A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

www.angewandte.org

Accepted Article

Title: Copper Catalyzed sp3 C-H Amidation: Sterically Driven Primary and Secondary C-H Site-Selectivity

Authors: Abolghasem Gus Bakhoda, Quan Jiang, Yosra Badiei, Jeffery A. Bertke, Thomas R. Cundari, and Timothy H. Warren

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201810556
Angew. Chem. 10.1002/ange.201810556

Link to VoR: http://dx.doi.org/10.1002/anie.201810556
http://dx.doi.org/10.1002/ange.201810556

WILEY-VCH

10.1002/anie.201810556

WILEY-VCH

Copper Catalyzed sp^3 C-H Amidation: Sterically Driven Primary and Secondary C-H Site-Selectivity

Abolghasem (Gus) Bakhoda,[a] Quan Jian,[b] Yosra M. Badiei,[a] Jeffery A. Bertke,[a] Thomas R. Cundari,[b]* and Timothy H. Warren[a]*

Abstract: Undirected sp^3 C−H functionalization reactions often follow site-selectivity patterns that mirror the corresponding C−H bond dissociation energies (BDEs). This often results in the functionalization of weaker 3° C−H bonds in the presence of stronger 2° and 1° bonds. An important, contemporary challenge is the development of catalyst systems capable of selectively functionalizing stronger 1° and 2° C−H bonds over 3° and benzylic C−H sites. Herein, we report a Cu catalyst that exhibits a high degree of 1° and 2° over 3° C-H bond selectivity in the amidation of linear and cyclic hydrocarbons with aroyl azides ArC(O)N$_3$. Mechanistic and DFT studies indicate that C−H amidation involves H−atom abstraction from R−H substrates by nitrene intermediates [Cu](κ^2−*N*,*O*−NC(O)Ar) to provide carbon−based radicals R• and copper(II)−amide intermediates [Cu^{II}]−NHC(O)Ar that subsequently capture radicals R• to form products R−NHC(O)Ar. These studies reveal important catalyst features required to achieve 1° and 2° C-H amidation selectivity in the absence of directing groups.

Catalyst-controlled site-selectivity that overcomes a substrate's innate preferences based on steric and electronic properties of individual C-H bonds in the absence of directing groups is a crucial challenge in the development of C-H functionalization.[1,2] In sp^3 C-H functionalization, selectivities often follow C-H bond strengths since a common mechanism involves H-atom abstraction (HAA) from the C-H bond.[1c] Thus, these reactions typically occur at weaker benzylic and allylic as well as more electron−rich 3° C−H bonds over stronger 1° and 2° C−H bonds.[1] The electrophilic nature of many HAA agents can further amplify selectivity towards electron-rich C-H bonds.[1,2b,2g-i] Recognizing that 3° C-H bonds are sterically somewhat hindered, however, suggests a strategy to achieve selective functionalization of more exposed 1° and 2° C-H bonds through catalyst-centered steric control.[1a-c,2g-j] Thus, the challenge becomes the design of a catalyst system potent enough to react with very strong 1° and 2° C-H bonds, yet with the capability to sterically differentiate among the wide range of C-H bonds typically found within substrate molecules.

Early, seminal work by Callot *et al*. demonstrated that 1° C-H bond selectivity for carbene insertion reactions of *n*-alkanes with ethyl diazoacetate catalyzed by [Rh(por)I] (where por = *meso*-tetraarylporphyrinato) increases with the increase of the sterics of the *ortho* groups of the *meso*-aryl rings.[3] In 2008, Che and co-workers showed that a sterically encumbered Rh–porphyrin catalyst demonstrates high 1° selectivity in carbenoid transfer reactions (Figure 1a).[4] Most recently, Davies group reported a new dirhodium catalyst that is highly effective for the functionalization of 1° C–H bonds with high levels of site- and enantioselectivity via [Rh]=CR$_2$ intermediates.[5a] By altering the sterics of the carboxylate ligands, site-selectivity can be tuned to prefer either 3°, 2° or 1° C–H bonds.[5]

