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Copper-catalyzed C_{sp^2}–H amidation of unactivated arenes by *N*-tosyloxycarbamates†

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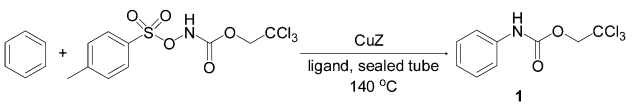
[(Neocuproine)Cu]PF_6 catalyzes the C–H amidation of unactivated arenes by *N*-tosyloxytrichloroethylcarbamates. Alkyl benzenes are selectively converted to aromatic amines and substituted arenes display variable regioselectivity.

Transition metal catalyzed C–H functionalization has revolutionized the chemist's approach to organic synthesis.[1,2] The ubiquitous presence of aromatic amines among natural products, pharmaceuticals, specialty chemicals and synthetic intermediates,[3,4] has recently stimulated efforts to develop efficient arene C–H amination reactions.[5,6] This methodology typically has relied on pre-installed metal-coordinating directing groups[7] to effect the reaction, which need to be removed post functionalization.

Reports of direct C–H N-functionalization of arenes lacking activating/directing groups, however, are sparse and limited in substrate and N-reagent scope.[8] The direct conversion of benzene to aniline using redox active transition metal oxides with NH_3/O_2 or hydroxylamine as N-reagents proceeds with moderate efficiency, but its substrate scope is unknown.[9] Transition metal-promoted arene amination by PhI=NTs has been catalyzed by: (1) $AuCl_3$[10] and (2) $Tp^{Br_3}Cu(MeCN)$,[11] but alkylaromatics undergo benzylic amination with both systems; (3) Cu(2,9-diaryl-phenanthroline)$_2^+$, which promotes amination of electron-rich arenes, but is ineffective for benzene;[12] and (4) a scorpionate Fe(II) complex,[13] which shows rare selectivity for aromatic over benzylic amination. Very recently, a regio- (*meta*- and *para*-) and chemo-selective C–H amination of arenes by phthalimide–$PhI(OAc)_2$/$Pd(OAc)_2$–P(*t*-Bu)$_3$ was reported.[14] Finally, metal-free oxidative C–H aminations[15] have shown sp^2-C–H selectivity for alkyl arene substrates.

Our pursuit of practical and economical C–H amination methodologies[16] and the cited precedents prompted us to evaluate the efficacy of aminating unactivated arenes by inexpensive copper catalysts and convenient pre-oxidized N-reagents, such as oxycarbamates, obviating the need for an external oxidant.[17–20] Herein we disclose a novel C–H amination of simple unactivated arenes employing synthetically versatile and conveniently deprotectable Troc-carbamate[21] as the N-reagent under Cu-catalysis.

We began by testing several catalyst/N-reagent combinations using benzene as the test substrate. Initial attempts with benzophenone *O*-acetyloxime[16a] and *N*-benzoylpiperidine[19b] as N-reagents and Cu(I)TC (TC = thiophene-2-carboxylate) did not yield any product. Based on the reactivity of oxycarbamates in Pd- and Rh-catalyzed directed arene C–H aminations,[20,21c] we shifted our focus to the use of *N*-tosyloxycarbamates. Gratifyingly, when *N*-tosyloxy-trichloroethylcarbamate was used as the N-reagent with 20 mol% Cu(I)TC in benzene as solvent at 140 °C, the *N*-phenylcarbamate **1** was detected in 15% yield, along with trichloroethanol and *O*-tosyltrichloroethanolate, derived from decomposition of the carbamate, as well as trace amounts of aminated toluenes (eqn (1)).‡



(1)

Various copper sources were then screened for catalytic activity. The best yield of **1** (*ca.* 45%, Table 1, entry 5) was obtained with $[Cu(CH_3CN)_4]PF_6$ (**A**) (20 mol%), while Cu(II) salts were generally found to be ineffective. Interestingly, increasing the catalyst loading did not improve the yield (Table 1, entries 5, 7 and 8). A screen of other first-row transition metal compounds gave no/low yields, *e.g.* 20% using $Fe(acac)_2$ and $Fe(OTf)_2(CH_3CN)_2$ (Table S1, ESI†).

