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Copper-Catalyzed Amination of Primary Benzylic C−H Bonds with Primary and Secondary Sulfonamides

David A. Powell* and Hope Fan

Merck Frosst Centre for Therapeutic Research, 16711 Trans Canada Highway, Kirkland, Québec H9H 3L1, Canada

david_powell2@merck.com

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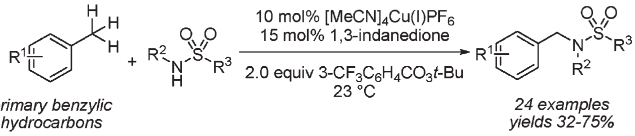

A room-temperature, copper-catalyzed amination of primary benzylic C−H bonds with primary and secondary sulfonamides is described. The reaction is applicable to the coupling of a range of primary and secondary benzylic hydrocarbons with a diverse set of sulfonamides and is tolerant of substitution on both coupling partners. Factors which influence the selectivity of C−H functionalization between primary and secondary sites are examined.

The direct transformation of C−H bonds into C−N bonds represents an efficient and attractive strategy for the synthesis of valuable nitrogen-containing molecules.[1] Transition-metal-catalyzed nitrene insertions into C−H bonds remain the most widely developed and impactful direct amination procedure,[2−4] although mechanistically distinct C−H amination strategies continue to be investigated.[5−8]

Despite significant progress within the C−H amination field, challenges remain. For example, methodologies for the amination of primary benzylic C−H bonds are relatively scarce.[4e,9] Primary benzylic hydrocarbons such as toluene typically afford unacceptably low yields under previously developed amination conditions, including our own (eq 1).[5b,10] Notable exceptions include recently described copper- and rhodium-catalyzed nitrene-based aminations,[4b,c,k,8b] in particular procedures utilizing only a single equivalent of hydrocarbon substrate.[4e,h] While clearly promising, these aminations procedures described few primary benzylic hydrocarbon substrates (typically only toluene) and utilize an optimized primary sulfonamide-based nucleophile. In addition, these methodologies, as a consequence of the

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(1) For some recent reviews of C−H bond oxidations, including aminations, see: (a) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061–5074. (b) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242–3272. (c) Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Rev.* **2008**, *108*, 3379–3394. (d) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439–2463. (e) Du Bois, J. *Chemtracts* **2005**, *18*, 1–13. (f) Espino, C. G.; Du Bois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed; Wiley-VCH: Weinheim, 2005; pp 379−416. (g) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657–669.

(2) For some recent reviews of metal-nitrene based aminations, see: (a) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905–2919. (c) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571–1586.

(3) Representative intramolecular metal-nitrene based aminations: (a) Fiori, K. W.; Espino, C. G.; Brodsky, B. H.; Du Bois, J. *Tetrahedron* **2009**, *65*, 3042–3051. (b) Kurokawa, T.; Kim, M.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2777–2779. (c) Olson, D. E.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 11248–11249. (d) Milczek, E.; Boudet, N.; Blakey, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6825–6828. (e) Lebel, H.; Leogane, O.; Huard, K.; Lectard, S. *Pure Appl. Chem.* **2006**, *78*, 363–375. (f) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073–1076. (g) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198–14199. (h) Zhang, J.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2005**, *46*, 5403–5408. (i) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378–15379. (j) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210–4212. (k) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 3610–3619. (l) Fruit, C.; Müller, P. *Helv. Chim. Acta* **2004**, *87*, 1607–1615. (m) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465–3468. (n) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935–6936. (o) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598–600. (p) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728–6729.

