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Iron Catalysed Cross-Couplings of Azetidines - Application to the Formal Synthesis of a Pharmacologically Active Molecule

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A protocol for the coupling of 3-iodoazetidines with Grignard reagents in the presence of an iron catalyst has been developed. A variety of aryl, heteroaryl, vinyl and alkyl Grignards were shown to participate in the coupling process to give the products in good to excellent yields. Furthermore, a short formal synthesis towards a pharmacologically active molecule was shown.

Small nitrogen-containing heterocycles are highly desirable structural motifs, which when installed within molecules can provide beneficial attributes sought after in both the agrochemical and pharmaceutical industries.[1] Within this family, azetidines are particularly interesting units since they possess a reasonable stability whilst providing strong molecular rigidity.[2] Azetidines can be found both in nature and in numerous practical applications with perhaps the highest-profile azetidine being azelnidipine which is sold as a calcium channel blocker.[3] Closely related to this, azetidines possessing aryl substitution at the 3-position are highly sought after compounds and have been found to display an array of pharmacological activities.[4]

Traditionally, 5- and 6-membered nitrogen-heterocycles have managed to find fame in commercial applications; however 4-membered azetidines have lagged behind their larger family members. We postulated that this may be due to the lack of synthetic methodology devoted to the incorporation and functionalisation of these structural units. The most typical procedure for the coupling of azetidines is through the use of palladium catalysis (Figure 1).[5] Operationally, the azetidine first has to be transformed to the corresponding organo-zinc complex followed by subsequent reaction with a suitable aryl iodide in the presence of a palladium catalyst and a phosphine ligand. Alternatively, nickel catalyzed procedures in the presence of a ligand have featured in reports which utilised either aryl boronic acids or aryl bromides with limited success.[6] Recently, a report by Ley has demonstrated the metal-free coupling between hydrazones and boronic acids.[7] In light of this, and building on our recent report on transition metal catalysis[8] we sought to unlock this constraint, and thus develop a more appealing method. We proposed to harness a cheap iron catalyst in the absence of any additional ligands and to use more readily available and easily prepared Grignard reagents. The last decade has seen rising interest in iron catalysis, which has led to the development of highly useful methodologies.[9] Unlike typical transition-metals, iron lies claim to existing in abundance, being relatively low-cost and possessing low toxicity. In particular, iron-catalyzed cross-coupling, usually with Grignard reagents has attracted an exceptional amount of attention.[10] Although the use of secondary alkyl halides as coupling partners is known,[11] cross-couplings of azetidine units under iron catalysis remains rare.[12]

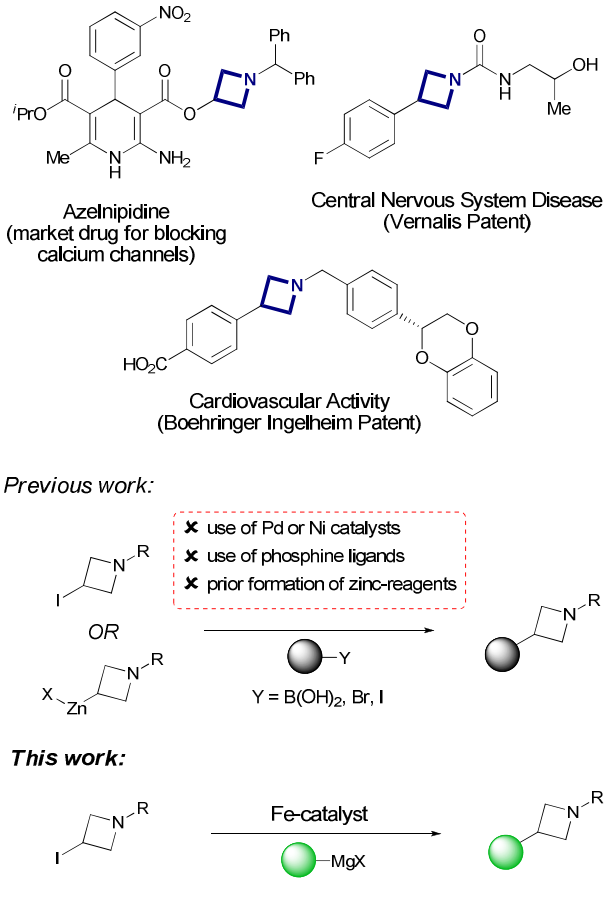
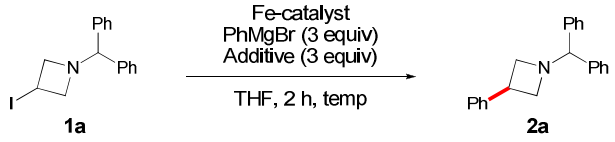


