ORGANIC
LETTERS

2006
Vol. 8, No. 26
6031−6034

Copper-Catalyzed Amidation of Allylic and Benzylic C—H Bonds

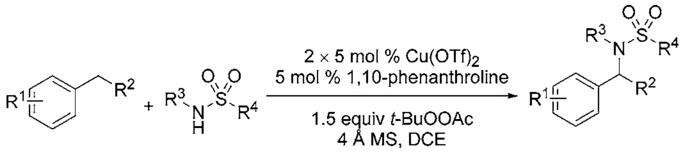
Guillaume Pelletier and David A. Powell*

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

david_powell2@merck.com

Received October 11, 2006

ABSTRACT



A copper-catalyzed amidation of allylic and benzylic C–H bonds with both primary and secondary sulfonamides is described. The reaction is applicable to the coupling of a diverse set of hydrocarbon species with aryl, heteroaryl, and alkyl sulfonamides and is tolerant of a variety of functional groups. Mechanistic insight has been gained through the isolation of a benzylic acetate intermediate, which was demonstrated to undergo facile conversion to the substituted sulfonamide product under copper catalysis.

The formation of C−N bonds is of fundamental importance in organic synthesis, owing to the high prevalence of nitrogen-containing molecules of natural and pharmaceutical relevance.[1] The vast majority of techniques for the introduction of C−N bonds rely on functional group interconversions for their synthesis. In contrast, the formation of new C−N bonds directly from C−H bonds represents an extremely attractive and efficient alternative.[2] Considerable achievements have been made within the past several years in order to effect amidation via a C−H activation strategy, particularly with regards to allylic and benzylic C−H bonds.[3−7]

For example, C−H amidation methodologies that proceed through transition metal-nitrene (imido) intermediates[8] have been demonstrated with a variety of metal catalysts, including

---

(1) *Modern Amination Reactions*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2000.

(2) For a recent review of oxidative functionalization of C−H bonds, see: Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439−2463.

(3) For some recent reviews of C−H bond amidations, see: (a) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518−3520. (b) Du, Bois, J. *Chemtracts* **2005**, *18*, 1−13. (c) Espino, C. G.; Du Bois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed; Wiley-VCH: Weinheim, 2005; pp 379−416. (d) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657−669.

(4) Representative intramolecular metal-nitrene-type amidations: (a) Kim, M.; Mulcahy, J. V.; Espino, C. G.; Du Bois, J. *Org. Lett.* **2006**, *8*, 1073−1076. (b) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198−14199. (c) Zhang, J.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2005**, *46*, 5403−5408. (d) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210−4212. (e) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378−15379. (f) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 3610−3619. (g) Fruit, C.; Müller, P. *Helv. Chim. Acta* **2004**, *87*, 1607−1615. (h) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3465−3468. (i) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935−6936. (j) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598−600. (k) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728−6729.

(5) Representative intermolecular metal-nitrene-type amidations: (a) Fructos, M. R.; Trofimenko, S.; Díaz-Requejo, M. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 11784−11791. (b) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048−9049. (c) 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. (d) Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 9561−9564. (e) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 3339−3342. (f) Yang, J.; Weinberg, R.; Breslow, R. *Chem. Commun.* **2000**, 531−532. (g) Au, S.-M.; Huang, J.-S.; Che, C.-M.; Yu, W.-Y. *J. Org. Chem.* **2000**, *65*, 7858−7864. (h) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233−2236. (i) Nägeli, I.; Baud, C.; Bernardinelli, G.; Jacquier, Y.; Moran, M.; Müller, P. *Helv. Chim. Acta* **1997**, *80*, 1087−1105. (j) Mahy, J. P.; Bedi, G.; Battioni, P.; Mansuy, D. *Tetrahedron Lett.* **1988**, *29*, 1927−1930. (k) Breslow, R.; Gellman, S. H. *J. Chem. Soc., Chem. Commun.* **1982**, 1400−1401.

