Nickel-Catalyzed Cross-Couplings of Unactivated Secondary and Tertiary Alkyl Halides and Photoinduced Copper-Mediated Asymmetric C–N Cross-Couplings

by

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B.S., Chemistry, 2006
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Submitted to the Department of Chemistry
on Partial Fulfillment of the Requirements for the Degree of

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ABSTRACT

Chapter 1 describes the development of two nickel-catalyzed Suzuki cross-coupling methodologies that employ alkyl halides as electrophiles. In Section 1.1, asymmetric γ-alkylation relative to a carbonyl group is achieved via the stereoconvergent cross-coupling of racemic secondary γ-chloroamides with primary alkylboranes. Section 1.2 describes the first Suzuki carbon-carbon bond-forming reaction using tertiary alkyl halides as electrophiles; specifically, unactivated tertiary alkyl bromides are cross-coupled with arylboranes.

Chapter 2 describes the establishment of photoinduced asymmetric copper-mediated C–N Ullmann-type coupling processes between racemic secondary alkyl halides and *N*-heterocycles. Preliminary yields and enantioselectivities for a reaction between secondary benzylic halides and carbazoles, with the use of a monodentate chiral phosphine ligand, are presented. The methodology is then extended to secondary α-haloamides, including α-halolactams, which are found to afford very promising yields and enantioselectivities.

Thesis Supervisor: Gregory C. Fu
Title: Altair Professor of Chemistry, California Institute of Technology

PREFACE

Portions of this thesis have appeared in the following publications:

"Catalytic Asymmetric γ-Alkylation of Carbonyl Compounds via Stereoconvergent Suzuki Cross-Couplings"
Zultanski, S. L.; Fu. G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362–15364.

"Nickel-Catalyzed Carbon–Carbon Bond-Forming Reactions of Unactivated Tertiary Alkyl Halides: Suzuki Arylations"
Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 624–627.

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First and foremost, I have a lot of appreciation for my advisor Greg, for fueling a lab with high standards of scientific rigor, and for having an insatiable curiosity toward exploring and developing novel methodologies. Science was never boring in this group, and many thanks to Greg for giving his students the independence to pursue their own research, yet providing guidance when it was needed. In the midst of working on challenging methodology projects, I always felt that the possibility for failure was very real, and ultimately, this was confidence building and it forced me to be strategic. Also, thanks to my committee members Mo and Steve, for their critical feedback over the course of my Ph.D.

I'm grateful to numerous friends in the Fu lab and at MIT for providing support and contributing to my growth as a scientist. In particular, I've learned a lot from postdocs Nathan Owston, Jackie Murphy and Nathan Schley. While the lab turnover has always been high due to a large number of postdocs, I've enjoyed the camaraderie of fellow graduate students Pam Lundin, Zhe Lu, Junwon Choi, Dan Ziegler, and Sarah Lee. Swager lab members Trisha Andrew and Jose Lobez were always there to watch the latest Lars von Trier flick with me. I miss MIT, but it's been a privilege to experience graduate school at Caltech as well. I hope to maintain long-lasting contact with acquaintances that I've made from both institutions, and hopefully I'll be fortunate enough to work with some of these folks in the future.

TABLE OF CONTENTS

ABBREVIATIONS

9-BBN	9-borabicyclo[3.3.1]nonane
ACN	acetonitrile
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
Bn	benzyl
Bpin	pinacolboryl
Bu	butyl
CFL	compact fluorescent lightbulb
cod	1,5-cyclooctadiene
d	doublet
diglyme	diethylene glycol dimethyl ether
DMA	dimethylacetamide
DMF	dimethylformamide
DMI	1,3-dimethyl-2-imidazolidinone
DMPEDA	*N'N'*-dimethyl-1,2-diphenylethylenediamine
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EPR	electron paramagnetic resonance
Eq	equation
equiv	equivalents
Et	ethyl
FT-IR	Fourier transform infrared spectroscopy
GC	gas chromatography
HPLC	high pressure liquid chromatography
Hz	hertz
LRMS	low resolution mass spectrometry
NHC	*N*-heterocyclic carbene
nm	nanometer
NMR	nuclear magnetic resonance
Ph	phenyl
Pr	propyl
pybox	2,6-bis(4,5-dihydrooxazol-2-yl)pyridine
q	quartet
r.t.	room temperature
s	singlet
s	sec (secondary)
SCE	saturated calomel electrode
SET	single electron transfer
SFC	supercritical fluid chromatography
SITCP	(11aR)-(+)-5,6,10,11,12,13-Hexahydro-5-phenyl-4H-diindeno[7,1-cd:1,7-ef]phosphocin
t	triplet
THF	tetrahydrofuran

CHAPTER 1

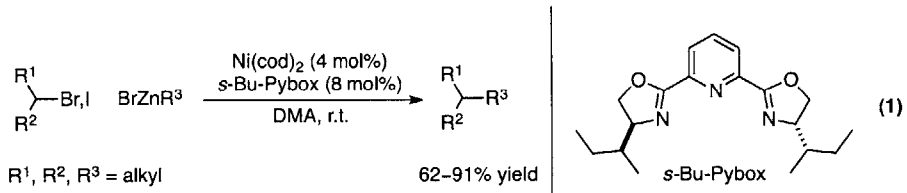
Nickel-Catalyzed Cross-Couplings of Unactivated Alkyl Halides

Section 1.1

Catalytic Asymmetric γ-Alkylation of Carbonyl Compounds via Stereoconvergent Suzuki Cross-Couplings

A. Introduction

Over the past two decades, nickel catalysts have been demonstrated to be highly versatile for alkyl–alkyl cross-coupling reactions.[1] Knochel and coworkers reported the first such process in 1995, specifically, a Negishi cross-coupling between unactivated primary alkyl halides and primary alkylzinc reagents.[2] Fu and coworkers disclosed in 2003 the first nickel-catalyzed cross-coupling using unactivated secondary alkyl halides; these were coupled with alkylzinc reagents to generate racemic products (eq 1).[3] While the reactivity of unactivated secondary alkyl



halides in cross-coupling reactions was explored by Kochi and Tamura in 1971 using silver and copper catalysts,[4] Fu's disclosure represents the first synthetically useful cross-coupling of unactivated secondary alkyl halides, where high selectivity for cross-coupling over undesired homocoupling processes is demonstrated. Subsequently, numerous reports have emerged detailing new nickel catalyst systems for cross-couplings of both activated and unactivated secondary alkyl halides, with various nucleophilic reaction partners.[5] Additionally, reports of iron-, cobalt-, palladium-, and copper-catalyzed cross-couplings of unactivated secondary alkyl

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[1] For relevant reviews, see: a) Rudolph, A.; Lautens, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 2656–2670. (b) Glorius, F. *Angew. Chem. Int. Ed.* **2008**, *47*, 8347–8349. (c) Hu, X. *Chem. Sci.* **2011**, *2*, 1867–1886. (d) Phapale, V. B.; Cárdenas, D. J. *Chem. Soc. Rev.* **2009**, *38*, 1598–1607.

[2] Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem. Int. Ed.* **1995**, *34*, 2723–2725.

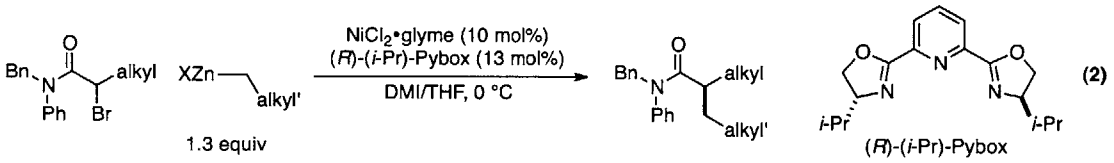
[3] Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726–14727.

[4] a) Ag: Tamura, M.; Kochi, J. *J. Am. Chem. Soc.* **1971**, *93*, 1483–1485. b) Cu: Tamura, M.; Kochi, J. *J. Am. Chem. Soc.* **1971**, *93*, 1485–1487.

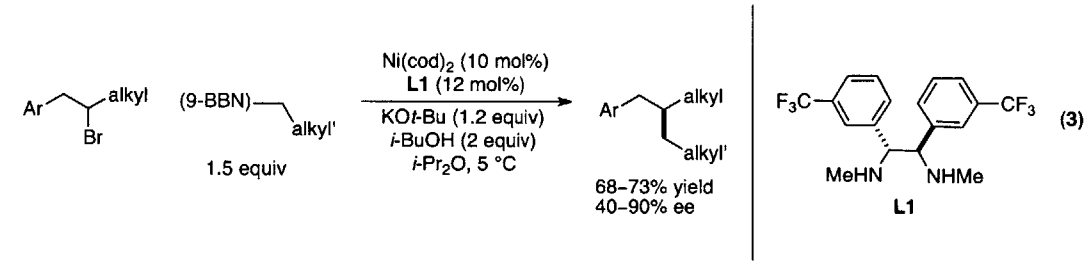
[5] Recent examples of nickel-catalyzed alkyl–alkyl cross-couplings: a) Cordier, C. J.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 10946–10949. (b) Binder, J. T.; Cordier, C. J.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 17003–17006. (c) Perez Garcia, P. M.; Di Franco, T.; Orsino, A.; Ren, P.; Hu, H. *Org. Lett.* **2012**, *14*, 4286–4289. (d) Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 9083–9090.

halides subsequently gained momentum,[1a, 6] however, thus far, asymmetric variants of these processes have yet to be reported.

The first catalytic asymmetric cross-coupling of secondary alkyl halides was reported by the Fu laboratory in 2005; in this Negishi reaction, racemic α-bromo amides were found to couple in a stereoconvergent manner with primary alkylzinc reagents (eq 2).[7] Several years thereafter, an asymmetric, stereoconvergent Suzuki–Miyaura cross-coupling reaction between unactivated racemic secondary alkyl halides, specifically, homobenzylic bromides, was disclosed (eq 3).[8]



(2)



(3)

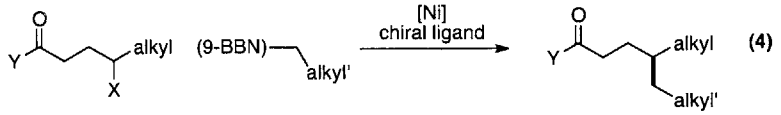
It is speculated that, in the case of unactivated, homobenzylic bromides, a secondary interaction between the aryl group on the electrophile with the chiral nickel catalyst enables high enantioselectivity. We questioned whether this "directing group" on the electrophile could be extended from a homobenzylic group to other functional groups, such as carbonyl groups, that would lead to more synthetically relevant products. In particular, while many methods exist for

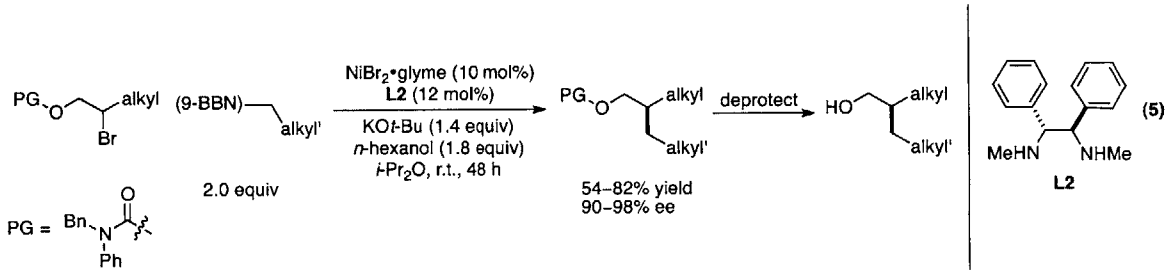
[6] For several recent examples, see: a) (Cu) Yang, C.-T.; Zhang, Z.-Q.; Liang, J.; Liu, J.-H.; Lu, X.-Y.; Chen, H.-H.; Liu, L. *J. Am. Chem. Soc.* **2012**, *134*, 11124–11127. b) (Fe) Hatakeyama, T.; Hashimoto, T.; Kathriarachchi, K. K. A. D. S.; Zenmyo, T.; Seike, H.; Nakamura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 8834–8837. c) (Pd) Xiao, B.; Liu, Z.-J.; Liu, L.; Fu, Y. *J. Am. Chem. Soc.* **2013**, *135*, 616–619.

[7] Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594–4595.

[8] Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694–6695.

catalytic asymmetric α- and β-alkylation relative to a carbonyl group,[9] there are a dearth of asymmetric γ-alkylation reactions;[10] we envisioned accessing this class of compounds via the asymmetric nickel-catalyzed cross-coupling of racemic γ-halo carbonyls with alkylboranes (eq 4).[11] Concurrently, a similar methodology to generate α-branched chiral alcohols from protected halohydrins was being explored; the nature of the protected halohydrin evolved from esters and ethers to carbamates, where optimal enantioselectivities were achieved (eq 5).[12]





Over the past several years, the Fu group has established that, indeed, a variety of functional groups can serve as directing groups on racemic unactivated secondary alkyl halides, enabling a diverse set of highly enantioselective nickel-catalyzed asymmetric alkyl–alkyl Suzuki–Miyaura reactions (eq 6, excluding the reactions previously described in eq 3–5).[13] Interestingly, while all reactions employ variants of a class of chiral *N,N*-dimethyl-1,2-

[9] a) Catalytic enantioselective α-alkylation reactions, leading references: MacMillan, D. W. C.; Watson, A. J. B. α-Functionalization of Carbonyl Compounds. In *Science of Synthesis*. De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Thieme: Stuttgart, Germany, 2010; Vol. 3, pp 677–745. (b) Catalytic enantioselective β-alkylation reactions, leading references: Nguyen, B. N.; Hii, K. K.; Syzmanski, W.; Janssen, D. B. Conjugate Addition Reactions. In *Science of Synthesis*. De Vries, J. G., Molander, G. A., Evans, P. A., Eds.; Thieme: Stuttgart, Germany, 2010; Vol. 1, pp 571–688.

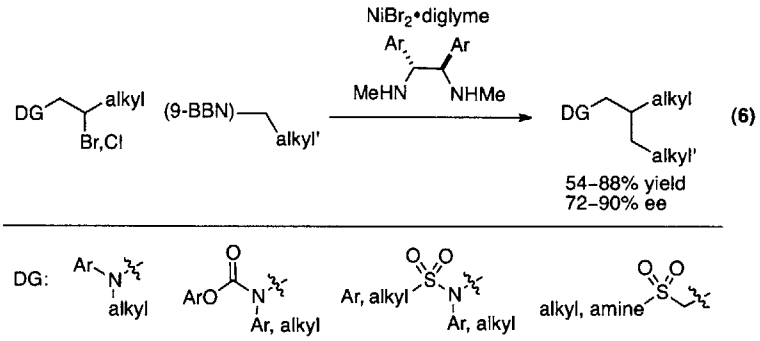
[10] For a recent example, see: Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 14231–14233.

[11] Zultanski, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 15362–15364.

[12] Owston, N. A.; Fu. G. C.; *J. Am. Chem. Soc.* **2010**, *132*, 11908–11909.

[13] a) Lu, Z.; Wilsily, A.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 8154–8157. b) Wilsily, A.; Tramutola, F.; Owston, N. A.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 5794–5797.

diarylethylene diamine ligands, homobenzylic bromides and β-chloro anilines provide the same sense of stereoselectivity in the products, and, in contrast, electrophiles containing carbonyl or sulfonyl groups in the γ-position relative to the halide (amides, carbamates, sulfonamides, sulfones) provide the opposite sense of stereoselectivity in the products.



It is postulated that the mechanism for stereoconvergence of the racemic unactivated alkyl halides to predominantly one enantiomer of product arises through the generation of an alkyl radical intermediate, via a single electron transfer oxidative addition mechanism.[14,15,16] In unpublished results, unactivated secondary alkyl chlorides react more rapidly than unactivated primary alkyl chlorides in a competition experiment; this order of reactivity provides circumstantial evidence for alkyl radical intermediates in nickel-catalyzed Suzuki cross-couplings. Secondly, unactivated alkyl tosylates are thus far not viable reaction partners; their poor reactivity is consistent with a radical oxidative addition mechanism. However, there is a lack of direct, observable evidence for the existence of radical intermediates. Stereoconvergence could also occur through nickel–alkyl bond homolysis, followed by recombination, in an entirely separate and subsequent step to oxidative addition. It should also be

[14] Nickel-catalyzed cross-coupling of *alkyl* halides involving SET was proposed by Espenson: Bakac, A.; Espenson, J. H. *J. Am. Chem. Soc.* **1986**, *108*, 719–723.

noted that for processes involving activated secondary alkyl halides (e.g., eq 2), other mechanistic possibilities for stereoconvergence are possible.

With respect to the overall reaction mechanism for nickel-catalyzed alkyl–alkyl cross-couplings, three possible single-metal catalytic cycles are depicted in Figure 1. Catalytic cycle **A** invokes a $Ni^{I/III}$ transmetalation-first pathway; this has been postulated by Vicic in the context of nickel/4,4',4"-tri-tert-butylterpyridine-catalyzed alkyl–alkyl Negishi cross-couplings using unactivated secondary alkyl iodides, and it has been supported by Phillips using density functional theory studies.[15, 16] Catalytic cycle **B** is a relatively less-discussed $Ni^{I/III}$ oxidative

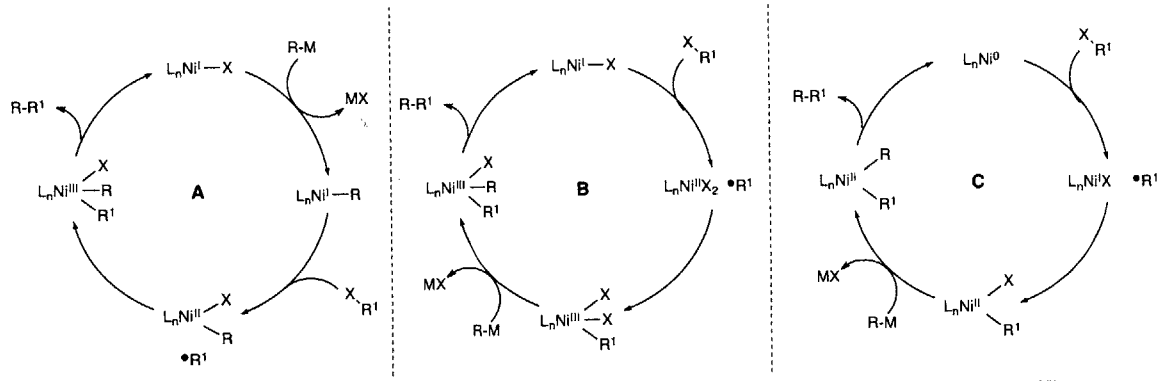


Figure 1. Possible single-metal mechanisms: A) Transmetalation-first $Ni^{I/III}$ cycle, B) Oxidative addition-first $Ni^{I/III}$ cycle, C) $Ni^{0/II}$ cycle.

addition-first pathway, and catalytic cycle **C**, a $Ni^{0/II}$ pathway, draws from the well-studied mechanism that is invoked for the majority of palladium-catalyzed cross-coupling reactions (however, in palladium systems, oxidative addition is most often proposed to occur via direct insertion, or via an S_N2 process in the case of primary alkyl halides).[17] Additionally, it is possible that for all three of these reaction pathways, bimetallic variants are in effect, where

[15] a) Anderson, T. J.; Jones, G. D.; Vicic, D. A. *J. Am. Chem. Soc.* **2004**, *126*, 8100–8101. b) Jones, G. D.; Martin, J. L.; McFarland, C.; Allen, O. R.; Hall, R. E.; Haley, A. D.; Brandon, R. J.; Konovalova, T.; Desrochers, P. J.; Pulay, P.; Vicic, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 13175–13183.
[16] Lin, X.; Phillips, D. L. *J. Org. Chem.* **2008**, *73*, 3680–3688.
[17] Metal-Catalyzed Cross-Coupling Reactions. de Meijere, A.; Diederich, F., Eds.; 2nd ed., Wiley-VCH: Weinheim, 2004.

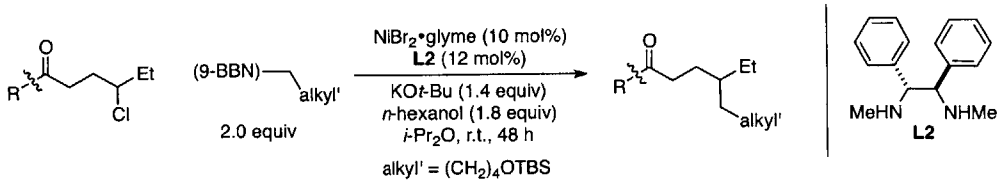
transmetalation occurs between two nickel species. It is also possible that radical chain processes are in effect; Hu has recently proposed a radical chain process for nickel-catalyzed alkyl–alkyl Kumada reactions.[18] It should be noted that, as a diverse set of nickel/ligand combinations have been successfully employed for different racemic and asymmetric cross-coupling reactions, using both activated and unactivated alkyl halides, it is unlikely that all of these processes converge on one general reaction mechanism. Efforts by coworkers in the Fu group to distinguish the reaction mechanisms of two specific nickel-catalyzed cross-coupling reactions are currently underway. Given the plethora of possible mechanisms, coupled with highly reactive proposed intermediates (syntheses of these intermediates is not trivial, and kinetic competence studies of these intermediates are difficult due to fast reaction times), lends to the formidable yet interesting challenge of accurately deciphering these catalytic cycles.

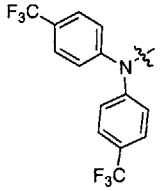
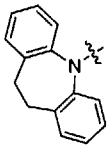
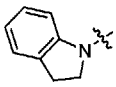
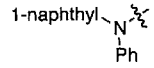
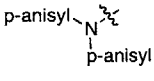
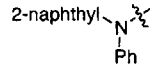
[18] Breitenfeld, J.; Ruiz, J.; Wodrich, M. D.; Hu, X. *J. Am. Chem. Soc.* [online early access]. DOI: 10.1021/ja4051923. Published online: July 18, 2013. http://dx.doi.org/10.1021/ja4051923. (accessed July 25, 2013).

B. Results and Discussion

In the early stages toward developing an asymmetric nickel-catalyzed cross-coupling reaction between γ-halo carbonyl compounds and alkylboranes, the identity of the carbonyl group on the electrophilic reaction partner was explored (Table 1). Because the mechanistic hypothesis for enantioselectivity in this reaction includes a secondary interaction of the carbonyl group with the chiral nickel catalyst, it was speculated that modifications to the carbonyl group could greatly influence stereochemical outcome. The reaction conditions used for Suzuki cross-couplings of masked halohydrins (eq 5) were employed in this initial survey of electrophiles.

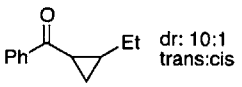
Table 1. Asymmetric Suzuki Reactions of Unactivated γ-Chloro Carbonyls: Effects of Variation of the Carbonyl Group.



entry	R-{-	ee (%)	yield (%)[a]	entry	R-{-	ee (%)	yield (%)[a]
1		nd	10	7		nd	10
2		75	83				
3		77	74	8		90	35
4		76	80				
5	 **2**	88	78	9		89	85
6		88	69	10		85	80

[a] The yields were determined by GC analysis with a calibrated internal standard.

A phenyl ketone was initially explored (Table 1, entry 1); the resulting low yield is attributed to formation of a considerable quantity of an undesired cyclopropyl phenyl ketone side-product (**1**). It is postulated that this side-product arose from deprotonation in the α-position relative to the carbonyl group, followed by an intramolecular S_N2 cyclization. This inspired movement to carbonyl groups with relatively less acidic α-protons. Esters were bypassed due to possible complications regarding transesterification in the presence of an alkoxide base; instead, amides were heavily explored.

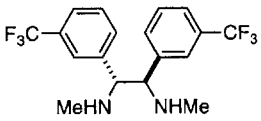


1

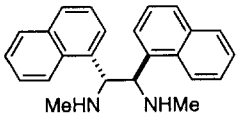
A Weinreb amide afforded good yield and a moderate, 75% ee (entry 2); a *N,N*-dialkylamide and a *N,N*-arylalkylamide offered comparable results with respect to yield and ee (entries 3 & 4). An improvement to 88% ee was observed with a *N,N*-diphenylamide (entry 5; **2**); this inspired further investigation of the class, *N,N*-diarylamides. A more electron-rich, *N,N*-bis(4-methoxyphenyl)amide offered no improvements (entry 6), and a more electron-poor, *N,N*-bis(4-(trifluoromethyl)phenyl)amide resulted in a low yield due to esterification of the electrophile and concurrent generation of bis(4-(trifluoromethyl)phenyl)amine (entry 7). A tethered variant of *N,N*-diphenylamide afforded a large reduction in yield (entry 8), and an effort to explore steric environment using *N,N*-naphthylphenylamides led to little or no improvement over the *N,N*-diphenylamide (entries 9 & 10). Therefore, other reaction parameters were investigated using *N,N*-diphenylamide **2**, which offered very promising preliminary results (78% yield, 88% ee; entry 5).

Variants of 1,2-diamine ligand **L2** were explored. Generally, monomethylation of the amines was necessary for reactivity; the demethylated variant of **L2** and the monoethylated variant of **L2** afforded <5% yield (this is general for all nickel-catalyzed Suzuki reactions with

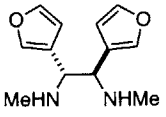
alkyl halides). The aryl backbone of **L2** was altered, and ligands **L1**, **L3**, and **L4** were surveyed.[19,20,21] However, when the reaction conditions from Table 1, entry 5 were employed with these ligands and numerous alkyl-(9-BBN) nucleophiles, comparable yields and enantioselectivities to **L2** were observed. Other aryl variants of **L2** led to greatly diminished enantioselectivities.



L1



L3

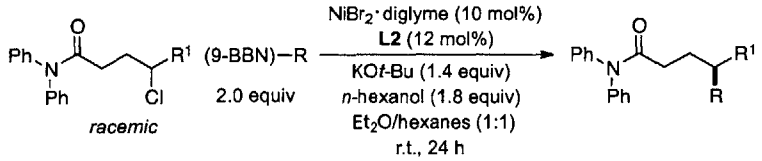


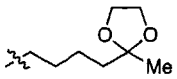
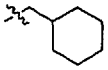
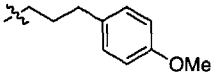
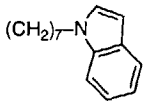
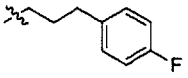
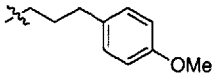
L4

In a survey of other reaction parameters, such as base, alcohol, nickel source, stoichiometry, temperature, and concentration, the optimal results were still obtained using the reaction conditions from Table 1, entry 5. However, it was determined that diethyl ether afforded comparable results to diisopropyl ether, and furthermore, a 1:1 ratio of diethyl ether:hexanes not only decreased the reaction time from 48 hours to 24 hours, but it also slightly increased enantioselectivity. The finalized reaction conditions are illustrated in Table 2 (Table 2, entry 3 can serve as a head-to-head comparison between the final reaction conditions and the conditions in Table 1, entry 5).

[19] **L1** is commercially available (Aldrich).
[20] For **L3** and **L4**, the unmethylated chiral diamines were synthesized according to a procedure from Chin: Kim, H.; Nguyen, Y.; Yen, C. P-H.; Chagal, L.; Lough, A. J.; Kim, B. M.; Chin, J. *J. Am. Chem. Soc.* **2008**, *130*, 12184–12191.
[21] The unmethylated chiral diamines were methylated according to a procedure from Alper: Kuznetsov, V. F.; Jefferson, G. R.; Yap, G. P. A.; Alper, H. *Organometallics* **2002**, *21*, 4241–4248.

Table 2. Catalytic Enantioselective γ-Alkylation of *N,N*-Diphenylamides via Stereoconvergent Suzuki Cross-Couplings: Scope of the Reaction Partners.



entry	R^1	R	ee (%)	yield (%)[b]
1	Me		85	63
2[c]	Me		90	54
3	Et	$(CH_2)_5$–OTBS	91	73
4	Et		89	80
5	Et		90	63
6[d]	Et	$(CH_2)_5$–CN	69	51
7	*n*-Bu		90	84
8	CH_2CH_2Ph		88	83
9	*i*-Bu	$(CH_2)_3$–Ph	82	61

[a] All data are the average of two experiments. [b] Yield of purified product. [c] 20% $NiBr_2$·diglyme and 24% **L2** were used. [d] The reaction was conducted in *i*-Pr_2O at 60 °C.

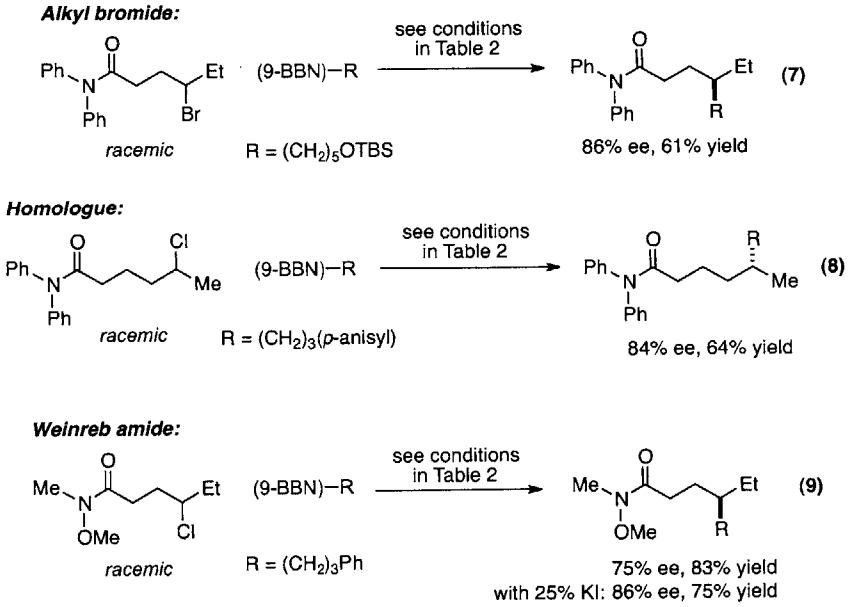
The scope of the reaction partners was explored under the optimized reaction conditions in Table 2. A wide variety of functional groups are compatible with this reaction, including an acetal, silyl ether, aryl ether,[22] and an aryl fluoride.[23] A nitrile suppressed reactivity at room temperature, but a modest yield of product was achieved at 60 °C, albeit with only modest enantioselectivity (entry 6). A β-branched alkyl-(9-BBN) reagent was also successfully

[22] For examples of nickel-catalyzed Suzuki reactions of aryl alkyl ethers, see: Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486–1495.

[23] For examples of nickel-catalyzed Suzuki reactions of aryl fluorides (perfluorinated arenes), see: Schaub, T.; Backes, M.; Radius, U. *J. Am. Chem. Soc.* **2006**, *128*, 15964–15965.

cross-coupled using higher catalyst loading (entry 2); to date, no other published asymmetric nickel-catalyzed alkyl–alkyl Suzuki reactions are able to tolerate a relatively sterically bulky, β-branched, alkyl-(9-BBN) reagent.

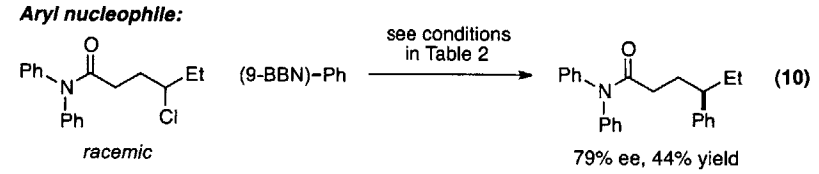
In addition to γ-chloro-diphenylamides, the corresponding bromides are also viable coupling partners, albeit in slightly lower yield and enantioselectivity (eq 7). Furthermore,

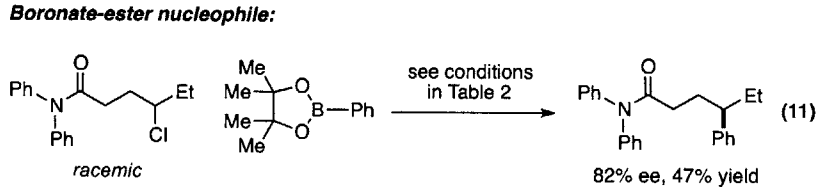


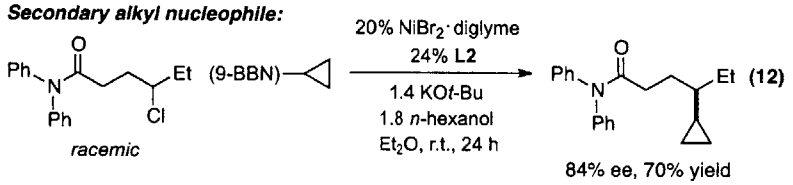
δ-alkylation was also achieved with good enantioselectivity when the homologous δ-chloro-diphenylamide was employed as a reaction partner (eq 8). Finally, while a Weinreb amide coupled with only modest enantioselectivity under the standard reaction conditions, a substoichiometric potassium iodide additive increased the enantioselectivity for this reaction from 75% ee to 86% ee (eq 9). Interestingly, enhanced enantioselectivity was not observed for other classes of electrophiles in the presence of potassium iodide or other salt additives.

With respect to the nucleophilic reaction partner, in our previous reports of asymmetric nickel-catalyzed Suzuki cross-coupling reactions using unactivated secondary alkyl electrophiles, only alkyl-(9-BBN) reagents were used as reaction partners.[12,13a] In this report, an

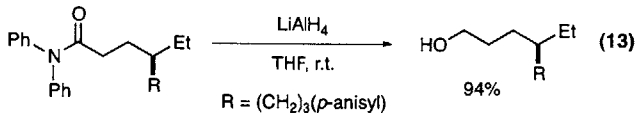
aryl-(9-BBN) reagent is also demonstrated to afford good enantioselectivity (eq 10). Additionally, an aryl boronate ester (eq 11), and a secondary alkyl-(9-BBN) reagent, cyclopropyl-(9-BBN), cross-couple with good enantioselectivity (eq 12).[24]

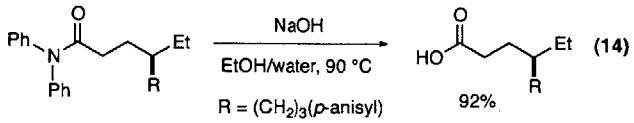




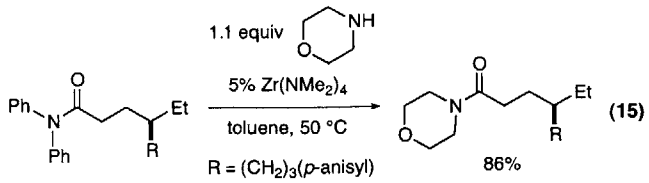


While Weinreb amides are known to be versatile functional groups, elaboration of *N,N*-diphenylamides is also fairly straightforward. Reduction, hydrolysis, and transamidation[25] reactions all proceed smoothly (eq 13–15).

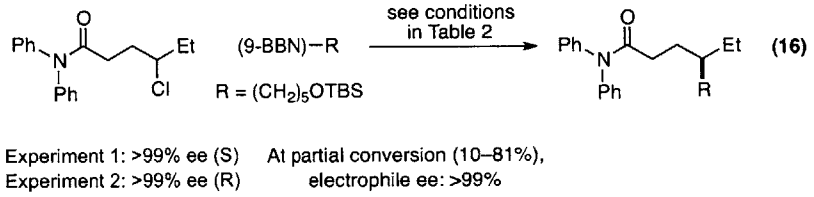




[24] However, cyclobutyl- and cyclopentyl-(9-BBN) did not provide cross-coupled products.
[25] For zirconium-catalyzed transamidation, see: Stephenson, N. A.; Zu, J.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 10003–10008.



While there is currently very little understanding of the overall reaction mechanism, it has been determined that the electrophile remains racemic throughout the course of the reaction, and the ee of the product remains constant, indicating that no kinetic resolution is occurring. Additionally, when the reaction is conducted with enantiopure electrophile, essentially no erosion of electrophile ee is observed in the course of the reaction, indicating that step 1 of oxidative addition (this is halide abstraction, in the case of the single electron transfer



mechanism that is under consideration), is irreversible (eq 16). Hopefully, with more detailed mechanistic studies, these observations will be able to contribute to a larger picture of the overall catalytic cycle.

C. Conclusion and Future Outlook

Stereoconvergent γ-alkylation of carbonyl compounds has been achieved via nickel-catalyzed Suzuki–Miyaura cross-couplings of γ-chloroamides with alkyl-(9-BBN) reagents. High enantioselectivity is proposed to originate through two-point binding of the electrophile to the nickel catalyst. The products are synthetically interesting because there is a dearth of methodology relating to asymmetric alkylation in the γ-position relative to a carbonyl group. Interestingly, δ-alkylation was also achieved with good enantioselectivity. Additionally, the asymmetric cross-coupling of a γ-chloroamide with cyclopropyl-(9-BBN) represents the first asymmetric cross-coupling reaction between secondary alkyl electrophiles and secondary alkyl nucleophiles.

Numerous asymmetric nickel-catalyzed cross-coupling reactions employing either classically activated or classically unactivated secondary alkyl halides have now been established. Future projects that fall within the realm of asymmetric cross-coupling with secondary alkyl halides may include more drastic changes to the nucleophilic reaction partner (e.g., enolates, non-carbon based nucleophiles, and secondary alkyl nucleophiles: for the latter, some progress has already been made[5a,5b]).

D. Experimental

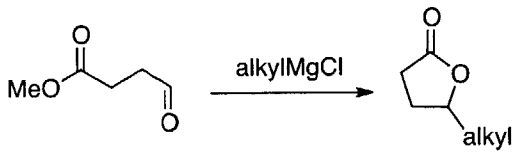
I. General Information

The following reagents were purchased and used as received: 9-BBN dimer (Aldrich), $NiBr_2$•diglyme (Aldrich; note: hygroscopic), ligands *(R,R)*-**L2** and *(S,S)*-**L2** (Acros, Aldrich), KO*t*-Bu (Aldrich), *n*-hexanol (anhydrous; Aldrich), Et_2O (anhydrous; Aldrich), and hexanes (anhydrous; Aldrich). The 1-alkenes (precursors to the nucleophiles) were purchased (Aldrich, Alfa Aesar) and purified by flash chromatography prior to use, or they were prepared according to literature procedures.

All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen. ^1H NMR and ^{13}C NMR data were collected on a Bruker Avance 400 spectrometer at ambient temperature. HPLC analyses were carried out on an Agilent 1100 series system with Daicel CHIRALCEL® columns (internal diameter 4.6 mm, column length 250 mm, particle size 5 μ). SFC analyses were carried out on an SFC ProNTo system with Daicel CHIRALCEL® columns (internal diameter 4.6 mm, column length 250 mm, particle size 5 μ).

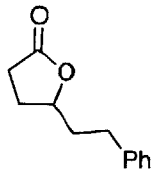
II. Preparation of Electrophiles

The procedures and yields have not been optimized.

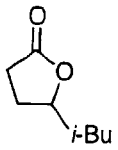


General Procedure A: Preparation of lactones. Anhydrous THF (170 mL) and then methyl 4-oxobutanoate (3.0 g, 24 mmol; Aldrich) were added to an oven-dried round-bottom flask. The reaction mixture was cooled to –78 °C, and the alkyl Grignard reagent (1.0 equiv) was added dropwise to the stirred solution. The reaction mixture was allowed to warm to room

temperature and then stirred for 1 hour. Next, the reaction was quenched by the addition of water (5 mL). A saturated aqueous solution of NH_4Cl (60 mL) was then added to the reaction mixture, which was stirred until it was homogeneous. The mixture was transferred to a separatory funnel, and the product was extracted with Et_2O (100 mL x2) and CH_2Cl_2 (100 mL). The combined organic extracts were washed with brine (100 mL x2), dried over magnesium sulfate, filtered, and concentrated to yield the γ-lactone, which was purified by flash chromatography with 10→60% Et_2O/hexanes.



5-Phenethyldihydrofuran-2(3*H*)-one [112606-95-8]. General procedure A was followed using phenylethylmagnesium chloride (24 mL; 1.0 M in THF; Aldrich), which furnished the lactone as a colorless oil (3.76 g, 83%). The spectral data match those described in the literature.[26]



5-Isobutyldihydrofuran-2(3*H*)-one [18432-37-6]. General procedure A was followed using isobutylmagnesium chloride (12 mL; 2.0 M in THF; Aldrich), which furnished the lactone as a colorless oil (2.15 g, 66%). The spectral data match those described in the literature.[27]

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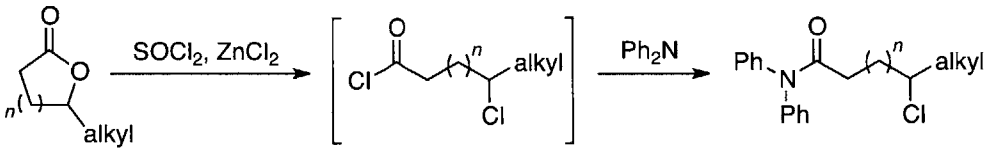
[26] Cossy, J.; Bargiggia, F.; Bouzbouz, S. *Org. Lett.* **2003**, *5*, 459–462.
[27] Pollack, J. A.; Clark, K. M.; Martynowicz, B. J.; Pridgeon, M. G.; Rycenga, M. J.; Stolle, K. E.; Taylor, S. K. *Tetrahedron: Asymmetry* **2007**, *18*, 1888–1892.

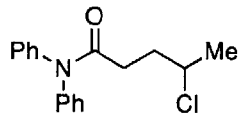


General Procedure B: Preparation of 3- and 4-chloro-*N*,*N*-diphenylamides.[28,29] Anhydrous $ZnCl_2$ (180 mg, 1.3 mmol; note: hygroscopic) was added to an oven-dried two-neck round-bottom flask, which was then capped with a septum and purged with nitrogen. Thionyl chloride (2.4 mL, 33 mmol) was added to the flask, followed by the lactone (30 mmol). The reaction mixture was stirred at 55 °C for 24 h, during which time it turned dark-brown and became viscous. The excess thionyl chloride was removed under reduced pressure, and the acid chloride was used in the next step without further purification.

The two-neck flask containing the acid chloride was equipped with a reflux condenser and purged with nitrogen. Next, anhydrous benzene (100 mL) and then the diarylamine (33 mmol) were added. The reaction mixture was refluxed for 6 h, and then it was allowed to cool to room temperature. Brine (100 mL) was added, and the mixture was transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with Et_2O (100 mL). The combined organic layers were washed with brine (100 mL), dried over magnesium sulfate, filtered, and concentrated to yield the γ- or δ-chloro-*N*,*N*-diarylamide. The product was purified by reverse-phase flash chromatography on C-18 silica gel with 10→100% acetonitrile/water, followed by normal-phase chromatography on silica gel with 10→70% Et_2O/hexanes, which furnished pure γ- or δ-chloro-*N*,*N*-diarylamide (alternatively, if the acid chloride is distilled prior to its use in the second step, purification by reverse-phase column chromatography is

[28] Reppe, W. et al. *Annalen der Chemie, Justus Liebigs* **1955**, *596*, 158–224.
[29] Wise, L. D.; Pattison, I. C.; Butler, D. E.; DeWald, H. A.; Lewis, E. P.; Lobbestael, S. J.; Nordin, I. C.; Poschel, B. P. H.; Coughenour, L. L.; *J. Med. Chem.* **1985**, *28*, 606–612.

unnecessary). The products are stable for at least 6 months when stored under an inert atmosphere at 0 °C.



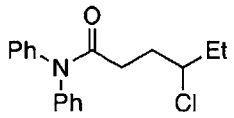
4-Chloro-*N,N*-diphenylpentanamide. The amide was prepared according to general procedure B, using γ-valerolactone and diphenylamine. White solid (5.14 g, 60%).

^{1}H NMR ($CDCl_3$) δ 7.33–7.22 (m, 10H), 4.13–4.05 (m, 1H), 2.45–2.42 (m, 2H), 2.22–2.14 (m, 1H), 1.93–1.83 (m, 1H), 1.47 (d, 3H, J = 6.4 Hz).

^{13}C NMR ($CDCl_3$) δ 172.1, 142.7, 130.0–125.0 (broad), 58.3, 35.7, 32.4, 25.6.

FT-IR (film) 3062, 2973, 2926, 1672, 1593, 1492, 1380, 1351, 1291, 756, 702 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{17}H_{19}ClNO$: 288, found: 288.



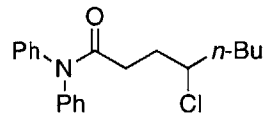
4-Chloro-*N,N*-diphenylhexanamide. The amide was prepared according to general procedure B, using γ-caprolactone and diphenylamine. White solid (6.02 g, 67%).

^{1}H NMR ($CDCl_3$) δ 7.33–7.23 (m, 10H), 3.91–3.88 (m, 1H), 2.46–2.43 (m, 2H), 2.30–2.23 (m, 1H), 2.01–1.94 (m, 1H), 1.87–1.76 (m, 2H), 0.98 (t, 3H, J = 7.2 Hz).

^{13}C NMR ($CDCl_3$) δ 172.2, 142.7, 129.7–126.4 (broad), 65.2, 33.6, 32.4, 31.9, 11.0.

FT-IR (film) 3063, 2969, 2936, 2878, 1673, 1594, 1492, 1452, 1381, 1272, 1162 cm^{-1}.

LRMS (EI) m/z ($M+H^+$) calcd for $C_{18}H_{21}ClNO$: 302, found: 302.



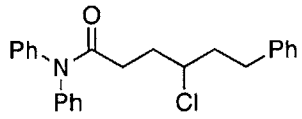
4-Chloro-*N*,*N*-diphenyloctanamide. The amide was prepared according to general procedure B, using γ-octanoic lactone and diphenylamine. White solid (5.50 g, 56%).

^{1}H NMR ($CDCl_3$) δ 7.33–7.23 (m, 10H), 3.95–3.93 (m, 1H), 2.46–2.43 (m, 2H), 2.23–2.18 (m, 1H), 1.86–1.82 (m, 1H), 1.69–1.64 (m, 2H), 1.46–1.44 (m, 1H), 1.36–1.24 (m, 3H), 0.86 (t, 3H, J = 7.2 Hz).

^{13}C NMR ($CDCl_3$) δ 172.2, 142.7, 128.7–126.4 (broad), 63.7, 38.5, 33.9, 32.3, 28.6, 22.3, 14.0.

FT-IR (film) 2957, 2871, 2360, 1674, 1594, 1492, 1379, 1280, 756, 701 cm^{-1}.

LRMS (EI) m/z ($M+H^+$) calcd for $C_{20}H_{25}ClNO$: 330, found: 330.



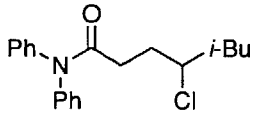
4-Chloro-*N*,*N*-6-triphenylhexanamide. The amide was prepared according to general procedure B, using 5-phenethyldihydrofuran-2(3*H*)-one and diphenylamine. White solid (3.89 g, 52%).

^{1}H NMR ($CDCl_3$) δ 7.34–7.14 (m, 15H), 3.94–3.90 (m, 1H), 2.84–2.80 (m, 1H), 2.72–2.69 (m, 1H), 2.46–2.43 (m, 2H), 2.22–2.20 (m, 1H), 2.02–1.92 (m, 3H).

^{13}C NMR ($CDCl_3$) δ 172.1, 142.7, 141.1, 130.0–125.0 (broad), 128.53, 128.50, 126.1, 62.7, 40.5, 34.0, 32.7, 32.2.

FT-IR (film) 3027, 2921, 2360, 2340, 1670, 1593, 1492, 1381, 1293, 1158, 700 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{24}H_{25}ClNO$: 378, found: 378.



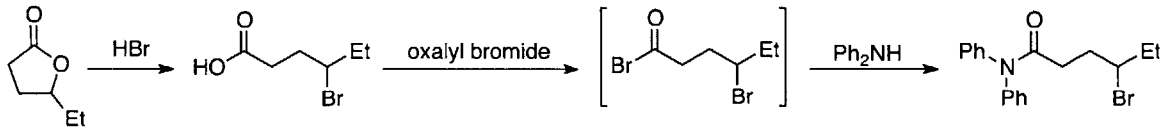
4-Chloro-6-methyl-*N*,*N*-diphenylheptanamide. The amide was prepared according to general procedure B, using 5-isobutyldihydrofuran-2(3*H*)-one and diphenylamine. White solid (2.40 g, 48%).

^{1}H NMR ($CDCl_3$) δ 7.34–7.23 (m, 10H), 4.02–4.00 (m, 1H), 2.48–2.44 (m, 2H), 2.21–2.18 (m, 1H), 1.88–1.81 (m, 2H), 1.67–1.60 (m, 1H), 1.46–1.41 (m, 1H), 0.88 (d, 3H, J = 6.4 Hz), 0.85 (d, 3H, J = 6.4 Hz).

^{13}C NMR ($CDCl_3$) δ 172.2, 142.7, 130.0–125.0 (broad), 61.8, 47.9, 34.2, 32.3, 25.3, 23.0, 21.4.

FT-IR (film) 2957, 2360, 1674, 1491, 1381, 1270, 756, 701 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{20}H_{25}ClNO$: 330, found: 330.



4-Bromo-*N*,*N*-diphenylhexanamide. In accordance with a literature procedure,[30] γ-caprolactone (8.0 g, 70 mmol) was added to a round-bottom flask containing HBr in AcOH (70 mL; 30% in AcOH). The flask was equipped with a reflux condenser, and the reaction mixture was stirred at room temperature for 2 hours and then at 70 °C for 5 hours. Next, the mixture was allowed to cool to room temperature, and then the AcOH was removed by rotary evaporation. CH_2Cl_2 (50 mL) and a solution of saturated sodium thiosulfate (50 mL) were then added, and the

[30] Sashida, H.; Nakayama, A.; Kaname, M. *Synthesis* **2008**, 3229–3236.

mixture was transferred to a separatory funnel, where the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (50 mL x2), and the combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, filtered, and concentrated to furnish 4-bromohexanoic acid (light-red oil). The product was used in the following step without further purification.

Anhydrous CH_2Cl_2 (240 mL) and then oxalyl bromide (20.4 g, 94.5 mmol; Aldrich) were added to an oven-dried round-bottom flask under nitrogen. The solution was cooled to 0 °C, and the unpurified 4-bromohexanoic acid (13.7 g, 70.1 mmol) was added. Next, DMF (1.1 mL, 14 mmol) was added dropwise, and the reaction was monitored at 0 °C for 2 h, at which time gas evolution ended. The reaction mixture was concentrated to remove the excess oxalyl bromide and CH_2Cl_2, affording 4-bromohexanoyl bromide, which was used without purification in the next step.

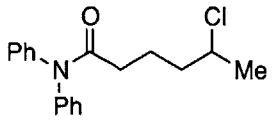
The flask was equipped with a reflux condenser and purged with nitrogen. Anhydrous benzene (240 mL) was added, followed by diphenylamine (11.8 g, 69.7 mmol). The reaction mixture was refluxed for 6 h, and then it was allowed to cool to room temperature. The mixture was transferred to a separatory funnel, and brine (100 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (100 mL). The combined organic layers were washed with brine (50 mL x2), dried over magnesium sulfate, filtered, and concentrated. The product was purified by flash chromatography (10→70% Et_2O/hexanes), which furnished 4-bromo-*N*,*N*-diphenylhexanamide as a white solid (15.0 g, 62% over three steps). This compound is stable for at least 3 months when stored under an inert atmosphere at 0 °C.

