Iron-Catalyzed Reactions and the Role

of Metal Contaminants

Julien Bonnamour

Iron-Catalyzed Reactions and the Role of Metal Contaminants

Von der Fakultät für Mathematik, Informatik und Naturwissenschaften der RWTH Aachen University zur Erlangung des akademischen Grades eines Doktors der Naturwissenschaften genehmigte Dissertation

vorgelegt von

Master of Science

Julien Bonnamour

aus Paris (France)

Diese Dissertation ist auf den Internetseiten der Hochschulbibliothek online verfügbar

This thesis presents the work carried out at the Institute of Organic Chemistry of RWTH Aachen University between October 2007 and July 2011 under the supervision of Prof. Dr. Carsten Bolm.

Parts of this work have already been published:

1) J. Bonnamour, C. Bolm
"Iron-Catalyzed Intramolecular *O*-Arylation: Synthesis of 2-Aryl Benzoxazoles"
Organic Letters **2008**, *10*, 2665.

2) J. Bonnamour, C. Bolm
"Iron Salts in the Catalyzed Synthesis of 5-Substituted 1H-Tetrazoles"
Chemistry, a European Journal **2009**, *15*, 4543.

3) J. Bonnamour, M. Piedrafita, C. Bolm
"Iron and Copper Salts in the Synthesis of Benzo[*b*]furans"
Advanced Synthesis and Catalysis **2010**, *352*, 1577.

4) J. Bonnamour, C. Bolm
"Iron(II) Triflate as Catalyst for the Synthesis of Indoles by Intramolecular C-H Amination"
Organic Letters **2011**, *13*, 2012.

Acknowledgments

First of all, I would like to thank my supervisor Prof. Dr. Carsten Bolm for giving me the opportunity to work in his group, for optimal working conditions and additionally for his enthusiastic interest in new results.

I thank the technical and administrative personnel of the Institute of Organic Chemistry RWTH Aachen. A great thank to Mrs. Ingrid Voss for her kindness and her help with the German administration. I would like to thank Rolf Winkels and Björn Dreindl for their kindness and the technician Susi Grünebaum and Pierre Winandy for their help in the preparation of starting materials.

I am really grateful to Arkaitz Correa for the guidance during the work on my thesis, his humour and also for his Spanish omelet! I wish to thank for so many reasons Ankur Pandey and Bernhard Füger that it would really be too long to mention here. My particular gratitude goes to Johannes Johansson for proof-reading and for his very useful suggestions, comments and much more. Thank you Maria Piedrafita for the fruitful collaboration.

I am thankful to Jenna Lynn Head, Nick Swisher and Ankur Pandey for proof-reading this thesis.

I am grateful to the sportive people such as the swimmers: Arkaitz Correa, Maria Piedrafita, Johannes Johansson, the professional ping-pong player Julien Buendia, and the basket team: Johannes Johansson, Ankur Pandey and Lianghua Zou.

De sincères remerciements se dirigent vers Julien Buendia pour sa jovialité, sa convivialité, ses connaissances et ses conseils avisés dans tous les domaines. Merci aussi à Mathieu Candy pour son aide lors de la rédaction de la thèse.

Thanks to Seong Jun Park, Julien Buendia for the nice ambiance in the 5.06 lab.

I would like to thank all the AK Bolm for the nice atmosphere in the group.

General Introduction

Transition metal-catalyzed cross-coupling reactions are recognized as one of the most valuable and versatile reactions for the formation of new bonds. For decades, palladium and copper have been the most utilized metals in cross-coupling chemistry. Nowadays, these metals are extensively and commonly used for catalysis in industry.[1]

Ecology and economics are two aspects which chemists should keep in mind. Within the last few decades the context has changed as times are becoming economically difficult and paying attention to how reactions affect the environment is now crucial. For these reasons it is important to develop alternative synthetic routes using cheaper and less hazardous catalysts.

Iron salts have interested chemists for several reasons. First of all, iron is cheap compared to palladium (1 kg $PdCl_2$ from Acros costs 30000 Euro, whereas 1 kg $FeCl_3$ from Acros costs about 30 Euro). Furthermore, iron is the fourth most abundant element and the second largest metallic component of earth's crust with 5%, following aluminum (8.1%). Iron salts generally present a low toxicity; iron oxide is used in Magnetic Resonance Imaging (MRI). Iron(III) sulfate, iron(II) sulfate monohydrate, and iron(II) sulfate heptahydrate, which are recognized as herbicides, are benign to human beings.[2] Since the middle of the 20th century, following the first iron catalysis by Kharasch in 1941,[3] iron-catalysis has been used more frequently and with wider applications.[4] However, further development is needed, as shown by the presented thesis.

The advantages of iron include its low toxicity, low price, environmentally friendly nature and being readily available. As iron has limited use in cross-coupling reactions forming carbon-

---

[1] For a review, see: a) C. Torborg, M. Beller, *Adv. Synth. Cat.* **2009**, *351*, 3027. b) A. Zapf, M. Beller, *Top. Catal.* **2002**, *19*, 101.

[2] For details see: Docket ID EPA-HQ-OPP-2008-0626-0003.

[3] M. S. Kharasch, P. O. Tawney, *J. Am. Chem. Soc.* **1941**, *63*, 2316.

[4] Reviews: a) C. Bolm, J. Legros, J. Le Paih, L. Zani, *Chem. Rev.* **2004**, *104*, 6217. b) A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624. c) A. Correa, O. García Mancheño, C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108. d) B. D. Sherry, A. Fürstner, *Acc. Chem. Res.* **2008**, *41*, 1500. e) S. Enthaler, K. Junge, M. Beller, *Angew. Chem.* **2008**, *120*, 3363; *Angew. Chem. Int. Ed.* **2008**, *47*, 3317. f) E. B. Bauer, *Curr. Org. Chem.* **2008**, *12*, 1341. g) S. Gaillard, J.-L. Renaud, *ChemSusChem* **2008**, *1*, 505. h) A. Fürstner, *Angew. Chem.* **2009**, *121*, 1390; *Angew. Chem. Int. Ed.* **2009**, *48*, 1364. i) W. M. Czaplik, M. Mayer, J. Cvengroš, A. Jacobi von Wangelin, *ChemSusChem* **2009**, *2*, 396. j) C. Bolm, *Nature Chem* **2009**, *1*, 420. k) A. A. O. Sarhan, C. Bolm, *Chem. Soc. Rev.* **2009**, *38*, 2730. l) L.-X. Liu ,*Curr. Org. Chem.* **2010**, *14*, 1099.

heteroatom bonds, we focused our investigations on the field of iron catalysis in click chemistry and on C-H bond activation. Also an iron-catalyzed carbon-heteroatom bond formation which is in a nascent stage of development is presented. This thesis visits the history of iron catalysis and its recent advances in chemistry in the past few years.

Iron in Cross-Coupling Reactions

1. Cross-Coupling

Organic chemistry is a vast domain of chemistry. It deals with all reactions between organic compounds and allows for the formation of complex molecules from simple substrates. Organic chemistry is present in all domains of every day life, from polymer production to medicine. In order to synthesize complex compounds, it is often necessary to make new C-C bonds, which can be difficult due to the stability of carbon compounds. Different methods are used; palladium cross-coupling is one of the most powerful. In 2010, Richard F. Heck, Ei-ichi Negishi and Akira Suzuki obtained the Nobel Prize for their work in this field.

2. Palladium

Cross-coupling with palladium(0) has been extensively documented; several well-known reactions such as the Buchwald-Hartwig amination, the Heck reaction, the Sonogashira-Hagihara coupling and the Suzuki reaction are all catalyzed by palladium (Scheme 1). The advantages of Pd-catalyzed reactions are their mild conditions and tolerance of a variety of functional groups.

Almost all types of bonds can be obtained by Pd-catalyzed cross-coupling: C-H, C-C, C-N, C-O, C-P, and C-Metal. The direct C-H cross-coupling with an aryl halide has the advantage that no precursor, such as a carbon-metal bond, is necessary. Various organometallic reagents have been used for C-C bond formations: Li (Murahashi),[5] B (Suzuki Miyaura),[6] Mg (Kumada-Corriu),[7] Al (Nozaki-Oshima, Negishi),[8] Si (Hiyama),[9] Cu (Normant),[10] Zn (Negishi),[11] Zr (Negishi),[12] and Sn (Stille).[13] Moreover, heteroatom-H bond such as N-H,[14] O-H,[15] P-H,[16] and S-H[17] are also coupled by Pd-catalyzed reactions (Scheme 1).

---

[5] M. Yamamura, I. Mritani, S. Murahashi, *J. Organomet. Chem.* **1975**, *95*, C39.

[6] A. Suzuki, *J. Organomet. Chem.* **1998**, *576*, 147

[7] S.I. Marahashi, M. Yamamura, K. Yanagisawa, N. Mita, K. Kondo, *J. Org. Chem.* **1979**, *44*, 2408.

[8] S. Baba, E. Negishi, *J. Am. Chem. Soc.* **1976**, *98*, 6729.

[9] Y. Hatanaka, T. Hiyama, *J. Am. Chem. Soc.* **1990**, *112*, 7793.

[10] A. Alexakis, J. K. Normant, *Tetrahedron Lett.* **1981**, *22*, 959.

[11] A. O. King, E. Negishi, *J. Org. Chem.* **1978**, *43*, 358.

[12] E. Negeshi, T. Tkahash, S. Baba, D. E. Van Horn, N. Okukado, *J. Am. Chem. Soc.* **1987**, *109*, 2393.

[13] J. K. Stille, *Angew. Chem.* **1986**, *98*, 504; *Angew. Chem. Int. Ed.* **1986**, *25*, 508.

[14] a) A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem.* **1995**, *107*, 1456; *Angew. Chem, Int. Ed. Engl.* **1995**, *34*, 1348. b) J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609.

[15] M. Palucki, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 10333.

[16] T. Hirao, T. Masunaga, Y. Ohshiro, T. Agawa, *Tetrahedron Lett.* **1980**, *21*, 3595.

[17] G. Y. Li, *Angew. Chem.* **2001**, *113*, 1561; *Angew. Chem, Int. Ed. Engl.* **2001**, *40*, 1513.

Scheme 1. Palladium-catalyzed cross-coupling.

$$R^1\text{-Metal} \xrightarrow[\text{Pd Catalyst}]{R^2\text{-X}} R^1\text{-}R^2 \xleftarrow[\text{Pd Catalyst}]{R^2\text{-X}} R^1\text{-H}$$
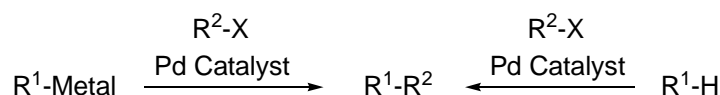
R^1 = Alkyl, alkenyl, vinyl, alkynyl, aryl
R^2 = Aryl, alkenyl, vinyl

3. Palladium versus Iron

A comparison between palladium and iron is important to point out the advantages and disadvantages of the two metals as catalysts. First of all, as mentioned above, an extensive work on palladium has been done. These reactions suffer from various disadvantages. They need ancillary ligands to create reactive species. Additionally palladium is toxic and environmentally hazardous. The price of palladium species is high, while the low cost of iron is one of its biggest advantages. Also, iron is beginning to be competitive amongst palladium in terms of reaction time and temperature. Moreover, iron is relatively nontoxic and environmentally friendly (LD_{50}(oral, rat): 895 mg/kg; LD_{50}(dermal, rabbit): >2000 mg/kg).[18] Most iron species are easy to handle because of their stability in moisture and air. They exist in various oxidation states Fe(-II), Fe(0), Fe(I), Fe(II), Fe(III), Fe(IV), Fe(V), and Fe(VI). Finally, palladium chemistry has been developed through decades of research whereas nature has been optimizing iron-enzymes for 3.6 billions of years. Various enzymes are now well-described: methane monooxygenase (MMO)[19], ribonucleotide reductase (RNR)[20], linoleoyl-CoA desaturase[21], Cytochrome P450[22], and Hemoglobin. This means that iron chemistry is both a biomimetic study and pure research in the laboratory.

4. History of Iron-Catalyzed Cross-Coupling Reactions

4.1. The Beginning of Iron Catalysis

The story of iron began in 1891 when Mond[23] and Berthelot[24] discovered one species of iron: pentacarbonyliron. In 1941, Kharasch[3] investigated the homocoupling of Grignard reagents by using different metals and observed that iron was successful in catalyzing this reaction.

---

[18] ClearTech, fiche signalétique, Chlorure Ferrique.

[19] H. Basch, K. Mogi, D. G. Musaev, K. Morokuma, *J. Am. Chem. Soc.* **1999**, *121*, 7249.

[20] D. Filatov, R. Ingemarson, A. Gräslund, L. Thelander, *J. Biol. Chem.* **1992**, *267*, 15816.

[21] T. Okayasu, M. Nagao, T. Ishibashi, Y Imai, *Arch. Biochem. Biophys.* **1981**, *206*, 21.

[22] B. Meunier, S. P. de Visser, S. Shalik, *Chem. Rev.* **2004**, *104*, 3947.

[23] L. Mond, F. Quincke, *J. Chem. Soc., Trans.* **1891**, *59*, 604.

[24] M. Berthelot, *C. R. Hebd. Seances Acad. Sci.* **1891**, *112*, 1343.

Scheme 2. Homocoupling of Grignard reagent by Kharasch.

Being awakened by those first results, chemists began to extend the scope of this reaction; in 1945 alkyl Grignard were coupled with benzyl bromide[25] and in 1953 with acetyl chloride.[26] In the 1950's with the boom of organometallic chemistry, Kealy and Pauson proposed a structure for the dicyclopentadienyl-iron,[27] but made a mistake in the structure by not considering the 18 electrons rule. Woodward noticed the failure, corrected the structure and gave the name Ferrocene to this entity.[28] At the same time Reppe developed a procedure for the reactions of acetylene with different substrates (Reppe synthesis) by using iron as a catalyst.[29]

4.2. Iron-Catalyzed Coupling with Grignard Reagents

In 1971, Kochi studied extensively iron-catalyzed cross-coupling of Grignard reagents with vinyl halides (Scheme 3).[30] The reaction was done at room temperature, however, 50 mol% of Fe(dbm)$_3$ were required.

Scheme 3. Iron-catalyzed cross-coupling of Grignard reagent with vinyl halides by Kochi.

He postulated a mechanism with a Fe(I)-Fe(III) cycle[31] several years later. The advantage of the reactions was their stereoselectivity. Unfortunately, several equivalents of bromide needed to be used (Scheme 4).

[25] G. Vavon, C. Chaminade, G. Quesnel, *Hebd. Seances Acad. Sci.* **1945**, *220*, 850.
[26] W. C. Percival, R. B. Wagner, N. C. Cook, *J. Am. Chem. Soc.* **1953**, *75*, 3731.
[27] T. J. Kealy, P. L. Pauson, *Nature* **1951**, *168*, 1039.
[28] G. Wilkinson, M. Rosenblum, M. C. Whiting, R. B. Woodward, *J. Am. Chem. Soc.* **1952**, *74*, 2125.
[29] W. Reppe, H. Vetter, *Justus Liebigs Ann. Chem.* **1953**, *582*, 133.
[30] a) J. K. Kochi, R. S. Smith, *J. Org. Chem.* **1976**, *41*, 502. b) M. Tamura, J. K. Kochi, *J. Am. Chem. Soc.* **1971**, *93*, 1487.
[31] J. K. Kochi, *J. Organomet. Chem.* **2002**, *653*, 11.

Scheme 4. Fe(I)-Fe(III) catalytic cycle by Kochi.
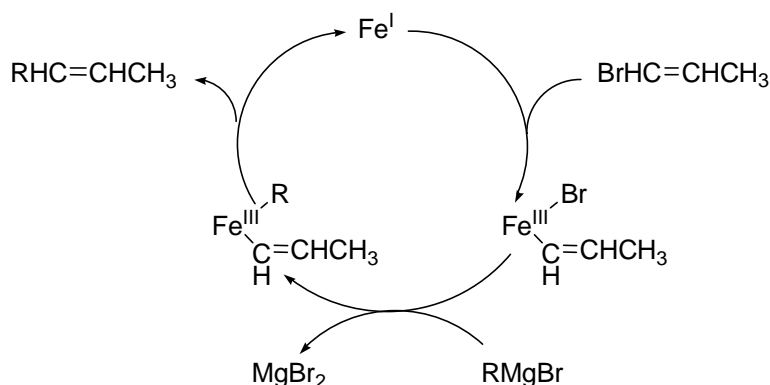
In 1983, Molander modified slightly Kochi's reaction.[32] His reaction permitted using a stoichiometric amount of Grignard reagent. The main drawback was that (*E*)-bromide gave a mixture of (*E*)- and (*Z*)-products. Yamamoto extended the scope of the reaction by using allylic phosphonates in 1991.[33] In 1998, a step forward was achieved by Cahiez by changing the source of iron.[34] Fe(acac)$_3$ was shown to be a suitable catalyst for the cross-coupling (Scheme 5).

Scheme 5. Iron-catalyzed cross-coupling of Grignard reagents with vinyl halides by Cahiez.
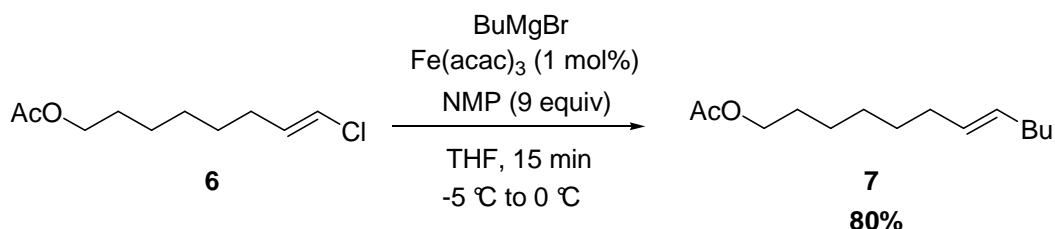
Over time, many advantages appeared, such as only 1 mol% of iron, high turn-over frequencies, high stereoselectivity, and broad scope. These conditions comprise a practical method for the cross-coupling of vinyl halides and alkyl Grignards.

In 2002, Fürstner used the same conditions and showed that alkyl Grignards could also be coupled with aryl halides.[35] He postulated a mechanism with a Fe(0)-Fe(-II) cycle (Scheme 6).[36]

---

[32] G. A. Molander, B. J. Rahn, D. C. Shubert, S. E. Bonde, *Tetrehaedron Lett.* **1983**, 5449.

[33] A. Yanagisawa, N. Nomura, H. Yamamoto, *Synlett* **1991**, 514.

[34] G. Cahiez, H. Avedissian, *Synthesis* **1998**, 1199.

[35] A. Fürstner, A. Leitner, M. Mendez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856.

[36] A. Fürstner, R. Martin, H. Krause, G. Seidel, R. Goddard, C. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 8773.

Scheme 6. Catalytic redox cycles by Fürstner.
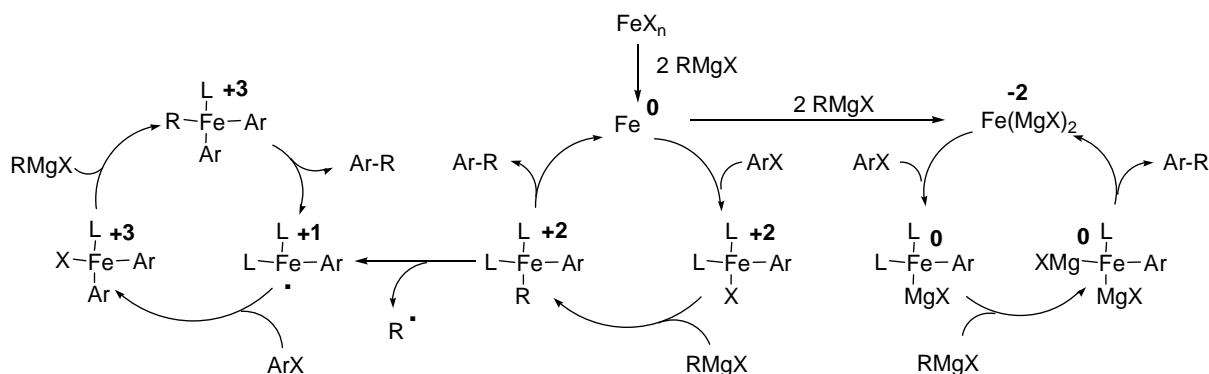
Later, other groups reported interesting results and expanded this field. Several findings have been made, such as the arylation of aryl halides[37] or of alkyl halides.[38]

It is striking that homocoupling compounds were mostly avoided and were considered to be non-interesting side products. In this context, Cahiez and coworker[39] published an iron-catalyzed homocoupling (Scheme 7).

Scheme 7. Iron-catalyzed homocoupling by Cahiez.
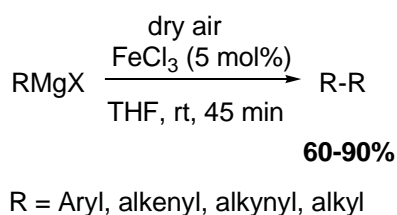
In this procedure, oxygen was used as an oxidant which coupled aryl and alkenyl Grignard reagents. More than being chemoselective, the reaction was highly stereoselective.

Daugulis reported a deprotonative dimerization of arenes with iron (Scheme 8).[40] In this case, the Grignard reagent is prepared *in situ*.

[37] a) T. Hatakeyama, M. Nakamura, *J. Am. Chem. Soc.* **2007**, *129*, 9844. b) C. Kofink, B. Blank, S. Pagano, N. Gotz, P. Knochel, *ChemComm* **2007**, 1954.

[38] a) M. Nakamura, K. Matsuo, S. Ito, E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686. b) R. Martin, A. Fürstner, *Angew. Chem.* **2004**, *116*, 4045; *Angew. Chem, Int. Ed.* **2004**, *43*, 3955. c) K. Dongol, H. Koh, M. Sau, C. Chai, *Adv. Synth. Catal.* **2007**, *349*, 1015.

[39] G. Cahiez, A. Moyeux, J. Buendia, C. Duplais, *J. Am. Chem. Soc.* **2007**, *129*, 13788.

[40] T. Truong, J. Alvarado, L. D. Tran, O. Daugulis, *Org. Lett.* **2010**, *12*, 1200.

Scheme 8. Iron-catalyzed deprotonative dimerization of arenes by Daugulis.

$$Ar\text{-}H \xrightarrow[\substack{\text{THF, } i\text{PrMgCl·LiCl,} \\ \text{tetramethylpiperidin,} \\ 0\ ^\circ\text{C - rt}}]{\text{FeCl}_3\ (10\ \text{mol\%}),\ O_2} Ar\text{-}Ar$$

Ar = *N*-Methylbenzimidazole **77%**
Tetrafluoropyridin **54%**
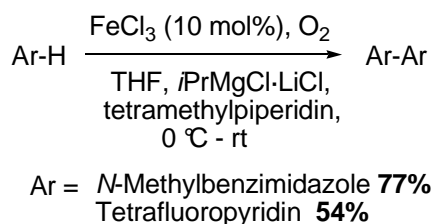
Iron(III) trichloride dimerized an arene under oxygen in THF at 0 °C. Moderate yields were obtained.

4.3. Iron-Catalyzed Coupling Reactions without Grignard Reagents

4.3.1. Organocopper Reagents

Sometimes, organocopper reagents can be used as alternatives for Grignards reagents. To achieve aryl-aryl cross-coupling, Knochel and coworker showed that by using 10 mol% $Fe(acac)_3$, a cross-coupling reaction between an organocopper and an aryl halide was possible (Scheme 9).[41]

Scheme 9. Iron-catalyzed coupling reactions of organocopper reagents by Knochel.

R^1 = CO_2Et, OMe, OTf

R^2 = CO_2Et, COPh, COMe, CN, $CONR_2$
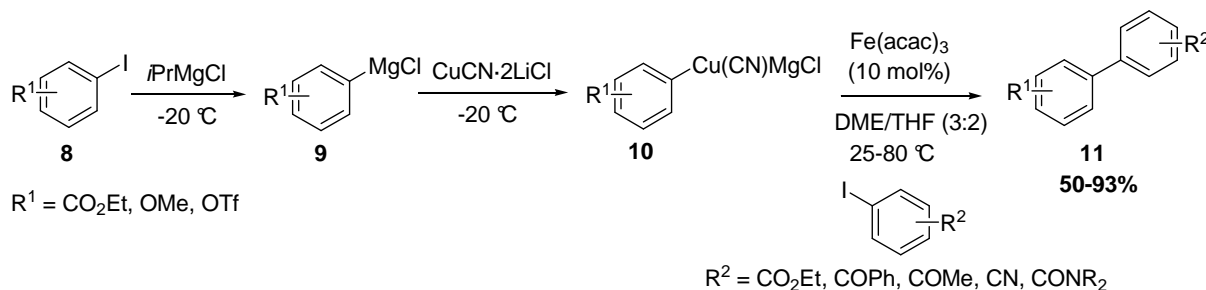
In this case, the homocoupling product, which was the main side product using Grignard reagents, disappeared almost completely. Good to excellent yields were obtained. On the other side, the scope was narrow. Only functionalized aryl and hetero aryl copper reagents can cross-couple with functionalized aryl iodides.

---

[41] I. Sapountzis, W. Lin, C. C. Kofink, C. Despotopoulou, P. Knochel, *Angew. Chem.* **2005**, *117*, 1599; *Angew. Chem. Int. Ed.* **2005**, *44*, 1654.

4.3.2 Organomanganese Reagents

In 1996, Cahiez found a new iron-catalyzed cross-coupling reaction using organomanganese reagents (Scheme 10).[42] Interestingly, changing I to Br or Cl did not affect the yield. This iron-catalyzed alkenylation of organomanganese reagents with alkenyl halides offered high yields with excellent stereoselectivity and furthermore I, Br and Cl could be used in this reaction.

Scheme 10. Iron-catalyzed cross-coupling with organomanganese reagents by Cahiez.
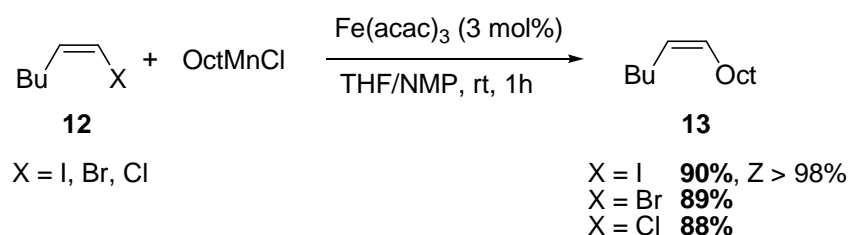
Fürstner showed that the reaction has a wide tolerance for different Mn-reagents, as all reagents of the types RMnX, R_2Mn, $R_3MnMgCl$ could be used (X = I, Br, Cl) (Scheme 11).[43] Aryl chlorides are coupled with alkyl organomanganese. In all cases excellent yields are obtained. This reaction is also chemoselective.

Scheme 11. Iron-catalyzed cross-coupling with organomanganese reagents by Fürstner.
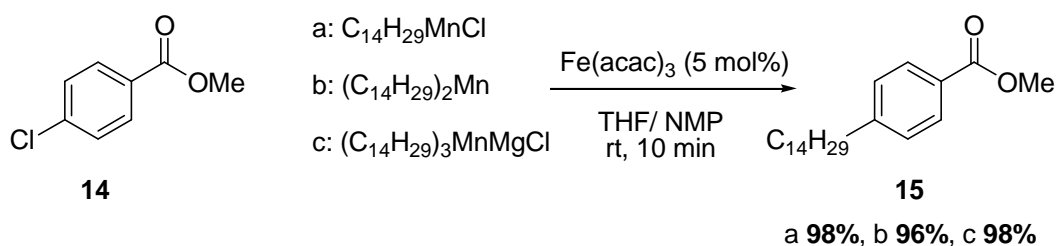
4.3.3 Organozinc Reagents

Iron-catalyzed reactions with organozinc reagents are more sporadic. Only a few examples have been reported. In 2002, Fürstner showed that iron(III) acac catalyzes a cross-coupling between an aryl chloride and an alkyl zinc-magnesium reagent (Scheme 12).[43]

---

[42] a) G. Cahiez, S. Marquais, *Tetrahedron Lett.* **1996**, *37*, 1773. b) G. Cahiez, S. Marquais, *Pure Appl. Chem.* **1996**, *68*, 53. For a review on organomanganese compounds, see: G. Cahiez, C. Duplais, J. Buendia, *Chem. Rev.* **2009**, *109*, 1434.

[43] A. Fürstner, A. Leitner, M. Mendez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124,* 13856.

Scheme 12. Iron catalyzed cross-coupling with organozinc reagents by Fürstner.
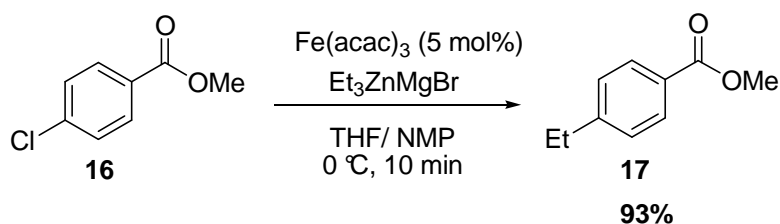
Knochel and coworkers used iron trichloride as a catalyst with the corresponding alkyl zinc reagents, which are able to cross-couple with acyl chloride (Scheme 13).[44] Good yields were obtained.

Scheme 13. Iron-catalyzed cross-coupling with organozinc reagents by Knochel.
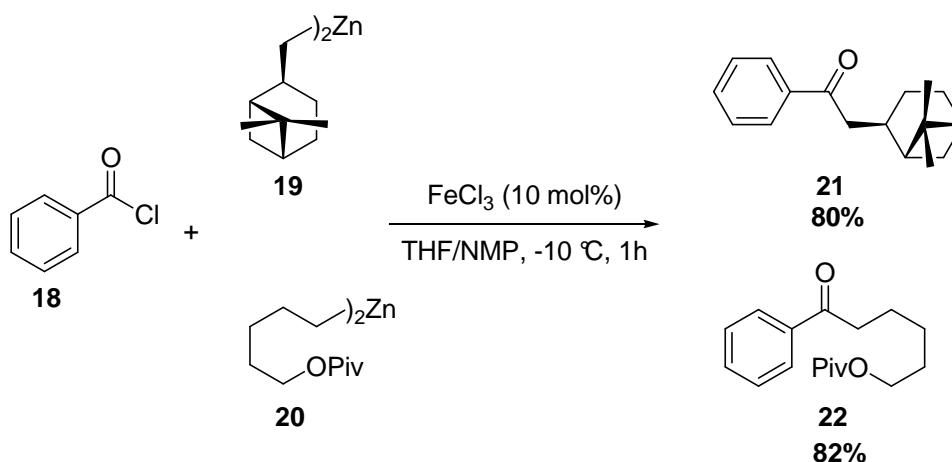
Iron proved to be useful in quite diverse cross-coupling reactions. The use of organometallic reagents has been in fashion in the last few decades. Nowadays, new reactions have replaced these organometallic reagents.

5. Iron-Catalyzed Reactions

5.1. Iron-Catalyzed Sonogashira-Hagihara Reaction

The Sonogashira-Hagihara reaction is a cross-coupling between a terminal alkyne and an aryl or vinyl halide, traditionally catalyzed by using palladium or a combination of palladium and copper. However, Bolm and coworkers have shown that this type of cross-coupling can be

---

[44] C. K. Reddy, P. Knochel, *Angew. Chem.* **1996**, *108*, 1812; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1700.

performed using copper[45] or iron.[46] The iron-catalyzed cyclization led to good and excellent yields. The base used was cesium carbonate, and the reaction time was 3 days (Scheme 14).

Scheme 14. Iron-catalyzed Sonogashira coupling by Bolm.

$$R\text{---}\!\!\equiv\!\!\text{---}H \;+\; Ar\text{---}I \xrightarrow[\substack{Cs_2CO_3,\ toluene \\ 135\ °C,\ 72\ h}]{\substack{FeCl_3\ (10\ mol\%) \\ DMEDA\ (20\ mol\%)}} R\text{---}\!\!\equiv\!\!\text{---}Ar$$

R = Ph, Et₃Si, 2-methoxynaphthalene, 3-toluene, Cy   **15-99.9%**
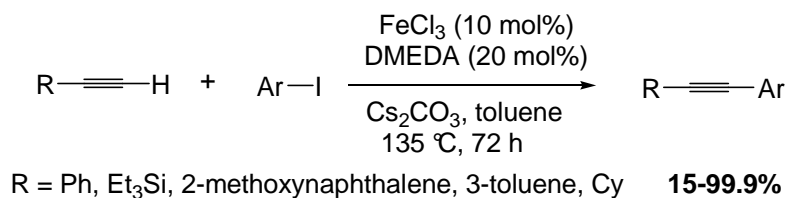
The couple iron(III) trichloride and DMEDA proved to be powerful in this kind of cross-coupling. Unfortunately, only aryl iodides could be used.

