C–H Functionalization

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Direct Azole Amination: C–H Functionalization as a New Approach to Biologically Important Heterocycles**

Alan Armstrong and James C. Collins*

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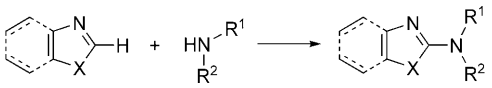
Five-membered heterocycles with amine substituents are employed widely in medicinal chemistry; for example, 2-aminothiazole derivatives are currently used as dopamine antagonists for Parkinson's disease (pramipexole), third-generation antibiotics (cefdinir), and anti-inflammatories (meloxicam). These motifs have classically been prepared by cyclocondensation reactions, forming the heterocyclic ring in the key step from two functionalized precursors (e.g. Hantszch aminothiazole synthesis). A much more direct and divergent synthetic approach to aminoheterocycles is by the selective formation of the heteroaryl–nitrogen bond. The development of the palladium-catalyzed Buchwald–Hartwig coupling[1] and mild variants of the analogous copper-catalyzed Ullmann and Goldberg couplings[2] have provided a robust and efficient approach for the amination of aryl and heteroaryl halides and sulfonates. The rapid and widespread adoption of these methods is evidenced by their advantages in both synthetic efficiency and simple access to novel chemical architectures. To further improve the efficiency of coupling-based approaches, a huge surge in interest has recently been directed towards C–H functionalization of at least one coupling partner, thus obviating the preparation of a preactivated substrate. Whereas direct intermolecular arylation of both aryl[3a] and heteroaryl[3b] functionality is now a well-developed area, the problems facing the analogous carbon–heteroatom bond-forming reactions such as hydroxylation,[3c] acetoxylation,[3d] and amination have only recently begun to be solved. Recent advances in C–H amination, from intramolecular to directed to intermolecular, have been the subject of recent reviews[4] and will not be covered here. Instead, this Highlight will focus on direct oxidative C–H amination as a highly efficient approach to amino-substituted azoles (Scheme 1) as well as overcoming challenges of reactivity and regioselectivity, as recent publications have demonstrated a variety of successful approaches to this problem.

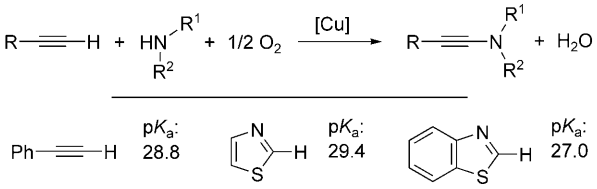
The pioneering development of a simple copper-catalyzed C–H amination was reported by Yu and co-workers,[5] using



Scheme 1. Direct oxidative amination of five-membered azoles.

$Cu(OAc)_2/O_2$ to effect the pyridine-directed functionalization of a C_{aryl}–H bond with a variety of anionic nucleophiles, including halogens, cyanide, alcohols, and sulfonamides. However, selective amination at C2 of azoles does not rely on the presence of a directing group, but instead relies on the discovery of C–H activation conditions that react preferentially at the electron-poor C2-position (as with the copper-catalyzed arylation developed by Daugulis et al.[6]).

Building upon the known Glaser–Hay oxidative dimerization of alkynes[7a] and the Chan–Lam oxidative coupling of arylboronic acids with amines,[7b] Stahl and co-workers have recently developed a copper-catalyzed direct oxidative amidation of alkynes[7c] (Scheme 2). The similarity in pK_a value



Scheme 2. Stahl's alkyne amidation as mechanistic precedent for copper-catalyzed direct oxidative amination of azoles.

between terminal alkyne protons ($pK_a = 29$[8a]) and the acidic C2-position of five-membered azoles ($pK_a = 25$–29[8b]) suggested that regioselective direct azole amination might also be possible. Further support for this idea is given by the recent development of the analogous direct thiolation of benzoxazole under CuI catalysis.[9]