^{1}H NMR ($CDCl_3$) δ 7.33–7.23 (m, 10H), 4.06–4.02 (m, 1H), 2.48–2.44 (m, 2H), 2.23–2.18 (m, 1H), 1.88–1.82 (m, 1H), 1.77–1.54 (m, 2H), 0.99 (t, 3H, J = 7.2 Hz).

^{13}C NMR ($CDCl_3$) δ 172.0, 142.6, 130.6–125.5 (broad), 60.0, 34.2, 34.5, 32.6, 12.1.

FT-IR (film) 3061, 2969, 1672, 1593, 1492, 1452, 1381, 1271, 756, 702 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{18}H_{21}BrNO$: 346, 348, found: 346, 348.



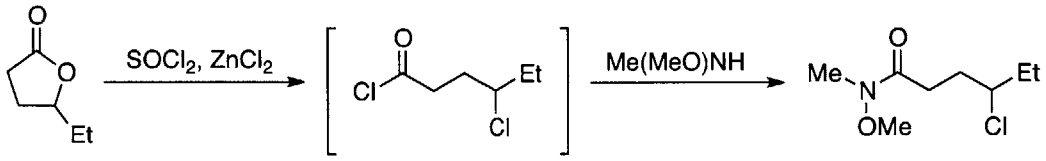
5-Chloro-*N*,*N*-diphenylhexanamide. The amide was prepared according to general procedure B, using δ-hexalactone and diphenylamine. White solid (3.70 g, 41%).

^{1}H NMR ($CDCl_3$) δ 7.34–7.23 (m, 10H), 3.91–3.88 (m, 1H), 2.46–2.43 (m, 2H), 2.23–2.18 (m, 1H), 1.88–1.82 (m, 1H), 1.77–1.54 (m, 2H), 1.00–0.96 (m, 3H).

^{13}C NMR ($CDCl_3$) δ 172.2, 142.7, 129.3–126.4 (broad), 65.2, 33.6, 32.4, 31.9, 11.0.

FT-IR (film) 3062, 3038, 2969, 2936, 1673, 1594, 1492, 1452, 1381, 1272, 1162 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{18}H_{21}ClNO$: 302, found: 302.



4-Chloro-N-methoxy-N-methylhexanamide. The first step was performed as described in general procedure B.

Next, *N,O*-dimethylhydroxylamine hydrochloride (1.9 g, 19 mmol) and Et_2O (30 mL) were added to a stirred 0 °C solution of potassium carbonate (6.6 g, 48 mmol) in water (30 mL). Then, 4-chlorohexanoyl chloride (4.0 g, 24 mmol) was added dropwise over 5 minutes. The reaction mixture was stirred at 0 °C for 30 minutes, and then it was diluted with Et_2O (50 mL) and brine (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (50

mL). The combined organic layers were washed with 1N HCl (30 mL), dried over magnesium sulfate, filtered, and concentrated. The product was purified by flash chromatography with 20→90% Et_2O/hexanes, which furnished the amide as a yellow oil (2.9 g, 79% yield for step 2). This compound is stable for at least 6 months when stored under an inert atmosphere at 0 °C.

^1H NMR ($CDCl_3$) δ 3.91–3.88 (m, 1H), 3.67 (s, 3H), 3.15 (s, 3H), 2.63 (t, 2H, J = 6.8 Hz), 2.16–2.12 (m, 1H), 1.90–1.70 (m, 3H), 1.01 (t, 3H, J = 7.2 Hz).

^{13}C NMR ($CDCl_3$) δ 173.3, 65.0, 61.0, 32.5, 31.9, 31.6, 28.6, 10.7.

FT-IR (film) 2969, 1775, 1666, 1417, 1386, 1178, 1120, 994, 848, 815 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{17}H_{17}ClNO$: 194, found: 194.

III. Preparation of *B*-alkyl-(9-BBN) Reagents

General procedure for preparation of *B*-alkyl-(9-BBN) reagents. In a nitrogen-filled glovebox, the olefin (6 mmol; purified) was added to 9-BBN dimer (3.0 mmol) in a 20-mL vial equipped with a stir bar. Et_2O was added to bring the concentration to 1.5 M of the organoborane, and the vial was sealed with a teflon-lined septum cap. The mixture was heated at 40 °C for 1.5 hours (outside of the glovebox) during which time it became homogenous. The solution was allowed to cool to room temperature. This solution could be stored in a glovebox at ambient temperature for 3 months without noticeable degradation.

Procedure for preparation of *B*-phenyl- and *B*-cyclopropyl-(9-BBN) reagents. These reagents were prepared according to a literature procedure[31] by reacting phenylmagnesium bromide (3.0 M in Et_2O; Aldrich), or cyclopropylmagnesium bromide (0.5 M in Et_2O; Aldrich) with *B*-MeO-(9-BBN). The resulting products were purified by distillation.

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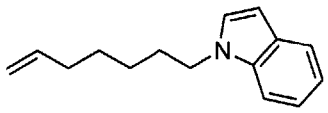
[31] Fang, G. Y.; Wallner, O. A.; Di Blasio, N.; Ginesta, X.; Harvery, J. N.; Aggarval, V. K. *J. Am. Chem. Soc.* **2007**, *129*, 14632–14639.



1-(Hept-6-en-1-yl)-1*H*-indole. The title compound was synthesized via a modification of a literature method.[32] Anhydrous DMF (7 mL) and indole (1.1 g, 9.4 mmol) were added to an oven-dried two-neck round-bottom flask under nitrogen. The reaction mixture was cooled to 0 °C and then NaH (0.21 g, 8.7 mmol) was added, followed by the dropwise addition of 7-bromo-hept-1-ene (2.0 g, 11.3 mmol). The reaction was warmed to room temperature and stirred for 5 hours. Next, water was added (10 mL), and the mixture was transferred to a separatory funnel. Brine (20 mL) was added, and the aqueous layer was extracted with Et_2O (50 mL x3). The combined organic extracts were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by flash chromatography with 5→40% hexanes/Et_2O, which furnished the 1-(hept-6-en-1-yl)-1*H*-indole as a red oil (1.0 g, 54%).

^{1}H NMR ($CDCl_3$) δ 8.05–8.04 (m, 1H), 7.67–7.65 (m, 1H), 7.59–7.53 (m, 1H), 7.51–7.50 (m, 1H), 7.34 (d, 1H, J = 2.2 Hz), 6.88–6.83 (m, 1H), 6.12–6.10 (m, 1H), 5.41–5.35 (m, 2H), 4.29 (t, 2H, J = 7.1 Hz), 2.38–2.36 (m, 2H), 2.11–2.04 (m, 2H), 1.75–1.68 (m, 2H), 1.64–1.53 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 139.0, 136.4, 129.1, 128.1, 121.7, 121.4, 119.6, 115.0, 109.8, 101.3, 46.6, 34.0, 30.5, 28.9, 26.8.

FT-IR (film) 3074, 2930, 2856, 1640, 1612, 1511, 1484, 1353, 1316, 910, 740 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{15}H_{20}N$: 214, found: 214.

[32] Xenon Pharmaceuticals, Inc. Spiro-Oxindole Compounds and Their Uses as Therapeutic Agents. WO2006/110917 A2, October 19, 2006; pp 74–75.

IV. Suzuki–Miyaura Cross-Couplings

General procedure for catalytic asymmetric γ-alkylations. In a nitrogen-filled glovebox, a solution of the organoboron reagent (670 μL, 1.0 mmol; 1.5 M) was added to a slurry of potassium *tert*-butoxide (78.5 mg, 0.70 mmol) and 1-hexanol (113 μL, 92 mg, 0.90 mmol) in a 4-mL vial equipped with a stir bar. The vial was sealed with a teflon-lined septum cap, and the mixture was stirred vigorously for 30 minutes and then used in the next step.

In a glovebox, $NiBr_2$•diglyme (17.6 mg, 0.050 mmol), *(R,R)*-**L2** (14.5 mg, 0.060 mmol), hexanes (3.1 mL), and Et_2O (1.4 mL) were added in turn to a 20-mL vial equipped with a stir bar. The vial was sealed with a teflon-lined septum cap, and the mixture was stirred vigorously for 45 minutes (a light-blue slurry forms). The solution of the activated organoborane reagent was then added to the slurry, and the vial was resealed and stirred for 30 minutes (the reaction mixture turns brown). The electrophile (0.50 mmol in 0.5 mL of Et_2O; purified) was added to the slurry via syringe, and the vial that contained the electrophile was then rinsed with additional Et_2O (0.5 mL), and this solution was added to the slurry. The mixture was sealed with a teflon-lined cap and stirred vigorously at room temperature for 24 hours (outside of the glovebox). Next, the reaction mixture was passed through a short plug of silica gel, eluting with Et_2O. The solution was concentrated to furnish an oil, which was purified by reverse-phase flash chromatography on C-18 silica gel with 10→110% acetonitrile/water. A second run was conducted with (*S,S*)-**L2**.

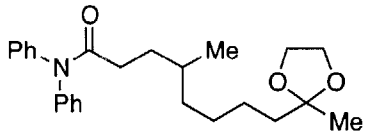
Glovebox-free procedure for catalytic asymmetric γ-alkylation (Table 2, entry 4). A 25-mL two-neck round-bottom flask equipped with a stir bar was capped with a septum and with a hose adaptor, which was connected to a Schlenk line. The flask was placed under vacuum and

flame-dried. The flask was then filled with nitrogen, and, under a positive pressure of nitrogen, 9-BBN dimer (732 mg, 3.0 mmol) was added. The flask was purged with nitrogen for 3 minutes, and then 1-allyl-4-methoxybenzene (890 mg, 6.0 mmol) was added via syringe. Next, anhydrous Et_2O was added by syringe to bring the concentration to 1.5 M, and the mixture was heated at 40 °C for 1.5 hours, during which time it became homogenous. The solution was allowed to cool to room temperature and then used in the next step.

A 50-mL two-neck round-bottom flask equipped with a stir bar was capped with a septum and with a hose adapter, which was connected to a Schlenk line. The flask was placed under vacuum and flame-dried. The flask was then filled with nitrogen, and, under a positive pressure of nitrogen, potassium *tert*-butoxide (78.5 mg, 0.70 mmol) was added. The flask was purged with nitrogen for 3 minutes, and then anhydrous 1-hexanol (92 mg, 113 μL, 0.90 mmol) and a solution of the *B*-alkyl-(9-BBN) reagent (670 μL, 1.0 mmol; 1.5 M) were added in turn via syringe. The resulting mixture was stirred vigorously for 30 minutes and then used in the next step.

A 50-mL two-neck round-bottom flask equipped with a stir bar was capped with a septum and with a hose adapter, which was connected to a Schlenk line. The flask was placed under vacuum and flame-dried. The flask was then filled with nitrogen, and, under a positive pressure of nitrogen, $NiBr_2$•diglyme (17.6 mg, 0.050 mmol) and (*R,R*)-**L2** (14.5 mg, 0.060 mmol) were added. The flask was purged with nitrogen for 3 minutes, and then anhydrous hexanes (3.1 mL) and Et_2O (1.4 mL) were added via syringe. The mixture was stirred vigorously for 45 minutes (a light-blue slurry forms). The solution of the activated *B*-alkyl-(9-BBN) reagent was then transferred to the slurry via cannula, and the reaction mixture was stirred for 30 minutes (the reaction mixture turns brown). The electrophile (151 mg, 0.50 mmol in 0.5 mL of Et_2O; in a

flame-dried flask under nitrogen) was added to this reaction mixture via syringe, and the flask that contained the electrophile was rinsed (under nitrogen) with an additional 0.5 mL of Et_2O, which was also added to the slurry via syringe. The reaction mixture was stirred vigorously under nitrogen for 24 hours at room temperature. Next, the mixture was passed through a short plug of silica gel, eluting with Et_2O. The solution was concentrated to furnish an oil, which was purified by reverse-phase flash chromatography on C-18 silica gel with 10→110% acetonitrile/water. Colorless oil (147 mg, 71%; 88% ee).



4-Methyl-8-(2-methyl-1,3-dioxolan-2-yl)-*N,N*-diphenyloctanamide (Table 2, Entry 1). This compound was prepared according to the general procedure, using 4-chloro-*N,N*-diphenylpentanamide (144 mg, 0.5 mmol) and a solution of the alkylborane prepared by hydroboration of 2-(but-3-en-1-yl)-2-methyl-1,3-dioxolane[33] with 9-BBN dimer (1.5 M in Et_2O; 670 μL, 1 mmol). Colorless oil.

First run: 125 mg (63%, 84% ee). Second run: 123 mg (62%, 85% ee).

The ee was determined by HPLC analysis (CHIRALPAK AD-H, 5% *i*-PrOH in hexanes; 1.0 mL/min; retention times (when *(R,R)*-**L2** is employed): 32.9 min (minor), 37.9 min (major)).

^{1}H NMR ($CDCl_3$) δ 7.33–7.21 (m, 10H), 3.92–3.87 (m, 4H), 2.25–2.19 (m, 2H), 1.71–1.61 (m, 1H), 1.58–1.54 (m, 2H), 1.49–1.40 (m, 1H), 1.30–1.15 (m, 9H), 1.08–0.99 (m, 1H), 0.71 (d, 3H, J = 6.8 Hz).

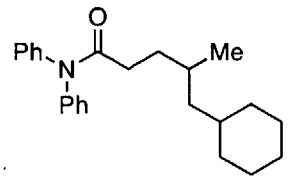
[33] Collins, P. W.; Gasiecki, A. F.; Perkins, W. E.; Gullikson, G. W.; Jones, P. H.; Bauer, R. F. *J. Med. Chem.* **1989**, *32*, 1001–1006.

^{13}C NMR ($CDCl_3$) δ 173.5, 143.0, 129.2–126.8 (broad), 110.1, 64.6 (2C), 39.2, 36.6, 33.0, 32.6, 32.3, 27.1, 24.3, 23.8, 19.4.

FT-IR (film) 3438, 2941, 2870, 1673, 1595, 1492, 1375, 1273, 1051, 757, 701 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{25}H_{34}NO_3$: 396, found: 396.

$[\alpha]^{25}_D = 0.61$ (*c* = 1.06, $CHCl_3$; obtained with (*S,S*)-**L2**).



5-Cyclohexyl-4-methyl-*N,N*-diphenylpentanamide (Table 2, Entry 2). This compound was prepared according to the general procedure, except that the catalyst loading was doubled: $NiBr_2$ • diglyme (35.2 mg, 0.10 mmol) and **L2** (29 mg, 0.12 mmol). 4-Chloro-*N,N*-diphenylpentanamide (144 mg, 0.50 mmol) was used, along with a solution of the alkylborane prepared by hydroboration of methylenecyclohexane with 9-BBN dimer (1.5 M in Et_2O; 670 μL, 1 mmol). White solid.

First run: 96 mg (55%, 90% ee). Second run: 91 mg (52%, 90% ee).

The ee was determined by HPLC analysis (CHIRALPAK AD-H, 2% *i*-PrOH in hexanes; 1.0 mL/min; retention times (when *(R,R)*-**L2** is employed): 19.3 min (minor), 25.0 min (major)).

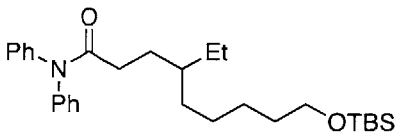
^{1}H NMR ($CDCl_3$) δ 7.34–7.25 (m, 10H), 2.31–2.17 (m, 2H), 1.65–1.62 (m, 6H), 1.44–1.36 (m, 2H), 1.20–1.15 (m, 4H), 1.05–0.95 (m, 1H), 0.95–0.88 (m, 1H), 0.88–0.70 (m, 5H).

^{13}C NMR ($CDCl_3$) δ 173.7, 143.1, 129.2–125.0 (broad), 44.9, 34.8, 34.0, 33.3, 33.0, 32.9, 29.2, 26.7, 26.4, 26.3, 19.6.

FT-IR (film) 2921, 2850, 2360, 1675, 1593, 1491, 1449, 1375, 1272, 755, 701 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{24}H_{32}NO$: 350, found: 350.

$[\alpha]^{24}_D = -1.2$ (*c* = 1.26, $CHCl_3$; obtained with (*S,S*)-**L2**).



9-((*tert*-Butyldimethylsilyl)oxy)-4-ethyl-*N,N*-diphenylnonanamide (Table 2, entry 3; eq 7). This compound was prepared according to the general procedure, using 4-chloro-*N,N*-diphenylhexanamide (151 mg, 0.5 mmol) and a solution of the alkylborane prepared by hydroboration of *tert*-butyldimethyl(pent-4-en-1-yloxy)silane[34] with 9-BBN dimer (1.5 M in Et_2O; 670 μL, 1 mmol). Colorless oil.

First run: 178 mg (76%, 90% ee). Second run: 168 mg (72%, 92% ee).

When 4-bromo-*N,N*-diphenylhexanamide is employed (173 mg, 0.5 mmol, **eq 7**): First run: 164 mg (60%, 86% ee). Second run: 166 mg (62%, 86% ee).

The ee was determined by HPLC analysis (CHIRALPAK AD-H, 1% *i*-PrOH in hexanes; 1.0 mL/min; retention times (when *(R,R)*-**L2** is employed): 12.6 min (minor), 13.2 min (major)).

^{1}H NMR ($CDCl_3$) δ 7.33–7.22 (m, 10H), 3.55 (t, 2H, *J* = 6.8 Hz), 2.22–2.18 (m, 2H), 1.61–1.56 (m, 2H), 1.45–1.42 (m, 2H), 1.19–1.10 (m, 9H), 0.86 (s, 9H), 1.06 (t, 3H, *J* = 7.2 Hz), 0.01 (s, 6H).

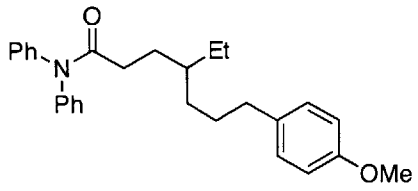
^{13}C NMR ($CDCl_3$) δ 173.7, 143.1, 129.3–126.6 (broad), 63.3, 38.5, 32.9, 32.8, 29.0, 26.3, 26.2, 26.0, 25.6, 18.4, 10.7, –4.9, –5.2.

FT-IR (film) 2929, 2857, 1676, 1594, 1492, 1462, 1360, 1255, 1098, 835, 775, 755, 701 cm^{-1}.

[34] Liang, B.; Negishi, E.-i. *Org. Lett.* **2008**, *10*, 193–195.

LRMS (EI) *m/z* (M+H–*t*-Bu$^+$) calcd for $C_{29}H_{46}NO_2Si$: 468, found: 411.

$[\alpha]^{24}_D$ = –0.84 (*c* = 1.1, $CHCl_3$; obtained with (*S,S*)-**L2**).



4-Ethyl-7-(4-methoxyphenyl)-*N,N*-diphenylheptanamide (Table 2, Entry 4). This compound was prepared according to the general procedure, using 4-chloro-*N,N*-diphenylhexanamide (151 mg, 0.5 mmol) and a solution of the alkylborane prepared by hydroboration of 1-allyl-4-methoxybenzene with 9-BBN dimer (1.5 M in Et_2O; 670 μL, 1 mmol). Colorless oil.

First run: 164 mg (79%, 89% ee). Second run: 166 mg (80%, 88% ee).

The ee was determined by HPLC analysis (CHIRALPAK AD-H, 10% *i*-PrOH in hexanes; 1.0 mL/min; retention times (when *(R,R)*-**L2** is employed): 17.2 min (minor), 18.4 min (major)).

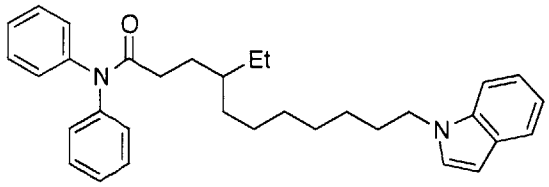
^{1}H NMR ($CDCl_3$) δ 7.33–7.20 (m, 10H), 7.02 (d, 2H, *J* = 8.4 Hz), 6.78 (d, 2H, *J* = 4.0 Hz), 3.76 (s, 3H), 2.43 (t, 2H, *J* = 6.8 Hz), 2.25–2.16 (m, 2H, *J* = 8.0 Hz), 1.61–1.54 (m, 2H), 1.49–1.41 (m, 2H), 1.30–1.18 (m, 5H), 0.77 (t, 3H, *J* = 7.6 Hz).

^{13}C NMR ($CDCl_3$) δ 173.7, 157.7, 143.1, 134.8, 129.3, 127.4–125.6 (broad), 113.7, 55.3, 38.4, 35.3, 32.8, 32.4, 29.0, 28.6, 25.6, 10.7.

FT-IR (film) 2931, 1674, 1594, 1558, 1540, 1512, 1491, 1456, 1245, 1177, 1035, 756, 702 cm^{-1}.

LRMS (EI) *m/z* (M+H$^+$) calcd for $C_{28}H_{34}NO_2$: 416, found: 416.

$[\alpha]^{24}_{D}$ = 1.8 (*c* = 1.26, $CHCl_3$; obtained with (*R*,*R*)-**L2**).



4-Ethyl-11-(1*H*-indol-1-yl)-*N*,*N*-diphenylundecanamide (Table 2, Entry 5). This compound was prepared according to the general procedure, using 4-chloro-*N*,*N*-diphenylhexanamide (151 mg, 0.5 mmol) and a solution of the alkylborane prepared by hydroboration of 1-(hept-6-en-1-yl)-1*H*-indole with 9-BBN dimer (1.5 M in Et_2O; 670 μL, 1 mmol). Yellow oil.

First run: 147 mg (61%, 89% ee). Second run: 154 mg (64%, 90% ee).

The ee was determined by SFC analysis (CHIRALPAK AD-H, 10% MeOH; 3.0 mL/min; retention times (when *(R,R)*-**L2** is employed): 43.0 min (major), 47.6 min (minor)).

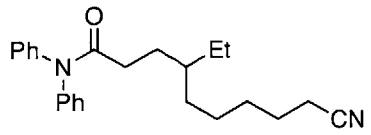
^{1}H NMR ($CDCl_3$) δ 7.66 (d, 1H, *J* = 8.0 Hz), 7.28–7.26 (m, 5H), 7.25–7.21 (m, 7H), 7.14–7.10 (m, 2H), 6.52–6.51 (m, 1H), 4.12 (t, 2H, *J* = 6.8 Hz), 2.26 (t, 2H, *J* = 7.6 Hz), 1.85–1.82 (m, 2H), 1.67–1.62 (m, 2H), 1.30–1.11 (m, 13H), 0.81 (t, 3H, *J* = 6.6 Hz).

^{13}C NMR ($CDCl_3$) δ 173.9, 143.3, 136.2, 129.4–127.2 (broad), 128.8, 128.0, 121.5, 121.2, 119.4, 109.6, 101.0, 46.6, 38.7, 33.0, 32.9, 30.5, 30.1, 29.5, 29.2, 27.2, 26.6, 25.8, 10.9.

FT-IR (film) 2926.6, 2855.0, 1672.8, 1592.3, 1490.9, 1463.8, 1314.6, 739.9, 701.6 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{33}H_{41}N_2O$: 481, found: 481.

$[\alpha]^{24}_{D}$ = 0.33 (*c* = 1.82, $CHCl_3$; obtained with (*S*,*S*)-**L2**).



9-Cyano-4-ethyl-*N,N*-diphenylnonanamide (Table 2, entry 6). This compound was prepared according to the general procedure, except that the reaction was heated to 60 °C in *i*-Pr_2O, using 4-chloro-*N,N*-diphenylhexanamide (151 mg, 0.5 mmol) and a solution of the alkylborane prepared by hydroboration of hex-5-enenitrile with 9-BBN dimer (1.5 M in i-Pr_2O; 670 μL, 1 mmol). Colorless oil.

First run: 94 mg (52%, 68% ee). Second run: 91 mg (50%, 70% ee).

The ee was determined by HPLC analysis (CHIRALPAK AD-H, 5% *i*-PrOH in hexanes; 1.0 mL/min; retention times (when *(R,R)*-**L2** is employed): 55.8 min (minor), 59.2 min (major)).

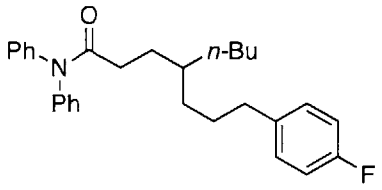
^{1}H NMR ($CDCl_3$) δ 7.28–7.18 (m, 10H), 2.28 (t, 2H, J = 7.2 Hz), 2.24–2.18 (m, 2H), 1.61–1.55 (m, 5H), 1.40–1.29 (m, 2H), 1.25–1.00 (m, 6H), 0.74 (t, 3H, J = 7.0 Hz).

^{13}C NMR ($CDCl_3$) δ 173.6. 143.0, 130.2–126.8 (broad), 119.9, 38.4, 32.7, 32.4, 29.0, 28.9, 25.7, 25.5, 25.3, 17.1, 10.7.

FT-IR (film) 2931, 2859, 1671, 1595, 1491, 1452, 1357, 1273, 757, 703 cm^{-1}.

MS (EI) *m/z* (M^+) calcd for $C_{24}H_{31}N_2O$: 363, found: 363.

$[\alpha]^{24}_D$ = −1.3 (c = 1.45, $CHCl_3$; obtained with (*R,R*)-**L2**).



4-(3-(4-Fluorophenyl)propyl)-*N,N*-diphenyloctanamide (Table 2, entry 7). This compound was prepared according to the general procedure, using 4-chloro-*N,N*-diphenyloctanamide (165 mg, 0.5 mmol) and a solution of the alkylborane prepared by hydroboration of 1-allyl-4-fluorobenzene with 9-BBN dimer (1.5 M in Et_2O; 670 μL, 1 mmol). Colorless oil.

First run: 134 mg (62%, 89% ee). Second run: 140 mg (65%, 90% ee).

The ee was determined by HPLC analysis (CHIRALPAK AD-H, 3% *i*-PrOH in hexanes; 1.0 mL/min; retention times (when *(R,R)*-**L2** is employed): 19.2 min (minor), 20.8 min (major)).

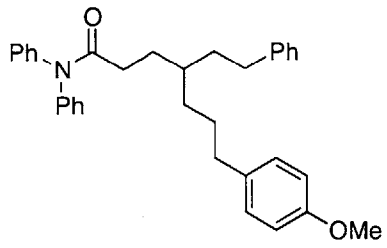
^{1}H NMR ($CDCl_3$) δ 7.32–7.20 (m, 10H), 7.07–7.03 (m, 2H), 6.93–6.89 (m, 2H), 2.46 (t, 2H, J = 7.6 Hz), 2.20–2.16 (m, 2H), 1.61–1.56 (m, 2H), 1.48–1.44 (m, 2H), 1.24–1.07 (m, 9H), 0.80 (t, 3H, J = 7.2 Hz).

^{13}C NMR ($CDCl_3$) δ 173.6, 161.2 (d, J = 964 Hz), 143.0, 138.2, 129.7, 129.6–126.6 (broad), 115.0, 114.8, 36.9, 35.5, 35.4, 33.1, 32.9, 29.4, 28.7, 28.4, 23.0, 14.1.

FT-IR (film) 2928, 2858, 2361, 2340, 1675, 1598, 1509, 1491, 1362, 1273, 1220, 1157, 832, 756, 702, 668 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{29}H_{35}FNO$: 432, found: 432.

$[\alpha]^{24}$ = 1.9 (c = 1.21, $CHCl_3$); obtained with (*S,S*)-**L2**).



7-(4-Methoxyphenyl)-4-phenethyl-*N*,*N*-diphenylheptanamide (Table 2, Entry 8). This compound was prepared according to the general procedure, using 4-chloro-*N*,*N*-6-triphenylhexanamide (189 mg, 0.5 mmol) and a solution of the alkylborane prepared by hydroboration of 1-allyl-4-methoxybenzene with 9-BBN dimer (1.5 M in Et_2O; 670 μL, 1 mmol). Colorless oil.

First run: 202 mg (82%, 88% ee). Second run: 206 mg (84%, 88% ee).

The ee was determined by HPLC analysis (CHIRALPAK AD-H, 3% *i*-PrOH in hexanes; 1.0 mL/min; retention times (when *(R,R)*-**L2** is employed): 56.7 min (minor), 65.3 min (major)).

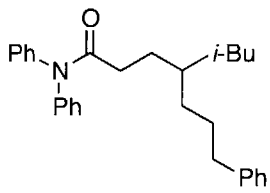
^{1}H NMR ($CDCl_3$) δ 7.33–7.14 (m, 13H), 7.07–7.02 (m, 4H), 6.81–6.79 (m, 2H), 3.77 (s, 3H), 2.48–2.43 (m, 4H), 2.25–2.20 (m, 2H), 1.70–1.68 (m, 2H), 1.54–1.35 (m, 5H), 1.22–1.19 (m, 2H).

^{13}C NMR ($CDCl_3$) δ 173.5, 157.7, 143.0, 142.9, 134.7, 130.0–125.0 (broad), 129.3, 128.4, 128.3, 125.7, 113.7, 55.3, 53.5, 36.6, 35.3, 32.9, 32.71, 32.66, 29.3, 28.5.

FT-IR (film) 2930, 2857, 1672, 1594, 1511, 1491, 1452, 1245, 1177, 1033, 756, 701 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{34}H_{38}NO_2$: 492, found: 492.

$[\alpha]^{24}_D$ = 0.84 (*c* = 1.12, $CHCl_3$); obtained with (*S*,*S*)-**L2**).



4-Isobutyl-N,N,7-triphenylheptanamide (Table 2, Entry 9). This compound was prepared according to the general procedure, using 4-chloro-6-methyl-*N,N*-diphenylheptanamide (165 mg, 0.5 mmol) and a solution of the alkyl borane prepared by hydroboration of allylbenzene with 9-BBN dimer (1.5 M in Et_2O; 670 μL, 1 mmol). Colorless oil.

First run: 124 mg (60%, 82% ee). Second run: 128 mg (62%, 82% ee).

The ee was determined by HPLC analysis (CHIRALPAK AD-H, 3% *i*-PrOH in hexanes; 1.0 mL/min; retention times (when *(R,R)*-**L2** is employed): 15.8 min (minor), 17.9 min (major)).

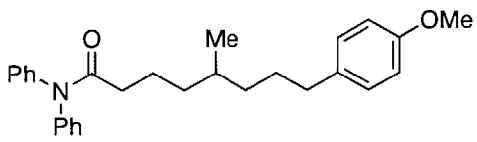
^{1}H NMR ($CDCl_3$) δ 7.32–7.10 (m, 15H), 2.48 (t, 2H, J = 7.6 Hz), 2.21–2.16 (m, 2H), 1.60–1.56 (m, 2H), 1.53–1.40 (m, 3H), 1.39–1.30 (m, 1H), 1.14–1.10 (m, 2H), 0.96–0.95 (m, 1H), 0.88–0.86 (m, 1H), 0.77–0.74 (m, 6H).

^{13}C NMR ($CDCl_3$) δ 173.7, 143.1, 142.7, 129.2–125.0 (broad), 128.5, 128.3, 125.7, 43.4, 36.4, 34.6, 33.3, 32.6, 29.6, 28.2, 25.2, 23.1, 22.9.

FT-IR (film) 2952, 2929, 2339, 2361, 1675, 1594, 1492, 1453, 1364, 1271, 755, 700 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{29}H_{36}NO$: 414, found: 414.

$[\alpha]^{24}_D$ = 0.79 (c = 1.07, $CHCl_3$); obtained with (*R,R*)-**L2**).



8-(4-Methoxyphenyl)-5-methyl-*N,N*-diphenyloctanamide (eq 8). This compound was prepared according to the general procedure, using 4-chloro-*N,N*-diphenylpentanamide (144 mg, 0.5 mmol) and a solution of the alkylborane prepared by hydroboration of 1-allyl-4-methoxybenzene with 9-BBN dimer (1.5 M in Et_2O; 670 μL, 1 mmol). Colorless oil.

First run: 131 mg (63%, 83% ee). Second run: 135 mg (65%, 84% ee).

The ee was determined by HPLC analysis (CHIRALPAK AD-H, 10% *i*-PrOH in hexanes; 1.0 mL/min; retention times (when *(R,R)*-**L2** is employed): 18.3 min (minor), 19.8 min (major)).

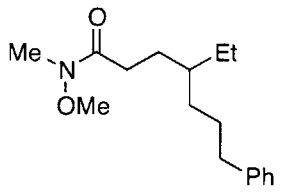
^{1}H NMR ($CDCl_3$) δ 7.33–7.21 (m, 10H), 7.04–7.02 (m, 2H), 6.80–6.78 (m, 2H), 3.76 (s, 3H), 2.44 (t, 2H, J = 7.6 Hz), 2.21–2.17 (m, 2H), 1.62–1.57 (m, 2H), 1.48–1.44 (m, 2H), 1.20–1.11 (m, 5H), 0.75–0.71 (m, 3H).

^{13}C NMR ($CDCl_3$) δ 173.6, 157.6, 143.0, 134.8, 129.2, 129.2–125.2 (broad), 113.7, 55.3, 38.4, 35.3, 32.8, 32.4, 29.0, 28.6, 25.5, 10.7.

FT-IR (film) 2931, 2858, 1674, 1594, 1512, 1491, 1457, 1374, 1246, 1035, 756, 702 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{28}H_{34}NO_2$: 416, found: 416.

$[\alpha]^{24}_D$ = 1.3 (c = 1.30, $CHCl_3$); obtained with (*R,R*)-**L2**).



4-Ethyl-N-methoxy-N-methyl-7-phenylheptanamide (eq 9). This compound was prepared according to the general procedure, except that potassium iodide (21 mg, 0.13 mmol) was added to the vial containing $NiBr_2$ • diglyme and **1** before solvent was added). 4-Chloro-*N*-methoxy-*N*-methylhexanamide (97 mg, 0.5 mmol) was used, along with a solution of the alkylborane prepared by hydroboration of allylbenzene with 9-BBN dimer (1.5 M in Et_2O; 670 μL, 1 mmol). Colorless oil.

First run: 87 mg (63%, 86% ee). Second run: 86 mg (62%, 86% ee).

The ee was determined by HPLC analysis (CHIRALPAK OJ-H, 1% *i*-PrOH in hexanes; 1.0 mL/min; retention times (when *(R,R)*-**L2** is employed): 14.2 min (minor), 15.0 min (major)).

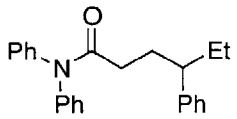
^{1}H NMR ($CDCl_3$) δ 7.24–7.22 (m, 2H), 7.16–7.12 (m, 3H), 3.62 (s, 3H), 3.14 (s, 3H), 2.56 (t, 2H, J = 7.6 Hz), 2.33 (t, 2H, J = 7.6 Hz), 1.62–1.54 (m, 4H), 1.33–1.24 (m, 5H), 0.86 (t, 3H, J = 7.2 Hz).

^{13}C NMR ($CDCl_3$) δ 175.0, 142.8, 128.4, 128.2, 125.6, 61.2, 38.5, 36.3, 32.5, 32.2, 29.4, 28.5, 27.9, 25.6, 10.8.

FT-IR (film) 2930, 1670, 1457, 1382, 1003, 747, 699 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{17}H_{28}NO_2$: 278, found: 278.

$[\alpha]^{24}_D$ = 0.42 (c = 4.40, $CHCl_3$); obtained with (*R,R*)-**L2**).



***N,N*-4-Triphenylhexanamide (eq 10 & 11).** This compound was prepared according to the general procedure, using 4-chloro-*N,N*-diphenylhexanamide (151 mg, 0.50 mmol), along with a solution of 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (**eq 11**; Aldrich, diluted to 1.5 M in Et_2O; 670 μL, 1.0 mmol). Colorless oil.

First run: 81 mg (47%, 83% ee). Second run: 81 mg (47%, 81% ee).

The ee was determined by HPLC analysis (CHIRALPAK AD-H, 3% *i*-PrOH in hexanes; 1.0 mL/min; retention times (when ligand *(R,R)*-**L2** is employed): 16.0 min (minor), 17.5 min (major)).

^{1}H NMR ($CDCl_3$) δ 7.28–7.00 (m, 15H), 2.41–2.40 (m, 1H), 2.09–2.03 (m, 3H), 1.85–1.75 (m, 1H), 1.62–1.48 (m, 2H), 0.72 (t, 3H, J = 7.2 Hz).

^{13}C NMR ($CDCl_3$) δ 173.2, 144.7, 142.8, 128.2, 127.8, 126.0, 130.0–125.0 (broad), 47.0, 33.3, 31.8, 29.8, 12.1.

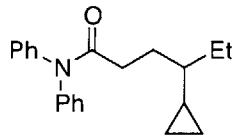
FT-IR (film) 3060, 2827, 1680, 1593, 1492, 1375, 1270, 756, 700 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{24}H_{26}NO$: 344, found: 344.

$[\alpha]^{25}_D$ = 11 (c = 1.80, $CHCl_3$); obtained with (*R,R*)-**L2**).

When *B*-phenyl-(9-BBN)[35] was employed instead of 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane (**eq 10**): First run: 75 mg (44%, 80% ee). Second run: 77 mg (45%, 78% ee).

[35] Fang, G. Y.; Wallner, O. A.; Di Blasio, N.; Ginesta, X.; Harvey, J. N.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2007**, *129*, 14632–14639.



4-Cyclopropyl-*N*,*N*-diphenylhexanamide (eq 12). This compound was prepared according to the general procedure, except that Et_2O was the only solvent (0.08 M) and the catalyst loading was doubled: $NiBr_2$ • diglyme (35.2 mg, 0.10 mmol) and **1** (29 mg, 0.12 mmol). 4-Chloro-6-methyl-*N*,*N*-diphenylheptanamide (165 mg, 0.50 mmol) was used, along with a solution of *B*-cyclopropyl-(9-BBN) (1.5 M in Et_2O; 670 μL, 1.0 mmol). Colorless oil.

First run: 108 mg (68%, 84% ee). Second run: 109 mg (71%, 83% ee).

The ee was determined by HPLC analysis (CHIRALPAK OJ-H, 1% *i*-PrOH in hexanes; 1.0 mL/min; retention times (when *(R,R)*-**L2** is employed): 14.2 min (minor), 15.0 min (major)).

^{1}H NMR ($CDCl_3$) δ 7.33–7.00 (m, 10H), 2.42–2.27 (m, 2H), 1.82–1.67 (m, 2H), 1.32–1.25 (m, 2H), 0.84 (t, 3H, J = 7.2 Hz), 0.44–0.39 (m, 1H), 0.32–0.29 (m, 3H), –0.03– –0.10 (m, 2H).

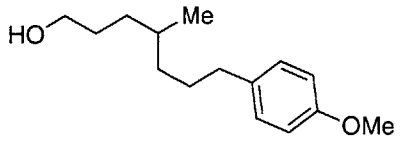
^{13}C NMR ($CDCl_3$) δ 173.8, 143.1, 129.3–126.5 (broad), 44.4, 33.2, 30.3, 27.5, 15.5, 11.3, 4.0, 3.6.

FT-IR (film) 2961, 2924, 1675, 1491, 1373, 1271, 756, 702, 693 cm^{-1}.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{21}H_{26}NO$: 308, found: 308.

$[\alpha]^{24}_D$ = –0.80 (c = 1.54, $CHCl_3$); obtained with (*S*,*S*)-**L2**).

V. Transformation of the Cross-Coupling Products



(*S*)-4-Ethyl-7-(4-methoxyphenyl)heptan-1-ol (eq 13). *(S)*-7-(4-Methoxyphenyl)-4-ethyl-*N,N*-diphenylheptanamide (100 mg, 0.24 mmol; 89% ee) and THF (13 mL) were added to an oven-dried two-neck round-bottom flask under nitrogen. This solution was cooled to 0 °C, and a solution of lithium aluminum hydride (1.45 mL, 2.9 mmol; 2.0 M in THF) was added dropwise with stirring. The mixture was allowed to warm to room temperature, and it was stirred for 12 h. The reaction mixture was then cooled to 0 °C, and the reaction was quenched by the addition of water (1 mL). The mixture was filtered through Celite, which was washed with THF. The filtrate was concentrated, and the residue was purified by flash chromatography with 10→70% Et_2O/hexanes, which furnished the product as a clear oil.

First run: 55 mg (92%, 88% ee). Second run: 57 mg (95%, 88% ee).

The ee was determined by HPLC analysis (CHIRALPAK IC, 2% *i*-PrOH in hexanes; 1.0 mL/min; retention times: 41.9 min (minor), 44.0 min (major)).

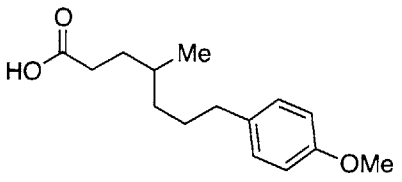
^{1}H NMR ($CDCl_3$) δ 7.07 (d, 2H, J = 8.0 Hz), 6.81–6.79 (m, 2H), 3.76 (s, 3H), 3.58 (t, 2H, J = 6.7 Hz), 2.50 (t, 2H, J = 8.0 Hz), 1.54 (s, 1H), 1.54–1.50 (m, 4H), 1.28–1.26 (m, 7H), 0.81 (t, 3H, J = 6.8 Hz).

^{13}C NMR ($CDCl_3$) δ 157.6, 134.9, 129.2, 113.7, 63.5, 55.3, 38.6, 35.5, 32.7, 30.0, 29.1, 28.9, 25.8, 10.8.

FT-IR (film) 3336 (broad), 2932, 2858, 2360, 2340, 1512, 1457, 1419, 1245, 1039, 829.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{16}H_{27}O_2$: 251, found: 251.

$[\alpha]^{24}_D$ = –2.0 (c = 2.67, $CHCl_3$).



***(S)*-4-Ethyl-7-(4-methoxyphenyl)heptanoic acid (eq 14).** *(S)*-7-(4-Methoxyphenyl)-4-ethyl-*N,N*-diphenylheptanamide (100 mg, 0.24 mmol; 89% ee), EtOH (7 mL), water (0.5 mL), and then sodium hydroxide (0.93 mg of a 30% w/w solution) were added to a 20-mL vial, which was then sealed with a septum cap and heated to 90 °C for 8 h. The reaction mixture was allowed to cool to room temperature, and then 2 N HCl (2 mL) was added. The mixture was transferred to a separatory funnel, to which Et_2O (50 mL) and brine (50 mL) were added. The layers were separated, and the aqueous layer was washed with Et_2O (50 mL x2). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated. The product was purified by flash chromatography with 10→70% Et_2O/hexanes, which furnished the product as a clear oil.

First run: 57 mg (90%, 88% ee). Second run: 59 mg (93%, 88% ee).

The ee was determined by HPLC analysis (CHIRALPAK IC, 1% *i*-PrOH in hexanes; 1.0 mL/min; retention time:s 24.7 min (major), 27.9 min (minor)).

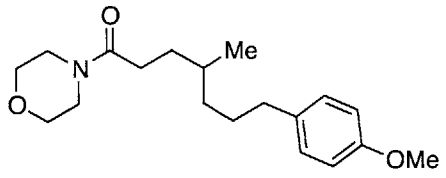
^{1}H NMR ($CDCl_3$) δ 7.04 (d, 2H, J = 8.4 Hz), 6.86 (d, 2H, J = 8.4 Hz), 3.77 (s, 3H), 2.51 (t, 2H, J = 7.6 Hz), 2.29 (t, 2H, J = 7.6 Hz), 1.61–1.51 (m, 4H), 1.29–1.26 (m, 5H), 0.81 (t, 3H, J = 6.8 Hz).

^{13}C NMR ($CDCl_3$) δ 180.1, 157.8, 134.9, 129.4, 113.9, 55.4, 38.4, 35.5, 32.5, 31.7, 28.8, 28.1, 25.6, 10.9.

FT-IR (film) 2932 (broad), 2859, 1708, 1512, 1457, 1300, 1245, 1177, 1039, 829.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{16}H_{26}O_3$: 265, found: 265.

$[\alpha]^{24}_{D} = -0.62$ ($c = 2.22$, $CHCl_3$).



***(S)*-4-Ethyl-7-(4-methoxyphenyl)-1-morpholinoheptan-1-one (eq 15)** (modified from a literature method).[24] In a nitrogen-filled glovebox, activated molecular sieves (20 mg; 4 Å), *(S)*-4-ethyl-7-(4-methoxyphenyl)-*N,N*-diphenylheptanamide (50 mg, 0.12 mmol; 89% ee), and toluene (0.36 mL; anhydrous, Aldrich) were added to a flame-dried 4-mL vial equipped with a stir bar. The mixture was stirred for 20 minutes, and then it was filtered through a 2 μm acrodisc filter into another flame-dried 4-mL vial equipped with a stir bar (the original vial was rinsed with toluene (0.1 mL x2, and the washings were filtered through the acrodisc into the second vial). Freshly distilled morpholine (23 μL, 0.27 mmol) was added to the vial by syringe. In another flame-dried 4-mL vial, a stock solution of $Zr(NMe_2)_4$ in anhydrous toluene was prepared (10.8 mg per 1.0 mL of toluene). This solution (143 μL, 1.6 mg, 0.0060 mmol) was added to the solution of amine and amide, immediately resulting in a light-yellow solution. The vial was sealed with a teflon-lined septum cap, and the mixture was stirred at 50 °C for 10 hours. The reaction mixture was then allowed to cool to room temperature, the solvent was removed, and the product was purified by reverse-phase flash chromatography on C-18 silica gel with 10→100% acetonitrile/water.

A second run was conducted using *(R)*-4-ethyl-7-(4-methoxyphenyl)-*N,N*-diphenylheptanamide and afforded *(R)*-4-ethyl-7-(4-methoxyphenyl)-1-morpholinoheptan-1-one.

First run: 35 mg (87%, 89% ee). Second run: 34 mg (85%, 89% ee).

The ee was determined by HPLC analysis (CHIRALPAK AD-H, 3% *i*-PrOH in hexanes; 1.0 mL/min; retention times (for *(S)*-4-Ethyl-7-(4-methoxyphenyl)-1-morpholinoheptan-1-one): 28.6 min (major), 30.7 min (minor)).

^{1}H NMR ($CDCl_3$) δ 7.05 (d, 2H, J = 5.2 Hz), 6.79 (d, 2H, J = 4.8 Hz), 3.75 (s, 3H), 3.64–3.57 (m, 5H), 3.38 (t, 2H, J = 5.2 Hz), 2.92 (d, 1H, J = 16.8 Hz), 2.50 (t, 2H, J = 7.6 Hz), 2.20 (t, 2H, J = 8 Hz), 1.58–1.50 (m, 4H), 1.29–1.28 (m, 5H), 0.81 (t, 3H, J = 7.1 Hz).

^{13}C NMR ($CDCl_3$) δ 172.1, 157.7, 134.7, 129.3, 113.7, 67.0, 66.7, 55.3, 46.0, 41.9, 38.6, 35.3, 32.3, 30.5, 28.6, 28.5, 25.7, 10.8.

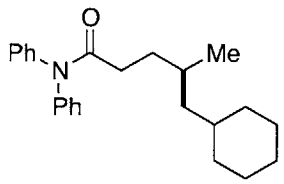
FT-IR (film) 2930, 2856, 2361, 2339, 1653, 1512, 1457, 1300, 1245, 1116, 1035, 830 cm $^{-1}$.

LRMS (EI) *m/z* ($M+H^+$) calcd for $C_{20}H_{32}NO_3$: 334, found: 334.

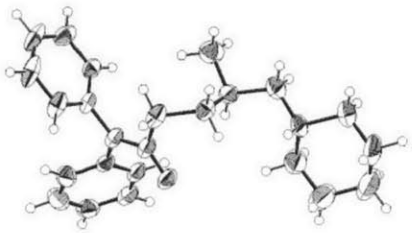
$[\alpha]^{24}_D$ = 0.97 (*c* = 0.95, $CHCl_3$); *(S)*-4-ethyl-7-(4-methoxyphenyl)-1-morpholinoheptan-1-one).

VI. Determination of Absolute Configuration

Assignment of absolute configuration of the γ-alkylated products. The absolute configuration of the product of entry 2 of Table 2 (using ligand *(S,S)*-**L2**) was determined by X-ray crystallography. The absolute configurations of the other γ-alkylated products were assigned by analogy.



The cross-coupling product was purified to >99% ee by chiral HPLC (CHIRALPAK AD-H). Crystals suitable for X-ray structural analysis were obtained by solvent evaporation of a pentane solution.