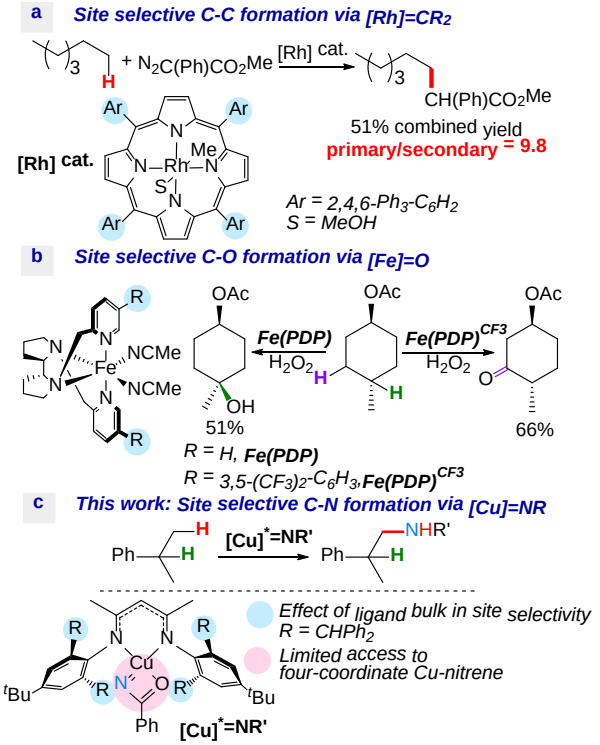


Figure 1. State of the art in site selective C-H functionalization controlled by catalyst structure.

Catalyst centered steric control may also override innate selectivity in C-H hydroxylations.[2g-i] White group reported that steric enhancement of a Fe(PDP) catalyst switches the selectivity from 3° to 2° C-H bonds due to decreased accessibility to the putative [Fe]=O intermediate (Figure 1b).[2g] Structurally related chiral Fe and Mn catalysts also become both more enantioselective through addition of steric bulk.[2d-e]

Despite these advances in redirecting C-H functionalization away from weaker C-H bonds in metal-carbene and -oxo based methods, progress with metal-nitrene based protocols has been much slower. In 2006 Peréz and coworkers reported that very bulky substituents in TpCu (Tp = tris(pyrazolyl)borate) catalysts could greatly favor C-H amination of cumene with PhI=NTs at the unactivated 1° site over the electronically favored 3° C-H bond.[6] Unfortunately, overall amination yields were low, despite using a large excess of the C-H substrate. Based on our development of discrete β-diketiminato copper nitrene complexes [Cu]$_2$(μ-NR') and

[a] M. Sc. A. Bakhoda, Dr. Y. M. Badiei, Dr. J. A. Bertke, Prof. Dr. T. H. Warren
Department of Chemistry, Georgetown University
Box 571227, Washington, DC 20057-1227 (USA)
E-mail: thw@georgetown.edu (T.H.W.)
[b] Q. Jiang, Prof. T. R. Cundari
Department of Chemistry, Center for Advanced Scientific Computing and Modeling (CASCaM) University of North Texas
Denton, TX 76203 (USA)
Email: t@unt.edu
Supporting information for this article is available on the WWW under http://dx.doi.org/....

10.1002/anie.201810556

[Cu]=NR' for stoichiometric and catalytic C-H amination with alkyl and aryl azides N_3R',[7] we felt that steric modification of the β-diketiminate ligand could result in the selective amination of stronger 1° C-H bonds provided that copper nitrenes with heightened reactivity could be generated.

To enhance the reactivity of our copper nitrene intermediates [Cu]=NR', we employed aroyl azides $ArC(O)N_3$ as potentially more electrophilic nitrene sources than alkyl or aryl azides.[8] Demonstrating the exceptional reactivity of a putative copper benzoylnitrene intermediate, addition of 1 equiv. $PhC(O)N_3$ (BzN_3, **2**) to 1 equiv. catalyst [Cl_2NN]Cu (**1**) in neat ethylbenzene at -35 °C gives the 2° C-H amination product in 70% yield (Figure 2b). Unfortunately, very low C-H amidation yields under catalytic conditions (see Supporting Information, Section 4) suggest that highly reactive [Cu](NC(O)Ph) intermediates undergo decomposition pathways that preclude catalysis. For instance, a 1:1 mixture of BzN_3 and [Cl_2NN]Cu in benzene gave the diazene BzN=NBz in 46% isolated yield. Coupled with C-H amination behavior in the presence of ethylbenzene, the formation of this diazene in the absence of a sp^3 R-H substrate suggests the generation of a [Cu](NC(O)Ph) intermediate that can dimerize or undergo an attack by excess BzN_3 with loss of N_2 to form BzN=NBz (**3**) (Figure 2b).

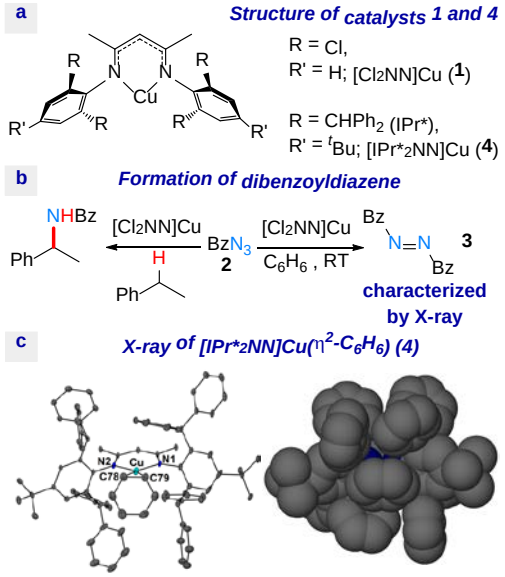
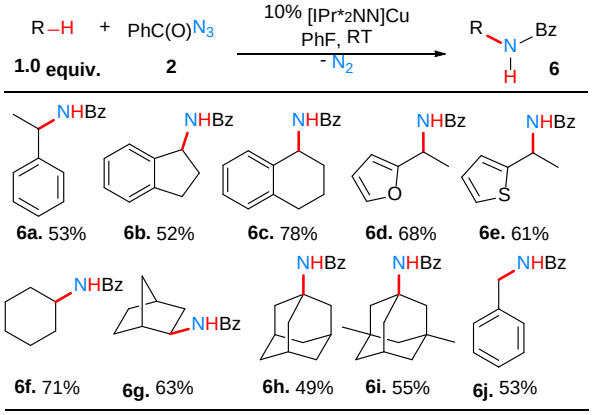