In the first report of direct azole amination, Mori and co-workers detailed the use of $Cu(OAc)_2$ as the preferred catalyst for the direct amination of benzothiazole (**1**) with *N*-methylaniline (**2**) under relatively mild reaction conditions, similar to those of Yu and co-workers (Scheme 3).[10] This reaction is tolerant of a range of relatively weak bases and copper ligands, with the best results being obtained using NaOAc and PPh_3 in xylene. An oxygen atmosphere allowed

[*] Prof. A. Armstrong, J. C. Collins
Department of Chemistry
Imperial College London
South Kensington, London SW7 2AZ (UK)
Fax: (+44) 20-7594-5804
E-mail: a.armstrong@imperial.ac.uk

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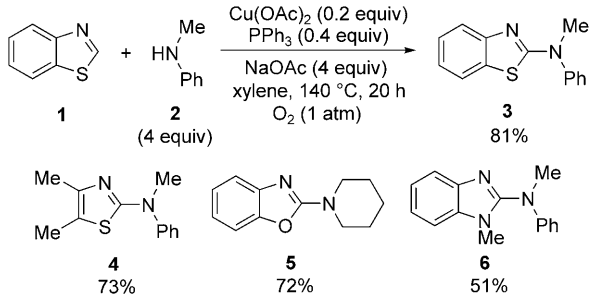
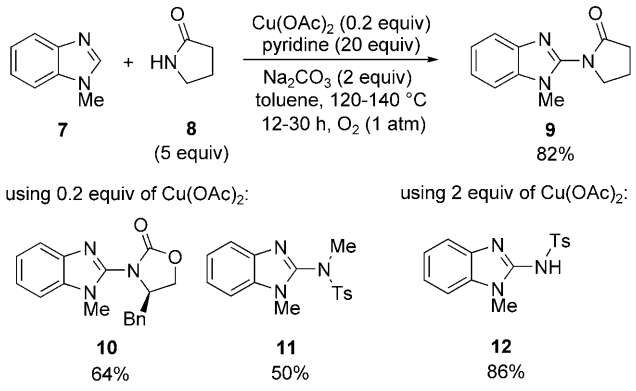


Scheme 3. Direct amination reaction conditions developed by Mori and co-workers, and selected examples of products (**3**–**6**) synthesized by this method.

for substoichiometric quantities of catalyst, with 20 mol% $Cu(OAc)_2$ delivering a reasonable yield and reaction time. These reaction conditions were extended to the amination of benzoxazole, *N*-methylbenzimidazole, and 4,5-dimethylthiazole, as well as for the use of secondary aliphatic amines and sulfonamides. The use of four equivalents of the amine nucleophile is necessary to prevent side reactions of the reactive organocopper intermediate, thus limiting the potential use of this method with amines that require significant synthetic investment in their preparation, and thereby diminishing the advantages in atom economy that favor the use of direct C–H amination.

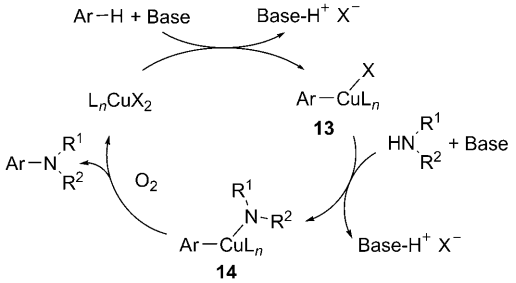
Wang and Schreiber recently developed closely related reaction conditions for the amidation of various heterocyclic compounds.[11] The optimized conditions (Scheme 4) also use 20 mol% $Cu(OAc)_2$ with a simple ligand (pyridine), weak inorganic base (Na_2CO_3), and nonpolar aromatic solvent (toluene). A range of amides (e.g. **8**), ureas, carbamates, and sulfonamides were found to efficiently amidate the C2-position of 1-methyl-benzimidazole (**7**), although primary amides and sulfonamides required the use of two equivalents of $Cu(OAc)_2$. Acyclic secondary amides were ineffective, reportedly as a result of steric hindrance. As before, a large excess of the nucleophile (five equivalents) was required to prevent a competing side reaction, which was identified in this case by Schreiber as the dimerization of benzimidazole.



