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Copper-Catalyzed Intermolecular Hydroamination of Alkenes

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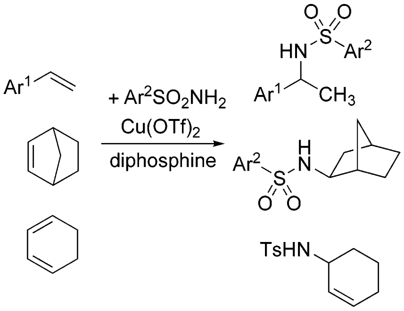
ABSTRACT



Regioselective additions of arylsulfonamides to vinylarenes, norbornene, and cyclohexadiene were achieved using a copper–diphosphine catayst under mild reaction conditions. These processes appear to be ligand-accelerated.

The addition of N−H bonds across alkenes (the hydroamination reaction) is an extremely attractive process for the production of amines. The uncatalyzed reaction is prohibited by a large activation energy barrier under ambient conditions, especially with electronically neutral alkene and/or non-nucleophilic NH substrates. With unsymmetrical alkenes, the reaction also poses additional regio- and stereoselectivity issues. Despite these considerable challenges, research in hydroamination catalysis has intensified significantly in recent years and has evolved into a highly competitive area of research.[1]

Among the number of intermolecular hydroamination reactions reported to date, the intermolecular addition of N−H to vinylarenes has been widely studied. These reactions can proceed with different regioselectivity, depending on the catalyst employed: anti-Markovnikov addition of aryl/alkylamines occurs in the presence of strong Brønsted bases,[2] organolanthanide,[3] rhodium,[4] or ruthenium[5] catalysts to furnish the linear product. Conversely, branched regioisomers result from the addition of aromatic amines effected by Pd(II)-diphosphine/triflic acid[6] or $TiCl_4$.[7] Thus far, general catalyzed additions of non-nucleophilic sulfonamides to vinylarenes are rare. Recently, Pt(II) and Au(I)/Ag(I) complexes have been reported to catalyze these additions, but only in low to moderate yields (45 and 51%).[8,9]

To the best of our knowledge, intermolecular hydroamination reactions catalyzed by copper complexes were only reported for reactions with alkenes containing electron-

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(1) For selected reviews within the last two years, see: (a) Hazari, N.; Mountford, P. *Acc. Chem. Res.* **2005**, *38*, 839. (b) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (c) Hultzsch, K. C. *Org. Biomol. Chem.* **2005**, *3*, 1819. (d) Xu, L. W.; Xia, C. G. *Eur. J. Org. Chem.* **2005**, 633. (e) Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673. (f) Beller, M.; Tillack, A.; Seayad. J. In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; VCH: Weinheim, 2004; Vol. 2, pp 403−414.

(2) Kumar, K.; Michalik, D.; Castro, I. G.; Tillack, A.; Zapf, A.; Arlt, M.; Heinrich, T.; Böttcher, H.; Beller, M. *Chem. Eur. J.* **2004**, *10*, 746.

(3) Ryu, J. S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584.

(4) Utsunomiya, M.; Kuwano, R.; Katwatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 5608.

(5) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2702.

(6) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546.

(7) Kaspar, L. T.; Fingerhut, B.; Ackermann, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 5972. Competing hydroarylation was observed using this catalyst.

(8) Qian, H.; Widenhoefer, R. A. *Org. Lett.* **2005**, *7*, 2635.

(9) Zhang, J.; Yang, C. G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798.

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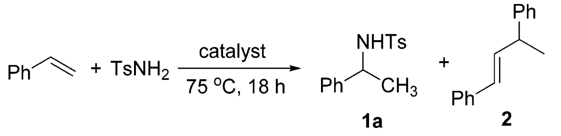
withdrawing substituents (Michael acceptors).[10] Following our recent discovery of copper(II) triflate as an effective catalyst for the addition of O−H bonds to norbornene,[11] we initiated a study to develop the corresponding hydroamination reactions. Herein, we provide the first examples of the copper-catalyzed addition of arylsulfonamides to vinyl arenes, norbornene, and 1,3-cyclohexadiene.