Figure 1 Previous works and this work in context

We began our study, inspired by Nakamura's original work[11a] by looking at the cross-coupling of phenyl magnesium bromide with 3-iodoazetidine **1a** to give the corresponding product **2a**. Initial optimisations of a variety of iron catalysts revealed $FeCl_3$ and $Fe(acac)_3$ to be suitable for the desired transformation with the latter performing slightly better (entries 1 and 2). A temperature screen revealed that the reaction produced marginally better yields at -20 ˚C and at -78 ˚C the reaction was completely switched off (entries 3-5). Our base line conditions always made use of TMEDA as an additive and its role in iron catalysis has been the subject of mechanistic studies.[13] In our hands, the use of alternative additives was briefly explored but no reactivity was observed in these cases (entries 6-8).

Table 1. Selected optimisation of catalyst, temperature and additive[a]



Entry	Catalyst (mol%)	Temp (˚C)	Additive	Yield (%)
1	$FeCl_3$ (5)	0	TMEDA	53
2	$Fe(acac)_3$ (5)	0	TMEDA	64
3	$Fe(acac)_3$ (10)	rt	TMEDA	67
4	$Fe(acac)_3$ (10)	-20	TMEDA	71
5	$Fe(acac)_3$ (10)	-78	TMEDA	-
6	$Fe(acac)_3$ (10)	-20	DABCO	-
7	$Fe(acac)_3$ (10)	-20	NMP	-
8	$Fe(acac)_3$ (10)	-20	Et_3N	-

[a]Yield of isolated product.

Figure 2 depicts the scope we explored with regards to azetidines coupling with Grignard reagents under the optimised conditions. In general, the coupling functions efficiently with a variety of Grignard reagents to yield the corresponding 3-substituted azetidines **2** in good yields. For unsubstituted phenyl and napthyl Grignard reagents, the reaction proceeded efficiently and performed almost identically with a variety of protecting groups on the nitrogen (**2a-c** and **2g-h**). This was also shown to be the case for 4-methyl substituted Grignard (**2d-f**). The reaction could also be scaled up in the case of **2a** to a 1 mmol procedure with no detrimental effects to the yield. On a practical note, we found that visualisation of the products containing the benzhydryl protecting group on thin layer chromatography (tlc) plates was much easier. For that sole reason, it was chosen to proceed with further examples using this group. Substitution at the 4-position of the aromatic was tolerated in good to modest yields (**2i-j**) whilst substitution at the 3-position was also equally accepted (**2k-l**). A bulky *i*Pr group at the 2-position (**2l**) was surprisingly well tolerated, delivering the product in excellent yields. The scope of the coupling reaction was next expanded to include alkyl, vinyl and various alternative aromatic Grignards. Pleasingly, we found that commercially available methyl magnesium bromide functioned as expected to give the corresponding product **2n** in 62% yield. Focusing on sp^2-hybridised partners, we were delighted to find both vinyl and di-methyl vinyl groups to undergo coupling (**2o-p**). Following this, we decided to explore the score of heterocyclic-Grignard reagents and found both 1,3-benzodioxole and Boc-protected indole to be suitable coupling components to yield the corresponding products (**2q** and **2s**) in good yields. To our delight, a

