C–H Functionalization

DOI: 10.1002/ange.201201921

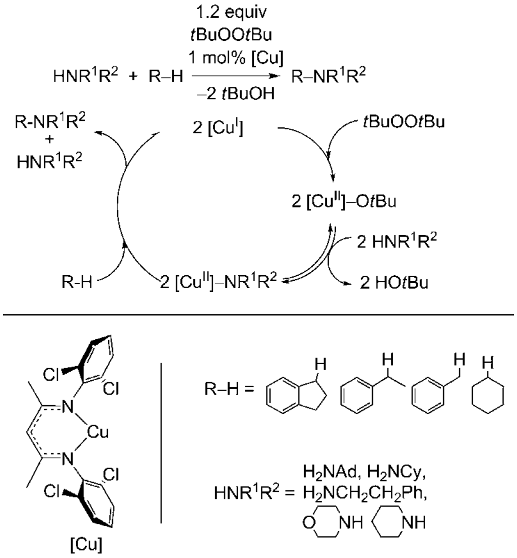
Catalytic C–H Amination with Aromatic Amines**

*Raymond T. Gephart III, Daria L. Huang, Mae Joanne B. Aguila, Graham Schmidt, Andi Shahu, and Timothy H. Warren**

The prevalence of basic nitrogen atoms in myriads of small molecules of biological interest motivates the development of methodologies to streamline the introduction of nitrogen atoms into organic molecules. C–H amination offers a potentially highly atom-economical approach, directly converting C–H into C–N bonds.[1] Prototypical nitrene-based routes[2] for C_{sp^3}–H amination typically employ the iminoiodinanes PhI=N(EWG) (EWG = SO_2R' or C(O)OR′) as nitrene transfer reagents with a range of catalysts to aminate C–H bonds in the substrates R-H to provide the corresponding secondary amines RNH(EWG). Though rhodium-[1e,3] and ruthenium-based[4] catalysts are perhaps most common, a growing number of catalyst systems employing Earth abundant first-row transition metals such as Mn,[5] Fe,[6,7] Co,[8] and Cu,[9] have been developed.

C–H amination with secondary amines HNR^1R^2 requires non-nitrene-based routes. Liu and co-workers[10] and White and co-workers[11] independently described allylic C–H amination with sulfonyl carbamates $MeOC(O)NHSO_2R$ in which cationic Pd–allyl complexes serve as key intermediates. Mildly basic diarylamines such as $HNAr_2$ also participate in allylic C–H amination,[12a] and *N*-fluorobis(phenylsulfonyl)imide (NFSI) may be used for palladium-catalyzed C–H amidation of substrates which possess directing donor groups.[12b] A 1,10-phenanthroline-based copper(I) catalyst employs $MeNHSO_2Ph$ with *t*BuOOR (R = O_2CMe, O_2CAr) as an oxidant to give tertiary sulfonylamines derived from allylic and benzylic substrates.[13,14] The near ubiquitous requirement of very strong electron-withdrawing groups on the nitrogen atom, however, severely limits the range of N-based functionalities that may be directly incorporated through C–H amination, though in some cases simple organic amides[9d] or imidazoles[7b] may be employed.

We recently showed that the β-diketiminato copper(I) complex $[\{(Cl_2NN)Cu\}_2(\mu\text{-benzene})]$ (**1**) catalyzes the amination of C_{sp^3}–H bonds of ethylbenzene, indane, and even the completely unactivated substrate cyclohexane with the primary alkylamines 1-adamantylamine, cyclohexylamine, and phenethylamine employing *t*BuOO*t*Bu as an oxidant (Scheme 1).[9b] Emphasizing the non-nitrene nature of this protocol, the secondary amines morpholine and piperidine may also be used. Through its isolation and reactivity studies, the copper(II) amide $[(Cl_2NN)Cu\text{-}NHAd]$ serves as a key intermediate that participates in both hydrogen atom abstraction (HAA) of the substrates R-H and capture of the resulting radical R• to give the C–H amination product R-NHAd.[9b]



Scheme 1. C–H amination with alkyl amines HNR^1R^2 catalyzed by $[(Cl_2NN)Cu]$ with proposed catalytic cycle.