5.2. Sonogashira-Type Reaction

Terminal alkynes can be cross-coupled with vinyl iodides. Li and coworkers found an enyne formation - iron-catalyzed - with the combination of $FeCl_3$, 1,10-phenanthroline and Cs_2CO_3 in toluene at 110 °C (Scheme 15).[47]

Scheme 15. Iron-catalyzed enyne formation by Li.
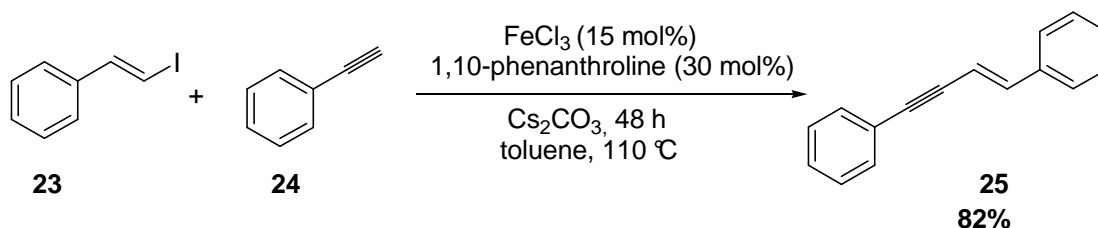
5.3. Coupling of Terminal Alkynes with Alcohols

Alkynes react with secondary alcohols to form substituted alkenyl halides. This C-C bond formation is interesting but not easy since the hydroxyl is a poor leaving group. An efficient and general method was published by Jana.[48] Alkenyl halides were synthesized in a one-pot reaction with various alcohols catalyzed by $FeCl_3$ or $FeBr_3$. Interestingly, both the regioselectivity and stereoselectivity were excellent (Scheme 16).

---

[45] E. Zuidema, C. Bolm, *Chem. Eur. J.* **2010**, *16*, 4181.

[46] M. Carril, A. Correa, C. Bolm, *Angew. Chem.* **2008**, *120*, 4940; *Angew. Chem. Int. Ed.* **2008**, *47*, 4862.

[47] X. Xie, X. Xu, H. Li, X. Xu, J. Yang, Y. Li , *Adv. Synth. Catal.* **2009**, *351*, 1263.

[48] S. Biswas, S. Maiti, U. Jana, *Eur. J. Org. Chem.* **2009**, 2354.

Scheme 16. Coupling of terminal alkynes with alcohols by Jana.

R^1, R^2 = Alkyl, alkenyl, alkynyl, aryl
R^3 = Alkyl, aryl

26-78%

E/Z = 71/29-100/0
X = Cl, Br
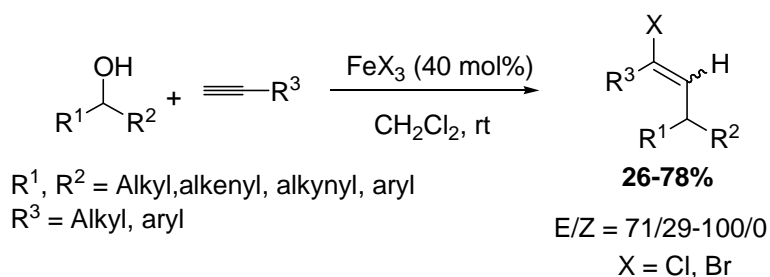
5.4. Coupling Reaction with Three Components

A complex molecule can be formed using a three component reaction, more precisely, alkynes, aldehydes and amines. Wang and coworkers found that ligand-free FeCl$_3$ catalyzes this reaction. Good to excellent yields were obtained (Scheme 17).[49]

Scheme 17. Three component reaction by Wang.

R, R^1 = Alkyl, aryl   R^2, R^3 = Alkyl benzyl   70-98%
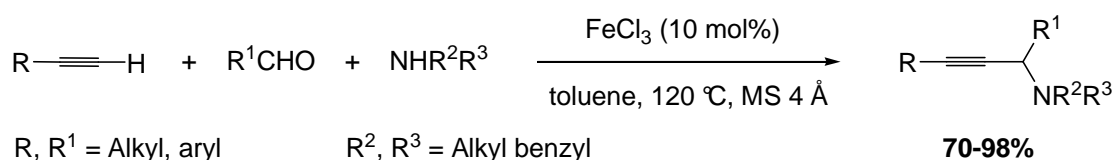
5.5. Iron-Catalyzed Mirozoki-Heck Reaction

Vogel and coworkers published a Mirozoki-Heck reaction catalyzed by iron(II) chloride.[50] They coupled aryl iodides with styrenes. The reaction proceeded well with iron(II) chloride and picolinic acid as a ligand in DMSO at 60 °C with *t*BuOK as a base. DMEDA as ligand was also possible. The stereoselectivity for the reaction between (hetero)aryl iodides and styrenes was high, only (*E*)-alkenes were formed. The use of aryl bromide lowered the yield of the reaction (Scheme 18).

Scheme 18. Iron-catalyzed Mirozoki-Heck reaction by Vogel.


X = I   87%
X = Br 19%
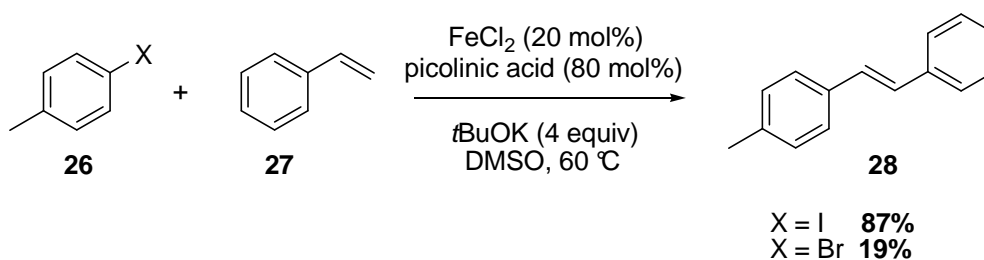
[49] P. Li, Y. Zhang, L. Wang, *Eur. Chem. J.* **2009**, *15*, 2045.
[50] R. Loska, C. M. Rao Volla, P. Vogel, *Adv. Synth. Catal.* **2008**, *350*, 2859.

5.6. Iron-Catalyzed Suzuki-Miyaura Reaction

The Suzuki-Miyaura reaction is a cross-coupling between an aryl halide and an organic boronic acid. Yu and coworkers, after their work on the direct arylation of inactivated arenes,[51] presented an iron-catalyzed *ortho*-arylation of pyrrole and pyridine (Scheme 19).[52]

**Scheme 19.** Iron-catalyzed Suzuki-Miyaura reaction by Yu.
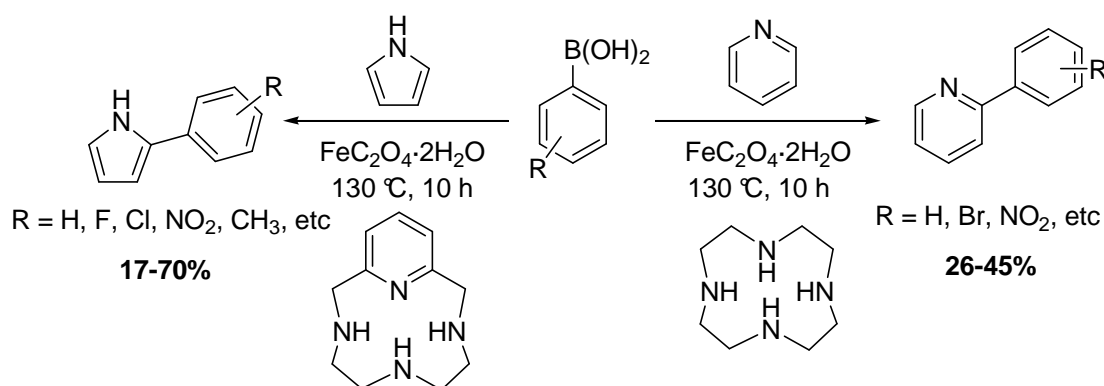
Most of the reactions gave moderate to good yields.

5.7. Iron-Catalyzed Arylations of Arenes with Aryl Halides

Iron-catalyzed arylations of arenes with aryl halides gave biaryls. Charette and Lei have reported this particular C-H activation.

In this work, no directing group was necessary for the iron-catalyzed arylation of arenes with aryl iodides.[53] Moreover, it was proven that iron was necessary only in catalytic amounts. Fe(OAc)$_2$ and bathophenanthroline catalyzed the reaction. The biaryl product was obtained with *t*BuOK as base, in benzene at 80 °C. Heteroaryl iodides and several aryl iodides provided the product in moderate to excellent yields. Nevertheless, aryl bromides did not give satisfactory yields (Scheme 20).

Scheme 20. Iron-catalyzed arylations of benzene with aryl iodides by Charette.
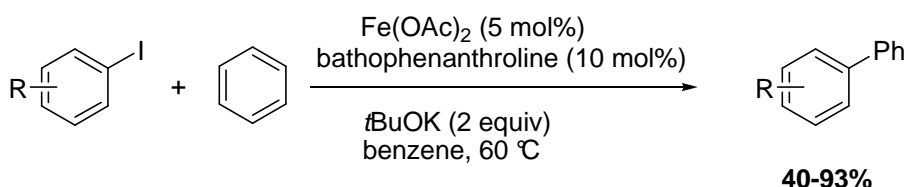
[51] J. Wen, J. Zhang, S.-Y. Shen, J. Li, X.-Q. Yu, *Angew. Chem.* **2008**, *120*, 4272; *Angew. Chem. Int. Ed.* **2008**, *47*, 8897.

[52] J. Wen, S. Qin, L.-F. Ma, L. A. Dong, J. Zhang, S.-S. Liu, Y.-S. Duan, S.-Y. Shen, C.-W. Hu, X.-Q. Yu, *Org. Lett.* **2010**, *12*, 2694.

[53] F. Vallée, J. J. Mousseau, A. B. Charrette, *J. Am. Chem.Soc.* **2010**, *132*, 1514.

Finally, Lei and coworkers, using FeCl₃ as a catalyst, DMEDA as a ligand and LiHMDS as a base, showed that aryl bromides give good yields.[54] Moreover, aryl iodides and aryl chlorides reacted well. It is interesting to note that electron-donating groups promoted the reaction whereas steric hinderance decreased the yield (Scheme 21).

Scheme 21. Iron-catalyzed arylation of arenes with aryl halides by Lei.
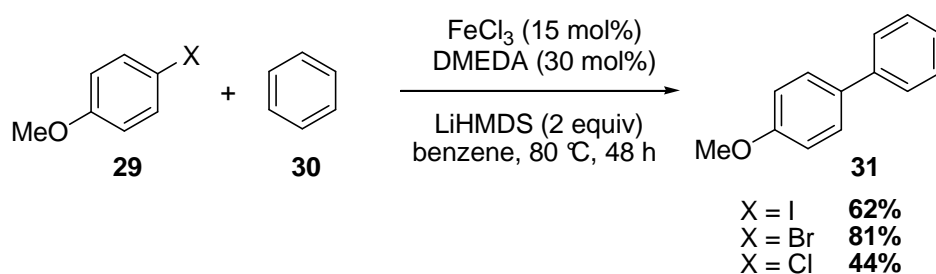
5.8. Hydrogenation and Reduction

Iron has been found to catalyze various hydrogenenation reactions.[55] Casey showed that the iron catalyst **33** hydrogenates ketones under mild conditions.[56] The acidic hydrogen attacks the polar double bond. The reaction is chemoselective, reducing the ketone but not the olefinic double bond (Scheme 22).

Scheme 22. Iron-catalyzed hydrogenation of ketones by Casey.
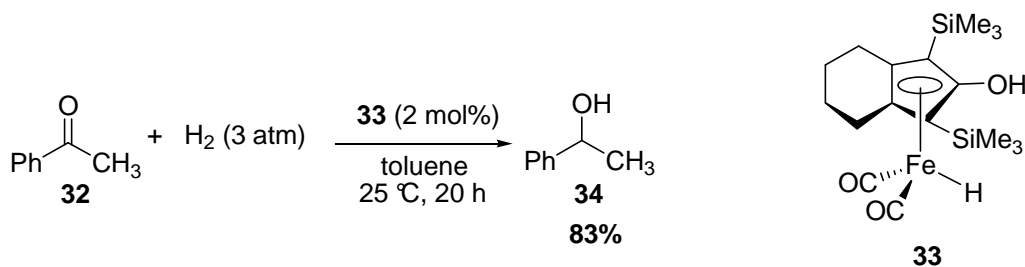
Morris *et al.* successfully reduced ketones enantioselectively with a tetra-dentate P-N-N-P ligand (Scheme 23).[57] The scope was broad, aromatic and nonaromatic ketones were usable.[58]

[54] W. Liu, H. Cao, A. Lei, *Angew. Chem.* **2010**, *122*, 2048; *Angew. Chem. Int. Ed.* **2010**, *49*, 2004.
[55] For review, see: R. H. Morris, *Chem. Soc. Rev.* **2009**, *38*, 2282.
[56] C. P. Casey, H. Guan, *J. Am. Chem. Soc.* **2007**, *129*, 5816.
[57] A. Mikhailine, A. J. Lough, R. H. Morris, *J. Am. Chem. Soc.* **2009**, *131*, 1394.
[58] N. Meyer, A. J. Lough, R. H. Morris, *Chem. Eur. J.* **2009**, *15*, 5605.

Scheme 23. Iron-catalyzed hydrogenation of ketones by Morris.

R^1 = H, Cl, OMe
R^2 = Me, Et, tBu, c-C$_4$H$_7$, c-C$_6$H$_{11}$
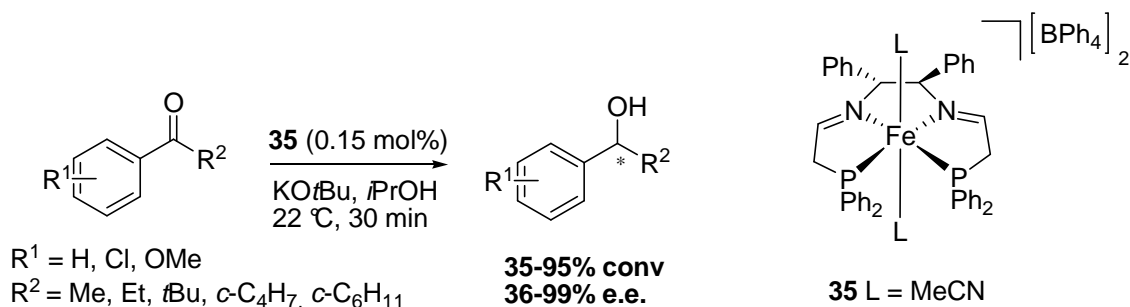
35 (0.15 mol%)
KOtBu, iPrOH
22 °C, 30 min

35-95% conv
36-99% e.e.

35 L = MeCN

Hydrosilylation is also possible. Yang and Tilley published a [Fe{N(SiMe$_3$)$_2$}$_2$]/Ph$_2$SiH$_2$ catalyzed hydrosilylation of ketones.[59] A wide range of ligands and various functional groups were tolerated (Scheme 24).

Scheme 24. Iron-catalyzed hydrosilylation of ketones by Tilley.

Fe[N(SiMe$_3$)$_2$]$_2$
(0.01-2.7 mol%)
C$_6$D$_6$, 23 °C

R^1 = Alkyl, aryl
R^2 = H, alkyl

up to 98%
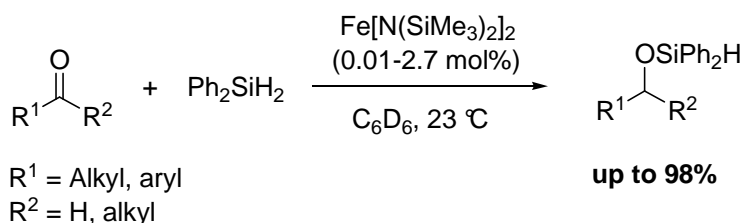
Another iron-catalyzed reaction was found by Enthaler.[60] The reductive amination promoted by iron(III) chloride with polymethylhydrosiloxane (PMHS) in THF for 6 hours at 60 °C gave secondary amines in excellent yields with a broad functional group tolerance (Scheme 25).

Scheme 25. Iron-catalyzed reductive amination by Enthaler.

FeCl$_3$ (5 mol%)
PMHS
THF, 60 °C, 6 h

R^1 = Alkyl, aryl, thiophene
R^2 = Aryl, benzyl

up to 97%

---
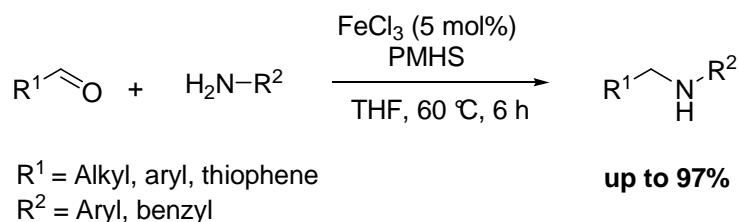
[59] J. Yang, T. D. Tilley, *Angew. Chem.* **2010**, *122*, 10384; *Angew. Chem. Int. Ed.* **2010**, *49*, 10186.
[60] S. Enthaler, *ChemCatChem* **2010**, *2*, 1411.

5.9. Cyclization Reaction

5.9.1. Prins Cyclization

Tetrahydropyrans can be synthesized by the powerful Prins cyclization.[61] Homoallylic alcohols react with aldehydes under acidic conditions and form cis-2,6-tetrahydropyran through an oxocarbenium species with excellent diastereoselectivity. Yu and coworker published an iron-catalyzed Prins cyclization of alkynyl diethyl acetals[62] and alkynyl aldehyde acetals.[63] Cyclization/halogenation of alkynyl acetals was achieved in high yield even at low temperature using FeX_3 as a catalyst (X = Cl or Br) (Scheme 26).

Scheme 26. Iron-catalyzed Prins cyclization by Yu.
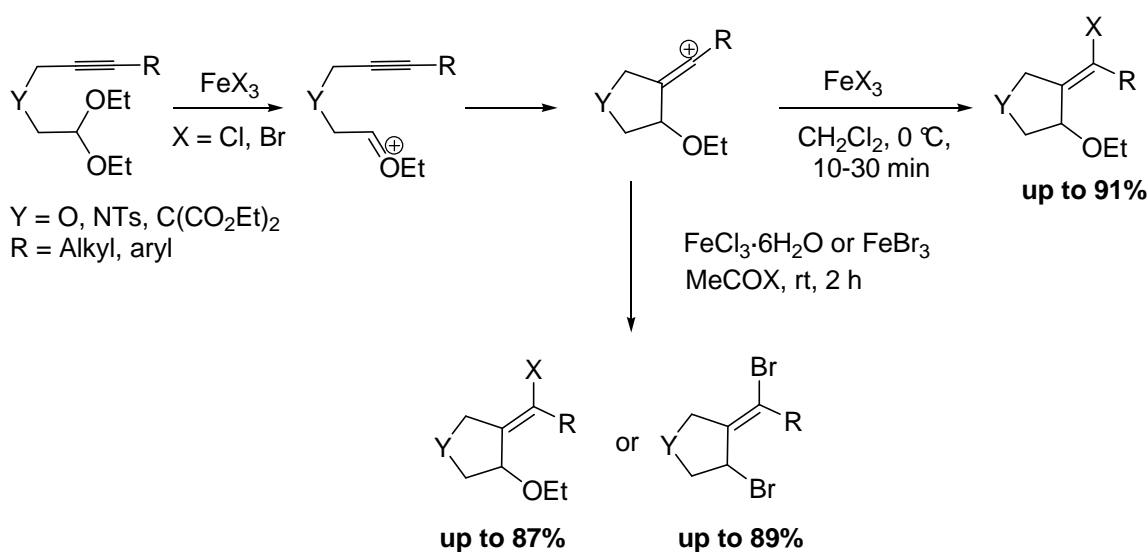
5.9.2. Other Cyclizations

Aminohydroxylations lead to aminoalcohols. Various methods have been presented using expensive and toxic metals such as osmium.[64] Catalyzing this reaction with iron gives several advantages. Yoon and Williamson have developed an iron-catalyzed method for the synthesis of aminoalcohols under mild conditions (Scheme 27).[65]

[61] For a review on Prins cyclization, see: L. E. Overman, L. D. Pennington, *J. Org. Chem.* **2003**, *68*, 7143.

[62] T. Xu, Z. Yu, L. Wang, *Org. Lett.* **2009**, *11*, 2113.

[63] T. Xu, Q. Yang, D. Li, J. Dong, Z. Yu, Y. Li, *Chem. Eur. J.* **2010**, *16*, 9264.

[64] K. B. Sharpless, A. O. Chong, J. Oshima, *J. Org. Chem.* **1976**, *41*, 177.

[65] K. S. Williamson, T. P. Yoon, *J. Am. Chem. Soc.* **2010**, *132*, 4570.

Scheme 27. Iron-catalyzed aminohydroxylation by Yoon.

Ar = 2,4-Cl$_2$Ph
36

R = Alkyl, alkene, alkyne, aryl

52-94%
37

cis:trans 1:1-10:1
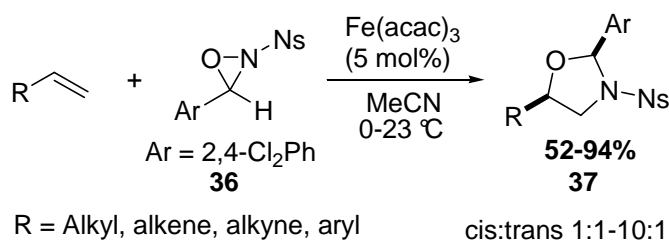
An oxaziridine reacts with an alkene in acetonitrile at 0 °C. Interestingly, the aminohydroxylation is regioselective.

5.10. Oxidation
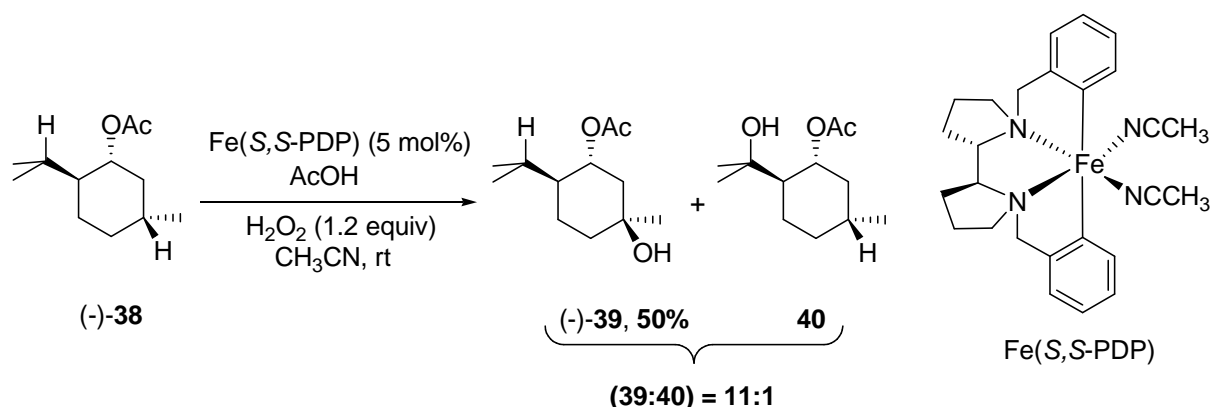
5.10.1. Oxidation of C-H Bond

Nowadays, C-H activation is a topic of big interest. The use of "green" and non-toxic oxidants has become an urgent goal in organic chemistry. Perhaps the most challenging aim is the oxidation of unfunctionalised C-H bonds that constitute large fractions of petroleum before cracking. In 2005, Bolm and coworkers[66] demonstrated a method for the oxidation of alkylarenes and cycloalkanes using $Fe(ClO_4)\cdot 6H_2O$ and hydrogen peroxide in acetonitrile at room temperature. Later, it was shown that the benzylic position could be oxidized with the cheap $FeCl_3\cdot 6H_2O$ using aqueous *tert*-butyl hydroperoxide.[67]

Selective oxidation of aliphatic C-H bond is difficult. Chen and White[68] published the oxidation of aliphatic C-H bond using $[Fe(S,S-PDP)(CH_3CN)_2](SbF_6)_2$. H_2O_2 was used as an oxidant. Also, the acetic acid was required as additive. By using this catalyst, the oxidation of a specific carbon could be calculated. The two main parameters were the steric and the electronical environment of the C-H bond to be oxidized. In fact, this hydroxylation proceeded at the most electron rich tertiary C-H bond. Surprisingly, if the C-H bond was at a stereogenic center, retention of configuration was observed (Scheme 28).

[66] C. Pavan, J. Legros, C. Bolm, *Adv. Synth. Catal.* **2005**, *347*, 703.
[67] M. Nakanishi, C. Bolm, *Adv. Synth. Catal.* **2007**, *349*, 861.
[68] M. S. Chen, C. White, *Science* **2007**, *318*, 783.

Scheme 28. Iron-catalyzed C-H oxidation by White.

Encouraged by these results, White and Chen continued their investigations in this direction and found a selective oxidation of secondary C-H bonds.[69] Three crucial parameters contributed to the selectivity of the reaction: steric and electronic. When synergistic effects of two or even three of them were observed, chemo- and diastereoselectivity of the oxidation went drastically higher.

On this subject, Ribas and Costas have also been successful oxidizing a tertiary C-H bond.[70] The conditions are rather similar to those used by White and Chen. The reaction took place in acetonitrile with H_2O_2 as an oxidant. Acetic acid is required. Again in this iron-catalyzed reaction, steric and electronic parameters promote the selectivity of the reaction.

5.10.2. Oxidation of Sulfur

The metal-catalyzed oxidation of sulfide to sulfoxide has been thoroughly explored, with special interest in the asymmetric versions of this reaction. Iron-catalyzed oxidation reactions are effective and enantioselective. In 2003, Legros and Bolm published an oxidation of sulfides with aqueous hydrogen peroxide.[71] One year later, they reported the same reaction with higher enantioselectivities.[72] Iron(III) acetylacetonate permitted successful oxidation in combination with a Schiff-base ligand (Scheme 29).

---

[69] M. S. Chen, M. C. White, *Science* **2010**, *327*, 566.

[70] L. Gómez, I. Garcia-Bosch, A. Company, J. Benet-Buchholz, A. Polo, X. Sala, X. Ribas, M. Costas, *Angew. Chem.* **2009**, *121*, 5830; *Angew. Chem. Int. Ed.* **2009**, *48*, 5720.

[71] J. Legros, C. Bolm, *Angew. Chem.* **2003**, *115*, 5645; *Angew. Chem. Int. Ed.* **2003**, *42*, 5487.

[72] J. Legros, C. Bolm, *Angew. Chem.* **2004**, *116*, 4321; *Angew. Chem. Int. Ed.* **2004**, *43*, 4225.

Scheme 29. Iron-catalyzed oxidation of sulfur by Bolm.

R^1 = Aryl
R^2 = Me, Et, Bn

up to **78%**, **96% ee**

41
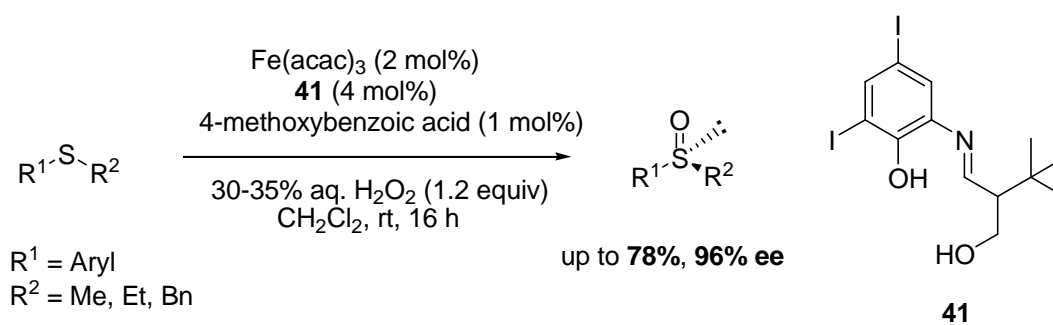
5.11. Metal Contaminants and Copper Catalysis[73]

In 2009, Buchwald and Bolm published the first paper dealing with metal contaminants in iron salts.[74] More precisely, effects of part-per-million (ppm) amounts of copper on different cross-couplings (*N*-, *C*-, *S*- arylation of aryliodides) catalyzed by iron salts were investigated. In all these particular cases, a comparison between 99.99% pure iron trichloride with the same amount of iron in addition to 5 or 10 ppm of copper was made. The former gave yields of up to 32%, on the other hand the latter provided yields of 42-99%.

In another paper, Bolm and Norrby reported a ppm copper loading in the C-N cross-coupling with aryl iodides.[75] It was demonstrated that each substrate required a certain amount of catalyst and a particular set of parameters.

Soon thereafter, several groups working on iron catalysis made test reactions with ppm amount of copper to prove that iron is actually the catalyst. For example, Li and coworkers working on an iron-catalyzed annulation showed that 1 mol% copper oxide formed 15% of the product whereas 92% of the product was obtained with iron trichloride.[76] The same group worked on an iron-catalyzed cascade reaction including a C-S cross-coupling.[77] It was observed that 0.001 mol% and 0.01 mol% CuI gave 61% and 57% product respectively. This could be compared to the results obtained with FeF_3, containing 0.000183 mol Cu/mol FeF_3, which gave a yield of 86%.

---

[73] For review on copper-catalyzed cross-coupling, see: a) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. b) W. Deng, L. Liu, Q.-X. Guo, *Chin. J. Org. Chem.* **2004**, *24*, 150. c) D. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450. d) F. Monnier, M. Taillefer, *Angew. Chem.* **2008**, *120*, 3140; *Angew. Chem. Int. Ed.* **2008**, *47*, 3096. e) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054. f) F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *121*, 7088; *Angew. Chem. Int. Ed.* **2009**, *48*, 6954. g) I. P. Beletskaya, V. P. Ananikov, *Chem. Rev.* **2011**, *111*, 1596.
[74] S. L. Buchwald, C. Bolm, *Angew. Chem.* **2009**, *121*, 5694; *Angew. Chem. Int. Ed.* **2009**, *48*, 5586.
[75] a) P.-F. Larsson, A. Correa, M. Carril, P-O. Norrby, C. Bolm, *Angew. Chem.* **2009**, *121*, 5801; *Angew. Chem. Int. Ed.* **2009**, *48*, 5691. b) P.-F. Larsson, P-O. Norrby, C. Bolm, *Chem. Eur. J.* **2010**, *16*, 13613.
[76] Z.-Q. Wang, Y. Liang, Y. Lei, M.-B. Zhou, J.-H. Li, *Chem. Comm.* **2009**, 5242.
[77] J.-W. Qiu, H.-G. Zhang, R.-Y. Tang, P. Zong, J.-H. Li, *Adv. Synth. Catal.* **2009**, *351*, 2319.

Recently, Wang and coworkers published a copper-catalyzed cross-coupling reaction with only 0.005 mol% of CuI.[78] 2-Aminobenzothiazoles were obtained in moderate to good yields (19-93%) with a high catalytic efficiency (TON up to 67000).

Shi and coworkers demonstrated a $C(sp^3)$-$C(sp^3)$ cross-coupling reaction of alcohols with alkenes.[79] They showed that the use of $FeCl_3$ (Aldrich; 99.99%) gave the same yield as $FeCl_3$ (Alfa Aesar; 98%). Moreover, adding various sources of copper such as CuI, $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$, CuO and Cu_2O did not have any effect on the yield. Li and coworkers tested several copper sources (CuBr, $CuBr_2$, CuCl, $CuCl_2$, CuI, $Cu(acac)_2$, $Cu(OAc)_2$, $CuSO_4 \cdot 5H_2O$, CuF_2) in the iron-catalyzed Pechmann condensation.[80] None provided product. In addition, $FeCl_3 \cdot 6H_2O$, which was purchased from Alfa Aesar (97%), Aldrich (97%) and KANTO (99%) proved that the yield was independent of the source or of the purity.

Wang and coworkers made a clear study of their case on the metal contaminant of iron.[81] They published an iron-catalyzed conversion of aryl halides to phenol (Table 1).

