Anti-Markovnikov hydroamination and hydrothiolation of electron-deficient vinylarenes catalyzed by well-defined monomeric copper(I) amido and thiolate complexes†

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Monomeric Cu(I) amido and thiolate complexes that are supported by the *N*-heterocyclic carbene ligand 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr) catalyze the hydroamination and hydrothiolation of electron-deficient vinylarenes with reactivity patterns that are consistent with an intermolecular nucleophilic addition of the amido/thiolate ligand of (IPr)Cu(XR) (X = NH or S; R = Ph, CH₂Ph) to free vinylarene.

The formation of C–S and C–N bonds *via* the addition of S–H/N–H bonds of thiols/amines across olefins is a promising atom efficient synthetic method.[1] Only a few transition metal catalysts for the regioselective hydroamination of styrenes have been reported.[2] Rarely observed "anti-Markovnikov" selectivity has been reported with Rh and Ru systems,[2e–h] while metal halides in combination with triflate salts or metal triflate systems catalyze "Markovnikov" addition of arylsulfonamides to vinylarenes and other olefins.[3] It is likely that many of these metal halide or triflate systems generate protic acid that functions as the active catalyst.[4] Similar to hydroamination, examples of transition metal catalyzed hydrothiolation of vinylarenes are relatively rare.[5]

We have recently prepared a series of monomeric Cu^I complexes with formally anionic heteroatomic ligands including amido, alkoxo, aryloxo and thiolate fragments.[6] Herein, we report that (IPr)Cu(X) {X = NHR or SR; IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, Chart 1} systems catalyze regioselective "anti-Markovnikov" hydroamination and hydrothiolation of activated vinylarenes.
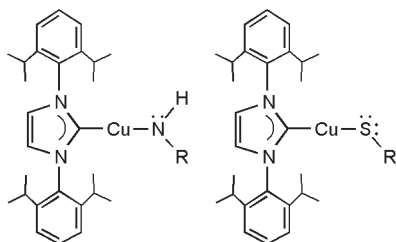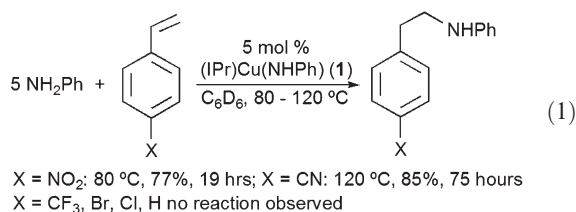

Chart 1 (IPr)Cu(X) [X = NHPh (**1**), NHCH₂Ph (**2**), SPh (**3**) or SCH₂Ph (**4**)] catalyst precursors.

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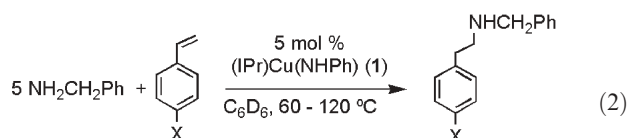
A benzene solution of 5 mol% (based on olefin) (IPr)Cu(NHPh) (**1**) with aniline and *para*-nitrostyrene produces the "anti-Markovnikov" product *N*-phenyl-*para*-nitrophenethylamine in 77% yield after 21 h at 80 °C (eqn 1). All yields given in eqn 1–5 have been determined by ^{1}H NMR spectroscopy against an internal standard. All organic products have been isolated and fully characterized, and isolated yields are provided in the ESI.† As previously discussed by Hartwig *et al.*, the use of excess amine is required to produce substantial or complete conversion.[7] *Control reactions in the absence of Cu catalyst do not result in hydroamination of vinylarene.*

$$5\ NH_2Ph\ +\ \text{(styrene, X)}\ \xrightarrow[\text{C}_6\text{D}_6,\ 80\ -\ 120\ ^\circ\text{C}]{\substack{5\ \text{mol}\,\%\\(\text{IPr})\text{Cu(NHPh)}\ (\mathbf{1})}}\ \text{(product, NHPh, X)}\quad (1)$$

X = NO₂: 80 °C, 77%, 19 hrs; X = CN: 120 °C, 85%, 75 hours
X = CF₃, Br, Cl, H no reaction observed

The reaction of aniline and *para*-cyanostyrene is also catalyzed by **1**, but a higher temperature (120 °C) and longer reaction time are required (eqn 1). Attempts at the catalytic hydroamination with aniline for vinylarenes that possess *para*-substituents with reduced electron-withdrawing ability do not yield new organic products. For example, heating solutions of **1** (C₆D₆) and aniline with *para*-X-styrene {where X = CF₃ ($\sigma_p{}^- = 0.65$), Br ($\sigma_p{}^- = 0.25$), Cl ($\sigma_p{}^- = 0.19$), or H ($\sigma_p{}^- = 0$)} to 120 °C results in no change after 48 h ($\sigma_p{}^-$ for NO₂ = 1.27 and CN = 1.00).