Aiming to extend our C–H amination protocol to aromatic amines H_2NAr, we were quite concerned that our system would instead catalyze their oxidation to diazenes ArN=NAr. Although first reported in 1955,[15] the use of copper(I) halides in pyridine for the aerobic oxidation of anilines into azobenzenes recently has been rediscovered as a versatile method for the synthesis of aromatic diazenes.[16] Indeed, early mechanistic studies suggested copper(II) anilides Cu^{II}–NHAr as key intermediates which are subject to bimolecular N–N coupling to give the hydrazines ArNH–NHAr en route to diazenes ArN=NAr (Scheme 2).[15b,c]

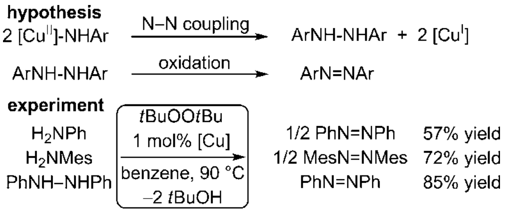
We began with scouting experiments employing 2,4,6-trimethylaniline (H_2NMes) with neat ethylbenzene as a substrate and *t*BuOO*t*Bu as an oxidant, catalyzed by 10 mol% [Cu] at 90°C. Despite the high conversion of the aniline (> 95%), the desired secondary amine PhCH(NHMes)Me is produced in only 21% yield accompanied by a significant amount of the diazene MesN=NMes. We find that decreasing the concentration of $[(Cl_2NN)Cu]$ either by lowering the loading of this catalyst (to 1 mol%) or increasing the solvent volume (to 20 mL) led to marked increases in the amount of

---

[*] R. T. Gephart III, D. L. Huang, M. J. B. Aguila, G. Schmidt, A. Shahu, Prof. T. H. Warren
Department of Chemistry, Georgetown University
Box 571227, Washington, DC 20057-1227 (USA)
E-mail: thw@georgetown.edu

[**] We acknowledge funding from the National Science Foundation (CHE-1012523) to T.H.W.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201201921.



Scheme 2. Oxidation of anilines and hydrazines by [Cu]/tBuOOtBu catalyst system gives diazenes.

the C–H amination product with a concomitant reduction in the diazene MesN=NMes (Figure 1; see Table S1 and Figures S1 and S2 in the Supporting Information).

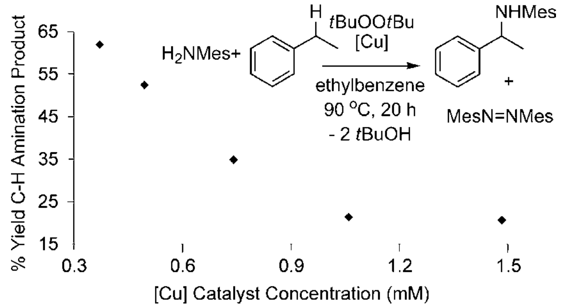


Figure 1. Dependence of product yield on catalyst concentration in the C–H amination of ethylbenzene by H_2NMes.

Based on the dramatic effect that the catalyst concentration has on diazene formation, we hypothesize that a bimolecular reaction occurs between two copper(II) anilido intermediates, [Cu^{II}]-NHMes (formed by reaction of [Cu^{II}]-OtBu with H_2NMes; see Scheme 1), to give MesNH–NHMes which may be subsequently oxidized to MesN=NMes (Scheme 2). Consistent with this hypothesis, PhNH–NHPh is oxidized to PhN=NPh under catalytic conditions (100% conversion, 85% diazene yield; Scheme 2). The reaction of H_2NPh or H_2NMes with tBuOOtBu in the presence of the catalyst [Cu] but in the absence of a C_{sp^3}–H substrate leads to complete consumption of the primary aromatic amine, thus forming PhN=NPh and MesN=NMes in 57 and 72% yield, respectively.

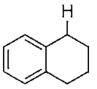
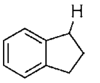
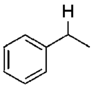
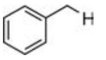
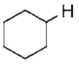
We then examined the dependence of the substrate C–H bond strength on the selectivity for C–H amination versus diazene formation when employing H_2NMes and tBuOOtBu with 1 mol% [Cu] at 90 °C (Table 1). The neat substrates cyclohexane (40% yield), toluene (18%), ethylbenzene (60%), indane (85%), and 1,2,3,4-tetrahydronaphthalene (95%) give C–H amination product yields that generally increase with decreasing C–H bond strength.

