQ alkaloids and its derivatives results particularly interesting.[133] Previous attempts to induce enantioselectivity using chiral ligands in the $BF_3{\cdot}OEt_2$ mediated reaction of chromene acetal with triorganoindium reagents were unsuccessful. Consequently, a diastereoselective approach based on the use of chiral auxiliaries was proposed for the oxidative coupling of THIQs. Installment of a bulky chiral moiety in the protecting group, near the reaction site for the nuclephilic addition, should in theory favor the approximation of the triorganoindium reagent from one of the faces of the molecule. Based on previous reports on the asymmetric

132 (*a*) Ying, B.-P.; Trogden, B. G.; Kohlman, D. T.; Liang, S. X.; Xu, Y.-C. *Org. Lett.* **2004**, *6*, 1523-1526. (*b*) Chu, L.; Qing, F.-L. *Chem Commun*. **2010**, *46*, 6285-6287.

133 Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.

addition reaction to pyridinium salts,[134] (–)-menthol and (–)-8-phenylmenthol were selected as chiral auxiliaries to test the oxidative coupling reaction of THIQs and triorganoindium reagents. For this purpose, THIQ **10** bearing (–)-menthol-carboxylate as protecting group was prepared by treatment of tetrahydroisoquinoline with the corresponding chiral chloroformate (see experimental part for the details). When the oxidative coupling reaction of **10** with tri-*p*-methoxyphenyllindium was performed at room temperature (Table 14, entry 1) the coupling product was obtained in 68 % yield, however, HPLC analysis revealed a 50:50 mixture of diastereomers in the product **10a**.

***Table 14**. Asymmetric oxidative cross-coupling reaction of THIQ **10** with tri-p-methoxyphenylindium.*



Entry	Conditions	Yield (%)[a]	d.r.[b]
1	r.t. 16 h	68	50: 50
2[c]	-78 °C, 16 h	62	50 : 50

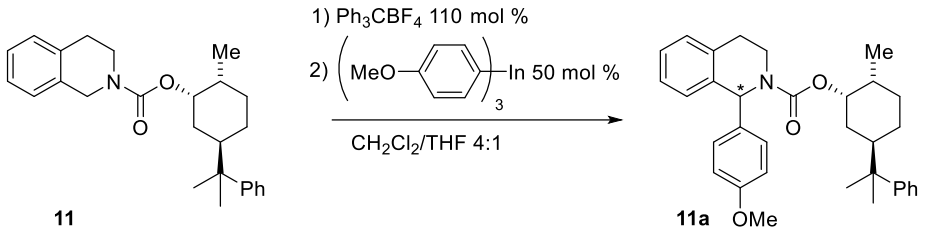
[a] Isolated yields. [b] d.r. determined by analytical HPLC. [c] R_3In solution added dropwise for 1 h.

The reaction was then performed at -78 °C, only to afford the same result as in the previous experiment (Table 14, entry 2).

THIQ **11** bearing the bulkier (–)-8-phenylmenthol was set to react with 50 mol% of tri-*p*-anisolylindium (Table 15). The reaction was initially carried out at room temperature, affording the coupling product in 81% yield, while analysis of the crude material using chiral HPLC revealed a ratio of diastereomers in product **11a** of 67:33 (Table 15, entry 1). In an attempt to increase the diastereomeric excess of the process, the reaction was performed at low temperature, although no improvement in the diasteromeric ratio was observed (Table 15, entry 2).

134 (*a*) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719-4728. (*b*) Peña-Lopez, M.; Martinez, M. M.; Sarandeses, L. A.; Pérez Sestelo, J. *Org. Lett.* **2010**, *12*, 852-854.

***Table 15**. Asymmetric oxidative cross-coupling reaction of THIQ **11** with tri-p-methoxyphenylindium.*



Entry	Conditions	Yield (%)[a]	d.r.[b]
1	r.t. 16 h	81	67: 33
2[c]	-78 °C, 16 h	51	65 : 35

[a] Isolated yields. [b] d.r. determined by analytical HPLC. [c] R_3In solution added dropwise for 1 h.

Despite the use of a bulky protecting group and low reaction temperature, no appreciable diastereomeric excess could be achieved for the reaction. Nonetheless, in the case of THIQ **11a** the main diastereomer could be isolated after bench column chromatography (see experimental part).

The reaction mechanism for the oxidative coupling reaction of THIQs with triorganoindium reagents was investigated. Formation of an iminium cation intermediate species via hydride abstraction by the trityl salt was proposed as the most plausible reaction pathway. Therefore, the observation of the iminium intermediate via NMR spectroscopy would provide evidence to support this mechanistic proposal. To this end, an experiment was performed in which a solution of THIQ **7** in CD_2Cl_2 (Figure 6) was treated with 110 mol% of Ph_3CBF_4 at room temperature, and then the resulting mixture was subject to ^1H NMR. Remarkably, all of **7** was consumed and the spectra of the corresponding iminium cation could be clearly appreciated (Figure 7). All of the signals had been displaced towards higher chemical shifts due to significant reduction of electron density. The new signal at 9.47 ppm corresponded to the iminium proton. Alongside the iminium cation, an equimolar quantity of Ph_3CH could be appreciated in the NMR spectrum (m, 7.17-7.35 ppm, 15H), thus indicating that the reaction mechanism is likely to proceed via hydride abstraction.

***Figure 6**. 300 MHz 1H NMR spectrum of **7** in CD_2Cl_2.*

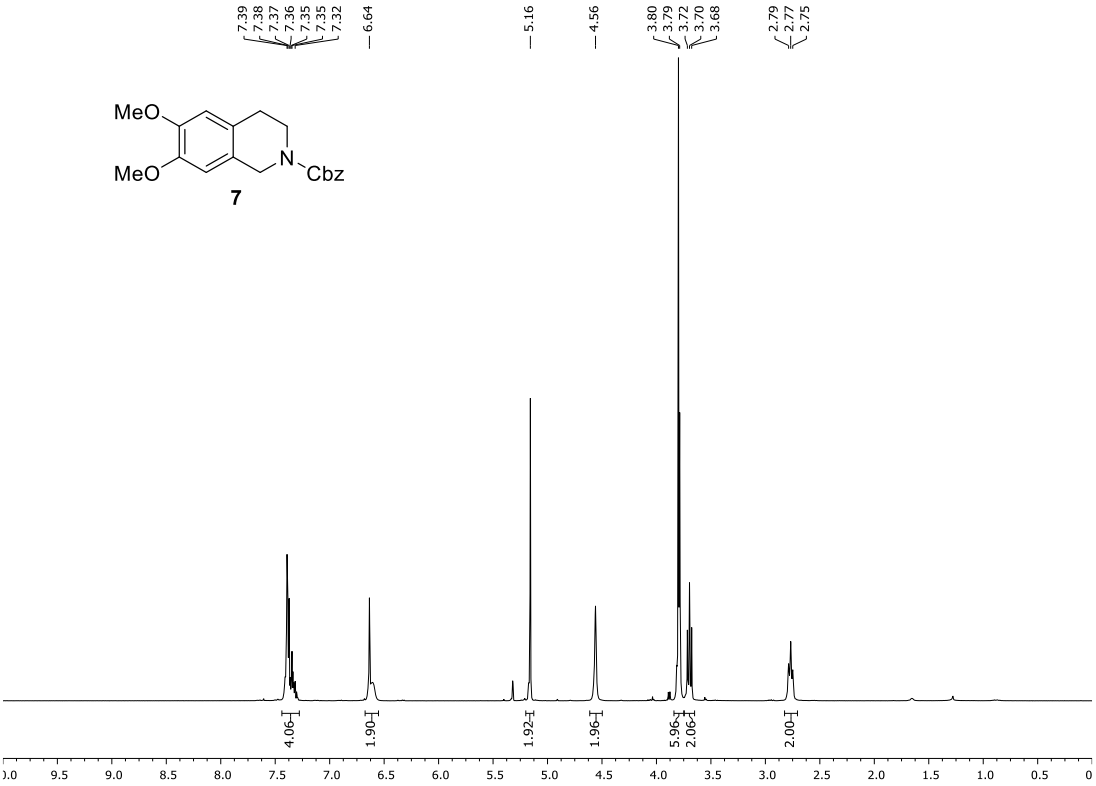
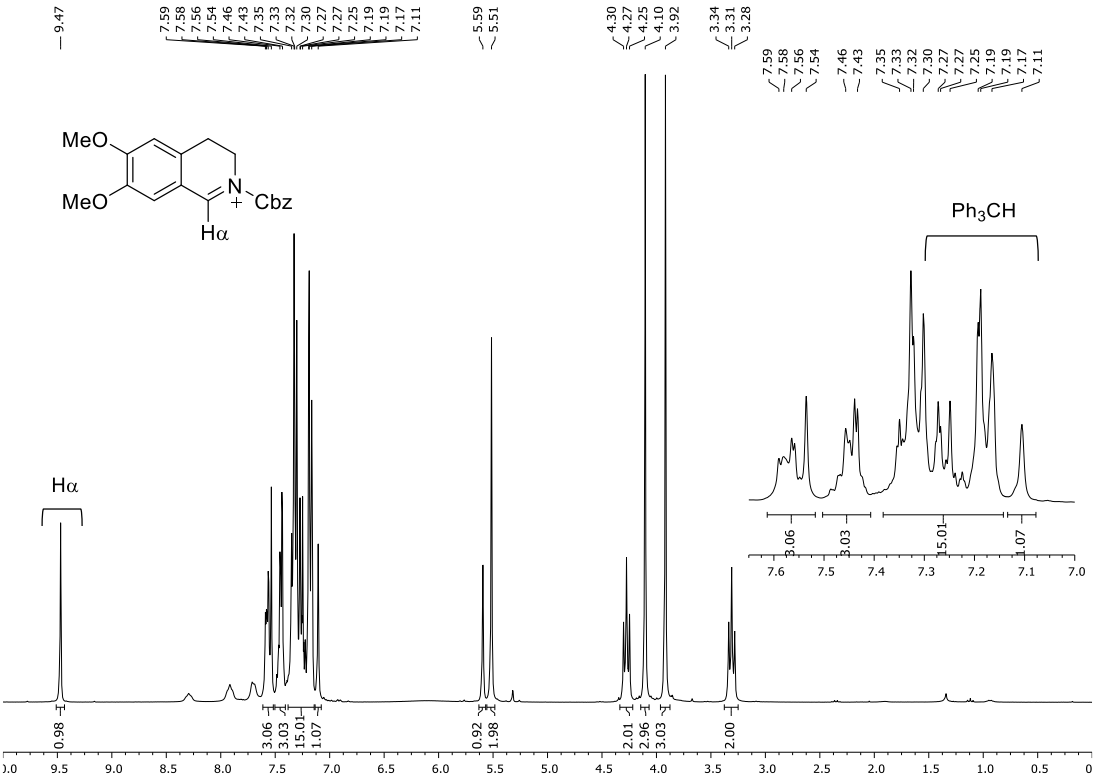
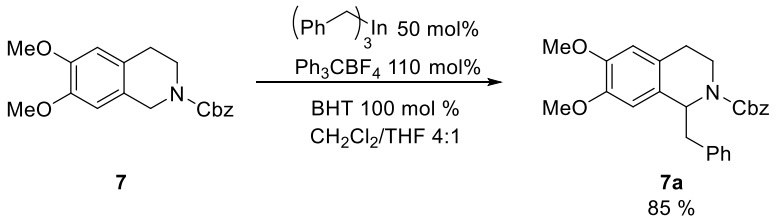


***Figure 7**. 300 MHz 1H NMR spectrum of the iminium cation after treatment of **7** with Ph_3CBF_4.*



The formation of the iminium intermediate is fast; the spectrum in figure 6 was acquired only 10 minutes after the treatment of **7** with the oxidant at room temperature. Also, it was found that an excess of oxidant had no further effect in the iminium intermediate, and when additional 200 mol% of Ph_3CBF_4 was added to the reaction media, the spectra of the intermediate remained unchanged, the only new signals observed corresponded to the excess trityl salt. Additionally, the reaction of **7** with tribenzylindium in the presence of one equivalent of radical scavenger butylated hydroxytoluene (BHT) afforded product **7d** in 85 % yield, thus possibly ruling out a reaction pathway involving radicals (Scheme 71).

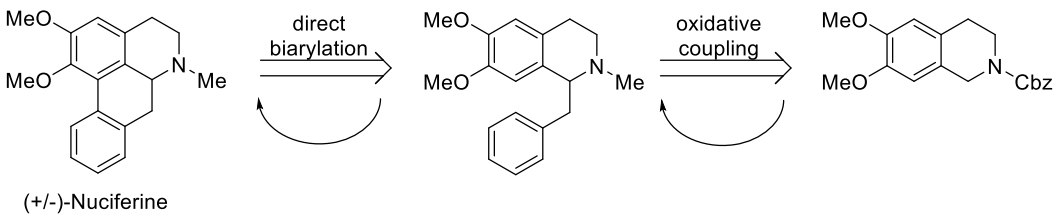
***Scheme 71**. Reaction of **7** in the presence of radical scavenger BHT.*



7 **7a** 85 %

To demonstrate the synthetic utility of the oxidative coupling of *N*-protected THIQs with triorganoindium reagents, the reaction was used for the synthesis of the racemic form of alkaloid Nuciferine, a natural product isolated from the plants *Nelumbo nucifera* and *Nymphaea caerulea*, and which exhibits a range of psychoactive properties.[135] The synthetic strategy for the construction of the tetracyclic core of the molecule was based on a combination of oxidative coupling reaction with tribenzylindium reagent followed by Pd-catalyzed direct biarylation (Scheme 72).

***Scheme 72**. Retrosynthetic scheme to access (±)Nuciferine.*

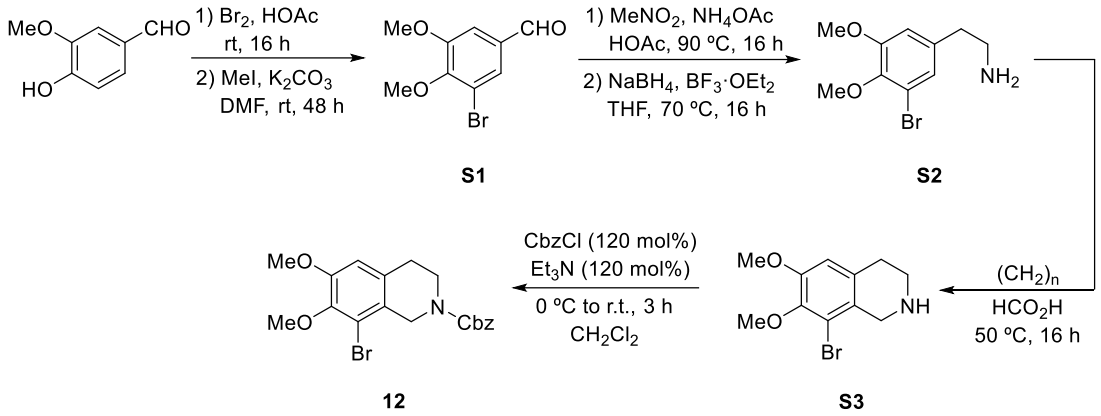


(+/-)-Nuciferine

135 (*a*) Munusamy, V.; Yap, B. K.; Buckle, M. J. C.; Doughty, S. W.; Chung, L. Y. *Chem. Biol. Drug. Des.* **2013**, *81*, 250-256. (*b*) Polkis, J. L.; Mulder, H. A.; Halquist, M. S.; Wolf, C. E.; Polkis, A.; Peace, M. R. *J. Psychoactive Drugs* **2017**, *49*, 175-181.

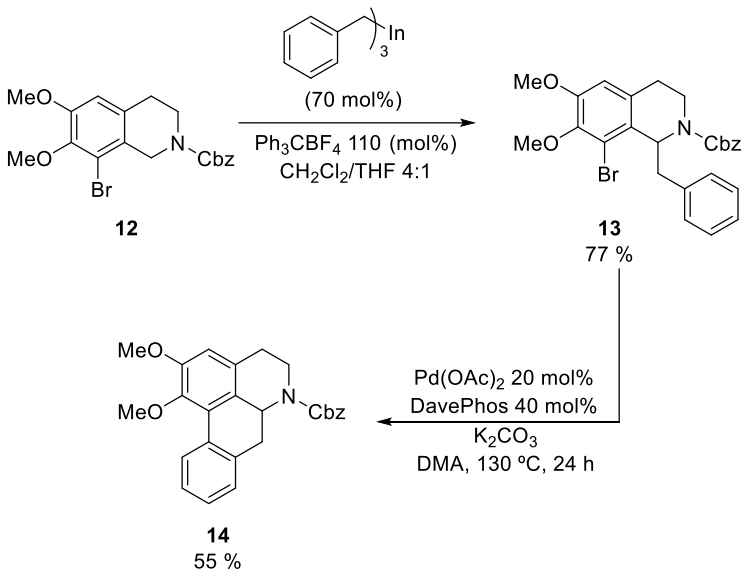
In an initial synthetic approach for (±)-Nuciferine, THIQ **12** bearing a bromine atom was prepared from vanillin following a known procedure (Scheme 73).[136]

***Scheme 73**. Preparation of THIQ **12**.*



THIQ **12** was then set to react with tribenzylindium under the optimized reaction conditions, however, product **13** was obtained in just 46 % yield; the lower than expected yield was probably caused by the presence of the electron-withdrawing bromine in the benzene ring of the substrate. When the amount of triorganoindium reagent was increased to 70 mol%, the yield of **13** could be improved towards 77 %. (Scheme 74).

***Scheme 74**. Initial synthetic route to access (±)Nuciferine.*

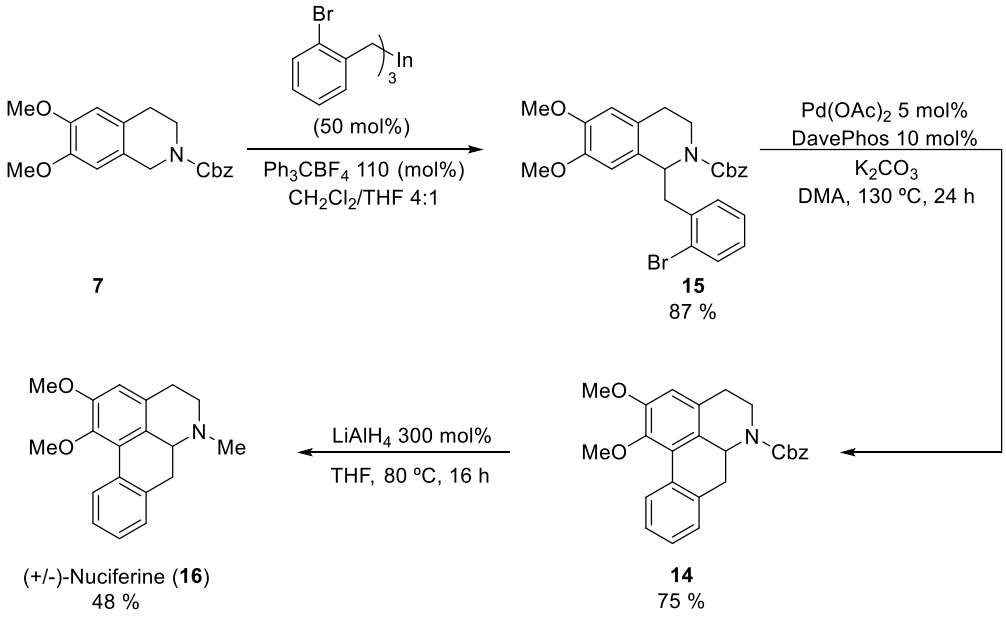


136 Ronson, T. O.; Kitsiou, C.; Unsworth, W. P.; Taylor, R. J.K. *Tetrahedron* **2016**, *72*, 6099-6106. For the synthesis of **12**, see the experimental part.

On the basis of similar works on the synthesis on aporphine alkaloids,[137] $Pd(OAc)_2$/DavePhos was chosen as the preferred catalytic system for the Pd-catalyzed biarylation reaction. However, for the reaction to proceed as much as 20 mol% of Pd loading was required, and this only led to a modest 55 % yield of **14**.

With the aim of improving the efficiency of the synthesis of (±)-Nuciferine, an alternative route was planned, this time placing the bromine atom in the benzylic group of the triorganonindium reagent (which was prepared from 2-bromobenzylmagnesium bromide). This would improve the oxidative coupling reaction by avoiding the presence of an electron-withdrawing group in the structure of the THIQ, while at the same time the biarylation should also proceed more efficiently in the presence of a lower catalytic load. For this purpose, THIQ **7** was set to react with 50 mol% of tris(2-bromobenzyl)indium reagent under oxidative conditions, affording **15** in 87 % yield (Scheme 75). Gratifyingly, this time the biarylation reaction of **15** proceeded in a good 75 % yield with just 5 mol % of the palladium catalyst. Finally, reduction of **14** with $LiAlH_4$ furnished (±)-Nuciferine (**16**) in 48 % yield.

***Scheme 75**. Revised synthetic route to access (±)Nuciferine.*



137 (*a*) Cuny, G. D. *Tetrahedron Lett.* **2003**, *44*, 8149-8152. (*b*) Lafrance M.; Blaquiere N.; Fagnou, K. *Eur. J. Org. Chem.* **2007**, 811-825.

In summary, a new transition-metal-free reaction of triorganoindium reagents with *N*-protected tetrahydroisoquinolines under oxidative conditions has been developed. The reaction allows different aryl, heteroaryl, akynyl, benzyl, and alkyl groups to be transferred under activation with stoichiometric Ph_3CBF_4, and using only 50 mol% of the triorganoindium reagents. Preliminary mechanistic studies suggest the formation of an iminium reaction intermediate, which was detected through NMR spectroscopy. Additionally, the reaction was used in the synthesis of aporphine alkaloid Nuciferine. These results show that the oxidative coupling reaction of THIQs with triorganoindium reagents can be applied successfully to the synthesis of biologically relevant substrates, while the ability to perform the reaction with a variety of different triorganoindium reagents enables the possibility of easily accessing libraries of THIQ derivatives.

2.4 Experimental Section.

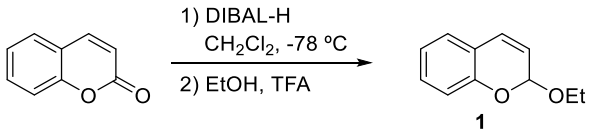
General Methods.

All reactions were carried out in flame-dried glassware, under argon using standard gas-tight syringes, cannulae and septa. THF was dried by distillation from sodium benzophenone ketyl. Dichloromethane and 1,2-dichloroethane were distilled from calcium hydride. Reaction temperatures refer to external bath temperatures. Commercially available reagents were used as received without further purification. Organolithium or Grignard reagents were titrated prior to use. Reactions were monitored by TLC using pre-coated silica gel plates (Alugram Xtra SIL G/UV_{254}, 0.20 mm thick), UV light as the visualizing agent and ethanolic phosphomolybdic acid as the developing agent. Flash column chromatography was performed with 230-400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 K using a Bruker Avance 300 MHz or a Bruker Avance 500 MHz spectrometer, and calibrated to the solvent peak. DEPT data were used to assign carbon types. Mass spectra were obtained with EI ionization at 70 eV or with ESI operating in positive ionization mode.

Preparation of Triorganoindium Reagents.

Triorganoindium compounds were prepared according to previously published methods[21] by treatment of the corresponding organolithium or Grignard reagent (3 equiv, ~0.5 M in THF) with a solution of $InCl_3$ (1 equiv, 0.45 M in THF) at –78 °C and warming to room temperature. Phenylacetylene, ethynyltrimethylsilane, thiophene, and benzothiophene were lithiated by treatment with *n*-BuLi (1 equiv) at -78 °C and warming to room temperature. Organolithium reagents derived from 2-bromonaphtalene β-bromostyrene, and cyclopropylbromide were prepared by metal-halogen exchange reaction with *t*-BuLi (2 equiv) at –78 °C.

Preparation of 2-Ethoxy-2*H*-chromene (1).[95]

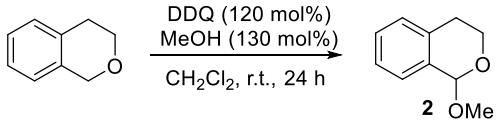


1

To a solution of coumarin (2 g, 13.7 mmol) in CH_2Cl_2 (40 mL), DIBAL-H (15 mL, 14.4 mmol, 1.0 M) was added drop wise for 1.5 h at –78 °C. The reaction was stirred for 2

h, warmed to 0 ºC, and then allowed to reach rt. The reaction mixture was diluted with EtOAc (100 mL) and water (100 mL). After filtration through Celite, the aqueous layer was extracted with EtOAc (2 × 50 mL) and the combined organic layer were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to yield a viscous yellow oil. The crude was redissolved in absolute EtOH (50 mL) and trifluoroacetic acid (40 μL, 0.54 mmol) was added. After 12 h stirring at rt, K_2CO_3 (100 mg, 0.72 mmol) was added. The mixture was filtered and the solvent evaporated under reduced pressure. The crude was purified by flash chromatography with silica gel (EtOAc/hexane 5:95, 3% Et_3N) to afford 1.642 g of **1** (68 %) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.25–7.18 (m, 1H), 7.14 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.96 (t, *J* = 7.2 Hz, 2H), 6.73 (d, *J* = 9.7 Hz, 1H), 5.86 (dd, *J* = 9.7, 3.7 Hz, 1H), 5.71 (d, *J* = 3.7 Hz, 1H), 4.00-3.90 (m, 1H), 3.73-3.63 (m, 1H), 1.22 (t, *J* = 7.1 Hz, 3H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 151.5 (C), 129.3 (CH), 127.1 (CH), 126.5 (CH), 121.4 (C), 120.8 (CH), 120.0 (CH), 116.5 (CH), 95.0 (CH), 63.5 (CH_2), 15.3 (CH_3); **MS** (EI) *m/z* 176 $[M]^+$ (18), 131 $[M - C_2H_5O]^+$ (100); **HRMS** (EI-magnetic sector) calcd for $C_{11}H_{12}O_2$ $[M]^+$ 176.0832, found 176.0828.

Preparation of 1-Methoxy-isochroman (2).[97]



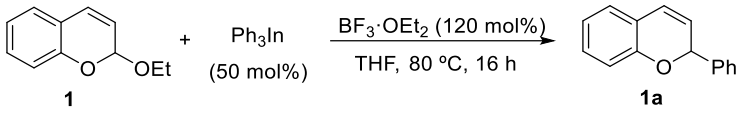
To a solution of DDQ (4.03 g, 17.9 mmol) in CH_2Cl_2 (140 mL), MeOH (0.8 mL, 19.4 mmol) and isochroman (1.9 mL, 14.9 mmol) were succesively added. The mixture was stirred at room temperature for 24 h, quenched with of saturated $NaHCO_3$ solution (100 mL) and filtered through Celite. The aqueous layer was extracted with CH_2Cl_2 (2 × 60 mL), and the combined organic layers washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude was purified by flash chromatography with silica gel (EtOAc/hexane 5:95, 3% Et_3N) to afford 2.127 g of **2** (87%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.27–7.23 (m, 3H), 7.15–7.13 (m, 1H), 5.47 (s, 1H), 4.15 (dt, *J* = 11.3, 3.4 Hz, 1H), 3.93 (dd, *J* = 11.3, 6.1 Hz, 1H), 3.57 (s, 3H), 3.05 (m, 1H), 2.65 (m, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 134.1 (C), 134.0 (C), 128.4 (CH), 128.15 (CH), 127.4 (CH), 126.3 (CH), 97.8 (CH), 57.8 (CH_2), 55.3 (CH_3), 28.0 (CH_2); **MS** (EI) *m/z*

164 $[M]^+$ (17), 163 $[M - H]^+$ (42), 133 $[M - CH_3O]^+$ (100); **HRMS** (EI-magnetic sector) calcd for $C_{10}H_{12}O_2$ $[M]^+$ 164.0754, found 164.0750.

General Procedure A for the $BF_3{\cdot}OEt_2$ Mediated Reaction of R_3In with 1 and 2.

To a solution of **1** or **2** (0.60 mmol) in dry THF (5 mL) at 0 °C, $BF_3{\cdot}OEt_2$ (0.091 mL, 0.72 mmol) was added. After 10 min stirring, a solution of R_3In (0.30 mmol, ~0.05 M) was added via cannula and the resulting mixture refluxed for 12 h. The crude was concentrated in vacuo, and Et_2O (30 mL) was added. The organic phase was successively washed with water (2 × 50 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by flash chromatography to afford, after concentration and high vacuum-drying, the corresponding coupling products (2-substituted chromenes)

2-Phenyl-2*H*-chromene (1a).[138]

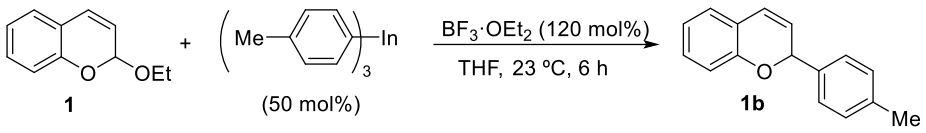


1 **1a**

Following the general procedure A, the reaction of **1** (106 mg, 0.60 mmol) with triphenylindium (6 mL, 0.05 M in THF, 0.30 mmol) and $BF_3{\cdot}OEt_2$ (0.091 mL, 0.72 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3% Et_3N), 114 mg of **1a** (91%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.50–7.44 (m, 2H), 7.43–7.33 (m, 3H), 7.13 (td, *J* = 7.8, 1.8 Hz, 1H), 7.03 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.89 (td, *J* = 7.4, 1.2 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.56 (dd, *J* = 9.8, 1.9 Hz, 1H), 5.94 (dd, *J* = 3.4, 1.9 Hz, 1H), 5.82 (dd, *J* = 9.8, 3.4 Hz, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 153.2 (C), 140.9 (C), 129.5 (CH), 128.6 (2 × CH), 128.3 (CH), 127.0 (2 × CH), 126.6 (CH), 124.8 (CH), 124.0 (CH), 121.3 (C), 121.2 (CH), 116.0 (CH), 77.2 (CH); **MS** (EI) *m/z* 208 $[M]^+$ (77) 207 $[M - H]^+$ (100), 131 $[M - C_6H_5]^+$ (47); **HRMS** (EI-magnetic sector) calcd for $C_{15}H_{12}O$ $[M]^+$ 208.0883, found 208.0877.

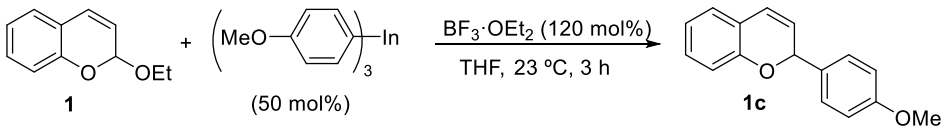
2-(4-Methylphenyl)-2*H*-chromene (1b).[139]

138 Kohari, Y.; Hoshino, Y.; Matsuyama, H.; Nakano, H. *Heterocycles*. **2010**, *82*, 843-850.
139 Zhang, T.; Huang, X.; Wu, L. *Eur. J. Org. Chem.* **2012**, 3507-3519.



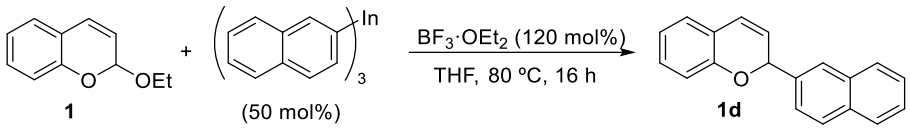
Following the general procedure A, the reaction of **1** (106 mg, 0.60 mmol) with tri-*p*-tolylindium (6 mL, 0.05 M in THF, 0.30 mmol) and $BF_3{\cdot}OEt_2$ (0.091 mL, 0.72 mmol) for 6 h at 23 °C afforded, after purification by flash chromatography (EtOAc/hexane 3:97, 3% Et_3N), 118 mg of **1b** (88%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.35 (d, *J* = 8.1 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.10 (td, *J* = 7.6, 1.5 Hz, 1H), 7.01 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.86 (td, *J* = 7.5, 1.2 Hz, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 6.53 (dd, *J* = 9.9, 1.5 Hz, 1H), 5.91-5.87 (m, 1 H), 5.79 (dd, *J* = 9.8, 3.4 Hz, 1H), 2.35 (s, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 153.2 (C), 138.2 (C), 137.9 (C), 129.4 (C), 129.3 (2 × CH), 127.1 (2 × CH), 126.5 (CH), 125.0 (CH), 123.9 (CH), 121.3 (C), 121.1 (CH), 116.0 (CH), 77.0 (CH), 21.2 (CH_3); **MS** (EI) *m/z* 222 $[M]^+$ (85), 221 $[M - H]^+$ (100), 207 $[M - CH_3]^+$ (42); **HRMS** (EI-magnetic sector) calcd for $C_{16}H_{14}O$ $[M]^+$ 222.1039, found 222.1030.

2-(4-Methoxyphenyl)-2*H*-chromene (1c).[139]



Following the general procedure A, the reaction of **1** (106 mg, 0.60 mmol) with tri-(4-methoxyphenyl)indium (10 mL, 0.030 M in THF, 0.30 mmol) and $BF_3{\cdot}OEt_2$ (0.091 mL, 0.72 mmol) for 3 h at 23 °C afforded, after purification by flash chromatography (EtOAc/hexane 3:97, 3% Et_3N) 120 mg of **1c** (84 %) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.43–7.37 (m, 2H), 7.12 (td, *J* = 7.8, 1.5 Hz, 1H), 7.03 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.94–6.90 (m, 2H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.8 (d, *J* = 8.1 Hz, 1H), 6.57 (dd, *J* = 9.9, 1.8 Hz, 1H), 5.89 (m, 1H), 5.81 (dd, *J* = 9.9, 3.6 Hz, 1H), 3.82 (s, 3H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 159.8 (C), 153.12 (C), 133.0 (C), 129.4 (CH), 128.6 (2 × CH), 126.5 (CH), 124.9 (CH), 124.0 (CH), 121.3 (C), 121.0 (CH), 116.0 (CH), 114 (2 × CH), 76.8 (CH), 55.3 (CH_3); **MS** (EI) *m/z* 238 $[M]^+$ (85), 237 $[M - H]^+$ (100); **HRMS** (EI-magnetic sector) calcd for $C_{16}H_{14}O_2$ $[M]^+$ 238.0988, found 238.0983.

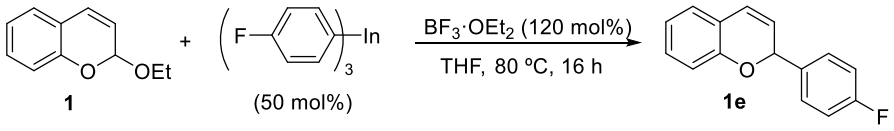
2-(Naphthalen-2-yl)-2*H*-chromene (1d).[97]



1 (50 mol%) 1d

Following the general procedure A, the reaction of **1** (106 mg, 0.60 mmol) with trinaphthylindium (12 mL, 0.025 M in THF, 0.30 mmol) and $BF_3{\cdot}OEt_2$ (0.091 mL, 0.72 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 1:99, 3% Et_3N), 104 mg of **1d** (67%) as white crystals. **MP** 80–81 °C (hexane); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ7.62 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.52–7.47 (m, 2H), 7.14 (td, *J* = 7.8, 1.5 Hz, 1H), 7.06 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.60 (dd, *J* = 9.8, 1.8 Hz, 1H), 6.10 (m, 1H), 5.89 (dd, *J* = 9.8, 3.4 Hz, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ153.2 (C), 138.1 (C), 133.3 (C), 133.2 (C), 129.5 (CH), 128.6 (CH), 128.2 (CH), 127.7 (CH), 126.6 (CH), 126.2 (CH), 126.0 (CH), 124.9 (CH), 124.7 (CH), 124.2 (CH), 121.3 (C), 121.2 (CH), 116.0 (CH), 77,3 (CH); **MS** (EI) *m/z* 258 $[M]^+$ (100), 257 $[M - H]^+$ (79); **HRMS** (EI-magnetic sector) calcd for $C_{19}H_{14}O$ $[M]^+$ 258.1039, found 258.1030.

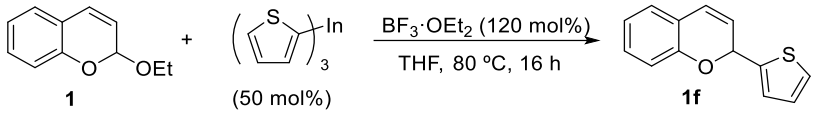
2-(4-Fluorophenyl)-2*H*-chromene (1e).[97]



1 (50 mol%) 1e

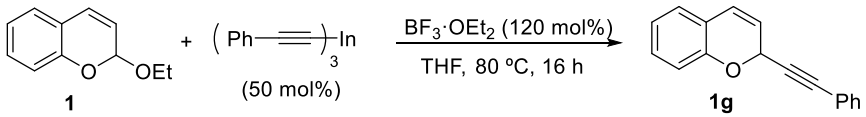
Following the general procedure A, the reaction of **1** (106 mg, 0.60 mmol) with tri-(4-fluorophenyl)indium (6 mL, 0.05 M in THF, 0.30 mmol) and $BF_3{\cdot}OEt_2$ (0.091 mL, 0.72 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3% Et_3N), 115 mg of **1e** (85%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ7.48–7.41(m, 2H), 7.13 (td, *J* = 7.8, 1.5 Hz, 1H), 7.09–7.04 (m, 2H), 7.04–7.01 (m, 1H), 6.88 (td, *J* = 7.4, 1.1 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.56 (dd, *J* = 9.9, 1.5 Hz, 1H), 5.94–5.89 (m, 1H), 5.78 (dd, *J* = 9.9, 3.6 Hz, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ163.7 (d, *J* = 245.3 Hz, C), 152.9 (C), 136.6 (d, *J* = 3Hz, C), 129.6 (CH), 129.0 (d, *J* = 8.3 Hz, 2 × CH), 126.6 (CH), 124.5 (CH), 124.3 (CH), 121.3 (CH), 121.2 (C), 116.0 (CH), 115.5 (d, *J* = 21.8 Hz, 2 × CH), 76.4 (CH); **MS** (EI) *m/z* 226 $[M]^+$ (68), 225 $[M - H]^+$ (100), 131 $[M - C_6H_4F]^+$ (73); **HRMS** (EI-magnetic sector) calcd for $C_{15}H_{11}OF$ $[M]^+$ 226.0788, found 226.0783.

2-(Thiophen-2-yl)-2*H*-chromene (1f).[140]



Following the general procedure A, the reaction of **1** (106 mg, 0.60 mmol) with tri(tiophen-2-yl)indium (8 mL, 0.0375 M in THF, 0.30 mmol) and $BF_3{\cdot}OEt_2$ (0.091 mL, 0.72 mmol) for 16 h at 80 ºC afforded, after purification by flash chromatography (EtOAc/hexane 2:98, 3% Et_3N) 95 mg of **1f** (74%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.29 (dd, *J* = 5.0, 1.8 Hz, 1H), 7.15–7.07 (m, 2H), 7.04 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.97 (dd, *J* = 5.0, 3.5 Hz, 1H), 6.88 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 6.6 (d, *J* = 9.9 Hz, 1H), 6.12 (d, *J* = 3.9 Hz, 1H), 5.93 (dd, *J* = 9.9, 3.9 Hz, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 152.5 (C), 143.7 (C), 129.5 (CH), 126.7 (CH), 126.6 (CH), 126.3 (CH), 126.1 (CH), 124.6 (CH), 123.9 (CH), 121.42 (CH), 121.38 (C), 116.41 (CH), 71.69 (CH); **MS** (EI) *m/z* 214 $[M]^+$ (85), 213 $[M - H]^+$ (100); **HRMS** (EI-magnetic sector) calcd for $C_{13}H_{10}OS$ $[M]^+$ 214.0447, found 214.0437.

2-(Phenylethynyl)-2*H*-chromene (1g).[141]

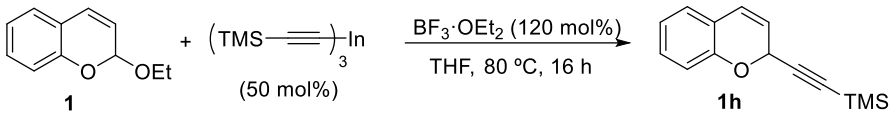


Following the general procedure A, the reaction of **1** (106 mg, 0.60 mmol) with tri(phenylethynyl)indium (8 mL, 0.0375 M in THF, 0.30 mmol) and $BF_3{\cdot}OEt_2$ (0.091 mL, 0.72 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 2:98, 3% Et_3N) 124 mg of **1g** (89%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.45–7.40 (m, 2H), 7.32–7.27 (m, 3H), 7.20 (td, *J* = 7.8, 1.8 Hz, 1H), 7.07 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.96 (m, 2H), 6.55 (d, *J* = 9.3 Hz, 1H), 5.87 (dd, *J* = 9.3, 3.9 Hz, 1H), 5.84 (d, *J* = 3.9Hz, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 152.5 (C), 131.9 (2 × CH), 129.5 (CH), 128.6 (CH), 128.2 (2 × CH), 126.8 (CH), 124.6 (CH), 122.2 (C), 122.1 (CH), 121.8 (CH), 121.4 (C), 116.5 (CH), 86.0 (C), 85.7 (C), 65.1 (CH); **MS** (EI) *m/z* 233 [M +

140 Xia, Y.; Zhang, Y.; Wang. J. *Org. Biomol. Chem.* **2014**, *12*, 9333-9336.
141 Wan, M.; Meng, Z.; Lou, H.; Liu, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 13845-13849.

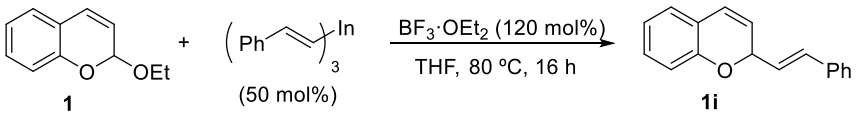
H]$^+$ (19), 232 [M]$^+$ (100); **HRMS** (EI-magnetic sector) calcd for $C_{17}H_{12}O$ [M]$^+$ 232.0883, found 232.0877.

2-(Trimethylsilylethynyl)-2*H*-chromene (1h).



Following the general procedure A, the reaction of **1** (106 mg, 0.60 mmol) with tris(trimethylsilylethynyl)indium (8 mL, 0.0375 M in THF, 0.30 mmol) and $BF_3{\cdot}OEt_2$ (0.091 mL, 0.72 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 2:98, 3% Et_3N) 116 mg of **1h** (85%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.15 (td, *J* = 7.5, 1.8 Hz, 1H), 7.01 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.92 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.90-6.86 (m, 1H), 6.47 (dd, *J* = 9.6, 1.8 Hz, 1H), 5.75 (dd, *J* = 9.6, 3.6 Hz, 1H), 5.59 (dd, *J* = 3.6, 1.8 Hz, 1H) 0.18 (s, 9H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 152.5 (C), 129.4 (CH), 126.7 (CH), 124.6 (CH), 122.2 (CH), 121.7 (CH), 121.3 (C), 116.4 (CH), 102.0 (C), 90.1 (C), 65.2 (CH), –0.3 (3 × CH_3); **MS** (EI) *m/z* 228 [M]$^+$ (92), 227 [M – H]$^+$ (85), 213 [M – CH_3]$^+$ (100); **HRMS** (EI-magnetic sector) calcd for $C_{14}H_{16}OSi$ [M]$^+$ 228.0965, found 228.0962.

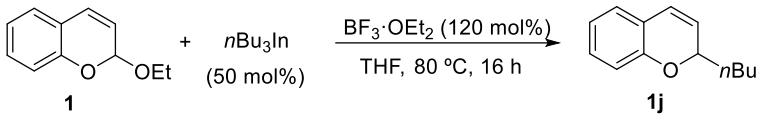
2-Styryl-2*H*-chromene (1i).[95]



Following the general procedure A, the reaction of **1** (106 mg, 0.60 mmol) with tri(2-styryl)indium (16 mL, 0.038 M in THF, 0.60 mmol, prepared from β-bromostyrene, *E*/*Z* 88:12) and $BF_3{\cdot}OEt_2$ (0.091 mL, 0.72 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3% Et_3N) 129 mg of **1i** (92%, *E*/*Z* 87:13) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.43–7.36 (m, 2H), 7.34–7.24 (m, 3H), 7.13 (td, *J* = 7.5, 1.5 Hz, 1H), 7.00 (dd, *J* = 7.2, 1.2 Hz, 1H), 6.94–6.86 (m, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 15.8 Hz, 1H), 6.50 (d, *J* = 9.6 Hz, 1H), 6.37 (dd, *J* = 15.8, 6.9 Hz, 1H), 5.80–5.89 (m, 0.26 H) 5.75 (dd, *J* = 9.6, 3.6 Hz, 1H), 5.51–5.46 (m, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 153.0 (C), 136.3 (C), 132.0 (CH), 129.3 (CH), 128.5 (2 × CH), 128.0 (CH), 127.2 (CH), 126.7 (2 × CH), 126.6 (CH), 124.2 (CH), 123.8 (CH),

121.6 (C), 121.2 (CH), 116.1 (CH), 75.6 (CH); **MS** (EI) *m/z* 234 $[M]^+$ (100), 233 $[M - H]^+$ (84); **HRMS** (EI-magnetic sector) calcd for $C_{17}H_{14}O$ $[M]^+$ 234.1039, found 234.1028.

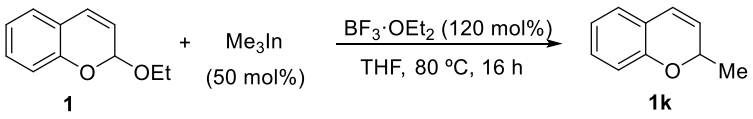
2-*n*-Butyl-2*H*-chromene (1j).[142]



1 1j

Following the general procedure A, the reaction of **1** (106 mg, 0.60 mmol) with tributylindium (6 mL, 0.05 M in THF, 0.30 mmol) and $BF_3{\cdot}OEt_2$ (0.091 mL, 0.72 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 1:99, 3% Et_3N), 47 mg of **1j** (42%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.11 (td, *J* = 7.5, 1.8 Hz, 1H), 6.97 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.85 (td, *J* = 7.5, 1.2 Hz, 1H), 6.80 (d, *J* = 7.5 Hz, 1H), 6.40 (d, *J* = 9.9 Hz, 1H), 5.70 (dd, *J* = 9.9, 3.3 Hz, 1H), 4.91-4.82 (m, 1H), 1.89–1.62 (m, 2H), 1.55–1.30 (m, 4H), 0.94 (t, *J* = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 153.6 (C), 129.0 (CH), 126.4 (CH), 126.0 (CH), 123.9 (CH), 122.0 (C), 120.9 (CH), 115.9 (CH), 75.2 (CH), 35.1 (CH_2), 27.0 (CH_2), 22.6 (CH_2), 14.0 (CH_3); **MS** (EI) *m/z* 188 $[M]^+$ (7), 131 $[M - C_4H_9]^+$ (100); **HRMS** (EI-magnetic sector) calcd for $C_{13}H_{16}O$ $[M]^+$ 188.1196, found 188.1193.

2-Methyl-2*H*-chromene (1k).[143]



1 1k

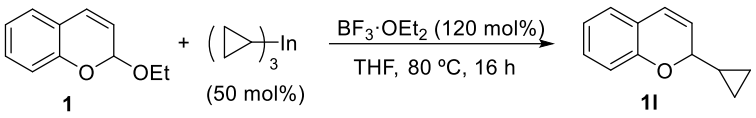
Following the general procedure A, the reaction of **1** (106 mg, 0.60 mmol) with trimethylindium (6 mL, 0.05 M in THF, 0.30 mmol) and $BF_3{\cdot}OEt_2$ (0.091 mL, 0.72 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 2:98, 3% Et_3N), 35 mg of **1k** (40%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.10 (td, *J* = 7.8, 1.8 Hz, 1H), 6.96 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.84 (td, *J* = 7.4, 1.2 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.38 (dd, *J* = 9.8, 1.8 Hz, 1H), 5.65 (dd, *J* = 9.8, 3.1 Hz), 5.06–4.96 (m, 1H), 1.45 (d, *J* = 6.6 Hz, 3H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 153.5

142 Wang, Q.; Finn, M.G. *Org. Lett.* **2000**, *2*, 4063-4065.

143 Hosokawa, T.; Yamashita, S.; Murahashi, S.-I.; Sonoda, A. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3662-3665.

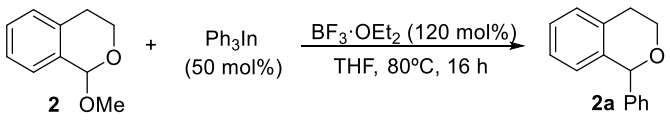
(C), 129.1 (CH), 126.9 (CH), 126.4 (CH), 123.7 (CH), 121.8 (C), 121.0 (CH), 115.9 (CH), 71.4 (CH), 21.3 (CH_3); **MS** (EI) *m/z* 146 $[M]^+$ (13), 131 $[M - CH_3]^+$ (100); **HRMS** (EI-magnetic sector) calcd for $C_{10}H_{10}O$ $[M]^+$ 146.0726, found 146.0726.

2-Cyclopropyl-2*H*-chromene (1l).



Following the general procedure A, the reaction of **1** (106 mg, 0.60 mmol) with tricyclopropylindium (8 mL, 0.0375 M in THF, 0.30 mmol) and $BF_3{\cdot}OEt_2$ (0.091 mL, 0.72 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 0.5:99.5, 3% Et_3N), 87 mg of **1l** (84%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.12 (td, *J* = 7.8, 1.5 Hz, 1H), 6.97(dd, *J* = 7.5, 1.8 Hz, 1H), 6.84 (t, *J* = 7.8 Hz, 2H), 6.43 (d, *J* = 9.9 Hz, 1H), 5.74 (dd, *J* = 9.9, 3.3 Hz, 1H), 4.24 (d, *J* = 8.4 Hz, 1H), 1.35–1.21 (m, 1H), 0.68–0.45 (m, 3H), 0.39–0.30 (m, 1H)); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 153.7 (C), 129.1 (CH), 126.4 (CH), 124.6 (CH), 124.2 (CH), 121.9 (C), 120.9 (CH), 115.9 (CH), 79.5 (CH), 15.8 (CH), 3.1 (CH_2), 1.3 (CH_2); **MS** (EI) *m/z* 172 $[M]^+$ (40), 131 $[M - C_3H_5]^+$ (100); **HRMS** (EI-magnetic sector) calcd for $C_{12}H_{12}O$ $[M]^+$ 172.0888, found 172.0883.

1-Phenyl-isochroman (2a). [144]

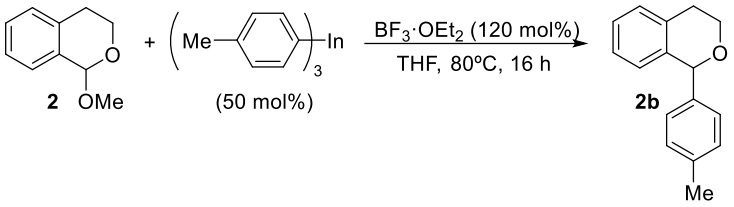


Following the general procedure A, the reaction of **2** (100 mg, 0.61 mmol) with triphenylindium (6 mL, 0.052 M in THF, 0.31 mmol) and $BF_3{\cdot}OEt_2$ (0.092 mL, 0.73 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3% Et_3N), 118 mg of **2a** (92%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.34–7.32 (m, 5H), 7.23–7.18 (m, 2H), 7.14–7.07 (m, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 5.77 (s, 1H), 4.27–4.20 (m, 1H), 4.01–3.93 (m, 1H), 3.23–3.13 (m, 1H), 2.83 (dt, *J* = 16.7, 4.2 Hz, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 142.3 (C), 137.4 (C), 133.9

144 Fujisaka, T.; Nojima, M.; Kusabayashi, S. *J. Org. Chem.* **1985**, *50*, 275-277.

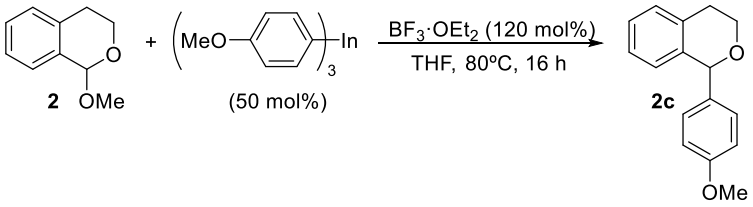
(C), 128.9 (2 × CH), 128.7 (CH), 128.4 (2 × CH), 128.1 (CH), 126.9 (CH), 126.6 (CH), 125.9 (CH), 79.7 (CH), 63.9 (CH_2), 28.9 (CH_2); **MS** (EI) *m/z* 210 $[M]^+$ (100), 209 $[M - H]^+$ (49); **HRMS** (EI-magnetic sector) calcd for $C_{15}H_{14}O$ $[M]^+$ 210.1039, found 210.1034.

1-(4-Methylphenyl)-isochroman (2b).[122]



Following the general procedure A, the reaction of **2** (100 mg, 0.61 mmol) with tri-*p*-tolylindium (6 mL, 0.052 M in THF, 0.31 mmol) and $BF_3{\cdot}OEt_2$ (0.092 mL, 0.73 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 2:98, 3% Et_3N), 123 mg of **2b** (90%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.23–7.12 (m, 6H), 7.11–7.04 (m, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 5.71 (s, 1H), 4.24–4.15 (m, 1H), 3.99–3.88 (m, 1H), 3.22–3.08 (m, 1H), 2.82 (dt, *J* = 16.2, 3.9 Hz, 1H), 2.35 (s, 3H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ139.3 (C), 137.8 (C), 137.5 (C), 133.9 (C), 129.1 (2 × CH), 128.8 (2 × CH), 128.7 (CH), 126.9 (CH), 126.5 (CH), 125.9 (CH), 79.4 (CH), 63.7 (CH_2), 28.8 (CH_2), 21.2 (CH_3); **MS** (EI) *m/z* 224 $[M]^+$ (100), 223 $[M - H]^+$ (47), 209 $[M - CH_3]^+$ (67); **HRMS** (EI-magnetic sector) calcd for $C_{16}H_{16}O$ $[M]^+$ 224.1190, found 224.1196.

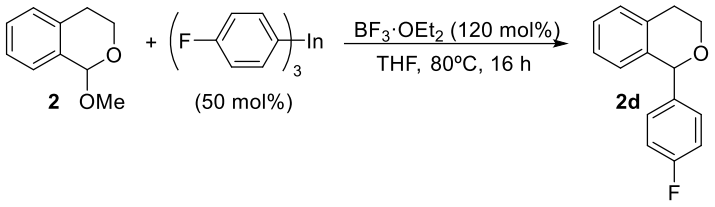
1-(4-Methoxyphenyl)-isochroman (2c).[101]



Following the general procedure A, the reaction of **2** (100 mg, 0.61 mmol) with tri-(4-methoxyphenyl)indium (10 mL, 0.031 M in THF, 0.31 mmol) and $BF_3{\cdot}OEt_2$ (0.092 mL, 0.73 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 2:98, 3% Et_3N), 123 mg of **2c** (84%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ7.28–7.22 (m, 2H), 7.21–7.16 (m, 2H), 7.13–7.06 (m, 1H), 6.93–6.86 (m, 2H), 6.78 (d, *J* = 7.5 Hz, 1H), 5.72 (s, 1H), 4.24–4.16 (m, 1H), 3.99–3.90 (m, 1H), 3.81

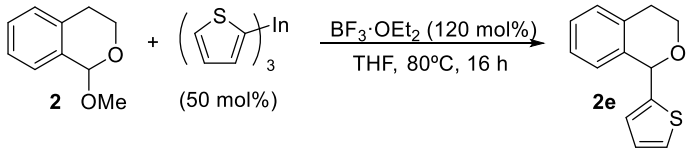
(s, 3H), 3.21–3.08 (m, 1H), 2.83 (dt, *J* = 16.5, 3.9 Hz, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 159.4 (C), 137.7 (C), 134.6 (C), 133.9 (C), 130.1 (2 × CH), 128.7 (CH), 127.0 (CH), 126.6 (CH), 125.9 (CH), 113.8 (2 × CH), 79.1 (CH), 63.7 (CH_2), 55.3 (CH_3), 28.9 (CH_2); **MS** (EI) *m/z* 240 $[M]^+$ (100), 239 $[M - H]^+$ (68), 209 $[CH_3O]^+$ (81); **HRMS** (EI-magnetic sector) calcd for $C_{16}H_{16}O_2$ $[M]^+$ 240.1145, found 240.1140.

1-(4-Fluorophenyl)-isochroman (2d).[122]



Following the general procedure A, the reaction of **2** (100 mg, 0.61 mmol) with tri-(4-fluorophenyl)indium (6 mL, 0.052 M in THF, 0.31 mmol) and $BF_3{\cdot}OEt_2$ (0.092 mL, 0.73 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3% Et_3N), 123 mg of **2d** (88%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.34–7.27 (m, 2H), 7.22–7.16 (m, 2H), 7.13–7.08 (m, 1H), 7.04 (t, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 7.5 Hz, 1H), 5.73 (s, 1H), 4.25–4.15 (m, 1H), 3.99–3.90 (m, 1H), 3.22–3.10 (m, 1H), 2.82 (dt, *J* = 16.2, 3.6 Hz, 1H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ162.5 (d, *J* = 244.9 Hz, C), 138.1 (d, *J* = 3.2 Hz, C), 137.2 (C), 133.8 (C), 130.6 (d, *J* = 8.2 Hz, 2 × CH), 128.8 (CH), 126.8 (CH), 126.7 (CH), 126.0 (CH), 115.3 (d, *J* = 21.3 Hz, 2 × CH), 78.9 (CH), 63.9 (CH_2), 28.8 (CH_2); **MS** (EI) *m/z* 228 $[M]^+$ (16), 83 $[M - C_{10}H_9O]^+$ (100); **HRMS** (EI-magnetic sector) calcd for $C_{15}H_{13}OF$ $[M]^+$ 228.0945, found 228.0940.

1-(Thiophen-2-yl)-isochroman (2e). [145]

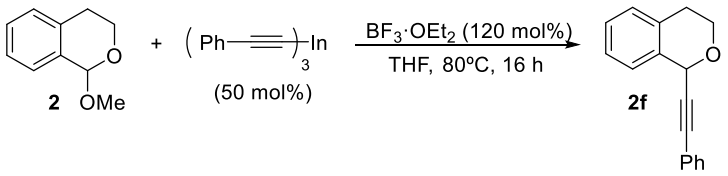


Following the general procedure A, the reaction of **2** (100 mg, 0.61 mmol) with tri(tiophen-2-yl)indium (8.2 mL, 0.038 M in THF, 0.31 mmol) and $BF_3{\cdot}OEt_2$ (0.092 mL, 0.73 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography

145 Chen, W.; Xie, Z.; Zheng, H.; Lou, H.; Liu, L. *Org. Lett.* **2014**, *16*, 5988-5991.

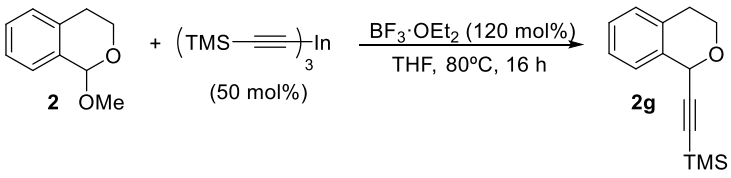
(EtOAc/hexane 3:97, 3% Et_3N), 98 mg of **2e** (71%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.32–7.29 (m, 1H), 7.23–7.12 (m, 3H), 7.02–6.96 (m, 3H), 6.06 (s, 1H), 4.18–4.10 (m, 1H), 4.00–3.90 (m, 1H), 3.01–2.87 (m, 2H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 146.0 (C), 136.3 (C), 133.5 (C), 128.8 (CH), 127.2 (CH), 127.0 (CH), 126.8 (CH), 126.2 (CH), 126.1 (CH), 125.9 (CH), 73.9 (CH), 62.4 (CH_2), 28.5 (CH_2); **MS** (EI) *m/z* 216 $[M]^+$ (100), 215 $[M - H]^+$ (37); **HRMS** (EI-magnetic sector) calcd for $C_{13}H_{12}OS$ $[M]^+$ 216.0603, found 216.0599.

1-Phenylethynyl-isochroman (2f).[146]



Following the general procedure A, the reaction of **2** (100 mg, 0.61 mmol) with tri(phenylethynyl)indium (8.2 mL, 0.038 M in THF, 0.31 mmol) and $BF_3{\cdot}OEt_2$ (0.092 mL, 0.73 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 2:98, 3% Et_3N), 117 mg of **2f** (82%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.49–7.43 (m, 2H), 7.38–7.33 (m, 1H), 7.33–7.28 (m, 3H), 7.25–7.20 (m, 2H), 7.17–7.12 (m, 1H), 5.78 (s, 1H), 4.37–4.26 (m, 1H), 4.08–3.98 (m, 1H), 2.96–2.89 (m, 2H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 134.9 (C), 132.8 (C), 131.8 (2 $\times$ CH), 129.0 (CH), 128.4 (CH), 128.2 (2 $\times$ CH), 127.2 (CH), 126.4 (CH), 126.0 (CH), 122.6 (C), 88.1 (C), 85.7 (C), 67.3 (CH), 62.7 (CH_2), 28.0 (CH_2); **MS** (EI) *m/z* 234 $[M]^+$ (92), 233 $[M - H]^+$ (77); **HRMS** (EI-magnetic sector) calcd for $C_{17}H_{14}O$ $[M]^+$ 234.1039, found 234.1032.

1-Trimethylsilylethynyl-isochroman (2g). [147]

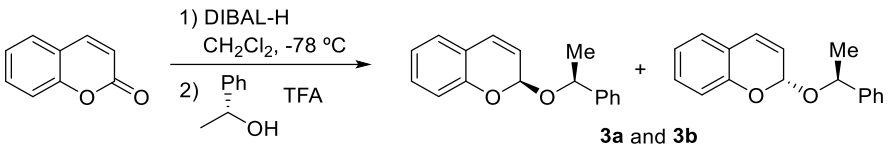


Following the general procedure A, the reaction of **2** (100 mg, 0.61 mmol) with tris(trimethylsilylethynyl)indium (8.4 mL, 0.037 M in THF, 0.31 mmol) and $BF_3{\cdot}OEt_2$

146 Correia, C.A.; Li, C.-J.; *Heterocycles* **2010**, *82*, 555-562.
147 Srinivas, H. D.; Maity, P.; Yap, G.; Watson, M. P. *J. Org. Chem.* **2015**, *80*, 4003-4016.

(0.092 mL, 0.73 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 3:97, 3% Et_3N), 97 mg of **2g** (70%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.33–7.27 (m, 1H), 7.25–7.17 (m, 2H), 7.16–7.07 (m, 1H), 5.54 (s, 1H), 4.30–4.20 (m, 1H), 4.00–3.90 (m, 1H), 2.88 (t, *J* = 5.9 Hz, 2H), 0.19 (s, 9H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 134.7 (C), 132.7 (C), 128.9 (CH), 127.2 (CH), 126.3 (CH), 126.0 (CH), 104.1 (C), 90.4 (C), 67.4 (CH), 62.8 (CH_2), 28.0 (CH_2), –0.2 (3 × CH_3); **MS** (EI) *m/z* 230 $[M]^+$ (40), 229 $[M - H]^+$ (34), 73 $[M - C_{11}H_9O]^+$ (100); **HRMS** (EI-magnetic sector) calcd for $C_{14}H_{18}OSi$ $[M]^+$ 230.1121, found 230.1113.

Preparation of (2*ξ*)-2-((1*S*)-1-phenylethoxy)-2*H*-chromene (3a and 3b).



3a and **3b**

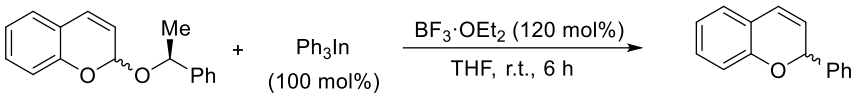
To a solution of coumarin (650 mg, 4.44 mmol) in CH_2Cl_2 (15 mL), DIBAL-H (4.66 mL, 4.66 mmol, 1.0 M) was added dropwise for 1.5 h at –78 °C. The reaction was stirred for 2 h, warmed to 0 °C, and then allowed to reach rt. The mixture was diluted with EtOAc (30 mL) and water (30 mL). After filtration through Celite, the aqueous layer was extracted with EtOAc (2 × 20 mL) and the resulting organic layer was washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated to yield a viscous yellow oil. The crude was dissolved in dry THF (20 mL) and (*R*)-1-phenylethanol (0.8 ml, 6.65 mmol) and trifluoroacetic acid (15 μL, 0.20 mmol) were added. After 12 h stirring at rt, K_2CO_3 (30 mg, 0.22 mmol) was added. The mixture was filtered and the solvent evaporated under reduced pressure. The crude was purified by flash chromatography (EtOAc/hexane 3:97, 3% Et_3N) to afford, after high vacuum drying, 490 mg of **3a** (44%) and 181 mg of **3b** (6%) as yellow oils (the absolute stereochemistry of diastereomers **3a** and **3b** was not determined).

3a: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.44–7.29 (m, 5H), 7.24 (td, *J* = 7.6 Hz, 1.8 Hz, 1H), 7.15 (dd, *J* = 7.5 Hz, 1.5 Hz, 1H), 7.05–6.93 (m, 2H), 6.74 (d, *J* = 9.6 Hz, 1H), 5.78 (dd, *J* = 9.6 Hz, 3.9 HZ, 1H), 5.52 (d, *J* = 3.6 Hz, 1H), 5.11 (q, *J* = 6.6 Hz, 1H), 1.41 (d, *J* = 6.6 Hz, 3H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 151.4 (C), 143.1 (C), 129.3 (CH), 128.6 (2 × CH), 127.7 (CH), 127.1 (CH), 126.53 (2 × CH), 126.48 (CH), 121.4 (CH), 120.9 (C), 120.2

(CH), 116.6 (CH), 92.3 (CH), 74.3 (CH) 24.2 (CH_3). **MS** (EI) *m/z* 252 $[M]^+$ (3), 105 [M – $C_{10}H_{11}O]^+$ (100); **HRMS** (EI-magnetic sector) calcd for $C_{17}H_{16}O_2$ $[M]^+$ 252.1145, found 252.1147.

3b: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ7.31–7.20 (m, 5H), 7.14–7.04 (m, 2H), 6.93 (td, *J* = 7.5 Hz, 1.2 Hz, 1H), 6.74 (d, *J* = 9.3 Hz, 1H), 6.41 (d, *J* = 8.1 Hz, 1H), 5.96–5.87 (m, 2H), 4.96 (q, *J* = 6.6 Hz, 1H), 1.53 (d, *J* = 6.6 Hz, 3H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ151.1 (C), 144.3 (C), 129.0 (CH), 128.1 (2 × CH), 127.0 (CH), 126.7 (CH), 126.6 (CH), 126.1 (2 × CH), 121.2 (CH), 120.6 (C), 119.9 (CH), 116.7 (CH), 94.6 (CH), 76.8 (CH), 23.2 (CH_3). **MS** (EI) *m/z* 252 $[M]^+$ (3), 105 [M – $C_{10}H_{11}O]^+$ (100); **HRMS** (EI-magnetic sector) calcd for $C_{17}H_{16}O_2$ $[M]^+$ 252.1145, found 252.1149.

Reaction of 3a and 3b with Ph_3In under $BF_3{\cdot}OEt_2$ activation.



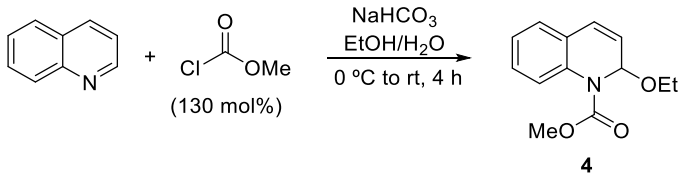
3a or **3b** **1a**

Following the general procedure A, the reaction of **3a** (100 mg, 0.40 mmol) with triphenylindium (8 mL, 0.05 M in THF, 0.40 mmol) and $BF_3{\cdot}OEt_2$ (0.061 mL, 0.48 mmol) for 6 h at r.t. afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3% Et_3N), 77 mg of **1a** (92%, er 48:52) as a colorless oil. Enantiomers were differentiated by HPLC using a chiral stationary phase (Chiralcel OJ-H) eluent 2-propanol/hexane 1:99, flow rate = 0.7 mL/min, λ = 280 nm, t_1 = 28 min, t_2 = 32 min.

Following the general procedure A, the reaction of **3b** (100 mg, 0.40 mmol) with triphenylindium (8 mL, 0.05 M in THF, 0.40 mmol) and $BF_3{\cdot}OEt_2$ (0.061 mL, 0.48 mmol) for 6 h at r.t. afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3% Et_3N), 79 mg of **1a** (94%, er 50:50) as a colorless oil. Enantiomers were discriminated by HPLC analysis using a chiral stationary phase (Chiralced OJ-H) eluent 2-propanol/hexane 1:99, flow rate = 0.7 mL/min, λ = 280 nm, t_1 = 30 min, t_2 = 34 min.

Preparation of methyl 2-ethoxyquinoline-1(2H)-carboxylate (4).[148]

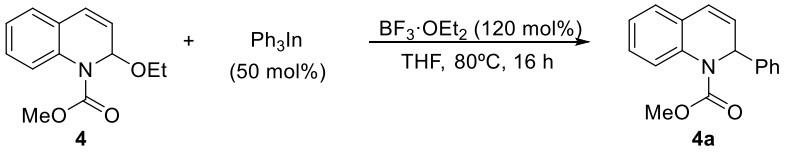
148 Shields, J. D.; Ahneman, D. T.; Graham, T. J. A.; Doyle, A. G. *Org. Lett.* **2014**, *16*, 142-145.



4

To a solution of quinoline (4.7 mL, 40 mmol) and $NaHCO_3$ (4.6 g, 54 mmol) in ethanol (12 mL) and water (1.5 mL), methyl chloroformate (4.0 mL, 54 mmol) was added dropwise at 0 °C. The reaction was warmed to room temperature and stirred for 4 h. Ice water (50 mL) was added and the resulting precipitate was filtered, washed with chilled water (100 mL) and dried. The crude material was recrystallized from Et_2O at -15 °C affording 3.43 g of **4** (37 %) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ7,30 (d, *J* = 1.8 Hz, 1H), 7.29–7.25 (m, 1H), 7.21 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.12 (td, *J* = 7.4, 1.2 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 6.14 (m, 2H), 3.86 (s, 3H), 3.68–3.56 (m, 2H), 1.13 (t, *J* = 7.0 Hz, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ155.4 (C), 133.7 (C), 127.73 (CH), 127.68 (CH), 126.9 (CH), 125.8 (C), 124.2 (2 × CH), 123.8 (CH), 78.3 (CH), 62.4 (CH_2), 53.3 (CH_3), 15.1 (CH_3). **MS** (EI) *m/z* 233 $[M]^+$ (4), 188 $[M - OEt]^+$ (100); **HRMS** (EI-magnetic sector) calcd for $C_{13}H_{15}O_3N$ $[M]^+$ 233.1046, found 233.1047.

Methyl 2-phenylquinoline-1(2H)-carboxylate (4a).[148]



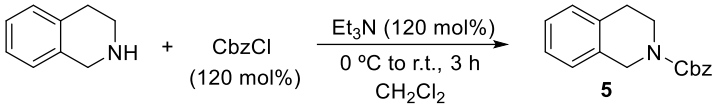
4 **4a**

Following the general procedure A, the reaction of **4** (100 mg, 0.43 mmol) with triphenylindium (6 mL, 0.036 M in THF, 0.22 mmol) and $BF_3{\cdot}OEt_2$ (0.064 mL, 0.52 mmol) for 16 h at 80 °C afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3% Et_3N), 59 mg of **4a** (43%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ7.51 (d, *J* = 6.9 Hz, 1H), 7.30–7.20 (m, 5H), 7.19–7.15 (m, 1H), 7.12 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.05 (td, *J* = 7.5, 1.2 Hz, 1H), 6.65 (m, 1H), 6.24–6.18 (m, 2H), 3.85 (s, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ155.2 (C), 139.6 (C), 134.7 (C), 128.5, (2 × CH), 127.1 (C), 127.0 (2 × CH), 126.3 (CH), 125.3 (CH), 124.6 (CH), 124.3 (CH), 55.6 (CH), 53.2 (CH_3). **MS** (EI) *m/z* 265 $[M]^+$ (59), 188 $[M - C_6H_6]^+$ (100).

General Procedure for the Protection of THIQs

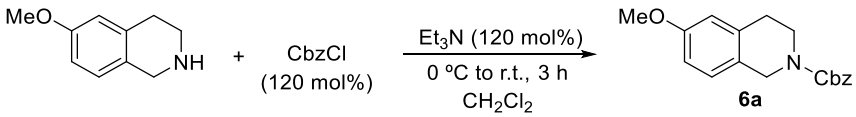
N-carboxybenzyl tetrahydroisoquinolines **5-11** were prepared by addition of the corresponding chloroformate (9.59 mmol) to a solution of tetrahydroisoquinoline (8 mmol) and triethylamine (1.34 mL, 9.59 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After 3 hours of stirring at rt, water (50 mL) was added. The organic phase was extracted with dichloromethane (2 × 20 mL). The combined organic extracts were washed with saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude was purified by flash chromatography to afford, after concentration and high-vacuum drying, the corresponding products.

Benzyl 3,4-dihydroisoquinoline-2(*1H*)-carboxylate (5).[149]



Following the general procedure, benzyl chloroformate (1.37 mL, 9.59 mmol) was added to a solution of terahydroisoquinoline (1.06 g, 8 mmol) and triethylamine (1.34 mL, 9.59 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After purification by flash chromatography (EtOAc/hexane 20:80, 3 % Et_3N) 1.00 g of **5** (47 %) was obtained as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.49–7.29 (m, 5H), 7.25–7.07 (m, 4H), 5.20 (s, 2H), 4.67 (s, 2H), 3.82–3.70 (m, 2H), 2.96–2.81 (m, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers seen) δ 155.5, 136.8, 134.6, 134.5, 133.5, 133.1, 128.8, 128.7, 128.5, 128.03, 127.97, 126.5, 126.3, 67.2, 45.8, 41.6, 41.4, 29.0, 28.8. **HRMS** (ESI) *m/z* calcd for $C_{17}H_{18}NO_2$ $[M + H]^+$ 268.1332, found 268.1342.

Benzyl 6-methoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (6a).[149]

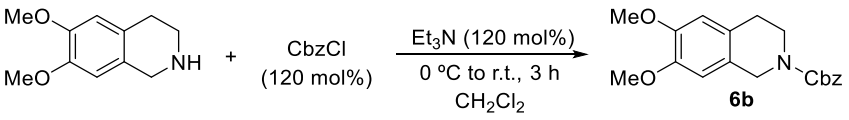


Following the general procedure, benzyl chloroformate (1.37 mL, 9.59 mmol) was added to a solution of 6-methoxy-1,2,3,4-tetrahydroisoquinoline (1.30 g, 8 mmol) and triethylamine (1.34 mL, 9.59 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After purification by flash chromatography (EtOAc/hexane 20:80, 3 % Et_3N) 1.19 g of **6a** (50 %) was

149 Yan, C.; Liu, Y.; Wang, Q. *RSC Adv.* **2014**, *4*, 60075-60078.

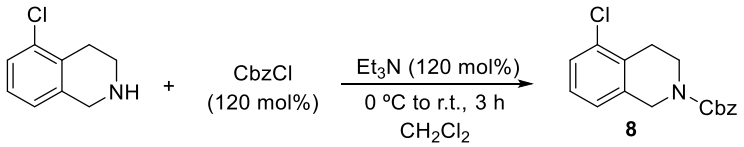
obtained as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ7.45–7.28 (m, 5H), 7.10–6.95 (m, 1H), 6.76 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.70–6.65 (m, 1H), 5.19 (s, 2H), 4.60 (s, 2H), 3.79 (s, 3H), 3.76–3.65 (m, 2H), 2.90–2.76 (m, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ158.3, 155.6, 136.9, 135.9, 128.6, 128.12, 128.06, 127.4, 125.5, 113.5, 112.7, 67.3, 55.4, 45.4, 41.6, 29.3. **HRMS** (ESI) *m/z* calcd for $C_{18}H_{19}NO_3Na$ $[M + Na]^+$ 320.1257, found 320.1260.

Benzyl 6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (6b). [150]



Following the general procedure, benzyl chloroformate (1.37 mL, 9.59 mmol) was added to a solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1.55 g, 8 mmol) and triethylamine (1.34 mL, 9.59 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After purification by flash chromatography (EtOAc/hexane 20:80, 3 % Et_3N) 1.41 g of **6b** (54 %) was obtained as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ7.44–7.27 (m, 5H), 6.67–6.52 (m, 2H), 5.18 (s, 2H), 4.58 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.77–3.65 (m, 2H), 2.84–2.70 (m, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ155.5, 147.8, 147.7, 136.9, 128.6, 128.1, 126.5, 126.3, 125.3, 124.8, 111.6, 109.1, 67.3, 56.0, 43.5, 41.8, 41.6, 28.5, 28.4. **HRMS** (ESI) *m/z* calcd for $C_{19}H_{22}NO_4Na$ $[M + H]^+$ 328.1543, found 328.1551.

Benzyl 5-chloro-3,4-dihydroisoquinoline-2(1H)-carboxylate (8).[125]

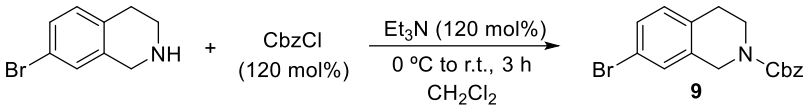


Following the general procedure, benzyl chloroformate (0.360 mL, 2.51 mmol) was added to a solution of 5-chloro-1,2,3,4-terahydroisoquinoline (0.350 g, 2.09 mmol) and triethylamine (0.350 mL, 2.51 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After purification by flash chromatography (EtOAc/hexane 20:80, 3 % Et_3N) 0.390 g of **8** (63 %) was

150 Kim, H. J.; Yoon, U. C.; Jung, Y.-S.; Park, N. S.; Cederstrom, E. N.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 860-863.

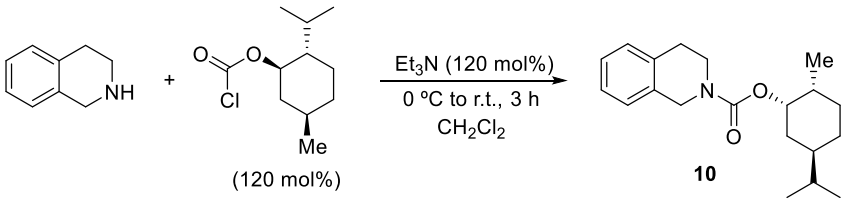
obtained as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.45–7.28 m(5H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.10 (td, *J* = 7.7, 1.9 Hz, 1H), 7.00 (m, 1H), 5.25–5.11 (m, 2H), 4.71–5.55 (m, 2H), 3.83–3.65 (m, 2H), 2.97–2.76 (m, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ 136.7, 135.6, 134.4, 132.6, 128.6, 128.2, 128.1, 127.3, 127.2, 124.8, 67.4, 45.8, 41.3, 26.6. **HRMS** (ESI) *m/z* calcd for $C_{17}H_{16}NO_2NaCl$ [M + Na]$^+$ 324.0761, found 324.0757.

Benzyl 7-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate (9).[149]



Following the general procedure, benzyl chloroformate (0.20 mL, 1.42 mmol) was added to a solution of 7-bromo-1,2,3,4-terahydroisoquinoline (0.250 g, 1.18 mmol) and triethylamine (0.20 mL, 1.42 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After purification by flash chromatography (EtOAc/hexane 20:80, 3 % Et_3N) 0.393 g of **9** (81 %) was obtained as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.46–7.17 (m, 7H), 7.0 (d, *J* = 8.4 Hz, 1H), 5.18 (s, 2H), 4.62 (s, 2), 3.80–3.62 (m, 2H), 2.85–2.73 (m, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ 155.5, 136.7, 133.6, 130.5, 129.7, 129.3, 128.7, 128.2, 128.1, 120.0, 67.5, 45.5, 41.4, 28.5. **HRMS** (ESI) *m/z* calcd for $C_{17}H_{16}NO_2NaBr$ [M + Na]$^+$ 368.0256, found 368.0256.

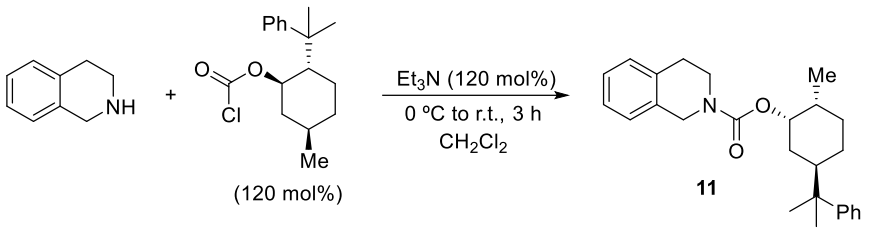
(1S,2R,5R)-5-isopropyl-2-methylcyclohexyl 3,4-dihydroisoquinoline-2(1H)-carboxylate (10).



Following the general procedure, (1*R*)-menthyl chloroformate (0.89 mL, 4.13 mmol) was added to a solution of 1,2,3,4-terahydroisoquinoline (0.500 g, 3.75 mmol) and triethylamine (0.57 mL, 4.13 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After purification by flash chromatography (EtOAc/hexane 10:90, 3 % Et_3N) 0.981 g of **10** (83 %) was obtained as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.23–7.07 (m, 4H), 4.70–4.53 (m, 3H), 3.75–3.63 (m, 2H), 2.91–2.78 (m, 2H), 2.14–2.03 (m, 1H),

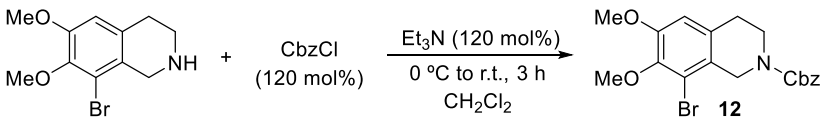
1.99–1.87 (m, 1H), 1.75–1.61 (m, 2H), 1.57–1.34 (m, 2H), 1.15–0.96 (m, 2H), 0.93–0.86 (m, 7H), 0.79 (d, *J* = 6.9 Hz, 3H). **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ155.5, 134.7, 128.7, 126.4, 126.2, 75.2, 47.4, 41.3, 34.4, 31.4, 29.0, 26.5, 23.7, 22.0, 20.8, 16.6. **HRMS** (ESI) *m/z* calcd for $C_{20}H_{30}NO_2$ $[M + H]^+$ 316.2271, found 316.2280.

(1S,2R,5R)-2-methyl-5-(2-phenylpropan-2-yl)cyclohexyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (11).



Following the general procedure, (1*R*)-8-phenylmenthyl chloroformate (0.607 g, 2.06 mmol) was added to a solution of 1,2,3,4-terahydroisoquinoline (0.230 g, 1.72 mmol) and triethylamine (0.29 mL, 2.06 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After purification by flash chromatography (EtOAc/hexane 5:95, 3 % Et_3N) 0.550 g of **11** (81 %) was obtained as a yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz, rotamers mixture) δ7.32–7.28 (m, 2H), 7.27–7.05 (m, 6H), 6.93–6.83 (m, 1H), 4.90–4.82 (m, 1H), 4.71–4.59 (m, 0.33H), 4.50–4.37 (m, 0.33H), 4.04–3.93 (m, 0.33H), 3.65–3.52 (m, 1H), 3.46–3.35 (m, 0.33H), 3.18–3.05 (m, 0.33H), 2.86–2.52 (m, 2.34H), 2.17–2.02 (m, 1H), 1.98–1.48 (m, 4H), 1.45–1.30 (m, 3.5H), 1.27–1.08 (m, 4H), 1.04–0.84 (m, 5.5H). **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 125 MHz, rotamers mixture) δ 154.7, 152.5, 152.3, 134.8, 134.6, 133.8, 133.5, 128.7, 128.51, 128.46, 127.9, 127.8, 126.4, 126.3, 126.2, 126.0, 125.9, 125.4, 125.3, 125.0, 75.2, 73.0, 51.0, 45.5, 44.6, 42.6, 40.9, 40.8, 39.8, 39.6, 34.8, 31.4, 29.2, 29.1, 28.0, 26.8, 26.7, 25.2, 23.8, 21.9. **HRMS** (ESI) *m/z* calcd for $C_{26}H_{34}NO_2$ $[M + H]^+$ 392.2584, found 392.2584.

Benzyl 8-bromo-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (12).



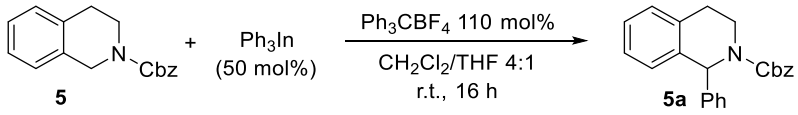
Following the general procedure, benzyl chloroformate (0.335 mL, 2.35 mmol) was added to a solution of 8-bromo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (0.53

g, 1.96 mmol) and triethylamine (0,34 mL, 2,35 mmol) in CH_2Cl_2 (20 mL) at 0 °C. After purification by flash chromatography (EtOAc/hexane 20:80, 3 % Et_3N) 0.64 g of **12** (80 %) was obtained as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.44–7.28 (m, 5H), 6.65 (s, 1H), 5.20 (s, 2H), 4.56 (s, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.74–3.64 (m, 2H), 2.80 (s, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ 155.4, 151.7, 145.0, 136.7, 131.7, 128.5, 128.0, 127.9, 117.8, 111.9, 67.2, 60.5, 56.1, 46.7, 41.1, 41.0, 29.1, 28.9. **HRMS** (ESI) *m/z* calcd for $C_{19}H_{21}NO_4Br$ $[M + H]^+$ 406.0648, found 406.0670.

General Procedure B for the Oxidative Cross-Coupling of THIQs with R_3In.

To a solution of triphenylcarbenium tetrafluoroborate (136 mg, 0.411 mmol) in CH_2Cl_2 (10 mL), *N*-protected THIQ (0.374 mmol) and R_3In (3 mL, 0.062 M in THF) were sequentially added at room temperature. The resulting mixture was left stirring overnight and then quenched with MeOH (1 mL). The solvent was concentrated in vacuo and Et_2O (20 mL) was added. The organic phase was washed with water (2 × 20 mL), saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to afford, after concentration and high-vacuum drying, the corresponding products.

Benzyl 1-phenyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (5a). [151]

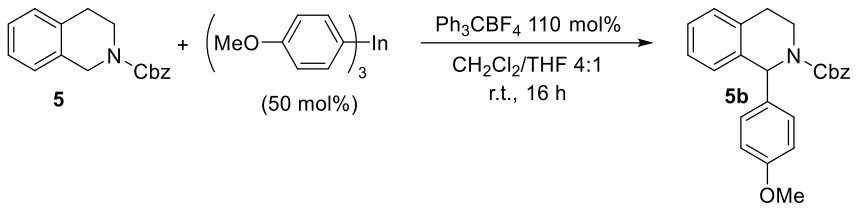


Following the general procedure B, the reaction of **5** (100 mg, 0.374 mmol) with triphenylindium (3 mL, 0.062 M in THF, 0.186 mmol) and triphenylcarbenium tetrafluoroborate (136 mg, 0.411 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3 % Et_3N) 74 mg of **5a** (58%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.53–7.01 (m, 14H), 6.65–6.22 (m, 1H), 5.40–5.10 (m, 2H), 4.30–3.98 (m, 1H), 3.43–3.23 (m, 1H), 3.13–2.91 (m, 1H), 2.88–2.69 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ 155.5, 142.7, 136.8,

151 Ludwig, M.; Hoesl, C. E.; Höfner, G.; Wanner, K. T. *Eur. J. Med. Chem.* **2006**, *41*, 1003-1010.

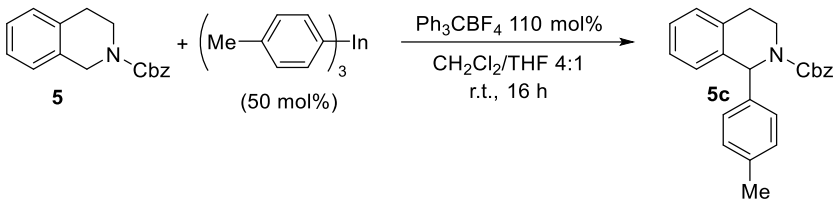
135.4, 135.1, 129.0, 128.6, 128.5, 128.4, 128.2, 127.5, 127.1, 126.3, 67.5, 57.9, 38.4, 28.6. **HRMS** (ESI) *m/z* calcd for $C_{23}H_{21}NO_2Na$ $[M + Na]^+$ 366.1470, found 366.1464.

Benzyl 1-(4-methoxyphenyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (5b).[125]



Following the general procedure B, the reaction of **5** (100 mg, 0.374 mmol) with tri-(4-methoxyphenyl)indium (3 mL, 0.062 M in THF, 0.186 mmol) and triphenylcarbenium tetrafluoroborate (136 mg, 0.411 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 10:90, 3 % Et_3N) 124 mg of **5b** (89%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.46–7.29 (m, 5H), 7.24–6.96 (m, 6H), 6.89–6.71 (m, 2H), 6.60–6.16 (m, 1H), 5.40–5.07 (m, 2H), 4.31–3.98 (m, 1H), 3.78 (s, 3H), 3.36–3.16 (m, 1H), 3.12–2.91 (m, 1H), 2.87–2.68 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ 158.8, 155.3, 136.7, 135.5, 134.9, 129.6, 128.9, 128.5, 128.0, 127.93, 127.91, 126.9, 126.1, 113.5, 67.3, 57.1, 55.2, 37.9, 28.5. **HRMS** (ESI) *m/z* calcd for $C_{24}H_{24}NO_3$ $[M + H]^+$ 374.1750, found 374.1748.

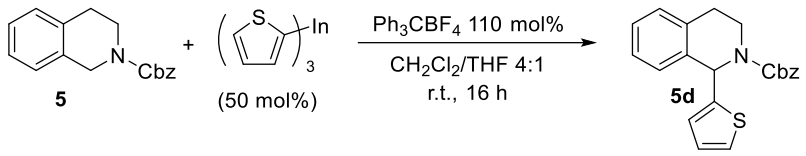
Benzyl 1-(p-tolyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (2c).[125]



Following the general procedure B, the reaction of **5** (100 mg, 0.374 mmol) with tri-*p*-tolylindium (3 mL, 0.062 M in THF, 0.186 mmol) and triphenylcarbenium tetrafluoroborate (136 mg, 0.411 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3 % Et_3N) 103 mg of **5c** (77%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.51–7.29 (m, 5H), 7.28–6.90 (m, 8H), 6.64–6.18 (m, 1H), 5.40–5.08 (m, 2H), 4.28–3.95 (m, 1H), 3.40–3.20 (m, 1H), 3.15–2.68 (m, 2H), 2.33 (s, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ 153.3,

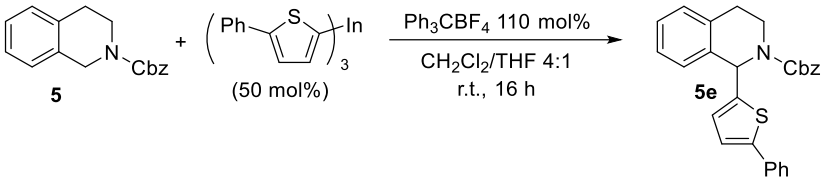
139.7, 137.1, 136.7, 135.5, 134.9, 129.3, 128.93, 128.85, 128.5, 128.4, 128.0, 127.4, 126.9, 126.1, 67.3, 57.5, 38.1, 28.6, 21.1. **HRMS** (ESI) *m/z* calcd for $C_{24}H_{24}NO_2$ $[M + H]^+$ 358.1801, found 358.1801.

Benzyl 1-(thiophen-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (5d).[125]



Following the general procedure B, the reaction of **5** (100 mg, 0.374 mmol) with tri-(thiophen-2-yl)indium (4 mL, 0.047 M in THF, 0.19 mmol) and triphenylcarbenium tetrafluoroborate (136 mg, 0.411 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 10:90, 3 % Et_3N) 111 mg of **5d** (80%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.45–7.30 (m, 5H), 7.27–7.12 (m, 5H), 6.95–6.85 (m, 1H), 6.84–6.47 (m, 2H), 5.34–5.15 (m, 2H), 4.36–3.99 (m, 1H), 3.51–3.23 (m, 1H), 3.14–2.70 (m, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ 155.3, 146.3, 136.6, 135.2, 134.6, 129.1, 128.6, 128.5, 128.2, 127.4, 126.7, 126.4, 126.2, 125.4, 67.6, 53.8, 38.5, 37.9, 28.5. **HRMS** (ESI) *m/z* calcd for $C_{21}H_{19}NO_2NaS$ $[M + Na]^+$ 372.1028, found 372.1033.

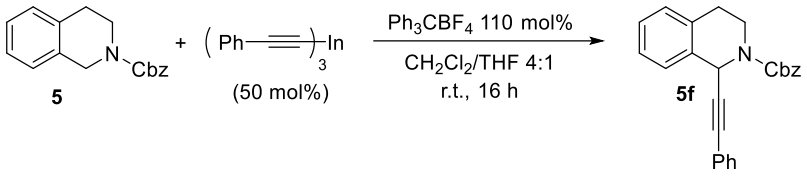
Benzyl 1-(5-phenylthiophen-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (5e).



Following the general procedure B, the reaction of **5** (100 mg, 0.374 mmol) with tris(5-phenylthiophen-2-yl)indium (4 mL, 0.047 M in THF, 0.19 mmol) and triphenylcarbenium tetrafluoroborate (136 mg, 0.411 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3 % Et_3N) 148 mg of **5e** (93%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.57–7.05 (m, 16H), 6.86–6.40 (m, 2H), 5.43–5.10 (m, 2H), 4.37–4.06 (m, 1H), 3.58–3.27 (m, 1H), 3.17–2.79 (m, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ 146.9, 145.6, 144.2, 136.6, 134.5, 134.2, 128.8, 128.6, 128.1, 127.9, 127.6, 127.45, 127.41, 127.3,

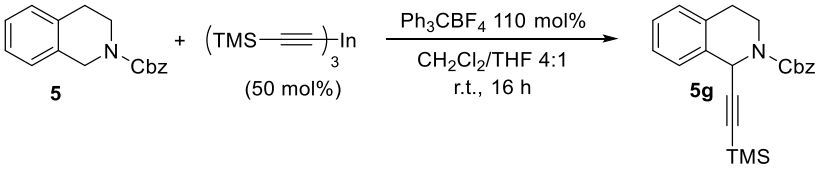
126.2, 125.7, 122.2, 67.4, 53.9, 38.4, 37.9, 29.7, 28.5, 28.4. **HRMS** (ESI) *m/z* calcd for $C_{27}H_{23}NO_2NaS$ $[M + Na]^+$ 448.1341, found 448.1353.

Benzyl 1-(phenylethynyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (5f).[125]



Following the general procedure B, the reaction of **5** (100 mg, 0.374 mmol) with tri(phenylethynyl)indium (4 mL, 0.047 M in THF, 0.19 mmol) and triphenylcarbenium tetrafluoroborate (136 mg, 0.411 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3 % Et_3N) 99 mg of **5f** (72%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.58–7.04 (m, 14H), 6.37–6.05 (m, 1H), 5.45–5.09 (m, 2H), 4.49–4.09 (m, 1H), 3.68–3.37 (m, 1H), 3.15–2.75 (m, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ 154.9, 136.8, 129.1, 128.5, 128.3, 128.1, 128.0, 127.9, 127.5, 127.3, 127.2, 126.6, 122.67, 122.64, 88.3, 83.3, 67.5, 47.4, 29.7, 28.4. **HRMS** (ESI) *m/z* calcd for $C_{25}H_{22}NO_2$ $[M + H]^+$ 368.1656, found 368.1645.

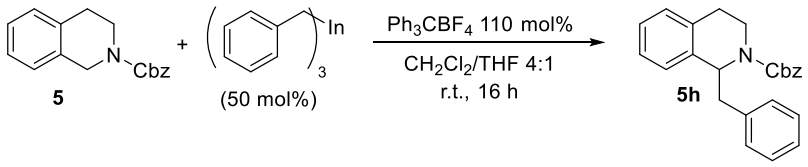
Benzyl 1-((trimethylsilyl)ethynyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (5g).[125]



Following the general procedure B, the reaction of **5** (100 mg, 0.374 mmol) with tris(trimethylsilylethynyl)indium (4 mL, 0.047 M in THF, 0.19 mmol) and triphenylcarbenium tetrafluoroborate (136 mg, 0.411 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3 % Et_3N) 83 mg of **5g** (61%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.45–7.27 (m, 6H), 7.24–7.08 (m, 3H), 6.10–5.80 (m, 1H), 5.43–5.05 (m, 2H), 4.40–4.06(m, 1H), 3.61–3.29 (m, 1H), 3.05–2.72 (m, 2H), 0.12 (s, 9H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ 155.0, 136.8, 129.2, 128.7, 128.2, 128.1, 128.0, 127.7, 127.4,

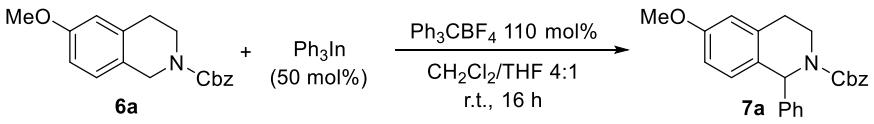
126.7, 104.5, 88.0, 67.6, 47.7, 28.5, 0.1. **HRMS** (ESI) *m/z* calcd for $C_{22}H_{26}NO_2Si$ [M + H]$^+$ 364.1727, found 364.1731.

Benzyl 1-benzyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (5g).[125]



Following the general procedure B, the reaction of **5** (100 mg, 0.374 mmol) with tribenzylindium (3 mL, 0.062 M in THF, 0.186 mmol) and triphenylcarbenium tetrafluoroborate (136 mg, 0.411 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3 % Et_3N) 124 mg of **5h** (93%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 500 MHz, rotamers mixture) δ 7.47–7.34 (m, 4H), 7.32–7.09 (m, 9H), 7.09–6.91 (m, 1H), 5.52–5.32 (m, 1H), 5.28–5.10 (m, 1H), 5.05–4.76 (m, 1H), 4.32-3.88 (m, 1H), 3.53–3.38 (m, 1H), 3.26–2.83 (m, 3H), 2.82–2.61 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 125 MHz, rotamers mixture) δ 155.5, 138.2, 138.0, 137.0, 136.55, 136.52, 134.43, 134.36, 129.8, 129.6, 129.1, 128.54, 128.51, 128.4, 128.3, 128.2, 128.1, 128.03, 127.98, 127.95, 127.8, 127.5, 127.29, 127.25, 126.9, 126.8, 126.54, 126.46, 126.1, 67.2, 67.0, 56.71, 56.66, 43.2, 42.8, 39.4, 38.1, 28.6, 28.5. **HRMS** (ESI) *m/z* calcd for $C_{24}H_{24}NO_2$ [M + H]$^+$ 358.1801, found 358.1806.

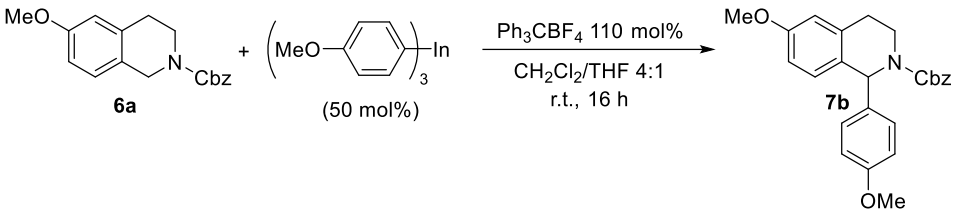
Benzyl 6-methoxy-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (7a).



Following the general procedure B, the reaction of **6a** (100 mg, 0.336 mmol) with triphenylindium (3 mL, 0.056 M in THF, 0.168 mmol) and triphenylcarbenium tetrafluoroborate (122 mg, 0.370 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 20:80, 3 % Et_3N) 65 mg of **7a** (52%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.55–7.09 (m, 10H), 7.07–6.88 (m, 1H), 6.86–6.70 (m, 2H), 6.58–6.18 (m, 1H), 5.38–5.10 (m, 2H), 4.26–3.97 (m, 1H), 3.82 (s, 3H), 3.38–3.18 (m, 1H), 3.11–2.88 (m, 1H), 2.86–2.66 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ 158.6, 155.5, 142.9, 136.9, 136.4, 129.6, 128.6, 128.43,

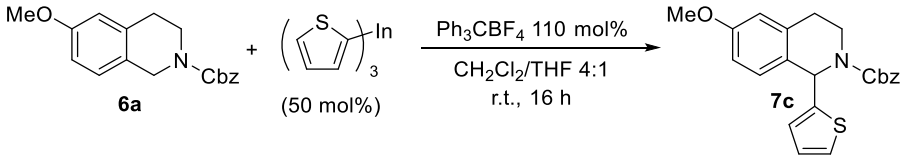
128.35, 128.1, 127.7, 127.5, 113.5, 112.6, 67.5, 57.5, 55.4, 38.3, 28.9. **HRMS** (ESI) *m/z* calcd for $C_{24}H_{24}NO_3$ $[M + H]^+$ 374.1750, found 374.1761.

Benzyl 6-methoxy-1-(4-methoxyphenyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (7b).



Following the general procedure B, the reaction of **6a** (100 mg, 0.336 mmol) with tri-(4-methoxyphenyl)indium (3 mL, 0.056 M in THF, 0.168 mmol) and triphenylcarbenium tetrafluoroborate (122 mg, 0.370 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 20:80, 3 % Et_3N) 122 mg of 7**b** (90%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.50–7.28 (m, 5H), 7.23–7.01 (m, 2H), 6.99–6.88 (m, 1H), 6.86–6.64 (m, 4H), 6.52–6.12 (m, 1H), 5.35–5.09 (m, 2H), 4.23–3.97 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.34–3.13 (m, 1H), 3.08–2.87 (m, 1H), 2.83–2.63 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ158.8, 158.3, 155.2, 136.8, 136.1, 135.1, 129.5, 128.5, 128.0, 127.7, 113.5, 113.3, 112.5, 67.3, 56.7, 37.7, 28.8. **HRMS** (ESI) *m/z* calcd for $C_{25}H_{26}NO_4$ $[M + H]^+$ 404.1856, found 404.1856.