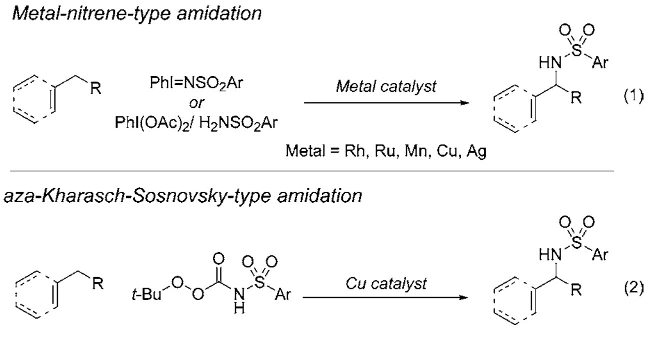
(6) (a) Kohmura, Y.; Kawasaki, K.-i.; Katsuki, T. *Synlett* **1997**, 1456−1458. (b) Smith, K.; Hupp, C. D.; Allen, K. L.; Slough, G. A. *Organometallics* **2005**, *24*, 1747−1755. (c) Clark, J. S.; Roche, C. *Chem. Commun.* **2005**, 5175−5177.

(7) For other strategies for the amination of allylic and benzylic C−H bonds, see: (a) Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4131−4146. (b) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1708.

(8) Review: (a) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905−2919. (b) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571−1586.

10.1021/ol062514u CCC: $33.50

Scheme 1. Catalytic Methods for C−H Bond Amidation



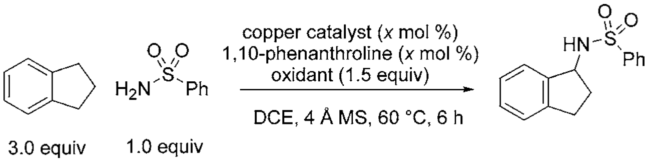
rhodium, ruthenium, and manganese (Scheme 1, eq 1). Although great strides have been made in intramolecular[4] amidation reactions, intermolecular[4e,5] couplings remain less advanced, often requiring an excess (>5 fold) of hydrocarbon component and proceeding in poor to modest yield. Furthermore, as a consequence of their mechanism, these amidation methodologies remain restricted to the coupling of primary amide components.

An intriguing alternative to the metal-nitrene-based amidation strategies is the copper-catalyzed allylic and benzylic amidation reaction first disclosed by Katsuki and coworkers[6a] (Scheme 1, eq 2). The reaction utilizes preformed peroxycarbamates, which serve as both the oxidant and amine component, and is based on a Kharasch−Sosnovsky reaction.[9] Although the reaction is conceptually a powerful complement to the metal-nitrene-type amidation methods, the requirement for presynthesized, unstable peroxycarbamates, combined with the narrow substrate scope and poor yields, severely limits the synthetic utility of this process.[6b] In addition, the course of the reaction (amidation versus oxidation) remains highly dependent on the electronic properties of the peroxycarbamate species as well as the ligand and hydrocarbon component used.[6c]

Inspired by these efforts as well as early reports by Kharasch,[10] we sought to develop a more general copper-catalyzed intermolecular amidation strategy that would be capable of coupling *both primary and secondary amide* reagents with a range of hydrocarbon species. Key to the merit of such a methodology would be the division of amide and oxidant into separate components, thereby circumventing the need for the presynthesis of unstable reagents.[6,8]

Our initial explorations focused on the intermolecular coupling reaction between indane and benzenesulfonamide (Table 1). Choice of copper catalyst[11] ($Cu(OTf)_2$) and oxidant[12] (*t*-BuOOAc) proved to be critical to the reaction efficiency. Although *t*-BuOOBz gave similar yields in the reaction of benzenesulfonamide with indane (entry 4 vs entry 5), we found the reaction of other hydrocarbon species with *t*-BuOOBz to be less general than that with *t*-BuOOAc. In addition, the acetic acid byproduct from the reaction with *t*-BuOOAc is easier to remove during the workup procedure than benzoic acid.