A key insight into diazene formation is revealed by monitoring the selectivity for C–H amination with a series of p-substituted anilines p-$XC_6H_4NH_2$ in neat ethylbenzene (Figure 2). Electron-withdrawing groups greatly enhance selectivity for C–H amination over diazene formation: the particularly electron-poor p-cyano derivative gives a yield of 95%. This trend follows both the Hammett-Brown σ^+ parameter ($R^2 = 0.99$) as well as the N–H bond strength for the parent aniline ($R^2 = 0.93$; see Figure S4 in the Supporting Information). Anilines possessing electron-withdrawing substituents are particularly resistant toward diazene formation. For instance, attempted oxidation of 2,4,6-$Cl_3C_6H_2NH_2$ with tBuOOtBu in benzene with 1 mol% [Cu] gives less than 5% of the corresponding diazene after 24 hours at 90 °C.

The reluctance of 2,4,6-$Cl_3C_6H_2NH_2$ to undergo oxidation to the corresponding diazene under our catalytic conditions identifies it as an excellent amine for the functionalization of challenging C–H substrates. In neat ethylbenzene and cyclohexane, C–H amination with 2,4,6-$Cl_3C_6H_2NH_2$ gives the corresponding N-alkyl-substituted anilines in 99 and 97% yield, respectively (Scheme 3). Thus, anilines possessing electron-withdrawing groups are especially effective in the functionalization of completely unactivated C_{sp^3}–H bonds.

Table 1: C–H amination of hydrocarbons with H_2NMes.[a]

$$H_2NMes + R\text{-}H \xrightarrow[\substack{90\ °C,\ 24\ h \\ -\ 2\ tBuOH}]{\substack{1.2\ equiv \\ tBuOOtBu \\ 1\ mol\%\ [Cu]}} R\text{-}NHMes$$

Entry	R–H	C–H BDE[b] [kcal mol^{-1}]	Yield [%]
1		83	95
2		85	85
3		87	60
4		90	18
5		97	40

[a] Reaction conditions: 1 mmol H_2NMes, 1.2 mmol tBuOOtBu, 20 mL neat substrate, 1 mol% [Cu], 90 °C, 24 h; ^1H NMR yields. [b] C–H BDEs from Ref. [17].

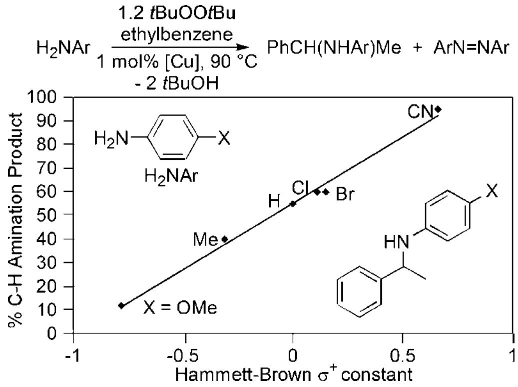
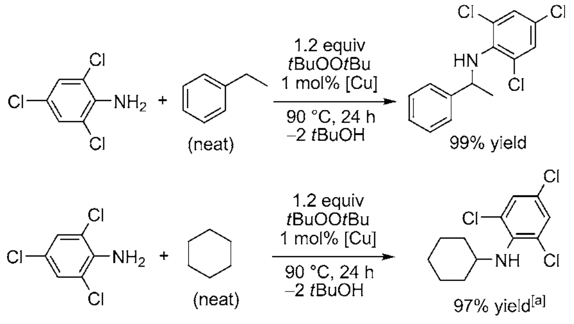


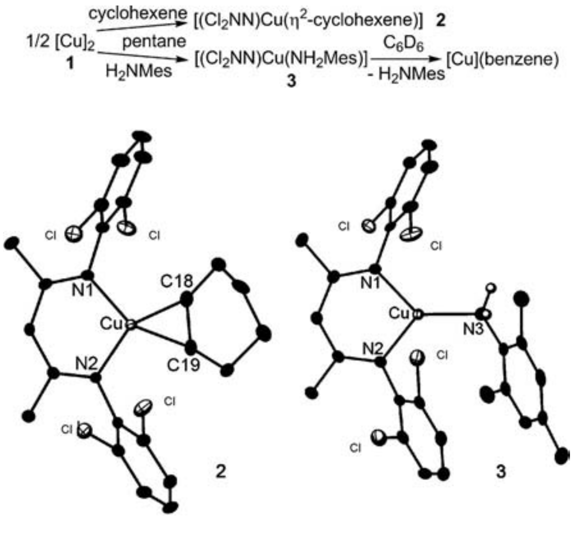
Figure 2. C–H amination product yields with a series of p-substituted anilines H_2NAr in neat ethylbenzene.