Table 1. Iron-catalyzed conversion of aryl halides to phenol by Wang.
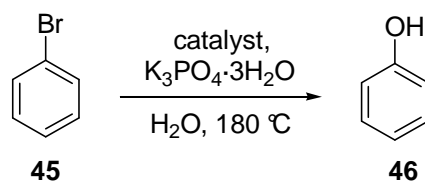
Entry	Purity of $FeCl_3$ (%)	Cu_2O (ppm)	GC yield (%)
1	98	-	88
2	99.99	-	91
3	99.99	10	86
4	99.99	100	89
5	-	100	3

No difference was observed between using $FeCl_3$ (98%) and $FeCl_3$ (99.99%) (Table 1, entries 1 and 2). In addition, copper(II) oxide has no effect on the reaction (Table 1, entries 3 and 4). The most important result is shown in Table 1, entry 5; without iron and with 100 ppm of

[78] Y.-L. Sun, Y. Zhang, X.-H. Cui, W. Wang, *Adv. Synth. Catal.* **2011**, *353*, 1174.
[79] S.-Y. Zhang, Y.-Q. Tu, C.-A. Fan, F.-M. Zhang, L. Shi, *Angew. Chem.* **2009**, *121*, 8917; *Angew. Chem. Int. Ed.* **2009**, *48*, 8761.
[80] X. Guo, R. Yu, H. Li, Z. Li, *J. Am. Chem. Soc.* **2009**, *131*, 17387.
[81] Y. Ren, L. Cheng, X. Tian, S. Zhao, J. Wang, C. Hou, *Tetrahedron Lett.* **2010**, *51*, 43.

copper, a very low amount of product is formed. This definitely proved that this reaction is iron-catalyzed.

Charette and coworker described the same type of study for their iron-catalyzed direct arylation of benzene (Table 2).[53] Lowering the purity of the iron source decreased the yield slightly. (Table 2, entries 1 and 2) On the other hand, with copper(II) acetate as the catalyst, less than 10% yield was obtained. This attend proved that copper has no effect on the reaction. Surprisingly, the addition of both iron and copper was detrimental and the yield dropped significantly (Table 2, entries 5 and 6).

Table 2. Fe and Cu catalysts in the direct arylation of benzene by Charette.
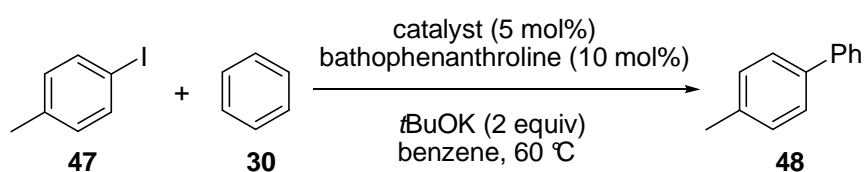
Entry	Catalyst	Purity (%)	GC yield (%)
1	Fe(OAc)$_2$	99.995	98
2	Fe(OAc)$_2$	97	91
3	Cu(OAc)$_2$	99	6
4	Cu(OAc)$_2$	97	9
5	Fe(OAc)$_2$ + Cu(OAc)$_2$	99.995 + 99	57
6	Fe(OAc)$_2$ + Cu(OAc)$_2$	99.995 + 97	48

Another example of proving that the reaction is catalyzed by iron is the work presented by Leadbeater and coworkers on the Suzuki-Miyaura coupling. It has been proven that only 50 part-per-billion (ppb) of Pd is enough to catalyze the reaction.[82] A study using ICP-MS showed that only 5.7 ppb of Pd were present in the sample of iron oxalate 99.999%.[52] Thus, it is highly probable that the Suzuki reaction is catalyzed by iron.

To be noted, Taillefer and coworkers published a NaOH-promoted hydrogen transfer. The reduction of the ketone was made with NaOH and propan-2-ol at reflux for 24 h. Even if

---

[82] R. K. Arvela, N. E. Leadbeater, M. S. Sangi, V. A. Williams, P. Granados, R. D. Singer, *J. Org. Chem.* **2005**, *70*, 161.

bases were promoting the H transfer, transition metal catalysts present in the commercially available bases could catalyze the reaction.[83]
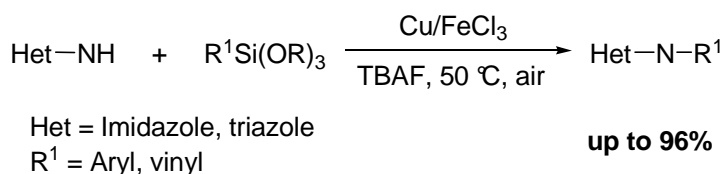
To conclude, copper in sub-molar quantities has an important impact on cross-coupling reaction. Its presence in most of the iron salts must not be ignored.

5.12. Iron-Catalyzed Coupling Reactions
5.12.1. Iron-Catalyzed Intermolecular *N*-Arylation

Taillefer and coworkers[84] described the *N*-arylation of pyrazoles using a combination of iron and copper. They showed that with 2 equivalents of cesium carbonate in DMF at 100 °C for 15 h, iron and copper are required for this transformation. Noteworthy is the fact that no ligand is necessary. To date, only copper can achieve the *N*-arylation without a ligand.[85] Li and coworkers[86] published a milder reaction - solvent-free - and with low catalyst loading (3 mol% FeCl$_3$ and 3 mol% Cu). The cocatalysis with iron and copper promotes a C-N cross-coupling between an arylsilane, as the electrophile, and imidazoles or triazoles. The main drawback of these protocols is the use of two metals (Scheme 30).[87]

Scheme 30. Copper/iron cocatalysis *N*-arylation by Li.

$$\text{Het}-\text{NH} \quad + \quad \text{R}^1\text{Si(OR)}_3 \quad \xrightarrow[\text{TBAF, 50 °C, air}]{\text{Cu/FeCl}_3} \quad \text{Het}-\text{N}-\text{R}^1$$

Het = Imidazole, triazole
R^1 = Aryl, vinyl

up to 96%

In 2007, Correa and Bolm developed conditions enabling iron to catalyze a cross-coupling - more precisely, an intermolecular *N*-arylation (Scheme 31).[88] The optimized conditions are iron(III) trichloride (10 mol%), DMEDA (20 mol%) and K$_3$PO$_4$ in toluene at 135 °C for 24 h. These conditions proved to be versatile.

[83] A. Ouali, J.-P. Majoral, A.-M. Caminade, M. Taillefer, *ChemCatChem.* **2009**, *1*, 504.

[84] a) M. Taillefer, N. Xia, A. Ouali, *Angew. Chem.* **2007**, *119*, 952; *Angew. Chem. Int. Ed.* **2007**, *46*, 934. Other iron/copper cocatalyzer *N*-arylation: b) Z. Wang, H. Fu, Y. Jiang, Y. Zhao, *Synlett* **2008**, 2540.

[85] Ligand-free copper catalyzed reactions: a) A. Correa, C. Bolm, *Adv Synth. Catal.* **2007**, *349*, 2673. b) E. Sperotto, J. G. de Vries, G. P. M. Van Klink, G. Van Koten, *Tetrahedron Lett.* **2007**, *48*, 7366. c) L. Zhu, P. Guo, G. Li, J. Lan, R. Xie, J. You, *J. Org. Chem.* **2007**, *72*, 8535. d) R. Zhu, L. Xing, X. Wang, C. Chemg, D. Su, Y. Hu, *Adv. Synth. Catal.* **2008**, *350*, 1253.

[86] R.-J. Song, C.-L. Deng, Y.-X. Xie, J.-H. Li, *Tetrahedron Lett.* **2007**, *48*, 7845.

[87] For review, see: Y. Su, W. Jia, N. Jiao, *Synthesis* **2011**, 1678.

[88] A. Correa, C. Bolm, *Angew. Chem.* **2007**, *119*, 9018; *Angew. Chem., Int. Ed.* **2007**, *46*, 8862.

Scheme 31. Iron-catalyzed C-N arylation by Bolm
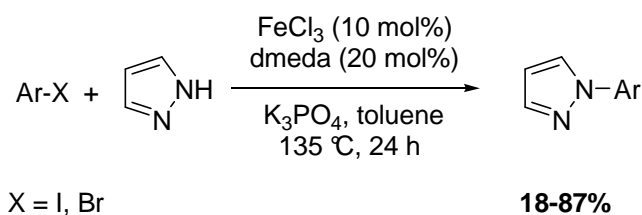
The scope of the reaction has been quickly extended to different nucleophiles such as indole, 7-azaindole, pyrrolidin-2-one and benzamide. On the other hand, aliphatic and aromatic amines were not suitable substrates. The same reaction also proceeded in water.[89]

The described conditions were applied to various nucleophiles: sulfoximines[90] and amides (aliphatic, aromatic and heteroaromatic substrates)[91]. Moreover, the corresponding intramolecular ring closure afforded heterocycles such as oxindole and quinolinone derivatives.[90] The main drawback is that nearly only aryl iodides gave satisfactory yields. Few particular aryl bromides could afford the desired products.

For this *N*-arylation, not only pyrazoles have been used but also simple amines in the presence of the catalytic couple Fe_2O_3 and *L*-proline with NaO*t*Bu as a base in DMSO have been reported by Liu and coworker.[92]

The C-N cross-coupling could also be catalyzed in aqueous media. Kwong and coworkers[93] showed that $FeCl_3 \cdot 6H_2O$ is an iron source for aqueous media. With $K_3PO_4 \cdot H_2O$ at reflux for 24 h, aryl iodides can be cross-coupled to pyrazoles.

Ynamide could be prepared by C-N cross-coupling. Zhang[94] published an *N*-alkynylation using $FeCl_3 \cdot 6H_2O$ with DMEDA as a ligand. This alkynylation was efficient with bromides and gave yields up to 97% (Scheme 32).

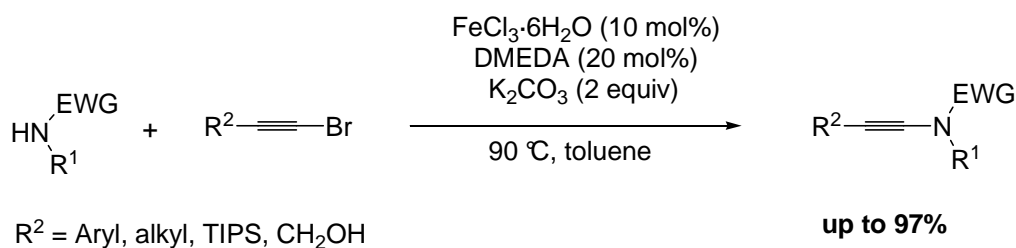[89] Y.-C. Teo, *Adv. Synth. Catal.* **2009**, *351*, 720.
[90] A. Correa, C. Bolm, *Adv. Synth. Catal.* **2008**, *350*, 391.
[91] A. Correa, S. Elmore, C. Bolm, *Chem.-Eur. J.* **2008**, *14*, 3527.
[92] D. Guo, H. Huang, J. Xu, H. Jiang, H. Liu, *Org. Lett.* **2008**, *10*, 4513.
[93] H. W. Lee, A. S. C. Chan, F. Y. Kwong, *Tetrahedron Lett.* **2009**, 5868.
[94] B. Yao, Z. Liang, T. Niu, Y. Zhang, *J. Org. Chem.* **2009**, *74*, 4630.

Scheme 32. *N*-alkynylation by Zhang.

R^2 = Aryl, alkyl, TIPS, CH$_2$OH

up to 97%

5.12.2. Iron-Catalyzed Intermolecular *S*-Arylation

S-Arylation is less studied than *N*-arylation, and thiols are more reactive and sensitive to oxidation, easily forming the corresponding disulfide. Conditions developed for the C-N iron cross-coupling were tested and optimized.[95] Finally, the best conditions for the C-S intermolecular cyclization differed only with the base. NaO*t*Bu proved to be more efficient than K$_3$PO$_4$ for this reaction (Scheme 33).

Scheme 33. Iron-catalyzed *S*-arylation of thiols with aryl halides by Bolm.

42   **8**   **43**
                          91%
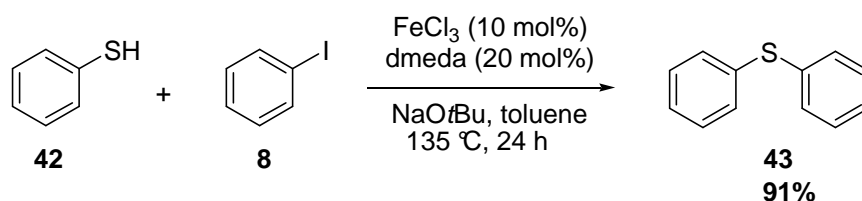
In this case, only aryl iodide could be used. The corresponding bromides and chlorides did not react at all.

An intramolecular version was developed by Li and coworkers.[77] This iron-catalyzed reaction is a cascade reaction which gave 2-aminobenzothiazoles. The couple FeF$_3$/1,10-phenanthroline gave moderate to excellent yields. Iodo and bromo arenes could be used (Scheme 34).

Scheme 34. Iron-catalyzed intramolecular *S*-arylation by Li.

X = I, Br

58-98%
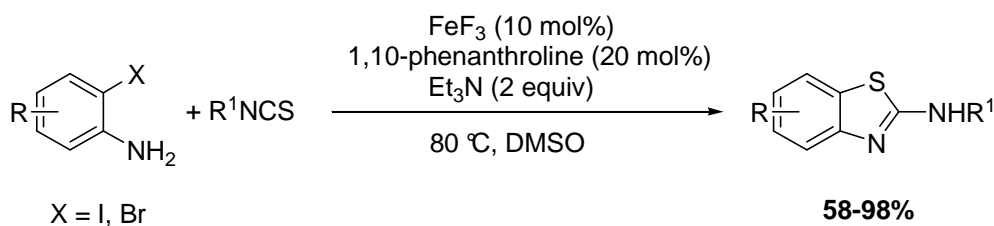
[95] A. Correa, M. Carril, C. Bolm, *Angew. Chem.* **2008**, *120*, 2922; *Angew. Chem. Int. Ed.* **2008**, *47*, 2880.

5.12.3. Iron-Catalyzed Intermolecular *O*-Arylation

It has now been shown that iron can catalyze cross-coupling of C-N, C-S and C-C bonds. Led by the results from studies of FeCl$_3$/DMEDA-catalyzed C-N cross-coupling, the C-O cross-coupling was investigated.[96] It was soon found that the conditions used for C-N cross-coupling could not be used for the coupling of C-O bonds. Thus, optimization of the reaction was performed with the result that another ligand must be used in this case. The ligand that gave the highest yield in combination with FeCl$_3$ was 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD). This new catalyst system is very powerful and gave yields up to 99% (Scheme 35).

Scheme 35. Iron-catalyzed *O*-arylation by Bolm.
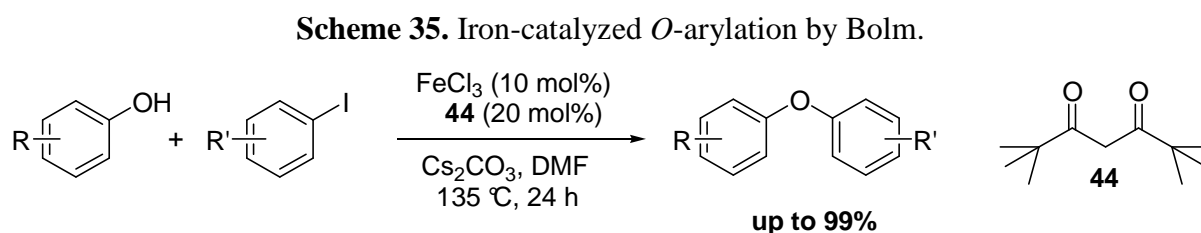
Aryl halides can be coupled with water using iron as a catalyst to form phenol derivatives. Wang and coworkers[81] published an iron-catalyzed conversion of inactivated aryl halides leading to phenols. Notable is the use of water as a solvent for this reaction. Aryl bromides and aryl iodides could be coupled with water to yield their corresponding phenol derivatives (Scheme 36).

Scheme36. Iron-catalyzed conversion of aryl halides to phenols by Wang.
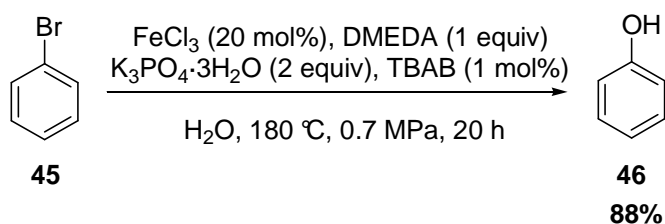
6. Conclusion

Along these lines, practical FeCl$_3$ cross-couplings of aryl halides in combination with appropriately chosen ligands have arisen. For example, C-N, C-S, C-C and C-O intermolecular cross-coupling with nitrogen, sulfur, carbon and oxygen containing nucleophiles, respectively, were described. More precisely, *N*-, *S*-, *C*-arylations efficiently proceeded in the presence of catalytic amounts of FeCl$_3$ and *N*,*N*′-dimethylethylendiamine

---

[96] O. Bistri, A. Correa, C. Bolm, *Angew. Chem.* **2008**, *120*, 596; *Angew. Chem., Int. Ed.* **2008**, *47*, 586

(DMEDA), whereas *O*-arylation required FeCl$_3$ and 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD). Along with these intermolecular cross-coupling reactions, the intramolecular variant was the next step.

Result and Discussion

I. Iron-Catalyzed Intramolecular *O*-Arylation

1. Benzoxazole

1.1. Introduction

Encouraged by the results obtained for the intermolecular *O*-arylations: FeCl$_3$ (10 mol%), TMHD (20 mol%), Cs$_2$CO$_3$ (2 equiv) in DMF at 135 °C, the same conditions were applied to intramolecular *O*-arylations (Scheme 37). The first reaction was the cyclization of benzamides or benzyl ketones to obtain benzoxazoles or benzofurans.

Scheme 37. Iron-catalyzed intramolecular *O*-arylation
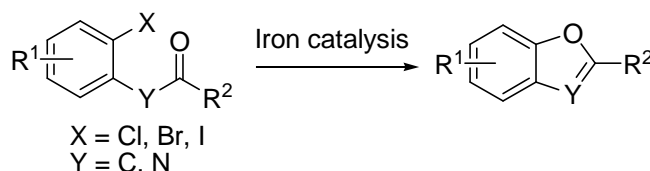
The reaction was performed using FeCl$_3$ (Acros; 98%) as catalyst. Both the compounds are present in natural products[97] and show interesting biological and therapeutical activities.[98] The preparation of 2-substituted benzoxazoles via *ortho*-aminophenols involves the use of either highly toxic reagent or harsh reaction conditions, for example, the use of strong acids and the need of high reaction temperatures.[99] More sustainable processes have recently overcome these drawbacks and are more efficient.[100] Copper-catalyzed intramolecular *O*-arylation reactions of *ortho*-haloanilides constitute a straightforward and elegant synthesis of a benzoxazole ring system.[101]

[97] a) B. H. Lipshutz, *Chem. Rev.* **1986**, *86*, 795. b) D. E. Fuerst, B. M. Stoltz, J. L. Wood, *Org. Lett.* **2000**, *2*, 3521.

[98] For benzoxazoles see: a) M. L. McKee, S. M. Kerwin, *Bioorg. Med. Chem.* **2008**, *16*, 1775. b) E. Oksuzoglu, B. Tekiner-Gulbas, S. Alper, O. Temiz-Arpaci, T. Ertan, I. Yildiz, N. Diril, E. Sener-Aki, I. Yalcin, *J. Enzyme Inhib. Med. Chem.* **2008**, *23*, 37. For benzo[*b*]furan see: L. De Luca, G. Nieddu, A. Porcheddu, G. Giacomelli, *Curr. Med. Chem.* **2009**, *16*, 1.

[99] For example, see: a) J. A. Seijas, M. P. Vazquez-Tato, M. R. Carballido-Reboredo, J. Crecente-Campo, L. Romar-Lopez, *Synlett* **2007**, 313. b) J. A. Seijas, M. P. Vazquez-Tato, M. R. Carballido-Reboredo, J. Crecente-Campo, L. Romar-Lopez, *Synlett* **2007**, 313.

[100] For example, see: a) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 12404. b) N. K. Downer-Riley, Y. A. Jackson, *Tetrahedron* **2007**, *61*, 10276.

[101] a) N. Barbero, M. Carril, R. SanMartin, E. Domınguez, *Tetrahedron* **2007**, *63*, 10425. b) P. Saha, T. Ramana, N. Purkait, M. A. Ali, R. Paul, T. Punniyamurthy, *J. Org.Chem.* **2009**, *74*, 8719. c) R. D. Viirre, G. Evindar, R. A. Batey, *J. Org. Chem.* **2008**, *73*, 3452.

Scheme 38. Copper-catalyzed intramolecular *O*-arylation by Batey.

49   **50**   **51**

R = Ph, 2-MePh, 2-thienyl, $nC_{11}H_{23}$ **56-77%**
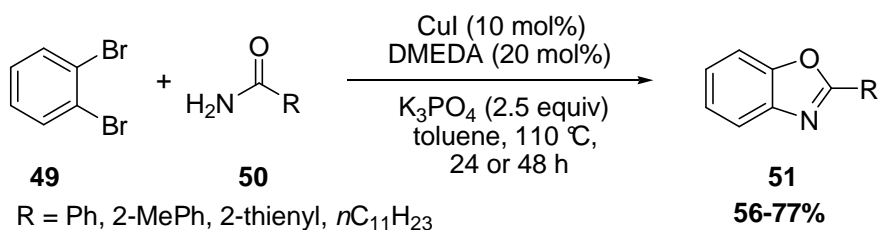
1.2. Study of Reaction

1.2.1. Influence of Temperature

N-(2-bromophenyl)benzamide (**52a**) was used as a model substrate for the optimization of the reaction conditions, which can be easily prepared by benzoylation of 2-bromoaniline. Heating a mixture of **52a** along with TMHD, Cs_2CO_3, DMF and $FeCl_3$ in DMF at 135 °C provided **51a** in 98% yield (Table 3, entry 1) which shows that these conditions fit perfectly also to intramolecular reactions. It is important to note that bromo derivatives as well as iodoarenes were employed for the intermolecular pathway. In the latter case more time was needed to ensure acceptable yields.[96] An experiment without $FeCl_3$ and ligand was performed. In this case, only 42% yield of **51a** could be isolated. It implies that the initial experiment is a sum of both nucleophilic substitutions and iron-catalyzed cyclizations.

Table 3. Influence of the temperature in the iron-catalyzed *O*-arylations of amide **52a**.

52a   **51a**
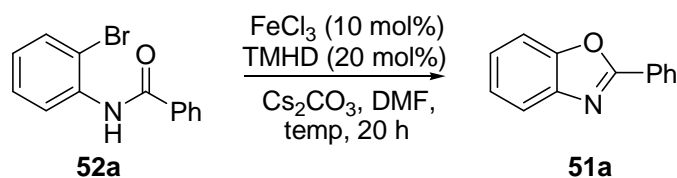
Entry	temp (°C)	51a[a] (%)
1	135	98 (42)
2	120	88 (traces)
3	110	66 (0)
4	80	22 (0)
5	60	0 (0)

[a]Yield of product after column chromatography; in parentheses, results from experiments performed in the absence of $FeCl_3$/TMHD.

The subsequent reactions were performed at lower temperatures to minimize aromatic substitution. Heating the reaction mixture at 120 °C afforded **51a** in 88% yield (Table 3, entry 2). Lowering the temperature further resulted in a drastic decrease of yield of **51a** (Table 3, entries 3-5).

1.2.2. Influence of Base

The crucial role of base and the solvent was revealed by conducting another set of experiments. Cs_2CO_3 gave the highest yield under the test conditions (Table 4, entry 1). Changing the base to K_3PO_4, K_2CO_3 and NaOtBu provided lowered yields of **51a** (Table 4, entries 2-4). No yield of **51a** was obtained in absence of a base (Table 4, entry 5).

Table 4. Influence of the base in the iron-catalyzed O-arylations of amide **52a**.

Entry	Base	51a[a] (%)
1	Cs_2CO_3	88
2	K_3PO_4	56
3	K_2CO_3	54
4	NaOtBu	13
5	none	0

[a]After column chromatography

1.2.3. Influence of Solvent

The influence of solvent on the outcome of the reaction was tested next.

Table 5. Influence of solvent in the iron-catalyzed O-arylations of amide **52a**.

Entry	Solvent	**51a**[a] (%)
1	DMF	88
2	Dioxane	72
3	DME	40

| 4	CH$_3$CN	65
5	Toluene	0

[a] After column chromatography

Using DMF as solvent, 88% of **51a** was obtained (Table 5, entry 1). The use of dioxane, DME and acetonitrile provided lowered yields of **51a** (Table 5, entries 2-4). No product was obtained when the reaction was performed in toluene (Table 5, entry 5). Thus, DMF was the optimal solvent for the reaction.

1.2.4. Influence of Different Iron Salts and Ligands

The next reactions focused on elucidating the effect of the catalyst composition on the benzoxazole formation, under the optimized conditions of base (Cs$_2$CO$_3$), solvent (DMF), and temperature (120 °C)

Table 6. Influence of nature of the catalyst in the intramolecular cyclization of **52a** to give benzoxazole **51a**.
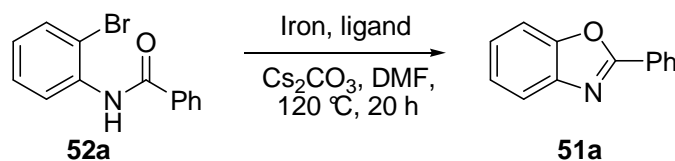
Entry	Iron source	Ligand	**51a**[a] (%)
1	FeCl$_3$	TMHD	88
2	none	TMHD	0
3	FeCl$_3$	none	0
4	FeCl$_3$	DMEDA	25
5	FeCl$_3$	*N*,*N*′-dimethylglycine	77
6	Fe$_2$O$_3$	TMHD	75
7	FeCl$_3$·6H$_2$O	TMHD	85
8	FeBr$_2$	TMHD	80
9	Fe(OAc)$_2$	TMHD	86
10	Fe(ClO$_4$)$_2$	TMHD	75

[a] After column chromatography

Conducting the reaction in presence of 10 mol% FeCl$_3$ and absence of a ligand did not provide the desired compound **51a**. Absence of FeCl$_3$ but presence of TMHD also failed to deliver the product **51a**. These results confirmed that both FeCl$_3$ as catalyst along with TMHD as ligand

are required for the process (Table 6, entries 2 and 3). FeCl$_3$ and TMHD was the best combination for this reaction (Table 6, entry 1). Ligands such as DMEDA or *N,N'*-dimethylglycine proved to be inferior, providing **51a** in 25% and 77% respectively (Table 6, entries 4 and 5). Some other iron(III) sources such as Fe$_2$O$_3$ and FeCl$_3$·6H$_2$O were also tested for the cyclization reaction and led to high yields (Table 6, entries 6 and 7). Iron(II) sources such as FeBr$_2$, Fe(OAc)$_2$ and Fe(ClO$_4$)$_2$ provided yields comparable to the FeCl$_3$ and TMHD combination (Table 6, entries 8-10). To sum up, this screening proved that the optimal conditions for the intramolecular *O*-arylation of **52a** were the use of FeCl$_3$, Cs$_2$CO$_3$, and TMHD in DMF at 120 °C.

1.3. Scope of the Reaction

Finally, the scope of the iron-catalyzed intramolecular *O*-arylation was evaluated. The chloro derivative **52c** of ortho-halobenzamide did not give any yield of the desired product under the optimized conditions (Table 7, entry 3). The iodo analogue of **52a**, under the same conditions, cyclized well, providing high yield of **51a** (Table 7, entry 2). In this reaction, the yield was driven by the nature of the substituent R^2, directly linked to the carbonyl moiety. Various substrates bearing different substituted aromatic motifs could be used. They offered good to high yields (Table 7, entries 1-7 and 9-11). Unfortunately, when substituent R^2 was vinylic or aliphatic group, no cyclization occurred (Table 7, entries 12-14).

Table 7. Iron-catalyzed synthesis of benzoxazole derivatives **51**[a].
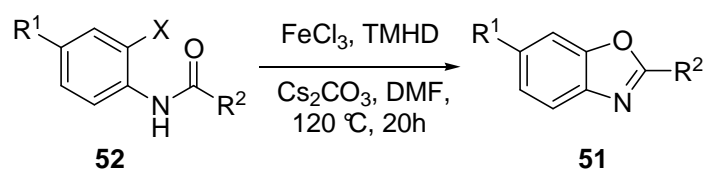
Entry	Substrate	R^1	R^2	X of **52**	Product	Yield (%)
1	**52a**	H	Ph	Br	**51a**	88
2	**52b**	H	Ph	I	**51a**	92
3	**52c**	H	Ph	Cl	**51a**	0
4	**52d**	H	4-Cl-Ph	Br	**51b**	75
5	**52e**	H	4-OMe-Ph	Br	**51c**	96
6	**52f**	H	3,4-diCl-Ph	Br	**51d**	65
7	**52g**	H	4-Br-Ph	Br	**51e**	92
8	**52h**	H	Mes	Br	**51f**	16[c]
9	**52i**	H	2-F-Ph	Br	**51g**	48[c]

10	**52j**	H	3-OMe-Ph	Br	**51h**	82
11	**52k**	F	Ph	Br	**51i**	89
12	**52l**	H	Et	Br	**51j**	0
13	**52m**	H	(Z) Prop-1-enyl	Br	**51k**	0
14	**52n**	H	(Z) Prop-1-enyl	I		0

[a]**52** (1 equiv), FeCl$_3$ (0.10 equiv), TMHD (0.20 equiv), Cs$_2$CO$_3$ (2.0 equiv), DMF (1 mL/mmol of **52**), 20 h. [b]After column chromatography. [c]Reaction time: 72 h

The presence of large substituent groups (R^2) on **52** lowered the yield (Table 7, entries 8 and 9). Using iodo-arene as electrophile or performing the cyclization for longer reaction times did not alter the outcome. Fluorene substitution (R^1) on **52** provided good yield (Table 7, entry 13).

In conclusion, an efficient iron-catalyzed intramolecular *O*-arylation leading to benzoxazole has been developed. The synthesis of benzofurans under these conditions provides an interesting prospect.

2. Benzofuran

2.1. Introduction

Benzofurans, like benzoxazoles are good candidates for drug design and industrial applications.[102] Electrophilic cyclizations of the corresponding *ortho*-alkenylphenols or alkynyl are possible for their synthesis.[103] Metal-free reactions between arynes and iodonium ylides[104] or cycloadditions starting from *ortho*-silylaryl triflates[105] have been employed. At low temperatures, boron trichloride-mediated cyclodehydrations reaction of 3-arylbenzo[*b*]furan was developed by Kim and coworkers.[106] Metal-catalyzed processes have also been described using palladium[107] or copper.[108] For example, Chen and Dormer reported a copper(I) iodide catalyzed ring closure of 2-haloaromatic ketones (Scheme 39).[108c] This methodology has also been extended to 2-haloaromatic aldehydes. Good to excellent yields

[102] D. Yue, T. Yao, R. C. Larock, *J. Org. Chem.* **2005**, *70*, 10292.

[103] a) M. C. Willis, D. Taylor, A. T. Gillmore, *Org. Lett.* **2004**, *6*, 4755. b) M. Yoshida, Y. Morishita, M. Fujita, M. Ihara, *Tetrahedron Lett.* **2004**, *45*, 1861. c) Y. Hu, Z. Yang, *Org. Lett.* **2001**, *3*, 1387.

[104] X.-C. Huang, Y.-L. Liu, Y. Liang, S.-F. Pi, F. Wang, J.-H. Li, *Org. Lett.* **2008**, *10*, 1525.

[105] a) Z. Liu, F. Shi, P. D. G. Martinez, C. Paminelli, R. C. Larock, *J. Org. Chem.* **2008**, *73*, 219. b) Y. K. Ramtohul, A. Chartrand, *Org. Lett.* **2007**, *9*, 1029. c) C. Xie, Y. Zhang, *Org. Lett.* **2007**, *9*, 781.

[106] I. Kim, S.-H. Lee, S. Lee, *Tetrahedron Lett.* **2008**, *49*, 6579.

[107] a) C. Martinex, R. Alvarez, J. M. Aurrecoechea, *Org. Lett.* **2009**, *11*, 1083. b) J. Farag, A. Kotschy, *Synthesis* **2009**, 85. c) For a review on palladium-catalyzed syntheses of benzofurans, see: S. Cacchi, G. Fabrizi, A. Goggiamani, *Curr. Org. Chem.* **2006**, *10*, 1423.

[108] a) A. C. Tadd, M. R. Fielding, M. C. Willis, *Tetrahedron Lett.* **2007**, *48*, 7578. b) M. Carril, R. SanMartin, I. Tellitu, E. Dominguez, *Org. Lett.* **2006**, *8*, 1467. c) C. Y. Chen, P. G. Dormer, *J. Org.Chem.* **2005**, *70*, 6964.

have been obtained. Iodo and bromo derivatives of ortho-halo aldehydes/ketones have also been proven to undergo cyclization under the same conditions.

Scheme 39. CuI-catalyzed intramolecular C-O cross-coupling by Dormer.