The effect of ligands and other additives on the amination reaction (eqn (1)) was assessed through screening reactions with various phosphines, amines, N-heterocycles and acids added to $Cu(AN)_4^+$ + L + TrocNHOTs/benzene (Table S2, ESI†). These revealed that the best ligands were dppf (57% yield) and neocuproine (2,9-dimethylphenanthroline, NC) (48%) (Table 1).[22] We were delighted to find that the amination efficiency using NC almost

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† Electronic supplementary information (ESI) available: Experimental procedure, characterization data, ^1H and ^{13}C spectra. See DOI: 10.1039/c3cc46412a

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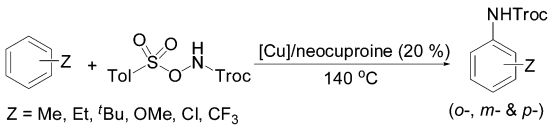
Table 1 Catalyst variation for the amination of benzene[a]

Entry	[Cu]/ligand loading (mol%)	Conversion[d] (%)	Yield[d] (%)
1	Cu(TC) (20)	73	16
2	Me_2S·CuBr (20)	—	10
3[b]	Cu_2O (10)	—	40
4	$Cu(OTf)_2$ (20)	35	11
5	**$[Cu(CH_3CN)_4](PF_6)$ (A) (20)**	**95**	**45**
6	$\{Cu(OTf)\}_2$·toluene (10)	50	20
7	**A** (30)	100	40
8	**A** (100)	38	17
9	**A** + dppf (20%)	100	57
10	**A** + phenanthroline (20%)	64	25
11	**A** + Neocuproine (20%)	100	48
12[c]	**A** + **Neocuproine (20%)**	**100**	**75 (57)**

[a] Reaction conditions: tosyloxycarbamate (0.138 mmol), [Cu] (0.027 mmol) and ligand (0.027 mmol) in benzene (*ca.* 0.5 mL) at 140 °C in sealed tube for 16 h. [b] After 48 h. [c] Reaction carried out in *ca.* 1 mL benzene. [d] Conversion and yield based on 1,3,5-trimethoxybenzene as an NMR reference. dppf = diphenylphosphinoferrocene, neocuproine (NC) = 2,9-dimethylphenanthroline.

doubled (*ca.* 75% yield) when the reaction solvent volume was doubled.



(2)

Having established effective benzene amination using the **A**–NC system, we proceeded to extend the method to other non-directing arenes (eqn (2), Fig. 1). Typically, a mixture of Troccarbamate (0.14 mmol) and **A**–NC (20 mol%) in the neat arene (*ca.* 1 mL) was stirred at 140 °C for 8 h to produce regioisomeric mixtures of the aminated arenes.§¶ The alkyl arenes, toluene and ethylbenzene, were successfully converted to their regioisomeric aromatic carbamates in good (59%) and moderate (44%) yields, respectively. Significantly, the reaction was highly chemoselective with no benzylic amination (C_{sp^3}–H) detected. In contrast the prior [Cu]/PhI=NTs systems give only benzylic amination products with alkyl arene substrates, while the [Fe]/PhI=NTs system results in benzylic and aromatic amination.[13] The isomer distribution for toluene showed the *ortho*-isomer dominating (*ca.* 50%) with lesser but nearly equal amounts of the *meta*- and *para* isomers. The toluene reaction also produced some alkyl arene dimers resulting from C_{sp^2}–C_{sp^3} homocoupling, while acetophenone, resulting from benzylic C–H oxidation, was detected with ethylbenzene.‖ With *tert*-butylbenzene only the *meta*- and *para* products were observed, probably the result

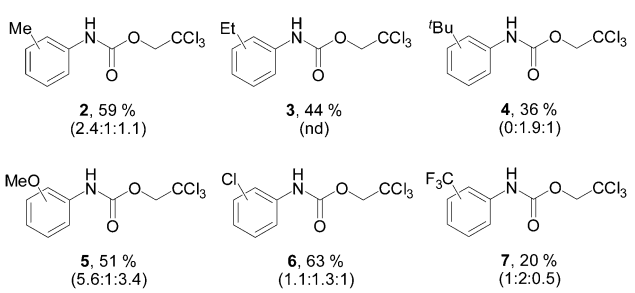


Fig. 1 Arene amination yields and (*o,m,p*) regioselectivity.