VII. ^{1}H NMR Spectra of Selected Compounds

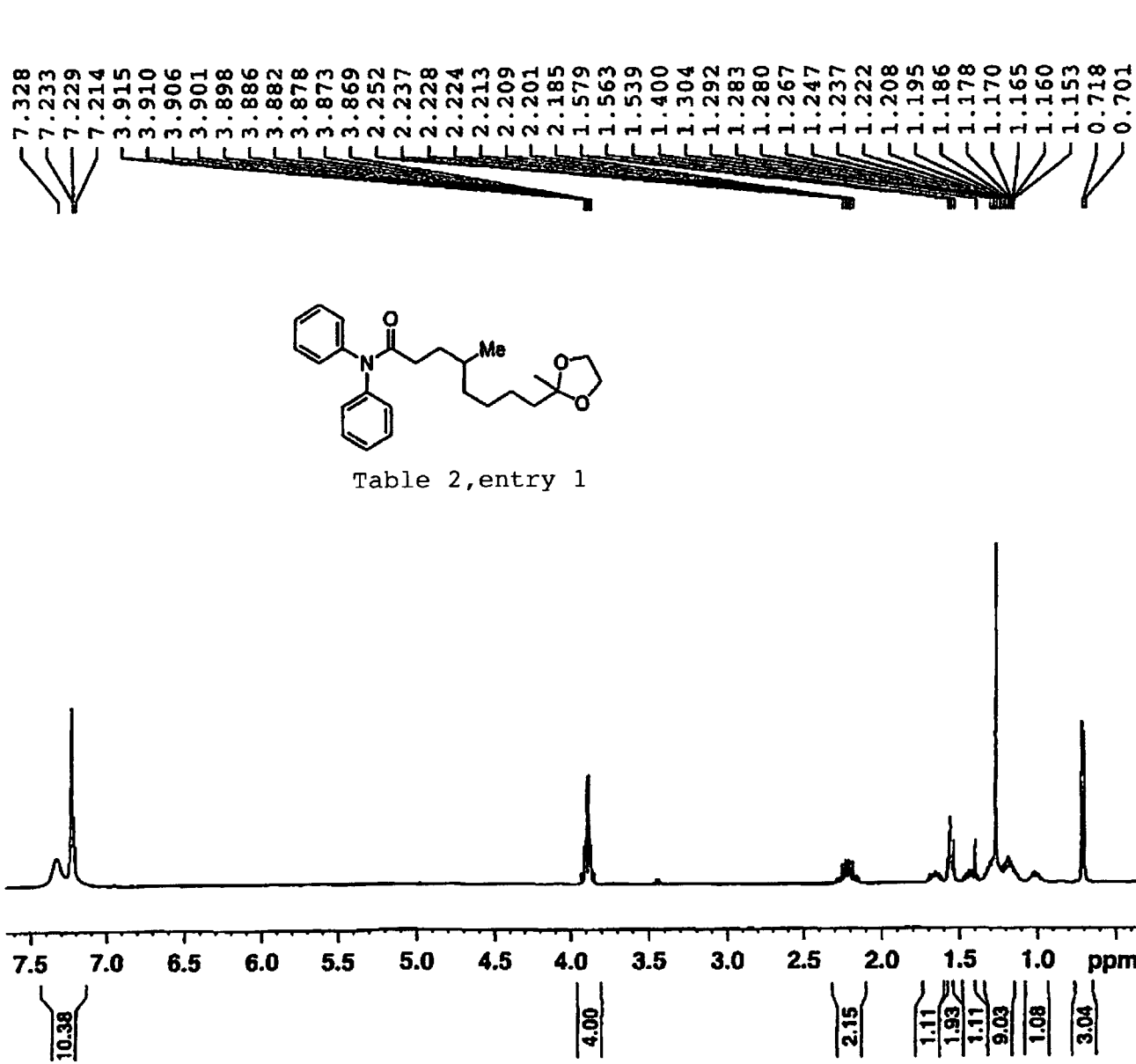


Table 2,entry 1

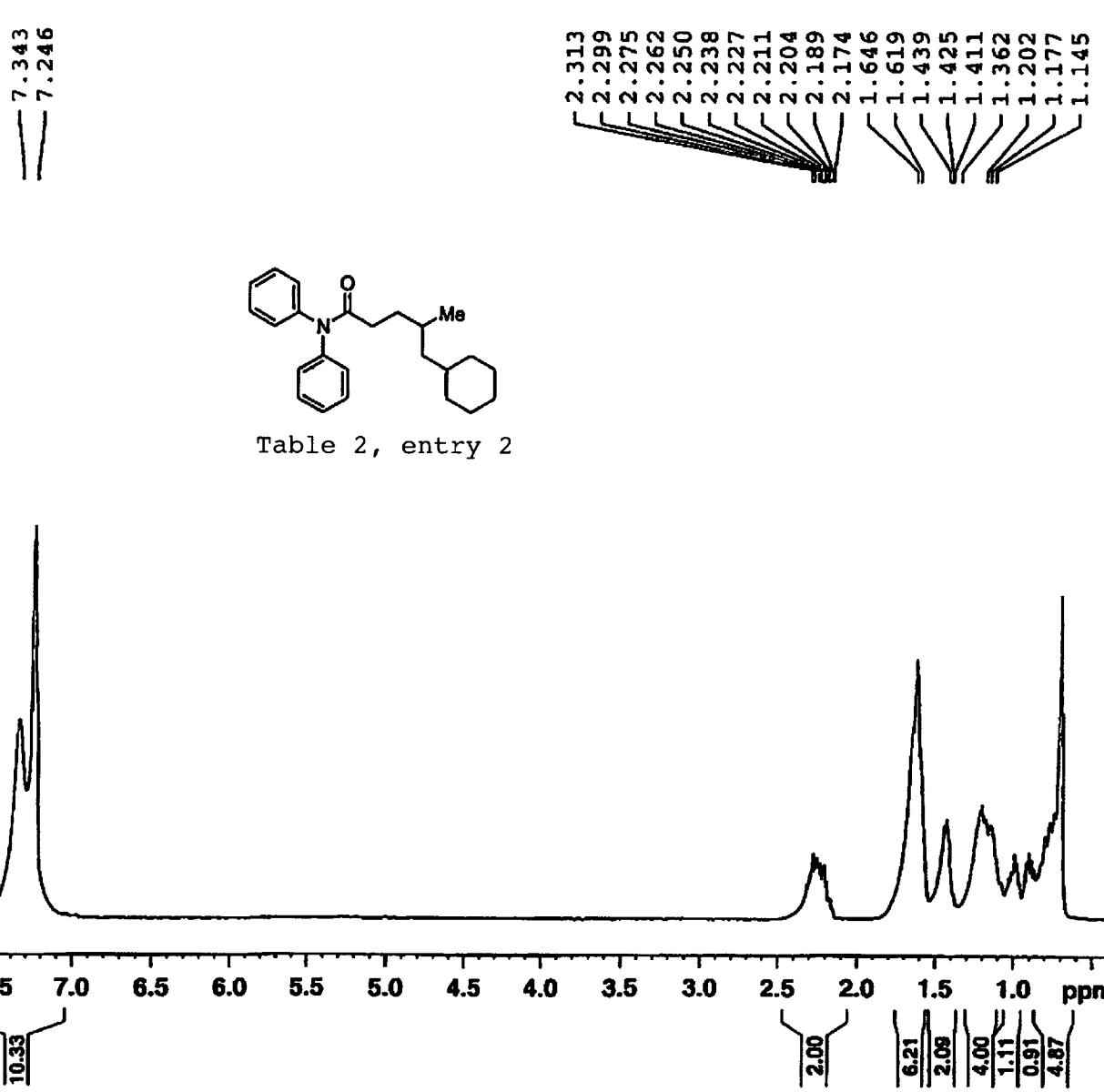


Table 2, entry 2

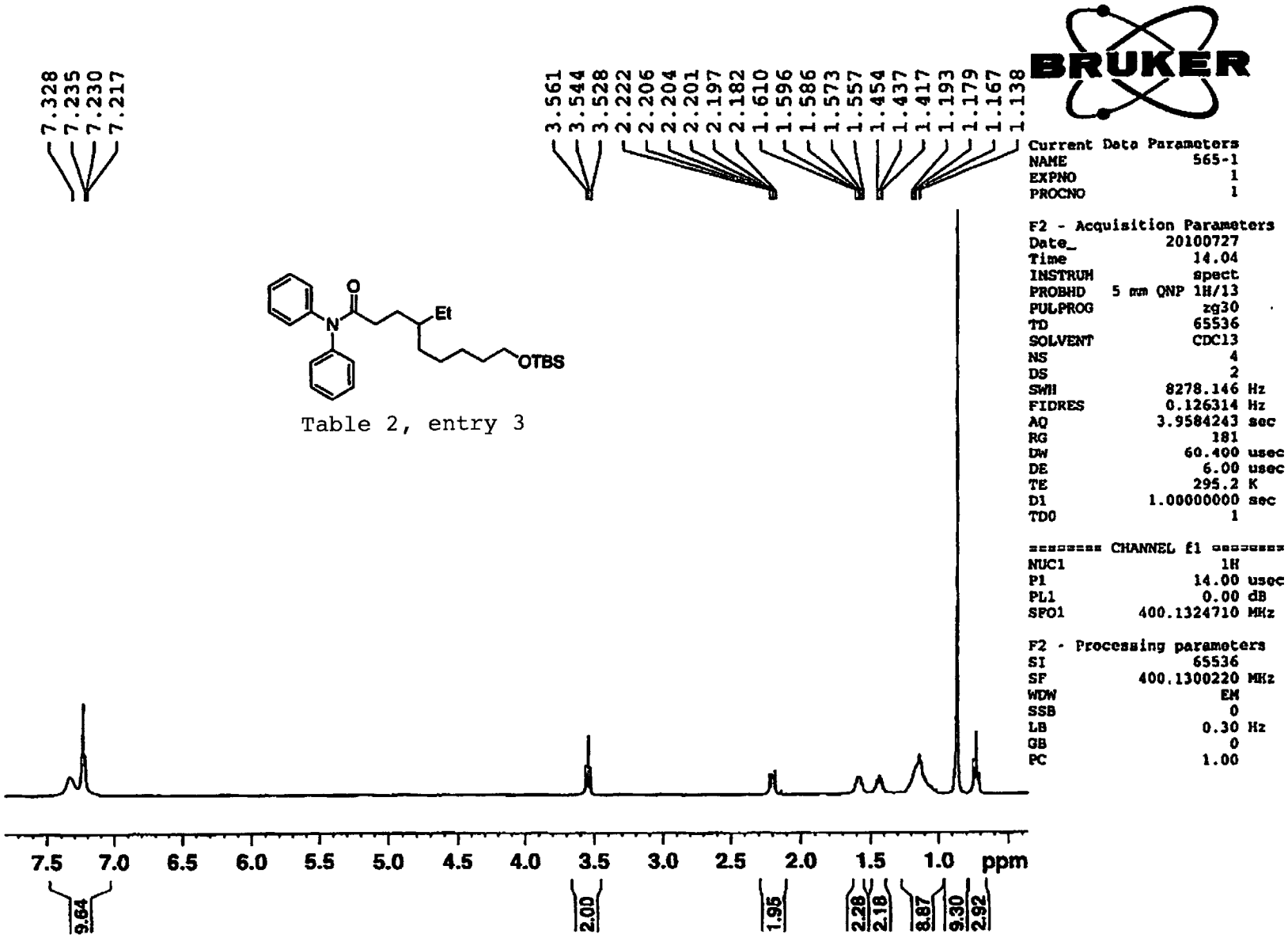


Table 2, entry 3

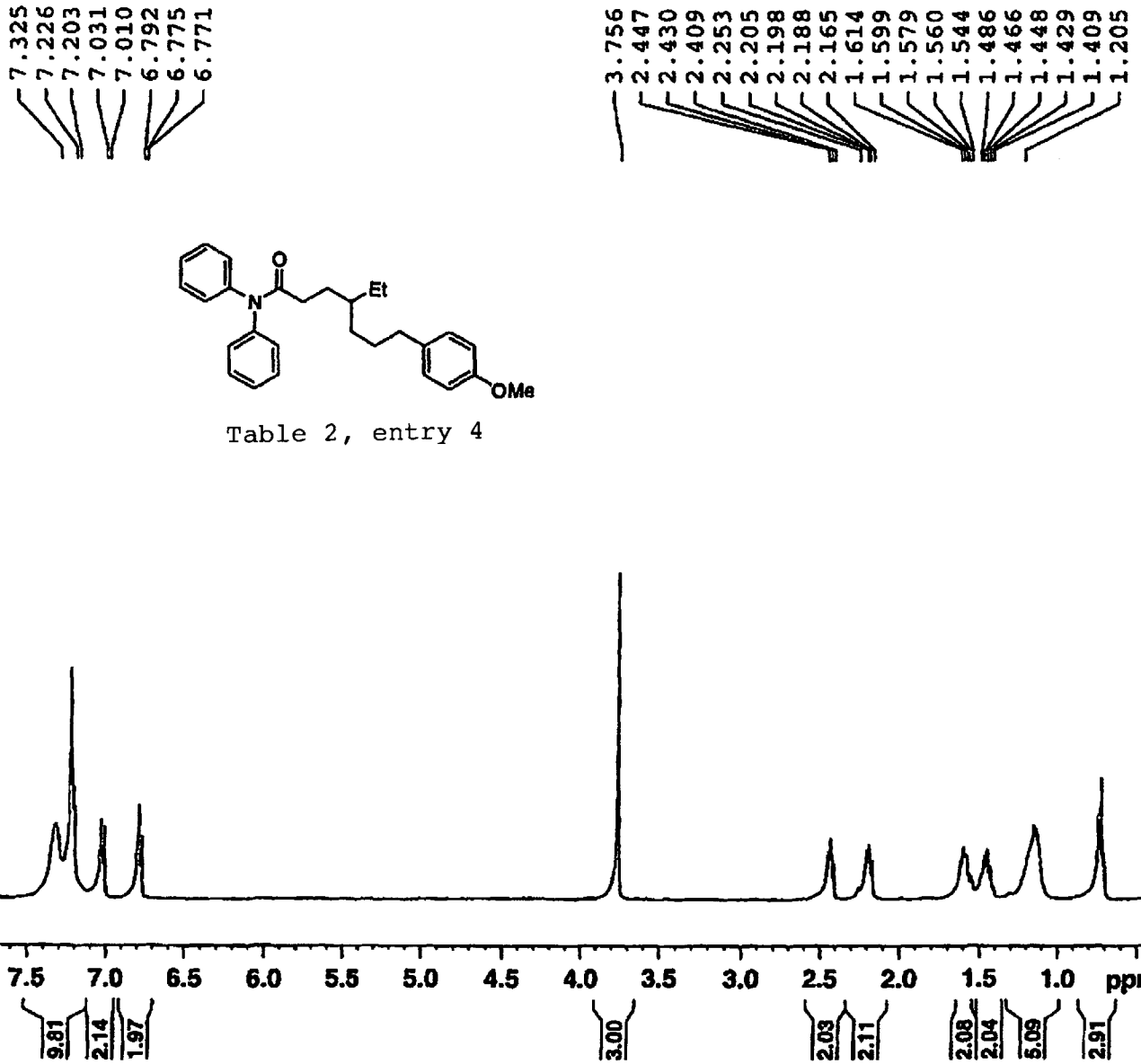


Table 2, entry 4

BRUKER

Current Data Parameters
NAME 550-1
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
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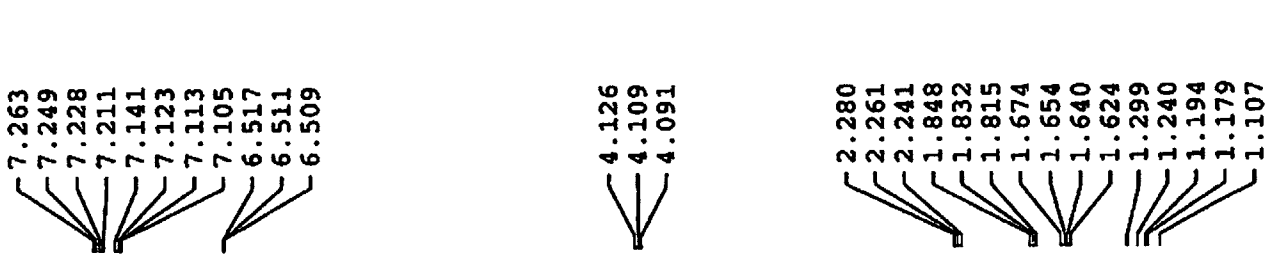
Time 14.30
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 7
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 128
DW 60.400 usec
DE 6.00 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 15.07 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 65536
SF 400.1300212 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



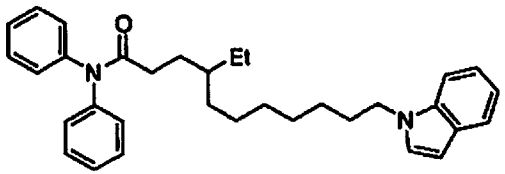
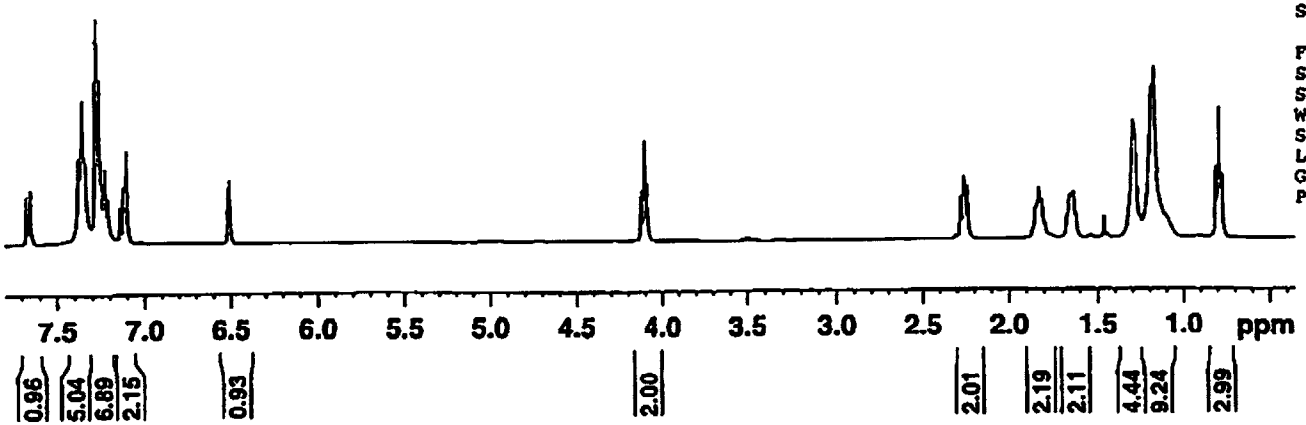


Table 2, entry 5



BRUKER

```
Current Data Parameters
NAME          787-1proton
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_              20110511
Time                   9.41
INSTRUM               spect
PROBHD   5 mm BBO BB-1H
PULPROG               zg30
TD                   65536
SOLVENT              CDCl3
NS                      10
DS                       2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                     25.4
DW                   60.400 usec
DE                    6.00 usec
TE                   296.2 K
D1              1.00000000 sec
TD0                     1

======== CHANNEL f1 ========
NUC1                   1H
P1                  15.07 usec
PL1                  0.00 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                   65536
SF            400.1300212 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.00
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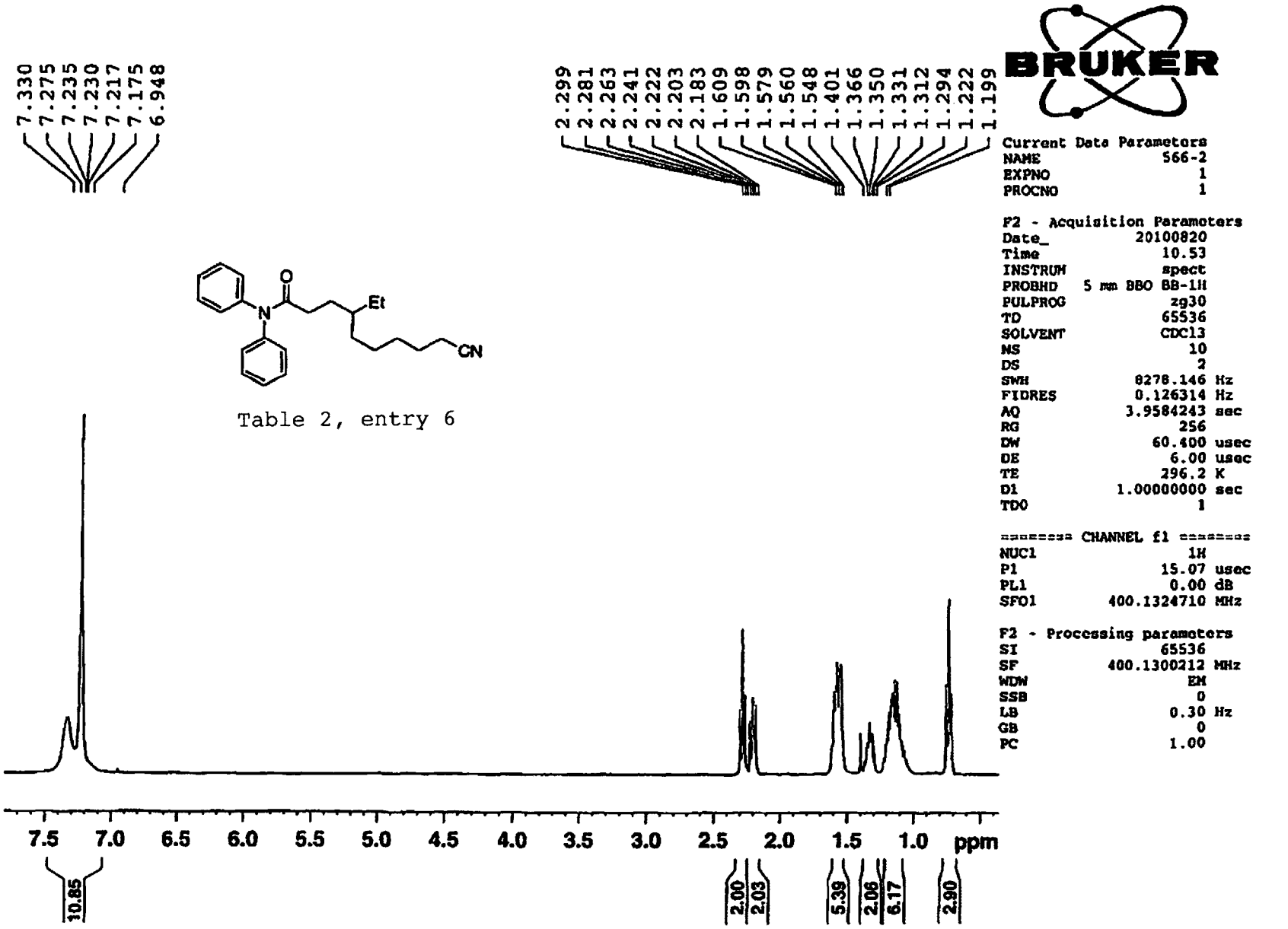
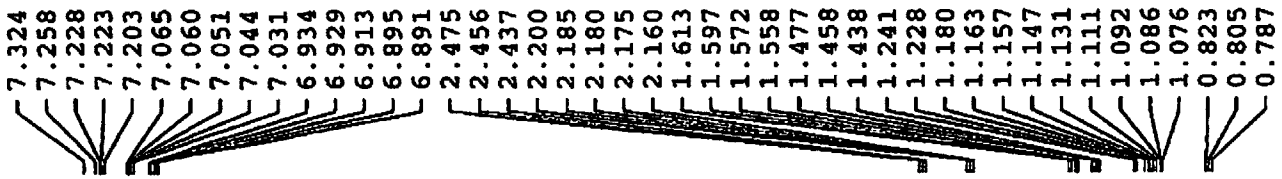


Table 2, entry 6



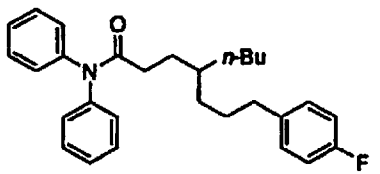


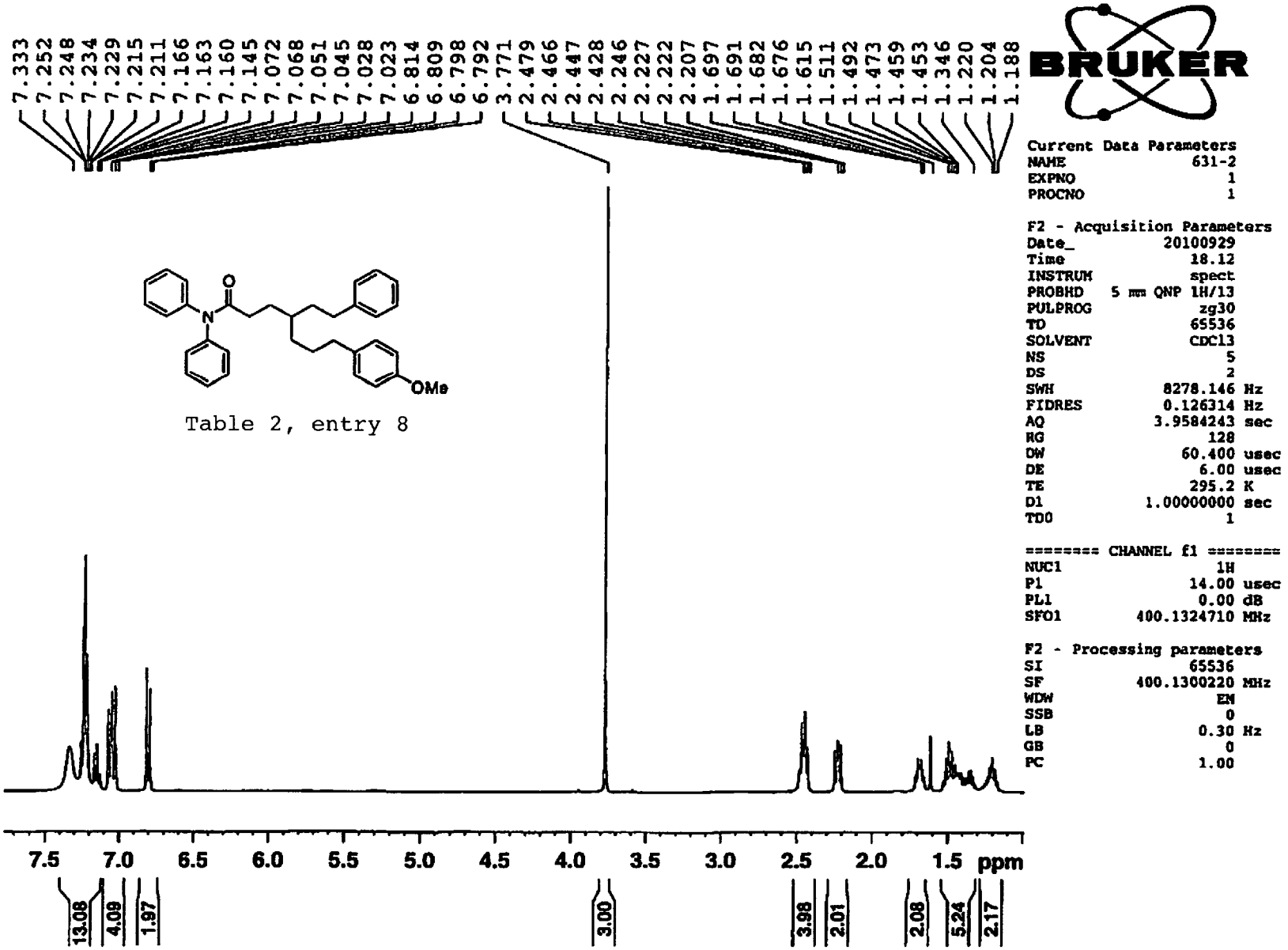
Table 2, entry 7


```
Current Data Paramoters
NAME                  584-2
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20100901
Time                  11.27
INSTRUM               spect
PROBHD   5 mm QNP 1H/13
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                        7
DS                        2
SWH               8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                      256
DW                 60.400 usec
DE                  6.00 usec
TE                  295.2 K
D1              1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    1H
P1                  14.00 usec
PL1                  0.00 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                    65536
SF            400.1300220 MHz
WDW                     EM
SSB                      0
LB                  0.30 Hz
GB                       0
PC                    1.00
```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7.229
7.215
7.211
7.166
7.163
7.160
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7.068
7.051
7.045
7.028
7.023
6.814
6.809
6.798
6.792
3.771
2.479
2.466
2.447
2.428
2.246
2.227
2.222
2.207
1.697
1.691
1.682
1.676
1.615
1.511
1.492
1.473
1.459
1.453
1.346
1.220
1.204
1.188
BRUKER
OMe
Table 2, entry 8
Current Data Parameters
NAME 631-2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100929
Time 18.12
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 5
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 128
DW 60.400 usec
DE 6.00 usec
TE 295.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 65536
SF 400.1300220 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
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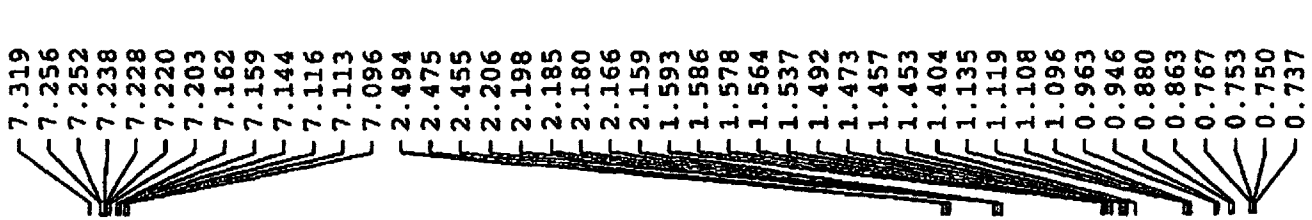
ppm
13.08
4.09
1.97
3.00
3.98
2.01
2.08
5.24
2.17



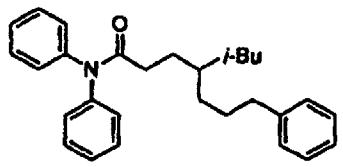
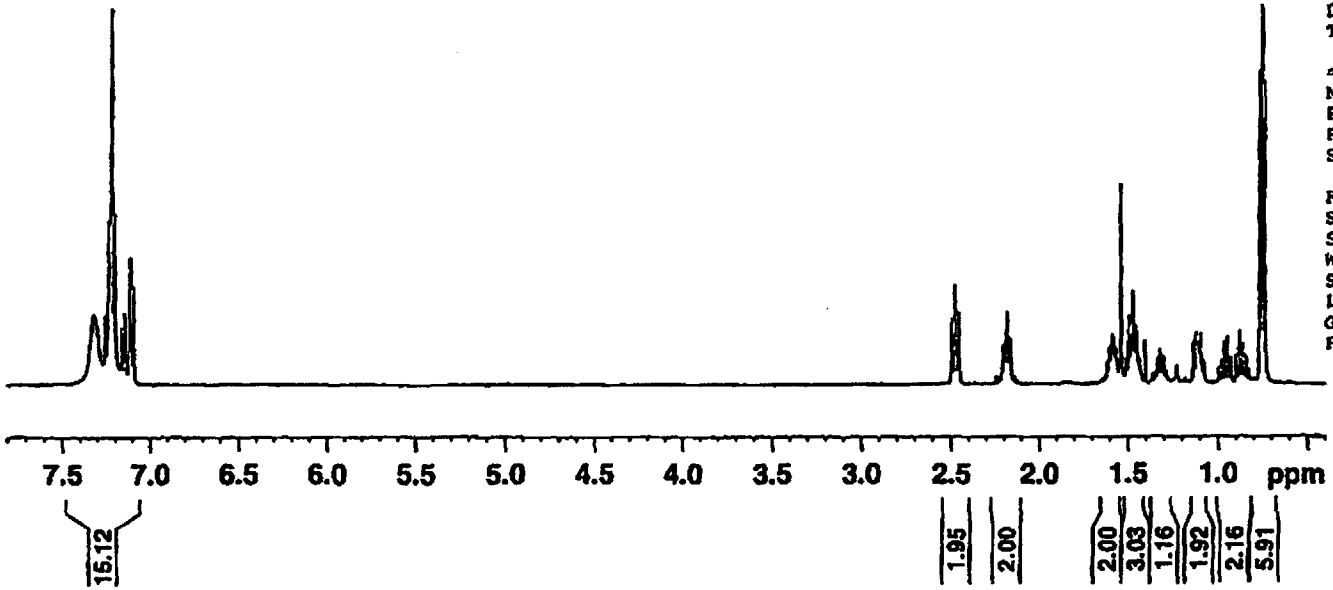


Table 2, entry 9



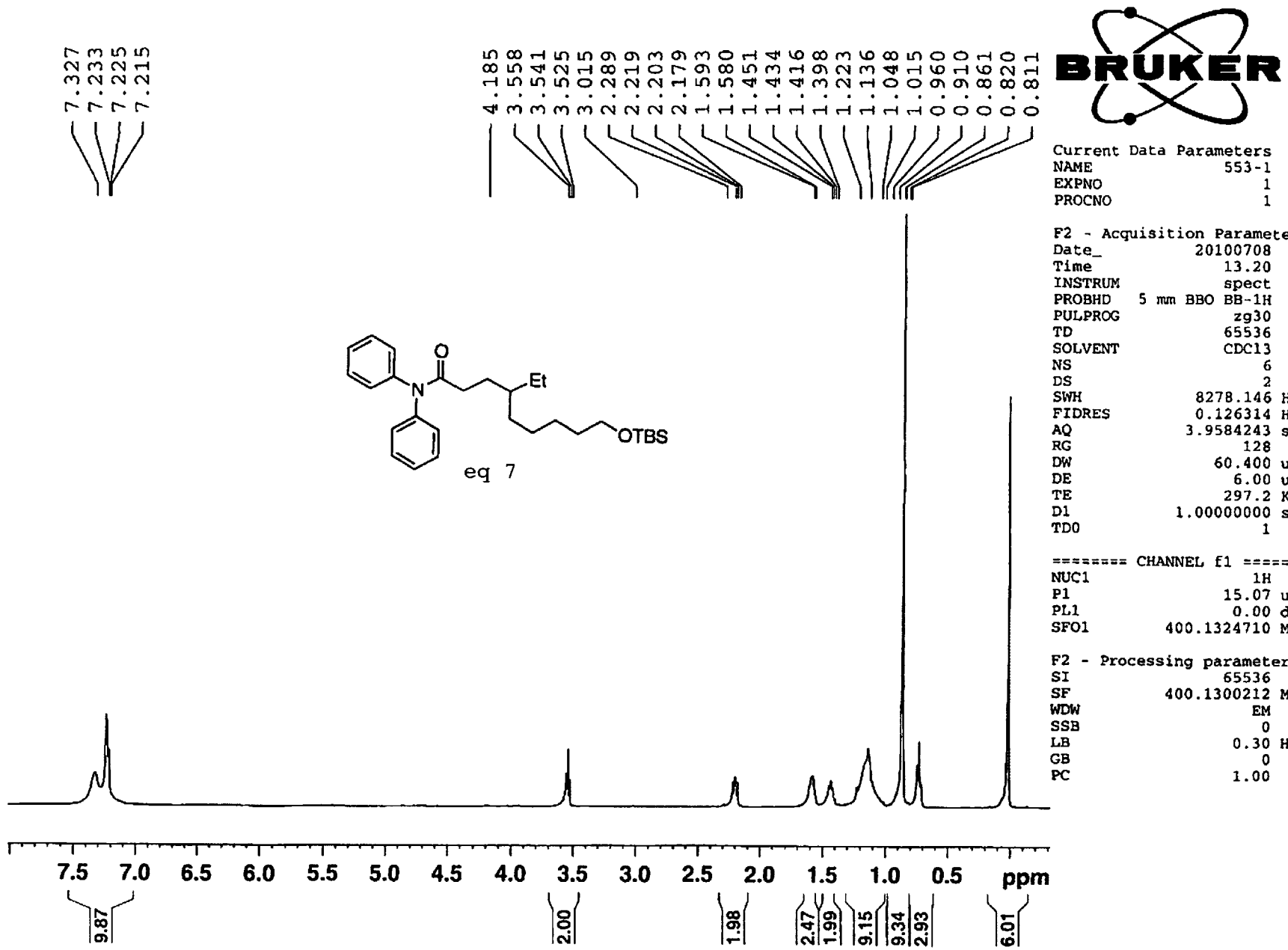
BRUKER

Current Data Parameters
NAME 664-1
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20101210
Time 11.31
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 2
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 203.2
DW 60.400 usec
DE 6.00 usec
TE 296.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 15.07 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 65536
SF 400.1300212 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



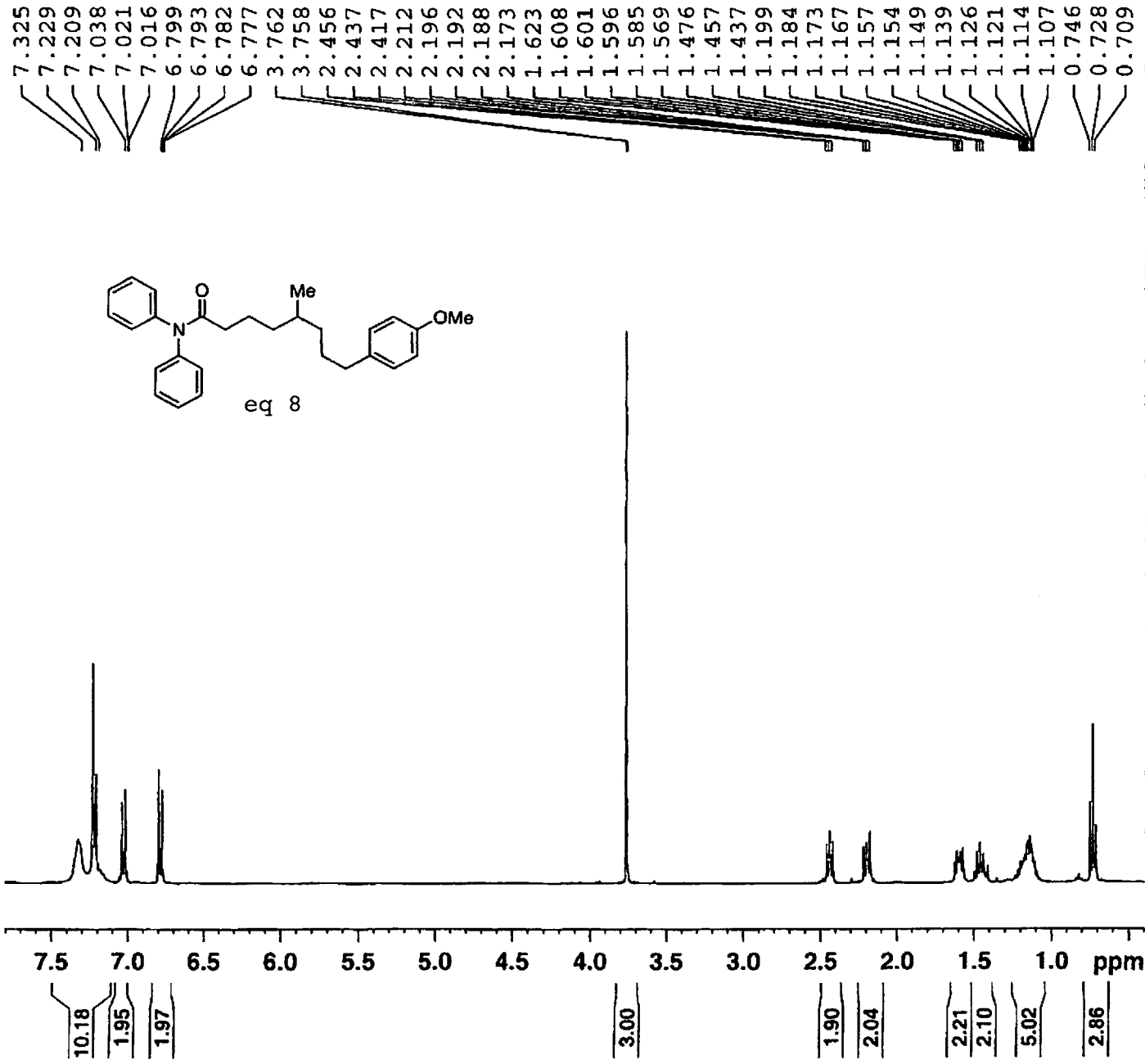
BRUKER

Current Data Parameters
NAME 553-1
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20100708
Time 13.20
INSTRUM spect
PROBHD 5 mm BBO BB-1H
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 6
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 128
DW 60.400 usec
DE 6.00 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 15.07 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 65536
SF 400.1300212 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



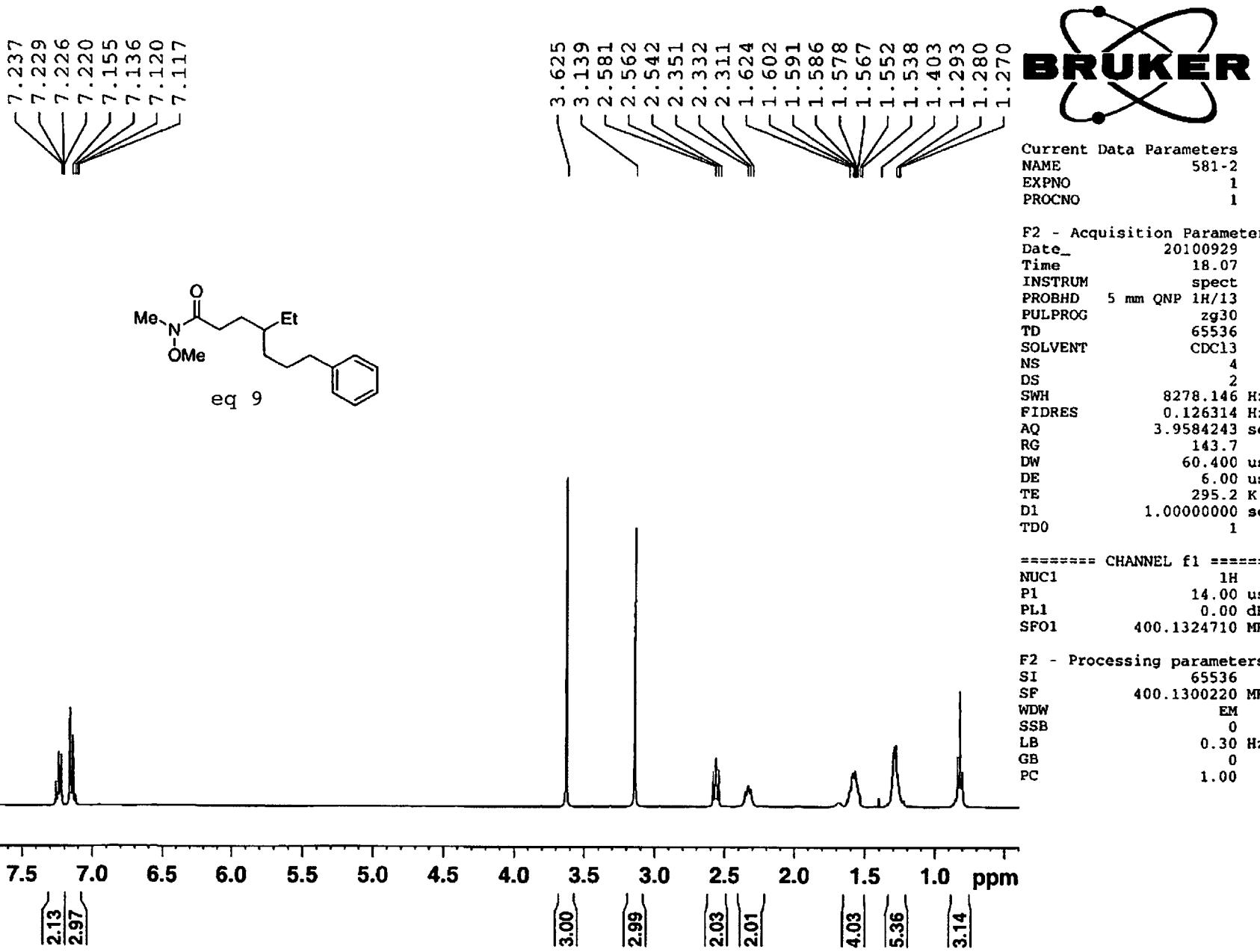
BRUKER

Current Data Parameters
NAME 589-1proton
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110310
Time 14.31
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 10
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 287.4
DW 60.400 usec
DE 6.00 usec
TE 683.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 65536
SF 400.1300220 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00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1.578
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1.552
1.538
1.403
1.293
1.280
1.270
BRUKER
Current Data Parameters
NAME 581-2
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20100929
Time 18.07
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 4
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 143.7
DW 60.400 usec
DE 6.00 usec
TE 295.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 65536
SF 400.1300220 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
Me
N
OMe
O
Et
eq 9
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6.0
5.5
5.0
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4.0
3.5
3.0
2.5
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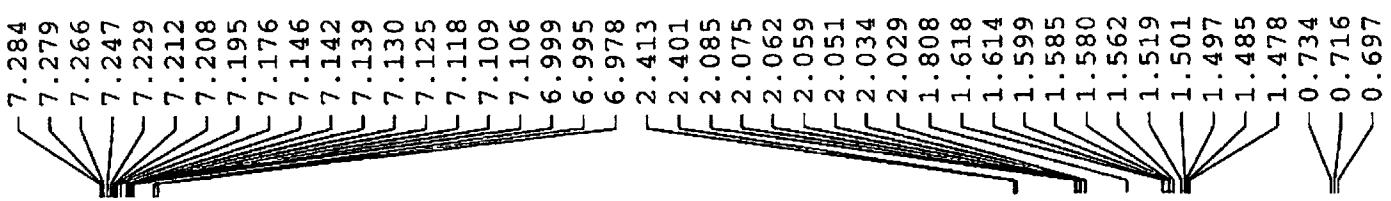
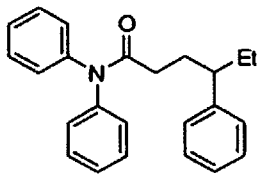
2.03
2.01
4.03
5.36
3.14





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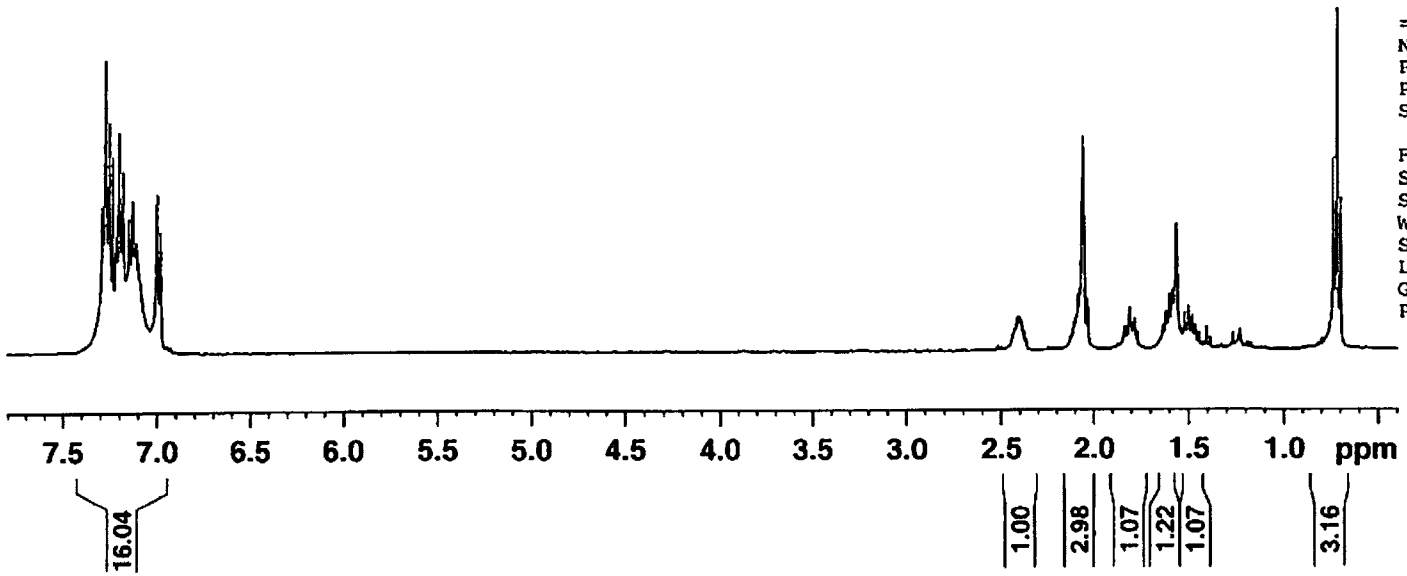
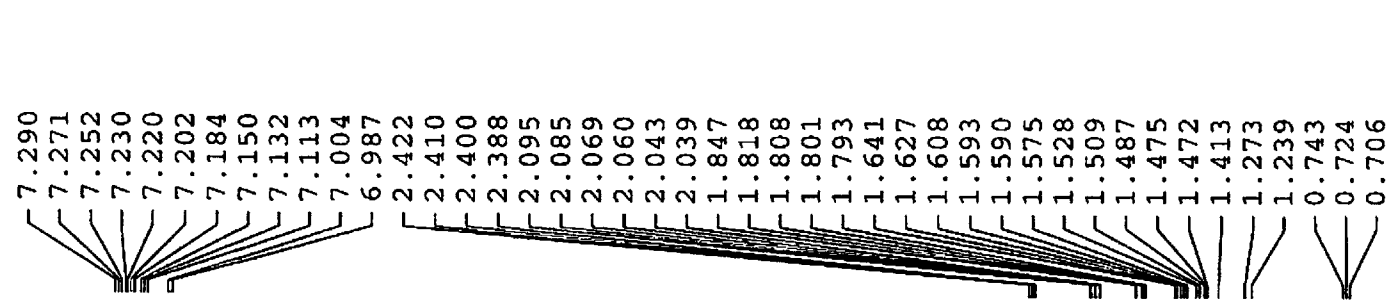


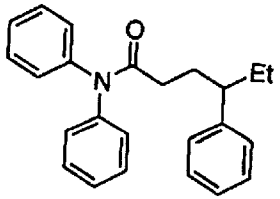

```
Current Data Parameters
NAME          852proton
EXPNO                 1
PROCNO                1

F2 - Acquisition Parameters
Date_          20110720
Time              17.53
INSTRUM           spect
PROBHD   5 mm QNP 1H/13
PULPROG             zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH            8278.146 Hz
FIDRES        0.126314 Hz
AQ            3.9584243 sec
RG               5160.6
DW               60.400 usec
DE                6.00 usec
TE               683.2 K
D1           1.00000000 sec
TD0                   1