X = Br, I
R¹ = H, alkyl, nitrile, ester
R² = H, alkyl, aryl

72-99%
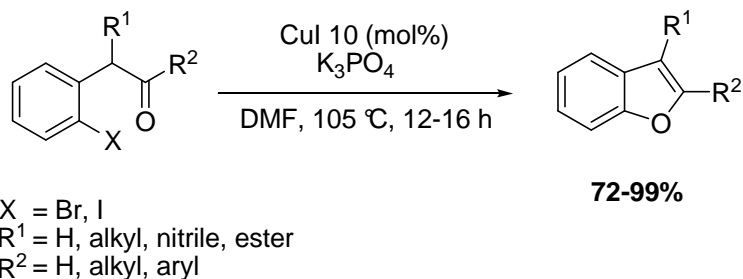
Recently, Zhao and Li published the use of iron trichloride, in the presence of strong oxidants, for the syntheses of functionalized benzo[*b*]furans.[109] Large amounts of FeCl$_3$ (2.5 equiv) was used for this purpose. Due to these inconveniences this procedure is not very attractive. The use of catalytic amount of iron salts that are cheaply available and also environmentally friendly for the intramolecular *O*-arylation for the formation of benzofurans presents an interesting challenge.

2.2. Study of Reaction

2.2.1. Influence of Base

The presence of a base is an important parameter in this reaction. Starting from the optimal conditions used for the intramolecular *N*-arylation reactions, several bases were tested (Table 8).

Table 8. Base and solvent screening.
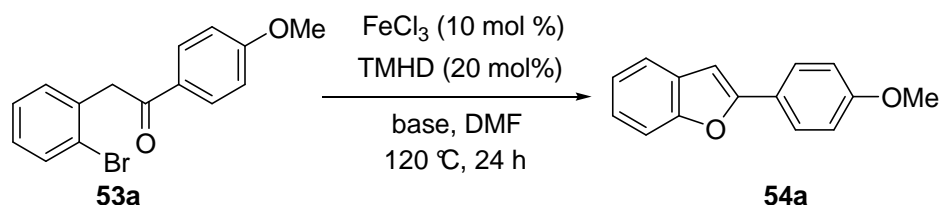
Entry	Base	**54a** (%)[a]
1	Cs$_2$CO$_3$	79
2	K$_3$PO$_4$	46

[109] a) Z. Liang, W. Hou, Y. Du, Y. Zhang, Y. Pan, D. Mao, K. Zhao, *Org. Lett.* **2009**, *11*, 4978. b) X. Guo, R. Yu, H. Li, Z. Li, *J. Am. Chem. Soc.* **2009**, *131*, 17387.

3	NaOH	7
4	K$_2$CO$_3$	39
5	NaHCO$_3$	traces
6	NaOtBu	traces
7	Na$_2$CO$_3$	traces

[a] After column chromatography

Interestingly, the target benzofuran **54a** was obtained in 79% yield using the same condition as during the formation of benzoxazole: FeCl$_3$ (10 mol%), TMHD (20 mol%) and Cs$_2$CO$_3$ (2 equiv) in DMF at 120 °C. The bases play a crucial role. Reactions with other bases, such as K$_3$PO$_4$, NaOH, K$_2$CO$_3$, NaHCO$_3$, NaOtBu, Na$_2$CO$_3$ under the same reaction conditions proved counter productive.

2.2.2. Influence of Solvent

Next the influence of solvent on the reaction was evaluated (Table 9). Using solvents other than DMF, lowered the yield of **54a** (Table 9, entry 2–4).

Table 9. Influence of the solvent.
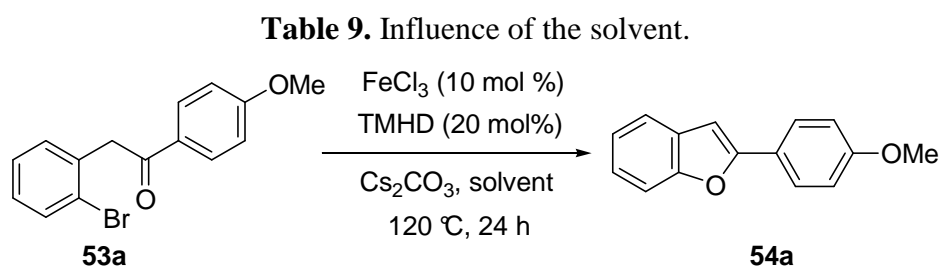
| Entry	Solvent	**54a** (%)[a]
1	DMF	79
2	CH$_3$CN	-
3	Dioxane	49
4	DMF/MeOH (9/1)	53

[a] After column chromatography

2.2.3. Influence of Ligand

Modifying the diketone to a ketoester **55** led to a decrease in yield. Good yields were obtained for the cyclization reaction with modification of the electronic properties of diketones (**56** and **59**). The use of 2-acetylcyclopentanone (**57**) and pentane-2,4-dione (**58**) as ligand lowered the

yields. Thus, previously employed TMHD as ligand proved to be the best ligand for the cyclization of the substrate (Scheme 40).

Scheme 40. Ligand screening.
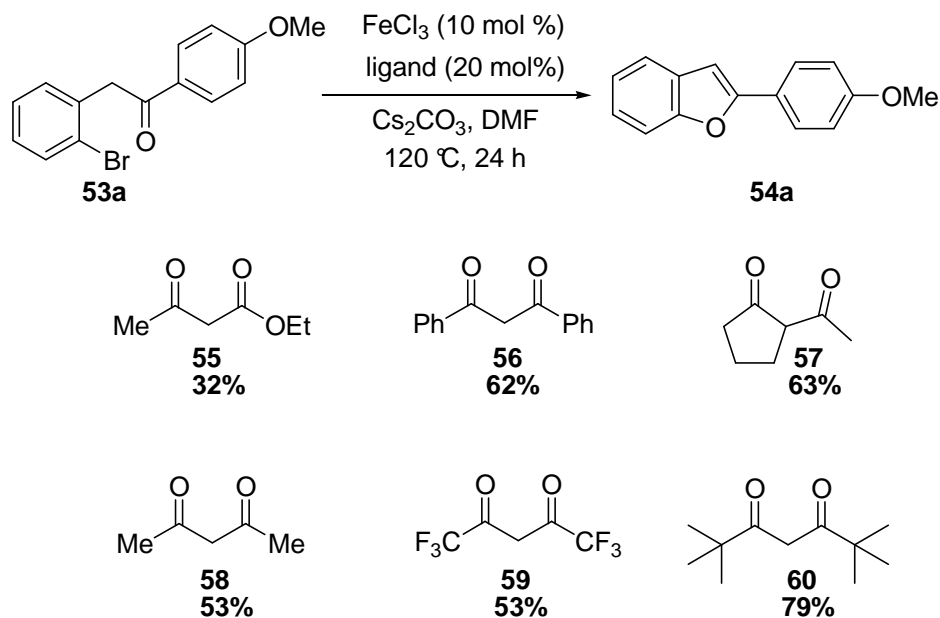
2.2.4. Influence of the Purity of the Catalyst

It has been shown that various reactions can be influenced by the presence of parts per million (ppm) quantities of copper (present in the iron salt).[45,74,75]

FeCl$_3$ (98% from Merck) was analyzed by atom absorption spectroscopy (AAS). The results showed that palladium (13.2 ppm), nickel (190 ppm), copper (344 ppm) and manganese (1720 ppm) were present. Therefore a test reaction for each of these metals was needed to check their reactivity for the cyclization reaction.

Table 10. Effects of metal dichlorides in cyclizations of **54a**.

Entry	Metal	ppm	Mol%	55a[a] (%)
1	FeCl$_3$ (98%)		10	79
2	-	-	-	8

3	CuCl$_2$	344	0.0088	60
4	MnCl$_2$·4H$_2$O	1720	0.0510	8
5	PdCl$_2$	13.2	0.0002	8
6	NiCl$_2$·6H$_2$O	190	0.0053	8

[a] Yield of the isolated product after flash chromatography.

2-(2-bromophenyl)-1-(4-methoxyphenyl)-ethanone (**53a**) was chosen as test substrate for this study. The reaction was performed under the optimized conditions: 10 mol% FeCl$_3$ with 20 mol% of 2,2,7,7-tetramethylhepta-2,5-dione (TMHD) and Cs$_2$CO$_3$ (2 equiv.) in DMF at 120 °C for 24 h. 2-Arylbenzo[*b*]furan **54a** was obtained in 79% yield (Table 10, entry 1). Absence of a metal-catalyst yielded **54a** in only 8%. Next, the quantity of other metal impurities found in FeCl$_3$ (98%) by AAS were applied for the cyclization reactions. MnCl$_2$·4H$_2$O, PdCl$_2$ and NiCl$_2$·6H$_2$O did not affect the cyclization reaction. Conversely, CuCl$_2$ with only 0.0088 mol% (344 ppm), gave 60% yield of benzofuran (Table 10, entry 3). This study demonstrated that copper, even in ppm quantities, can efficiently catalyze the reaction. We decided to further examine the role of this metal in combination with iron. Different mixtures of high purity of copper chloride and iron trichloride were applied to this cyclization reaction.

Table 11. Effect of FeCl$_3$/CuCl$_2$ mixtures on the synthesis of **54a** starting from **53a**.

Entry	Mol% of FeCl$_3$[a]	Mol% of CuCl$_2$[a]	Yield [%][b]
1	10	0.0088	79
2	0.1	0.0088	68
3	0.0088	0.0088	65
4	0	0.0088	60
5	0	0.02	63
6	0	0.03	67
7	0	0.04	77
8	0	0.05	79
9	0.0088	0	8
10[c]	10	0	79

[a] With a purity of 99.995% (Aldrich). [b] Yield of the isolated product after flash chromatography. [c] Using a stock solution of FeCl$_3$ in DMF.

The addition of 10 mol% of FeCl$_3$ (99.995%) and 0.0088 mol% of CuCl$_2$ which corresponded to the same amount present in the FeCl$_3$ (98%) led to the same yield of 79% (Table 10, entry

1 and Table 11, entry 1). Lowering the catalyst loading of FeCl$_3$ to 0.1 and 0.0088 mol% decreased the yield slightly 68% and 65%, respectively (Table 11, entry 2 and 3). On the other hand, increasing CuCl$_2$ loading in absence of FeCl$_3$, provided higher yields (Table 11, entry 4-8). These results show that copper salts have a predominant impact on this reaction. Using high purity FeCl$_3$ in low catalyst loading (0.0088 mol%) had no impact on the reaction (Table 11, entry 9). The catalyst loading of 10 mol% gave 79% yield (Table 11, entry 10). Surprisingly, no differences were observed using iron(III) chloride with 98% purity and iron(III) chloride with 99.995% purity. In conclusion, iron trichloride with high purity was used and proved to be equally efficient (Table 11, entry 10).

2.3. Scope of the Reaction

Finally, the scope of the intramolecular *O*-arylation for the formation of benzofurans was investigated. The highest yield of **54a** was obtained using FeCl$_3$ (Merck; 98%) (Table 10, entry 1).
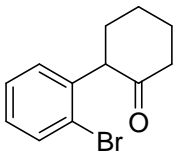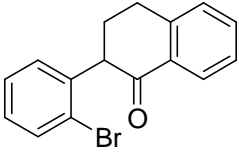
Electron-donating groups in the *para*-position of the carbonyl-substituted arene (Table 12, entries 1–5) afforded good yields (up to 87%). As anticipated, the presence of an electron-withdrawing chloro group decreased the yield of the product to 25% (entry 6). Interestingly, increasing the steric hinderance does not affect the formation of the product as shown by the cyclization of **53e**, which was obtained in 89% yield (entry 5). 2,3-Disubstituted benzo[*b*]furans **54g** and **54h** were isolated in 33% and 76% yields respectively (entries 7 and 8). A methoxy substituent in *para*-position to the bromo group (**53k–n**) lowered the yield compared to the unsubstituted aryl benzyl ketones (Table 12, entries 11–14). These results were obtained with FeCl$_3$ (98%).

Table 12. Substrate scope in the benzo[*b*]furan syntheses.
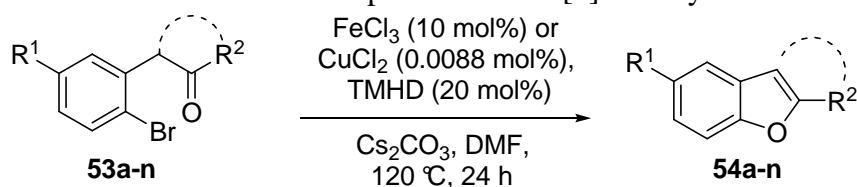
Entry	R^1	R^2	Substrate	Product	Yield [%][a]
1	H	4-OMe-Ph	**53a**	**54a**	79 (60)
2	H	4-SMe-Ph	**53b**	**54b**	72 (67)
3	H	4-Me-Ph	**53c**	**54c**	59 (50)
4	H	4-*t*Bu-Ph	**53d**	**54d**	54 (42)
5	H	Mes	**53e**	**54e**	87 (69)

6	H	4-Cl-Ph	**53f**	**54f**	25 (16)
7	H		**53g**	**54g**	33 (30)
8	H		**53h**	**54h**	76 (60)
9	H	2,3-dihydro-1H-inden-5-yl	**53i**	**54i**	75 (45)
10	H	5,6,7,8-tetrahydronaphthalen-2-yl	**53j**	**54j**	81 (36)
11	OMe	4-OMe-Ph	**53k**	**54k**	47 (42)
12	OMe	4-SMe-Ph	**53l**	**54l**	30 (10)
13	OMe	4-Me-Ph	**53m**	**54m**	36 (31)
14	OMe	Mes	**53n**	**54n**	66 (59)

[a] Yield of the isolated product after flash chromatography; in parentheses, results from experiments performed with 0.0088 mol% of $CuCl_2$ (99.995%; Aldrich).

To investigate if 0.0088 mol% of copper had an effect, experiments were repeated in the presence of the appropriate amount of $CuCl_2$ (with 99.995% purity). Generally, with respect to the substitution pattern, the same trend was observed but with significantly lower yields. The benzo[*b*]furans **54l** and **54e** were obtained in 10% and 69 % yields, respectively (Table 12, entries 12 and 5).

In conclusion, 10 mol% iron and 0.0088 mol% copper both show a strong activity for the intramolecular C-O cross-coupling in the formation of benzofurans.

II. Iron Salts in Click Chemistry

1. Introduction

The aim of this work was the investigation of role of iron in reactions along with azides and nitriles. Thus iron-catalyzed "Click-reactions" was investigated. According to the green chemistry guideline, iron could be considered as the metal of choice for such reactions.

"Click chemistry" was introduced by Sharpless[110] in 2001. According to the principles of "Click chemistry", it has to be wide in scope, modular, has to generate small amounts of side products which should be non-toxic and removable by non-chromatographic methods like crystallization and distillation. Additionally these reactions should give high yields, be stereospecific, and present high atom economy. Conditions for the process have to be simple, the starting material and the reagents must be readily available and the solvent should be avoided or easily removable. High thermodynamic forces (> 20 kcal/mol) drive these reactions. This definition fits to following classes of reactions: nucleophilic substitution of strained rings like epoxides and aziridines, carbonyl condensation reactions like formation of oximes and hydrazones from aldehydes and carbon-heteroatom bond formation like the cycloadditions of unsaturated molecules.

The most studied example, for the latter reaction type, is the Huisgen's 1,3-dipolar cycloaddition. It is also named as the "cream of the crop" in "Click chemistry". Rolf Huisgen first reported this cycloaddition reaction in 1961.[111] A great improvement of this reaction was achieved by K. Barry Sharpless and Morten Meldal by the use of a catalytic amount of copper.[112,113] This copper(I) catalysis was a great step for this cycloaddition reaction in terms of regioselectivity (Scheme 41).

Scheme 41. Huisgen's 1,3-dipolar cycloaddition by Sharpless.

---
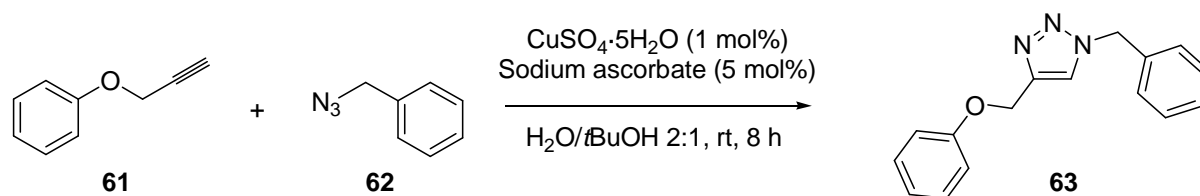
[110] H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.
[111] R. Huisgen, *Proceedings of the Chemical Society of London* **1961**, 357.
[112] V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2708; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.
[113] C. W. Tornoe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057

2. Syntheses of 1,2,3-Triazoles

The first trials were performed using phenylacetylene and benzylazide in acetonitrile for 24 h. At room temperature none of the iron catalysts tested was active. Heating the reaction mixture at 50 °C (Table 13), a ratio of 60% of **65** and 40% of **66** was obtained consistently (Table 13, entries 6-9).

Table 13. Syntheses of 1,2,3-triazoles.
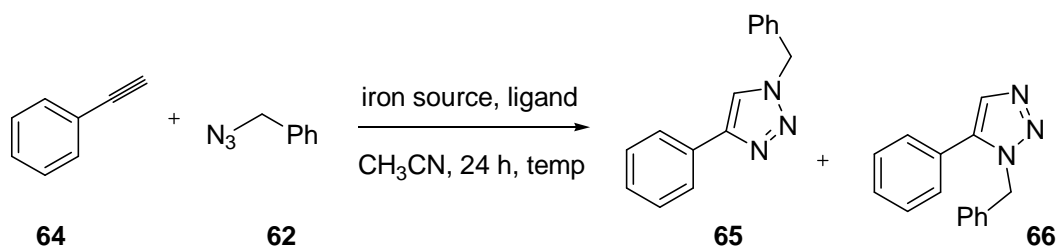
Entry	Iron (10 mol%)	Ligand	temp (°C)	GC Yield (%)
1	FeCl$_3$	-	rt	SM
2	FeCl$_3$	TMHD	rt	SM
3	FeBr$_2$	-	rt	SM
4	Fe(OAc)$_2$	-	rt	SM
5	-	-	rt	SM
6	FeCl$_3$	-	50	60% **65**, 40% **66**
7	FeBr$_2$	-	50	60% **65**, 40% **66**
8	Fe(OAc)$_2$	-	50	60% **65**, 40% **66**
9	-	-	50	60% **65**, 40% **66**

In another study on iron-catalyzed "Click chemistry", the reaction of *para*-fluoroethynylbenzene with trimethylsilyl azide was tested. The starting material was recovered when the reaction was performed at room temperature or at elevated temperature (60 °C) even after 24 hours. Some traces of the product appeared in the non-catalyzed reaction at 80 °C. This reaction was very slow. Thus, after 3 days at 100 °C, 29% of product was observed. Surprisingly, the starting material was recovered using Fe(OAc)$_2$ (Table 14, entries 1, 3, 5 and 7).

Table 14. Cyclization of triazoles.
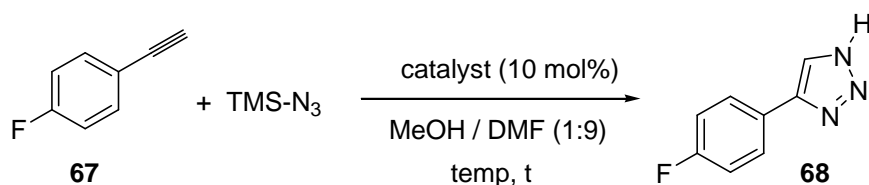
Entry	catalyst	t (h)	temp (°C)	Yield (^{19}F)
1	Fe(OAc)$_2$	24	rt	SM
2	-	24	rt	SM
3	Fe(OAc)$_2$	24	60	SM
4	-	24	60	SM
5	Fe(OAc)$_2$	24	80	SM
6	-	24	80	3%
7	Fe(OAc)$_2$	72	100	SM
8	-	72	100	29%

The formation of tetrazoles using iron-catalyzed "Click chemistry" was investigated next.

3. Synthesis of Tetrazoles

3.1. Introduction

Historically, tetrazoles have been synthesized before triazoles. Their first synthesis was reported in 1901 by Hantzsch and Vagt.[114] Tetrazoles were obtained by reaction of hydrazoic acid and hydrogen cyanide. At the end of the 20th century, most of 5-substituted 1H-tetrazoles were prepared by a reaction between azides and nitriles.[115] Sharpless, who described the concept of "Click chemistry", realized that 1H-tetrazoles could be synthesized by metal catalysis. The catalysis was accomplished with 0.5 to 1.0 equivalents of Zn(II) salts. Also, the addition of sodium azide to nitriles was possible.[116] Later, Yamamoto and coworkers provided a method to access tetrazoles by a reaction of trimethylsilyl azide (TMS-N$_3$), with nitriles, in presence of Cu$_2$O (2.5 mol%), in a 9:1 mixture of DMF and MeOH at 80 °C (Scheme 42).[117]

[114] A. Hantzsch, A. Vagt, *Ann.* **1901***, 314*, 339.

[115] a) V. Aureggi, G. Sedelmeier, *Angew. Chem.* **2007**, *119*, 8592; *Angew. Chem. Int. Ed.* **2007**, *46*, 8440. b) L. Bosch, J. Vilarrasa, *Angew. Chem.* **2007**, *119*, 4000; *Angew. Chem. Int. Ed.* **2007**, *46*, 3926. c) D. P. Curran, S. Hadida, S.-Y. Kim, *Tetrahedron* **199**9, *55*, 8997. d) K. Koguro, T. Oga, S. Mitsui, O. Orita, *Synthesis* **1998**, 910. e) S. J. Wittenberger, B. G. Donner, *J. Org. Chem.* **1993**, *58*, 4139. f) B. E. Huff, M. A. Staszak, *Tetrahedron Lett.* **1993**, *34*, 8011. g) J. V. Duncia, M. E. Pierce, J. B. Santella III, *J. Org. Chem.* **1991**, *56*, 2395.

[116] a) Z. P. Demko, K. B. Sharpless, *J. Org. Chem.* **2001**, *66*, 7945. b) Z. P. Demko, K. B. Sharpless, *Org. Lett.* **2002**, *4*, 2525. c) F. Himo, Z. P. Demko, L. Noodleman, K. B. Sharpless, *J. Am. Chem. Soc.* **2002**, *124*, 12210. d) F. Himo, Z. P. Demko, L. Noodleman, K. B. Sharpless, *J. Am. Chem. Soc.* **2003**, *125*, 9983.

[117] T. Jin, F. Kitahara, S. Kamijo, Y. Yamamoto, *Tetrahedron Lett.* **2008**, *49*, 2824.

Scheme 42. Synthesis of tetrazoles by Yamamoto.

R = Alkyl, benzyl, aryl **36-96%**
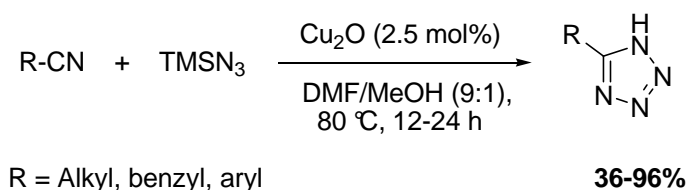
The reaction has wide applicability and alkyl, benzyl and aryl substituted nitriles can be used. Tetrazoles are widely spread in different domains: photographic agents, explosives and pharmaceutical chemistry as bioisosteres of carboxylic acid groups, which are metabolically stable.[118,119]

Attempts at using iron for 'Click chemistry'' was encouraged by the fact that several different metals are already available for this type of reaction and the use of iron would only increase the scope of the reaction.

3.2. Study of the Reaction

3.2.1. Influence of the Iron Source

para-Trifluorotoluonitrile (**69**) was chosen as the starting material in presence of trimethylsilyl azide. Using conditions developed by Yamamoto, various iron salts were screened in DMF/MeOH (9:1) at 80 °C (Table 15).

Table 15. Influence of the iron source.
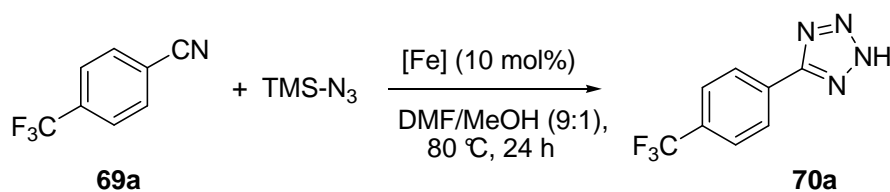
Entry	Iron source	Yield of **70a** [%][a]
1	FeCl$_3$ [b]	76
2	FeCl$_3$·6H$_2$O [c]	72

[118] a) S. Wu, A. Fluxe, J. Sheffer, J. M. Janusz, B. E. Blass, R. White, C. Jackson, R. Hedges, M. Muawsky, B. Fang, G. M. Fadayel, M. Hare, L. Djandjighian, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6213. b) M. B. Talawar, A. P. Agrawal, M. Anniyappan, D. S. Wani, M. K. Bansode, G. M. Gore, *J. Hazard. Mater.* **2006**, *137*, 1074. c) H. Xue, Y. Gau, B. Twamley, J. M. Shreeve, *Chem. Mater.* **2005**, *17*, 191. d) R. N. Bulter in *Comprehensive Heterocyclic Chemistry, Vol. 4* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon, Oxford 1996, p. 791. e) V. A. Ostrovskii, M. S. Pevznert, T. P. Kofmna, M. B. Shcherbinin, I. V. Tselinskii, *Targets Heterocycl. Syst.* **1993**, *3*, 467. f) G. I. Koldobskii, V. A. Ostrovskii, *Usp. Khim.* **1994**, *63*, 847.

[119] a) H. A. McKie, S. Friedland, F. Hof, *Org. Lett.* **2008**, *10*, 4653. b) R. J. Herr, *Bioorg. Med. Chem.* **2002**, *10*, 3379. c) H. Singh, A. S. Chawla, V. K. Kapoor, D. Paul, R. K. Malhotra, *Prog. Med. Chem.* **1980**, *17*, 151.

3	$Fe(ClO_4)_2$ [d]	80
4	$FeBr_2$ [e]	87
5	$Fe(NTf)_2$ [d]	86
6	$Fe(OTf)_2$ [d]	87
7	$Fe(OAc)_2$ [f]	91
8	$Fe(OAc)_2$ [g]	87

[a]After column chromatography. [b]$FeCl_3$ (98%; Merck) [c]$FeCl_3 \cdot 6H_2O$ (98%; Grüssing GmbH). [d]Iron source prepared according the literature. [e]$FeBr_2$ (98%; Aldrich). [f]$Fe(OAc)_2$ (95%; Acros). [g]$Fe(OAc)_2$ (99.995%; Aldrich).

The difference in oxidation states of iron catalyst or the counterion did not alter the outcome of the reaction greatly. Yields were in the range of 72% to 91% (Table 15, entries 1-8). The click-type cycloaddition catalyzed by $Fe(OAc)_2$ (Acros; 95%) afforded the highest yield of tetrazole (91%). Atom absorption spectroscopy proved that neither $Fe(OAc)_2$ (Acros; 95%) nor $Fe(OAc)_2$ (Aldrich; 99.995%) had any copper impurities (with the detection sensibility at 1 ppm).

3.2.2. Influence of Azide

Other azide derivatives were also tested (Table 16), but neither tosylazide nor benzylazide gave satisfactory yields.

Table 16. Cyclization of tetrazoles.
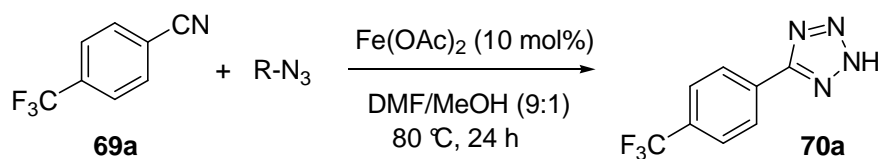
Entry	R	Yield of **70a** (%)[a]
1	TMS	91
2	Ts	14
3	Bn	-

[a]After column chromatography

3.2.3. Influence of Temperature

Temperature plays an important role in these reactions. It is well-known that at high temperatures the cyclization can occur without catalyst (> 60 °C). Lowering the temperature

led to decreased yields (Table 17, entries 1-4). Test reactions were also conducted without the catalyst. These results showed that the cycloaddition occurred in an uncatalyzed manner (Table 17, entries 1–5; data in parentheses). However, the iron-catalyzed cyclization led to much higher yields.

Table 17. Influence of temperature.
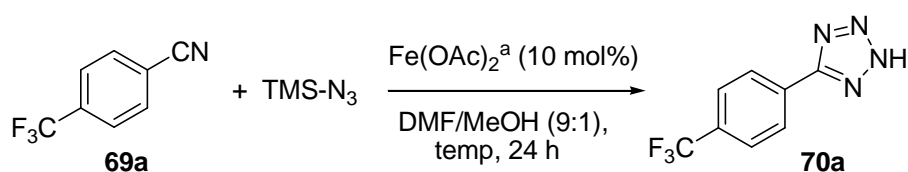
Entry	temp (°C)	Yield of **70a** (%)[b]
1	100	88 (47)
2	90	89 (42)
3	80	91 (37)
4	70	59 (15)
5	60	35 (5)

[a]Fe(OAc)$_2$ (95%; Acros). [b]In parentheses, results from reactions performed in the absence of iron.

3.2.4. Influence of Solvent

The role of other solvents for the synthesis of tetrazoles was also examinated (Table 18). The use of pure DMF provided decreased yield of **70** (56%) as compared to the use of 9:1 DMF/MeOH (91%). Reactions in other solvents remained unsuccessful (Table 18, entries 3–9).

Table 18. Influence of solvent.
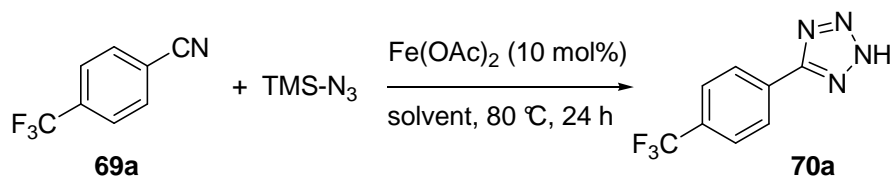
Entry	Solvent	Yield of **70** (%)[a]
1	DMF/MeOH (9:1)	91
2	DMF	56
3	MeOH	-
4	water	-
5	DME	-

6	dioxane	traces
7	toluene	-
8	THF	-
9	THF/water (9:1)	-

[a]After column chromatography

3.3. Scope of the Reaction

Finally, the scope of the reaction was investigated. The cyclization proceeded well and gives high to excellent yield for a wide variety of aryl nitriles. Electron-withdrawing groups are benefical and permitted the formation of **70e** and **70l** in 96% and >99% yields, respectively (Table 19, entries 5 and 12). However, a nitro group at the *ortho*-position restricted the formation of tetrazole (Table 19, entry 10). The same trend was observed with an *ortho*-bromo-substituted tetrazole **70g** which was obtained in only 15% yield (Table 19, entry 7). Electron-donating substituents at the *meta* and *para*-positions afforded good yields. Non-aromatic nitriles did not give any product (Table 19, entries 15 and 16). The reaction proceeded well in presence of Fe(OAc)$_2$ (99.995% purity), but slightly less yield of the product was obtained in comparison to Fe(OAc)$_2$ (95% purity). We did not determine if the difference of activity was due to metal salt consistencies or unknown contaminants.

Table 19. Iron-catalyzed synthesis of 5-substituted 1H-tetrazoles.

R-CN + TMS-N$_3$ $\xrightarrow[\text{DMF/H}_2\text{O (9:1),}~80\,°C,\,24\,h]{\text{Fe(OAc)}_2~(10~\text{mol\%})}$ **70a-p**

69a-p

Entry	Substrate	R	Product	Yield of **70** (%)[a]
1	**69a**	4-CF$_3$-Ph	**70a**	91 (87)
2	**69b**	Ph	**70b**	56 (22)
3	**69c**	4-I-Ph	**70c**	68 (53)
4	**69d**	4-vinyl-Ph	**70d**	37 (11)
5	**69e**	4-NO$_2$-Ph	**70e**	96 (86)
6	**69f**	4-OH-Ph	**70f**	41 (7)
7	**69g**	2-Br-Ph	**70g**	15 (11)
8	**69h**	4-Me-Ph	**70h**	57 (42)
9	**69i**	4-Cl-Ph	**70i**	70 (64)
10	**69j**	2-NO$_2$-Ph	**70j**	67 (48)

11	**69k**	Naphth	**70k**	58 (56)
12	**69l**	3,4-diNO$_2$-Ph	**70l**	>99 (>99)
13	**69m**	Thiophen	**70m**	74 (43)
14	**69n**	2,2-diMe-2H-chromen-6-yl	**70n**	53 (49)
15	**69o**	4-OMe-benzyl	**70o**	-
16	**69p**	5-cyclohexenyl	**70p**	-

[a]After column chromatography; in parentheses, results from experiments performed with Fe(OAc)$_2$ (99.995%; Aldrich)

4. Conclusion

In conclusion, iron salts as catalyst for "Click reactions" have been proven effective.