Initially, 10 mol % of copper(II) triflate was used in the reaction between toluenesulfonamide and styrene. Gratifyingly, product formation was observable at 75 °C (Table 1, entry 1)—a lower temperature than that required by other catalysts. Despite the modest yield (42%), the branched 1-phenethyltosylamide **1a** was obtained as the only product. To validate the unique reactivity of the catalyst, a set of control experiments were conducted in the presence of other copper salts, as well as triflic acid. The results show that the combination of the triflate counteranion (entries 2 and 3) and the +2 oxidation state (entries 4−6) is crucial for catalytic activity. Notably, triflic acid alone gave a very low yield of **1a** under these conditions, with concomitant formation of a styrene dimer **2** (entry 7). Hence, we rule out a process catalyzed solely by the Brønsted acid.[12]

Table 1. Reactions between Styrene and Toluenesulfonamide[a]



entry	catalyst (loading/mol %)	$TsNH_2$/styrene	**1a**:**2**[b] (%)
1	$Cu(OTf)_2$ (10)	2:1	42[c]
2	$CuSO_4$ (10)	2:1	–
3	$Cu(OAc)_2$ (10)	2:1	–
4	$[Cu(NCMe)_4]PF_6$ (10)	2:1	–
5	CuBr (10)	2:1	–
6	CuI (10)	2:1	–
7	TfOH (20)	2:1	14:15
8	$Cu(OTf)_2$/(±)-BINAP (10)	2:1	98[c]
9	$Cu(OTf)_2$/(±)-BINAP (5)	2:1	97[c]
10	$Cu(OTf)_2$/(±)-BINAP (1)	2:1	93[c]
11	$Cu(OTf)_2$/(±)-BINAP (10)	1:1	70[c]
12	$Cu(OTf)_2$/(±)-BINAP (10)	1:2	72[c]
13	$Cu(OTf)_2$/(±)-BINAP (10)	1:4	75[c]

[a] Typical procedure: $TsNH_2$ (number of equivalents indicated), styrene (1 mmol), solvent (1 mL), 75 °C, 18 h. [b] Isolated yield after purification by column chromatography, duplicated to within ±3%. [c] Dimer **2** was not detected in the reaction mixture (^1H NMR).

Significantly, ligand screening revealed that the copper-catalyzed process is greatly enhanced by the addition of BINAP ligand (entry 8). Consequently, the catalyst loading can be reduced to 1 mol % before any adverse effect became noticeable (entries 9 and 10).

An excess of $TsNH_2$ is needed for the high yield—using an equivalent/excess of styrene leads to a lower yield of **1a**, although the formation of the dimer **2** remained negligible (<5%) under these reaction conditions. Significantly, increased stoichiometry of styrene has very little effect (entries 11−13), implying that the alkene is not involved in the rate-determining step.

The scope of the reaction was subsequently examined by introducing electronically different substituents to the substrates (Table 2). 4-Nitrobenzenesulfonamide ($NsNH_2$) was employed in this part of the study, as the nosyl (Ns) moiety is often used as a protecting and activating group in the synthesis of secondary amines.[13]

Using 5 mol % catalytic loading, the addition proceeded smoothly to afford the branched regioisomer with moderate to excellent yields in most cases. The reactions of $TsNH_2$ with styrene and electron-deficient 4-fluorostyrene gave fast and high-yielding reactions (entries 1 and 2), while the reaction of 4-chlorostyrene was somewhat slower (entry 3). The introduction of methyl groups has a retarding effect (entries 4 and 5), although moderate yields can be obtained by prolonging the reaction time. Similarly, the addition of $TsNH_2$ to 2-vinylnaphthalene also proceeded with an acceptable yield (entry 7). In comparison, the addition of the less nucleophilic $NsNH_2$ is generally slower, although the relative activity remained broadly similar: Best yields were obtained with the unsubstituted and 4-fluoro-styrenes (entries 8 and 9), and moderate yields with 4-chloro- and 4-methylstyrenes (entries 10 and 12).