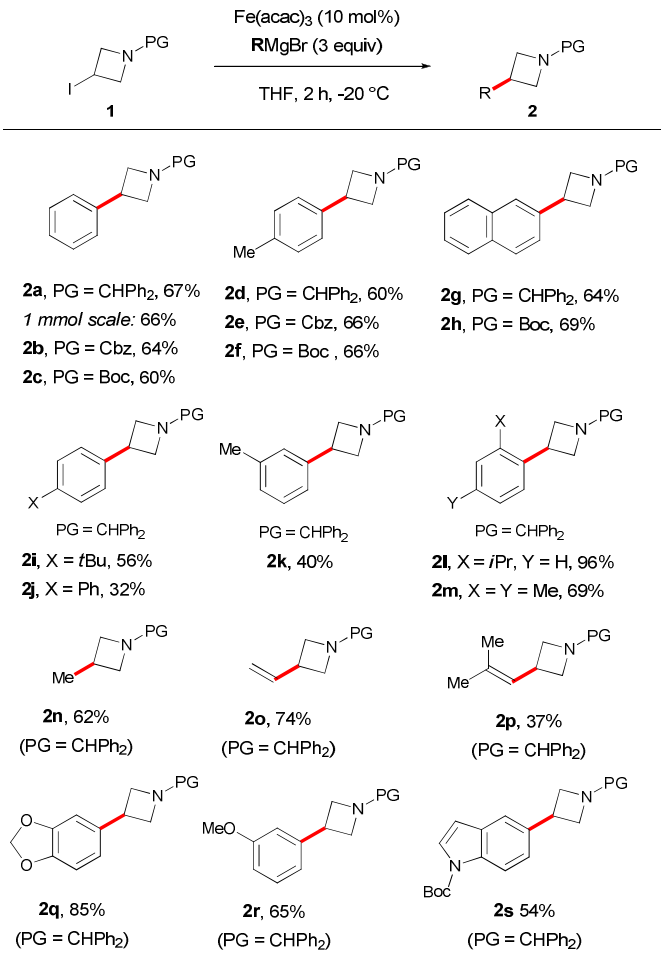


Figure 2. Azetidine cross-couplings with Grignard reagents.

pyridine-derived Grignard also delivered the desired product (**2s**) albeit in a lower yield. We propose that the most likely mechanism of this reaction follows the classically established pathway of an Fe(I)/Fe(III) couple, whereby an Fe(I) species is initially generated by reduction by the Grignard reagent followed by straight-forward oxidative addition, transmetallation and finally reductive elimination steps to complete the cycle.[14] It should however be appreciated that the mechanism described may well be simplified, and the exact nature of the iron species is unknown and could be dependent on the nature of Grignard reagent used.[15]

To demonstrate the potential and benefit of this methodology, we sought to utilize our conditions for the preparation of a pharmacologically active molecule. We choose compound **6** as a suitable challenge, which was recently filed under a patent by Vernalis Research Limited for possessing activity against central nervous system (CNS) disorders.[4b] Their synthesis of this compound (and other structurally related molecules) commences with commercially available ketone azetidin-3-one **3** (Figure 4). Treatment with (4-fluorophenyl)magnesium bromide **4** yields the corresponding addition product, which can be reacted with mesyl chloride to yield the mesylated alcohol. Finally, raney nickel is used to de-oxygenate the substrate and yield **5** in an overall combined yield of 41%. It should be noted that completing these three steps requires two days and two chromatography steps. Our improved route starts from the commercially available iodide **1a**, however the

corresponding alcohol, which is cheaper, can also be used and transformed into the iodide in one step. Using our developed conditions directly on **1a** yields the intermediate **5** in 61%; which can be transformed into the desired compound **6** by a simple protecting group swap.