Although we have not been able to isolate the Cu^I amido complex formed from benzylamine, (IPr)Cu(NHCH₂Ph) (**2**), this system can likely be generated *in situ* upon reaction of (IPr)Cu(NHPh) and benzylamine. The combination of **1** and benzylamine at 100 °C produces a new (IPr)Cu system and free aniline. Attempted isolation of **2** results in decomposition (see the ESI†). Use of **1** as catalyst precursor with benzylamine extends the range of substituted styrenes that undergo hydroamination to the *p*-CF₃ compound (eqn 2). Thus, the transformations with benzylamine are successful when the *para* substituent of the vinylarene is nitro, cyano or perfluoromethyl (eqn 2), while the analogous reaction of the *p*-CF₃–styrene with aniline does not undergo reaction after 7 days (120 °C). Apparently, complex **1** is not sufficiently reactive to enter the catalytic cycle for the less activated perfluoromethyl styrene, and we presume that catalysis with the *p*-CF₃–styrene and benzylamine occurs *via* initial formation of complex **2**. For catalysis with benzylamine, yields by ^{1}H NMR are quantitative for X = CN or CF₃.

$5\ NH_2CH_2Ph\ +$ [p-substituted styrene, X] $\xrightarrow[C_6D_6,\ 60\ -\ 120\ ^\circ C]{\substack{5\ mol\ \% \\ (IPr)Cu(NHPh)\ (1)}}$ [product: 4-X-benzyl CH$_2$NHCH$_2$Ph] $\qquad (2)$

X = NO$_2$: 60 °C, 65%, 22 hrs; X = CN: 80 °C, >95%, 6 hrs;
X = CF$_3$: 120 °C, >95%, 86 hrs; X = Br, H, Cl, no reaction observed

In addition to control reactions in the absence of Cu amido complexes, which do not give the hydroamination product (see above), we attempted to catalyze these reactions with lithium amido or pyridine as base. Under conditions identical to the Cu-catalyzed reactions shown in eqn 1, aniline/*para*-nitrostyrene and aniline/*para*-cyanostyrene do not react in the presence of 5 mol% [Li][NHPh]. Likewise, attempted reaction (again, under conditions analogous to the Cu-catalyzed reactions) of benzylamine with *para*-cyanostyrene and aniline with *para*-nitrostyrene in the presence of pyridine do not give the hydroamination product.
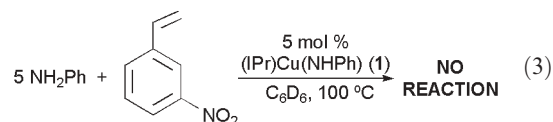
Several mechanisms have been elucidated for transition metal catalyzed hydroamination (and related reactions) of olefins. For example, early transition metal imido complexes have been proposed to undergo initial net [2 + 2] cycloaddition of olefins.[8] Hydroamination of olefins by late transition metal systems have been proposed to occur by olefin coordination and subsequent nucleophilic addition of the amine,[1a] formation of a π–arene complex and activation toward nucleophilic addition of the amine,[2h] olefin insertion into M–NR$_2$ bonds,[1a] and formation of η^3-allyl complexes (for styrenes) followed by amine addition to the allyl ligand.[2a,c]

The hydroamination reactions catalyzed by complexes **1** and **2** appear to be dependent upon the electron withdrawing ability of the *para*-substituent of the vinylarene. For the closely related addition of aniline to acrylonitrile, we have reported evidence supporting a pathway that involves rate-determining nucleophilic addition of the amido ligand of (IPr)Cu(NHPh) to *free* acrylonitrile.[6c] Similarly, we suggest that a related mechanism may be operative for the hydroamination of vinylarenes in which the rate-determining step is *intermolecular* nucleophilic addition of the heteroatom to free vinylarene (Scheme 1). Although the data are limited, the relative predilection toward hydroamination of vinylarenes as a function of the *para*-substituent (*i.e.*, reactivity observed only for more electron-withdrawing groups) is consistent with the proposed pathway. In addition, the more nucleophilic benzylamine reacts with the *p*-NO$_2$ and *p*-CN vinylarenes at lower temperature than does aniline, and benzylamine reacts with the *p*-CF$_3$ while aniline does not (eqn 1–2). Furthermore, although
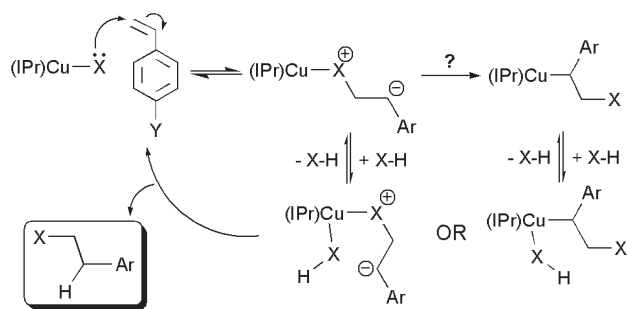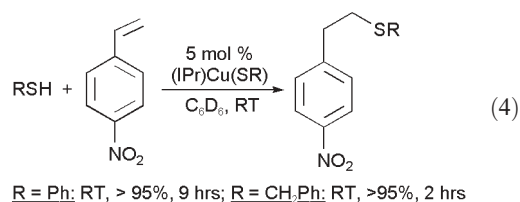
catalytic conversion of aniline and *p*-NO$_2$–styrene is successful, attempted catalysis with aniline and *m*-NO$_2$–styrene fails to yield hydroamination at temperatures up to 100 °C after 24 h (eqn 3).