Additions to electron-rich 4-methoxystyrene are noteworthy. The reactions were very sluggish, and competitive dimerization of the vinylarene was observed, leading to mixtures of products (entries 6 and 13). Interestingly, attempted addition of $NsNH_2$ to vinylnaphthalene led exclusively to the formation of the dimer (entry 14).

Despite these limitations, the performance of the copper catalyst still surpasses other catalysts reported for the same reaction, such as the aforementioned platinum and gold catalysts, and NBS.[14]

The overall reactivity and the regioselectivity of the system suggest the reaction between a benzylic cation intermediate and nucleophilic arylsulfonamide. In the absence of the sulfonamide, either $Cu(OTf)_2$ or triflic acid can catalyze the formation of styrene dimer **2** at 75 and 85 °C, respectively. Thus, the involvement of a Brønsted acid in the catalytic cycle cannot be completely ruled out. This is further supported by the fact that the reaction between styrene and $TsNH_2$ is sequested in the presence of noncoordinating bases such as $CuCO_3$ and K_2CO_3 (10 mol %).

On the basis of these observations, a catalytic cycle is tentatively proposed (Scheme 1). We assume ligand exchange occurs between the catalyst and arylsulfonamide to generate a copper−sulfonamide intermediate **4**. This releases triflic acid that protonates the vinylarene, furnishing a benzylic

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[10] For example, see: Munro-Leighton, C.; Blue, E. D.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2006**, *128*, 1446.

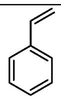
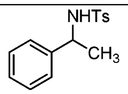
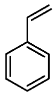
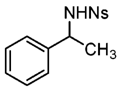
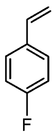
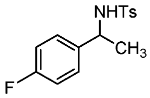
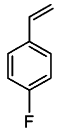
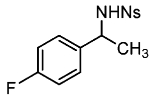
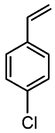
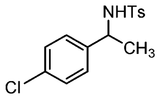
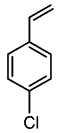
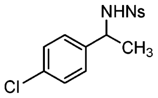
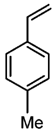
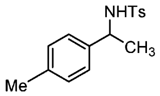
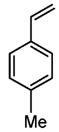
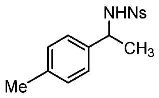
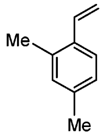
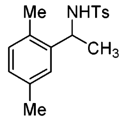
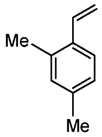
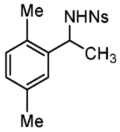
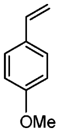
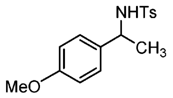
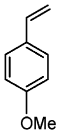
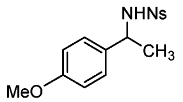
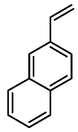
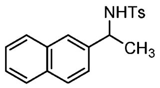
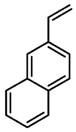
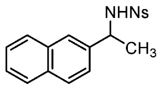
[11] Taylor, J. G.; Whittall, N.; Hii, K. K. *Chem. Commun.* **2005**, 5103.

[12] Strong Brønsted acids catalyze competitive hydroamination and hydroarylation reactions between styrene and aniline at 135 °C: Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542.

[13] (a) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353. (b) Fukuyama, T.; Jow, C. K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

[14] NBS (20 mol %) catalyzes the addition of sulfonamides to activated styrenes containing OMe or SMe groups only: Talluri, S. K.; Sudalai, A. *Org. Lett.* **2005**, *7*, 855.