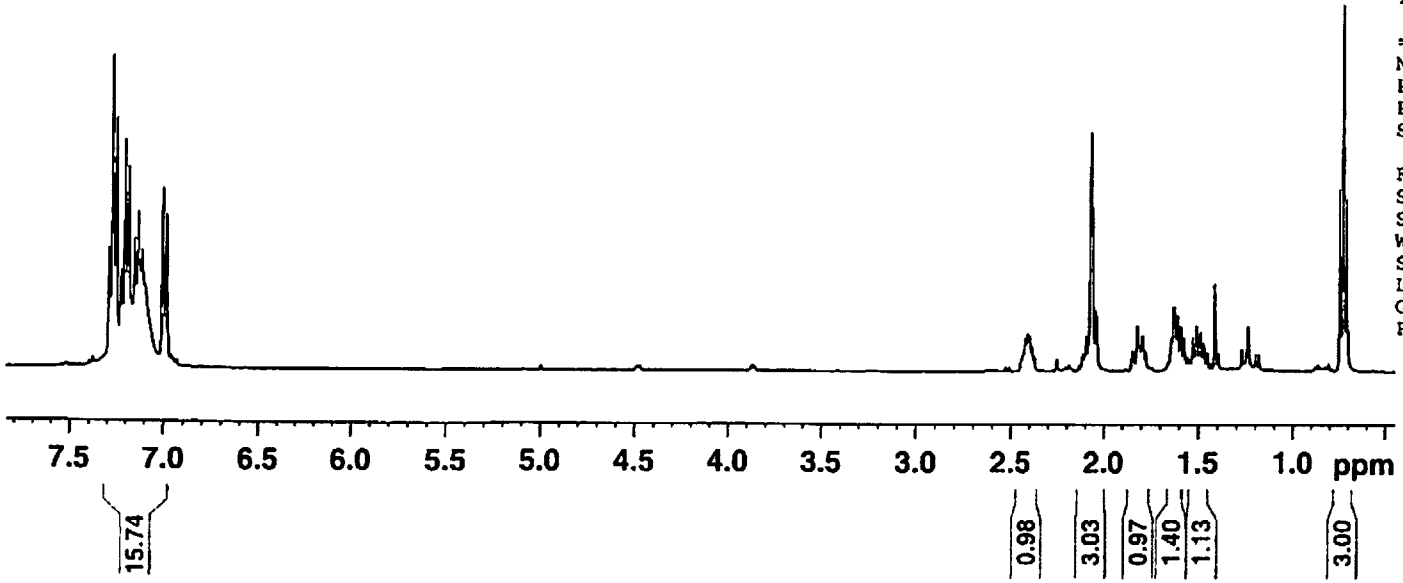
======== CHANNEL f1 ========
NUC1                 1H
P1                14.00 usec
PL1                0.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                65536
SF          400.1300220 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
```





eq 11

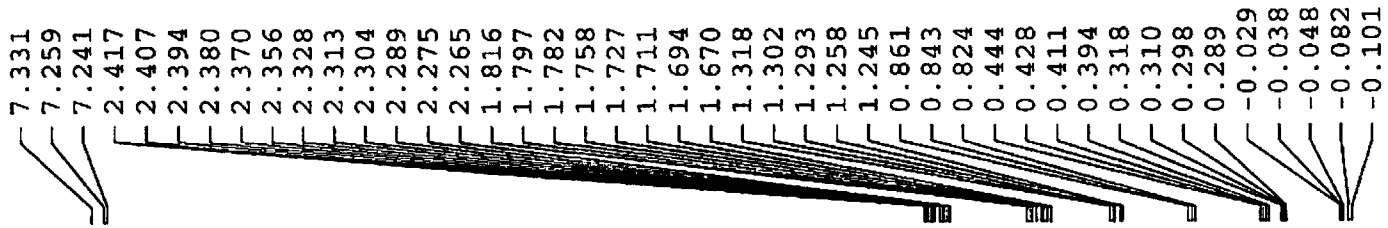


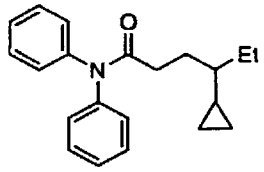
Current Data Parameters
NAME 858-1
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110822
Time 15.25
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 3
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 3251
DW 60.400 usec
DE 6.00 usec
TE 683.2 K
D1 1.00000000 sec
TD0 1

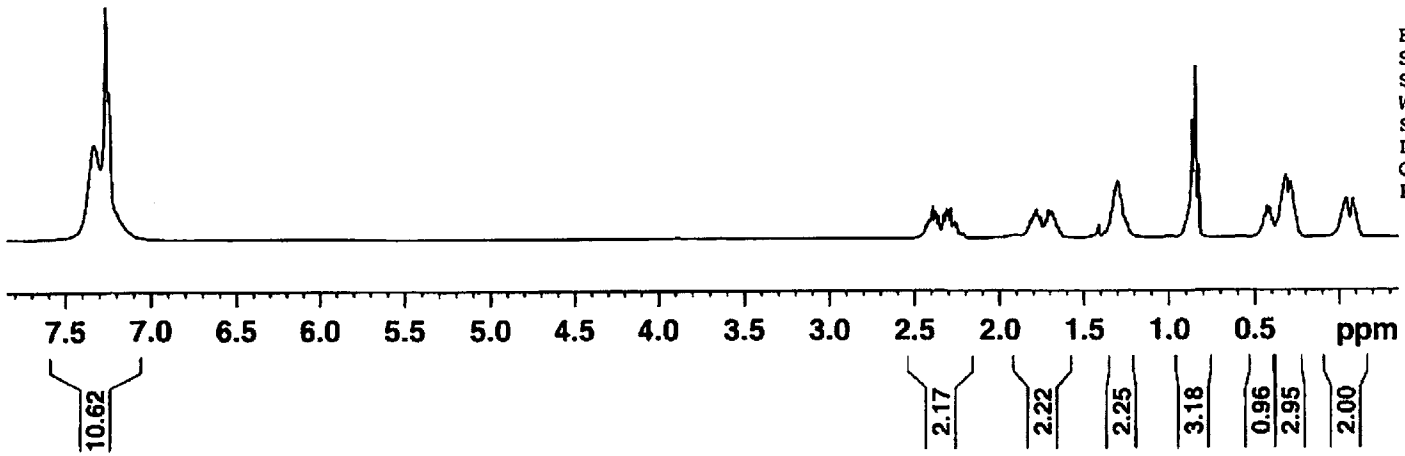
======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 65536
SF 400.1300220 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00





eq 12

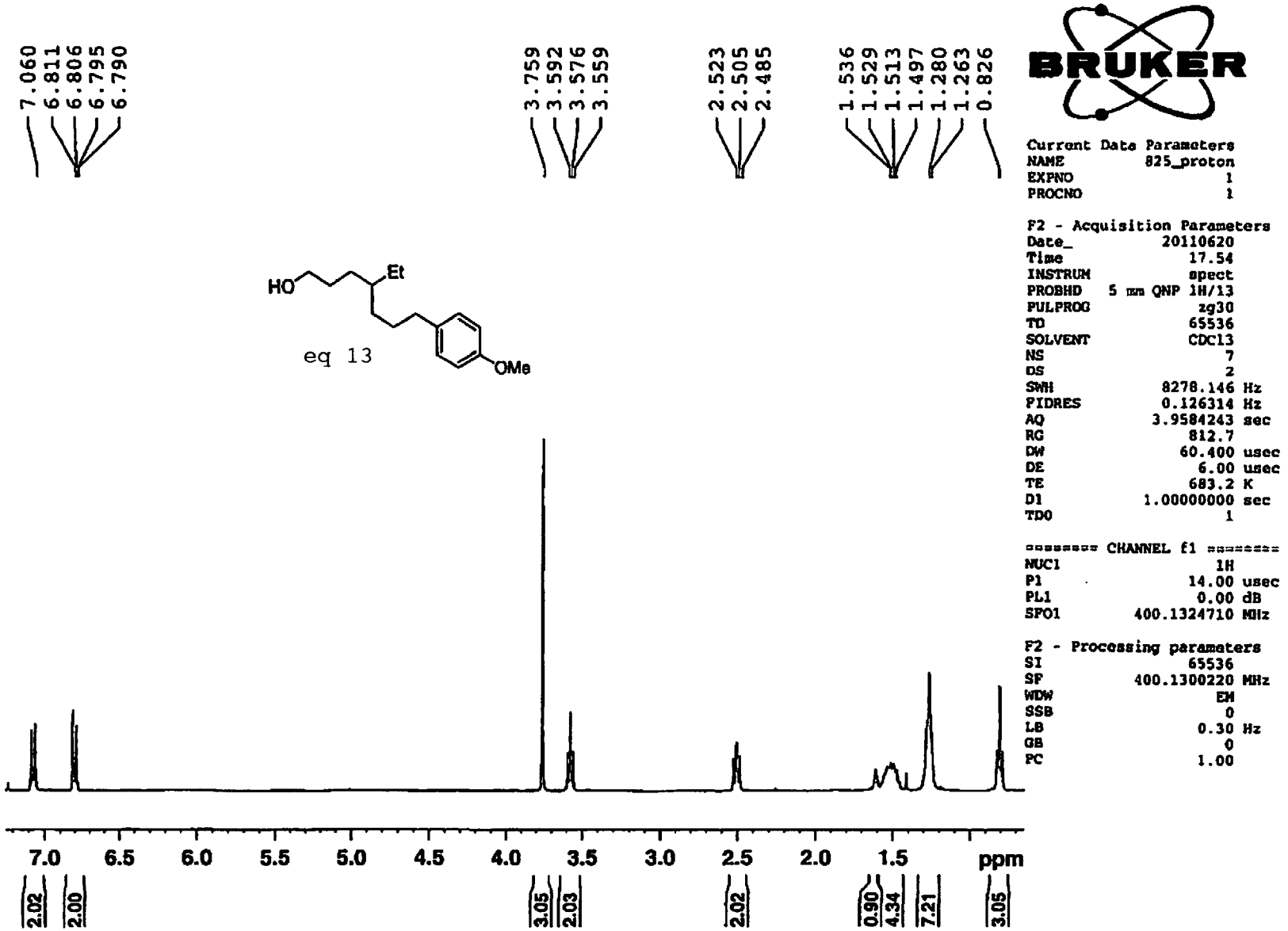


Current Data Parameters
NAME 815-2proton
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110530
Time 14.14
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 4
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9584243 sec
RG 114
DW 60.400 usec
DE 6.00 usec
TE 683.2 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 14.00 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 65536
SF 400.1300220 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00



BRUKER

Current Data Parameters
NAME 825_proton
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 20110620
Time 17.54
INSTRUM spect
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 65536
SOLVENT CDCl3
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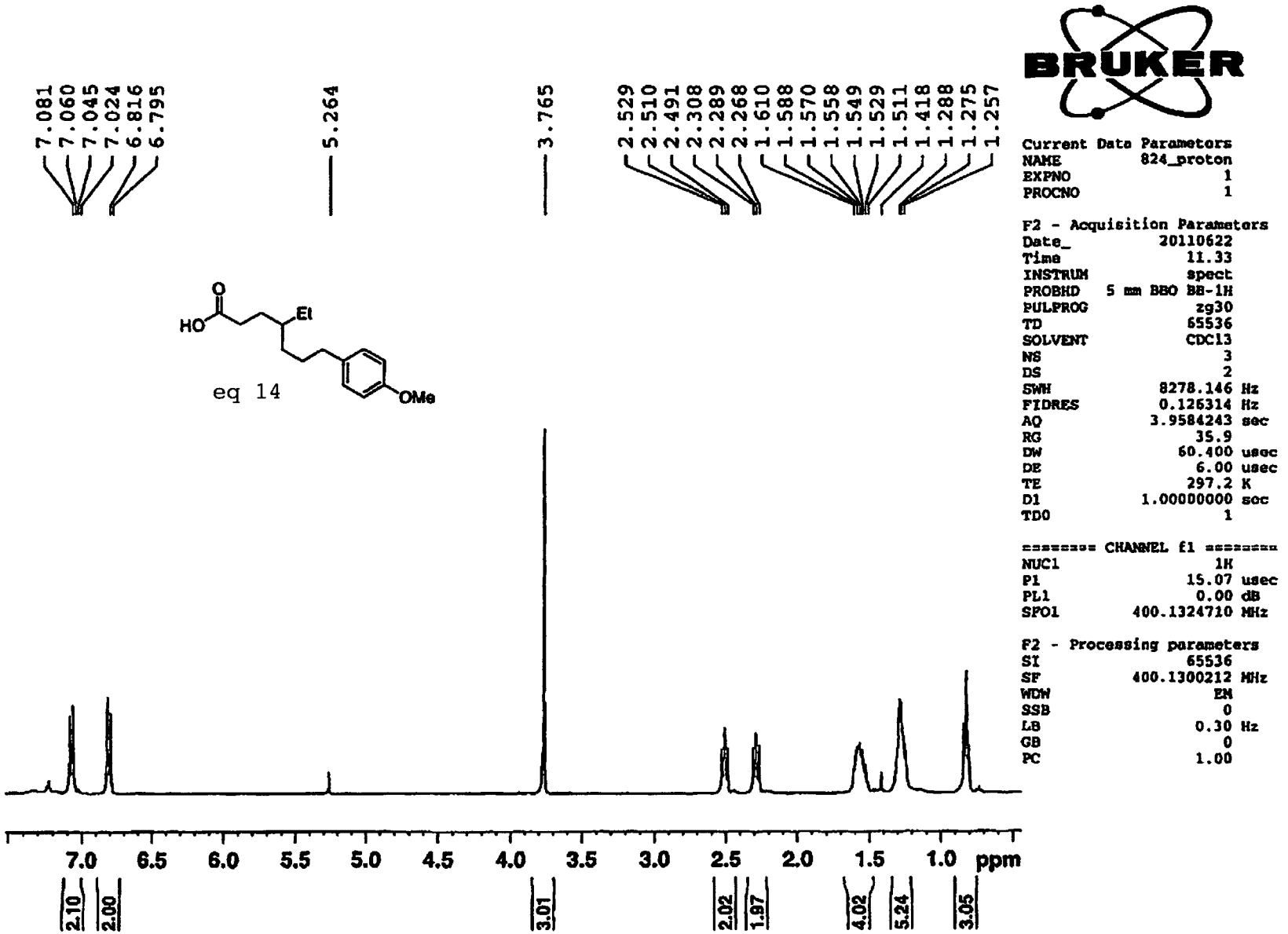
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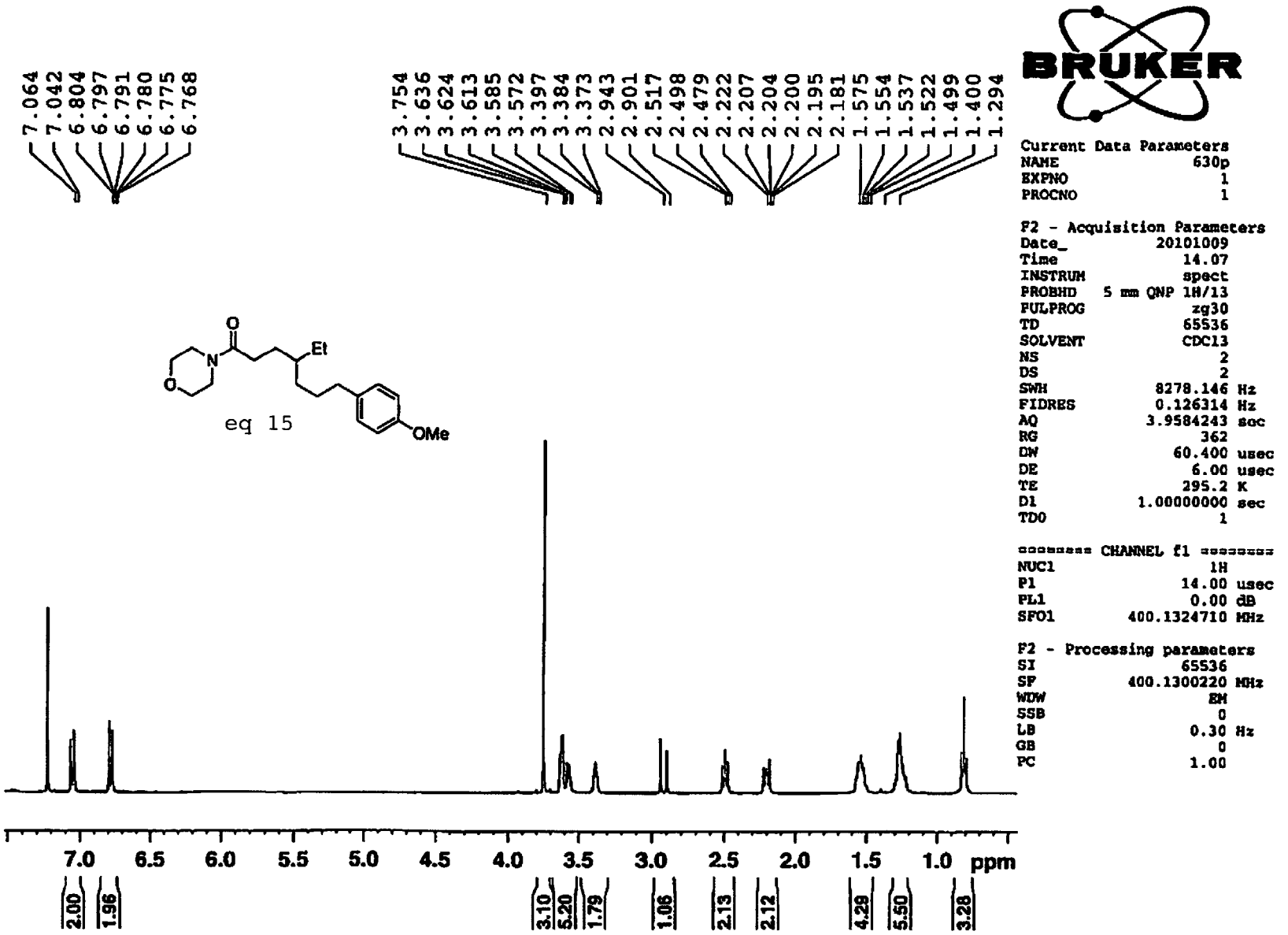

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Section 1.2

Nickel-Catalyzed Carbon–Carbon Bond-Forming Reactions of Unactivated Tertiary Alkyl Halides: Suzuki Arylations

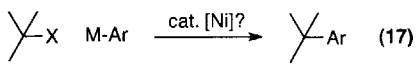
A. Introduction

While considerable progress has been made in the area of metal-catalyzed cross-couplings of primary and secondary alkyl electrophiles over the past two decades,[1] there are only a handful of reports on cross-couplings of tertiary alkyl electrophiles. The challenges often associated with cross-coupling tertiary alkyl halides include their susceptibility to decomposition through elimination pathways, as well as the low propensity of tertiary alkyl halides toward oxidative addition through S_N2 or direct insertion pathways. Notably, Oshima has disclosed cross-couplings of unactivated tertiary alkyl halides with indenyllithium (Ag catalyst), cyclopentadienylmagnesium (Cu), benzylmagesium (Ag), allylmagnesium (Co, Cu and Ag), and allyl- and benzylzinc reagents (Ag).[36] There are still considerable improvements to be made; in Oshima's reports, functional group tolerance on the electrophilic reaction partner is generally unexplored, and the nucleophile scope is limited to one or two specific nucleophiles per report.

The Fu group and others propose that in nickel-catalyzed cross-couplings of secondary alkyl halides, oxidative addition occurs via a single electron transfer pathway; halide abstraction generates a secondary alkyl radical that subsequently combines with nickel (Oshima proposes radical intermediates as well, in the case of his silver, cobalt and copper catalysts).[1c,1d,15,16,18] We speculated that tertiary alkyl halides, which could generate relatively stable tertiary alkyl radicals in the course of a single electron transfer oxidative addition pathway, may be suitable

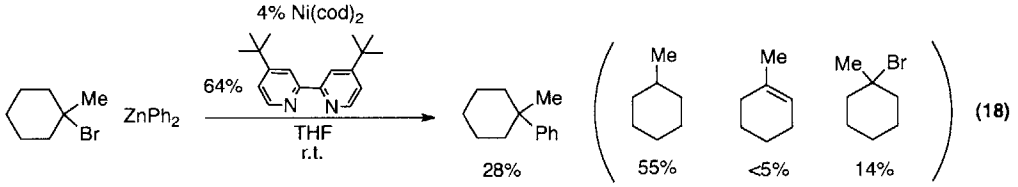
[36] For examples of cross-couplings (not Heck reactions or other related processes) that provide >50% yield with an unactivated tertiary alkyl halide other than a 1-haloadamantane (which cannot eliminate HX), see: (a) allylmagnesium (cobalt): Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.*, **2002**, *41*, 4137–4139; Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J.* **2004**, *10*, 5640–5648. (b) allyl- and benzylmagnesium (silver): Someya, H.; Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 969–971; Mitamura, Y.; Someya, H.; Yorimitsu, H.; Oshima, K. *Synlett* **2010**, 309–312. (c) cyclopentadienylmagnesium (copper): Sai, M.; Someya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2008**, *10*, 2545–2547. (d) allylmagnesium (copper): Sai, M.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 1194–1196. (e) allyl- and benzylzinc (silver): Mitamura, Y.; Asada, Y.; Murakami, K.; Someya, H.; Yorimitsu, H.; Oshima, K. *Chem. Asian J.* **2010**, *5*, 1487–1493. (f) indenyllithium (silver): Someya, H.; Yorimitsu, H.; Oshima, K. *Tetrahedron*, **2010**, *66*, 5993–5999.

candidates for nickel-catalyzed cross-coupling processes. With respect to choice of nucleophilic reaction partner, aryl nucleophiles were initially targeted (eq 17); alkyl, alkenyl, and alkynyl nucleophiles were considered to be potentially more challenging coupling partners, due to their ability to undergo side reactions such as β-hydride elimination (alkyl & and alkenyl nucleophiles) and migratory insertion (alkenyl & alkynyl nucleophiles).

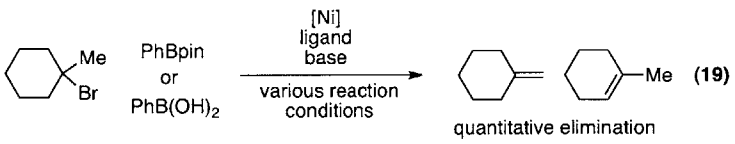


(17)

In 2004, the Fu group explored nickel-catalyzed Negishi cross-couplings of unactivated tertiary alkyl halides with organozinc reagents. After a one-year investigation of diarylzinc reagents, arylzinc halides, and, briefly, alkylzinc halides, the best result that was achieved employed an unactivated tertiary alkyl bromide, diphenylzinc and 64% ligand loading; the cross-coupled product was attained in 28% yield (eq 18). Hydrodehalogenation of the tertiary alkyl bromide was the predominant side-product, and in cases with reduced ligand loading, hydrodehalogenation was even more problematic. Suzuki cross-couplings using phenyl-Bpin and



(18)



(19)

phenylboronic acid were also attempted, but quantitative elimination of the tertiary alkyl bromide was observed (eq 19). This is likely caused by the presence of alkoxide base in the reaction mixture, which is required to activate boranes for Suzuki cross-couplings. Additionally,

various *activated* tertiary alkyl halides were explored in the Fu group in 2008, but either no product, or substantial product due to background reactions, was observed.

By 2011, the Fu group had reported several methods for nickel-catalyzed Suzuki couplings of secondary alkyl halides with 9-BBN reagents.[8,11,12,13,37,38] Interestingly, while earlier reports of nickel-catalyzed reactions with secondary alkyl halides and *boronic acids* use an excess of alkoxide base relative to the boronic acid,[39] in all reports using 9-BBN reagents, less alkoxide base is required relative to the 9-BBN reagent. Additionally, it was established that the reaction conditions with 9-BBN reagents and alkoxides are not highly Brønsted basic, due to complexation of the alkoxide to the trivalent borane.[36] Thus, it was speculated that it may be possible to develop a nickel-catalyzed Suzuki cross-coupling of unactivated tertiary alkyl halides with aryl-(9-BBN) reagents. Indeed, in preliminary studies where an unactivated tertiary alkyl bromide was stirred with an equivalent of phenyl-(9-BBN) and an equivalent of a primary alkoxide base in diethyl ether at room temperature (the phenyl-(9-BBN) and the base were premixed for ten minutes prior to addition of the electrophile), relatively little electrophile decomposition was observed over the course of ten hours.

Prior to the initiation of this project, a nickel-catalyzed reaction was being developed in the Fu group where alkyl halides were cross-coupled with bis(pinacolato)diboron to generate alkyl boronic esters. It was found that not only unactivated primary and secondary alkyl halides were viable cross-coupling partners, but that unactivated tertiary alkyl bromides reacted to form tertiary boronic esters.[40] However, when bis(pinacolato)diboron was substituted with phenyl-

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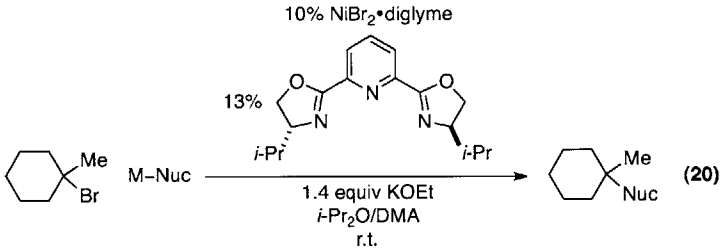
[37] Saito, B.; Fu. G. C.; *J. Am. Chem. Soc.* **2007**, *129*, 9602–9603.
[38] Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027–11029.
[39] a) Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340–1341. b) González-Bobez, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360–5361.
[40] Dudnik, A. S.; Fu, G. C. *J. Am. Chem. Soc.* **2012**, *134*, 10693–10697.

(9-BBN) in the effort to develop a C–C bond-forming reaction, none of the desired product was obtained (eq 20).



M–Nuc	yield (%)
pinB–Bpin	67%
(9-BBN)–Ph	0%

Thus, efforts were turned toward developing a tertiary alkyl carbon–carbon bond-forming process from the ground up, beginning with an exploration of ligands.

B. Results and Discussion

The project commenced with a survey of ligand classes that have been utilized for other nickel-catalyzed cross-coupling reactions with alkyl electrophiles, including pybox, diamine, amino alcohol, bisoxazoline, terpyridine and bipyridine ligands (Figure 2). The reaction conditions chosen for this ligand screen were based on common conditions for nickel-catalyzed Suzuki–Miyaura cross-couplings of unactivated *secondary* alkyl halides. While reactions with unactivated secondary alkyl halides typically proceed at room temperature, the reaction temperature chosen here was 70 °C, as it was postulated that tertiary alkyl electrophiles might have more sluggish reactivity compared to secondary alkyl electrophiles. While most ligands in this screen afforded 1-2% GC calibrated yields, bathophenanthroline resulted in 3% yield, and, most promisingly, 2,2'-bypyridine afforded a leading 5% yield. Importantly, bathophenanthroline and 2,2'-bypyridine were the only ligands surveyed that afforded yields

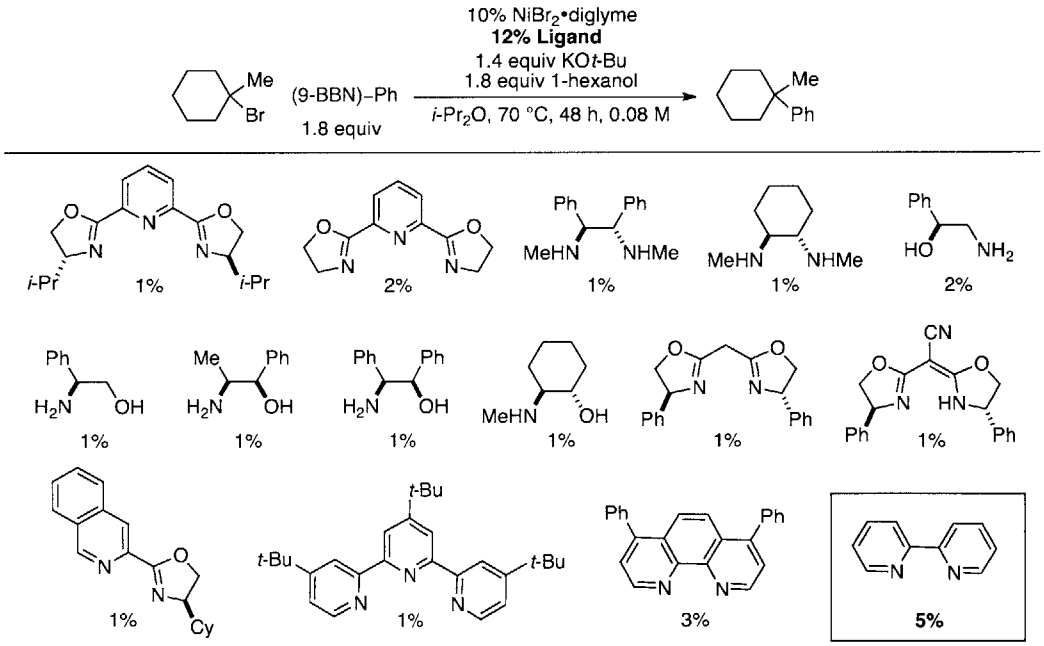
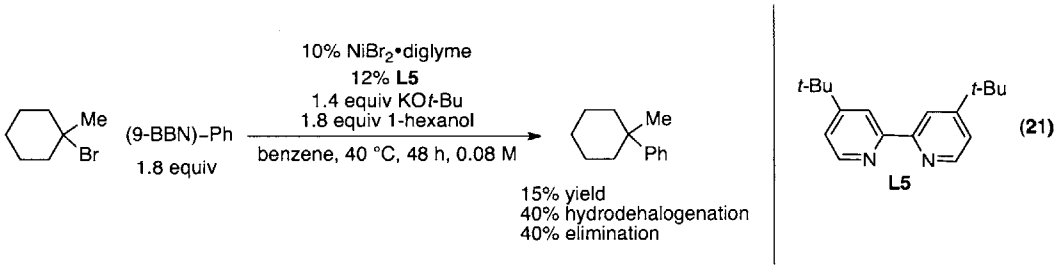


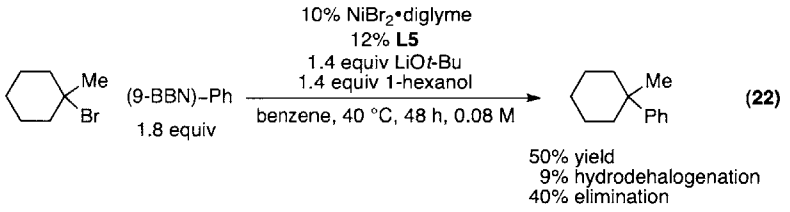
Figure 2. Yields in an initial ligand screen using common reaction conditions for nickel-catalyzed Suzuki reactions with unactivated *secondary* alkyl halides.

above a background reaction conducted in the presence of nickel and in the absence of a ligand.

The fate of the tertiary alkyl bromide was monitored by GC analysis and used as a predictive tool for improving the reaction conditions. The reaction in Figure 2 with 2,2'-bypyridine resulted in complete electrophile conversion, partitioned between approximately 70% elimination, 25% hydrodehalogenation, and 5% product formation. The starting material conversion, coupled with the large degree of decomposition via elimination, served as an impetus to explore lower reaction temperatures. Hydrodehalogenation was postulated to result from tertiary alkyl radical abstraction of a hydrogen atom from the solvent, diisopropyl ether; this resulted in a movement toward solvents that do not contain abstractable hydrogen atoms, such as benzene, trifluorotoluene, hexanes, and *t*-amyl alcohol. A ligand survey of bathophenanthroline variants and 2,2'-bypyridine variants, employing the aforementioned changes to reaction conditions, resulted in a new lead of 15% yield in benzene, using the ligand 4,4'-d*i*-*tert*-butyl-2,2'-bipyridyl (**L5**; eq 21).

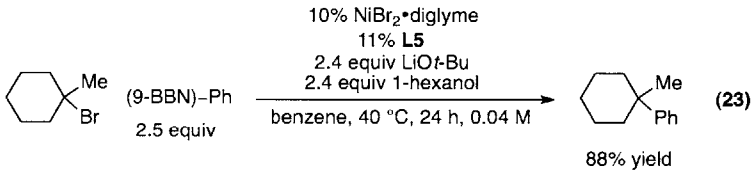


Under these improved reaction conditions, hydrodehalogenation of the tertiary alkyl bromide in benzene was still problematic. For reasons that are difficult to rationalize, the hydrodehalogenated side product was dramatically reduced after substituting KO*t*-Bu with LiO*t*-Bu, resulting in a new lead of 50% yield (eq 22).



(22)

Additional alterations to the reaction parameters, particularly, decreasing concentration and increasing the equivalents of nucleophile, base, and alcohol, led to the optimized reaction conditions (88% yield; eq 23). It should be noted that, while optimization from Figure 2 to the

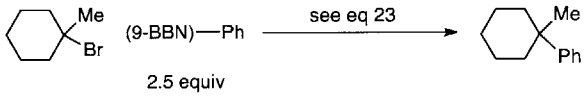


(23)

final reaction conditions appears to be relatively straightforward, there were also numerous failed attempts to optimize this reaction through more drastic variations to the reaction conditions. Regarding the aryl nucleophile, diphenylzinc, Grignard reagents, a cyclic triolborate, phenyl boronic acid, numerous phenyl boronic esters, and numerous silyl reagents were explored; these reagents resulted in yields from 0–5%. Additionally, in the course of optimization, solvents and ligands that initially appeared to be possible contenders with benzene and 4,4'-di-*tert*-butyl-2,2'-bipyridine were continuously reexamined under the concurrent leading reaction conditions. However, high yields were never observed with solvents trifluorotoluene, *t*-amyl alcohol, or hexanes, and phenanthroline and 2,2'-bipyridine variants always afforded inferior results compared to 4,4'-di-*tert*-butyl-2,2'-bipyridine.

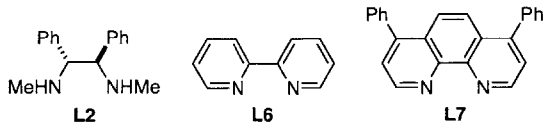
As illustrated in Table 3, no reaction occurs in the absence of nickel (entry 2), and in the presence of nickel and in the absence of ligand, no catalyst turnover is achieved (entry 3). The presence of the base, LiO*t*-Bu, is required for reactivity (entry 4), and, interestingly, under the finalized reaction conditions, substituting LiO*t*-Bu with K- or NaO*t*-Bu results in only trace

Table 3. Optimized conditions for the nickel-catalyzed cross-coupling of tertiary alkyl halides, and the effects of changes to the reaction parameters.



entry	variation from the "standard" conditions	yield (%)[a]
1	none	**88**
2	no $NiBr_2$·diglyme	<2
3	no **L5**	8
4	no LiO*t*-Bu	<2
5	**L2**, instead of **L5**	7
6	**L6**, instead of **L5**	72
7	**L7**, instead of **L5**	63
8	KO*t*-Bu or NaO*t*-Bu, instead of LiO*t*-Bu	<2
9	toluene, instead of benzene	45
10	cyclohexane, instead of benzene	34
11	Et_2O, instead of benzene	13
12	1.8 equiv of (9-BBN)–Ph[b]	62
13	5% $NiBr_2$·diglyme, 5.5% **L5**	53
14	0.1 equiv H_2O	89

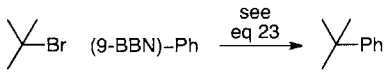
[a] The yield was determined by GC analysis versus a calibrated internal standard (average of two experiments).
[b] 1.7 equiv LiO*t*-Bu, 1.7 equiv *i*-BuOH.

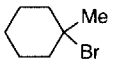
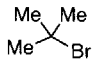
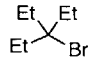
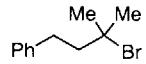
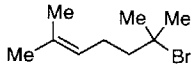
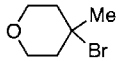
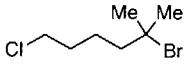
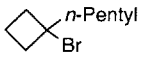
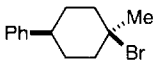


yield (entry 8). A 1,2-diamine, DMPEDA, which has been used for all other reports of nickel-catalyzed cross-couplings of unactivated secondary halides with 9-BBN reagents, affords little product in the cross-coupling of unactivated tertiary alkyl halides (entry 5). Ligands 2,2'-bipyridine and bathophenanthroline do lead to product formation, albeit in lower yields compared to *tert*-butyl-2,2'-bipyridine (entries 6 and 7). For the solvents toluene, cyclohexane,

and diethyl ether, product formation proceeds in considerably lower yields (entries 9–11). Additionally, lower catalyst loading and reduced equivalents of nucleophile resulted in lower yields (entries 12 and 13). Lastly, the reaction is not highly moisture sensitive (entry 14); however, the reaction is quite air sensitive.

Table 4. Cross-couplings of tertiary alkyl bromides with Ph-(9-BBN): Scope of the electrophile.

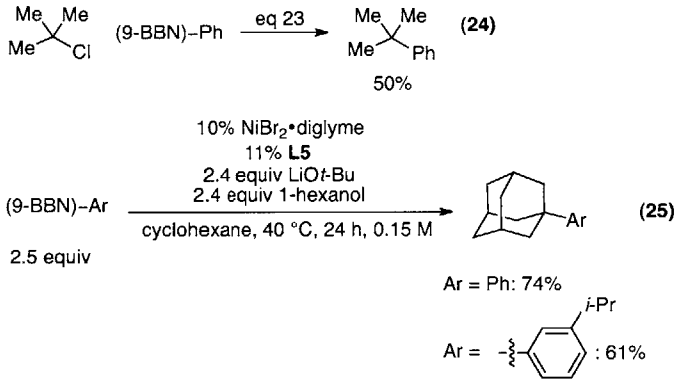


entry	tertiary alkyl bromide	yield (%)[a]
1		84
2		71 (84)[b]
3		70
4		86
5		76
6		57
7		67
8		53
9		73[c]

[a] Isolated yields (averages of two experiments). [b] Yield in parentheses is a GC yield using a calibrated internal standard. [c] Product is a 1.2:1 ratio of diastereomers.

The scope of the reaction with respect to the electrophile was preliminarily examined during the course of reaction optimization, in order to ensure that it would extend beyond 1-bromo-1-methylcyclohexane. Table 4 depicts the electrophile scope under the final reaction conditions. In addition to 1-bromo-1-methylcyclohexane (entry 1), *t*-butylbromide (entry 2) and more hindered 3-bromo-3-ethylpentane (entry 3) are suitable substrates. Furthermore, the functional groups aryl, alkenyl, ether, and primary alkyl chloride are well tolerated (entries 4–7). An electronically distinct tertiary cyclobutyl bromide can be coupled (entry 8). Lastly, the cross-coupling of a single diastereomer of a tertiary alkyl bromide leads to a mixture of two product diastereomers (1.2:1; entry 9), consistent with the hypothesis that oxidative addition occurs through a tertiary alkyl radical intermediate.

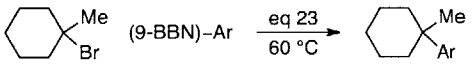
With respect to successes with other unactivated tertiary alkyl halides, a preliminary study revealed that cross-coupling product can be achieved with an unactivated tertiary alkyl chloride; however, the yield is rather low compared to the corresponding bromide (eq 24, GC calibrated yield). Furthermore, while unactivated tertiary alkyl iodides were found to decompose by elimination under the reaction conditions, 1-iodoadamantane, which is incapable of decomposing by elimination, was a viable substrate in the cross-coupling reaction (eq 25). Interestingly, this substrate exhibited a strong background reaction with benzene when it was used as the solvent, which was tested by running a reaction in benzene-d_6. Therefore, this reaction was instead optimized in cyclohexane, where the reaction concentration was increased to 0.15 M. 1-Bromoadamantane, in contrast, was completely unreactive in both benzene and cyclohexane.

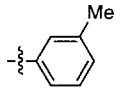
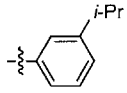
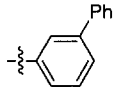
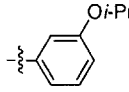
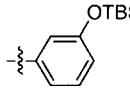


Under the optimized reaction conditions, classically activated tertiary alkyl halides were also tested. Tertiary benzylic chloride (2-chloropropan-2-yl)benzene provided no cross-coupled product, and a considerable amount of electrophile homocoupling was observed. Several tertiary bromides containing carbonyl groups in the α-position relative to the bromide resulted in electrophile decomposition, and no cross-coupled product.

A major limitation to the scope of unactivated tertiary alkyl bromides for this reaction rests on the stability of the tertiary alkyl bromide itself. Some functional groups are merely not tolerated in the presence of an unactivated tertiary alkyl bromide (e.g., amines), and therefore, these electrophiles cannot be synthesized. While a tertiary alkyl bromide containing a dialkylketone was successfully synthesized, the substrate began to decompose upon standing within an hour after purification. Additionally, it is most straightforward to purify unactivated tertiary alkyl bromides by distillation, but this purification method has limitations with respect to molecular weight. The compounds can be purified by flash chromotagraphy, however, fast flow rates must be used in order to limit decomposition by elimination (therefore, automated chromatography is recommended).

Table 5. Cross-couplings of tertiary alkyl bromides with Ar-(9-BBN): Scope of the nucleophile.



entry	Ar	yield (%)[a]
1		60
2		61
3		74
4		57
5		54

[a] Isolated yields (averages of two experiments).

The scope of the nucleophilic reaction partner proved to be more challenging to develop compared to the electrophile scope. Interestingly, some aryl-(9-BBN) substrates containing meta-substitution were successful reaction partners (Table 5). Phenyl-(9-BBN) substrates containing alkyl, aryl, and alkoxy substitution in the meta-position were found to be viable. Fortunately, this set of products is particularly interesting, because they cannot be accessed directly through Friedel-Crafts reactions. The optimal temperature for these reactions was determined to be 60 °C; otherwise, the reaction conditions are the same as those with

phenyl-(9-BBN) in eq 23.

Numerous other aryl-(9-BBN) reagents were synthesized and tested; however, these substrates afforded little to no product formation (Figure 3). Limitations with respect to the nucleophile scope remain difficult to rationalize. Rather then having a common theme for their lack of reactivity, different nucleophiles may fail for a variety of reasons, including varied steric or electronic natures, as well as the presence of readily abstractable hydrogens on the nucleophile, which may not be well-tolerated in the presence of a proposed tertiary alkyl radical reaction intermediate.

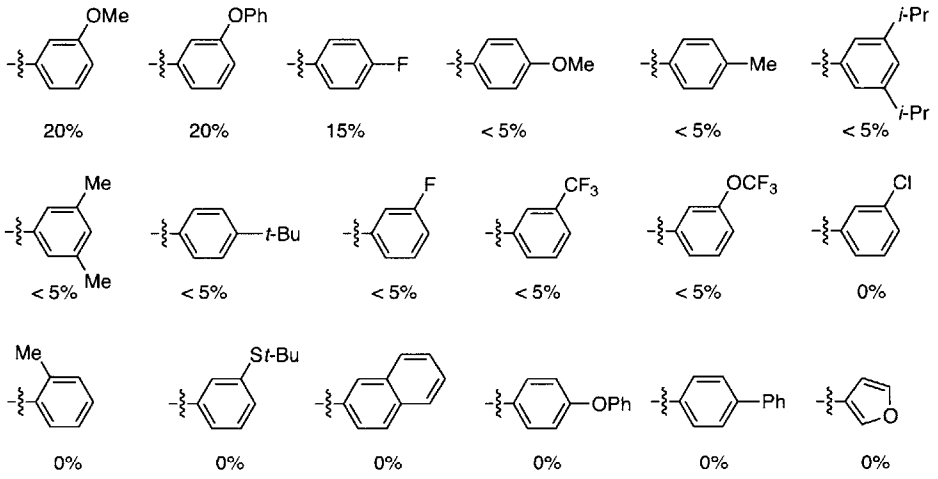
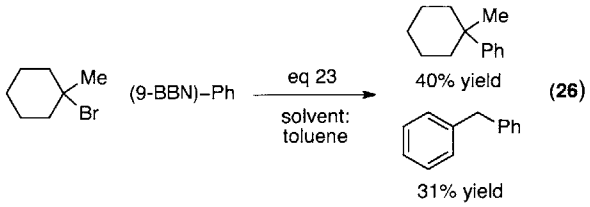


Figure 3. Yields of nonviable nucleophiles tested under the reaction conditions in eq 23 (60 °C).

When the tertiary alkyl halide cross-coupling reaction was conducted in toluene instead of benzene, a large quantity of the side-product diphenylmethane was isolated, in addition to a low yield of the desired cross-coupled product (eq 26). The formation of diphenylmethane



(26)

provides support for the existence of a tertiary radical intermediate in this cross-coupling reaction, which, in the presence of toluene, is capable of abstracting a hydrogen atom from toluene to generate a tolyl radical intermediate. This intermediate could then react with phenyl-(9-BBN) to generate diphenylmethane. Nickel-catalyzed cross-couplings of *secondary* alkyl halides are all conducted in solvents that contain abstractable hydrogen atoms. The fact that, in the case of tertiary alkyl halides, toluene is a problematic solvent, attests to presumably long-lived tertiary radical intermediates that undergo slow bond formation with nickel, and thus have a propensity to participate in side-reactions. Another possibility is that the bond between nickel and a tertiary alkyl group is likely to be weak, and therefore, homolysis to generate tertiary alkyl radicals, at some stage along the catalytic cycle, occurs readily.

C. Conclusion and Future Outlook

The first Suzuki–Miyaura cross-coupling of tertiary alkyl halides has been described. Specifically, unactivated tertiary alkyl bromides are coupled with aryl-(9-BBN) reagents using a nickel/bipyridine catalyst system. The use of a solvent, benzene, that does not contain readily abstractable hydrogen atoms, was found to be critical for the success of this reaction, which is postulated to occur through a tertiary radical intermediate. Additionally, as tertiary alkyl halides are prone to decomposition via elimination under Brønsted basic reaction conditions, it was important to attenuate the basicity of this Suzuki reaction by employing 9-BBN reagents, which strongly coordinate an alkoxide that is required for transmetalation.

With respect to reaction scope, movement to systems that employ tertiary alkyl electrophiles that are less prone to elimination could enable an expansion of functional group tolerance. The increased stability of these electrophiles could arise from the nature of the leaving group (e.g., using ethers in place of halides), or due to the presence of stabilizing neighboring groups (e.g., replace a generic alkyl group with a $-CF_3$ group: this was briefly explored in our group and may warrant a return in the future). It remains difficult to propose how to improve nucleophile scope, but in the exploration of new catalyst systems for cross-coupling tertiary alkyl halides, new insights may lead to improved scope.

D. Experimental

I. General Information

The following reagents were purchased and used as received: $NiBr_2$•diglyme (Aldrich; note: hygroscopic), 4,4'-di-*tert*-butyl-2,2'-bipyridine (Aldrich), LiO*t*-Bu (Aldrich, 97%; Strem, 98%), *i*-BuOH (Aldrich; anhydrous), benzene (Aldrich; anhydrous), 2-bromo-2-methylpropane (Aldrich), and 2-chloro-2-methylpropane (Aldrich). Other tertiary alkyl bromides were prepared from the corresponding alcohols, using LiBr and HBr.[41]

All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen. GC analyses were obtained on an HP 6890 Series GC System with a DB-1 column (length 30 m, internal diameter 0.25 mm).

II. Preparation of Electrophiles

The procedure and the yields have not been optimized.

General procedure. In accordance with the literature procedure,[41] at 0 °C, hydrobromic acid (2 equiv) was added dropwise to a round-bottom flask containing lithium bromide (2 equiv), and the tertiary alcohol (1 equiv). The mixture was stirred for 2 h and monitored for disappearance of starting material by GC. The solution was then transferred to a separatory funnel, where the crude tertiary bromide was extracted twice with diethyl ether, dried with magnesium sulfate, filtered and concentrated. The tertiary bromide was distilled under reduced pressure (employment of a vigreux column is suggested; the crude bromides are prone to bumping under reduced pressure).