$5\ NH_2Ph\ +$ [*m*-NO$_2$ styrene] $\xrightarrow[C_6D_6,\ 100\ ^\circ C]{\substack{5\ mol\ \% \\ (IPr)Cu(NHPh)\ (1)}}$ **NO REACTION** $\qquad (3)$

As an additional confirmation of the importance of the nucleophile, we attempted hydrothiolation of *para*-nitrostyrene with (IPr)Cu(SR)/thiols, which are presumably more nucleophilic than the (IPr)Cu(NHR)/amine analogs. Similar to the hydroamination reactions, using (IPr)Cu(SR) {R = Ph (**3**) or CH$_2$Ph (**4**)} as catalyst affords the hydrothiolation of the activated *p*-NO$_2$ compound *at room temperature* (eqn 4). *Under these conditions* (*i.e.*, <80 °C), reactions with less electron-withdrawing groups (*e.g.*, X = CN, CF$_3$, Br, Cl or H) do not proceed to products.

$RSH\ +$ [p-NO$_2$ styrene] $\xrightarrow[C_6D_6,\ RT]{\substack{5\ mol\ \% \\ (IPr)Cu(SR)}}$ [product: 4-NO$_2$-benzyl CH$_2$CH$_2$SR] $\qquad (4)$

R = Ph: RT, > 95%, 9 hrs; R = CH$_2$Ph: RT, >95%, 2 hrs

In an effort to demonstrate the potential utility of these Cu catalysts, we have prepared *N*-methyl-*N*-benzyl-*para*-nitrophenethylamine as shown in eqn 5. This compound is a precursor to a class III antiarrhythmic agent and has been prepared in four steps (overall yield 77%) from commercially available reagents in reaction sequences that incorporate HBr, HCl, benzene, ethanol, MeI, acetonitrile, benzaldehyde, potassium borohydride, formaldehyde and formic acid.[9] Using (IPr)Cu(NHPh) as catalyst, we have synthesized and isolated the amine in a single step from commercially available reagents (eqn 5). By ^{1}H NMR, the reaction proceeds to ∼70% yield, and the amine has been isolated in ∼50% yield. Although our unoptimized yield is lower than the previous process, the procedure is simpler and generates fewer byproducts and waste.

$5\ NH(Me)CH_2Ph\ +$ [p-NO$_2$ styrene] $\xrightarrow[C_6D_6,\ 60\ ^\circ C]{\substack{5\ mol\ \% \\ (IPr)Cu(NHPh)\ (1)}}$ [product: 4-NO$_2$-C$_6$H$_4$-CH$_2$CH$_2$-N(Me)(CH$_2$Ph)] $\qquad (5)$

70%

In summary, we have reported well-defined monomeric Cu(I) amido and thiolate complexes that catalyze the addition of N–H and S–H bonds of amines and thiols to activated vinylarenes. The anti-Markovnikov selectivity, which has only rarely been achieved with transition metal catalysts, is consistent with a mechanism that involves intermolecular X–C (X = N or S) bond formation and is inconsistent with transformations catalyzed by Brønsted acid impurities. Although non-catalyzed additions of amines to activated vinylarenes in polar solvents have been reported,[10] such transformations were not accessible with aniline or alkyl anilines, nor have they been reported for activating groups other than nitro. The Cu-catalyzed reactions likely resemble simple base-catalyzed olefin hydroamination,[1f] while potentially offering the flexibility of transition metal catalysis [*via* adjustment of ligand(s) and metal oxidation state] and milder reaction conditions (most base-catalyzed hydroamination reactions of vinylarenes occur at higher