(4) Representative intermolecular metal-nitrene based aminations: (a) Lu, H.; Subbarayan, V.; Tao, J.; Zhang, X. P. *Organometallics* **2010**, *29*, 389–393. (b) Badiei, Y. M.; Dinescu, A.; Dai, X.; Palomino, R. M.; Heinemann, F. W.; Cundari, T. R.; Warren, T. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9961–9964. (c) Huard, K.; Lebel, H. *Chem.—Eur. J.* **2008**, *14*, 6222–6230. (d) Kalita, B.; Lamar, A. A.; Nicholas, K. M. *Chem. Commun.* **2008**, 4291–4293. (e) Liang, C.; Collet, F.; Robert-Peillard, F.; Müller, P.; Dodd, R. H.; Dauban, P. *J. Am. Chem. Soc.* **2008**, *130*, 343–350. (f) Li, Z.; Capretto, D. A.; Rahaman, R.; He, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 5184–5186. (g) Harden, J. D.; Ruppel, J. V.; Gao, G.-Y.; Zhang, X. P. *Chem. Commun.* **2007**, 4644–4646. (h) Bhuyan, R.; Nicholas, K. M. *Org. Lett.* **2007**, *9*, 3957–3959. (i) Lebel, H.; Huard, K. *Org. Lett.* **2007**, *9*, 639–642. (j) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562–568. (k) Fructos, M. R.; Trofimenko, S.; Díaz-Requejo, M. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 11784–11791. (l) Reddy, R. P.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 5013–5016. (m) Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641–4644. (n) Leung, S. K.-Y.; Tsui, W.-M.Huang, J.-S.; Che, C.-M.; Liang, J.-L.; Zhu, N. *J. Am. Chem. Soc.* **2005**, *127*, 16629–16640. (o) Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 9561–9564. (p) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 3339–3342. (q) Chanda, B. M.; Vyas, R.; Bedekar, A. V. *J. Org. Chem.* **2001**, *66*, 30–34. (r) Albone, D. P.; Aujla, P. S.; Taylor, P. C. *J. Org. Chem.* **1998**, *63*, 9569–9571.

(5) Metal-peroxycarbamate and perester based C−H aminations: (a) Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2007**, *9*, 3813–3816. (b) Pelletier, G.; Powell, D. A. *Org. Lett.* **2006**, *8*, 6031–6034. (c) Smith, K.; Hupp, C. D.; Allen, K. L.; Slough, G. A. *Organometallics* **2005**, *24*, 1747–1755. (d) Clark, J. S.; Roche, C. *Chem. Commun.* **2005**, 5175–5177. (e) Kohmura, Y.; Kawasaki, K.-i.; Katsuki, T. *Synlett* **1997**, 1456–1458.

(6) Metal-*N*-halosuccinimide based C−H aminations: (a) Liu, X.; Zhang, Y.; Wang, L.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2008**, *73*, 6207–6212. (b) Wang, Z.; Zhang, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2008**, *10*, 1863–1866.

(7) Palladium-catalyzed allylic C−H aminations: (a) Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707–11711. (b) Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11701–11706. (c) Liu, G.; Yin, G.; Wu, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4733–4736. (d) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 7274–7276.

(8) Other representative saturated C−H bond amination strategies: (a) Allen, C. P.; Benkovics, T.; Turek, A. K.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 12560–12561. (b) Fan, R.; Li, W.; Pu, D.; Zhang, L. *Org. Lett.* **2009**, *11*, 1425–1428. (c) Zalatan, D. N.; Du Bois, J. *Synlett* **2009**, 143–146. (d) Zhao, B.; Du, H.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 7220–7221. (e) Chouthaiwale, P. V.; Suryavanshi, G.; Sudalai, A. *Tetrahedron Lett.* **2008**, *49*, 6401–6403. (f) Ragaini, F.; Penoni, A.; Gallo, E.; Tollari, S.; Gotti, C. L.; Lapadula, M.; Mangioni, E.; Cenini, S. *Chem.—Eur. J.* **2003**, *9*, 249–259.

(9) Some of the increased challenge associated with oxidations of primary over secondary benzylic C−H bonds may be attributable to differences in bond-dissociation energies between these types of substrates, see refs 4b, 4n, and Bryant, J. R.; Mayer, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 10351–10361.

(10) The amination of toluene with a variety of transition metal catalysts are reported to proceed in 9−30% yields even when toluene is used in large excess as the solvent. See Supporting Information for further details.

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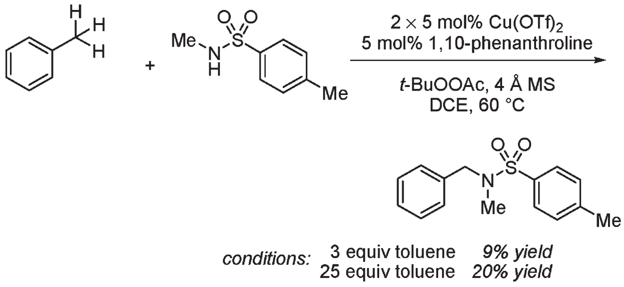
metal-nitrenoid intermediate, remain restricted to amination with primary amide species. Development of general methodologies for the amination of primary benzylic C−H bonds with demonstrated scope for a variety of hydrocarbon and sulfonamide substrates remains desirable.