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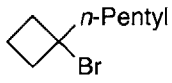
[41] Masada, H.; Murotani, Y. *Bull. Chem. Soc. Jpn.*, **1980**, *53*, 1181–1182.



1-Bromo-1-pentylcyclobutane. This compound was made according to the general procedure, using 1-pentylcyclobutanol (71.3 mmol).[42] The product was distilled at 73 °C at 20 Torr. Colorless oil (10.6 g, 52.0 mmol, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.67–2.60 (m, 2H), 2.38–2.31 (m, 2H), 2.20–2.09 (m, 1H), 1.87–2.77 (m, 3H), 1.49–1.42 (m, 2H), 1.35–1.25 (m, 4H), 0.87 (t, 3H, J = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 69.0, 44.1, 40.1, 31.6, 25.8, 22.6, 17.1, 14.1.

FT-IR (film) 2932, 2859, 1466, 1240, 1140, 856, 424, 407 cm^{-1}.

LRMS (EI) *m/z* (M^+) calcd for $C_9H_{17}Br$: 204, 206, found: 204, 206.

III. Preparation of *B*-Aryl-(9-BBN) Reagents

The procedures and the yields have not been optimized.

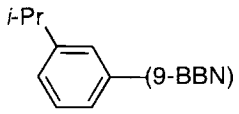
Whereas we routinely purified the aryl-(9-BBN) reagents by distillation, we have determined that the reagents can be used without purification by distillation, at the expense of a ~10% reduction of yield in the cross-coupling reaction.

General Procedure for the synthesis of non-commercially available arylmagnesium bromides. Magnesium turnings (417 mg, 17.2 mmol, 1.1 equiv) and a crystal of iodine were added to a flame-dried two-neck round-bottom flask under a positive pressure of nitrogen. The dry magnesium turnings and iodine were allowed to stir under the nitrogen atmosphere for 2 h. THF (anhydrous; 20 mL) was added, and the reaction was allowed to stir until the iodine color

[42] Leroux, Y.; Normant, H. *Comptes Rendus des Seances de l'Academie des Sciences, Serie C: Sciences Chimiques,* **1967**, *265*, 1472–1474.

disappeared. A solution of the aryl bromide (17.2 mmol) in 4 mL of anhydrous THF was then added dropwise over 5 min. The mixture was stirred at 40 °C for 3 h. The reaction was then titrated according to a literature procedure,[43] and the Grignard reagent in THF was used directly in the synthesis of the corresponding aryl-(9-BBN) reagent.

General Procedure for the synthesis of aryl-(9-BBN) reagents from arylmagnesium bromides. The aryl-(9-BBN) reagents were prepared by following a literature procedure for the synthesis of phenyl-(9-BBN) via the reaction of phenylmagnesium bromide with *B*-methoxy-(9-BBN) (Aldrich; 1 M in hexanes).[35] (m-Tolyl)-(9-BBN) was also prepared according to a literature procedure.[44]



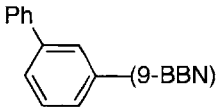
(1s,5s)-9-(3-Isopropylphenyl)-9-borabicyclo[3.3.1]nonane. Prepared from 3-(isopropylphenyl)magnesium bromide (25.1 mmol). The product was distilled at 96°C at 100 mTorr. Colorless oil (3.2 g, 13.4 mmol, 53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.91 (m, 2H), 7.57–7.50 (m, 2H), 3.10 (sept, 1H, J = 6.7 Hz), 2.44–2.42 (m, 2H), 2.18–2.06 (m, 6H), 2.00–1.91 (m, 4H), 1.43 (d, 6H, J = 8.0 Hz), 1.49–1.36 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 132.8, 132.3, 131.0, 128.1, 34.4, 34.3, 29.3, 24.2, 23.6.

^{11}B NMR (128 MHz, $CDCl_3$) δ 80.

[43] Krasovskiy, A.; Knochel, P. *Synthesis*, **2006**, *5*, 890–891.
[44] Lundin, P. M.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 11027–11029.

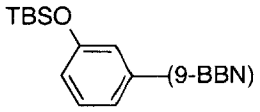


(1s,5s)-9-([1,1'-Biphenyl]-3-yl)-9-borabicyclo[3.3.1]nonane. Prepared from [1,1'-biphenyl]-3-ylmagnesium bromide (21.4 mmol). The product was distilled at 135 °C at 150 mTorr. Colorless oil (1.7 g, 6.3 mmol, 29%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22–8.21 (m, 1H), 8.00–7.98 (m, 1H), 7.83–7.80 (m, 1H), 7.68–7.50 (m, 3H), 7.49–7.41 (m, 2H), 7.40–7.37 (m, 1H), 2.40–2.37 (m, 2H), 2.11–1.98 (m, 6H), 1.93–1.83 (m, 4H), 1.41–1.33 (m, 2H).

^{13}C NMR (400 MHz, $CDCl_3$) δ 141.4, 140.9, 133.5, 133.4, 131.6, 128.8, 128.5, 127.32, 127.26, 34.2, 29.4, 23.5.

^{11}B NMR (400 MHz, $CDCl_3$) δ 80.

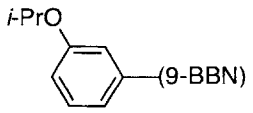


(3-((1s,5s)-9-Borabicyclo[3.3.1]nonan-9-yl)phenoxy)(tert-butyl)dimethylsilane. Prepared from (3-((tert-butyldimethylsilyl)oxy)phenyl)magnesium bromide (19.4 mmol). The literature procedure was modified as follows: after (3-((*tert*-butyldimethylsilyl)oxy)phenyl)magnesium bromide was added to the solution of *B*-methoxy-(9-BBN) in diethyl ether, the resultant mixture was stirred for 48 h before continuing to the next step of the reaction. The product was distilled at 165 °C at 500 mTorr. Colorless oil (2.0 g, 6.1 mmol, 31%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.57 (m, 1H), 7.46–7.43 (m, 1H), 7.38–7.34 (m, 1H), 7.08–7.04 (m, 1H), 2.28–2.25 (m, 2H), 2.07–1.96 (m, 6H), 1.88–1.80 (m, 4H), 1.38–1.31 (m, 2H), 1.03 (s, 9H), 0.24 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 129.0, 127.5, 125.6, 124.4, 34.2, 29.4, 25.8, 23.5, 18.3, 4.3.

^{11}B NMR (128 MHz, $CDCl_3$) δ 81.



(1s,5s)-9-(3-Isopropoxyphenyl)-9-borabicyclo[3.3.1]nonane. Prepared from 3-(isopropoxyphenyl)magnesium bromide (23.0 mmol). The literature procedure was modified as follows: after 3-(isopropoxyphenyl)magnesium bromide was added to the solution of *B*-methoxy-(9-BBN) in diethyl ether, the resultant mixture was stirred for 48 h before continuing to the next step of the reaction. The product was distilled at 124°C at 510 mTorr. Colorless oil (2.5 g, 8.3 mmol, 36%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.58 (m, 1H), 7.55–7.54 (m, 1H), 7.43 (t, 1H, J = 8.0 Hz), 7.15–7.12 (m, 1H), 4.67 (sept, 1H, J = 6.0 Hz), 2.32–2.30 (m, 2H), 2.15–2.04 (m, 6H), 1.92–1.86 (m, 4H), 1.42 (d, 6H, J = 4.0 Hz), 1.38–1.32 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 129.1, 126.8, 121.8, 120.0, 69.7, 34.2, 29.4, 23.5, 22.1.

^{11}B NMR (128 MHz, $CDCl_3$) δ 81.

IV. Suzuki–Miyaura Cross-Couplings

General procedure for activation of *B*-aryl-(9-BBN) reagents. In a nitrogen-filled glovebox, the *B*-aryl-9-BBN reagent (2.50 mmol, 2.5 equiv) was added to a slurry of lithium *tert*-butoxide (192 mg, 2.40 mmol, 2.4 equiv), *i*-BuOH (178 mg, 222 μL, 2.40 mmol, 2.4 equiv), and benzene (1 mL) in a 4 mL vial equipped with a magnetic stir bar. The vial was sealed with a PTFE-lined septum cap, and the mixture was stirred vigorously for 20 minutes and used immediately in the subsequent cross-coupling reaction.

General Procedure A (Table 4 and eq 23). In a nitrogen-atmosphere glovebox, $NiBr_2$•diglyme (35.5 mg, 0.1 mmol, 0.1 equiv) and 4,4'-di-tert-butyl-2,2'-bipyridine **L5** (30.0 mg, 0.11 mmol, 0.11 equiv) were added to a 30 mL vial equipped with a magnetic stir bar. Benzene (24 mL, anhydrous) was added, the vial was sealed with a PTFE-lined septum cap, and the resultant mixture was stirred vigorously for 2 h (a light green slurry forms). The solution of activated *B*-aryl-(9-BBN) reagent was then added to the slurry, and the reaction vial was again sealed with a PTFE-lined cap and stirred for 20 minutes (the reaction mixture turns dark green). The tertiary alkyl halide (1.0 mmol, 1 equiv) was then added to the slurry via microsyringe (neat). The resultant mixture was resealed and stirred vigorously at 40 °C for 24 hours (outside of the glovebox). Next, the reaction mixture was filtered through a plug of silica gel, which was rinsed with diethyl ether, and the filtrate was concentrated using rotary evaporation. The crude product was purified by column chromatography.

General Procedure B (Table 5). General procedure A was followed, except that the reaction was heated to 60 °C, instead of 40 °C.

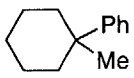
General Procedure C (1-iodoadamantane, eq 25). General procedure A was followed, except that cyclohexane (anhydrous; 1.0 mL) was used in place of benzene for the activation of the aryl-(9-BBN), and that cyclohexane (anhydrous; 5.7 mL) was used in place of benzene for the cross-coupling.

Glovebox-free procedure: Cross-coupling of phenyl-(9-BBN) with 1-bromo-1-methylcyclohexane. A 250-mL two-neck round-bottom flask equipped with a stir bar was connected to the outer joint of a swivel frit, and the outer joint on the other end of the swivel frit was connected to a 250-mL one-neck round-bottom flask, also equipped with a stir bar. The swivel frit was connected to a high-vacuum line and the entire apparatus was flame-dried under vacuum with a torch. The apparatus was allowed to cool under vacuum overnight. In the two-neck flask, phenyl-(9-BBN) was synthesized according the literature procedure (10 mmol scale).[35] At the end of the reaction, the crude mixture of phenyl-(9-BBN), magnesium salts, and hexanes was filtered into the 250-mL one-neck flask using the swivel frit under a gentle vacuum, to give a clear solution of phenyl-(9-BBN) in hexanes. The hexanes were removed under high vacuum, and the resulting crude phenyl-(9-BBN) continued to dry under vacuum for 1 hour.

A 25-mL two-neck pear-shaped Schlenk flask equipped with a stir bar was flame-dried with a torch under high vacuum and allowed to cool to room temperature. Under a positive atmosphere of nitrogen gas, LiO*t*-Bu (192 mg, 2.40 mmol, 2.4 equiv) was added, and the flask was capped and then further dried under high vacuum for 30 minutes. Under an atmosphere of nitrogen gas, *i*-BuOH (178 mg, 222 μL, 2.40 mmol, 2.4 equiv, anhydrous), newly synthesized

crude phenyl-(9-BBN) (495 mg, 2.5 mmol, density = 1 g/mL) and benzene (1 mL, anhydrous) were added to the flask, which was subsequently purged with nitrogen for 5 minutes, and the cloudy mixture was allowed to stir for 20 minutes.

A 100-mL two-neck round-bottom Schlenk flask equipped with a stir bar was flame-dried with a torch under high vacuum and allowed to cool to room temperature. Under a positive atmosphere of nitrogen gas, $NiBr_2$•diglyme (35.5 mg, 0.1 mmol, 0.1 equiv) and 4,4'-di-*tert*-butyl-2,2'-bipyridine **L5** (30.0 mg, 0.11 mmol, 0.11 equiv) were added, and the flask was capped and then further dried under high vacuum (stirring) for 30 minutes. Under an atmosphere of nitrogen gas, benzene (24 mL, anhydrous) was added to the flask, which was subsequently purged with nitrogen for 5 minutes, and the nickel/ligand mixture was allowed to stir at room temperature for 2 hours (light green slurry). The activated phenyl-(9-BBN) was then transferred via syringe to the nickel/ligand slurry, which was allowed to stir for 20 minutes (dark green reaction mixture). Then, neat 1-bromo-1-methylcyclohexane (177 mg, 1 mmol) was added to the reaction, which was purged with nitrogen for 5 minutes and then heated to 40 °C for 24 hours. On completion, 100 μL of pentadecane (internal standard to obtain a calibrated yield by GC) was added to the reaction, and the reaction mixture was filtered through a plug of silica, with diethyl ether. The filtrate was concentrated using rotary evaporation. GC analysis revealed a yield of 70%. The yield of a corresponding reaction, set up in a glovebox with non-distilled phenyl-(9-BBN), was 76%.



(1-Methylcyclohexyl)benzene [828-45-5] (Table 4, entry 1). This compound was prepared according to general procedure A, using 1-bromo-1-methylcyclohexane (177 mg, 1.0

mmol) and phenyl-(9-BBN) (495 mg, 2.5 mmol). Purification: Biotage, silica, 100% hexanes. Colorless oil.

First run: 148 mg (85%). Second run: 144 mg (83%).

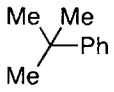
On a larger scale: 1-bromo-1-methylcyclohexane (5.65 mmol): 807 mg (82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.36 (m, 2H), 7.33–7.28 (m, 2H), 7.18–7.14 (m, 1H), 2.03–1.98 (m, 2H), 1.60–1.43 (m, 8H), 1.18 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 128.4, 126.9, 125.4, 38.1, 30.8, 30.5, 26.6, 22.9.

FT-IR (film) 3087, 3057, 2930, 2857, 1600, 1495, 1466, 1445, 1374, 1299, 1076, 1026, 963, 859, 761, 699, 580, 544, 529 cm^{-1}.

LRMS (EI) *m/z* (M^+) calcd for $C_{13}H_{18}$: 174, found: 174.



***tert*-Butylbenzene [98-06-6] (Table 4, entry 2).** This compound was prepared according to general procedure A, using 2-bromo-2-methylpropane (112 μL, 1.0 mmol; Aldrich) and phenyl-(9-BBN) (495 mg, 2.5 mmol). Purification: Biotage, silica, 100% hexanes. Colorless oil.

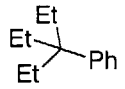
First run: 94 mg (70%); GC calibrated yield: 86%. Second run: 97 mg (72%); GC calibrated yield: 82%. The product is volatile.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.58 (m, 2H), 7.51–7.47 (m, 2H), 7.37–7.36 (m, 1H), 1.53 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 128.3, 125.7, 125.4, 34.8, 31.9.

FT-IR (film) 2963, 2950, 762 cm^{-1}.

LRMS (EI) *m/z* (M^+) calcd for $C_{10}H_{14}$: 134, found: 134.



(3-Ethylpentan-3-yl)benzene [4170-84-7] (Table 4, entry 3). This compound was prepared according to general procedure A, using 3-bromo-3-ethylpentane (179 mg, 1.0 mmol) and phenyl-(9-BBN) (495 mg, 2.5 mmol). Purification: Biotage, silica, 100% hexanes. Colorless oil.

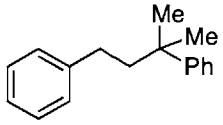
First run: 126 mg (72%). Second run: 119 mg (68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.31 (m, 4H), 7.18–7.16 (m, 1H), 1.69 (q, 6H, J = 8.0 Hz), 0.66 (t, 9H, J = 8.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 127.8, 126.9, 125.1, 43.7, 28.7, 8.0.

FT-IR (film) 3089, 3059, 3022, 2966, 2937, 2878, 1559, 1540, 1496, 1446, 1457, 1376, 1083, 1032, 1011, 753, 698 cm^{-1}.

LRMS (EI) *m/z* (M^+) calcd for $C_{13}H_{20}$: 176, found: 176.



(3-Methylbutane-1,3-diyl)dibenzene [1520-43-0] (Table 4, entry 4). This compound was prepared according to general procedure A, using (3-bromo-3-methylbutyl)benzene (227 mg, 1.0 mmol) and phenyl-(9-BBN) (495 mg, 2.5 mmol). Purification: Biotage, silica, 100% hexanes. Colorless oil.

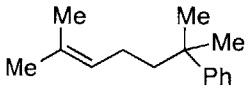
First run: 195 mg (87%). Second run: 190 mg (85%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.43 (m, 2H), 7.40–7.36 (m, 2H), 7.29–7.12 (m, 6H), 2.42–2.38 (m, 2H), 2.01–1.95 (m, 2H), 1.50 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 143.2, 128.4, 128.3, 125.9, 125.6, 46.8, 38.0, 31.4, 29.1.

FT-IR (film) 3086, 3061, 3026, 2963, 2863, 2361, 1602, 1496, 1454, 1386, 1366, 1071, 1031, 762, 698, 408 cm^{-1}.

LRMS (EI) m/z (M^+) calcd for $C_{17}H_{20}$: 224, found: 224.



(2,6-Dimethylhept-5-en-2-yl)benzene (Table 4, entry 5). This compound was prepared according to general procedure A, using 6-bromo-2,6-dimethylhept-2-ene (205 mg, 1.0 mmol) and phenyl-(9-BBN) (495 mg, 2.5 mmol). Purification: Biotage, silica, 100% hexanes. Colorless oil.

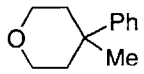
First run: 151 mg (75%). Second run: 155 mg (77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.23 (m, 4H), 7.16–7.14 (m, 1H), 5.04 (t, 2H, J = 8.0 Hz), 1.75–1.69 (m, 2H), 1.65–1.63 (m, 5H), 1.48 (s, 3H), 1.31 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 131.1, 128.0, 125.9, 125.4, 124.9, 44.6, 37.7, 28.9, 25.7, 23.6, 17.5.

FT-IR (film) 2965, 2926, 1496, 1446, 1385, 1366, 764, 699 cm^{-1}.

LRMS (EI) m/z (M^+) calcd for $C_{15}H_{22}$: 202, found: 202.



4-Methyl-4-phenyltetrahydro-2H-pyran [67768-01-8] (Table 4, entry 6). This compound was prepared according to general procedure A, using 4-bromo-4-methyltetrahydro-2H-pyran (179 mg, 1.0 mmol) and phenyl-(9-BBN) (495 mg, 2.5 mmol). Purification: Biotage, reverse phase silica (C-18), 40→100% ACN/water, followed by Biotage, normal phase silica, 10→80% Et_2O/hexanes. Colorless oil.

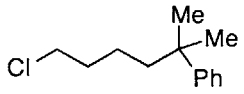
First run: 102 mg (58%). Second run: 97 mg (55%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.24 (m, 4H), 7.16–7.10 (m, 1H), 3.74–3.57 (m, 4H), 2.09–2.00 (m, 2H), 1.72–1.69 (m, 2H), 1.22 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 128.5, 125.8, 125.6, 64.5, 37.6, 35.6, 29.2.

FT-IR (film) 3058, 2955, 2857, 2361, 1601, 1496, 1445, 1389, 1299, 1246, 1177, 1108, 1033, 1014, 865, 764, 701, 548, 425, 415 cm^{-1}.

LRMS (EI) m/z (M^+) calcd for $C_{12}H_{16}O$: 176, found: 1764.



(6-Chloro-2-methylhexan-2-yl)benzene (Table 4, entry 7). This compound was prepared according to general procedure A, using 5-bromo-1-chloro-5-methylhexane (214 mg, 1.0 mmol) and phenyl-(9-BBN) (495 mg, 2.5 mmol). Purification: Biotage, silica, 100% hexanes. Colorless oil.

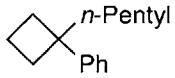
First run: 140 mg (67%). Second run: 141 mg (67 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.28 (m, 4H), 7.19–7.17 (m, 1H), 3.44 (t, 2H, J = 8.0 Hz), 1.71–1.60 (m, 4H), 1.31 (s, 6H), 1.24–1.18 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 128.1, 125.8, 125.5, 44.9, 43.8, 37.7, 33.3, 28.9, 22.2.

FT-IR (film) 2961, 2868, 1497, 1445, 1387, 1367, 1311, 1031, 765, 700, 652, 569 cm^{-1}.

LRMS (EI) m/z (M^+) calcd for $C_{13}H_{19}Cl$: 210, found: 210.



(1-Pentylcyclobutyl)benzene (Table 4, entry 8). This compound was prepared according to general procedure A, using 1-bromo-1-pentylcyclobutane (205 mg, 1.0 mmol) and phenyl-(9-BBN) (495 mg, 2.5 mmol). Purification: Biotage, silica, 100% hexanes. Colorless oil.

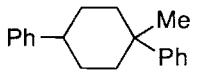
First run: 105 mg (52%). Second run: 113 mg (54%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.25 (m, 2H), 7.18–7.09 (m, 3H), 2.40–2.31 (m, 2H), 2.17–2.03 (m, 3H), 1.86–1.72 (m, 3H), 1.27–1.12 (m, 4H), 1.06–0.98 (m, 2H), 0.82 (t, 3H, J = 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 127.7, 125.7, 124.9, 46.5, 42.7, 32.8, 32.3, 24.2, 22.6, 16.0, 14.1.

FT-IR (film) 3024, 2928, 2856, 1601, 1495, 1466, 1446, 764, 700, 563, 419, 410 cm^{-1}.

LRMS (EI) m/z (M^+) calcd for $C_{15}H_{22}$: 202, found: 202.



(1-Methylcyclohexane-1,4-diyl)dibenzene (Table 4, entry 9). This compound was prepared according to general procedure A, using ((1s,4s)-4-bromo-4-methylcyclohexyl)benzene (cis, dr >20:1, 253 mg, 1.0 mmol) and phenyl-(9-BBN) (495 mg, 2.5 mmol). Purification:

Biotage, reverse phase silica (C-18), 40→100% ACN/water. White solid. Product is an unseparated mixture of diastereomers with a 1.2:1 ratio.

First run: 181 mg (72%). Second run: 185 mg (74 %).

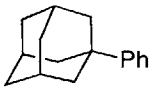
^{1}H NMR (300 MHz, $CDCl_3$); diastereomer 1: δ 7.38–6.93 (m, 10H), 6.78–6.75 (m, 9H), 1.27 (s, 3H).

^{1}H NMR (300 MHz, $CDCl_3$); diastereomer 2: δ 7.38–6.93 (m, 10H), 6.78–6.75 (m, 9H), 1.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 147.44, 147.39, 147.2, 128.6, 128.5, 128.3, 127.0, 126.9, 126.5, 126.1, 125.9, 125.7, 125.4, 125.2, 44.7, 44.2, 38.3, 38.09, 38.05, 36.6, 35.5, 30.6, 30.2, 24.5.

FT-IR (film) 3085, 3058, 3025, 2928, 2857, 1943, 1869, 1800, 1602, 1581, 1494, 1450, 1376, 1098, 1077, 1032, 1023, 964, 762 cm^{-1}.

LRMS (EI) *m/z* (M^+) calcd for $C_{19}H_{22}$: 250, found: 250.



(3r,5r,7r)-1-Phenyladamantane [780-68-7] (eq 25). This compound was prepared according to general procedure C, using 1-iodoadamantane (262 mg, 1 mmol) and phenyl-(9-BBN) (495 mg, 2.5 mmol). Purification: Biotage, silica, 100% hexanes. White solid.

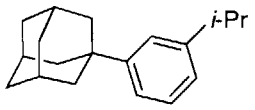
First run: 157 mg (74%). Second run: 155 mg (73%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.22 (m, 4H), 7.13–7.07 (m, 1H), 2.07–2.01 (m, 3H), 1.86–1.85 (m, 6H), 1.76–1.64 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 128.1, 125.5, 124.8, 43.2, 36.8, 36.2, 29.0.

FT-IR (film) 2924, 2904, 2847, 1443, 1245, 907, 752 cm^{-1}.

LRMS (EI) *m/z* (M^+) calcd for $C_{16}H_{20}$: 212, found: 212.



(3r,5r,7r)-1-(3-Isopropylphenyl)adamantane [183967-44-4] (eq 25). This compound was prepared according to general procedure C, using 1-iodoadamantane (262 mg, 1 mmol) and (1s,5s)-9-(3-isopropylphenyl)-9-borabicyclo[3.3.1]nonane (601 mg, 2.5 mmol). Purification: Biotage, silica, 100% hexanes. Colorless oil.

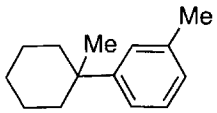
First run: 158 mg (62%). Second run: 150 mg (59%).

^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.20 (m, 3H), 7.10–7.07 (m, 1H), 2.98–2.89 (m, 1H), 2.14–2.10 (m, 3H), 1.96–1.95 (m, 6H), 1.85–1.78 (m, 6H), 1.31–1.27 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 148.4, 128.0, 123.4, 123.2, 122.3, 43.2, 36.9, 36.2, 34.4, 29.0, 24.2.

FT-IR (film) 2958, 2903, 2847, 1604, 1487, 1449, 1317, 1103, 976, 787, 705 cm^{-1}.

LRMS (EI) *m/z* (M^+) calcd for $C_{19}H_{26}$: 254, found: 254.



1-Methyl-3-(1-methylcyclohexyl)benzene [14962-11-9] (Table 5, entry 1). This compound was prepared according to general procedure B, using 1-bromo-1-methylcyclohexane (177 mg, 1 mmol) and (1s,5s)-9-(m-tolyl)-9-borabicyclo[3.3.1]nonane (530 mg, 2.5 mmol). Purification: Biotage, silica, 100% hexanes. Colorless oil.

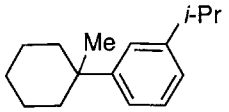
First run: 112 mg (60%). Second run: 115 mg (61%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.21 (m, 3H), 7.03–6.99 (m, 1H), 2.38 (s, 3H), 2.05–1.98 (m, 2H), 1.60–1.45 (m, 8H), 1.20 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 137.5, 128.1, 126.6, 126.0, 122.9, 37.9, 37.8, 30.3, 26.4, 22.7, 21.8.

FT-IR (film) 3023, 2929, 2856, 1587, 1605, 1492, 1467, 1454, 1374, 1302, 784, 705 cm^{-1}.

LRMS (EI) m/z (M^+) calcd for $C_{14}H_{20}$: 188, found: 188.



1-Isopropyl-3-(1-methylcyclohexyl)benzene [14962-14-2] (Table 5, entry 2). This compound was prepared according to general procedure B, using 1-bromo-1-methylcyclohexane (177 mg, 1 mmol) and (1s,5s)-9-(3-isopropylphenyl)-9-borabicyclo[3.3.1]nonane (601 mg, 2.5 mmol). Purification: Biotage, silica, 100% hexanes. Colorless oil.

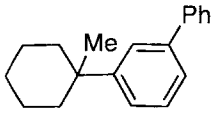
First run: 134 mg (62%). Second run: 127 mg (59%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.20 (m, 3H), 7.09–7.05 (m, 1H), 2.97–2.88 (m, 1H), 2.06–1.99 (m, 2H), 1.65–1.42 (m, 8H), 1.29 (d, 6H, J = 6.0 Hz), 1.22 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 148.5, 128.0, 124.2, 123.3, 123.0, 38.0, 37.9, 30.3, 26.4, 24.2, 22.7.

FT-IR (film) 2957, 2929, 2859 1601, 1489, 1456, 792, 706 cm^{-1}.

LRMS (EI) m/z (M^+) calcd for $C_{16}H_{24}$: 216, found: 216.



3-(1-Methylcyclohexyl)-1,1'-biphenyl (Table 5, entry 3). This compound was prepared according to general procedure B, using 1-bromo-1-methylcyclohexane (177 mg, 1 mmol) and (1s,5s)-9-([1,1'-biphenyl]-3-yl)-9-borabicyclo[3.3.1]nonane (686 mg, 2.5 mmol). Purification: Biotage, reverse phase silica (C-18), 40→100% ACN/water. Colorless oil.

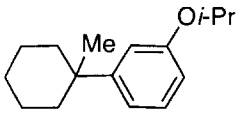
First run: 183 mg (73%). Second run: 187 mg (75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.60 (m, 3H), 7.49–7.33 (m, 6H), 2.13–2.05 (m, 2H), 1.70–1.44 (m, 8H), 1.26 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 142.0, 141.1, 128.7, 128.6, 127.3, 127.1, 125.0, 124.9, 124.2, 38.1, 38.0, 30.6, 26.4, 22.7.

FT-IR (film) 3029, 2929, 2856, 1598, 1481, 1466, 1449, 1410, 1075, 894, 798, 756 cm^{-1}.

LRMS (EI) *m/z* (M^+) calcd for $C_{19}H_{22}$: 250, found: 250.



1-Isopropoxy-3-(1-methylcyclohexyl)benzene (Table 5, entry 4). This compound was prepared according to general procedure B, using 1-bromo-1-methylcyclohexane (177 mg, 1 mmol) and (1s,5s)-9-(3-isopropoxyphenyl)-9-borabicyclo[3.3.1]nonane (641 mg, 2.5 mmol). Purification: Biotage, reverse phase silica (C-18), 40→100% ACN/water. Colorless oil.

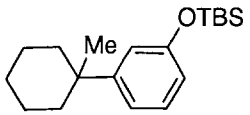
First run: 133 mg (57%). Second run: 130 mg (56%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.20 (m, 1H), 6.98–6.91 (m, 2H), 6.73–6.69 (m, 1H), 4.60–4.51 (m, 1H), 2.02–1.95 (m, 2H), 1.59–1.42 (m, 8H), 1.35 (d, 6H, J = 9.0 Hz), 1.18 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 152.0, 128.9, 118.2, 114.6, 111.7, 69.6, 38.0, 37.9, 30.5, 26.4, 22.7, 22.2.

FT-IR (film) 2975, 2930, 2857, 1605, 1579, 1487, 1467, 1452, 1383, 1372, 1289, 1239, 1188, 1122, 1000, 985, 961, 873, 773 cm^{-1}.

LRMS (EI) *m/z* (M^+) calcd for $C_{16}H_{24}O$: 232, found: 232.



***tert*-Butyldimethyl(3-(1-methylcyclohexyl)phenoxy)silane (Table 5, entry 5).** This compound was prepared according to general procedure B, using 1-bromo-1-methylcyclohexane (177 mg, 1 mmol) and (3-((1s,5s)-9-borabicyclo[3.3.1]nonan-9-yl)phenoxy)(*tert*-butyl)dimethylsilane (821 mg, 2.5 mmol). Purification: Biotage, reverse phase silica (C-18), 40→100% ACN/water. Colorless oil.

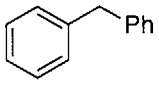
First run: 164 mg (54%). Second run: 161 mg (53%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (t, 1H, J = 12.0 Hz), 6.78–6.75 (m, 1H), 6.65 (t, 1H, J = 3.0 Hz), 6.47–6.43 (m, 1H), 1.80–1.72 (m, 2H), 1.37–1.22 (m, 8H), 0.96 (s, 3H), 0.79 (s, 9H), 0.00 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 155.5, 128.9, 118.8, 118.0, 116.8, 37.9, 37.9, 30.5, 26.4, 25.8, 22.7, 18.3, 4.4.

FT-IR (film) 2929, 2858, 1600, 1581, 1487, 1472, 1361, 1302, 1251, 1190, 1002, 981, 953, 874, 835, 781 cm^{-1}.