Scheme 4. Direct amidation conditions developed by Wang and Schreiber, and selected examples of products (**9**–**12**) synthesized by this method. Bn = benzyl, Ts = 4-toluenesulfonyl.

Interestingly, Schreiber reports that the use of amines in this reaction leads to significant dimerization in every case, and is attributed to strong electron-donation by the amine nucleophile and its unfavorable deprotonation. Alternatively, weak amide nucleophiles such as phthalimide were also unreactive, thus suggesting the need to find a balance between the opposing properties of nucleophilicity and N–H acidity. The scope of the C–H coupling partner was extended to similar acidic, fully substituted azoles. No examples were reported that tested the expected regioselectivity of the reaction. Modified reaction conditions also allowed the direct amidation of fluorobenzenes, albeit in low yields, in a direct parallel with the pK_a-dependent copper-catalyzed C–H arylation developed by Daugulis.[6]

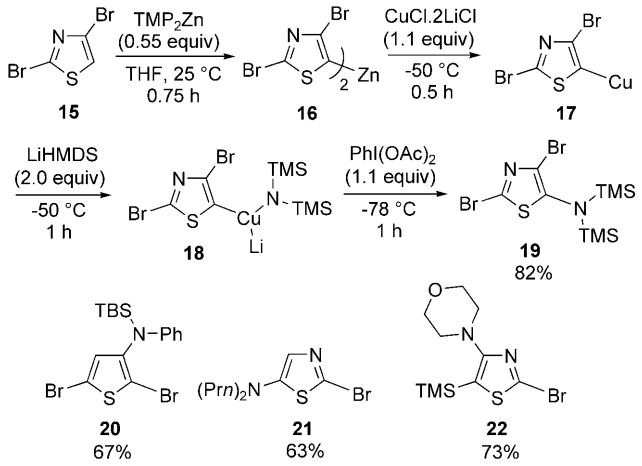
The mechanism proposed by both Mori and Schreiber (Scheme 5) is directly analogous to that proposed by Stahl for the amidation of alkynes; formation of organocopper intermediate **13** by deprotonation, coordination of the nucleophile (→**14**), and then reductive elimination with the catalyst regenerated by molecular oxygen.



Scheme 5. Proposed mechanism of direct oxidative amination.

An alternative, noncatalytic approach to copper-mediated heterocycle C–H amination has recently been reported by Knochel and co-workers,[12] essentially dividing the proposed catalytic cycle described above into its component steps by sequential addition of the reagents. Building on similar previous work, Knochel's oxidative amination started with the formation of a heterocyclic anion (**16**) by deprotonation of **15** using TMP_2Zn (Scheme 6). Addition of CuCl·2 LiCl formed the expected organocopper intermediate **17**, which was then further coordinated by the addition of two equivalents of the deprotonated amine nucleophile and gave an amidocuprate (**18**). A stoichiometric quantity of PhI-$(OAc)_2$ oxidant was then required in the final step to promote reductive elimination of the aminated heterocycle.

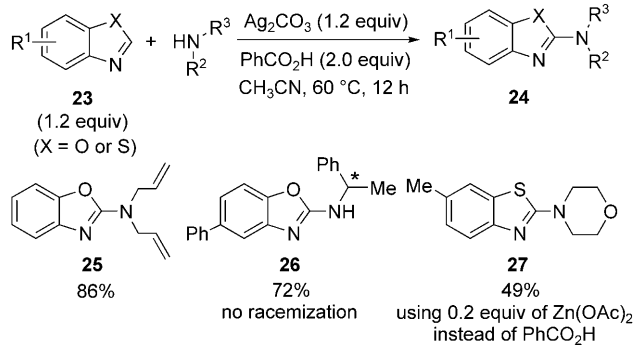
Good yields are obtained for the amination of a variety of heterocycles, using both secondary and protected primary amines, and the reaction can be scaled up efficiently. This approach to aminoheterocycles is clearly not as simple as those discussed previously, and requires a precise sequence of reagents at low temperatures, rigorously dry conditions, and stoichiometric quantities of the copper salt and oxidant. Furthermore, the excess of the deprotonated amine nucleophile is likely to cause side reactions with any other electrophilic functionality. The key benefits to this methodology lie