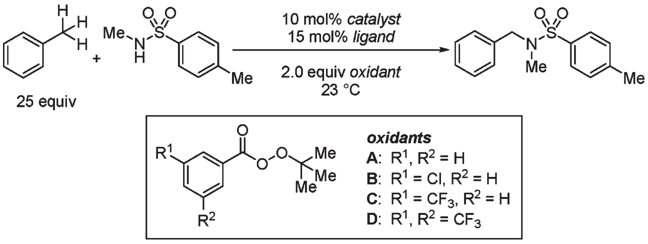
(1)

Given the paucity of methodologies available for the direct amination of primary benzylic C−H bonds, we focused our attention toward this goal. Conscious of the ascendant utility of C−H aminations in total synthesis,[11] we sought a methodology that would demonstrate sufficient scope under mild reaction conditions.

Commencing from our previous work,[5b] an investigation of various reaction parameters was conducted for the model reaction between toluene and *N*-methyl toluenesulfonamide (Table 1). After substantial efforts, reaction conditions were discovered that allowed amination to proceed under mild conditions and at room temperature (entry 8).

Copper catalyst (entry 1) and oxidant[12] are essential components of the reaction. The 1,3-indanedione additive also plays a role enhancing the overall yield of the reaction (entry 6 vs entry 3). Although 1,3-diketones capable of bidentate coordination (entry 5) are known ligands for copper-catalyzed C−N bond formation,[13] the role of 1,3-indanedione in this reaction remains unclear; a working hypothesis is that it may be serving as a monocoordinate ligand for copper. Despite further efforts, improvements in the yield of amination product (∼50−55%) could not be attained using commercially available oxidants such as *t*-BuOOAc or *t*-BuOOBz (**A**, entry 6). On the basis of work by Andrus,[14] we explored a variety of *tert*-butyl peroxybenzoate based oxidants containing electron-withdrawing substituents (**B**−**D**, entries 7−9).[15] Overall, an electron-withdrawing 3-trifluoromethyl substituted peroxybenzoate oxidant **C** afforded higher yields and was used for subsequent aminations (entry 8). It has been proposed that the electron-withdrawing substituent may serve to weaken the perester bond, thereby reducing the energy barrier required for the formation of the *tert*-butoxy radical.[14] Other copper catalysts (entries 10 and 11) were significantly less effective as compared to $[MeCN]_4Cu(I)PF_6$, with the exception of $Cu(OTf)_2$, and previously disclosed iron catalysts[6b] are not capable of effecting the transformation (entry 12). Unfortunately, reducing the amount of the toluene hydrocarbon resulted in diminished yields (entries 13 and 14).

TABLE 1. Exploration of Reaction Parameters on the Amination of Toluene with *N*-Methyl Toluenesulfonamide



entry	catalyst	ligand	oxidant	yield, %[a]
1	none	no ligand	**A**	< 2
2	$Cu(OTf)_2$	no ligand	**A**	23
3	$[MeCN]_4Cu(I)PF_6$	no ligand	**A**	33
4	$[MeCN]_4Cu(I)PF_6$	batho-phenanthroline	**A**	33[b]
5	$[MeCN]_4Cu(I)PF_6$	1,3-diphenylpropanedione	**A**	52
6	$MeCN]_4Cu(I)PF_6$	1,3-indanedione	**A**	55
7	$[MeCN]_4Cu(I)PF_6$	1,3-indanedione	**B**	65
8	$\mathbf{[MeCN]_4Cu(I)PF_6}$	**1,3-indanedione**	**C**	**70**
9	$[MeCN]_4Cu(I)PF_6$	1,3-indanedione	**D**	49
10	$CuCl_2$, $Cu(OAc)_2$ CuI or $Cu(ClO_4)_2$	1,3-indanedione	**C**	< 15
11	$Cu(OTf)_2$	1,3-indanedione	**C**	63
12	$FeBr_3$ or $FeCl_2$	1,3-indanedione	**C**	< 2
13	$[MeCN]_4Cu(I)PF_6$	1,3-indanedione	**C**	28[c]
14	$[MeCN]_4Cu(I)PF_6$	1,3-indanedione	**C**	47[d]

[a] Determined by ^{1}H NMR analysis versus an internal standard. [b] 5 mol % ligand was used. [c] 5 equiv of toluene was used. [d] 10 equiv of toluene was used.