Scheme 3. C–H amination of hydrocarbons with H_2NAr^{Cl3}. Yields determined by ^1H NMR spectroscopy. [a] Isolated in 95 % yield.

These observations reveal a combination of factors required to achieve high C–H amination yields with modest C–H substrate loadings: a) low catalyst concentrations to prevent bimolecular N–N coupling, b) anilines with electron-poor substituents, and c) substrates with somewhat lower C–H bond strengths.

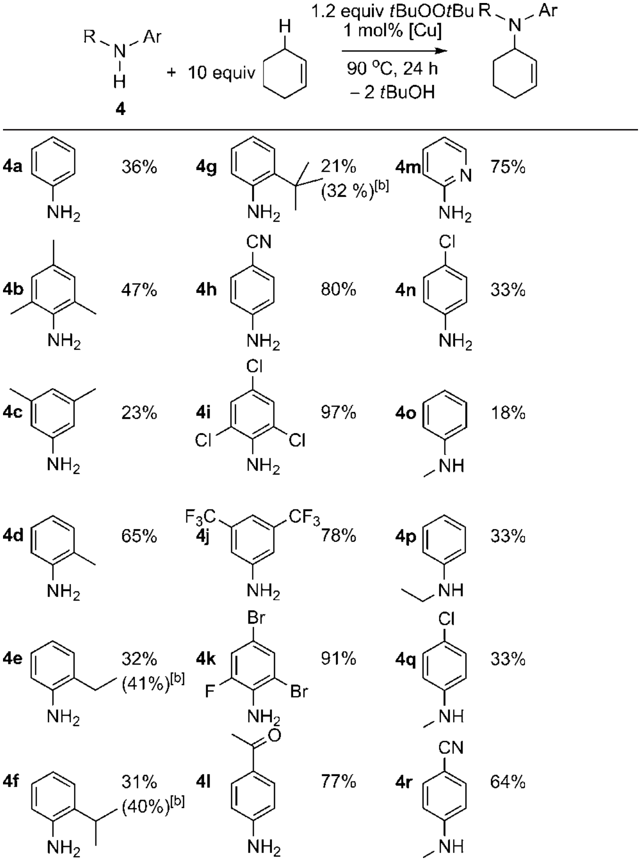
We examined a broader range of anilines with cyclohexene which possesses a C–H bond of modest strength (C–H BDE ≈ 82 kcal mol^{-1}).[17] We were initially surprised at the low conversions of anilines (1 mmol scale) in C–H amination when performed in neat cyclohexene ca. 20 mL). Since alkenes may bind to copper(I) complexes,[18] we considered inhibition by coordination of cyclohexene to the [(Cl_2NN)Cu] catalyst. Indeed, the cyclohexene adduct [(Cl_2NN)Cu(η^2-cyclohexene)] (**2**) readily forms upon addition of cyclohexene to **1** in [D_6]benzene (Scheme 4; see Figures S9 and S11 in the Supporting Information). Thus, cyclohexene binds more strongly to the [Cu^I] center than benzene and may adversely affect catalyst performance by impeding the oxidation of [Cu^I] by *t*BuOO*t*Bu (Scheme 1). In contrast, [(Cl_2NN)Cu(NH_2Mes)] (**3**), isolated by addition of H_2NMes to **1** in pentane, readily loses H_2NMes in [D_6]benzene, thus indicating that aniline substrates and products do not likely inhibit catalytic C–H amination (Scheme 4; Figures S10 and S12).



Scheme 4. X-ray structures of **2** and **3** illustrate coordination of cyclohexene and H_2NMes to the [(Cl_2NN)Cu] catalyst.[23] The thermal ellipsoids are shown at 50 % probability. See full crystallographic details in the Supporting Information.