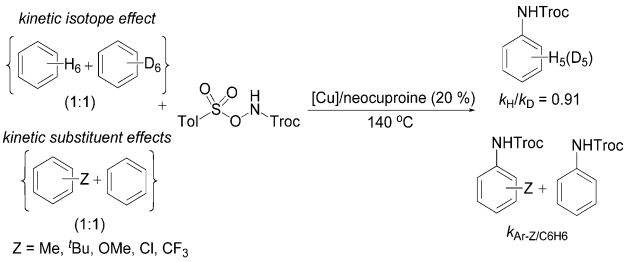


Fig. 2 Kinetic isotope and substituent effects.

of steric effects with the bulky *tert*-butyl group blocking *ortho*-functionalization. On the other hand the electron-rich arene anisole, showed regioselectivity more typical of an electrophilic substitution (*ortho* > *para* > *meta*), while the electron-poor chlorobenzene produced an equimolar mixture of the three regioisomers. This contrasts with the selectivity observed for copper catalyzed aminations with TsN=IPh, which furnished only *ortho*/*para* isomers with anisole and chlorobenzene.[11a,12] With electron poor trifluorotoluene, a modest yield of *ca.* 20% was obtained, favouring the *meta*-isomer. The conditions, yields and regioselectivities observed with the TrocNHOTs–NC–Cu^+ system are comparable to the best observed with other [M]/N-reagents for amination of simple arenes.[10–13]

To gain insight into the nature of the reactive species in the reaction, several mechanistic probes were applied. A kinetic isotope effect (KIE) study using an equimolar amount of benzene and benzene-d_6 exhibited a marginally inverse KIE of 0.9 (±0.1) (Fig. 2), indicating that C–H bond-breaking is not involved in the rate limiting step. This contrasts with many metal promoted C–H functionalization processes, which often display large primary isotope effects.[23]

Relative reactivity studies were carried out through competition experiments with an equimolar mixture of each of several arenes with benzene to establish the electronic nature of the reaction. The electron rich arenes, toluene and anisole, were found to react faster than benzene, k_{rel} of 3.2 and 7.2, suggestive of electrophilic character for the intermediate effecting their amination. The subdued reactivity of *tert*-butylbenzene may be due to the limited accessibility of the *ortho* positions. Surprisingly, the electron-poor chlorobenzene was also found to react faster than benzene (k_{rel}. = 8.8). A Hammett plot of $k_{Ar–X}/k_{benz}$ *vs.* σ_p values for these substrates was thus non-linear (Fig. 3), suggestive of a

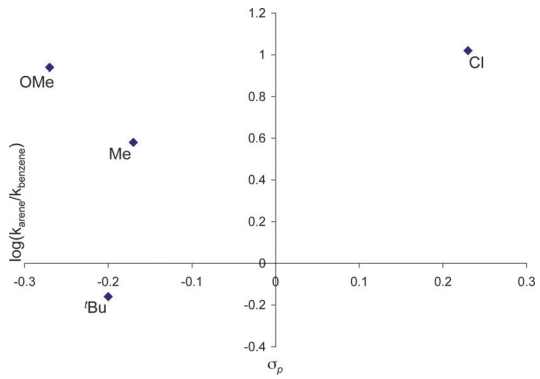


Fig. 3 Hammett plot of relative arene reactivity *vs.* σ_p.

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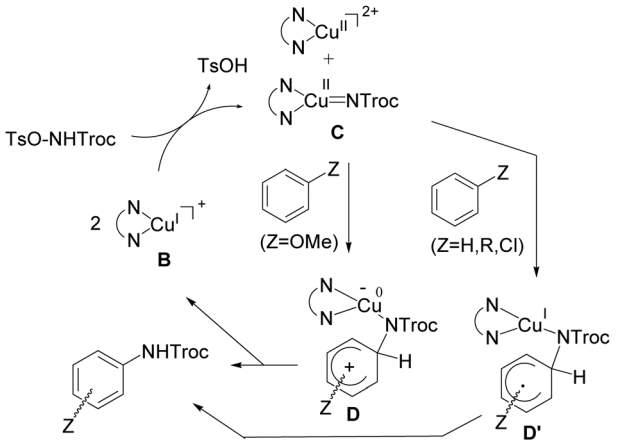

Scheme 1 Possible catalytic pathway for aromatic amidation.

change in mechanism or rate-limiting step, depending on the electronic character of the substituent.[24,25]

Mechanistic aspects of copper catalyzed C–H functionalization are currently of high interest.[26] One of several conceivable pathways consistent with the observed substrate-dependent regioselectivities, kinetic isotope effect, and relative arene reactivities, and side products is shown in Scheme 1. Suggested stages include: (a) generation of a Cu(II)-imido species **C** *via* OA and redox disproportionation; (b) addition of electrophilic radicaloid **D** to the arene, either by electrophilic (two electron) attack to give adduct **D** or by radical attack to produce **D′**, depending on the arene electronic character; and (c) C–H to N–H transfer with (phen)Cu^+ elimination and aryl carbamate formation.