III. Iron(II) Triflate as Catalyst for the Synthesis of Indoles by Intramolecular C-H Amination

1. Introduction

Indole derivatives are important heterocycles because they display interesting biological activities.[120] For decades azides have been used by chemists to prepare indoles by intramolecular cyclization. In 1971 the first contribution in this field was reported by Hemetsberger and Knittel, who discovered that cyclization of α-azidoacrylates resulted in the formation of indoles (Scheme 43).[121]

Scheme 43. Cyclization of α-azidoacrylates by Hemetsberger and Knittel.
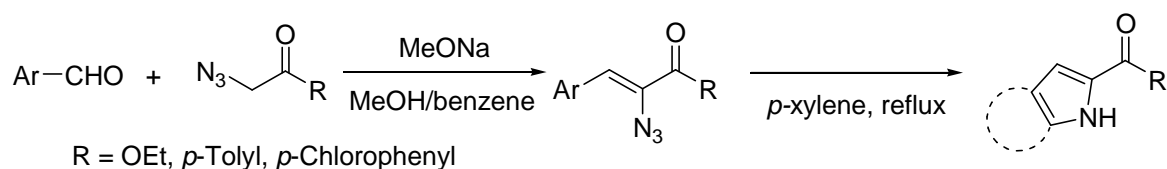
The starting material was obtained by condensation of α-azidocarbonyls with aldehydes n the presence of sodium methoxide. Then, the resulting azidoacrylic esters were heated at reflux in *p*-xylene. This thermolysis enabled the cyclization to from indoles. However, this reaction is known to proceed via nitrenes. Reactions at high temperatures must be avoided for economic, practical and safety reasons.[122] Using a metal to catalyze the cyclization becomes important in order to perform the reaction under milder conditions. In this way, Driver and coworker described the same indole-forming reaction using rhodium(II) perfluorobutyrate as the catalyst (Scheme 44).[123]

---

[120] For biological activities of indoles, see: a) R. J. Sundberg, *Indoles*; Academic Press: London, 1996. b) V. Sharma, P. Kumar, J. Pathak, *Heterocycl. Chem.* **2010**, *47*, 491.

[121] H. Hemetsberger, D. Knittel, *Monatsh. Chem.* **1972**, *103*, 194.

[122] J. Wiss, C. Fleury, U. Onken, *Org. Process Res. Dev.* **2006**, *10*, 349.

[123] a) B. J. Stokes, H. Dong, B. E. Leslie, A. L. Pumphrey, T. G. Driver, *J. Am. Chem. Soc.* **2007**, *129*, 7500. For related work on carbazole formations, see: b) B. J. Stokes, B. Jovanovic, H. Dong, K. J. Richert, R. D. Riell, T. G. Driver, *J. Org. Chem.* **2009**, *74*, 3225. c) B. J. Stokes, K. J. Richert, T. G. Driver, *J. Org. Chem.* **2009**, *74*, 6442.

Scheme 44. Cyclization of α-azidoacrylates with rhodium by Driver.

R$_1$ = H, OMe, Me, Cl
R$_2$ = H, Cl, Br, OMe
R$_3$ = H, OMe, Me, i-Pr, t-Bu, Cl, Br, CF$_3$

71

71-98%

72
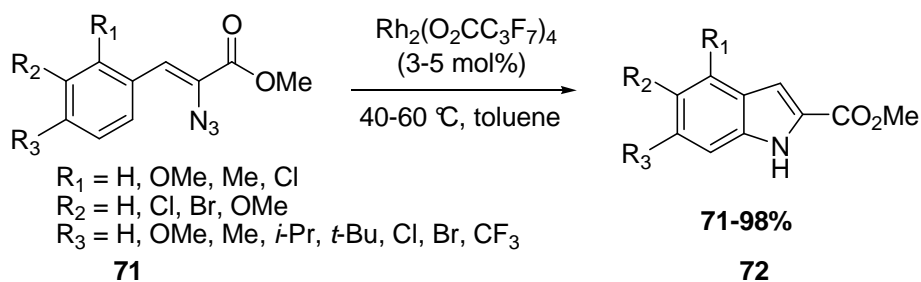
In the presence of the rhodium catalyst, the cyclization of α-azidoacrylates has a lower thermal barrier to activation, with a required temperature range between 40 and 60 °C. However, rhodium is a very expensive transition metal, and it would be of great interest to find a more economical alternative.

The idea was to use environmentally friendly, non-toxic and cheap iron as a metal of choice for this intramolecular C-H amination.

2. Study of the Reaction

2.1. Influence of Catalyst

Methyl phenylazidoacrylate (**71**) was used as a starting material as representative of azido-ester derivatives to form 2-carboxy-substituted indole (**72**). Finding a suitable iron catalyst was the critical obstacle for this reaction. Several iron sources were tested. Neither iron chlorides, Fe(acac)$_3$ or FeBr$_3$ gave any product when heated with **71**. The use of iron(II) triflate, which had previously been proven to be a highly efficient and robust catalyst superior to other iron salts in the imination of sulfoxides,[124] led to the desired product in 46% yield (Table 20).

Table 20. Influence of catalyst.

71a

72a
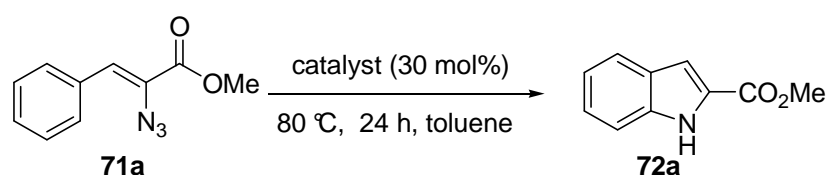
Entry	Catalyst (30 mol%)	Yield of **72a** (%)[a]
1	FeCl$_2$	-

[124] a) O. Garcia Mancheño, J. Dallimore, A. Plant, C. Bolm, *Org. Lett.* **2009**, *11*, 2429. b) O. Garcia Mancheño, J. Dallimore, A. Plant, C. Bolm, *Adv. Synth. Catal.* **2010**, *352*, 309.

2	FeCl$_3$	-
3	Fe(acac)$_3$	-
4	FeBr$_3$	-
5	Fe(OTf)$_2$	46

[a] After column chromatography.

In this case, iron(II) triflate was chosen for further evaluation since it was the only catalyst to give the desired product.

2.2. Influence of Solvent

After choosing the catalyst, the solvent used for the reaction was evaluated (Table 21).

Table 21. Iron-catalyzed C-H amination of azide **72a**: influence of solvent.
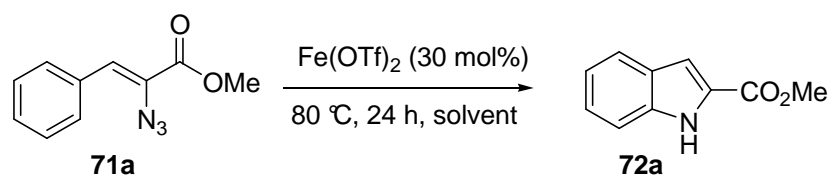
Entry	Solvent	Yield of **72a** (%)[a]
1	DMF	-
2	acetonitrile	-
3	EtOH	-
4	water	-
5	hexane	58
6	toluene	46
7	xylene	38
8	DME	63
9	dioxane	26
10	diethyl ether	16
11	MTBE	28
12	THF	78 (75)[b]
13	chloroform	46
14	anisole	41

[a] After column chromatography. [b] In parentheses, the result from an experiment performed with 10 mol% of iron triflate.

Reactions performed in protic solvents such as ethanol and water and polar aprotic solvents such as DMF and acetonitrile did not give any of the desired product (Table 21, entries 1-4). Nonpolar solvents afforded moderate to good yields (Table 21, entries 5-7). Ethereal solvents afforded the indole ester in yields up to 78% (Table 21, entries 8-12). The best result was obtained in THF (Table 21, entry 12). Lowering the catalyst loading to 10 mol% in THF did not significantly affect the yield, and under the optimized conditions the indole was obtained in 75% yield. Other solvents such as chloroform and anisole, gave the desired product in only moderate yields (Table 21, entries 13 and 14).

2.3. Influence of Copper

To insure that the active catalyst in the formation of indole contained iron, different test reactions were performed (Table 22).

Table 22. Influence of catalyst.
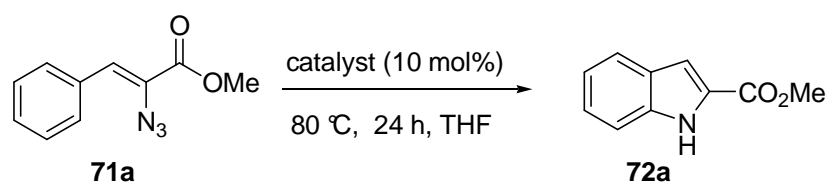
Entry	Catalyst (10 mol%)	Yield (%)^a
1	-	-
2	TfOH	-
3	TfONa	-
4	CuOTf	-
5	Cu(OTf)$_2$	-

^{a} After column chromatography

Without catalyst, no product was observed (Table 22, entry 1). Triflic acid and sodium triflate were tested and no product was observed (Table 22, entries 2 and 3). After considering possible contamination of iron by traces of copper, reactions with copper(I) triflate and copper(II) triflate were performed. Neither led to cyclization (Table 22, entries 4 and 5).

2.4. Influence of Temperature

The second parameter to be screened for this iron catalysis was the temperature. Having a mild temperature is important for cost, conveniency, practical and safety reasons.

Table 23. Influence of temperature.
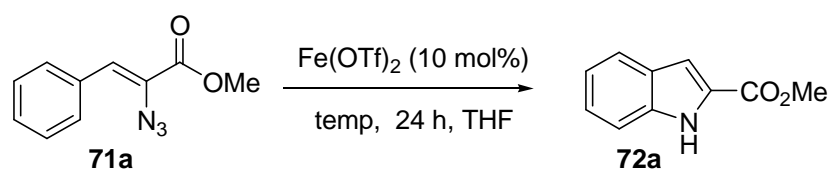
Entry	temp (°C)	Yield (%)^a
1	80	75 (40)^b
2	60	24
3	rt	0

^{a} After column chromatography. ^{b} In parentheses, the result from an experiment performed with 1 mol% of iron triflate.

The yield dropped significantly when only 1 mol% of the catalyst was used in the reaction (Table 23, entry 1). Lowering the temperature to 60 °C decreased the yield sharply (Table 23, entry 2). At room temperature the desired reaction did not occur and the starting material was recovered.

3. Scope of the Reaction

Finally, the scope of the reaction with respect to the starting azido ester was investigated. Generally, good to excellent yields were obtained when substrates bearing a variety of substituents on the aryl ring were used (Table 24).

Table 24. Synthesis of indole derivatives.
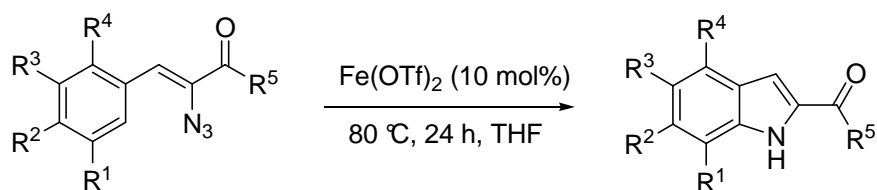
Entry	R^1	R^2	R^3	R^4	R^5	72	Yield (%)^a
1	H	H	H	H	OMe	**72a**	75
2	H	OMe	H	H	OMe	**72b**	74
3	H	Me	H	H	OMe	**72c**	77
4	H	tBu	H	H	OMe	**72d**	83
5	H	CF$_3$	H	H	OMe	**72e**	60
6	H	F	H	H	OMe	**72f**	72
7	H	Cl	H	H	OMe	**72g**	56
8	H	Ph	H	H	OMe	**72h**	80

9	H	H	H	OMe	OMe	**72i**	70
10	H	OMe	OMe	H	OMe	**72j**	88
11	H	OBn	OMe	H	OMe	**72k**	99
12	H	O-CH$_2$-O		H	OMe	**72l**	97
13	H	CH=CH-O		H	OMe	**72m**	99
14	CH=CH-CH=CH		H	H	OMe	**72n**	98
15	CH=CH-CH=CH		H	H	(*L*)-OMethyl	**72o**	93
16	H	OMe	H	H	O*i*Pr	**72p**	35

a After column chromatography.

When a substituent positioned *para* to the azido ester group was such as a methoxy, alkyl, fluoride, trifluoromethyl, halide or phenyl, the reaction led to the corresponding indole in good yields (Table 24, entries 2-8). A substituent *ortho* to the ester did not have an effect, thus **72i** was obtained in 70% yield (Table 24, entry 9 vs entry 2). Disubstituted arenes at the *para* and *meta* positions gave indoles in excellent yields as a single isomer (Table 24, entries 10-13). As an exception, **72o** cyclized differently (Table 24, entry 15). To our delight, isopropyl and menthyl esters could be successfully used (Table 24, entries 14 and 16).

4. Conclusion

Various indoles can be obtained by the intramolecular reaction of azides using iron(II) triflate as the catalyst. The main advantages are that the reaction is performed under mild conditions (80 °C), and that the catalyst is environmentally friendly and cheap. Also, an investigation of the scope of the reaction showed that various functional groups were tolerated and excellent yields could be obtained.

Summary and Outlooks

The main aim of this work was to discover new and convenient reactions using cheap and relatively benign iron as an efficient transition metal catalyst.

In the first part of this work, we demonstrated that the conditions used for the iron-catalyzed intermolecular C-O cross-coupling could also be applied to intramolecular reactions. Thus, this method represents an interesting pathway for the synthesis of benzoxazoles and benzofurans (Scheme 45).

Scheme 45. Iron-catalyzed intramolecular *O*-arylation.
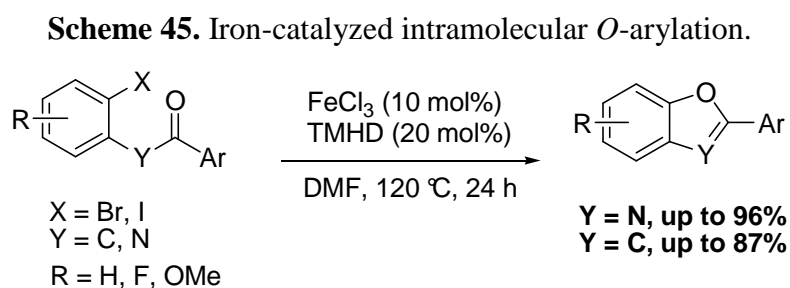
The most important parameter of the reaction was the temperature. To avoid nucleophilic aromatic substitution (SNAr), the coupling had to be performed at 120 °C. We believe that increasing the temperature would cause a non-metal catalyzed SNAr pathway to predominate. In this C-O intramolecular cyclization, the use of TMHD as a ligand afforded the best yield. First, use of ligands such as DMEDA or *N*,*N'*-dimethylglycine gave the corresponding product in low yield. Ligands structurally close to TMHD, diketone-like moieties, were used but none of them gave a yield as high as TMHD. Various sources of iron were tested; in all cases, high yields were obtained. The oxidation state of iron did not influence the reaction, and the use of iron(II) and iron(III) compounds is possible in this reaction. An examination of the influence of impurities was performed. Manganese, palladium and nickel had no influence. However, copper(II) chloride seemed to be highly active in 344 ppm amounts. To prove that iron catalyzed the reaction, iron(III) chloride 99.995% was used and gave the best yield. The scope of this C-O intramolecular cyclization is quite broad with respect to substitution on the azido-ester aryl group. Unfortunately, alkyl or alkenyl derivatives were not usable.

53

Bromo and iodo arenes were easily converted to the corresponding product. However chloro derivatives did not react. An interesting goal for future work would be C-O bond formation by direct C-H bond activation.

In the second part of this thesis, an iron-catalyzed "Click reaction" for the synthesis of triazoles and tetrazoles was reported. The formation of tetrazoles is possible using iron(II) acetate (Scheme 46).

Scheme 46. Iron-catalyzed synthesis of tetrazoles.

$$Ar\text{-}CN \ + \ TMS\text{-}N_3 \ \xrightarrow[\substack{DMF/MeOH \ (9:1), \\ 80 \ °C, \ 24 \ h}]{Fe(OAc)_2 \ (10 \ mol\%)} \ Ar\overset{N=N}{\underset{N}{\diagup}}NH$$

up to 99%
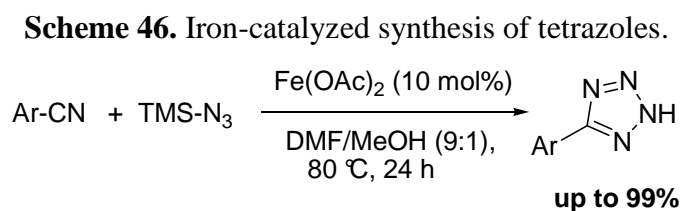
Various iron salts were tested in this Click reaction. The oxidation state of iron could be II or III. In both cases, the yields of tetrazoles were approximately equal. Our optimal choice catalyst was iron(II) acetate, since it gave an excellent yield and no traces of copper were found in it. Different azides were examined. Trimethylsilylazide gave the best yield. Both the temperature and the solvent were important. Surprisingly, reactions in a mixture of DMF/MeOH (9:1) afforded the best result. In the scope of the reaction, various aryl derivatives have been employed. The main drawback is that alkyl derivates did not lead to any product. To solve this problem, it might be interesting to switch to an aryl azide compound since the iron chemistry seems to be dependent on aryl substrates.

A number of conditions for the cyclization of triazoles were tested, but none were satisfying. Iron did not provide a better yield than the metal-free conditions. A subject of further investigation for this iron "Click chemistry" would be the use of internal alkynes.

In the last part of the present work, an improved synthesis of indoles by iron-catalyzed intramolecular C-H amination was described (Scheme 47).

Scheme 47. Iron-catalyzed C-H amination of azide.
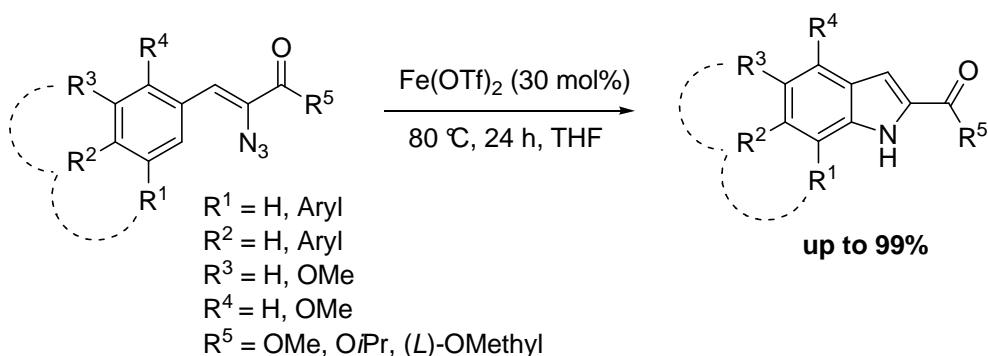
Several iron sources were tested and surprisingly, only iron(II) triflate catalyzed the reaction efficiently. Since traces of copper were detected in the iron salt, some test reactions were performed with different copper sources. Neither copper(I) nor copper(II) were active. The scope of this iron-catalyzed C-H amination is quite broad. The main drawback is that the presence of an ester group is necessary. Further study is certainly needed to perform an intermolecular version of the reaction.

Another critical point is that copper is present in very small quantities in almost all iron salts. Nevertheless, we proved throughout this work that even if its presence increases the yield in some cases, iron is the main species responsible for all these reactions.

Since the first example of iron catalysis described by Kochi, organic chemistry has entered in the Iron Age. Industrial chemists are always searching for cheap, environmentally benign, selective and high turn-over frequency catalysts for more efficient processes. For these kinds of applications, iron is probably the most promising alternative. Its low price, moderate toxicity and ready availability lead it during these last decades on the phase of a significant growth. The reactions developed in this thesis are bringing new information on iron behavior. However, the use of iron remains less developed than noble metals such as palladium. As soon as the mechanisms are understood, iron's role in organic synthesis will become much more important.

Experimental Part

1. General Techniques

All the synthetic operations described in the present experimental part including reactions, work-ups and chromatographic separations were carried out in a well ventilated hood according to the current safety dispositions.

Air and moisture sensitive reactions were conducted under an inert atmosphere of argon using Schlenk techniques. All glass was oven dried prior to use, then filled with argon. The addition of liquid (reagents and solvents) was performed with a syringe through a septum or dropping funnel. Solids were added under gentle stream of argon.

2. Solvents

Solvents for anhydrous reactions were dried and purified according to standard techniques.[125]

CH_2Cl_2:   Simple destillation, followed by destillation from calcium hydride.

Toluene: Destillation from sodium-benzophenone ketyl radical.

THF: Pre-drying on KOH/Al_2O_3, followed by destillation from sodium-benzophenone ketyl radical.

Ethyl acetate (EtOAc), diethyl ether (Et_2O), and *n*-pentane for flash column chromatography were distilled before use. DMF, MeOH, 1,2-dichloroethane, DMSO and acetonitrile were HPLC- or reagent grade and were used as received.

3. Determination of the Physical Properties of the Synthesized Compounds

3.1. ^{1}H NMR Spectroscopy

^{1}H NMR spectra were recorded either on a *Varian* Gemini 300 spectrometer (300 MHz) or on a *Varian* Inova 400 spectrometer (400 MHz). Chemical shifts are given in ppm relative to tetramethylsilane (TMS, 0.00 ppm). Solvent residual peaks (chloroform, 7.26 ppm; dimethylsulfoxide 2.50 ppm) were used as internal standard. Coupling patterns are described by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Coupling costants (*J*) are given in Herz (Hz).

---

[125] W. L. F. Armarego, D. D. Perrin, *Purification of Laboratory Chemicals*, Butterworth-Heinemann, Oxford, **1996**.

3.2. ^{13}C NMR Spectroscopy

^{13}C NMR spectra were recorded either on a *Varian* Gemini 300 spectrometer (75 MHz) or on a *Varian* Inova 400 spectrometer (100 MHz). Chemical shifts are given in ppm and were determined by comparison with solvent residual peaks (chloroform, 7.26 ppm; dimethylsulfoxide 2.50 ppm).

3.3. ^{19}F NMR Spectroscopy

^{19}F NMR spectra were recorded either on a *Varian* Gemini 300 spectrometer (282 MHz) or on a *Varian* Inova 400 spectrometer (376 MHz).

3.4. Mass Spectroscopy

Mass spectra were recorded on a *Varian* MAT 212 or on a *Finnigan* MAT 95 spectrometer with EI (electronic impact) ionization, at a 70 eV ionization potential. Peaks are listed according to their *m/z* value. High resolution mass spectra (HRMS) were recorded on a *Finnigan* MAT 95 spectrometer.

3.5. GC-MS Measurements

GC-MS measurements were conducted with the following instrument: GC (HP 6890 Series), MSD 5973, column: HP-5 MS (30 m × 0.25 mm × 0.25 μm); carrier gas: He, constant flow, 200 °C.

3.6. Elemental Analysis

Elemental analyses were performed using a *Heraeus* CHN-O-Rapid instrument.

3.7. Melting Point

Melting points were measured in open glass capillaries with a *Büchi* B-540 apparatus and were uncorrected.

4. Chromatographic Methods

4.1. Preparative Column Chromatography

Purifications by Flash Column Chromatography were carried out in glass columns (10-50 mm diameter) according to STILL, 320 using *Merck* silica gel 60, particle size 0.040-0.063 mm (230-400 mesh).

4.2. Thin Layer Chromatography (TLC)

Support: TLC aluminum sheets silica gel 60 F_{254} (*Merck*) with a fluorescent indicator.

Detection:

      1) Exposition to UV-light (λ = 254 nm).

      2) Treatment with an acidic aqueous solution of ammonium molybdate tetrahydrate

      $[(NH_4)_6Mo_7O_{24}]\cdot 4H_2O$ and cerium sulfate tetrahydrate $[Ce(SO_4)]\cdot 4H_2O$ (Mostain).

      3) Treatment with a basic aqueous solution of potassium permanganate ($KMnO_4$).

5. Synthesis of 2-Aryl Benzoxazoles

General Procedure for Amidation:

To a solution of *ortho*-haloaniline (9.16 mmol, 1.0 equiv) in dry CH_2Cl_2 (20 mL) at room temperature acyl chloride was added (10.01 mmol, 1.1 equiv). The reaction mixture was stirred overnight then diluted with CH_2Cl_2 (50 mL). The organic layer was washed with 5% $NaHCO_3$ (2 x 50 mL), dried over $MgSO_4$ and the solvent was removed *in vacuo*.

The product was carried on to next step without any further purification in most cases. However, if necessary, a silica gel column chromatography was performed.

N-(2-bromophenyl)benzamide (52a)
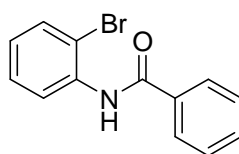
Following the general procedure, the product was obtained as a white solid in 85% yield.

**^{1}H NMR (400 MHz, CDCl$_3$):** δ = 8.60 (dd, 1H, *J* = 8.2 Hz, *J* = 1.5 Hz), 8.54 (br s, 1H), 7.94-8.02 (m, 2H), 7.52-7.67 (m, 4H), 7.42 (td, 1H, *J* = 8.0 Hz, *J* = 1.4 Hz), 7.06 (td, 1H, *J* = 8.2 Hz, *J* = 1.5 Hz).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 165.3, 135.9, 134.6, 132.3, 132.2, 129.0, 128.6, 127.1, 125.3, 121.8, 113.8.

M. p. = 107.2-107.9 °C.

All spectral data correspond to those given in the literature.[126]

---

[126] D. A. Ames, A. Opalko, *Tetrahedron* **1984**, *40*, 1919.

N-(2-iodophenyl)benzamide (52b)
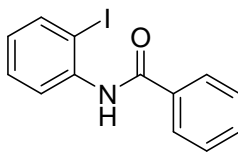
Following the general procedure, the product was obtained as a yellowish solid in 89% yield.

**¹H NMR (300 MHz, CDCl₃):** δ = 8.46 (dd, 1H, *J* = 8.2 Hz, *J* = 1.5 Hz), 8.30 (br s, 1H), 7.98-8.01 (m, 2H), 7.82 (dd, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz), 7.48-7.63 (m, 3H), 7.40 (td, 1H, *J* = 8.2 Hz, *J* = 1.5 Hz), 6.88 (td, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz).

¹³C NMR (75 MHz, CDCl₃): δ = 165.4, 138.9, 138.3, 134.5, 132.3, 129.5, 129.0, 127.2, 126.1, 121.8, 90.3.

M. p. = 133.4-134.3 °C.

All spectral data correspond to those given in the literature.[127]

N-(2-chlorophenyl)benzamide (52c)
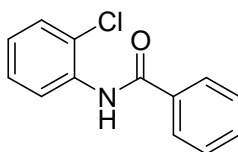
Following the general procedure, the product was obtained as a white solid in 95% yield.

¹H NMR (300 MHz, CDCl₃): δ = 8.56 (dd, 1H, *J* = 8.2 Hz, *J* = 1.5 Hz), 8.45 (br s, 1H), 7.87-7.95 (m, 2H), 7.45-7.61 (m, 3H), 7.40 (dd, 1H, *J* = 8.0 Hz, *J* = 1.4 Hz), 7.32 (td, 1H, *J* = 8.0 Hz, *J* = 1.4 Hz), 7.07 (td, 1H, *J* = 8.2 Hz, *J* = 1.5 Hz).

¹³C NMR (75 MHz, CDCl₃): δ = 165.3, 134.8, 134.6, 132.2, 129.1, 129.0, 127.9, 127.1, 124.8, 123.1, 121.6.

M. p. = 97.8-98.5 °C.

All spectral data correspond to those given in the literature.[128]

N-(2-bromophenyl)-4-chlorobenzamide (52d)
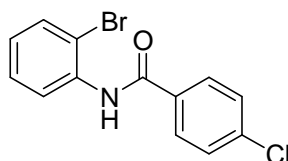
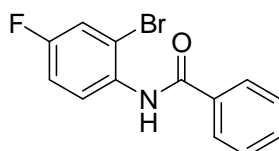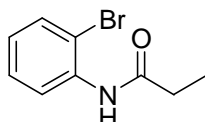Following the general procedure, the product was obtained as a white solid in 92% yield.

[127] B. S. Thyagarajan, N. Kharasch, H. B. Lewis, W. Wolf, *Chem. Comm. (London)* **1967**, *13*, 614.
[128] P. A. S. Smith, *J. Am. Chem. Soc.* **1954**, *76*, 431.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.56 (dd, 1H, J = 8.2 Hz, J = 1.5 Hz), 8.43 (br s, 1H), 7.88-7.95 (m, 2H), 7.63 (dd, 1H, J = 8.1 Hz, J = 1.4 Hz), 7.51-7.58 (m, 2H), 7.42 (td, 1H, J = 8.5 Hz, J = 1.4 Hz), 7.07 (td, 1H, J = 7.8 Hz, J = 1.5 Hz).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 164.2, 138.6, 135.6, 133.0, 132.3, 129.3, 128.6, 128.6, 125.5, 121.8, 113.8.

M. p. = 134.2-135.5 °C.

All spectral data correspond to those given in the literature.[129]

N-(2-bromophenyl)-4-methoxybenzamide (52e)
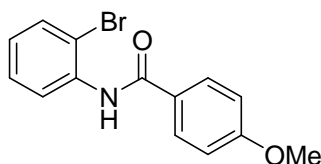
Following the general procedure, the product was isolated by silica gel column chromatography (CH$_2$Cl$_2$) as a white solid in 97% yield.

^{1}H NMR (300 MHz, CDCl$_3$): δ =8.59 (dd, 1H, J = 8.2Hz, J = 1.4 Hz), 8.43 (br s, 1H), 7.91-7.98 (m, 2H), 7.61 (dd, 1H, J = 8.2 Hz, J = 1.5 Hz), 7.40 (td, 1H, J = 8.0 Hz, J = 1.4 Hz), 7.00-7.08 (m, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 164.8, 162.8, 136.0, 132.2, 129.0, 128.5, 126.8, 125.0, 121.7, 114.2, 113.7, 55.5.

M. p. = 147-148°C.

All spectral data correspond to those given in the literature.[130]

N-(2-bromophenyl)-3,4-dichlorobenzamide (52f)
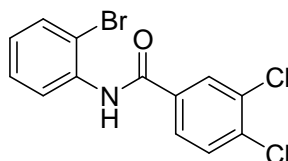
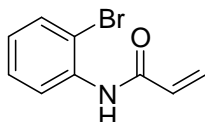Following the general procedure, the product was obtained as a yellowish solid in 94% yield.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.49 (dd, 1H, J = 8.0 Hz, J = 1.5 Hz), 8.38 (br s, 1H), 8.06 (d, 1H, J = 8.2 Hz), 7.76 (dd, 1H, J = 8.2 Hz, J = 1.5 Hz), 7.58-7.66 (m, 2H), 7.41 (td, 1H, J = 8.0 Hz, J = 1.5 Hz), 7.07 (td, 1H, J = 8.2 Hz, J = 1.5 Hz).

[129] J. I. G. Cadogan, D. M. Smith, J. B. Thomson, *J. Chem. Soc., Perkin Trans 1* **1972**, *11*, 1296.

[130] N. Itoh, T. Sakamoto, E. Miyazawa, Y. Kikugawa, *J. Org. Chem.* **2002**, *67*, 7424.

^{13}C NMR (100 MHz, CDCl$_3$): δ = 163.1, 136.8, 135.3, 134.3, 133.6, 132.4, 131.0, 129.5, 128.6, 126.0, 125.8, 122.0, 114.0.

M. p. = 127 °C.

All spectral data correspond to those given in the literature.[131]

4-bromo-N-(2-bromophenyl)benzamide (52g)
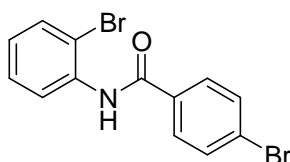
Following the general procedure, the product was obtained as a yellowish solid in 87% yield.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.55 (dd, 1H, *J* = 8.2 Hz, *J* = 1.5 Hz), 8.43 (br s, 1H), 7.81-7.87 (m, 2H), 7.62-7.74 (m, 2H), 7.62 (dd, 1H, *J* = 8.1 Hz, *J* = 1.5 Hz), 7.40 (td, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz), 7.07 (td, 1H, *J* = 8.2 Hz, *J* = 1.5 Hz).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 164.3, 135.6, 133.4, 132.3, 132.2, 128.7, 128.6, 127.1, 125.5, 121.8, 113.8.