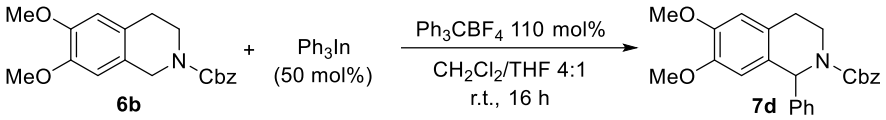
Benzyl-6-methoxy-1-(thiophen-2-yl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (7c).



Following the general procedure B, the reaction of **6a** (100 mg, 0.336 mmol) with tri-(thiophen-2-yl)indium (4 mL, 0.042 M in THF, 0.168 mmol) and triphenylcarbenium tetrafluoroborate (122 mg, 0.370 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 5:95, 3 % Et_3N) 101 mg of **7c** (79%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.51–7.27 (m, 5H), 7.23–7.16(m, 1H), 7.16–6.97(m, 1H), 6.95–6.92 (m, 4H), 6.62–6.34 (m, 1H), 5.33–5.13 (m, 2H), 4.33–

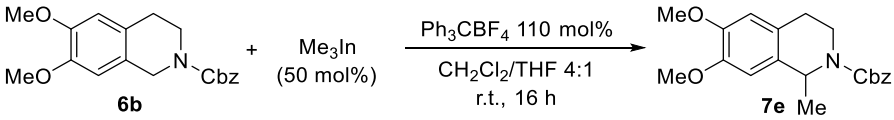
3.81 (m, 1H), 3.81 (s, 3H), 3.49–3.16 (m, 1H), 3.08–2.68 (m, 2H). **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ 158.8, 146.8, 136.8, 135.9, 129.6, 128.6, 128.2, 128.14, 128.09, 126.6, 126.4, 125.4, 113.5, 112.7, 67.6, 55.4, 53.4, 38.2, 37.8, 28.9. **HRMS** (ESI) *m/z* calcd for $C_{22}H_{22}NO_3S$ $[M + H]^+$ 380.1314, found 380.1331.

Benzyl 6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (7d). [152]



Following the general procedure B, the reaction of **6b** (100 mg, 0.305 mmol) with triphenylindium (3 mL, 0.051 M in THF, 0.153 mmol) and triphenylcarbenium tetrafluoroborate (110 mg, 0.335 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 30:70, 3 % Et_3N) 98 mg of **7d** (80%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.52–7.06 (m, 10H), 6.67 (s, 1H), 6.60–6.15 (m, 2H), 5.40–5.08 (m, 2H); 4.27–4.00 (m, 1H), 3.89 (s, 3H), 3.75 (s, 3H), 3.39–3.11 (m, 1H), 3.09–2.84 (m, 1H), 2.77–2.57 (m, 1H). **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ 155.4, 148.2, 147.6, 142.6, 136.8, 128.6, 128.3, 128.1, 128.01, 127.97, 127.5, 127.1, 126.9, 111.4, 111.2, 67.4, 57.4, 56.05, 55.98, 37.9, 28.1. **HRMS** (ESI) *m/z* calcd for $C_{25}H_{26}NO_4$ $[M + H]^+$ 404.1856, found 404.1872.

Benzyl 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (7e). [153]



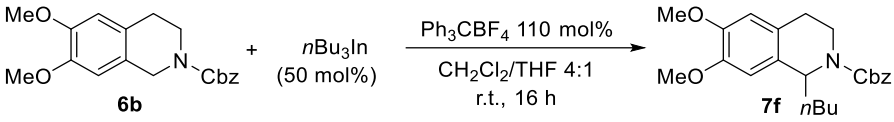
Following the general procedure B, the reaction of **6b** (100 mg, 0.305 mmol) with trimethylindium (4.5 mL, 0.034 M in THF, 0.153 mmol) and triphenylcarbenium tetrafluoroborate (110 mg, 0.335 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 15:85, 3 % Et_3N) 63 mg of **7e** (61%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.47–7.28 (m, 5H), 6.68–6.47 (m, 2H), 5.37–5.05 (m, 3H), 4.37–4.03 (m, 1H), 3.85 (s, 6H), 3.42-3-13 (m, 1H), 3.00–2.75 (m,

152 Dunetz, J. R.; Ciccolini, R. P.; Fröling, M.; Paap, S. M.; Allen, A. J.; Holmes, A. B.; Tester, J. W.; Danheiser, R. L. *Chem. Commun.* **2005**, 4465-4467.

153 Pinet, S.; Chavant, P. Y.; Averbuch-Pouchot, M.-T.; Vallée, Y. *J. Chem. Research (S)* **2001**, 65-67.

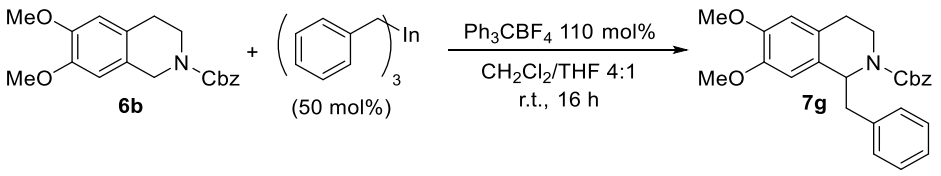
1H), 2.73–2.54 (m, 1H), 1.45 (d, *J* = 6.6 Hz, 3H). **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ155.2, 155.0, 147.7, 137.0, 130.6, 130.1, 128.6, 128.1, 126.1, 125.7, 111.5, 109.8, 67.3, 67.1, 56.1, 56.0, 50.2, 37.9, 37.5, 28.6, 28.5, 22.4, 21.9. **HRMS** (ESI) *m/z* calcd for $C_{20}H_{24}NO_4$ $[M + H]^+$ 342.1699, found 342.1714.

Benzyl 1-butyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (7f).



Following the general procedure B, the reaction of **6b** (100 mg, 0.305 mmol) with tributhylindium (3 mL, 0.051 M in THF, 0.153 mmol) and triphenylcarbenium tetrafluoroborate (110 mg, 0.335 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 15:85, 3 % Et_3N) 97 mg of **7f** (83%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 7.50–7.27 (m, 5H), 6.71–6.47 (m, 2H), 5.34–4.97 (m, 3H), 4.34–4.02 (m, 1H), 3.84 (s, 6H), 3.44–3.14 (m, 1H), 3.03–2.76 (m, 1H), 2.73–2.53 (m, 1H), 1.94–1.59 (m, 2H), 1.55–1.15 (m, 4H), 1.02–0.77 (m, 3H). **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ155.7, 147.8, 147.5, 137.1, 136.8, 130.4, 130.0, 128.5, 128.3, 128.1, 128.0, 127.8, 126.1, 125.8, 111.7, 111.5, 110.3, 110.0, 67.3, 67.1, 56.1, 56.0, 54.7,. 54.6, 38.2, 37.5, 36.8, 36.6, 28.8, 28.7, 28.3, 27.9, 22.7, 14.2. **HRMS** (ESI) *m/z* calcd for $C_{23}H_{30}NO_4$ $[M + H]^+$ 384.2169, found 384.2164.

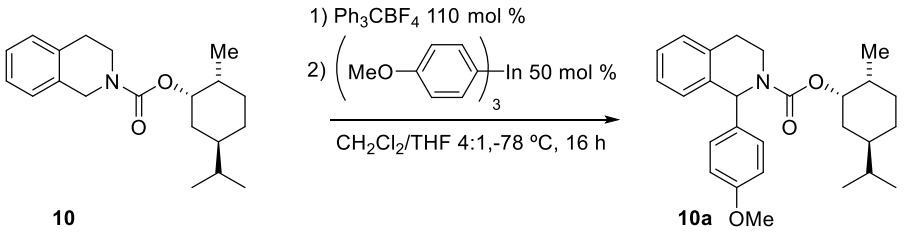
Benzyl 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (7g).[125]



Following the general procedure B, the reaction of **6b** (100 mg, 0.305 mmol) with tribenzylindium (3 mL, 0.051 M in THF, 0.153 mmol) and triphenylcarbenium tetrafluoroborate (110 mg, 0.335 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 20:80, 3 % Et_3N) 118 mg of **7g** (93%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz, rotamers mixture) δ7.44–7.29 (m, 4H), 7.28–7.15 (m, 4H), 7.14–6.98 (m, 2H), 6.67–6.52 (m, 1H), 6.28–6.07 (m, 1H), 5.37–5.10 (m, 2H), 5.07–4.82 (m, 1H), 4.28–4.06 (m, 1H), 3.90–3.80 (m, 3H), 3.73–3.55 (m, 3H), 3.50–3.29 (m,

1H), 3.25–3.06 (m, 1H), 3.05–2.52 (m, 3H). **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 125 MHz, rotamers mixture) δ155.5, 147.9, 147.8, 147.1, 147.0, 138.4, 138.3, 137.1, 136.7, 130.1, 129.8, 128.61, 128.55, 128.44, 128.38, 128.32, 128.28, 128.11, 128.06, 127.9, 126.6, 126.5, 126.4, 126.2, 115.0, 111.2, 110.7, 110.4, 67.4, 67.1, 56.5, 56.0, 55.9, 55.8, 43.3, 42.8, 39.4, 38.4, 28.3, 28.2. **HRMS** (ESI) *m/z* calcd for $C_{26}H_{28}NO_4$ $[M + H]^+$ 418.2012, found 418.2022.

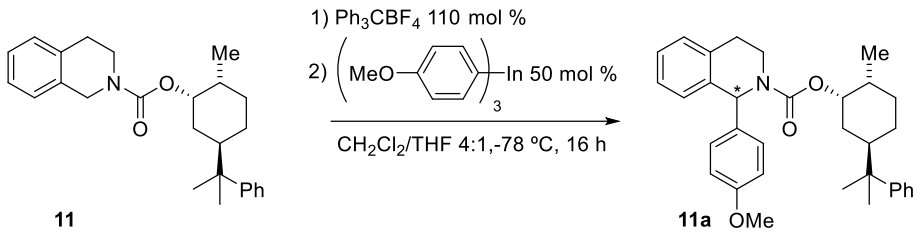
Reaction of 10 with R_3In under oxidative conditions.



To a solution of triphenylcarbenium tetrafluoroborate (115 mg, 0.350 mmol) and **10** (100 mg, 0.317 mmol) in CH_2Cl_2 (10 mL), a solution of tri-(4-methoxyphenyl)indium (3 mL, 0.053 M in THF) was added dropwise for 1 h at -78 °C. The resulting mixture was left stirring overnight at -78 °C and then quenched with MeOH (1 mL). The solvent was concentrated in vacuo and Et_2O (20 mL) was added. The organic phase was washed with water (2 $\times$ 20 mL), saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexane 5:95, 3 % Et_3N) to afford, after concentration and high-vacuum drying, 83 mg of **10a** (62%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ7.23–7.08 (m, 5H), 7.04 (d, *J* = 9.3 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.55–6.09 (m, 1H), 4.74–4.58 (m, 1H), 4.22–3.92 (m, 1H), 3.78 (s, 3H), 3.33–3.07 (m, 1H), 3.05–2.86 (m, 1H), 2.84–2.68 (m, 1H), 2.13–2.00 (m, 1H), 1.96–1.77 (m, 1H), 1.74–1.61 (m, 1H), 1.57–1.32 (m, 2H), 1.10–0.98 (m, 2H), 0.93–0.84 (m, 6H), 0.81–0.70 (m, 3H).). **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ158.9, 155.4, 136.1, 136.0, 135.5, 135.4, 135.2, 129.7, 129.0, 128.7, 127.0, 126.9, 126.2, 126.1, 113.7, 113.6, 75.4, 55.4, 47.8, 47.7, 41.9, 41.7, 34.6, 34.5, 31.6, 28.9, 28.7, 26.6, 23.9, 22.2, 21.1, 21.0, 16.7. **HRMS** (ESI) *m/z* calcd for $C_{27}H_{36}NO_3$ $[M + H]^+$ 422.2689, found 422.2697.

Diastereomers were discriminated by HPLC analysis using a chiral stationary phase (Chiralcel OD-H) eluent 2-propanol/hexane 2:98, flow rate = 0.7 mL/min, λ = 254 nm, t_1 = 6.7 min, t_2 = 7.1 min.

Reaction of 11 with R_3In under oxidative conditions.

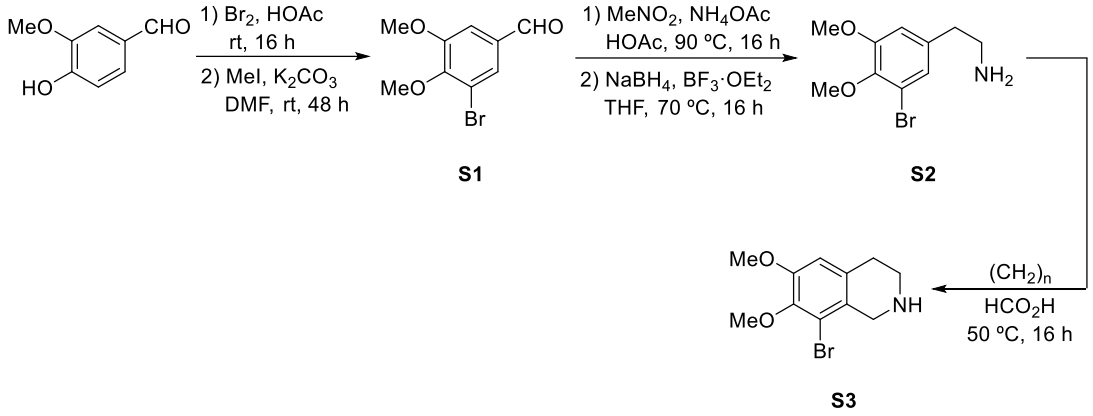


To a solution of triphenylcarbenium tetrafluoroborate (92 mg, 0.280 mmol) and **11** (100 mg, 0.255 mmol) CH_2Cl_2 (10 mL), a solution of tri-(4-methoxyphenyl)indium (3 mL, 0.043 M in THF) was added dropwise for 1 h at -78 °C. The resulting mixture was left stirring overnight at -78 °C and then quenched with MeOH (1 mL). The solvent was concentrated in vacuo and Et_2O (20 mL) was added. The organic phase was washed with water (2 $\times$ 20 mL), saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexane 5:95, 3 % Et_3N) to afford, after concentration and high-vacuum drying, 65 mg of **11a** (51%, dr 67:33) as a colorless oil. Major diastereomer isolated. **^{1}H NMR** ($CDCl_3$, 500 MHz, rotamers mixture) δ 7.35–7.25 (m, 3H), 7.21–7.09 (m, 5H), 7.06–6.85 (m, 5H), 6.80–6.69 (m, 1.4H), 6.62–6.55 (m, 0.4H), 6.39–6.35 (m, 0.5H), 4.92-4.79 (m, 1.4H), 4.20–4.12 (m, 0.4H), 3.88–3.73 (m, 3H), 3.20–3.10 (m, 0.4H), 3.00–2.88 (m, 0.5H), 2.82–2.70 (m, 1H), 2.69–2.59 (m, 0.5H), 2.52–2.44 (m, 0.5H), 2.42–2.30 (m, 0.5H), 2.20–2.00 (m, 1H), 1.93–1.66 (m, 3H), 1.57–1.43 (m, 1H), 1.37–1.10 (m, 7H), 0.99-0.84 (m, 4H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 100 MHz, rotamers mixture) δ 158.9, 154.4, 152.6, 152.3, 147.0, 136.04, 135.97, 135.8, 135.5, 135.3, 134.9, 129.9, 129.7, 129.1, 128.8, 128.7, 128.6, 128.1, 128.0, 127.9, 127.7, 127.4, 126.8, 126.4, 126.0, 125.7, 125.3, 125.2, 125.1, 124.6, 113.42, 113.38, 75.6, 75.1, 56.7, 56.5, 55.4, 55.3, 51.4, 51.1, 42.5, 42.4, 39.6, 39.5, 37.9, 36.8, 34.9, 31.4, 29.8, 29.5, 29.3, 29.1, 28.7, 26.72, 26.65, 23.7, 23.5, 21.9. **HRMS** (ESI) *m/z* calcd for $C_{33}H_{40}NO_3$ $[M + H]^+$ 498.3002, found 498.3011.

Diastereomers were discriminated by HPLC analysis using a chiral stationary phase (Chiralcel OD-H) eluent 2-propanol/hexane 10:90, flow rate = 0.7 mL/min, λ = 254 nm, t_1 = 6.1 min, t_2 = 6.5 min.

Synthesis of (+/-)-Nuciferine.

Synthesis of Compound S3.[136]



3-Bromo-4,5-dimethoxybenzaldehyde (S1).

To a solution of *o*-vanillin (3 g, 19.73 mmol) in AcOH (35 mL), Br_2 (1.25 mL, 24.4 mmol) was added dropwise at 0 °C. After 2 h, the solution was warmed to rt and stirred overnight. Addition of cold water (50 mL) resulted in a white precipitate that was filtered and dried under vacuum. The solid was re-dissolved in DMF (35 mL) with K_2CO_3 (3.6 g, 26 mmol), and MeI (1.3 mL, 20.8 mmol) was added dropwise during 1 h. The reaction was left stirring at rt for 48 h, and then water (50 mL) and Et_2O (50 mL) were added. The organic phase was washed with water (5 $\times$ 10 mL), saturated NaCl solution (50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 3.77 g of **S1** (78%, 2 steps) as a white solid**. ^{1}H NMR** ($CDCl_3$, 300 MHz) δ 9.85 (s, 1H), 7.66 (d, *J* = 1.79 Hz, 1H), 7.39 (d, *J* = 1.76 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 190.0 (HC=O), 154.3 (C), 152.0 (C), 132.2 (C), 128.9 (CH), 118.1 (C), 110.2 (CH), 61.0 (CH_3), 56.4 (CH_3).

2-(3-Bromo-4,5-dimethoxyphenyl)ethan-1-amine (S2).

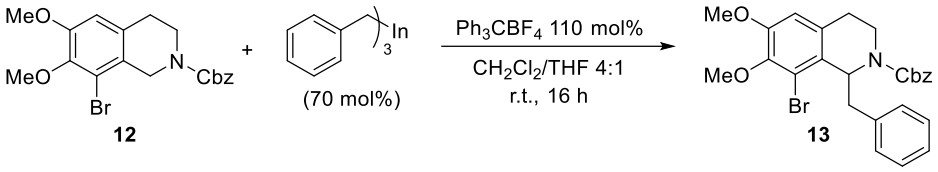
To a solution of **S1** (3 g, 12.24 mmol) and ammonium acetate (1.41 g, 18.36 mmol) in AcOH (25 mL), $MeNO_2$ (2 mL, 36.72 mmol) was added and the reaction was warmed to 90 °C and stirred overnight. After cooling to room temperature, water (50 mL) and

EtOAc (50 mL) were added. The aqueous phase was extracted with EtOAc (2 × 50 mL) and the combined organic extracts were washed with saturated $NaHCO_3$ solution (2 × 100 mL) and saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a yellow solid that was next used without further purification. The resulting solid was slowly added in portions to a mixture of $NaBH_4$ (1.50 g, 39.6 mmol) and $BF_3{\cdot}OEt_2$ (4.90 mL, 39.6 mmol) in THF (35 mL) at 0 °C, and then refluxed overnight. The reaction was cooled to 0 °C and water (20 mL) was added. The solution was basified to pH 10 by addition of 2.0 M solution of NaOH. The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo affording an orange oil that was purified by flash chromatography with silica gel (5:95 MeOH/CH_2Cl_2, 3% Et_3N) to yield 2.64 g of **S2** (83%, 2 steps) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 6.97–6.93 (m, 1H), 6.69–6.65 (m, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 2.93 (t, *J* = 6.81 Hz, 2H), 2.65 (t, *J* = 6.8 Hz, 2H), 1.29 (s, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 156.3 (C), 144.9 (C), 137.2 (C), 124.8 (CH), 117.6 (C), 112.5 (CH), 60.6 (CH_3), 56.2 (CH_3), 43.4 (CH_2), 39.6 (CH_2).

8-Bromo-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (S3).

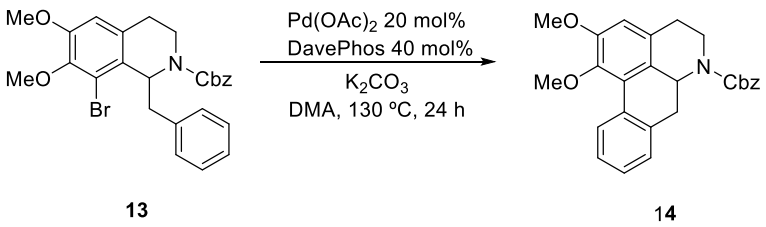
A mixture of **S3** (1 g, 3.84 mmol) and paraformaldehyde (115 mg, 3.84 mmol) in formic acid (20 mL) was stirred overnight at 50 °C. The reaction was cooled to 0 °C and water (20 mL) was added. The solution was basified to pH 10 by addition of 2.0 M solution of NaOH and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford 763 mg of **S3** (73%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 6.60 (s, 1H), 3.90 (s, 2H), 3.83 (s, 3H), 3.81 (s, 3H), 3.05 (t, *J* = 5.9 Hz, 2H), 2.72 (t, *J* = 5.9 Hz, 2H), 1.72 (s, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 151.6 (C), 144.7 (C), 132.3 (C), 127.9 (C), 118.1 (C), 112.4 (CH), 60.6 (CH_3), 56.2 (CH_3), 48.9 (CH_2), 43.4 (CH_2), 29.5 (CH_2).

Benzyl-1-benzyl-8-bromo-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (13).



To a solution of triphenylcarbenium tetrafluoroborate (180 mg, 0.541 mmol) in CH_2Cl_2 (10 mL), **12** (200 mg, 0.492 mmol) and tribenzylindium (5.5 mL, 0.063 M, 0.344 mmol) were sequentially added at room temperature. The resulting mixture was left stirring overnight and then quenched with MeOH (1 mL). The solvent was concentrated in vacuo and Et_2O (20 mL) was added. The organic phase was washed with water (2 × 20 mL), saturated NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/hexane 20:80, 3 % Et_3N) to afford, after concentration and high-vacuum drying, 188 mg of **13** (77%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz, rotamers mixture) δ 7.38–7.20 (m, 8H), 7.17–7.05 (m, 2H), 6.71–6.60 (m, 1H), 5.76–5.72 (m, 0.34H), 5.63–5.56 (m, 0.64H), 5.13–5.08 (m, 0.34H), 5.03–4.98 (m, 0.33H), 4.94–4.86 (m, 0.64H), 4.68–4.60 (m, 0.64H), 4.27–4.20 (m, 0.64H), 3.91–3.83 (m, 6.6H), 3.63–3.52 (m, 1H), 3.45–3.38 (m, 0.35H), 3.33–3.27 (m, 0.64H), 2.99–2.82 (m, 1.6H), 2.78–2.66 (m, 1H), 2.49–2.41 (0.33H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 125 MHz, rotamers mixture) δ 155.43, 155.38, 152.3, 152.2, 145.18, 145.15, 138.4, 138.1, 137.0, 137.6, 131.8, 131.7, 129.6, 129.5, 129.3, 129.1, 128.5, 128.4, 128.2, 128.0, 127.9, 127.7, 127.5, 126.6, 126.5, 118.7, 118.4, 112.1, 111.8, 67.04, 67.01, 60.68, 60.66, 56.5, 56.2, 56.0, 39.5, 39.4, 38.5, 37.2, 28.4, 28.2. **HRMS** (ESI) *m/z* calcd for $C_{26}H_{26}NO_4NaBr$ $[M + Na]^+$ 518.0937, found 518.0944.

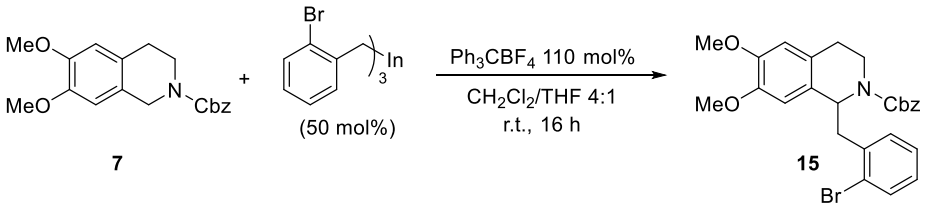
Benzyl-1,2-dimethoxy-4,5,6a,7-tetrahydro-6*H*-dibenzo[*de*,*g*]quinoline-6-carboxylate (14).



To a mixture of $Pd(OAc)_2$ (14.5 mg, 0.065 mmol), DavePhos (51.2 mg, 0.13 mmol), and dried K_2CO_3 powder (89 mg, 0.646 mmol) in 20 mL of DMA, a solution of **13** (160

mg, 0.323 mmol) in 3 mL of DMA was added via cannula and the reaction was stirred at 130 ºC for 24 h. After cooling to room temperature, Et_2O (150 mL) was added and the organic phase was washed with water (5× 20 mL), brine (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo, to afford after purification by flash chromatography (EtOAc/hexane 10:90, 3 % Et_3N) 73 mg of **14** (55%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, rotamers mixture) δ 8.44 (d, *J* = 7.8 Hz, 1H), 7.47–7.18 (m, 8H), 6.68 (s, 1H), 5.35–5.25 (m, 1H), 5.22–5.11 (m, 1H), 4.85–4.74 (m, 1H), 4.57–4.43 (m, 1H), 3.90 (s, 3H), 3.67 (s, 3H), 3.10–2.80 (m, 4H), 2.73–2.61 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz, rotamers mixture) δ 155.3, 152.2, 145.8, 136.9, 136.8, 131.8, 129.7, 128.62, 128.59, 128.4, 128.1, 127.9, 127.8, 127.7, 127.2, 126.2, 111.6, 67.2, 60.2, 56.1, 51.8, 39.1, 30.5. HRMS (ESI-time of flight) *m/z* calcd for $C_{26}H_{26}NO_4$ $[M + H]^+$ 416.1861, found 416.1863.

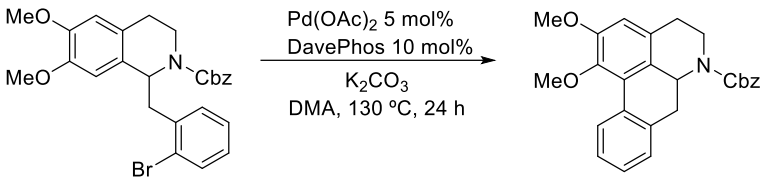
Benzy1-(2-bromobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (15).



Following the general procedure B, the reaction of **7** (200 mg, 0.611 mmol) with tris(2-bromobenzyl)indium (4.5 mL, 0.068 M, 0.306 mmol) and triphenylcarbenium tetrafluoroborate (223 mg, 0.672 mmol) afforded, after purification by flash chromatography (EtOAc/hexane 20:80, 3 % Et_3N) 264 mg of 1**5** (87%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 500 MHz, rotamers mixture) δ 7.55–7.48 (m, 0.40H), 7.44–7.40 (m, 0.66H), 7.37–7.27 (m, 3.70H), 7.20–7.11 (m, 2.70H), 7.09–6.99 (m, 1.70H), 6.64–6.61 (m, 1.40H), 6.60–6.58 (m, 0.30H), 6.40–6.37 (m, 0.30H), 5.51–5.45 (m, 0.30H), 5.44–5.38 (m, 0.67H), 5.13–5.01 (m, 0.60H), 4.91–4.86 (m, 0.66H), 4.56–4.52 (m, 0.65H), 4.40–4.32 (m, 0.67H), 4.10–4.02 (m, 0.30H), 3.87–3.83 (m, 3H), 3.80–3.77(m, 2H), 3.70–3.67 (m, 1H), 3.56–3.49 (m, 0.30H), 3.46–3.37 (m, 0.67H), 3.33–3.25 (m, 1H), 3.23–3.16 (m, 0.30H), 3.11–3.03 (m, 0.67H), 2.98–2.89 (m, 0.68H), 2.87–2.79 (m, 0.30H), 2.75–2.65 (m, 1H).). **^{13}C{^{1}H} NMR** ($CDCl_3$, 125 MHz, rotamers mixture) δ 155.3, 147.9, 147.8, 147.3, 147.1, 137.8, 136.9, 136.2, 132.7, 132.6, 131.7, 128.9,

128.7, 128.5, 128.28, 128.26, 128.21, 128.16, 128.13, 127.92, 127.89, 127.8, 127.3, 127.2, 126.2, 126.1, 125.5, 125.1, 111.3, 111.0, 109.8, 67.2, 66.9, 55.90, 55.88, 55.8, 54.7, 54.0, 42.7, 42.0, 38.8, 37.5, 28.2, 28.1. **HRMS** (ESI) *m/z* calcd for $C_{26}H_{27}NO_4Br$ [M + H]$^+$ 496.1123, found 496.1132.

Benzyl-1,2-dimethoxy-4,5,6a,7-tetrahydro-6*H*-dibenzo[*de*,*g*]quinoline-6-carboxylate (14).

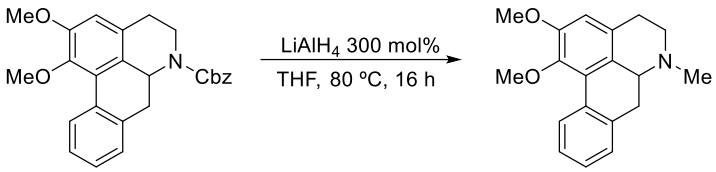


15 **14**

To a mixture of $Pd(OAc)_2$ (5 mg, 0.020 mmol), DavePhos (16 mg, 0.040 mmol), and dried K_2CO_3 powder (111 mg, 0.806 mmol) in DMA (25 mL), a solution of **15** (200 mg, 0.403 mmol) in DMA (4 mL) was added via cannula and the reaction was stirred at 130 °C for 24 h. After cooling to rt, Et_2O (150 mL) was added and the organic phase was washed with water (5× 20 mL), saturated NaCl solution (100 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo, to afford after purification by flash chromatography (EtOAc/hexane 10:90, 3 % Et_3N) 125 mg of **14** (75%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz, rotamers mixture) δ 8.44 (d, *J* = 7.8 Hz, 1H), 7.47–7.18 (m, 8H), 6.68 (s, 1H), 5.35–5.25 (m, 1H), 5.22–5.11 (m, 1H), 4.85–4.74 (m, 1H), 4.57–4.43 (m, 1H), 3.90 (s, 3H), 3.67 (s, 3H), 3.10–2.80 (m, 4H), 2.73–2.61 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz, rotamers mixture) δ 155.3, 152.2, 145.8, 136.9, 136.8, 131.8, 129.7, 128.62, 128.59, 128.4, 128.1, 127.9, 127.8, 127.7, 127.2, 126.2, 111.6, 67.2, 60.2, 56.1, 51.8, 39.1, 30.5. **HRMS** (ESI) *m/z* calcd for $C_{26}H_{26}NO_4$ [M + H]$^+$ 416.1861, found 416.1863.

1,2-Dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[*de*,*g*]quinoline (16).[154]

154 Rossini, A. F. C.; Muraca, A. C.; Casagrande, G. A.; Raminelli, C. *J. Org. Chem.* **2015**, *80*, 10033-10040.



14 **16**

To a suspension of $LiAlH_4$ (28 mg, 0.735 mmol) in THF (15 mL), a solution of **14** (102 mg, 0.245 mmol) in THF (5 mL) was added at 0 °C. The mixture was heated to 80 °C and left stirring overnight. The reaction was quenched by addition of EtOAc (15 mL), and chilled water (15 mL), and then it was filtered through celite. The solution was basified to pH 10 by addition of 2.0 M solution of NaOH and the aqueous phase was extracted with EtOAc (2 $\times$ 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo to afford after purification by flash chromatography (MeOH/CH_2Cl_2 2:98, 3 % Et_3N) 35 mg of **16** (48%) as a yellow solid. **MP** 160–161 °C . **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.29 (d, *J* = 7.9 Hz, 1H), 7.29–7.10 (m, 3H), 6.56 (s, 1H), 3.81 (s, 3H), 3.59 (s, 3H), 3.17–2.90 (m, 4H), 2.67–2.52 (m, 2H), 2.47 (s, 3H), 2.44–2.37 (m, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 152.1 (C), 145.3(C), 136.6 (C), 132.3 (C), 128.8 (C), 128.4 (CH), 128.1 (C), 128.0 (CH), 127.4 (CH), 127.1 (CH), 127.0 (C), 111.4 (CH), 62.5 (CH), 60.3 (CH_3), 56.0 (CH_3), 53.4 (CH_2), 44.1 (CH_3), 35.2 (CH_2), 29.3 (CH_2). **HRMS** (ESI) *m/z* calcd for $C_{19}H_{22}NO_2$ $[M + H]^+$ 296.1650, found 296.1660.

Chapter 3.

Synthesis and Structural Studies of Solid, Bench-Stable Triorganoindium Reagents.

3.1 Introduction.

Triorganoindium reagents participate in transition-metal catalyzed cross-coupling reactions with a wide variety of electrophiles. In contrast with other types of organometallic reagents, triorganoindium species possess high chemoselectivity. Additionally, triorganoindium reagents show high atom-efficiency because the three organic groups attached to the indium metal center may be transferred in the process. These features have prompted a steady increase in the use of triorganoindium reagents for organic synthesis.[18] Despite these advantages, the use of triorganoindium reagents is still limited by the fact that they must be *in situ* prepared, since attempts to isolate and store these reagents lead to decomposition.[155] In addition, reactions involving triorganoindium reagents require the use of ethereal solvents, which may result incompatible with additives or other reagents present in the reaction media. Therefore, the preparation of indium organometallic species with enhanced stability and with the potential to be isolated or stored, would constitute an important advance in the field on indium organometallic chemistry and its application in organic synthesis. In this sense, other species used as nucleophilic counterparts in cross-coupling reactions, such as boron or zinc reagents are also air and moisture sensitive, and strategies to access bench-stable variants of these compounds have been developed.[156] In the case of indium, the preparation of organometallic complexes that show enhanced stability by coordination with nitrogen or phosphorus donors has been reported, although the reactivity of this type of compounds for cross-coupling reactions has remained unexplored.[157]

155 Yasuda, M.; Haga, M.; Baba, A. *Organometallics* **2009**, *28*, 1998-2000.

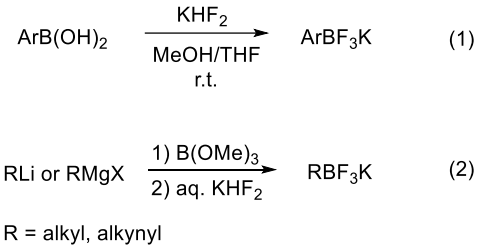
156 (*a*) Benische, A.; Ellwart, M.; Becker, M.; Knochel, P. *Synthesis* **2016**, *48*, 1101-1107 (*b*) Lennox, A. J. J.; Lloyd-Jones, G.C. *Chem. Soc. Rev.* **2014**, *43*, 412-443. (*c*) Molander, G. A. *J. Org. Chem.* **2015**, *80*, 7837-7848.

157 (*a*) Schumann, H.; Kaufmann, J.; Wassermann, B. C.; Girgsdies, F.; Jaber, N.; Blum, J. *Z. Anorg. Allg. Chem.* **2002**, *628*, 971-978. (*b*) Schumann, H.; Girgsdies, F.; Heymer, B.; Kaufmann, J.; Marschall, C.; Wassermann, W. *Z. Anorg. Allg. Chem.* **2007**, *633*, 2268-2273.

3.1.1 Solid-Stable Organoboron Reagents.

Since the discovery of the Suzuki-Miyaura reaction,[158] organoboranes have been widely used in transition-metal-catalyzed reactions, particularly in palladium-catalyzed cross-coupling reactions. Nonetheles, many organoboranes are not stable under atmospheric conditions, specially alkyl and alkynyl boranes.[159] This lack of stability is due to the vacant orbital on the boron, which can be attacked by oxygen or water.[160] One solution emerged with the development of potassium organotrifluoroborates. These reagents showed exceptional stabilities towards nucleophilic compounds as well as air and moisture, and the majority of them could be stored indefinitely at room temperature. More importantly, this stability does not hamper their reactivity in transition-metal-catalyzed cross-coupling reactions.[156c,161] Potassium organotrifluoroborates are obtained by reaction of the corresponding boronic acids with potassium bifluoride.[162] For example, aryl trifluoroborates can be accessed in a straightforward manner by treatment of arylboronic acids with potassium bifluoride in aqueous methanol (Scheme 76). Alkyl and alkynyl trifluoroborates are prepared by transmetalation reaction from organolithium or Grignard reagents with a borate ester and subsequent treatment with potassium bifluoride (Scheme 76).[163]

***Scheme 76**. Preparation of potassium organotrifluoroborates.*



Because of their stability and excellent performance, the use of organotrifluoroborate salts have become widespread for Suzuki cross-coupling

158 Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483.

159 (*a*) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544-4568. (*b*) Miyaura, N. *Metal-Catalyzed Cross-Coupling Reactions 2nd Ed.* Wiley-VCH. Weinheim, **1998**.

160 Davies, A. G.; Roberts, B. P.; *Chem. Commun.* **1966**, *0*, 298-299.

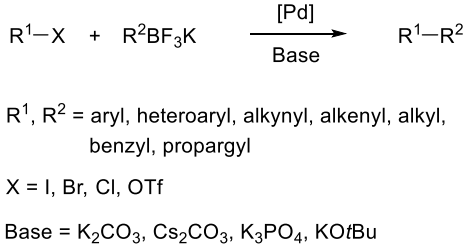
161 Molander, A. G.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275-286.

162 Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020-3027.

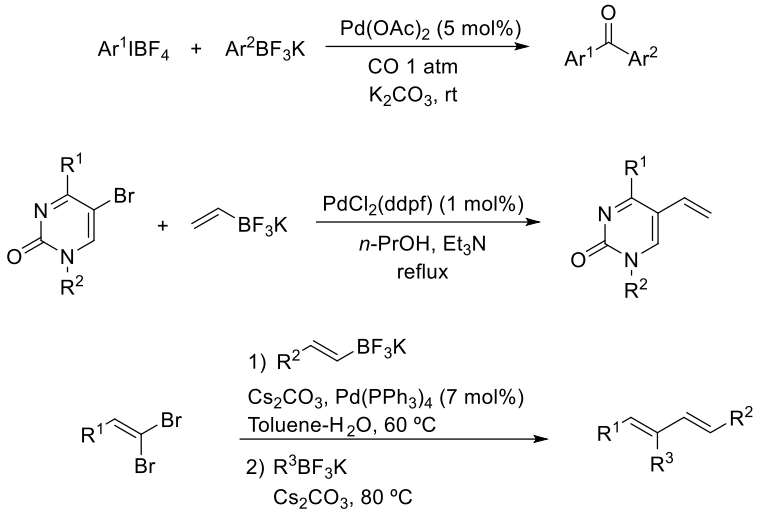
163 Pawelke, G.; Heyder, F.; Burger, H. *J. Organomet. Chem.* **1979**, *178*, 1-4.

reactions, and thus it is possible to react aryl, alkenyl, alkyl, allyl, and alkynyl trifluoroborates with diverse organic halides or triflates (Scheme 77).[164] Among these reactions it is possible to find carbonilative cross-coupling with electron-deficient heteroaromatic susbtrates, or sequential cross-coupling reactions (Scheme 78).[165]

Scheme 77. *Pd-catalyzed cross-coupling reaction of potassium organotrifluoroborates*



Scheme 78. *Representative examples of Suzuki couplings using RBF_3K.*



Throughout these processes, organotrifluoroborates can be handled conveniently under atmospheric air without special precautions affording similar reaction yields to those obtained with the corresponding organoboron species, such as boronic acids. Nonetheless, potassium organotrifluoroborates may show solubility issues requiring highly polar solvents or mixtures of solvents.[166] Palladium-catalyzed cross-coupling

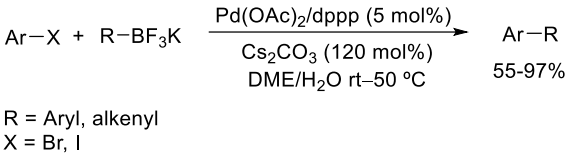
164 (*a*) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288-325. (*b*) Lennox, A. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412-443.

165 (*a*) Xia, M.; Chen, C.-Z. *J. Chem. Res. (S)* **1999**, 400-401. (*b*) Puentener, K.; Scalone, M. (Hoffman-La Roche AG) EP Patent 1057831, **2000**. (*c*) Molander, G. A.; Yokoyama, Y. *J. Org. Chem.* **2006**, *71*, 2493-2498.

166 Lima, F.; Kabeshov, M. A.; Tran, D. N.; Battilocchio C.; Sedelmeier, J.; Sedelmeier, G; Schenkel, B.; Ley, S. V. *Angew. Chem. Int. Ed.* **2016**, *55*, 14085-14089.

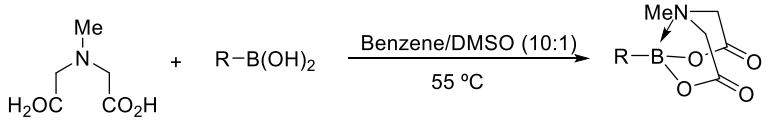
reactions using organotrifluoroborates can be carried out using protic solvents and amines as bases.[167] For example, aryl and alkenyl potassium trifluoroborates can react with aryl or heteroaryl iodides and bromides using aqueous dimethoxyethane as solvent (Scheme 79).

***Scheme 79**. Palladium-catalyzed cross-coupling reactions of RBF_3K performed in aqueous DME.*



An important strategy for the stabilization of boron reagents is the protection of boronic acids as *N*-methyliminodiacetic acid (MIDA) boronates.[168] These compounds have been shown air stable when stored on the laboratory bench, while they can take part in palladium-catalyzed cross-coupling reactions with yields similar to those achieved using boronic acids.[169] MIDA boronates can be synthesized from the corresponding boronic acids and methyliminodiacetic acid in a DMSO/benzene mixture (Scheme 80).[170] Aryl, heteroaryl, alkenyl, and alkyl boronates can be accessed using this protocol. The stability of MIDA boronates comes from its strong coordinative B-N bond, resulting from donation of the Lewis basic lone pair on the nitrogen to the Lewis acidic boron. The stability of these species is such that they have shown to be compatible with silica gel chromatography conditions.[159]

***Scheme 80**. Preparation of MIDA boronates.*



These reagents react efficiently under palladium catalysis with a wide variety of substrates. One of the most difficult substrates to cross-couple is the 2-pirydyl

167 (*a*) Batey, R. A.; Quach, T. D. *Tetrahedron Lett.* **2001**, *42*, 9099-9103. (*b*) Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302-4314.

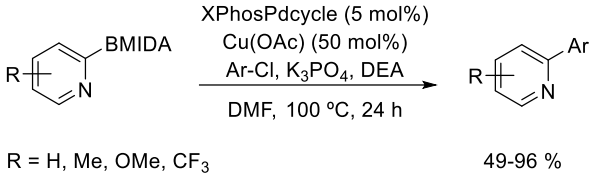
168 (*a*) Gillis, E. P.; Burke, M. D. *Aldrichim Acta* **2009**, *42*, 17-27. (*b*) Li, J.; Grillo, A. S.; Burke, M.D. *Acc. Chem. Res.* **2015**, *48*, 2297-2307.

169 Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009,** *131*, 6961-6963.

170 Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716-6717.

moiety, as the corresponding boronic acid is notoriously unstable towards protodeboronation. However, the use of MIDA enables the isolation of 2-pyridyl-MIDA boronate as a crystalline, air-sable solid which can be subsequently used for the palladium-catalyzed synthesis of a range of 2-aryl pyridines in moderate to excellent yields (Scheme 81).[171] This strategy has been used to access important synthetic products such as terpyridines used as ligands in catalysis, dye sensitizers, or bioactive compounds in drug research.[172]

***Scheme 81**. Synthesis of 2-aryl pyridines by cross-coupling reaction of 2-pyridyl MIDA boronates.*



In cross-coupling reactions involving MIDA boronates, the active species is actually the boronic acid that results from basic hydrolysis of the MIDA boronate. Mechanistic studies have demonstrated that the vacant p orbital in boron is required during the transmetalation step of the Suzuki cross-coupling reaction.[173] Moreover, competitive experiments using MIDA boronates and the corresponding boronic acids showed a preferential reactivity of the boronic acid.[167] Therefore, adjustment of reaction temperature and base choice can result in a slow hydrolysis rate of the MIDA boronate. This approach can be used to keep a low concentration of the more unstable boronic acid and thus minimize undesired side-reactions such as protodeboronation.

Boronoamides have also been developed as reagents for Suzuki couplings that show enhanced stability.[174] In these reagents boron is bonded to two amide moieties, and

171 Dick, G. R.; Woerly, E. M.; Burke, M. D. *Angew. Chem. Int. Ed.* **2012**, *51*, 2667-2672.

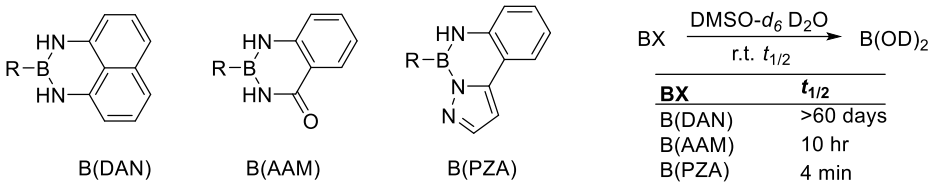
172 (*a*) Guo, P.; Zhang, H.; Zhou, J.; Gallou, F.; Parmentier, M.; Wang, H. *J. Org. Chem.* **2018**, *83*, 7523-7527. (*b*) Colucci, C.; Manfredi, N.; Salamone, M.; Ruffo, R.; Lobello, M. G.; De Angelis, F.; Abbotto, A. *J. Org. Chem.* **2012**, *77*, 7945-7956. (*c*) Laulhe, S.; Blackburn, J. M.; Roizen, J. L. *Org. Lett.* **2016**, *18*, 4440-4443.

173 (*a*) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461-470. (*b*) Miyaura, N. *J. Organomet. Chem.* **2002**, *653*, 54-57.

174 Noguchi, H.; Hojo, K.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 758-759.

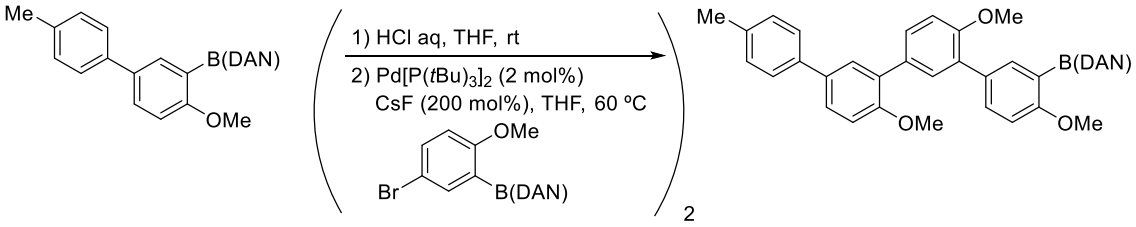
three types of ligands have been reported: 1,8-diaminonaphtalene (DAN), anthranlinamide (AAM), and 2-(pyrazol-5-yl)-aniline (PZA) (Figure 8).[175]

***Figure 8**. Stability of different boronoamide reagents towards hydrolysis.*



DAN exhibits the greatest stability towards hydrolysis. The lone pair donation from nitrogen to boron reduces the Lewis acidity at boron making it more stable. Carbonyl conjugation in the case of AAM, and nitrogen aromaticity in the case of PZA reduce this lone pair donation, thus making the reagents less stable towards hydrolysis. DAN boronoamides are stable towards aqueous work-up and silica gel column chromatography; however, for the cross-coupling reaction they must be first converted to the corresponding boronic acid. Unlike MIDA boronates, DAN boronoamides resist base promoted hydrolysis, while deprotection can be achieved upon treatment with dilute aqueous acid solution. These characteristics have made DAN boronoamides particularly useful reagents for iterative Suzuki cross-coupling reactions aimed at the synthesis of polyaromatic compounds (Scheme 82).

***Scheme 82**. Iterative Suzuki coupling reactions using DAN boronoamides.*

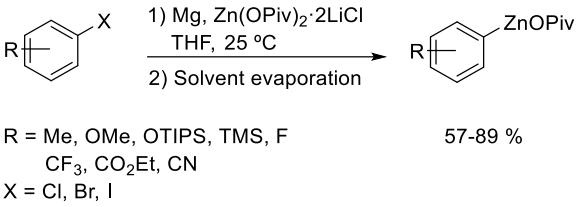


175 (*a*) Ihara, H.; Koyanagi, M.; Suginome, M. *Org. Lett.* **2011**, *13*, 2662-2665. (*b*) Koyanagi, M.; Eichenauer, N.; Ihara, H.; Yamamoto, T.; Suginome, M. *Chem. Lett.* **2013**, *42*, 541-543. (*c*) Kamio, S.; Kageyuki, I.; Osaka, I.; Hatano, S.; Abe, M. Yoshida, H. *Chem. Commun.* **2018**, *54*, 9290-9293.

3.1.2 Solid-Stable Organozinc Reagents.

The group of Prof. Knochel has recently developed strategies for the stabilization of zinc organometallic reagents which are used in the Negishi cross-coupling reaction. Zinc reagents of the type RZnX (X = halide) or R_2Zn are highly sensitive to moisture and air, and this represents a serious drawback for its application in the laboratory or at the industrial scale. The preparation of solid-salt stabilized organozinc pivalates by treatment of different aryl, heteroaryl, and benzyl magnesium halides with $Zn(OPiv)_2 \cdot 2LiCl$ affords, after solvent evaporation, solid RZn(OPiv) reagents that can be manipulated under air atmosphere (Scheme 83).[176]

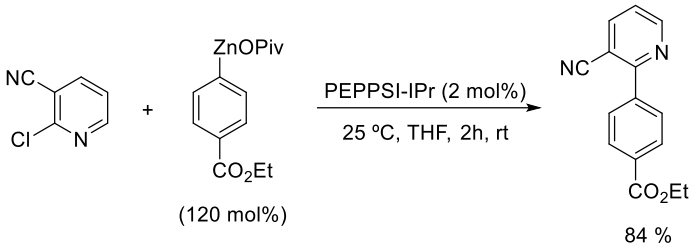
***Scheme 83**. Synthesis of solid, salt-stabilized organozinc pivalates.*



Contrary to regular organozinc reagents that are highly viscous oils, organozinc pivalates are loose powders that can be stored under argon indefinitely without losing their reactivity in Negishi reactions. Additionally, they can be handled under atmospheric air for short times without causing appreciable decrease in reaction yields. Generally, organozinc pivalates show a similar reactivity to organozinc halides or diorganozincs. The cross-coupling of organozinc pivalates proceeds in mild conditions and tolerates the presence of different functional groups, such as nitrile or ester (Scheme 84).[156a]

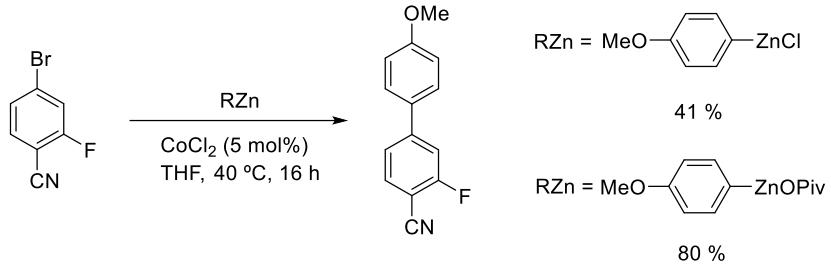
176 (*a*) Bernhardt, S.; Manolikakes, G.; Kunz, T.; Knochel, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 9205-9209. (*b*) Chen, Y.-H.; Ellwart, M.; Malakhov, V.; Knochel, P. *Synthesis* **2017**, *49*, 3215-3223. (*c*) Stathakis, C. I.; Bernhardt, S.; Quint, V.; Knochel P. *Angew. Chem. Int. Ed.* **2012**, *51*, 9428-9432.

***Scheme 84**. Pd-catalyzed cross-coupling reaction of organozinc pivalates.*



In some instances, organozinc pivalates can outperform the more conventional organozinc regents, like in the cobalt-catalyzed cross-coupling of arylzinc reagents to generate biaryls, in which organozinc pivalates double the yield when compared to the corresponding arylzinc halides (Scheme 85).[177] The reaction proceeds with a wide substrate scope, including several electron-deficient *N*-heterocyclic halides that react smoothly with organozinc pivalates to afford the expected cross-coupling products.

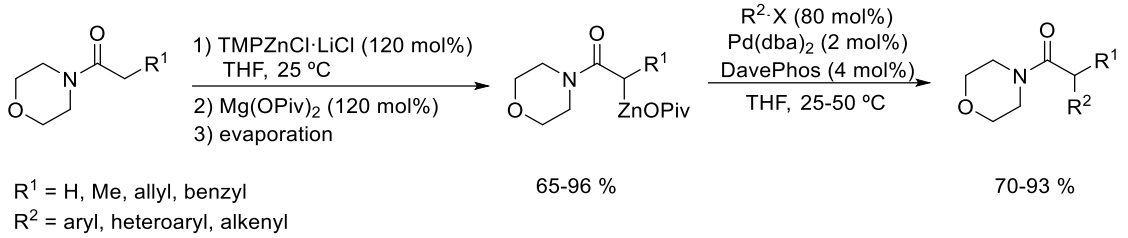
***Scheme 85**. Organozinc pivalates vs arylzinc halides in Co-catalyzed cross-coupling.*



The group of Prof. Knochel has also extended this stabilization strategy to the synthesis of zinc amide enolates, which can also remain reactive after long-term storage under argon or after short exposure to atmospheric air.[178] These reagents can be prepared by treatment of the corresponding amide with TMPZnCl·LiCl followed by the addition of $Mg(OPiv)_2$. The best results in terms of stability are obtained when using *N*-morpholino acetamide. Subsequent Pd-catalyzed cross-coupling reaction can be carried out with diverse electron-rich or electron-deficient electrophiles in good yields (Scheme 86).

177 Hamman, J. M.; Lutter, F. H.; Haas, D.; Knochel, P. *Angew. Chem. Int. Ed.* **2017**, *56*, 1082-1086.
178 Chen Y.-H.; Ellwart, M.; Toupalas, G.; Ebe, Y.; Knochel, P. *Angew. Chem. Int. Ed.* **2017**, *56*, 1-6.

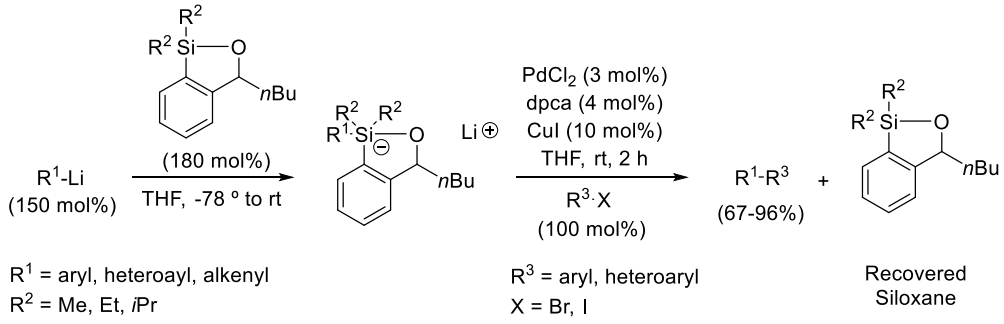
***Scheme 86**. Preparation of stabilized zinc amide enolates and subsequent Negishi reaction.*



3.1.3 Other Solid-Stable Nucleophiles.

The group of Prof. Amos B. Smith has developed a new class of silicon reagents, termed siloxane-transfer reagents, that enable the cross-coupling of organolithium reagents under transition-metal catalysis.[179] Although reaction protocols for the cross-coupling of organolithium compounds have been successfully established,[180] there are still significant limitations associated to the use of these reagents in cross-coupling, including extensive formation of homocoupling products which often requires slow addition, or competitive nucleophilic addition reactions. The development of siloxane-transfer reagents permits room temperature Pd-catalyzed cross-coupling of aryl, heteroaryl, or alkenyl lithium species (Scheme 87). Interestingly, these silicon reagents have proven to be bench stable and can be recovered from the reaction media through column chromatography.

***Scheme 87**. Siloxane-transfer reagents for the cross-coupling of RLi.*

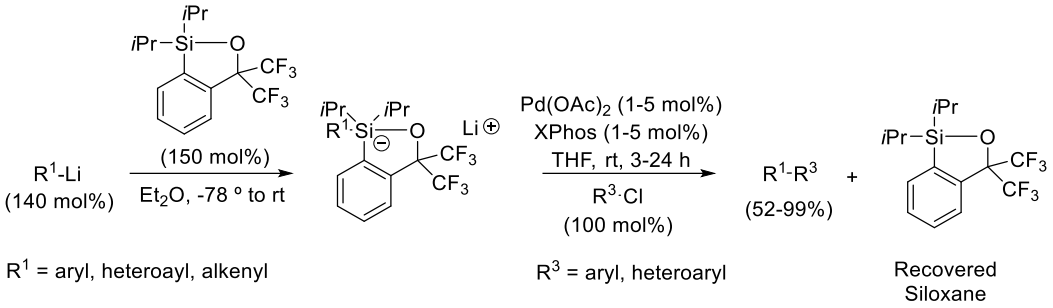


179 (*a*) Smith III, A. B.; Hoye, A. T.; Martinez-Solorio, D.; Kim, W.-S.; Tong, R. *J. Am. Chem. Soc.* **2012**, *134*, 4533-4536. (*b*) Martinez-Solorio, D.; Hoye, A. T.; Nguyen, M. H.; Smith III, A. B. *Org. Lett.* **2013**, *15*, 2454-2457. (*c*) Nguyen, M. H.; Smith III, A. B. *Org. Lett.* **2014**, *16*, 2070-2073.

180 (*a*) Giannerini, M.; Fañanás-Mastral, M.; Feringa, B. L. *Nat. Chem.* **2013,** *5*, 667-672. (*b*) Vila, C.; Hornillos, V.; Giannerini, M.; Fañanás-Mastral, M.; Feringa, B. L. *Chem. Eur. J.* **2014**, *20*, 13078-13083. (*c*) Murahashi, S.-L. *J. Organomet. Chem.* **2002**, *653*, 27-33.

In a series of more recent developments, siloxane-tranfer reagents have been shown capable of reacting with aryl and heteroaryl chlorides, which are ideal electrophiles due to low cost and widespread availability (Scheme 88).[181] The presence of the geminal CF_3 groups at the benzylic position of the new transfer reagents increase the barrier for the regeneration of the lithium reagents, further inhibiting the formation of formation of homocoupling products.

***Scheme 88**. Siloxane-tranfers agents for cross-coupling of RLi with aryl chlorides.*



3.1.4 Solid Organoindium Reagents.

From a structural point of view, indium(III) organometallics in the solid phase show structures with different coordination geometries mainly depending on the size of the organic groups attached to indium and the donor properties of ligands present.[182] In the crystal structure of isolated triorganoindium compounds, the three organic groups attached to indium are distributed along an equatorial plane, while significant intermolecular interactions exist between indium and neighboring organic groups in the axial plane, giving rise to distorted trigonal planar dispositions, as in the case of trimethyl or triphenylindium.[183]

The synthesis of triorganoindium compounds from more reactive organometallics such as organolithium or Grignard reagents in ethereal solvents normally afford the corresponding adducts with one molecule of solvent.[184] In these cases, the affinity of triorganoindium reagents for the donor solvent molecule is considerable, making the adducts difficult to break. However, in the case of very bulky organic groups attached

181 Martinez-Solorio, D.; Melillo, B.; Sanchez, L.; Liang, Y.; Lam, E.; Houk, K. N.; Smith III, A. B. *J. Am. Chem. Soc.* **2016**, *138*, 1836-1839.

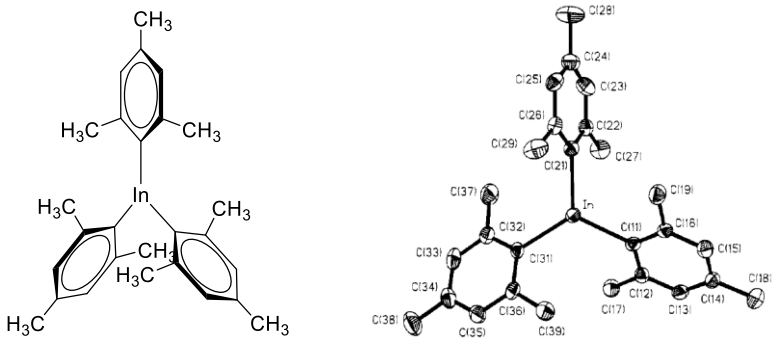
182 Banger, K. K. *Encyclopedia of Inorganic and Bioinorganic Chemistry.* **2015** John Wiley & Sons.

183 (*a*) Malone, J. F.; McDonald, W. S. *J. Chem. Soc. D.* **1969**, *0*, 591-592. (*b*) Blake, A. J.; Cradock, S. *J. Chem. Soc. Dalton Trans.* **1990**, 2393-2396.

184 Bregadve, V. I.; Golubinskaya, L. M.; Kozyrkin, B. I. *J. Clust. Sci.* **2002**, *13*, 631-636.

to indium, like trimesitylindium, the crystalline compound has been isolated without solvent molecule (Figure 9).[185]

***Figure 9**. Crystal structure of trimesitylindium(III).*



Most triorganoindium compounds isolated as crystalline solids are heteroleptic species. The use of different reagent precursors for the synthesis of triorganoindium compounds affords mixtures of complexes in solution that then engage in redistribution equilibria, which finally favor the more thermodynamically stable homoleptic complexes. Therefore, only few examples of crystalline heteroleptic triorganoindium compounds have been reported.[186]

The study of organonindium halides has received considerable attention.[187] They can be prepared through different synthetic methods such as methatesis reaction from organolithium reagents with indium(III) halides, where stoichiometric control can afford the desired organoindium halide. Sterically hindered organoindium halides have been used for the preparation of base-free Group 13 hydride complexes (Scheme 89).[188]

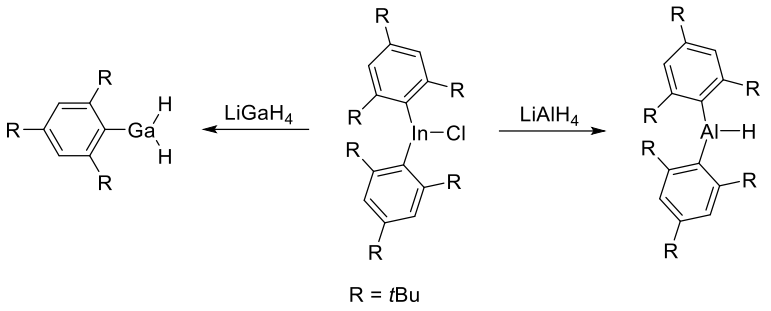
185 (*a*) Leman, J. T.; Barron, A. R. *Organometallics* **1989**, *8*, 2214-2219. (*b*) Robinson, G. H.; Li, X.-W.; Pennington, W. T. *J. Organomet. Chem.* **1995**, *501*, 399-402.

186 Beachley, O. T.; MacRae, D. J.; Kovalevsky, A.Y.; Zhang, Y.; Li. X. *Organometallics* **2002**, *21*, 4632-4640.

187 (*a*) Miller, S. B.; Jelus, B. L.; Brill, T. B. *J. Organomet. Chem.* **1975**, *96*, 1-14. (*b*) Estrela dos Santos, J.; Peppe, C.; Brown, M. A.; Tuck, D. G. *Organometallics* **1996**, *15*, 2201-2204. (*c*) Neumüller, B. *Coord. Chem. Rev.* **1997**, *158*, 69-101. (*d*) Clovis, P.; Nobrega, J. A.; Zaldini, Hernandes, M.; Luiz Longo, R.; Tuck, D. G. *J. Organomet. Chem.* **2001**, *626*, 68-75.

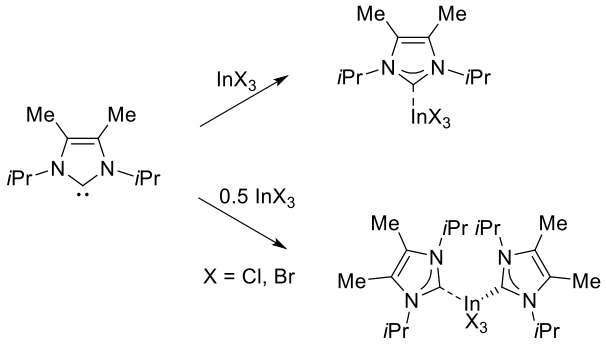
188 West, R. *Advances in Organometallic Chemistry*, Vol. 53. Academic Press, New York, **2006**.

***Scheme 89**. Sterically hindered organoinidum halides for the synthesis of Group 13 hydride complexes.*



Indium(III) halide salts coordinate with stable imidazolydene carbene derivatives to afford organoindium halides.[189] Depending on the amount of indium halide added, different coordination modes can be observed, resulting in either the tetrahedral 1:1 adduct or the 1:2 bipyramidal trigonal (Scheme 90).

***Scheme 90**. Formation of organoindium carbene derivatives.*

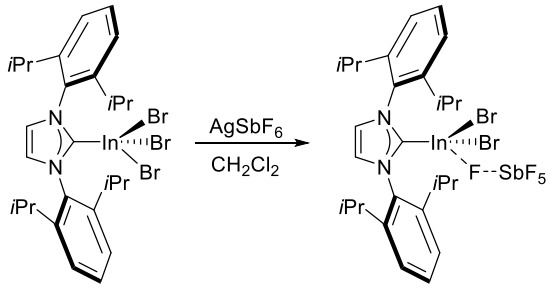


Recently, a carbene organoindium halide complex has been synthesized and characterized. [190] It shows catalytic activity towards the activation of triple bonds in hydroarylation and cycloisomerization reactions (Scheme 91). Interestingly, this species is air-stable, in contrast with indium(III) halides which are highly hygroscopic and must be handled under inert atmosphere conditions.

189 (*a*) De Fremont, P.; Marion, N.; Nolan, S. P. *Coord. Chem. Rev.* **2009**, *253*, 862-892. (*b*) Ball, G. E.; Cole, M. L.; McKay, A. I. *Dalton Trans* **2012**, *41*, 946-952.

190 (*a*) Michelet, B.; Colard-Itte, J.-R.; Thiery, G.; Guillot, R.; Bour, C.; Gandon, V. *Chem. Commun.* **2015**, *51*, 7401-7404. (*b*) Bastien, M.; Tang, S.; Thiery, G.; Monot, J.; Li, H.; Guillot, R.; Bour, C.; Gandon, V. *Org. Chem. Front.* **2016**, *3*, 1603-1613.

***Scheme 91**. Air-stable cationic carbene organoindium complex.*



Organoindium compounds behave as Lewis acids forming adducts with electron-donating, oxygen, nitrogen, or phosphorus species. One of the most noticeable differences between coordinated and uncoordinated R_3In is the associated reduced reactivity due to the saturation of the indium metal coordination sphere. The stability of these adducts varies accordingly with the donor strength of the Lewis bases involved. Determinations of the enthalpy of dissociation of $Me_3M{\cdot}L$ (where M = Al, Ga, In) in the vapor phase have shown a relative donor strength order where the strongest adducts involved the formation of a dative metal-nitrogen bond (Scheme 92).[191]

***Scheme 92**. Relative donor strength of typical Lewis bases forming adducts with Me_3M (M = Al, Ga, In).*

$$Me_3N > Me_3P > Me_2O > Me_2S > Me_2Se > Me_2Te$$

The relative stabilities of these adducts have been studied by allowing different bases to compete for the organometallic species. For example, mixing $Me_3In{\cdot}OEt_2$ with trimethylphosphine yields the phosphine-indium adduct. Similarly, trimethylamine displaces trimethylphosphine from $Me_3In{\cdot}PMe_3$. Additionally, the stabilities of various indium alkyl derivatives have been studied using differential scanning calorimetry (DSC).[192] DSC in conjunction with thermogravimetric analysis coupled with FTIR or GC-MS can aid in providing a mechanism for the decomposition pathway of such compounds.

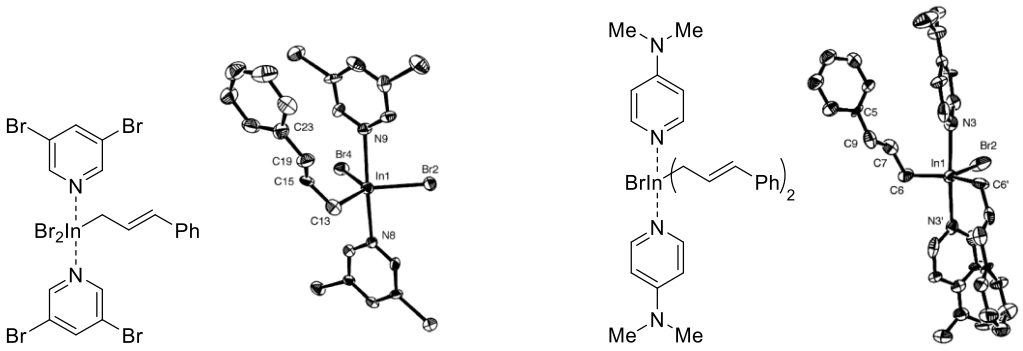
191 Bahr, G.; Muller, G. E. *Chem. Ber.* **1955**, *88*, 251-264.

192 Duffy, S.; Nolan, P. F.; Rushworth, S. A.; Leese, A. B.; Jones, A. C. *Adv. Mater. Opt. Electron.* **1997**, *7*, 233-240.

The study of the thermal properties, stability, and structure of several adducts of trimethylindium with nitrogen or phosphorus Lewis bases has been reported.[193]Coordination with nitrogen or phosphorus donors results in increased stability towards air and moisture for organoindium compounds. This feature has been used in the generation of more stable precursors during the synthesis of ultra-pure trimethylindium in the semiconductors and electronic industry.[194]

The incorporation of nitrogen ligands has enabled the isolation of the allylindium reagent, making it possible to unambiguously establish its structure based on X-ray diffraction spectroscopy.[195] The use of bulky and strongly coordinating 4-dimethylaminopyridine (DMAP) and 3,5-dibromopyridine resulted in the stabilization of the allylindium species generated from the reaction of indium metal with allyl halide (Figure 10). More importantly, the isolated species react with aldehydes to afford the corresponding allylic alcohols. Previous to this work, structural proposals for allylindium were based solely on NMR data, and this species was believed to be a sesquihalide or a mixture of (allyl)dihalogenoindium/allylindium.[196]

***Figure 10**. Stabilization of allylindium reagents by coordination with pyridine ligands.*



193 (*a*) Bradley, D. C.; Hamilton, P. A.; Harding, I. S.; Morton, N. W.; Rankin, D. W. H.; Robertson, H. E.; Vaghjiani, J. *Proc. R. Soc. Lond.* **1997**, *453*, 2123-2137. (*b*) Foster, D. G.; Rushworth, S. A.; Cole-Hamilton, D. J.; Cafferty, R.; Harrison, J.; Parkes, P. *J. Chem. Soc. Dalton Trans.* **1988**, *0*, 7-11. (*c*) Thomas, F.; Bauer, T.; Schulz, S.; Nieger, M. *Z. Anorg. Allg. Chem.* **2003**, *629*, 2018-2027.

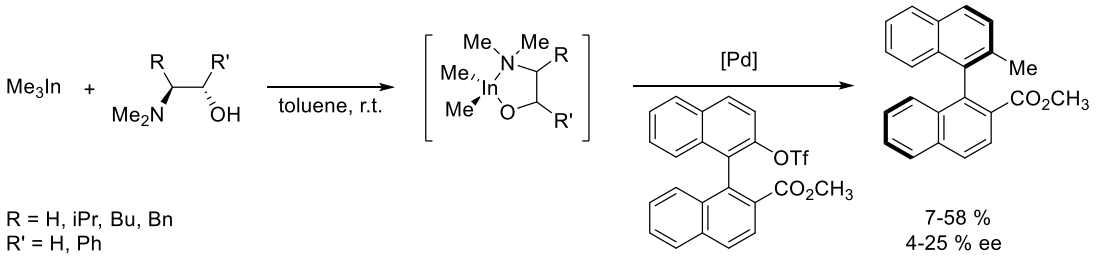
194 (*a*) Jense, K. F.; Hirai, T.; Wahl, G.; Pauleau, Y. *Chemistry for Electronic Materials.* **1993**. Elsevier. (*b*) Farrow, R. F. C.; Parkin, S. S. P.; Dobson, P. J.; Neave, J. H.; Arrott, A. S. *Thin Film Growth Techniques for Low Dimensional Structures*. **2013**. Springer Science & Business Media.

195 Yasuda, M.; Haga, M.; Baba, A. *Eur. J. Org. Chem.* **2009**, 5513-5517.

196 (*a*) Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *58*, 1831-1833. (*b*) Araki, T.; Shimuzu, T. S.; Johar, S.; Jin, Y.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2538-2542. (*c*) Law, M. C.; Cheung, T. W.; Wong, K. Y.; Chan, T. H. *J. Org. Chem.* **2007**, *72*, 923-929.

Regarding the use of indium organometallic reagents stabilized by coordination with donor ligands in transition-metal catalyzed cross-coupling reactions, the only existing precedent comes from the group of Prof. Schumann, in which intramolecularly stabilized trimethylindium derivatives were prepared and set to react with biaryl triflates under Pd catalysis.[157a] These reagents were obtained by treating Me_3In with chiral dimethylaminoethanol or its derivatives. The resulting complexes showed to decompose slowly under atmospheric air and were used in the Pd-catalyzed cross-coupling reaction with 2-carboxymethoxy-1,1-binaphtyl-2'-trifltate, affording modest yields and enantiomeric excesses (Scheme 93).

***Scheme 93**. Preparation and reactivity of intramolecularly stabilized trimethylindium derivatives.*



3.2 Results and Discussion.

3.2.1 Stabilization of Triorganoindium Reagents by Means of Coordination with Donor Ligands.

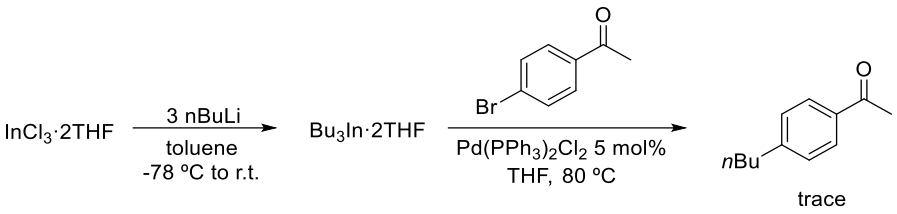
As mentioned before, triorganoindium reagents are widely used in transition-metal catalyzed cross-coupling reactions, and are valued for their chemoselectivity, versatility, and atom economy derived from their ability to transfer the three organic groups attached to indium. Nonetheless, triorganoindium compounds are air and moisture sensitive reagents that must be prepared shortly before their use. Unlike the case of other organometallic nucleophilic reagents used in cross-coupling, no solid, stable variants of triorganoindium reagents have been developed to date. Therefore, we have set our aim at developing more stable and easier to handle triorganoindium reagents, and to systematically test their suitability in cross-coupling reactions. To this end, we envisioned the use of adequate donor ligands to form more stable adducts, that maintain the same reactivity of triorganoindium species towards transition-metal-catalyzed cross-coupling.

We began our investigation with the preparation of triorganoindium reagents using the minimum amount of THF in the reaction media. The necessary use of large quantities of THF or other ethereal solvents can be a disadvantage in many types of reactions. If successful, with this strategy THF could simply become an additive and not the reaction solvent.

Based on the reported structure of the $InCl_3$ complex with THF,[197] in which two molecules of THF are coordinated to indium, we attempted the preparation of tributylindium from a solution of $InCl_3$ in toluene containing two equivalents of THF (Scheme 94). Thus, a solution of $InCl_3$·2THF in toluene was added three equivalents of *n*BuLi (in toluene) at -78 °C. However, temperature increase resulted in decomposition of the resulting triorganoindium, and ensuing cross-coupling reaction afforded only trace amounts of product.

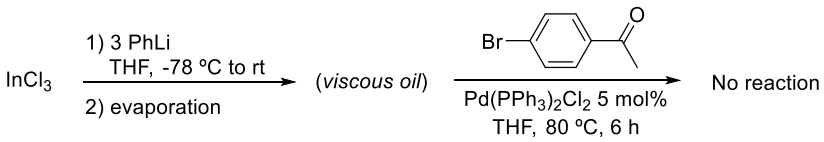
197 Self, M. F.; McPhail, A. T.; Wells, R. L. *Polyhedron*, **1993**, *12*, 455-459.

***Scheme 94**. Attempted preparation of Bu_3In from $InCl_3$·2THF and subsequent cross-coupling.*



It seemed that the use of only two equivalents of THF was not enough to ensure the formation and stability of tributylindium, and therefore the cross-coupling reaction failed. Likewise, when triphenylindium was prepared in THF and then the solvent was evaporated, the result was a viscous oily substance that when re-dissolved proved to be unreactive in palladium-catalyzed cross-coupling with 4-bromoacetophenone (Scheme 95).

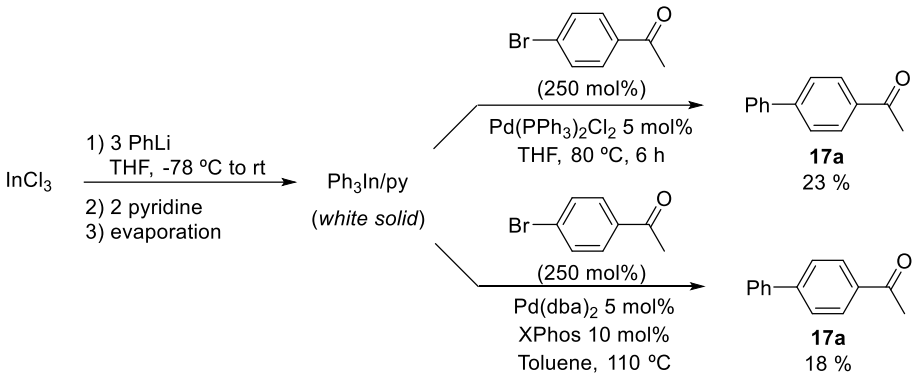
***Scheme 95.** Attempted cross-coupling reaction with Ph_3In after solvent evaporation.*



After these results, we decided to explore the use of a nitrogen donor for the formation of a stronger Lewis acid-base adduct with the triorganoindium reagent. Consequently, the preparation of Bu_3In in toluene was attempted by addition of two equivalents of pyridine to $InCl_3$, but the resulting mixture proved to be insoluble. Moreover, when pyridine was added to a solution of $InCl_3$·2THF in toluene, an insoluble precipitate was formed immediately, probably due to the displacement of THF by the more Lewis basic pyridine. A different strategy was then envisioned: If pyridine forms a much more stable adduct with indium, then it might be possible that after the evaporation of THF from a R_3In solution, the resulting residue might not decompose and the cross-coupling reaction product could be obtained in a reasonable yield. Consequently, a solution of Ph_3In in THF was prepared and then two equivalents of pyridine were added (Scheme 96). The solvent was evaporated and a white solid was obtained. Remarkably, when this solid was re-dissolved, it underwent palladium catalyzed cross-coupling reaction with 4-bromoacetophenone affording

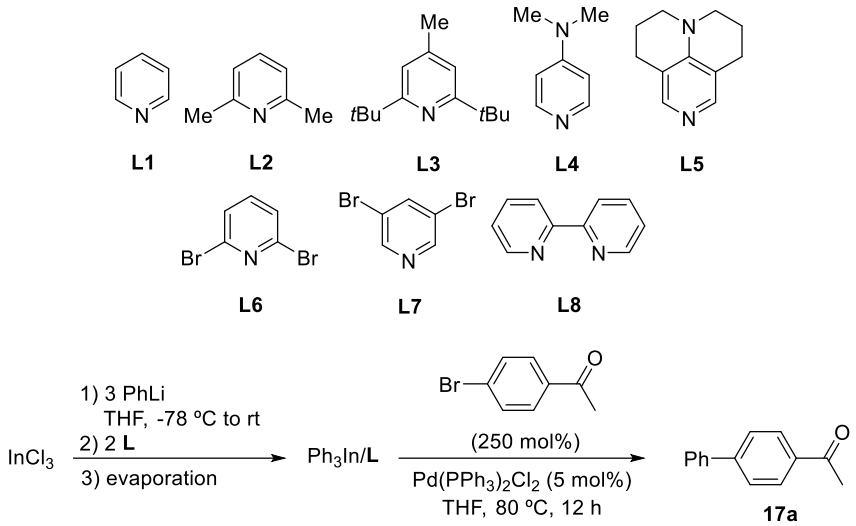
the corresponding product **17a** in 18% isolated yield. The coupling reaction was also carried out in toluene, affording a similar product yield.

***Scheme 96**. Cross-coupling reaction of Ph_3In complex with pyridine performed in THF or toluene.*



From this results, by using pyridine it had become possible to evaporate THF and obtain a solid that proved to remain reactive in palladium-catalyzed cross-coupling, albeit affording low yields. After these encouraging results, we decided to test different pyridines and investigate the effect on triphenylindium after the removal of THF. The goal would be to find an adequate ligand that allowed the isolation of a solid reactive species. Ideally the resulting compound should exhibit a similar performance in cross-coupling reactions than the *in situ* prepared triorganoindium reagents. For this purpose, two equivalents of pyridine ligands **L1-L8** were added to a solution of Ph_3In in THF. In each case, the solvent was evaporated affording the corresponding solid residue, which was stored under Ar for a period of 24 hours and re-dissolved in THF to be finally subjected to Pd-catalyzed cross-coupling reaction with 4-bromoacetophenone (Table 16). The efficiency and adequacy of the ligand would be measured in terms of the yield of cross-coupled product **17a** obtained from the solid reagent. For ligands **L2** and **L3**, only 15 and 5 % of the cross-coupling product **17a** was observed (Table 16, entries 3 and 4). In these cases, increased sterics likely weakened the complex formed between the triorganoindium and the pyridine. The more electron-rich 4-dimethylaminopyridine (DMAP) **L4** afforded the best results, leading to cross-coupled product **17a** in 55 % yield (Table 16, entry 5). Unexpectedly, **L5** (9-azajulolidine) afforded a lower yield than DMAP or pyridine (Table 16, entry 6).

***Table 16**. Screening of different pyridine ligands for the preparation of a solid Ph_3In/L reagent.*



Entry	Ligand	Yield of **17a** (%)[a]
1	–	–
2	**L1**	23
3	**L2**	15
4	**L3**	5
5	**L4**	55
6	**L5**	11
7	**L6**	–
8	**L7**	–
9	**L8**	–

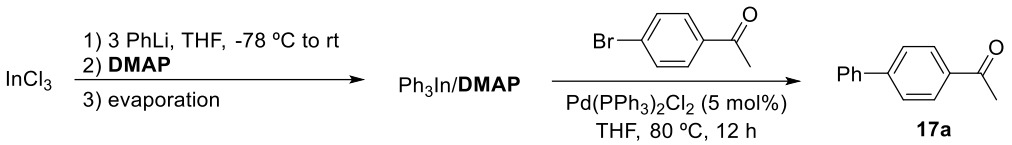
[a] Isolated yield.

The use of dibromo pyridines **L6** and **L7** did not afford any of the cross-coupled product **17a** (Table 16, entries 7 and 8). Likewise, the use of bipyridine **L8** did not provide any of **17a** (Table 16, entry 9).

The next step was to optimize the reaction with the Ph_3In/DMAP complex (Table 17). During the initial screening two equivalents of ligand were added in each case, because Lewis acid-base adducts involving indium compounds and nitrogen donors have been reported with either 1:1 and 2:1 stoichiometry. At this point, the stoichiometry of the Ph_3In/DMAP complex had not been established yet. Interestingly, when only one equivalent of DMAP (with respect to Ph_3In) was

employed (Table 17, entry 2), the yield of cross-coupled product **17a** was virtually the same as in the case where two equivalents of DMAP were used (Table 17, entry 1).

***Table 17**. Optimization of the cross-coupling reaction using Ph_3In/DMAP.*

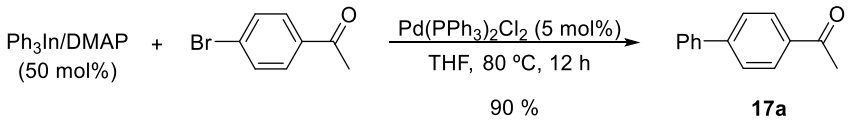


Entry	mol% of DMAP (with respect to Ph_3In)	mol% of Ph_3In/DMAP (with respect to electrophile)	Yield of **17a** (%)[a]
1	200	40	55
2	100	40	53
3	100	70	quantitative
4	100	50	91

[a] Isolated yield.

When the amount of Ph_3In/DMAP complex used for the cross-coupling reaction was increased to 70 mol%, the yield of cross-coupled product **17a** was quantitative (Table 17, entry 3). Using 50 mol%, a 91 % yield of the cross-coupling **17a** was obtained (Table 17, entry 4). Additionally, after the solid Ph_3In/DMAP complex was exposed to atmospheric air, it still proved capable of taking part in the palladium catalyzed cross-coupling reaction of 4-bromoacetophenone, and remarkably, almost the same yield of product **17a** could be obtained (Scheme 97).

***Scheme 97**. Cross-coupling reaction using solid reagent* Ph_3In/DMAP *after exposure to atmospheric air.*

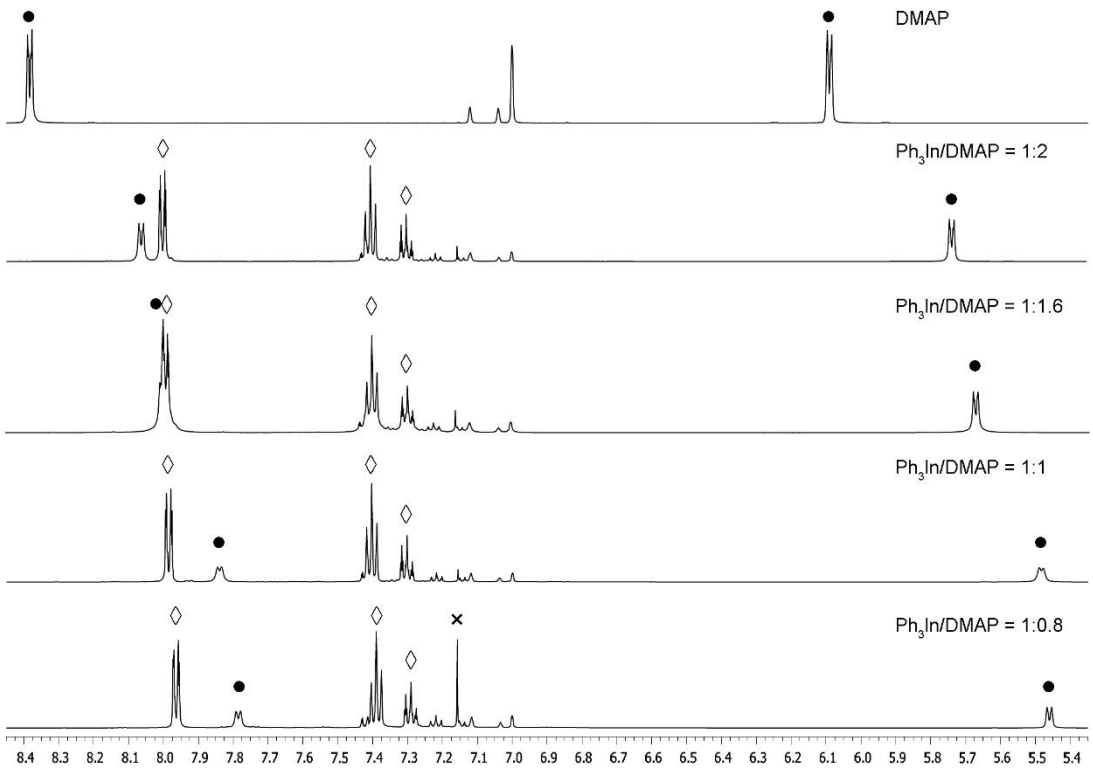


This result shows that formation of an adduct with DMAP not only prevents decomposition of the triorganoindium reagent during the solvent evaporation step, but it also provides protection against reaction with oxygen and moisture. Like in the case of coordinatively stabilized boron reagents such as MIDA boronates, interaction of the vacant orbital in the indium reagent with the nitrogen lone pair of the pyridine reduces the reactivity towards water or oxygen. More importantly, the enhanced

stability in the indium reagent does not prevent it from taking part efficiently in palladium-catalyzed cross-coupling reactions.

Then, we analyzed the structure of the triorganoindium reagent resulting from the mixture of Ph_3In with different quantities of DMAP using NMR spectroscopy (Figure 11). When less than one equivalent of DMAP was employed, the signal corresponding to benzene at 7.16 ppm was significant, meaning that part of the Ph_3In decomposed giving rise to benzene. When at least one equivalent of DMAP was employed, only traces of benzene could be detected. The NMR signals of the coordinated ligand were displaced towards lower chemical shifts in comparison to the free ligand as a consequence of changes in its electron density after coordination with Ph_3In. As the quantity of DMAP was increased, the NMR chemical shifts moved towards the value of the uncoordinated ligand.

Figure 11. *^{1}H NMR experiments on different mixtures of Ph_3In and DMAP.*

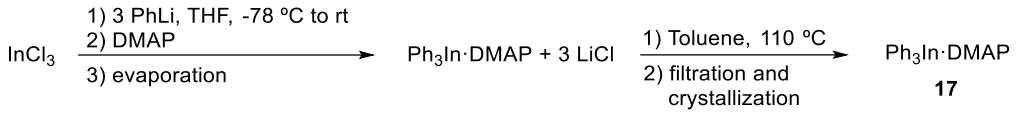


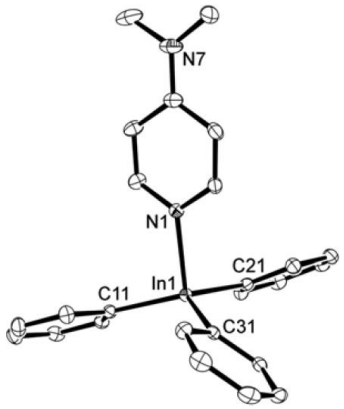
Experiments performed with toluene-d_8. • DMAP. ◊ Ph_3In. × Benzene

In order to characterize the Ph_3In/DMAP complex, it was purified by extraction with boiling toluene to eliminate lithium chloride, then filtered, and crystals were slowly grown from a toluene/hexane mixture at 4 °C (Scheme 98). Crystals suitable for

single-crystal X-ray diffraction were obtained, which showed that triphenylindium is coordinated to only one molecule of DMAP. The crystals showed a trigonal pyramidal structure where the ideal plane formed by the phenyl groups and the indium atom is distorted by the DMAP ligand, resulting in a N-In-C angle of around 100 °C. The In-N distance was 2.27 Å, and the In-C distance was 2.17 Å.

***Scheme 98**. Purification of compound **17** for X-ray diffraction spectroscopy.*

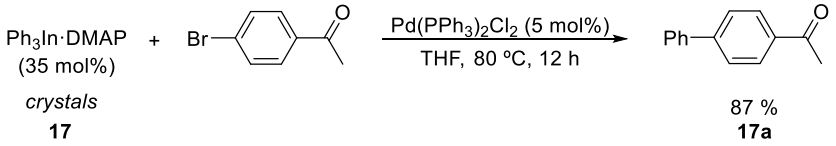




ORTEP drawing of **17** showing 40 % probability displacement of ellipsoids.

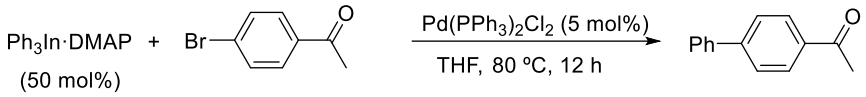
Interestingly, when crystals of **17** were used for the palladium-catalyzed cross-coupling of 4-bromoacetophenone, only 35 mol% of the reagent was necessary to achieve a high yield of product **17a** (Scheme 99). This yield is similar to those previously reported using *in situ* prepared triphenylindium in THF solution, which demonstrates that complex **17** can transfer efficiently the three organic groups attached to indium. Additionally, this result also demonstrates that the palladium-catalyzed cross-coupling reaction using triorganoindium reagents does not require the presence of lithium salts in the reaction media.

***Scheme 99**. Palladium-catalyzed cross-coupling reaction using crystals of **17**.*



The solid reagent Ph_3In·DMAP had shown to withstand exposure to atmospheric air without an appreciable decrease in cross-coupling product yield. Therefore, it was decided to investigate in more detail the stability of **17**. For this purpose, compound **17** was prepared by addition of DMAP to a solution of Ph_3In followed by evaporation of the solvent, without performing any further purification. The resulting white powder was stored under Ar and used for the palladium-catalyzed cross-coupling reaction of 4-bromoacetophenone. Each time a portion of reagent **17** was taken, it was exposed to atmospheric air and then stored under argon. The effect caused by storage time and repeated exposure to air of **17** was upon the reaction yield was registered (Table 18).

***Table 18**. Effect of storage time and exposure to air of **17** on the yield of cross-coupled product.*



Entry	Days after preparation of **17**	Yield of **17a** (%)[a]
1	3	91
2	5	88
3	7	93
4	14	84
5	21	82
6	28	78
7	45[b]	95[b]

[a] Isolated yield. [b] Reaction performed with purified crystals of **17**.

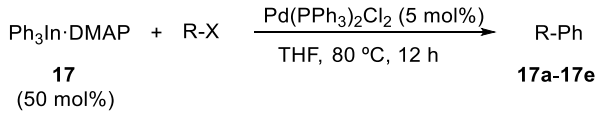
The solid reagent **17** maintained similar reactivity over a period of four weeks affording good yields of cross-coupled product **17a** (Table 18, entries 1-6). During this time, Ph_3In·DMAP remained stored under argon on the laboratory bench while (deliberately) suffering occasional exposure to atmospheric air during its handling. Coordination of DMAP to triphenylindium is likely to reduce considerably its tendency towards reacting with moisture or oxygen, therefore decomposition happens very slowly. This is in sharp contrast with the sensitivity of triphenylindium reagent in THF solution, where trace amounts of moisture cause immediate decomposition of the organometallic, and seriously affect the yield of any subsequent cross-coupling

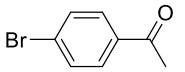
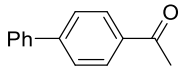
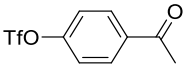
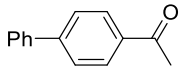
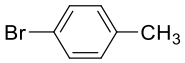
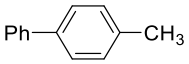
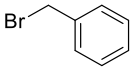
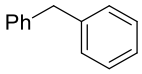
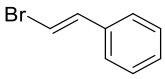
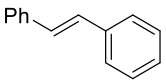
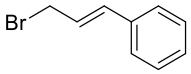
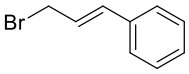
reaction. Ph_3In·DMAP could be conveniently weighted on the laboratory balance without the need of glovebox or any other special protective measures. More interestingly, when reagent **17** was used in its purified and crystalline form, it afforded an almost quantitative yield of **17a** after having been stored for 45 days (Table 18, entry 7). Purification of **17** eliminates the highly hygroscopic lithium salts and is likely to further slow down its decomposition rate.

The next step was to study the reactivity of this novel R_3In·DMAP reagent in cross-coupling with a variety of electrophiles. Therefore, reagent **17** was set to react with a collection of substrates and yields were calculated after isolation of the cross-coupling product by column chromatography (Table 19). Under the previously developed reaction conditions for the cross-coupling of triorganoindium reagents, the reaction of **17** proceeded well with 4-bromotoluene, affording the corresponding cross-coupled product **17b** in an excellent 92 % yield (Table 19, entry 3). Interestingly, the use of triflate as leaving group in the electrophile did not have any detrimental effect in the reaction performance (Table 19, entry 2). The cross-coupling reaction was also carried out over benzyl bromide, affording diphenylmethane **17c** in 81 % yield (Table 19, entry 4). Finally, the cross-coupling of **17** with bromostyrene and with cinnamyl bromide, afforded the corresponding products **17d** and **17e** in good yields (Table 19, entries 5 and 6 respectively). Overall, the cross-coupling with the different electrophiles lead in all cases to the desired reaction products in high yields.

From a practical point of view, performing the reactions with reagent **17** was relatively simple in comparison with the use of *in situ* generated triphenylindium; setting the reaction involved weighting and introducing three solid reagents (catalyst, electrophile, and **17**) in the reaction vessel, flushing with argon, and dissolving with THF. By contrast, the use of *in situ* generated triphenylindium involves careful handling of hygroscopic $InCl_3$ and performing the transmetallation step with organolithium or Grignard reagents at low temperature shortly before the cross-coupling reaction.

***Table 19**. Palladium-catalyzed cross-coupling reaction of **17** with various electrophiles.*

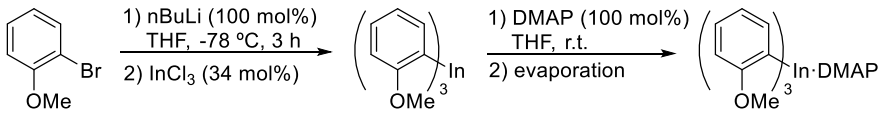


Entry	R-X	Product	Yield (%)[a]
1		 **17a**	91
2		 **17a**	92
3		 **17b**	94
4		 **17c**	81
5		 **17d**	88
6		 **17e**	87

[a] Isolated yield.

Having successfully prepared the Ph_3In·DMAP complex and after testing its reactivity in palladium-catalyzed cross-coupling reactions, the protocol was extended to other triorganoindium reagents. Triarylindium complex **18,** derived from 2-bromoanisole, was prepared following a similar procedure; one equivalent of DMAP was added to the corresponding triorganoindium solution in THF at room temperature and then the solvent was evaporated (Scheme 100). In order to highlight the practical advantage of using solid triorganoindium compounds over in-situ prepared reagents in solution, reagent **18** would be latter used in palladium cross-coupling reactions without further purification.

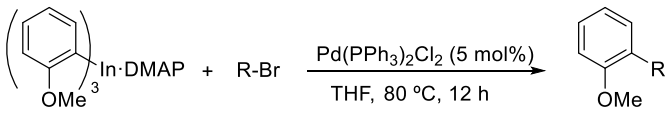
***Scheme 100**. Preparation of solid triorganoindium reagent **18**.*



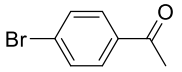
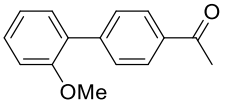
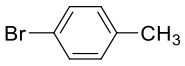
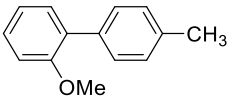
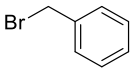
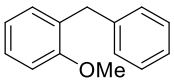
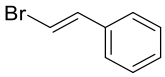
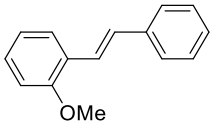
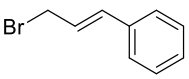
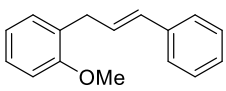
18

The resulting waxy solid **18** was kept under argon and then used in palladium catalyzed cross-coupling reactions with the same series of electrophiles as previously (Table 20). The reaction with 4-bromoacetophenone and 4-bromotoluene took place efficiently affording products **18a** and **18b** in 84 and 96 % yield, respectively (Table 20, entries 1-2). The coupling proceeded well with other bromides; benzyl bromide, bromostyrene, and cinnamyl bromide were cross-coupled affording the corresponding products in good yields (Table 20, entries 3-5).

***Table 20**. Palladium-catalyzed cross-coupling reaction of **18** with various electrophiles.*



18 (50 mol%) → **18a-18e**

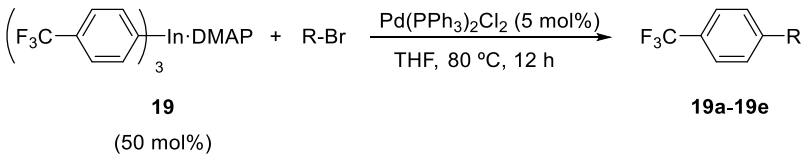
Entry	R-Br	Product	Yield (%)[a]
1		 **18a**	84
2		 **18b**	96
3		 **18c**	87
4		 **18d**	92
5		 **18e**	88

[a] Isolated yield.

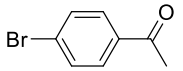
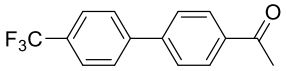
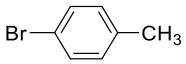
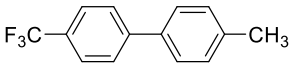
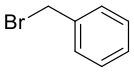
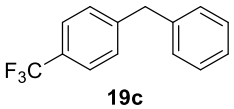
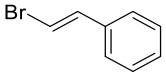
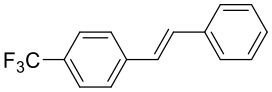
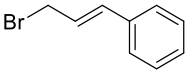
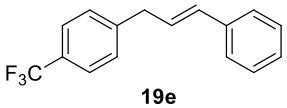
The reactivity of reagent **18** decreased more rapidly than in the case of compound **17**; after five days stored on the laboratory bench under argon, the palladium-catalyzed cross-coupling reaction of 4-bromoacetophenone using 50 mol% of **18** afforded only 56 % yield of product **18a** while a significant part of the electrophile was recovered unchanged. Possibly, increased sterics in **18** because of the methoxy group adjacent to the organometallic bond might weaken the coordination with DMAP resulting in reduced stabilization.