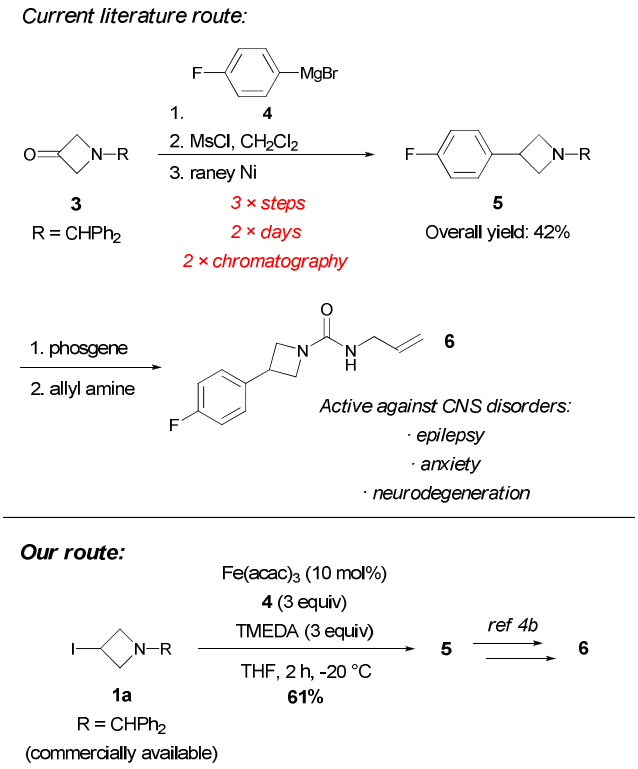


Figure 4. Optimised synthetic route to a pharmacologically active molecule

In conclusion, we have developed a mild and efficient procedure for the coupling of azetidines at the 3-position with a number of different Grignard reagents. The Grignard scope includes aryl, vinyl, alkyl and heterocyclic variants which can either be freshly-prepared or used directly from commercial sources. Furthermore, we have utilised our conditions to improve the formal synthesis of an active compound against CNS-disorders. Given the large array of azetidine compounds accommodated in the patent literature, we envision this protocol to be highly amenable towards synthesising libraries of substrates within the pharmaceutical industry.

Notes and references

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(1) (a) J. Slade, J. Bajwa, H. Liu, D. Parker, J. Vivelo, G.-P. Chen, J. Calienni, E. Villhauer, K. Prasad, O. Repic and T. J. Blacklock, *Org. Process Res. Dev.* **2007**, *11*, 825; (b) G. B. Evans, R. H. Furneaux, B. Greatrex, A. S. Murkin, V. L. Schramm and P. C. Tyler, *J. Med. Chem.* **2008**, *51*, 948; (c) A. R. Pinder, *Nat. Prod. Rep.* **1992**, *9*, 491.

(2) (a) N. H. Cromwell and B. Phillips, *Chem. Rev.* **1979**, *79*, 331; (b) A. Brandi, S. Cicchi and F. M. Cordero, *Chem. Rev* **2008**, *108*, 3988; (c) F. Couty and G. Evano, *Synlett* **2009**, 3053.

(3) Y. Yagil, M. Miyamoto, L. Frasier, K. Oizumi and H. Koike, *Am. J. Hypertens.* **1994**, *7*, 637.

(4) (a) A Reaxys search performed in November 2014 for azetidines with this general structural motif which had reported pharmacological activity resulted in 1000+ hits, mostly from patent literature; (b) D. R. Adams, J. Bentley, C. D. Bodkin, I. A. Cliffe, J. E. P. Davidson, H. L. Mansell, N. J. Monck, R. G. Shepherd, J. M., Shepherd, U.S. Patent 6831078, 2004; (c) S. R. Brunette, A. Abeywardane, M. J. Burke, S. R. Kapadia, T. M. Jr. Kirrane, M. R. Netherton, H. Razavi, S. Rodriguez, A. Saha, R. Sibley, K. Smith Keenan, L. Lana, H. Takahashi, M. R. Turner, J.-P. Wu, E. R. R. Young, Q. Zhang, Q. Zhang, R. M. Zindell, WO2013/134226 A1, 2013,

(5) S. Billotte, *Synlett* **1998**, 379.

(6) (a) M. A. J. Duncton, M. A. Estiarte, D. Tan, C. Kaub, D. J. R. O'Mahony, R. J. Johnson, M. Cox, W. T. Edwards, M. Wan, J. Kincaid and M. G. Kelly, *Org. Lett.* **2008**, *10*, 3259; (b) G. A. Molander, K. M. Traister and B. T. O'Neill, *J. Org. Chem.* **2014**, *79*, 5771; (c) G. A. Molander, K. M. Traister and B. T. O'Neill, *J. Org. Chem.* **2014**, *79*, 5771.

(7) D. M. Allwood, D. C. Blakemore, A. D. Brown and S. V. Ley, *J. Org. Chem.* **2013**, *79*, 328.