M. p. = 138.5-139.5 °C.

All spectral data correspond to those given in the literature.[131]

N-(2-bromophenyl)-2,4,6-trimethylbenzamide (52h)
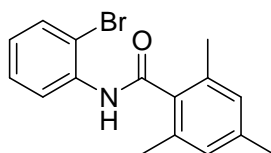
Following the general procedure, the product was obtained as a yellowish solid in 64% yield.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.55 (dd, 1H, *J* = 8.3 Hz, *J* = 1.5 Hz), 7.72 (br s, 1H), 7.55 (dd, 1H, *J* = 8.1 Hz, *J* = 1.5 Hz), 7.40-7.34 (m, 1H), 7.04-6.99 (m, 1H), 6.90 (s, 1H), 2.36 (s, 6H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 168.7, 139.1, 135.6, 134.6, 134.3, 132.3, 128.5, 128.4, 125.5, 122.4, 133.7, 21.1, 19.3.

M. p. = 100.2-100.6 °C.

HRMS (ESI): *m/z* calculated for C$_{16}$H$_{16}$ON^{79}BrNa 340.0308, found 340.0305.

---

[131] G. Evindar, R. A. Batey, *J. Org. Chem.* **2006**, *71*, 1802.

N-(2-bromophenyl)-2-fluorobenzamide (52i)
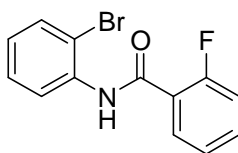
Following the general procedure, the product was obtained as a yellowish solid in 79% yield.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.08 (d, *J* = 15,2 Hz, 1H), 8.55 (dt, *J* = 5.9 Hz, *J* = 11.8 Hz, 1H), 8.21-8.14 (m, 1H), 7.57-7.45 (m, 2H), 7.36-7.24 (m, 2H), 7.20-7.12 (m, 1H), 7.02-6.96 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 162.1, 161.1, 158.8, 136.1, 134.0, 132.4, 132.3, 126. 9 (*J* = 217 Hz), 125.1, 122.4, 121.0, 116.3, 113.7.

M. p. = 94.3-94.8 °C.

HRMS (ESI): *m/z* calculated for C$_{13}$H$_9$ON^{79}BrFNa 315.9744, found 315.9748.

N-(2-bromophenyl)-3-methoxybenzamide (52j)
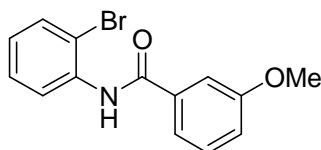
Following the general procedure, the product was obtained as a yellowish solid in 86% yield.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.57-8.51 (m, 1H), 8.45 (s, 1H), 7.57 (dd, 1H, *J* = 8.0 Hz, *J* = 1.3 Hz), 7.53-7.33 (m, 6H), 7.13-7.08 (m, 1H), 7.05-6.97 (m, 1H), 3.88 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 165.1, 160.1, 136.1, 135.8, 132.3, 129.9, 128.5, 125.3, 121.7, 118.7, 118.4, 113.7, 112.6, 55.5.

M. p. = 93.9–94.6 °C.

HRMS (ESI): *m/z* calculated for C$_{14}$H$_{12}$O$_2$N^{79}BrK 343.9683, found 343.9684.

N-(2-bromo-4-fluorophenyl)benzamide (52k)

Following the general procedure, the product was isolated by silica gel column chromatography (CH$_2$Cl$_2$/pentane 1:1) as a white solid in 68% yield.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.55 (dd, 1H, *J* = 9.2 Hz, *J* = 5.6 Hz), 8.36 (br s, 1H), 7.93-8.00 (m, 2H), 7.52-7.67 (m, 3H), 7.38 (dd, 1H, *J* = 7.8 Hz, *J* = 2.9 Hz), 7.11-7.20 (m, 1H).

^{13}**C NMR (75 MHz, CDCl$_3$):** δ = 165.3, 158.6 (d, J = 248.5 Hz), 134.4, 132.4, 132.3, 129.0, 127.1, 122.9 (d, J = 8.1 Hz), 119.4 (d, J = 25.6 Hz), 115.4 (d, J = 21.6 Hz), 113.8 (d, J = 9.8 Hz).

M. p. = 140.8-141.4 °C.

All spectral data correspond to those given in the literature.[131]

N-(2-bromophenyl)propionamide (52l)

Following the general procedure, the product was obtained as a yellowish solid in 92% yield.

^{1}**H NMR (300 MHz, CDCl$_3$):** δ = 8.41 (d, 1H, J = 8.0 Hz), 7.67 (br s, 1H), 7.56 (dd, 1H, J = 8.0 Hz, J = 1.4 Hz), 7.35 (td, 1H, J = 8.0 Hz, J = 1.5 Hz), 7.00 (td, 1H, J = 8.0 Hz, J = 1.5 Hz), 2.51 (q, 2H, J = 7.5 Hz), 1.32 (t, 3H, J = 7.5 Hz).

^{13}**C NMR (75 MHz, CDCl$_3$):** δ = 171.9, 135.7, 132.2, 128.4, 125.0, 121.9, 113.3, 31.0, 9.6.

M. p. = 89-91 °C.

All spectral data correspond to those given in the literature.[131]

(Z)-N-(2-bromophenyl)but-2-enamide (52m)

Following the general procedure, the product was obtained as a white solid in 94% yield.

^{1}**H NMR (300 MHz, CDCl$_3$):** δ = 8.44 (d, 1H, J = 8.2 Hz), 7.67 (br s, 1H), 7.55 (dd, 1H, J = 8.0 Hz, J = 1.4 Hz), 7.28-7.37 (m, 1H), 6.94-7.08 (m, 2H), 5.98-6.08 (m, 1H), 1.95 (dd, 3H, J = 6.9 Hz, J = 1.6 Hz).

^{13}**C NMR (75 MHz, CDCl$_3$):** δ = 163.8, 142.2, 135.9, 132.2, 128.4, 125.4, 125.1, 122.0, 113.5, 17.9.

M. p. = 80-82 °C.

All spectral data correspond to those given in the literature.[132]

---

[132] K. Jones, M. Thompson, C. Wright, *J. Chem. Soc., Chem. Comm.* **1986**, *2*, 115.

(Z)-N-(2-iodophenyl)but-2-enamide (52o)
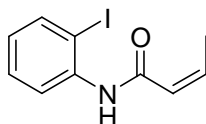
Following the general procedure, the product was obtained as a white solid in 92% yield.

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.29 (d, 1H, J = 8.1 Hz), 7.77-7.73 (m, 1H), 7.42 (br s, 1H), 7.35-7.29 (m, 1H), 6.99 (dq, J = 6.9 Hz, J = 15.1 Hz, 1H), 6.84-6.78 (m, 1H), 5.99 (dq, 1H, J = 1.7 Hz, J = 15.1 Hz), 1.92 (dd, J = 6.9 Hz, J = 1.7 Hz, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 163.8, 142.1, 138.8, 138.3, 129.3, 125.8, 125.4, 121.9, 90.0, 17.9.

M. p. = 95.2-96.1 °C.

HRMS (ESI): *m/z* calculated for C$_{10}$H$_{10}$ONINa 309.9699, found 309.9700.

General Procedure for Intramolecular *O*-Arylation to Give Benzoxazoles:

A sealable tube equipped with a magnetic stir bar was charged with the *N*-(2-bromophenyl)benzamide (1.0 equiv), Cs$_2$CO$_3$ (2.0 equiv) and FeCl$_3$ (0.1 equiv; Acros; 98%). The aperture of the tube was then covered with a rubber septum, and an argon atmosphere was established. 2,2,6,6-Tetramethyl-3,5- heptanedione (0.2 equiv) and DMF (1 mL/mmol of benzamide) were added by using syringe. The septum was then replaced by a teflon-coated screw cap, and the reaction vessel was placed in an oil bath heated to 120 °C. After stirring at this temperature for 20 h, the heterogeneous mixture was cooled to room temperature and diluted with dichloromethane. The resulting solution was directly filtered through a pad of celite and concentrated to yield the product, which was purified by silica gel chromatography to afford the corresponding benzoxazole. The identity and purity of the product was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis.
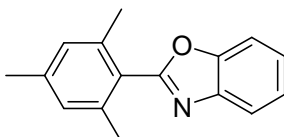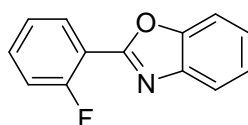
2-phenylbenzo[*d*]oxazole (51a)
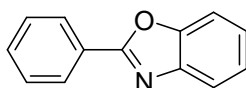
Following the general procedure using *N*-(2-bromophenyl)benzamide (100 mg, 0.36 mmol) provided 54 mg (75% yield) of the coupling product as a white solid after purification by flash chromatography (CH$_2$Cl$_2$/pentane 1:1).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.33-7.39 (m, 2H), 7.50-7.57 (m, 2H), 7.58-7.62 (m, 1H), 7.75-7.85 (m, 1H), 8.25-8.32 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 110.6, 120.1, 124.6, 125.1 127.1, 127.7, 128.9, 131.5, 142.1, 150.7, 163.0.

All spectral data correspond to those given in the literature.[131]

2-(4-chlorophenyl)benzo[*d*]oxazole (51b)
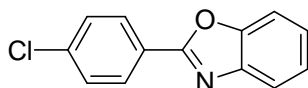
Following the general procedure using *N*-(2-bromophenyl)-4-chlorobenzamide (100 mg, 0.32 mmol) provided 55 mg (75% yield) of the coupling product as a white solid after purification by flash chromatography (CH$_2$Cl$_2$/pentane 1:1).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.25-7.31 (m, 2H), 7.39-7.44 (m, 2H), 7.46-7.52 (m, 1H), 7.66-7.71 (m, 1H), 8.08-8.12 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 110.6, 120.1, 124.7, 125.3, 125.6, 128.4, 128.8, 129.0, 129.2, 137.7, 142.0, 150.7, 162.0.

All spectral data correspond to those given in the literature.[133]

2-(4-methoxyphenyl)benzo[*d*]oxazole (51c)
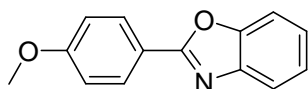
Following the general procedure using *N*-(2-bromophenyl)-4-methoxybenzamide (100 mg, 0.33 mmol) provided 70 mg (96% yield) of the coupling product as a white solid after purification by flash chromatography (CH$_2$Cl$_2$/pentane 1:1).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.87 (s, 3H), 7.01 (d, 2H, *J* = 8,7 Hz), 7.27-7.35 (m, 2H), 7.51-7.56 (m, 1H), 7.70-7.77 (m, 1H), 8.19 (d, 2H, *J* = 8,7 Hz).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 55.5, 110.4, 114.3, 119.6, 119.7, 124.4, 124.6, 129.3, 142.2, 150.6, 162.2, 163.0.

All spectral data correspond to those given in the literature.[133]

---

[133] J.-Z. Zhang, Q. Zhu, X. Huang, *Synth.. Commun.* **2002**, *32*, 2175.

2-(3,4-dichlorophenyl)benzo[*d*]oxazole (51d)
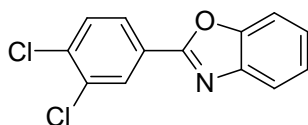
Following the general procedure using *N*-(2-bromophenyl)-3,4-dichlorobenzamide (100 mg, 0.29 mmol) provided 50 mg (65% yield) of the coupling product as a white solid after purification by flash chromatography (CH$_2$Cl$_2$/pentane 1:1).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.22-7.25 (m, 2H), 7.33-7.40 (m, 2H), 7.54-7.62 (m, 1H), 7.73-7.79 (m, 1H), 8.07 (dt, 1H, *J* = 1.9, 8.5 Hz), 8.34 (t, 1H, *J* = 1.9 Hz).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 110.6, 120.1, 124.9, 125.5, 126.4, 126.9, 129.3, 130.9, 133.5, 141.8, 150.6, 160.8.

All spectral data correspond to those given in the literature.[134]

2-(4-bromophenyl)benzo[*d*]oxazole (51e)
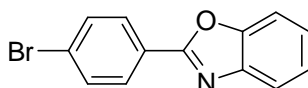
Following the general procedure using 4-bromo-*N*-(2-bromophenyl)benzamide (100 mg, 0.35 mmol) provided 65 mg (92% yield) of the coupling product as a white solid after purification by flash chromatography (CH$_2$Cl$_2$/pentane 1:1).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.31-7.37 (m, 2H), 7.52-7.57 (m, 1H), 7.61-7.66 (m, 2H), 7.71-7.77 (m, 1H), 8.07-8.11 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 110.6, 120.1, 124.7, 125.4, 126.0, 126.2, 129.1, 132.2, 141.9, 150.7, 162.0.

All spectral data correspond to those given in the literature.[135]

2-mesitylbenzo[*d*]oxazole (51f)

[134] V. V. Somayajulu, N. V. Subba Rao, *Current Sci. (India)* **1956**, *25*, 86.

[135] R. S. Pottorf, N. K. Chadha, M. Katkevics, V. Ozola, E. Suna, H. Ghane, T. Regberg, M. R. Player, *Tetrahedro. Lett.* **2002**, *44*, 175.

Following the general procedure using *N*-(2-bromophenyl)-2,4,6-trimethylbenzamide (100 mg, 0.32 mmol) provided 12 mg (16% yield) of the coupling product as a white solid after purification by flash chromatography (CH$_2$Cl$_2$/pentane 1:1).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.33 (s, 6H), 2.39 (s, 3H), 7.00 (s, 2H), 7.36-7.44 (m, 2H), 7.56-7.64 (m, 1H), 7.80-7.90 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 20.3, 21.3, 110.6, 120.2, 122.4, 124.2, 124.9, 125.0, 128.6, 132.4, 138.5, 140.3, 141.7, 150.6, 163.5.

All spectral data correspond to those given in the literature.[136]

2-(2-fluorophenyl)benzo[*d*]oxazole (51g)

Following the general procedure using *N*-(2-bromophenyl)-2-fluorobenzamide (100 mg, 0.34 mmol) provided 35 mg (48% yield) of the coupling product as a white solid after purification by flash chromatography (CH$_2$Cl$_2$/pentane 1:1).

^{19}F NMR (376 MHz, CDCl$_3$): δ = -110.2.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.24-7.27 (m, 1H), 7.28-7.34 (m, 1H), 7.35-7.42 (m, 2H), 7.49-7.56 (m, 1H), 7.60-7.65 (m, 1H), 7.81-7.87 (m, 1H), 8.21-8.27 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 110.7, 115.5, 117.0 (d, J^{CF} = 21 Hz), 120.4, 124.4 (d, J^{CF} = 3.8 Hz), 124.7, 125.5, 130.5, 133.0 (d, J^{CF} = 9.1 Hz), 141.7, 150.4, 159.5, 161.0.

All spectral data correspond to those given in the literature.[137]

2-(3-methoxyphenyl)benzo[*d*]oxazole (51h)
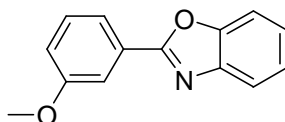
Following the general procedure using *N*-(2-bromophenyl)benzamide (100 mg, 0.33 mmol) provided 72 mg (82% yield) of the coupling product as a white solid after purification by flash chromatography (CH$_2$Cl$_2$/pentane 1:1).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 3.94 (s, 3H), 7.08-7.14 (m, 1H), 7.34-7.41 (m, 2H), 7.45 (dd, 1H, *J* = 8.0, 8.0 Hz), 7.58-7.64 (m, 1H), 7.77-7.84 (m, 2H), 7.86-7.90 (m, 1H).

[136] H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 12404.
[137] G. Altenhoff, F. Glorius, *Adv. Synth. Catal.* **2004**, *346*, 1161.

¹³C NMR (100 MHz, CDCl₃): δ = 55.5, 110.6, 111.9, 118.4, 120.0, 124.6, 125.2, 128.4, 130.0, 142.1, 150.8, 160.0, 163.0.

All spectral data correspond to those given in the literature.[138]

6-fluoro-2-phenylbenzo[*d*]oxazole (51i)
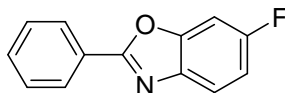
Following the general procedure using *N*-(2-bromo-4-fluorophenyl)benzamide (100 mg, 0.34 mmol) provided 65 mg (89% yield) of the coupling product as a white solid after purification by flash chromatography (CH₂Cl₂/pentane 1:1).

¹⁹F NMR (376 MHz, CDCl₃): δ = -115.1.

¹H NMR (400 MHz, CDCl₃): δ = 7.10 (td, 1H, *J* = 9.4, 2.5 Hz), 7.31 (dd, 1H, *J* = 8.0, 2.5 Hz), 7.48-7.56 (m, 3H), 7.67-7.72 (m, 1H), 8.18-8.25 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 98.7 (d, *J*^CF = 28 Hz), 112.5 (d, *J*^CF = 24 Hz), 120.2 (d, *J*^CF = 9.9 Hz), 126.9, 127.4, 129.0, 131.6, 138.4, 150.6 (d, *J*^CF = 14 Hz), 159.4, 161.8, 163.6.

All spectral data correspond to those given in the literature.[139]

6. Synthesis of Benzofurans

General Procedure for Synthesis of the Starting Materials by Friedel-Crafts Acylations of 2-Bromophenyl Acetyl Chloride[140]
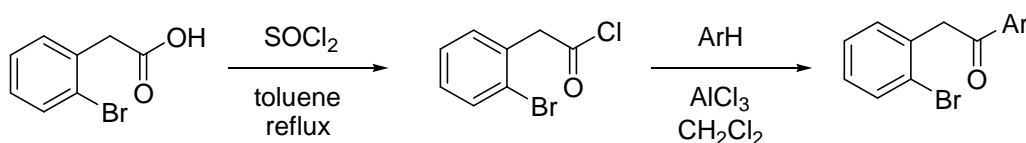
A solution of 2-bromophenyl acetic acid (1 equiv, 1.07 g, 5 mmol) and thionyl chloride (2 equiv, 0.85 mL, 10 mmol) in toluene (12 mL) in a round-bottomed flask was refluxed for 2 hours. Then, the mixture was evaporated under reduced pressure to dryness and the residue re-disolved in dichloromethane (15 mL). The arene (2.2 equiv, 11 mmol) was added and the mixture was then cooled to 0 °C. Subsequently, AlCl₃ (1.2 eq, 800 mg, 6 mmol) was added portionwise, keeping the reaction temperature below 10 °C. The mixture was warmed to room

[138] R. Ips, M. Lachaize, O. Albert, M. Dupont, *Chimica Therapeutica* **1971**, *6*, 126.
[139] A. Hari, C. Karan, W. C. Rodrigues, B. L. Miller, *J. Org. Chem.* **2001**, *66*, 991.
[140] C. Chen, P. G. Dormer, *J. Org. Chem* **2005**, *70*, 6964.

temperature and stirred at this temperature for 2 h. Then, it was poured into 1N HCl (15 mL), and the CH_2Cl_2 layer was separated, dried with $MgSO_4$ and concentrated in vacuum to give crude product as a solid. The product was recrystallized from MTBE/pentane 1:1 to afford the correspondent bromoketone.

2-(2-bromophenyl)-1-(4-methoxyphenyl)ethanone (53a)
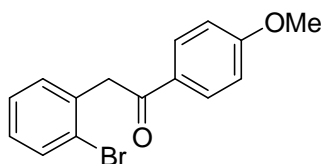
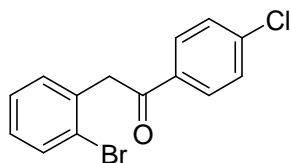Following the general procedure to yield the title compound as a white solid (74%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.03-7.99 (m, 2H), 7.59-7.55 (m, 1H), 7.28-7.20 (m, 2H), 7.15-7.09 (m, 1H), 6.90-6.98 (m, 2H), 4.38 (s, 2H), 3.86 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 194.8, 163.6, 135.2, 132.7, 131.6, 130.6, 129.6, 128.6, 127.5, 125.0, 113.8, 55.6, 45.5.

M. p. = 84.4 °C; lit. m. p. = 91-92 °C.

All spectral data correspond to those given in the literature.[140]

2-(2-bromophenyl)-1-(4-(methylthio)phenyl)ethanone (53b)
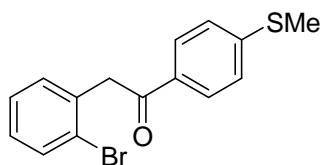
Following the general procedure to yield the title compound as a yellow pale solid (68%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.98-7.92 (m, 2H), 7.62-7.56 (m, 1H), 7.32-7.24 (m, 4H), 7.18-7.10 (m, 1H), 4.41 (s, 2H), 2.52 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 195.4, 146.2, 135.1, 132.8, 132.9, 132.8, 131.6, 128.8, 128.7, 127.5, 125.1, 45.5, 14.8.

M. p. = 84.2-84.8 °C; lit. m. p. = 85-87 °C.

All spectral data correspond to those given in the literature.[140]

2-(2-bromophenyl)-1-*p*-tolylethanone (53c)
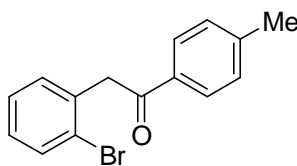
Following the general procedure to yield the title compound as a yellow oil (82%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.97 (m, 2H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.30-7.25 (m, 4H), 7.17-7.15 (m, 1H), 4.44 (s, 2H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 196.0, 144.2, 135.2, 134.1, 132.8, 132.7, 131.7, 129.4, 128.5, 127.5, 125.1, 45.79, 21.87.

All spectral data correspond to those given in the literature.[140]

2-(2-bromophenyl)-1-mesitylethanone (53d)
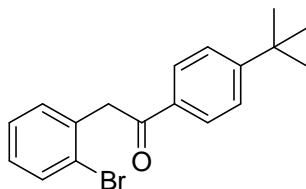
Following the general procedure (3 mmol scale) using mesitylene (2.2 equiv, 1.5 mL) to yield the title compound as a pale yellow solid (51%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.60 (d, *J* = 8.0 Hz, 1H), 7.33-7.25 (m, 2H), 7.19-7.14 (m, 1H), 6.86 (s, 2H), 4.23 (s, 2H), 2.30 (s, 3H), 2.28 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 205.5, 138.9, 138.6, 133.7, 132.9, 132.8, 131.8, 128.9, 128.5, 127.5, 125.4, 51.63, 21.22, 19.45.

M. p. = 103.5-104.5 °C.

HRMS (EI): *m/z* calculated for C$_{17}$H$_{17}$O^{79}Br 316.0457, found 316.0457.

2-(2-bromophenyl)-1-(4-*tert*-butylphenyl)ethanone (53e)
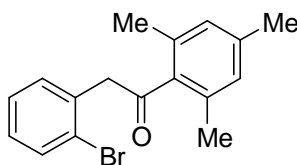
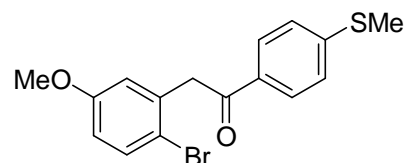Following the general procedure to yield the title compound as a tan solid (45%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.95-7.90 (m, 2H), 7.54-7.50 (m, 1H), 7.46-7.41 (m, 2H), 7.25-7.16 (m, 1H), 7.12-7.05 (m, 1H), 4.37 (s, 2H), 1.28 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 195.8, 157.0, 135.1, 135.0, 132.7), 131.6, 129.1, 128.6, 128.3, 127.6, 127.4, 125.6, 45.8, 31.2.

M. p. = 71.1-71.9 °C.

HRMS (ESI): *m/z* calculated for C$_{18}$H$_{19}$O^{79}BrNa 353.0512, found 353.0511.

2-(2-bromophenyl)-1-(4-chlorophenyl)ethanone (53f)

Following the general procedure (3 mmol scale) using chlorobenzene (2.2 equiv, 0.67 mL) to yield the title compound as a white solid (15%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.98 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 3.5 Hz, 1H), 7. 46 (d, *J* = 8.5 Hz, 2H), 7.30-7.22 (m, 2H), 7.16 (td, *J* = 7.8 Hz, *J* = 1.5 Hz, 1H), 4.41 (s, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 195.1, 139.7, 134.9, 134.6, 132.8, 131.5, 129.7, 129.1, 129.0, 127.6, 125.0, 45.82.

M. p. = 94.0-94.5 °C; lit. m. p. = 76-77 °C.

All spectral data correspond to those given in the literature.[141]

2-(2-bromophenyl)-1-(2,3-dihydro-1H-inden-5-yl)ethanone (53i)
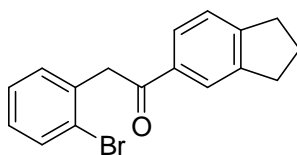
Following the general procedure to yield the title compound as a white solid (10%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.92-7.89 (m, 1H), 7.86-7.82 (m, 1H), 7.59-7.56 (m, 1H), 7.33-7.21 (m, 3H), 7.16-7.10 (m, 1H), 4.42 (s, 2H), 2.98-2.92 (m, 4H), 2.14-2.06 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 196.1, 150.5, 144.9, 135.3, 135.1, 132.7, 131.7, 128.6, 127.5, 126.9, 125.1, 124.4, 124.2, 45.9, 33.2, 32.7, 25.5.

M. p. = 67.0 °C.

HRMS (EI): *m/z* calculated for C$_{17}$H$_{16}$O^{79}Br 315.0379, found 315.0375.

---

[141] J. Farago, A. Kotschy, *Synthesis* **2009**, 85.

2-(2-bromophenyl)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethanone (53j)
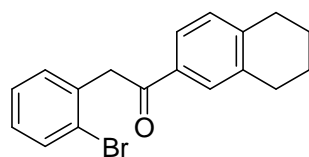
Following the general procedure to yield the title compound as a white solid (11%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.76-7.72 (m, 2H), 7.59-7.55 (m, 1H), 7.29-7.20 (m, 2H), 7.16-7.09 (m, 2H), 4.40 (s, 2H), 2.84-2.77 (m, 4H), 1.83-1.78 (m, 4H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 196.1, 143.4, 137.5, 135.2, 134.1, 132.7, 131.6, 129.4, 129.2, 128.6, 127.4, 125.4, 125.1, 45.7, 29.8, 29.5, 23.1, 22.9.

M. p. = 101.5-102.3 °C.

HRMS (ESI): *m/z* calculated for C$_{18}$H$_{18}$O^{79}Br 329.0536, found 329.0535.

2-(2-bromo-5-methoxyphenyl)-1-(4-methoxyphenyl)ethanone (53k)
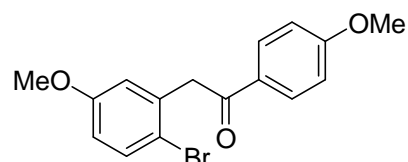
Following the general procedure to yield the title compound as a tan solid (38%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.03-7.97 (m, 2H), 7.46-7.42 (d, *J* = 8.8 Hz, 1H), 6.96-6.90 (m, 2H), 6.79-6.76 (d, *J* = 3.0 Hz, 1H), 6.71-6.66 (dd, *J* = 3.0 Hz, *J* = 8.8 Hz, 1H), 4.33 (s, 2H), 3.87 (s, 3H), 3.73 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 195.1, 163.7, 159.1, 136.3, 133.4, 130.9, 129.8, 117.3, 115.6, 114.7, 114.0, 55.7, 55.6, 45.8.

M. p. = 116.9-117.7 °C.

HRMS (ESI): *m/z* calculated for C$_{16}$H$_{16}$O$_3$^{79}Br 335.0277, found 335.0275.

2-(2-bromo-5-methoxyphenyl)-1-(4-(methylthio)phenyl)ethanone (53l)

Following the general procedure to yield the title compound as a yellow pale solid (10%).

¹H NMR (400 MHz, CDCl₃): δ = 7.94-7.90 (m, 2H), 7.46-7.42 (m, 1H), 7.28-7.23 (m, 1H), 6.79-6.76 (d, J = 3.0 Hz, 1H), 6.71-6.66 (dd, J = 3.0 Hz, J = 8.8 Hz, 1H), 4.33 (s, 2H), 3.73 (s, 3H), 2.50 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 195.2, 158.8, 146.2, 135.9, 133.2, 132.8, 128.8, 125.0, 117.2, 115.4, 114.5, 55.5, 45.8, 14.9.

M. p. = 95.8-96.4 °C.

HRMS (ESI): m/z calculated for C₁₆H₁₆⁷⁹BrO₂S 351.0049, found 351.0047.

2-(2-bromo-5-methoxyphenyl)-1-p-tolylethanone (53m)
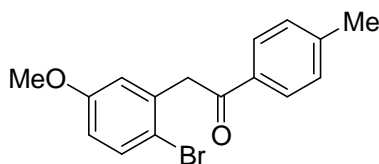
Following the general procedure to yield the title compound as a white solid (64%).

¹H NMR (400 MHz, CDCl₃): δ = 7.94-7.90 (d, J = 8.0 Hz, 2H), 7.46-7.42 (d, J = 8.8 Hz, 1H), 7.28-7.24 (d, J = 8.0 Hz, 1H), 6.79-6.77 (d, J = 3.0 Hz, 1H), 6.71-6.67 (dd, J = 3.0 Hz, J = 8.8 Hz, 1H), 4.36 (s, 2H), 3.74 (s, 3H), 2.40 (s, 3H).

¹³C NMR (75 MHz, CDCl₃): δ = 195.9, 158.9, 144.2, 136.0, 134.1, 133.2, 129.4, 128.5, 117.2 , 115.5, 114.5, 55.4, 45.8, 21.7.

M. p. = 79.8-80.8 °C.

HRMS (ESI): m/z calculated for C₁₆H₁₅O₂⁷⁹Br 341.0148, found 341.0149.

2-(2-bromo-5-methoxyphenyl)-1-mesitylethanone (53n)
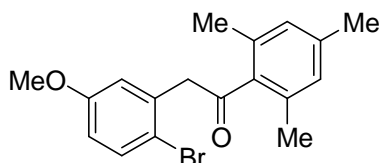
Following the general procedure to yield the title compound as a yellow solid (34%).

¹H NMR (300 MHz, CDCl₃): δ = 7.50-7.55 (d, J = 8.8 Hz, 2H), 6.68-6.64 (m, 2H), 6.81-6.70 (m, 2H), 4.18 (s, 2H), 3.78 (s, 3H), 2.29 (s, 3H), 2.27 (s, 6H).

¹³C NMR (75 MHz, CDCl₃): δ = 205.5, 158.9, 139.0, 138.6, 134.5, 133.4, 132.8, 128.6, 117.5, 115.8, 114.4, 55.5, 51.7, 21.1, 19.3.

M. p. = 93.1-93.5 °C.

HRMS (ESI): m/z calculated for C₁₈H₁₉O₂⁷⁹BrNa 369.0461, found 369.0461.

General Procedure for Synthesis of Starting Materials 53g and 53h by α-Arylation of Ketones[142]

Under argon Cs_2CO_3 (2.2 equiv, 4.3 g, 13.2 mmol) was added to a dried flask charged with $Pd_2(dba)_3$ (0.5 mol%, 27 mg, 0.03 mmol) and XANTPHOS (1.2 mol%, 42 mg, 0.07 mmol). The flask was evacuated and back-filled with argon three times. The reagents were suspended in anhydrous dioxane and 1-bromo-2-iodobenzene (1 equiv, 0.77 mL, 6 mmol) and the ketone (2 equiv) were added under argon. The reaction was heated to 80 ºC for 24 hours. After cooling to room temperature the reaction mixture was diluted with diethyl ether and water. The product was extracted with diethyl ether. The combined organic extracts were washed with brine, dried with $MgSO_4$, filtered and reduced in *vacuo*. The product was purified via flash chromatography to yield the title compound.

2-(2-bromophenyl)cyclohexanone (53g)
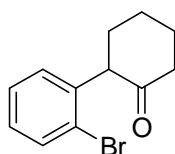
Following the general procedure using cyclohexanone (1.24 mL), the product was purified via flash chromatography (pentene/diethyl ether 10:1) to yield the title compound as a white solid (15%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.48 (d, *J* = 7.9 Hz, 1H), 7.25-7.18 (m, 1H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.04 (t, *J* = 7.3 Hz, 1H), 4.03 (dd, *J* = 12.8 and 5.2 Hz, 1H), 2.49-2.45 (m, 2H), 2.23-2.11 (m, 2H), 1.98-1.70 (m, 4H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 208.7, 138.4, 132.6, 128.4, 127.4, 127.2, 125.2, 56.7, 42.6, 34.4, 27.9, 25.8.