During this investigation, we prepared other functionalized aryl $R_3In{\cdot}DMAP$ reagents including an electron-withdrawing group attached to the phenyl ring (**19**). Complex **19** was prepared from 1-bromo-4(-trifluoromethyl)benzene by halogen-lithium exchange and treatment with $InCl_3$. Addition of one equivalent of DMAP, followed by solvent evaporation afforded **19** as a waxy residue. The reactivity of compound **19** in palladium-catalyzed cross-coupling towards different electrophiles was investigated (Table 21).

Table 21*. Palladium-catalyzed cross-coupling reactions of* ***19****.*



19 (50 mol%) **19a-19e**

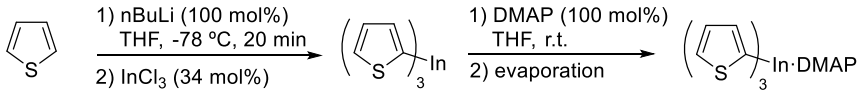
Entry	R-Br	Product	Yield (%)[a]
1		 **19a**	81
2		 **19b**	86
3		 **19c**	77
4		 **19d**	84
5		 **19e**	89

[a] Isolated yield.

The cross-coupling reactions proceeded in good yields, affording the corresponding products.The complex **19** showed less stable over time in comparison to Ph_3In·DMAP (**17**); one week after the preparation of **19** the yield of **19a** decreased to less than 50%.

The preparation of heteroaromatic R_3In·DMAP reagents was also investigated. Thiophene-containing organometallic complex **20** was prepared following the same procedure used for compounds **17**-**19** (Scheme 101).

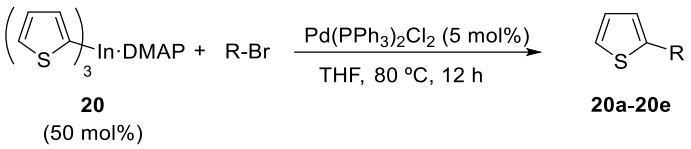
Scheme 101*. Preparation of solid triorganoindium reagent* ***20****.*

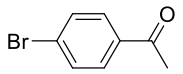
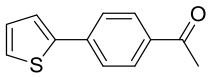
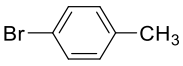
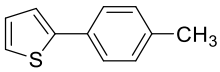
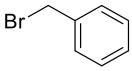
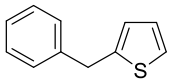
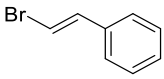
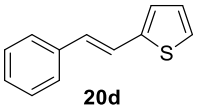
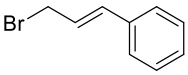
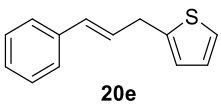


20

Compound **20** was then used in a series of palladium-catalyzed cross-coupling reactions with different electrophiles (Table 22). The reaction with 4-bromoacetophenone proceeded well, affording compound **20a** in a good 76% yield (Table 22, entry 1). Reaction with 4-bromotoluene also led to cross-coupling **20b** in good yield (Table 22, entry 2). Reactions with the benzyl, alkenyl, and cinnamyl bromides took place efficiently with the corresponding cross-coupling products being obtained (Table 22, entries 3-5). Remarkably, solid triorganoindium reagent **20** resulted to be very stable over time. Three weeks after its preparation, it was still possible to obtain high yields of products **20a** and **20b** using compound **20**. Thus, the stability of **20** was comparable to that of solid reagent **17.**

***Table 22**. Palladium-catalyzed cross-coupling reaction of **20** with various electrophiles.*

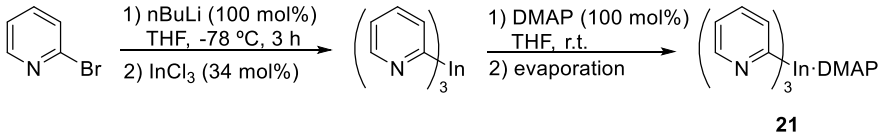


Entry	R-Br	Product	Yield (%)[a]
1		 **20a**	76
2		 **20b**	87
3		 **20c**	80
4		 **20d**	84
5		 **20e**	89

[a] Isolated yield.

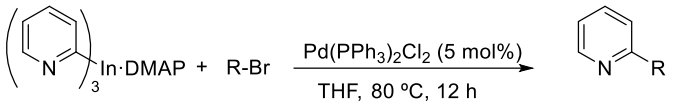
The preparation of a solid triorganoindium reagent with pyridine was also carried out. Compound **21** was prepared from 2-bromopyridine (Scheme 102). The resulting solid triorganoindium reagent **21** turned to be very sensitive towards air and moisture. After its preparation, reagent **21** had the aspect of a green powder under argon; once the reagent was exposed to atmospheric air, its color changed first to yellow and then finally to red in a matter of hours. The reactivity of **21** in palladium-catalyzed cross-coupling was studied. The cross coupling reaction with **21** afforded good yields with all the different electrophiles involved (Table 23). These results were obtained employing reagent **21** within the first twelve hours after its preparation. Once compound **21** was exposed to air, reaction yields decreased significantly in a matter of hours, to the point that after 24 hours none of the cross-coupling products could be obtained.

***Scheme 102**. Preparation of solid triorganoindium reagent **21**.*

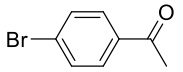
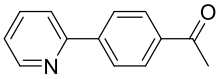
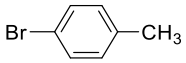
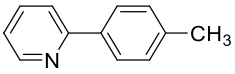
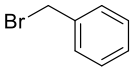
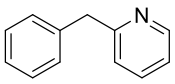
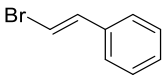
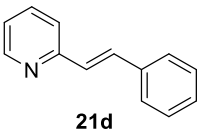
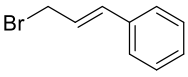
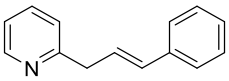


21

***Table 23**. Palladium-catalyzed cross-coupling reaction of **21** with various electrophiles.*



21 (50 mol%) — **21a-21e**

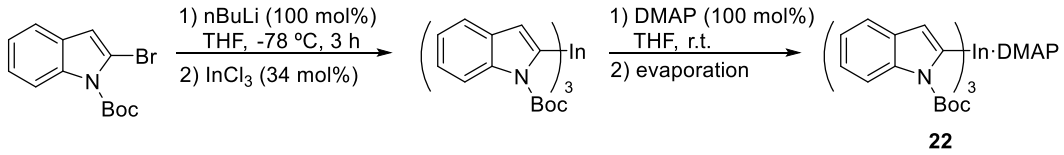
Entry	R-Br	Product	Yield (%)[a]
1		 **21a**	93
2		 **21b**	95
3		 **21c**	82
4		 **21d**	71
5		 **21e**	88

[a] Isolated yield.

The R_3In·DMAP solid reagent **22** containing indole was prepared from *N*-Boc protected 2-indole (Scheme 103). Like in the case of pyridine reagent **21**, complex **22** resulted to be very sensitive towards exposure to atmospheric air. When stored under argon, complex **22** had the aspect of a green to brown powder, however, soon after being exposed to moist air it turned into a red, viscous oil. Nevertheless, we studied the reactivity of **22** in palladium-catalyzed cross-coupling with the usual electrophiles. The cross-coupling of **22** with 4-bromoacetophenone afforded product **22a** in 85% yield (Table 24, entry 1). Likewise, reaction with bromotoluene and bromostyrene afforded the corresponding products **22b** and **22c** in 82 and 88% yield

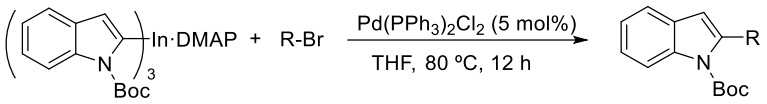
respectively (Table 24, entries 2 and 3). The cross-coupling reactions with benzyl and cinnamyl bromide using reagent **22** were not attempted due to the low stability of the corresponding organoindium reagent.

***Scheme 103**. Preparation of solid triorganoindium reagent **22**.*

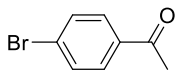
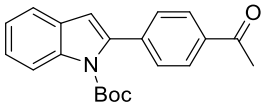
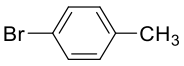
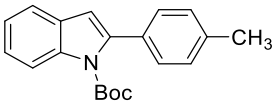
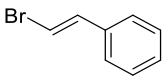
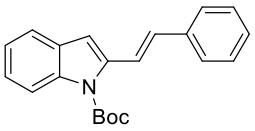


22

***Table 24**. Palladium-catalyzed cross-coupling reaction of **22** with various electrophiles.*



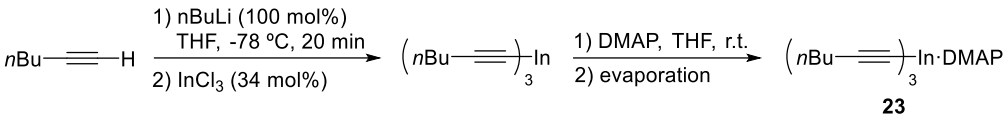
22 (50 mol%) **22a-22c**

Entry	R-Br	Product	Yield (%)[a]
1		 **22a**	85
2		 **22b**	82
3		 **22c**	88

[a] Isolated yield.

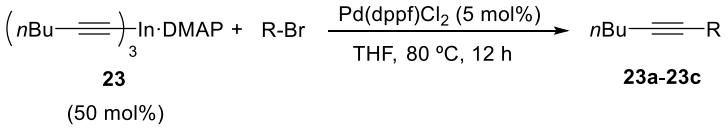
With the aim of extending the methodology to other types of triorganonindium reagents, the preparation of a $R_3In·DMAP$ species with an alkynyl group was planned. An alkynyl triorganoinidum compound derived from 1-hexyne was successfully coordinated to DMAP affording a solid (**23**) that was stored on the laboratory bench under argon and later used in cross-coupling reactions (Scheme 104).

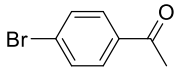
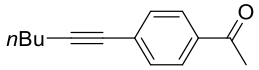
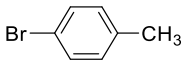
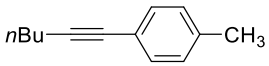
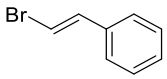
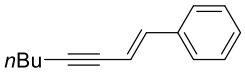
***Scheme 104**. Preparation of solid triorganoindium reagent **23**.*



The cross-coupling reactions with reagent **23** were carried out using $Pd(ddpf)Cl_2$ instead of $Pd(PPh_3)Cl_2$ since according to previously reported results, it is the catalyst of choice when alkynyl triorganoindium reagents are involved (Table 25).[7] Compound **23** maintained its reactivity for a few days after its preparation, then its appearance changed from yellow to colorless and the yields of cross-coupled products dropped sharply.

***Table 25**. Palladium-catalyzed cross-coupling reaction of **23** with various electrophiles.*

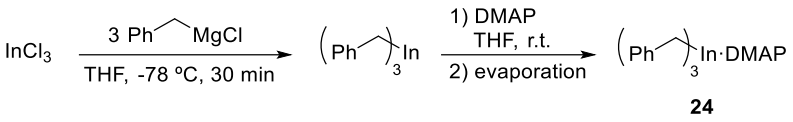


Entry	R-Br	Product	Yield (%)[a]
1		 **23a**	92
2		 **23b**	93
3		 **23c**	80

[a] Isolated yield.

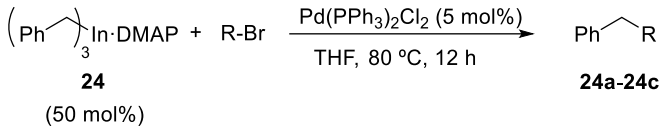
Tribenzylidium reagent **24** was also prepared, this time from the corresponding Grignard reagent (Scheme 105). Solid organoindium **24** was reacted with 4-bromoacetophenone affording product **24a** in 68 % yield (Table 26, entry 1). The solid complex was also set to react with cinnamyl bromide and product **24b** was obtained in 58 % yield (Table 26, entry 2). Interestingly, these represented the first examples of palladium-catalyzed cross-coupling reaction using tribenzylindium reagent, as this type of triorganoindium reagent had not been used before in this context. Finally, organoindium **24** was also set to react with 2-bromobenzonitrile, affording product **24c** in 71 % yield (Table 26, entry 3).

***Scheme 105**. Preparation of solid triorganoindium reagent **24**.*

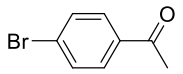
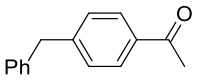
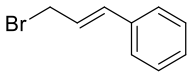
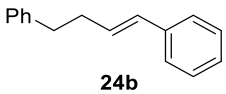
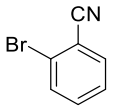
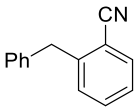


24

***Table 26**. Palladium-catalyzed cross-coupling reaction of **24** with various electrophiles.*



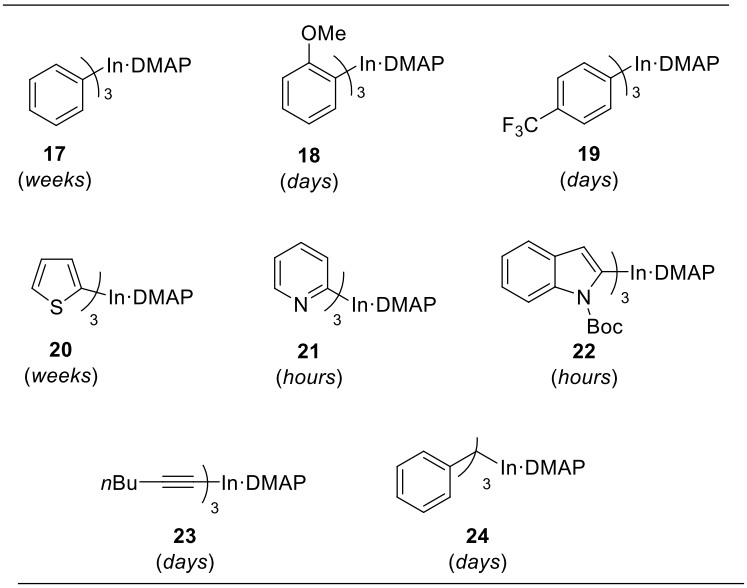
24 (50 mol%) — **24a-24c**

Entry	R-Br	Product	Yield (%)
1		 **24a**	68[a]
2		 **24b**	58[b]
3		 **24c**	71[a]

[a] Isolated yield. [b] Yield estimated by ^{1}H NMR.

The results obtained showed that it is possible to prepare solid triorganoindium reagents using DMAP as ligand. These reagents contained aromatic, heteroaromatic, alkynyl, and a benzyl group, and took part efficiently in palladium-catalyzed cross-coupling reactions with different electrophiles. The strong coordinative bond formed between indium and the aromatic nitrogen of DMAP gives the resulting species enough stability to withstand exposure to atmospheric air. This stability varies depending on the organic group, presumably due to electronic and steric factors (Figure 12). The more stable compounds were **17** and **20**, which showed little variation in the yield of the cross-coupled products for weeks after their preparation. Other reagents such as 2-anisole derived **18** or alkyne-containing **23** were able to sustain high reaction yields only for a few days. The more electron-deficient nitrogen-containing pyridine and indole compounds **21** and **22** were the more sensitive, resulting totally decomposed a few hours after being exposed to atmospheric air.

***Figure 12**. Different $R_3In·DMAP$ reagents and their observed stability.*

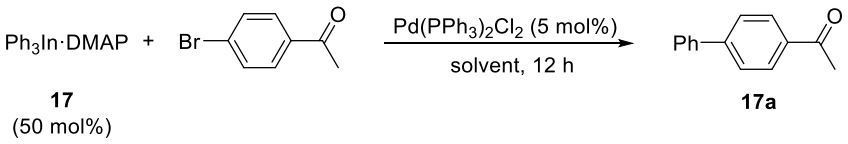


LiCl is omitted for clarity.

Despite the differences in stability of the resulting compounds, the availability of solid triorganoindium reagents provides important advantages. It is now possible to prepare and store the triorganoindium reagents for later use, and if necessary they can be exposed to air without appreciable decomposition, at least in the short term. It is easier to handle these compounds and experiments require less time for set up, for example they can be especially useful during reaction optimization studies that normally require multiple simultaneous reactions.

Another important feature from the use of $R_3In·DMAP$ reagents is the ability to perform cross-coupling reactions in non-ethereal solvents. Preliminary experiments had shown that the cross-coupling reaction could be carried out using toluene, a non-coordinating solvent, therefore it was decided to investigate the use of different solvents for the palladium-catalyzed cross-coupling reaction of compound **17** (Table 27).

***Table 27**. Palladium-catalyzed cross-coupling of $Ph_3In{\cdot}DMAP$ (**17**) using different solvents.*



17
(50 mol%)

17a

Entry	Solvent	Temperature	Yield of **17a** (%)[a]
1	toluene	110 °C	55
2	CH_2Cl_2	40 °C	62
3	1,2-dichloroethane	80 °C	64
4	1,1,2,2-tetrechloroethane	110 °C	45
5	DMF	120 °C	93
6	CH_3CN	80 °C	34

[a] Isolated yield.

The cross-coupling of compound **17** with 4-bromoacetophenone in toluene afforded product **17a** in 55 % yield (Table 27, entry 1). More interestingly, the reaction could be carried out using various halogenated solvents with acceptable yields (Table 27, entries 2-4). Additionally, the reaction of **17** was performed using DMF leading to **17a** in an excellent 93 % yield (Table 27, entry 5), while the use of CH_3CN afforded a more discreet 34 % yield.

3.2.2 Pd-Catalyzed Reactions of R_3In·DMAP and Aryne Precursors.

The results obtained show that R_3In·DMAP reagents possess enhanced stability when compared to classically prepared triorganoindium reagents and that they can react under palladium catalysis in a variety of solvents. After these findings, we decided to further explore the reactivity of the new solid triorganoindium reagents. Therefore, in collaboration with the group of Profs. Enrique Guitian and Dolores Pérez, from the University of Santiago de Compostela, we decided to investigate the reaction of R_3In·DMAP with aryne precursors under palladium catalysis.

Arynes are the highly reactive species derived from an aromatic ring by removal of two ortho substituents, and they constitute important intermediates involved in many types of processes including Diels-Alder reactions, dipolar cycloadditions, or insertion reactions that enable the synthesis of a wide array of organic molecules.[198] The use of 2-trimethylsilyl triflates as aryne precursors under mild conditions has favored the development of a variety of transition-metal-mediated aryne carbon-carbon bond forming processes.[199] Among these reactions, intermolecular carbopalladation of benzyne intermediates using π-allyl palladium complexes constitutes an important strategy for the construction of diverse 1,2-functionalized arenes.[200] In this context, boronic acids, stannanes, and silanes have been used in three-component reactions with allyl chlorides in the presence of aryne precursors under palladium catalysis (Scheme 106). [201]

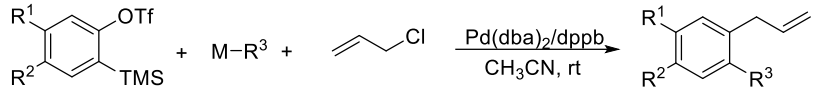
198 (*a*) Bhunia, A.; Reddy, Y. S.; Biju, A. T.; *Chem. Soc. Rev.* **2012**, *41*, 3140-3152. (*b*) García López, J. A.; Greaney, M. F. *Chem. Soc. Rev.* **2016**, *45*, 6766-6798. (*c*) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550-3577.

199 Some recent examples: (*a*) Zuo, Z.; Wang, H.; Diao, Y.; Ge, Y.; Liu, J.; Luan, X. *ACS Catal.* **2018**, *8*, 11029-11034. (*b*) Duan, S.; Cheng, B.; Duan, X.; Bao, B.; Li, Y.; Zhai, H. *Org. Lett.* **2018**, *20*, 1417-1420. (*c*) Garve, L. K. B.; Werz, D. B. *Org. Lett.* **2015**, *17*, 596-599.

200 (*a*) Yoshikawa, E.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2000**, *39*, 173-175. (*b*) Henderson, J. L.; Edwards, A. S.; Greaney, M. F. *J. Am. Chem. Soc.* **2006**, *128*, 7426-7427.

201 (*a*) Jayanth, T. T.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2005**, *7*, 2921-2924. (*b*) Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2004**, *6*, 2821-2824. (*c*) Jayanth, T. T.; Cheng, C.-H. *Angew. Chem. Int. Ed.* **2007**, *46*, 5921-5924. (*d*) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C.-H. *Angew. Chem. Int. Ed.* **2009**, *48*, 391-394.

Scheme 106. *Pd-catalyzed three-component reaction of different organometallic species with aryne precursors and allyl chlorides.*

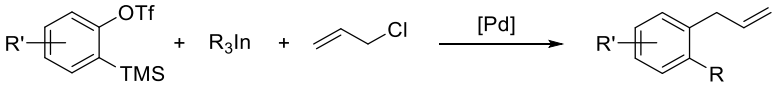


R^1, R^2 = H, Me
R^3 = aryl, alkynyl
M = $B(OH)_2$, $SnBu_3$, $Si(OMe)_3$

68-88 %

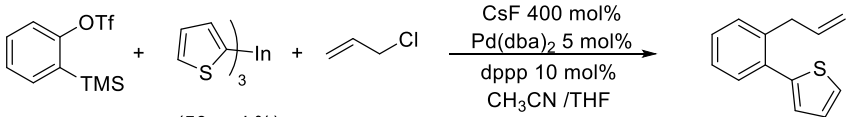
In this sense, triorganoindium reagents have the potential to take part efficiently in this type of palladium-catalyzed reaction. Therefore, as part of the ongoing effort to expand the synthetic utilities of triorganoindium reagents in organic chemistry, we decided to investigate the reaction of triorganoindium reagents with aryne precursors and allyl chlorides under palladium catalysis (Scheme 107).

Scheme 107*. Pd-catalyzed reaction of R_3In with aryne precursors in the presence of allyl chlorides.*



As part of a preliminary study, trithiophenylindium was reacted with 2-trimethylsilyl triflate in the previously reported conditions for the reaction of boronic acids (Scheme 108). However, only trace amounts of the expected product **25** could be detected. Reaction failure was attributed to the poor solubility of CsF in the reaction media due to the presence of THF employed for the preparation of the indium reagent. Although other fluoride sources such as TBAF were employed, appreciable quantities of **25** could not be obtained. The previously cited works highlight solvent and fluoride source choice as critical factors for the reaction to proceed.

Scheme 108*. Three-component reaction of R_3In, allyl chloride, and aryne precursor under Pd catalysis.*

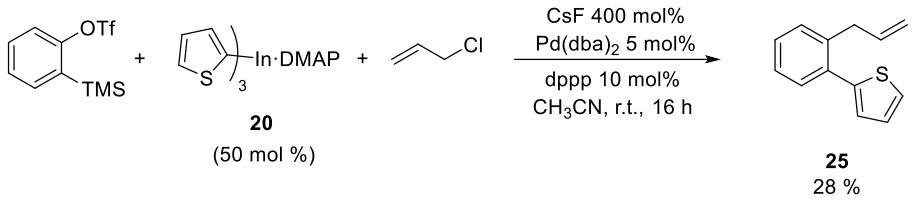


25
trace

On the other hand, the newly developed R_3In·DMAP reagents can be used in solvents other than THF, and therefore, we decided to test the reaction again this time

employing solid triorganoindium reagent **20** and CH_3CN as the only solvent (Scheme 109).

***Scheme 109**. Three-component reaction using a solid triorganoindium reagent.*

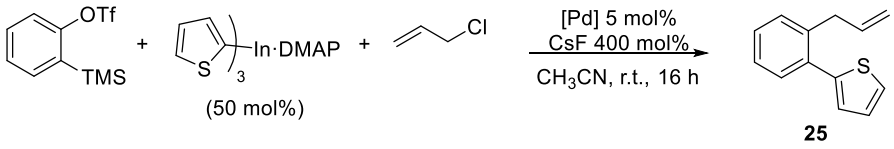


20
(50 mol %)

25
28 %

Gratifyingly, allyl thiophenyl benzene **25** was obtained in 28 % yield. This result demonstrates the utility of the newly developed $R_3In{\cdot}DMAP$ reagents, enabling reactions that otherwise would be unfeasible with the *in situ* generated triorganoindium. After this initial result, the different variables involved in the reaction were optimized in order to improve product yield. Previously, in the coupling reactions with boronic acids and stannanes, the choice of the phosphine ligand had significant effects upon reaction yield. Therefore, we screened various bidentate phosphine ligands while maintaining constant the remaining reaction conditions (Table 28).

***Table 28**. Screening of bidentate phosphines for the three-component reaction of $R_3In{\cdot}DMAP$, allyl chloride, and aryne under Pd catalysis.*



(50 mol%)

25

Entry	[Pd] (mol%)	Ligand (mol%)	Yield of **25**[a]
1	$Pd(dba)_2$ (5)	dppe (10)	36
2	$Pd(dba)_2$ (5)	dppp (10)	28
3	$Pd(dba)_2$ (5)	DPEPhos (10)	44
4	$Pd(dba)_2$ (5)	–	9
5	$Pd(PPh_3)_4$ (5)	–	28
6	–	–	–

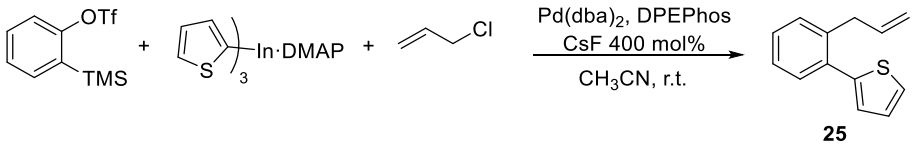
[a] Isolated yield.

In this study, three different bidentate phosphines were tested in combination with $Pd(dba)_2$ in 2:1 proportion (Table 28, entries 1-3). The best results were initially obtained with DPEPhos while using a palladium catalyst load of 5 mol%. Absence of

a phosphine ligand led only to a residual amount of allyl thiophenyl benzene **25** (Table 28, entry 4) while performing the reaction without palladium resulted in none of **25** (Table 28, entry 6). The use of $Pd(PPh_3)_4$ as catalyst afforded a modest 28% yield of isolated product **25**.

Then, we studied other variables involved in the reactions (Table 29). We studied the effect of the amount of triorganoindium reagent, and found that increasing the quantity towards 70 mol% did not have an impact on the reaction yield (Table 29, entry 1). Surprisingly, we also observed that decreasing the amount of $R_3In{\cdot}DMAP$ to only 35 mol% afforded the same yield (Table 29 entry 2). Reaction work-up after 6 h resulted in somewhat lower product yield compared to running the reaction overnight (Table 29, entry 4).

***Table 29**. Optimization of reaction conditions for the three-component reaction of $R_3In{\cdot}DMAP$.*



Entry	$R_3In{\cdot}DMAP$(mol%)	$Pd(dba)_2$(mol %)	DPEPhos (mol%)	Reaction time (h)	Yield[a]
1	70	5	10	16	42
2	35	5	10	16	42
3	35	5	10	2	28
4	35	10	10	6	38
5	35	10	20	16	62

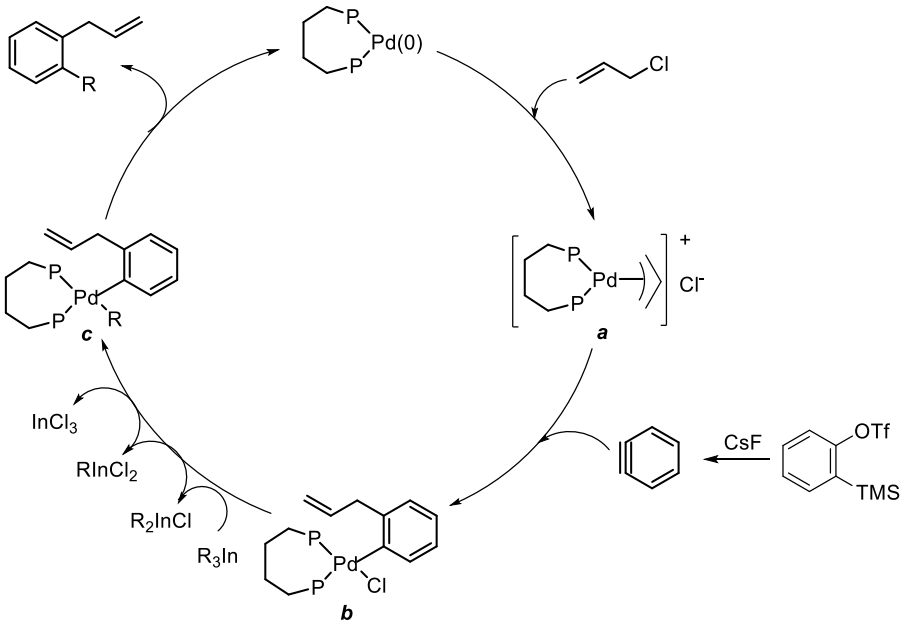
[a] Isolated yield.

At this point it was hypothesized that the observed low yields were due to the Pd-catalyzed reaction not occurring rapidly enough. Moreover, despite the relatively low reaction output, only trace amounts of aryne precursor was recovered in each case. Consequently, the amount of catalyst loading was doubled (Table 29, entry 5) resulting in an appreciable increase of reaction performance, leading to **25** in 62% isolated yield.

After these results, a reaction mechanism was proposed (Figure 13), which involved oxidative addition of allyl chloride to Pd(0) as the first step to give π-allyl palladium complex ***a***. Then, the benzyne species generated from the reaction of trimethylsilyl

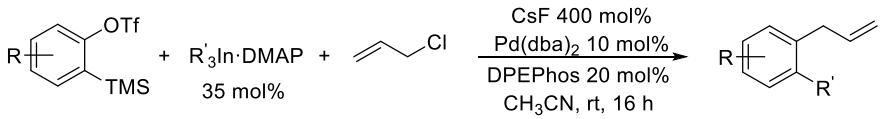
triflate in the presence of CsF would undergo insertion into ***a*** to afford aryl palladium intermediate ***b***. Transmetallation of the organoindium with palladium gives intermediate ***c***. Product yield of 62% using just 35 mol% of the triorganoindium reagent indicates that more one organic group is transferred in the process. Finally, ***c*** would undergo reductive elimination, affording the reaction product while the active catalyst is regenerated.

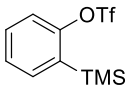
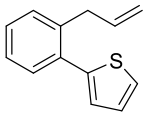
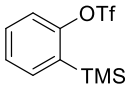
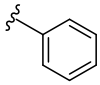
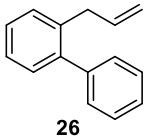
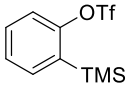
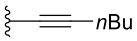
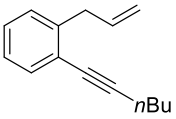
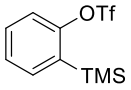
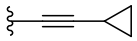
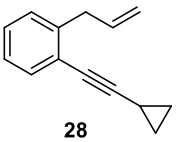
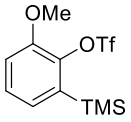
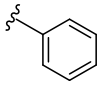
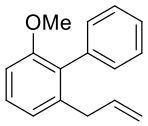
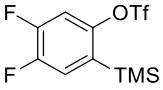
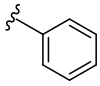
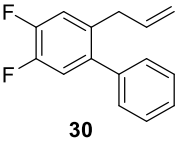
Figure 13*. Proposed catalytic cycle for the Pd-catalyzed multicomponent reaction of R_3In·DMAP.*



With the optimized conditions in hand, other R_3In·DMAP reagents and aryne precursors were employed (Table 30).

***Table 30**. Palladium-catalyzed multi-component reaction using different R_3In·DMAP reagents and aryne precursors.*



Entry	Precursor	R'	Product	Yield (%)[a]
1			 **25**	62
2			 **26**	54
3			 **27**	39
4			 **28**	43
5			 **29**	31[b]
6			 **30**	46

[a] Isolated yield. [b] 2-allyl-3-methoxy isomer was also obtained from the reaction as minor product.

The use of Ph_3In·DMAP afforded the corresponding reaction product **26** in 56 % yield (Table 30, entry 2). The reaction was also carried out using alkynyl indium reagents, and products **27** and **28** were obtained in moderate yields (Table 30, entries 3 and 4). When R_3In·DMAP reagents bearing alkyl or benzyl groups were used, only trace amounts of the reaction products could be obtained. The reaction was also performed using the more electron-rich 2-methoxy-6-trimethylsilyl-phenyltriflate as aryne precursor, and product **29** could be obtained in 31 % yield, along with the 2-allyl-3-methoxy isomer.

Although reaction yields were generally moderate, to the best of knowledge, these represent the first examples of the reaction of indium organometallics with benzyne species. The process involves the simultaneous formation of two new carbon-carbon bonds in a single synthetic step, and the results obtained so far indicate that it can be performed with aryl, heteroaryl, and alkynyl reagents. The reaction has the potential to access benzene derivatives furnished with a variety of different functionalities. More importantly, this reaction was possible because of the newly developed $R_3In{\cdot}DMAP$ reagents which can be stored and manipulated as solids and can be used with different types of organic solvents. Thus, this is an example of how $R_3In{\cdot}DMAP$ can be used in reactions that were once considered to be incompatible with triorganoindium reagents, and therefore they have the potential to further expand the utility of indium organometallics in organic synthesis.

3.3 Experimental Section.[202]

Synthesis and isolation of Ph_3In·DMAP (17).

To a solution of $InCl_3$ (487 mg, 2.20 mmol) in THF (15mL), PhLi (3.67 mL, 6.60 mol, 1.8 M in dibutyl ether) was added dropwise at –78 °C. After 30 min the reaction was warmed to rt, and stirred for an additional 30 min. A solution of 4-dimethylaminopyridine (269 mg, 2.20 mmol) in THF (5mL) was added via cannula. After 1 h of stirring, the solvent was evaporated in vacuo to afford a white to yellow solid that was extracted with refluxing toluene. The extract was filtered and the solvent was evaporated in vacuo to afford **17** as a white solid (753 mg, 73% yield). Crystals suitable for X-ray diffraction spectroscopy were obtained from a toluene/hexane 3:1 mixture after one week of storage at 4 °C. **^{1}H NMR** (toluene-d_8, 500 MHz) δ7.97 (d, *J* = 7.2 Hz, 6H); 7.82 (d, *J* = 5.3 Hz, 2H); 7.39 (t, *J* = 7.2 Hz, 6H); 7.29 (t, *J* = 7.4 Hz, 3H); 5.43 (d, *J* = 7.2 Hz, 2H); 1.96 (s, 6H). **^{13}C{^{1}H} NMR** (toluene-d_8, 125 MHz) δ155.2 (C); 154.6 (3 × C); 148.8 (3 × CH); 140.1 (2 × CH); 128.5 (2 × CH); 127.8 (6 × CH); 107.2 (6 × CH); 38.4 (2 × CH_3). Anal. Cald for $C_{25}H_{25}InN_2$: C, 64.12; H, 5.38; N, 5.98. Found: C, 63.72; H, 5.24; N, 5.92.

General method for the preparation of R_3In·DMAP reagents.

To a solution of $InCl_3$ (487 mg, 2.20 mmol) in THF (15 mL), the corresponding organolithium or Grignard reagent (6.60 mmol, THF solution) was added dropwise at –78 °C. After 30 min the reaction was warmed to room temperature, and stirred for an additional 30 min. A solution of 4-dimethylaminopyridine (269 mg, 2.20 mmol) in THF (5 mL) was added via cannula. After 1 h of stirring, the solvent was evaporated in vacuo to afford a solid that was subsequently stored under argon.

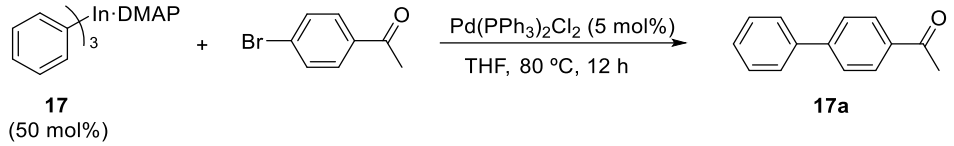
General method for the palladium-catalyzed cross-coupling reaction with R_3In·DMAP.

A mixture of electrophile (0.5 mmol), solid R_3In·DMAP (0.25 mmmol), and Pd catalyst (0.025 mmol) was placed in a Schlenk tube, dissolved in THF (5 mL), and refluxed for 16 h. The crude was concentrated in vacuo, and Et_2O (30 mL) was added. The organic phase was successively washed with water (50 mL, two portions) and brine (30 mL),

202 For General Experimental Methods, see section 2.3.

dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to afford, after concentration and high vacuum-drying, the corresponding products.

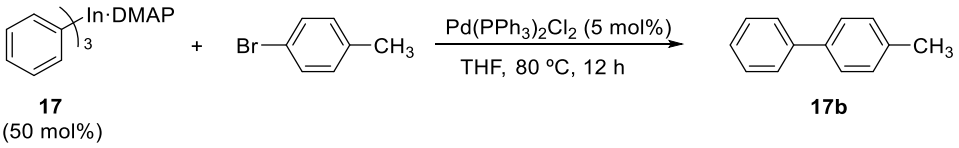
1-(4-Bromophenyl)ethan-1-one (17a).[203]



17 (50 mol%) **17a**

Following the general procedure, the reaction of 4-bromoacetophenone (99 mg, 0.5 mmol) with **17** (149 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 5:95), 89 mg of **17a** (91%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2 H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.51–7.37 (m, 3H), 2.64 (s, 3H)); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 197.7 (C), 145.8 (C), 139.9 (C), 135.9(C), 129.0 (2 × CH), 128.9 (2 × CH), 128.2 (CH), 127.3 (2 × CH), 127.2 (2 × CH), 26.6 (CH_3). **MS** (EI) *m/z* 196 $[M]^+$ (61), 181 $[M - CH_3]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{14}H_{12}O$ $[M]^+$ 196.0883, found 196.0881.

4-Methyl-1,1'-biphenyl (17b).[203]

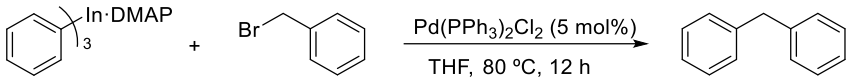


17 (50 mol%) **17b**

Following the general procedure, the reaction of 1-bromo-4-methylbenzene (86 mg, 0.5 mmol) with **17** (149 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 1:99), 79 mg of **17b** (94%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.68–7.61 (m, 2H), 7.60 (d, *J* = 8.1 Hz, 2H), 7.48(t, *J* = 7.2 Hz, 2H), 7.42–7.34 (m, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 2.46 (s, 3H)); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 141.2 (C), 138.4 (C), 137.0 (C), 129.5 (2 × CH), 128.7 (2 × CH), 127.03 (2 × CH), 127.01 (3 × CH), 21.1 (CH_3). **MS** (EI) *m/z* 168 $[M]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{13}H_{12}$ $[M]^+$ 168.0934, found 168.0935.

203 I. J. S. Fairlamb, A. R. Kapdi, A. F. Lee, *Org. Lett.* **2004**, *6*, 4435–4438.

Diphenylmethane (17c).[204]

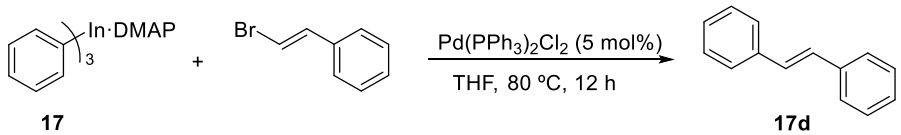


17
(50 mol%)

17c

Following the general procedure, the reaction of benzyl bromide (86 mg, 0.5 mmol) with **17** (149 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 1:99), 68 mg of **17c** (81%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.40–7.22 (m, 10 H), 4.05 (s, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 141.2 (2 × C), 129.0 (4 × CH), 128.5 (4 × CH), 126.1 (2 × CH), 42.0 (CH_2). **MS** (EI) *m/z* 168 $[M]^+$ (70), 167 $[M - H]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{13}H_{12}$ $[M]^+$ 168.0934, found 168.0928.

(*E*)-1,2-Diphenylethene (17d).[205]



17
(50 mol%)

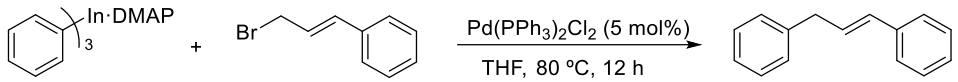
17d

Following the general procedure, the reaction of β-bromostyrene (92 mg, 0.5 mmol) with **17** (149 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 2:98), 79 mg of **17d** (88%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.56 (d, *J* = 7.1 Hz, 4H), 7.40 (t, *J* = 7.1 Hz, 4H), 7.34–7.26 (m, 2H), 7.16 (s, 2H); **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 137.4 (2 × C), 128.73 (2 × CH), 128.68 (4 × CH), 127. 6 (2 × CH), 126. 5 (4 × CH). **MS** (EI) *m/z* 180 $[M]^+$ (100). HRMS (EI-magnetic sector) calcd for $C_{14}H_{12}$ $[M]^+$ 180.0934, found 180.0928.

(*E*)-1,3-Diphenylpropene (17e).[204]

204 E. Alacid, C. Nájera, *Org. Lett.* **2008**, *10*, 5011–5014.

205 R. Bandari, T. Höche, A. Prager, K. Dirnberger, M. R. Buchmeiser, *Chem. Eur. J.* **2010**, *16*, 4650–4658.

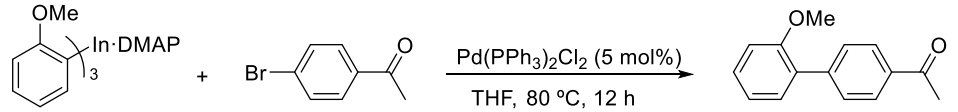


17
(50 mol%)

17e

Following the general procedure, the reaction of cinnamyl bromide (99 mg, 0.5 mmol) with **17** (149 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 2:98), 84 mg of **17e** (87%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.47–7.20 (m, 10H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.48–6.37 (m, 1H), 3.66 (d, *J* = 6.3 Hz, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 140.2 (C), 137. 5 (C), 131.1 (CH), 129.3 (CH), 128.7 (2 × CH), 128.5 (4 × CH), 127.1 (CH), 126.23 (CH), 126.18 (2 × CH), 39.4 (CH_2).). **MS** (EI) *m/z* 194 $[M]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{15}H_{14}$ $[M]^+$ 194.1090, found 194.1084.

1-(2'-Methoxy-[1,1'-biphenyl]-4-yl)ethan-1-one (18a).[206]



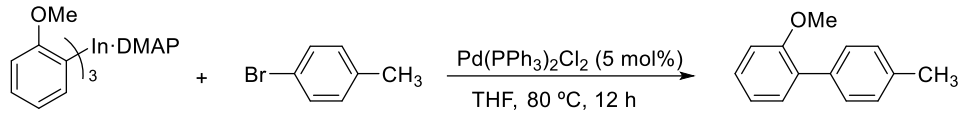
18
(50 mol%)

18a

Following the general procedure, the reaction of 4-bromoacetophenone (99 mg, 0.5 mmol) with **18** (171 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 10:90), 95 mg of **18a** (84%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.01 (d, *J* = 8.1 Hz, 2H), 7.65 (d, *J* = 8.1 Hz, 2H), 7.43–7.30 (m, 2H), 7.12–6.97 (m, 2H) 3.83 (s, 3H), 2.64 (s, 3H**). ^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 197.7 (C), 156.5 (C), 143.6 (C), 135.5 (C), 130.7 (CH), 129.7 (2 × CH), 129.49 (CH), 129.44 (C), 128.1 (2 × CH), 121.0 (CH), 111.4 (CH), 55.6 (CH_3), 26.6 (CH_3). **MS** (EI) *m/z* 226 $[M]^+$ (77), 211 $[M - CH_3]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{15}H_{14}O_2$ $[M]^+$ 226.0988, found 226.0983.

2-Methoxy-4'-methyl-1,1'-biphenyl (18b).[207]

206 K. L. Billingsley, T. E. Barder, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 5359–5363.
207 S. Thapa, P. Basnet, S. K. Gurung, R. Giri, *Chem. Commun.* **2015**, *51*, 4009–4012.

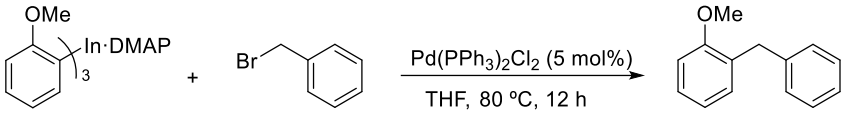


18
(50 mol%)

18b

Following the general procedure, the reaction of 1-bromo-4-methylbenzene (86 mg, 0.5 mmol) with **18** (171 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 5:95), 95 mg of **18b** (96%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.57–7.48 (m, 2H), 7.44–7.28 (m, 4H), 7.16–7.02 (m, 2H) 3.88 (s, 3H), 2.48 (s, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 156.6 (C), 136.6 (C), 135.7 (C), 130.9 (CH), 130.8 (C), 129.5 (2 × CH), 128.8 (2 × CH), 128.4 (CH), 120.9 (CH), 111.3 (CH), 55.6 (CH_3), 21.3 (CH_3). **MS** (EI) *m/z* 198 $[M]^+$ (100), 183 $[M - CH_3]^+$ (33), 168 $[M - OCH_3]^+$ (39). **HRMS** (EI-magnetic sector) calcd for $C_{14}H_{14}O$ $[M]^+$ 198.1039, found 198.1048.

1-Benzyl-2-methoxybenzene (18c).[208]



18
(50 mol%)

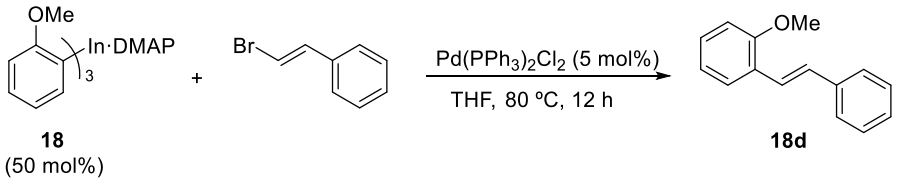
18c

Following the general procedure, the reaction of benzyl bromide (86 mg, 0.5 mmol) with **18** (171 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 5:95), 86 mg of **18c** (87%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.37–7.19 (m, 6H), 7.12 (d, *J* = 7.3 Hz, 1H), 6.92 (t, *J* = 7.7 Hz, 2H), 4.04 (s, 2H), 3.86 (s, 3H**). ^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 157.4 (C), 141.1 (C), 130.4 (CH), 129.7 (C), 129.0 (2 × CH), 128.3 (2 × CH), 127.4 (CH), 125.8 (CH), 110.4 (CH), 55.4 (CH_3), 35.9 (CH_2). **MS** (EI) *m/z* 198 $[M]^+$ (100), 183 $[M - CH_3]^+$ (28), 167 $[M - OCH_3]^+$ (27). **HRMS** (EI-magnetic sector) calcd for $C_{14}H_{14}O$ $[M]^+$ 198.1039, found 198.1035.

(*E*)-1-Methoxy-2-styrylbenzene (18d).[209]

208 P. Maity, D. M. Shacklady-McAtee, G. P. A. Yap, E. R. Sirianni, M. P. Watson, *J. Am. Chem. Soc.* **2013**, *135*, 280–285.

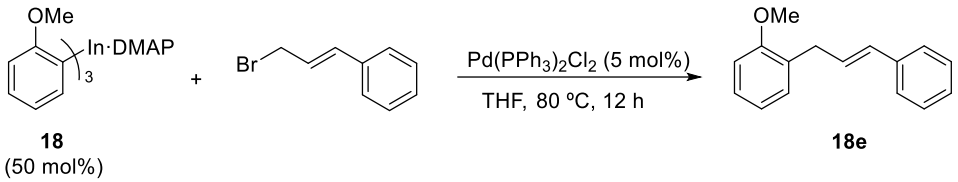
209 J. F. Guastavino, M. E. Budén, R. A. Rossi, *J. Org. Chem.* **2014**, *79*, 9104–9111.



18 (50 mol%) **18d**

Following the general procedure, the reaction of β-bromostyrene (92 mg, 0.5 mmol) with **18** (171 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 5:95), 97 mg of **18d** (92%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ7.65 (d, *J* = 7.7 Hz, 1H), 7.62–7.48 (m, 3H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.2Hz, 2H), 7.17 (d, *J* = 16.4 Hz, 1H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 3.93 (s, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ157.0 (C), 138.0 (C), 129.1 (CH), 128.7 (CH), 128.6 (2 × CH), 127.4 (CH), 126.6 (2 × CH), 126.5 (C), 126.4 (CH), 123.5 (CH), 120.8 (CH), 110.0 (CH), 55.5 (CH_3). **MS** (EI) *m/z* 210 $[M]^+$ (100), 167 $[M - C_2H_3O]^+$ (17). **HRMS** (EI-magnetic sector) calcd for $C_{15}H_{14}O$ $[M]^+$ 210.1039, found 210.1038.

1-Cinnamyl-2-methoxybenzene (18e).[210]

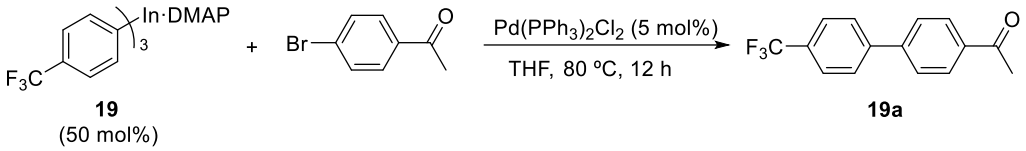


18 (50 mol%) **18e**

Following the general procedure, the reaction of cinnamyl bromide (99 mg, 0.5 mmol) with **18** (171 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 2:98), 99 mg of **18e** (88%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ7.45–7.15 (m, 7H), 7.02–6.84 (m, 2H), 6.55–6.34 (m, 2H), 3.88 (s, 3H), 3.58 (d, *J* = 5.3 Hz, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ157. 3 (C), 137.8 (C), 130.7 (CH), 129.8 (CH), 128.9 (CH), 128.7 (C), 128.4 (2 × CH), 127.4 (CH), 126.9 (CH), 126.1 (2 × CH), 120.5 (CH), 110.4 (CH), 55.4 (CH_3), 33.4 (CH_2). **MS** (EI) *m/z* 224 $[M]^+$ (100), 193 $[M - OCH_3]^+$ (34). **HRMS** (EI-magnetic sector) calcd for $C_{16}H_{16}O$ $[M]^+$ 224.1196, found 224.1193.

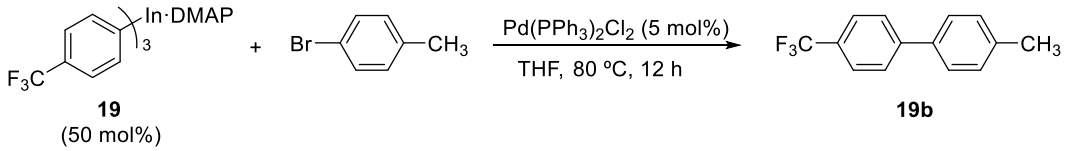
210 R. Riveiros, R. Tato, J. Pérez Sestelo, L. A. Sarandeses, *Eur. J. Org. Chem.* **2012**, *2012*, 3018–3023.

1-(4'-(Trifluoromethyl)-[1,1'-biphenyl]-4-yl)ethan-1-one (19a).[211]



Following the general procedure, the reaction of 4-bromoacetophenone (99 mg, 0.5 mmol) with **19** (200 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 10:90), 107 mg of **19a** (81%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.06 (d, *J* = 8.5 Hz, 2H), 7.75–7.64 (m, 6H), 2.65 (s, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 197.5 (C), 144.1 (C), 143.3 (C), 136.6 (C), 130.2 (q, *J* = 32.6 Hz, C), 129.0 (2 × CH), 127.6 (2 × CH), 127.4 (2 × CH) 125.9 (q, *J* = 3.7 Hz, 2 × CH), 122.3 (C), 26.7 (CH_3). **MS** (EI) *m/z* 264 $[M]^+$ (34), 249 $[M - CH_3]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{15}H_{11}OF_3$ $[M]^+$ 264.0757, found 264.0745.

4-Methyl-4'-(trifluoromethyl)-1,1'-biphenyl (19b).[212]

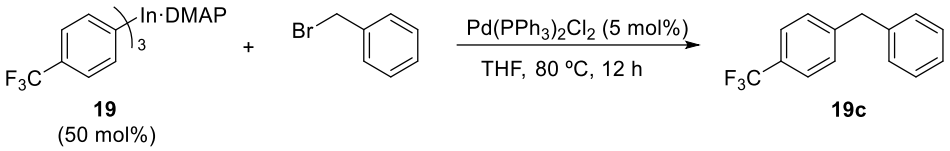


Following the general procedure, the reaction of 1-bromo-4-methylbenzene (86 mg, 0.5 mmol) with **19** (200 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 1:99), 101 mg of **19b** (86%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.71–7.65 (m, 4H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 144.6 (C), 138.1 (C), 136.9 (C), 129.7 (2 × CH), 129.0 (q, *J* = 32.3 Hz, C), 127.14 (2 × CH), 127.08 (2 × CH), 125.6 (q, *J* = 3.8 Hz, 2 × CH), 124.3 (q, *J* = 270.1 Hz, CF_3), 21.1 (CH_3). **MS** (EI) *m/z* 236 $[M]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{14}H_{11}F_3$ $[M]^+$ 236.0807, found 236.0806.

211 A. Prastaro, P. Ceci, E. Chiancone, A. Boffi, R. Cirilli, M. Colone, G. Fabrizi, A. Stringaro, S. Cacchi, *Green Chem.* **2009**, *11*, 1929–1932.

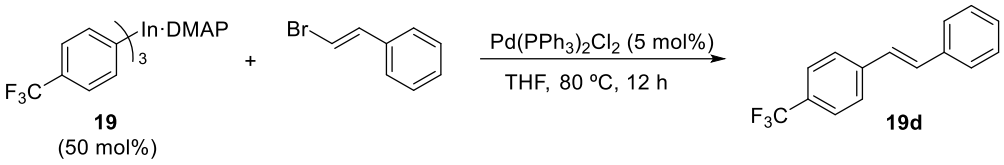
212 D. Gauthier, S. Beckendorf, T. M. Gøgsig, A. T. Lindhardt, T. Skrydstrup, *J. Org. Chem.* **2009**, *74*, 3536–3539.

1-Benzyl-4-(trifluoromethyl)benzene (19c).[213]



Following the general procedure, the reaction of benzyl bromide (86 mg, 0.5 mmol) with **19** (200 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 2:98), 91 mg of **19c** (77%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.39–7.16 (m, 7H), 4.1 (s, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 145.2 (C), 140.0 (C), 129.2 (2 × CH), 128.9 (2 × CH), 128,7 (C), 128.7 (2 × CH), 126.4 (CH), 125.4 (q, *J* = 3.8 Hz, 2 × CH), 126.1 (q, *J* = 270 Hz, CF_3), 41.7 (CH_3). **MS** (EI) *m/z* 236 $[M]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{14}H_{11}F_3$ $[M]^+$ 236.0807, found 236.0813.

(*E*)-1-Styryl-4-(trifluoromethyl)benzene (19d).[214]

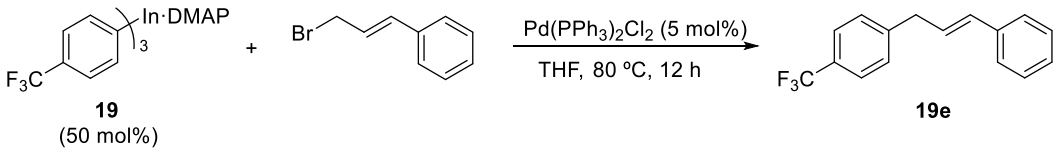


Following the general procedure, the reaction of β-bromostyrene (92 mg, 0.5 mmol) with **19** (200 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 2:98), 104 mg of **19d** (84%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7,67–7.60 (m, 4H), 7.59–7.53 (m, 2H), 7.45–7.32 (m, 3H), 7.22 (d, *J* = 16.4 Hz, 1H), 7.14 (d, *J* = 16.4 Hz, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 140.8 (C), 136.6 (C), 131.2 (CH), 129.5 (C), 129.0 (C), 128.8 (2 × CH), 128.3 (CH), 127.1 (CH), 126.8 (2 × CH), 126.6 (2 × CH), 125 (q, *J* = 3.8 Hz, 2 × CH). **MS** (EI) *m/z* 248 $[M]^+$ (100), 179 $[M - CF_3]^+$ (37). **HRMS** (EI-magnetic sector) calcd for $C_{15}H_{11}F_3$ $[M]^+$ 248.0807, found 248.0801.

1-Cinnamyl-4-(trifluoromethyl)benzene (19e).[214]

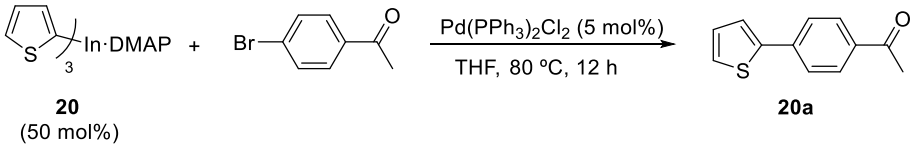
213 J. R. Schmink, N. E. Leadbeater, *Org. Lett.* **2009**, *11*, 2575–2578.

214 M. Peña-López, L. A. Sarandeses, J. Pérez Sestelo, *Eur. J. Org. Chem.* **2013**, *2013*, 2545–2554.



Following the general procedure, the reaction of cinnamyl bromide (99 mg, 0.5 mmol) with **19** (200 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 2:98), 117 mg of **19e** (89%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ7.60 (d, *J* = 8.0 Hz, 2H), 7.44–7.21 (m, 7H), 6.51 (d, *J* = 16.0 Hz, 1H), 6.42–6.28 (m, 1H), 3.63 (d, *J* = 6.7 Hz, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ144.3 (C), 137.1 (C), 132.0 (CH), 129.0 (2 × CH), 129.2 (q, *J* = 32.2 Hz, C), 128.6 (2 × CH), 127.9 (CH), 127.4 (CH), 126.2 (2 × CH), 125.4 (q, *J* = 3.7 Hz, 2 × CH), 122.5 (C), 39.1 (CH_2). **MS** (EI) *m/z* 262 $[M]^+$ (100), 193 $[M - CF_3]^+$ (58). **HRMS** (EI-magnetic sector) calcd for $C_{16}H_{13}F_3$ $[M]^+$ 262.0964, found 262.0956.

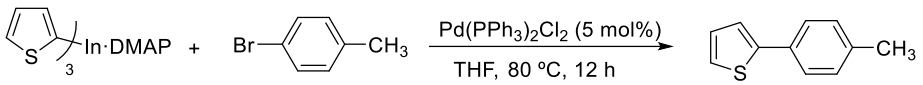
1-(4-(Thiophen-2-yl)phenyl)ethan-1-one (20a).[215]



Following the general procedure, the reaction of 4-bromoacetophenone (99 mg, 0.5 mmol) with **20** (153 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 10:90), 77 mg of **20a** (76%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ7.95 (d, *J* = 8.6 Hz, 2H), 7.68 (d, *J* = 8.6 Hz, 2H), 7.42 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.36 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.11 (dd, *J* = 5.1, 3.6 Hz, 1H), 2.60 (s, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ197.3 (C), 142.9 (C), 138.8 (C), 135.7 (C), 129.1 (2 × CH), 128.4 (CH), 126.4 (CH), 125.6 (2 × CH), 124.6 (CH), 26.5 (CH_3). **MS** (EI) *m/z* 202 $[M]^+$ (58), 187 $[M - CH_3]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{12}H_{10}OS$ $[M]^+$ 202.0447, found 202.0441.

2-(*p*-Tolyl)thiophene (20b).[216]

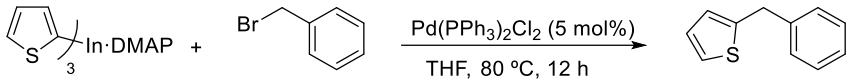
215 N. Miyaura, Y. Yamamoto, M. Takizawa, X.-Q. Yu, *Heterocycles* **2010**, *80*, 359–368.
216 M. L. N. Rao, D. Banerjee, R. J. Dhanorkar, *Synlett* **2011**, *2011*, 1324–1330.



20 (50 mol%) **20b**

Following the general procedure, the reaction of 1-bromo-4-methylbenzene (86 mg, 0.5 mmol) with **20** (153 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 10:90), 76 mg of **20b** (87%) as a white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53 (d, *J* = 8.1 Hz, 2H), 7.30–7.24 (m, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.08 (dd, *J* = 5.1, 3.6 Hz, 1H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 75 MHz) δ 144.6 (C), 137.3 (C), 131.6 (C), 129.5 (2 × CH), 127.9 (CH), 125.9 (2 × CH), 124.3 (CH), 122.6 (CH), 21.2 (CH_3). MS (EI) *m/z* 174 $[M]^+$ (100), 173 $[M - H]^+$ (46). HRMS (EI-magnetic sector) calcd for $C_{11}H_{10}S$ $[M]^+$ 174.0498, found 174.0495.

2-Benzylthiophene (20c).[217]



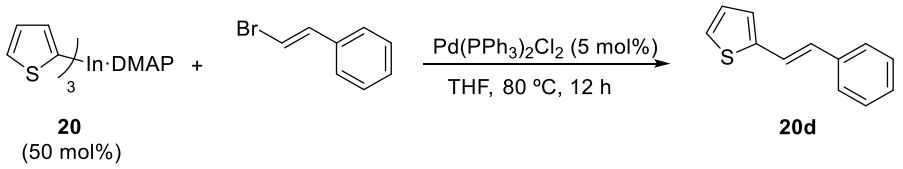
20 (50 mol%) **20c**

Following the general procedure, the reaction of benzyl bromide (86 mg, 0.5 mmol) with **20** (153 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 5:95), 70 mg of **20c** (80%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ7.40–7.21 (m, 5H), 7.18 (dd, *J* = 5.1, 1.2 Hz, 1H). 6.97 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.87–6.82 (m, 1H), 4.20 (s, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 144.0 (C), 140.4 (C), 128.60 (2 × CH), 128.55 (2 × CH), 126.8 (CH), 126.5 (CH), 125.2 (CH), 123.9 (CH), 36.1 (CH_2). **MS** (EI) *m/z* 174 $[M]^+$ (100), 173 $[M - H]^+$ (80). **HRMS** (EI-magnetic sector) calcd for $C_{11}H_{10}S$ $[M]^+$ 174.0498, found 174.0492.

(*E*)-2-Styrylthiophene (20d).[218]

217 N. Henry, C. Enguehard-Gueiffier, I. Thery, A. Gueiffier, *Eur. J. Org. Chem.* **2008**, *2008*, 4824–4827.

218 C.-Z. Yao, Q.-Q. Li, M.-M. Wang, X.-S. Ning, Y.-B. Kang, *Chem. Commun.* **2015**, *51*, 7729–7732.

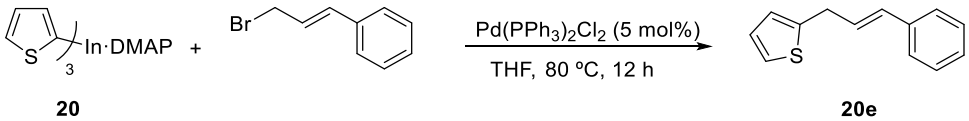


20
(50 mol%)

20d

Following the general procedure, the reaction of β-bromostyrene (92 mg, 0.5 mmol) with **20** (153 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 5:95), 78 mg of **20d** (84%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.50 (d, *J* = 7.2 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.33–7.20 (m, 3H), 7.11 (d, *J* = 3.4 Hz, 1H), 7.04 (dd, *J* = 5.0, 3.4 Hz, 1H), 6.98 (d, *J* = 16.0 Hz, 1H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 142.9 (C), 137.0 (C), 128.7 (2 × CH), 128.4 (CH), 127.6 (2 × CH), 126.3 (2 × CH), 126.1 (CH), 124.3 (CH), 121.8 (CH). **MS** (EI) *m/z* 186 $[M]^+$ (100), 185 $[M - H]^+$ (66). **HRMS** (EI-magnetic sector) calcd for $C_{12}H_{10}S$ $[M]^+$ 186.0498, found 186.0497.

2-Cinnamylthiophene (20e).[216]



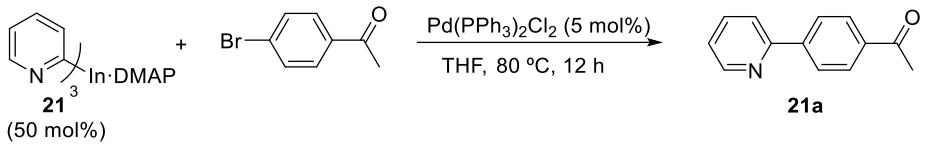
20
(50 mol%)

20e

Following the general procedure, the reaction of cinnamyl bromide (99 mg, 0.5 mmol) with **20** (153 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 5:95), 89 mg of **20e** (89%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.46–7.22 (m, 5H), 7.20 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.99 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.93–6.86 (m, 1H), 6.55 (d, *J* = 15.7 Hz, 1H), 6.40 (dt, *J* = 15.7, 6.6 Hz, 1H), 3.77 (d, *J* = 6.6 Hz, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 143.1 (C), 137.2 (C), 131.4 (CH), 128.5 (2 × CH), 128.2 (CH), 127.3 (CH), 126.9 (CH), 126.3 (2 × CH), 124.7 (CH), 123.8 (CH), 33.4 (CH_2). **MS** (EI) *m/z* 200 $[M]^+$ (100), 199 $[M - H]^+$ (38). **HRMS** (EI-magnetic sector) calcd for $C_{13}H_{12}S$ $[M]^+$ 200.0654, found 200.0650.

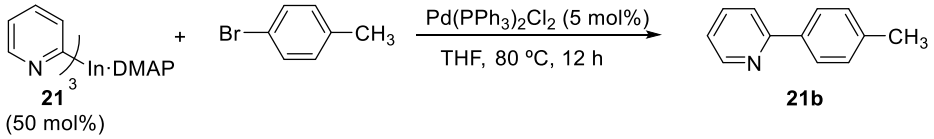
1-(4-(Pyridin-2-yl)phenyl)ethan-1-one (21a).[219]

219 T. Nokami, Y. Tomida, T. Kamei, K. Itami, J.-I. Yoshida, *Org. Lett.* **2006**, *8*, 729–731.



Following the general procedure, the reaction of 4-bromoacetophenone (99 mg, 0.5 mmol) with **21** (150 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 20:80), 107 mg of **21a** (93%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.74–8.70 (m, 1H), 8.12–8.00 (m, 4H), 7.81–7.75 (m, 2H), 7.32–7.22 (m, 1H), 2.63 (s, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 197.8 (C), 156.0 (C), 149.9 (CH), 143.6 (C), 137.1 (C), 136.9 (CH), 128.8 (2 × CH), 127.0 (2 × CH), 122.9 (CH), 120.1 (CH), 26.7 (CH_3). **MS** (EI) *m/z* 197 $[M]^+$ (42), 182 $[M - CH_3]^+$ (100), 154 $[M - C_2H_3O]^+$ (46). **HRMS** (EI-magnetic sector) calcd for $C_{13}H_{11}NO$ $[M]^+$ 197.0835, found 197.0833.

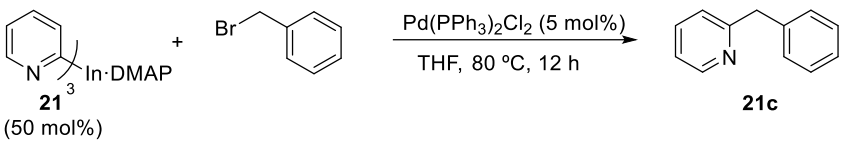
2-(*p*-Tolyl)pyridine (21b).[219]



Following the general procedure, the reaction of 1-bromo-4-methylbenzene (86 mg, 0.5 mmol) with **21** (150 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 20:80), 80 mg of **21b** (95%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.73–8.65 (m, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.78–7.67 (m, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.25–7.17 (m, 1H), 2.42 (s, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 157.5 (C), 149.6 (CH), 138.9 (C), 136.62 (C), 136.60 (CH), 129.4 (2 × CH), 126.7 (2 × CH), 121.7 (CH), 120.2 (CH), 21.2 (CH_3). **MS** (EI) *m/z* 169 $[M]^+$ (100), 168 $[M - H]^+$ (45**). HRMS** (EI-magnetic sector) calcd for $C_{12}H_{11}N$ $[M]^+$ 169.0886, found 169.0884.

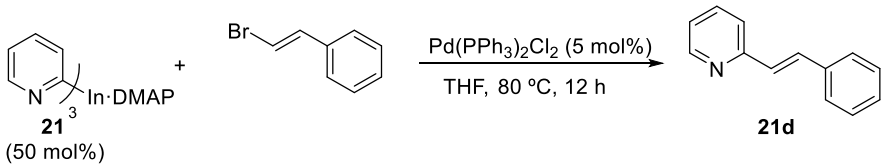
2-Benzylpyridine (21c).[220]

220 R. Shang, Z.-W. Yang, Y. Wang, S.-L. Zhang, L. Liu, *J. Am. Chem. Soc.* **2010**, *132*, 14391–14393.



Following the general procedure, the reaction of benzyl bromide (86 mg, 0.5 mmol) with **21** (150 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 20:80), 69 mg of **21c** (82%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.55 (dd, *J* = 5.4, 1.6 Hz, 1H), 7.57 (td, *J* = 7.7, 1.8Hz, 1H), 7.36–7.17 (m, 5H), 7.15–7.06 (m, 2H), 4.16 (s, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 161.0 (C), 149.3 (CH), 139.5 (C), 136.5 (CH), 129.1 (2 × CH), 128.6 (2 × CH), 126.4 (CH), 123.1 (CH), 121.2 (CH), 44.7 (CH_2). **MS** (EI) *m/z* 169 $[M]^+$ (25), 168 $[M - H]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{12}H_{10}N$ $[M- H]^+$ 169.0808, found 169.0804.

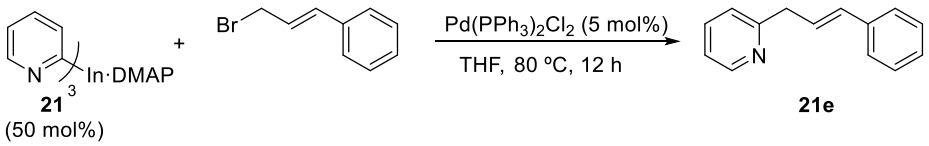
(*E*)-2-Styrylpyridine (21d).[221]



Following the general procedure, the reaction of β-bromostyrene (92 mg, 0.5 mmol) with **21** (150 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 25:75), 64 mg of **21d** (71%) as a white solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.62 (d, *J* = 4.8 Hz, 1H), 7.72–7.54 (m, 4H), 7.38 (t, *J* = 7.8 Hz, 3H), 7.34–7.25 (m, 1H), 7.23–7.08 (m, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 155.6 (C), 149.7 (CH), 136.7 (C), 136.5 (CH), 132.7 (CH), 128.7 (2 × CH), 128.3 (CH), 128.0 (CH), 127.1 (2 × CH), 122.07 (CH), 122.03 (CH). **MS** (EI) *m/z* 181 $[M]^+$ (22), 180 $[M - H]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{13}H_{10}N$ $[M - H]^+$ 180.0808, found 180.0806.

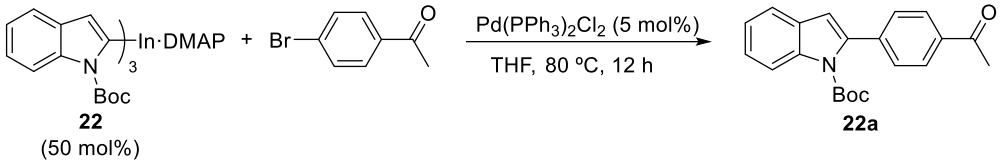
(*E*)-2-Cynnamylpyridine (21e).[222]

221 J. F. Cívicos, D. A. Alonso, C. Nájera, *Adv. Synth. Catal.* **2011**, *353*, 1683–1687.
222 Z. Cui, X. Shang, X.-F. Shao, Z.-Q. Liu, *Chem. Sci.* **2012**, *3*, 2853–2858.



Following the general procedure, the reaction of innamyl bromide (99 mg, 0.5 mmol) with **21** (150 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 20:80), 86 mg of **21e** (88%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.56 (d, *J* = 4.9 Hz, 1H), 7.62 (td, *J* = 7.6, 1.8 Hz, 1H), 7.42–7.34 (m, 2H), 7.32–7.10 (m, 5H), 6.60–6.38 (m, 2H), 3.74 (d, *J* = 6.3 Hz, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 160.2 (C), 149.4 (CH), 137.2 (C), 136.5 (CH), 131.9 (CH), 128.5 (2 × CH), 127.4 (CH), 127.2 (CH), 126.2 (2 × CH), 122.8 (CH), 121.3 (CH), 42.1 (CH_3). **MS** (EI) *m/z* 195 $[M]^+$ (90), 194 $[M - H]^+$ (100), 118 $[M - C_6H_5]^+$ (34). **HRMS** (EI-magnetic sector) calcd for $C_{14}H_{13}N$ $[M- H]^+$ 195.1043, found 195.1039.

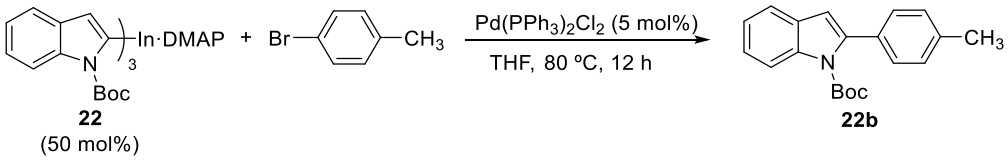
***tert*-Butyl 2-(4-acetylphenyl)-1*H*-indole-1-carboxylate (22a).** [223]



Following the general procedure, the reaction of 4-bromoacetophenone (99 mg, 0.5 mmol) with **22** (253 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 10:90), 142 mg of **22a** (85%) as a yellow solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.23 (d, *J* = 8.34 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 2H), 7.61–7.49 (m, 3H), 7.41–7.23 (m, 2H), 6.64 (s, 1H), 2.65 (s, 3H), 1.36 (s, 9H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 197.5 (C), 150.0 (C), 139.6 (C), 139.3 (C), 137.7 (C), 136.0 (C), 129.1 (C), 128.7 (2 × CH), 127.8 (2 × CH), 124.9 (CH), 123.2 (CH), 120.8 (CH), 115.3 (CH), 111.1 (CH), 84.0 (C), 27.7 (3 × CH_3), 26.7 (CH_3). **MS** (EI) *m/z* 335 $[M]^+$ (16), 235 $[M - C_5H_9O_2]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{21}H_{21}NO_3$ $[M]^+$ 335.1516, found 335.1514.

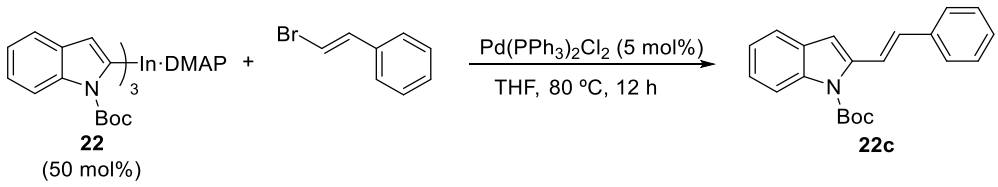
***tert*-Butyl 2-(*p*-tolyl)-1*H*-indole-1-carboxylate (22b).**[217]

223 M. A. Pena, J. Pérez Sestelo, L. A. Sarandeses, *J. Org. Chem.* **2007**, *72*, 1271–1275.



Following the general procedure, the reaction of 1-bromo-4-methylbenzene (86 mg, 0.5 mmol) with **22** (253 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 10:90), 126 mg of **22b** (82%) as a yellow solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ8.25 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 7.5 Hz, 1H), 7.40–7.22 (m, 6H), 6.57 (s, 1H), 2.45 (s, 3H), 1.39 (s, 9H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ150.3 (C), 140.7 (C), 137.41 (C), 137.38 (C), 132.0 (C), 129.3 (C), 128.6 (2 × CH), 128.5 (2 × CH), 124.1 (CH), 122.9 (CH), 120.4 (CH), 115.2 (CH), 109.7 (CH), 83.4 (C), 27.6 (3 × CH_3), 21.3 (CH_3). **MS** (EI) *m/z* 307 $[M]^+$ (22), 207 $[M - C_5H_9O_2]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{20}H_{21}NO_2$ $[M]^+$ 307.1567, found 307.1572.

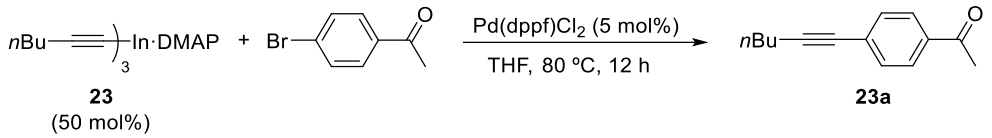
***tert*-Butyl (*E*)-2-styryl-1*H*-indole-1-carboxylate (22c).**[224]



Following the general procedure, the reaction of β-bromostyrene (92 mg, 0.5 mmol) with **22** (253 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 5:95), 141 mg of **22c** (88%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ8.17 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 16.4 Hz, 1H), 7.60–7.53 (m, 3H), 7.40 (t, J = 7.2 Hz, 2H), 7.35–7.22 (m, 3H), 6.89 (s, 1H), 1.74 (s, 9H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ150.7 (C), 139.6 (C), 137.2 (C), 137.0 (C), 130.6 (CH), 129.5 (C), 128.7 (2 × CH), 127.8 (CH), 126.7 (2 × CH), 124.2 (CH), 123.0 (CH), 120.8 (CH), 120.3 (CH), 115.7 (CH), 106.7 (CH), 84.1 (C), 28.4 (3 × CH_3). **HRMS** (EI-magnetic sector) calcd for $C_{21}H_{21}NO_2$ $[M]^+$ 319.1567, found 319.1574.

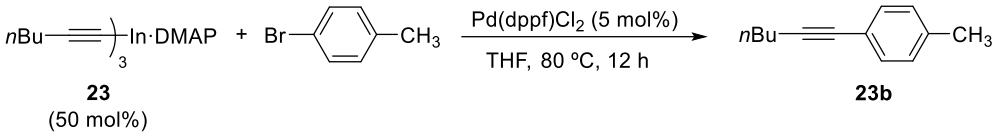
1-(4-(Hex-1-yn-1-yl)phenyl)ethan-1-one (23a).[225]

224 K. Masuda, T. Ohmura, M. Suginome, *Organometallics* **2011**, *30*, 1322–1325.
225 G. A. Molander, B. W. Katona, F. Machrouhi, *J. Org. Chem.* **2002**, *67*, 8416–8423.



Following the general procedure, the reaction of 4-bromoacetophenone (99 mg, 0.5 mmol) with **23** (152 mg, 0.25 mmol) and Pd(dppf)Cl_2 (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 5:95), 92 mg of **23a** (92%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.88 (d, *J* = 8.5Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 2.56 (s, 3H), 2.42 (t, *J* = 6.97 Hz, 2H), 1.66–1.40 (m, 4H), 0.94 (t, *J* = 7.3 Hz, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 193.3 (C), 135.6 (C), 131.6 (2 × CH), 129.1 (C), 128.1 (2 × CH), 94.3 (C), 80.1 (C), 30.6 (CH_2), 26.5 (CH_3), 22.0 (CH_2), 19.2 (CH_2), 13.6 (CH_3). **MS** (EI) *m/z* 200 $[M]^+$ (31), 185 $[M - CH_3]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{14}H_{16}O$ $[M]^+$ 200.1196, found 200.1196.

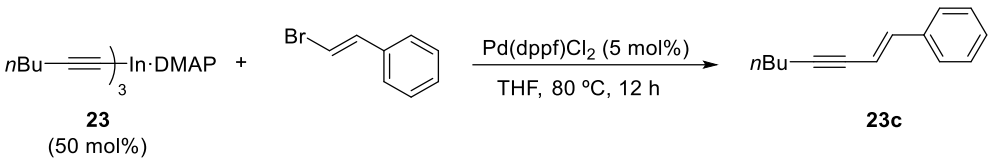
1-(Hex-1-yn-1-yl)-4-methylbenzene (23b).[226]



Following the general procedure, the reaction of 1-bromo-4-methylbenzene (86 mg, 0.5 mmol) with **23** (152 mg, 0.25 mmol) and Pd(dppf)Cl_2 (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 1:99), 80 mg of **23b** (93%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.31 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 2.42 (t, *J* = 6.9 Hz, 2H), 2.34 (s, 3H), 1.67–1.43 (m, 4H), 0.97 (t, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 137.3 (C), 131.4 (2 × CH), 128.9 (2 × CH), 121.0 (C), 89.6 (C), 80.6 (C), 30.9 (CH_2), 22.0 (CH_2), 21.4 (CH_3), 19.1 (CH_2), 13.6 (CH_3). **MS** (EI) *m/z* 172 $[M]^+$ (44), 157 $[M - CH_3]^+$ (55), 129 $[M - C_3H_7]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{13}H_{16}$ $[M]^+$ 172.1247, found 172.1239.

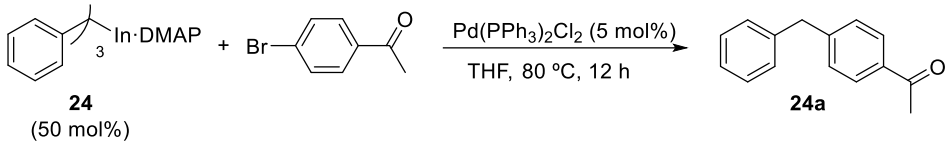
(*E*)-Oct-1-en-3-yn-1-ylbenzene (23c).[227]

226 S. Kankala, R. Vadde, C. S. Vasam, *Org. Biomol. Chem.* **2011**, *9*, 7869–7876.
227 Y.-Y. Lin, Y.-J. Wang, J.-H. Cheng, C.-F. Lee, *Synlett* **2012**, *23*, 930–934.



Following the general procedure, the reaction of β-bromostyrene (92 mg, 0.5 mmol) with **23** (152 mg, 0.25 mmol) and $Pd(dppf)Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 2:98), 74 mg of **23c** (80%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.41–7.21 (m, 5H), 6.87 (d, *J* = 16.2 Hz, 1H), 6.16 (dt, *J* = 16.2, 2.3 Hz, 1H), 2.38 (td, *J* = 6.9, 2.2 Hz, 2H), 1.63–1.38 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 139.9 (CH), 136.6 (C), 128.6 (2 × CH), 128.2 (CH), 126.0 (2 × CH), 108.9 (CH), 93.0 (C), 79.7 (C), 30.9 (CH_2), 22.0 (CH_2), 19.3 (CH_2), 13.6 (CH_3). **MS** (EI) *m/z* 184 $[M]^+$ (63), 141 $[M - C_3H_7]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{14}H_{16}$ $[M]^+$ 184.1247, found 184.1239.

1-(4-Benzylphenyl)ethan-1-one (24a).[228]

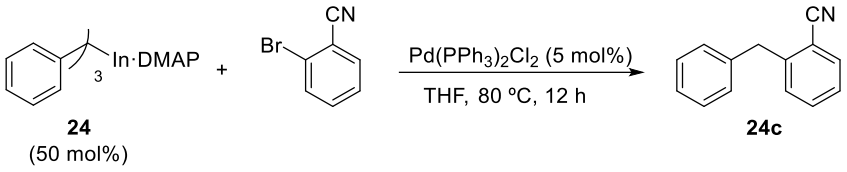


Following the general procedure, the reaction of 4-bromoacetophenone (99 mg, 0.5 mmol) with **24** (159 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 5:95), 71 mg of **24a** (68%) as a colorless solid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.90 (d, *J* = 8.3 Hz, 2H), 7.35–7.16 (m, 7H), 4.05 (s, 2H), 2.59 (s, 3H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 197.8 (C), 146.8 (C), 140.0 (C), 135.2 (C), 129.1 (2 × CH), 128.9 (2 × CH), 128.6 (4 × CH), 126.4 (CH), 41.9 (CH_2), 26.6 (CH_3). **MS** (EI) *m/z* 210 $[M]^+$ (81), 195 $[M - CH_3]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{15}H_{14}O$ $[M]^+$ 210.1039, found 210.1037.

1-(4-Benzylphenyl)ethan-1-one (24c).[229]

228 G. A. Molander, T. Ito, *Org. Lett.* **2001**, *3*, 393–396.

229 T. Itou, Y. Yoshimi, T. Morita, Y. Tokunaga, M. Hatanaka, *Tetrahedron* **2009**, *65*, 263–269.



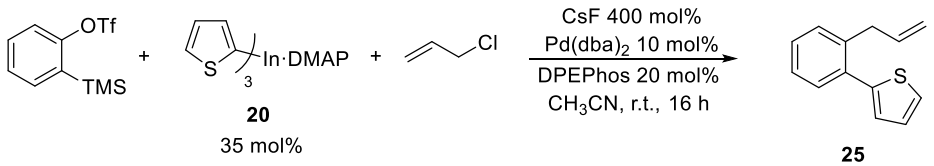
24 (50 mol%) **24c**

Following the general procedure, the reaction of 2-bromobenzonitrile (91 mg, 0.5 mmol) with **24** (159 mg, 0.25 mmol) and $Pd(PPh_3)_2Cl_2$ (18 mg, 0.025 mmol) afforded, after purification by column chromatography (EtOAc/hexane 10:90), 69 mg of **24c** (71%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.65 (d, *J* = 7.7 Hz, 1H), 7.52 (td, *J* = 7.7, 1.4 Hz, 1H), 7.38–7.21 (m, 7H), 4.23 (s, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 145.0 (C), 138.8 (C), 132.92 (CH), 132.91 (CH), 130.1 (CH), 129.0 (2 × CH), 128.7 (2 × CH), 126.8 (CH), 126.7 (CH), 118.2 (C), 112.6 (C), 40.2 (CH_2). **MS** (EI) *m/z* 193 $[M]^+$ (100). **HRMS** (EI-magnetic sector) calcd for $C_{14}H_{11}N$ $[M]^+$ 193.0886, found 193.0888.

General procedure for the palladium-catalyzed three-component reaction of arynes, R_3In·DMAP reagents, and allyl chloride.

To a suspension of cesium fluoride (204 mg, 1.34 mmol), $Pd(dba)_2$ (19 mg, 0.0336 mmol), and DPEPhos (36 mg, 0.0672 mmol) in CH_3CN (8 mL), solid triorganoindium reagent (0.118 mmol), allyl chloride (0.030 mL, 0.370 mmol) and aryne precursor (0.336 mmol) were sequentially added. After the reaction was stirred overnight at rt, the solvent was eliminated under reduced pressure and the resulting residue was extracted with AcOEt (20 mL), washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo, to afford after purification by flash column chromatography the corresponding products.

2-(2-allylphenyl)thiophene (25).[195a]

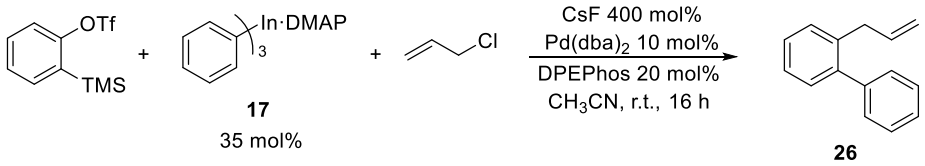


20 35 mol% **25**

Following the general procedure, the reaction of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (100 mg, 0.336 mmol) and **20** (57 mg, 0.118 mmol) afforded after purification by column chromatography with *n*-hexane, 42 mg (62%) of **25** as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.43 (d, *J* = 7.4 Hz, 1H), 7.38–7.23 (m, 4H), 7.13–7.03 (m, 2H), 6.07–5.89 (m, 1H), 5.08 (dd, *J* = 10.1, 1.5 Hz, 1H), 4.98 (dd,

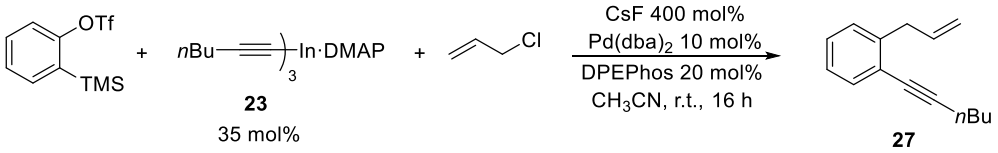
J = 17.0, 1.5 Hz, 1H), 3.51 (dt, *J* = 6.2, 1.6 Hz, 2H). **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 75 MHz) δ142.7 (C), 138.3 (C), 137.7 (CH), 134.3 (C), 131.2 (CH), 130.2 (CH), 128.2 (CH), 127.2 (CH), 126.7 (CH), 126.3 (CH), 125.4 (CH), 116.1 (CH_2), 37.9 (CH_2). **HRMS** (EI-magnetic sector) *m/z* calcd for $C_{13}H_{12}S$ $[M]^+$ 200.0654, found 200.0655.

2-allyl-1,1'-biphenyl (26).[201a]



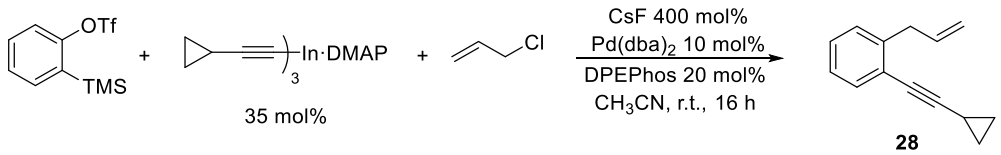
Following the general procedure, the reaction of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (100 mg, 0.336 mmol) and **17** (55 mg, 0.118 mmol) afforded after purification by column chromatography with *n*-hexane, 35 mg (54%) of **26** as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ7.47–7.23 (m, 9H), 5.99–5.85 (m, 1H), 5.04 (dd, *J* = 10.1, 1.8 Hz, 1H), 4.94 (dd, *J* = 17.0, 1.8 Hz, 1H), 3.37 (d, *J* = 6.4 Hz, 2H). **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 75 MHz) δ142.1 (C), 141.8, (C), 137.9 (CH), 137.3 (C), 130.2 (CH), 129.8 (CH), 129.4 (2 × CH), 128.1 (2 × CH), 127.5 (CH), 127.0 (CH), 126.2 (CH), 115.9 (CH_2), 37.6 (CH_2). **HRMS** (EI-magnetic sector) *m/z* calcd for $C_{15}H_{14}$ $[M]^+$ 194.1090, found 194.1091.

1-allyl-2-(hex-1-yn-1-yl)benzene (27).[201b]



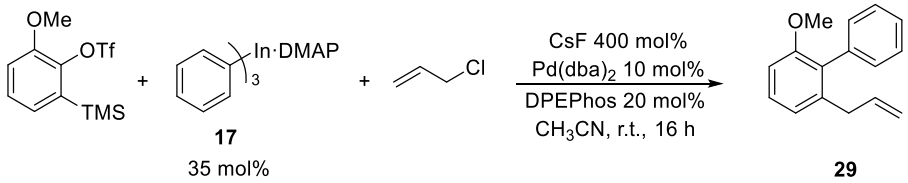
Following the general procedure, the reaction of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (100 mg, 0.336 mmol) and **23** (57 mg, 0.118 mmol) afforded after purification by column chromatography with *n*-hexane, 26 mg (39%) of **27** as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ7.41–7.35 (m, 1H), 7.25–7.10 (m, 3H), 6.10–5.90 (m, 1H), 5.14–5.01 (m, 2H), 3.55 (d, *J* = 6.7 Hz, 2H), 2.45 (t, *J* = 6.8 Hz, 2H), 1.68–1.43 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H). **$^{13}C\{^{1}H\}$ NMR** ($CDCl_3$, 75 MHz) δ141.9 (C), 137.0 (CH), 132.3 (CH), 128.7 (CH), 127.8 (CH), 126.1 (CH), 123.7 (C), 115.8 (CH_2), 94.5 (C), 79.2 (C), 38.9 (CH_2), 31.1 (CH_2), 22.2 (CH_2), 19.4 (CH_2), 13.8 (CH_3). **HRMS** (EI-magnetic sector) *m/z* calcd for $C_{15}H_{18}$ $[M]^+$ 198.1403, found 198.1398.

1-allyl-2-(cyclopropylethynyl)benzene (28).



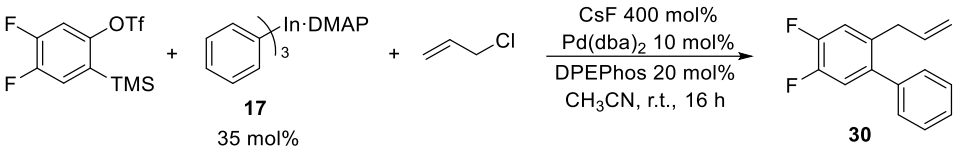
Following the general procedure, the reaction of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (100 mg, 0.336 mmol) and tris(cyclopropylethynyl)indium·DMAP (51 mg, 0.118 mmol) afforded after purification by column chromatography with *n*-hexane, 26 mg (43%) of **28** as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.41–7.34 (m, 1H), 7.24–7.07 (m, 3H), 6.08–5.88 (m, 1H), 5.15–5.02 (m, 2H), 3.53 (dt, *J* = 6.8, 1.5 Hz, 2H), 1.56–1.43 (m, 1H), 0.95–0.74 (m, 4H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 142.0 (C), 136.9 (CH), 132.3 (CH), 128.7 (CH), 127.8 (CH), 126.1 (CH), 123.5 (C), 115.9 (CH_2), 97.6 (C), 74.3 (C), 38.89 (CH_2), 38.88 (CH), 8.9 (2 × CH_2). **HRMS** (EI-magnetic sector) *m/z* calcd for $C_{14}H_{14}$ $[M]^+$ 182.1090, found 182.1081.

2-allyl-6-methoxy-1,1'-biphenyl (29).



Following the general procedure, the reaction of 2-methoxy-6-(trimethylsilyl)phenyl trifluoromethanesulfonate (110 mg, 0.336 mmol) and **17** (55 mg, 0.118 mmol) afforded after purification by column chromatography (Et_2O/*n*-hexane 0.5/99.5) 21 mg (31%) of **29** as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.42–7.29 (m, 5H), 7.27–7.20 (m, 1H), 6.93–6.85 (m, 2H), 6.04–5.86 (m, 1H), 4.93 (dd, *J* = 10.1, 1.7 Hz, 1H), 4.79 (dd, *J* = 17.1, 1.7 Hz, 1H), 3.87 (s, 3H), 3.31 (dt, *J* = 5.9, 1.6 Hz, 2H). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 143.7 (C), 141.8 (C), 137.6 (CH), 129.4 (2 × CH), 129.0 (C), 128.0 (2 × CH), 127.0 (CH), 126.8 (CH), 122.6 (CH), 114.6 (CH_2), 109.5 (CH), 55.8 (CH_3), 31.7 (CH_2). **HRMS** (EI-magnetic sector) *m/z* calcd for $C_{16}H_{16}O$ $[M]^+$ 224.1196, found 224.1192.

2-allyl-4,5-difluoro-1,1'-biphenyl (30).

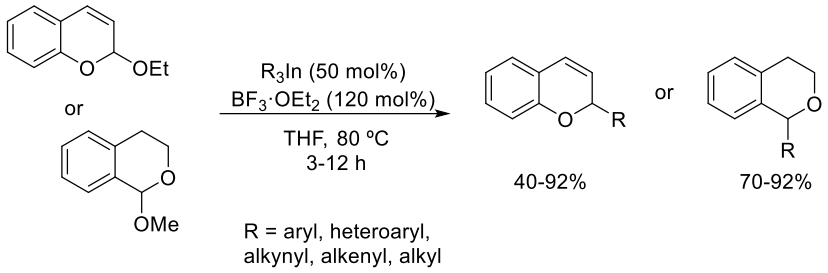


Following the general procedure, the reaction of 4,5-difluoro-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (112 mg, 0.336 mmol) and **17** (55 mg, 0.118 mmol) afforded after purification by column chromatography with *n*-hexane, 32 mg (46%) of **30** as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.48–7.37 (m, 3H), 7.32–7.24 (m, 2H), 7.17–7.01 (m, 2H), 5.94–5.77 (m, 1H), 5.08 (dd, *J* = 10.1, 1.5 Hz, 1H), 4.96 (dd, *J* = 17.0, 1.7 Hz, 1H), 3.28 (d, *J* = 6.3 Hz, 2H).). **^{13}C{^{1}H} NMR** ($CDCl_3$, 75 MHz) δ 149.6 (dd, *J* = 245.9, 12.3 Hz, C), 148.5 (dd, *J* = 245.3, 12.5 Hz, C), 139.8 (d, *J* = 1.4 Hz, C), 138.7 (dd, *J* = 5.6, 3.6 Hz, C), 136.9 (CH), 134.2 (dd, *J* = 5.4, 3.6 Hz, C), 129.2 (2 × CH), 128.4 (2 × CH), 127.6 (CH), 118.7 (d, *J* = 16.8 Hz, CH), 118.2 (d, *J* = 16.8 Hz, CH), 116.7 (CH_2), 36.9 (CH_2). **HRMS** (EI-magnetic sector) *m/z* calcd for $C_{15}H_{11}F_2$ $[M]^+$ 230.0902, found 230.0902.

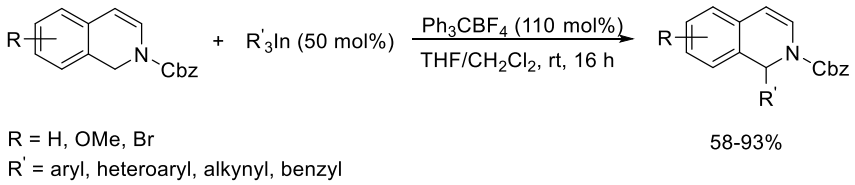
Conclusions

As a result of the research work conducted throughout this Thesis, the following general conclusions have been reached:

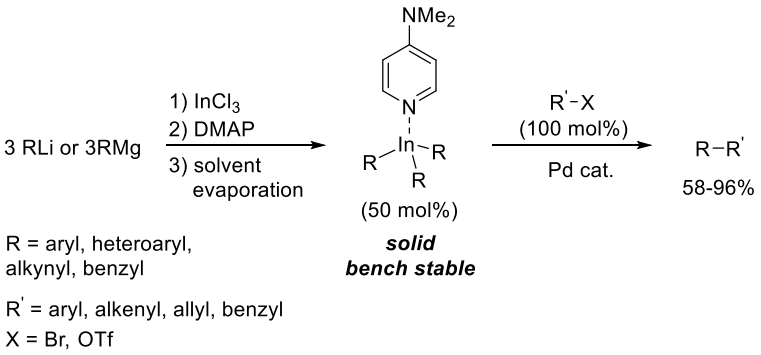
1. A new transition-metal-free cross-coupling reaction of triorganoindium reagents with chromene and isochroman acetals mediated by $BF_3{\cdot}OEt_2$ has been developed. The reaction afforded 2-substituted chromenes and 1-substituted isochromans, respectively in good yields. The reaction proceeds with a variety of triorganoindium reagents (aryl, heteroaryl, alkynyl, alkenyl, alkyl) using only 50 mol% of the organometallic, thus demonstrating the efficiency of these species. Preliminary mechanistic studies show the reaction is likely to proceed via an oxonium intermediate.



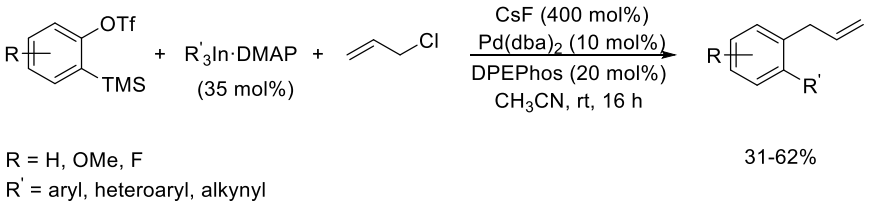
2. A new oxidative coupling of triorganoindium reagents with *N*-Cbz-tetrahydroisoquinolines in the presence of Ph_3CBF_4 has been developed. The reaction afforded the corresponding 1-substituted tetrahydroisoquinolines in good yields upon using only 50 mol% of the triorganoindium reagents. Mechanist studies suggest a hydride abstraction by the oxidant to generate an iminium ion that reacted with the indium reagents. The synthetic utility of the reaction was further established by its application to the synthesis of aporphine alkaloid (±) Nuciferine.



3. Bench-stable solid triorganoindium compounds have been prepared by coordination with 4-dimethylaminopyridine (DMAP). The solid R_3In·DMAP complexes are obtained from the corresponding solution of R_3In in quantitative yield and can be stored up to several weeks. These reagents show excellent reactivity in palladium-catalyzed cross-coupling reactions with organic electrophiles.



4. The newly developed solid triorganoindium reagents have been employed in a palladium-catalyzed reaction with aryne precursors. This constitutes the first example of a reaction involving indium organometallics and aryne species. In this process, two new carbon-carbon bonds are formed in a single synthetic step.



Annex I.

Summary in Spanish.

Introducción.

Esta Tesis Doctoral se enmarca dentro de un proyecto que tiene como objetivo lograr el desarrollo de nuevas aplicaciones para los compuestos organometálicos de indio en Síntesis Orgánica. En este sentido, a lo largo de las últimas dos décadas ha habido un incremento constante en el uso de los organometálicos de indio en diferentes tipos de reacciones dentro de la Química Orgánica, incluyendo reacciones de adición a electrófilos de distinta naturaleza, reacciones de acoplamiento cruzado catalizadas por metales de transición o en reacciones de activación de enlaces múltiples.[18] El desarrollo de métodos eficaces y simples para la preparación de organometálicos de indio ha hecho posible la generalización de su uso y por tanto el desarrollo de un importante número de nuevas metodologías sintéticas.[5,6] Los compuestos organoíndicos poseen una serie de propiedades que los hacen especialmente atractivos frente a otros compuestos organometálicos, como por ejemplo la elevada quimioselectividad que muestran, derivada de su baja nucleofilia, la cual permite llevar a cabo reacciones en presencia de grupos funcionales sensibles. Otras características igualmente importantes son la baja toxicidad de los compuestos de indio, o la alta economía atómica en el caso de los compuestos triorganoíndicos, donde es posible la transferencia de los tres grupos orgánicos enlazados al centro metálico.