A subtle change in the catalytic reaction conditions allows the isolation of cyclohexene C–H amination products in up to 97 % yield (Table 2). The use of 10 equivalents of cyclohexene, 1 equivalent of the aniline **4**, and 1.2 equivalents of *t*BuOO*t*Bu with 1 mol % [Cu] catalyst under essentially solventless conditions enables C–H amination with a wide range of anilines. Both electron-rich and electron-poor anilines participate in C–H amination, though the presence of electron-withdrawing groups typically enhances the product yield.

Table 2: C–H amination of cyclohexene with aniline derivatives.[a]



4a	36%	**4g**	21% (32 %)[b]	**4m**	75%
4b	47%	**4h**	80%	**4n**	33%
4c	23%	**4i**	97%	**4o**	18%
4d	65%	**4j**	78%	**4p**	33%
4e	32% (41%)[b]	**4k**	91%	**4q**	33%
4f	31% (40%)[b]	**4l**	77%	**4r**	64%

[a] Reaction conditions: 1 mmol aniline, 1.2 mmol *t*BuOO*t*Bu, 10 mmol cyclohexene, 1 mol % [Cu], 90 °C. Aniline structures are shown and the yields are those of the isolated products. [b] Used 5 mol % [Cu] and yield was determined by ^1H NMR spectroscopy.

When considering anilines with electron-releasing methyl substituents, those that provide modest steric hindrance to the N atom (**4b** and **4d**) result in higher yields. Anilines with larger *o*-alkyl substituents (**4e–g**), however, gave lower yields because of limited conversion of the aniline substrates, perhaps reflecting a sluggishness in the formation or C–H amination reactivity of the putative [Cu^{II}]-NHAr intermediates. Increasing the catalyst loading to 5 mol % modestly increased the amination yields to 41, 40, and 32 % (^1H NMR) for *o*-Et-, *o*-*i*Pr-, and *o*-*t*Bu-substituted anilines, respectively (**4e–g**). In the case of the *o*-Et and *o*-*i*Pr derivatives, the conversion of aniline substantially increased, but so too did the formation of the corresponding diazene. Little diazene was observed for the *o*-*t*Bu-substituted aniline (**4g**); conversion of this sterically demanding aniline was a concern at both low (1 mol %) and high (5 mol %) catalyst loadings.

Anilines possessing electron-withdrawing groups provide excellent C–H amination yields (**4h–m**). Notably, catalysis was not inhibited by 2-aminopyridine which is known to form a variety of coordination compounds through κ^2-*N*,*N* binding to metals in its anionic form.[19] In contrast, no C–H amination product with 4-nitroaniline was observed, perhaps as a result of interaction of the nitro group with the metal center.[20]

To demonstrate this catalysis proceeds through a non-nitrene-based mechanism, we surveyed a small range of N-alkyl-substituted anilines (**4o–r**). Paralleled in the series of primary aromatic amines, the presence of an electron-withdrawing group enhances the yield (**4r**). Oxidation of these secondary aromatic amines to the corresponding imines may compete with C–H amination as previously observed in the amination of cyclohexane with morpholine using this catalyst system.[9b]

In conclusion, we present the first general use of anilines in the C–H amination of a range of substrates with C_{sp^3}–H bonds. Previous related, though isolated, examples involve polyfluorinated arenes possessing acidic C_{sp^2}–H bonds with electron-poor anilines[21] or sterically hindered bromoarenes which undergo C–H functionalization of an *o*-*t*Bu group under attempted Buchwald–Hartwig cross-coupling with anilines.[22]

The copper(I) catalyst $[\{(Cl_2NN)Cu\}_2(\text{benzene})]$ in conjunction with the mild oxidant *t*BuOO*t*Bu enables the direct use of a variety of commercially available anilines in C–H amination. Even strong, unactivated C_{sp^3}–H bonds may be efficiently functionalized by using low catalyst loadings and electron-poor anilines which suppress diazene formation. We rationalize these findings to result from the competition between the involvement of putative $[Cu^{II}]$-NHAr intermediates in C–H functionalization vs. their undesired bimolecular coupling which appears to be disfavored for electron-poor anilines. Future studies target the isolation of discrete copper(II) anilides $[(Cl_2NN)Cu\text{-}NHAr]$ and an examination of their reactivity patterns to lay a concrete mechanistic foundation for this unique C–H amination system that tolerates both alkyl and arylamines.