M. p. = 57.0-58.0 °C; lit. m. p. = 57.0-58.3 °C.

All spectral data correspond to those given in the literature.[142]

2-(2-bromophenyl)-3,4-dihydronaphthalen-1(2H)-one (53h)

---
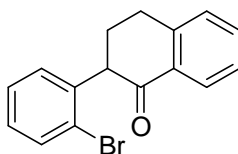
[142] M. C. Willis, D. Taylor, A. T. Gillmore, *Org. Lett.* **2004**, *6*, 4755.

Following the general procedure using α-tetralone and sodium *tert*-butoxide as the base, heating at 100 °C for 24 hours. The product was purified via flash chromatography (pentane/diethyl ether 10:1) to yield the title compound as a viscous yellow oil (76%).

¹H NMR (400 MHz, CDCl₃): δ = 8.00 (dd, *J* = 7.5 and 1.3 Hz, 1H), 7.46 (td, *J* = 7.5 and 1.3, 1H), 7.36 (td, *J* = 7.5 and 1.6 Hz, 1H), 7.22-7.11 (m 3H), 7.04-6.96 (m, 2H), 4.17 (dd, *J* = 11.9 and 4.9 Hz, 1H), 3.09-3.01 (m, 1H), 2.90 (dt, *J* = 16.6 and 4.0 Hz, 1H), 2.35-2.18 (m, 2H).

¹³C NMR (100 MHz, CDCl₃): δ = 196.8, 143.9, 139.7, 133.5, 132.9, 132.8, 129.7, 129.5, 128.5, 127.8, 127.6, 126.8, 125.5, 54.5, 30.6, 29.5.

All spectral data correspond to those given in the literature.[142]

General Procedure for Intermolecular *O*-Arylations to Give Benzo[*b*]furans

A sealed tube equipped with a magnetic stir bar was charged with the 2-(2-bromophenyl)ketone (1.0 equiv, 0.32 mmol), Cs_2CO_3 (2.0 equiv, 0.64 mmol) and $FeCl_3$ (0.1 equiv, 0.03 mmol; Acros; 98%). The aperture of the tube was then covered with a rubber septum, and an argon atmosphere was established. 2,2,6,6-Tetramethyl-3,5-heptanedione (TMHD, 0.2 equiv, 0.06 mmol) and DMF (1 mL) were added via syringe. The septum was replaced by a teflon-coated screw cap, and the reaction vessel was heated at 120 °C. After stirring at this temperature for 24 h, the heterogeneous mixture was cooled to room temperature, diluted with dichloromethane and filtered through a pad of celite. The solution was concentrated to give the product, which was purified by silica gel chromatography to yield the benzo[*b*]furan. The identity and purity of the product was confirmed by ¹H NMR and ¹³C NMR spectroscopic analysis and exact mass determination.

2-(4-methoxyphenyl)benzo[*b*]furan (54a)
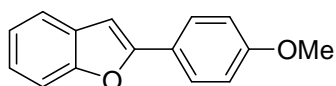
Following the general procedure using 2-(2-bromophenyl)-1-(4-methoxyphenyl)ethanone (98 mg, 0.32 mmol) and $FeCl_3$ (Acros; 98%) provided 57 mg (79%) of the coupling product as a white solid after purification by flash chromatography (CH_2Cl_2/pentane 1:3).

**¹H NMR (400 MHz, CDCl₃):** δ = 7.74-7.69 (m, 2H), 7.49-7.45 (m, 1H), 7.44-7.40 (m, 1H), 7.20-7.10 (m, 2H), 6.92-6.87 (m, 2H), 6.81-6.79 (m, 1H), 3.77 (s, 3H).

^{13}**C NMR (100 MHz, CDCl$_3$):** δ = 159.9, 156.0, 154.6, 129.4, 126.4, 123.7, 123.3, 122.8, 120.5 , 114.2, 111.0, 99.7, 55.4.

M. p. = 146.2-147.2 °C; lit. m. p. = 154-155 °C.

All spectral data correspond to those given in the literature.[140]

2-(4-(methylthio)phenyl)benzo[*b*]furan (54b)
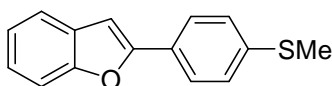
Following the general procedure using 2-(2-bromophenyl)-1-(4-(methylthio)phenyl)ethanone (103 mg. 0.32 mmol) and FeCl$_3$ (Acros; 98%) provided 55 mg (72%) of the coupling product as a white solid after purification by flash chromatography (CH$_2$Cl$_2$/pentane 1:1).

^{1}**H NMR (400 MHz, CDCl$_3$):** δ = 7.78-7.74 (m, 2H), 7.57-7.46 (m, 2H), 7.32-7.17 (m, 4H), 6.96 (s, 1H), 2.51 (s, 3H).

^{13}**C NMR (100 MHz, CDCl$_3$):** δ = 155.5, 154.7, 139.2, 129.2, 127.2, 126.4, 125.2, 124.1, 122.9, 120.8, 111.1, 100.9, 15.7.

M. p. = 163.5-163.5 °C; lit. m. p. = 159 °C.

All spectral data correspond to those given in the literature.[140]

2-*p*-tolylbenzofuran (54c)
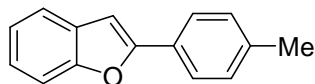
Following the general procedure using 2-(2-bromophenyl)-1-p-tolylethanone (92 mg, 0.32 mmol) and FeCl$_3$ (Acros; 98%) provided 39 mg (59%) of the coupling product as a white solid after purification by flash chromatography (pentane).

^{1}**H NMR (400 MHz, CDCl$_3$):** δ = 7.66 (d, *J* = 8.2 Hz), 7.48-7.41 (m, 2H), 7.18-7.13 (m, 4H), 6.86 (s, 1H), 2.30 (s, 3H).

^{13}**C NMR (100 MHz, CDCl$_3$):** δ = 156.1, 154.7, 138.6, 129.5, 129.3, 127.7, 124.9, 124.0, 122.8, 120.7, 111.1, 100.6, 21.5.

M. p. = 128.3-129.1 °C.

All spectral data correspond to those given in the literature.[143]

---

[143] C. Pan, J. Yu, Y. Zhou, Z. Wang, M.-M. Zhou, *Synlett* **2006**, 1657.

2-(4-*tert*-butylphenyl)benzo[*b*]furan (54d)
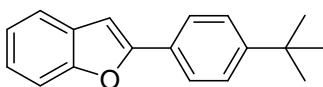
Following the general procedure using 2-(2-bromophenyl)-1-(4-tert-butylphenyl)ethanone (106 mg, 0.32 mmol) and FeCl$_3$ (Acros; 98%) provided 43 mg (54%) of the coupling product as a white solid after purification by flash chromatography (pentane).

**^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.83-7.78 (m, 2H), 7.59-7.56 (m, 1H), 7.55-7.51 (m, 1H), 7.50-7.46 (m, 2H), 7.30-7.20 (m, 2H), 6.98-6.96 (m, 1H), 1.21 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 156.1, 154.8, 151.7, 129.3, 127.7, 125.7, 124.7, 124.0, 122.8, 120.7, 111.1, 100.7, 34.9, 31.4.

M. p. = 127.8-128.4 °C; lit. m. p. = 132 °C.

All spectral data correspond to those given in the literature.[144]

2-mesitylbenzofuran (54e)
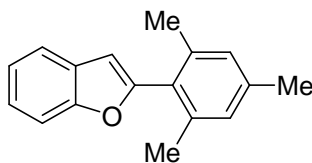
Following the general procedure using 2-(2-bromophenyl)-1-mesitylethanone (100 mg, 0.32 mmol) and FeCl$_3$ (Acros; 98%) provided 63 mg (87%) of the coupling product as a white solid after purification by flash chromatography (pentane).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.53-7.51 (m, 1H), 7.42-7.41 (m, 1H), 7.21-7.12 (m, 2H), 6.87 (s, 2H), 6.54 (s, 1H), 2.25 (s, 3H), 2.14 (s, 6H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 155.1, 154.8, 139.0, 138.4, 128.9, 128.4, 127.7, 123.7, 122.6, 120.7, 111.2, 106.1, 21.2, 20.5.

M. p. = 49.4-49.7 °C; lit. (oil).

All spectral data correspond to those given in the literature.[140]

2-(4-chlorophenyl)benzofuran (54f)

---
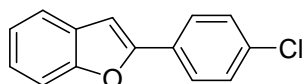
[144] J. Astoin, P. Demerseman, A. Riveron, R. Royer, *J. Het. Chem.* **1977**, *14*, 867.

Following the general procedure using 2-(2-bromophenyl)-1-(4-chlorophenyl)ethanone (99 mg, 0.32 mmol) and FeCl₃ (Acros; 98%) provided 18 mg (25%) of the coupling product as a white solid after purification by flash chromatography (pentane).

^{1}H NMR (300 MHz, CDCl₃): δ = 7.80-7.77 (m, 2H), 7.60-7.56 (m, 1H), 7.52-7.49 (m, 1H), 7.43-740 (m, 2H), 7.30-7.23 (m, 2H), 7.01 (s, 1H).

^{13}C NMR (75 MHz, CDCl₃): δ = 154.9, 154.8, 134.3, 129.1, 129.0, 126.3, 126.1, 124.6, 123.1, 121.0, 111.2, 101.8.

M. p. = 143.2-144.2 °C.

All spectral data correspond to those given in the literature.[143]

1,2,3,4-tetrahydrodibenzo[*b,d*]furan (54g)
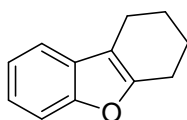
Following the general procedure using 2-(2-bromophenyl)cyclohexanone (81 mg, 0.32 mmol) and FeCl₃ (Acros; 98%) provided 18 mg (33%) of the coupling product as a colourless oil after purification by flash chromatography (pentane).

^{1}H NMR (300 MHz, CDCl₃): δ = 7.34-7.31 (m, 2H), 7.13-7.10 (m, 2H), 2.69-2.64 (m, 2H), 2.58-2.52 (m, 2H), 1.89-1.76 (m, 4H).

^{13}C NMR (75 MHz, CDCl₃): δ = 154.3, 154.0, 128.8, 122.9, 122.1, 118.3, 112.8, 110.7, 23.4, 22.9, 22.7, 20.4.

All spectral data correspond to those given in the literature.[142]

5,6-dihydrobenzo[*b*]naphtho[2,1-*d*]furan (54h)
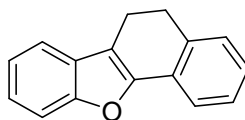
Following the general procedure using 2-(2-bromophenyl)-3,4-dihydronaphthalen-1(2H)-one (96 mg, 0.32 mmol) and FeCl₃ (Acros; 98%) provided 53 mg (76%) of the coupling product as a white solid after purification by flash chromatography (pentane / diethyl ether 9:1).

^{1}H NMR (400 MHz, CDCl₃): δ = 7.65 (d, *J* = 7.4Hz, 1H), 7.51-7.46 (m, 2H), 7.29-717 (m, 5H), 3.08 (t, *J* = 7.7 Hz, 2H), 3.00 (t, *J* = 7.9 Hz, 2H).

^{13}C NMR (100 MHz, CDCl₃): δ = 155.2, 151.7, 135.9, 128.3, 128.0, 127.8, 127.6, 126.8, 124.0, 122.7, 120.5, 119.1, 114.1, 111.4, 28.8, 19.5.

M. p. = 51.9-52.5 °C; lit. (oil).

All spectral data correspond to those given in the literature.[142]

2-(2,3-dihydro-1H-inden-5-yl)benzo[*b*]furan (54i)
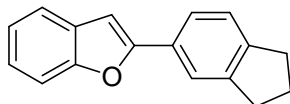
Following the general procedure using 2-(2-bromophenyl)-1-(2,3-dihydro-1H-inden-5-yl)ethanone (101 mg, 0.32 mmol) and FeCl$_3$ (Acros; 98%) provided 56 mg (75%) of the coupling product as a white solid after purification by flash chromatography (pentane).

**^{1}H NMR (400 MHz, CDCl$_3$):** δ = 7.75-7.72 (m, 1H), 7.67-7.63 (m, 1H), 7.58-7.54 (m, 1H), 7.53-7.49 (m, 1H), 7.31-7.19 (m, 3H), 6.95 (s, 1H), 3.00-2.91 (m, 4H), 2.32 (m, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 186.5, 156.6, 154.7, 145.1, 144.8, 129.4, 128.5, 124.6, 123.9, 123.1, 122.8, 120.9, 120.7, 111.0, 100.4, 32.9, 25.5.

M. p. = 92.2-92.8 °C.

HRMS (EI): *m/z* calculated for C$_{17}$H$_{14}$O 234.1039, found 234.1034.

2-(5,6,7,8-tetrahydronaphthalen-2-yl)benzo[*b*]furan (54j)
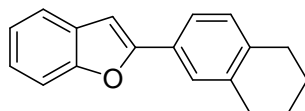
Following the general procedure using 2-(2-bromophenyl)-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethanone (105 mg, 0.32 mmol) and FeCl$_3$ (Acros; 98%) provided 64 mg (81%) of the coupling product as a white solid after purification by flash chromatography (pentane).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.51-7.40 (m, 4H), 7.21-7.09 (m, 2H), 7.07-7.02 (m, 1H), 6.81 (s, 1H), 2.80-2.65 (m, 4H), 1.79-1.70 (m, 4H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 156.4, 154.8, 138.0, 137., 129.6, 129.4 127.7, 125.5, 123.9, 122.8, 122.2, 120.7, 111.7, 110.5, 29.5, 29.4, 23.2, 25.1.

M. p. = 98.0-98.7 °C.

HRMS (EI): *m/z* calculated for C$_{18}$H$_{16}$O 248.1196; found 248.1187.

5-methoxy-2-(4-methoxyphenyl)benzo[*b*]furan (54k)
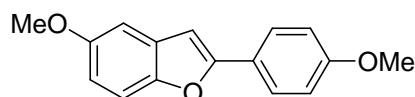
Following the general procedure using 2-(2-bromo-5-methoxyphenyl)-1-(4-methoxyphenyl)ethanone (97 mg, 0.32 mmol) and FeCl$_3$ (Acros; 98%) provided 33 mg (47%) of the coupling product as a white solid after purification by flash chromatography (CH$_2$Cl$_2$/pentane 1:1).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.79-7.75 (m, 2H), 7.40-7.37 (d, J = 8.9 Hz, 1H), 7.03-7.01 (d, J = 2.6 Hz, 2H), 6.99-6.95 (m, 1H), 6.87-6.84 (dd, J = 2.6 Hz, J = 8.9 Hz, 1H), 6.83 (s, 1H), 3.86 (ds, 6H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 159.9, 156.9, 156.0, 149.7, 130.0, 126.3, 123.4, 114.2, 112.3, 111.4, 103.2, 99.9, 55.9, 55.4.

M. p. = 154.8-155.6 °C; lit. m. p. = 163 °C.

All spectral data correspond to those given in the literature.[145]

5-methoxy-2-(4-(methylthio)phenyl)benzo[*b*]furan (54l)
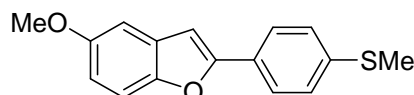
Following the general procedure using 2-(2-bromo-5-methoxyphenyl)-1-(4-(methylthio)phenyl)ethanone (112 mg, 0.32 mmol) and FeCl$_3$ (Acros; 98%) provided 26 mg (30%) of the coupling product as a white solid after purification by flash chromatography (CH$_2$Cl$_2$/pentane 1:1).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.70-7.66 (m, 2H), 7.34-7.30 (d, J = 8.9 Hz, 1H), 7.20-7.15 (m, 2H), 7.25-7.21 (m, 2H), 6.96-6.94 (d, J = 2.6 Hz, 1H), 6.85-6.83 (m, 1H), 6.82-6.78 (dd, J = 2.6 Hz, J = 8.9 Hz, 1H), 3.78 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 156.3, 156.0, 149.7, 139.1, 129.8, 127.2, 126.4, 125.1, 112.8, 111.5, 103.2, 101.0, 56.0, 15.7.

M. p. = 166.5-167.3 °C.

HRMS (EI): *m/z* calculated for C$_{16}$H$_{15}$O$_2$S 271.0787, found 271.0787.

5-methoxy-2-*p*-tolylbenzo[*b*]furan (54m)
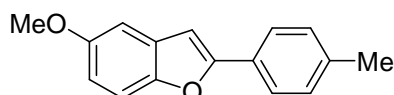
[145] A. Guy, J. P. Guette, G. Lang, *Synthesis* **1980**, 222.

Following the general procedure using 2-(2-bromo-5-methoxyphenyl)-1-*p*-tolylethanone (102 mg, 0.32 mmol) and FeCl$_3$ (Acros; 98%) provided 27 mg (36%) of the coupling product as a tan solid after purification by flash chromatography (CH$_2$Cl$_2$/pentane 1:3).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.68-7.64 (m, 2H), 7.34-7.30 (m, 1H), 7.20-7.15 (m, 2H), 6.96-6.94 (d, *J* = 2.6 Hz, 1H), 6.84-6.82 (m, 1H), 6.81-6.77 (dd, *J* = 2.6 Hz, *J* = 8.9 Hz, 2H), 3.78 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 156.9, 155.9, 149.7, 138.5, 129.8, 129.4, 127.8, 124.8, 112.6, 111.5, 103.2, 100.7, 56.0, 21.5.

M. p. = 123.0-124.0 °C; lit. m. p. = 126.0-126.5 °C.

All spectral data correspond to those given in the literature.[146]

2-mesityl-5-methoxybenzo[*b*]furan (54n)
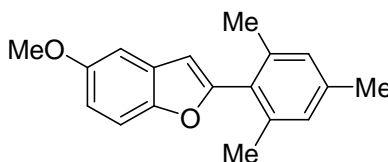
Following the general procedure using 2-(2-bromo-5-methoxyphenyl)-1-mesitylethanone (111 mg, 0.32 mmol) and FeCl$_3$ (Acros; 98%) provided 57 mg (66%) of the coupling product as a white solid after purification by flash chromatography (CH$_2$Cl$_2$/pentane 1:3).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.33-7.29 (d, *J* = 8.9 Hz, 1H), 7.99-7.02 (d, *J* = 2.6 Hz, 1H), 6.89-6.87 (s, 2H), 6.84-6.79 (dd, *J* = 2.6 Hz, *J* = 8.9 Hz, 1H), 3.79 (s, 3H), 2.26 (s, 3H), 2.15 (s, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 155.8, 155.7, 149.7, 138.9, 138.3, 129.3, 128.3, 127.7, 112.3, 111.6, 106.2, 103.2, 56.0, 21.3, 20.6.

M. p. = 103.6-104.6 °C.

HRMS (EI): *m/z* calculated for C$_{18}$H$_{19}$O$_2$ 267.1380, found 267.1380.

7. Synthesis of 5-Substituted 1H-Tetrazoles

General Procedure for Synthesis of 5-Substituted 1H-Tetrazoles

A sealable tube equipped with a magnetic stir bar was charged with arylnitrile (1.0 equiv) and Fe(OAc)$_2$ (0.1 equiv; Aldrich; 95%). A rubber septum was used to cover the aperture of the tube, an argon atmosphere was established, and trimethylsilyl azide (1.5 equiv) and a 9:1 DMF-MeOH solution (1 mL) were added using a syringe. Then, a teflon-coated screw cap

---

[146] A. E. Siegrist, H. R. Meyer, *Helv. Chim. Acta* **1969**, *52*, 1282.

replaced the rubber septum, and the reaction vessel was heated at 80 °C. After stirring at this temperature for 24 h, the mixture was cooled to room temperature and diluted with ethyl acetate. The resulting solution was washed with 1 N HCl, dried over anhydrous Na_2SO_4 and concentrated. An aqueous solution of NaOH (0.25 N) was added to the residue, and the mixture was stirred for 30 min at room temperature. The resulting solution was washed with ethyl acetate, and then 1 N HCl was added until the pH value of the water layer became 1. The aqueous layer was extracted with ethyl acetate three times, and the combined organic layers were washed with 1 N HCl. The organic layer was dried over anhydrous Na_2SO_4 and concentrated. The identity and purity of the product was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis.

5-(4-(trifluoromethyl)phenyl)-2H-tetrazole (70a)
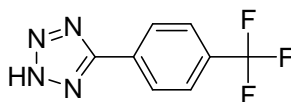
Following the general procedure using 4-(trifluoromethyl)benzonitrile (100 mg, 0.58 mmol) provided 112.9 mg (91% yield) of the cycloaddition product as a white solid after extraction.

^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 8.22 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.5 Hz, 2H).

^{13}C NMR (100 MHz, d$_6$-DMSO): δ = 155.7, 131.3 (q, J = 32.1 Hz), 128.9, 128.1, 126.6, 124.2 (q, J = 271 Hz).

M.p. = 221-222 °C; lit. m. p. = 218-219 °C.

All spectral data correspond to those given in the literature.[147]

5-phenyltetrazole (70b)
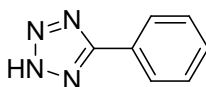
Following the general procedure using benzonitrile (100 mg, 0.97 mmol) provided 79.4 mg (56% yield) of the cycloaddition product as a white solid after extraction.

^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 8.02-7.98 (m, 2H), 7.58-7.54 (m, 3H).

^{13}C NMR (100 MHz, d$_6$-DMSO): δ = 155.8, 131.6, 129.8, 127.3, 124.7.

M.p. = 210-211 °C; lit. m. p. = 215-216 °C.

All spectral data correspond to those given in the literature.[116a]

---

[147] J. H. Markgraf, S. H. Brown, M. W. Kaplinsky, R. G. Peterson, *J. Org. Chem.* **1964**, *29*, 2629.

5-(4-iodophenyl)-2H-tetrazole (70c)
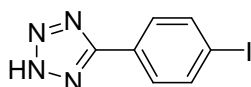
Following the general procedure using 4-iodobenzonitrile (100 mg, 0.44 mmol) provided 80.8 mg (68% yield) of the cycloaddition product as a white solid after extraction.

^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 7.98-7.94 (m, 2H), 7.80-7.76 (m, 2H).

^{13}C NMR (100 MHz, d$_6$-DMSO): δ = 138.7, 129.1, 124.2, 98.9.

M.p. = 269-271 ° C; lit. m. p. = 270-271 °C.

All spectral data correspond to those given in the literature.[148]

5-(4-vinylphenyl)-2H-tetrazole (70d)
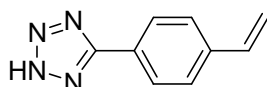
Following the general procedure using 4-vinylbenzonitrile (100 mg, 0.77 mmol) provided 49.3 mg (37% yield) of the cycloaddition product as a yellow solid after extraction.

^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 8.00-7.96 (m, 2H), 7.69-7.65 (m, 2H), 6.78 (dd, *J* = 11.0, 17.7 Hz, 1H), 5.96 (d, *J* = 17.7 Hz, 1H), 5.37 (d, *J* = 11.0 Hz, 1H).

^{13}C NMR (100 MHz, d$_6$-DMSO): δ = 154.9, 139.6, 135.6, 127.1, 126.9, 132.2, 116.4.

M. p. = 213-215 °C.

HRMS (ESI): *m/z* calculated for $C_9H_8N_4$ 172.0744, found 172.0746.

5-(4-nitrophenyl)tetrazole (70e)
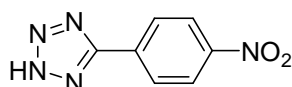
Following the general procedure using 4-nitrobenzonitrile (100 mg, 0.68 mmol) provided 123.9 mg (96% yield) of the cycloaddition product as a white solid after extraction.

^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 8.45-8.40 (m, 2H), 8.30-8.26 (m, 2H).

^{13}C NMR (100 MHz, d$_6$-DMSO): δ = 156.1, 149.1, 131.5, 128.6, 125.0.

M. p. = 218-220 °C; lit. m. p. = 220 °C.

All spectral data correspond to those given in the literature.[116a]

---

[148] a) J. Kaczmarek, H. Smagowski, Z. Grzonka, *J. Chem. Soc. Perkin Trans. 2* **1979**, *12*, 1670. b) J. Ciarkowski, J. Kaczmarek, Z. Grzonka, *Org. Magn. Res.* **1979**, *12*, 631.

5-(4-hydroxyphenyl)tetrazole (70f)
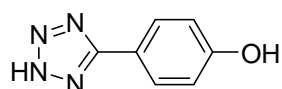
Following the general procedure using 4-hydroxybenzonitrile (100 mg, 0.84 mmol) provided 55.8 mg (41% yield) of the cycloaddition product as a white solid after extraction.

^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 10.15 (br, 1H), 7.84-7.81 (m, 2H), 6.94-6.89 (m, 2H).

^{13}C NMR (100 MHz, d$_6$-DMSO): δ = 160.0, 154.7, 128.7, 116.1, 114.6.

M. p. =. 238-240 °C; lit. m. p. = 234-236 °C.

All spectral data correspond to those given in the literature.[116a]

5-(2-bromophenyl)-2H-tetrazole (70g)
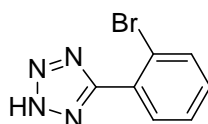
Following the general procedure using 2-bromobenzonitrile (100 mg, 0.55 mmol) provided 18.5 mg (15% yield) of the cycloaddition product as a white solid after extraction.

^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 7.85 (dd, J = 7.7, 1.5 Hz, 1H), 7.70 (dd, J = 7.5, 1.9 1H), 7.61-7.51 (m, 2H).

^{13}C NMR (100 MHz, d$_6$-DMSO): δ = 154.5, 133.4, 132.5, 131.9, 128.1, 126.3, 121.6.

M. p. =178-179 °C; lit. m. p. = 181-183 °C.

All spectral data correspond to those given in the literature.[149]

5-*p*-tolyl-2H-tetrazole (70h)
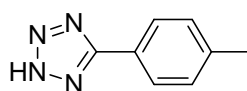
Following the general procedure using 4-methylbenzonitrile (100 mg, 0.85 mmol) provided 78.0 mg (57% yield) of the cycloaddition product as a white solid after extraction.

^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 7.91-9.87 (m, 2H), 7.40-7.36 (m, 2H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, d$_6$-DMSO): δ = 154.9, 141.0, 129.8, 126.7, 121.2, 21.1.

M. p. = 246-248 °C; lit. m. p. = 248-249 °C.

All spectral data correspond to those given in the literature.[150]

---

[149] a) S. J. Wittember, B. G. Donner, *J. Org. Chem.* **1993**, *58*, 4139; b) J. Kaczmarek, Z. Grzonka, *Polish J. Chem.* **1980**, *54*, 1297.

5-(4-chlorophenyl)tetrazole (70i)
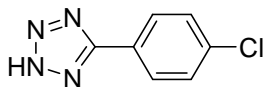
Following the general procedure using 4-chlorobenzonitrile (100 mg, 0.73 mmol) provided 91.9 mg (70% yield) of the cycloaddition product as a white solid after extraction.
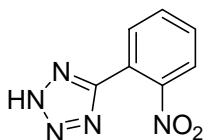
^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 8.00 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H).

^{13}C NMR (100 MHz, d$_6$-DMSO): δ = 155.3, 136.3, 129.9, 129.0, 123.6.

M. p. = 252-254 °C; lit. m. p. = 252-253 °C.

All spectral data correspond to those given in the literature. [148]

5-(2-nitrophenyl)-2H-tetrazole (70j)

Following the general procedure using 2-nitrobenzonitrile (100 mg, 0.68 mmol) provided 86.5 mg (67% yield) of the cycloaddition product as a grey solid after extraction.

^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 8.19-8.15 (m, 1H), 7.92-7.85 (m, 3H).

^{13}C NMR (100 MHz, d$_6$-DMSO): δ = 154.1, 148.6, 134.1, 132.8, 131.9, 125.2, 119.7.

M. p. =158-161 °C; lit. m. p. = 159-161 °C.

All spectral data correspond to those given in the literature. [151]

5-(2-naphthyl)tetrazole (70k)
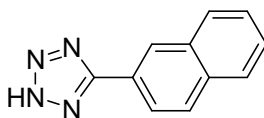
Following the general procedure using 2-naphthonitrile (100 mg, 0.65 mmol) provided 74.3 mg (58% yield) of the cycloaddition product as a white solid after extraction.

---

[150] a) N. B. Richard, C. G. Victor, *J. Chem. Soc., Perkin Trans. 1* **1981**, 390. b) R. N. Butler, T. M. McEvoy, *J. Chem. Soc., Perkin Trans. 2* **1978**, 1087.
[151] J. M. McManus, M. R. Herbst, *J. Org. Chem.* **1959**, *24*, 1044.

^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 8.64-8.61 (m, 1H), 8.13-8.03 (m, 3H), 8.01-7.93 (m, 1H), 7.65-7.58 (m, 2H).

^{13}C NMR (100 MHz, d$_6$-DMSO): δ = 155.5, 134.3, 133.0, 129.6, 129.0, 128.3, 128.3, 127.7, 127.4, 124.1, 122.0.

M. p. = 202-204 °C; lit. m. p. = 205-207 °C.

All spectral data correspond to those given in the literature.[116a]

5-(3,5-dinitrophenyl)-2H-tetrazole (70l)
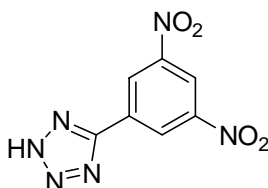
Following the general procedure using 3,5-dinitrobenzonitrile (100 mg, 0.52 mmol) provided 121.9 mg (>99% yield) of the cycloaddition product as a white solid after extraction.

^{1}H NMR (300 MHz, d$_6$-DMSO): δ = 9.10 (d, J = 2.2 Hz, 2H), 7.78 (d, J = 2.2 Hz, 1H).

^{13}C NMR (100 MHz, d$_6$-DMSO): δ = 155.3, 149.1, 128.6, 127.1, 120.5.

M. p. = 176-177 °C; lit. m. p. = 178-179 °C.

All spectral data correspond to those given in the literature.[152]

5-(thiophen-3-yl)-2H-tetrazole (70m)
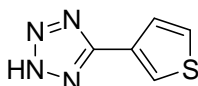
Following the general procedure using thiophene-3-carbonitrile (100 mg, 0.92 mmol) provided 100.4 mg (72% yield) of the cycloaddition product as a white solid after extraction.

^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 8.24 (dd, J = 3.0, 1.4 Hz, 1H), 7.78 (dd, J = 5.2, 3.0 Hz, 1H), 7.62 (dd, J = 5.2, 1.4 Hz, 1H).

^{13}C NMR (100 MHz, d$_6$-DMSO): δ = 151,8, 129.2, 127.8, 126.4, 125.4.

M. p. = 243-245 °C; lit. m. p. = 244-246 °C.

All spectral data correspond to those given in the literature.[153]

5-(2,2-dimethyl-2H-chromen-6-yl)-2H-tetrazole (70n)

---

[152] B. S. Jursic, B. W. Leblanc, *J. Het. Chem.* **1998**, *35*, 405.
[153] B. Elpern, F. C. Nachod, *J. Am. Chem. Soc.* **1950**, *72*, 3379.
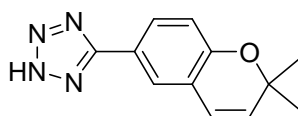
Following the general procedure using 2,2-dimethyl-2H-chromene-6-carbonitrile (100 mg, 0.54 mmol) provided 65.3 mg (53% yield) of the cycloaddition product as a white solid after extraction.

^{1}H NMR (400 MHz, d$_6$-DMSO): δ = 7.36 (dd, *J* =8.4, 2.2 Hz, 1H), 7.23 (dd, *J* = 2.2 Hz, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 6.27 (d, *J* = 9.9 Hz, 1H), 5.68 (d, *J* = 9.9 Hz, 1H), 1.45 (s, 6H).

^{13}C NMR (100 MHz, d$_6$-DMSO): δ = 155.2, 132.5, 128.4, 125.5, 121.9, 121.4, 117.2, 117.0, 77.6, 28.4.

M. p. = 195-197 °C.

All spectral data correspond to those given in the literature.[154]

8. Synthesis of Indoles

General Procedure for the Preparation of the Aryl Azidoacrylates

The required aryl azidoacrylates were prepared in one step by condensation of methyl azidoacetate and aromatic or heteroaromatic aldehydes following the method reported by Driver and coworkers.[123] The yields were not optimized.

To a cooled (–20 °C) solution of NaOMe (0.70 g, 13.0 mmol, 1.52 equiv) in MeOH (20 mL) was added a solution of the aldehyde (8.6 mmol, 1 equiv) and methyl azidoacetate (3.0 g, 25.9 mmol, 3 equiv) in MeOH 20mL dropwise over 20 minutes. The resulting reaction mixture was warmed to –10 °C. After 4 h, the heterogeneous mixture was diluted with water (20 mL) and diethyl ether (20 mL). The aqueous phase was extracted with diethyl ether (2 x 20 mL), and the combined organic phases were washed with distilled water (2 x 20 mL) and brine (20 mL). The resulting organic phase was dried over MgSO$_4$, and the heterogeneous mixture was filtered. The filtrate was concentrated *in vacuo* to afford a light yellow oil. Purification by flash chromatography (EtOAc/diethyl ether or CH$_2$Cl$_2$/pentane) afforded the product.