Los compuestos triorganoíndicos han encontrado su uso más importante en la reacción de acoplamiento cruzado catalizada por metales de transición, descubierta en 1999 por el grupo de los Profs. Luis Sarandeses y José Pérez Sestelo.[7] Desde entonces se han utilizado sobre todo en reacciones catalizadas por Pd con una amplia variedad de electrófilos incluyendo haluros arílicos o heteroarílicos, bromuros bencílicos, cloruros de ácido, o haluros de alquenilo, entre otros.[21-35] Asimismo, la variedad de grupos orgánicos que pueden transferirse al electrófilo es también notable, incluyendo aromáticos, heteroaromáticos, alquinílicos, alquílicos, o alquenílicos. Muchas de estas reacciones pueden llevarse a cabo empleando una cantidad subestequiométrica del reactivo triorganoíndico, lo que indica que los tres grupos orgánicos unidos al indio se transfieren en la reacción, poniendo de manifiesto la elevada economía atómica del proceso.[7,20] No obstante, pese a la versatilidad y

eficiencia de los compuestos triorganoíndicos, existen aún ciertas limitaciones en cuanto a su uso, como por ejemplo la sensibilidad a la humedad y al oxígeno que hace necesaria su preparación poco antes de emplearse en las reacciones y que dificulta su almacenamiento. Por otro lado, la gran mayoría de aplicaciones de los compuestos triorganoíndicos se basan exclusivamente en reacciones catalizadas por metales de transición, y prácticamente no se han desarrollado métodos alternativos. Por todo ello, el trabajo desarrollado en esta Tesis Doctoral busca dar respuesta a dichas limitaciones y ampliar por tanto la utilidad de los compuestos triorganoíndicos en el ámbito de la Química Orgánica. En primer lugar, se aborda el desarrollo de nuevas metodologías con compuestos triorganoíndicos en ausencia de metales de transición, enfocadas hacia la funcionalización de moléculas heterocíclicas. En segundo lugar, se estudia el desarrollo de reactivos triorganoíndicos con mayor estabilidad y más fácil manejo, compatibles con su uso en diversas condiciones de reacción.

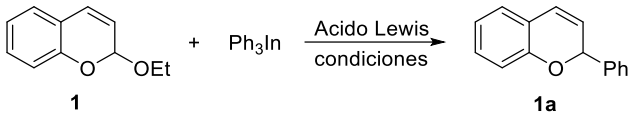
Reacciones de Acoplamiento Cruzado de Reactivos Triorganoíndicos con Cromenos, Isocromanos y Tetrahidroisoquinolinas en Ausencia de Metales de Transición.

En los últimos años se han dado a conocer una serie de nuevas metodologías de reacción basadas en la generación de intermedios oxonio o iminio altamente electrofílicos que reaccionan con nucleófilos de distinta naturaleza (incluyendo organometálicos de magnesio, zinc, estaño u organoboranos) permitiendo la generación de nuevos enlaces carbono-carbono.[94-102] Este tipo de reacciones pueden ser llevadas a cabo mediante catálisis con metales de transición, o bien en ausencia de los mismos bajo activación con ácidos de Lewis, condiciones oxidantes o fotocatálisis. En este contexto y teniendo en cuenta los antecedentes al respecto, los compuestos triorganoíndicos se presentan como candidatos idóneos para desarrollar este tipo de reacciones en ausencia de metales de transición.

Por todo ello, decidimos investigar la reacción de acetales de cromeno con reactivos triorganoíndicos bajo activación con ácidos de Lewis. El cromeno es un motivo de estructural de marcada relevancia, puesto que se encuentra presente tanto en fármacos como en productos naturales con actividad biológica. La reacción del acetal

de cromeno **1** con trifenilindio se estudió en presencia de varios ácidos de Lewis (Tabla 1).

*Tabla 1. Cribado de ácidos de Lewis y optimización de las condiciones para la reacción de **1** con trifenilindio.*



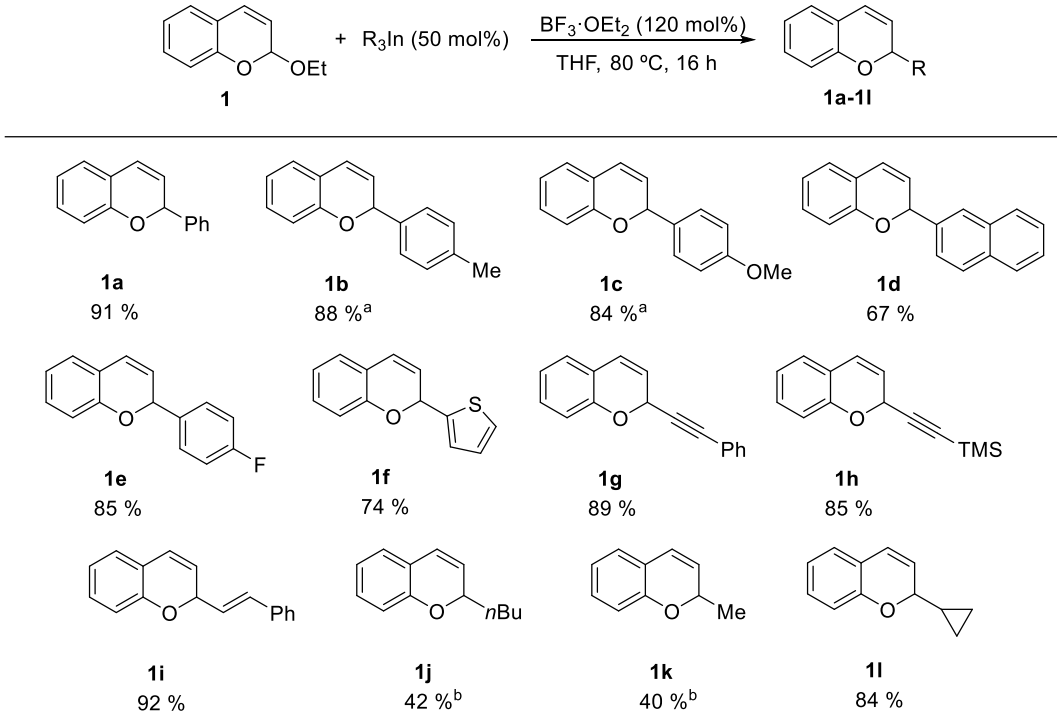
1 **1a**

Entr.	mol % Ph_3In	Ácido de Lewis (mol%)	Cond. Reacción	Rend. (%)[a]
1	50	–	THF, t.a. to 80 °C, 16 h	–
2	50	TMSOTf (120)	THF, 80 °C, 16 h	–
3	50	$Cu(OTf)_2$ (120)	THF, 80 °C, 16 h	–
4	50	$Yb(OTf)_3$ (120)	THF, 80 °C, 16 h	33
5	50	$InBr_3$ (120)	THF, 80 °C, 16 h	6
6	100	$BF_3{\cdot}OEt_2$ (200)	THF, t.a, 16 h	92
7	100	$BF_3{\cdot}OEt_2$ (120)	THF, r.t, 16 h	92
8	40	$BF_3{\cdot}OEt_2$ (120)	THF, r.t., 16 h	56
9	40	$BF_3{\cdot}OEt_2$ (120)	THF, 80 °C, 16 h	65
10	50	$BF_3{\cdot}OEt_2$ (120)	THF, 80 °C, 16 h	91
11	50	$BF_3{\cdot}OEt_2$ (20)	THF, 80 °C, 16 h	10

[a] Rendimiento calculado en función del producto aislado.

Se observó que la reacción tiene lugar al emplear $BF_3{\cdot}OEt_2$, y que, tras una optimización de las condiciones de reacción, es posible llevarla a cabo en buen rendimiento empleando sólo un 50 mol% del reactivo triorganoíndico. Este resultado indica que más de un grupo orgánico enlazado al indio es transferido durante el proceso. Con las condiciones de reacción optimizadas, se estudió la versatilidad de la reacción empleando diferentes R_3In (Figura 1). Los resultados obtenidos indican que la reacción puede llevarse a cabo con diferentes tipos de R_3In, permitiendo la transferencia de grupos aromáticos, heteroaromáticos, alquinílicos, alquenínilicos e incluso alquílicos. Cuando la reacción se llevó a cabo con grupos aromáticos ricos en electrones fue posible obtener un elevado rendimiento incluso a temperatura ambiente (Figura 1, productos **1b** y **1c**). También es destacable que al llevar a cabo la reacción con el triorganoíndico alquenílico, se obtuvo el producto de reacción sin que se produjera isomerización del doble enlace (Figura 1, producto **1f**).

*Figura 1. Estudio de la reacción de **1** empleando diferentes reactivos triorganoíndicos.*

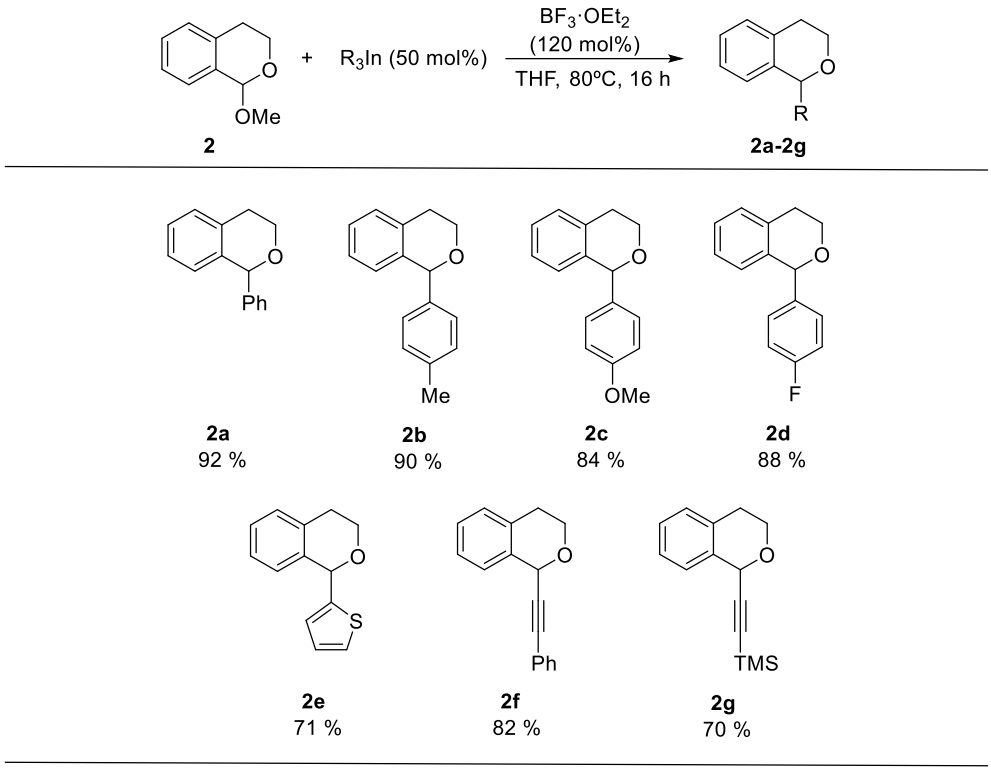


[a] Reacciones llevadas a cabo a t.a. [b] Regioisómero mayoriatario aislado, 65% rendiento total, ratio C-2/C-4 : 65/35.

Finalmente, en el caso de los triorganoíndicos alquílicos, trimetilindio y tributilindio, se observa pérdida de la regioselectividad en la reacción dando lugar a una mezcla del cromeno 2-substituido y 4-substituido aproximadamente en proporción 2:1 (Figura 1, productos **1j** y **1k**). Curiosamente, al emplear el reactivo triorganoíndico derivado del ciclopropilo, no se observa dicha pérdida de regioselectividad, quizá debido a la peculiar naturaleza del enlace en el anillo de ciclopropilo.

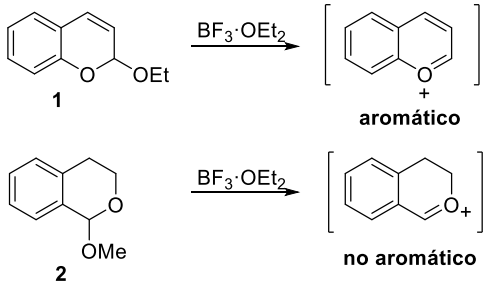
Una vez establecida la reacción para el acetal de cromeno, decidimos extender la metodología sintética a otro compuesto benzoheterocíclico igualmente relevante, el isocromano. La reacción del acetal de isocromano **2** con trifenilindio en presencia de $BF_3{\cdot}OEt_2$ dio lugar al producto de reacción esperado **2a** en buen rendimiento. Al igual que en el caso del acetal de cromeno, la reacción requiere de por lo menos una cantidad estequiométrica del ácido de Lewis. Empleando las condiciones de reacción ya optimizadas se llevó a cabo la reacción con diferentes reactivos triorganoíndicos (Figura 2). La reacción del acetal de isocromano con trifenilindio y otros reactivos triorganoíndicos arílicos condujo a los correspondientes 1-arilisocromanos en buenos rendimientos (Figura 2, **2a**-**2g**).

*Figura 2. Estudio de la reacción del acetal de isocromano **2** con diferentes reactivos triorganoínicos.*



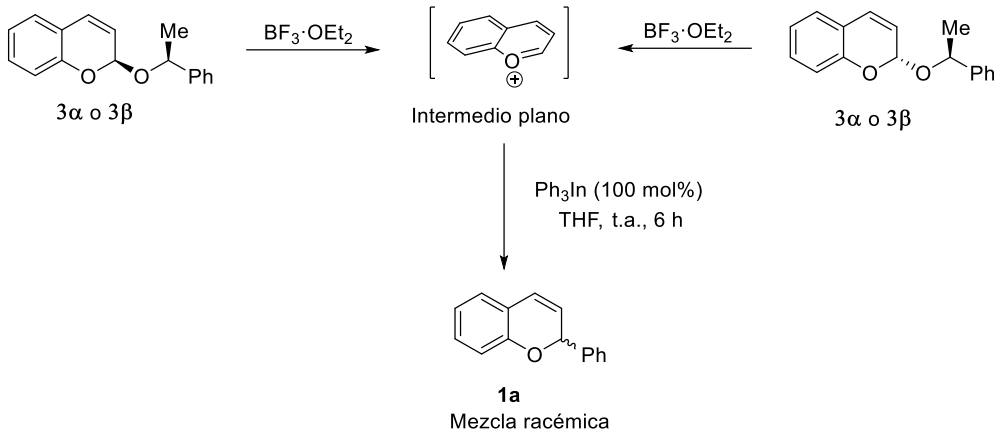
A partir de los resultados obtenidos, se observó que el acetal de isocromano presentó menor reactividad que el acetal de cromeno. En el caso del isocromano, fué necesario calentar a reflujo para que las reacciones tuvieran lugar incluso cuando se emplearon triorganoíndicos arílicos ricos en electrones. Además, la reacción no tuvo lugar con triorganoíndicos alquenílicos o alquílicos. La diferencia de reactividad podría explicarse por las diferencias entre los intermedios de reacción oxonio propuestos para ambos sustratos (Figura 3). En el caso del acetal de cromeno, la generación del intermedio oxonio está más favorecida porque se trata de una especie aromática, mientras que en el acetal de isocromano no.

*Figura 3. Intermedios de reacción propuestos para **1** y para **2**.*



Con el propósito de investigar el mecanismo de reacción, se diseñó un experimento basado en la reacción por separado de los dos disatereoisómeros del acetal de cromeno de *R*-1-feniletanol cada uno con el centro quiral en alfa al oxígeno definido (Figura 4).

Figura 4. Experimento con acetales de cromeno quirales.



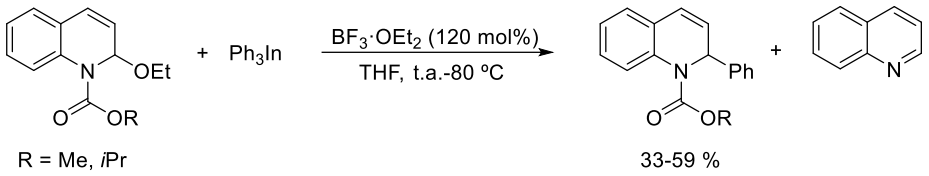
En cada caso, la reacción condujo a la mezcla racémica del producto, con lo cual podría afirmarse que la reacción transcurre a través de la especie de tipo oxonio propuesta, ya que el ataque del organometálico de indio puede tener lugar por cualquiera de las dos caras del intermedio.

Finalmente, y puesto que una importante proporción de los cromenos e isocromanos que existen como fármacos o como productos con actividad biológica relevante, se encuentran presentes como un único enantiómero, exploramos la posibilidad de llevar a cabo esta reacción de manera enantioselectiva. Para ello se llevó a cabo la reacción en presencia de varios ligandos quirales, aunque los resultados obtenidos no fueron los deseados, siendo imposible obtener excesos enantioméricos apreciables.

A continuación, decidimos también extender esta nueva reacción a sustratos benzoheterocíciclos nitrogenados. En esta familia de compuestos se encuentran un gran número de moléculas con interés biológico y aplicaciones terapéuticas y por tanto el desarrollo de nuevas metodologías constituye un campo de trabajo importante.[111] En consecuencia, ensayamos la reacción de reactivos triorganoíndicos promovida por $BF_3{\cdot}OEt_2$ estequiométrico sobre acetales mixtos de quinolina (Figura

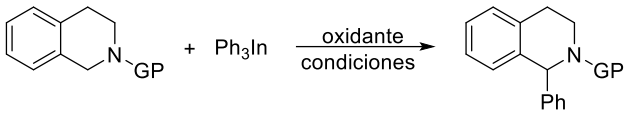
5). No obstante, observamos que, en vez de dar lugar al producto deseado, una parte significativa del compuesto de partida perdía el grupo protector para regenerar quinolina. Aumentar el impedimento estérico en el grupo protector o la variación de la temperatura en la reacción no consiguieron mitigar el problema.

Figura 5. Reacción de acetales mixtos de quinolina con Ph_3In mediante activación con $BF_3{\cdot}OEt_2$.



A raíz de estos resultados, planteamos una estrategia alternativa, basada en la activación C-H de la posición adyacente al nitrógeno en tetrahidroisoquinolinas *N*-protegidas mediante el uso de condiciones oxidantes. En años recientes, la funcionalización selectiva de la posición C-1 ha surgido como alternativa viable para la síntesis de tetrahidroisoquinolinas, llevada a cabo tanto en presencia como en ausencia de metales de transición.[120] De esta manera, se investigó la reacción de la tetrahidroisoquinolina con trifenilindio variando oxidantes, grupo protector y condiciones de reacción (Tabla 2). Las reacciones fueron llevadas a cabo en diclorometano o dicloroetano, usando THF como codisolvente, puesto que éste último es necesario en la preparación de los reactivos triorganoíndicos. Oxidantes como 2,3-dicloro-5,6-diciano-1,4-benzoquinona (DDQ) o derivados de iodo hipervalente (PIFA) no dieron lugar al producto de reacción (Tabla 2, entradas 1 y 2). En cambio, el uso del perclorato de tritilo condujo a la 1-fenil-tetrahidroisoquinolina **5a**, con un rendimiento del 56% (Tabla 2, entrada 3). Asimismo, el empleo de tetrafluoroborato de tritilo (comercialmente disponible, a diferencia del perclorato) proporcionó un rendimiento similar de **5a** (Tabla 2, entrada 4). No obstante, la variación de los tiempos de reacción, temperatura, cantidad de triorganoíndico o cantidad de oxidante, no mejoraron el rendimiento de la reacción (Tabla2, entradas 5-8). Cabe destacar el efecto del grupo protector en la reacción; ya que cuando se sustituyó el benciloxicarbonilo por el *tert*-butoxicarbonilo o por el tosilo, la reacción no tuvo lugar (Tabla 2, entradas 9 y 10).

Tabla 2. Optimización de las condiciones de reacción de la tetrahidroisoquinolina N-protegida con Ph_3In bajo codiciones oxidantes.

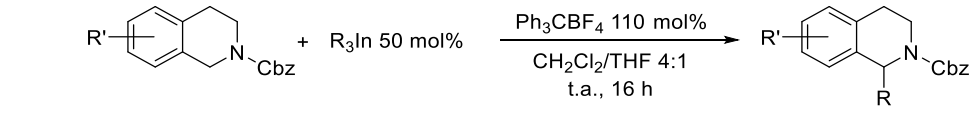


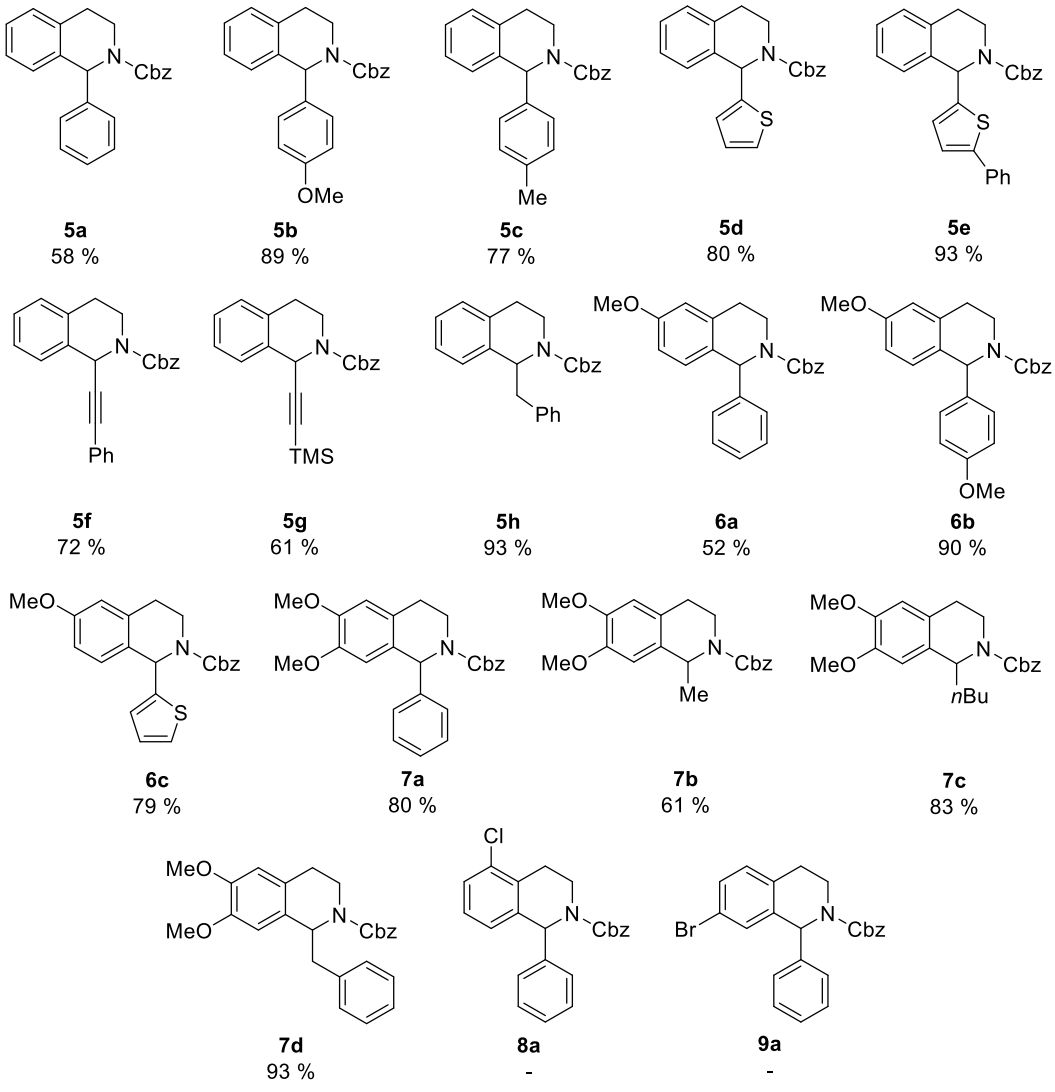
Entr.	Oxidante (mol%)	Ph_3In (mol%)	Grupo Protector	Condiciones	Rend.(%)[a]
1	DDQ (110)	50	Cbz	CH_2Cl_2/THF, t.a., 16 h	–
2	PIFA (110	50	Cbz	CH_2Cl_2/THF, t.a.,16 h	–
3	Ph_3CClO_4 (110)	50	Cbz	CH_2Cl_2/THF, t.a., 16 h	56
4	Ph_3CBF_4 (110)	50	Cbz	CH_2Cl_2/THF t.a., 16 h	58
5	Ph_3CBF_4 (110)	50	Cbz	CH_2Cl_2/THF, t.a.,72 h	44
6	Ph_3CBF_4 (110)	50	Cbz	DCE/THF, 80 °C, 16 h	52
7	Ph_3CBF_4 (110)	100	Cbz	CH_2Cl_2/THF, t.a., 16 h	66
8	Ph_3CBF_4 (110)	50	Cbz	CH_2Cl_2/THF, t.a., 16 h	51
9	Ph_3CBF_4 (110)	50	Boc	CH_2Cl_2/THF, t.a.,16 h	–
10	Ph_3CBF_4 (110)	50	Ts	CH_2Cl_2/THF, t.a.,16 h	–

[a] Rendimiento calculado en función del producto aislado.

Se estudió la reacción con distintos reactivos triorganoíndicos así como el efecto de diferentes sustituyentes en el anillo aromático de la tetrahidroisoquinolina (Figura 6). Al llevar a cabo la reacción con triorganoíndicos arílicos con grupos dadores en el anillo aromático, el rendimento de la reacción fue mayor (Figura 6, **5b** y **5c**). Asimismo, la reacción con reactivos triorganoíndicos derivados del tiofeno, 2-feniltiofeno, fenilacetileno, trimetilsililacetileno y bencilo dieron lugar a rendimientos también mayores que en el caso del trifenilindio (Figura 6, **5d**-**5h**). Al llevar a cabo la reacción con la 6-metoxi-tetrahidroisoquinolina **6** en presencia de varios reactivos triorganoíndicos aromáticos y heteroaromáticos los resultados fueron comparables a los obtenidos con **5** (Figura 6, **6a**-**6c**). Al emplear la 6,7-dimetoxi-tetrahidroisoquinolina **7**, se obtuvo un alto rendimiento con trifenilindio (Figura 6, **7a**) e incluso fue posible llevar a cabo la reacción con triorganoíndicos alquílicos (Figura, **7b** y **7c**). No obstante, la reacción con las tetrahidroisoquinolinas **8** y **9**, con grupos haluro en el anillo aromático, no tuvo lugar, recuperándose los compuestos de partida en cada caso. Estos resultados indican que la reactividad de la tetrahidroisoquinolina aumenta con la riqueza electrónica en el anillo aromático.

Figura 6. Estudio del efecto de diferentes reactivos triorganoíndicos y grupos funcionales en el rendimiento de la reacción de tetrahidroisoquinolinas.

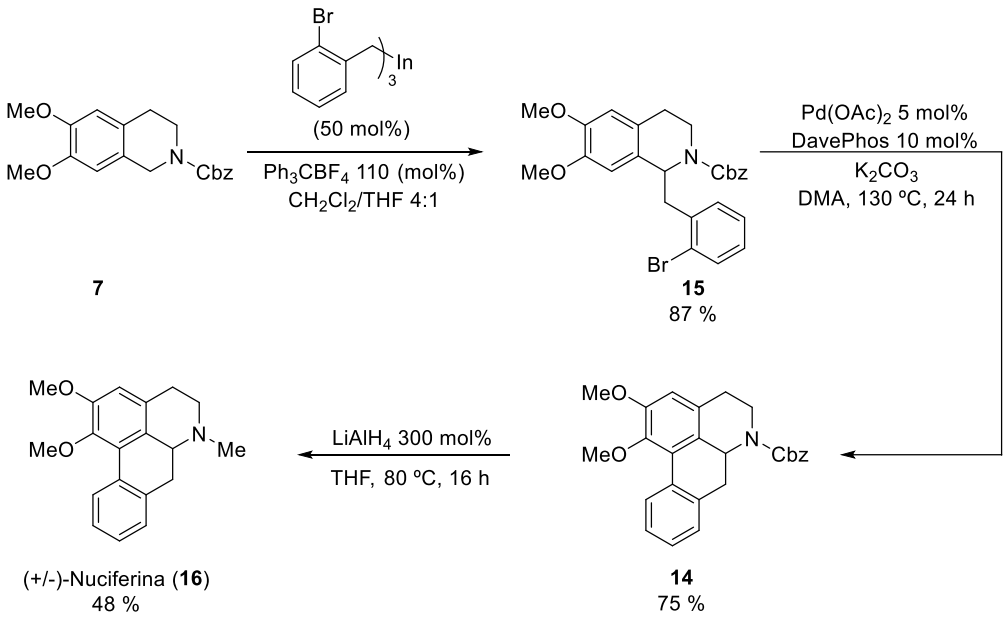




Los resultados muestran que es posible llevar a cabo la funcionalización de diversas tetrahidroisoquinolinas *N*-protegidas con reactivos triorganoíndicos bajo condiciones oxidantes y en ausencia de metales de transición. No es necesaria la presencia de un grupo saliente en el sustrato, la reacción transcurre directamente sobre el enlace C-H del carbono bencílico adyacente al átomo de nitrógeno. Los resultados muestran además que pueden alcanzarse buenos rendimientos con cantidades subestequiométricas del reactivo triorganoíndico, lo cual constituye un nuevo ejemplo de la alta economía atómica de estas especies.

Para demostrar la utilidad sintética de esta nueva reacción, decidimos abordar la síntesis de un producto natural, la Nuciferina,[135] alcaloide dibenzoquinolínico derivado de la planta *Nelumbo nucifera* con propiedades psicoactivas (Figura 7). Para ello, planteamos una ruta sintética de tres pasos que incluye la funcionalización del carbono C-1 de 6,7-dimetoxitetrahidroisoquinolina con un reactivo triorganoíndico en las condiciones de reacción optimizadas. La reacción con el reactivo triorganoíndico permitió instalar el grupo 2-bromobencilo en buen rendimiento dando lugar al compuesto **15**. A continuación se llevó a cabo una reacción de biarilación catalizada por Pd que dio lugar a la estructura tetracíclica de dibenzoisoquinolina **14**, y finalmente la reducción con $LiAlH_4$ condujo a la (±)Nuciferina (**16**).

Figura 7. Sintesis de (±)Nuciferina.



Como parte de nuestra investigación de la reactividad de tetrahidroisoquinolinas, decidimos emplear grupos protectores quirales con el objetivo de llevar a cabo la reacción de manera diasteroselectiva. Para ello se emplearon carbamatos derivados del (–)-mentol y el (–)-8-fenilmentol, aunque los excesos diastereoméricos no pasaron del 34% en el mejor de los casos, incluso llevando a cabo las reacciones a -78 °C.

Por último, se hicieron experimentos para estudiar el intermedio de reacción propuesto de tipo iminio. En este sentido, fue posible observar dicho intermedio mediante espectroscopia de RMN al tratar la tetrahidroisoquinolina con Ph_3CBF_4 en diclorometano deuterado. Asimismo, se comprobó que la adición de inhibidores radicalarios al medio de reacción no afectaba al transcurso de la misma, por lo que puede descartarse un posible mecanismo radicalario.

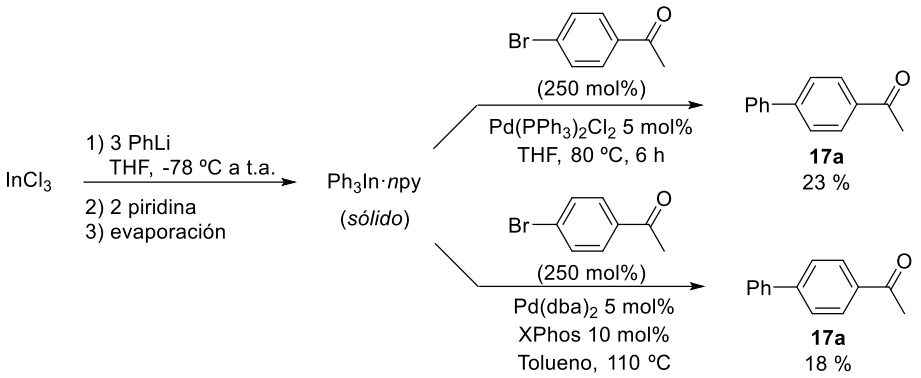
Síntesis de Reactivos Triorganoíndicos Sólidos y Estudio de la Reactividad en Reacciones de Acoplamiento Cruzado Catalizadas por Paladio.

Tal y como se ha mencionado ya anteriormente, los compuestos triorganoíndicos participan en reacciones de acoplamiento cruzado de forma eficiente con una amplia variedad de sustratos, mostrando elevada selectividad y tolerancia a distintos grupos funcionales. Sin embargo, existen ciertas limitaciones importantes en cuanto al uso de los compuestos triorganoíndicos, entre ellas el hecho de que éstos deben ser preparados poco antes de emplearse en las reacciones y siempre en disolventes como THF o Et_2O.[19,155] En algunos casos, como por ejemplo los organometálicos de zinc, se han desarrollado reactivos que son estables en ausencia de disolventes, que se pueden almacenar como sólidos fácilmente manipulables, e incluso en ausencia de atmósfera inerte.[156] En este trabajo se planteó el desarrollo de estrategias para la estabilización de reactivos triorganoíndicos, que faciliten su manejo y almacenamiento y que además permitan el empleo de condiciones de reacción hasta ahora incompatibles con los mismos.

La afinidad de los compuestos de In(III) por bases de Lewis con átomos dadores de nitrógeno o fósforo para dar lugar a complejos estables es conocida.[193] En la industria de semiconductores, la formación de aductos estables con aminas terciarias es una técnica habitual en la obtención de trimetilindio de alta pureza.[194] Asimismo, la coordinación con ligandos dadores de nitrógeno o fósforo ha permitido el aislamiento y elucidación estructural de organometálicos de In(III).[195] Teniendo en cuenta estos precedentes, decidimos investigar la preparación de reactivos triorganoíndicos de mayor estabilidad mediante formación de aductos con bases de Lewis adecuadas. Teniendo en cuenta la gran afinidad del indio por ligandos nitrogenados, se estudió

la adición de dos equivalentes de piridina a trifenilindio en disolución de THF (Figura 8).

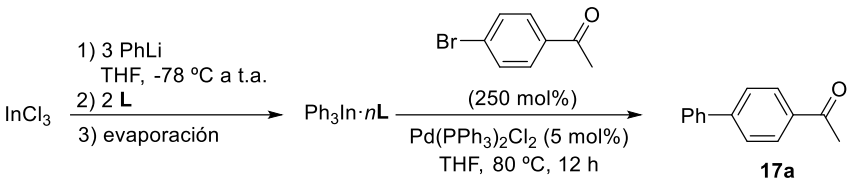
Figura 8. Aislamiento de un complejo de Ph_3In con piridina y posterior reacción de acoplamiento cruzado.



No se observó la formación de un precipitado en la disolución, pero la evaporación del disolvente dio lugar a un sólido, que pudo ser re-disuelto en THF o en tolueno y que resultó ser reactivo en una reacción de acoplamiento cruzado catalizada por paladio dando lugar a **17a** con un rendimiento moderado. Este resultado demostró que la coordinación con piridina permitía la obtención de un compuesto que podía aislarse como un sólido y que mantenía su reactividad en reacciones de acoplamiento cruzado.

A continuación, se estudió el efecto de diferentes piridinas a la hora de formar complejos estables y aislables con el trifenilindio (Tabla 3). El empleo de piridinas más impedidas estericamente condujo a rendimientos más bajos que en el caso de la piridina, probablemente debido a la formación de aductos menos estables con el indio (Tabla 3, entradas 3 y 4). El mejor resultado se obtuvo al emplear la 2-dimetilaminopiridina (DMAP) como ligando, que condujo a la obtención de **17a** en un 55% de rendimiento. Otras piridinas, con grupos sustractores de carga en el anillo aromático, no dieron lugar a compuestos aislables que mostraran reactividad en cross-coupling (Tabla 3, entradas 7 y 8).

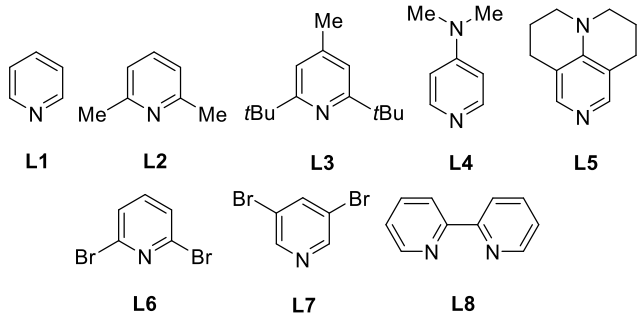
Tabla 3. Estudio del efecto de diferentes piridinas en la estabilización de Ph_3In.



17a

Entrada	Ligando	Rend. **17a** (%)[a]
1	–	–
2	**L1**	23
3	**L2**	15
4	**L3**	5
5	**L4**	55
6	**L5**	11
7	**L6**	–
8	**L7**	–
9	**L8**	–

[a]Rendimiento calculado en función del producto aislado.

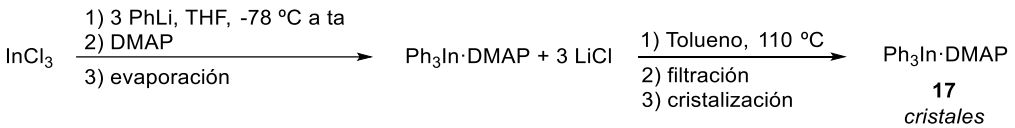


L1 **L2** **L3** **L4** **L5**

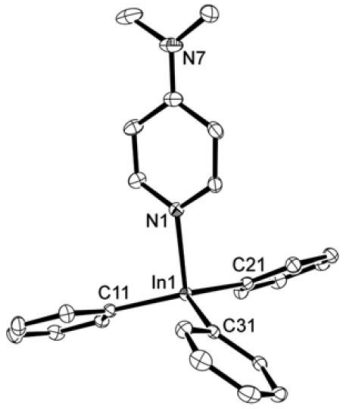
L6 **L7** **L8**

Para establecer la estructura del complejo formado por trifenilindio con DMAP, se obtuvieron cristales adecuados para difracción de rayos-X de monocristal a partir de una disolución de hexano/tolueno (Figura 9).

Figura 9. Obtención de cristales de Ph_3In·DMAP para difracción de rayos-X.



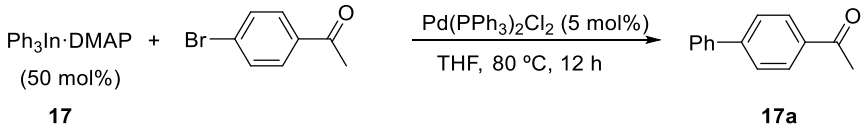
Los datos de espectroscopia de rayos-X indican que una molécula de DMAP se coordina al átomo de indio en una estructura piramidal trigonal distorsionada, en donde las distancias interatómicas In-C son de 2.17 Å y la distancia In-N es de 2.27 Å.



ORTEP con un 40 % de probabilidad de los elipsoides.

La formación de un complejo con DMAP permite aislar al trifenilindio como un sólido tras la evaporación del disolvente. Decidimos investigar durante cuánto tiempo permanecía siendo reactivo el Ph_3In·DMAP en reacciones de acoplamiento cruzado tras su preparación (Tabla 4). En estas reacciones, se empleó el sólido obtenido tras la evaporación del THF sin llevar a cabo ninguna purificación posterior.

Tabla 4. Reactividad en el tiempo de Ph_3In·DMAP.



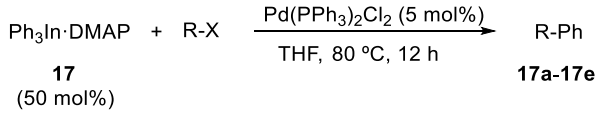
Entrada	Dias tras la preparación de **17**	Rend. **17a** (%)[a]
1	3	91
2	5	88
3	7	93
4	14	84
5	21	82
6	28	78
7	45[b]	95[b]

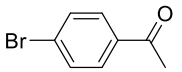
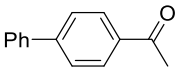
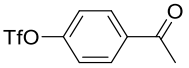
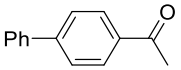
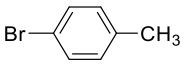
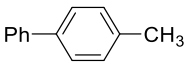
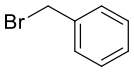
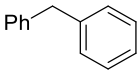
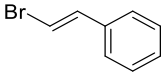
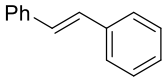
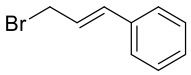
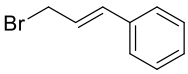
[a] Rendimiento calculado en función del producto aislado. [b] Reacción llevada a cabo con cristales purificados de **17**.

Sorprendentemente, el complejo siguió dando buenos rendimientos del producto de acoplamiento cruzado hasta cuatro semanas después de su preparación. Además, a la hora de llevar a cabo cada una de las reacciones, el triorganoíndico sólido se expuso al aire atmosférico sin que esto tuviera un efecto significativo en el rendimiento.

Se estudió la reacción catalizada por Pd del triorganoíndico sólido $Ph_3In{\cdot}DMAP$ con diferentes electrófilos con el objetivo de comparar su reactividad con la del trifenilindio preparado *in situ* en disolución de THF (Tabla 5).

*Tabla 5. Reactividad de **17** en reacciones de acoplamiento cruzado catalizadas por Pd con distintos electrófilos.*



Entrada	R-X	Producto	Rend. (%)[a]
1		 **17a**	91
2		 **17a**	92
3		 **17b**	94
4		 **17c**	81
5		 **17d**	88
6		 **17e**	87

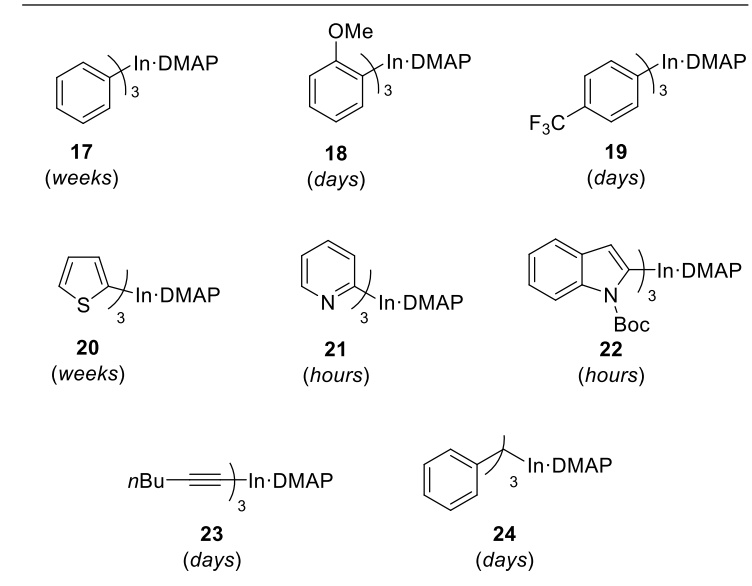
[a] Rendimiento calculado en función del producto aislado.

Los resultados fueron comparables a los reportados con el trifenilindio preparado *in situ.* La reacción tuvo lugar de forma satisfactoria con 4-bromotolueno, dando lugar al producto **17b** con un 92% de rendimiento (Tabla 5, entrada 3). El uso de triflato como grupo saliente condujo prácticamente al mismo de rendimiento de reacción que al emplear bromuro (Tabla 5, entrada 2). La reacción también tuvo lugar con bromuro de bencilo, obteniéndose el compuesto **17c** con un rendimiento del 81% (Tabla 5, entrada 4). Asimismo, la reacción de acoplamiento cruzado pudo llevarse a

cabo con un alqueno, el β-bromoestireno, y con bromuro de cinamilo, para dar lugar a los correspondientes productos **17d** y **17e** con rendimientos del 88% y 87% respectivamente (Tabla 5, entradas 5 y 6).

A continuación, decidimos extender la metodología a otros compuestos triorganoíndicos sólidos y estudiar tanto su estabilidad en el tiempo como su reactividad en reacciones de acoplamiento cruzado. Para ello, se prepararon otros triorganoíndicos arílicos, derivados del 2-anisol (**18**) y el 4-trifluorometilbenceno (**19**). A diferencia del $Ph_3In{\cdot}DMAP$, la reactividad de estos compuestos se redujo considerablemente al cabo de unos días después de su preparación. Por otro lado, el triorganoíndico sólido preparado a partir del tiofeno (**20**) demostró ser capaz de participar en reacciones de acoplamiento cruzado con 4-bromoacetofenona con altos rendimientos de manera consistente hasta casi cuatro semanas después de su preparación. En cambio, los triorganoíndicos sólidos preparados a partir de piridina (**21**) e indol (**22**), mantuvieron su reactividad apenas durante unas horas y además mostraron ser especialmente sensibles a la exposición al aire atmosférico.

Figura 10. Compuestos triorganoíndicos sólidos y su estabilidad.



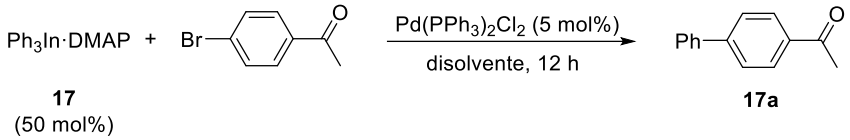
LiCl omitido para mayor claridad.

También se preparó un triorganoíndico sólido con un grupo alquino, derivado del 1-hexino (**23**) así como el reactivo derivado del tribencilindio (**24**). Al margen de las diferencias en la estabilidad, los compuestos sólidos triorganoíndicos reaccionaron

satisfactoriamente con bromuros arílicos, bencílicos, alquenílicos y alílicos, obteniéndose en la mayoría de los casos rendimientos semejantes a los obtenidos con los triorganoíndicos preparados *in situ*. Los resultados ponen de manifiesto la utilidad práctica de este nuevo tipo de reactivos organometálicos de indio.

Finalmente, se investigó la compatibilidad de los R_3In·DMAP en otros disolventes diferentes del THF. Para ello, se hizo reaccionar Ph_3In·DMAP con 4-bromoacetofenona empleando diferentes disolventes (Tabla 6). Aunque con rendimientos más bajos que en el caso de THF, la reacción pudo llevarse a cabo en tolueno y con varios disolventes halogenados. Curiosamente, el empleo de DMF condujo al producto de reacción con un rendimiento elevado (Tabla 6, entrada 5).

*Tabla 6. Reacciones de acoplamiento cruzado de **17** empleando diferentes disolventes.*



17
(50 mol%)

17a

Entrada	Disolvente	Temperatura (°C)	Rend. **17a** (%)[a]
1	tolueno	110	55
2	CH_2Cl_2	40	62
3	1,2-dicloroetano	80	64
4	1,1,2,2-tetracloroetano	110	45
5	DMF	120	93
6	CH_3CN	80	34

[a] Rendimiento calculado en función del producto aislado.

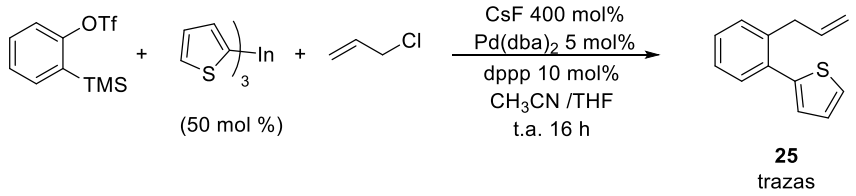
Una de las principales limitaciones en el uso de los compuestos triorganoíndicos ha sido la necesidad de emplear THF como disolvente, o por lo menos como co-disolvente, en el medio de reacción. Los resultados obtenidos demuestran que mediante el empleo de los R_3In·DMAP esta limitación puede superarse.

A raíz de estos resultados, decidimos explorar el uso de los R_3In·DMAP en reacciones donde las condiciones habituales de preparación de los compuestos triorganoíndicos resultan poco favorables. De esta manera, y en colaboración con el grupo de los Profs Dolores Pérez y Enrique Guitián de la Universidad de Santiago de Compostela, investigamos la reactividad de los R_3In·DMAP en presencia de precursores de arino

bajo catálisis de Pd. Los arinos son intermedios muy reactivos que participan de manera eficiente en diferentes tipos de procesos de generación de enlaces carbono-carbono.[198] Los arinos pueden generarse en condiciones suaves a partir de 2-trimetilsilil-fenil-trifluorometanosulfonatos en presencia de ion fluoruro.[199] En años recientes, se ha demostrado que bajo estas condiciones es posible la generación de arinos y su posterior reacción con diferentes organometálicos bajo catálisis con metales de transición.[200,201] Por lo tanto, decidimos estudiar la reacción de los compuestos triorganoíndicos en presencia de intermedios arino y cloruro de alilo bajo catálisis de Pd.

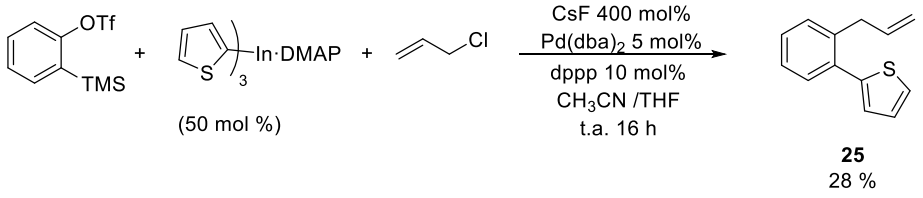
Estudios preliminares nos llevaron a la conclusión de que la presencia de THF, necesario en la preparación *in situ* de los compuestos triorganoíndicos, prácticamente inhibía la reacción, dando lugar solamente a trazas del producto **25** (Figura 11). El empleo de fuentes alternativas de fluoruro como TBAF o KF/éter-corona no supuso mejora alguna.

Figura 11. Reacción de R_3In con arino y cloruro de alilo bajo catálisis de Pd.



Sin embargo, al emplear el R_3In·DMAP fue posible llevar a cabo la reacción empleando solamente acetonitrilo como disolvente, lo cual esta vez condujo al producto **25** en un rendimiento del 28% (Figura 12).

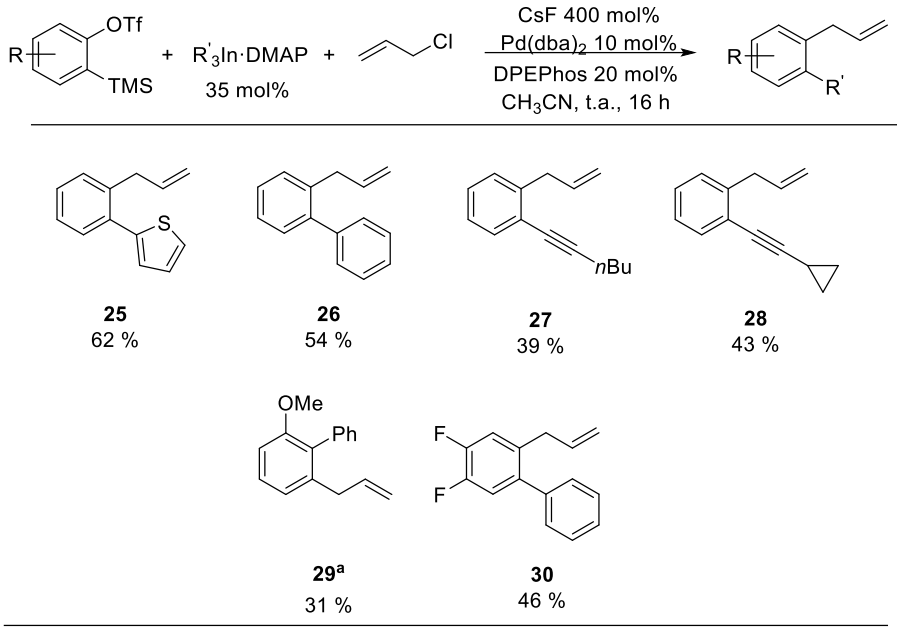
Figura 12. Reacción de R_3In·DMAP con arino y cloruro de alilo bajo catálisis de Pd.



Tras optimizar las condiciones de reacción, se encontró que empleado una carga catalítica del 10 mol% de Pd/DPEPhos, el producto de reacción **25** se podía obtener con un rendimiento del 62%. Además, en la reacción se usa un 35% mol del reactivo

triorganoíndico, lo cual indica que más de un grupo orgánico unido al indio se transfiere en el proceso. Se emplearon varios triorganoíndicos sólidos en las condiciones de reacción, lo cual demuestra la versatilidad de la reacción (Figura 13).

Figura 13. Reacción de organometálicos de indio sólidos con varios precursores de arino bajo catálisis de Pd.



25
62 %

26
54 %

27
39 %

28
43 %

29[a]
31 %

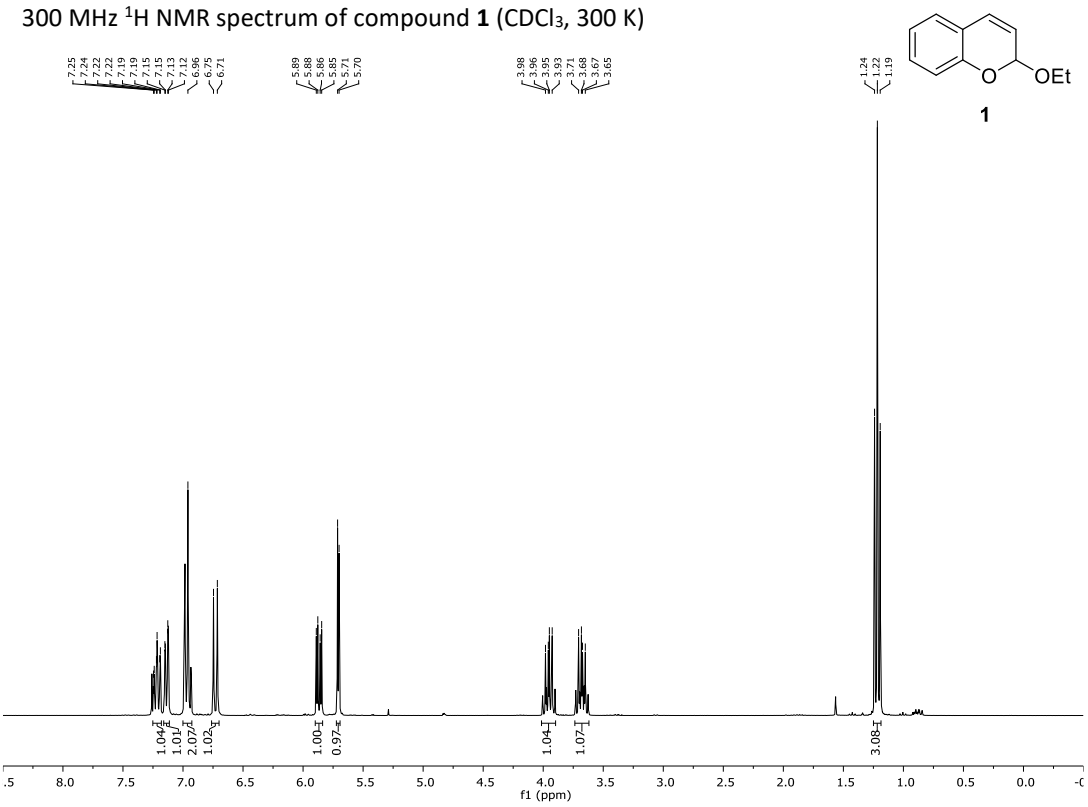
30
46 %

Pese a los rendimientos relativamente bajos de la reacción, es necesario tener en cuenta que se trata de un proceso donde se generan de manera simultánea dos enlaces carbono-carbono, y además se trata del primer ejemplo de reacción de organometálicos de indio con intermedios de tipo arino. Además, la reacción ha sido posible gracias al desarrollo de los organometálicos de indio sólidos, que han demostrado su utilidad en condiciones que normalmente resultan ser incompatibles con disoluciones de triorganoíndicos en THF.

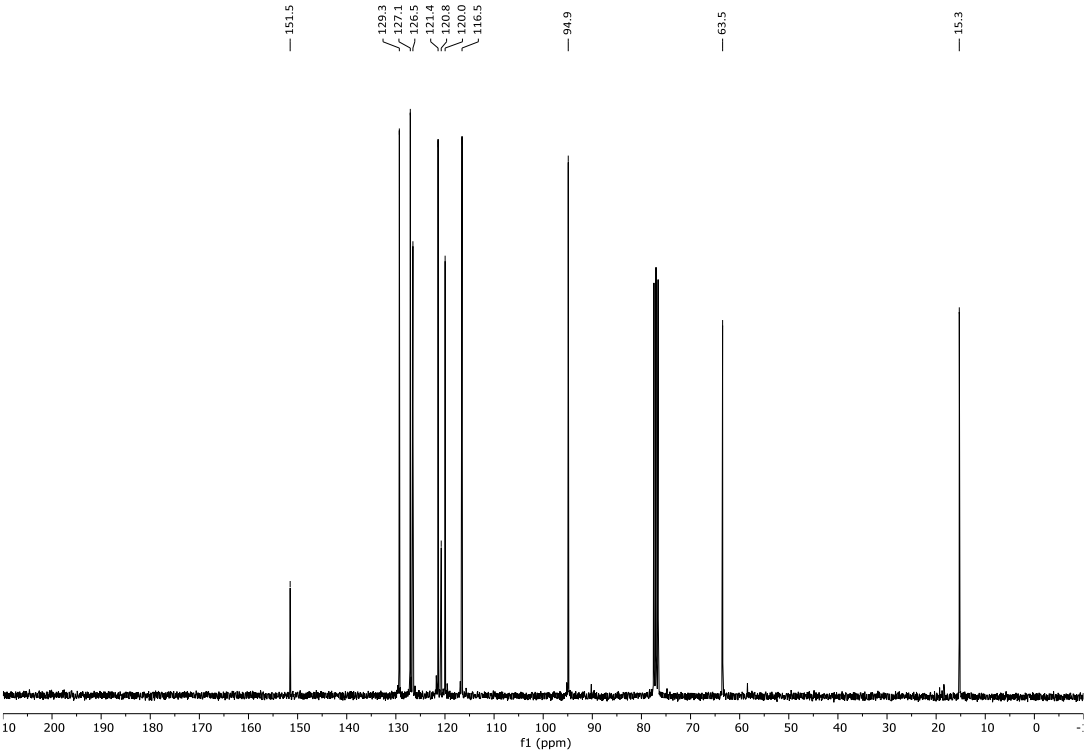
Annex II.

NMR Spectra.

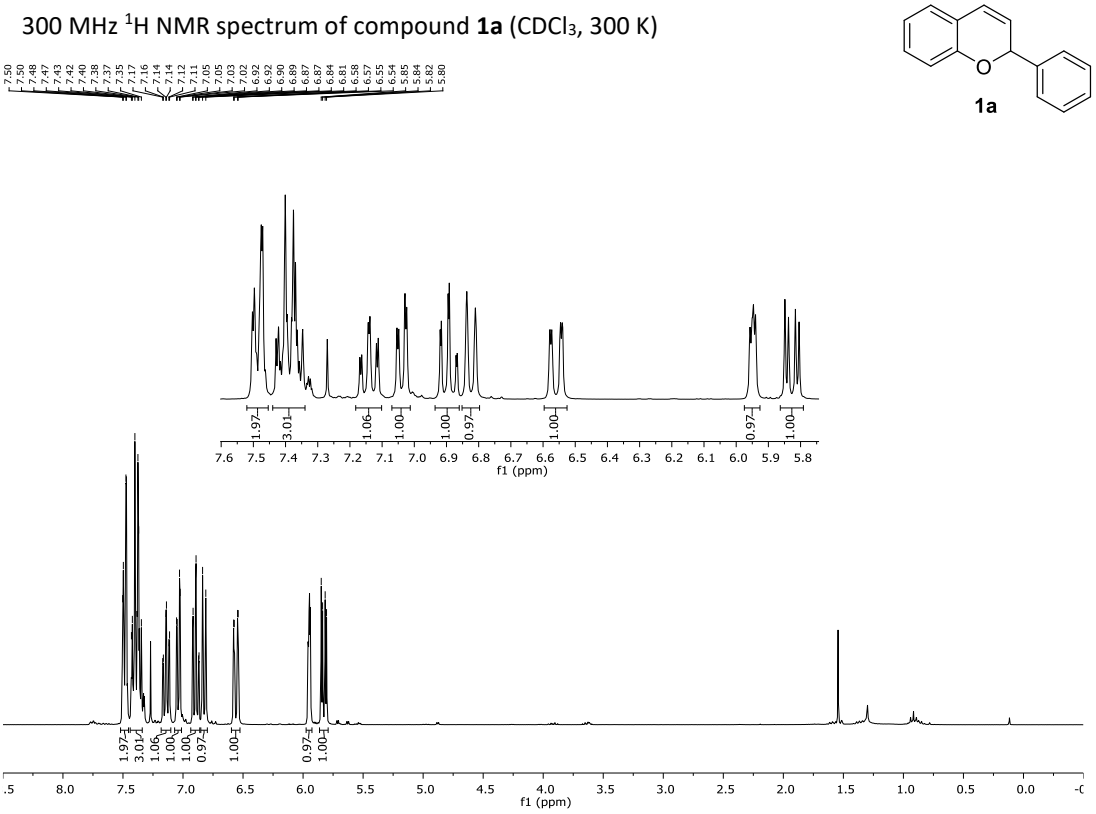
300 MHz ^{1}H NMR spectrum of compound **1** ($CDCl_3$, 300 K)



75 MHz ^{13}C NMR spectrum of compound **1** ($CDCl_3$, 300 K)

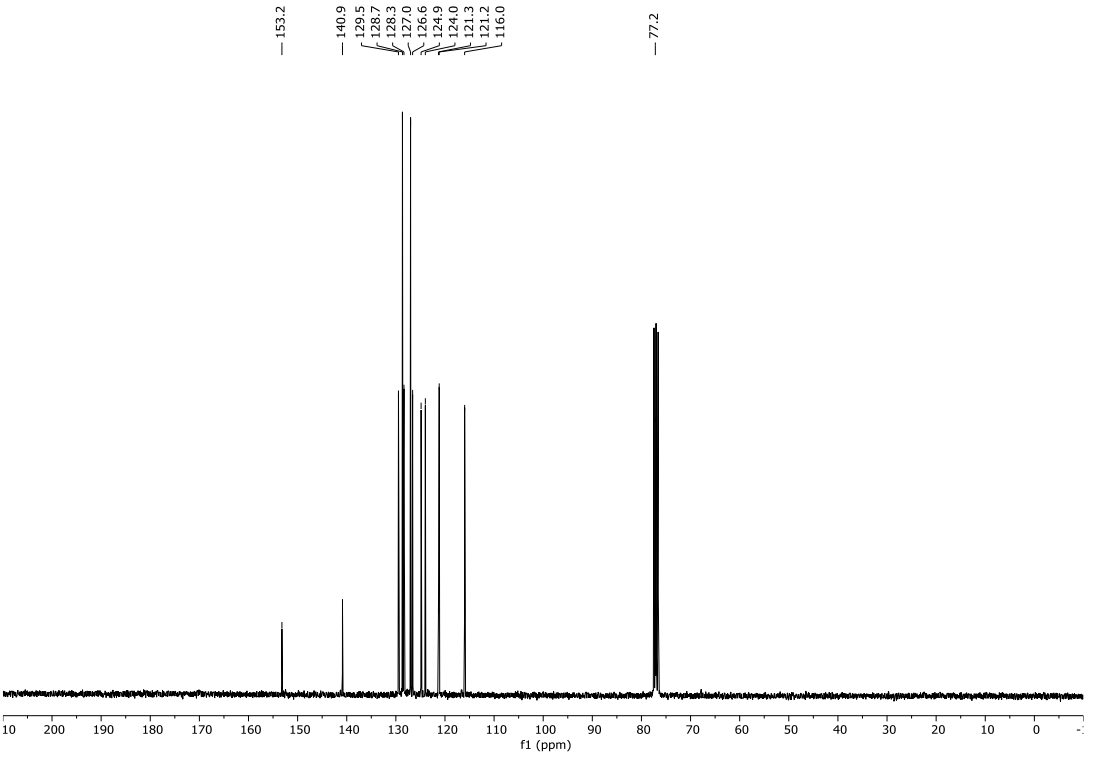


300 MHz ^{1}H NMR spectrum of compound **1a** ($CDCl_3$, 300 K)

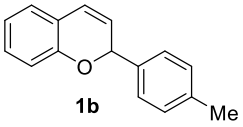


1a

75 MHz ^{13}C NMR spectrum of compound **1a** ($CDCl_3$, 300 K)

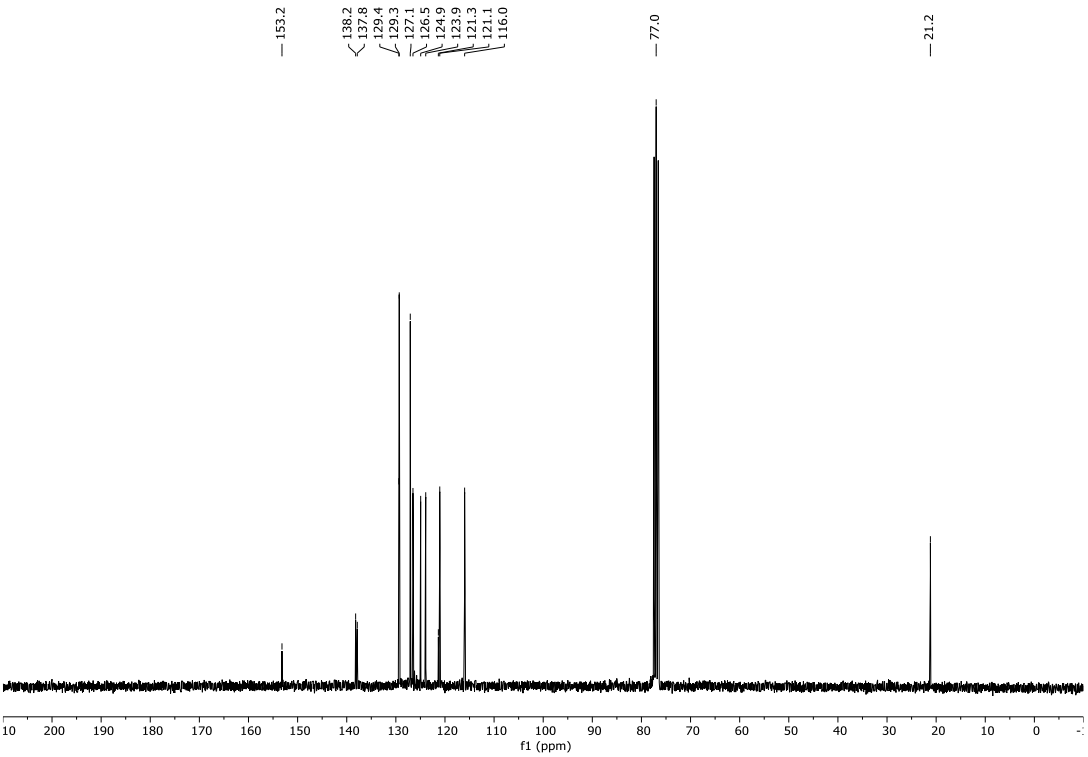


300 MHz ^{1}H NMR spectrum of compound **1b** ($CDCl_3$, 300 K)

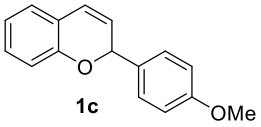


1b

75 MHz ^{13}C NMR spectrum of compound **1b** ($CDCl_3$, 300 K)

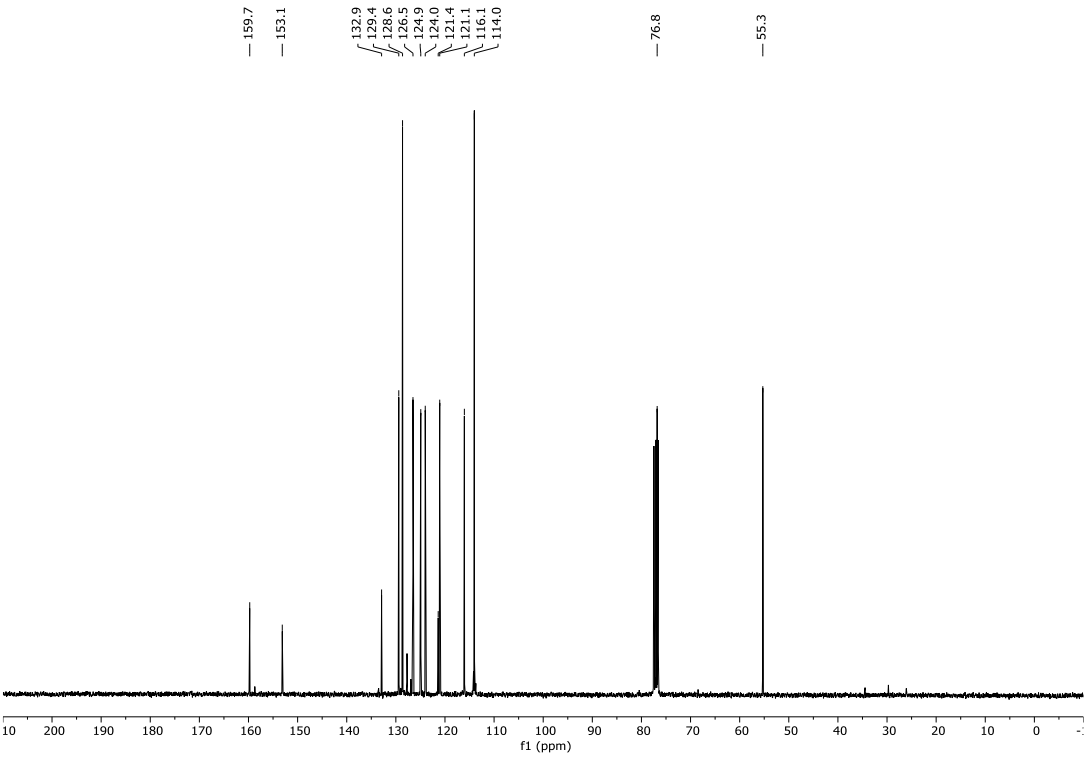


300 MHz ^{1}H NMR spectrum of compound **1c** ($CDCl_3$, 300 K)

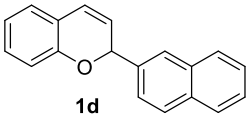


1c

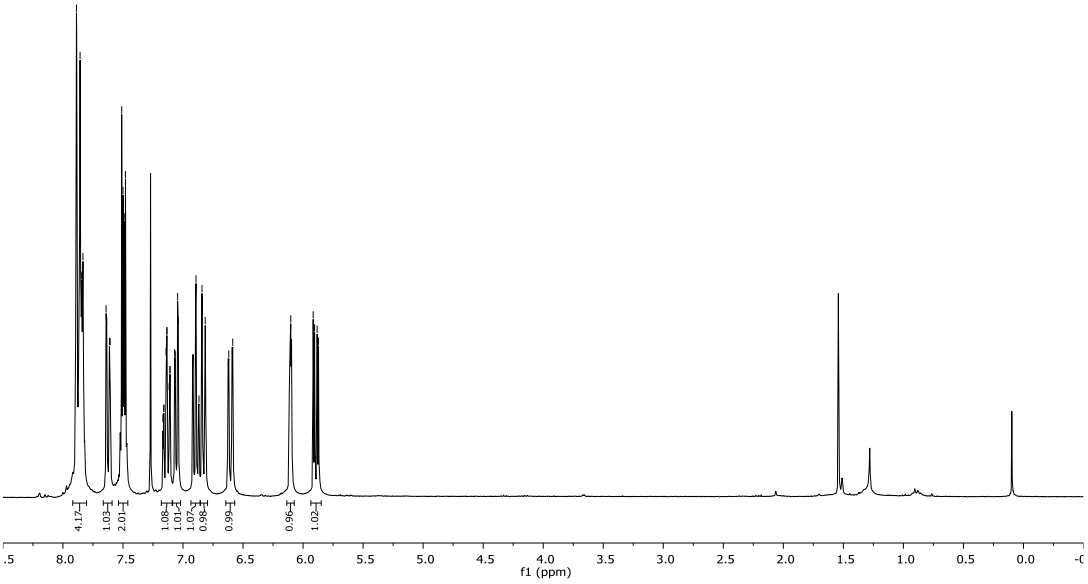
75 MHz ^{13}C NMR spectrum of compound **1c** ($CDCl_3$, 300 K)



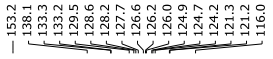
300 MHz ^{1}H NMR spectrum of compound **1d** ($CDCl_3$, 300 K)

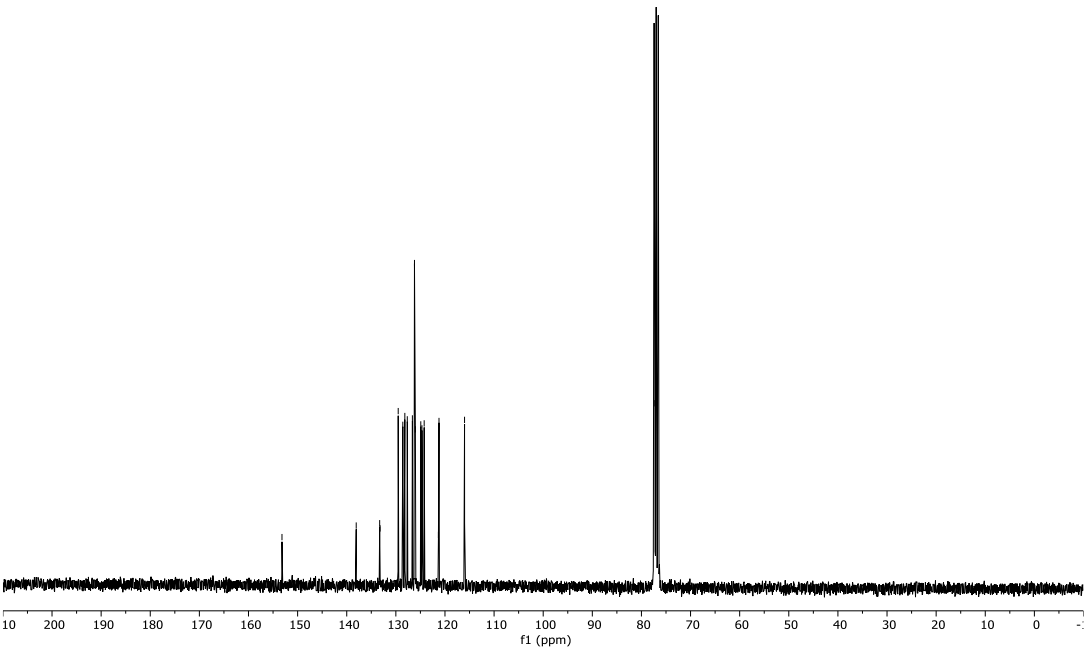


1d

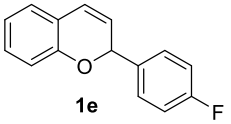


75 MHz ^{13}C NMR spectrum of compound **1d** ($CDCl_3$, 300 K)

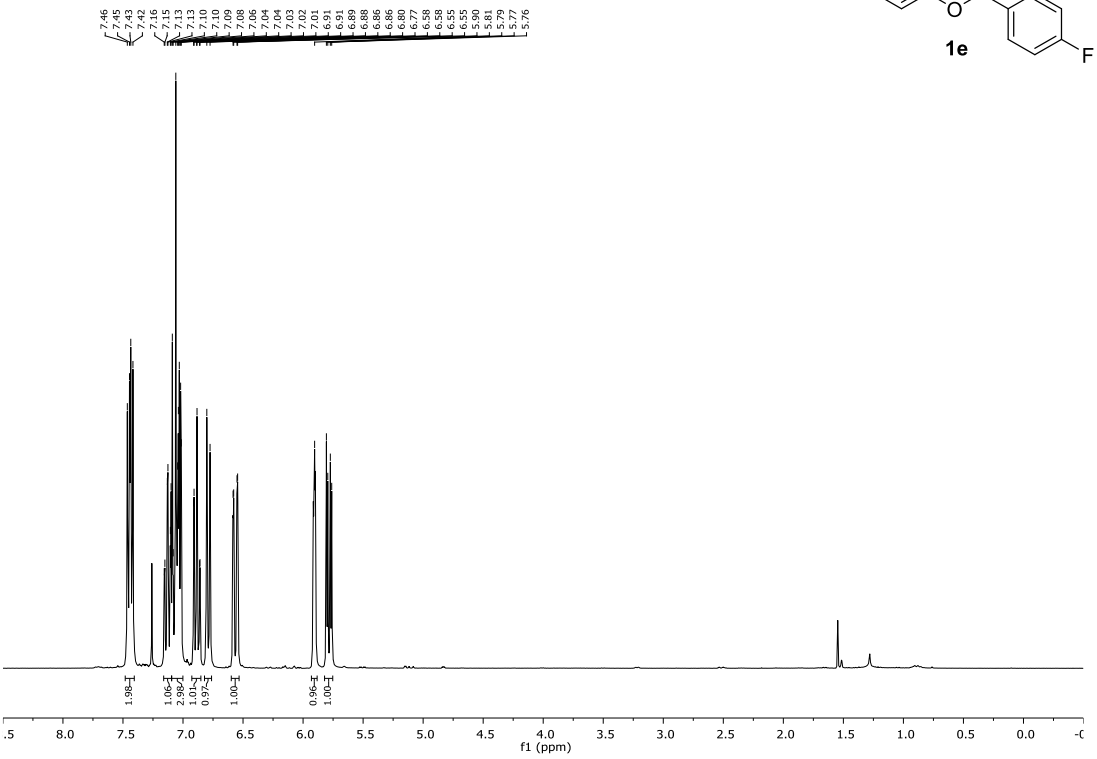




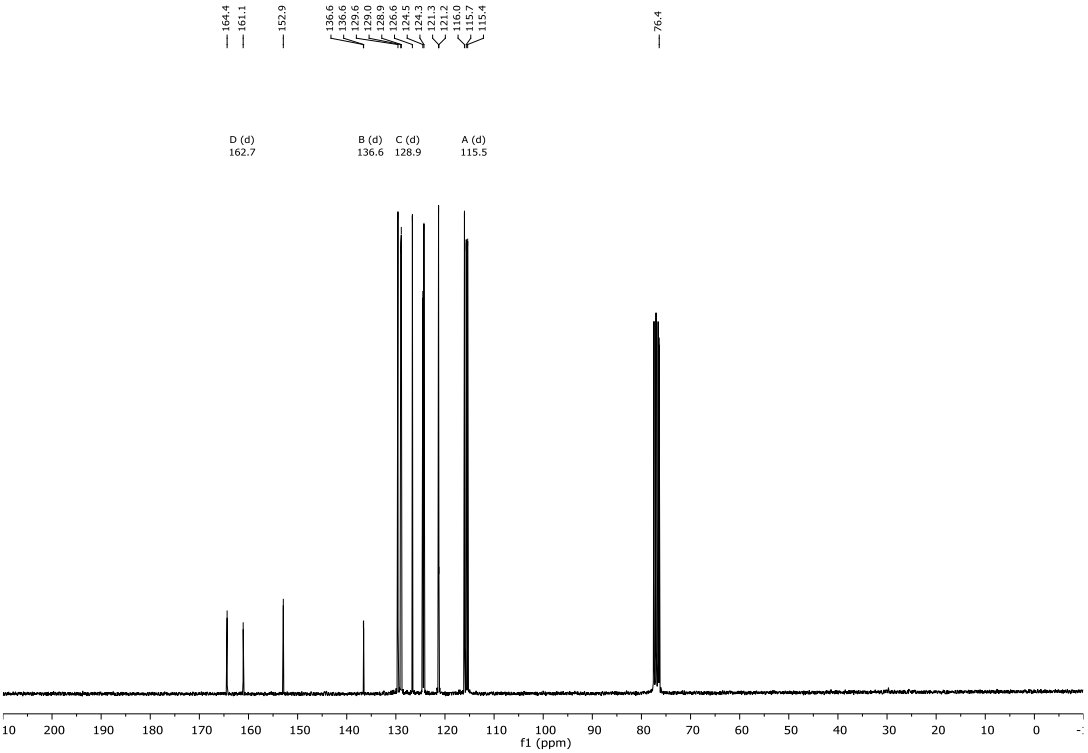
300 MHz ^{1}H NMR spectrum of compound **1e** ($CDCl_3$, 300 K)



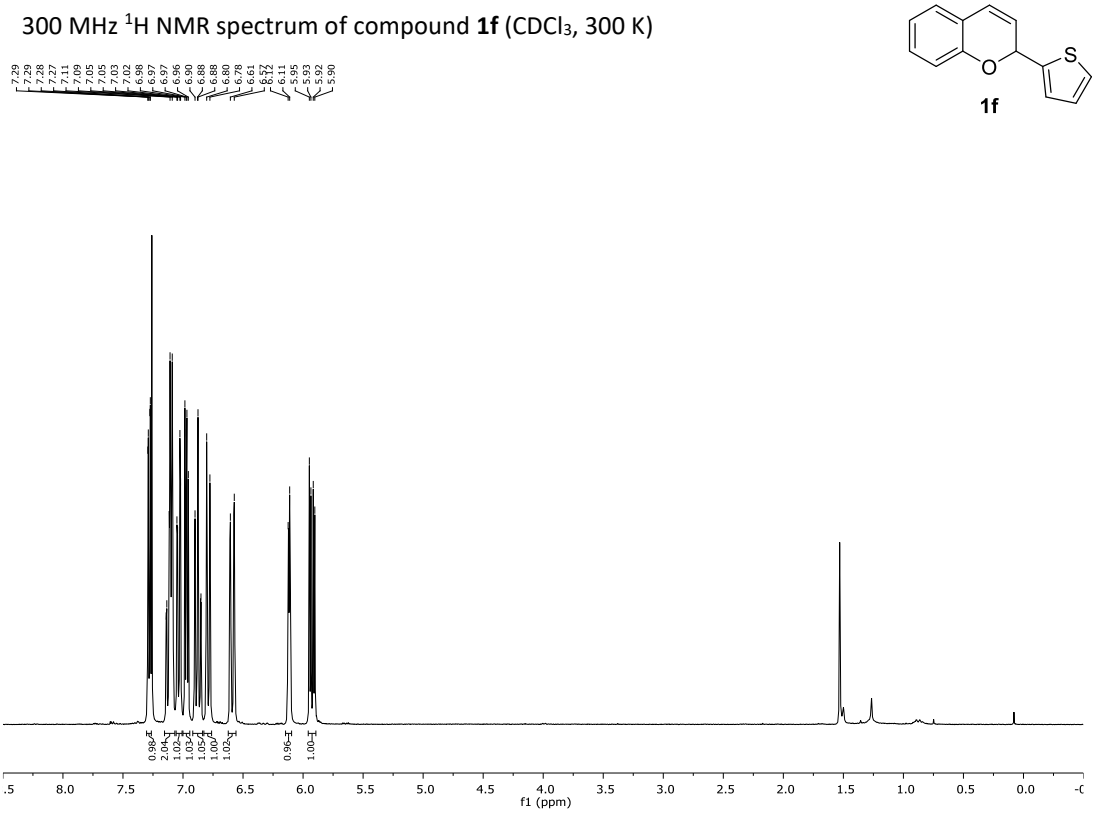
1e



75 MHz ^{13}C NMR spectrum of compound **1e** ($CDCl_3$, 300 K)

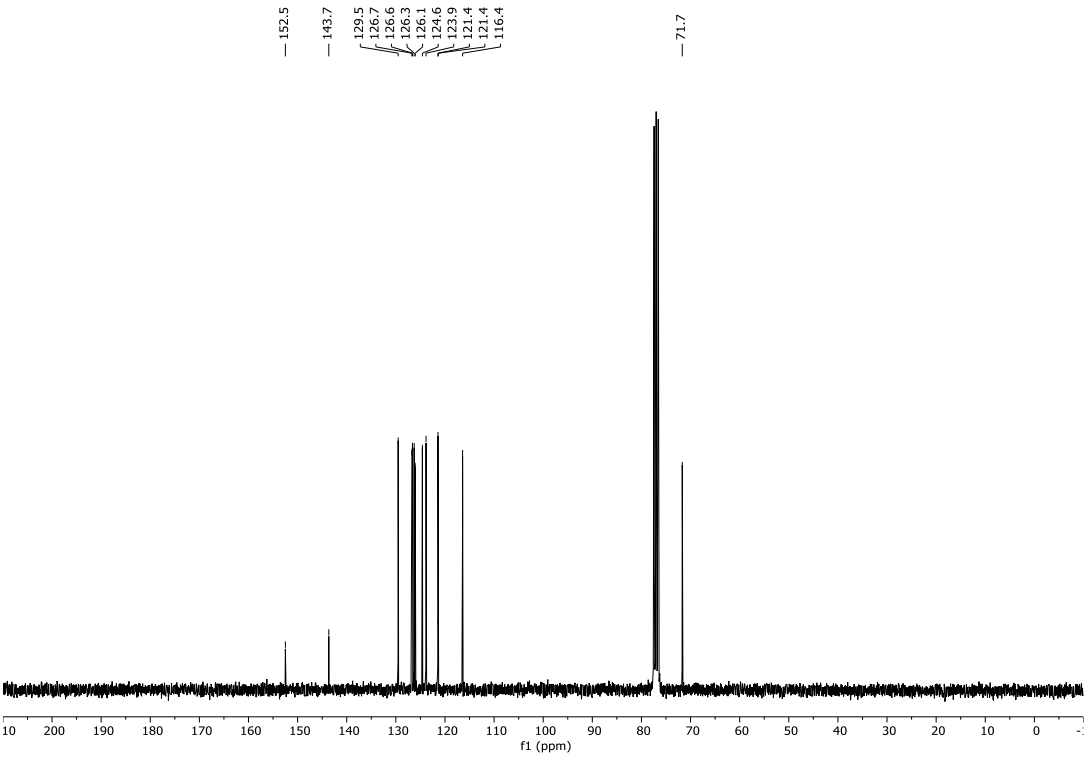


300 MHz ^{1}H NMR spectrum of compound **1f** ($CDCl_3$, 300 K)

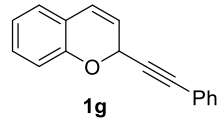


1f

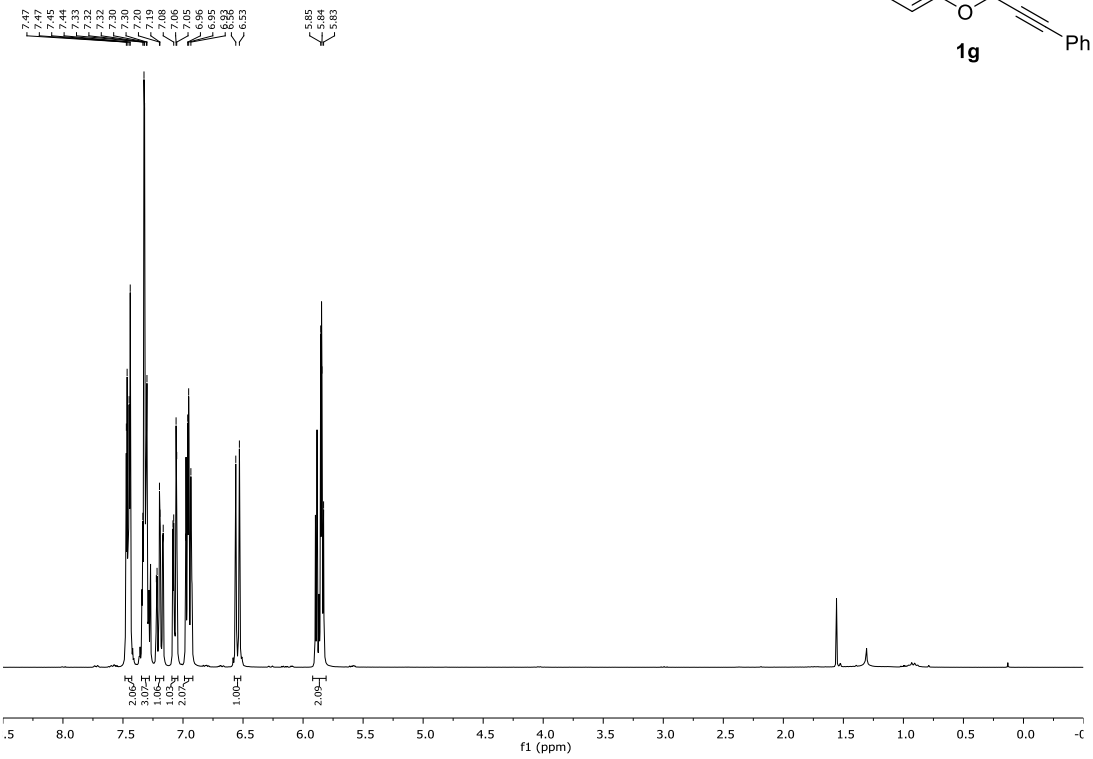
75 MHz ^{13}C NMR spectrum of compound **1f** ($CDCl_3$, 300 K)



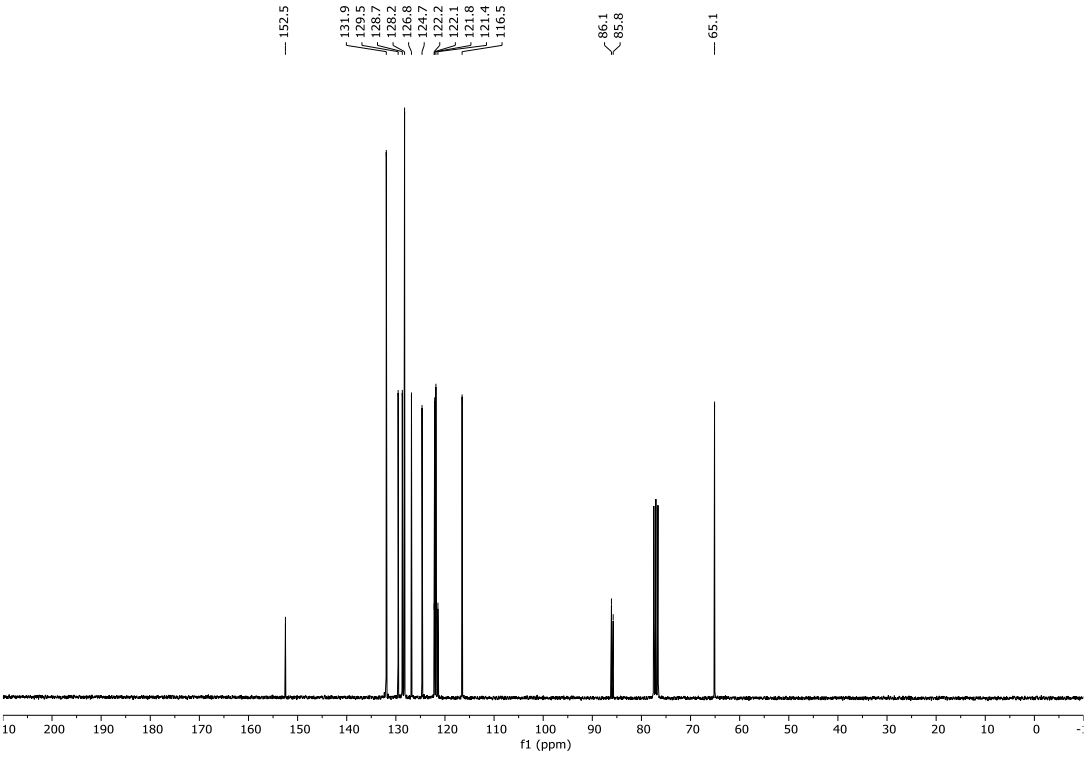
300 MHz ^{1}H NMR spectrum of compound **1g** ($CDCl_3$, 300 K)



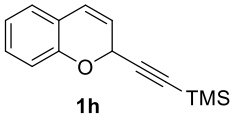
1g



75 MHz ^{13}C NMR spectrum of compound **1g** ($CDCl_3$, 300 K)

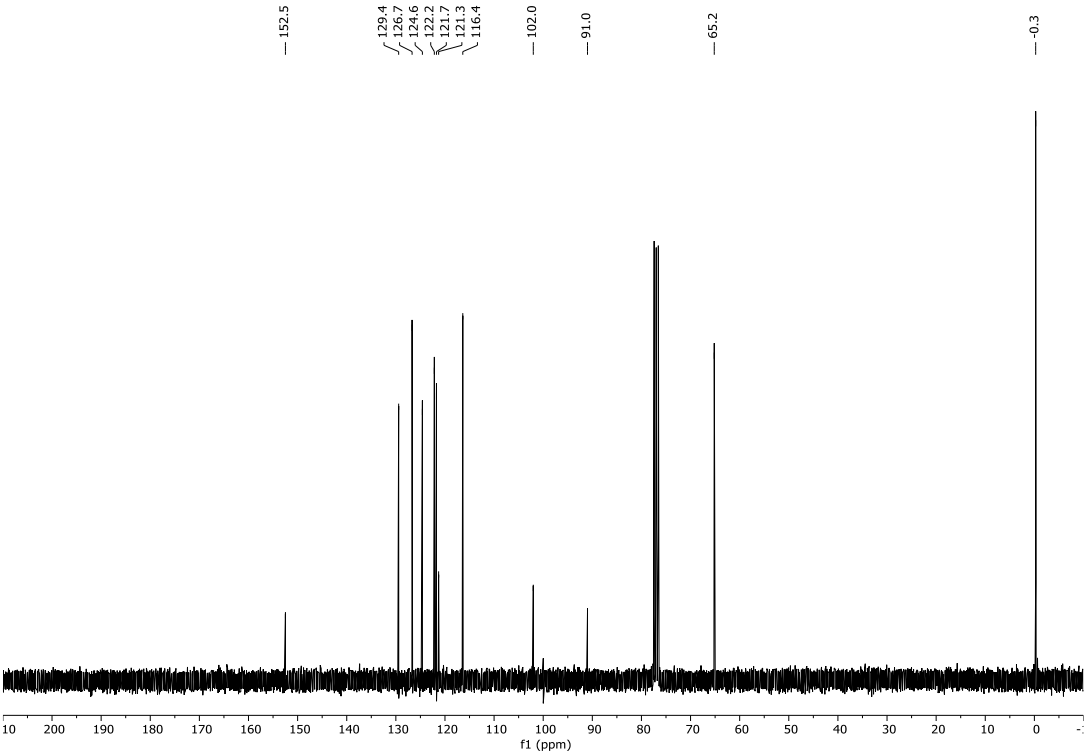


300 MHz ^{1}H NMR spectrum of compound **1h** ($CDCl_3$, 300 K)

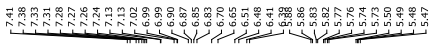


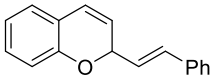
1h

75 MHz ^{13}C NMR spectrum of compound **1h** ($CDCl_3$, 300 K)

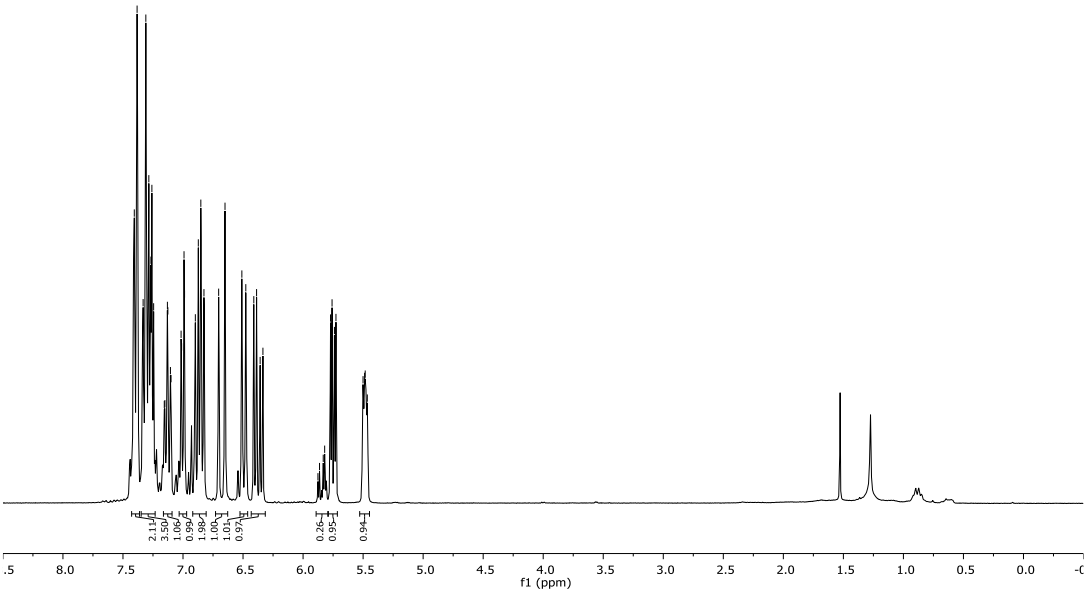


300 MHz ^{1}H NMR spectrum of compound **1i** ($CDCl_3$, 300 K)

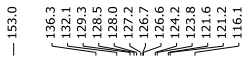


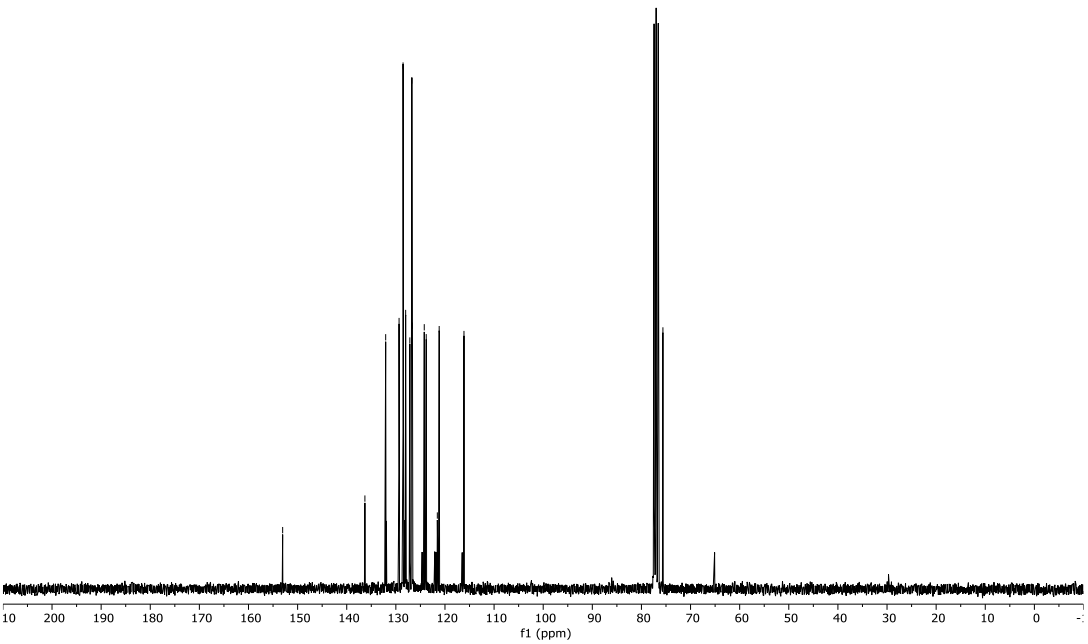


1i
E/Z 87:13

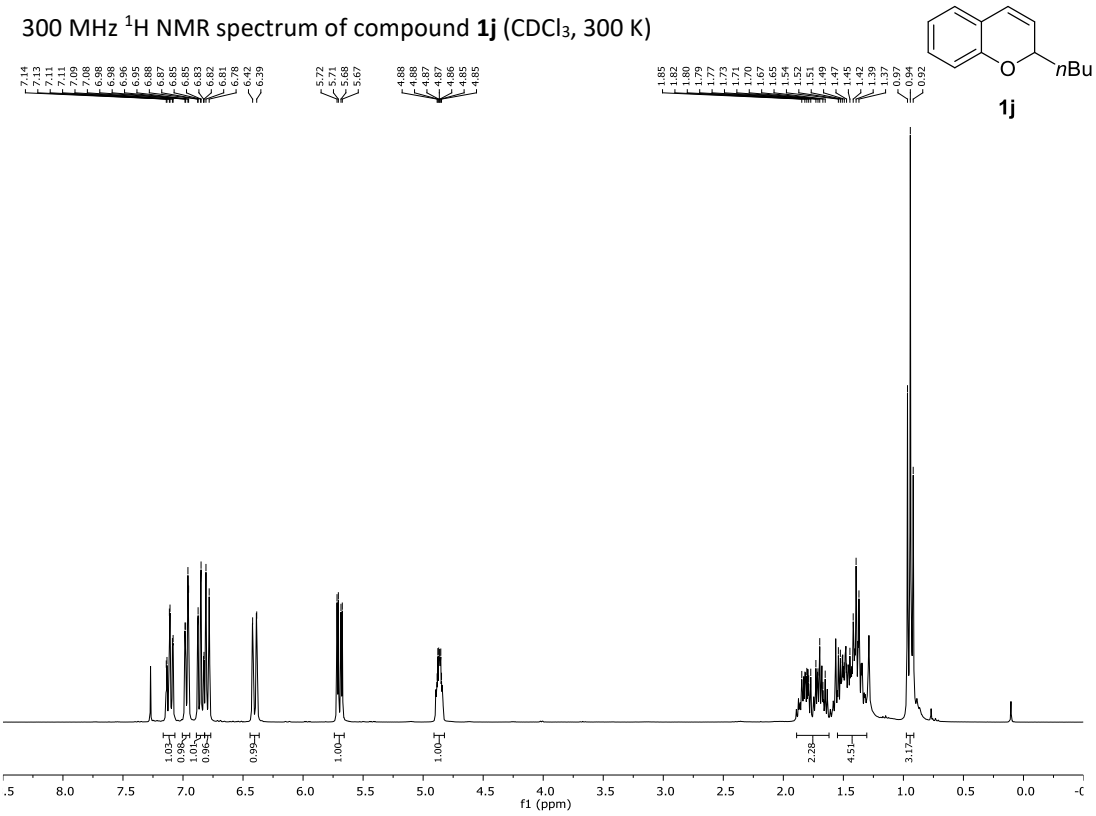


75 MHz ^{13}C NMR spectrum of compound **1i** ($CDCl_3$, 300 K)

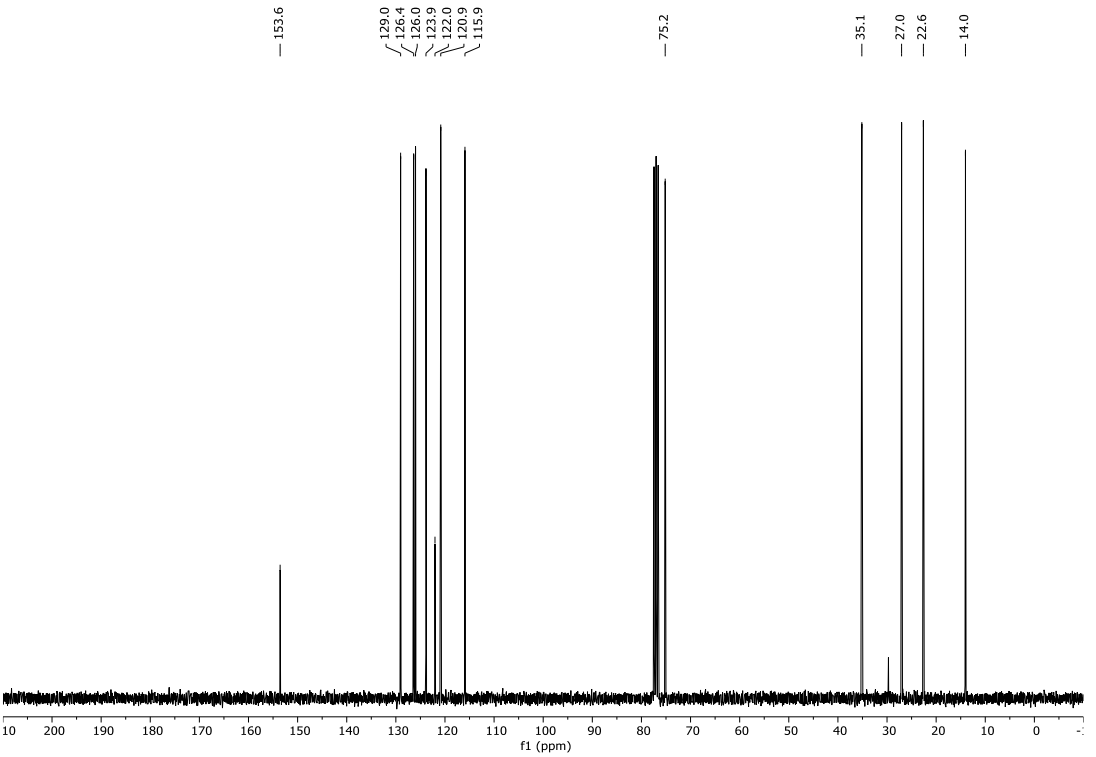




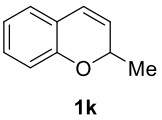
300 MHz ^{1}H NMR spectrum of compound **1j** ($CDCl_3$, 300 K)