Having established suitable reaction conditions for the amination of a representative primary benzylic hydrocarbon (toluene), the range of capable sulfonamide coupling partners was next examined (Table 2). Distinct from metal-nitrene based amination procedures,[2−4] this copper-based amination methology proceeds with both primary and secondary sulfonamides. Compared to secondary sulfonamides or electron-rich sulfonamides, lower yields were obtained with primary sulfonamides (entry 3) or with aryl sulfonamides substituted with electron-withdrawing groups (entries 7−9). In addition to sulfonamide nucleophilicity, steric factors influence the reaction, with the corresponding *N*-ethyl (entry 10) and *N*-cyclopropyl (entry 11) 4-toluenesulfonamides affording lower yields in comparison to the *N*-methyl analogue (entry 1). Unfortunately amides and carbamates, such as *tert*-butyl carbamate or *N*-methyl benzamide, were found to be unacceptable coupling partners in this reaction (yield < 10%).[16] The remaining mass balance in

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(11) (a) Kang, S.; Lee, H.-K. *J. Org. Chem.* **2010**, *75*, 237–240. (b) Mulcahy, J. V.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 12630–12631. (c) Wang, S.; Romo, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1284–1286. (d) Liu, Y.; Xiao, W.; Wong, M.-K.; Che, C.-M. *Org. Lett.* **2007**, *9*, 4107–4110. (e) Fleming, J. J.; Du Bois, J. *J. Am. Chem. Soc.* **2006**, *128*, 3926–3927. (f) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510–11511. (g) Wehn, P. M.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 12950–12951. (h) Trost, B. M.; Gunzner, J. L.; Dirat, O.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 10396–10415. (i) Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1998**, *120*, 4039–4040.

(12) Other oxidants, including *t*-BuOO*t*-Bu, *m*-CPBA, and $PhI(OAc)_2$ yielded < 5% of the amination product.

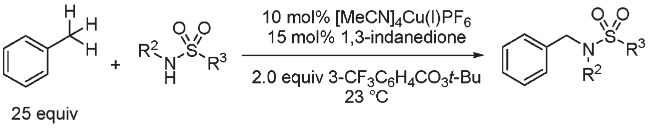
(13) For some representative examples, see: (a) Xia, N.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 337–339. (b) Xi, Z.; Liu, F.; Zhou, Y.; Chen, W. *Tetrahedron* **2008**, *64*, 4254–4259. (c) Shafir, A.; Lichtor, P. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3490–3491. (d) de Lange, B.; Lambers-Verstappen, M. H.; Schmieder-van de Vondervoort, L.; Sereinig, N.; de Rijk, R.; de Vries, A. H. M.; de Vries, J. G. *Synlett* **2006**, 3105–3109. (e) Shafir, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 8742–8743.

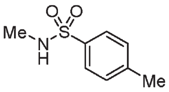
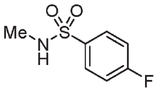
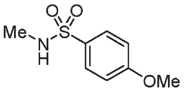
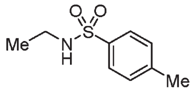
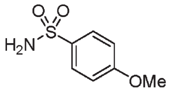
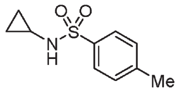
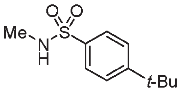
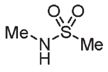
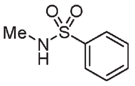
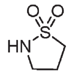
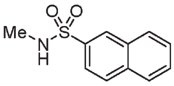
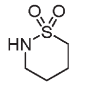
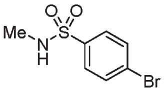
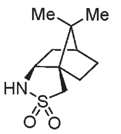
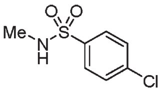
(14) Andrus, M. B.; Chen, X. *Tetrahedron* **1997**, *53*, 16229–16240.

(15) These oxidants could readily be synthesized in gram quantities in a single step, commencing from commercially available reagents. See Supporting Information for further details.