(Z)-methyl 2-azido-3-phenylacrylate (71a)

[154] K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G.-Q. Cao, S. Barluenga, H. J. Mitchell, *J. Am. Chem. Soc.* **2000**, *122*, 9939.
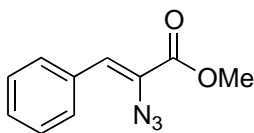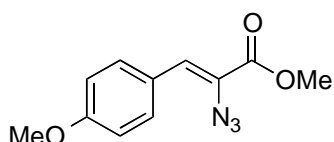
Following the general procedure, purification with CH$_2$Cl$_2$/pentane 1:1 to yield the title compound as a white solid (40%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.82 - 7.80 (m, 2H), 7.41 - 7.29 (m, 3H), 6.92 (s, 1H), 3.92 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 164.0, 133.1, 130.6, 129.5, 128.5, 125.6, 125.3, 52.9.

All spectral data correspond to those given in the literature.[123a]
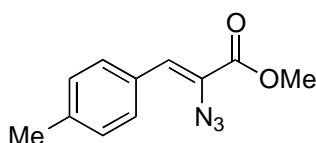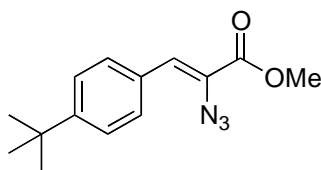

(Z)-methyl 2-azido-3-(4-methoxyphenyl)acrylate (71b)

Following the general procedure, purification with CH$_2$Cl$_2$ to yield the title compound as a light yellow oil (40%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.77 (d, J = 8.6 Hz, 2H), 6.91 - 6.85 (m, 3H), 3.88 (s, 3H), 3.82 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 164.3, 160.5, 132.4, 126.0, 125.7, 123.1, 113.9, 55.3, 52.7

All spectral data correspond to those given in the literature.[123a]

(Z)-methyl 2-azido-3-p-tolylacrylate (71c)

Following the general procedure, purification with CH$_2$Cl$_2$/pentane 1:1 to yield the title compound as a yellow solid (22%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.68 (d, J = 8.2 Hz, 2H), 7.18 (d, J = 8.2 Hz, 2H), 6.89 (s, 1H), 3.89 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 164.1, 139.9, 130.6, 130.4, 129.2, 125.8, 124.4, 52.9, 21.6.

All spectral data correspond to those given in the literature.[123a]

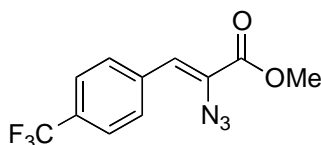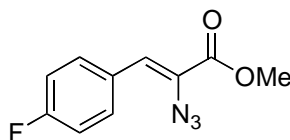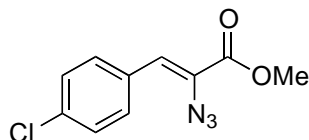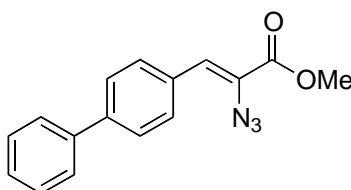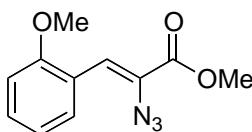**(Z)-methyl 2-azido-3-(4-*tert*-butylphenyl)acrylate (71d)**

Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a yellow oil (25%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.76 – 7.70 (m, 2H), 7.42 – 7.36 (m, 2H), 6.93 (s, 1H), 3.90 (s, 3H), 1.35 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 164.1, 153.0, 130.4, 130.3, 125.7, 125.5, 124.6, 52.8, 34.8, 31.1.

All spectral data correspond to those given in the literature.[123a]

(Z)-methyl 2-azido-3-(4-(trifluoromethyl)phenyl)acrylate (71e)

Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield the title compound as orange solid (21%).

^{19}F NMR (376 MHz, CDCl$_3$): δ = –62.9.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.88 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H), 6.87 (s, 1H), 3.91 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 163.6, 136.5, 130.8, 127.5, 125.4, 125.3, 123.9 (q, J^{CF} = 270 Hz), 123.2, 53.1.

All spectral data correspond to those given in the literature.[123a]

(Z)-methyl 2-azido-3-(4-fluorophenyl)acrylate (71f)

Following the general procedure; purification with CH_2Cl_2/pentane 1:9 to yield the title compound as a orange oil (27%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.81 - 7.75 (m, 2H), 7.07 - 7.00 (m, 2H), 7.83 (s, 1H), 3.88 (s, 3H).

^{13}**C NMR (100 MHz, CDCl$_3$):** δ = 164.0 (d, J = 30.9 Hz), 161.7, 132.6 (d, J = 8.3 Hz), 124.9 (d, J = 2.6 Hz), 124.2, 115.5 (d, J = 21.6 Hz), 52.9.

HRMS (ESI): (–N$_2$) m/z calculated for C$_{10}$H$_8$O$_2$NF 193.0534, found 193.0534.

(Z)-methyl 2-azido-3-(4-chlorophenyl)acrylate (71g)

Following the general procedure, purification with CH$_2$Cl$_2$/pentane 3:1 to yield the title compound as a yellow solid (33%).

^{1}**H NMR (400 MHz, CDCl$_3$):** δ = 7.73 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 6.85 (s, 1H), 3.89 (s, 3H).

^{13}**C NMR (100 MHz, CDCl$_3$):** δ = 163.7, 135.1, 131.7, 131.6, 128.7, 125.8, 124.0, 53.1.

All spectral data correspond to those given in the literature.[123a]

(Z)-methyl 2-azido-3-(4-benzylphenyl)acrylate (71h)

Following the general procedure, purification with CH$_2$Cl$_2$/pentane 1:1 to yield the title compound as a yellow solid (32%).

^{1}**H NMR (400 MHz, CDCl$_3$):** δ = 7.89 (d, J = 8.6 Hz, 2H), 7.64 - 7.60 (m, 4H), 7.47 - 7.42 (m, 2H), 7.39 - 7.34 (m, 1H), 6.95 (s, 1H), 3.52 (s, 3H).

^{13}**C NMR (100 MHz, CDCl$_3$):** δ = 164.0, 142.0, 140.2, 132.2, 131.1, 127.8, 127.1, 127.0, 126.9, 125.2, 125.1, 52.9.

HRMS (ESI): m/z calculated for C$_{16}$H$_{13}$O$_2$N$_3$ 279.1002, found 279.1008.

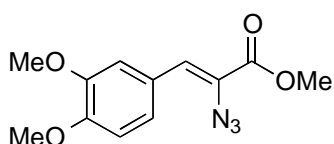### (Z)-methyl 2-azido-3-(2-methoxyphenyl)acrylate (71i)

Following the general procedure, purification with CH$_2$Cl$_2$ to yield the title compound as a yellow pale solid (25%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.17 (dd, J = 7.8 Hz, J = 1.7 Hz, 1H), 7.38 (s, 1H), 7.35 - 7. 28 (m, 1H), 7.02 - 6.96 (m, 1H), 6.89 (dd, J = 8.5 Hz, J = 0.9 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 164.2, 157.6, 130.8, 130.6, 125.0, 122.0, 120.3, 119.6, 110.4, 55.6, 52.8.

All spectral data correspond to those given in the literature.[123a]
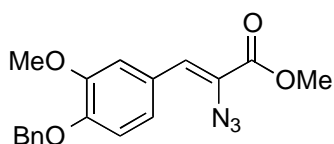
(Z)-methyl 2-azido-3-(3,4-dimethoxyphenyl)acrylate (71j)

Following the general procedure, purification with CH$_2$Cl$_2$/pentane 1:1 to yield the title compound as a yellow pale solid (36%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.49 (d, J = 2.0 Hz, 1H), 7.34 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H), 6.87 - 6.83 (m, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.88 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 164.2, 150.2, 148.6, 126.2, 125.9 125.0, 123.2, 112.9, 110.7, 55.90, 55.88, 52.8.

All spectral data correspond to those given in the literature.[123a]

### (Z)-methyl 2-azido-3-[4-(benzyloxy)-3-methoxyphenyl]acrylate (71k)

Following the general procedure, purification with Et$_2$O/pentane 1:3 to yield the title compound as a yellow solid (31%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 7.45 - 7.43 (m, 1H), 7.38 - 7.18 (m, 6H), 7.82 - 7.78 (m, 2H), 5.12 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 164.2, 149.4, 149.1, 136.6, 128.6, 128.0, 127.2, 126.5, 125.8, 124.7, 123.3, 113.5, 113.1, 70.8, 56.0, 52.8.

HRMS (ESI): *m/z* calculated for C$_{18}$H$_{17}$O$_4$N$_3$Na 362.1111, found 362.1117.

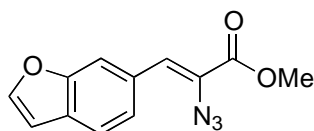### (Z)-methyl 2-azido-3-(benzo[d][1,3]dioxol-5-yl)acrylate (71l)
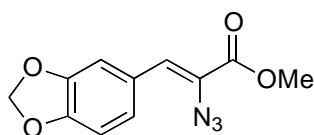
Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a orange pale solid (36%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.54 (d, *J* = 1.7 Hz , 1H), 7.15 (dd, *J* = 8.2 Hz, *J* = 1.7 Hz, 1H), 6.82 - 6.77 (m, 2H), 5.98 (s, 2H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 164.1, 148.6, 147.7, 127.5, 126.5, 125.6, 123.4, 109.8, 108.3, 101.5, 52.8.

HRMS (ESI): *m/z* calculated for $C_{11}H_9O_4N_3$ 274.0588, found 247.0588.

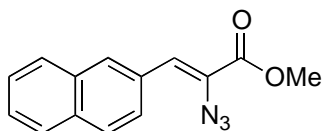### (Z)-methyl 2-azido-3-(benzofuran-6-yl)acrylate (71m)

Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a white solid (38%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.15 (d, *J* = 1.6 Hz, 1H), 7.68 (dd, *J* = 1.6 Hz, *J* = 8.7 Hz, 1H), 7.62 (d, *J* = 2.2 Hz, 1H), 7.47 (d, *J* = 8.7 Hz, 1H), 7.00 (s, 1H), 6.77 (d, *J* = 2.2 Hz, 1H), 3.89 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 164.1, 155.2, 145.9, 128.2, 127.7, 127.5, 126.2, 124.0, 123.8, 111.4, 106.9, 52.8.

HRMS (ESI): *m/z* calculated for $C_{12}H_9O_3N_3$ 243.0638, found 243.0639.

(Z)-methyl 2-azido-3-(naphthalen-2-yl)acrylate (71n)

Following the general procedure; purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a yellow pale solid (41%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.26 (s, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.88 - 7.78 (m, 3H), 7.52 - 7.46 (m, 2H), 7.05 (s, 1H), 3.92 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 164.0, 133.5, 133.1, 131.0, 130.7, 128.7, 128.0, 127.6, 127.3, 127.2, 126.4, 125.6, 125.4, 52.9.

All spectral data correspond to those given in the literature.[123a]

General Procedure for the Transesterification

In an oven-dried three neck-flask charged with argon, the alcohol (1 equiv) was dissolved in THF (40 mL). Then *n*BuLi (1 equiv, 1.6 N in THF) was added slowly at 0 °C. After 20 min, the ester (1 equiv) dissolved in THF (2 mL) was added slowly while stirring vigorously. After the addition of the ester, the reaction mixture was allowed to warm to room temperature, and stirring was continued for 2 h. Then, water (20 mL) was added. The mixture was extracted with CH$_2$Cl$_2$ (3 x 20 mL), washed several times with water and concentrated on vaccuo. The product was purified by silica gel colunm chromatography to yield the corresponding ester. The identity and purity of the product was confirmed by ^{1}H and ^{13}C NMR.

(Z)-[(1R,2S,5R)-2-isopropyl-5-methylcyclohexyl]2-azido-3-(naphthalen-2-yl)acrylate (71o)
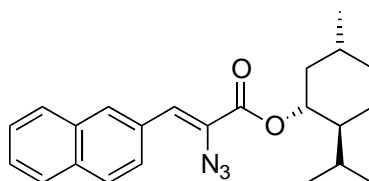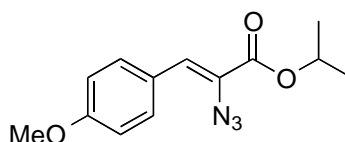

Following the general procedure; purification with CH$_2$Cl$_2$/pentane 1:1 to yield the title compound as a yellow oil (66%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.28 (s, 1H), 7.97 (dd, *J* = 8.7 Hz, *J* = 1.7 Hz, 1H), 7.89 - 7.79 (m, 3H), 7.46 - 7.53 (m, 2H), 7.06 (s, 1H), 4.95 (td, *J* = 10.9 Hz, *J* = 4.4 Hz, 1H), 2.20 - 2.12 (m, 1H), 2.03 - 1.95 (m, 1H), 1.79 - 1.70 (m, 2H), 1.63 – 1.50 (m, 2H), 1.21 - 1.07 (m, 2H), 1.00 - 0.92 (m, 6H), 0.85 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 163.2, 133.5, 133.1, 131.0, 128.7, 128.0, 127.6, 127.4, 127.1, 126.4, 126.0, 125.1, 76.8, 47.1, 40.8, 34.2, 31.5, 26.5, 23.6, 22.0, 20.8, 16.5.

HRMS (ESI): *m/z* calculated for C$_{23}$H$_{27}$O$_2$N$_3$ 377.2098, found 377.2102.

(Z)-isopropyl 2-azido-3-(4-methoxyphenyl)acrylate (71p)

Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a yellow oil (44%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.78 (d, J = 8.9 Hz, 2H), 6.89 (d, J = 8.9 Hz, 2H), 6.84 (s, 1H), 5.18 (hept, J = 6.2 Hz, 1H), 3.81 (s, 3H), 1.35 (d, J = 6.2 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 163.3, 160.4, 132.3, 126.1, 125.1, 123.6, 113.9, 70.0, 55.3, 21.8.

HRMS (ESI): m/z calculated for $C_{13}H_{15}O_3N_3$ 261.1108, found 261.1113.

General Procedures for Metal-Catalyzed Cyclization of the Aryl Azidoacrylates

A sealable tube equipped with a magnetic stir bar was charged with the aryl azidoacrylates (100 mg, 1.0 equiv) and Fe(OTf)$_2$ (10 mol %; abcr; 98%). The aperture of the tube was then covered with a rubber septum and an argon atmosphere was established. THF (1 mL) was added by using a syringe. The septum was then replaced by a teflon-coated screw cap, and the reaction vessel was placed in an oil bath (80 °C). After stirring at this temperature for 24 h, the mixture was cooled to room temperature and diluted with dichloromethane. The resulting solution was directly filtered through a pad of celite, washed with water, extracted with dichloromethane and concentrated to yield the product, which was purified by silica gel chromatography to yield the corresponding indole as a white solid. The identity and purity of the product was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis.

methyl 1H-indole-2-carboxylate (72a)
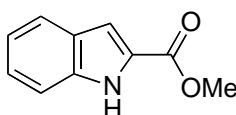
Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a white solid (75%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.29 (br s, 1H), 7.71 (dd, J = 8.1 Hz, J = 1.9 Hz, 1H), 7.47 - 7.43 (m, 1H), 7.38 - 7.31 (m, 1H), 7,26 - 7.24 (m, 1H), 7.20 - 7.14 (m, 1H), 3.98 (s, 3H).
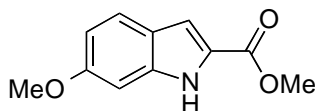
^{13}C NMR (100 MHz, CDCl$_3$): δ = 162.7, 137.0, 127.5, 127.1, 125.4, 122.6, 120.8, 112.0, 108.8, 52.0.

M. p. = 152.5-153.0 °C; lit. m. p. = 150-151 °C.

All spectral data correspond to those given in the literature.[155,156]

---

[155] M. Sechi, M.Derudas, R. Dallocchio, A. Dessi, A. Bacchi, L. Sannia, F. Carta, M. Palomba, O. Ragab, C. Chan, R. Shoemaker, S. Sei, R. Dayam, N. Neamati, *J. Med. Chem.* **2004**, *47*, 5298.

methyl 6-methoxy-1H-indole-2-carboxylate (72b)

Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a white solid (74%).
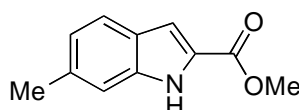
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.91 (br s, 1H), 7.55 - 7.41 (m, 1H), 7.14 - 7.15 (m, 1H), 6.82 - 6.79 (m, 2H), 3.92 (s, 3H), 3.84 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 162.4, 158.9, 138.0, 126.0, 123.4, 121.8, 112.3, 109.2, 93.7, 55.5, 51.8.

M. p. = 118.5-119.0 °C; lit. m. p. = 117-118 °C.

All spectral data correspond to those given in the literature.[123a,156]

methyl 6-methyl-1H-indole-2-carboxylate (72c)

Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a white solid (77%).
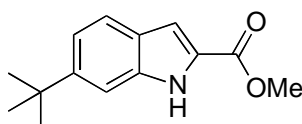
^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.81 (br s, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.19 - 7.15 (m, 2H), 7.00 - 6.95 (m, 1H), 3.92 (s, 3H), 2.46 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 162.5, 137.3, 135.7, 126.5, 125.3, 122.9, 122.1, 111.5, 108.8, 51.9, 21.9.

M. p. = 128.2-128.7 °C; lit. 128-129 °C.

All spectral data correspond to those given in the literature.[123a,157]

methyl 6-*tert*-butyl-1H-indole-2-carboxylate (72d)

Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a white solid (83%).

[156] K. Yamazaki, Y. Nakamura, Y. Kondo, *J. Org. Chem.* **2003**, *68*, 6011.
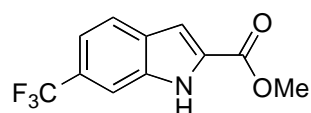[157] K. Dirk, *Synthesis* **1985**, 186.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.05 (br s, 1H), 7.61 (d, J = 8.6 Hz, 1H), 7.41 (s, 1H), 7.26 - 7.23 (m, 1H), 7.18 - 7.16 (m, 1H), 3.94 (s, 3H), 1.38 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 162.6, 149.1, 137.3, 126.8, 125.2, 122.0, 119.6, 108.6, 107.8, 51.9, 35.0, 31.5.

M. p. = 156.2-157.0 °C.

All spectral data correspond to those given in the literature.[123a]

methyl 6-(trifluoromethyl)-1H-indole-2-carboxylate (72e)

Following the general procedure, purification with CH$_2$Cl$_2$/pentane 1:1 to yield the title compound as a white solid (60%).

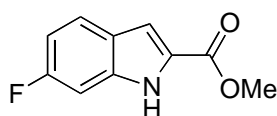**^{19}F NMR (282 MHz, CDCl$_3$)** δ = −62.0.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.32 (br s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.72 (s, 1H), 7.37 (dd, J = 8.5 Hz, J = 1.3 Hz, 1H), 7.25 - 7.24 (m, 1H), 3.97 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 162.1, 135.5, 129.3 (q, J = 32.1 Hz), 127.4, 127.2, 124.7 (q, J = 271.9 Hz), 123.3, 117.3 (q, J = 3.24 Hz), 109.6 (q, J = 4.6 Hz), 108.5, 52.4.

M. p. = 169.8–170.8 °C.

All spectral data correspond to those given in the literature.[123a]

methyl 6-fluoro-1H-indole-2-carboxylate (72f)

Following the general procedure, purification with CH$_2$Cl$_2$/pentane 1:1 to yield the title compound as a white solid (72%).

^{1}H NMR (300 MHz, CDCl$_3$): δ = 9.18 (br s, 1H), 7.60 (dd, J = 8.8 Hz, J = 5.3 Hz, 1H), 7.19 (dd, J = 2.1 Hz, J = 1.0 Hz, 1H), 7.10 - 7.05 (m, 1H), 6.95 - 6.87 (m, 1H), 3.94 (s, 3H).
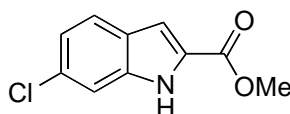
^{13}C NMR (75 MHz, CDCl$_3$): δ = 162.3, 161.8 (d, J = 240.9 Hz), 137.0 (d, J = 12.8 Hz), 127.7, 124.1, 123.8 (d, J = 10.4 Hz), 110.5 (d, J = 25.3 Hz), 109.0, 97.8 (d, J = 26.1 Hz), 52.1.

M. p. = 166.5-167.0 °C; lit. m. p. = 156 °C.

HRMS (EI): m/z calculated for C$_{10}$H$_8$O$_2$NF 193.0534, found 193.0534.

All spectral data correspond to those given in the literature.[158]

methyl 6-chloro-1H-indole-2-carboxylate (72g)

Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield to yield the title compound as a white solid (56%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.00 (br s, 1H), 7.58 (d, J = 8.6 Hz, 1H), 7.41 (m, 1H), 7.17 (m, 1H), 7.13 (dd, J = 8.6 Hz, J = 1.8 Hz, 1H), 3.93 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 162.1, 137.0, 131.4, 127.8, 126.0, 123.5, 121.9, 111.7, 108.8, 52.1.

M. p. = 176.8-178.5 °C; lit. m. p. = 180-181 °C.

All spectral data correspond to those given in the literature.[123a,157]

methyl 6-phenyl-1H-indole-2-carboxylate (72h)

Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a white solid (80%).
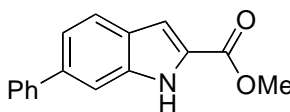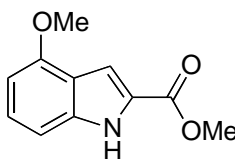
^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.02 (s br, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.59 - 7.51 (m, 3H), 7.40 - 7.21 (m, 3H), 7.30 - 7.25 (m, 1H), 7.18 - 7.15 (m, 1H), 3.88 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 162.4, 141.6, 138.9, 137.4, 128.8, 127.6, 127.4, 127.2, 126.8, 122.8, 121.0, 110.1, 108.7, 52.1.

M. p. = 153.0-154.0 °C.

HRMS (EI): *m/z* calculated for $C_{16}H_{12}O_2N$ 250.0863, found: 250.0866.

methyl 4-methoxy-1H-indole-2-carboxylate (72i)

---

[158] J. B. Blair, D. Kurrasch-Orgaugh, D. Marona-Lewicka, M. G. Cumbay, V. J. Watts, E. L. Barker, D. E Nichols, *J. Med. Chem.* **2000**, *43*, 4701.

Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a white solid (49%).
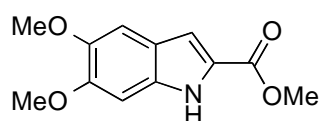
¹H NMR (400 MHz, CDCl₃): δ = 9.14 (br s, 1H), 7.34 (d, J = 2.2 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.49 (d, J = 7.8 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 162.5, 154.6, 138.3, 126.4, 125.8, 119.0, 106.5, 104.8, 99.7, 55.3, 51.9.

M. p. = 142.3-142.8 °C; lit. m. p. = 147-148 °C.

All spectral data correspond to those given in the literature.[123a]

methyl 5,6-dimethoxy-1H-indole-2-carboxylate (72j)

Following the general procedure; purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a white solid (88%).
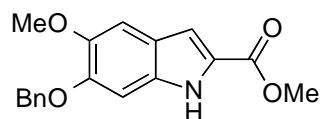
¹H NMR (400 MHz, CDCl₃): δ = 8.92 (br s, 1H), 7.10 - 7.08 (m, 1H), 7.02 (s, 1H), 6.83 (s, 1H), 3.90 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ = 162.3, 150.1, 146.2, 132.1, 125.5, 120.4, 108.8, 102.5, 93.8, 56.1, 55.9, 51.7.

M. p. = 169.3-170.0 °C; lit. m. p. = 164-166 °C.

All spectral data correspond to those given in the literature.[123a,159]

methyl 6-(benzoyloxy)-5-methoxy-1H-indole-2-carboxylate (72k)

Following the general procedure; purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a white solid (99%).

¹H NMR (400 MHz, CDCl₃): δ = 8.77 (br s, 1H), 7.36 (d, J = 7.1 Hz, 2H), 7.31 - 7.25 (m, 2H), 7.24 - 7.19 (m, 1H), 7.03 - 7.01 (m, 1H), 6.99 (s, 1H), 6.75 (s, 1H), 5.11 (s, 2H), 3.84 (s, 3H), 3.81 (s, 3H).
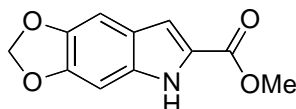
¹³C NMR (100 MHz, CDCl₃): δ = 162.5, 149.1, 146.7, 136.8, 132.0, 128.6, 127.9, 127.1, 125.8, 120.9, 108.7, 103.1, 96.4, 71.1, 56.3, 51.7.

---

[159] R. F. Chapman, G. A. Swan, *J. Chem. Soc.* **1970**, 865.

M. p. = 155.3-156.1 °C.

HRMS (EI): *m/z* calculated for $C_{18}H_{17}O_4NNa$ 334.1050, found 334.1049.

methyl 5H-[1,3]dioxolo[4,5-*f*]indole-6-carboxylate (72l)

Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a white solid (97%).

¹H NMR (400 MHz, CDCl₃): δ = 8.84 (br s, 1H), 7.02 (m, 1H), 6.92 (s, 1H), 6.75 (s, 1H), 5.94 (s, 2H), 3.84 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 162.2, 148.0, 144.2, 132.8, 125.8, 121.6, 109.1, 101.0, 99.8, 91.8, 51.8.

M. p. = 195.8-196.6 °C; lit. m. p. = 194-195 °C.

All spectral data correspond to those given in the literature.[155]

methyl 5H-furo[2,3-*f*]indole-6-carboxylate (72m)

Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a white solid (99%).
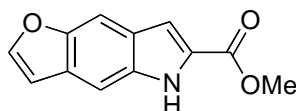
¹H NMR (400 MHz, CDCl₃): δ = 9.5 (br s, 1H), 7.67 (d, *J* = 2.1 Hz, 1H), 7.55 (d, *J* = 8.9 Hz, 1H), 7.37 (d, *J* = 8.9 Hz, 1H), 7.33 (d, *J* = 2.1 Hz, 1H), 7.02 - 7.00 (m, 1H), 3.97 (s, 3H).

¹³C NMR (100 MHz, CDCl₃): δ = 162.6, 154.5, 143.8, 130.4, 125.6, 123.0, 118.8, 112.2, 110.3, 107.1, 103.7, 52.0.

M. p. = 178.5-179.0 °C.

HRMS (EI): *m/z* calculated for $C_{12}H_8O_3N$ 214.0499, found 214.0504.

methyl 1H-benzo[*g*]indole-2-carboxylate (72n)

Following the general procedure, purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a white solid (98%).
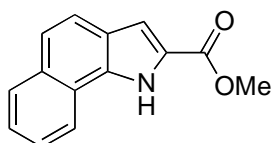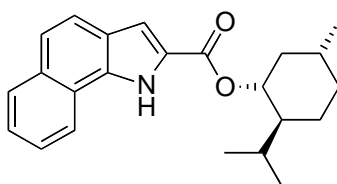
^{1}H NMR (300 MHz, CDCl$_3$): δ = 9.94 (br s, 1H), 8.21 - 8.17 (m, 1H), 7.92 – 7.88 (m, 1H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.59 - 7.47 (m, 3H), 7.32 (d, *J* = 2.1 Hz, 1H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 162.5, 132.9, 132.0, 128.9, 126.0, 125.6, 125.5, 123.8, 122.1, 121.8, 121.3, 120.5, 110.3, 52.1.

M. p. = 211.0-211.5 °C; lit. m. p. = 168-170 °C.

All spectral data correspond to those given in the literature.[123a,160]

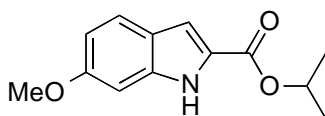**(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 1H-benzo[*g*]indole-2-carboxylate (72o)**

Following the general procedure; purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a tranparent oil (93%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 10.20 (br s, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.93 - 7.89 (m, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.58 - 7.48 (m, 3H), 7.35 (d, *J* = 2.1 Hz, 1H), 7.35 (td, *J* = 4.5 Hz, *J* = 10.9 Hz, 1H), 2.20 - 2.12 (m, 1H), 2.03 - 1.95 (m, 1H), 1.79 - 1.70 (m, 2H), 1.63 - 1.45 (m, 2H), 1.21 - 1.10 (m, 2H), 1.00 - 0.84 (m, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 162.0, 132.9, 132.0, 128.8, 126.2, 125.9, 125.5, 123.8, 122.0, 121.9, 121.2, 120.7, 110.0, 75.1, 47.3, 41.1, 34.3, 31.4, 26.6, 23.8, 22.0, 20.7, 16.7.

HRMS (EI): *m/z* calculated for $C_{23}H_{26}O_2N$ 348.1958, found 348.1967.

isopropyl 6-methoxy-1H-indole-2-carboxylate (72p)

Following the general procedure; purification with CH_2Cl_2/pentane 1:1 to yield the title compound as a white solid (35%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.90 (br s, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.14 (d, *J* = 2.1 Hz, 1H), 7.83 - 7.78 (m, 2H), 5.26 (hept, *J* = 6.2 Hz, 1H), 3.86 (s, 3H), 1.37 (d, *J* = 6.2 Hz, 6H).

[160] S. Itoh, Y. Fukui, M. Ogino, S. Haranou, M. Kamatsu, Y. Ohshiro, *J. Org. Chem.* **1992**, *57*, 2788.

^{13}C NMR (100 MHz, CDCl$_3$): δ = 161.6, 158.8, 137.8, 126.8, 123.3, 121.9, 112.2, 108.8, 93.7, 68.3, 55.4, 22.0.

M. p. = 154.0-155.0 °C.

HRMS (EI): *m/z* calculated for C$_{13}$H$_{15}$O$_3$N 233.1047, found 233.1044.

Appendix

List of Abbreviations

Ac	acetyl
aq.	aqueous (solution)
Ar	aromatic substituent
Bn	benzyl
br	broad (NMR signal)
Bu	butyl
*t*Bu	*tert*-butyl
Cy	cyclohexyl
δ	chemical shift
dba	dibenzylideneacetone
DCM	dichloromethane
DMF	*N,N*-dimethylformamide
DMEDA	*N,N′*-dimethylethylene diamine
DMSO	dimethylsulfoxide
ee	enantiomeric excess
EI	electronic impact (in mass spectroscopy)
equiv	equivalent
Et	ethyl
eV	electronvolt
HRMS	high resolution mass spectroscopy
ICP-MS	inductively coupled plasma mass spectrometry
J	coupling constant (in NMR spectroscopy)
L	ligand
M	molar
Me	methyl
Mes	2,4,6-trimethylphenyl (mesityl)
mol	mole
M. p.	melting point
MPa	mega pascal

MS	mass spectroscopy
MTBE	methyl-*tert*-butylether
N	normal (concentration)
Naphth	naphthyl
NMR	nuclear magnetic resonance (spectroscopy)
PMHS	polymethylhydrosiloxane
ppb	parts per billion
ppm	parts per million
*i*Pr	*iso*-propyl
rt	room temperature
THF	tetrahydrofuran
TIPS	triisopropylsilane
TMHD	2,2,6,6-tetramethyl-3,5- heptanedione
TMS	trimethylsilyl
Ts	tosyl
XANTPHOS	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

2. Curriculum Vitae

Personnal Information

Name: Julien Bonnamour

Date of Birth: 31/01/1983

Place of Birth: Paris

Nationality: French

Education and background

2007-2011   **RWTH Aachen University**, Institute of Organic Chemistry
Prof. Dr. Carsten Bolm
Ph.D. work in Organic Chemistry on *Iron-Catalyzed Reactions and the Role of Metal Contaminants*

2007   6 months **CNRS-BioCIS Molécules Fluorées et Chimie Médicinale** - Université Paris-Sud XI, Faculté de Pharmacie de Châtenay-Malabry
Director: D. Bonnet-Delpon
Synthesis of new trifluoromethyl amino compounds

2006   3 months **CNRS-BioCIS Molécules Fluorées et Chimie Médicinale** - Université Paris-Sud XI, Faculté de Pharmacie de Châtenay-Malabry
Director: D. Bonnet-Delpon
Synthesis of fluorinated triazole compounds by click chemistry

2004   2 months **CNRS-BioCIS Synthèse Organique et Pharmacochimie de Composés d'Intérêt Biologique** - Université Paris-Sud XI, Faculté de Pharmacie de Châtenay-Malabry
Director: C. Cavé
Synthesis of peroxydes with potential antimalarial activity