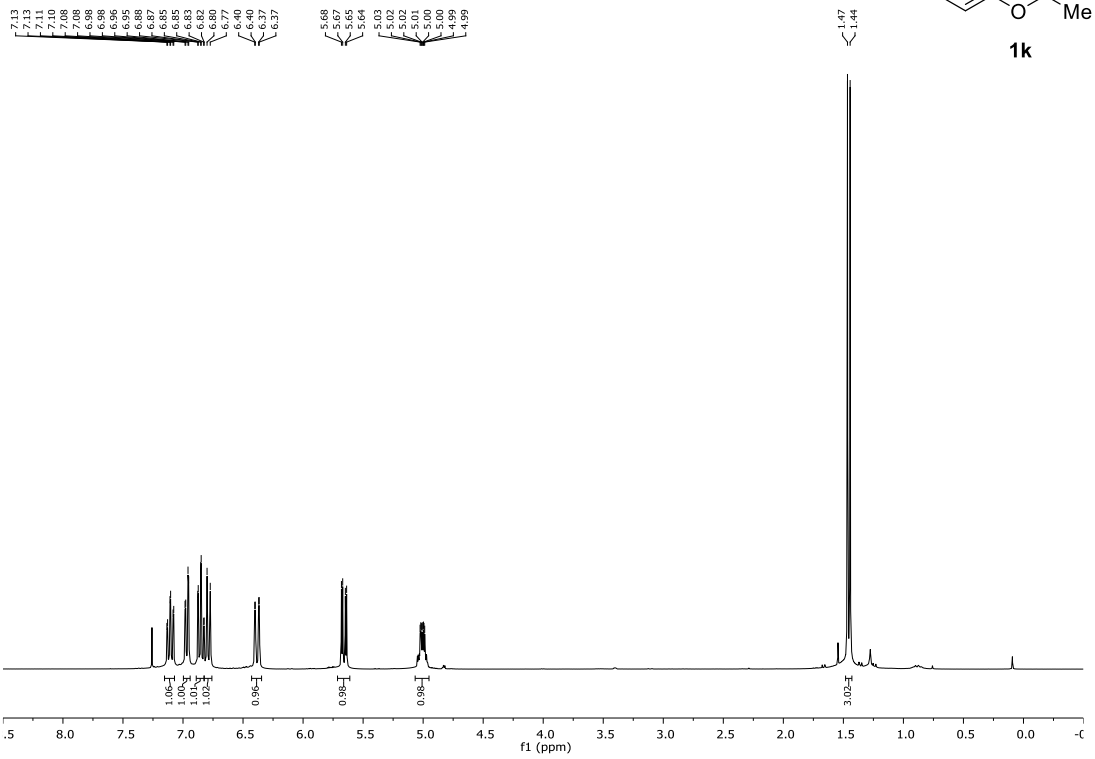
75 MHz ^{13}C NMR spectrum of compound **1j** ($CDCl_3$, 300 K)



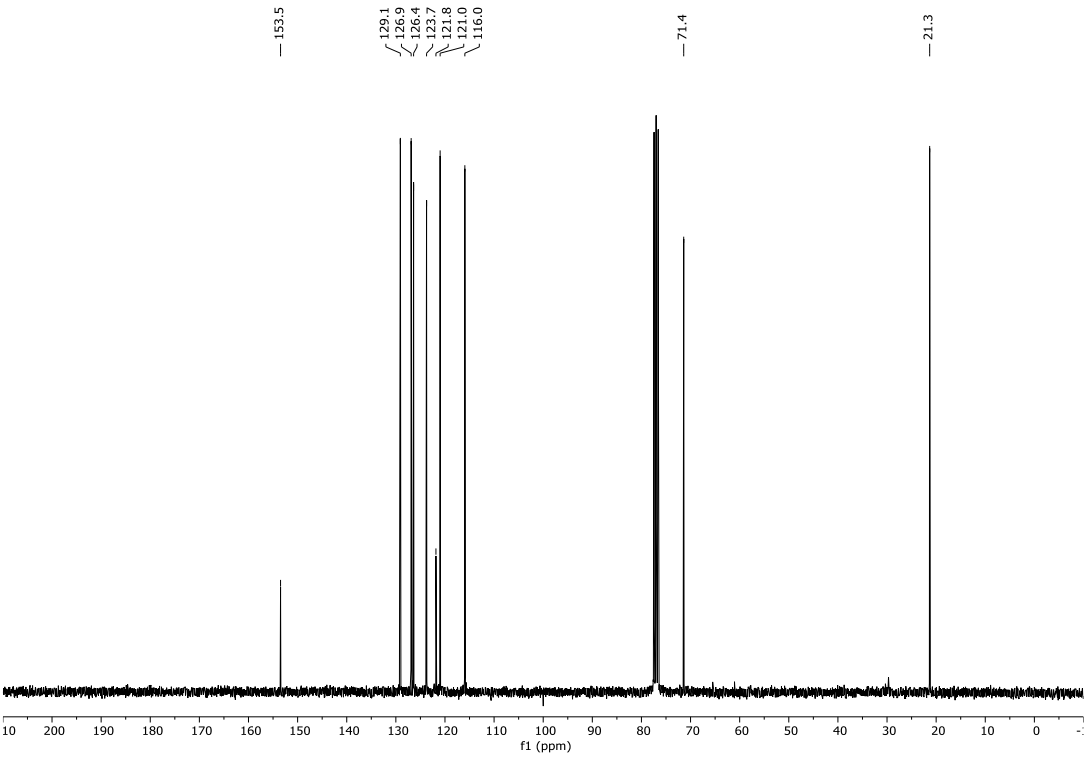
300 MHz ^{1}H NMR spectrum of compound **1k** ($CDCl_3$, 300 K)



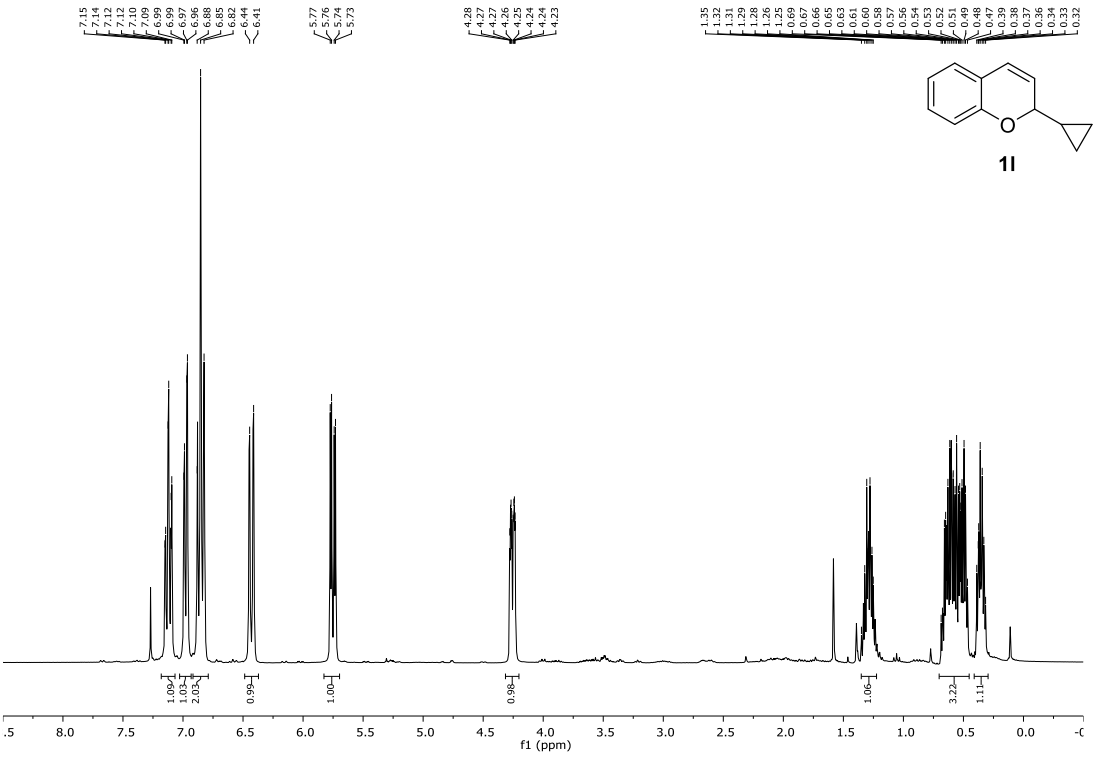
1k



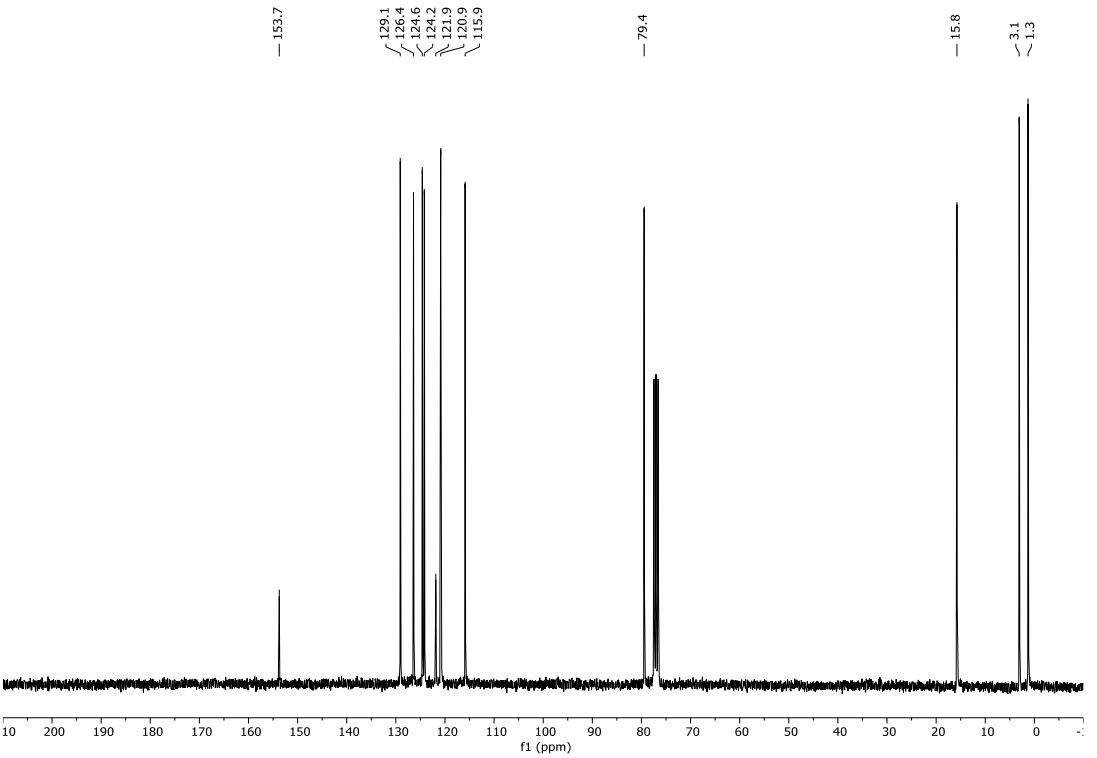
75 MHz ^{13}C NMR spectrum of compound **1k** ($CDCl_3$, 300 K)



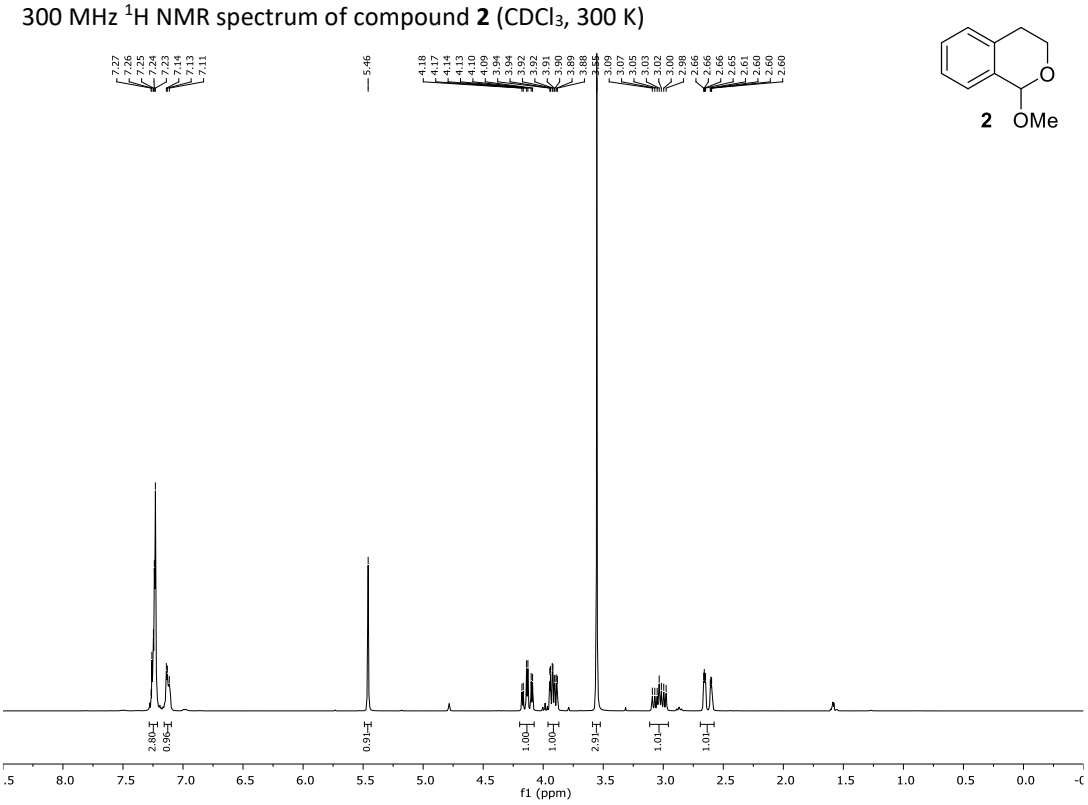
300 MHz ^{1}H NMR spectrum of compound **1l** ($CDCl_3$, 300 K)



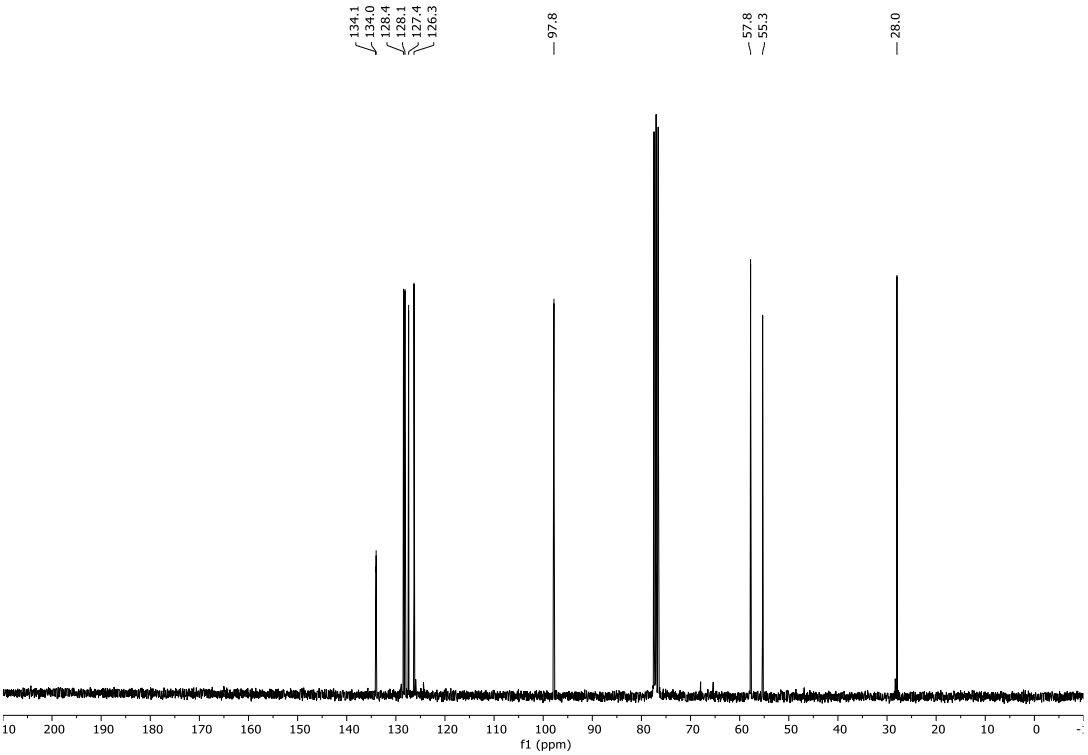
75 MHz ^{13}C NMR spectrum of compound **1l** ($CDCl_3$, 300 K)



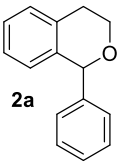
300 MHz ^{1}H NMR spectrum of compound **2** ($CDCl_3$, 300 K)



75 MHz ^{13}C NMR spectrum of compound **2** ($CDCl_3$, 300 K)

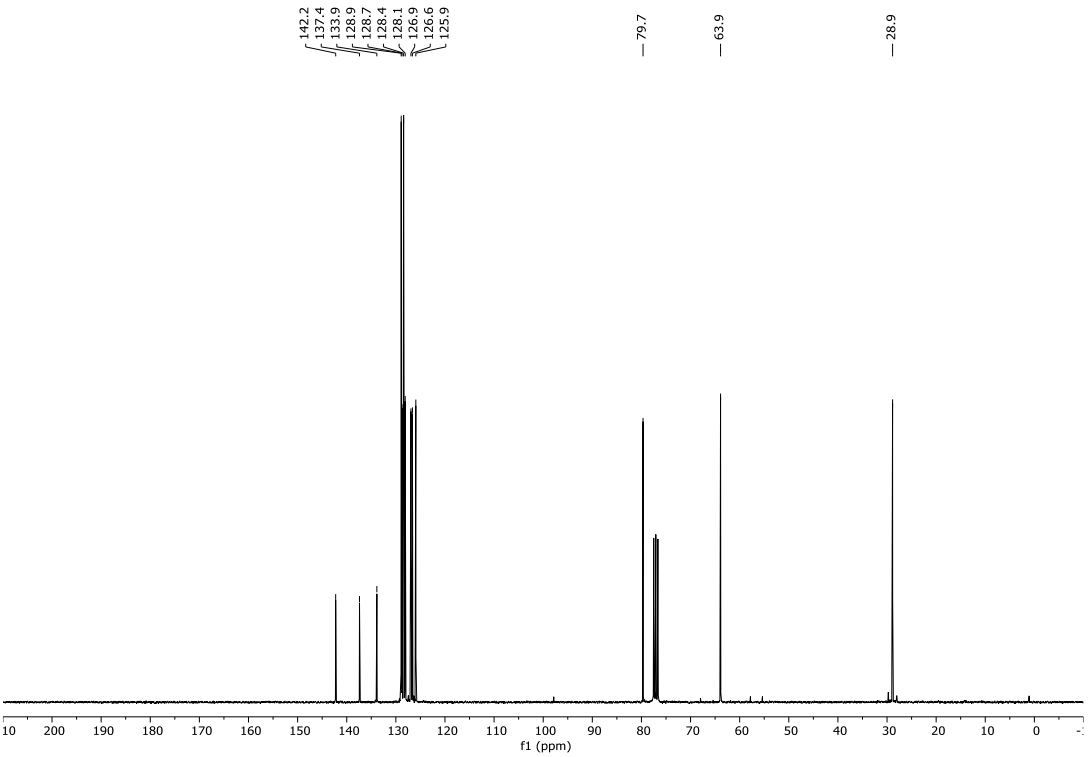


300 MHz ^{1}H NMR spectrum of compound **2a** ($CDCl_3$, 300 K)

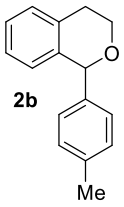


2a

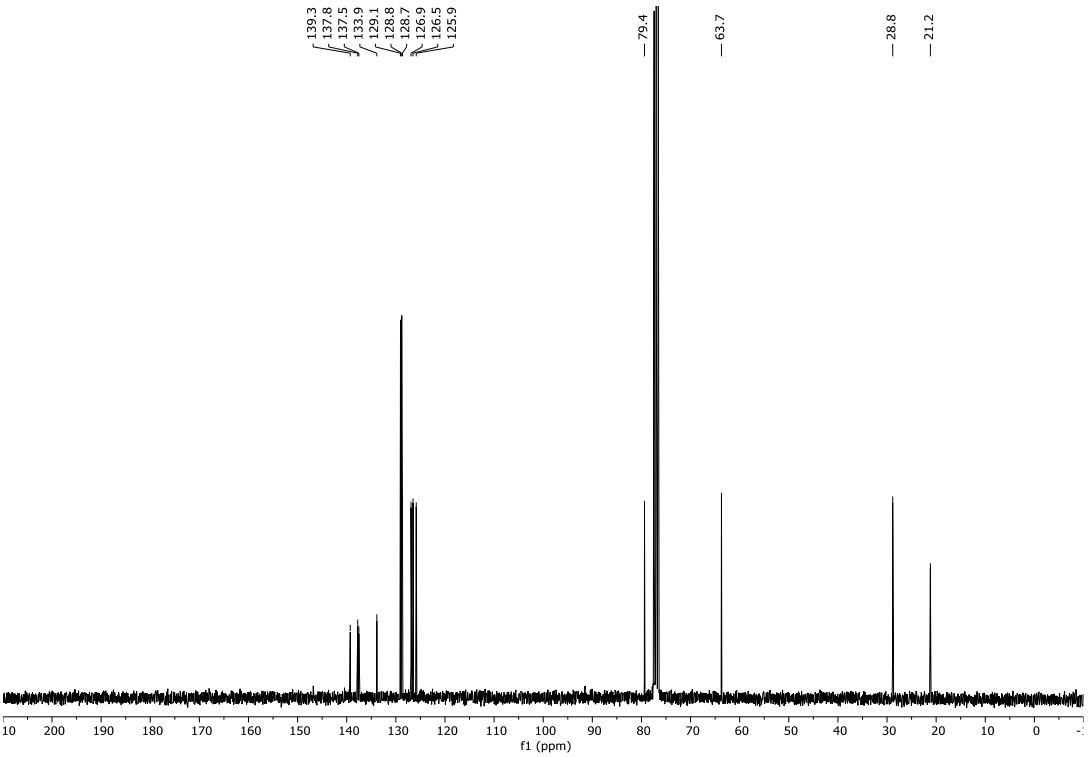
75 MHz ^{13}C NMR spectrum of compound **2a** ($CDCl_3$, 300 K)



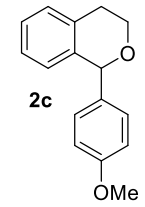
300 MHz ^{1}H NMR spectrum of compound **2b** ($CDCl_3$, 300 K)



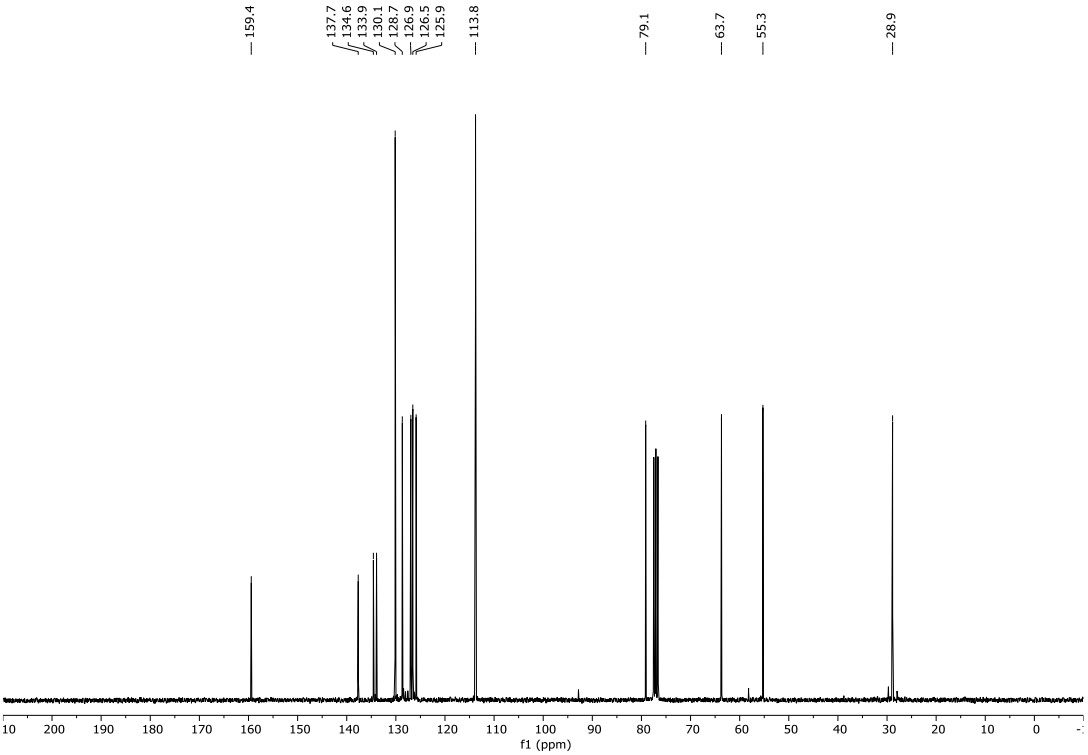
75 MHz ^{13}C NMR spectrum of compound **2b** ($CDCl_3$, 300 K)



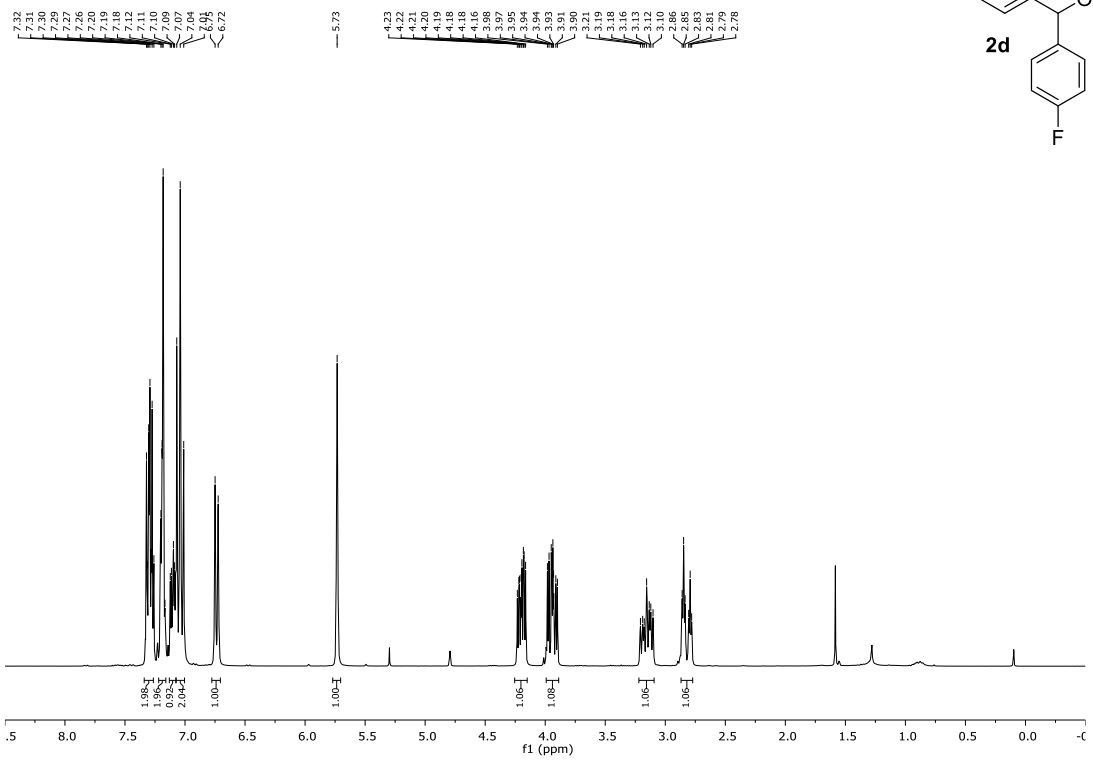
300 MHz ^{1}H NMR spectrum of compound **2c** ($CDCl_3$, 300 K)



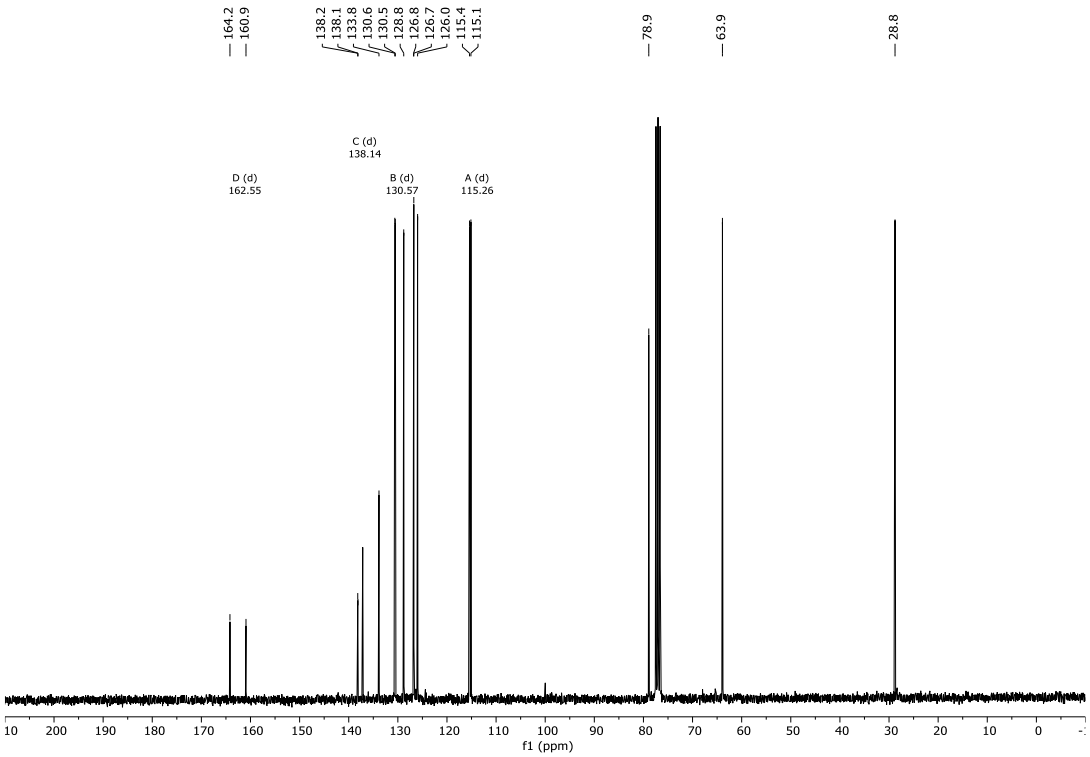
75 MHz ^{13}C NMR spectrum of compound **2c** ($CDCl_3$, 300 K)



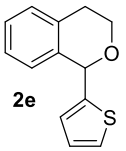
300 MHz ^{1}H NMR spectrum of compound **2d** ($CDCl_3$, 300 K)



75 MHz ^{13}C NMR spectrum of compound **2d** ($CDCl_3$, 300 K)

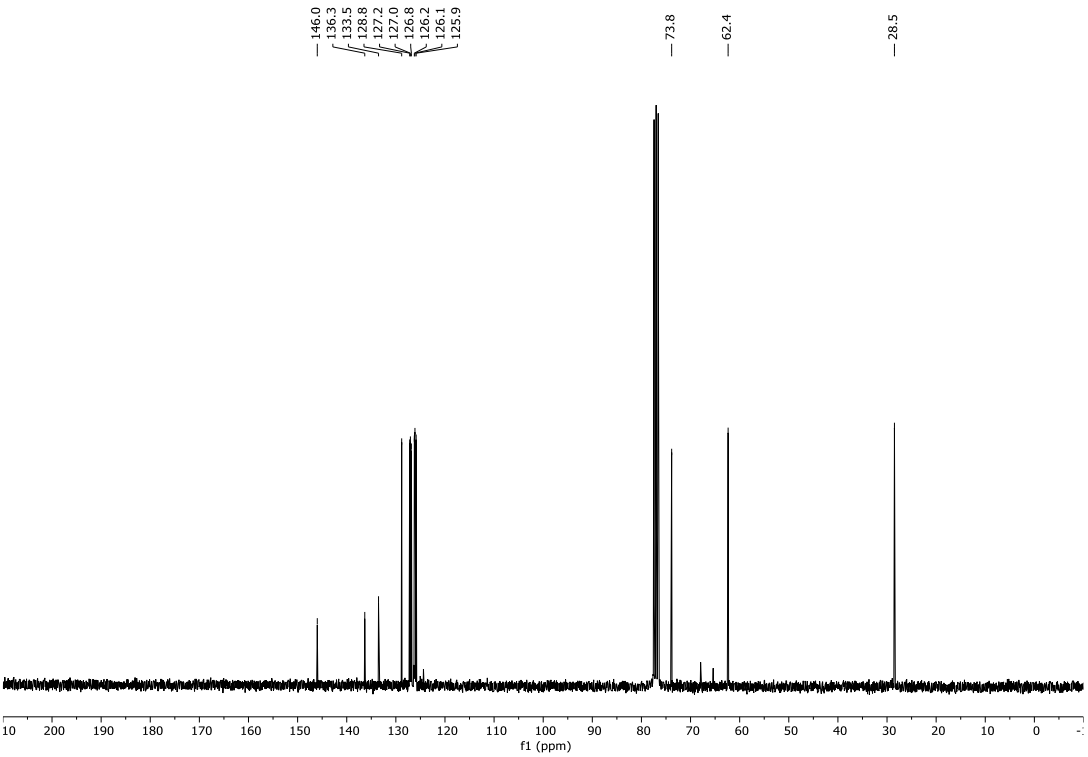


300 MHz ^{1}H NMR spectrum of compound **2e** ($CDCl_3$, 300 K)

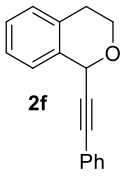


2e

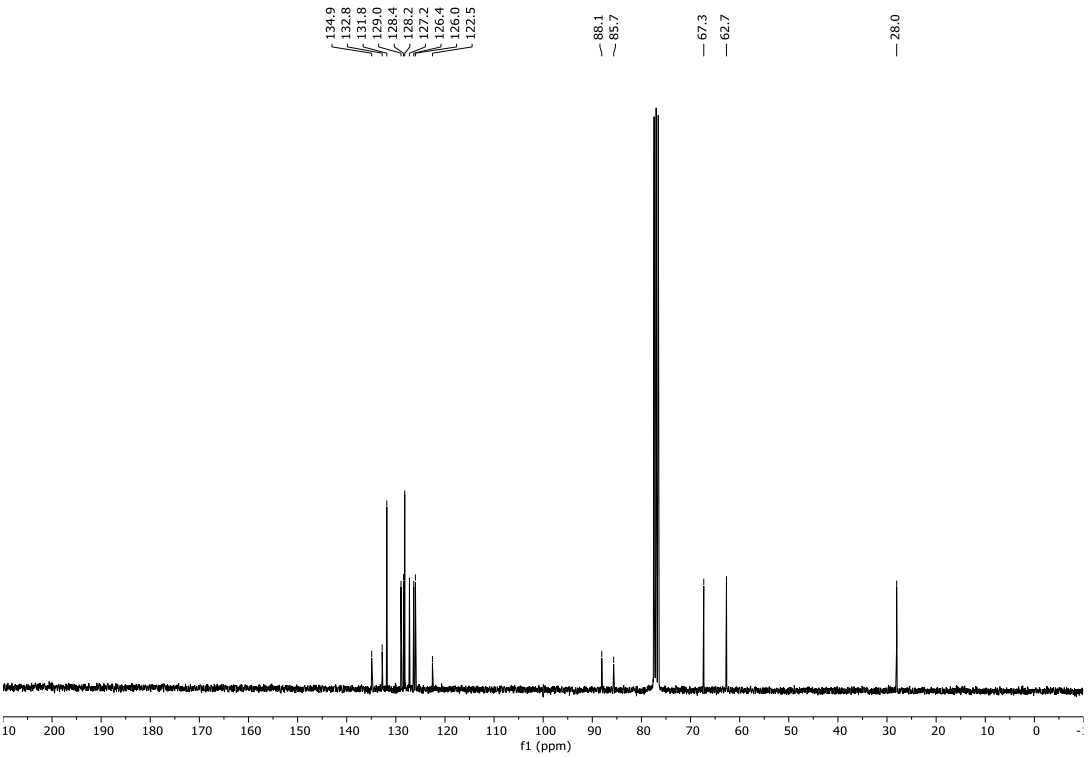
75 MHz ^{13}C NMR spectrum of compound **2e** ($CDCl_3$, 300 K)



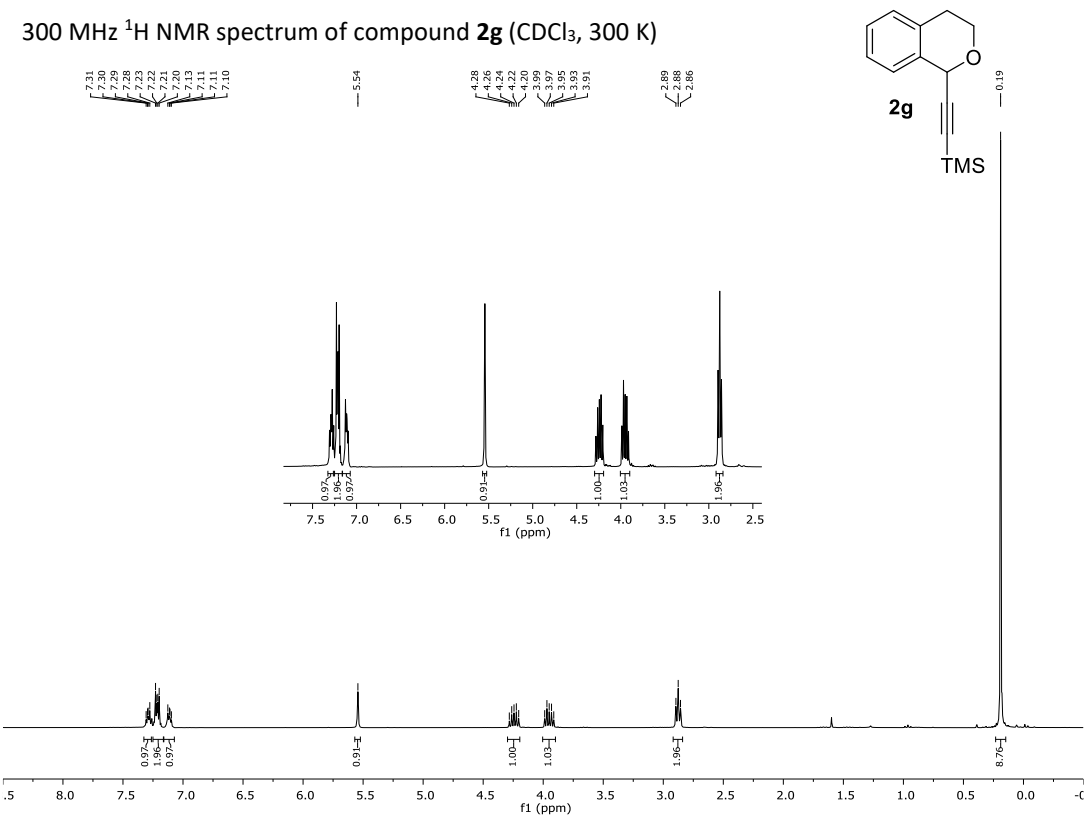
300 MHz ^{1}H NMR spectrum of compound **2f** ($CDCl_3$, 300 K)



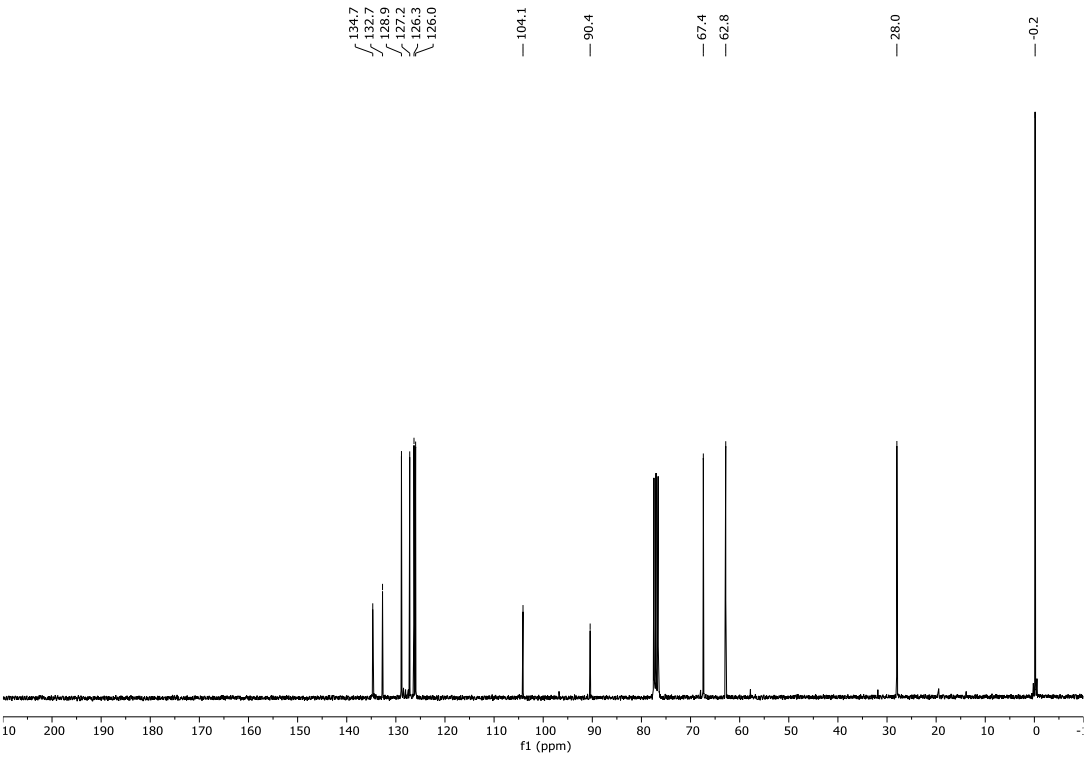
75 MHz ^{13}C NMR spectrum of compound **2f** ($CDCl_3$, 300 K)



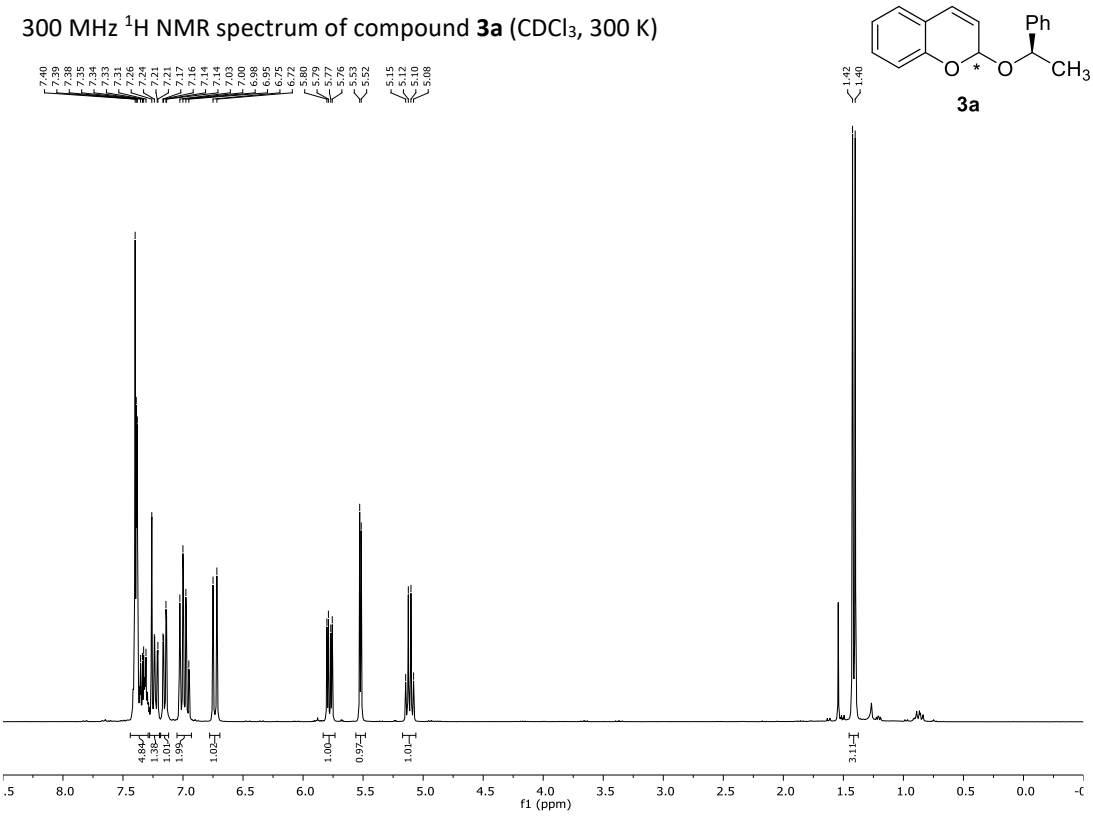
300 MHz ^{1}H NMR spectrum of compound **2g** ($CDCl_3$, 300 K)



75 MHz ^{13}C NMR spectrum of compound **2g** ($CDCl_3$, 300 K)

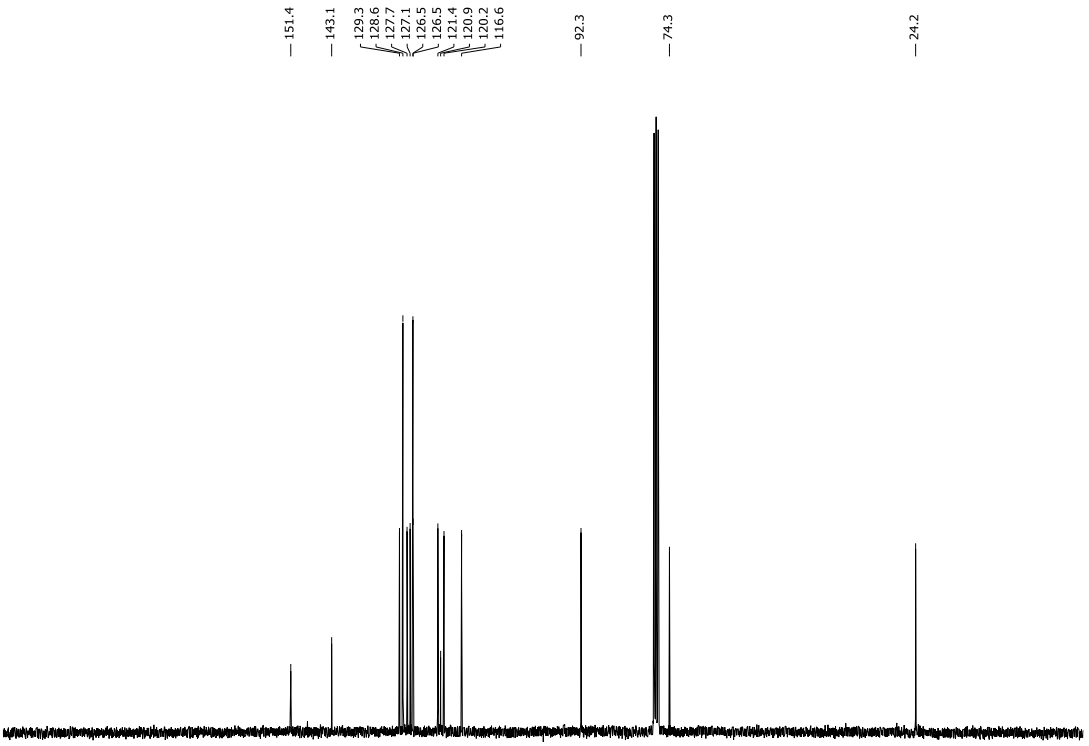


300 MHz ^{1}H NMR spectrum of compound **3a** ($CDCl_3$, 300 K)

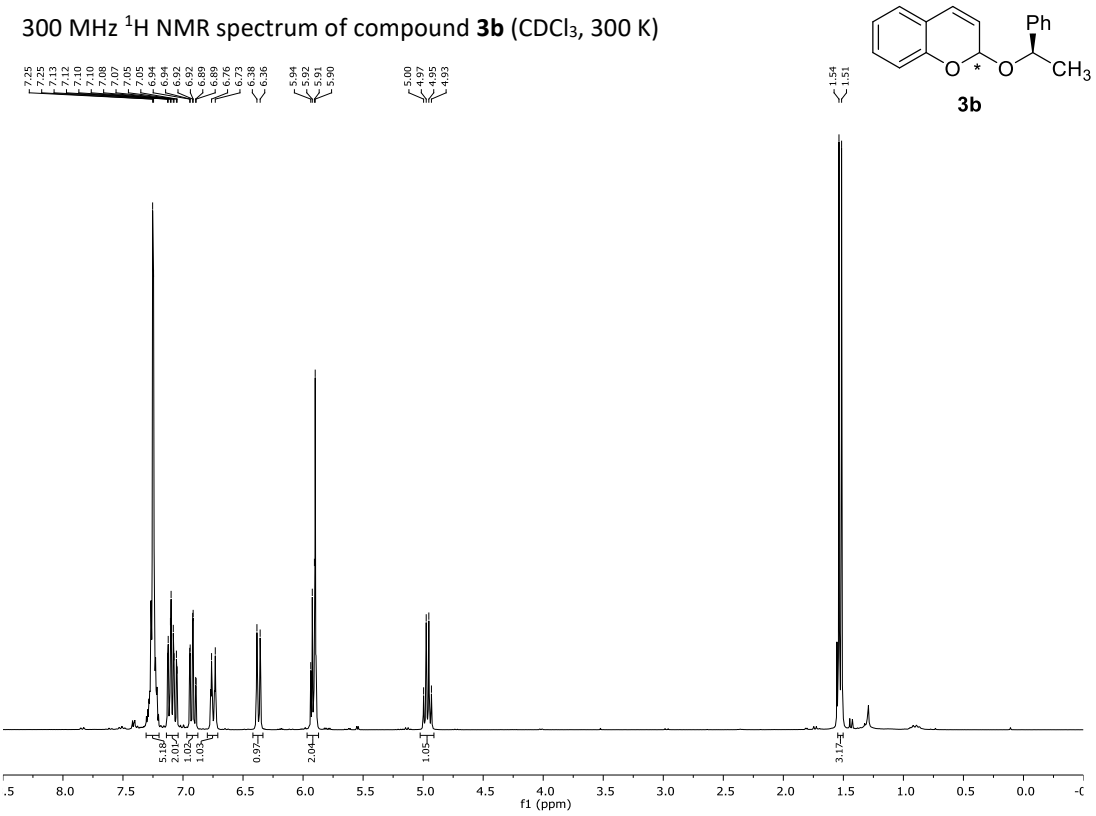


3a

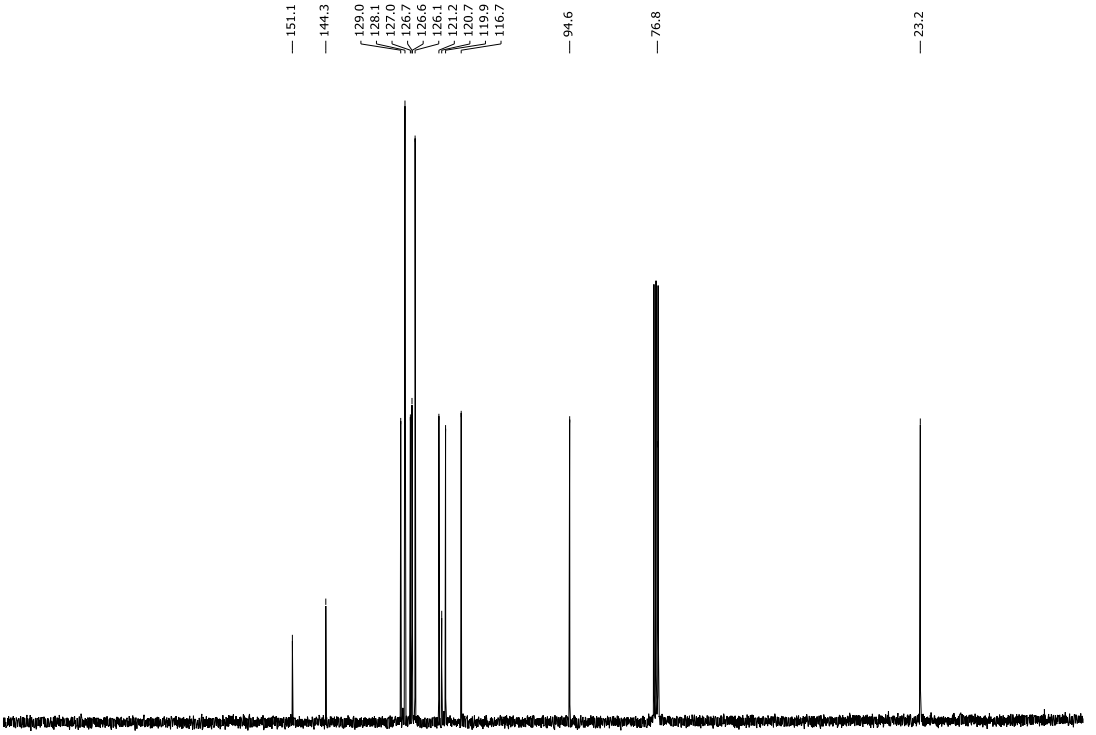
75 MHz ^{13}C NMR spectrum of compound **3a** ($CDCl_3$, 300 K)



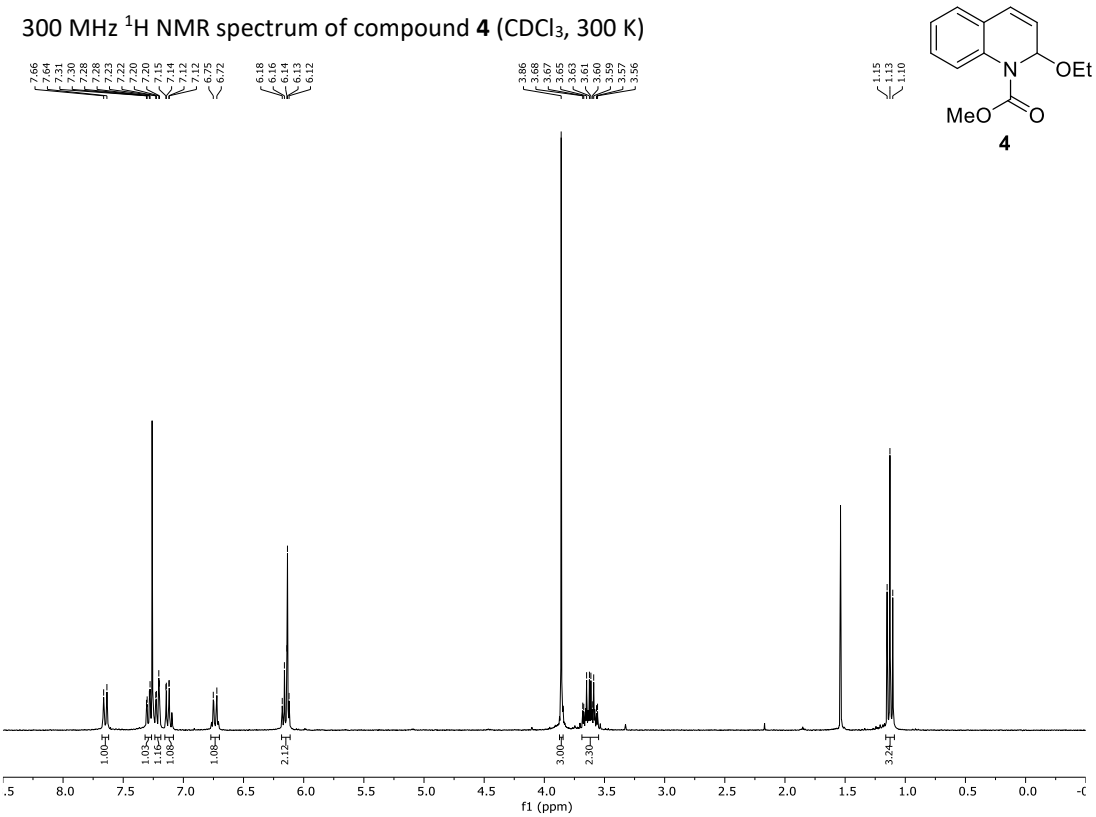
300 MHz ^{1}H NMR spectrum of compound **3b** ($CDCl_3$, 300 K)



75 MHz ^{13}C NMR spectrum of compound **3b** ($CDCl_3$, 300 K)

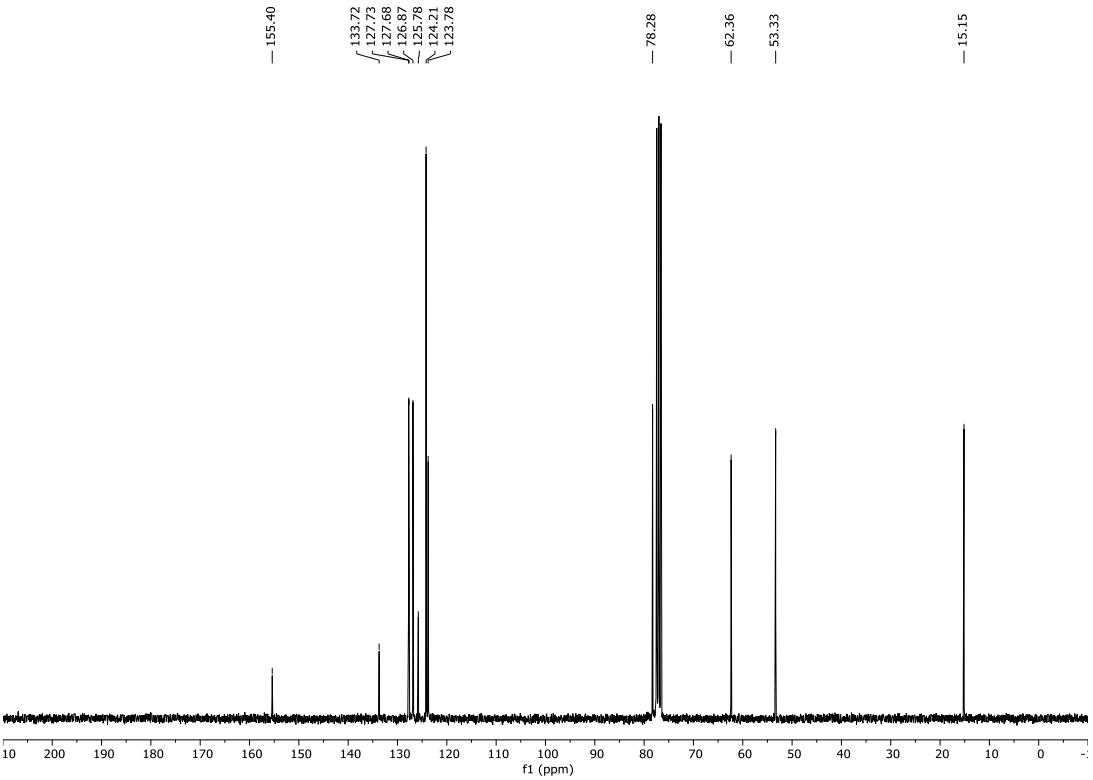


300 MHz ^{1}H NMR spectrum of compound **4** ($CDCl_3$, 300 K)

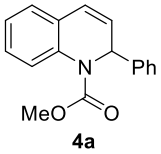


4

75 MHz ^{13}C NMR spectrum of compound **4** ($CDCl_3$, 300 K)

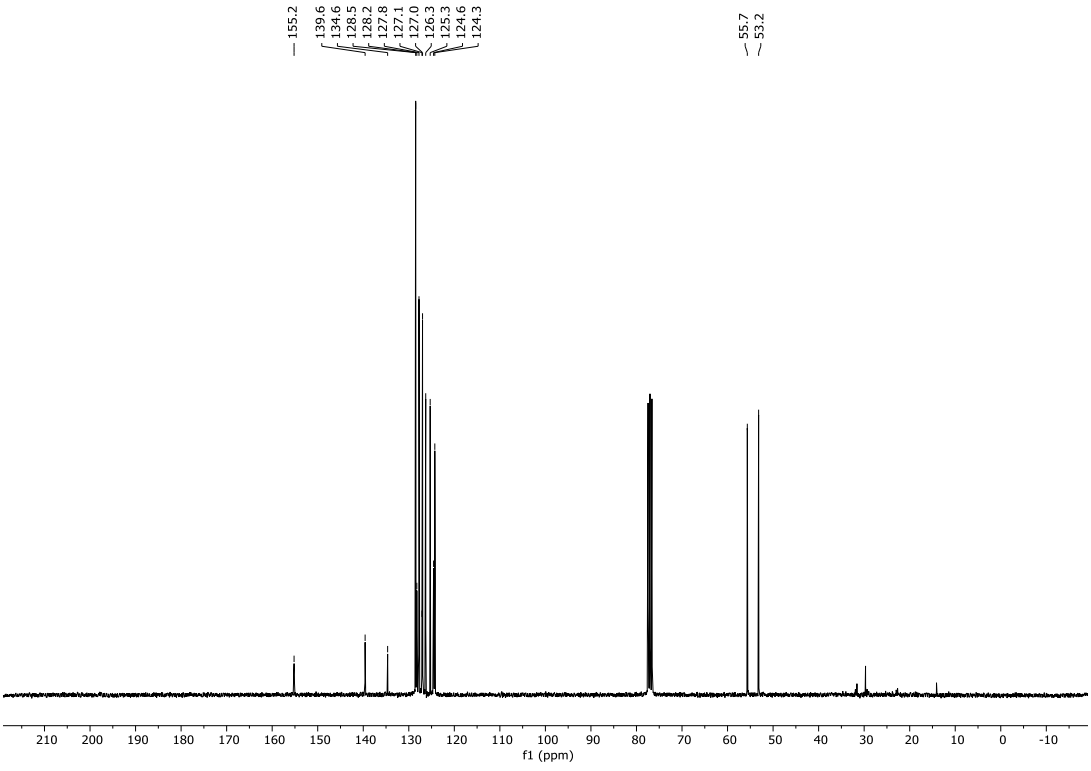


300 MHz ^{1}H NMR spectrum of compound **4a** ($CDCl_3$, 300 K)

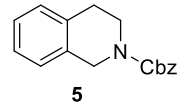


4a

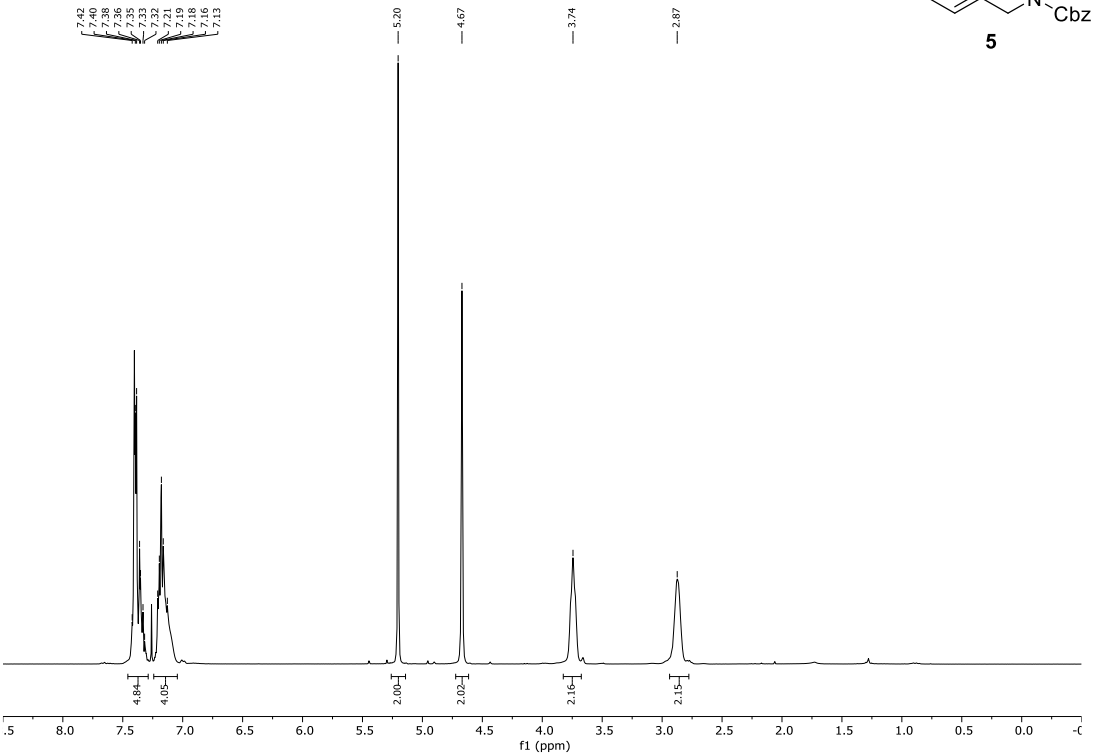
75 MHz ^{13}C NMR spectrum of compound **4a** ($CDCl_3$, 300 K)



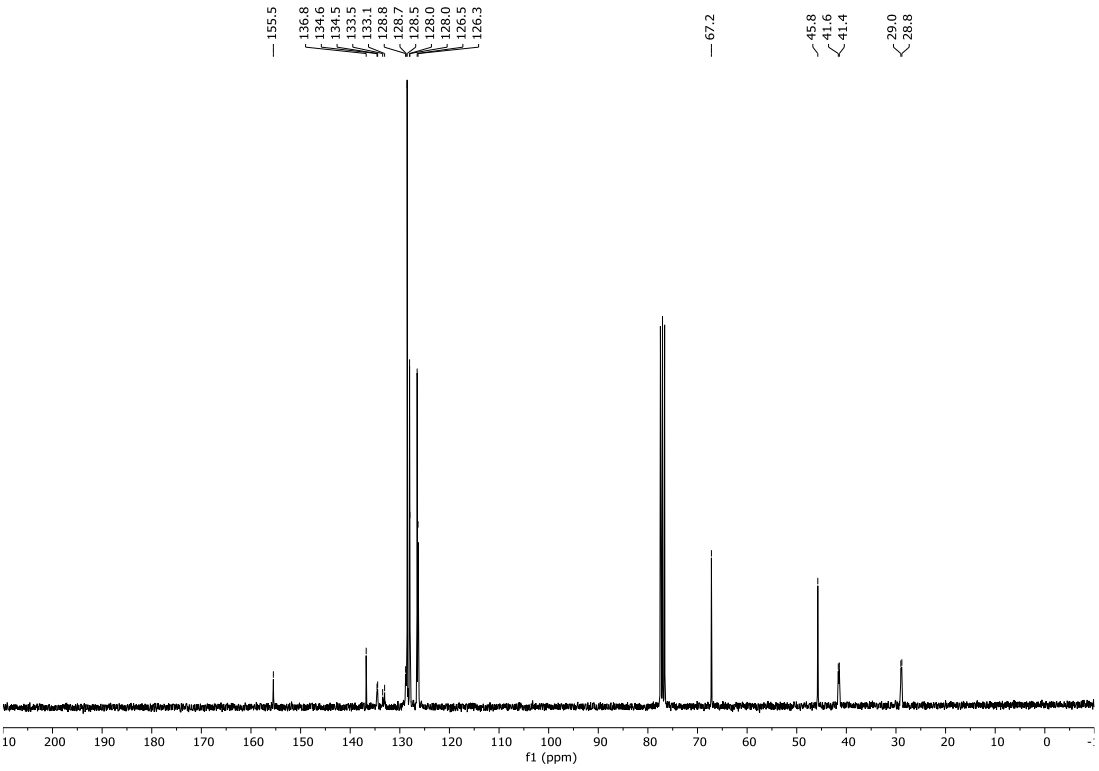
300 MHz ^{1}H NMR spectrum of compound **5** ($CDCl_3$, 300 K)



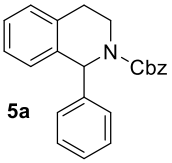
5



75 MHz ^{13}C NMR spectrum of compound **5** ($CDCl_3$, 300 K)

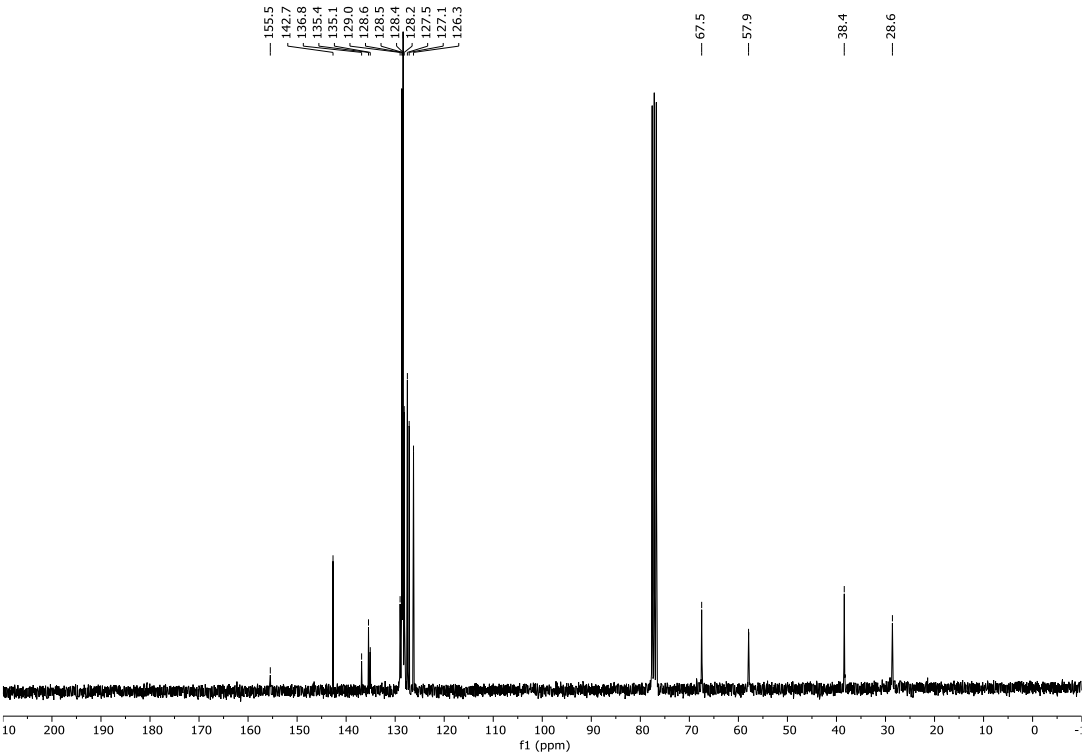


300 MHz ^{1}H NMR spectrum of compound **5a** ($CDCl_3$, 300 K)

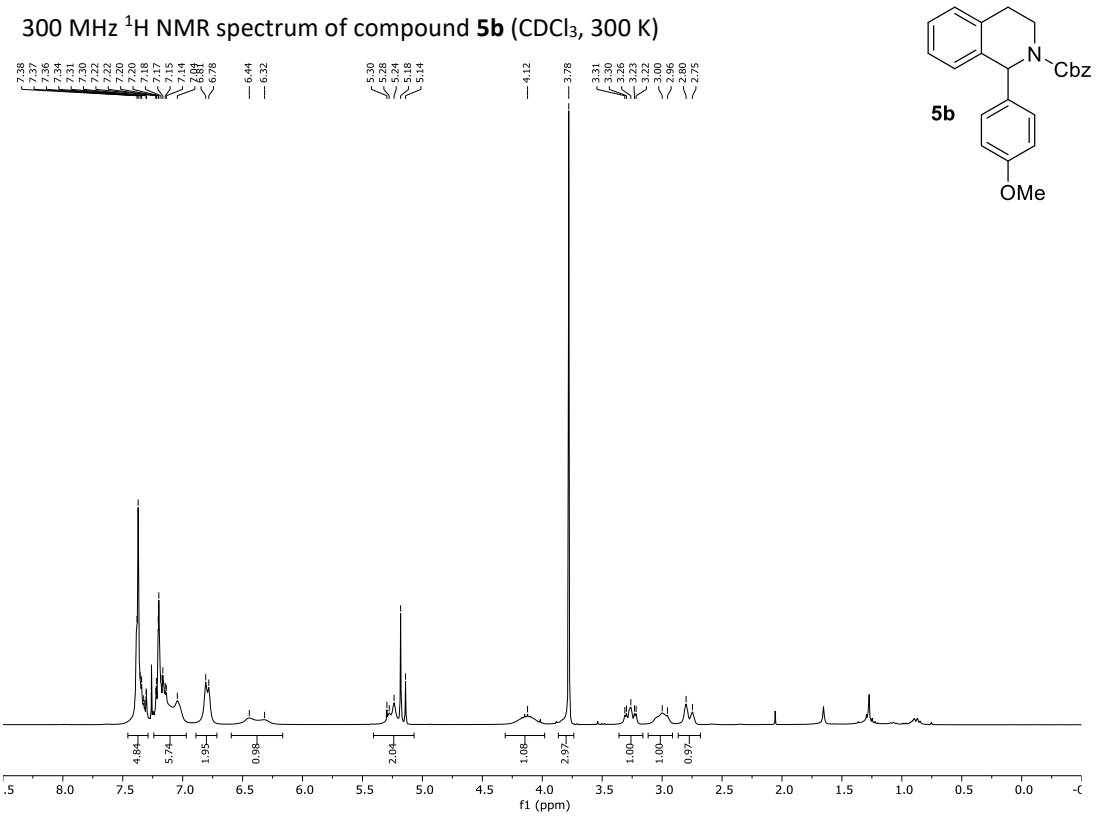


5a

75 MHz ^{13}C NMR spectrum of compound **5a** ($CDCl_3$, 300 K)

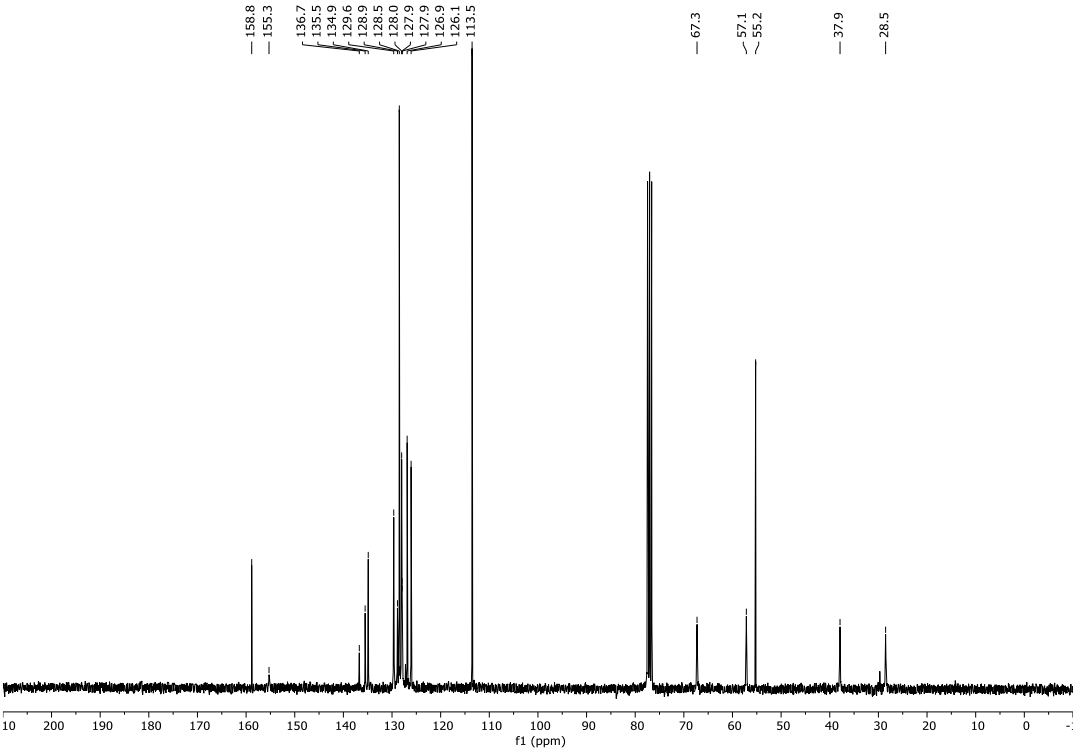


300 MHz ^{1}H NMR spectrum of compound **5b** ($CDCl_3$, 300 K)

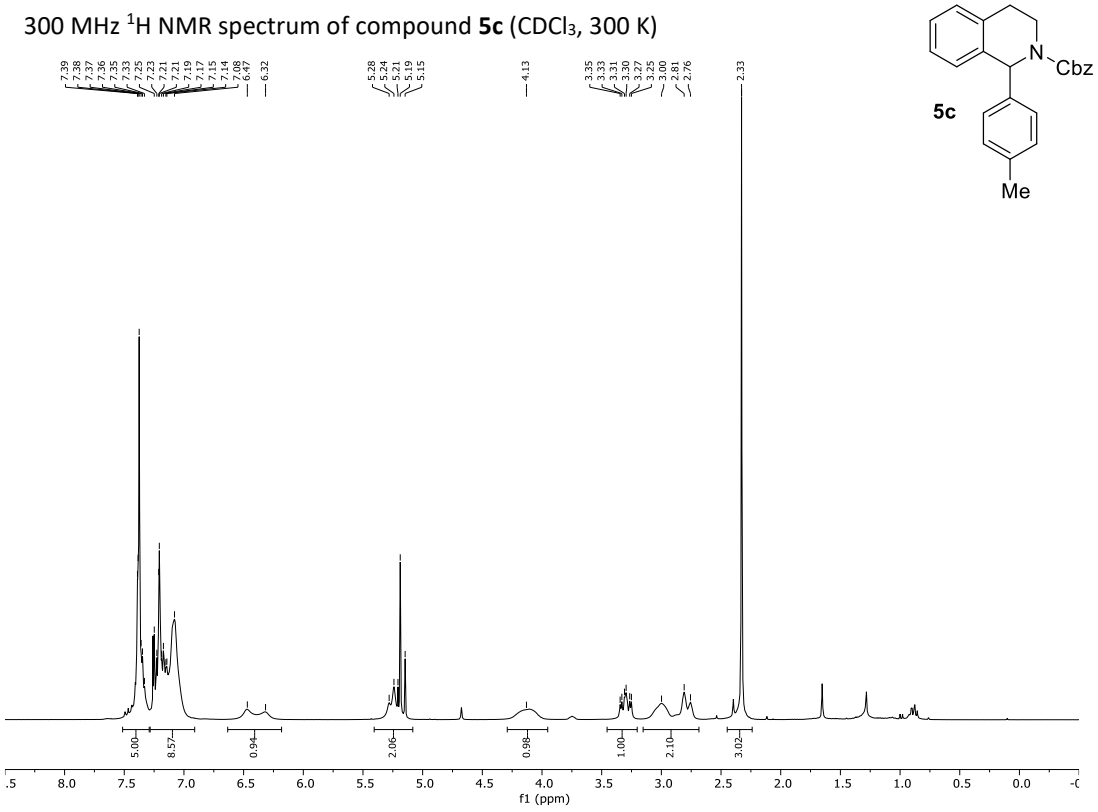


5b

75 MHz ^{13}C NMR spectrum of compound **5b** ($CDCl_3$, 300 K)

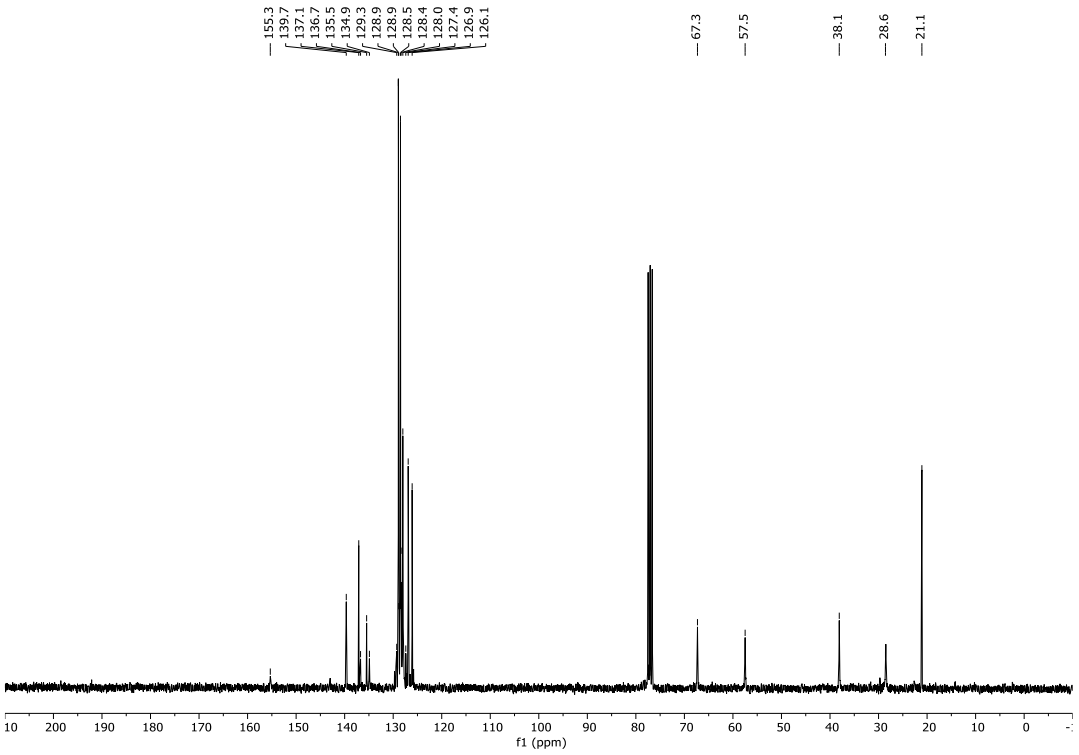


300 MHz ^{1}H NMR spectrum of compound **5c** ($CDCl_3$, 300 K)

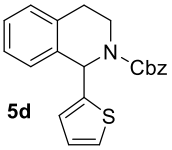


5c

75 MHz ^{13}C NMR spectrum of compound **5c** ($CDCl_3$, 300 K)

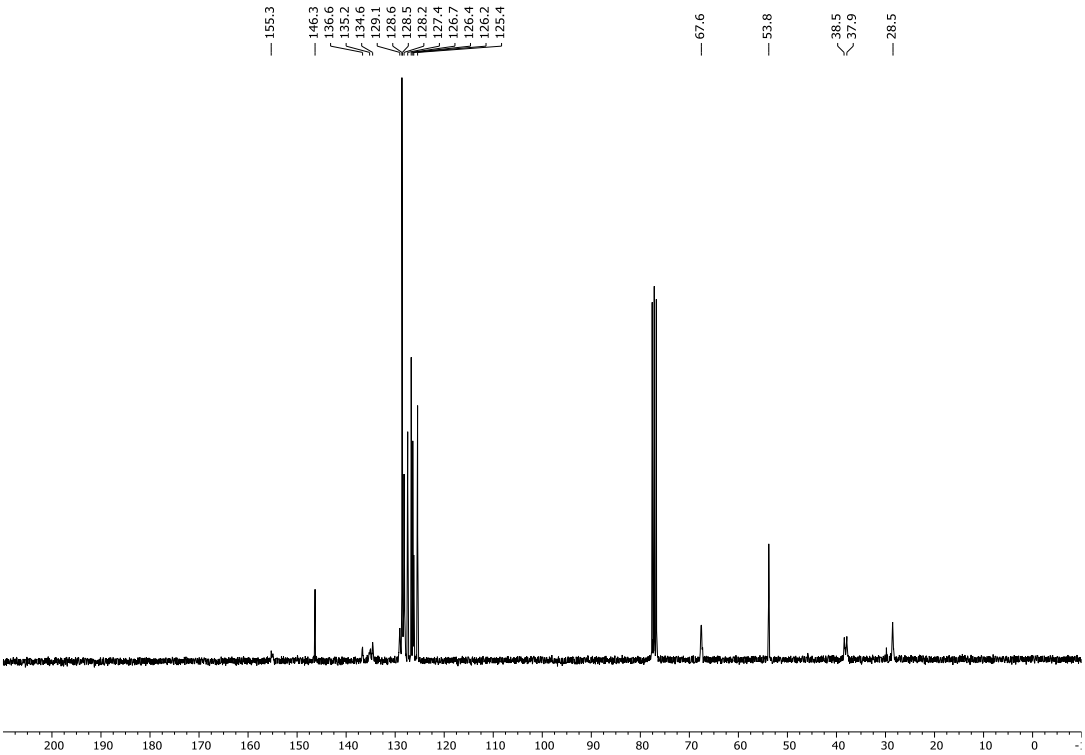


300 MHz ^{1}H NMR spectrum of compound **5d** ($CDCl_3$, 300 K)

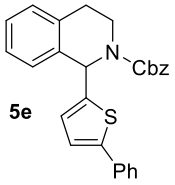


5d

75 MHz ^{13}C NMR spectrum of compound **5d** ($CDCl_3$, 300 K)

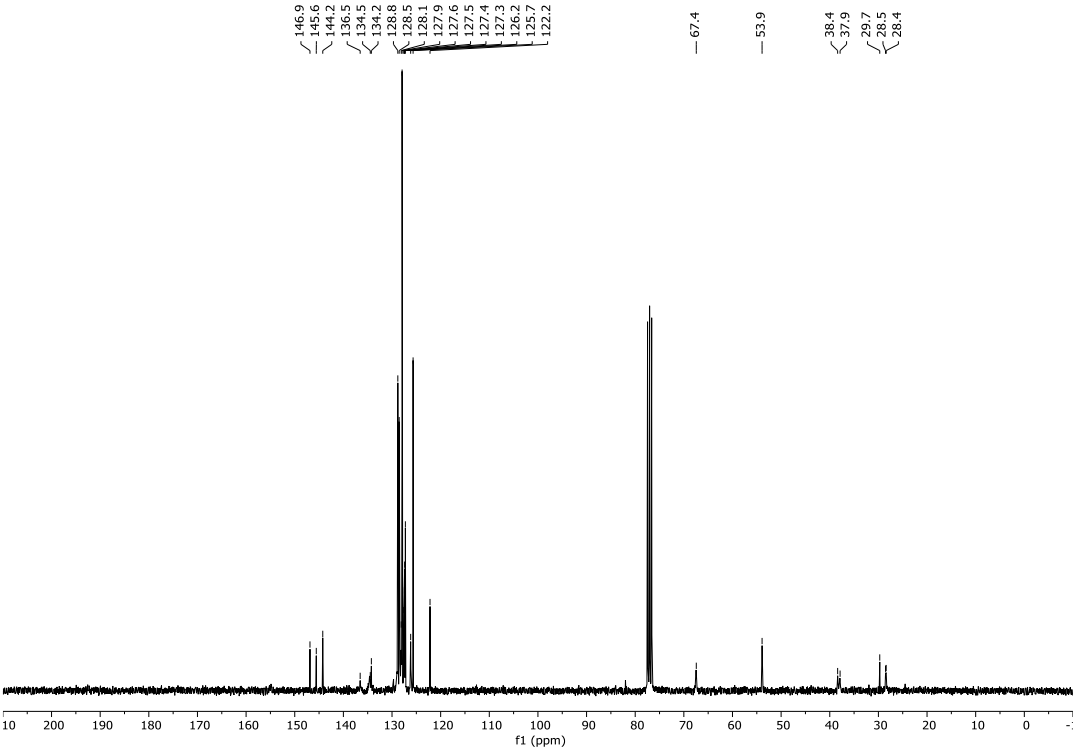


300 MHz ^{1}H NMR spectrum of compound **5e** ($CDCl_3$, 300 K)

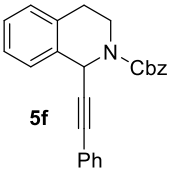


5e

75 MHz ^{13}C NMR spectrum of compound **5e** ($CDCl_3$, 300 K)

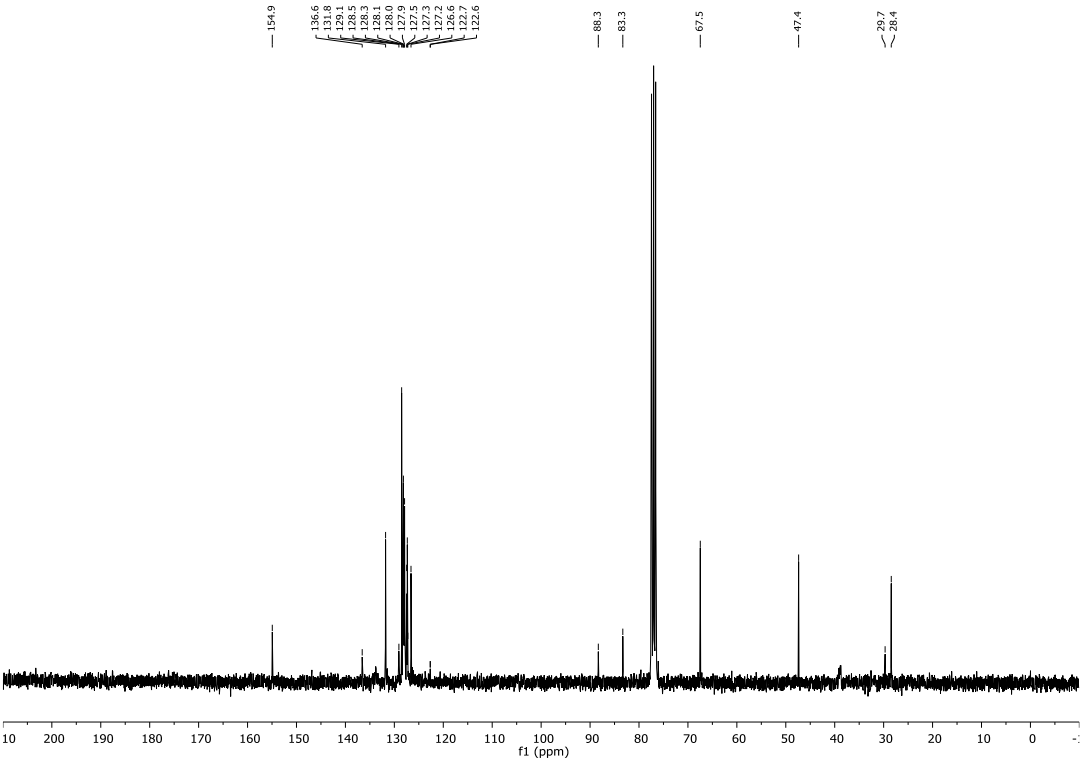


300 MHz ^{1}H NMR spectrum of compound **5f** ($CDCl_3$, 300 K)

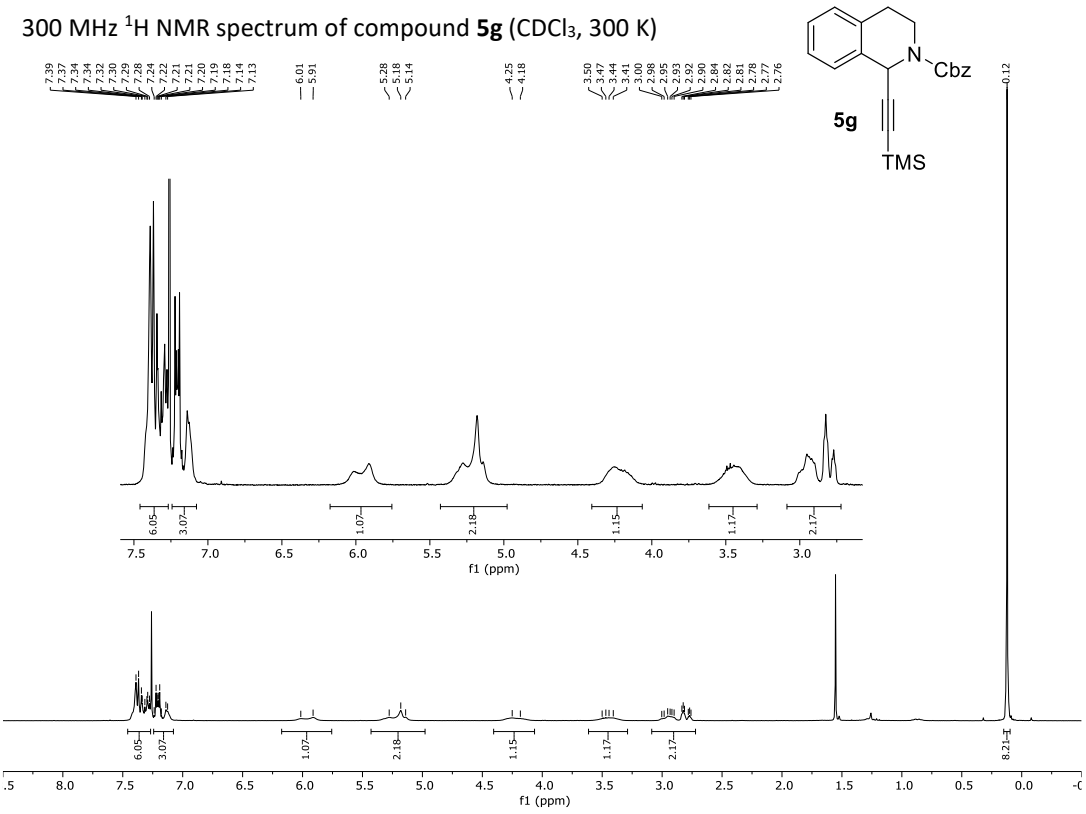


5f

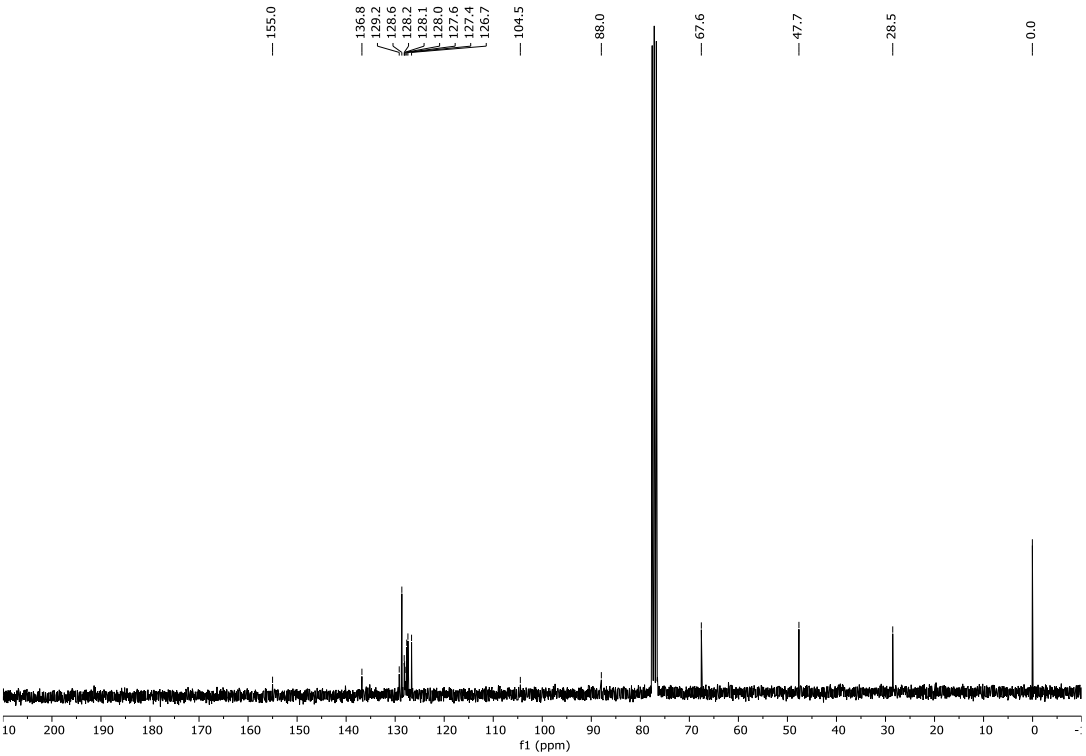
75 MHz ^{13}C NMR spectrum of compound **5f** ($CDCl_3$, 300 K)



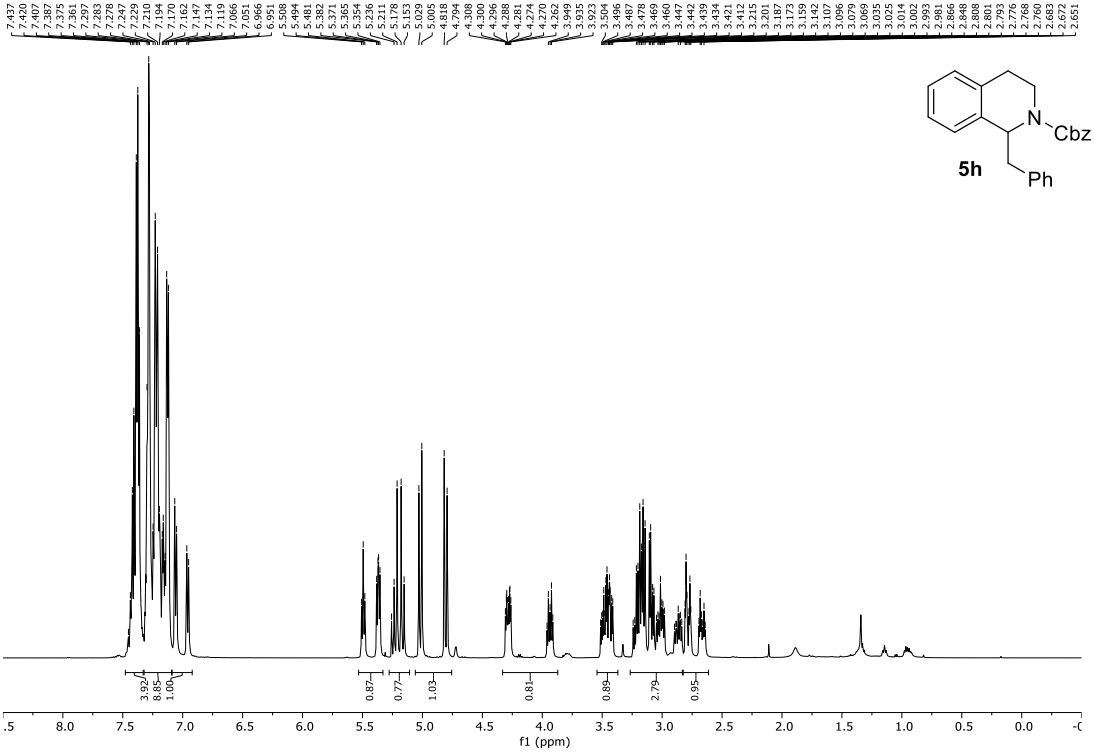
300 MHz ^{1}H NMR spectrum of compound **5g** ($CDCl_3$, 300 K)