(8) (a) M. Leiendecker, C.-C. Hsiao, L. Guo, N. Alandini and M. Rueping, *Angew. Chem., Int. Ed.* **2014**, *53*, 12912.(b) M. Rueping, W. Ieawsuwan, *Synlett* **2007,** 247-250

(9) (a) C. Bolm, J. Legros, J. Le Paih and L. Zani, *Chem. Rev* **2004**, *104*, 6217; (b) A. Fuerstner and R. Martin, *Chem. Lett.* **2005**, *34*, 624; (c) E. B. Bauer, *Curr. Org. Chem.* **2008**, *12*, 1341; (d) A. Correa, O. Garcia Mancheno and C. Bolm, *Chem. Soc. Rev.* **2008**, *37*, 1108; (e) B. D. Sherry and A. Fuerstner, *Acc. Chem. Res.* **2008**, *41*, 1500; (f) W. M. Czaplik, M. Mayer, J. Cvengroš and A. J. von Wangelin, *ChemSusChem* **2009**, *2*, 396; (g) C.-L. Sun, B.-J. Li and Z.-J. Shi, *Chem. Rev* **2011**, *111*, 1293; (h) F. Jia and Z. Li, *Org. Chem. Front.* **2014**, *1*, 194.

(10) (a) A. Fuerstner, A. Leitner, M. Mendez and H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856; (b) T. Hatakeyama and M. Nakamura, *J. Am. Chem. Soc.* **2007**, *129*, 9844; (c) G. Cahiez and H. Avedissian, *Synthesis* **1998**, 1199.

(11) (a) M. Nakamura, K. Matsuo, S. Ito and E. Nakamura, *J. Am. Chem. Soc.* **2004**, *126*, 3686; (b) M. Nakamura, S. Ito, K. Matsuo and E. Nakamura, *Synlett* **2005**, 1794; (c) R. B. Bedford, D. W. Bruce, R. M. Frost, J. W. Goodby and M. Hird, *Chem. Commun.* **2004**, 2822; (d) R. B. Bedford, D. W. Bruce, R. M. Frost and M. Hird, *Chem. Commun.* **2005**, 4161; (e) R. B. Bedford, M. Betham, D. W. Bruce, A. A. Danopoulos, R. M. Frost and M. Hird, *J. Org. Chem.* **2006**, *71*, 1104; (f) G. Cahiez, V. Habiak, C. Duplais and A. Moyeux, *Angew. Chem., Int. Ed.* **2007**, *46*, 4364; (g) A. Rudolph and M. Lautens, *Angew. Chem., Int. Ed.* **2009**, *48*, 2656.

(12) (a) C. W. Cheung, P. Ren and X. Hu, *Org. Lett.* **2014**, *16*, 2566; (b) B. Barré, L. Gonnard, R. Campagne, S. Reymond, J. Marin, P. Ciapetti, M. Brellier, A. Guérinot and J. Cossy, *Org. Lett.* **2014**, *16*, 6160.

(13) (a) D. Noda, Y. Sunada, T. Hatakeyama, M. Nakamura and H. Nagashima, *J. Am. Chem. Soc.* **2009**, *131*, 6078; (b) R. B. Bedford, P. B. Brenner, E. Carter, P. M. Cogswell, M. F. Haddow, J. N. Harvey, D. M. Murphy, J. Nunn and C. H. Woodall, *Angew. Chem., Int. Ed.* **2014**, *53*, 1804.

(14) (a) R. S. Smith and J. K. Kochi, *J. Org. Chem.* **1976**, *41*, 502; (b) J. Kleimark, A. Hedstroem, P.-F. Larsson, C. Johansson and P.-O. Norrby, *ChemCatChem* **2009**, *1*, 152; (c) Q. Ren, S. Guan, F. Jiang and J. Fang, *J. Phys. Chem. A* **2013**, *117*, 756; (d) A. Hedstroem, E. Lindstedt and P.-O. Norrby, *J. Organomet. Chem.* **2013**, *748*, 51; (e) R. Schoch, W. Desens, T. Werner and M. Bauer, *Chem. Eur. J.* **2013**, *19*, 15816; (f) G. Lefevre and A. Jutand, *Chem. Eur. J.* **2014**, *20*, 4796.

(15) A. Fürstner, R. Martin, H. Krause, G. Seidel, R. Goddard and C. W. Lehmann, *J. Am. Chem. Soc.* **2008**, *130*, 8773.