Table 1. Exploration of Reaction Parameters on the Amidation of Indane with Benzenesulfonamide



entry	catalyst	ligand	oxidant	yield %[a]
1	none	5 mol %	*t*-BuOOAc	0[b]
2	$Cu(OAc)_2$ (10 mol %)	10 mol %	*t*-BuOOAc	8[b]
3	$Cu(OTf)_2$ (10 mol %)	10 mol %	*t*-BuOOH	20[b]
4	$Cu(OTf)_2$ (10 mol %)	10 mol %	*t*-BuOOBz	48
5	$Cu(OTf)_2$ (10 mol %)	10 mol %	*t*-BuOOAc	49
6	$Cu(OTf)_2$ (10 mol %)	10 mol %	*t*-BuOOAc [addition over 6 h]	63
7	**$Cu(OTf)_2$** **(2 × 5 mol %)**	**5 mol %**	***t*-BuOOAc** **[addition over 6 h]**	**73**
8	$Cu(OTf)_2$ (2 × 5 mol %)	5 mol %	*t*-BuOOAc [addition over 6 h]	35[b,c]
9	$Cu(OTf)_2$ (2 × 5 mol %)	5 mol %	*t*-BuOOAc [addition over 6 h]	41[d]

[a] Isolated yield. [b] Determined by HPLC analysis versus a calibrated internal standard (average of two runs). [c] Reaction conducted at room temperature. [d] 1.0 equiv of indane was used.

Further improvements in yield could be realized through slow addition of the oxidant via syringe pump over 6 h (entry 6). Finally, by adding the copper catalyst in two portions of 5 mol %, first at the start of the reaction and then after 3 h, we were able to generate the amidation product in a reasonable 73% isolated yield (entry 7).[13,14]

With a suitable set of reaction conditions developed, we then investigated the range of sulfonamide coupling partners that could be employed (Table 2). Gratifyingly, *both primary and secondary sulfonamides* reacted with indane under the copper-catalyzed amidation procedure. This distinguishes the current methodology as one of the few allylic and benzylic C−H bond amidation processes in which secondary amide components can be employed.[15]

---

(9) (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.

(10) A single example of a copper-catalyzed amidation of cyclohexene with phthalimide in the presence of *tert*-butyl hydroperoxide (14% yield) was described by Kharasch almost 50 years ago: Kharasch, M. S.; Fono, A. *J. Org. Chem.* **1958**, *23*, 325−326.

(11) Other copper catalysts including $CuCl_2$, $Cu(MeCN)_4PF_6$, $Cu[BF_4]_2$, and CuOTf·benzene were less effective in the amidation reaction.

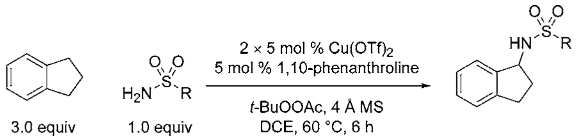
(12) Other oxidants including $PhI(OAc)_2$ and chloramine-T gave lower yields of product.

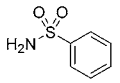
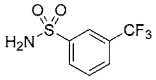
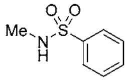
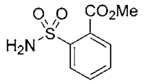
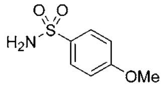
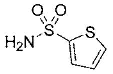
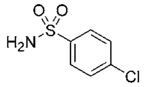
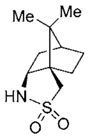
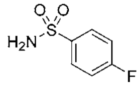
(13) Yields in the absence of 1,10-phenanthroline ligand are only slightly lower (64% by HPLC); however, use of an excess of ligand (20 mol %) results in dramatically diminished yields.

(14) We suspect the $Cu(OTf)_2$ catalyst may be deactivated or decomposing in the presence of an excess of the oxidant.

(15) The only other examples of similar amidation reactions with secondary amides were conducted with phthalimide[10] and saccharin[6b].