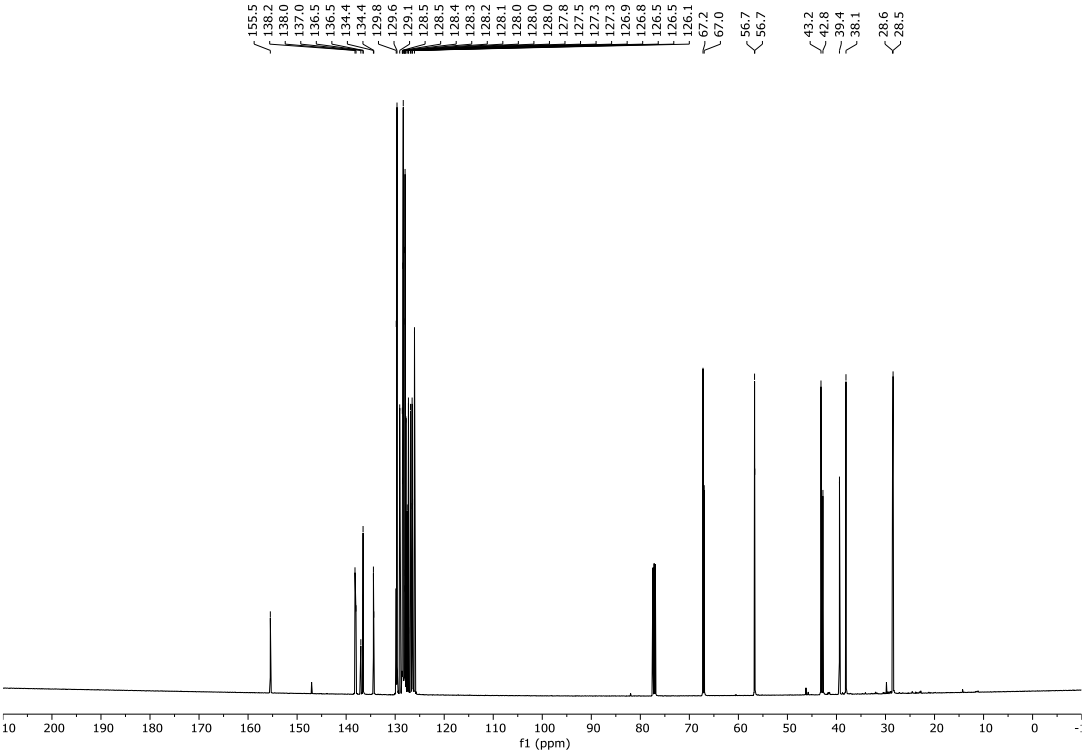
75 MHz ^{13}C NMR spectrum of compound **5g** ($CDCl_3$, 300 K)



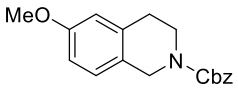
500 MHz ^{1}H NMR spectrum of compound **5h** ($CDCl_3$, 300 K)



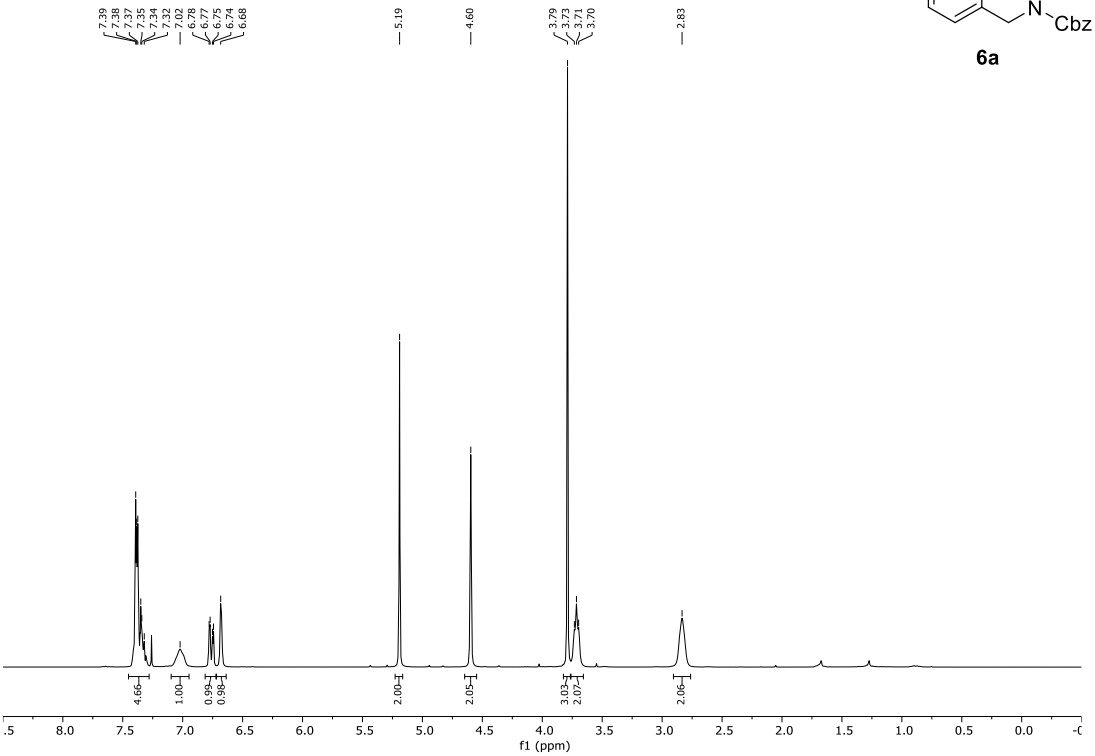
125 MHz ^{13}C NMR spectrum of compound **5h** ($CDCl_3$, 300 K)



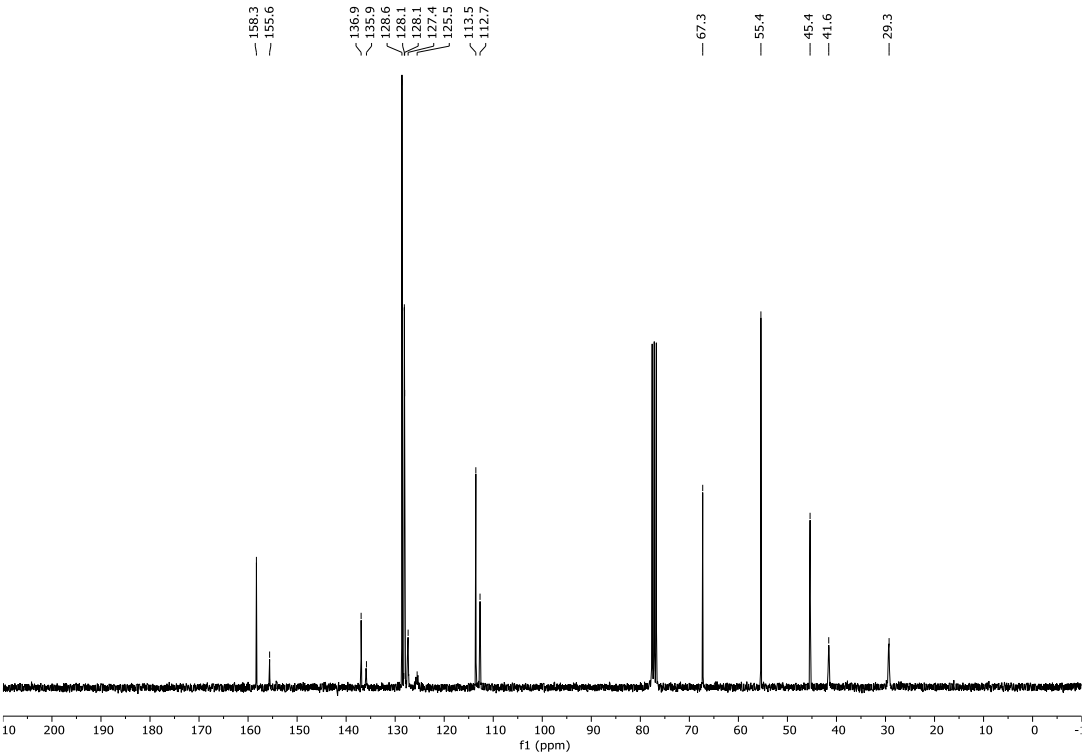
300 MHz ^{1}H NMR spectrum of compound **6a** ($CDCl_3$, 300 K)



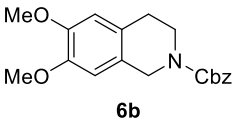
6a



75 MHz ^{13}C NMR spectrum of compound **6a** ($CDCl_3$, 300 K)

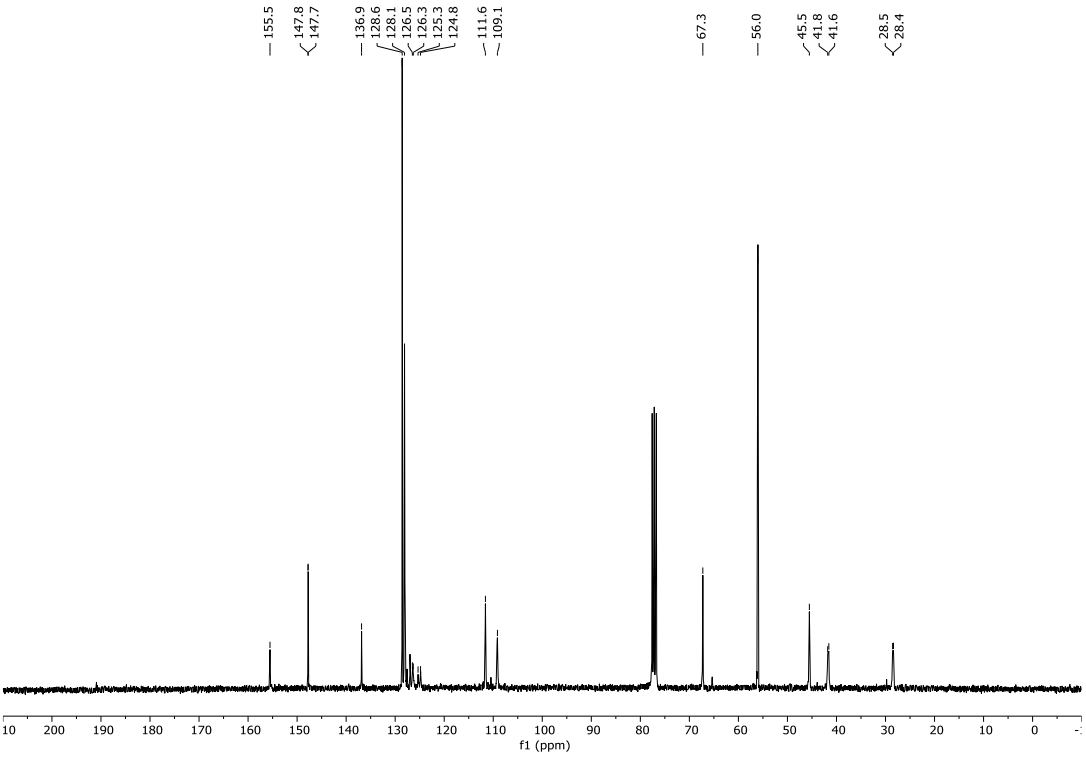


300 MHz ^{1}H NMR spectrum of compound **6b** ($CDCl_3$, 300 K)

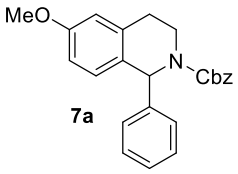


6b

75 MHz ^{13}C NMR spectrum of compound **6b** ($CDCl_3$, 300 K)

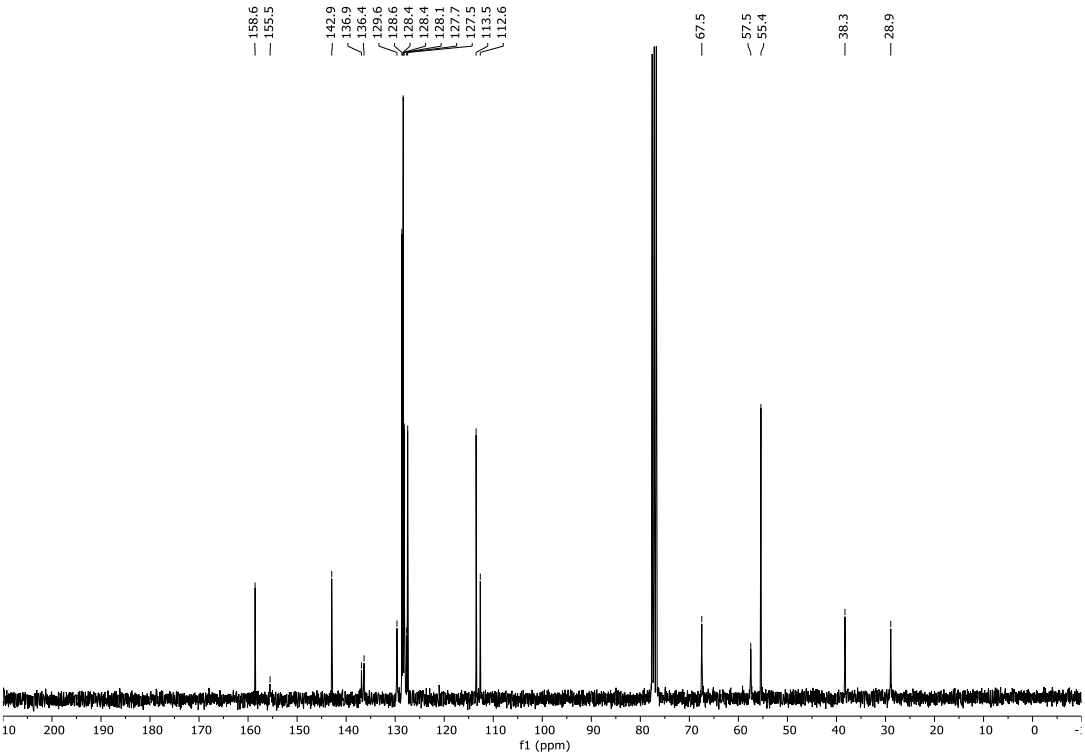


300 MHz ^{1}H NMR spectrum of compound **7a** ($CDCl_3$, 300 K)

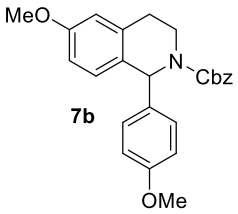


7a

75 MHz ^{13}C NMR spectrum of compound **7a** ($CDCl_3$, 300 K)

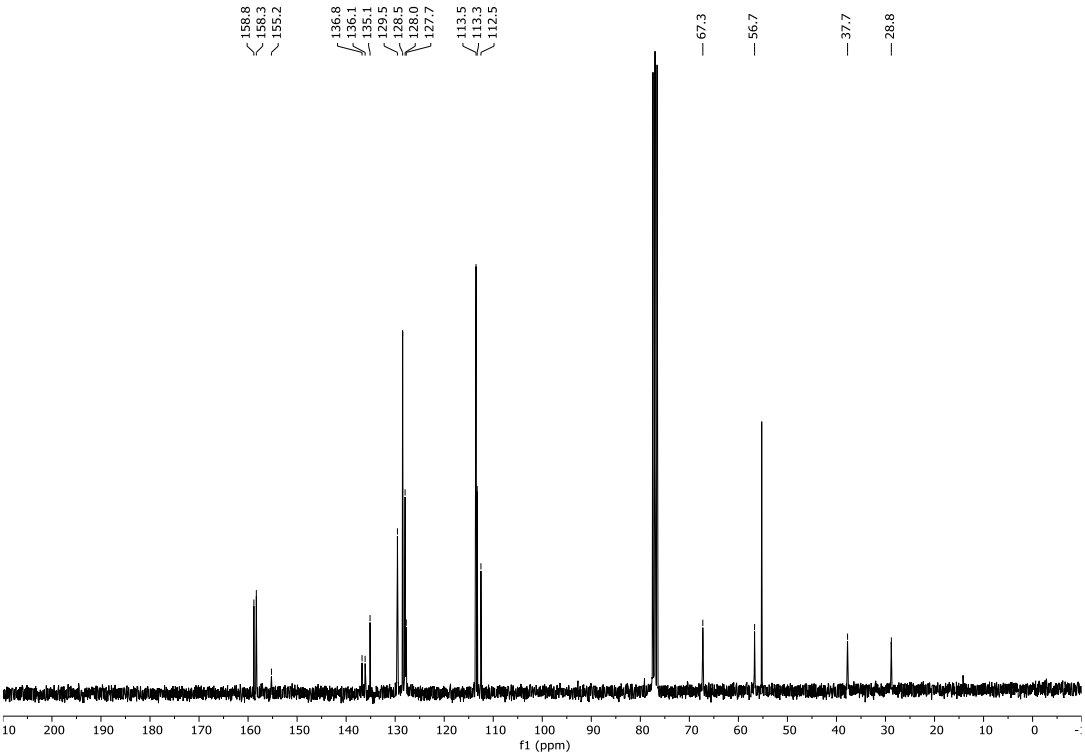


300 MHz ^{1}H NMR spectrum of compound **7b** ($CDCl_3$, 300 K)

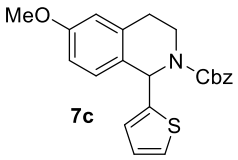


7b

75 MHz ^{13}C NMR spectrum of compound **7b** ($CDCl_3$, 300 K)

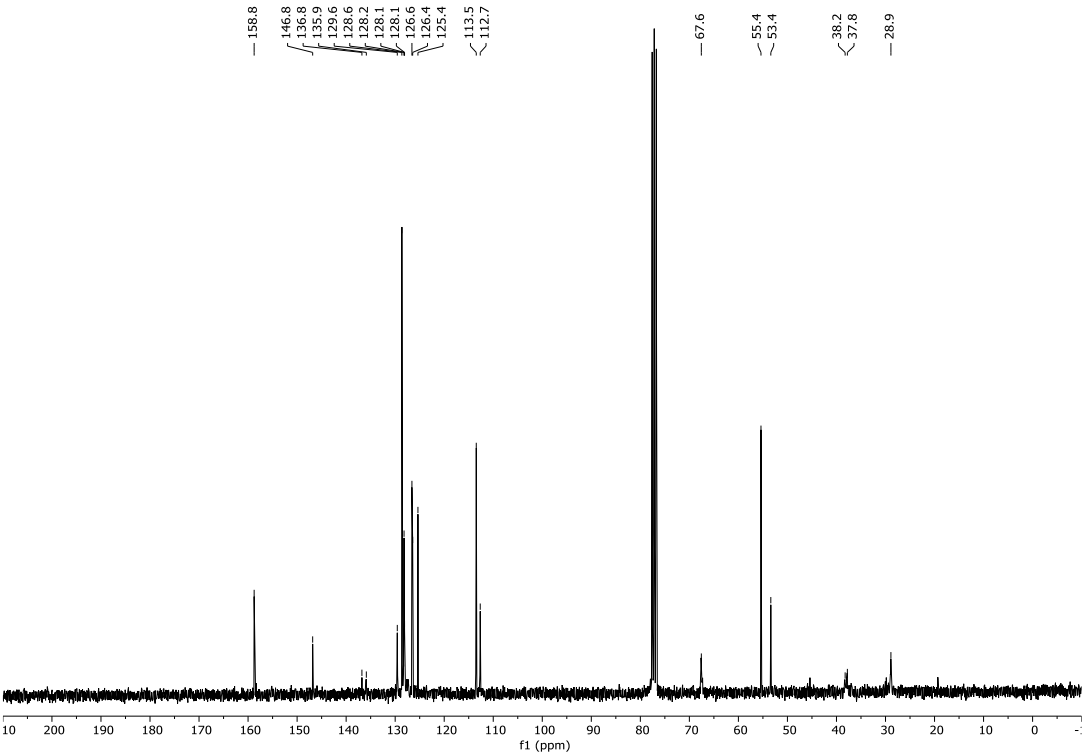


300 MHz ^{1}H NMR spectrum of compound **7c** ($CDCl_3$, 300 K)

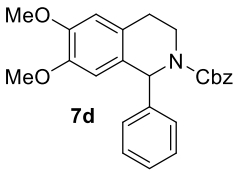


7c

75 MHz ^{13}C NMR spectrum of compound **7c** ($CDCl_3$, 300 K)

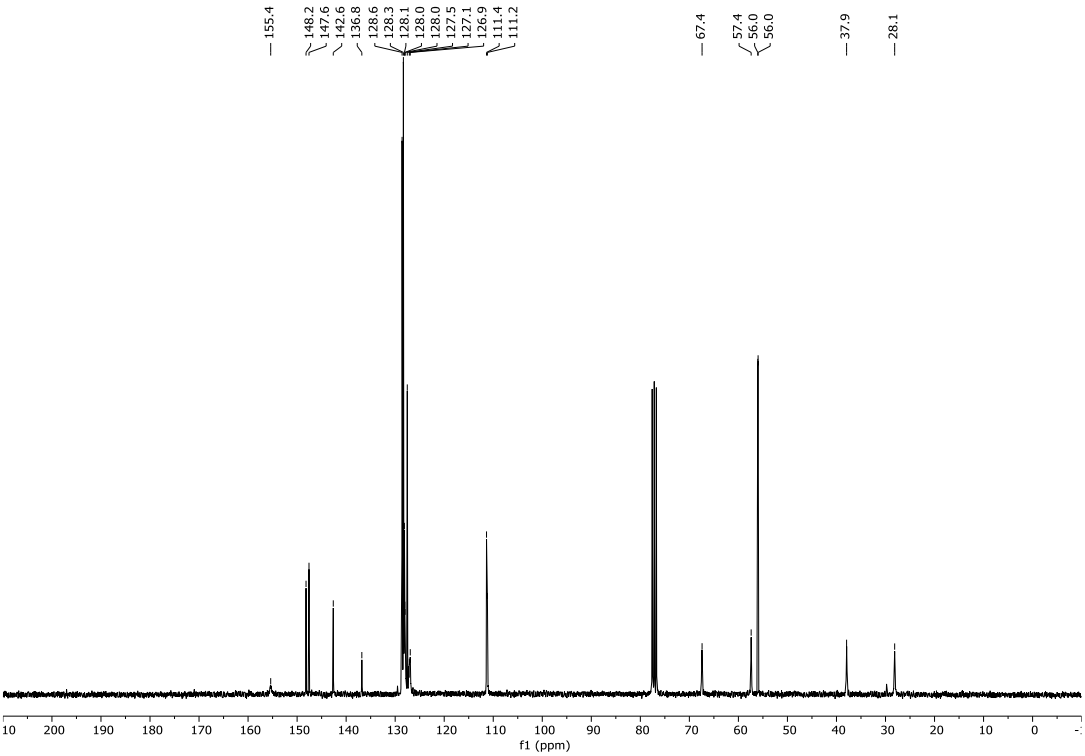


300 MHz ^{1}H NMR spectrum of compound **7d** ($CDCl_3$, 300 K)

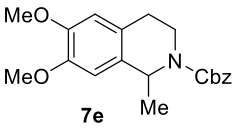


7d

75 MHz ^{13}C NMR spectrum of compound **7d** ($CDCl_3$, 300 K)

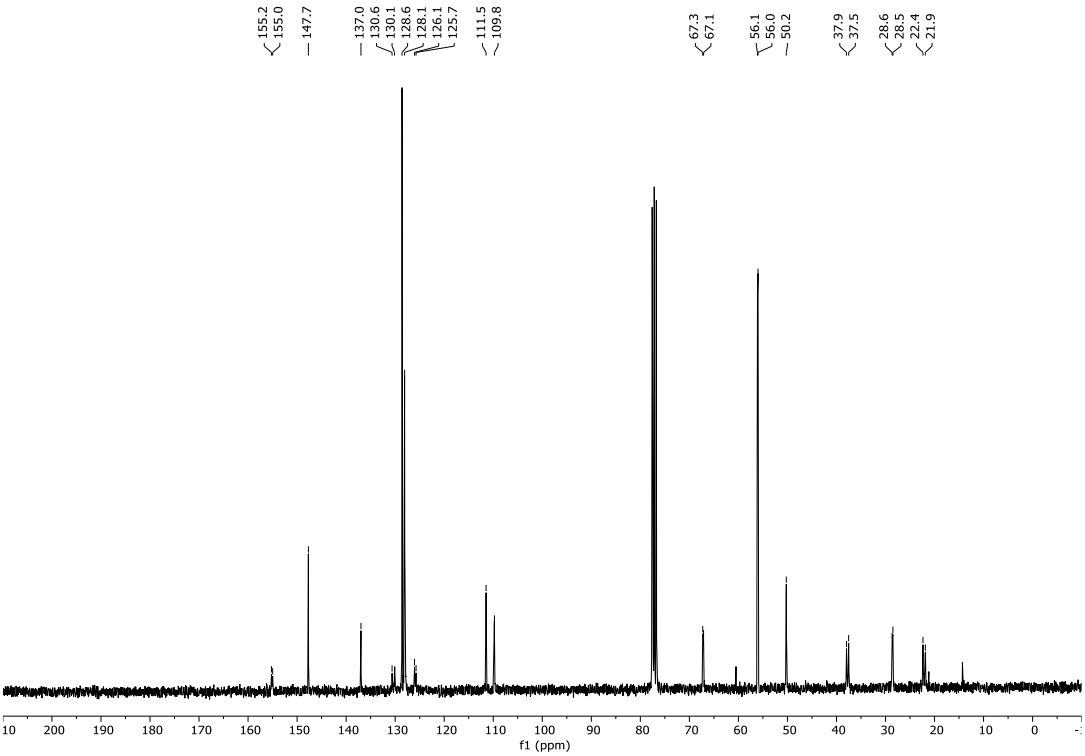


300 MHz ^{1}H NMR spectrum of compound **7e** ($CDCl_3$, 300 K)

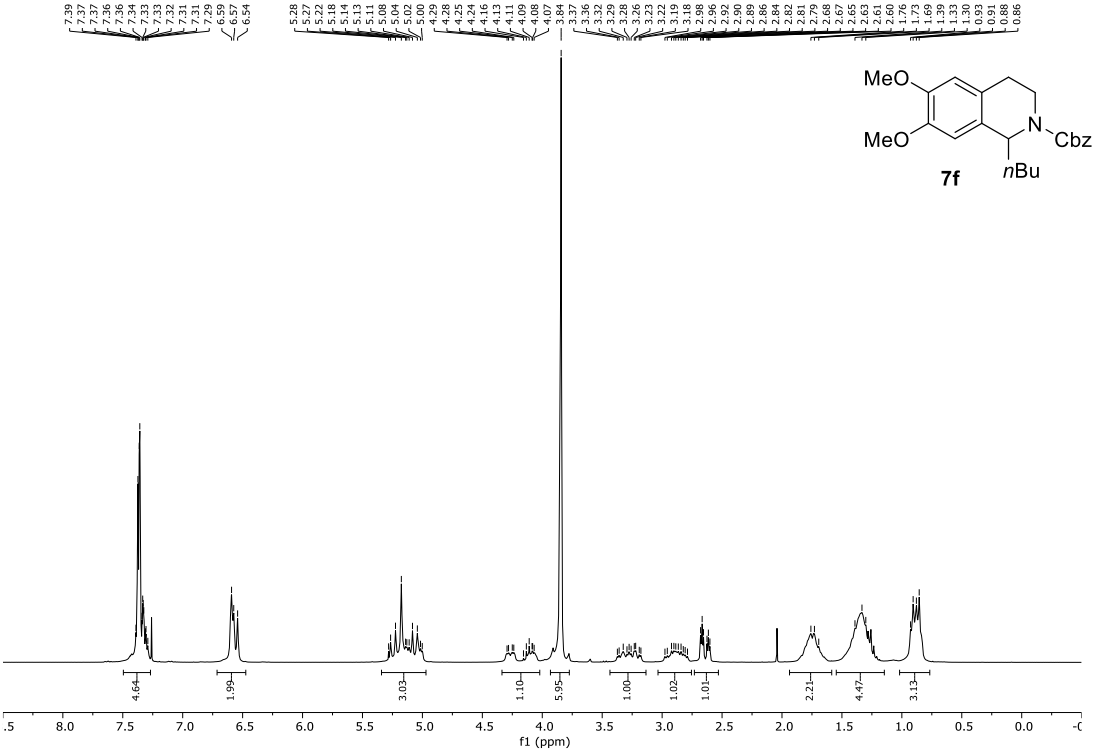


7e

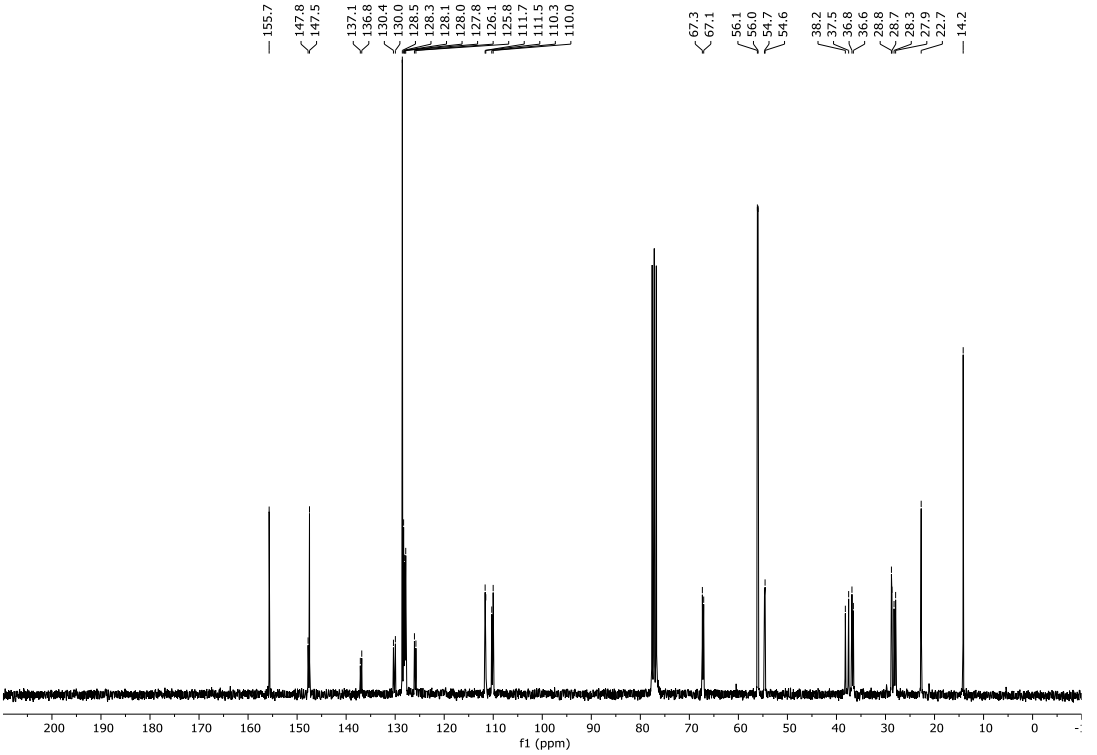
75 MHz ^{13}C NMR spectrum of compound **7e** ($CDCl_3$, 300 K)



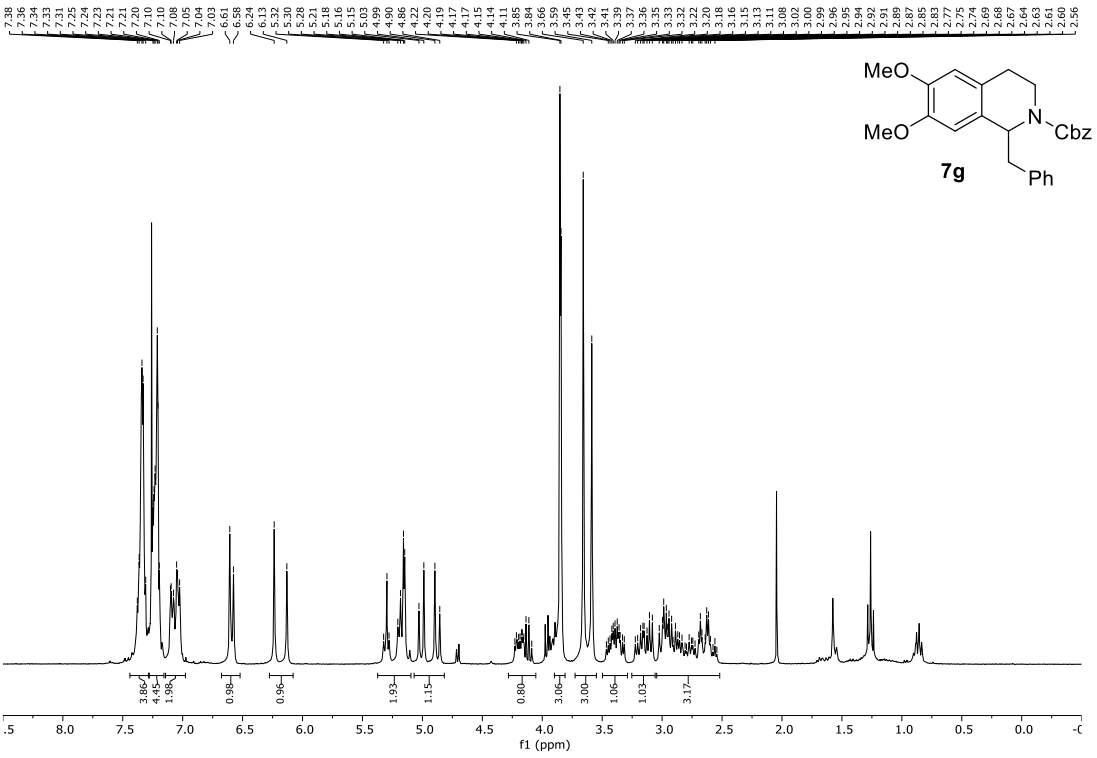
300 MHz ^{1}H NMR spectrum of compound **7f** ($CDCl_3$, 300 K)



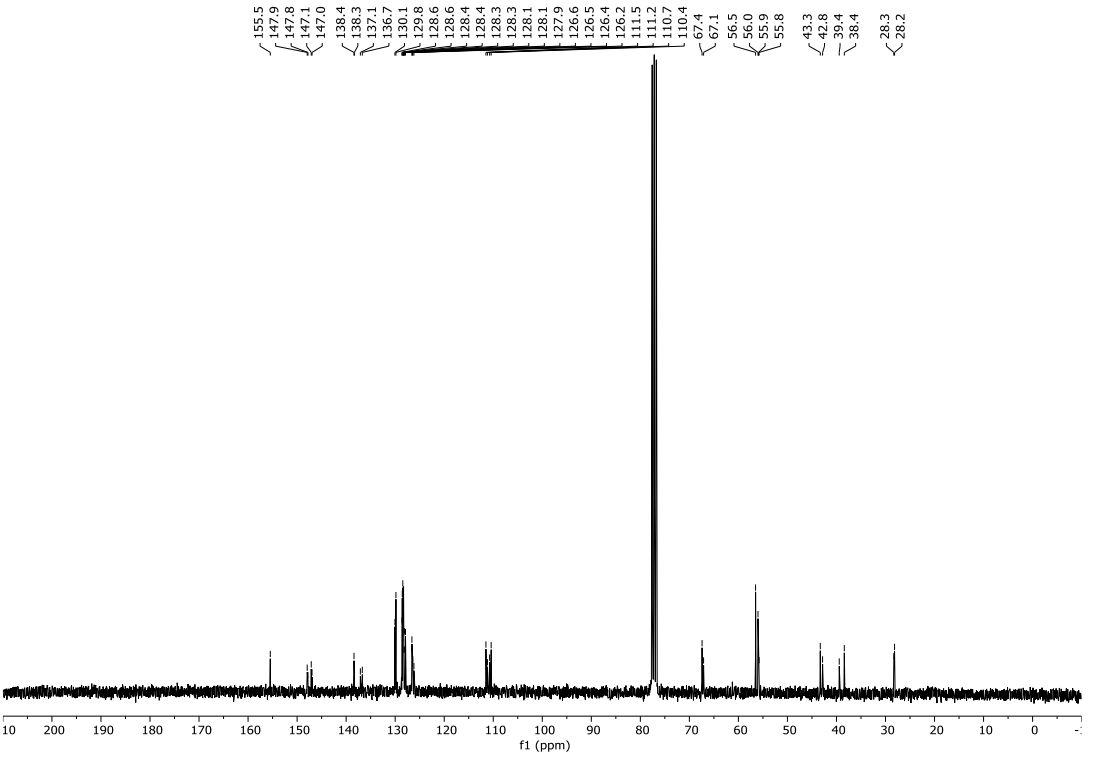
75 MHz ^{13}C NMR spectrum of compound **7f** ($CDCl_3$, 300 K)



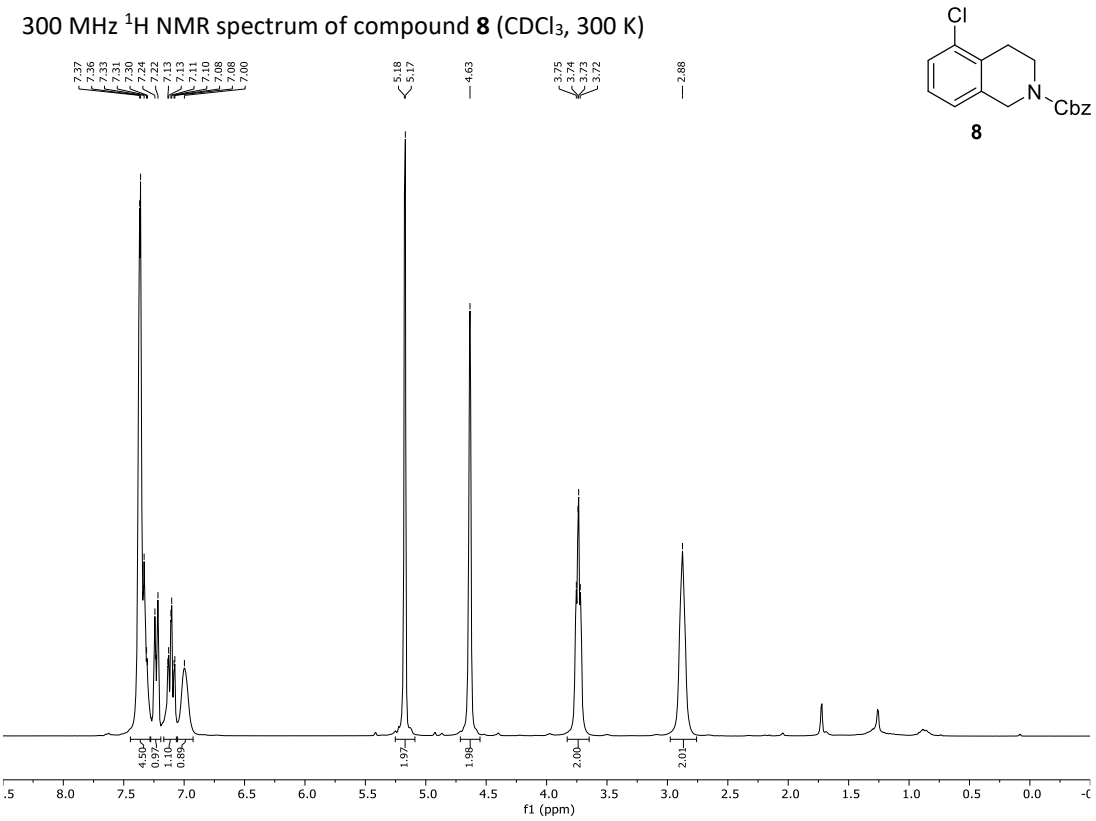
500 MHz ^{1}H NMR spectrum of compound **7g** ($CDCl_3$, 300 K)



125 MHz ^{13}C NMR spectrum of compound **7f** ($CDCl_3$, 300 K)

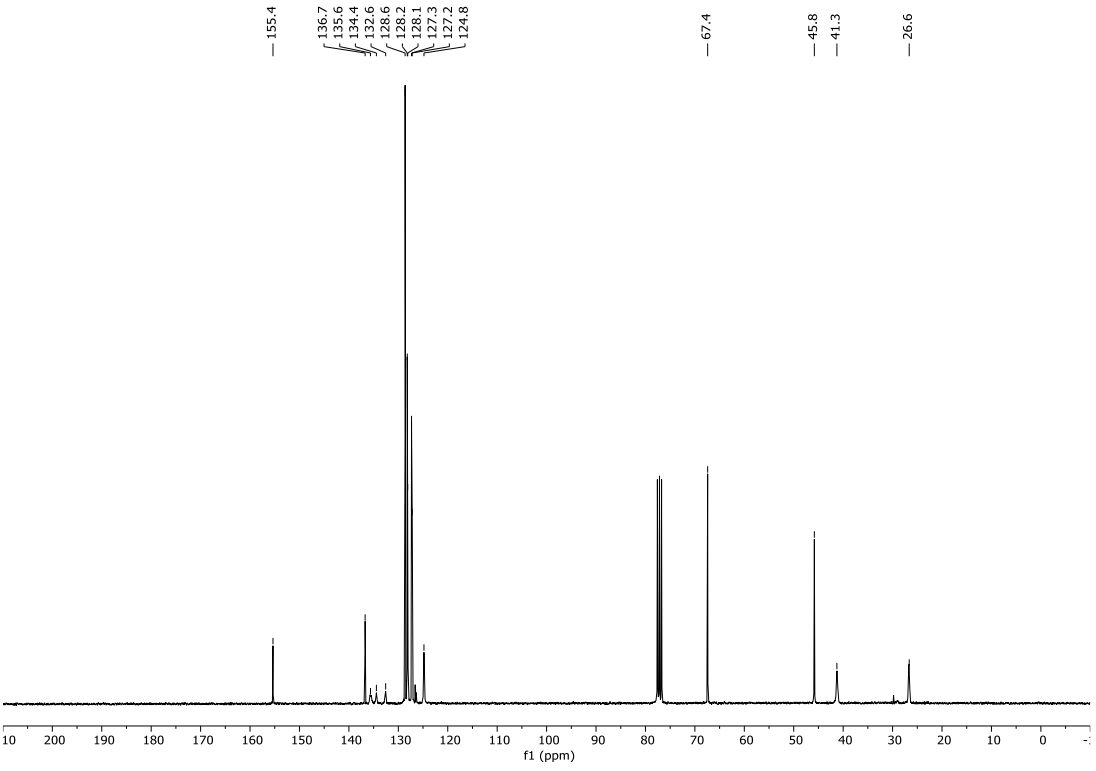


300 MHz ^{1}H NMR spectrum of compound **8** ($CDCl_3$, 300 K)

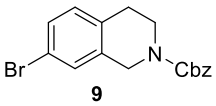


8

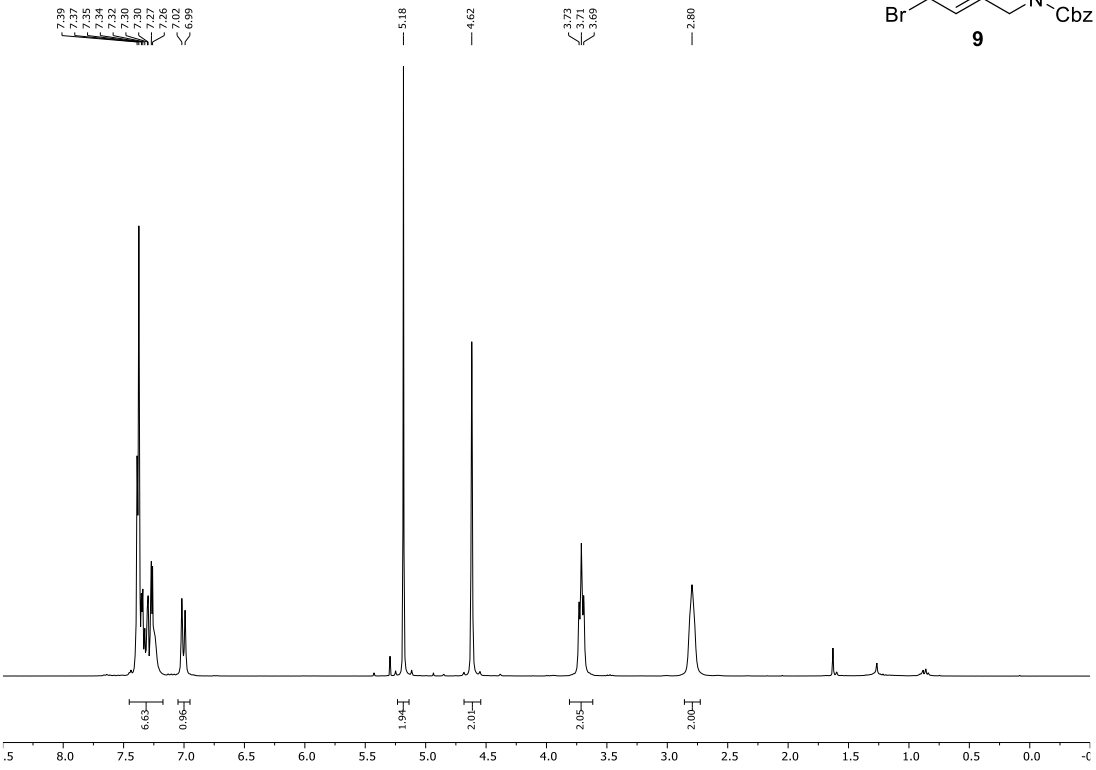
75 MHz ^{13}C NMR spectrum of compound **8** ($CDCl_3$, 300 K)



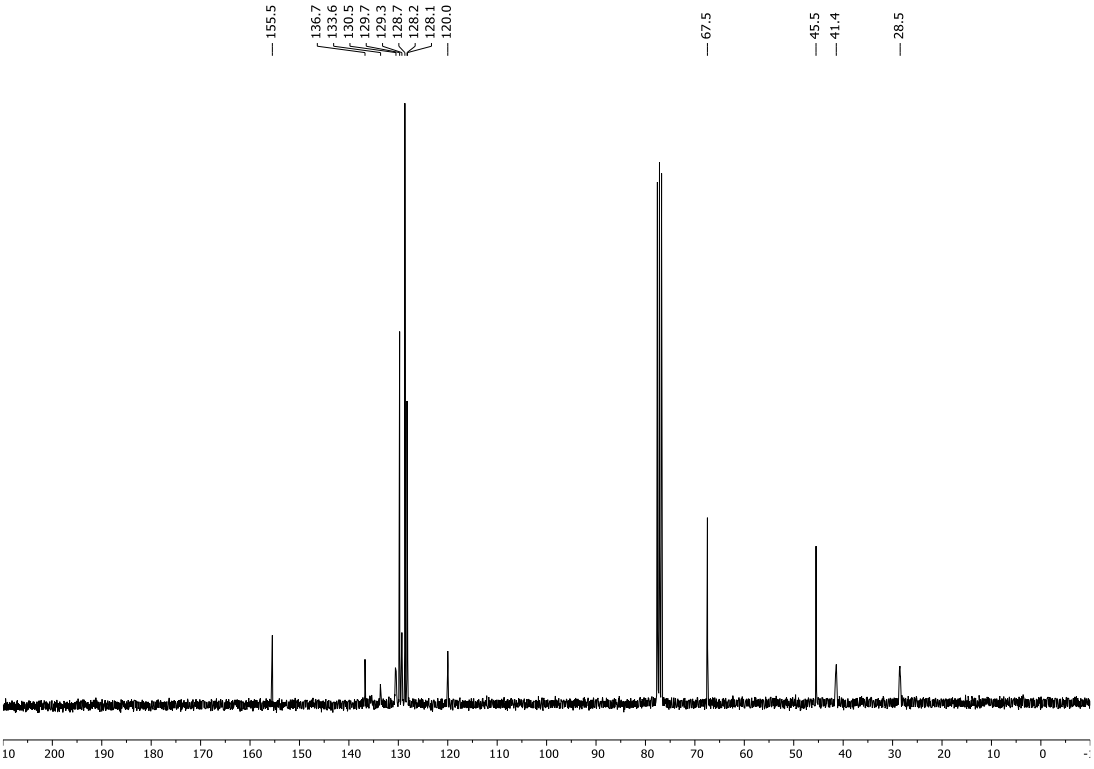
300 MHz ^{1}H NMR spectrum of compound **9** ($CDCl_3$, 300 K)



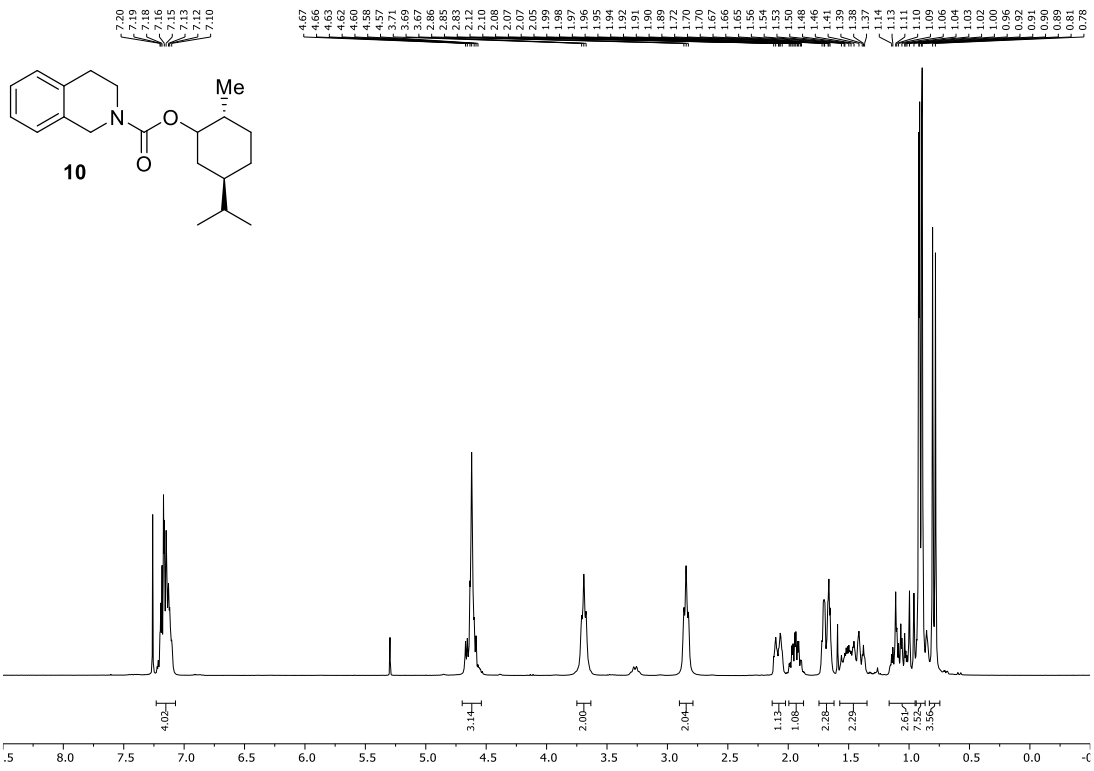
9



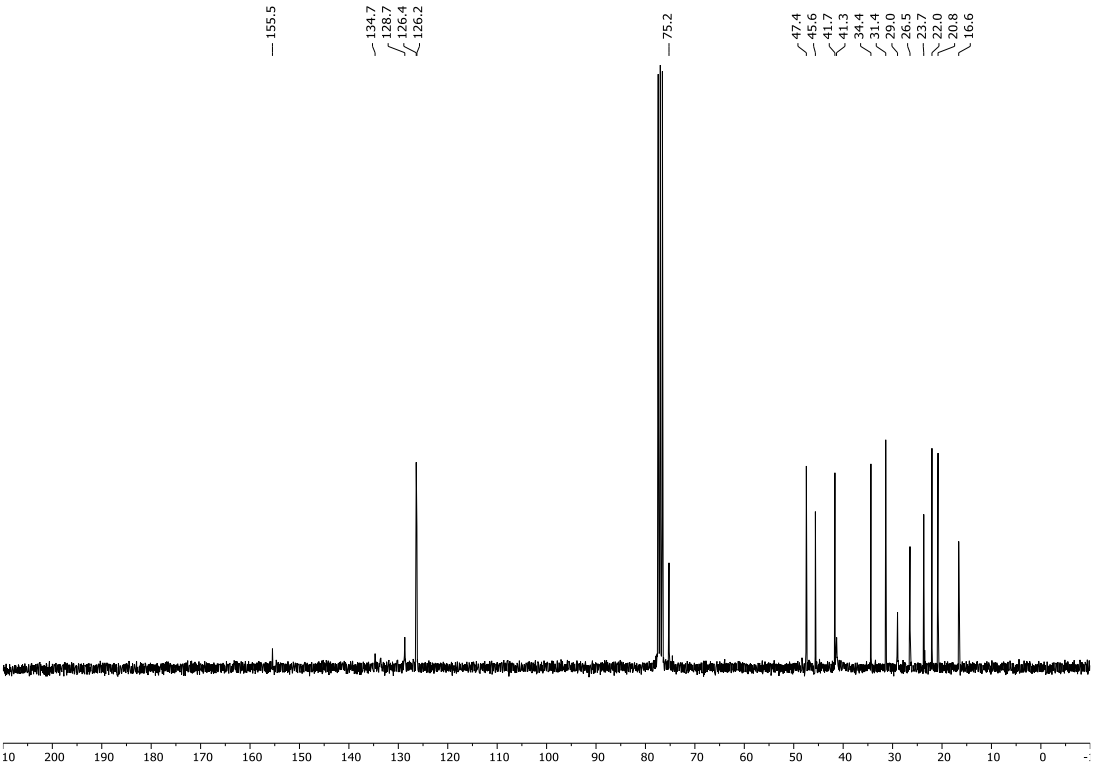
75 MHz ^{13}C NMR spectrum of compound **9** ($CDCl_3$, 300 K)



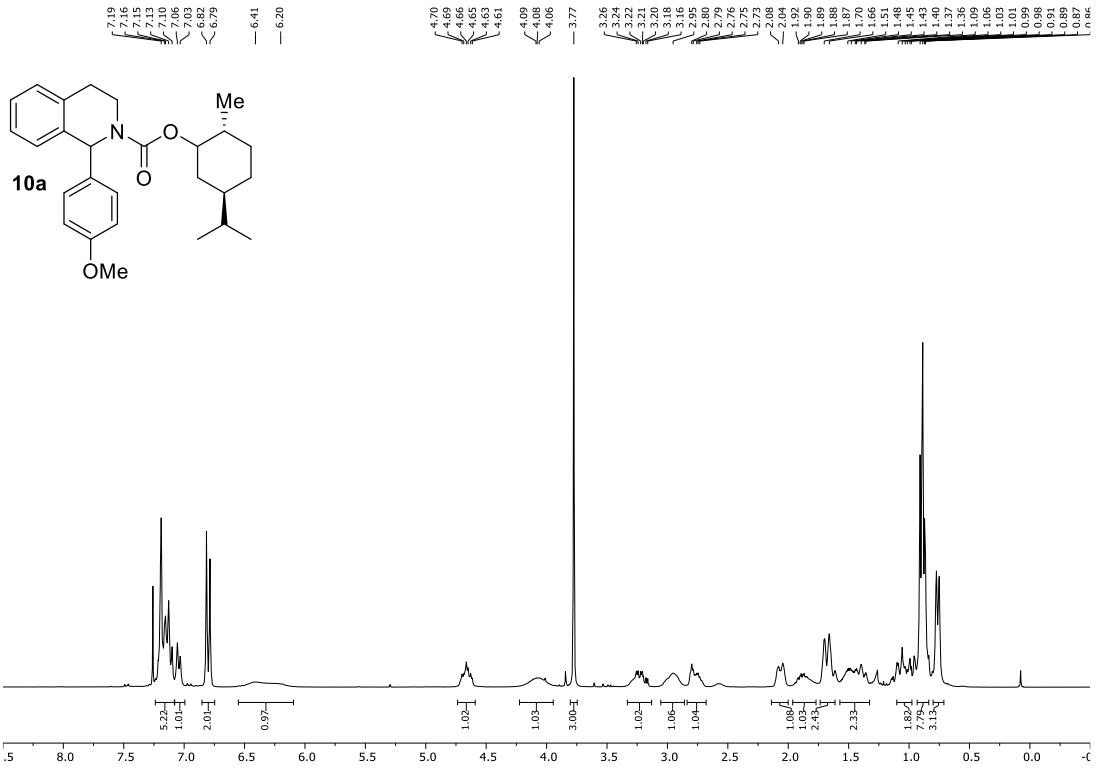
300 MHz ^{1}H NMR spectrum of compound **10** ($CDCl_3$, 300 K)



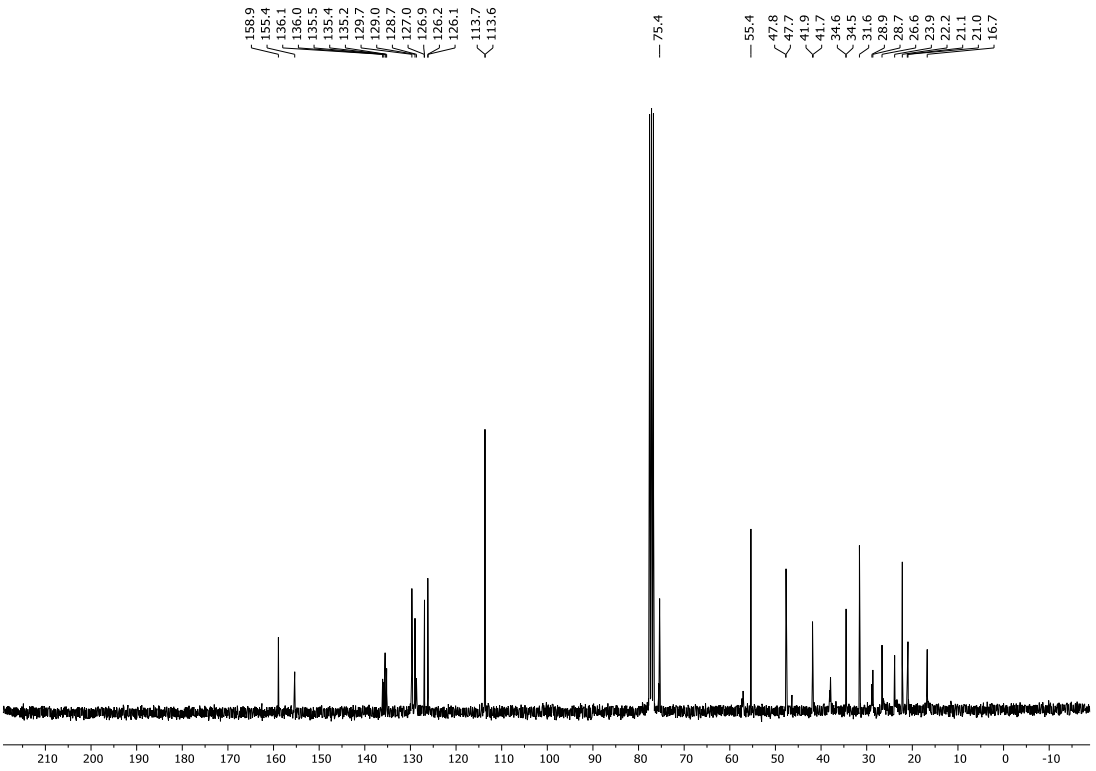
75 MHz ^{13}C NMR spectrum of compound **10** ($CDCl_3$, 300 K)



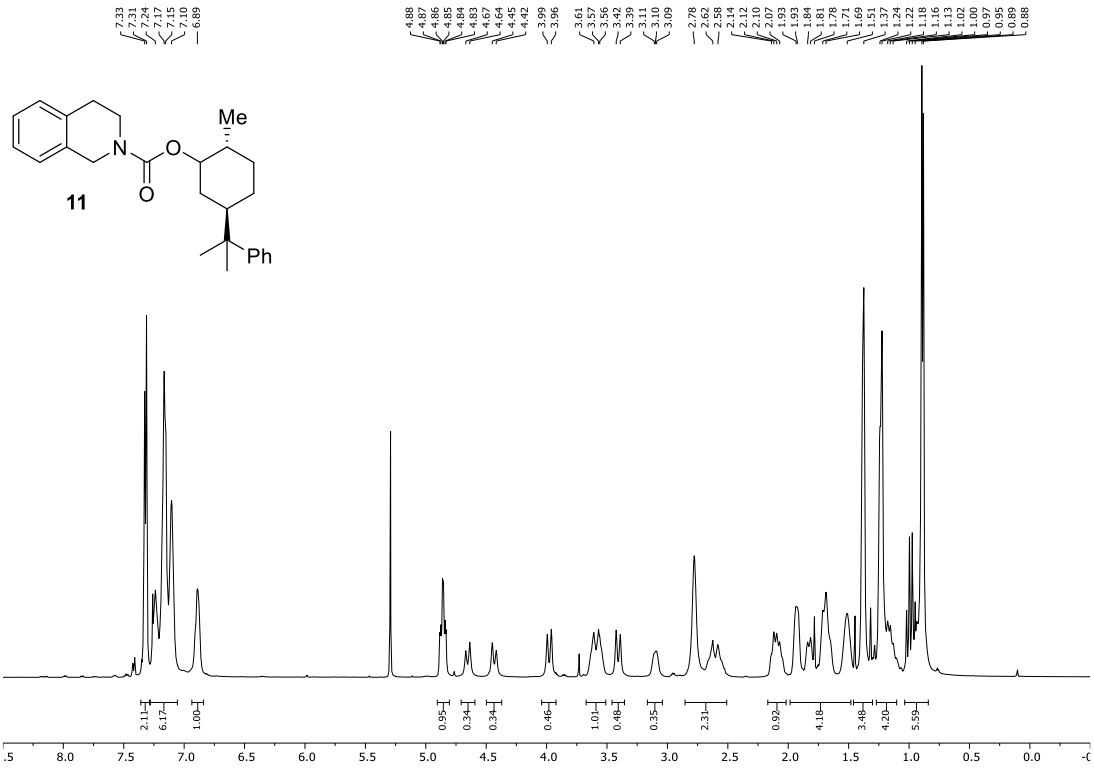
300 MHz ^{1}H NMR spectrum of compound **10a** ($CDCl_3$, 300 K)



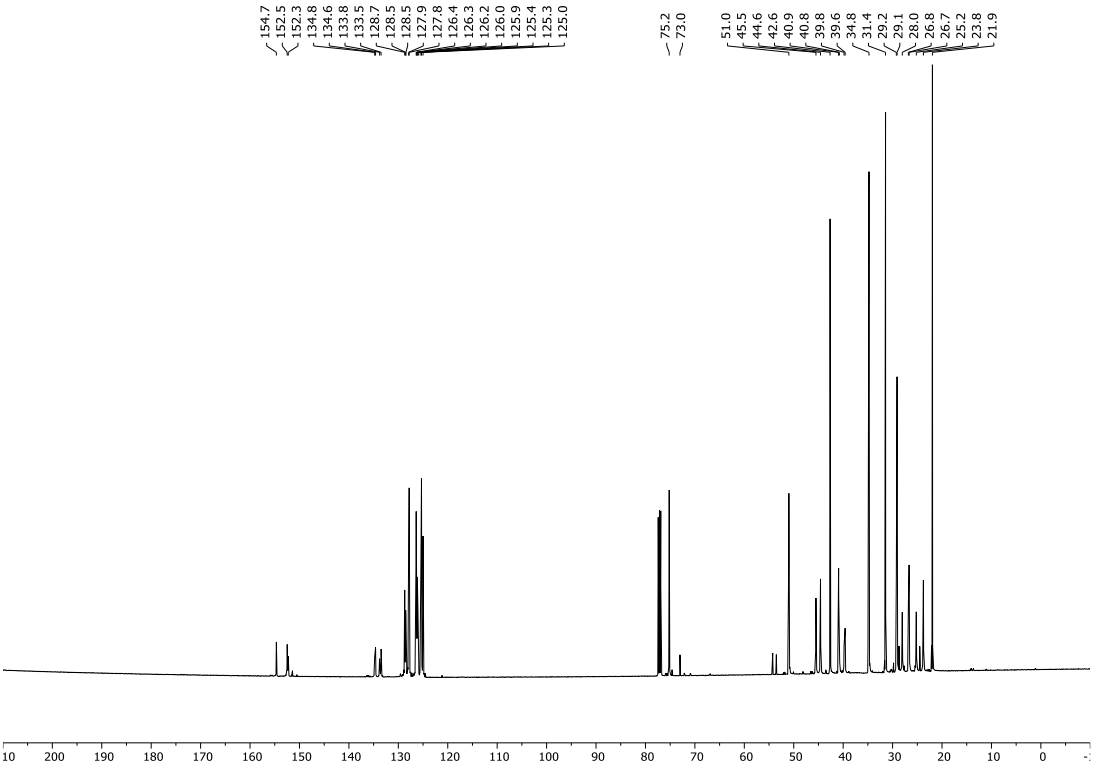
75 MHz ^{13}C NMR spectrum of compound **10a** ($CDCl_3$, 300 K)



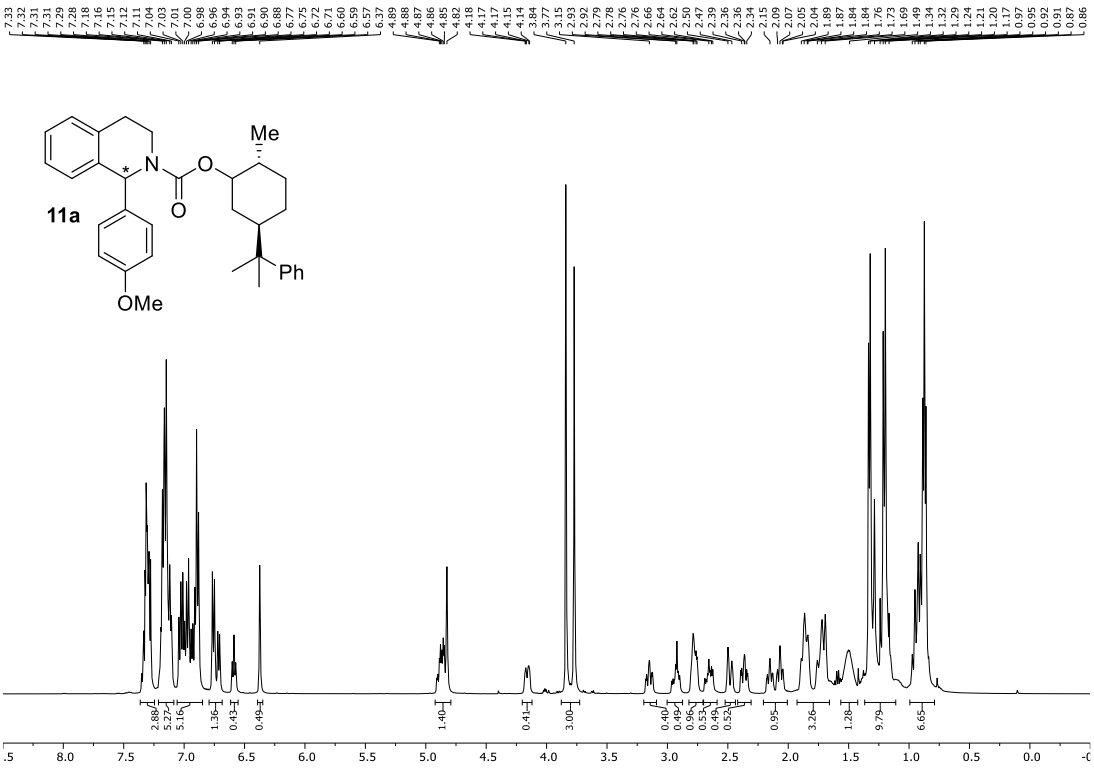
500 MHz ^{1}H NMR spectrum of compound **11** ($CDCl_3$, 300 K)



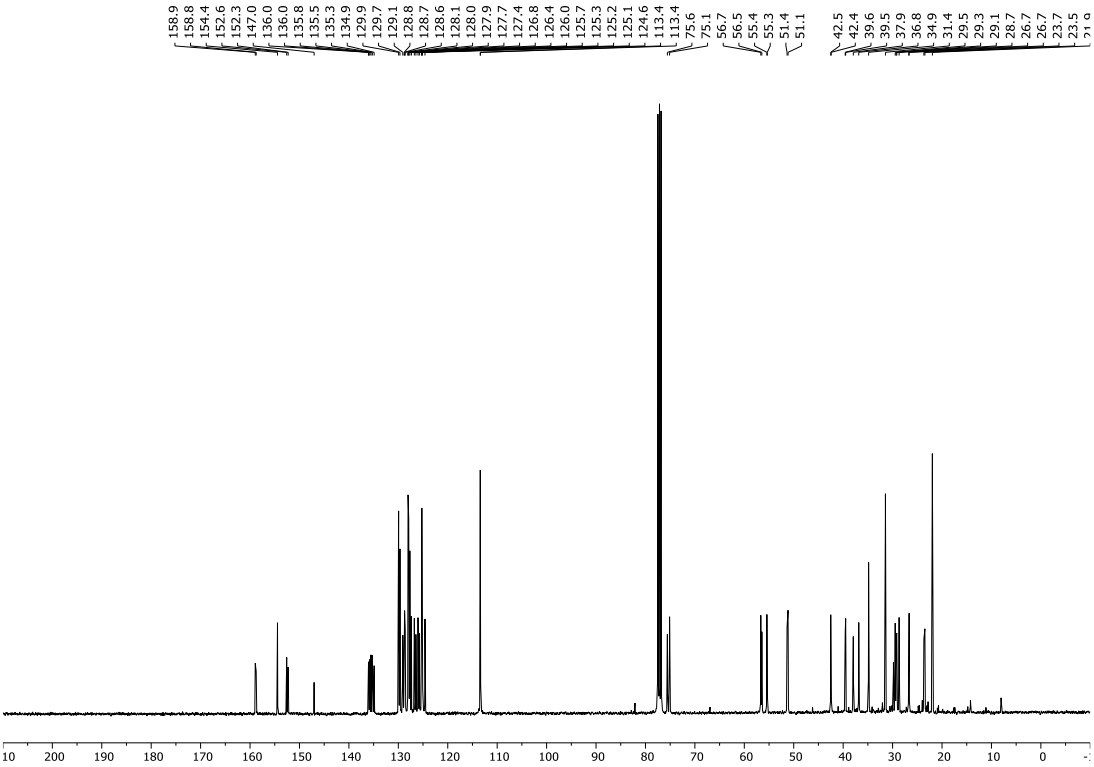
125 MHz ^{13}C NMR spectrum of compound **11** ($CDCl_3$, 300 K)



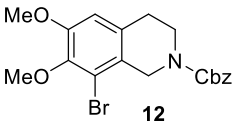
500 MHz ^{1}H NMR spectrum of compound **11a** ($CDCl_3$, 300 K)



100 MHz ^{13}C NMR spectrum of compound **11a** ($CDCl_3$, 300 K)

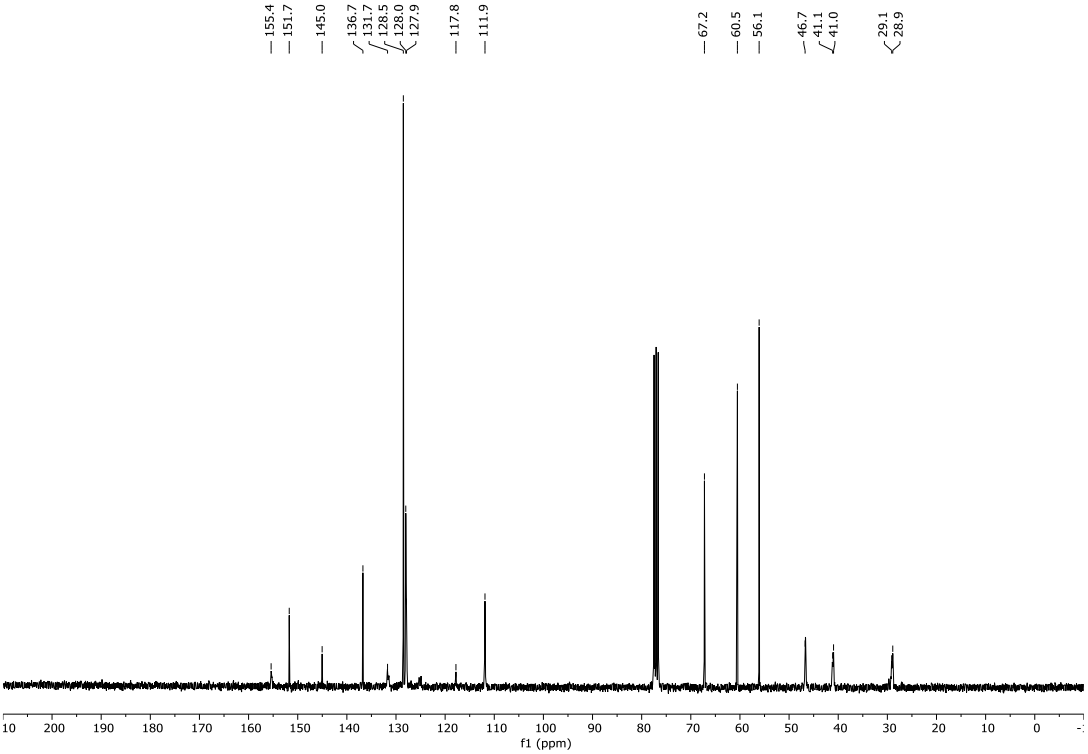


300 MHz ^{1}H NMR spectrum of compound **12** ($CDCl_3$, 300 K)

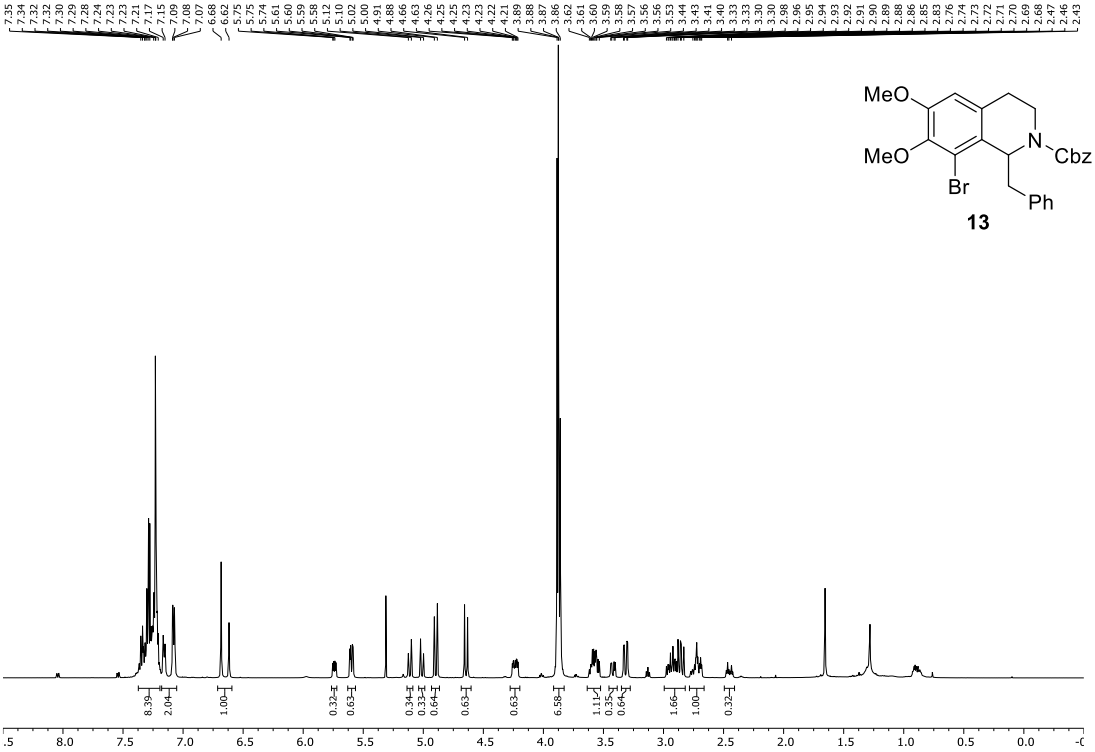


12

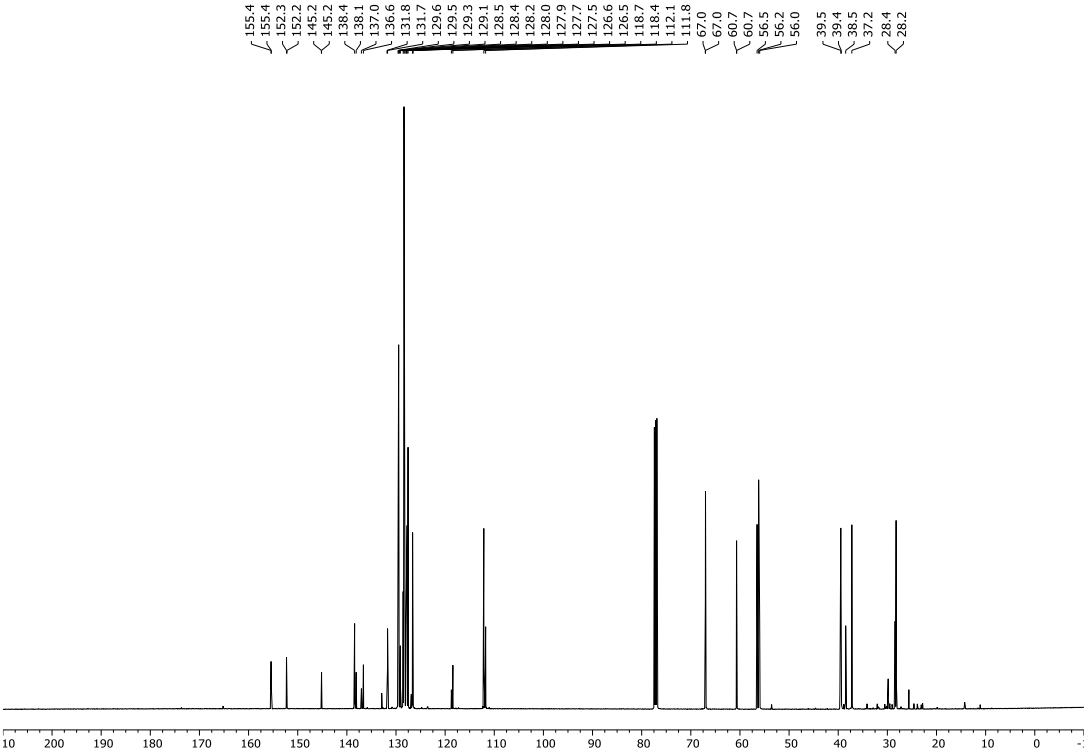
75 MHz ^{13}C NMR spectrum of compound **12** ($CDCl_3$, 300 K)



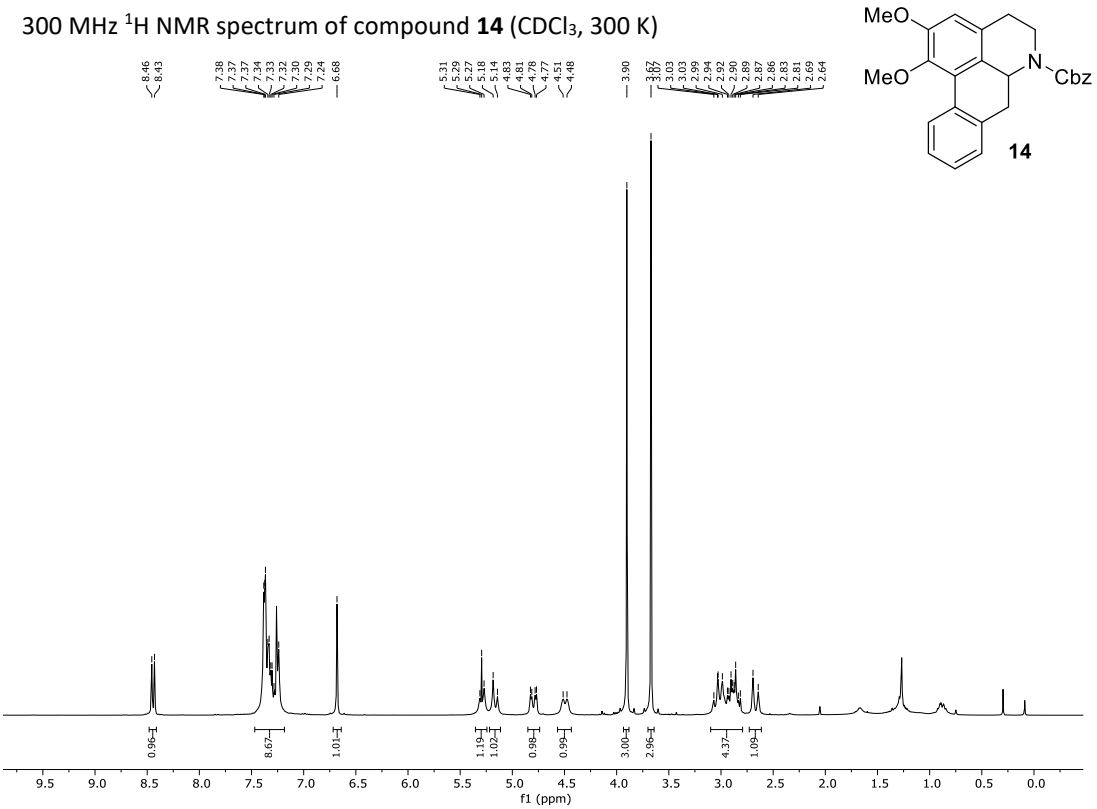
500 MHz ^{1}H NMR spectrum of compound **13** ($CDCl_3$, 300 K)



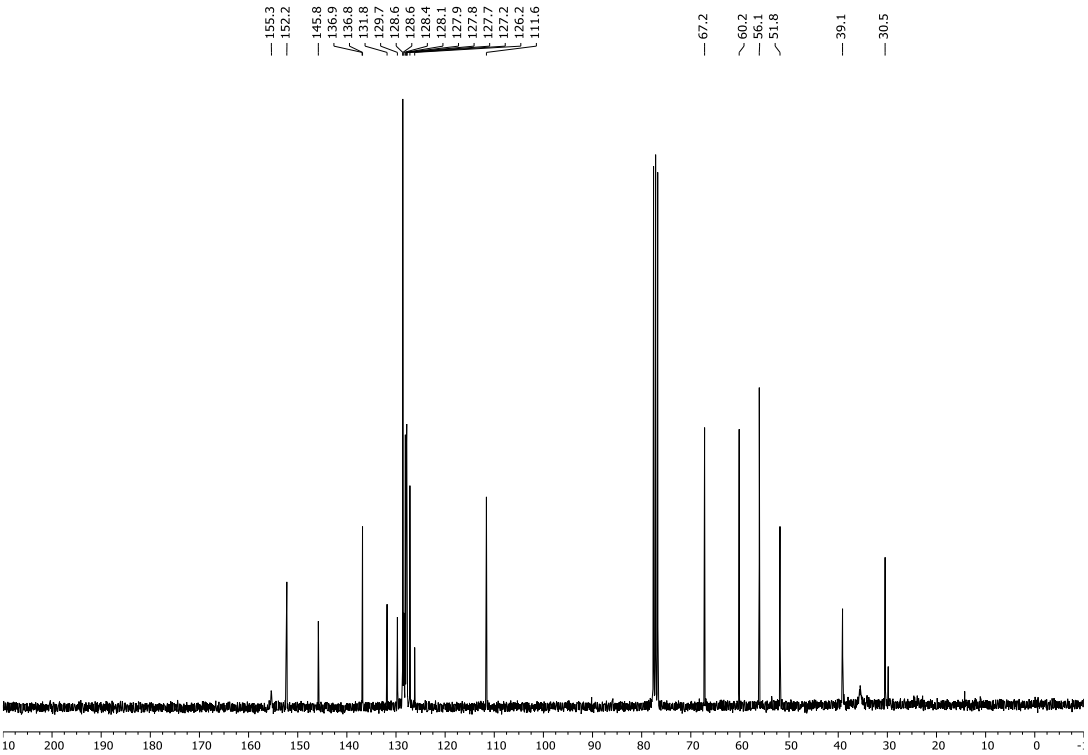
125 MHz ^{13}C NMR spectrum of compound **13** ($CDCl_3$, 300 K)



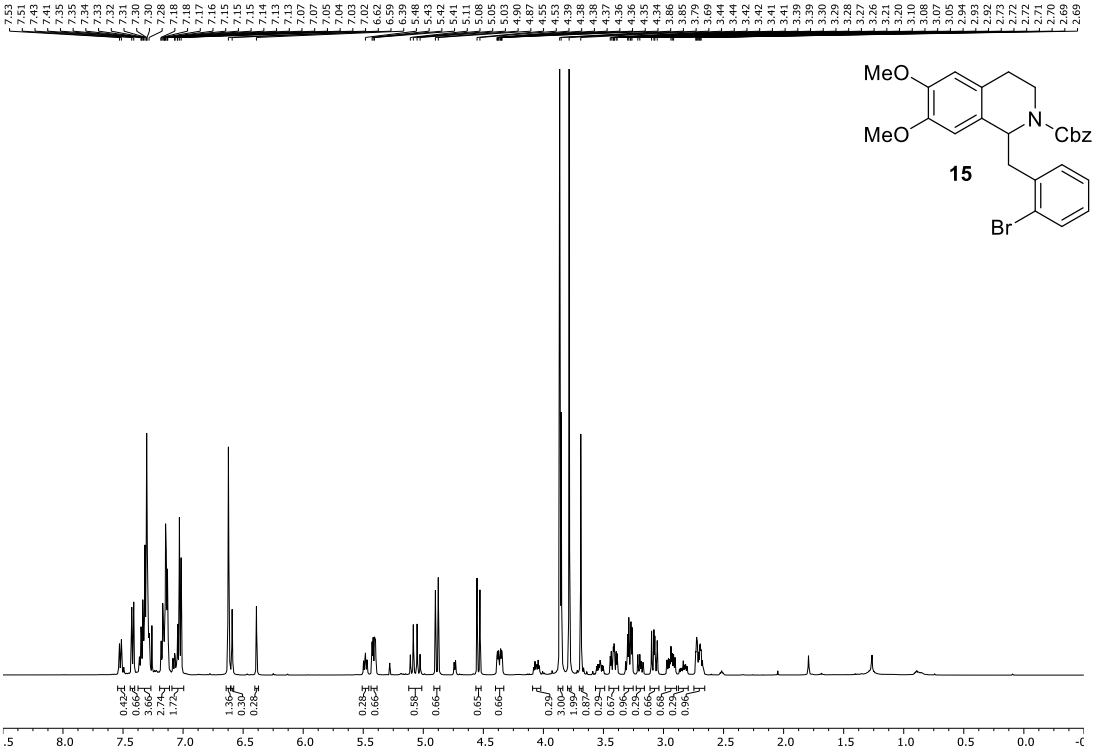
300 MHz ^{1}H NMR spectrum of compound **14** ($CDCl_3$, 300 K)



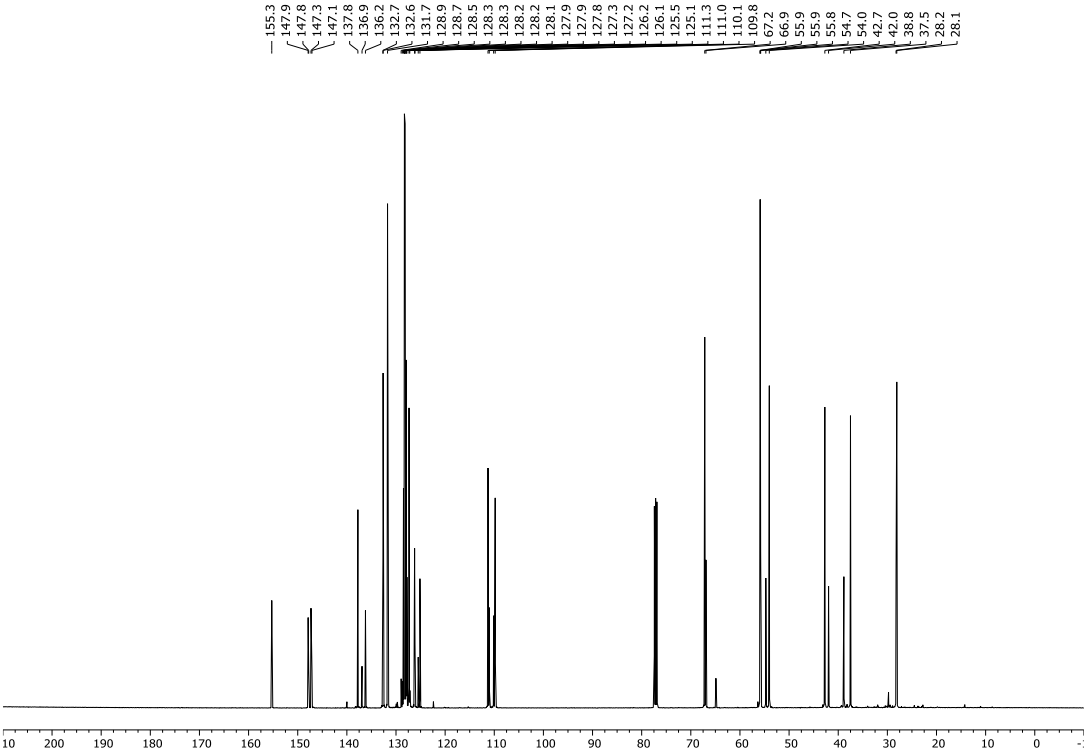
75 MHz ^{13}C NMR spectrum of compound **14** ($CDCl_3$, 300 K)



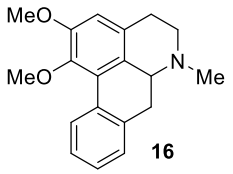
500 MHz ^{1}H NMR spectrum of compound **15** ($CDCl_3$, 300 K)



125 MHz ^{13}C NMR spectrum of compound **15** ($CDCl_3$, 300 K)

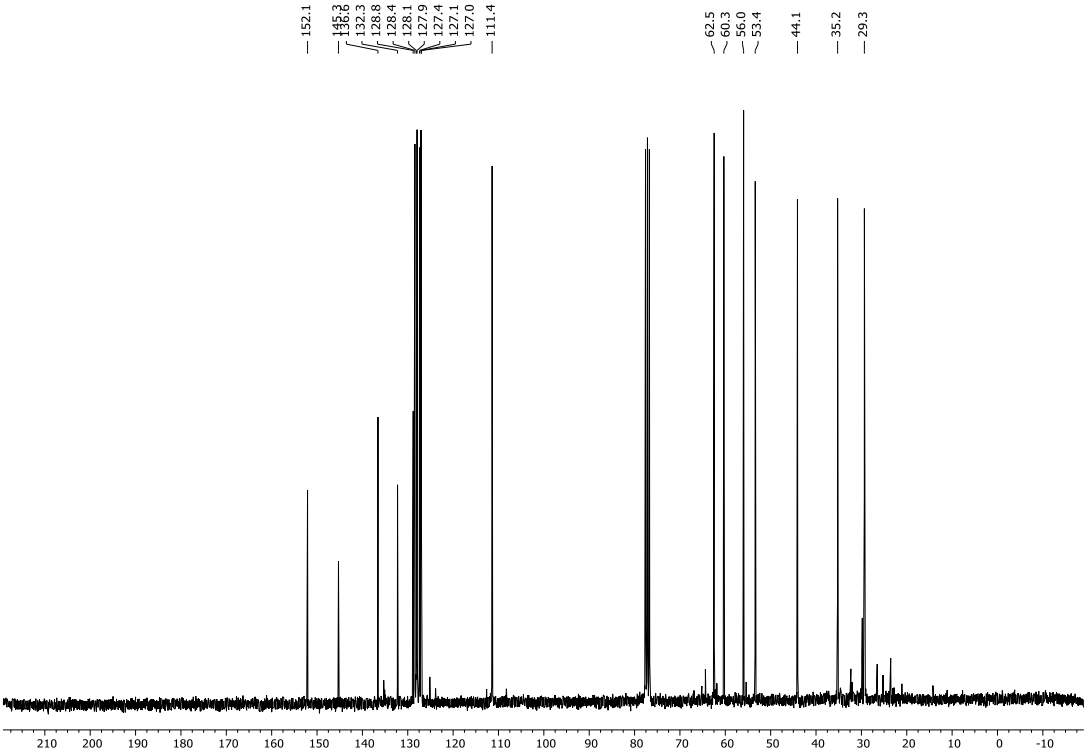


300 MHz ^{1}H NMR spectrum of compound **16** ($CDCl_3$, 300 K)

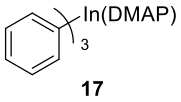


16

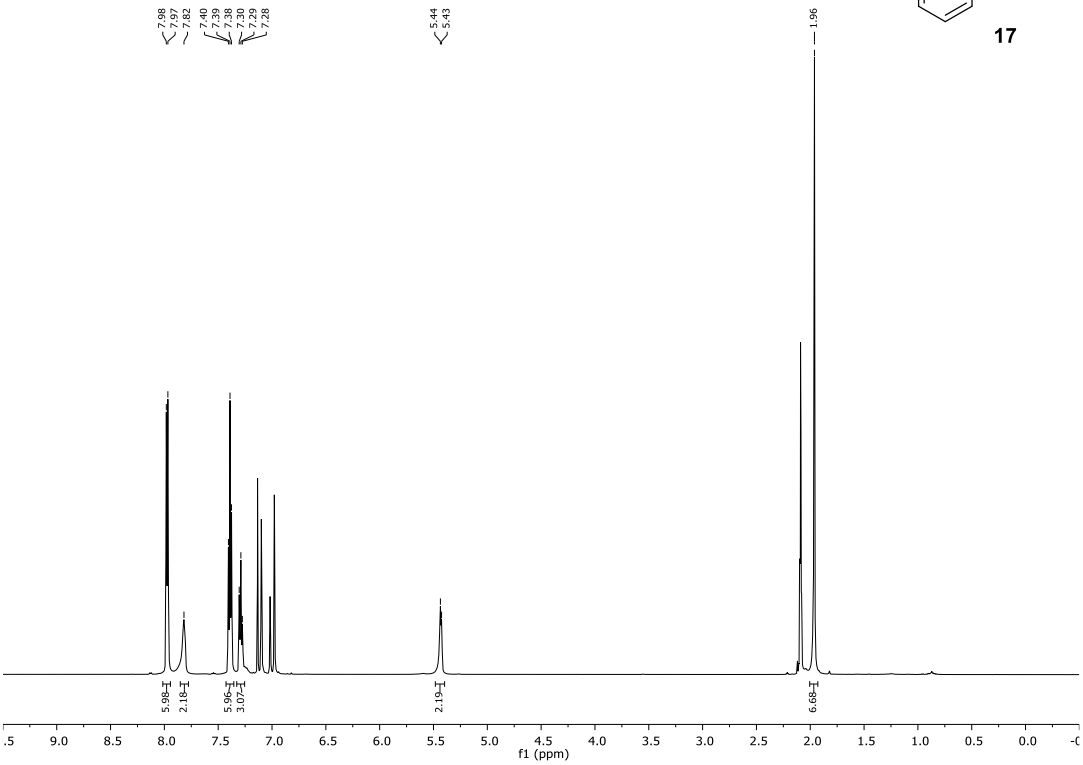
75 MHz ^{13}C NMR spectrum of compound **16** ($CDCl_3$, 300 K)



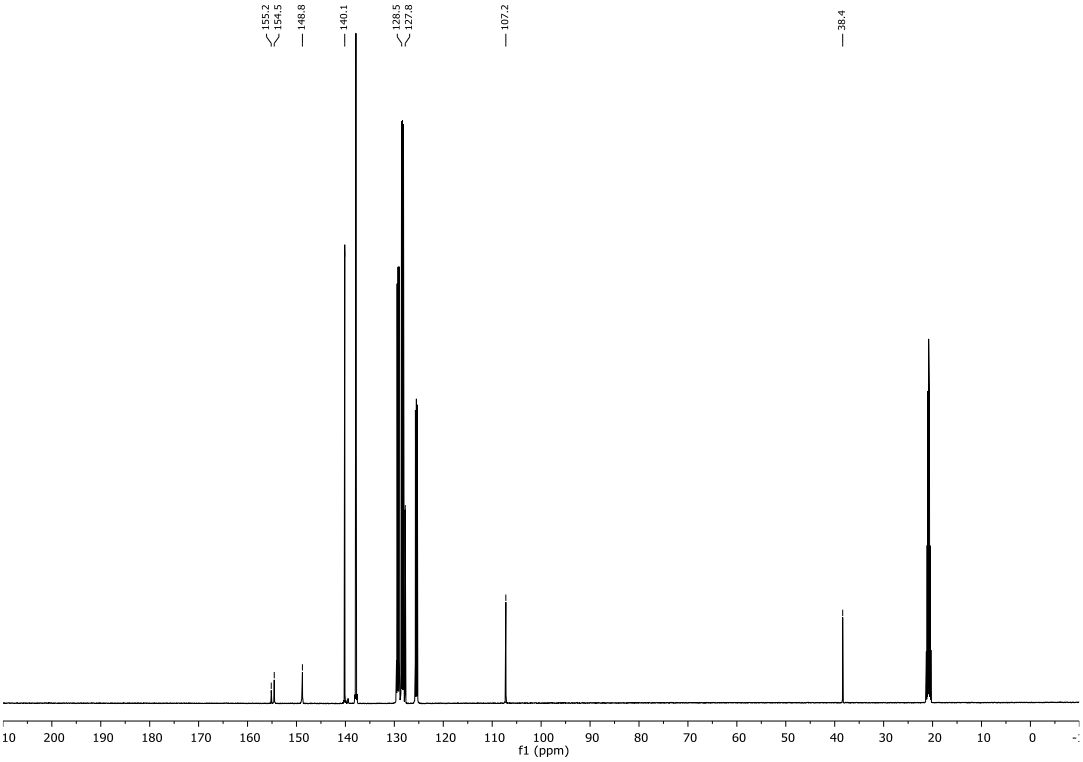
500 MHz ^{1}H NMR spectrum of compound **17** (toluene-d_8, 300 K)



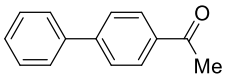
17



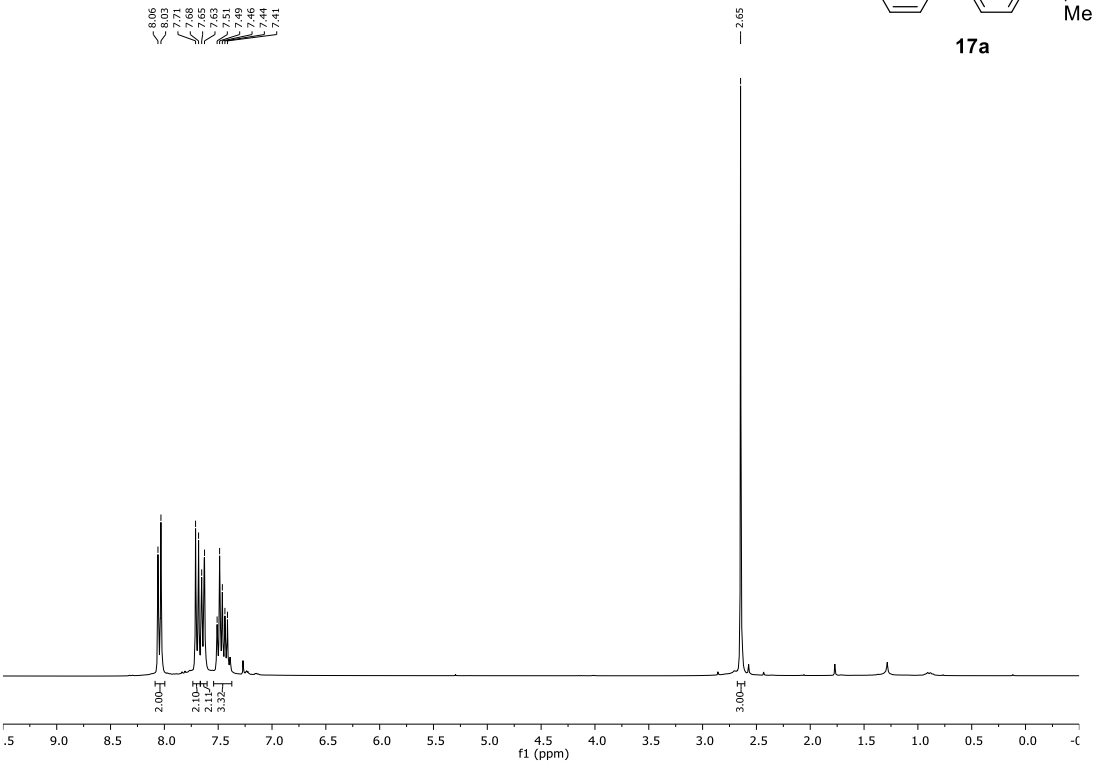
125 MHz ^{13}C NMR spectrum of compound **17** (toluene-d_8, 300 K)



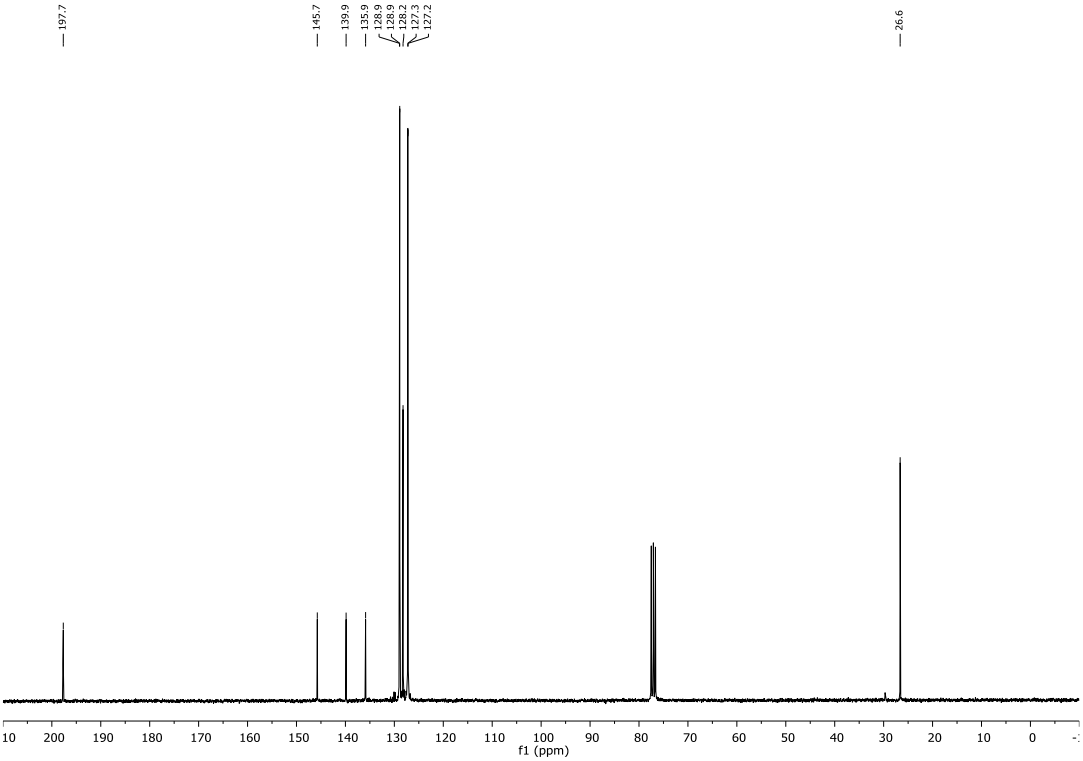
300 MHz ^{1}H NMR spectrum of compound **17a** ($CDCl_3$, 300 K)