(16) Attempted reaction of *N*-(*p*-toluenesulfonyl)-*p*-toluenesulfonimidamide or 2,2,2-trichloroethoxysulfonamide under the reaction conditions afforded < 10% of the desired product as determined by ^{1}H NMR analysis of the unpurified reaction mixture.

TABLE 2. Copper-Catalyzed Amination of Toluene with Various Primary and Secondary Sulfonamides



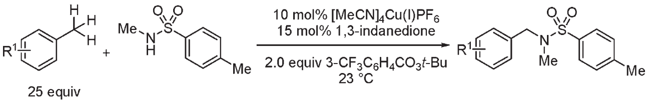
entry	sulfonamide	yield %[a]	entry	sulfonamide	yield %[a]
1		72	9		45
2		72	10		35
3		32	11		48
4		71	12		41
5		52	13		54
6		56	14		75
7		56	15		62
8		46			

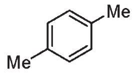
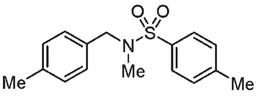
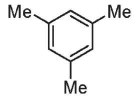
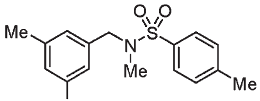
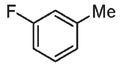
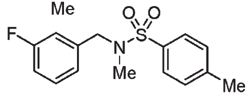
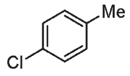
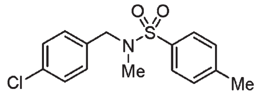
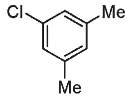
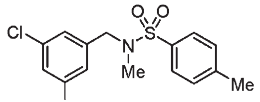
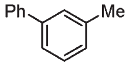
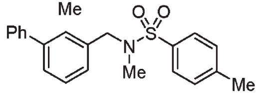
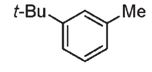
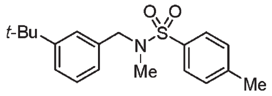
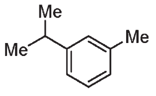
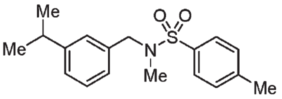
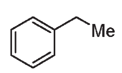
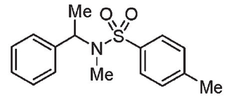
[a] Isolated yield.

this reaction primarily consisted of the sulfonamide and hydrocarbon starting materials. Applying heat (50 °C) to reactions that afforded lower yield (e.g., entry 3) did not result in further improvements in yields.

Within the few described procedures for amination of primary benzylic hydrocarbons,[4b,c,e,h,k,8b] little exploration as to the scope of viable hydrocarbon components have been disclosed. Additional primary benzylic substrates beyond toluene were explored in order to delineate the hydrocarbon scope (Table 3). In general, comparable yields were obtained with a variety of primary benzylic hydrocarbon coupling partners, including those containing electron-donating (entries 1, 2, 7, 8) or modestly electron-withdrawing substituents (entries 3−5). Notable is the selectivity observed in the amination of 3-isopropyltoluene, where amination is observed exclusively at the primary benzylic position over the tertiary benzylic position. Ethylbenzene, a secondary benzylic hydrocarbon, can be aminated under these conditions; however, an excess of hydrocarbon is still required (entry 9).

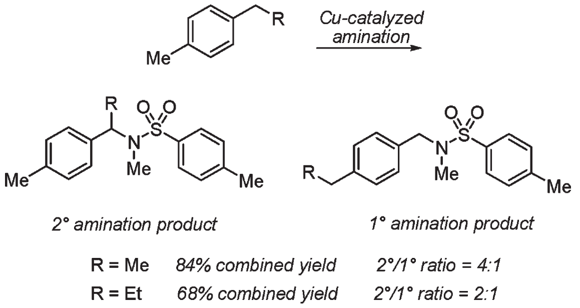
TABLE 3. Copper-Catalyzed Amination of Various Primary Benzylic Hydrocarbons with *N*-Methyl 4-Toluenesulfonamide



entry	hydrocarbon	product	yield %[a]
1			61
2			56
3			63
4			63
5			61
6			71
7			66
8			39[b]
9			64 59[c] 33[d]

[a] Isolated yield. [b] Only regioisomeric amination product as observed by ^{1}H NMR analysis of the unpurified reaction mixture. [c] 10 equiv of ethylbenzene was utilized. [d] 3 equiv of ethylbenzene was utilized.