Received: March 10, 2012

Keywords: amination · anilines · C–H functionalization · copper · synthetic methods

---

[1] a) F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun.* **2009**, 5061; b) F. Collet, C. Lescot, P. Dauban, *Chem. Soc. Rev.* **2011**, *40*, 1926; c) D. N. Zalatan, J. Du Bois, *Top. Curr. Chem.* **2010**, *292*, 347; d) X. P. Zhang, H. Lu, *Chem. Soc. Rev.* **2011**, *40*, 1899; e) J. Du Bois, *Org. Process Res. Dev.* **2011**, *15*, 758; f) T. A. Ramirez, B. Zhao, Y. Shi, *Chem. Soc. Rev.* **2012**, *41*, 931.

[2] F. Collet, C. Lescot, C. Liang, P. Dauban, *Dalton Trans.* **2010**, *39*, 10401.

[3] a) K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562; b) C. Liang, F. Collet, F. Robert-Peillard, P. Muller, R. H. Dodd, P. Dauban, *J. Am. Chem. Soc.* **2008**, *130*, 343; c) K. Huard, H. Lebel, *Chem. Eur. J.* **2008**, *14*, 6222; d) H. Lebel, K. Huard, S. Lectard, *J. Am. Chem. Soc.* **2005**, *127*, 14198.

[4] a) J.-L. Liang, S.-X. Yuan, J.-S. Huang, W.-Y. Yu, C.-M. Che, *Angew. Chem.* **2002**, *114*, 3615; *Angew. Chem. Int. Ed.* **2002**, *41*, 3465; b) S. K.-Y. Leung, W.-M. Tsui, J.-S. Huang, C.-M. Che, J.-L. Liang, N. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 16629; c) E. Milczek, N. Boudet, S. Blakey, *Angew. Chem.* **2008**, *120*, 6931; *Angew. Chem. Int. Ed.* **2008**, *47*, 6825; d) S. Fantauzzi, E. Gallo, A. Caselli, F. Ragaini, N. Casati, P. Macchi, S. Cenini, *Chem. Commun.* **2009**, 3952; e) M. E. Harvey, D. G. Musaev, J. Du Bois, *J. Am. Chem. Soc.* **2011**, *133*, 17207.

[5] J. Zhang, P. W. H. Chan, C.-M. Che, *Tetrahedron Lett.* **2005**, *46*, 5403.

[6] a) Z. Wang, Y. Zhang, H. Fu, Y. Jiang, Y. Zhao, *Org. Lett.* **2008**, *10*, 1863; b) Y. Liu, C.-M. Che, *Chem. Eur. J.* **2010**, *16*, 10494.

[7] a) E. R. King, E. T. Hennessy, T. A. Betley, *J. Am. Chem. Soc.* **2011**, *133*, 4917; b) Q. Xia, W. Chen, H. Qiu, *J. Org. Chem.* **2011**, *76*, 7577.

[8] a) V. Lyaskovskyy, A. I. Olivos Suarez, H. Lu, H. Jiang, X. P. Zhang, B. de Bruin, *J. Am. Chem. Soc.* **2011**, *133*, 12264; b) H. Lu, J. Tao, J. E. Jones, L. Wojitas, X. P. Zhang, *Org. Lett.* **2010**, *12*, 1248; c) H. Lu, V. Subbarayan, J. Tao, X. P. Zhang, *Organometallics* **2010**, *29*, 389; d) A. Caselli, E. Gallo, S. Fantauzzi, S. Morlacchi, F. Ragaini, S. Cenini, *Eur. J. Inorg. Chem.* **2008**, 3009.

[9] a) Y. M. Badiei, A. Dinescu, X. Dai, R. M. Palomino, F. W. Heinemann, T. R. Cundari, T. H. Warren, *Angew. Chem.* **2008**, *120*, 10109; *Angew. Chem. Int. Ed.* **2008**, *47*, 9961; b) S. Wiese, Y. M. Badiei, R. T. Gephart, S. Mossin, M. S. Varonka, M. M. Melzer, K. Meyer, T. R. Cundari, T. H. Warren, *Angew. Chem.* **2010**, *122*, 9034; *Angew. Chem. Int. Ed.* **2010**, *49*, 8850; c) T. H. Warren (Georgetown University), PCT Int. Appl. WO 2010028159, **2010**; d) X. Liu, Y. Zhang, L. Wang, H. Fu, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2008**, *73*, 6207; e) D. N. Barman, P. Liu, K. N. Houk, K. M. Nicholas, *Organometallics* **2010**, *29*, 3404; f) A. N. Vedernikov, K. G. Caulton, *Chem. Commun.* **2004**, 162; g) C. W. Hamilton, D. S. Laitar, J. P. Sadighi, *Chem. Commun.* **2004**, 1628; h) M. M. Díaz-Requejo, T. R. Belderraín, M. C. Nicasio, S. Trofimenko, P. J. Pérez, *J. Am. Chem. Soc.* **2003**, *125*, 12078; i) M. R. Fructos, S. Trofimenko, M. M. Díaz-Requejo, P. J. Pérez, *J. Am. Chem. Soc.* **2006**, *128*, 11784.