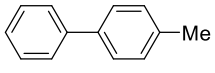
17a



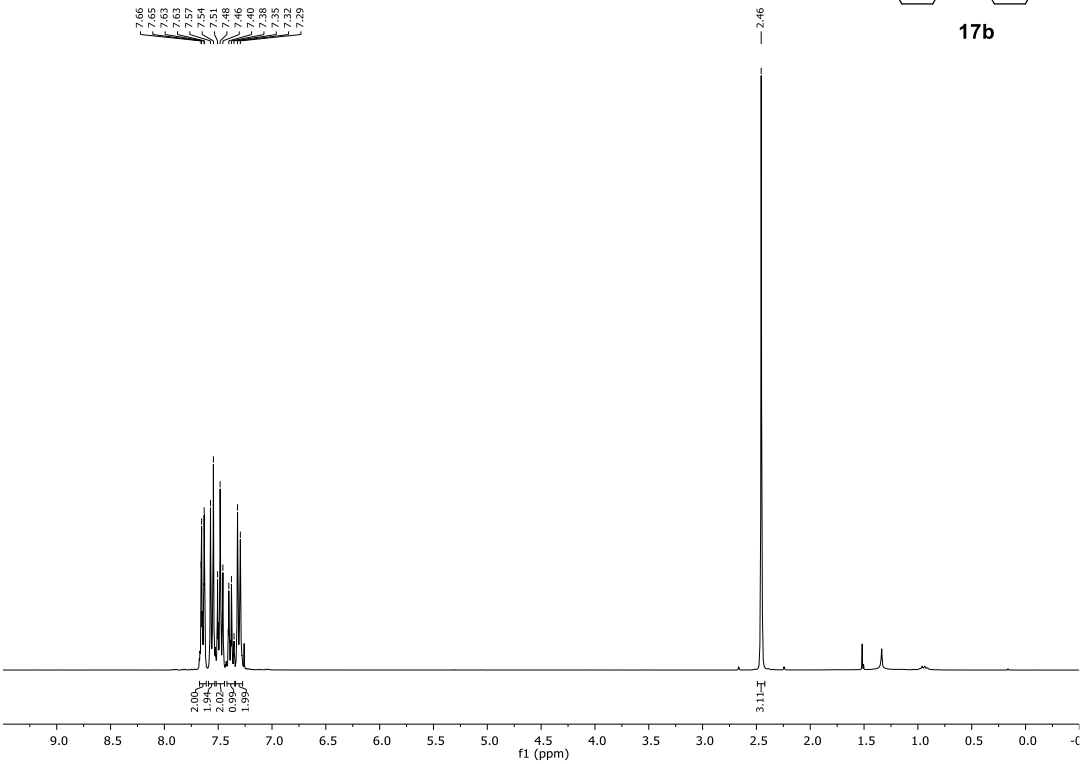
75 MHz ^{13}C NMR spectrum of compound **17a** ($CDCl_3$, 300 K)



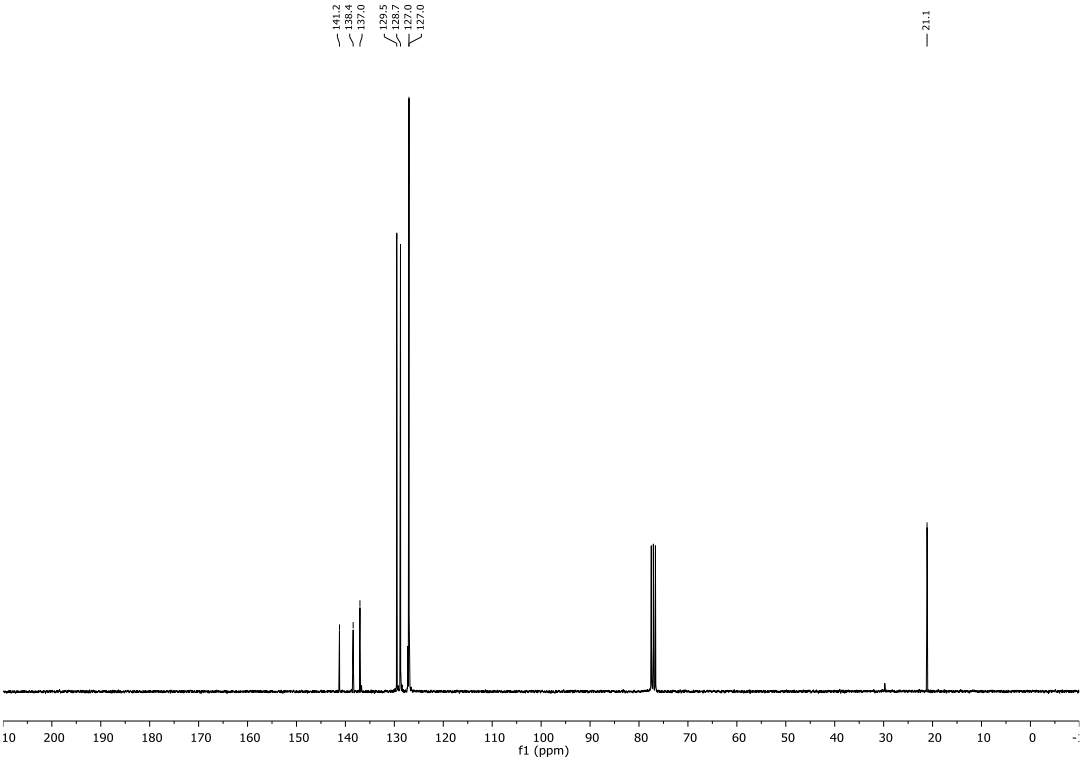
300 MHz ^{1}H NMR spectrum of compound **17b** ($CDCl_3$, 300 K)



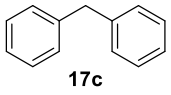
17b

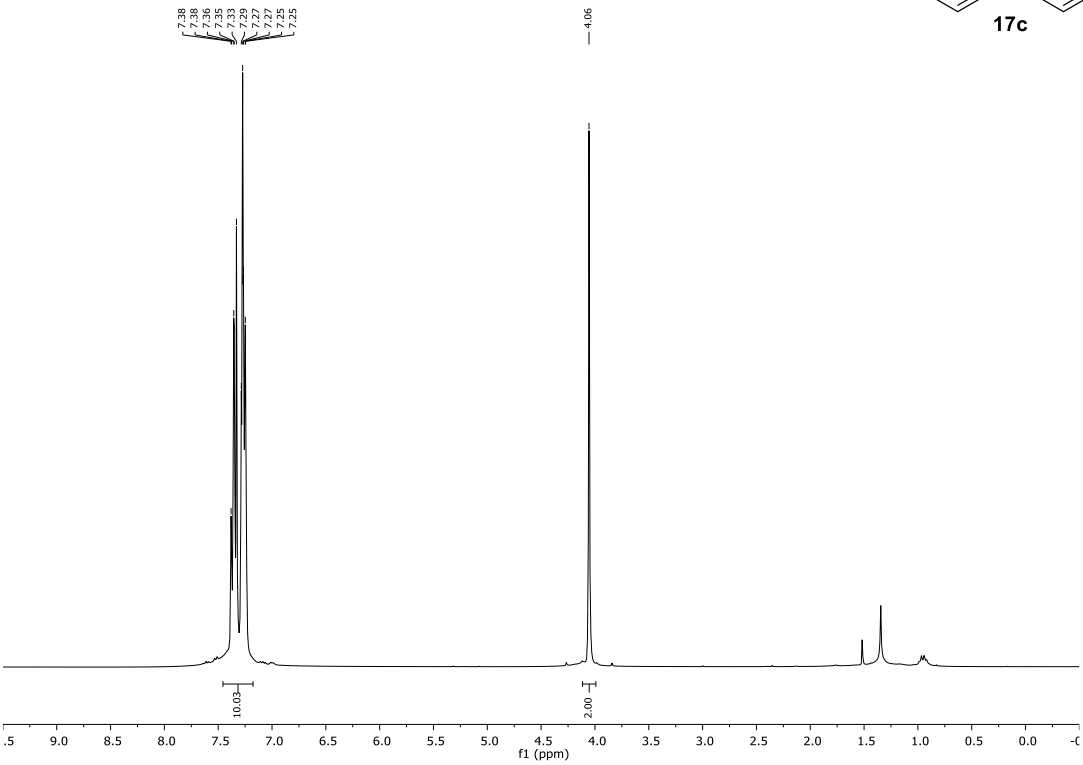


75 MHz ^{13}C NMR spectrum of compound **17b** ($CDCl_3$, 300 K)

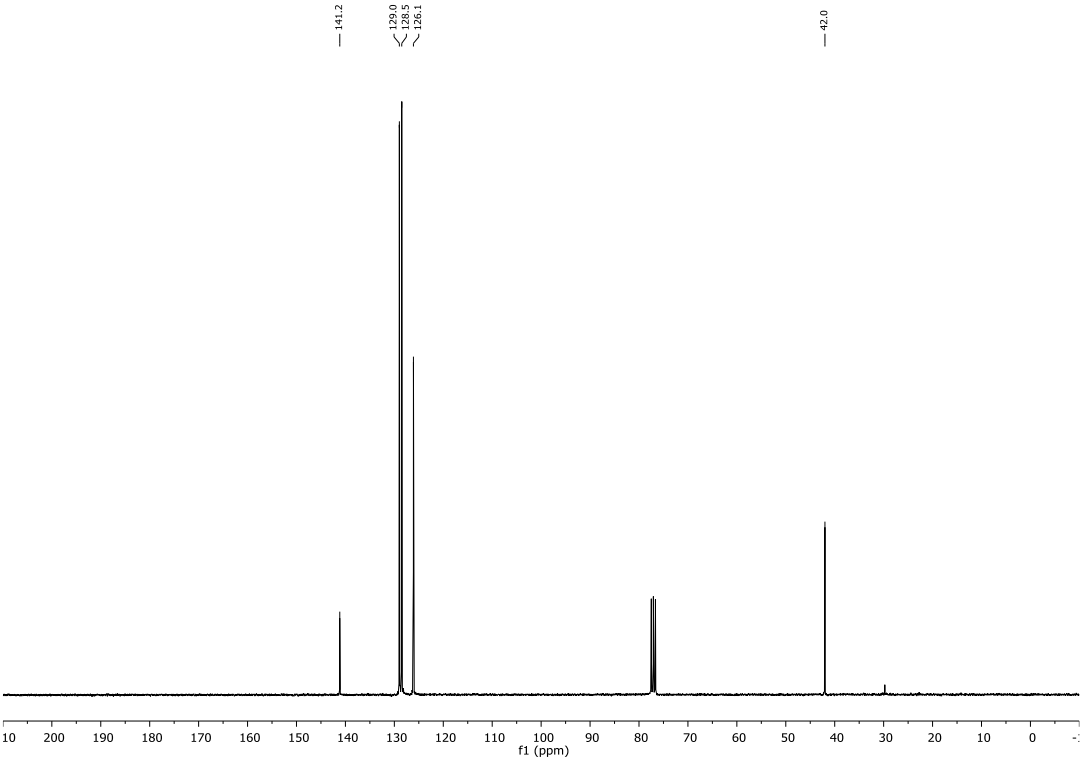


300 MHz ^{1}H NMR spectrum of compound **17c** ($CDCl_3$, 300 K)

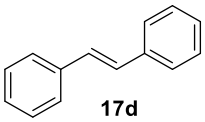




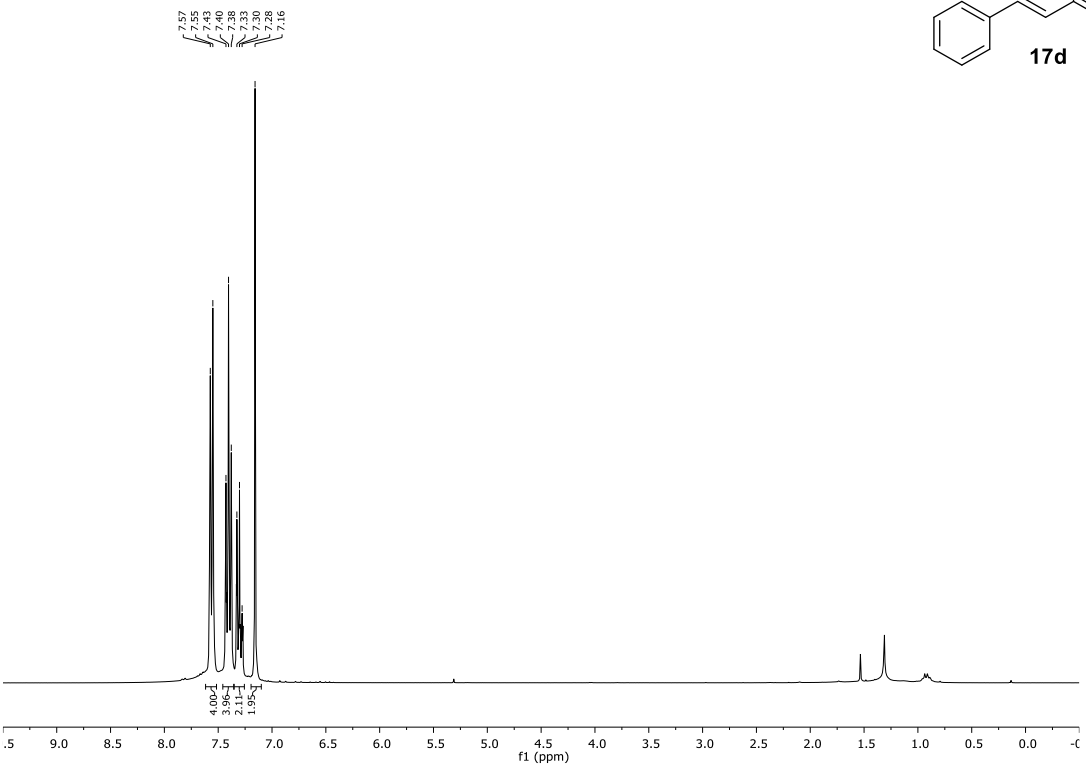
75 MHz ^{13}C NMR spectrum of compound **17c** ($CDCl_3$, 300 K)



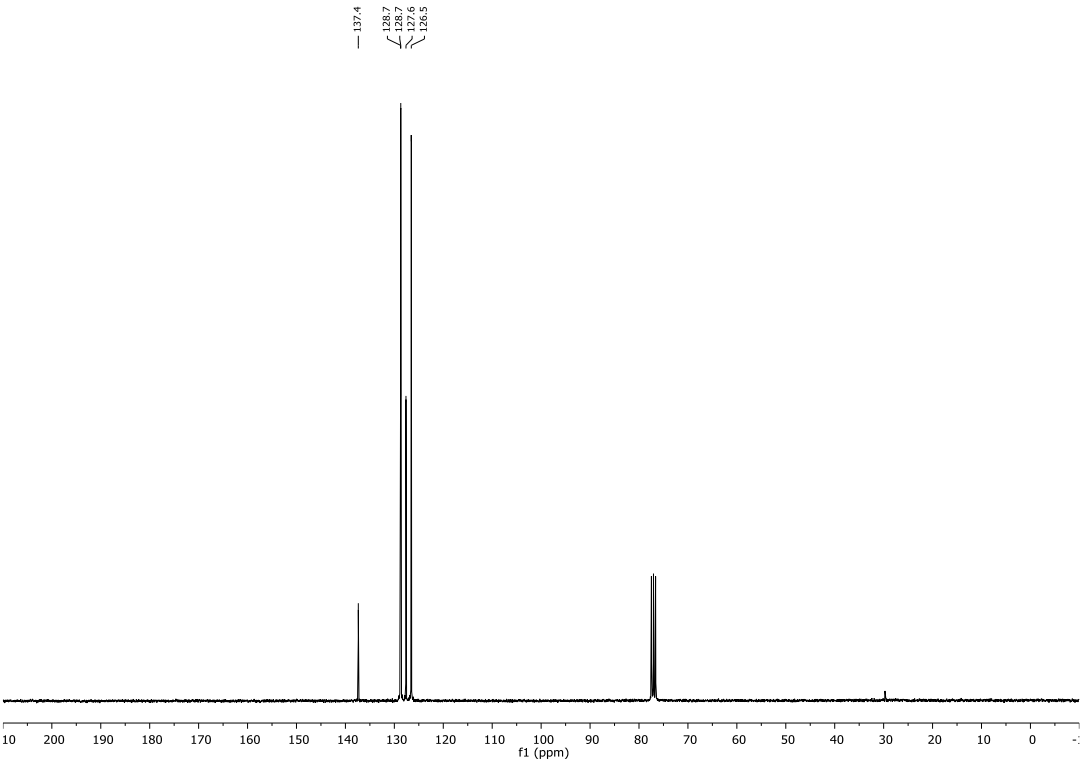
300 MHz ^{1}H NMR spectrum of compound **17d** ($CDCl_3$, 300 K)



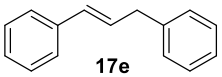
17d

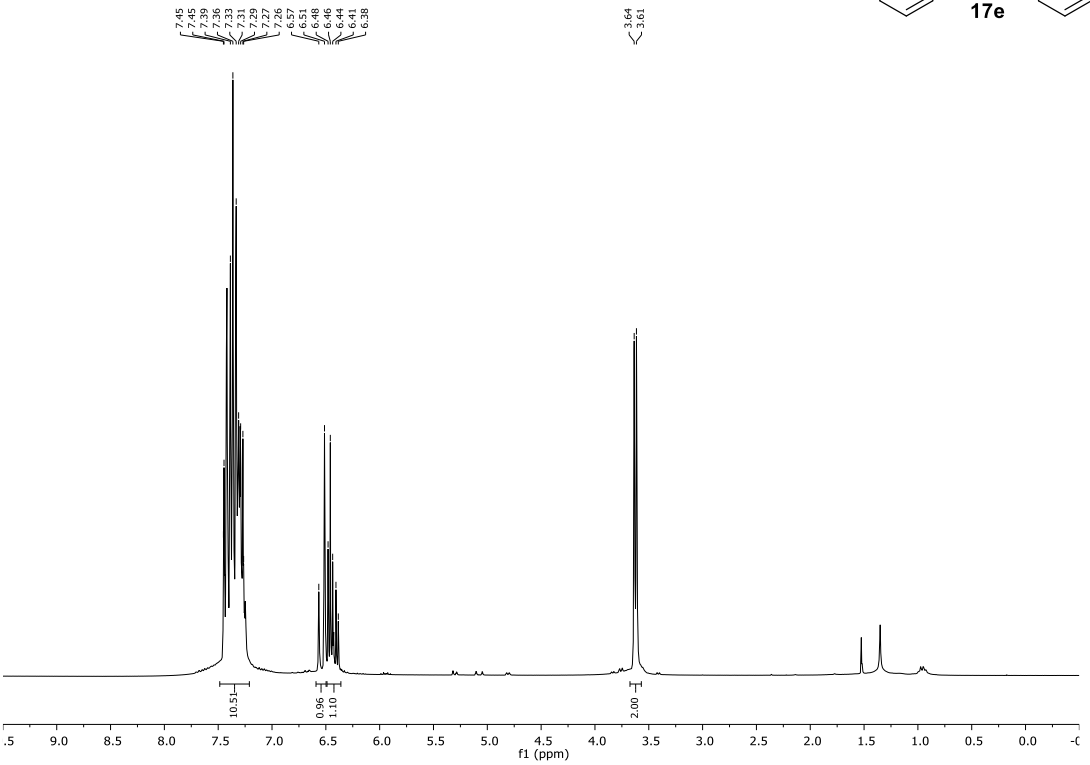


75 MHz ^{13}C NMR spectrum of compound **17d** ($CDCl_3$, 300 K)

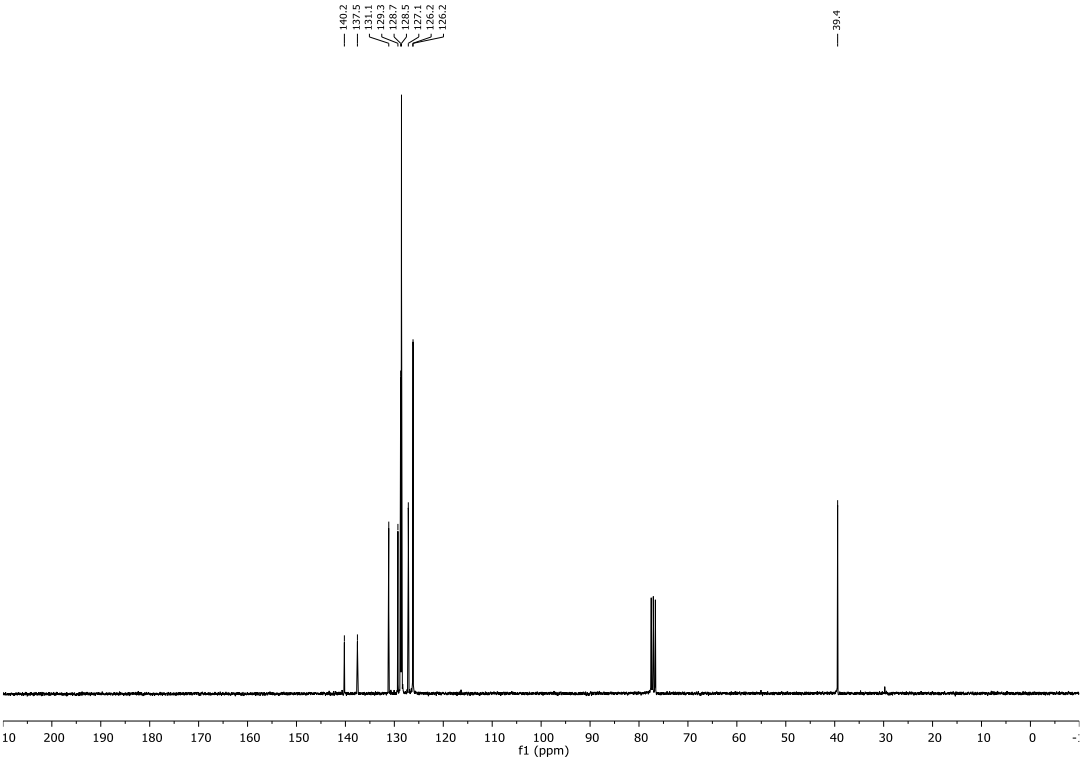


300 MHz ^{1}H NMR spectrum of compound **17e** ($CDCl_3$, 300 K)

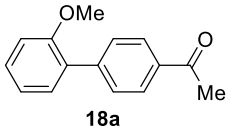




75 MHz ^{13}C NMR spectrum of compound **17e** ($CDCl_3$, 300 K)

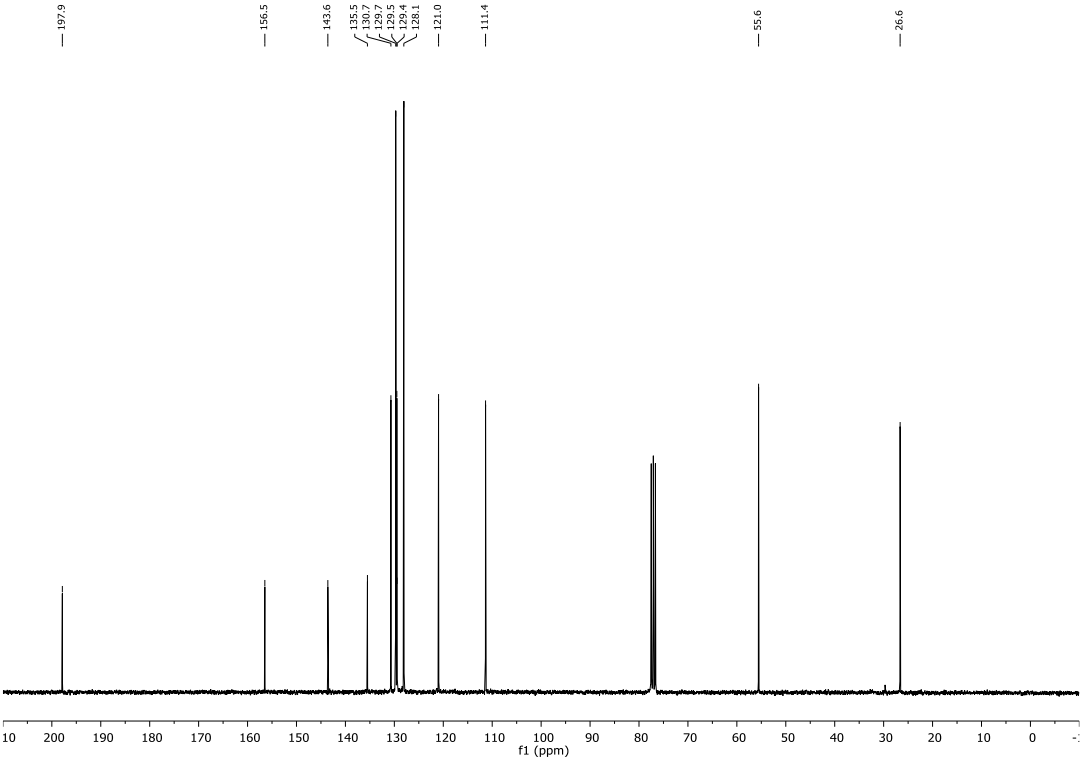


300 MHz ^{1}H NMR spectrum of compound **18a** ($CDCl_3$, 300 K)

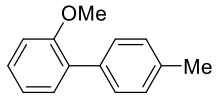


18a

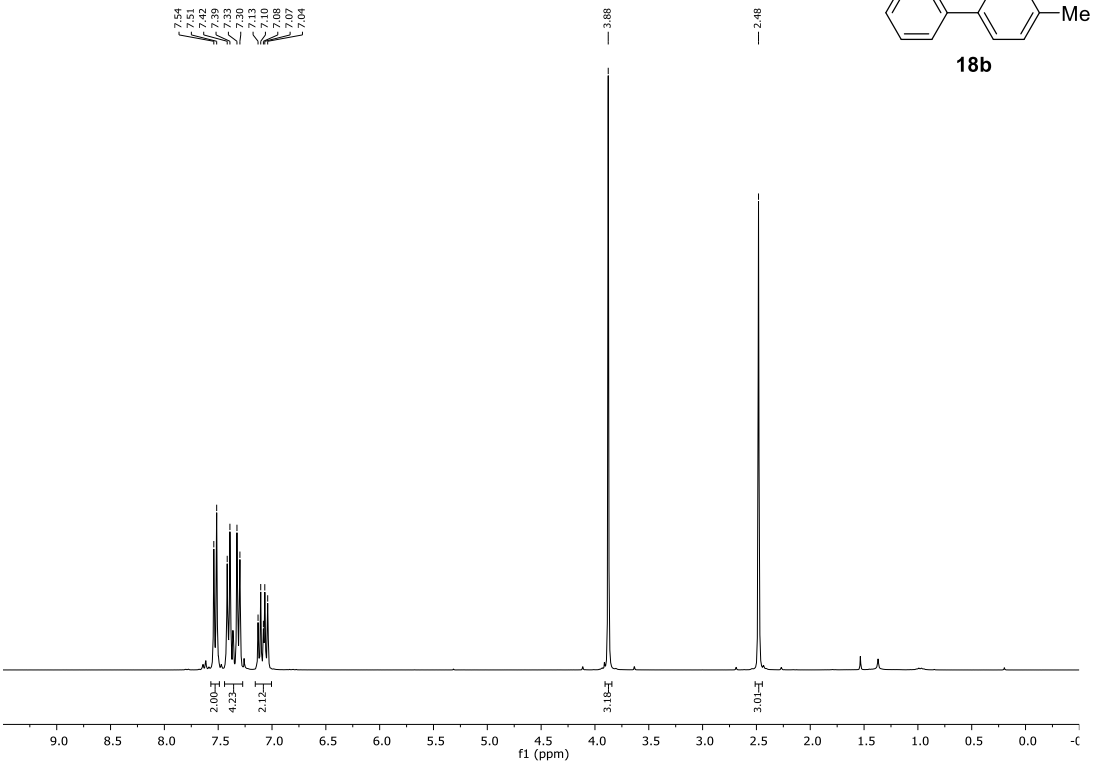
75 MHz ^{13}C NMR spectrum of compound **18a** ($CDCl_3$, 300 K)



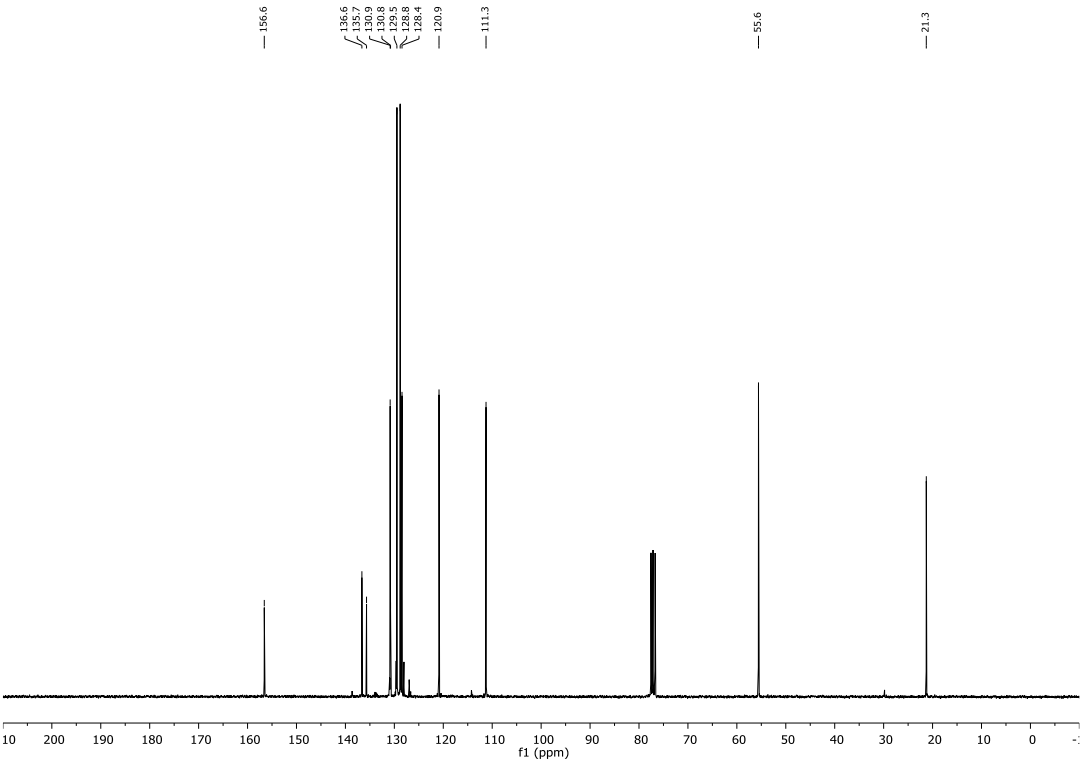
300 MHz ^{1}H NMR spectrum of compound **18b** ($CDCl_3$, 300 K)



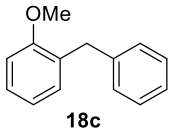
18b



75 MHz ^{13}C NMR spectrum of compound **18b** ($CDCl_3$, 300 K)

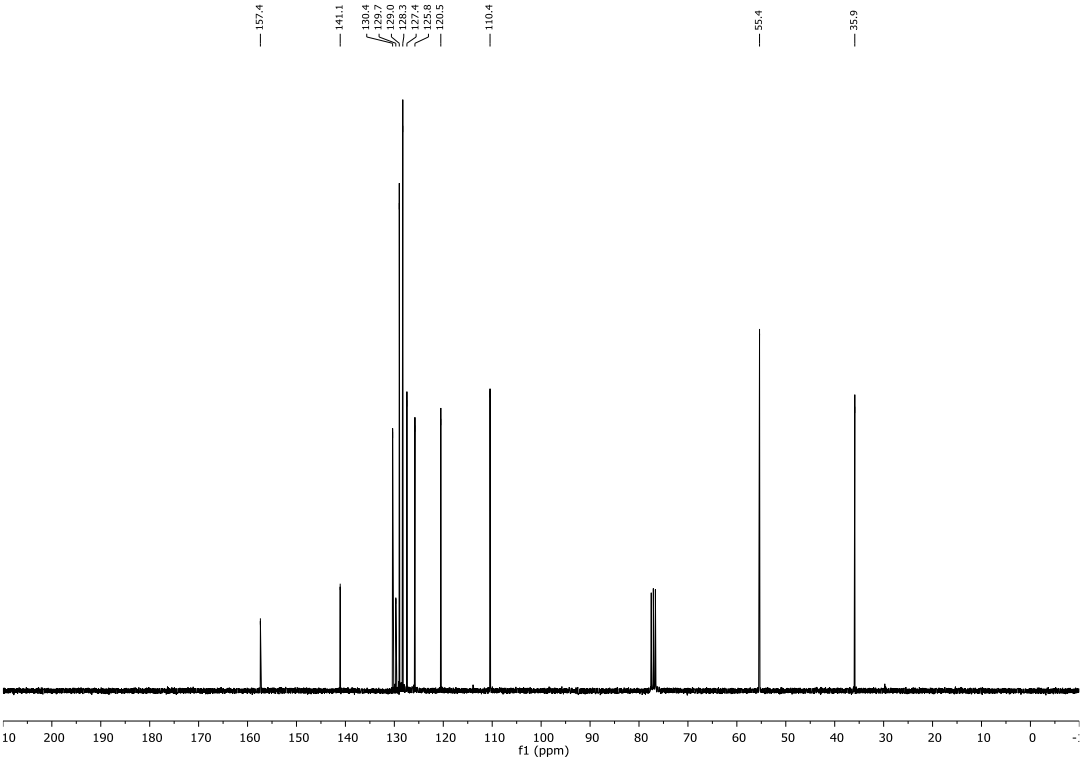


300 MHz ^{1}H NMR spectrum of compound **18c** ($CDCl_3$, 300 K)

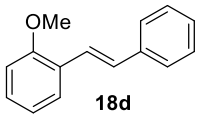


18c

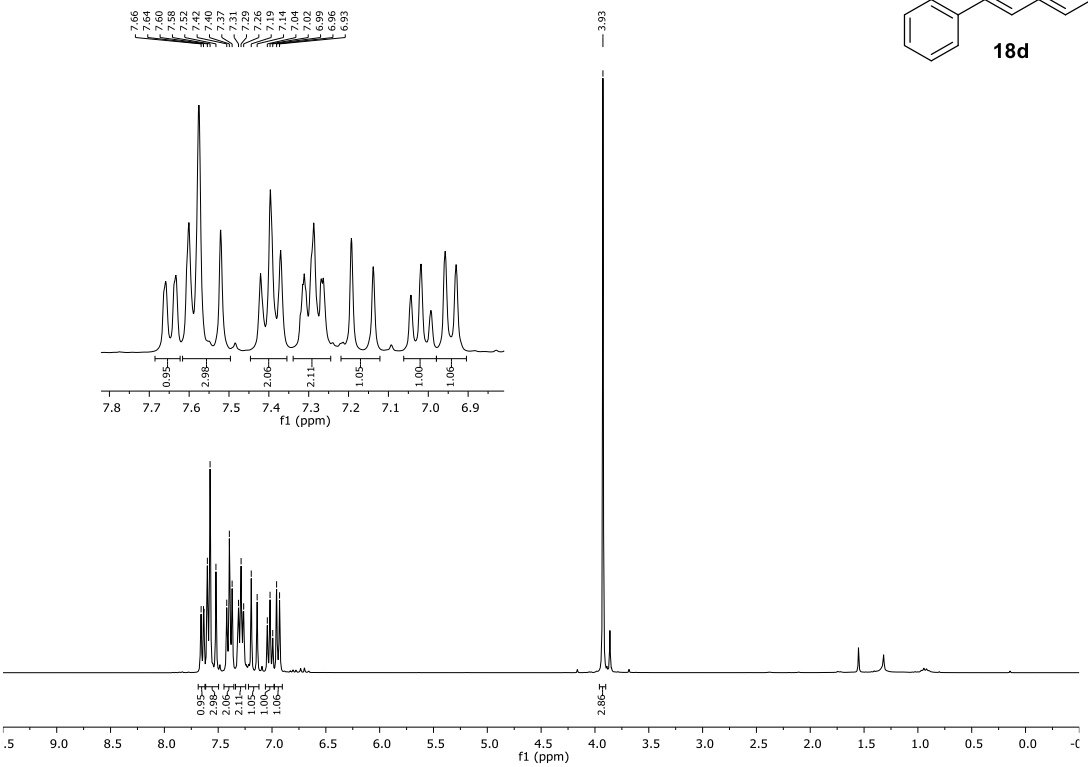
75 MHz ^{13}C NMR spectrum of compound **18c** ($CDCl_3$, 300 K)



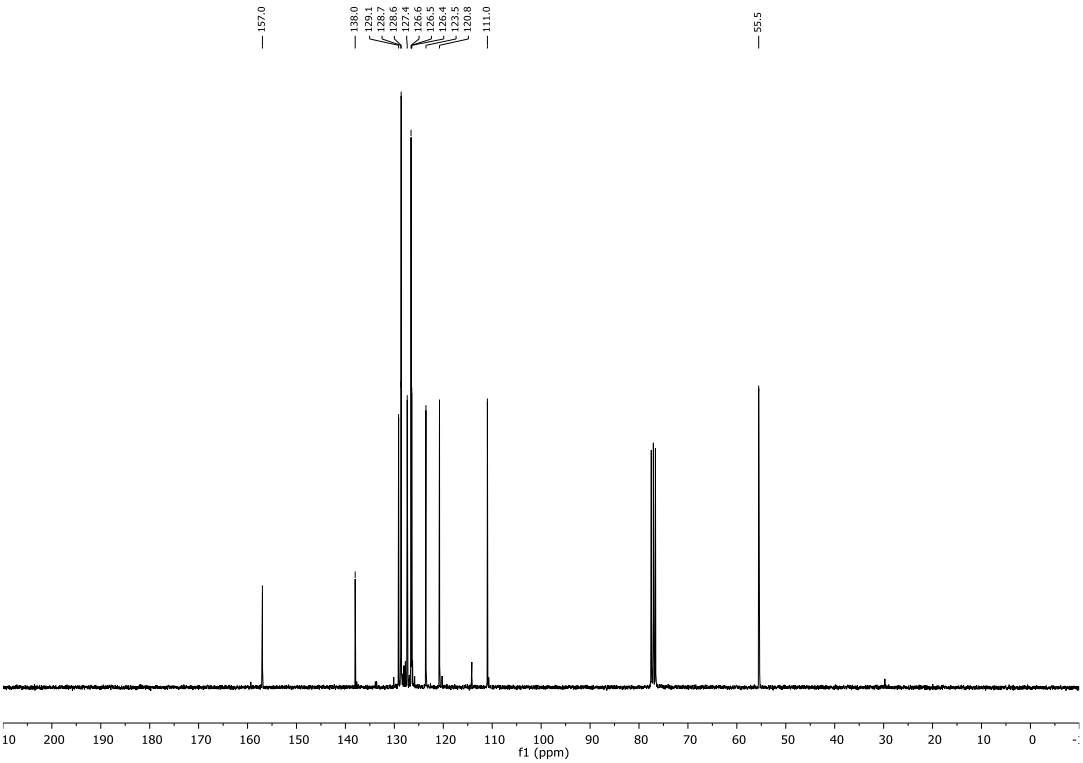
300 MHz ^{1}H NMR spectrum of compound **18d** ($CDCl_3$, 300 K)



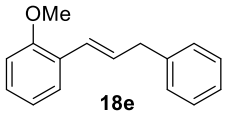
18d



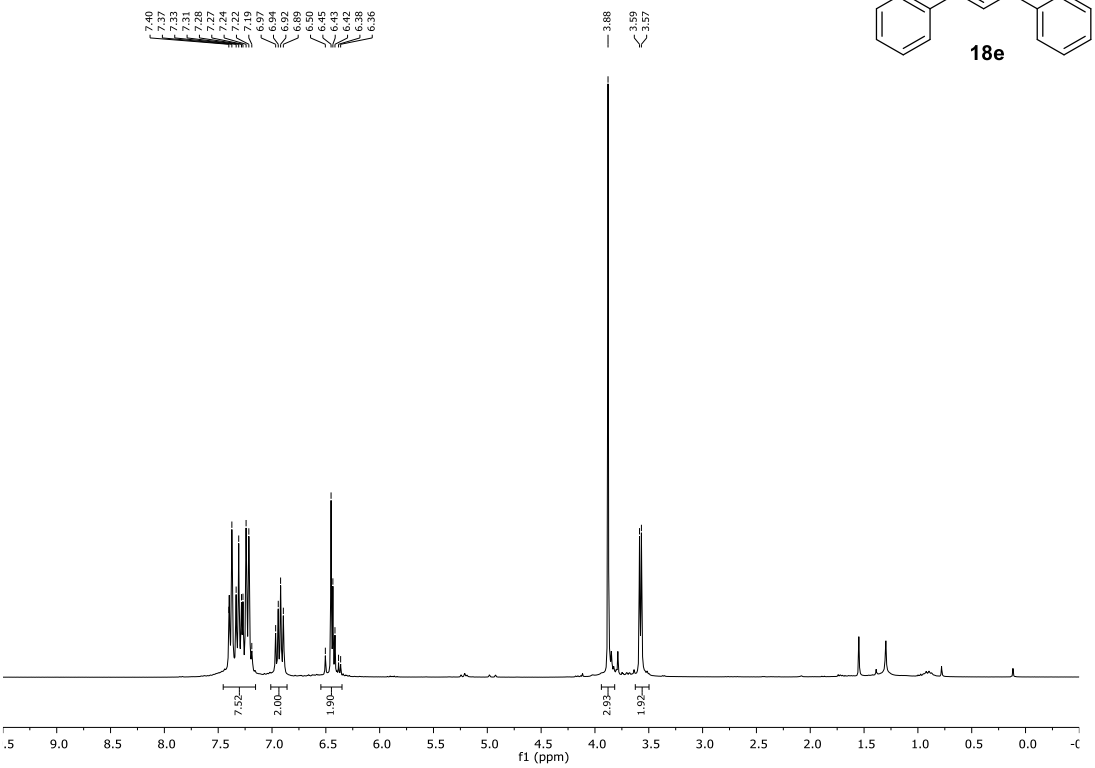
75 MHz ^{13}C NMR spectrum of compound **18d** ($CDCl_3$, 300 K)



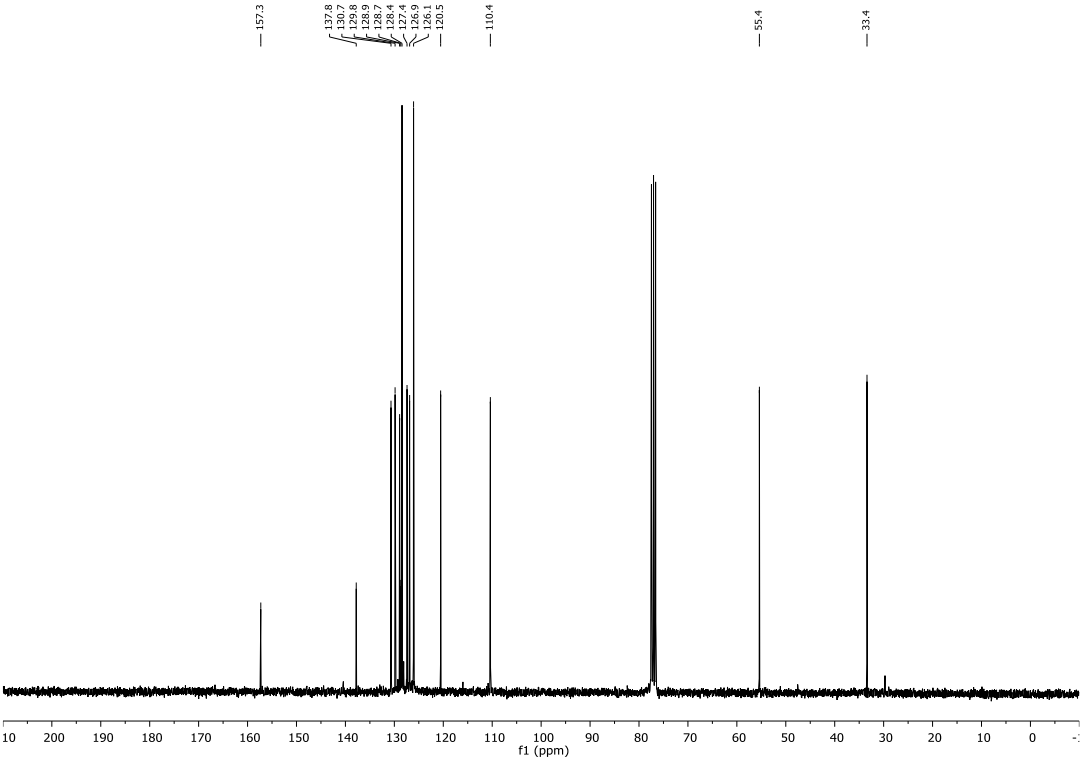
300 MHz ^{1}H NMR spectrum of compound **18e** ($CDCl_3$, 300 K)



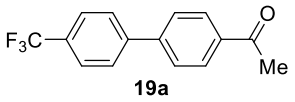
18e



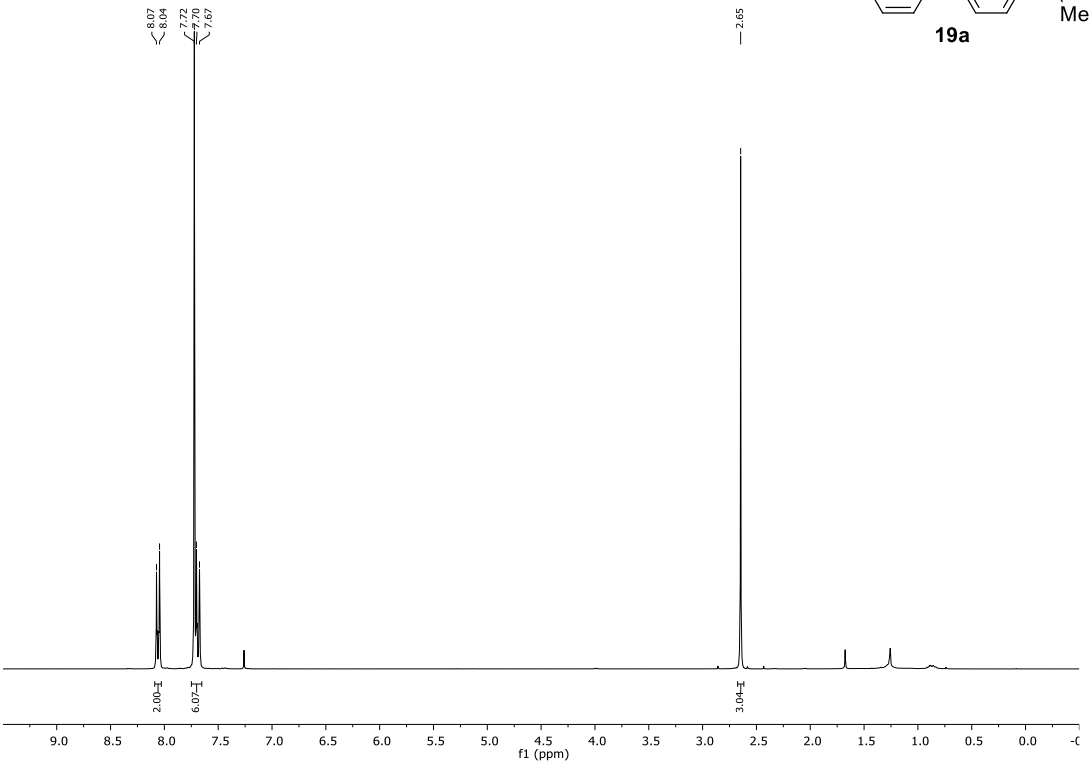
75 MHz ^{13}C NMR spectrum of compound **18e** ($CDCl_3$, 300 K)



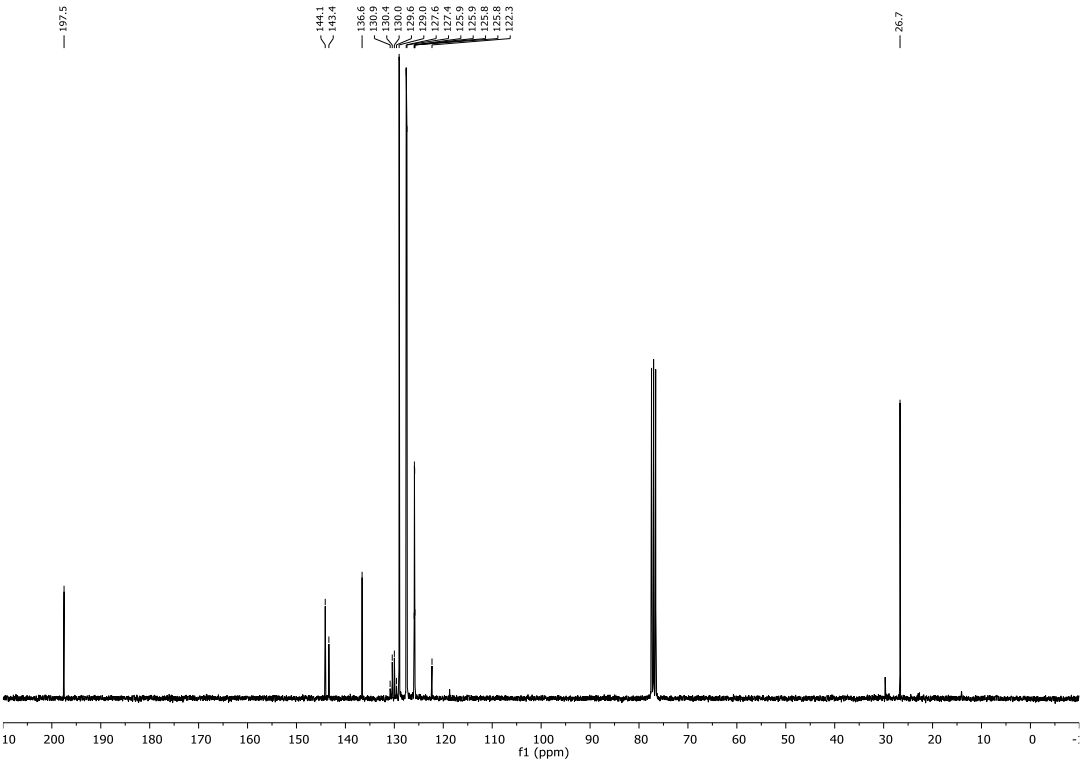
300 MHz ^{1}H NMR spectrum of compound **19a** ($CDCl_3$, 300 K)



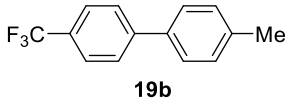
19a



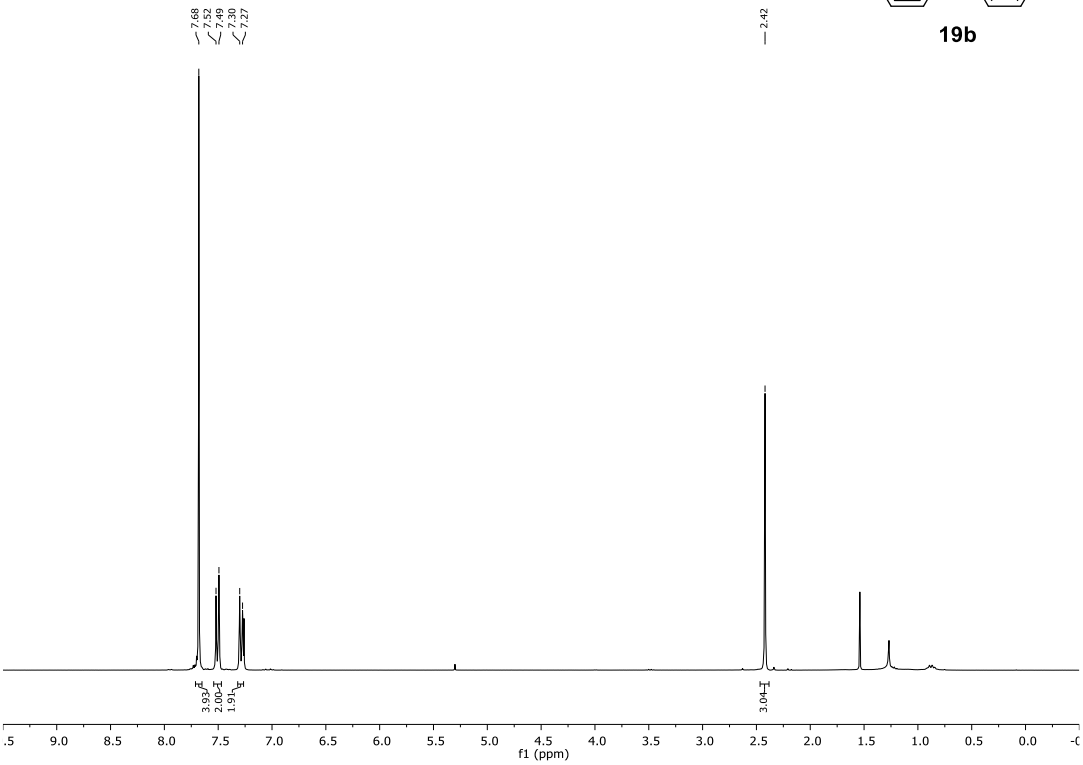
75 MHz ^{13}C NMR spectrum of compound **19a** ($CDCl_3$, 300 K)



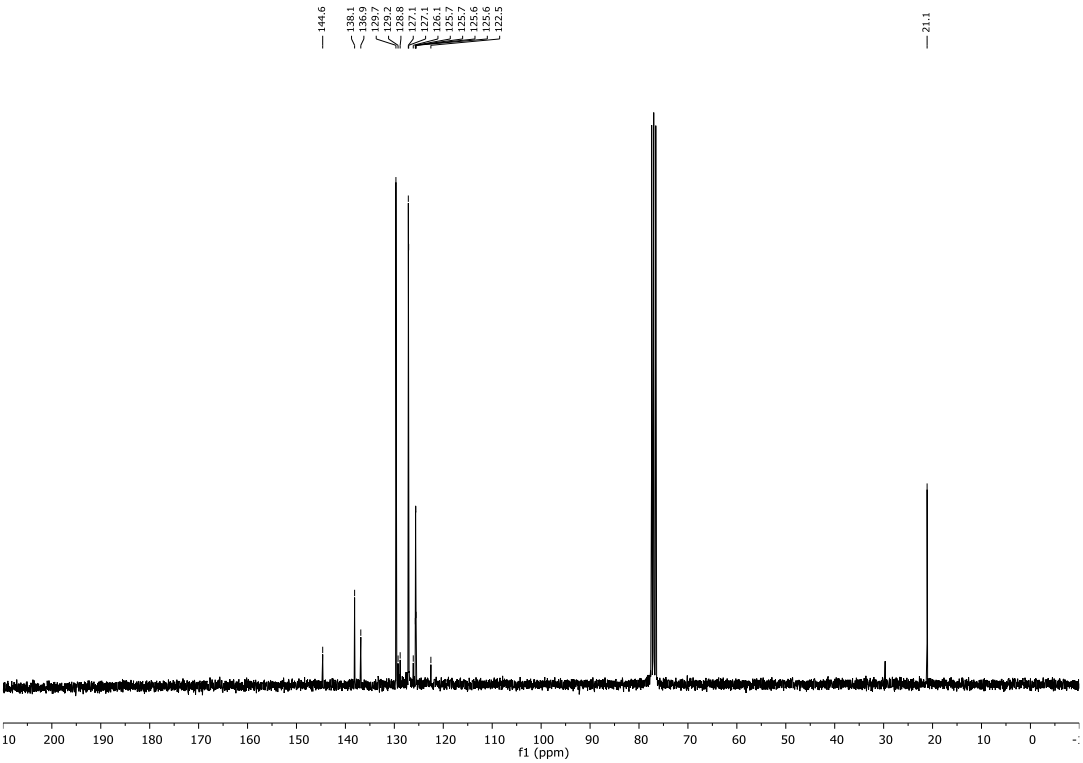
300 MHz ^{1}H NMR spectrum of compound **19b** ($CDCl_3$, 300 K)



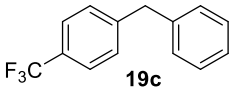
19b



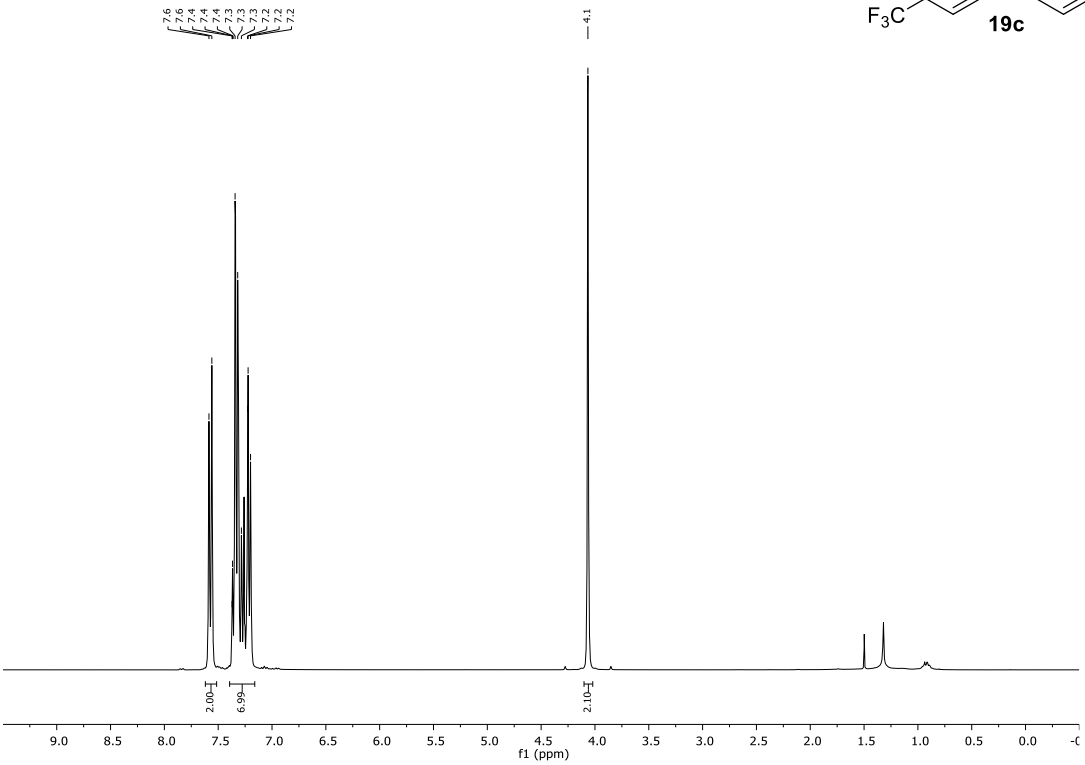
75 MHz ^{13}C NMR spectrum of compound **19b** ($CDCl_3$, 300 K)



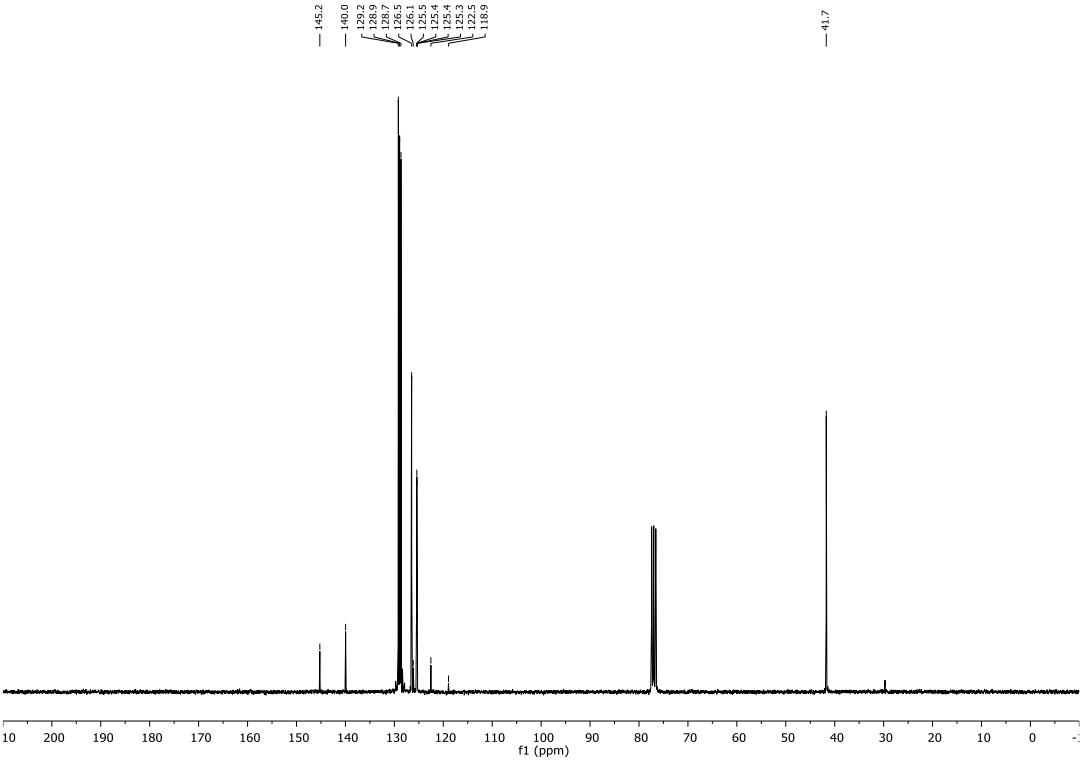
300 MHz ^{1}H NMR spectrum of compound **19c** ($CDCl_3$, 300 K)



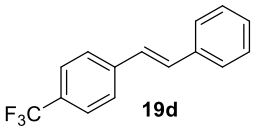
19c



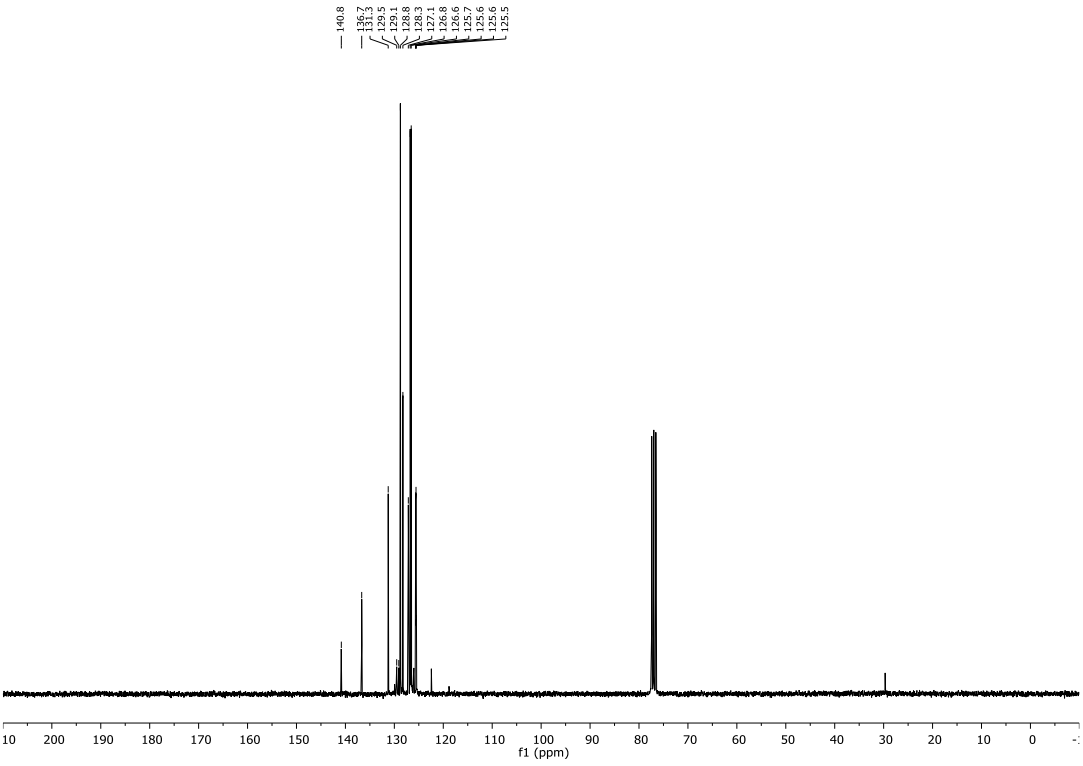
75 MHz ^{13}C NMR spectrum of compound **19c** ($CDCl_3$, 300 K)



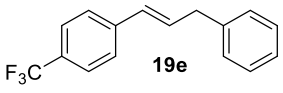
300 MHz ^{1}H NMR spectrum of compound **19d** ($CDCl_3$, 300 K)

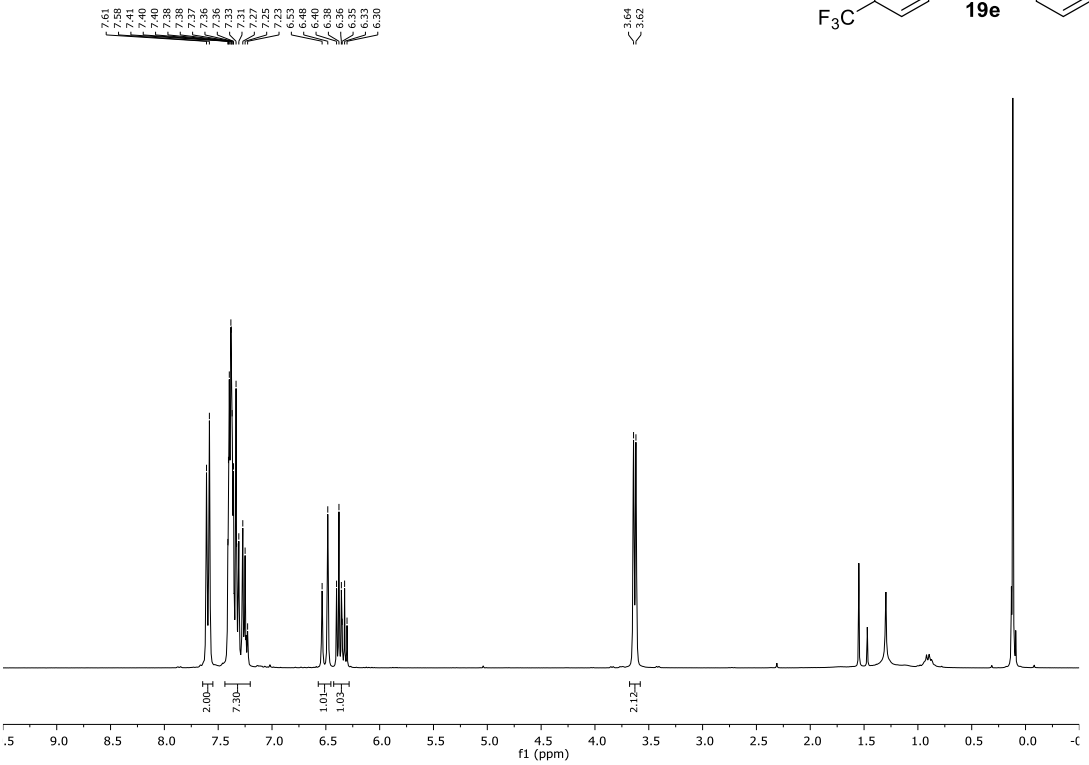


75 MHz ^{13}C NMR spectrum of compound **19d** ($CDCl_3$, 300 K)

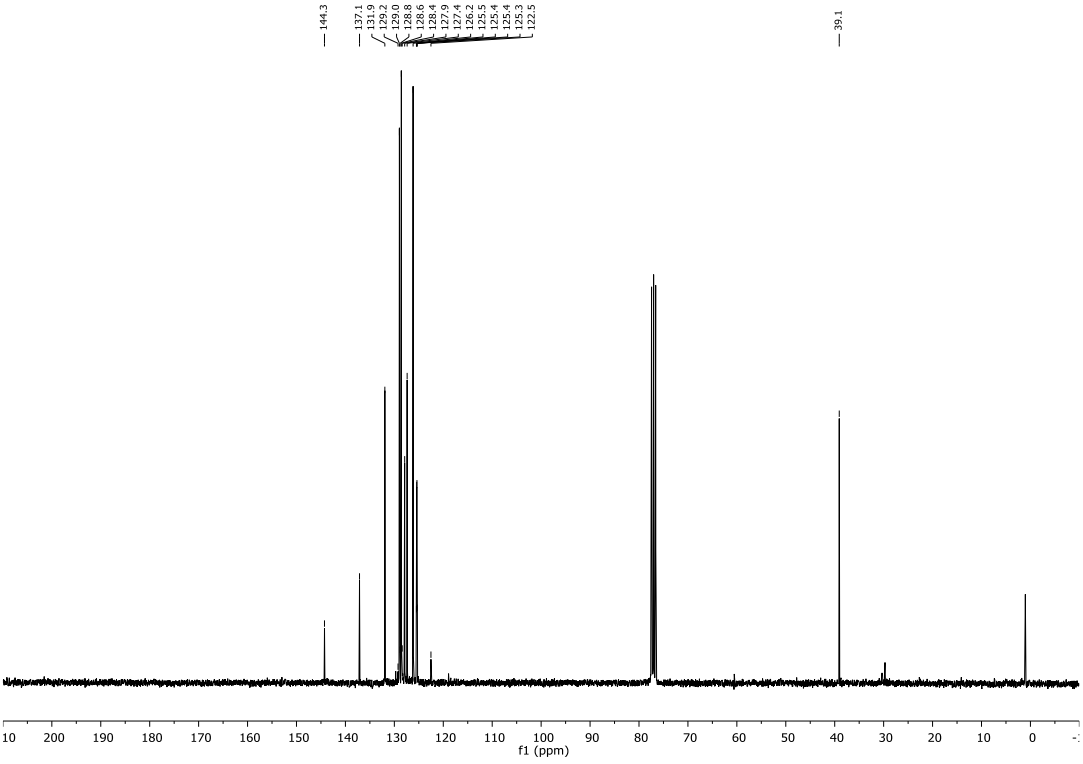


300 MHz ^{1}H NMR spectrum of compound **19e** ($CDCl_3$, 300 K)

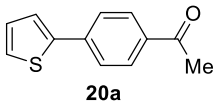




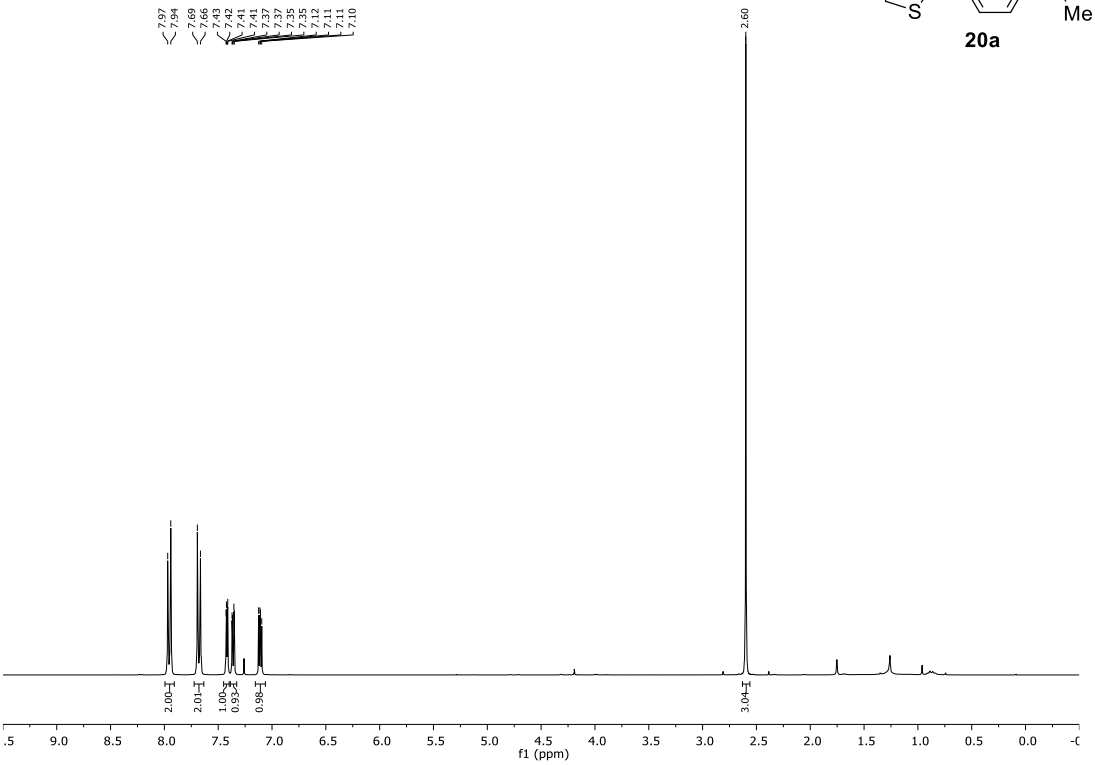
75 MHz ^{13}C NMR spectrum of compound **19e** ($CDCl_3$, 300 K)



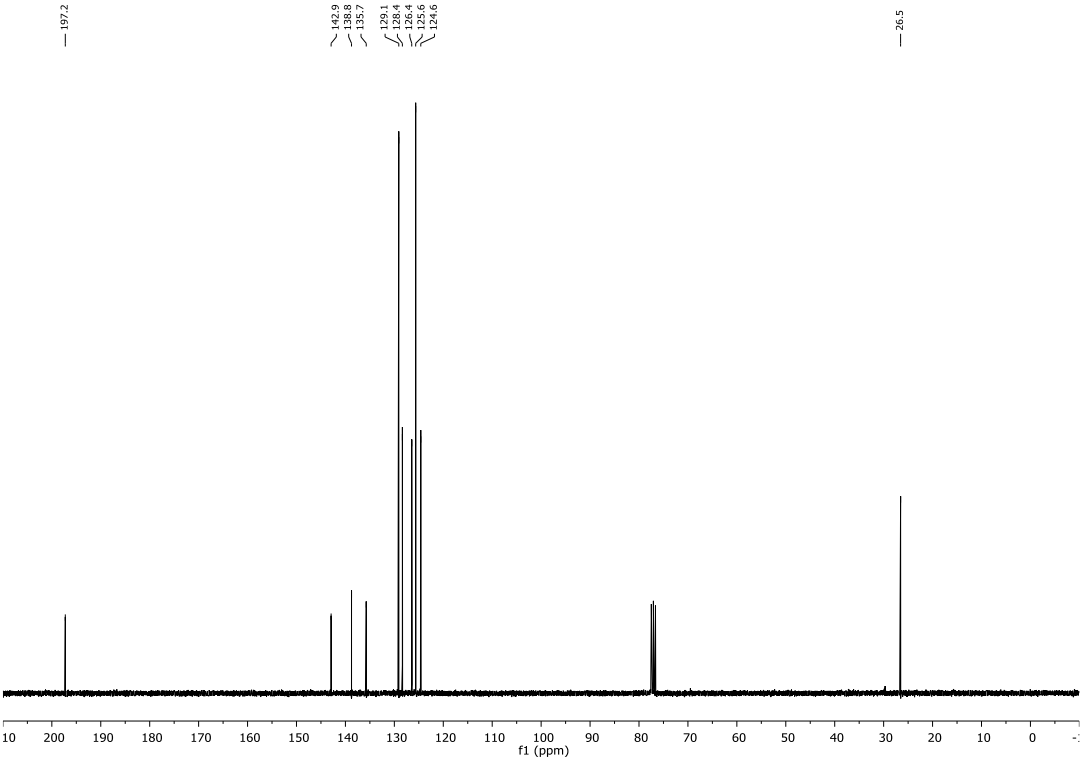
300 MHz ^{1}H NMR spectrum of compound **20a** ($CDCl_3$, 300 K)



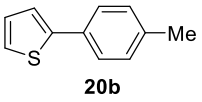
20a



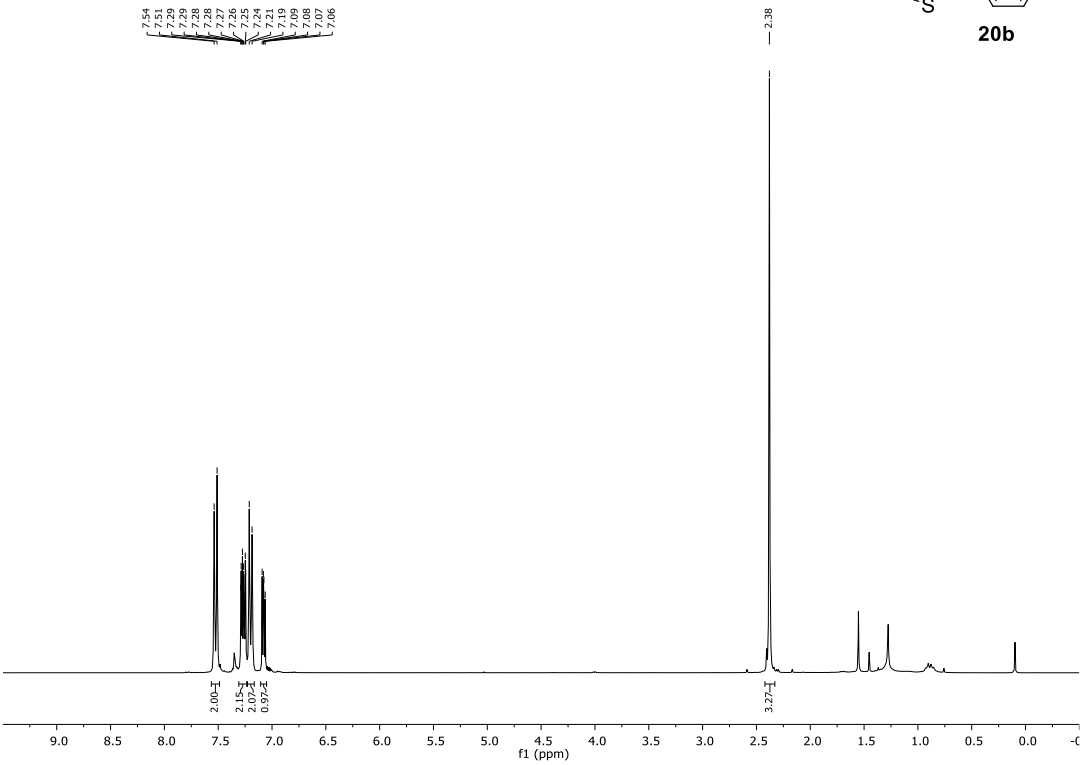
75 MHz ^{13}C NMR spectrum of compound **20a** ($CDCl_3$, 300 K)



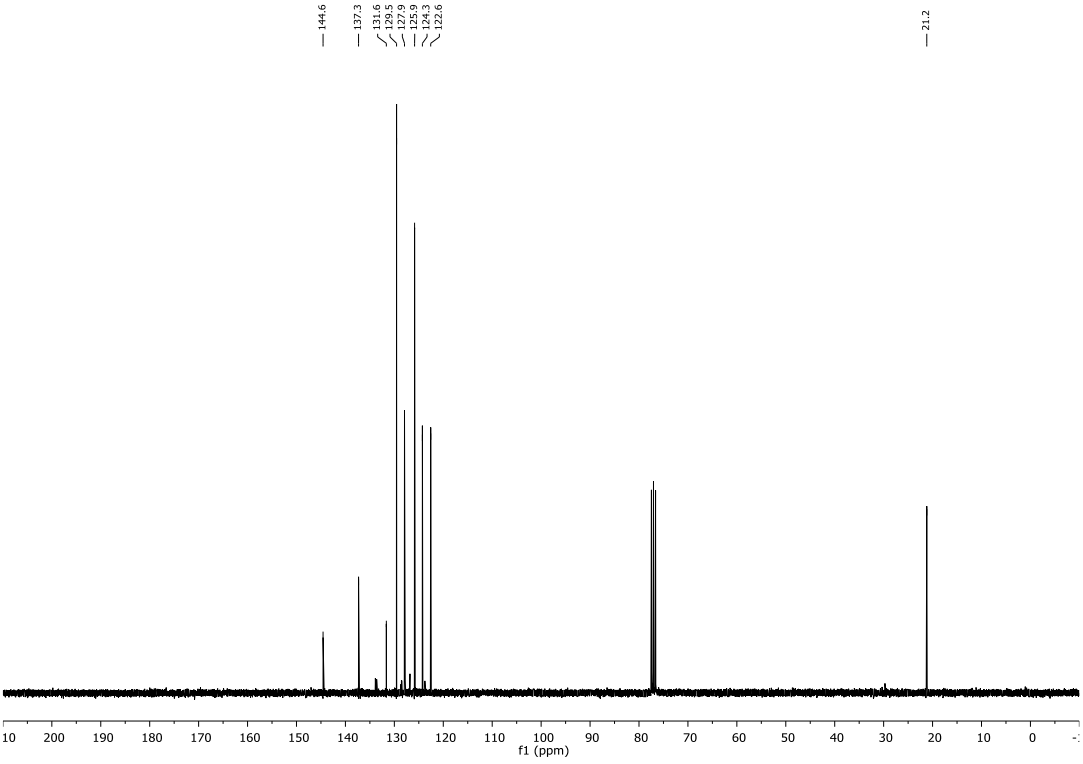
300 MHz ^{1}H NMR spectrum of compound **20b** ($CDCl_3$, 300 K)



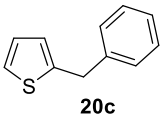
20b



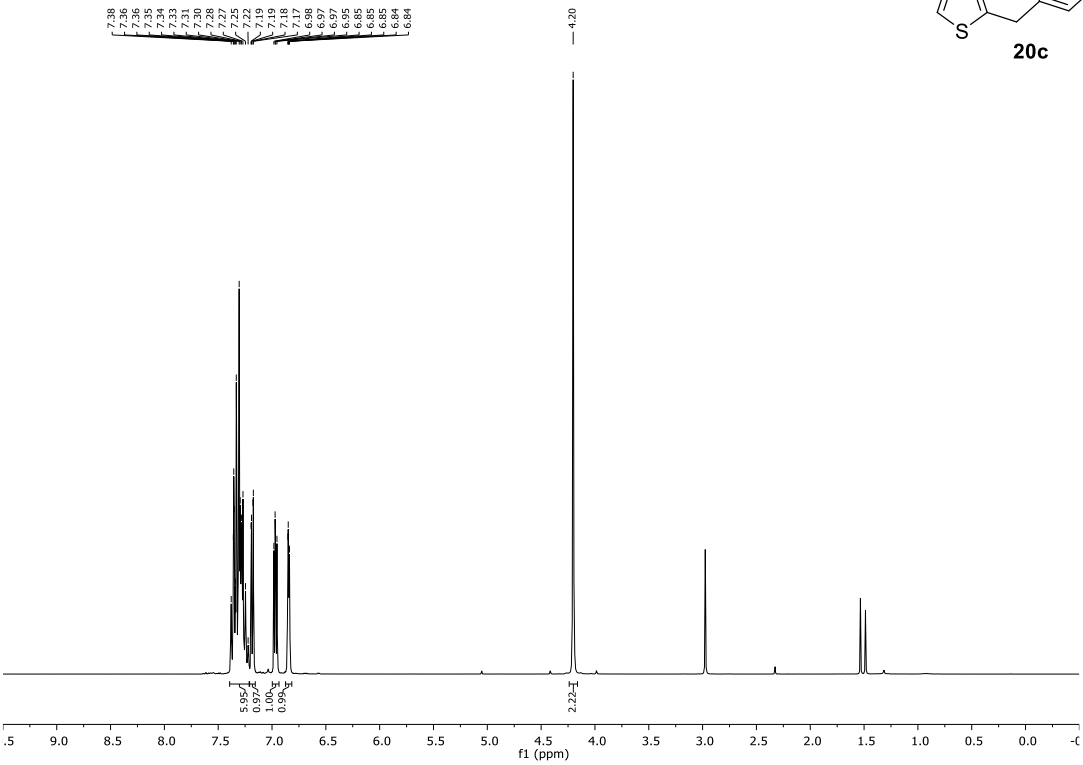
75 MHz ^{13}C NMR spectrum of compound **20b** ($CDCl_3$, 300 K)



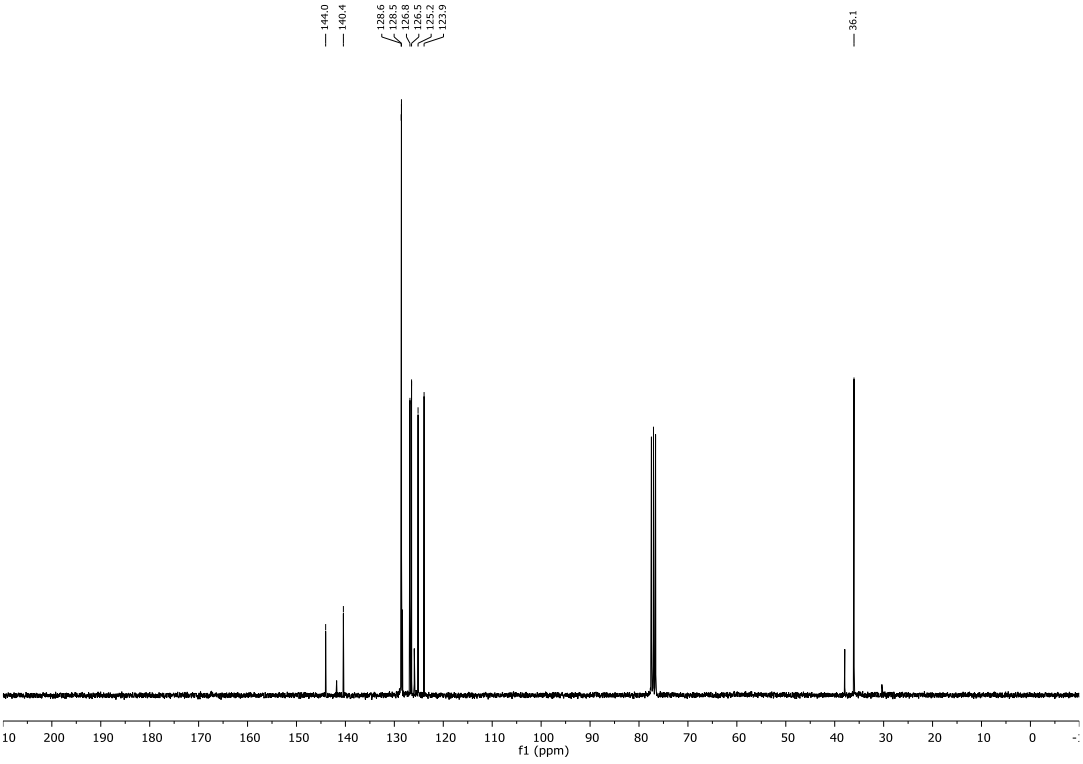
300 MHz ^{1}H NMR spectrum of compound **20c** ($CDCl_3$, 300 K)



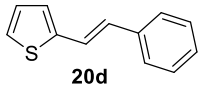
20c



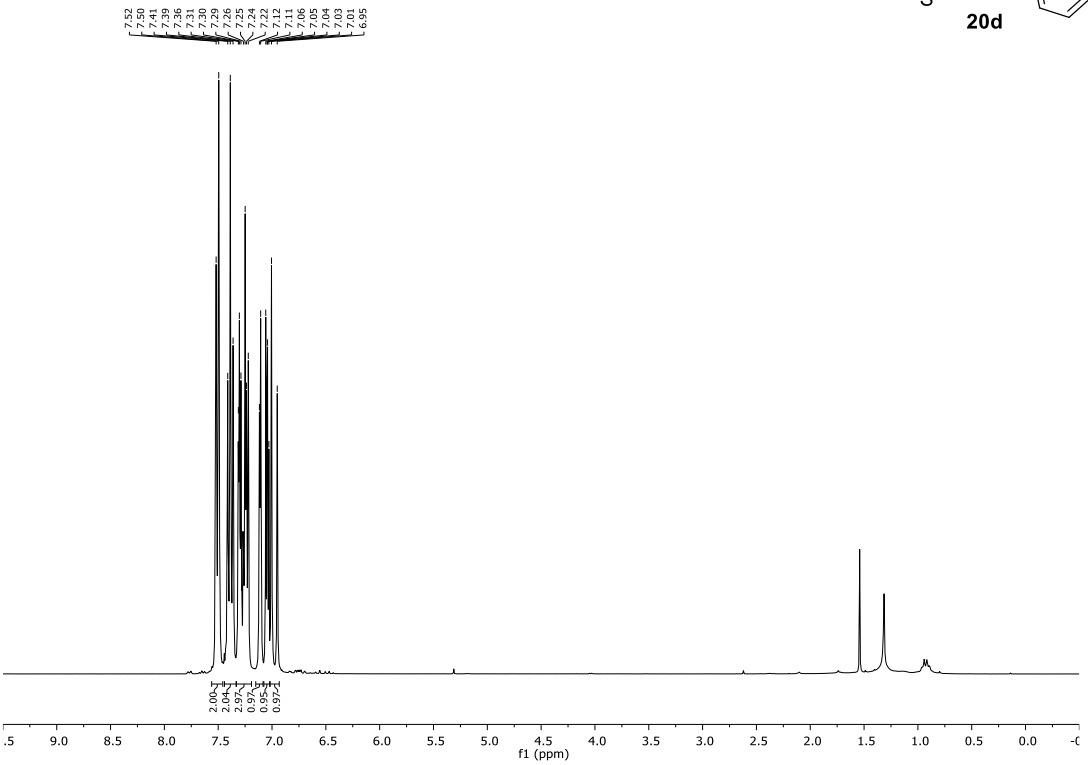
75 MHz ^{13}C NMR spectrum of compound **20c** ($CDCl_3$, 300 K)



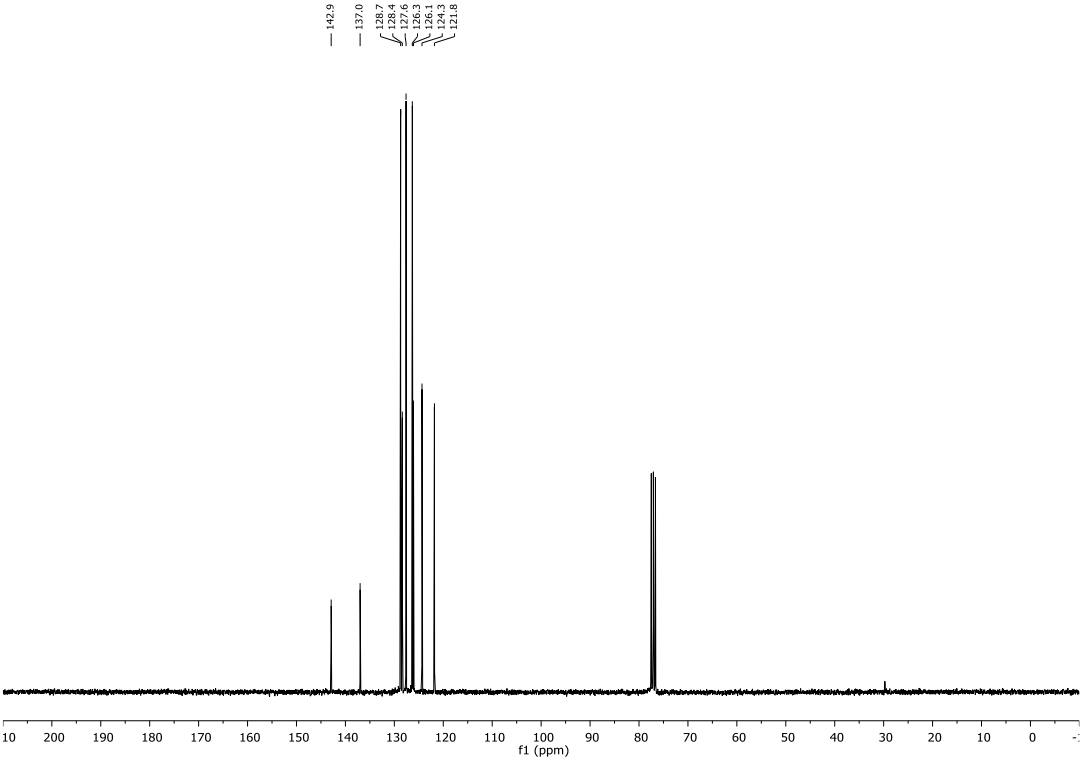
300 MHz ^{1}H NMR spectrum of compound **20d** ($CDCl_3$, 300 K)



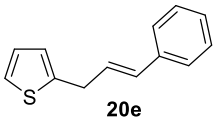
20d



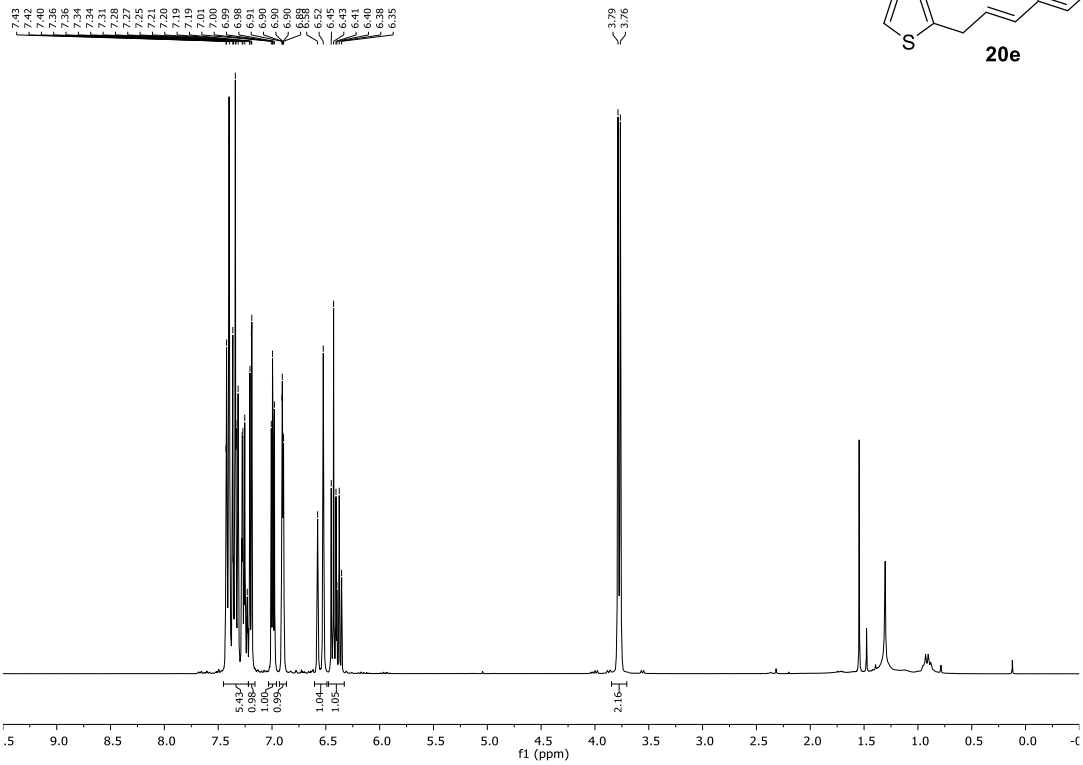
75 MHz ^{13}C NMR spectrum of compound **20d** ($CDCl_3$, 300 K)



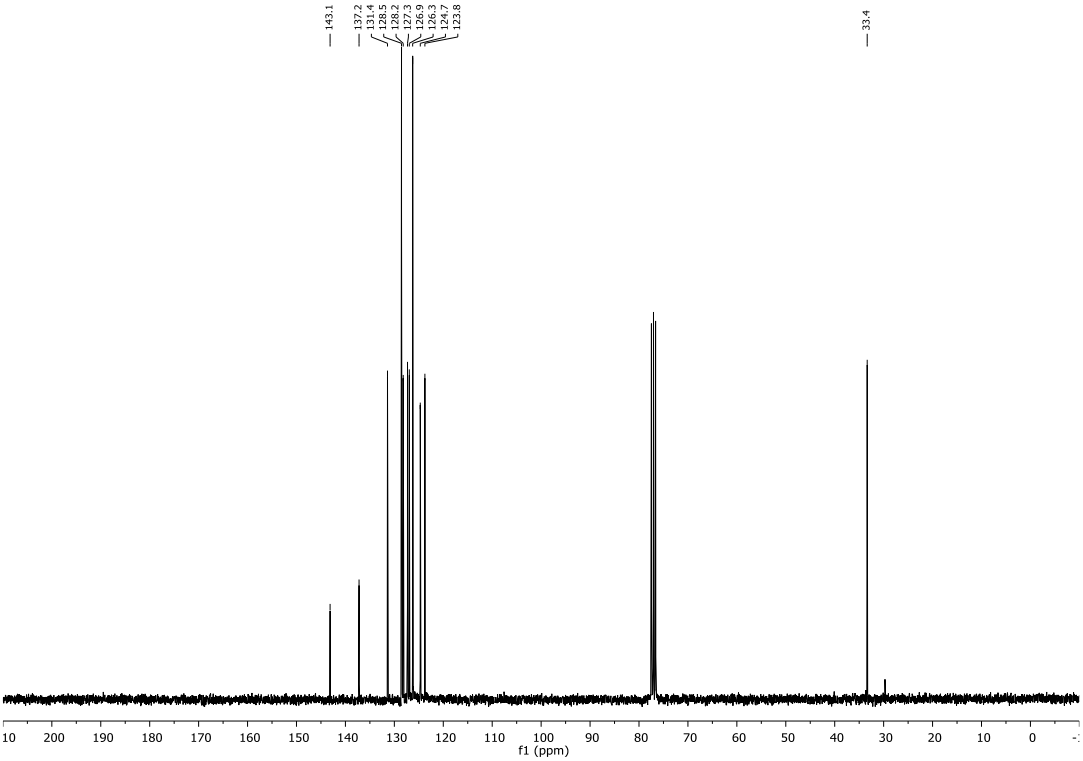
300 MHz ^{1}H NMR spectrum of compound **20e** ($CDCl_3$, 300 K)



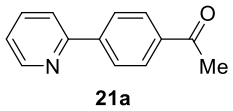
20e



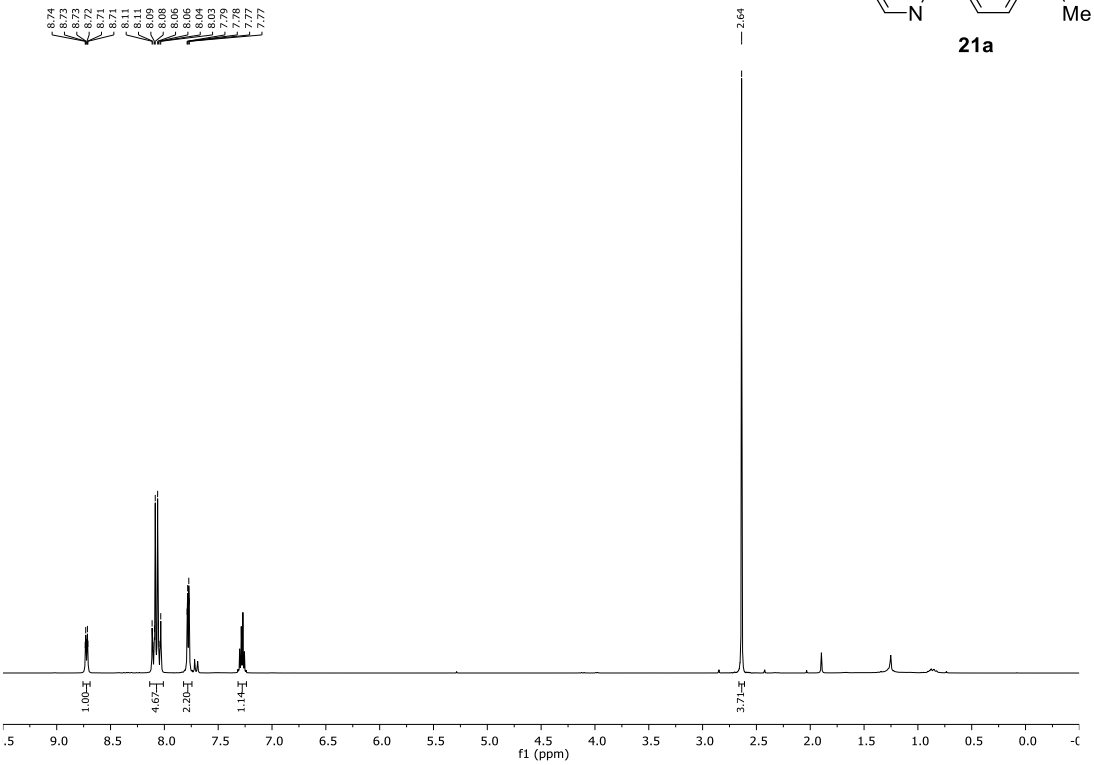
75 MHz ^{13}C NMR spectrum of compound **20e** ($CDCl_3$, 300 K)