The (NC)Cu^+–TsONHTroc system, employing an inexpensive catalyst and convenient N-reagent, promotes moderately efficient C–H amination of arenes lacking coordinating substituents and exhibits high selectivity for aromatic *vs.* benzylic substitution.

Notes and references

‡ Aminated toluene products derive from copper mediated decomposition of the N-reagent; these were detected with all arene substrates.
§ Sample procedure: to a stirred mixture of A (0.010 g, 0.026 mmol) and NC (0.005 g, 0.024 mmol) in the arene (*ca.* 1 mL) was added *N*-tosyltroccarbamate (0.050 g, 0.138 mmol) and the mixture was allowed to stir at 140 °C for 8 h. The reaction mixture was cooled to room temperature, filtered through a pad of silica washing with CH_2Cl_2 and the filtrate concentrated under vacuum. The residue was purified by silica chromatography using 5–15% Et_2O in hexanes to obtain the regioisomeric mixture of aminated arenes. The isomer ratio was determined by NMR using 1,3,5-trimethoxybenzene as a reference.
¶ Isomeric products were identified either by partial chromatographic separation or independent synthesis. See ESI† for details of identification.
‖ Alkyl arene side products are minimized in reactions at lower temperatures (100 °C), but with lower conversion. The acetophenone product from ethylbenzene is minimized by reaction in degassed ethylbenzene with 3 Å molecular sieves under Ar.