[10] a) G. Liu, G. Yin, L. Wu, *Angew. Chem.* **2008**, *120*, 4811; *Angew. Chem. Int. Ed.* **2008**, *47*, 4733; b) L. Wu, S. Qiu, G. Liu, *Org. Lett.* **2009**, *11*, 2707.

[11] a) S. A. Reed, A. R. Mazzotti, M. C. White, *J. Am. Chem. Soc.* **2009**, *131*, 11701; b) G. T. Rice, M. C. White, *J. Am. Chem. Soc.* **2009**, *131*, 11707.

[12] a) Y. Shimizu, Y. Obora, Y. Ishii, *Org. Lett.* **2010**, *12*, 1372; b) A. Iglesias, R. Álvarez, Á. R. de Lera, K. Muñiz, *Angew. Chem.* **2012**, *124*, 2268; *Angew. Chem. Int. Ed.* **2012**, *51*, 2225.

[13] G. Pelletier, D. A. Powell, *Org. Lett.* **2006**, *8*, 6031.

[14] D. A. Powell, H. Fan, *J. Org. Chem.* **2010**, *75*, 2726.

[15] a) A. P. Terent'ev, Y. D. Mogilyanskii, *Dolklady Akad. Nauk USSR* **1955**, *103*, 91; b) K. Kinoshita, *Bull. Chem. Soc. Jpn.* **1959**, *32*, 777; c) K. Kinoshita, *Bull. Chem. Soc. Jpn.* **1959**, *32*, 780.

[16] a) W. Lu, C. Xi, *Tetrahedron Lett.* **2008**, *49*, 401; b) M. Zhang, R. Zhang, A.-Q. Zhang, X. Li, H. Liang, *Synth. Commun.* **2009**, *39*, 3428; c) C. Zhang, N. Jiao, *Angew. Chem.* **2010**, *122*, 6310; *Angew. Chem. Int. Ed.* **2010**, *49*, 6174.

[17] Y.-R. Luo, Handbook of Bond Dissociation Energies in Organic Compounds, CRC Press, Boca Raton, FL, **2002**.

[18] a) A related β-diketiminato complex binds ethylene and styrene: X. Dai, T. H. Warren, *Chem. Commun.* **2001**, 1998; b) for

a review of coinage metal alkene complexes with tris(pyrazolyl)borate ligands, see: H. V. R. Dias, C. J. Lovely, *Chem. Rev.* **2008**, *108*, 3223.

[19] a) R. Kempe, *Eur. J. Inorg. Chem.* **2003**, 791; b) S. Deeken, G. Motz, R. Kempe, *Z. Anorg. Allg. Chem.* **2007**, *633*, 320.

[20] a) Nitrosoaromatics (ArNO) bind well to Cu^I β-diketiminates: S. Wiese, P. Kapoor, K. D. Williams, T. H. Warren, *J. Am. Chem. Soc.* **2009**, *131*, 18105; b) nitroarene ($ArNO_2$) coordination to β-diketiminato fragments has been computationally considered: A. B. Kazi, T. R. Cundari, E. Baba, N. J. DeYonker, A. Dinescu, L. Spaine, *Organometallics* **2007**, *26*, 910.

[21] H. Zhao, M. Wang, W. Su, M. Hong, *Adv. Synth. Catal.* **2010**, *352*, 1301.

[22] J. Pan, M. Su, S. J. Buchwald, *Angwew. Chem.* **2011**, *123*, 8806; *Angew. Chem.* **2011**, *123*, 8806; *Angew. Chem. Int. Ed.* **2011**, *50*, 8647.

[23] CCDC 876017 (**2**) and CCDC 876018 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.