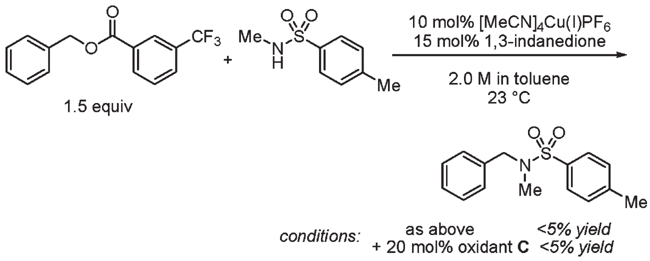
SCHEME 1. Exploration of C−H Amination Selectivity between Primary and Secondary Benzylic Sites[a]



[a] Isolated yield of combined products. Secondary/primary ratio determined by ^{1}H NMR analysis of the unpurified reaction mixture.

Intrigued by the selectivity observed with 3-isopropyltoluene, the following two experiments were conducted with 4-ethyltoluene and 4-*n*-propyltoluene (Scheme 1). Copper-catalyzed amination was explored under the developed reaction conditions, and selectivity for amination at the primary and secondary benzylic positions was determined by ^{1}H NMR analysis of the unpurified reaction mixture. Reaction of *N*-methyl 4-toluenesulfonamide with 4-ethyltoluene gave a 4:1 mixture of products in favor of amination at

SCHEME 2. Reaction of Benzyl 3-(Trifluoromethyl)benzoate



the secondary benzylic position.[17] Increasing the steric hindrance of the secondary benzylic site resulted in a diminished selectivity of 2:1 for the secondary position. As with previous C−H aminations, this copper-catalyzed procedure remains sensitive to steric effects, with selectivity favoring reaction at a secondary benzylic C−H > primary benzylic C−H > tertiary benzylic C−H.[18,19]

We have previously demonstrated that a benzylic acetate intermediate, the product of a Kharasch−Sosnovsky reaction,[20] can be converted to a sulfonamide product under copper-catalyzed conditions.[5b,21] Interestingly, when benzyl 3-(trifluoromethyl)benzoate was subjected to the copper-catalyzed reaction conditions, none of the amination product was obtained (Scheme 2). This disparate result suggests that benzoate esters, formed via a competing Kharasch−Sosnovsky reaction, do not serve as viable intermediates in the current amination methodology.[22] Further studies are required to support a mechanistic hypothesis; however, on the basis of the established Kharasch-Sosnovsky reaction,[20] we favor a mechanism that involves initial formation of a benzylic radical. Formation of a C−N bond may then proceed via a transient carbocation.[23] The benzylic carbocation intermediate is likely generated directly from the benzylic radical,[24] as the described reaction conditions are not sufficient to induce carbocation formation from the benzyl benzoate (Scheme 2).

In conclusion, we have developed a room-temperature, copper-catalyzed procedure for the amination of primary benzylic hydrocarbons with sulfonamide substrates. Furthermore, the reaction proceeds with both primary and secondary sulfonamides and is suitable for the coupling of an assortment of benzylic hydrocarbon species under mild conditions. A significant limitation of the current procedure remains the need for an excess (25 equiv) of the hydrocarbon component. However, given the shortage of established methodologies for amination at a primary benzylic position, this work demonstrates proof-of-principle that such aminations can proceed under mild conditions and through mechanisms distinct from metal-nitrene based processes. Further investigations aimed at reducing the amount of hydrocarbon species required to effect the transformation remain ongoing.