LRMS (EI) m/z (M^+) calcd for $C_{19}H_{32}OSi$: 304, found: 304.



Diphenylmethane [101-81-5] (eq 26). This compound was prepared according to general procedure A (except that toluene was used in place of benzene), using 1-bromo-1-methylcyclohexane (177 mg, 1.0 mmol), and phenyl-(9-BBN) (495 mg, 2.5 mmol). Purification: Biotage, reverse-phase silica (C-18), 40→100% ACN/water, followed by Biotage, silica, 100% hexanes. Colorless oil.

First run: 48 mg (29%). Second run: 53 mg (32%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.19 (m, 10H), 4.02 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 129.1, 128.6, 126.2, 42.1.

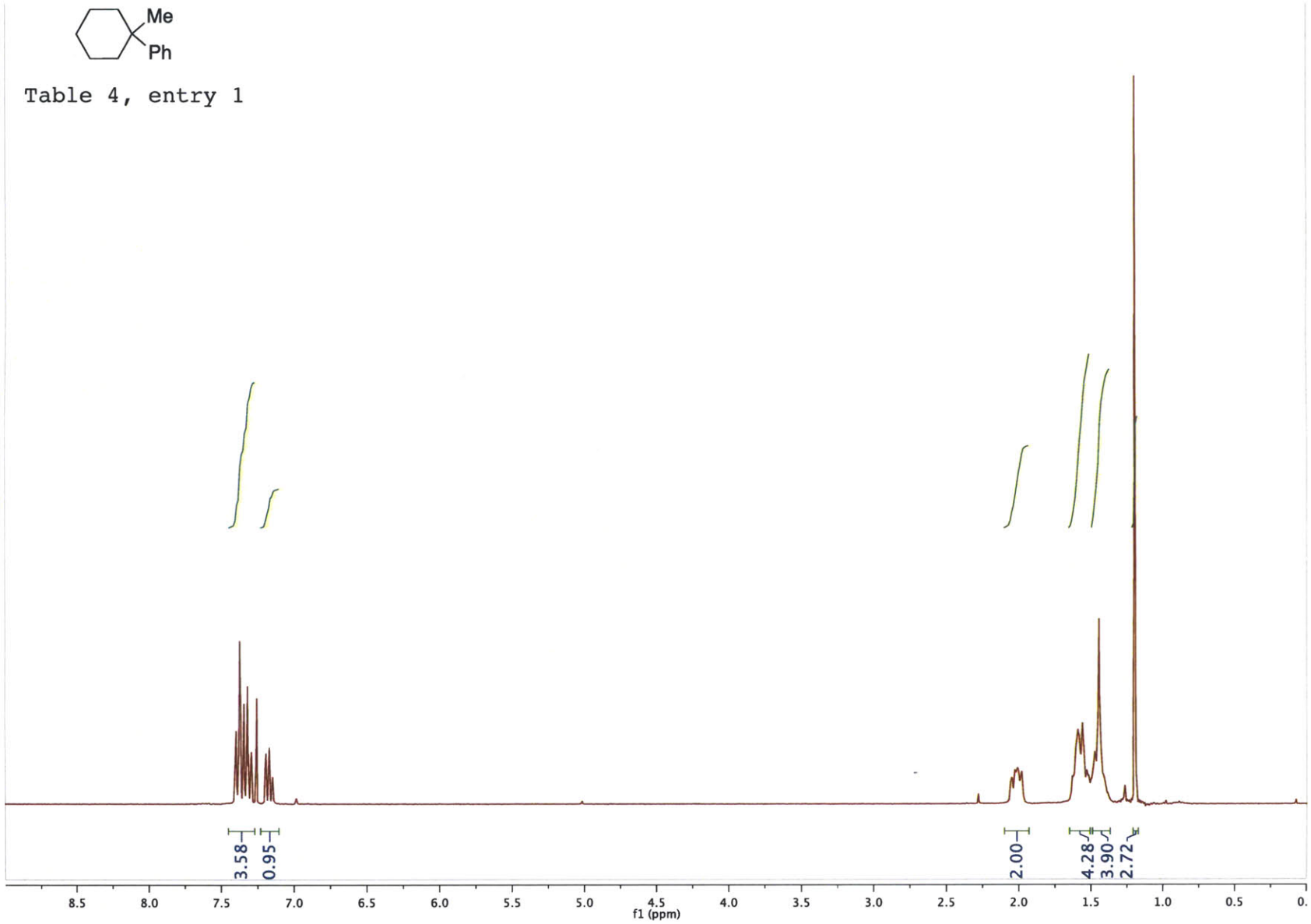
FT-IR (film) 3084, 3061, 3026, 2906, 1076, 1029, 736 cm^{-1}.

LRMS (EI) *m/z* (M^+) calcd for $C_{13}H_{12}$: 168, found: 168.

The direct cross-coupling product, (1-methylcyclohexyl)benzene, was also isolated using the aforementioned purification procedure.

First run: 66 mg (38%). Second run: 72 mg (41%).

V. ^{1}H NMR Spectra of Selected Compounds


Me
Ph
Table 4, entry 1
3.58
0.95
2.00
4.28
3.90
2.72
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

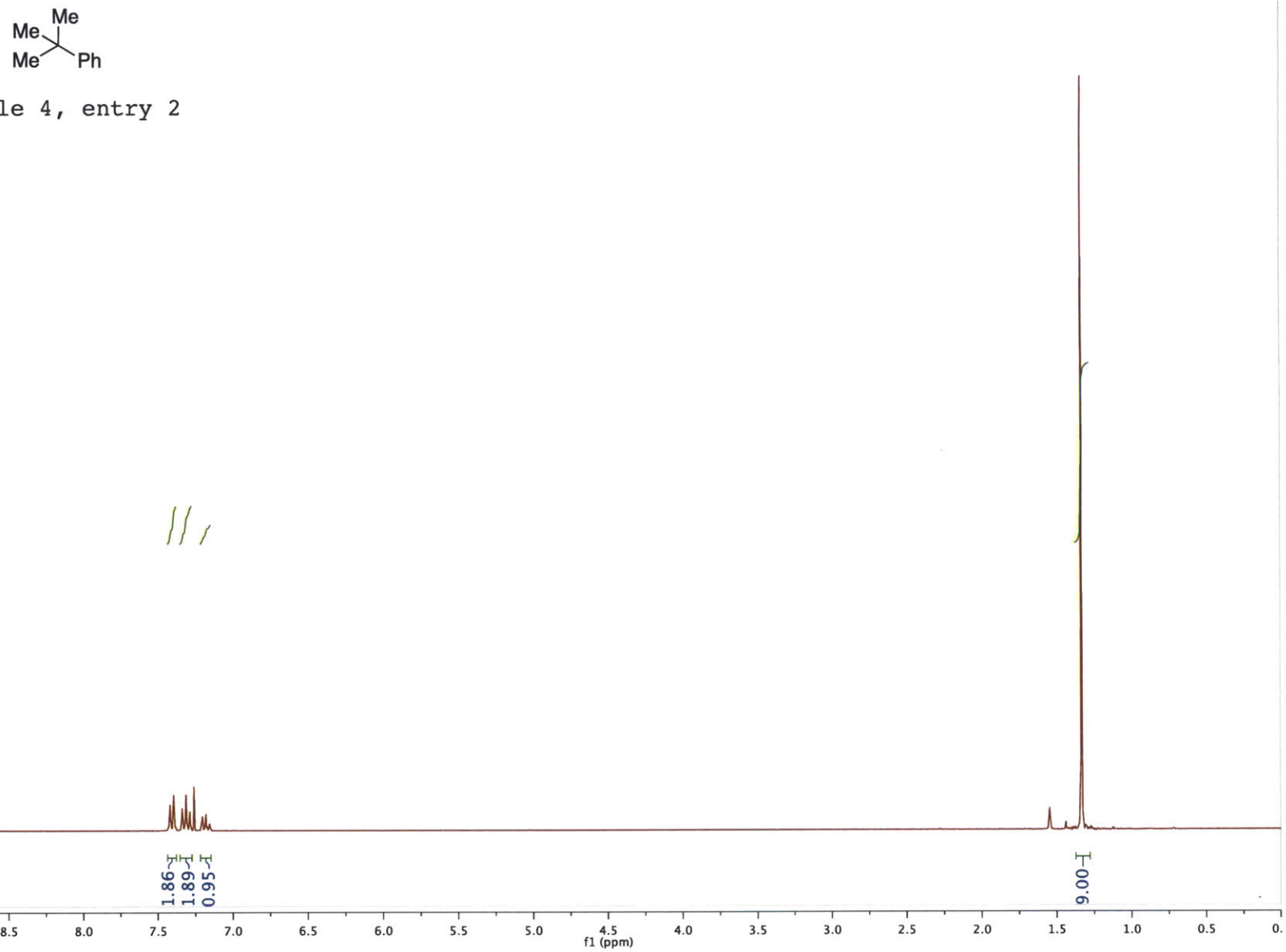


Table 4, entry 2

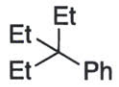
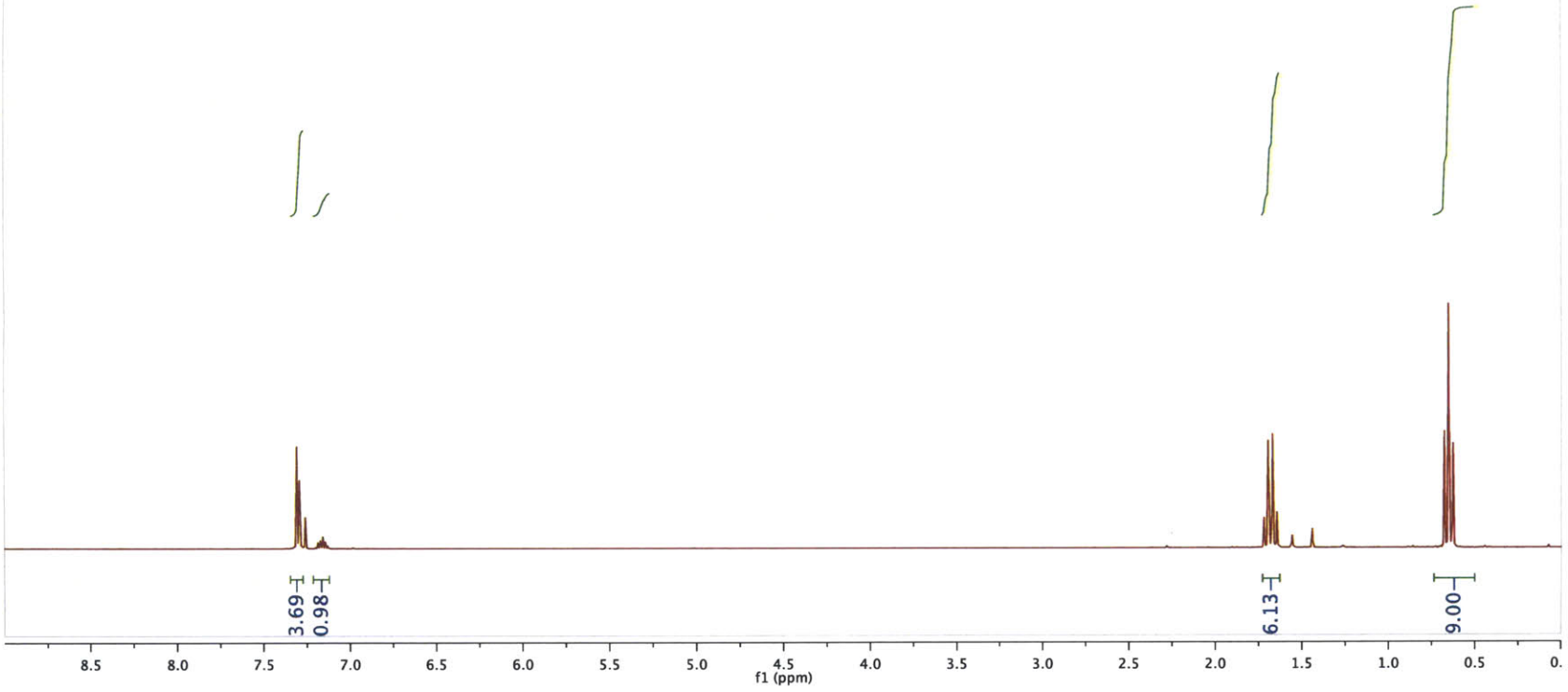


Table 4, entry 3



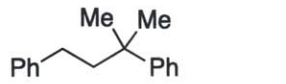
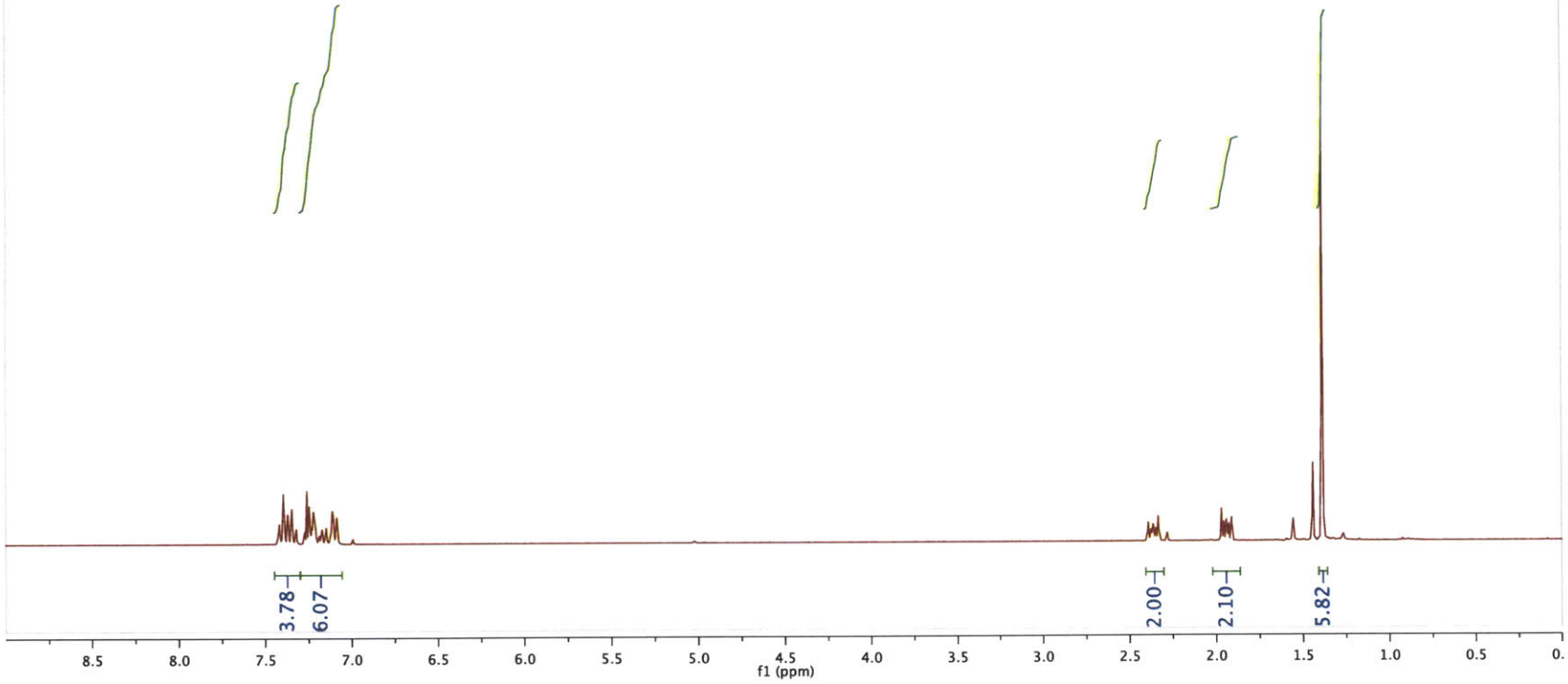


Table 4, entry 4



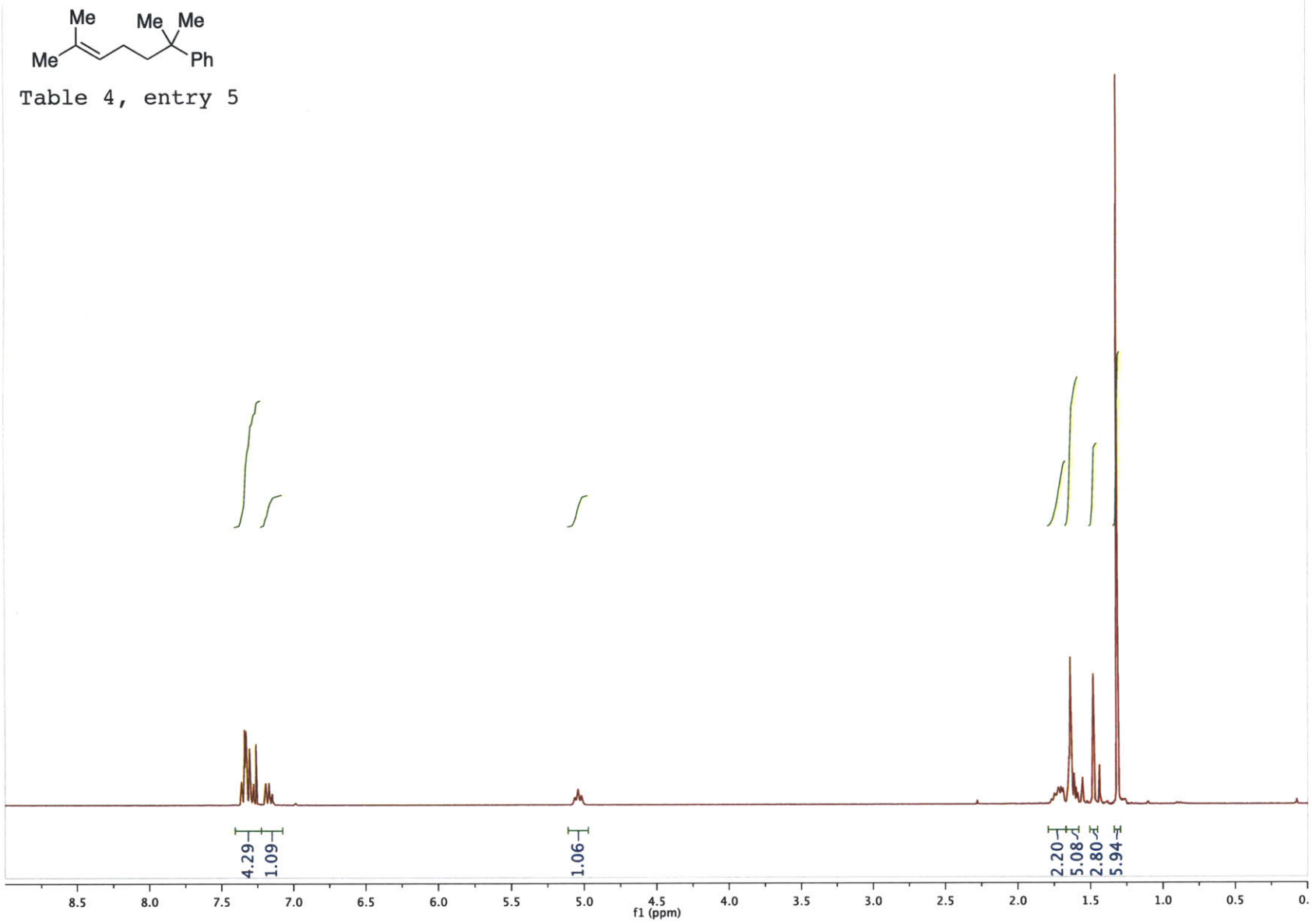
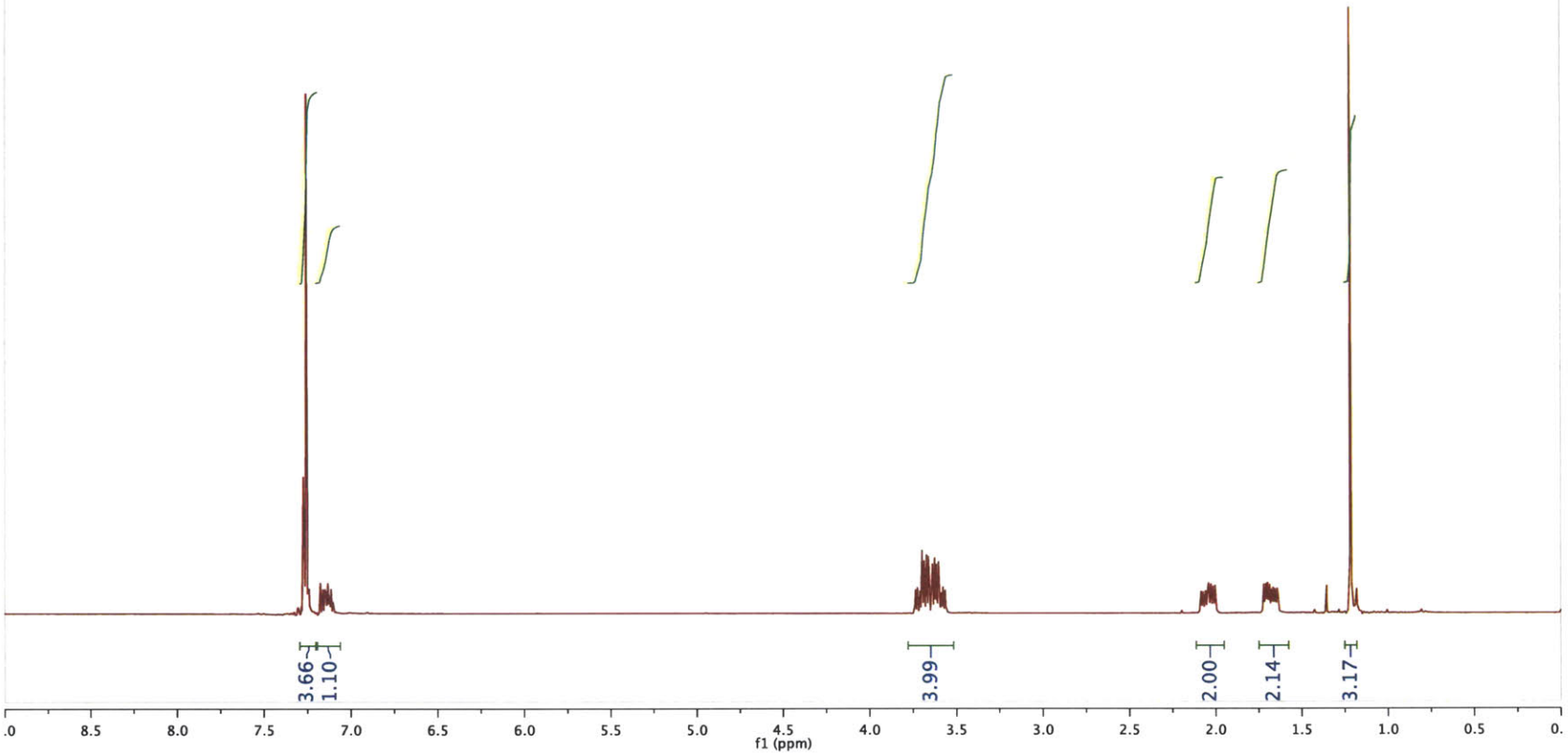
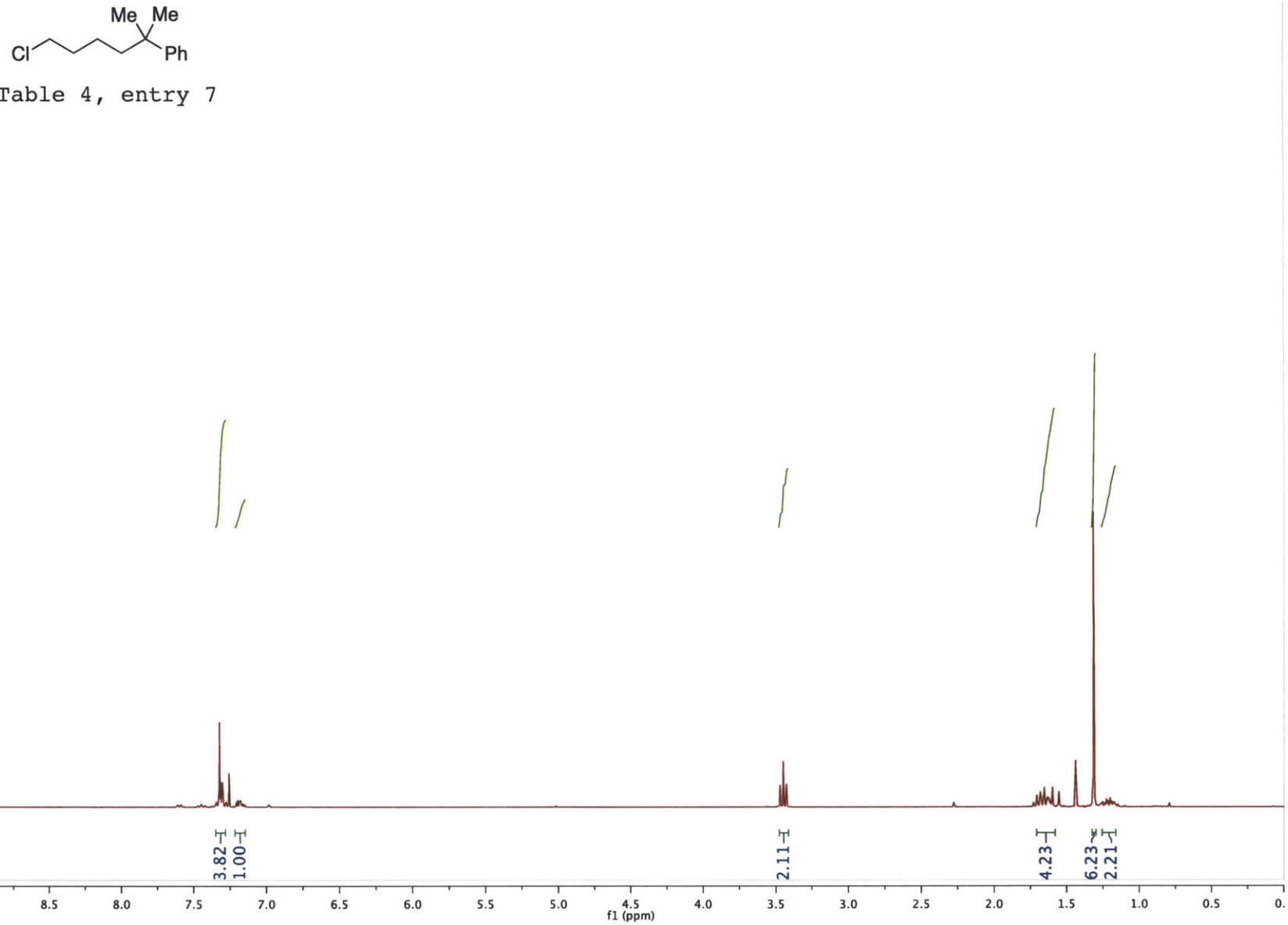

Me
Me
Me
Me
Ph
Table 4, entry 5
4.29
1.09
1.06
2.20
5.08
2.80
5.94
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
f1 (ppm)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.

Table 4, entry 6




Me Me
Cl
Ph
Table 4, entry 7
3.82
1.00
2.11
4.23
6.23
2.21
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
f1 (ppm)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.

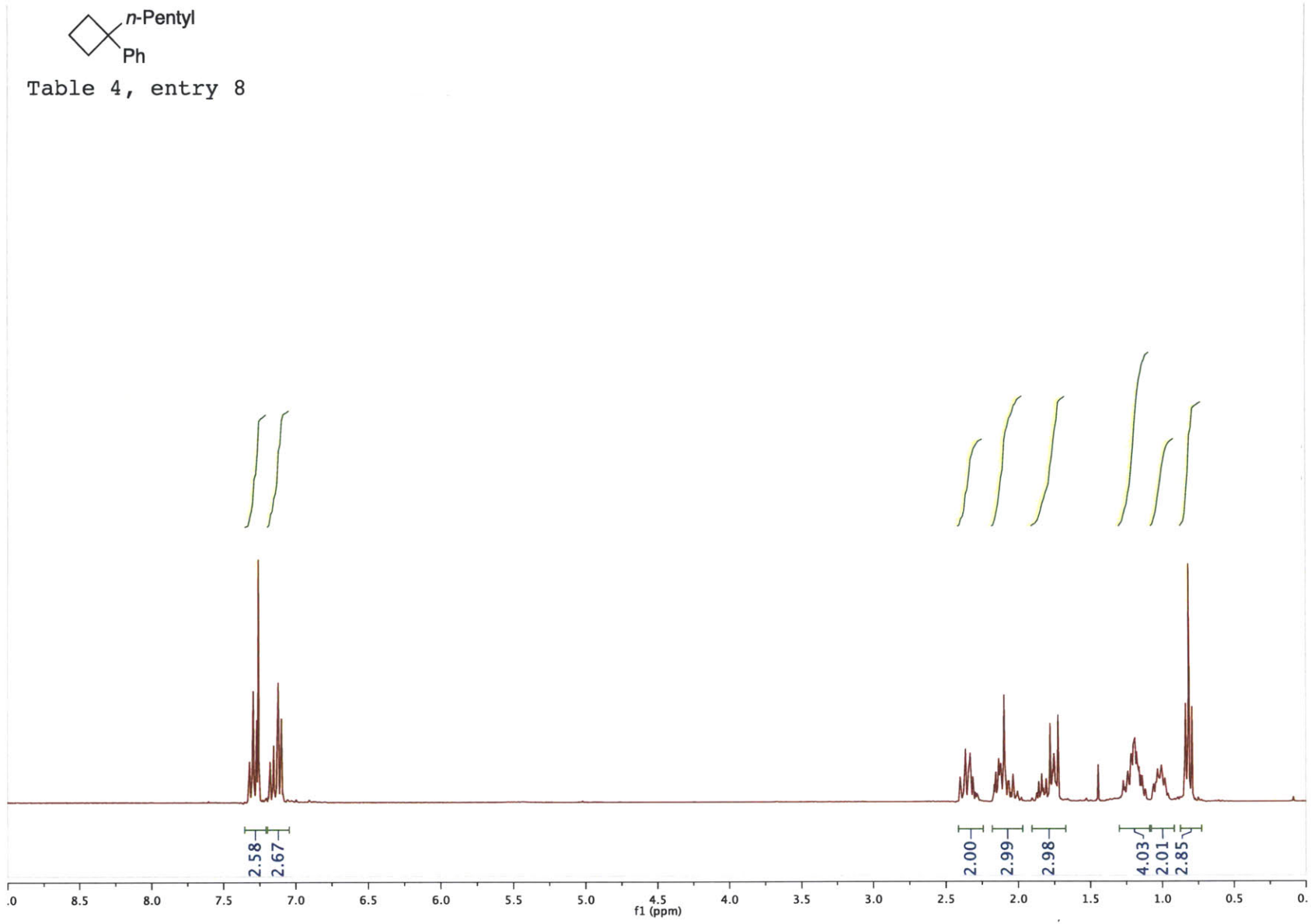
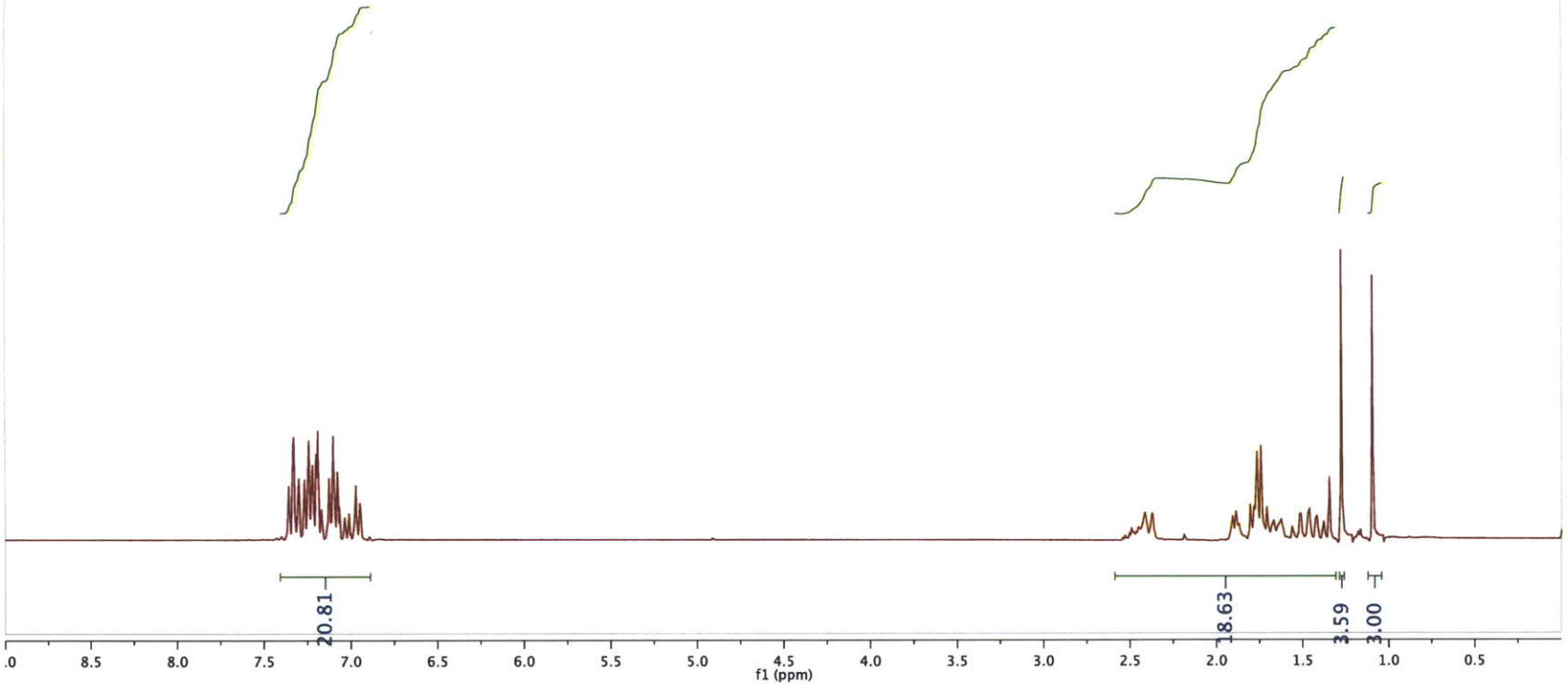
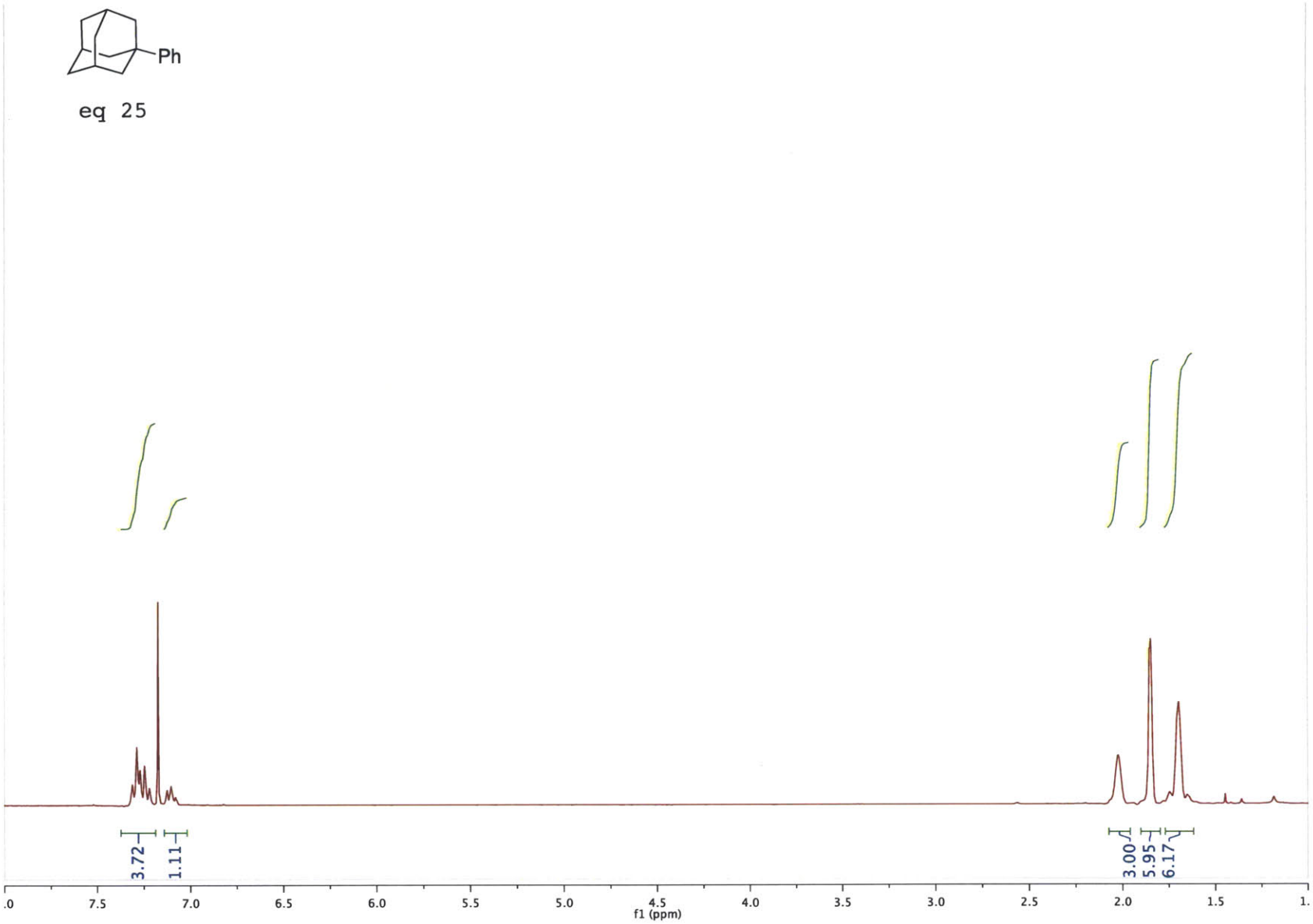

n-Pentyl
Ph
Table 4, entry 8
2.58
2.67
2.00
2.99
2.98
4.03
2.01
2.85
f1 (ppm)

Table 4, entry 9

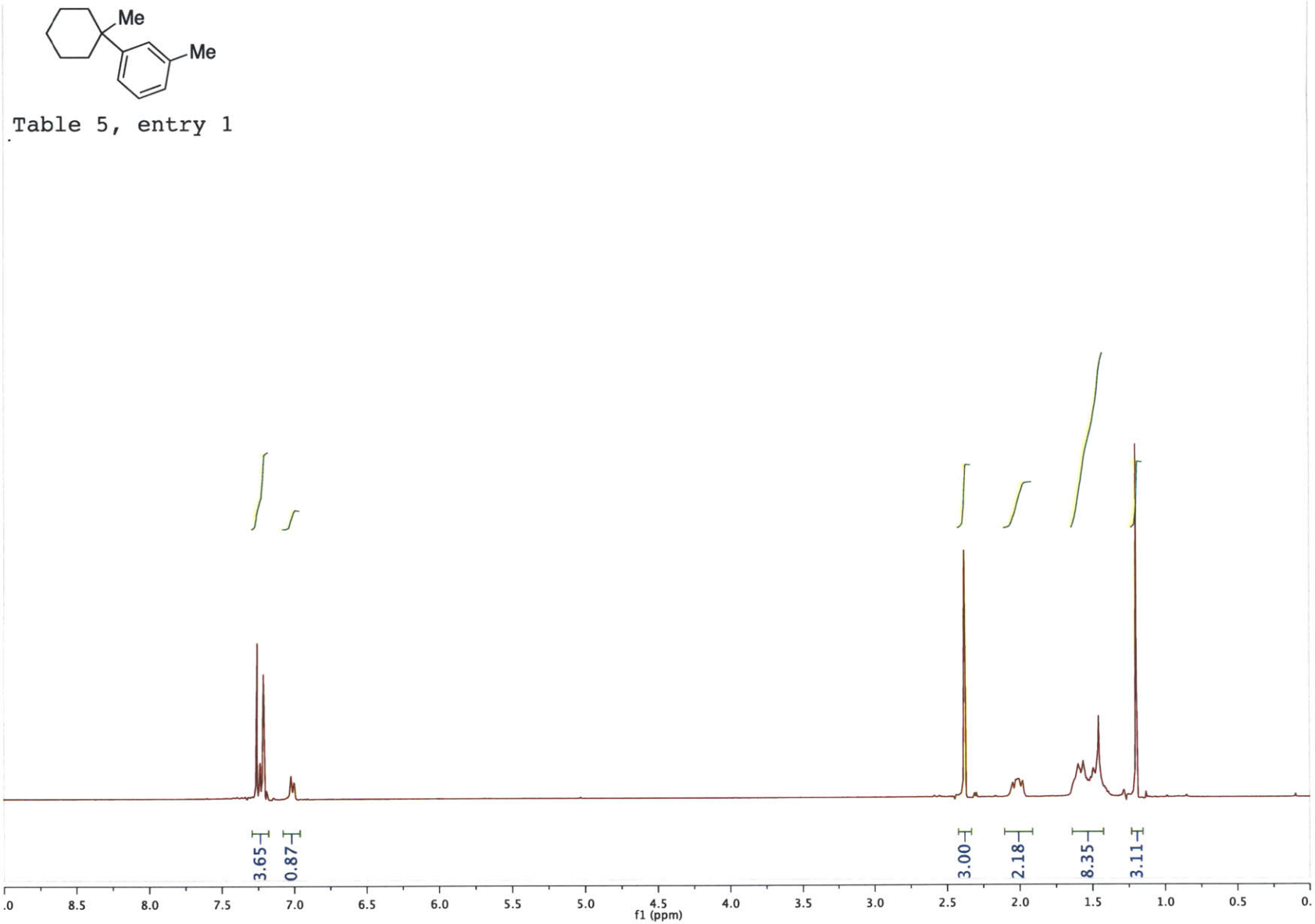



Ph
eq 25
3.72
1.11
3.00
5.95
6.17
7.5
7.0
6.5
6.0
5.5
5.0
4.5
f1 (ppm)
4.0
3.5
3.0
2.5
2.0
1.5

i-Pr

eq 25

3.67
1.17
1.13
2.98
5.80
6.00
6.34
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


Me
Me
Table 5, entry 1
3.65
0.87
3.00
2.18
8.35
3.11
f1 (ppm)

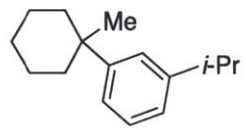
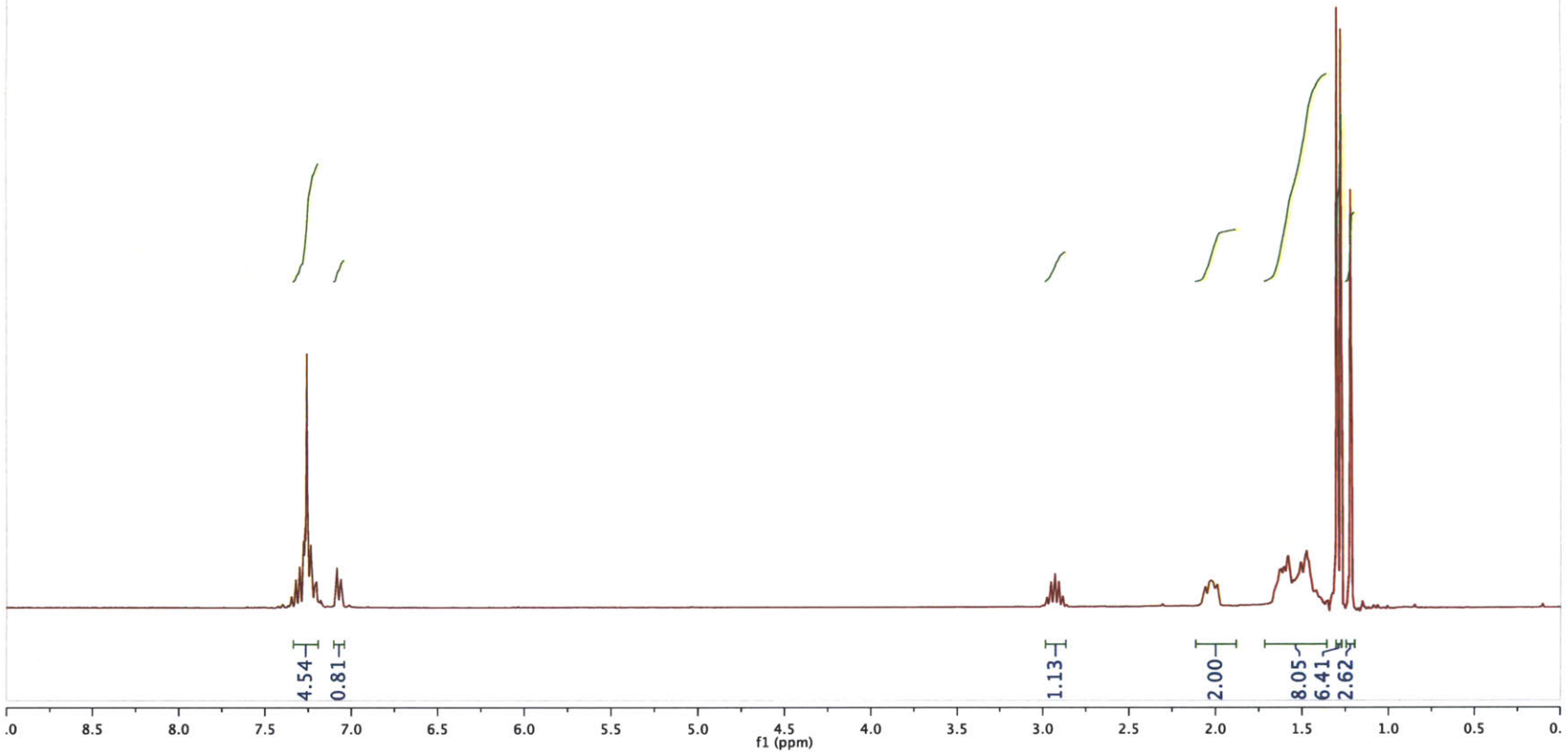
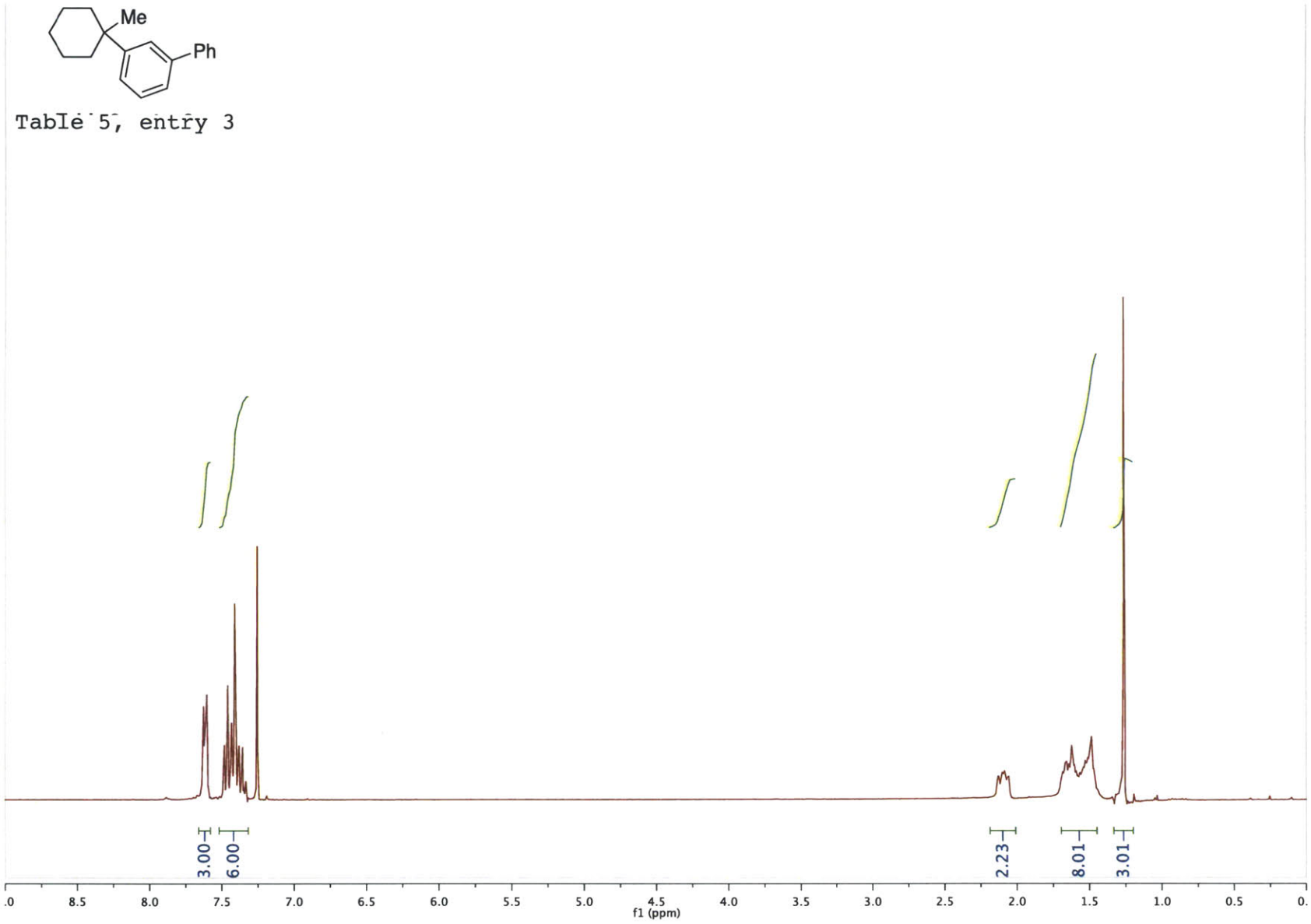


Table 5, entry 2




Me
Ph
Table 5, entry 3
3.00
6.00
2.23
8.01
3.01
f1 (ppm)

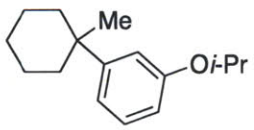
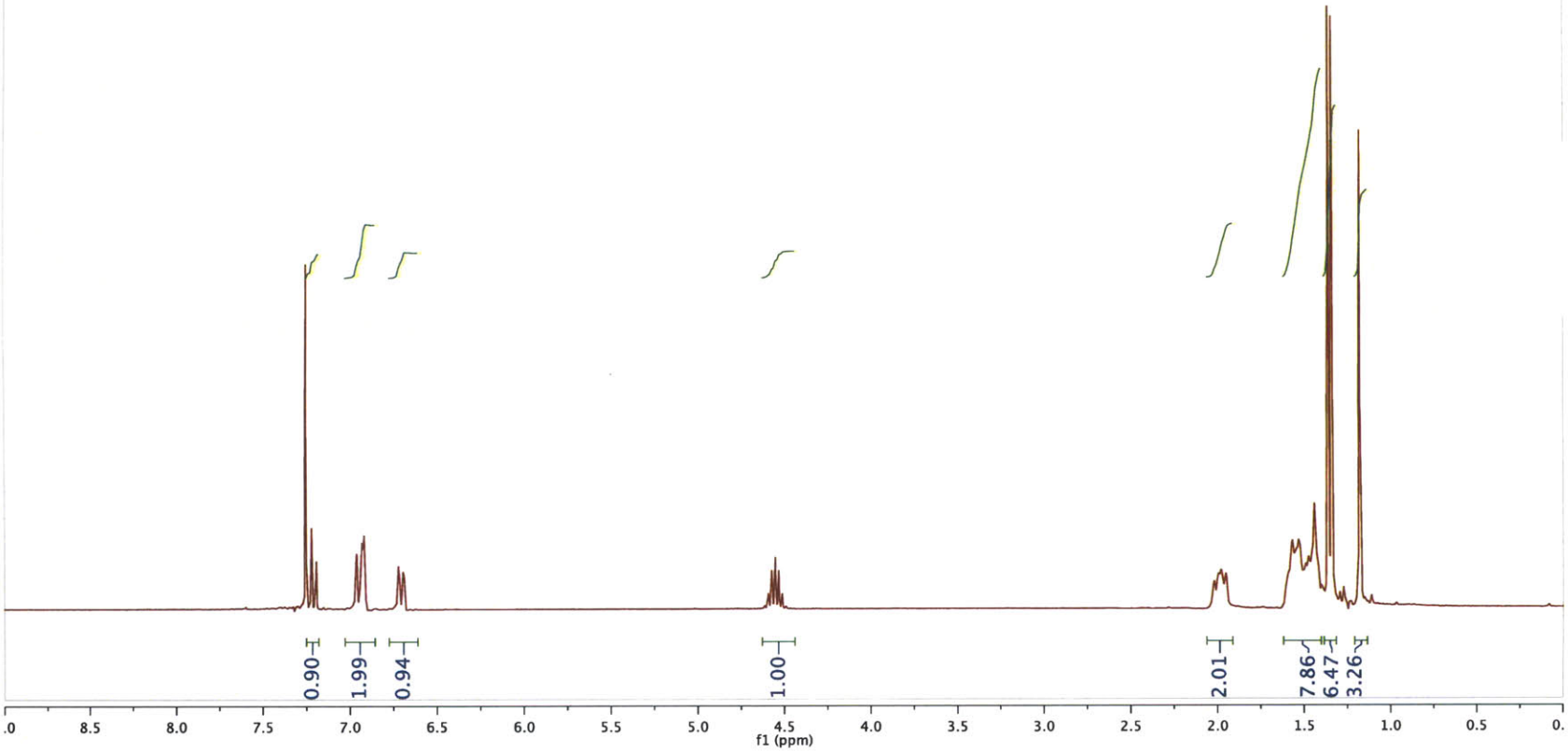


Table 5, entry 4



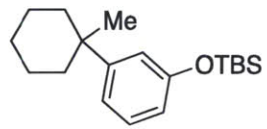
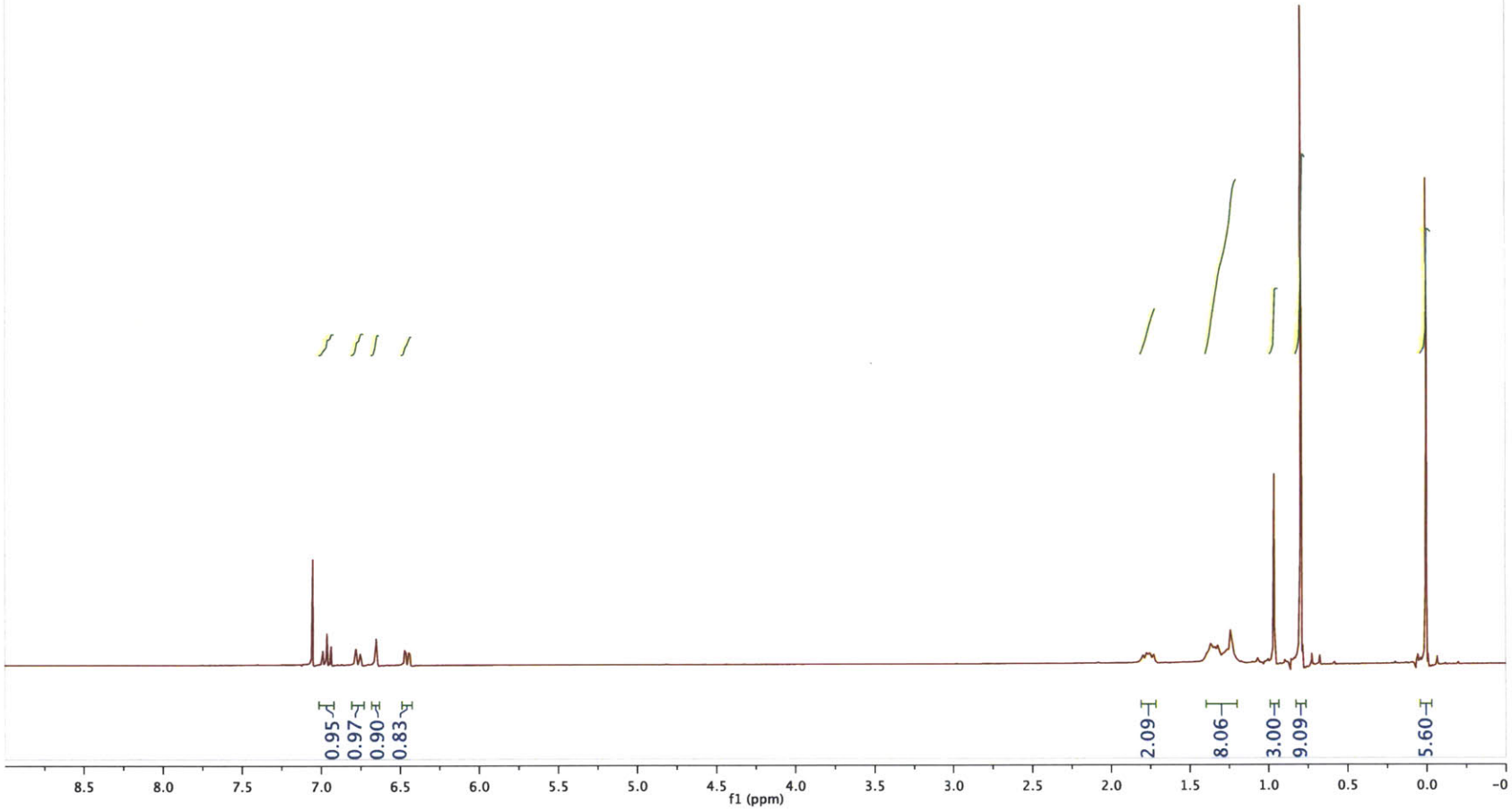
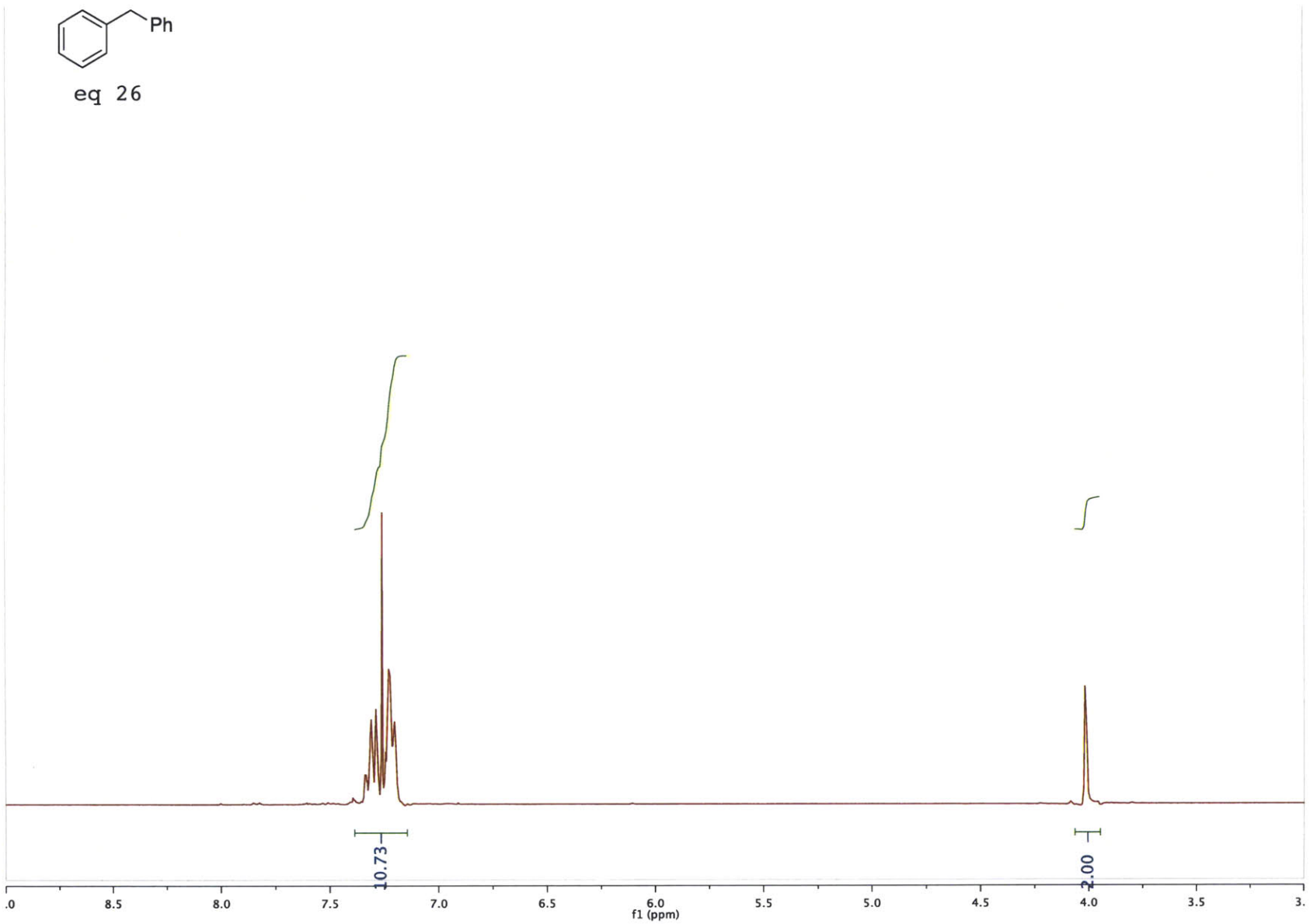


Table 5, entry 5



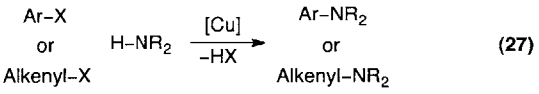

Ph
eq 26
10.73
2.00
8.5
8.0
7.5
7.0
6.5
6.0
f1 (ppm)
5.5
5.0
4.5
4.0
3.5

CHAPTER 2

Photoinduced Copper-Mediated Asymmetric C–N Couplings of Secondary Benzylic Halides and Secondary α-Haloamides with Carbazoles

A. Introduction

The first copper-mediated carbon–nitrogen bond-forming reaction between amines and aryl halides was reported by Ullmann in 1903.[45] A catalytic variant of this process, which included anilines and amides as nucleophiles, followed shortly thereafter by Goldberg in 1906.[46] Over the course of the next century, variants of these processes were typically conducted in high temperatures of up to 210 °C, resulting in a lack of generality with respect to reaction scope. In the 21st century, the introduction of new catalytic copper/ligand systems has enabled the use of milder, user-friendlier reaction conditions;[47] this has subsequently led to a dramatic expansion of reaction partner scope as well as functional group tolerance for Ullmann C–N bond-forming reactions. Presently, a range of aryl and alkenyl halides can be successfully cross-coupled with various *N*-heterocycles, amides, and amines using catalytic amounts of copper (eq 27).[48]



(27)

NR_2 = *N*-heterocycles, amides, anilines, alkylamines, ureas

With respect to the mechanism of these processes, Cu–N bond-formation is generally believed to occur first, followed by oxidative addition of the electrophilic reaction partner. Both concerted and single electron transfer pathways for oxidative addition have been proposed for

[45] Ullmann, F. *Ber. Deutsch. Chem. Ges.* **1903**, *36*, 2382.
[46] Goldberg, I. *Ber. Deutsch. Chem. Ges.* **1906**, *39*, 1691.
[47] For several seminal reports, see: a) Buchwald, S. L.; Klapars, A.; Antilla, J. C.; Job. G. E.; Wolter, M.; Kwong, F. Y.; Nordmann, G.; Hennessey, E. J., WO02/085838 (priority number US 0286268, **2001**). b) Taillefer, M.; Cristau, H.-J.; Cellier, P. P.; Cellier, J.-F.; Spindler, Env. SAU2001-1009 and SAU2001-01044; patents Fr2833947-WO0353225 (Pr. Nb. Fr 2001 16547). c) Taillefer, M.; Cristau, H.-J.; Cellier, P. P.; Spindler, J. F.; Ouali, A. Fr2840303-WO03101966 (Pr. Nb. Fr200206717).
[48] For recent reviews on Ullmann couplings, see: a) Monnier, F.; Taillefer, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971. b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131.

different catalyst systems.[49,50] While single electron pathways have been supported by computational studies on specific systems, no direct experimental evidence for single electron transfer oxidative addition has been observed in the case of thermal Ullmann C–N bond-forming reactions.

In 2012, Peters and Fu disclosed a photoinduced copper-mediated C–N bond-forming reaction between aryl halides and photoluminescent copper(I) carbazolide complex **3** (eq 28).[51,52] The reaction can be conducted with iodobenzene at room temperature using a 13-watt compact

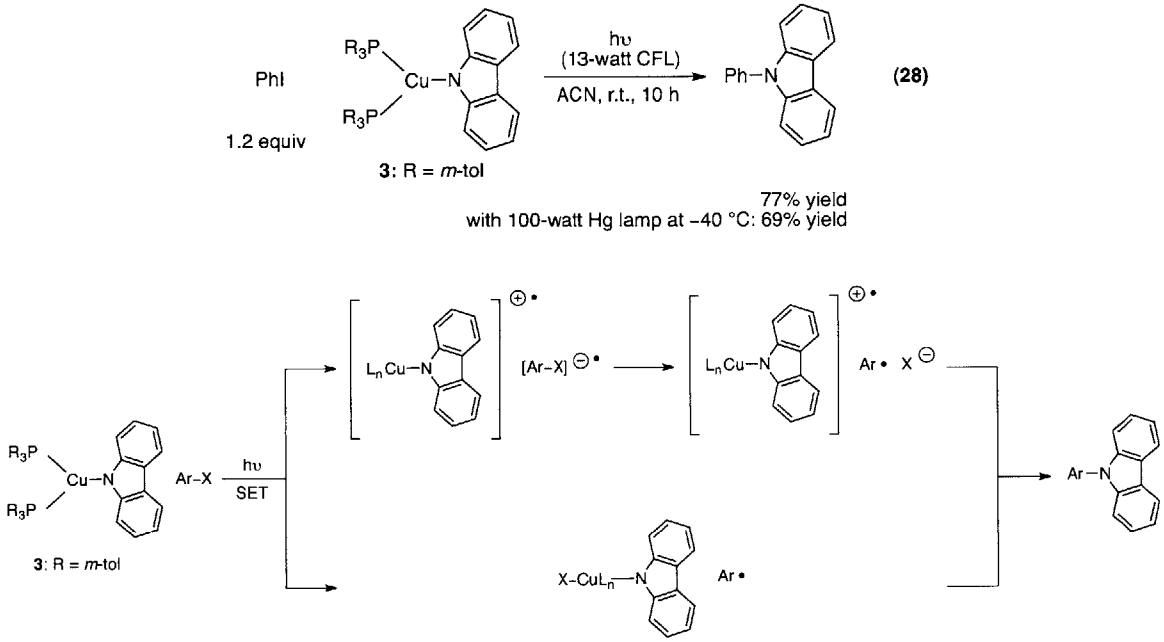


Figure 4. Outline of possible single electron transfer pathways for photoinduced C–N bond formation from **3** and an arylhalide. Top pathway: Outer sphere electron transfer. Bottom pathway: Inner sphere electron transfer.

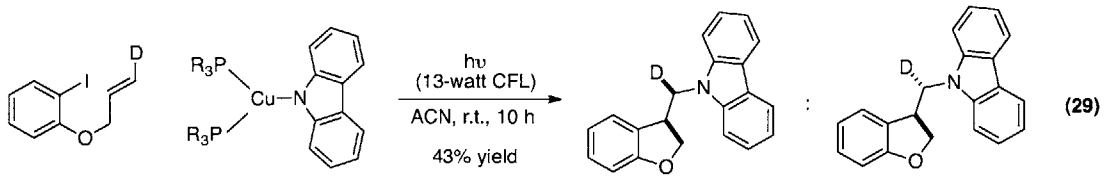
[49] Support for a concerted pathway in the context of specific systems: a) Tye, J. W.; Weng, Z.; Johns, A. M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 9971–9983. b) Giri, R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 15860–15863.

[50] Computational support for a single electron transfer pathway in the context of specific systems: Jones, G. O.; Liu, P.; Houk, K. N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 6205–6213.

[51] Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. *Science* **2012**, *338*, 647–651.

[52] For photoluminescence studies on closely related complexes to **3**, see: Lotito, K. J.; Peters, J. C. *Chem. Commun.* **2010**, *46*, 3690–3692.

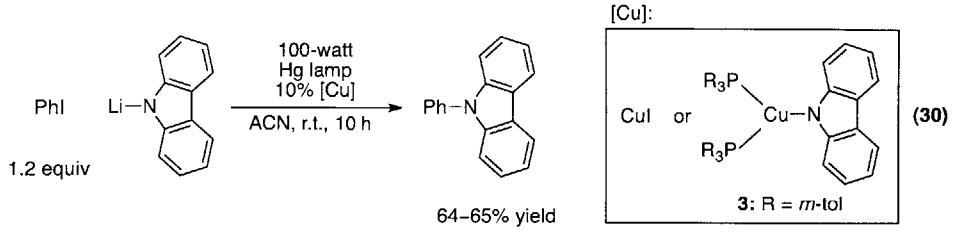
fluorescent light bulb, and at –40 °C, an almost comparable yield can be achieved using a 100-watt mercury lamp. In this process, a combination of experimental evidence is consistent with a single electron pathway for oxidative addition, which involves the intermediacy of an organic radical (possible single electron mechanisms are illustrated in Figure 4). Firstly, the origin of the undesired side-products that have been observed in this reaction can be traced to abstraction of a hydrogen atom from the solvent, acetonitrile, to generate cyanomethyl radicals. Succinonitrile, presumably arising from the homocoupling of cyanomethyl radicals, is observed in >5% yield. Additionally, when the reaction is conducted in deuterated acetonitrile, monodeuterated benzene is observed. EPR data are also consistent with a single electron transfer mechanism. Lastly, in an experiment involving a deuterium-labeled radical probe, the observation of a 1:1 diastereomeric mixture of cyclized products provides strong evidence for the intermediacy of an organic radical (eq 29).



2 **3**: R = *m*-tol **4** : **5** **(29)**

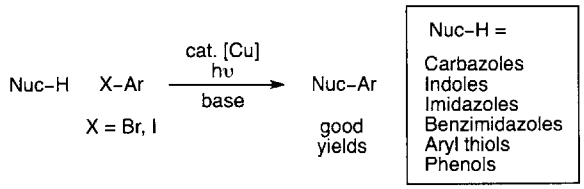
dr: 1:1

The report by Peters and Fu also discloses a photoinduced copper-*catalyzed* cross-coupling between iodobenzene and lithium carbazolide, where copper complex **3** or simple copper(I) iodide are suitable precatalysts (eq 30). Efforts to explore the scope and synthetic



(30)

utility of related copper-catalyzed processes between aryl halides and various nucleophiles have commenced. A successful photoinduced, copper-catalyzed methodology for the cross-coupling of aryl halides with aryl thiols was recented reported;[53] additional reports on photoinduced copper-catalyzed couplings of aryl halides with various *N*-heterocycles, as well as phenols, are imminent (eq 31).



(31)

The radical probe experiment in equation 29 indicates that an alkyl radical can react productively to lead to C–N bond-formation. Thus, the Fu and Peters groups considered the likelihood of successfully developing a photoinduced copper-catalyzed process using alkyl halides as electrophiles. Based on reduction potentials, this seems reasonable: Copper complex **3** is roughly estimated to have a reduction potential of –2.6 V versus SCE in acetonitrile,[51] and the outer-sphere reduction potentials of unactivated primary and secondary alkyl chlorides, bromides, and iodides have been reported to range from approximately –0.9 to –1.2 versus SCE in acetonitrile.[54] Indeed, alkyl halides do turn out to be successful coupling partners for these processes. Our groups have recently reported the photoinduced copper-catalyzed coupling of secondary (and sterically bulky primary) alkyl iodides with carbazoles.[55] Additionally, in unpublished work, primary amides have been found to be suitable coupling partners with unactivated secondary bromides and iodides. Preliminary results indicate that, upon further optimization, indoles and pyrroles may also be viable reaction partners (eq 32).

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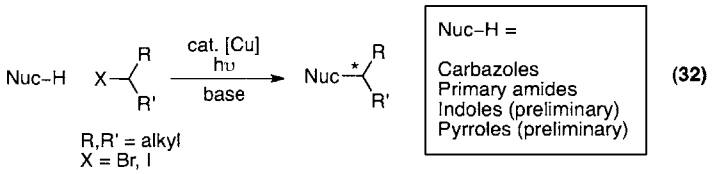
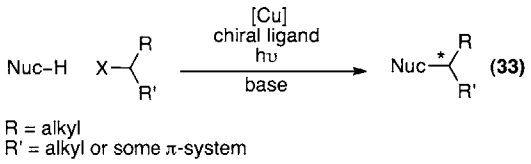
[53] Uyeda, C.; Tan, Y.; Fu, G. C.; Peters, J. C. *J. Am. Chem. Soc.* **2013**, *135*, 9548–9552.
[54] Isse, A. A.; Lin, C. Y.; Coote, M. L.; Gennaro, A. *J. Phys. Chem. B* **2011**, *115*, 678–684.
[55] Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 5129–5133.



(32)

Given that secondary alkyl halides have been demonstrated as suitable reaction partners, coupled with the hypothesis that oxidative addition in these processes occurs via a single electron transfer pathway that generates organic radical intermediates, we were inclined to explore the possibility of developing stereoconvergent asymmetric Ullmann cross-couplings between racemic secondary alkyl halides and various nucleophiles, aided by a chiral ligand (eq 33). The

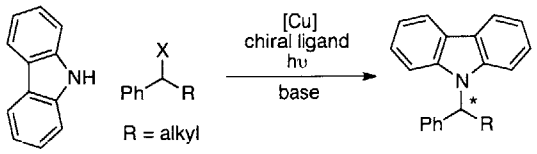


(33)

development of these processes would demonstrate a great precedent for the unique utility of photoinduced Ullmann coupling reactions, because these classes of enantioenriched coupling products are currently inaccessible via thermal Ullmann reactions.

We decided that it would be logical to first attempt to develop a copper-*mediated* asymmetric process, in order to gain a general understanding of reactivity without inviting the additional complications that may arise from catalysis. Carbazoles were selected as the first class of nucleophilic reaction partners to explore, because at the time, they were demonstrated to cross-couple with unactivated secondary alkyl iodides in good yields. Secondary benzylic halides were considered as the first class of electrophilic reaction partners to explore: We

speculated that a chiral copper complex might be better able to differentiate between the aryl and the alkyl group on a benzylic radical intermediate, as compared to differentiation between two



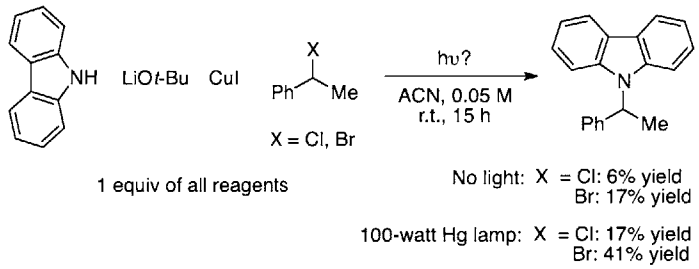
(34)

alkyl groups in the case of unactivated secondary alkyl halides. Additionally, with respect to using secondary α-halo carbonyls as reaction partners, we anticipated that excitation of the carbonyl group might lead to undesired side reactions. Thus, the project commenced between secondary benzylic halides and carbazoles (eq 34).

B. Results and Discussion

1. Experimental Design

Prior to exploring reactions that include chiral ligands, initial efforts for this project focused on establishing that copper-mediated photoinduced bond-formation between secondary benzylic halides and carbazoles is possible. First, experiments in the absence of light were conducted in order to monitor for S_N2-type background reactions (eq 35). As a starting point, the reaction conditions that were chosen for these experiments closely mimicked those conditions previously reported for photoinduced copper-catalyzed C–N coupling between alkyl iodides and carbazoles; acetonitrile was selected as the solvent, lithium *tert*-butoxide as the base, and copper (I) iodide as the copper source. Using the electrophile (1-chloroethyl)benzene, the background reaction after fifteen hours at room temperature was a promisingly low 6% yield, while with (1-bromoethyl)benzene[56], the background reaction increased to 17% yield.



(35)

These experiments were then conducted in the presence of a 100-watt mercury lamp, and for both (1-chloroethyl)benzene and (1-bromoethyl)benzene, higher yields were observed in the presence of the lamp, establishing that a photoinduced copper-mediated cross-coupling between secondary benzylic halides and carbazoles is possible (eq 35). It should be noted that the mercury lamp generates a considerable amount of heat, and therefore, the reactions were set up in a crycocool that maintained an ethanol bath at room temperature. Due to the fairly low background

[56] For the preparation of this compound, see: Art, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482–10483.

reaction observed with (1-chloroethyl)benzene, this electrophile was selected over (1-bromoethyl)benzene for further studies that employed chiral ligands.

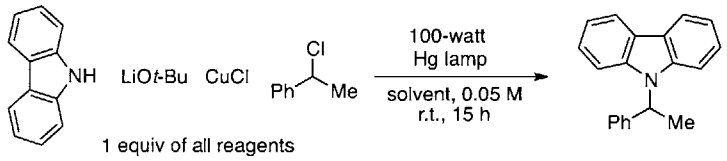
While attempting to initiate a stoichiometric copper(I) iodide/chiral ligand screen in acetonitrile, it immediately became apparent that, generally, the solubility of the combination of these reagents in acetonitrile was low. Most reactions were extremely viscous and heterogeneous; this is obviously problematic in the context of attempting to realize a photoinduced process. Attention was turned toward identifying solvents that are potentially more solubilizing than acetonitrile. At this time, it was also decided to move from copper(I) iodide to copper(I) chloride, in order to bypass potential Finkelstein reactions that could occur in the presence of an iodide. Table 6 depicts photoinduced copper-mediated reactions in DMSO, DMA, and DMF; background reactions in the absence of light were also monitored. Additionally, a rough depiction of the reaction setup is provided in Figure 5. The vial numbers provided in Table 6 correspond to vial locations with respect to the mercury lamp in Figure 5.

The first observation is that the reaction affords product in all three solvents, with very low-yielding background reactions in the absence of light. It is not necessarily important that these reactions afford product in the absence of a chiral ligand, since the ultimate goal is to develop an asymmetric process using a chiral ligand-bound copper complex. However, it is somewhat reassuring that product formation is observed in these reactions; if no yield was observed, we could not rule out that the solvent is incompatible with the copper-mediated process; in this case, all subsequent ligand screens could be in vain.

The second observation is that, with the current reaction setup, due to the 45° angle of the mercury lamp over the dewar, vial location is important. For example, drastically different yields are obtained for reactions in DMSO for vials 2 versus 3. Vial 3, while closer to the mercury

lamp, most likely has a lower yield due to obstruction of light from the vial's cap. In order to attain interpretable, reproducible results, the reaction setup had to be modified.

Table 6. Photoinduced Copper-Mediated C–N bond-formation in DMSO, DMA and DMF; Vial # denotes vial location in Figure 5.



1 equiv of all reagents

Vial #	Solvent	Yield (%)*
1	ACN (control experiment)	16
2	DMSO	69
3	DMSO	37
4	DMSO (no light)	1
5	DMA	34
6	DMA	19
7	DMA (no light)	3
8	DMF	20
9	DMF	25
10	DMF (no light)	3

*GC calibrated yields.

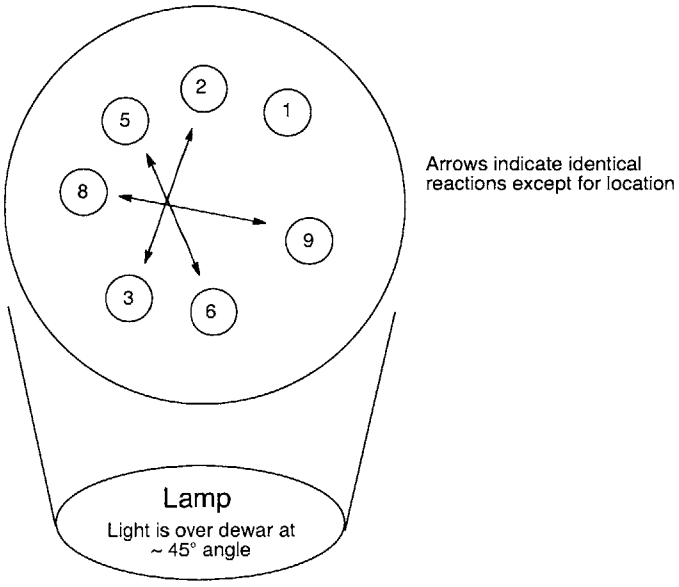


Figure 5. First-generation lamp and cryocool set-up, corresponding to the reactions in Table 6.

In an alternative setup, the mercury lamp is no longer angled over the dewar; instead, it is positioned directly over the dewar, facing straight down (Figure 6). Therefore, regardless of vial location, all vials are presumably exposed to a similar intensity of light. In this setup, vials are placed upside down in order to limit the obstruction of light from their caps; the caps are Teflon-lined and were found to maintain a reliable seal while immersed in an ethanol bath. With this setup, nine reactions were conducted in DMSO in various vial locations, and all nine reactions afforded 59–62% GC calibrated yields. Thus far, this reaction setup has been used for the duration of the project. It should be noted that the reaction in Figure 6 is also viable in a photobox when irradiated with a 350 nm light source. However, the lamp/cryocool setup was considered to be more useful, because the reaction temperature with this setup is an easily adjustable parameter. Being able to access low temperatures was postulated to potentially become very important in the context of developing an asymmetric process.

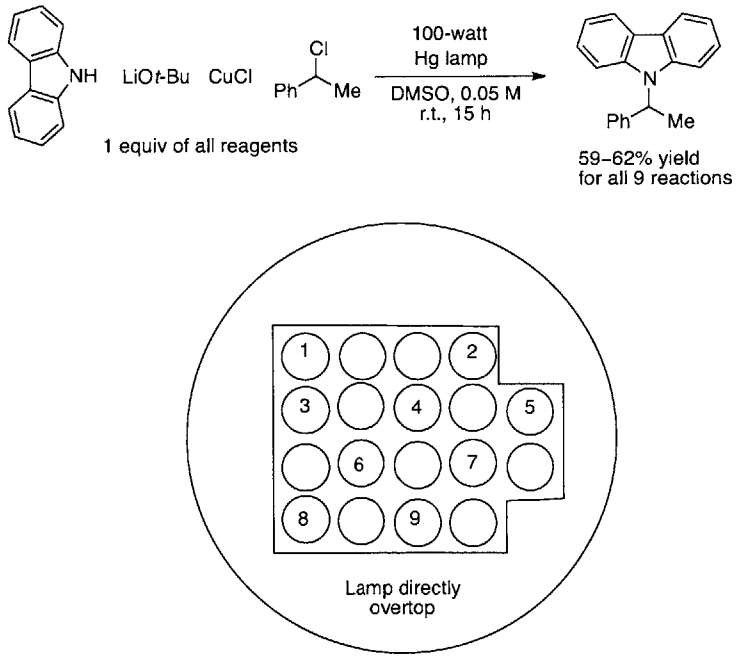
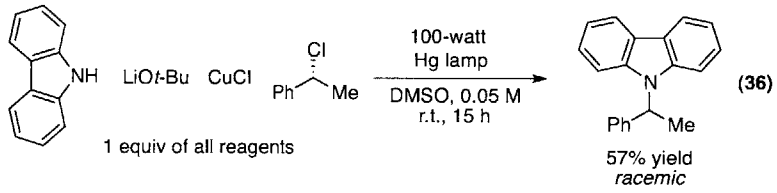


Figure 6. Second-generation reaction setup, in order to ensure reproducible results across vial locations.

Before moving forward and attempting reactions in DMSO with chiral ligands, we wanted to ensure that, in the course of the photoinduced copper-mediated reaction, the reaction mechanism allows for both enantiomers of the racemic secondary benzylic chloride to form one enantiomer of product. In order for this to happen, the mechanism of oxidative addition must not proceed via retention or inversion. To test this, enantiopure (*R*)-(1-chloroethyl)benzene[57] was synthesized and used in a reaction (eq 36). The resulting product was racemic, indicating that oxidative addition does not proceed with retention or inversion (or, that there is an alternative, more complicated mechanism for interconversion of the electrophile). This experiment validates the potential development of a stereoconvergent process.



(36)

2. Asymmetric Cross-Couplings of Secondary Benzylic Chlorides with Carbazoles

With reaction conditions and a reaction setup established, an examination of chiral ligands in DMSO commenced (Figure 7). Regarding the general procedure for these reactions with chiral ligands, lithium *tert*-butoxide and carbazole were first premixed for ten minutes in order to ensure the clean formation of lithium carbazolide. In a separate vial, copper(I) chloride and the chiral ligand were premixed for thirty minutes. The solution of lithium carbazolide was then added to the copper(I) chloride/chiral ligand mixture, and this was premixed for an additional thirty minutes prior to adding the electrophile and finally, turning on the mercury lamp.

[57] This was accessed via chlorination of commercially available (*R*)-(+)-1-phenylethanol: De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, *4*, 553–555.

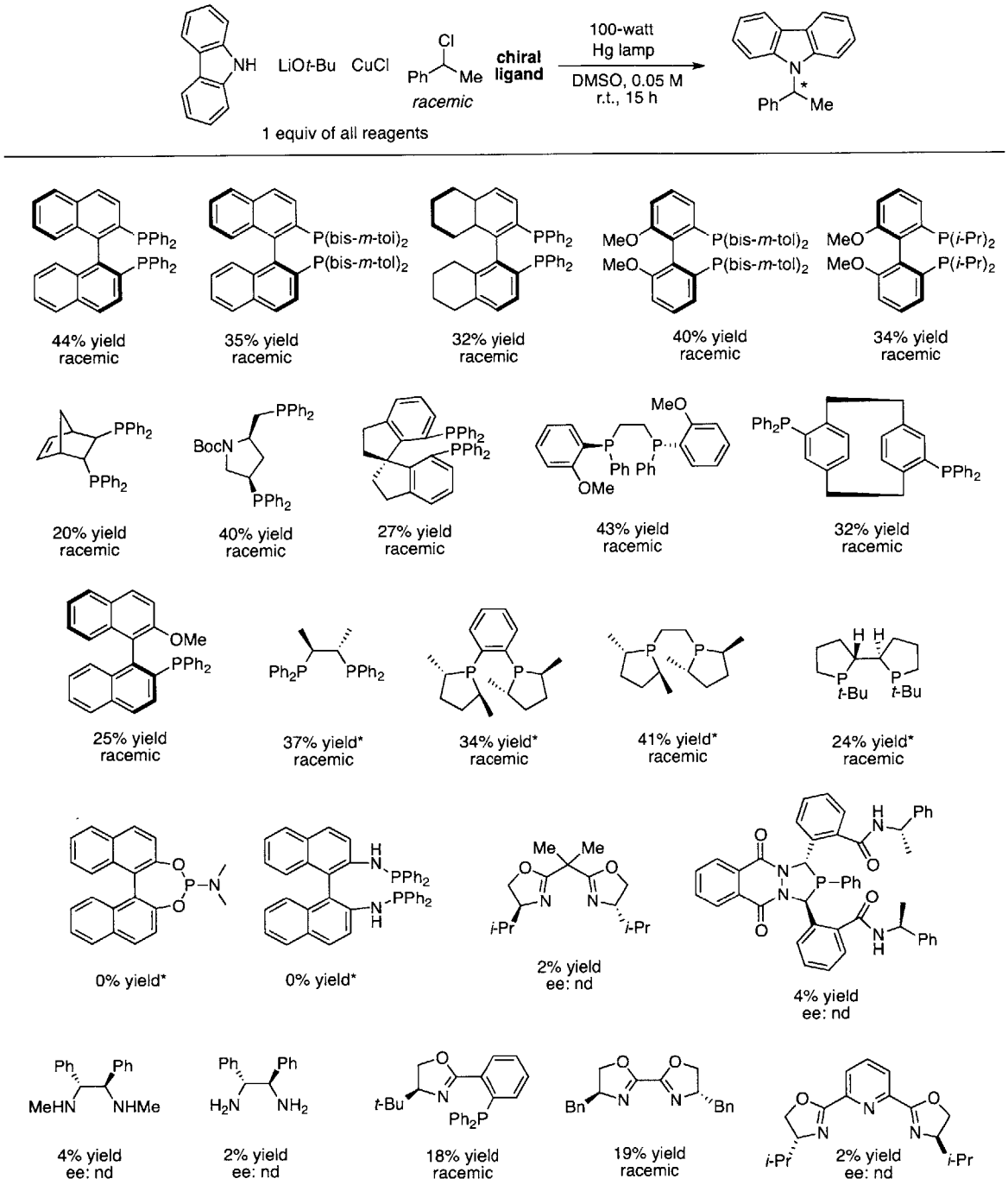
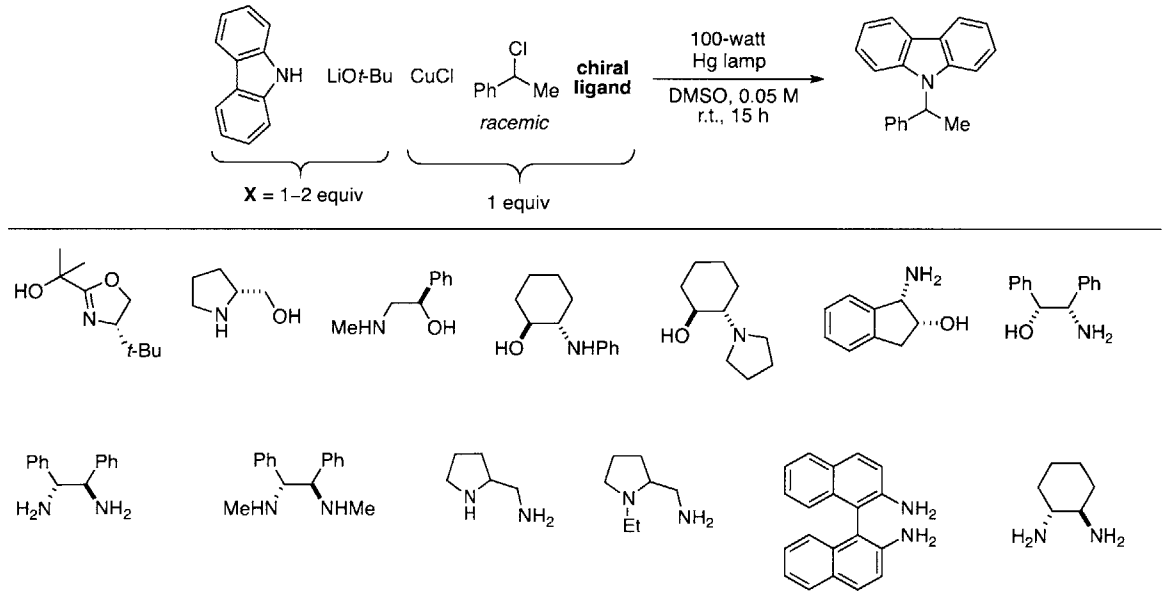


Figure 7. Examination of ligands. Yields are GC calibrated. *Denotes reactions run in 1:1 DMSO:ACN.

Many ligand classes were explored in Figure 7, including phosphines, diamines, and bisoxazoline ligands. Unfortunately, in all reactions that afforded product, the products were racemic.

Because the reactions in this first ligand screen were racemic, we surmised that the chiral ligands might be dissociating from copper, and that employing potentially anionic ligands may allow for stronger ligand coordination to copper. In Figure 8, amino alcohols and diamine ligands were screened in the presence of either one or two equivalents of carbazole and LiO*t*-Bu (generating lithium carbazolide in situ). In cases where a second equivalent of lithium carbazolide is present, deprotonation of a ligand-bound copper species was speculated to be possible. However, the difference in yield proved to be marginal when using one versus two equivalents of lithium carbazolide for a given chiral ligand, and all of the reactions in Figure 8 afforded racemic product. The amino alcohols in Figure 8 were also deprotonated with sodium



Conclusion: With **X** = 1 or 2 equiv, yields for this screen vary from 5–50%; all products are **racemic**.

Figure 8. Survey of ligands, with varying quantities of carbazolide (allowing for the potential generation of anionic ligands). Yields are GC calibrated.

hydride and then tested in reactions, but again, only racemic products were observed.

Indolides as nucleophiles were also explored in the absence and presence of chiral ligands. In the absence of chiral ligands, in solvents ACN, DMSO, and benzene, product was observed in less than 10% yield. In the presence of chiral ligands, yields were similarly low, and therefore, enantioenrichment was not determined. Electrophiles 2-bromo- and 2-chloropropanenitrile were also examined. In the absence and presence of chiral ligands, product formation was observed, but all products were racemic.

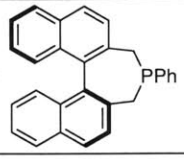
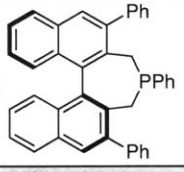
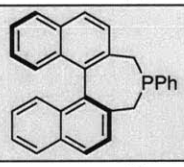
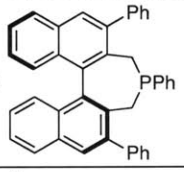
We are fortunate to possess a sizable library of chiral phosphepine ligands, which have been successfully employed in the group for asymmetric nucleophilic catalysis.[58] Two phosphepine ligands with varying degrees of steric bulk were surveyed in DMSO and benzene, for the coupling of (1-chloroethyl)benzene with carbazole. Benzene was selected as a second solvent because these reactions in DMSO turned out to have limited solubility. The first observation of enantioenrichment, specifically, 10% ee, 16% yield, was observed using ligand **L8**[59] in benzene (Table 7, entry 3). Unfortunately, efforts to reproduce this result were met with failure, and racemic product was observed over several attempts.

[58] For a recent example,and for the preparation of **L9**, see: Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293–12297.

[59] For the preparation of **L8**, see: Junge. K.; Hagemann, B.; Enthaler, S.; Spannenberg, A.; Michalik, M.; Oehme, G.; Monsees, S.; Riermeier, T.; Beller, M. *Tetrahedron: Asymmetry*, **2004**, *15*, 2621–2631.

Table 7. Survey of Chiral Phosphepine Ligands in DMSO and Benzene.

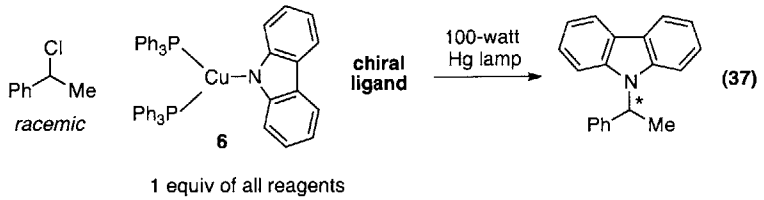
1 equiv of all reagents

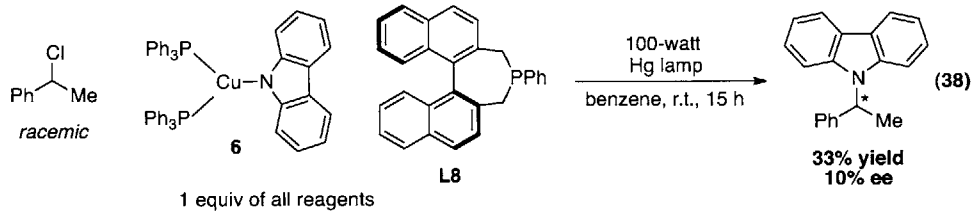
Entry	Ligand	Solvent	Yield (%)*	ee (%)
1	L8 	DMSO	56	0
2	L9 	DMSO	52	0
3	L8 	Benzene	16	10
4	L9 	Benzene	11	0

* Yields are GC calibrated.

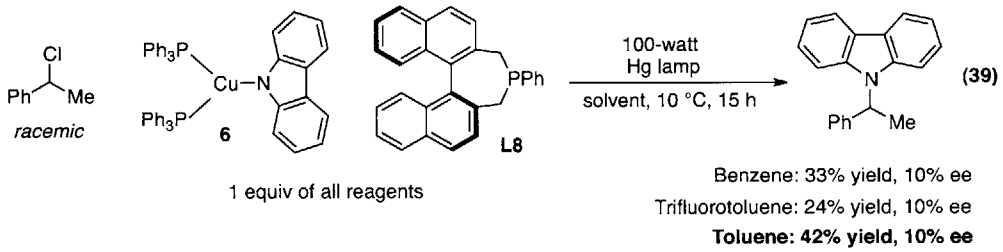
At this point, we questioned the design of our reaction. We postulated that perhaps transmetalation of lithium carbazolide to various chiral ligand-bound copper chloride complexes is a problematic step that could result in dissociation of the chiral ligand. This might help to explain the observation of only racemic products in reactions with a variety of chiral ligands. It also might explain the problem in reproducing the lead result of 10% ee (however, it was difficult to try to validate this hypothesis by attempting to detect free phosphepine ligand by ^{31}P NMR, because this reaction is very heterogeneous). We decided to continue with a new experimental design that uses premade copper carbazolide complex **6**; therefore, the potentially

problematic step, transmetalation, can be avoided (eq 37). In this general procedure, the copper complex and the chiral ligand are premixed prior to the addition of the electrophile. With this approach, we were pleased to find that we could again achieve 10% ee, and this result was very reproducible (eq 38).



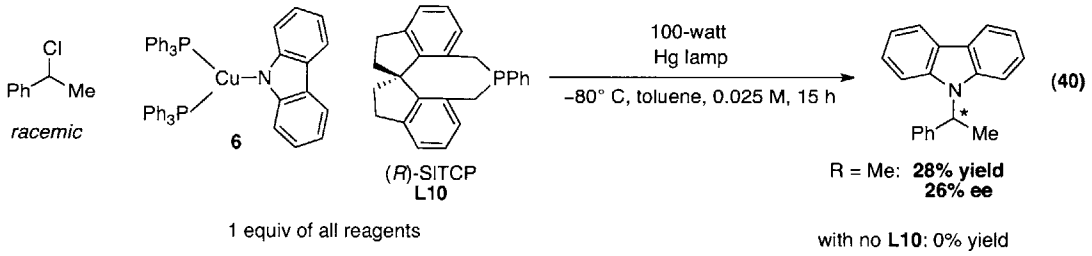