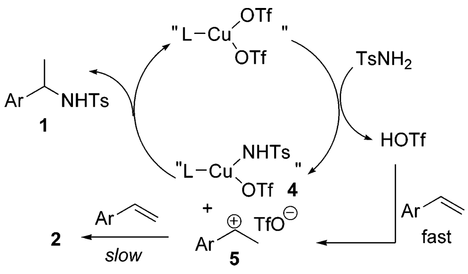
Table 2. Cu-Catalyzed Hydroamination of Vinylarenes with Arylsulfonamides[a]

entry	alkene	$ArSO_2NH_2$	product	yield[b] (%)	entry	alkene	$ArSO_2NH_2$	product	yield[b] (%)
1		$TsNH_2$	 **1a**	97[c]	8		$NsNH_2$	 **3a**	95
2		$TsNH_2$	 **1b**	95[c]	9		$NsNH_2$	 **3b**	83
3		$TsNH_2$	 **1c**	83	10		$NsNH_2$	 **3c**	62
4		$TsNH_2$	 **1d**	67	11		$NsNH_2$	 **3d**	63
5		$TsNH_2$	 **1e**	54	12		$NsNH_2$	 **3e**	43
6		$TsNH_2$	 **1f**	32 (29)[d]	13		$NsNH_2$	 **3f**	26 (32)[d]
7		$TsNH_2$	 **1g**	70	14		$NsNH_2$	 **3g**	- (75)[d]

[a] General reaction conditions: $Cu(OTf)_2$ (0.05 mmol), (±)-BINAP (0.05 mmol), $Ar_2SO_2NH_2$ (2.0 mmol), vinylarene (1.0 mmol), 1,4-dioxane, 75 °C, 36 h. [b] Isolated yield (based on vinylarene) after purification by column chromatography, duplicated to within ±3%. [c] Reaction time = 18 h. [d] Calculated by ^1H analysis of reactions mixtures. Value in parentheses corresponds to the yield of dimer (based on vinylarene).

cation. The TfO^- anion is envisaged to play an important role in the bond formation; for example, by enhancing the nucleophilicity of the amide through hydrogen bonding and/or stabilizing the cationic intermediate through ion pairing. In this catalytic model, formation of styrene dimer **2** results from the reaction of **5** with vinylarene, which becomes competitive when the sulfonamide addition (rate-determining step) is slow, as is the case when an electron-deficient sulfonamide and/or electron-rich vinylarene (weaker nucleophile and electrophile, respectively) were employed.

Scheme 1. Proposed Catalytic Cycle



Thus far, reactions performed with optically pure *R*-BINAP did not lead to any significant enantiomeric excess in the product under these conditions (<5%). This led us to speculate that the reaction may be reversible. To verify the reversibility of the C−N bond formation,[15] the configurational stability of optically pure (*S*)-**1a**[16] was examined with and without added (±)-BINAP ligand (Scheme 2).[17] Surprisingly, while the stereointegrity of (*S*)-**1a** was retained in the latter case, it deteriorated slowly in the presence of the

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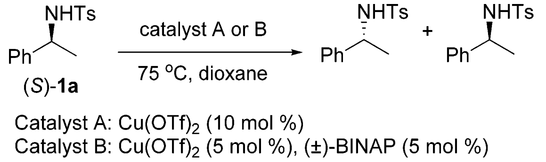
(15) Results of crossover experiments were inconclusive: With or without added ligand, a mixture of **3a**/$TsNH_2$ showed very little (<1%) crossover product, whereas **1a**/$NsNH_2$ showed a mixture of crossover products (CI-MS). This could be the result of substitution reactions.