Experimental Section

General Procedure for the Copper-Catalyzed Amination of Primary Benzylic C−H Bonds with Sulfonamides. Preparation of *N*-Benzyl-4-methoxy-*N*-methyl-benzenesulfonamide (Table 2, entry 2). Into a 20 mL vial equipped with a magnetic stir bar were weighed [MeCN]$_4$Cu(I) PF$_6$ (74 mg, 0.2 mmol, 10 mol %), 1,3-indanedione (44 mg, 0.3 mmol, 15 mol %), and *N*-methyl 4-methoxybenzenesulfonamide (402 mg, 2.0 mmol, 1.0 equiv). The mixture was diluted with toluene (5.3 mL, 50 mmol, 25 equiv) and stirred at room temperature for 15 min. After this time, the 3-CF$_3$C$_6$H$_4$CO$_3$*t*-Bu oxidant (1.05 g, 4.0 mmol, 2.0 equiv) was added in a single addition via syringe. The vial was placed under an atmosphere of nitrogen and fitted with a septum or Teflon-coated cap. After 3 days of stirring at room temperature, the resulting mixture was poured into a 125 mL separatory funnel containing aqueous sodium carbonate (75 mL), and the mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over MgSO$_4$, filtered, and concentrated under reduced vacuum. The desired product was purified by column chromatography through silica gel, eluting with a gradient of 100% hexanes to 20% ethyl acetate in hexanes to afford the title compound as an off-white solid (417 mg, 72% yield). Mp 117−118 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.81 (2H, d, J = 9.0 Hz), 7.38−7.31 (5H, m), 7.05 (2H, d, J = 9.0 Hz), 4.14 (2H, s), 3.92 (3H, s), 2.60 (3H, s); ^{13}C NMR (100 MHz, CDCl$_3$) δ 162.9, 135.7, 129.6, 129.0, 128.6, 128.4, 127.9, 114.3, 55.6, 54.1, 34.3; IR (KBr) ν 3002, 2846, 1595, 1455, 1339, 1305, 1261, 1153, 736, 560 cm^{-1}; HRMS (ESI$^+$) *m*/*z* calcd for C$_{15}$H$_{17}$NO$_3$SNa [M + Na]$^+$ 314.0821, found 314.0824.

Acknowledgment. This paper is dedicated in memory of Professor Keith Fagnou. We are grateful to Merck Frosst for providing financial support to H.F. during his undergraduate work term and colleagues for helpful discussions, in particular Austin Chen, Jason Burch, and Ernest Lee.

Supporting Information Available: Experimental procedures and compound characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Varying levels of selectivity have been observed in previous aminations with 4-ethyltoluene. For example, a secondary:primary selectivity of 3:1 was observed in the Cu(I)-catalyzed reaction of 4-ethyltoluene with PhI=NTs, while ZnBr$_2$ afforded only the secondary product; see ref 4d. A secondary:primary:tertiary selectivity of 6:1:2 was observed with a Tp^{Br3}Cu-(NCMe) catalyst with PhI=NTs; see ref 4k. In contrast, a Rh-catalyst/sulfonimidamide system observed amination exclusively at the secondary carbon; see ref 4e.

(18) For a discussion of C−H bond reactivity and steric effects in Rh-nitrene aminations, see ref 4j. With Cu-nitrene aminations, see refs 4e, 4h, 4k.

(19) Interestingly, a gold catalyst has recently been described that favors nitrene insertion into sp^2 C−H bonds over benzylic sp^3 C-H bonds; see: Li, Z.; Capretto, D. A.; Rahaman, R. O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058–12059.

(20) For leading reviews and references on the Kharasch−Sosnovsky reaction, see: (a) Andrus, M. B.; Lashley, J. C. *Tetrahedron* **2002**, *58*, 845–866. (b) Eames, J.; Watkinson, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3567–3571. (c) Kharasch, M. S.; Sosnovsky, G. *J. Am. Chem. Soc.* **1958**, *80*, 756.

(21) (a) Powell, D. A.; Pelletier, G. *Tetrahedron Lett.* **2008**, *49*, 2495–2498. (b) Borduas, N.; Powell, D. A. *J. Org. Chem.* **2008**, *73*, 7822–7825.

(22) Under the current amination conditions, < 20% of benzyl 3-(trifluoromethyl)benzoate was detected in the ^{1}H NMR spectrum of the unpurified reaction mixture.

(23) Alternatively, carbon−nitrogen bond formation may proceed from an Cu(III) species. Aminations that proceed via aryl-Cu(III)-N species have recently been described, and Cu(III) intermediates have been proposed in other Cu-catalyzed allylic aminations; see refs 5a, 5c, and Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196–9197.

(24) For recent examples of aminations which proceed via postulated carbocations, see: (a) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409–413. (b) Sreedhar, B.; Reddy, P. S.; Reddy, M. A.; Neelima, B.; Arundhathi, R. *Tetrahedron Lett.* **2007**, *48*, 8174–8177.