Exploring the reaction temperature was prioritized in the attempt to improve enantioselectivity. Due to benzene's high freezing point, it was desirable to explore solvents with lower freezing points. Benzene, trifluorotoluene and toluene were examined at 10 °C. Despite concern that toluene would be a problematic solvent for a postulated radical process, it afforded an improved yield of 42%, and comparable ee to benzene and trifluorotoluene (eq 39).

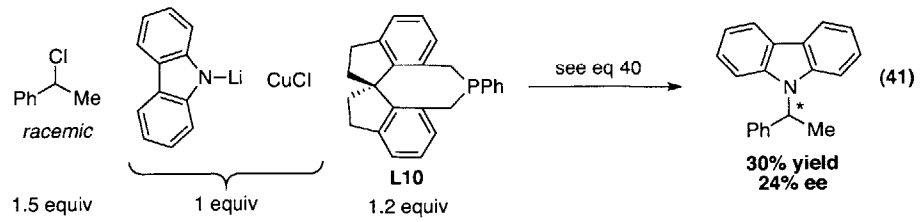


The reaction temperature was reduced to −80 °C, the low-temperature limit for the cryocool. Reaction concentration and numerous phosphepine ligands, as well as other chiral

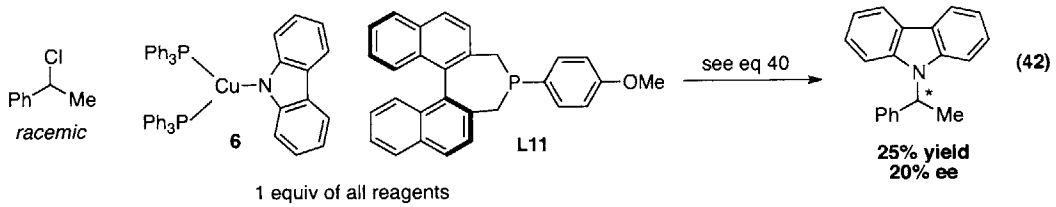
dialkylarylphosphine ligands, were examined. A clear negative correlation was observed between temperature and enantioselectivity. We achieved a new best result with the commercially available spirocyclic phosphine ligand, (*R*)-SITCP (**L10**); this affords 26% ee and 28% yield (eq 40). It should be noted that, in moving from (1-chloroethyl)benzene to more hindered (1-chloropropyl)benzene, comparable yield and enantioselectivity is observed. Additionally, in the absence of ligand **L10**, no product is observed under the conditions outlined in equation 40. This reaction is homogeneous from beginning to end.

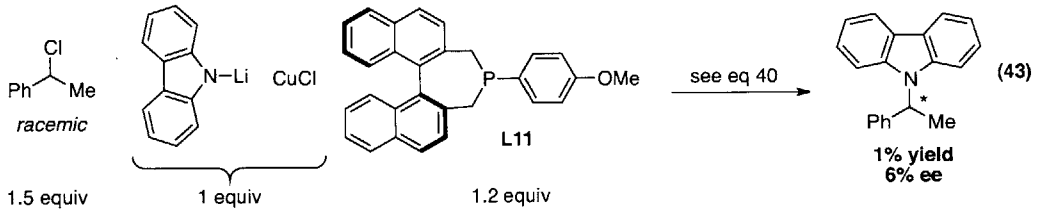


Upon achieving these results, the reaction was attempted without copper carbazolide complex **6**, and instead using the original protocol beginning with copper(I) chloride/lithium carbazolide (eq 41). In this case, instead of using carbazole and lithium *tert*-butoxide in the reaction, lithium carbazolide was premade and used directly as a white salt. **L10** was premixed with copper(I) chloride for thirty minutes (homogeneous after thirty minutes). Subsequently, lithium carbazolide was added, and the mixture was allowed to stir for an additional thirty minutes (slightly turbid, presumably due to the generation of LiBr, but otherwise the mixture appears to be homogeneous). Gratifyingly, under these conditions, the yield and enantioselectivity were comparable to the results in equation 40.



However, when ligand **L11** was compared in the case of both protocols (eq 42 & 43), drastically different results were observed; the yield and ee for the reaction using copper(I) chloride/lithium carbazolide were much lower than the corresponding reaction with premade copper carbazolide complex **6**. Notably, in contrast to **L10**, when **L11**[60] is premixed with copper(I) chloride in equation 43, the mixture remains heterogeneous. After lithium carbazolide is added, the mixture is still very hetereogeneous over the course of thirty minutes. We speculate that the poor reaction outcome in equation 43 arises from this heterogeneity, which could cause transmetalation to be a problematic step. This relationship between homogeneity and good



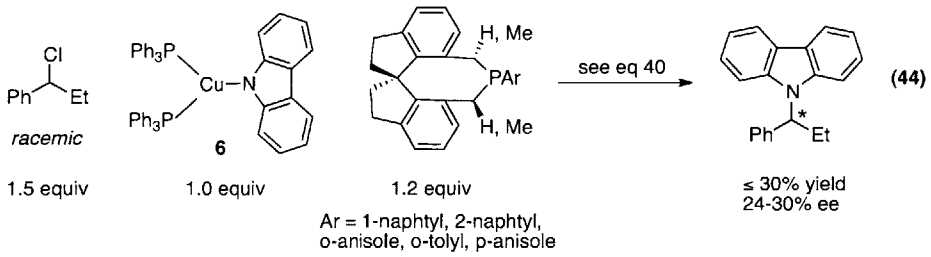


reactivity for reactions beginning with copper(I) chloride/lithium carbazolide was also observed for other phosphepine ligands – hetereogeneous reactions using copper(I) chloride generally

[60] For the preparation of **L11**, see: Enthaler, S.; Erre, G.; Junge, K.; Michalik, D.; Spannenberg, A.; Marras, F.; Gladiali, S.; Beller, M. *Tetrahedron: Asymmetry* **2007**, *18*, 1288–1298.

afforded poor results compared to analogous reactions using copper complex **6**. This observation validates the decision to examine all chiral ligands using copper carbazolide complex **6** instead of copper(I) chloride and lithium carbazolide.

Further efforts to optimize the result of 26–28% ee in equation 40 were fairly fruitless. Using two equivalents of **L10** only had a marginal effect on the reaction outcome (1–2% improvement in ee). Ethereal solvents were comparable to toluene; other solvents were inferior. Variation of the benzylic electrophile (i.e., substitution on the aryl ring, and cyclic variants) gave comparable results to (1-chloroethyl)benzene. A ligand screen of variants to **L10** was undertaken (eq 44). In conclusion, ligands containing substitution on the aryl ring afforded comparable enantioselectivities to the parent ligand **L10**, and methylation in the benzylic position of this scaffold had no effect on enantioselectivity. Yields varied, but were no greater than 30%.



A very broad ligand survey was undertaken: All previously examined ligands were reexamined (BINAP-type, oxazolines, diamines, etc.) and several new chiral ligand classes were explored, such as amino acids, deprotonated amino acids, and some commercially available chiral carbenes. All reactions that afforded <5% yield at –80 °C were also run at 0 °C in order to generate high enough yields so that enantioselectivity could be assayed. Most of these ligands completely suppressed reactivity. Bidentate triarylphosphine ligands such as BINAP afforded yields, but all products were racemic. Three new ligand classes were found to afford some

enantioselectivity: Trialkylphosphepine ligands **L12–L13**[61,62] resulted in low yields and ee's; phosphinamine ligand **L14**[63] afforded a relatively high ee of 42%, but the yield was suppressed to 6%; and lithiated amino alcohol **L15** afforded 14% ee at 0 °C (Figure 9). Subsequently, a large screen of deprotonated amino alcohols, varying the cation, was untaken. However, **L15** afforded the only enantioenriched result (reproducibly).

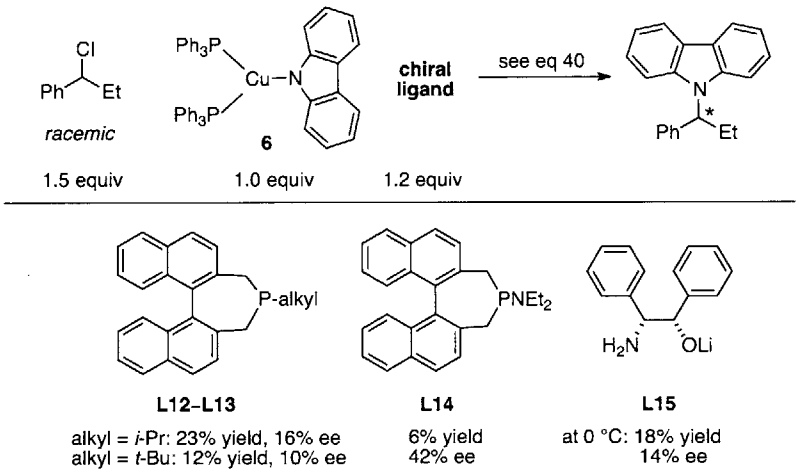
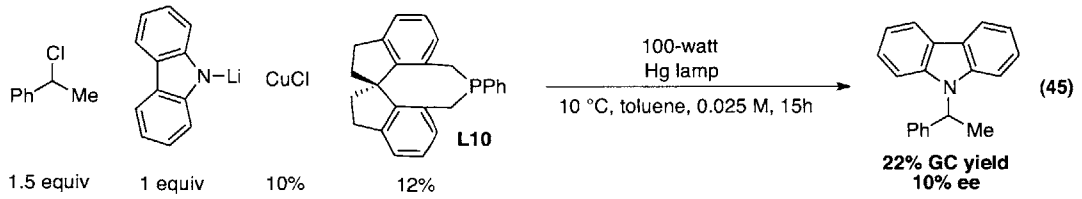


Figure 9. Other ligand classes that afford some enantioselectivity.

At this point, optimization of photoinduced copper-mediated C–N bond-formation between secondary benzylic chlorides and carbazoles was put on hold. A catalytic variant of the reaction was attempted at –80 °C, but no product formation was observed. However, upon running the catalytic reaction at 10 °C, product was formed in 22% yield and 10% ee (eq 45). While these results are modest, they indicate that: A) catalyst turnover was achieved (one), and B) some enantioselectivity was maintained (the ligand didn't completely dissociate in the presence of excess lithium carbazolide). The corresponding stoichiometric reaction at 10 °C affords 15% ee. The erosion of enantioselectivity from the stoichiometric to the catalytic reaction

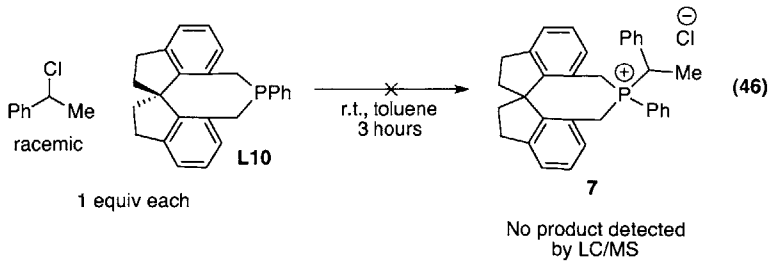
[61] For the preparation of **L12**, see ref. 60.
[62] For the preparation of **L13**, see ref. 59.
[63] For the preparation of **L14**, see: Junge, K.; Oehme, G.; Monsees, A.; Riermeier, T.; Dingerdissen, U.; Beller, M. *J. Organomet. Chem.* **2003**, *675*, 91–96.

might be partially due to ligand dissociation from copper; instead, along with a minor racemic S_N2 background reaction with lithium carbazolide in the catalytic case (1–2%). Upon finding a more enantioselective stoichiometric system, catalysis will be attempted again.



Regarding the reaction mechanism, our leading hypothesis invokes a similar mechanism to that proposed in the photoinduced copper-mediated cross-coupling of iodobenzene and carbazole (Figure 4): Single electron transfer oxidative addition generates a benzylic radical intermediate, which combines with a chiral copper complex, followed by reductive elimination (direct C–N bond formation between the benzylic radical intermediate and the chiral copper complex is also possible). Other possible mechanisms involve an S_N2 reaction between ligand **L10** and the benzylic chloride. In one case, the resulting chiral cationic species could form a tight ion pair with an anionic Cu(carbazolide)$_2$ species,[64] that might further react productively with a secondary benzylic chloride in an asymmetric process. In another case, the S_N2 reaction between **L10** and the benzylic chloride could be a kinetic resolution, where the resulting cationic species is an intermediate that further reacts with a copper carbazolide species, via another S_N2 reaction, to form enantioenriched product. However, when **L10** was mixed with (1-chloroethyl)benzene for three hours in toluene, no reaction occurred (eq 46). Additionally, at the end of the photoinduced copper-mediated cross-coupling reaction, cationic species **7** was not observed by LC/MS. Lastly, at the end of the cross-coupling reaction, remaining (1-chloroethyl)benzene is always racemic, which is inconsistent with a kinetic resolution pathway.

[64] It has been demonstrated that in the case of photoinduced copper-catalyzed cross-coupling of secondary alkyl iodides and carbazoles, Li[Cu(carbazolide)$_2$] is a chemically competent species: see ref. 55.

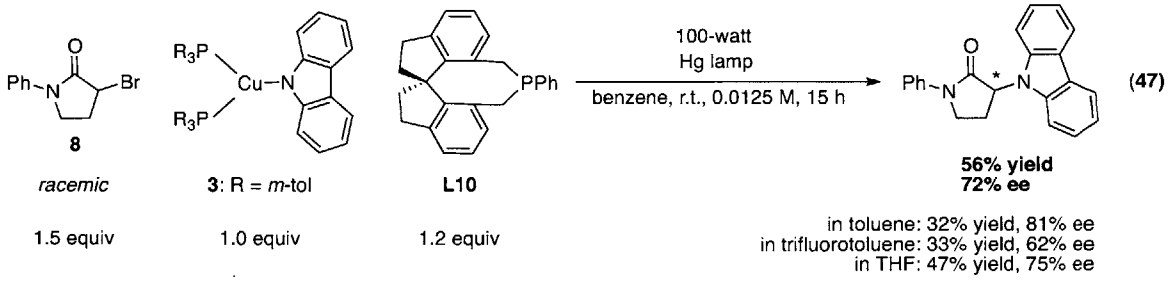


(46)

3. Asymmetric Cross-Couplings of α-Haloamides and α-Halolactams with Carbazoles

Under the best reaction conditions for the coupling of secondary benzylic chlorides with carbazole (eq 40), other electrophiles and nucleophiles were explored. Once again, reactivity with an indole was poor; only trace yield was observed, even in a reaction at room temperature. 2-bromo and 2-chloropropionitrile afforded racemic products. Unactivated electrophiles such as those described in equations 3 and 5 (Chapter 1) were tried, but only trace yields were observed, even in reactions at room temperature. An ee assay was obtained for the unactivated electrophile containing a carbamate in equation 5, despite the very low yield, but the product was racemic (this reaction was run at room temperature).

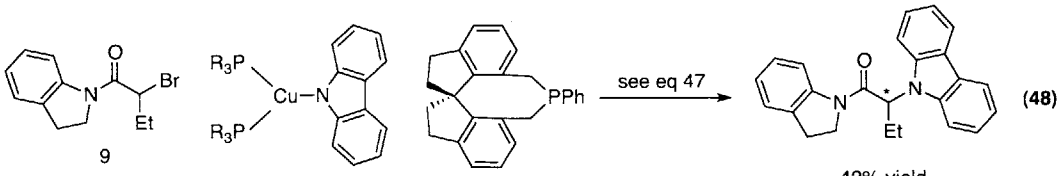
Upon exploring α-haloamides, very promising results were obtained. Under the room temperature reaction conditions illustrated in equation 47, α-bromo-γ-lactam **8** was cross-coupled with copper carbazolide complex **3** in benzene to afford product in 56% yield, 72% ee. Other solvents were surveyed: Toluene affords 81% ee, but the yield was reduced to



(47)

33%. In general, across all α-haloamides that have now been examined, yields in toluene are inferior to yields in benzene, which leads us to speculate that abstraction of a benzylic hydrogen on toluene by a secondary alkyl radical intermediate could be occurring. Trifluorotoluene results in inferior yield and ee, and THF offers comparable ee to benzene, albeit the yield is lower.

We next turned our attention to acyclic amide electrophiles. Thus far, amide **9** affords 42% yield, 71% ee (eq 48; note: based on a simultaneous control experiment that afforded a lower yield than usual, the yield of the reaction in eq 48 is most likely higher than 42%). A *N,N*-diphenylamide, an *N,N*-dialkylamide and a Weinreb amide all afford lower enantioselectivities compared to **9** (50s–60s). It is worth mentioning that, in contrast to lactam **8**, which gives comparable ee in benzene and THF, THF and other ethereal solvents have consistently resulted in reduced enantioselectivities for *acyclic* amide electrophiles. It should also be noted that at the end of all of these reactions, the remaining electrophiles are racemic.



(48)

In a survey of chiral ligands, **L10** provides the highest enantioselectivities for these amide electrophiles, although close variants of **L10** (i.e., eq 44) have yet to be examined. In toluene, these reactions are not viable at −80 °C, but intermediate temperatures still need to be explored, and solvents should be explored simultaneously at these lower temperatures. Thus far, head-to-head bromide and chloride electrophiles lead to comparable yield and ee. It will doubtlessly be possible to systematically optimize these results, and there are numerous reaction parameters remaining to explore.

C. Conclusion and Future Outlook

Photoinduced, copper-mediated asymmetric C–N cross-coupling reactions between racemic secondary alkyl electrophiles and carbazoles have been established. The commercially available chiral phosphine ligand, SITCP, was found to induce modest enantioselectivity (20s–30s) for secondary benzylic electrophiles, and good enantioselectivity (70s, with yields in the 40s–50s) for α-haloamides and α-halo-γ-lactams. In the development of these processes, the most effective strategy for surveying chiral ligands involved using premade copper complexes $(PPh_3)_2Cu$(carbazolide) **6** or $(P(m\text{-tol})_3)_2Cu$(carbazolide) **3**, and, presumably, displacing the triarylphosphine ligands in situ with more strongly coordinating chiral ligands. Once the ligand (R)-SITCP **L10** was identified using this strategy, more user-friendly reaction conditions that circumvent the use of a premade copper complex were developed for cross-coupling secondary benzylic halides, involving **L10**, copper(I) chloride, lithium carbazolide and the desired electrophile. These conditions will be tested shortly with α-haloamides and α-halolactams.

It is expected that fine-tuning of the ligand, in addition to an exploration of solvents, temperatures and concentrations, will be the path forward for the final optimization of the cross-coupling reaction between carbazolides and α-haloamides/α-halolactams. The scope of these electrophiles also needs to be further explored (with particular attention to varying lactam ring size).

Regarding the possibility for catalysis: While the S_N2 background reaction (in the absence of light) for the stoichiometric in copper process is very low with α-bromoamides at room temperature (tested in toluene and THF), under similar reaction conditions, yet in the absence of copper and in the presence stoichiometric lithium carbazolide, a strong S_N2 reaction is observed. This contributes to the challenge of developing catalytic asymmetric reaction

conditions. With tuning of temperature and solvent, along with movement to chloride electrophiles, it may be possible to develop a catalytic in copper process between lithium carbazolide and α-chloroamides or α-chlorolactams.

In the long term, in the interest of expanding the catalysis to include nucleophiles that, once deprotonated, are even more prone to S_N2 reactions with alkyl halides than carbazoles (e.g., indoles, pyrroles) it may become extremely important to establish reaction conditions that successfully employ weak bases (e.g., carbonates, phosphates), which are only able to deprotonate *N*-heterocycles upon their coordination to copper. If this is not possible, another potential way to avoid the S_N2 problem is to employ deprotonated nucleophiles containing particular countercations that still enable transmetalation, yet slow the rate of S_N2 processes.

D. Experimental

I. General Information

The following reagents were purchased and used as received: CuCl (Aldrich; note: hygroscopic), (*R*)-SITCP (Strem; note: air sensitive), PPh_3 (Acros), P(*m*-tol)$_3$ (Acros), 1-(chloroethyl)benzene (TCI America), 3-bromo-1-phenylpyrollidin-2-one **8** (Fluka; currently discontinued). Carbazole (Acros) was recrystallized twice from ethanol prior to use. Lithium carbazolide,[64] $(PPh)_3Cu$(carbazolide) **6**,[65] (P(*m*-tol$_3$))$_2$(carbazolide) **3**,[66] 1-(chloropropyl)benzene,[67] and 2-bromo-(1-indolin-1-yl)butan-1-one **9**[68] were prepared according to literature procedures. All solvents were deoxygenated and dried by sparging with argon followed by passage through an activated alumina column from PPT (Nashua, NH).

All reactions were carried out in oven-dried glassware under an atmosphere of nitrogen. HPLC analyses were carried out on an Agilent 1100 series system with Daicel CHIRALCEL® columns (internal diameter 4.6 mm, column length 250 mm, particle size 5 μ). GC analyses were obtained on an HP 6890 Series GC System with a DB-1 column (length 30 m, internal diameter 0.25 mm). LC/MS analyses were obtained on an Agilent 1290 series UHPLC with an Agilent Eclipse Plus C18 column (internal diameter 2.1 mm, column length 50 mm, particle size 1.8 μ), and a 6140 quadrupole MS.

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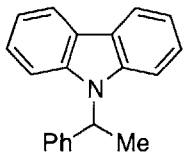
[65] See ref. 52.
[66] See ref. 51.
[67] De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, *4*, 553–555.
[68] See ref. 44.

II. Photoinduced Copper-Mediated Asymmetric C–N Couplings with Secondary Alkyl Halides and Carbazoles

General Procedure A (eq 40). In a nitrogen-atmosphere glovebox, copper complex **6** (18.8 mg, 0.025 mmol, 1.0 equiv) and (*R*)-SITCP **L10** (8.8 mg, 0.025 mmol, 1.0 equiv) were added to a 4-mL borosilicate vial equipped with a magnetic stir bar. Toluene (0.8 mL, anhydrous) was added, the vial was sealed with a Teflon-lined septum cap, and the resultant solution was stirred for 30 minutes. The solution was then added to another 4-mL borosilicate vial, equipped with a magnetic stirbar, containing the electrophile (0.038 mmol, 1.5 equiv); the vial that had contained the mixture of **6** and **L10** was rinsed with toluene (0.2 mL, anhydrous), and this was also added to the reaction mixture containing the electrophile. This vial was capped with a Teflon-lined septum cap, removed from the glovebox, and secured upside-down in a plastic vial rack immersed in a dewar containing a –80 °C ethanol bath which is maintained by a crycool and rests above a stir plate. The reaction was stirred for 2 minutes in order to equilibrate to –80 °C. Then, a 100-watt mercury lamp was placed directly above the dewar, facing straight down (see Figure 6). The entire apparatus was covered in aluminum foil, the mercury lamp was turned on, and the reaction was allowed to stir at –80 °C for 15 hours.

The reaction was then removed from the –80 °C bath, quenched with 5 μL acetic acid, and an internal standard, pentadecane (6.9 μL, 0.025 mmol, 1.0 equiv) was added. The mixture was filtered through a plug of silica, eluting with diethyl ether. The yield was then calculated by calibrated GC analysis. The filtrate was then concentrated using rotary evaporation, and the crude product was purified (for HPLC analysis) by preparatory TLC.



9-(1-Phenylethyl)-9*H*-carbazole (eq 40). This compound was prepared according to general procedure A, using (1-chloroethyl)benzene (5.0 μL, 0.038 mmol). Purification: Preparatory TLC, silica, 95% hexanes: 5% diethyl ether. 28% GC calibrated yield, 26% ee.

The ee was determined by HPLC analysis: CHIRALPAK OD-H, 4% *i*-PrOH in hexanes, 1.0 mL/min, retention times: 8.5 min (minor) and 10.8 min (major).

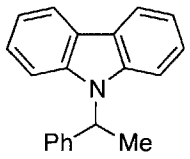
LRMS (EI; LC/MS) *m/z* ($M+H^+$) calcd for $C_{20}H_{17}N$: 272, found: 271, 272.

Note: The product retention time on HPLC, LC/MS, GC, and TLC (Rf) matches that of the independently synthesized authentic product (**10**, see SI, part III).

General Procedure B (eq 41). In a nitrogen-atmosphere glovebox, copper(I) chloride (5.0 mg, 0.05 mmol, 1.0 equiv) and (*R*)-SITCP **L10** (21.2 mg, 0.06 mmol, 1.2 equiv) were added to a 4-mL borosilicate vial equipped with a magnetic stir bar. Toluene (1.0 mL, anhydrous) was added, the vial was sealed with a Teflon-lined septum cap, and the resultant mixture was stirred for 30 minutes (the mixture becomes homogeneous). The solution was then added to another 4-mL borosilicate vial, equipped with a magnetic stirbar, containing lithium carbazolide•1.2 THF (13.0 mg, 0.05 mmol, 1.0 equiv); the vial that had contained the mixture of CuCl and **L10** was rinsed with toluene (0.5 mL, anhydrous), and this was also added to the reaction mixture containing lithium carbazolide. This vial was then sealed with a Teflon-lined septum cap, and the resultant mixture was stirred for 30 minutes (the mixture becomes slightly turbid, most likely due to LiBr, but is otherwise homogenous). The solution was then added to another 4-mL borosilicate vial, equipped with a magnetic stirbar, containing the electrophile (0.075 mmol, 1.5

equiv); the previous vial was rinsed with toluene (0.5 mL, anhydrous), and this was also added to the reaction mixture containing the electrophile. This vial was capped with a Teflon-lined septum cap, removed from the glovebox, and secured upside-down in a plastic vial rack immersed in a dewar containing a –80 °C ethanol bath which is maintained by a crycool and rests above a stir plate. The reaction was stirred for 2 minutes in order to equilibrate to –80 °C. Then, a 100-watt mercury lamp was placed directly above the dewar, facing straight down (see Figure 6). The entire apparatus was covered in aluminum foil, the mercury lamp was turned on, and the reaction was allowed to stir at –80 °C for 15 hours.

The reaction was then removed from the –80 °C bath, quenched with 5 μL acetic acid, and an internal standard, pentadecane (13.8 μL, 0.05 mmol, 1.0 equiv) was added. The mixture was filtered through a plug of silica, eluting with diethyl ether. The yield was then calculated by calibrated GC analysis. The filtrate was then concentrated using rotary evaporation, and the crude product was purified (for HPLC analysis) by preparatory TLC.



9-(1-Phenylethyl)-9*H*-carbazole (eq 41). This compound was prepared according to general procedure B, using (1-chloroethyl)benzene (10.0 μL, 0.075 mmol). Purification: Preparatory TLC, silica, 95% hexanes: 5% diethyl ether. 30% GC calibrated yield, 24% ee.

The ee was determined by HPLC analysis: CHIRALPAK OD-H, 4% *i*-PrOH in hexanes, 1.0 mL/min, retention times: 8.4 min (minor) and 10.9 min (major).

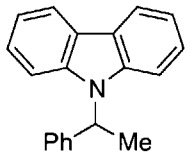
LRMS (EI; LC/MS) *m/z* ($M+H^+$) calcd for $C_{20}H_{17}N$: 272, found: 271, 272.

Note: The product retention time on HPLC, LC/MS, GC, and TLC (Rf) matches that of the independently synthesized authentic product (**10**, see SI, part III).

General Procedure C (eq 45; catalytic reaction). In a nitrogen-atmosphere glovebox, copper(I) chloride (5.0 mg, 0.05 mmol, 0.1 equiv) and (*R*)-SITCP **L10** (21.2 mg, 0.06 mmol, 0.12 equiv) were added to a 20-mL borosilicate vial equipped with a magnetic stir bar. Toluene (15.0 mL, anhydrous) was added, the vial was sealed with a Teflon-lined septum cap, and the resultant mixture was stirred for 60 minutes (the mixture becomes homogeneous). The solution was then added to a 40-mL borosilicate vial, equipped with a magnetic stirbar, containing lithium carbazolide•1.2 THF (133.0 mg, 0.50 mmol, 1.0 equiv); the vial that had contained the mixture of CuCl and **L10** was rinsed with toluene (5.0 mL, anhydrous), and this was also added to the reaction mixture containing lithium carbazolide. To the mixture was then added the electrophile (0.75 mmol, 1.5 equiv). The vial was capped with a Teflon-lined septum cap, removed from the glovebox, and secured upside-down with copper wire in a dewar containing a 10 °C ethanol bath which is maintained by a crycool and rests above a stir plate. The reaction was stirred for 2 minutes in order to equilibrate to 10 °C. Then, a 100-watt mercury lamp was placed directly above the dewar, facing straight down (see Figure 6). The entire apparatus was covered in aluminum foil, the mercury lamp was turned on, and the reaction was allowed to stir at 10 °C for 15 hours.

The reaction was then removed from the 10 °C bath, quenched with 50 μL acetic acid, and an internal standard, pentadecane (138.0 μL, 0.5 mmol, 1.0 equiv) was added. The mixture was filtered through a plug of silica, eluting with diethyl ether. The yield was then calculated by

calibrated GC analysis. The filtrate was then concentrated using rotary evaporation, and the crude product was purified (for HPLC analysis) by preparatory TLC.



9-(1-Phenylethyl)-9*H*-carbazole (eq 45). This compound was prepared according to general procedure C, using (1-chloroethyl)benzene (100.0 μL, 0.75 mmol). Purification: Preparatory TLC, silica, 95% hexanes: 5% diethyl ether. 22% GC calibrated yield, 10% ee.

The ee was determined by HPLC analysis: CHIRALPAK OD-H, 4% *i*-PrOH in hexanes, 1.0 mL/min, retention times: 8.6 min (minor) and 10.9 min (major).

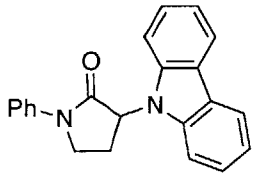
LRMS (EI; LC/MS) *m/z* ($M+H^+$) calcd for $C_{20}H_{17}N$: 272, found: 271, 272.

Note: The product retention time on HPLC, LC/MS, GC, and TLC (Rf) matches that of the independently synthesized authentic product (**10**, see SI, part III).

General Procedure D (eq 47 & 48). In a nitrogen-atmosphere glovebox, copper complex **3** (21.0 mg, 0.025 mmol, 1.0 equiv) and (*R*)-SITCP **L10** (10.6 mg, 0.03 mmol, 1.2 equiv) were added to a 4-mL borosilicate vial equipped with a magnetic stir bar. Benzene (1.8 mL, anhydrous) was added, the vial was sealed with a Teflon-lined septum cap, and the resultant solution was stirred for 30 minutes. The solution was then added to another 4-mL borosilicate vial, equipped with a magnetic stirbar, containing the electrophile (0.038 mmol, 1.5 equiv); the vial that had contained the mixture of **3** and **L10** was rinsed with benzene (0.2 mL, anhydrous), and this was also added to the reaction mixture containing the electrophile. This vial was capped with a Teflon-lined septum cap, removed from the glovebox, and secured upside-down in a