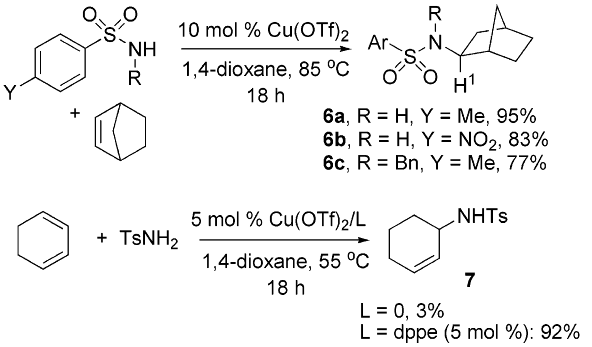
Scheme 2. Product Racemization Study



diphosphine (84% ee after 24 h). These experiments suggest that the ligand lowers the energy barrier of the copper-catalyzed process, rendering it reversible at 75 °C.

Preliminary studies have shown that the copper catalyst can also effect the addition of $TsNH_2$ to norbornene (Scheme 3). For example, the addition to the strained olefin furnished the hydroamination product **6a** in excellent yield. The efficiency of the system compares favorably with recent reports where 10 mol % of $[(COD)Pt(OTf)_2]$ was employed under similar conditions (>95% GC yield)[18] or 5 mol % of $Ph_3PAuCl/AgOTf$ at 85 °C (89%).[19] Furthermore, additions of electron-deficient 4-nitrophenylsulfonamide and *N*-benzyl-4-toluenesulfonamide can also be realized, giving products **6b** and **6c** in good yields. As was the case with O−H additions,[11] the reactions favor the exclusive formation of the *exo*-isomer (NMR spectroscopy).[20]

Scheme 3. Addition of Arylsulfonates to Norbornene and 1,3-Cyclohexadiene



Following recent reports of the addition of carbamates and sulfonamides to 1,3-dienes catalyzed by bimetallic systems $Bi(OTf)_3/[Cu(CH_3CN)_4]PF_6$[21] and $Ph_3PAuCl/AgOTf$,[22] the effectiveness of the copper catalyst in these additions was examined. Preliminary studies show a dramatic ligand acceleration effect. While $Cu(OTf)_2$ alone is ineffective for the addition of $TsNH_2$ to 1,3-cyclohexadiene at 55 °C, the presence of dppe induced catalytic turnovers to furnish the product **7a** in 92% yield. This observation emphasizes the importance of ligand in this catalytic system.

In summary, using a catalyst generated from copper(II) trifluoromethanesulfonate/diphosphine, regioselective additions of arylsulfonamides to vinylarenes, norbornene, and 1,3-cyclohexadiene can be achieved. The copper(II) catalyst was procured cheaply from commercial sources and stored and handled in air without recourse to gloveboxes. All these reactions can also be performed in air, using unpurified reagent-grade solvent. These practical simplicities provide ample justification of further explorations of its application in hydroamination and other olefin heterofunctionalization processes.

Acknowledgment. We are grateful to GSK and EPSRC for studentship support (J.G.T.).

Supporting Information Available: Experimental procedures, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Prepared by the tosylation of commercially available *S*-(−)-1-phenylethylamine.

(17) Enantiopurity of **1a** was assessed by chiral HPLC (Conditions: Chiralcel OD-H, *i*-PrOH/hexane 10: 90, flow rate 0.6 mL/min, $t_R = 16.8$ min, $t_S = 20.4$ min).

(18) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640.

(19) Four equivalents of styrene were needed for the Au-catalyzed reaction, which proceeded with 51% yield in 14 h (ref 9).

(20) Coupling between H-1 and its adjacent bridgehead methine proton is conspicuously absent (COSY spectrum of **6a** provided in the Supporting Info). This ^3J coupling is typically <1 Hz for an *endo*-proton and 4 Hz for an *exo*-proton. See: (a) Laszlo, P.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1964**, *86*, 1171−1179. (b) Franz, J. E.; Osuch, C.; Dietrich, M. W. *J. Org. Chem.* **1964**, *29*, 2922−2927.

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