Scheme 1 Proposed mechanism for hydroamination and hydrothiolation of vinylarenes [X = NHPh (**1**), NHCH$_2$Ph (**2**), SPh (**3**) or SCH$_2$Ph (**4**); Y = electron withdrawing group].
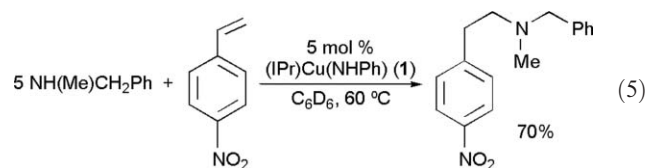
temperatures, often >150 °C).[1f] To our knowledge, reports of transition metal catalyzed "anti-Markovnikov" hydroamination of styrenes are limited to Ru and Rh, which are relatively expensive metals. Even though more active catalysts will be required for general synthetic utility, the development of Cu catalysts that are active for the hydroamination of activated vinyl arenes is a first step toward relatively inexpensive metals.

Notes and references

1 (a) T. E. Müller and M. Beller, *Chem. Rev.*, 1998, **98**, 675–703; (b) M. Beller, J. Seayad, A. Tillack and H. Jiao, *Angew. Chem., Int. Ed.*, 2004, **43**, 3368–3398; (c) S. Hong and T. Marks, *Acc. Chem. Res.*, 2004, **37**, 673–686; (d) J. F. Hartwig, *Pure Appl. Chem.*, 2004, **76**, 507–516; (e) J.-J. Brunet and D. Neibecker, in *Catalytic Hetero-functionalization: From Hydroamination to Hydrozirconation*, ed. A. Togni and H. Grützmacher, Wiley-VCH, Weinheim, 2001; pp. 91–132; (f) J. Seayad, A. Tillack, C. Hartung and M. Beller, *Adv. Synth. Catal.*, 2002, **344**, 795–813.

2 (a) U. Nettekoven and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 1166–1167; (b) M. Utsunomiya and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 14286–14287; (c) L. K. Vo and D. A. Singleton, *Org. Lett.*, 2004, **6**, 2469–2472; (d) K. Li, P. N. Horton, M. B. Hursthouse and K. K. Hii, *J. Organomet. Chem.*, 2003, **665**, 250–257; (e) M. Utsunomiya, R. Kuwano, M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 5608–5609; (f) M. Beller, H. Trauthwein, M. Eichberger, C. Breindl, J. Herwig, T. E. Müller and O. R. Thiel, *Chem.–Eur. J.*, 1999, **5**, 1306–1319; (g) M. Utsunomiya and J. F. Hartwig, *J. Am. Chem. Soc.*, 2004, **126**, 2702–2703; (h) J. Takaya and J. F. Hartwig, *J. Am. Chem. Soc.*, 2005, **127**, 5756–5757; (i) L. T. Kaspar, B. Fingerhut and L. Ackermann, *Angew. Chem., Int. Ed.*, 2005, **44**, 5972–5974.

3 (a) J. G. Taylor, N. Whittall and K. K. Hii, *Org. Lett.*, 2006, **8**, 3561–3564; (b) J. Zhang, C.-G. Yang and C. He, *J. Am. Chem. Soc.*, 2006, **128**, 1798–1799; (c) L. T. Kaspar, B. Fingerhut and L. Ackermann, *Angew. Chem., Int. Ed.*, 2005, **44**, 5972–5974; (d) H. Qin, N. Yamagiwa, S. Matsunaga and M. Shibasaki, *Chem.–Asian J.*, 2007, **2**, 150–154.

4 D. C. Rosenfeld, S. Shekhar, A. Takemiya, M. Utsunomiya and J. F. Hartwig, *Org. Lett.*, 2006, **8**, 4179–4182.

5 T. Kondo and T.-a. Mitsudo, *Chem. Rev.*, 2000, **100**, 3205–3220.

6 (a) C. Munro-Leighton, E. D. Blue and T. B. Gunnoe, *J. Am. Chem. Soc.*, 2006, **128**, 1446–1447; (b) L. A. Goj, E. D. Blue, S. A. Delp, T. B. Gunnoe, T. R. Cundari, A. W. Pierpont, J. L. Petersen and P. D. Boyle, *Inorg. Chem.*, 2006, **45**, 9032–9045; (c) C. Munro-Leighton, S. A. Delp, E. D. Blue and T. B. Gunnoe, *Organometallics*, 2007, **26**, 1483–1493.

7 A. M. Johns, N. Sakai, A. Ridder and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 9306–9307.

8 B. F. Straub and R. G. Bergman, *Angew. Chem., Int. Ed.*, 2001, **40**, 4632–4635.

9 H. Liu, M. Ji, X. Luo, J. Shen, X. Huang, W. Hu, H. Jiang and K. Chen, *J. Med. Chem.*, 2002, **45**, 2953–2969.

10 W. J. Dale and G. Buell, *J. Org. Chem.*, 1956, **21**, 45–47.