Scheme 6. Reaction conditions for oxidative amination developed by Knochel and co-workers, and selected examples of products (**19**–**22**) synthesized by this method. HMDS = 1,1,1,3,3,3-hexamethyldisilazane, TBS = *tert*-butyldimethylsilyl, THF = tetrahydrofuran, TMP = tetramethylpiperidide, TMS = trimethylsilyl.

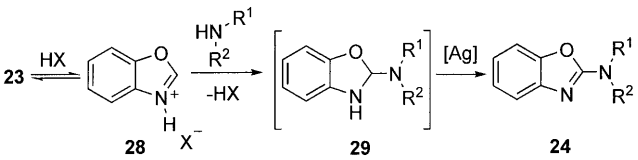
in its flexibility. The compatibility of the deprotonation using TMP_2Zn with halides and silanes allows for the synthesis of highly functionalized heterocyclic cores (such as **22**) that can be rapidly elaborated by further coupling processes. The use of stronger bases also extends the scope from azole amination at C2 to less acidic heterocycles and electron-rich positions, which are not as amenable to the more common Buchwald–Hartwig coupling.

An alternative mechanistic approach to azole amination at C2 has been recently reported by Chang and co-workers,[13] and resulted from the unexpected discovery that attempted direct benzoxazole (**23**; X = O) amidation with formamides results in the C2-aminated product **24**, through decarbonylation to give an amine nucleophile. This reaction required the use of an excess of Ag_2CO_3 under acidic conditions. As expected, switching to using amines (and thus bypassing the slow formamide decarbonylation) led to a significant increase in reaction efficiency, thus allowing the use of much lower temperatures than the analogous copper-catalyzed processes above (Scheme 7).



Scheme 7. Direct amination conditions developed by Chang and co-workers, and selected examples of products (**25**–**27**) synthesized by this method.

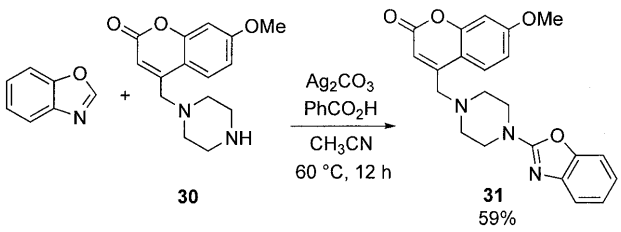
The proposed mechanism for this reaction (Scheme 8) involves protonation of the heterocycle by the acid additive (**23**→**28**), the pK_a value of which has been shown to be



Scheme 8. Chang's proposed mechanism for silver-mediated direct amination of benzoxazole.

crucial. Attack by the amine group results in a 2-aminobenzoxazoline intermediate **29**, which is then oxidatively rearomatized by Ag_2CO_3. Importantly, the absence of an unstable organometallic intermediate in the amination mechanism allows for the use of 0.8–1 equivalents of the amine nucleophile. Along with the low temperature, this is the key advantage of this method over the copper-based alternatives. Another consequence of this alternative mechanism is the dependence of the reaction on having both a suitably nucleophilic amine and electrophilic heterocycle, although within these constraints the reaction scope encompasses a wide variety of aliphatic amines, and an example of benzothiazole amination is included. Interestingly, the benzothiazole is aminated to give **27** using a substoichiometric quantity of $Zn(OAc)_2$ as a Lewis acid catalyst, thus replacing the Brønsted acid additive (Scheme 7). Chang notes that investigations into Lewis acid catalysis are underway, thus potentially allowing for an increase in substrate scope, functional group tolerance, and amine reactivity. The proposed role of the stoichiometric silver salt as the oxidant also could allow for the use of an alternative catalytic oxidant that could be regenerated by molecular oxygen. If this were possible, it would result in a very simple and mild catalyst system for azole amination at C2. The power of this method is exemplified in the synthesis of biologically active benzoxazole **31** by the heteroarylation of a highly functionalized piperazine (**30**; Scheme 9), thus illustrating both the synthetic power of direct C–H amination and the applicability of Chang's approach to medicinal chemistry.