plastic vial rack immersed in a dewar containing a room temperature ethanol bath which is maintained by a crycool and rests above a stir plate. Then, a 100-watt mercury lamp was placed directly above the dewar, facing straight down (see Figure 6). The entire apparatus was covered in aluminum foil, the mercury lamp was turned on, and the reaction was allowed to stir at room temperature for 15 hours.

The reaction was then removed from the ethanol bath, quenched with 5 μL acetic acid, and an internal standard was added. The mixture was filtered through a plug of silica, eluting with diethyl ether. The yield was then calculated using either calibrated GC or LC analysis. The filtrate was then concentrated using rotary evaporation, and the crude product was purified (for HPLC analysis) by preparatory TLC.

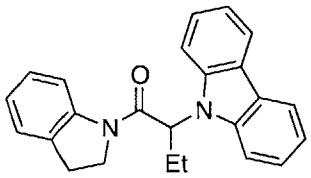


3-(9H-Carbazol-9-yl)-1-phenylpyrrolidin-2-one (eq 47). This compound was synthesized according to general procedure D, using 3-bromo-1-phenylpyrollidin-2-one **8** (9.0 mg, 0.038 mmol). The internal standard added to this reaction was pentadecane (6.9 μL, 0.025 mmol, 1.0 equiv); the yield was calculated by calibrated GC analysis. Purification: Preparatory TLC, silica, 50% hexanes: 50% diethyl ether. 56% GC calibrated yield, 72% ee.

The ee was determined by HPLC analysis: CHIRALPAK IC, 20% *i*-PrOH in hexanes, 1.0 mL/min, retention times: 36.0 min (minor) and 42.5 min (major).

LRMS (EI; LC/MS) *m/z* ($M+H^+$) calcd for $C_{22}H_{18}N_2O$: 327, found: 327.

Note: The product retention time on HPLC, LC/MS, GC, and TLC (Rf) matches that of the independently synthesized authentic product (**11**, see SI, part III).



2-(9H-Carbazol-9-yl)-1-(indolin-1-yl)butan-1-one (eq 48). This compound was synthesized according to general procedure D, using 2-bromo-(1-indolin-1-yl)butan-1-one **9** (10.2 mg, 0.038 mmol). The internal standard added to this reaction was anisole (5.4 μL, 0.05 mmol, 2.0 equiv); the yield was calculated by calibrated LC analysis (this compound does not elute on GC). Purification: Preparatory TLC, silica, 50% hexanes: 50% diethyl ether. 42% LC calibrated yield, 71% ee.

The ee was determined by HPLC analysis: CHIRALPAK AD-H, 3% *i*-PrOH in hexanes, 1.0 mL/min, retention times: 24.3 min (major) and 26.0 min (minor).

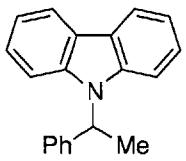
LRMS (EI; LC/MS) *m/z* ($M+H^+$) calcd for $C_{24}H_{22}N_2O$: 355, found: 355.

Note: The product retention time on HPLC, LC/MS and TLC (Rf) matches that of the independently synthesized authentic product (**12**, see SI, part III).

IV. Syntheses and Full Characterization of Authentic Products

General Procedure E. Potassium *tert*-butoxide (41.5 mg, 0.37 mmol, 1 equiv) and carbazole (62.0 mg, 0.37 mmol, 1 equiv) were added to a 20-mL vial equipped with a stir bar. The flask was capped with a septum cap and purged with nitrogen. THF (10 mL, anhydrous) was added, and the reactants were stirred for 20 minutes. The benzylic electrophile was added via

syringe (0.37 mmol, 1 equiv). The reaction was allowed to stir at 60 °C for 24 h. The reaction was allowed to cool to room temperature, and filtrate was then concentrated using rotary evaporation. The crude product was purified by column chromatography (Biotage, silica) with 0→60% diethyl ether/hexanes.



9-(1-phenylethyl)-9*H*-carbazole (10). This compound was prepared according to general procedure E, using (1-chloroethyl)benzene (49 μL, 0.37 mmol). Yield: 24 mg (24%).

HPLC assay for this racemic compound: CHIRALPAK OD-H, 4% *i*-PrOH in hexanes, 1.0 mL/min, retention times: 9.4 min and 11.0 min (there was a difference in time of several months between this assay and the corresponding enantioenriched assays, hence the slight shift in retention times).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.6 (dd, 2H, J = 7.7, 1.1), 7.41–7.23 (m, 11H), 6.11 (q, 1H, J = 7.1 Hz), 2.03 (d, 3H, J = 6.0 Hz).

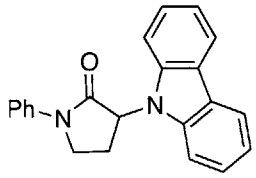
^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 139.8, 128.7, 127.3, 126.5, 125.5, 123.4, 120.3, 119.0, 110.1, 52.3, 17.4.

FT-IR 1481, 1451, 1327, 1224, 1154, 1086, 770, 749, 723 (film) cm^{-1}.

LRMS (EI; LC/MS) *m/z* ($M+H^+$) calcd for $C_{20}H_{17}N$: 272, found: 271, 272.

General Procedure F. The electrophile (0.37 mmol, 1 equiv) and lithium carbazolide•1.2 THF (96 mg, 0.37 mmol, 1 equiv) were added to a 4-mL vial equipped with a stir bar. The vial was capped with a septum cap and purged with nitrogen. THF (3 mL,

anhydrous) was added, and the reaction was allowed to stir at 60 °C for 24 h. The reaction was allowed to cool to room temperature, and filtrate was then concentrated using rotary evaporation. The crude product was purified by column chromatography (Biotage, silica) with 10→100% diethyl ether/hexanes.



3-(9H-Carbazol-9-yl)-1-phenylpyrrolidin-2-one (11). This compound was prepared according to general procedure F, using 3-bromo-1-phenylpyrollidin-2-one **8** (89 mg, 0.37 mmol). Yield: 56 mg (46%).

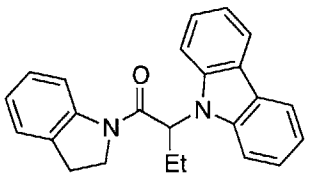
HPLC assay for this racemic compound: CHIRALPAK IC, 20% *i*-PrOH in hexanes, 1.0 mL/min, retention times: 34.9 min and 41.4 min.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, 2H, J = 6.0 Hz), 7.8 (d, 2H, J = 6.0 Hz), 7.49–7.41 (m, 4H), 7.35–7.23 (m, 5H), 5.61 (t, 1H, J = 10.1 Hz), 4.10–4.06 (m, 2H), 2.72–2.63 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 139.2, 129.1, 125.8, 125.3, 123.7, 120.6, 119.7, 119.6, 119.2, 56.1, 44.9, 23.2 (Missing 1C).

FT-IR 1705, 1598, 1484, 1455, 1389, 1306, 1240, 750, 723 (film) cm^{-1}.

LRMS (EI; LC/MS) *m/z* ($M+H^+$) calcd for $C_{22}H_{18}N_2O$: 327, found: 327.



2-(9H-Carbazol-9-yl)-1-(indolin-1-yl)butan-1-one (12). This compound was prepared according to general procedure F, using 2-bromo-(1-indolin-1-yl)butan-1-one **9** (99 mg, 0.37 mmol). Yield: 54 mg (41%).

HPLC assay for this racemic compound: CHIRALPAK AD-H, 3% *i*-PrOH in hexanes, 1.0 mL/min, retention times: 24.9 min and 26.6 min.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (d, 1H, J = 8.1 Hz), 8.11 (d, 2H, J = 6.0 Hz), 7.60 (d, 2H, J = 8.3 Hz), 7.48–7.43 (m, 2H), 7.29–7.18 (m, 3H), 7.07–6.96 (m, 2H), 5.27–5.22 (m, 1H), 3.90 (td, 1H, J = 9.9, 4.4 Hz), 3.04–2.84 (m, 2H), 2.73–2.64 (m, 1H), 2.54–2.30 (m, 2H), 0.84 (t, 3H, J = 7.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 143.0, 139.7, 131.1, 127.4, 126.1, 124.4, 124.2, 123.2, 120.5, 119.6, 117.4, 109.6, 59.1, 47.7, 28.4, 23.5, 11.0

FT-IR (film) 3046, 2969, 1781, 1654, 1597, 1481, 1453, 1405, 1336, 1326, 1221, 1157, 909, 751, 725 cm^{-1}.

LRMS (EI; LC/MS) *m/z* ($M+H^+$) calcd for $C_{24}H_{22}N_2O$: 355, found: 355.

III. HPLC and ^{1}H NMR Spectra of Selected Compounds

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Acq. Instrument	: Instrument 1	Inj Volume	: 15 µl
Different Inj Volume from Sequence !		Actual Inj Volume	: 10 µl
Acq. Method	: C:\HPCHEM\1\METHODS\OD-04-20.M		
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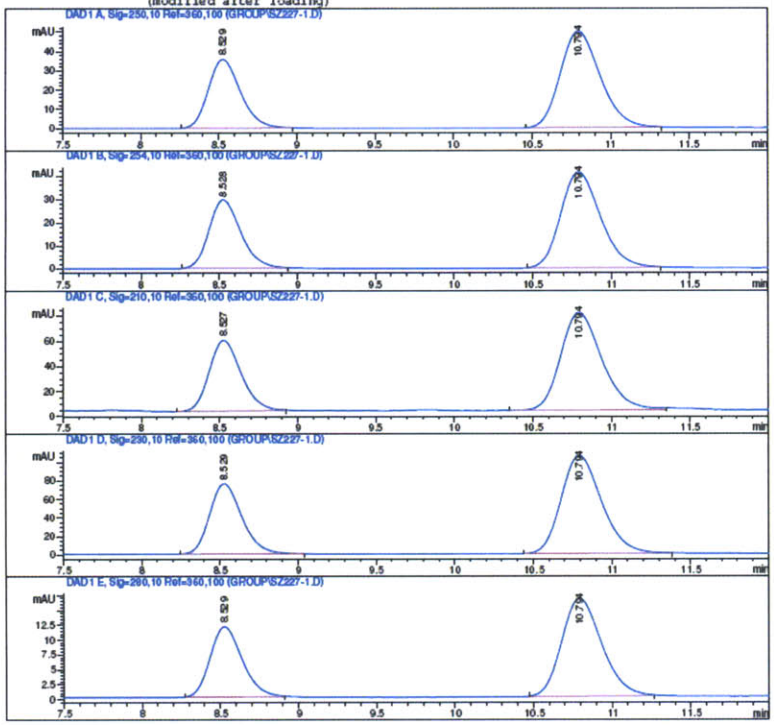

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Area Percent Report

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Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.529	BB	0.2224	516.67139	35.79851	36.7221
2	10.794	BB	0.2744	890.30341	49.84429	63.2779
Totals :				1406.97479	85.64280	

Results obtained with enhanced integrator!

Signal 2: DAD1 B, Sig=254,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.528	BB	0.2220	426.79135	29.64708	36.6582
2	10.794	BB	0.2763	737.45459	41.29683	63.3418
Totals :				1164.24594	70.94391	

Results obtained with enhanced integrator!

Signal 3: DAD1 C, Sig=210,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.527	VB	0.2179	814.59924	56.59964	36.0492
2	10.794	VB	0.2849	1439.48828	78.13263	63.7030
3	14.412	BV	0.0610	5.59816	1.33158	0.2477
Totals :				2259.68568	136.06385	

Results obtained with enhanced integrator!

Signal 4: DAD1 D, Sig=230,10 Ref=360,100

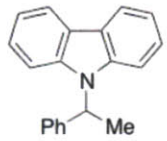
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.529	BB	0.2227	1098.08679	75.93232	36.7039
2	10.794	BB	0.2751	1893.66113	105.66508	63.2961
Totals :				2991.74792	181.59740	

Results obtained with enhanced integrator!

Signal 5: DAD1 E, Sig=280,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.529	BB	0.2197	170.23125	11.84487	36.7483
2	10.794	BB	0.2733	293.00418	16.49063	63.2517
Totals :				463.23543	28.33551	

Results obtained with enhanced integrator!



eq 40

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Acq. Instrument : Instrument 1 Inj Volume : 5 µl
Different Inj Volume from Sequence ! Actual Inj Volume : 10 µl
Acq. Method : C:\HPCHEM\1\METHODS\ODH-0440.M
Last changed : 5/17/2012 8:24:53 PM by JTM
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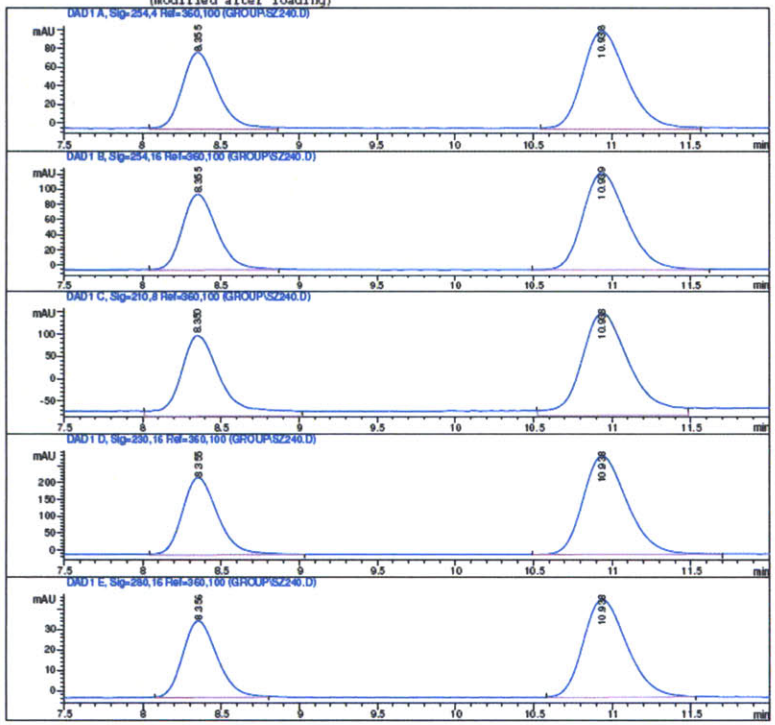


Data File C:\HPCHEM\1\DATA\GROUP\SZ240.D

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.355	VB	0.2417	1282.34583	82.33479	38.1968
2	10.938	VB	0.2921	2074.86157	105.18024	61.8032
Totals :				3357.20740	187.51502	

Results obtained with enhanced integrator!

Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.355	VB	0.2388	1527.29004	99.63960	38.0760
2	10.939	VB	0.3008	2483.87451	127.74691	61.9240
Totals :				4011.16455	227.38651	

Results obtained with enhanced integrator!

Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.350	VV	0.2654	3296.47192	180.23219	40.1427
2	10.938	VV	0.3149	4915.41260	228.58635	59.8573
Totals :				8211.88452	408.81854	

Results obtained with enhanced integrator!

Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.355	BB	0.2391	3561.01514	229.45567	38.5914
2	10.938	VB	0.2989	5666.46240	291.39731	61.4086
Totals :				9227.47754	520.85298	

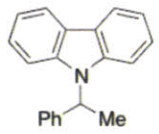
Results obtained with enhanced integrator!

Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.356	BB	0.2350	569.29224	37.51745	38.0610
2	10.938	BB	0.2934	926.44586	47.96332	61.9390
Totals :				1495.73810	85.48077	

Results obtained with enhanced integrator!

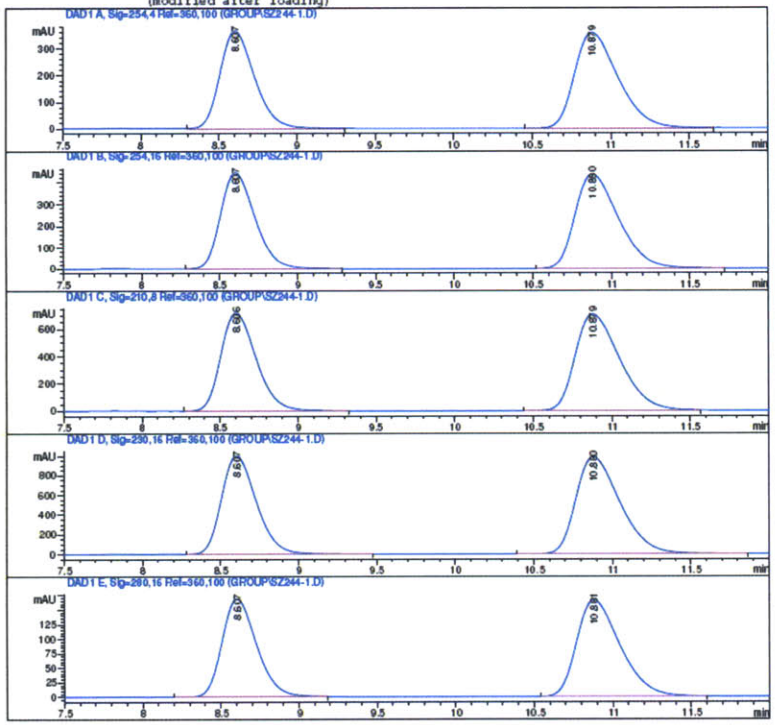
*** End of Report ***



eq 41

Data File C:\HPCHEM\1\DATA\GROUP\SZ244-1.D

Injection Date	: 2/4/2013 12:54:51 PM	Seq. Line	: 12
Sample Name	:	Location	: Vial 1
Acq. Operator	: JTM	Inj	: 1
Acq. Instrument	: Instrument 1	Inj Volume	: 5 µl
Different Inj Volume from Sequence !		Actual Inj Volume	: 10 µl
Acq. Method	: C:\HPCHEM\1\METHODS\ODH-0420.M		
Last changed	: 2/4/2013 12:53:45 PM by JTM (modified after loading)		
Analysis Method	: C:\HPCHEM\1\METHODS\IA-1020.M		
Last changed	: 8/13/2013 10:46:12 PM by TMB (modified after loading)		



Data File C:\HPCHEM\1\DATA\GROUP\SZ244-1.D

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.607	BV	0.2386	5720.22705	365.46887	45.0102
2	10.879	VV	0.2930	6988.49707	359.18396	54.9898
Totals :				1.27087e4	724.65283	

Results obtained with enhanced integrator!

Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.607	VB	0.2396	6909.12451	443.91464	44.9057
2	10.880	BB	0.2982	8476.73828	437.24805	55.0943
Totals :				1.53859e4	881.16269	

Results obtained with enhanced integrator!

Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.606	VV	0.2480	1.15216e4	722.82343	44.9908
2	10.879	VV	0.3015	1.40872e4	710.07629	55.0092
Totals :				2.56087e4	1432.89972	

Results obtained with enhanced integrator!

Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.607	VB	0.2414	1.56965e4	998.74359	44.8985
2	10.880	VB	0.3002	1.92635e4	984.77979	55.1015
Totals :				3.49600e4	1983.52338	

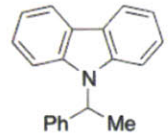
Results obtained with enhanced integrator!

Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.607	BB	0.2401	2597.00928	168.22852	44.7752
2	10.881	BB	0.2970	3203.09937	166.09877	55.2248
Totals :				5800.10864	334.32729	

Results obtained with enhanced integrator!

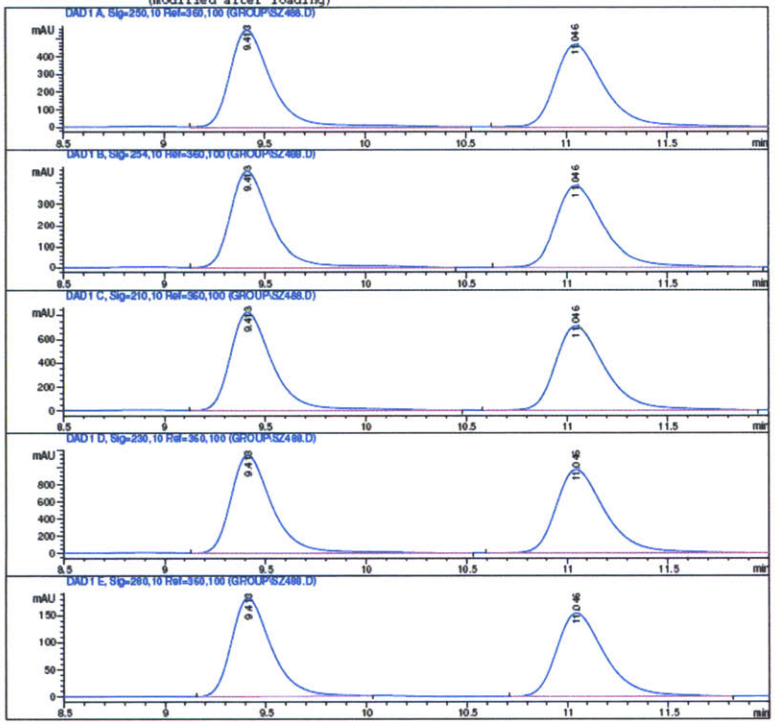
*** End of Report ***



eq 45

Data File C:\HPCHEM\1\DATA\GROUP\SZ488.D

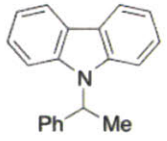
Injection Date	: 8/14/2013 2:00:36 AM	Seq. Line	: 1
Sample Name	:	Location	: Vial 1
Acq. Operator	: MK	Inj	: 1
Acq. Instrument	: Instrument 1	Inj Volume	: 15 µl
Different Inj Volume from Sequence !		Actual Inj Volume	: 1 µl
Acq. Method	: C:\HPCHEM\1\METHODS\OD-04-40.M		
Last changed	: 8/14/2013 1:59:18 AM by MK (modified after loading)		
Analysis Method	: C:\HPCHEM\1\METHODS\OJ-10-20.M		
Last changed	: 8/13/2013 10:43:06 PM by MK (modified after loading)		



Data File C:\HPCHEM\1\DATA\GROUP\SZ488.D

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs



10

Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.413	VB	0.2168	7866.17822	550.18707	50.0398
2	11.046	BB	0.2545	7853.67969	466.24896	49.9602
Totals :				1.57199e4	1016.43604	

Results obtained with enhanced integrator!

Signal 2: DAD1 B, Sig=254,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.413	VB	0.2164	6482.79297	454.45325	50.0259
2	11.046	BB	0.2562	6476.09082	385.16144	49.9741
Totals :				1.29589e4	839.61469	

Results obtained with enhanced integrator!

Signal 3: DAD1 C, Sig=210,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.413	VV	0.2222	1.21956e4	826.30603	49.7948
2	11.046	VV	0.2644	1.22961e4	708.78693	50.2052
Totals :				2.44917e4	1535.09296	

Results obtained with enhanced integrator!

Signal 4: DAD1 D, Sig=230,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.413	VB	0.2163	1.62963e4	1143.16467	49.9006
2	11.046	BB	0.2564	1.63612e4	972.12799	50.0994
Totals :				3.26575e4	2115.29266	

Results obtained with enhanced integrator!

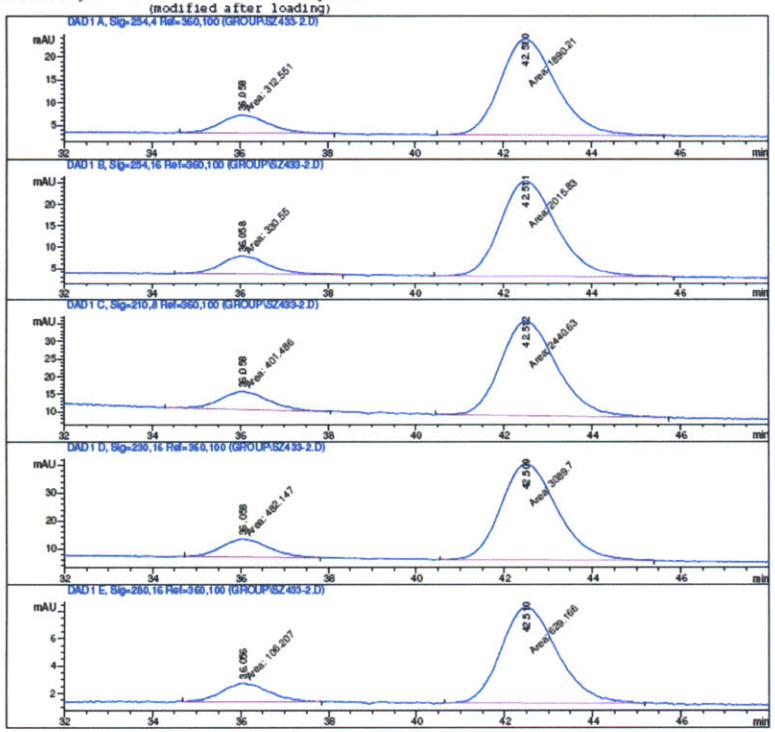
Signal 5: DAD1 E, Sig=280,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.570	PP	0.2613	20.53890	1.01830	0.4072
2	9.413	PB	0.2077	2475.95215	180.84976	49.0835
3	11.046	BB	0.2518	2547.87646	153.37793	50.5093
Totals :				5044.36752	335.24599	

Results obtained with enhanced integrator!

Data File C:\HPCHEM\1\DATA\GROUP\SZ433-2.D

Injection Date	: 7/1/2013 5:40:06 PM	Seq. Line	: 2
Sample Name	:	Location	: Vial 2
Acq. Operator	: TMB	Inj	: 1
Acq. Instrument	: Instrument 1	Inj Volume	: 5 µl
Different Inj Volume from Sequence !	Actual	Inj Volume	: 10 µl
Acq. Method	: C:\HPCHEM\1\METHODS\IC-2050.M		
Last changed	: 5/17/2012 7:46:04 PM by JTM		
Analysis Method	: C:\HPCHEM\1\METHODS\IA-1020.M		
Last changed	: 8/13/2013 7:14:24 PM by TMB		
	(modified after loading)		



Data File C:\HPCHEM\1\DATA\GROUP\SZ433-2.D

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.058	MM	1.2841	312.55051	4.05660	14.1890
2	42.510	MM	1.4990	1890.20837	21.01684	85.8110
Totals :				2202.75888	25.07344	

Results obtained with enhanced integrator!

Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.058	MM	1.2892	330.55002	4.27325	14.0877
2	42.511	MM	1.5028	2015.82776	22.35588	85.9123
Totals :				2346.37778	26.62913	

Results obtained with enhanced integrator!

Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.058	MM	1.2714	401.48627	5.26294	14.1263
2	42.512	MM	1.5029	2440.62866	27.06579	85.8737
Totals :				2842.11493	32.32872	

Results obtained with enhanced integrator!

Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.058	MM	1.2370	482.14734	6.49593	13.4985
2	42.509	MM	1.4930	3089.70288	34.49015	86.5015
Totals :				3571.85022	40.98609	

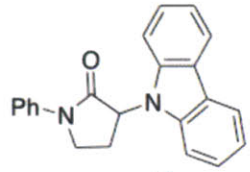
Results obtained with enhanced integrator!

Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	36.056	MM	1.2624	106.20746	1.40223	14.4427
2	42.510	MM	1.4869	629.16565	7.05220	85.5573
Totals :				735.37311	8.45443	

Results obtained with enhanced integrator!

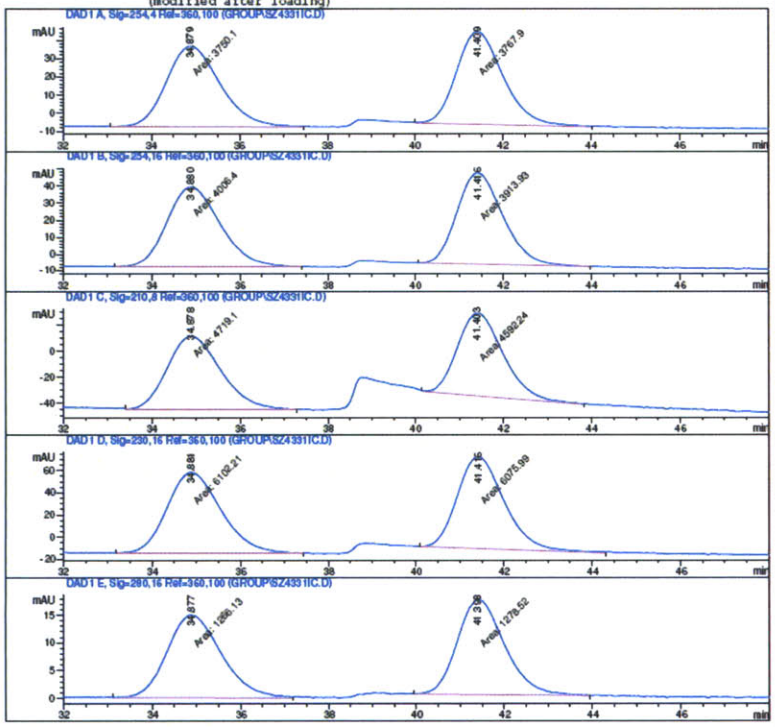
*** End of Report ***



eq 47

Data File C:\HPCHEM\1\DATA\GROUP\SZ4331IC.D

Injection Date	: 7/1/2013 1:36:35 PM	Seq. Line	: 2
Sample Name	:	Location	: Vial 1
Acq. Operator	: TMB	Inj	: 1
Acq. Instrument	: Instrument 1	Inj Volume	: 5 µl
Different Inj Volume from Sequence !	Actual Inj Volume	: 10 µl	
Acq. Method	: C:\HPCHEM\1\METHODS\IC-1050.M		
Last changed	: 7/1/2013 2:10:02 PM by TMB (modified after loading)		
Analysis Method	: C:\HPCHEM\1\METHODS\IA-1020.M		
Last changed	: 8/13/2013 7:10:39 PM by TMB (modified after loading)		



Data File C:\HPCHEM\1\DATA\GROUP\SZ4331IC.D

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.879	MM	1.4185	3750.10254	44.06201	49.8816
2	41.409	MM	1.2420	3767.90063	50.56122	50.1184
Totals :				7518.00317	94.62323	

Results obtained with enhanced integrator!

Signal 2: DAD1 B, Sig=254,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.880	MM	1.4227	4006.39917	46.93439	50.5838
2	41.416	MM	1.2227	3913.92554	53.35227	49.4162
Totals :				7920.32471	100.28666	

Results obtained with enhanced integrator!

Signal 3: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.878	MM	1.3994	4719.10205	56.20377	50.6812
2	41.403	MM	1.2062	4592.23682	63.45277	49.3188
Totals :				9311.33887	119.65654	

Results obtained with enhanced integrator!

Signal 4: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.881	MM	1.4093	6102.21045	72.16672	50.1077
2	41.416	MM	1.2315	6075.98584	82.23231	49.8923
Totals :				1.21782e4	154.39902	

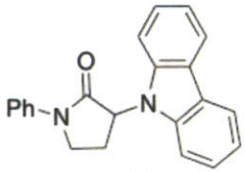
Results obtained with enhanced integrator!

Signal 5: DAD1 E, Sig=280,16 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	34.877	MM	1.4201	1266.12561	14.85952	49.7564
2	41.398	MM	1.2452	1278.52209	17.11285	50.2436
Totals :				2544.64771	31.97237	

Results obtained with enhanced integrator!

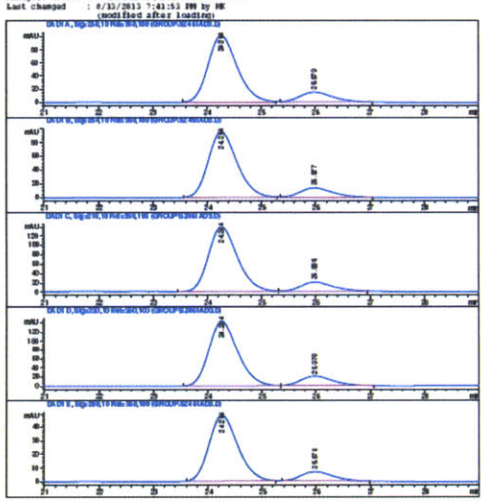
*** End of Report ***



11

Data File C:\HPCHEM\1\DATA\GROUP\SI461A01.D

Injection Date : 7/23/2013 11:50:41 PM Seq. Line : 6
Sample Name : Location : Vial 60
Acq. Operator : CE Inj : 1
Acq. Instrument : Instrument 1 Inj Volume : 35 µl
Different Inj Volume from Sequence ! Actual Inj Volume : 10 µl
Acq. Method : C:\HPCHEM\1\METHODS\AD-03-60.M
Last changed : 9/9/2011 8:37:40 PM by MB
Analysis Method : C:\HPCHEM\1\METHODS\OJ-10-20.M
Last changed : 8/13/2013 7:41:53 PM by ME
(modified after loading)



Instrument 1 8/13/2013 7:42:20 PM ME

Data File C:\HPCHEM\1\DATA\GROUP\SI461A01.D

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=250,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.264	BB	0.5740	3797.21641	101.62165	85.5094
2	25.979	BB	0.6065	643.57341	14.94112	14.4904
Totals :				4441.39001	116.57297	

Results obtained with enhanced integrator!

Signal 2: DAD1 B, Sig=254,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.264	BB	0.5800	3557.69978	95.19507	85.5123
2	25.977	BB	0.5965	602.75201	13.99581	14.4877
Totals :				4160.45172	109.19018	

Results obtained with enhanced integrator!

Signal 3: DAD1 C, Sig=210,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.264	VB	0.5346	5197.31055	138.85276	85.0286
2	25.985	BV	0.5004	858.42188	20.25065	14.1754
Totals :				6055.73242	159.15141	

Results obtained with enhanced integrator!

Signal 4: DAD1 D, Sig=230,10 Ref=360,100

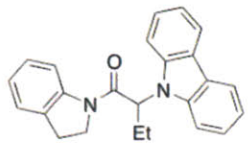
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.264	BB	0.5706	5322.65967	142.22550	85.4654
2	25.978	BB	0.5957	906.65833	21.88118	14.5546
Totals :				6229.31000	163.22667	

Results obtained with enhanced integrator!

Signal 5: DAD1 E, Sig=288,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.264	BB	0.5677	1798.64288	48.28748	86.4861
2	25.976	BB	0.5611	280.75574	6.83724	13.5139

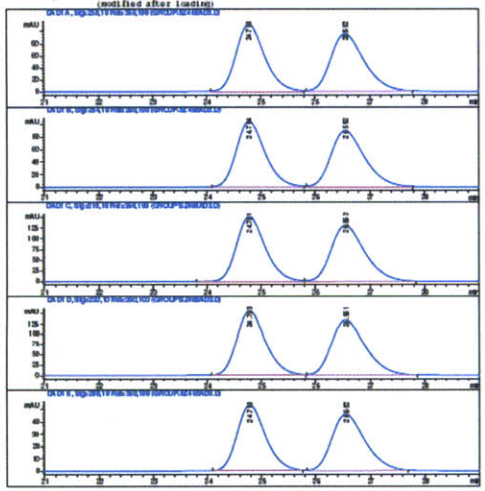
Instrument 1 8/13/2013 7:42:20 PM ME



eq 48

Data File C:\HPCHEM\1\DATA\GROUP\SI466ADS.D

Injection Date	: 7/23/2013 10:49:38 PM	Seq. Line	: 5
Sample Name	:	Location	: Vial 59
Acq. Operator	: CE	Inj	: 1
Acq. Instrument	: Instrument 1	Inj Volume	: 15 µl
Different Inj Volume from Sequence :		Actual Inj Volume	: 5 µl
Acq. Method	: C:\HPCHEM\1\METHODS\AD-80-60.M		
Last changed	: 9/5/2013 8:27:46 PM by ME		
Analysis Method	: C:\HPCHEM\1\METHODS\OJ-10-20.M		
Last changed	: 8/13/2013 7:42:23 PM by ME		
	(modified after loading)		



Instrument 1 8/13/2013 7:44:25 PM ME

Data File C:\HPCHEM\1\DATA\GROUP\SI466ADS.D

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.783	BB	0.3628	4085.42432	111.15942	49.9912
2	26.552	BB	0.6479	4086.26646	95.38821	50.0088
Totals :				8172.30078	206.54804	

Results obtained with enhanced integrator!

Signal 2: DAD1 B, Sig=254,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.784	BB	0.5606	3825.76196	104.13499	49.9961
2	26.552	BB	0.6414	3826.36475	89.38497	50.0039
Totals :				7652.12671	193.51997	

Results obtained with enhanced integrator!

Signal 3: DAD1 C, Sig=230,10 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.781	VV	0.5529	5647.08888	151.58543	50.2840
2	26.553	VB	0.6200	5601.10262	130.17645	49.7960
Totals :				1.12489e4	281.76188	

Results obtained with enhanced integrator!

Signal 4: DAD1 D, Sig=230,10 Ref=360,100

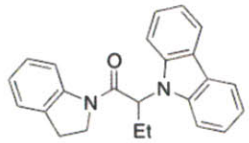
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.783	BB	0.5627	5713.36963	155.50003	49.9323
2	26.551	BB	0.6565	5728.07861	133.52866	50.0677
Totals :				1.14422e4	289.02869	

Results obtained with enhanced integrator!

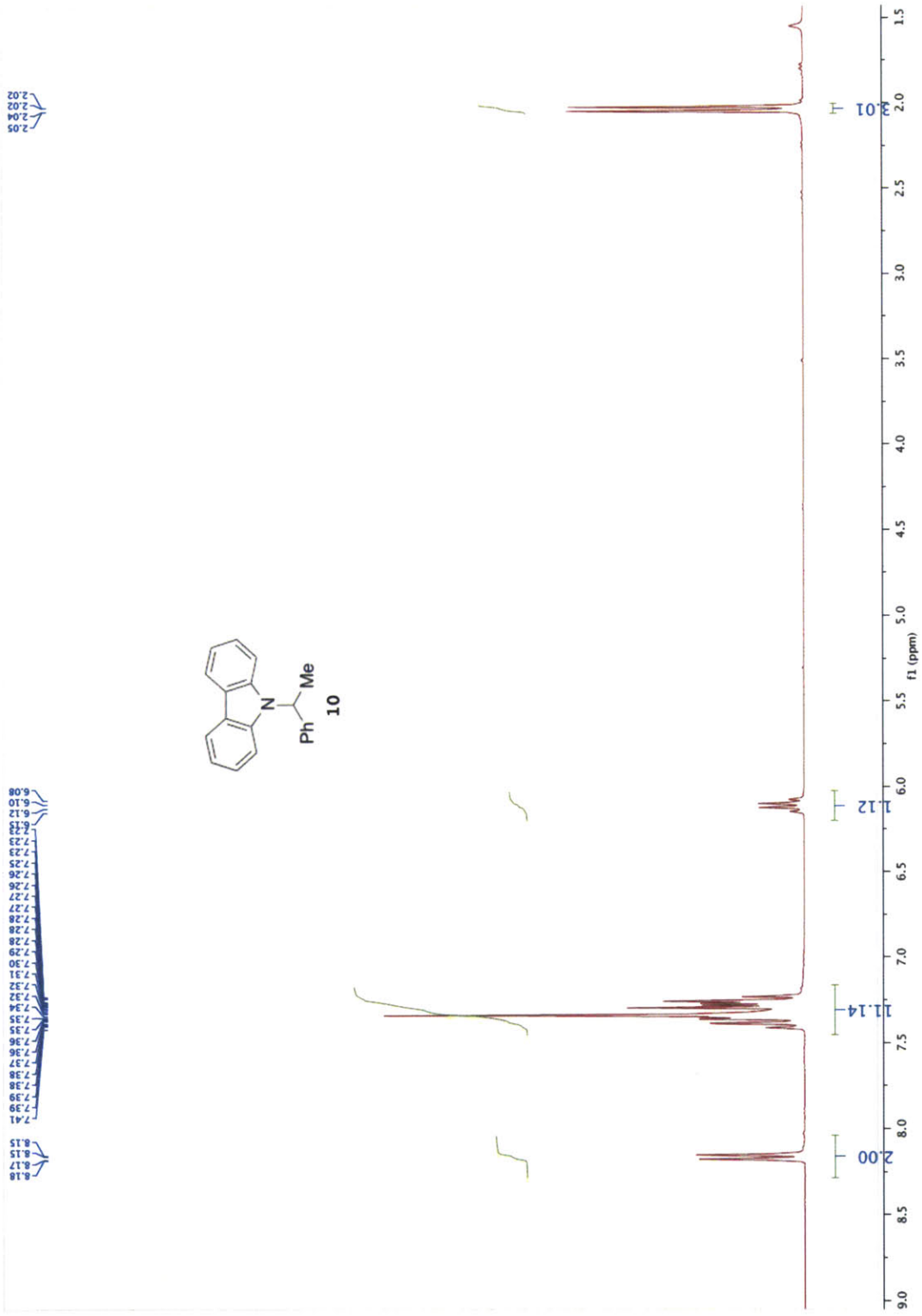
Signal 5: DAD1 E, Sig=288,10 Ref=360,100

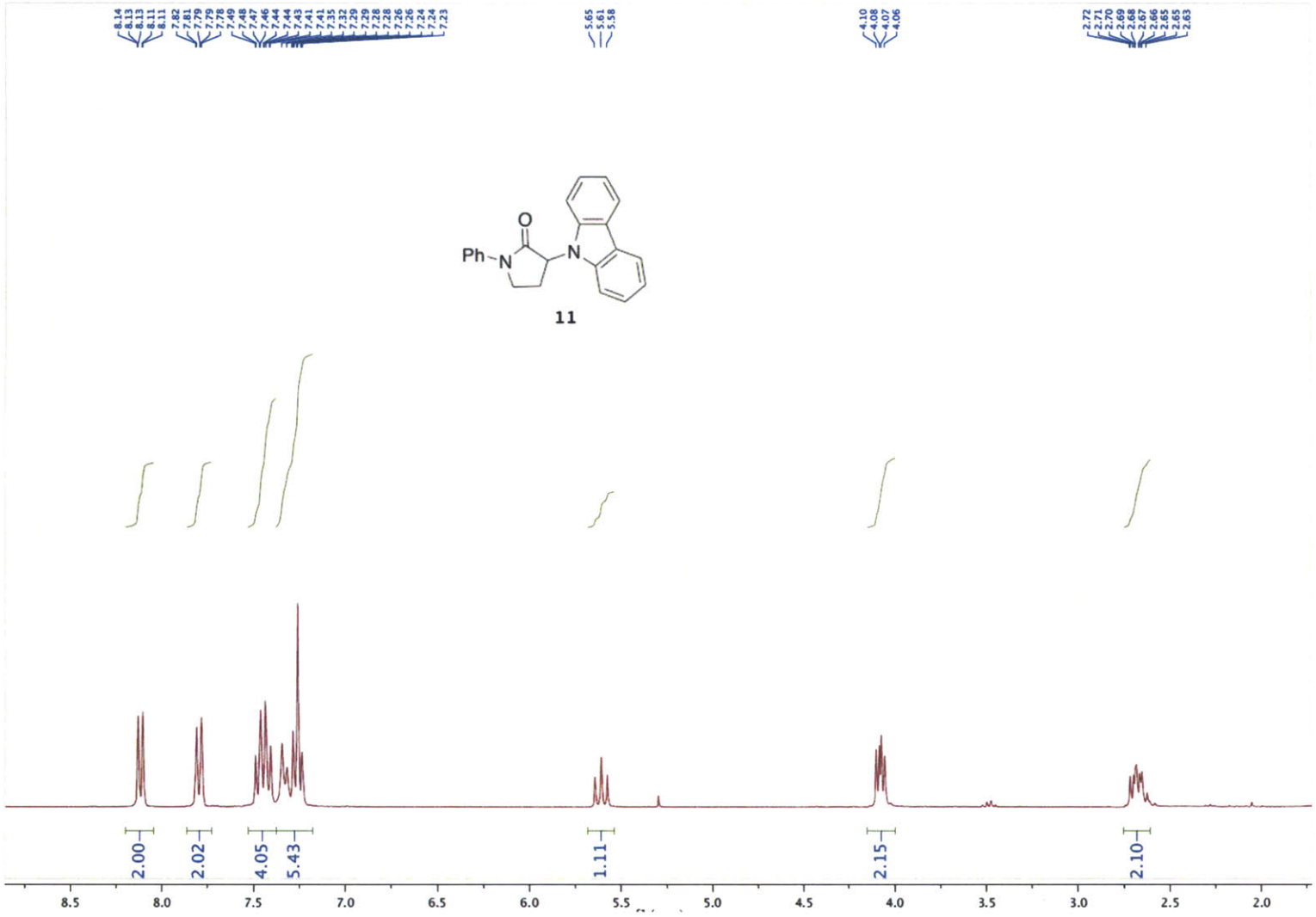
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	2.967	PB	0.1168	14.28281	1.58826	0.2414
2	14.669	PV	0.2378	41.04837	2.57208	1.0859
3	15.091	VB	0.3249	142.15623	6.50621	3.4177

Instrument 1 8/13/2013 7:44:25 PM ME



12


Ph
Me
10
f1 (ppm)


8.14
8.13
8.13
8.11
8.11
7.82
7.81
7.79
7.79
7.78
7.49
7.48
7.47
7.46
7.44
7.44
7.43
7.41
7.41
7.35
7.32
7.29
7.29
7.28
7.28
7.26
7.25
7.24
7.24
7.23
5.65
5.61
5.58
4.10
4.08
4.07
4.06
2.72
2.71
2.70
2.69
2.68
2.67
2.66
2.65
2.65
2.63
O
Ph
N
N
11
2.00
2.02
4.05
5.43
1.11
2.15
2.10
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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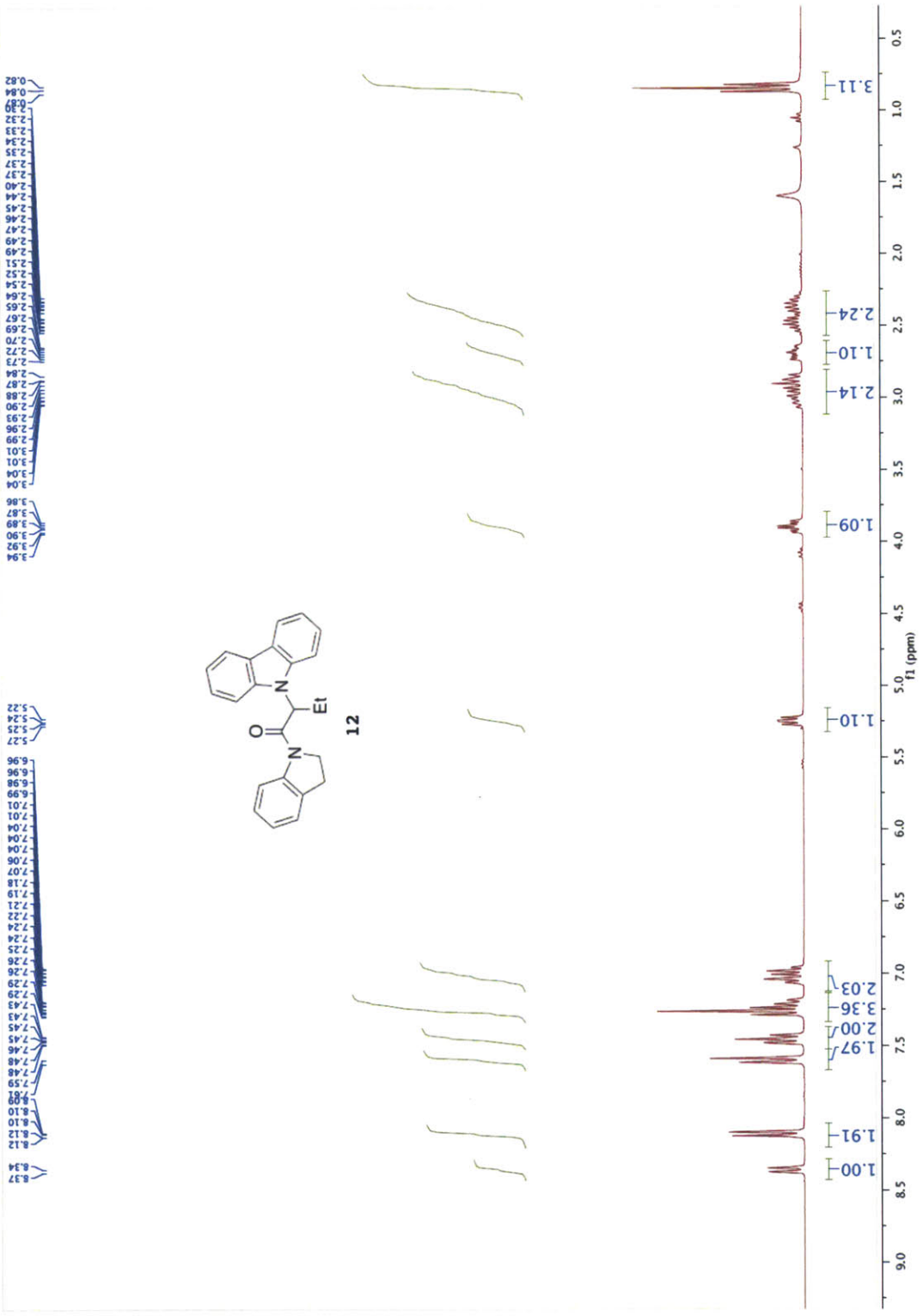
4.5
4.0
3.5
3.0
2.5
2.0


Et
O
N
N
12
f1 (ppm)

Curriculum Vitae

SUSAN L. ZULTANSKI

EDUCATION

CALIFORNIA INSTITUTE OF TECHNOLOGY
Visiting Graduate Student, June 2012 – September 2013
Advisor: Professor Gregory C. Fu

MASSACHUSETTS INSTITUTE OF TECHNOLOGY
Ph.D. Organic Chemistry, August 2008 – September 2013
Advisor: Professor Gregory C. Fu

UNIVERSITY OF ROCHESTER
B.S. Chemistry, *magna cum laude*, September 2002 – May 2006
Advisors: Professor Alison J. Frontier & Professor Kara L. Bren

PROFESSIONAL EXPERIENCE

Merck Research Laboratories, Boston, MA
Medicinal Chemist, October 2006 – July 2008
Supervisor: Dr. Christian Fischer

PUBLICATIONS

(4) **Nickel-Catalyzed Suzuki–Miyaura Arylations of Unactivated Tertiary Alkyl Bromides**
J. Am. Chem. Soc. **2013**, *135*, 624–627.
Zultanski, S. L.; Fu, G. C.

(3) **Catalytic Asymmetric γ-Alkylation of Carbonyl Compounds via Stereoconvergent Suzuki Cross-Couplings**
J. Am. Chem. Soc. **2011**, *133*, 15362–15364.
Zultanski, S. L.; Fu, G. C.

(2) **Triazoloamides as Potent γ-Secretase Modulators with Reduced hERG Liability**
Bioorg. Med. Chem. Lett. **2012**, *22*, 3140–3146.
Fischer, C.; Zultanski, S. L.; Zhou, H.; Methot, J. L.; Shah, S.; Nuthall, H.; Hughes, B. L.; Smotrov, N.; Hill, A.; Szewczak, A. A.; Moxham, C. M.; Bays, N.; Middleton, R. E.; Munoz, B.; Shearman, M. S.

(1) **Triazoles as γ-Secretase Modulators**
Bioorg. Med. Chem. Lett. **2011**, *21*, 4083–4087.
Fischer, C.; Zultanski, S. L.; Zhou, H.; Methot, J. L.; Brown, C.; Mampreian, D. M.; Schell, A. J.; Shah, S.; Nuthall, H.; Hughes, B. L.; Smotrov, N.; Kenific, C. M.; Cruz, J. C.; Walker, D.; Bouthillette, M.; Nikov, G. N.; Savage, D. F.; Jeliazkova-Mecheva, V. V.; Diaz, D.; Szewcsak, A. A.; Bays, N.; Middleton, R. E.; Munoz, B.; Shearman, M. S.

PATENTS

Triazole Derivatives for Treating Alzheimer's Disease and Related Conditions
PCT Int. Appl. (2008). WO 2008156580.
Fischer, C.; Munoz, B.; Zultanski, S.; Methot, J.; Zhou, H.; Brown, C. W.

PRESENTATIONS

(4) **Nickel-Catalyzed Suzuki–Miyaura Cross-Couplings of Unactivated Tertiary Alkyl Bromides with Aryl-(9-BBN) Reagents**
Oral Presentation: Caltech Chemistry & Chemical Engineering Student Seminar Day; Pasadena, CA (October 2012).

(3) **Nickel-Catalyzed Suzuki–Miyaura Cross-Couplings of Unactivated Tertiary Alkyl Bromides with Aryl-(9-BBN) Reagents**
Oral presentation: 244th ACS National Meeting; Philadelphia, PA (August 2012).

(2) **Nickel-Catalyzed Asymmetric Alkyl-Alkyl Suzuki–Miyaura Cross-Couplings of Racemic γ-Chloroamides**
Poster presentation: 42nd National Organic Chemistry Symposium; Princeton, NJ (June 2011).

(1) **Nickel-Catalyzed Asymmetric Alkyl-Alkyl Suzuki–Miyaura Cross-Couplings of Raemic γ-Chloroamides**
Oral Presentation: 239th ACS National Meeting; San Francisco, CA (March 2010).

GRADUATE FELLOWSHIPS

- Merck Summer Graduate Fellowship (June 2010 – August 2010)
- Robert T. Haslam Departmental Fellowship (September 2008 – June 2009)