Table 2. Copper-Catalyzed Amidation of Indane with Primary and Secondary Sulfonamides



entry	sulfonamide	yield[a] (%)	entry	sulfonamide	yield[a] (%)
1		73	6		70
2		78	7		76
3		60	8		67
4		71	9		86[b]
5		69			

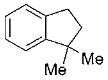
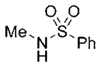
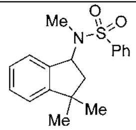
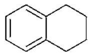
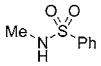
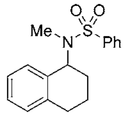
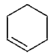
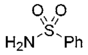
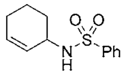
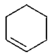
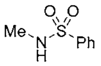
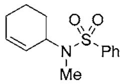
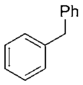
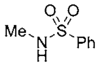
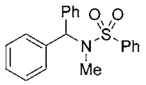
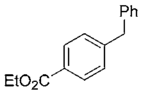
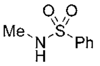
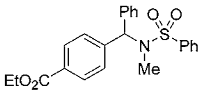
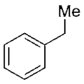
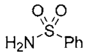
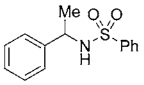
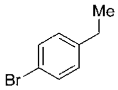
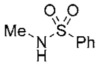
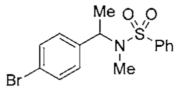
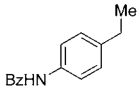
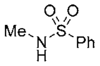
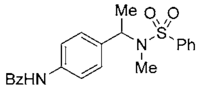
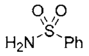
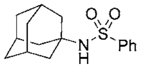
[a] Isolated yield. [b] Indane product was obtained as a 1:1 mixture of diastereomers.

Overall, the yields remain relatively consistent with sulfonamides of varying electronic and steric properties; the electron-rich *p*-methoxybenzenesulfonamide (entry 3), the electron-deficient *m*-trifluoromethansulfonamide (entry 6), and the *ortho*-substituted carbomethoxybenzenesulfonamide (entry 7) all yielded amidation products in 60−76% yields. Heteroaromatic 2-thiophenylsulfonamide (entry 8) was also tolerated in the copper-catalyzed amidation methodology. Finally, amidation with a chiral sultam (entry 9) proceeded in 86% yield, demonstrating that alkyl sulfonamides are also suitable reaction partners. Here, the indane product was formed as a 1:1 mixture of diastereomers that were separated by column chromatography and analyzed by X-ray crystallography to ascertain the absolute stereochemistry at the benzylic center.

Of technical significance, the reaction is operationally facile to conduct; all reagents were weighed and handled without the need for rigorous exclusion of air or moisture. In addition, few byproducts were detected in the crude reaction mixture,[16] with the exception of small amounts (typically <5%) of the *N*,*N*-bis-indanylsulfonamide product observed in the couplings of primary sulfonamides.

The Cu(OTf)$_2$/*t*-BuOOAc system could also be applied to the amidation of a range of hydrocarbon species with both primary and secondary sulfonamides (Table 3). For example, the direct generation of C−N bonds in 1,1-dimethylindane (entry 1) and tetrahydronapthalene (entry 2) occurs in reasonable yields under the general reaction conditions.

Table 3. Copper-Catalyzed Amidation of Various Hydrocarbon Components with Primary and Secondary Sulfonamides

entry	hydrocarbon	sulfonamide	product	yield %[a]
1				63
2				54
3				75
4				61
5				50[b]
6				47[b]
7				60[b]
8				49[b]
9				64[b]
10				56[b,c]

[a] Isolated yield. [b] Reaction conducted at 80 °C. [c] The 2-adamantane sulfonamide regioisomer was formed in <5% yield as determined by ^{1}H NMR analysis.

Amidation of the allylic C−H bonds of cyclohexene was realized both with benzenesulfonamide (entry 3) and *N*-methylbenzenesulfonamide (entry 4). In contrast to several metal-nitrene-based amidation reactions,[8] no aziridination product could be detected in the crude reaction mixture.[17] The method could also be applied to acyclic hydrocarbons as well as cyclic hydrocarbons. Thus diphenylmethane (entries 5 and 6) as well as ethylbenzene derivatives (entries 7−9) serve as suitable reaction partners in this transformation. Notably, the amidation procedure tolerates a variety of functional groups on the hydrocarbon component, including an ester (entry 6), aryl bromide (entry 8), and amide (entry 9). The reaction is chemoselective for C−N bond formation