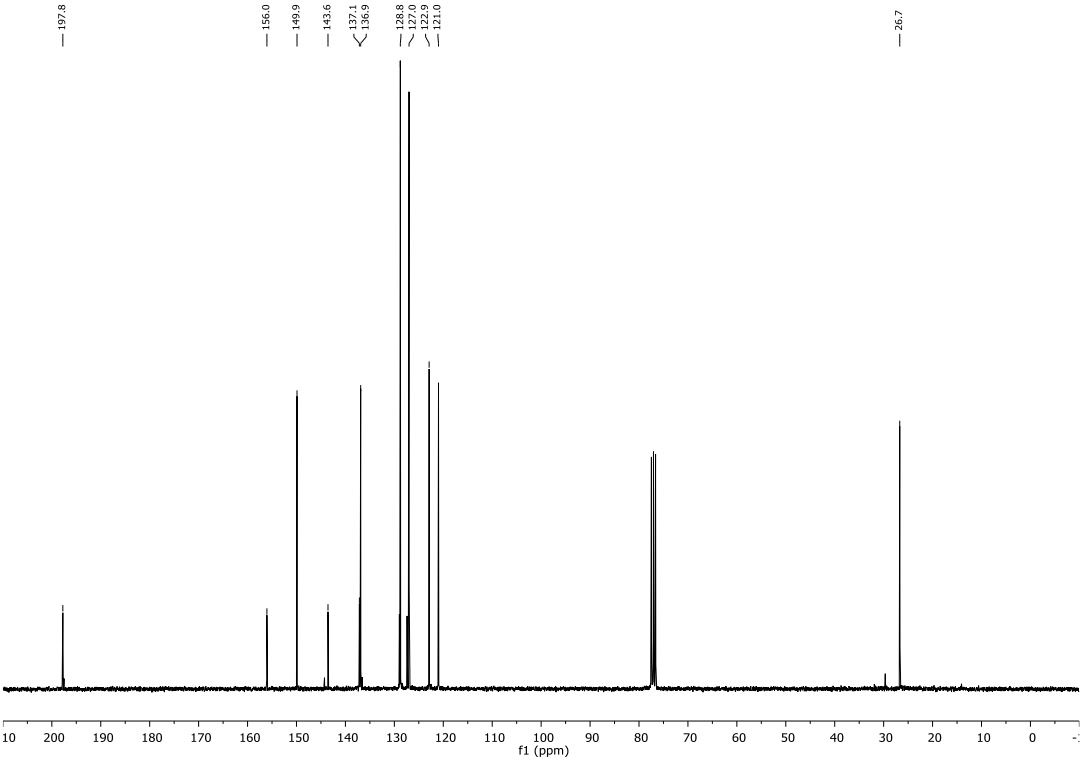
300 MHz ^{1}H NMR spectrum of compound **21a** ($CDCl_3$, 300 K)



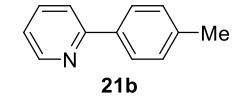
21a



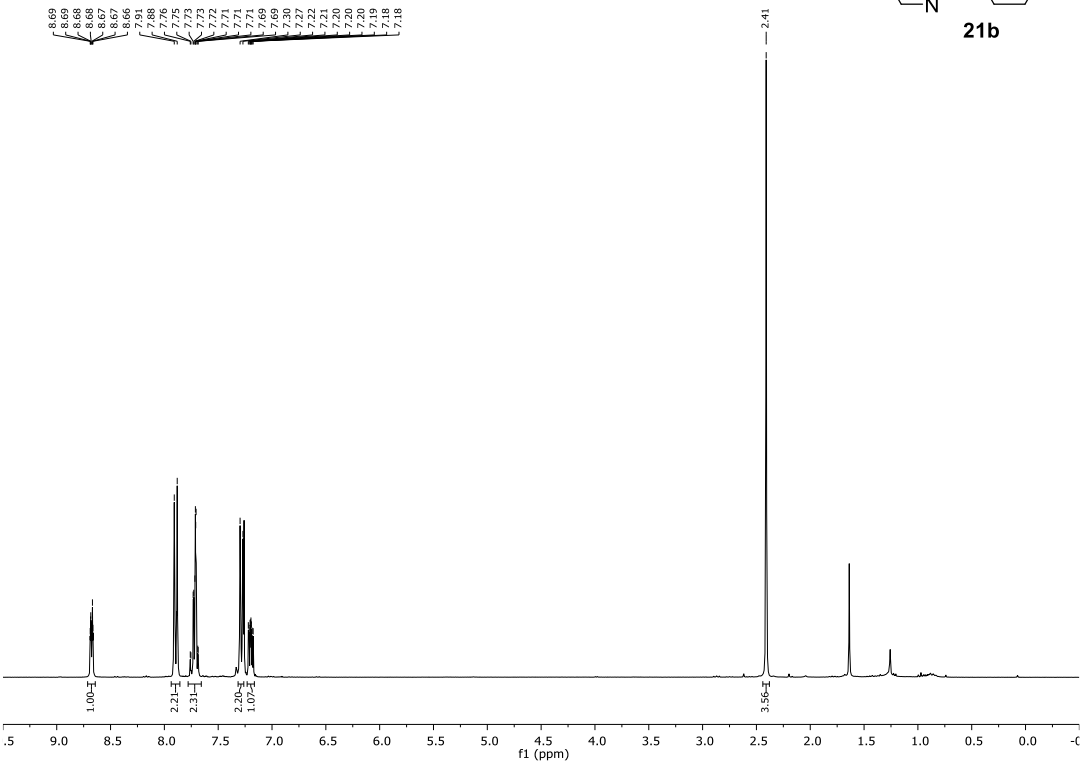
75 MHz ^{13}C NMR spectrum of compound **21a** ($CDCl_3$, 300 K)



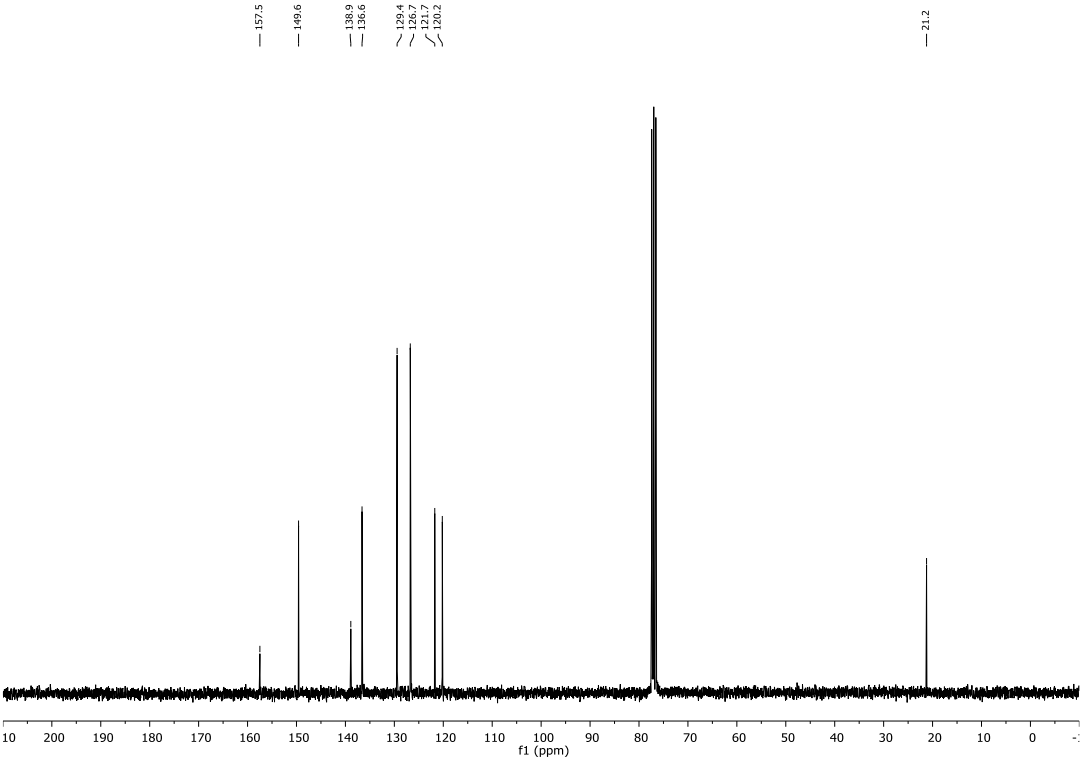
300 MHz ^{1}H NMR spectrum of compound **21b** ($CDCl_3$, 300 K)



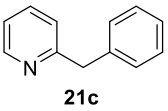
21b



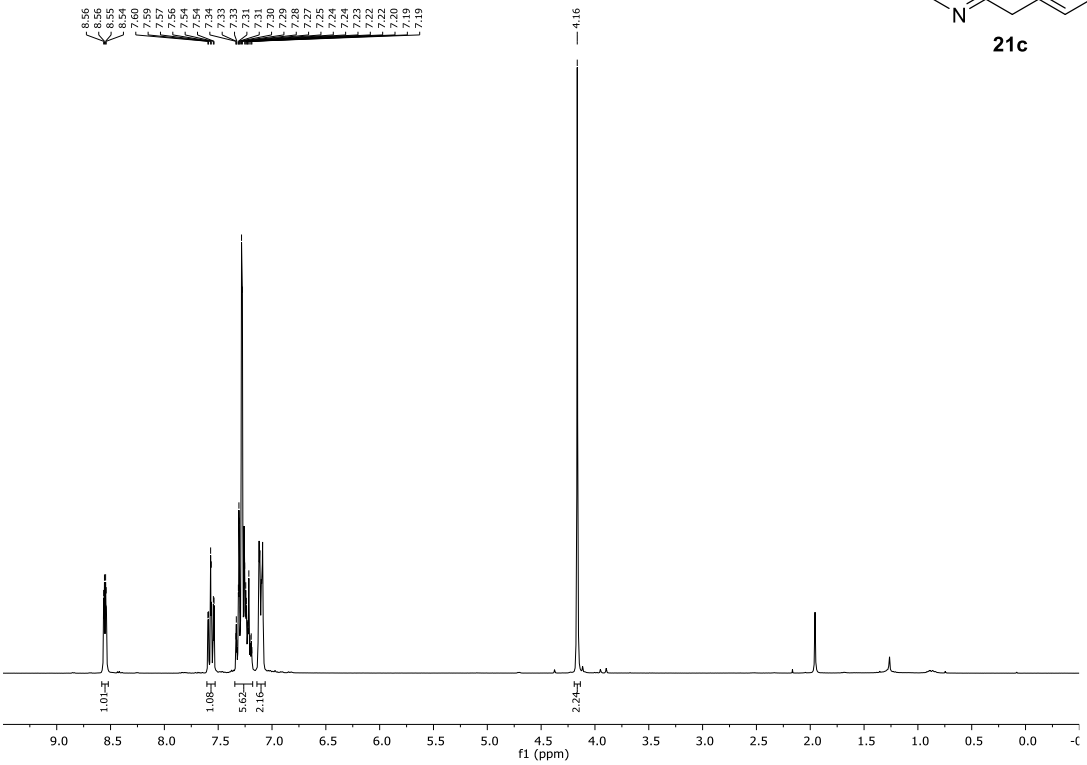
75 MHz ^{13}C NMR spectrum of compound **21b** ($CDCl_3$, 300 K)



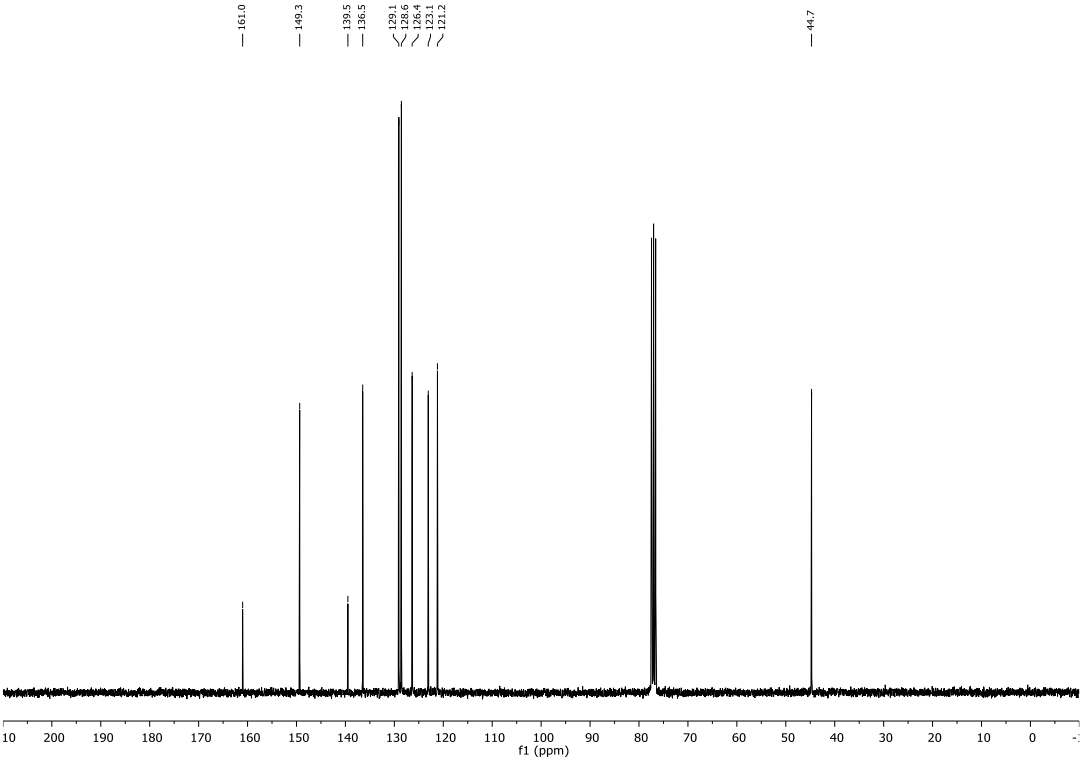
300 MHz ^{1}H NMR spectrum of compound **21c** ($CDCl_3$, 300 K)



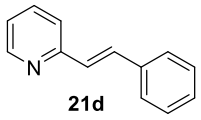
21c



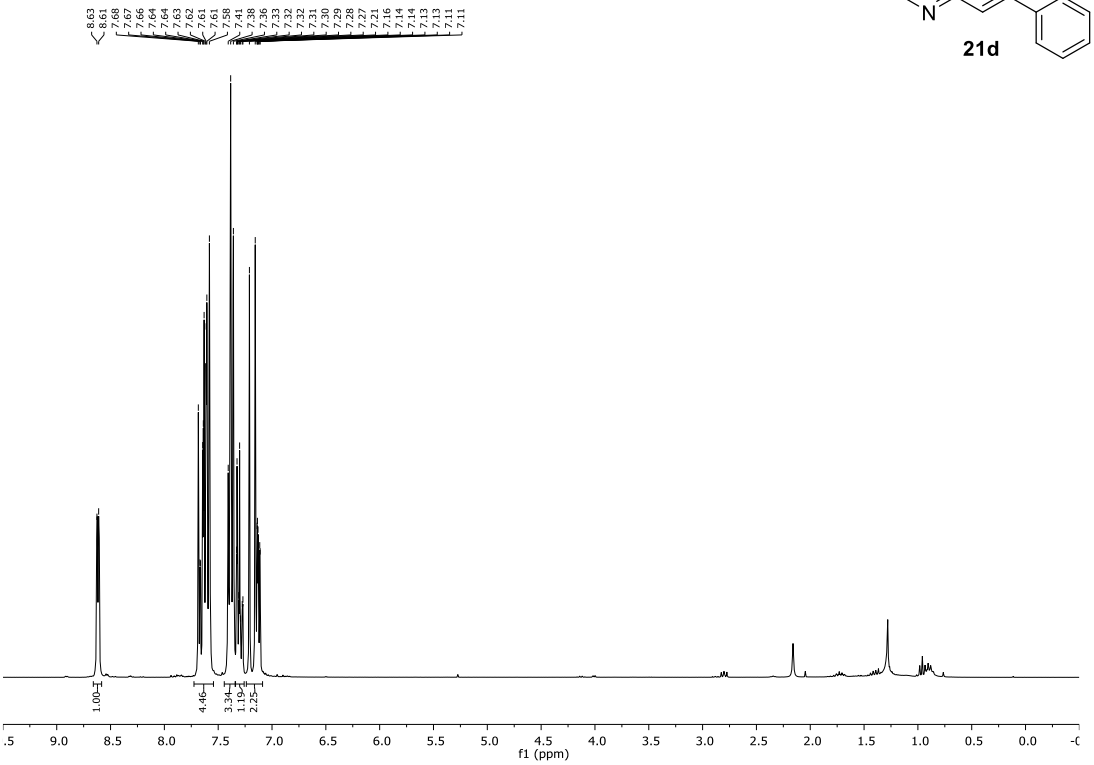
75 MHz ^{13}C NMR spectrum of compound **21c** ($CDCl_3$, 300 K)



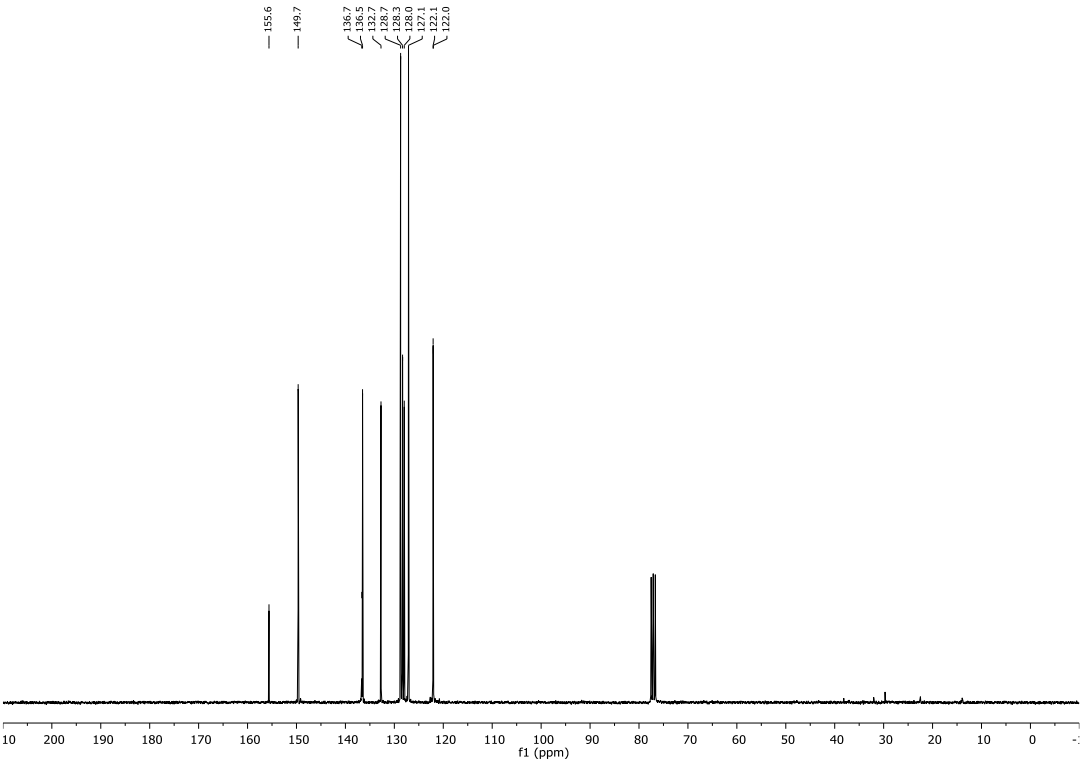
300 MHz ^{1}H NMR spectrum of compound **21d** ($CDCl_3$, 300 K)



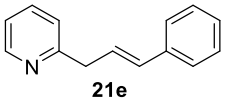
21d



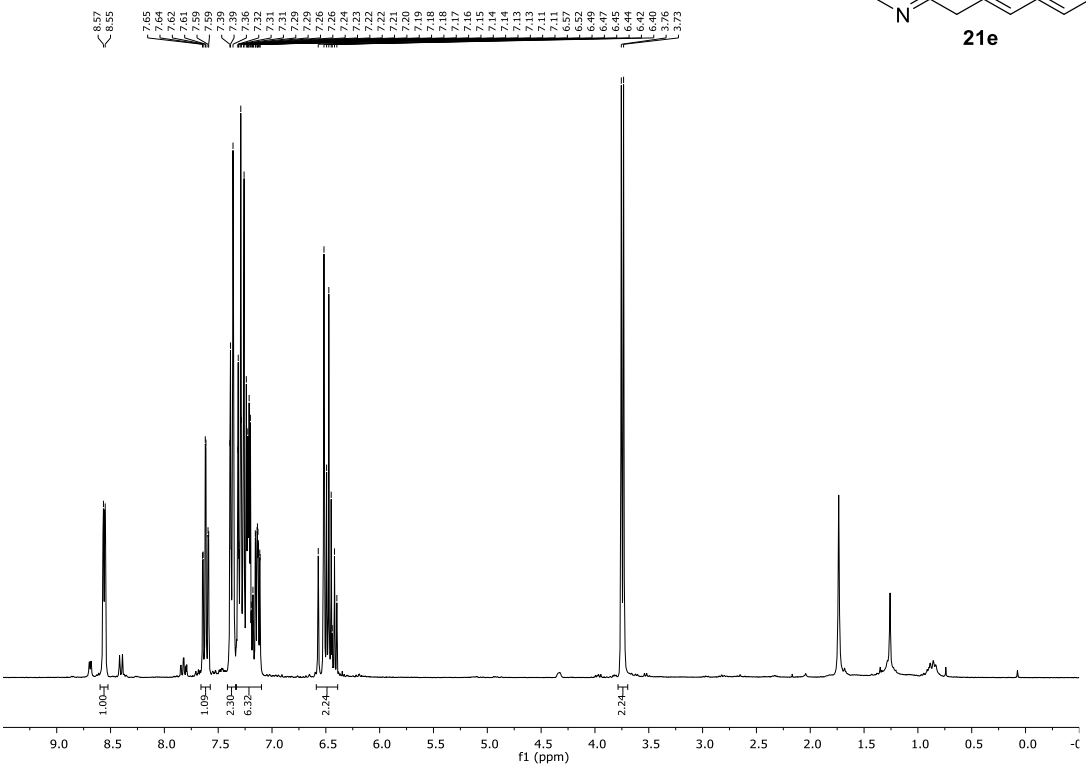
75 MHz ^{13}C NMR spectrum of compound **21d** ($CDCl_3$, 300 K)



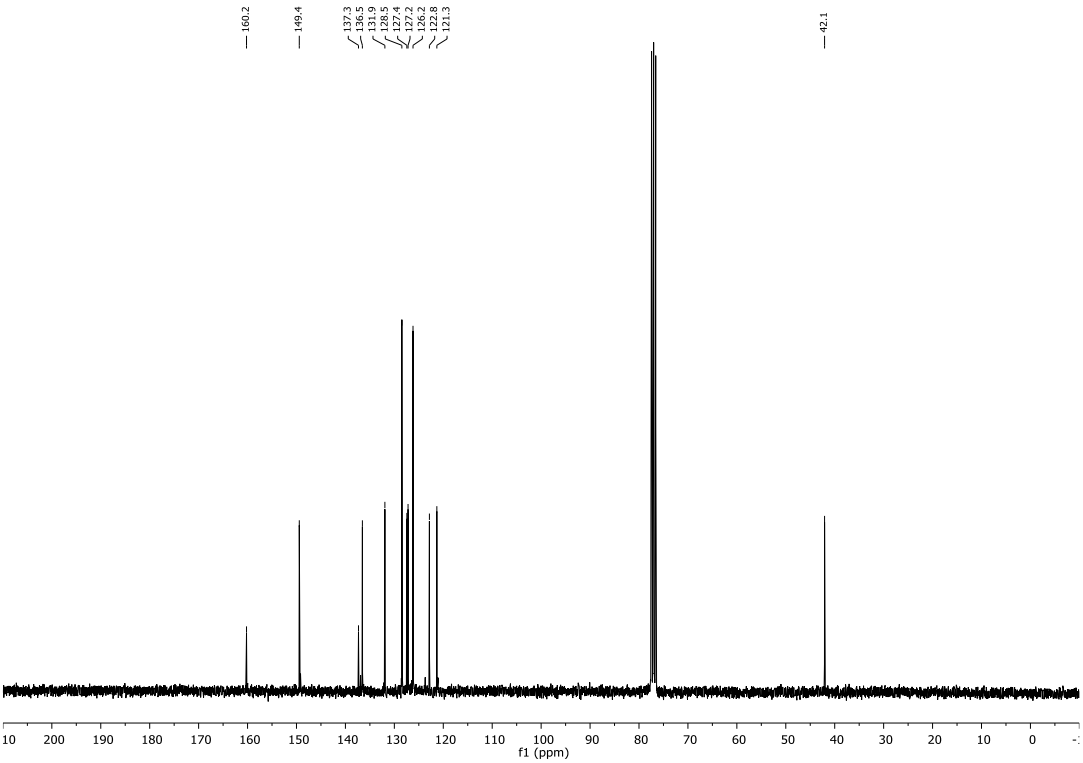
300 MHz ^{1}H NMR spectrum of compound **21e** ($CDCl_3$, 300 K)



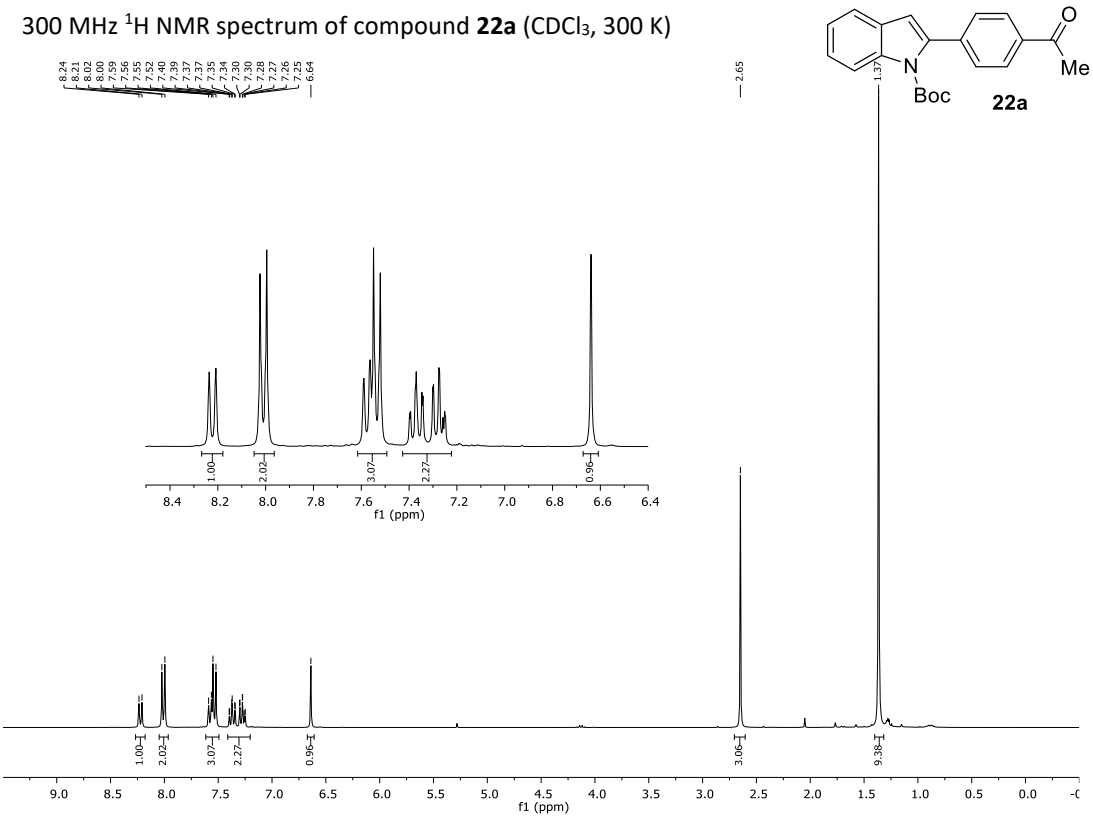
21e



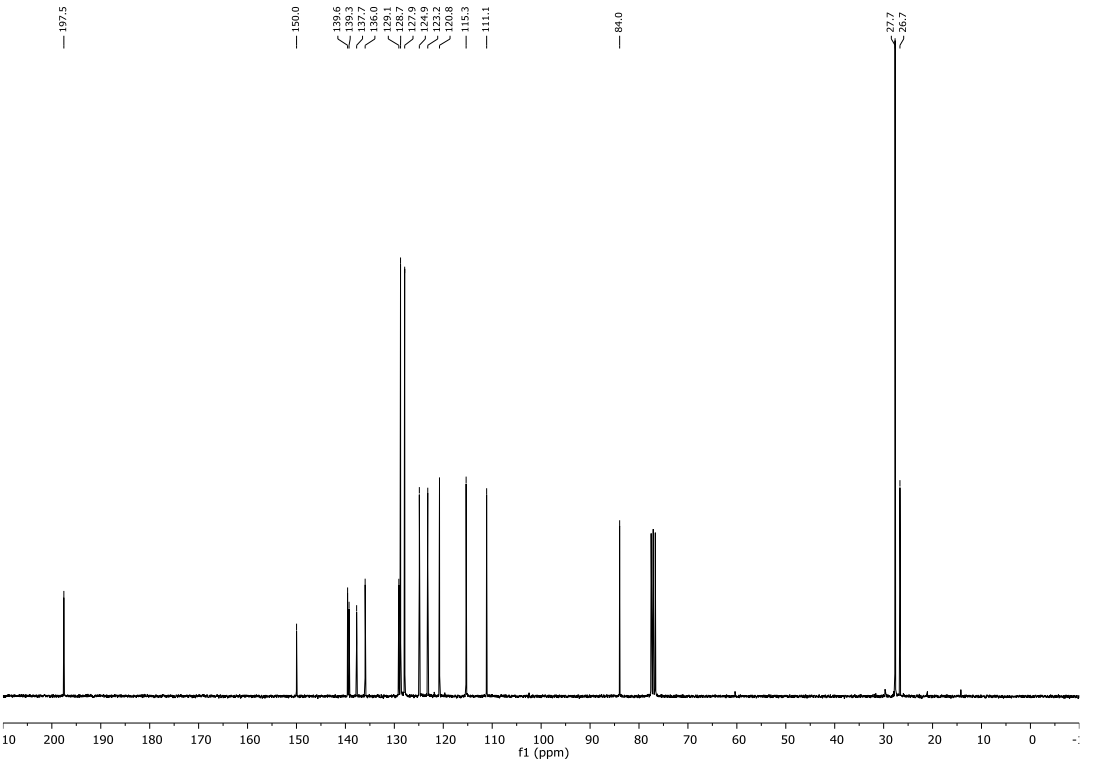
75 MHz ^{13}C NMR spectrum of compound **21d** ($CDCl_3$, 300 K)



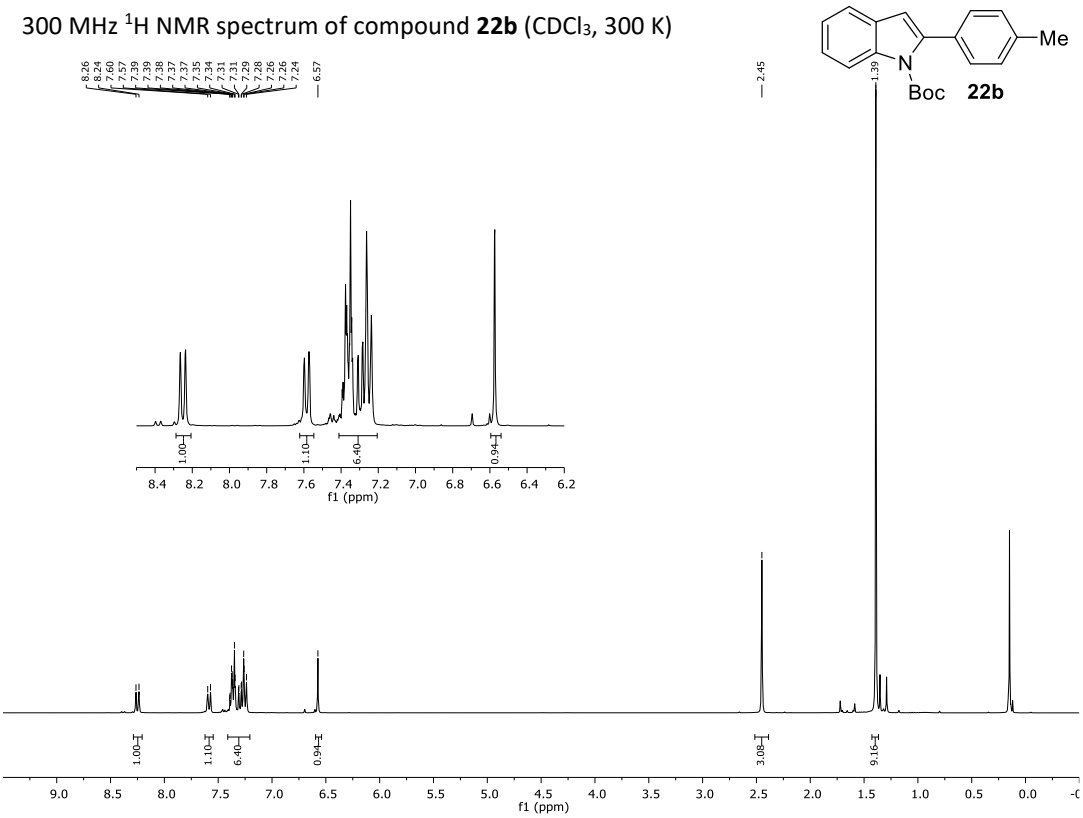
300 MHz ^{1}H NMR spectrum of compound **22a** ($CDCl_3$, 300 K)



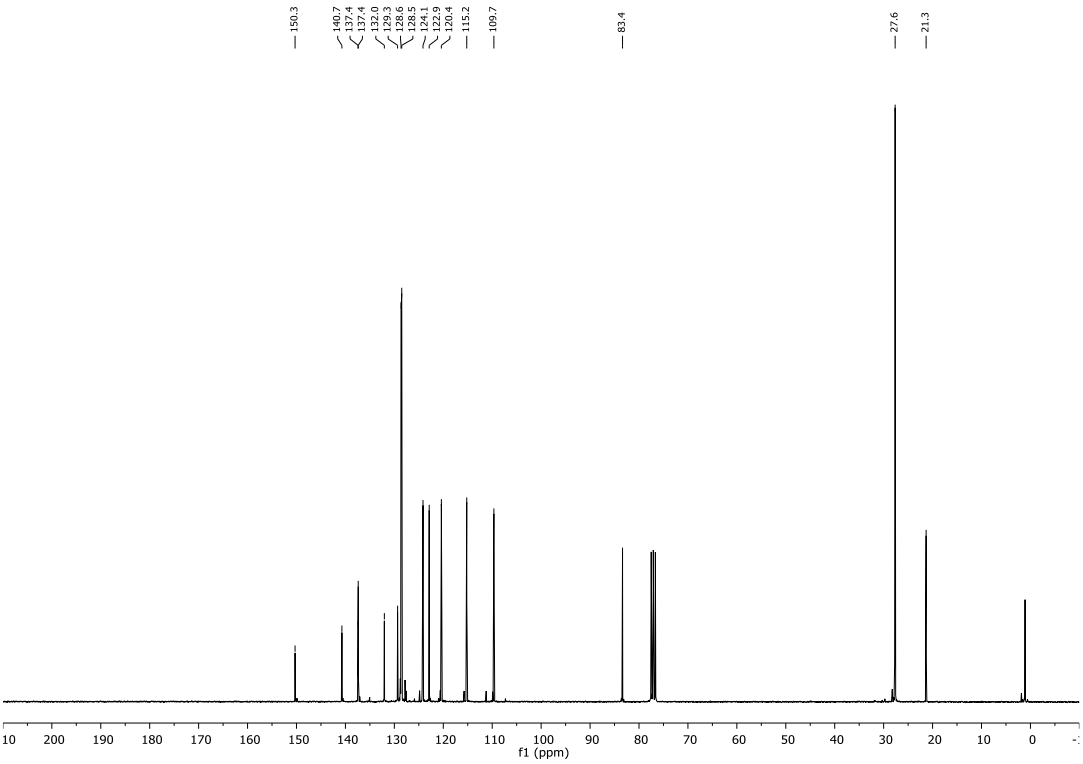
75 MHz ^{13}C NMR spectrum of compound **22a** ($CDCl_3$, 300 K)



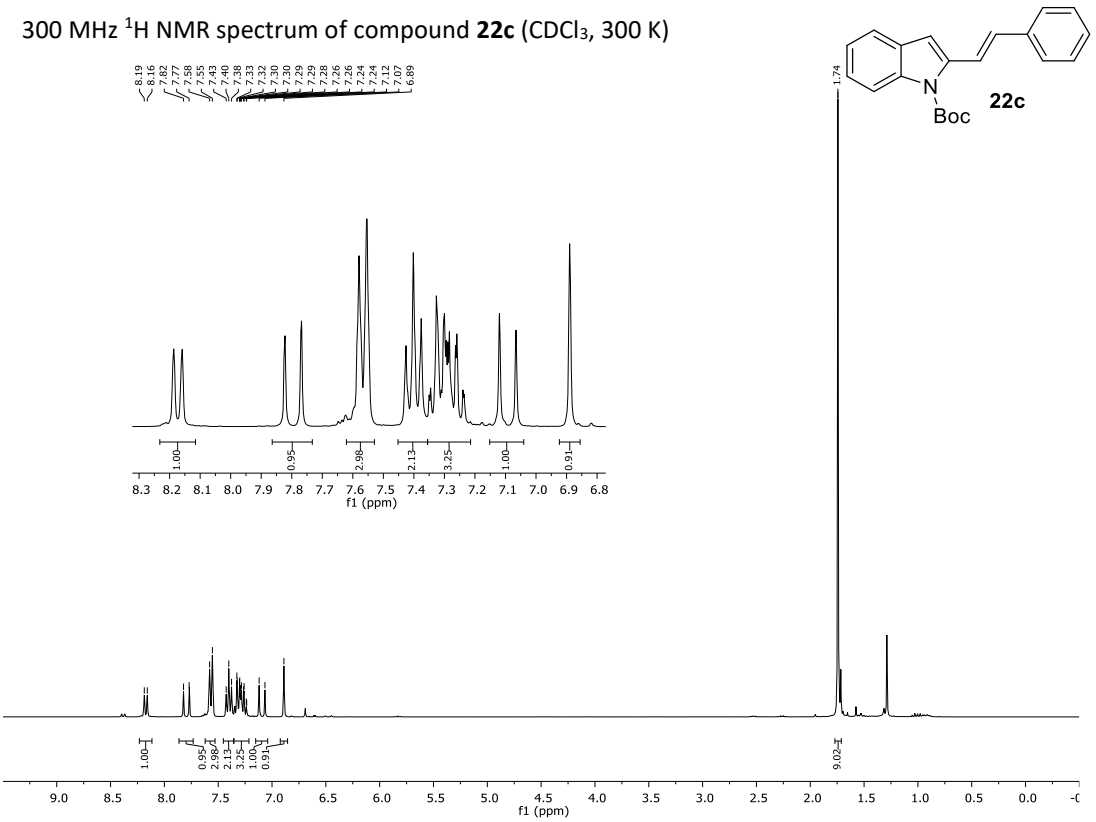
300 MHz ^{1}H NMR spectrum of compound **22b** ($CDCl_3$, 300 K)



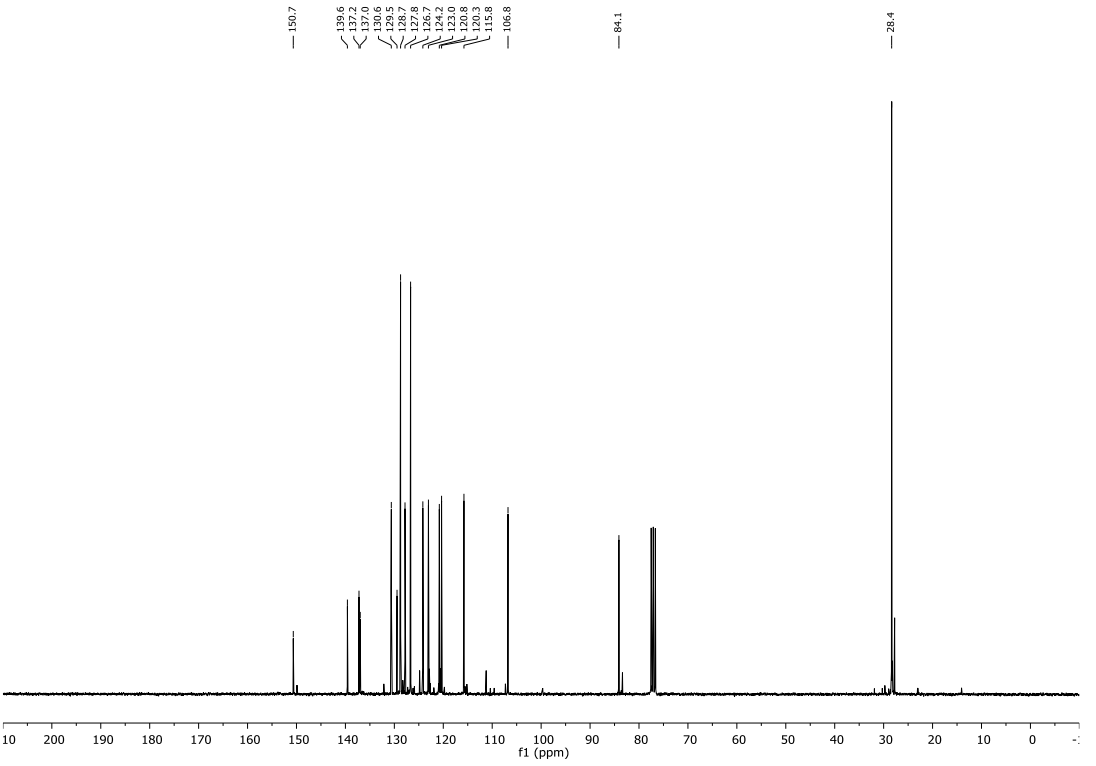
75 MHz ^{13}C NMR spectrum of compound **22b** ($CDCl_3$, 300 K)



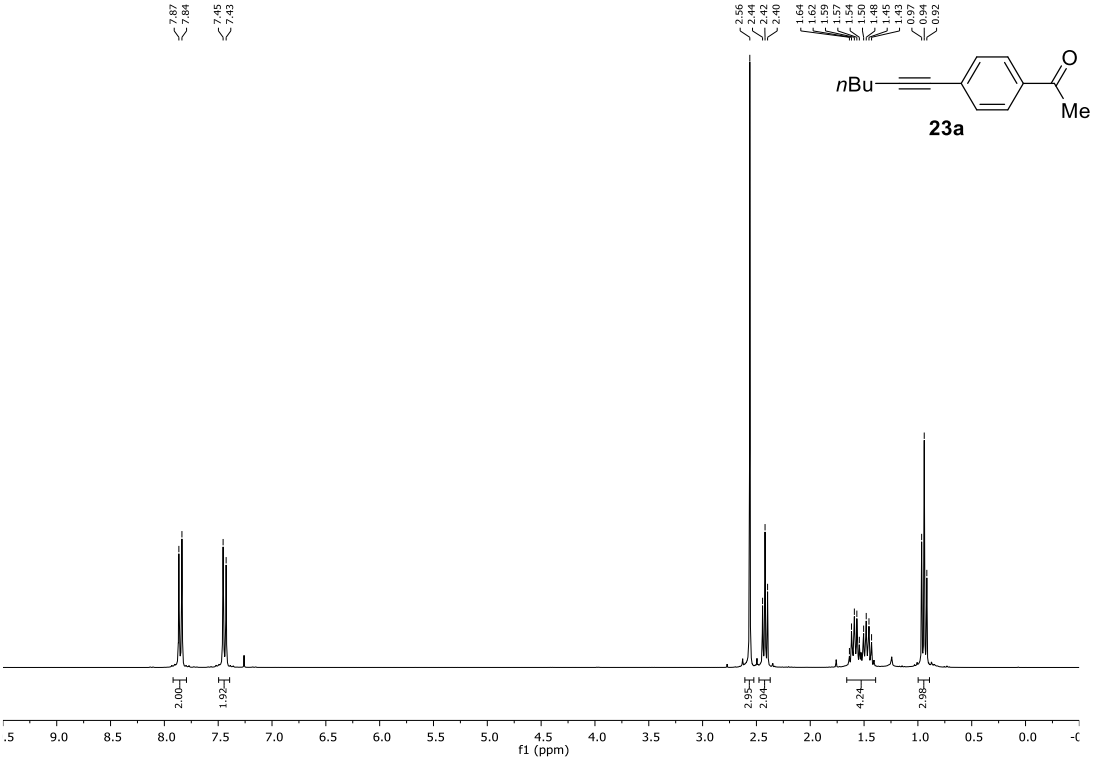
300 MHz ^{1}H NMR spectrum of compound **22c** ($CDCl_3$, 300 K)



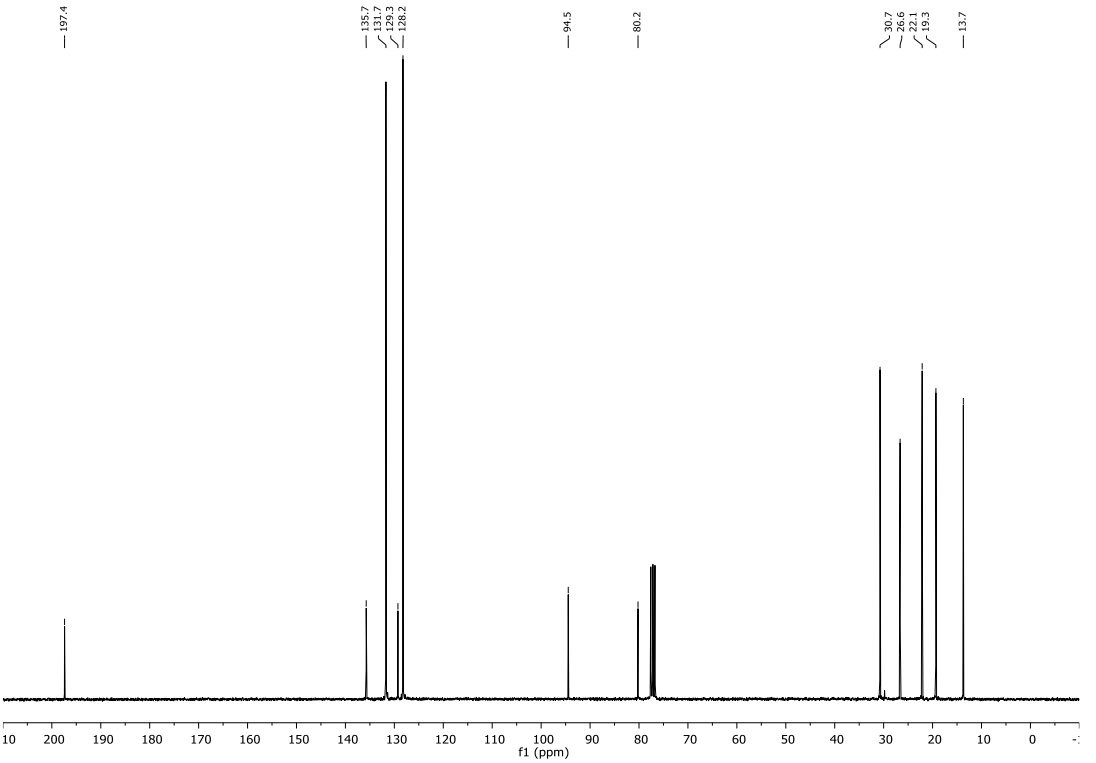
75 MHz ^{13}C NMR spectrum of compound **22c** ($CDCl_3$, 300 K)



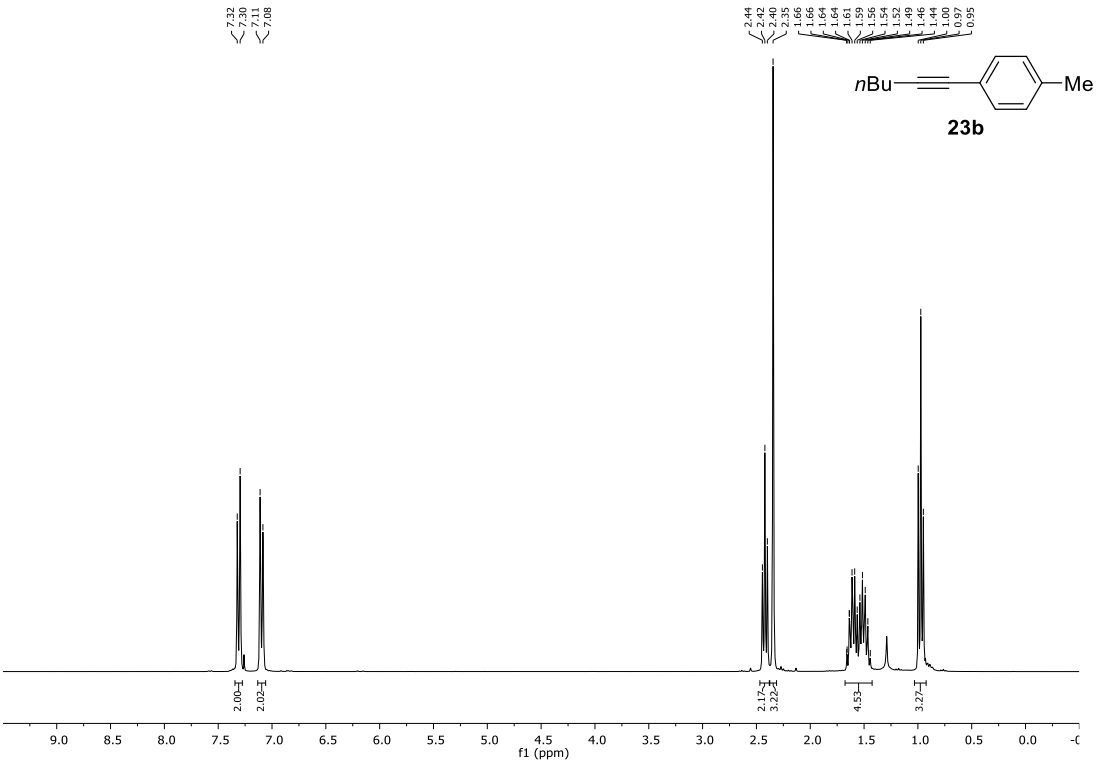
300 MHz ^{1}H NMR spectrum of compound **23a** ($CDCl_3$, 300 K)



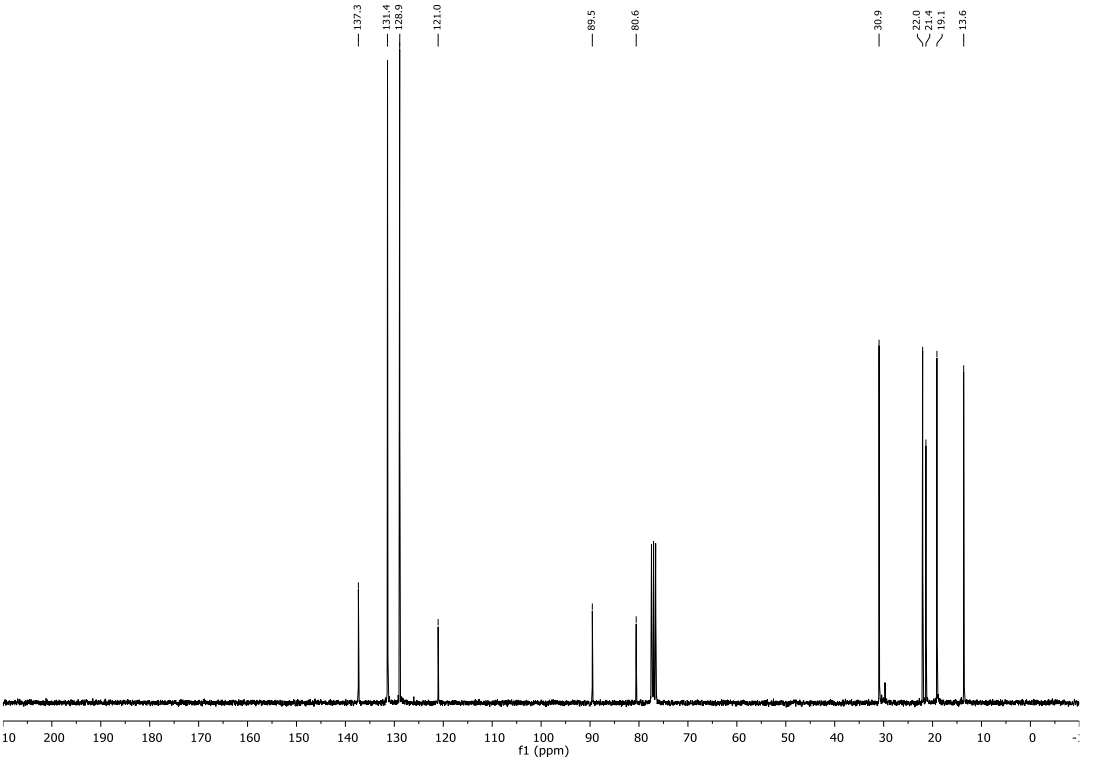
75 MHz ^{13}C NMR spectrum of compound **23a** ($CDCl_3$, 300 K)



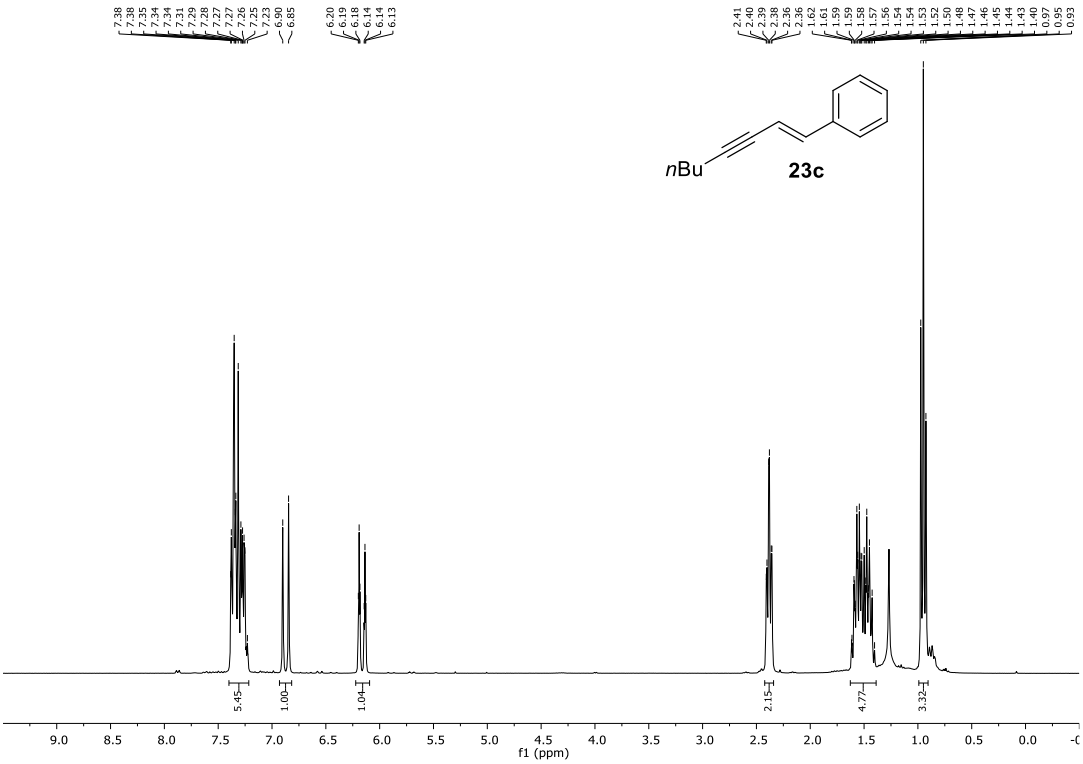
300 MHz ^{1}H NMR spectrum of compound **23b** ($CDCl_3$, 300 K)



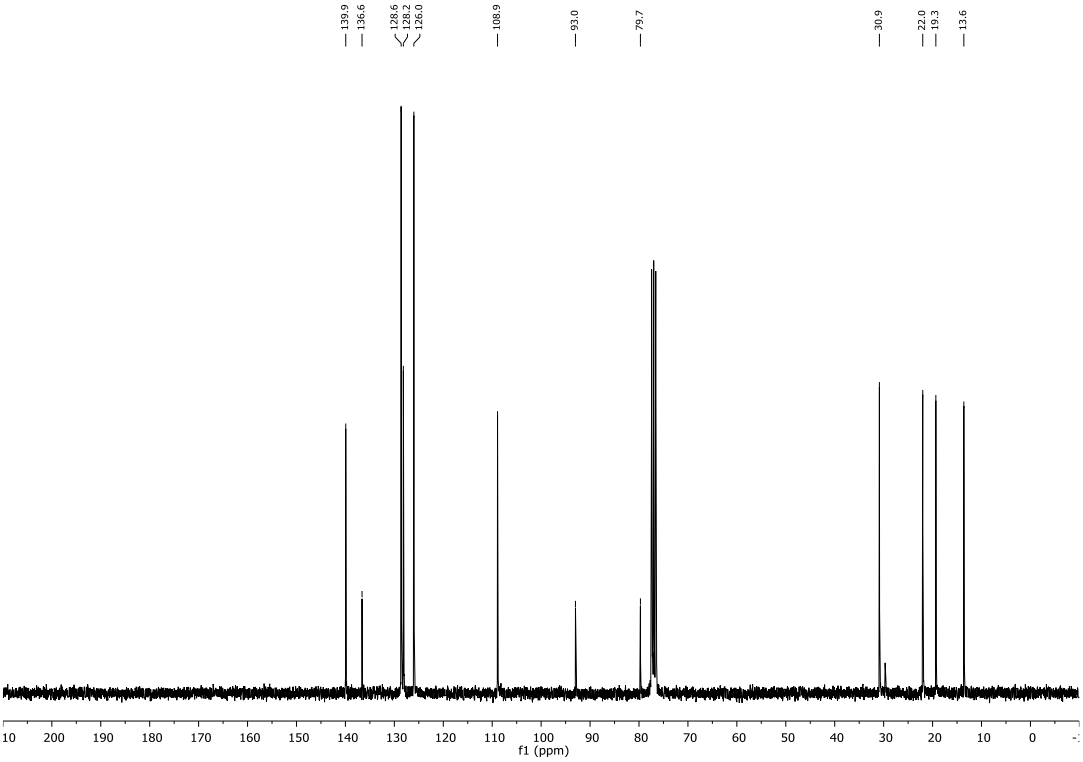
75 MHz ^{13}C NMR spectrum of compound **23b** ($CDCl_3$, 300 K)



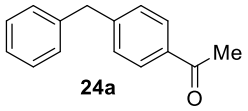
300 MHz ^{1}H NMR spectrum of compound **23c** ($CDCl_3$, 300 K)



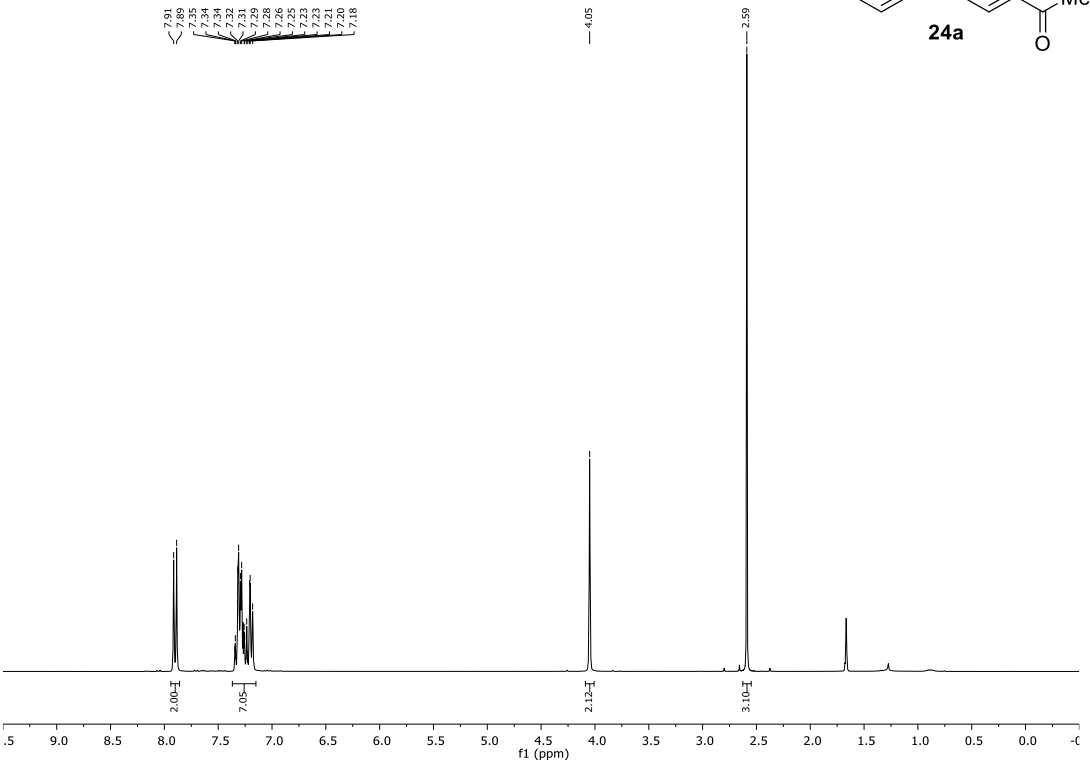
75 MHz ^{13}C NMR spectrum of compound **23c** ($CDCl_3$, 300 K)



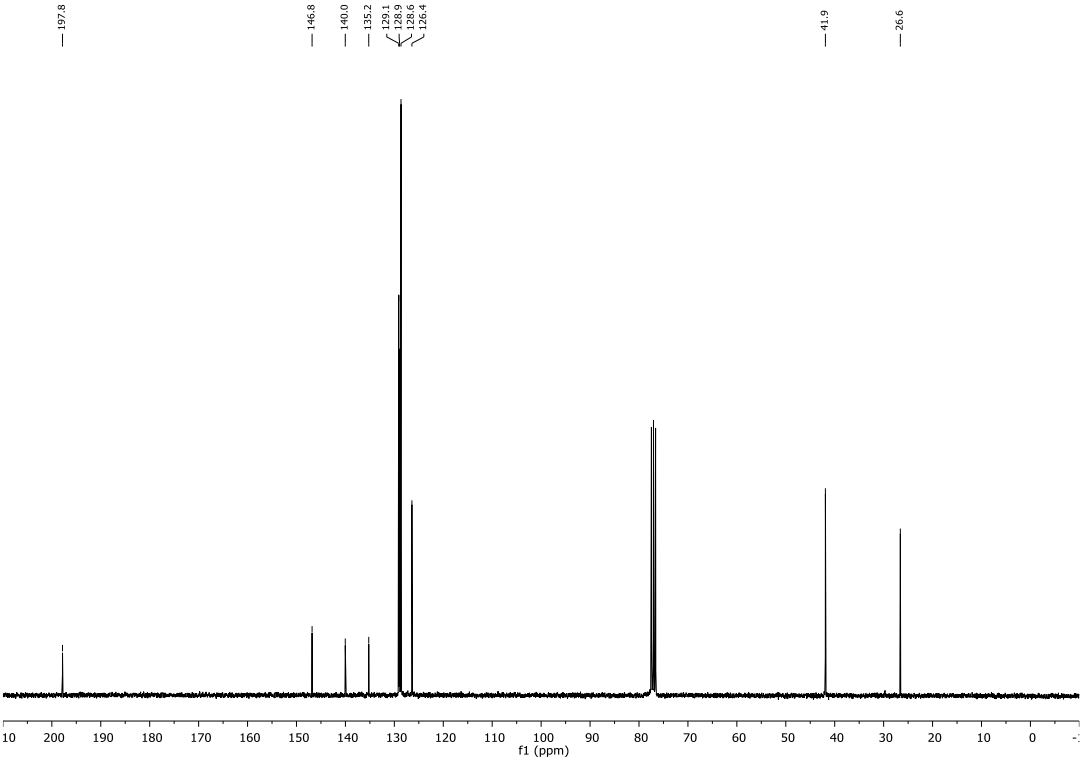
300 MHz ^{1}H NMR spectrum of compound **24a** ($CDCl_3$, 300 K)



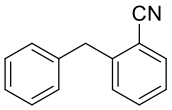
24a



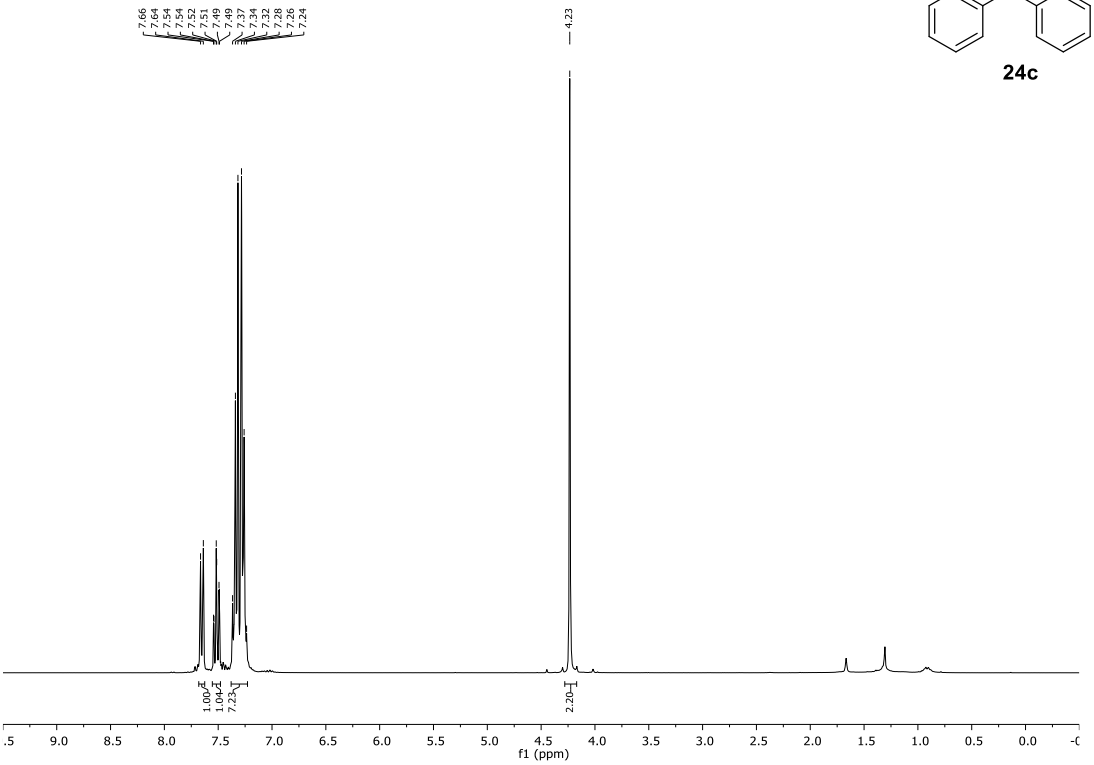
75 MHz ^{13}C NMR spectrum of compound **24a** ($CDCl_3$, 300 K)



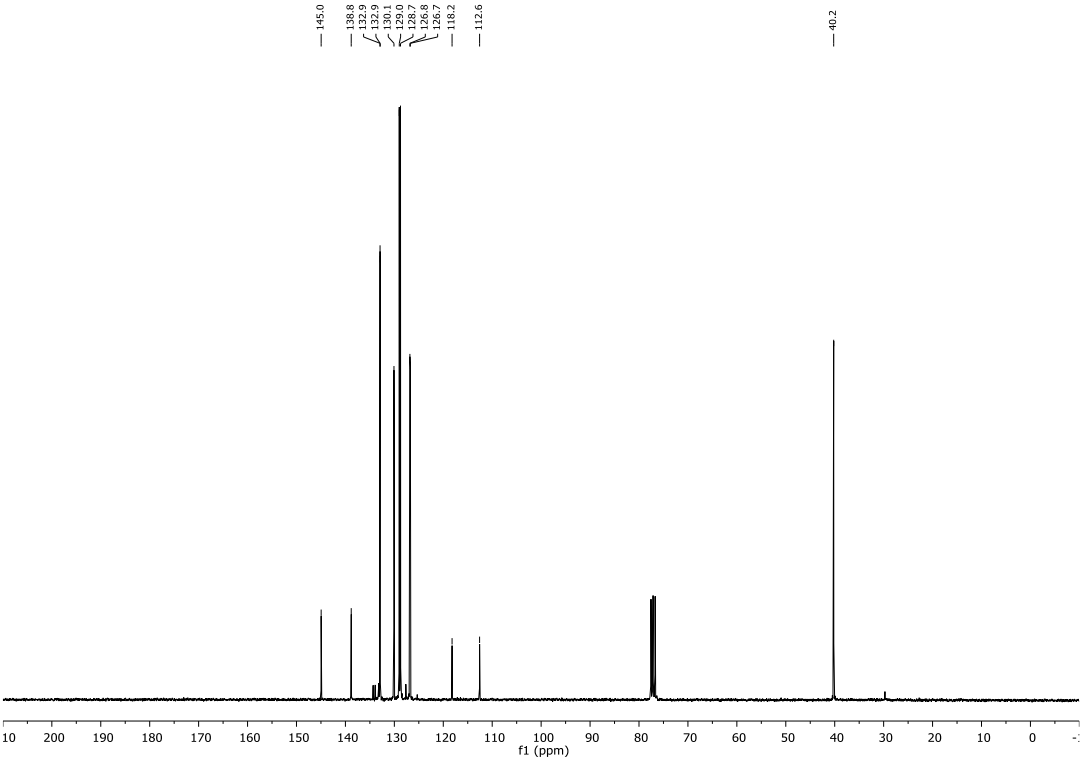
300 MHz ^{1}H NMR spectrum of compound **24c** ($CDCl_3$, 300 K)



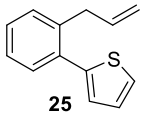
24c



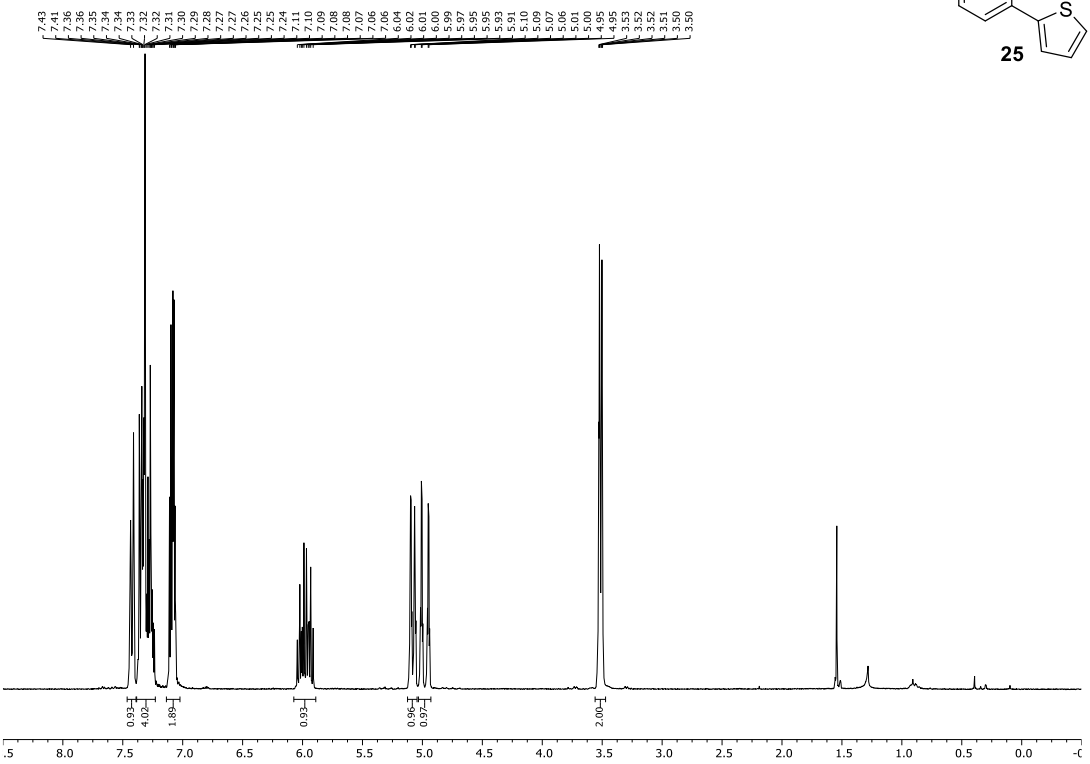
75 MHz ^{13}C NMR spectrum of compound **24c** ($CDCl_3$, 300 K)



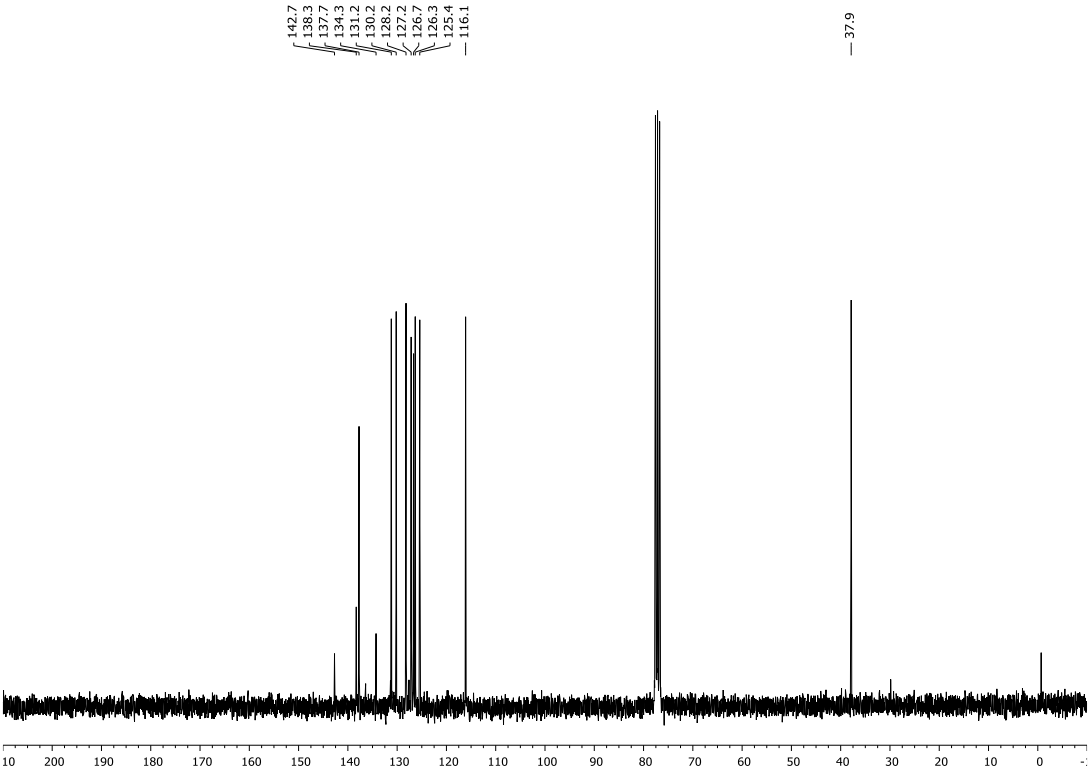
300 MHz ^{1}H NMR spectrum of compound **25** ($CDCl_3$, 300 K)



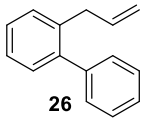
25



75 MHz ^{13}C NMR spectrum of compound **25** ($CDCl_3$, 300 K)

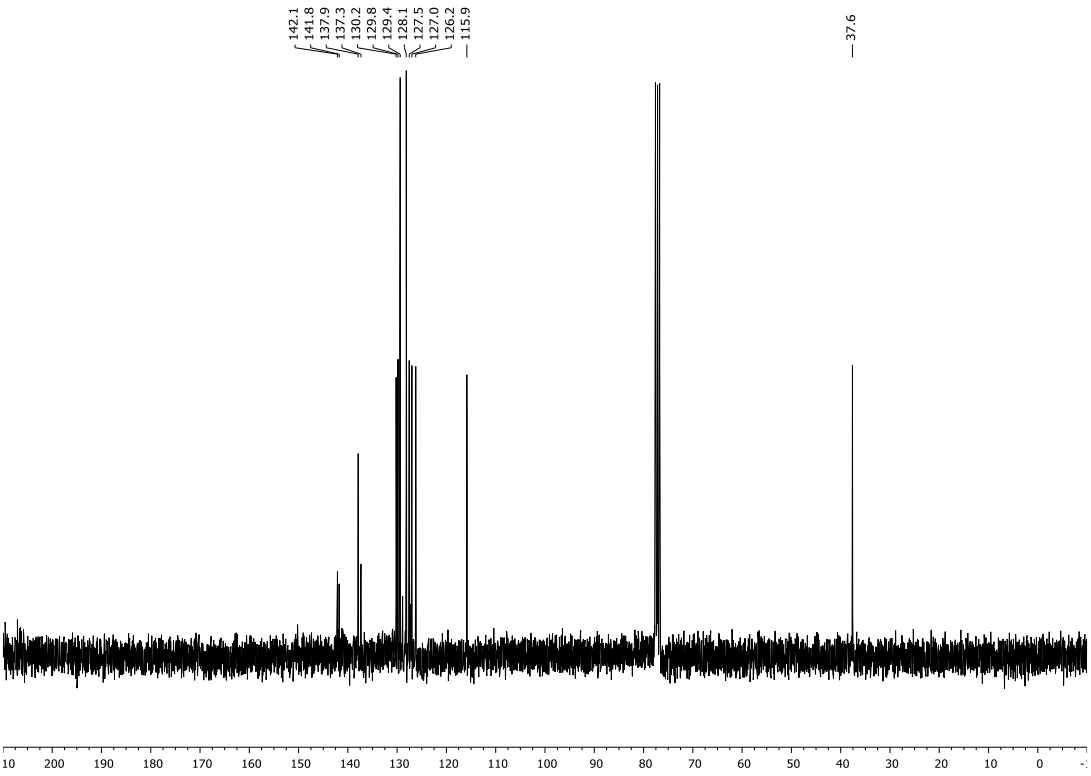


300 MHz ^{1}H NMR spectrum of compound **26** ($CDCl_3$, 300 K)

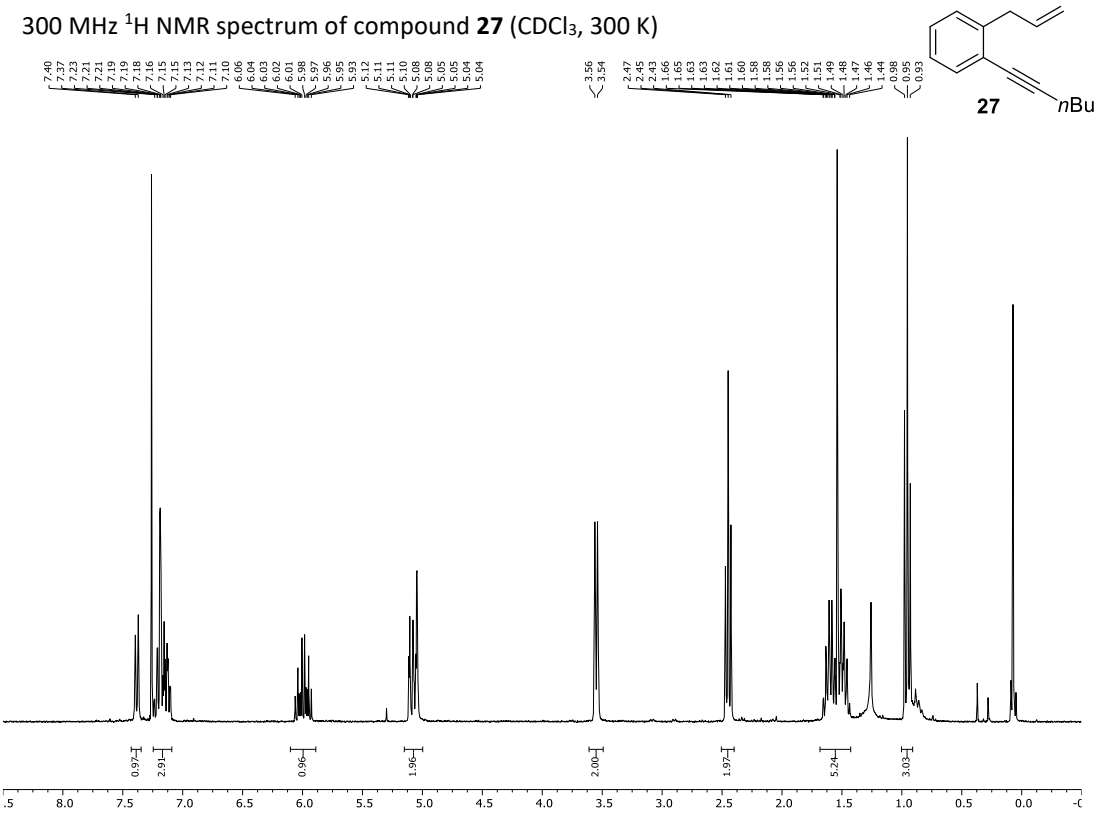


26

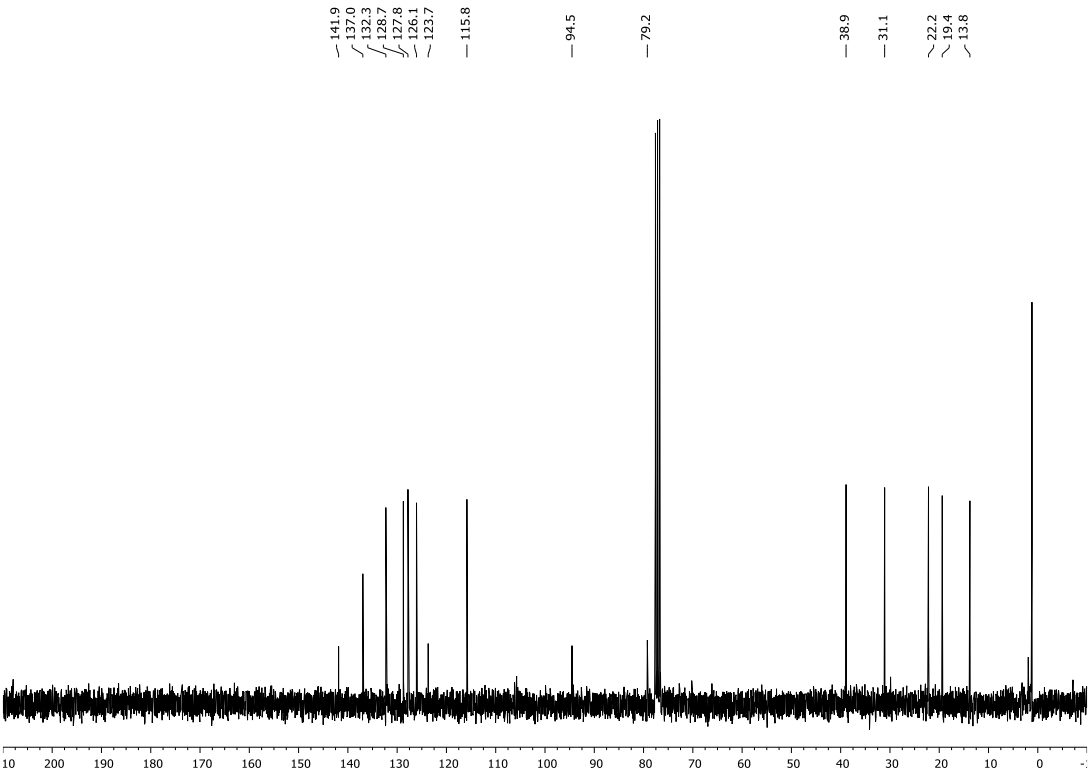
75 MHz ^{13}C NMR spectrum of compound **26** ($CDCl_3$, 300 K)



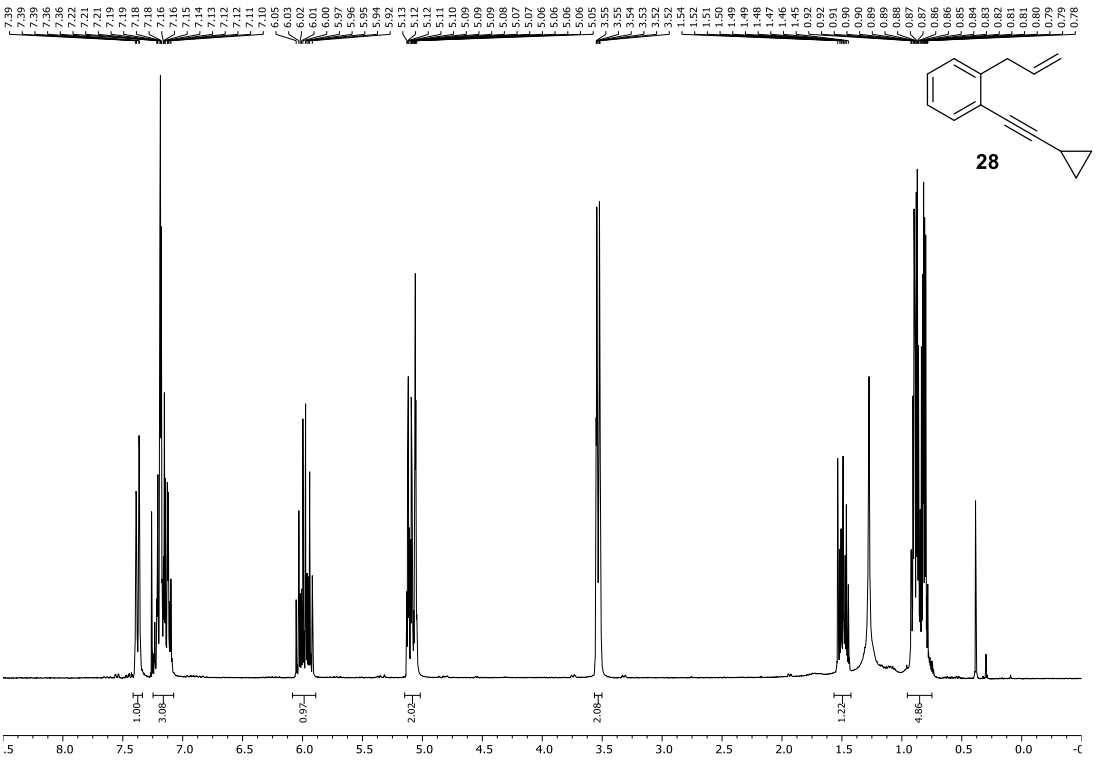
300 MHz ^{1}H NMR spectrum of compound **27** ($CDCl_3$, 300 K)



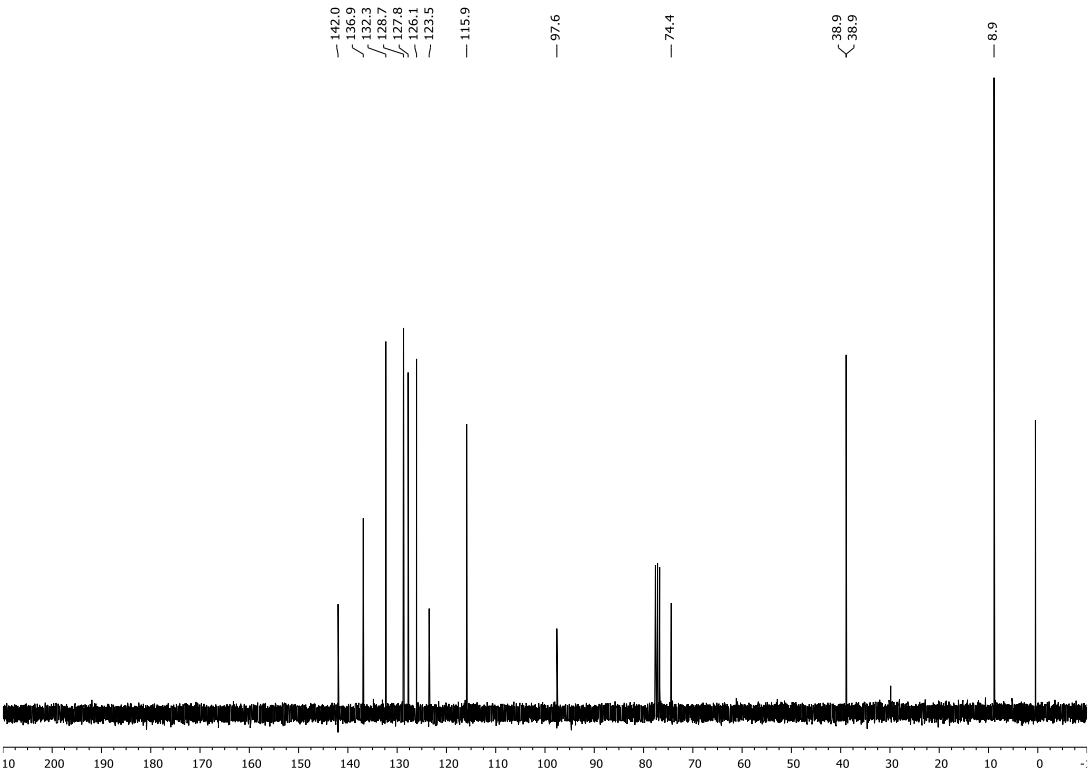
75 MHz ^{13}C NMR spectrum of compound **27** ($CDCl_3$, 300 K)



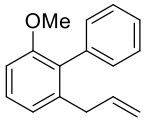
300 MHz ^{1}H NMR spectrum of compound **28** ($CDCl_3$, 300 K)



75 MHz ^{13}C NMR spectrum of compound **28** ($CDCl_3$, 300 K)

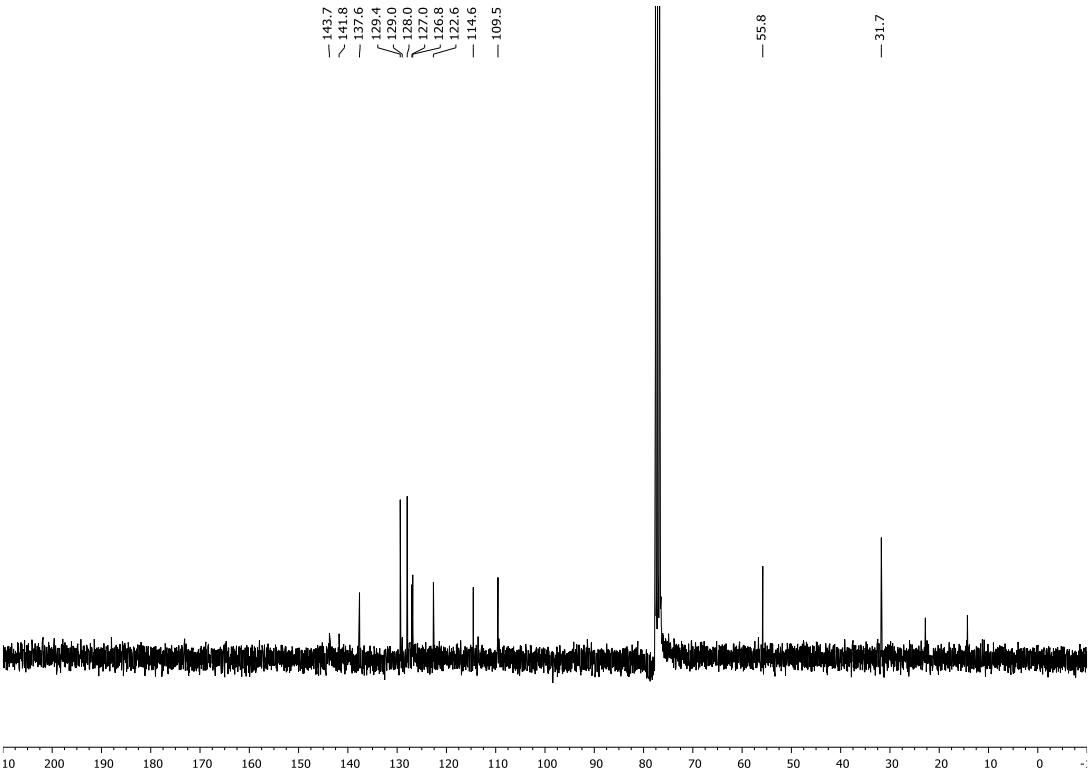


300 MHz ^{1}H NMR spectrum of compound **29** ($CDCl_3$, 300 K)

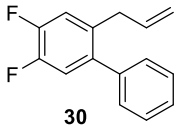


29

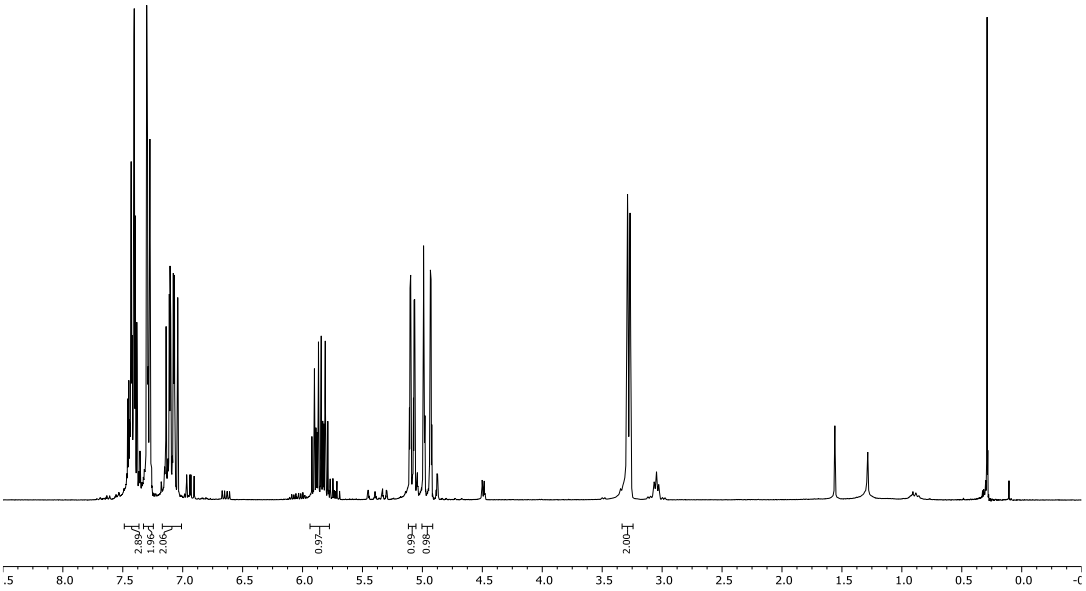
75 MHz ^{13}C NMR spectrum of compound **29** ($CDCl_3$, 300 K)



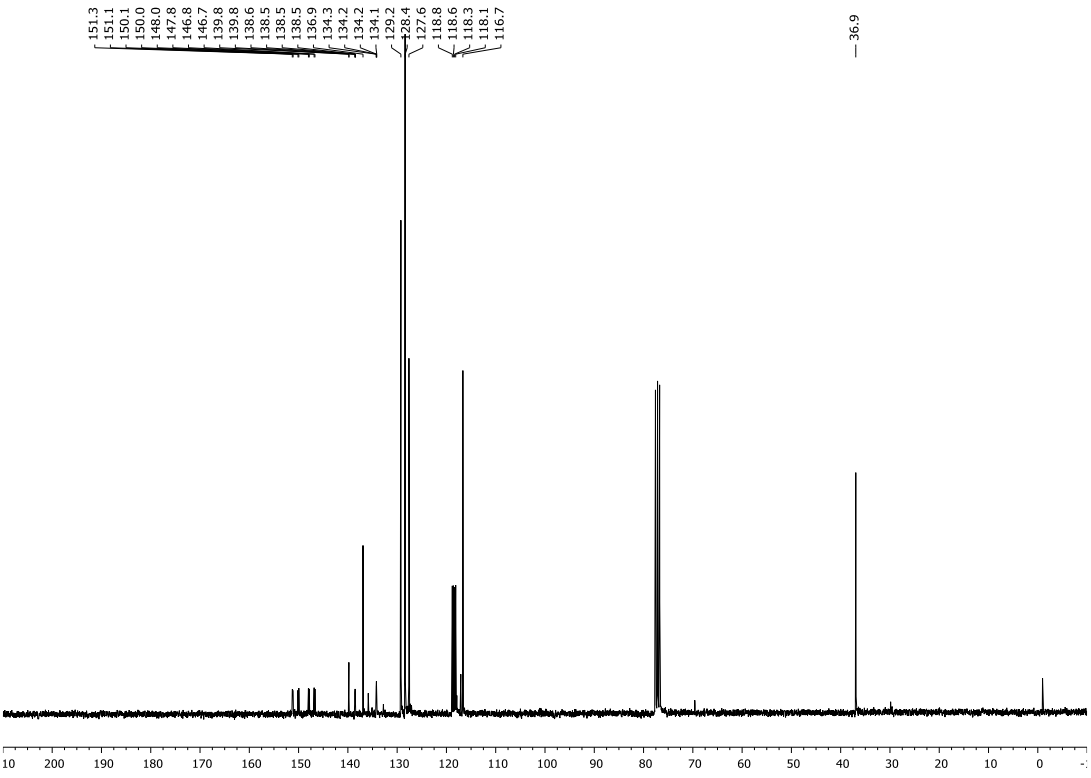
300 MHz ^{1}H NMR spectrum of compound **30** ($CDCl_3$, 300 K)



30



75 MHz ^{13}C NMR spectrum of compound **30** ($CDCl_3$, 300 K)



Annex III.

X-Ray Diffraction Spectroscopic Data.

X-Ray diffraction spectroscopic data for compound **17**

Table 1. Crystal data and structure refinement for shelx.

Identification code	shelx	
Empirical formula	$C_{25}H_{25}InN_2$	
Formula weight	468.29	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 12.3494(7) Å	α= 90°
	b = 12.6121(7) Å	β= 98.628(3)°
	c = 13.8333(8) Å	γ = 90°
Volume	2130.2(2) $Å^3$	
Z	4	
Density (calculated)	1.460 Mg/m^3	
Absorption coefficient	1.121 mm^{-1}	
F(000)	952	
Crystal size	0.220 x 0.150 x 0.070 mm^3	
Theta range for data collection	1.668 to 33.221°	
Index ranges	-18<=h<=19, -19<=k<=18, -20<=l<=21	
Reflections collected	100422	
Independent reflections	8141 [R(int) = 0.0531]	
Completeness to theta = 25.242°	100.0 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8141 / 0 / 255	
Goodness-of-fit on F^2	1.052	
Final R indices [I>2sigma(I)]	R1 = 0.0294, wR2 = 0.0552	
R indices (all data)	R1 = 0.0430, wR2 = 0.0590	
Largest diff. peak and hole	0.543 and -0.410 $e.Å^{-3}$	

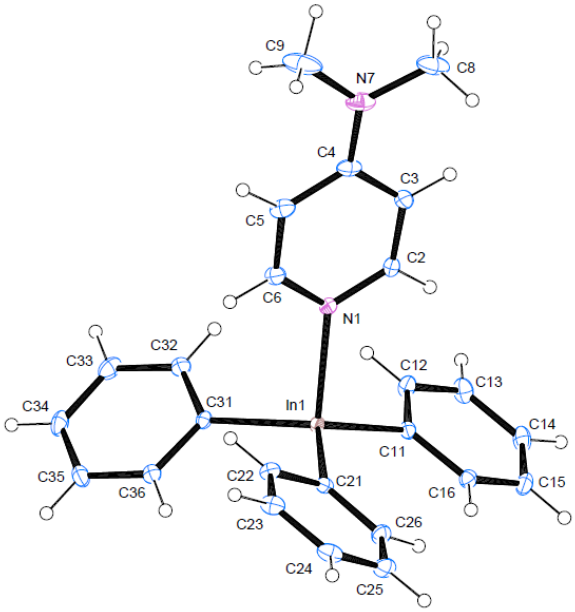


Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for shelx. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
In(1)	2705(1)	1722(1)	6827(1)	14(1)
N(1)	2651(1)	3220(1)	5909(1)	17(1)
C(2)	1749(1)	3825(1)	5726(1)	22(1)
C(3)	1629(1)	4650(1)	5073(1)	25(1)
C(4)	2478(2)	4900(1)	4537(1)	23(1)
C(5)	3428(2)	4273(1)	4741(1)	25(1)
C(6)	3469(1)	3467(1)	5408(1)	22(1)
N(7)	2373(1)	5700(1)	3873(1)	32(1)
C(8)	1335(2)	6266(2)	3644(1)	40(1)
C(9)	3272(2)	6055(2)	3405(2)	53(1)
C(11)	1337(1)	1971(1)	7618(1)	17(1)
C(12)	1353(1)	2791(1)	8299(1)	22(1)
C(13)	502(1)	2946(2)	8838(1)	26(1)
C(14)	-393(1)	2275(2)	8712(1)	26(1)
C(15)	-432(1)	1449(1)	8052(1)	24(1)
C(16)	417(1)	1303(1)	7513(1)	19(1)
C(21)	2604(1)	536(1)	5676(1)	17(1)
C(22)	3433(1)	510(1)	5093(1)	21(1)
C(23)	3404(2)	-188(1)	4309(1)	25(1)
C(24)	2532(2)	-877(1)	4083(1)	25(1)

C(25)	1699(2)	-873(1)	4648(1)	25(1)
C(26)	1742(1)	-179(1)	5438(1)	22(1)
C(31)	4355(1)	1863(1)	7622(1)	15(1)
C(32)	4711(1)	2757(1)	8175(1)	22(1)
C(33)	5739(2)	2799(2)	8744(1)	28(1)
C(34)	6441(1)	1941(2)	8770(1)	28(1)
C(35)	6118(1)	1048(1)	8217(1)	24(1)
C(36)	5090(1)	1015(1)	7654(1)	18(1)