1 (*a*) S. Rousseaux, B. Liegault and K. Fagnou, *Modern Tools for the Synthesis of Complex Bioactive Molecules*, 2012, p. 1; (*b*) K. M. Engle and J.-Q. Yu, *Org. Chem.*, 2012, 279; (*c*) C. M. White, *Synlett*, 2012, 2746; (*d*) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651.
2 *Metal-Catalyzed Cross-Coupling Reaction*, F. Diederich and P. J. Stang, ed., Wiley VCH, Weinheim, 1998.
3 (*a*) A. Armstrong and J. C. Collins, *Angew. Chem., Int. Ed.*, 2010, **49**, 2282; (*b*) F. Collet, R. H. Dodd and P. Dauban, *Chem. Commun.*, 2009, 5061.
4 (*a*) W. C. P. Tsang, N. Zheng and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 14560; (*b*) H. M. L. Davies and M. S. Long, *Angew. Chem., Int. Ed.*, 2005, **44**, 3518.
5 (*a*) Y. Tan and J. F. Hartwig, *J. Am. Chem. Soc.*, 2010, **132**, 3676; (*b*) J. A. Jordan-Hore, C. C. C. Johansson, M. Gulias, E. M. Beck and M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 16184; (*c*) M. Wasa and J.-Q. Yu, *J. Am. Chem. Soc.*, 2008, **130**, 14058.
6 (*a*) N. Matsuda, K. Hirano, T. Satoh and M. Miura, *Synthesis*, 2012, 1792; (*b*) J. Wang, J.-T. Hou, J. Wen, J. Zhang and X.-Q. Yu, *Chem. Commun.*, 2011, **47**, 3652.
7 (*a*) C. Wang and Y. Huang, *Synlett*, 2013, 0145; (*b*) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (*c*) S. I. Kozhushkov and L. Ackermann, *Chem. Sci.*, 2013, **4**, 886; (*d*) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112**, 5879; (*e*) J. Wencel-Delord, T. Droge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740.
8 N. Kuhl, M. N. Hopkinson, J. Wencel-Dolard and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 10236.
9 (*a*) S. Singha and K. M. Parida, *Catal. Sci. Technol.*, 2011, **1**, 1496; (*b*) L. F. Zhu, B. Guo, D. Y. Tang, X. K. Hu, G. Y. Li and C. W. Hu, *J. Catal.*, 2007, **245**, 446; (*c*) N. Hoffmann and M. Muhler, *Catal. Lett.*, 2005, **103**, 155; (*d*) N. I. Kuznetsova, L. I. Kuznetsova, L. G. Detusheva, V. A. Likholobov, G. P. Pez and H. Cheng, *J. Mol. Catal. A: Chem.*, 2000, **161**, 1; (*e*) J. Becker and W. F. Hölderich, *Catal. Lett.*, 1998, **54**, 125.
10 Z. Li, D. A. Capretto, R. O. Rahaman and C. He, *J. Am. Chem. Soc.*, 2007, **129**, 12058.
11 (*a*) M. R. Fructos, S. Trofimenko, M. M. Diaz-Requejo and P. J. Perez, *J. Am. Chem. Soc.*, 2006, **128**, 11784; (*b*) M. M. Diaz-Requejo, T. R. Belderrain, M. C. Nicasio, S. Trofimenko and P. J. Perez, *J. Am. Chem. Soc.*, 2003, **125**, 12078.
12 C. W. Hamilton, D. S. Laitar and J. P. Sadighi, *Chem. Commun.*, 2004, 1628.
13 S. Liang and M. P. Jensen, *Organometallics*, 2012, **31**, 8055.
14 R. Shrestha, P. Mukherjee, Y. Tan, Z. C. Litman and J. F. Hartwig, *J. Am. Chem. Soc.*, 2013, **135**, 8480.
15 (*a*) R. Samanta, J. O. Bauer, C. Strohmann and A. P. Antonchick, *Org. Lett.*, 2012, **14**, 5518; (*b*) A. A. Kantak, S. Potavathri, R. A. Barham, K. M. Romano and B. DeBoef, *J. Am. Chem. Soc.*, 2011, **133**, 19960; (*c*) H. J. Kim, J. Kim, S. H. Cho and S. Chang, *J. Am. Chem. Soc.*, 2011, **133**, 16382.
16 (*a*) A. John and K. M. Nicholas, *Organometallics*, 2012, **31**, 7914; (*b*) A. A. Lamar and K. M. Nicholas, *J. Org. Chem.*, 2010, **75**, 7644; (*c*) D. N. Barman, P. Liu, K. N. Houk and K. M. Nicholas, *Organometallics*, 2010, **29**, 3404.
17 (*a*) Z. Shi, C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3381; (*b*) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2011, **50**, 11062.
18 (*a*) C. Grohmann, H. Wang and F. Glorius, *Org. Lett.*, 2012, **14**, 656; (*b*) K.-H. Ng, Z. Zhou and W.-Y. Yu, *Org. Lett.*, 2012, **14**, 272.
19 (*a*) N. Matsuda, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2011, **13**, 2860; (*b*) E. J. Yoo, S. Ma, T.-S. Mei, S. L. Chan and J.-Q. Yu, *J. Am. Chem. Soc.*, 2011, **133**, 7652.
20 K.-H. Ng, A. S. C. Chan and W.-Y. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 12862.
21 Oxycarbamates in aziridination: (*a*) H. Lebel, M. Parmentier, O. Leogane, K. Ross and C. Spitz, *Tetrahedron*, 2012, **68**, 3396; benzylic amination: (*b*) H. Lebel and K. Huard, *Org. Lett.*, 2007, **9**, 639; in directed aromatic amination: (*c*) C. Grohmann, H. Wang and F. Glorius, *Org. Lett.*, 2013, **15**, 3014. Deprotecting the Troc group; (*d*) E. Vellemäe, V. Stepanov and U. Mäeorg, *Synth. Commun.*, 2010, **40**, 3397 and cited references.
22 Neither product **1** nor consumption of the N-reagent were detected when PhH/Troccarbamate were heated at 140 °C without (NC)Cu^+.
23 X. Chen, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 12634.
24 B. I. Stokes, K. J. Richert and T. G. Driver, *J. Org. Chem.*, 2009, **74**, 6442.
25 A Hammett plot of log k_{rel} *vs.* the radical substituent parameter TE is also non-linear (see ESI†). (*a*) Y.-D. Wu, C.-L. Wong, K. W. K. Chan, G.-Z. Ji and X.-K. Jiang, *J. Org. Chem.*, 1996, **61**, 746; (*b*) S.-M. Au, J.-S. Huang, C.-M. Che and W.-Y. Yu, *J. Org. Chem.*, 2000, **65**, 7858.
26 (*a*) A. M. Suess, M. Z. Ertem, C. J. Cramer and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 9797; (*b*) M. J. B. Aguila, Y. M. Badiei and T. H. Warren, *J. Am. Chem. Soc.*, 2013, **135**, 9399; (*c*) G. Lefèvre, G. Franc, A. Tlili, C. Adamo, M. Taillefer, I. Ciofini and A. Jutand, *Organometallics*, 2012, **31**, 7694.