These recent developments employ mechanistically and strategically different approaches to direct heterocycle amination that will undoubtedly find application in chemical synthesis and medicinal chemistry. Further investigations will



Scheme 9. Synthesis of anti-HIV and antitumor piperazine **31** by direct amination.

likely result in improvements in catalyst loading and substrate scope, thereby extending the usefulness of this method. Additionally, further insights into the mechanistic details, particularly of Chang's silver-mediated amination, may allow for the rational design of superior catalytic systems. In this Highlight, we have drawn attention to an emerging area within the changing field of functionalized heterocycle synthesis: from convergent late-stage cyclocondensation to divergent transition-metal-catalyzed functionalization of simple heterocyclic cores.

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[1] J. P. Wolfe, S. Wagaw, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805; J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534.
[2] S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.
[3] a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; b) F. Bellina, R. Rossi, *Tetrahedron* **2009**, *65*, 10269; c) S. Taktak, M. Flook, B. M. Foxman, L. Que Jr. , E. V. Rybak-Akimova, *Chem. Commun.* **2005**, 5301; Y.-H. Zhang, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 14654; for copper-catalyzed heterocycle synthesis by C–O bond formation, see: S. Ueda, H. Nagasawa, *Angew. Chem.* **2008**, *120*, 6511; *Angew. Chem. Int. Ed.* **2008**, *47*, 6411; S. Ueda, H. Nagasawa, *J. Org. Chem.* **2009**, *74*, 4272; d) A. R. Dick, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 2300; L. V. Desai, H. A. Malik, M. S. Sanford, *Org. Lett.* **2006**, *8*, 1141.
[4] Review of C–H amination: F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061; see also T.-S. Mei, X. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 10806; review of C–H amination for heterocycle synthesis: P. Thansandote, M. Lautens, *Chem. Eur. J.* **2009**, *15*, 5874.
[5] X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790; for a similar reaction involving a stoichiometric quantity of $Cu(OAc)_2$, see: T. Uemura, S. Imoto, N. Chatani, *Chem. Lett.* **2006**, *35*, 842.
[6] O. Daugulis, H.-Q. Do, D. Shabashov, *Acc. Chem. Res.* **2009**, *42*, 1074.
[7] a) P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632; b) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941; c) T. Hamada, X. Ye, S. S. Stahl, *J. Am. Chem. Soc.* **2008**, *130*, 833.
[8] a) F. G. Bordwell, G. E. Drucker, N. H. Andersen, A. D. Denniston, *J. Am. Chem. Soc.* **1986**, *108*, 731; b) R. W. Taft, F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 463.
[9] S.-i. Fukuzawa, E. Shimizu, Y. Atsuumi, M. Haga, K. Ogata, *Tetrahedron Lett.* **2009**, *50*, 2374.
[10] D. Monguchi, T. Fujiwara, H. Furukawa, A. Mori, *Org. Lett.* **2009**, *11*, 1607.
[11] Q. Wang, S. L. Schreiber, *Org. Lett.* **2009**, *11*, 5178.
[12] M. Kienle, C. Dunst, P. Knochel, *Org. Lett.* **2009**, *11*, 5158.
[13] S. H. Cho, J. Y. Kim, S. Y. Lee, S. Chang, *Angew. Chem.* **2009**, *121*, 9291; *Angew. Chem. Int. Ed.* **2009**, *48*, 9127.