---

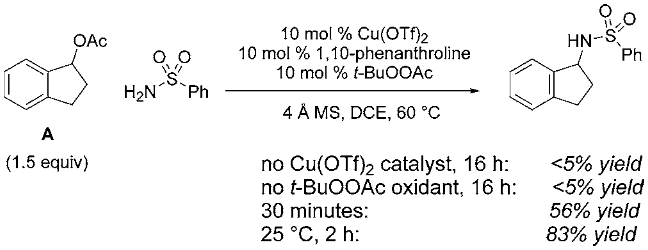
[16] For those reactions that proceeded in only moderate yield, the remaining mass balance consisted of primarily the sulfonamide and hydrocarbon starting materials.

[17] (a) Dauban, P.; Dodd, R. H. *Org. Lett.* **2000**, *2*, 2327−2329. (b) Albone, D. P.; Aujla, P. S.; Taylor, P. C. *J. Org. Chem.* **1998**, *63*, 9569−9571. (c) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742−2753.

with a secondary sulfonamide in the presence of a secondary benzamide (entry 9). Finally, amidation of the C−H bonds of adamantane could be achieved (entry 10). Here reaction occurs preferentially at the bridgehead position, affording the 1-adamantyl sulfonamide in 56% yield and greater than 95:5 regioselectivity.

Acetate **A** has been observed in minor quantities (<5% by HPLC, MS) during the course of our amidation reaction, presumably forming via a direct Kharasch−Sosnovsky reaction with the *tert*-butylperacetate oxidant. To help ascertain whether **A** is a potential intermediate in this reaction, we explored the coupling of 1-indanyl acetate **A** with benzensulfonamide under our copper-catalyzed conditions (Scheme 2). Reaction of **A** with the sulfonamide occurs very rapidly at room temperature within 2 h, giving an 83% isolated yield of product. This reaction does not proceed in the absence of copper, even at elevated temperatures (<5% yield). Interestingly, this coupling requires catalytic quantities of *both copper and tert-butylperacetate oxidant* in order to proceed, suggesting proper oxidation state of the copper catalyst is an important requirement for reactivity. While these observations do not preclude a mechanistic pathway in which product formation occurs directly from the hydrocarbon species, we have demonstrated that an intermediate benzylic acetate **A** can be converted to product under the copper-catalyzed conditions.[18,19]

Scheme 2. Reaction of 1-Indenyl Acetate with Benzensulfonamide



In conclusion, we have demonstrated a copper-catalyzed amidation of allylic and benzylic C−H bonds with sulfonamides that tolerates functionality on both coupling partners. This methodology serves as a complement to the metal-nitrene-type amidation processes in that both primary and secondary amides can be utilized. Further investigations into more active and robust copper catalysts and extension to other amide coupling components[20] is ongoing.

Acknowledgment. We thank Zahir Sadikali (Merck Frosst) for conducting preliminary experiments, NSERC for an undergraduate research award to G.P., Nancy N. Tsou and Richard G. Ball at Merck Research Laboratories (Rahway) for X-ray crystallographic analysis, and the McGill University Mass Spectroscopy Unit for HRMS analysis.

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

OL062514U

---

[18] A third mechanistic possibility involves oxidation of the hydrocarbon species to an alkene, followed by a copper-catalyzed hydroamination, although diphenylmethane and adamantane, for which alkene intermediates are unlikely, are reactive under our conditions. See: Taylor, J. G.; Whittall, N.; Hii, K. K. *Org. Lett.* **2006**, *8*, 3561−3564.

[19] To our knowledge, this copper-catalyzed amidation reaction of a benzylic acetate has not previously been observed; however, copper-catalyzed aminations of allylic halides are known. See: Baruah, J. B.; Samuelson, A. G. *Tetrahedron* **1991**, *47*, 9449−9454.

[20] Under the optimized conditions described in table 1, amidation of indane with benzamide or *tert*-butyl carbamate proceeds in only 5% and 12% yields, respectively.