Figure 2. Development of hindered β-diketiminato copper catalyst **4** for sp^3 C-H amidation with BzN_3.

To discourage bimolecular interactions between transient acylnitrene intermediates [Cu](NC(O)Ph) that could lead to N-N coupling, we synthesized a novel copper(I) β-diketiminate complex [IPr*NN]Cu(η^2-benzene) (**4**) that features extremely sterically demanding *o*-$CHPh_2$ and *p*-^{t}Bu substituents on the β-diketiminato *N*-aryl groups. Deprotonation of the free β-diketimine [IPr^*_2NN]H (**5**) with *n*-BuLi to give [IPr^*_2NN]Li followed reaction of CuCl in benzene provided **4** in 72% yield. A space-filling model of the X-ray structure of **4** makes apparent the considerable steric influence of the four *o*-$CHPh_2$ substituents (Figure 2c).

Preliminary screening experiments that employed ethylbenzene and benzoyl azide (BzN_3) in a 1 : 1 ratio in fluorobenzene (PhF) catalyzed by 10 mol% **4** at RT showed complete conversion of the azide, but produced the desired amide PhCH(NHC(O)Ph)Me in only 29% yield with a significant amount of benzamide $PhC(O)NH_2$ (57%). Slow addition of $PhC(O)N_3$, however, led to a significant increase in the C-H amidation yield to 57% with a concomitant decrease in the undesired parent benzamide $PhC(O)NH_2$ (14%). Slow addition techniques have been used in other C-H functionalization protocols where the reactive intermediates are susceptible to dimerization or degradation or to simulate high catalyst loadings.[9] The use of the highly electrophilic aroyl azide $PhC(O)N_3$ enables C-H amidation at RT; in contrast, scouting experiments with the aryl azide PhN_3 under similar conditions reveal only PhN=NPh formation.

Table 1. Benzylic, 2° and 3° C-H amidation by **4**.

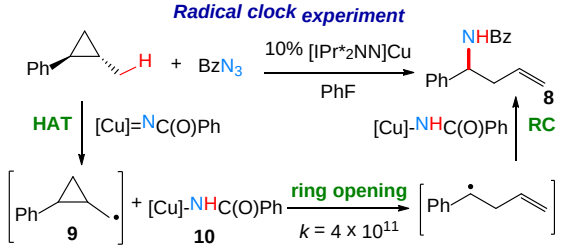


Conditions: RT, slow addition of BzN_3 solution (4.1 M in PhF, 0.01 mL/min). Isolated yields.

Both benzylic as well as unactivated 2° C-H bonds undergo amidation upon slow addition of BzN_3 catalyzed by 10 mol% **4** as presented in Table 1. Notably, good yields are obtained with using the R-H substrates as the limiting reagent (1.0 equiv.) at room temperature. Benzylic C-H bonds undergo smooth C-H amidation (entries **6a**-**6e**). This catalytic system functionalizes the unactivated 2° C-H bonds of cyclohexane (BDE = 99.5 kcal/mol)[10] (entry **6f**) in 71% yield. Likewise, amidation of norbornane at 2° C-H bonds (entry **6g**) gives the *exo* regioisomer (dr = 13:1; crude ^{1}H NMR), which may be isolated in 63% yield. On the other hand, adamantane and 1,3-dimethyladamantane underwent selective amidation at the 3° C-H sites to provide the benzamide products **6h** and **6i**. The latter furnished the *N*-benzoyl derivative of the Alzheimer's disease medication memantine in 55% yield.

We note that **4** catalyzes C-H amidation with many aroyl azides $ArC(O)N_3$ under analogous conditions (Table S1), though sterically hindered azides such as anthracene 9-carbonyl azide give lower yields. A curious finding is that 2-picolinoyl azide leads to only a trace amount of the C-H amidation product (entry **7o**). We hypothesize that pyridyl group coordination inhibits azide activation. Consistent with this observation, we find that addition of 2-picoline to **4** gives [IPr_2*NN]Cu(2-picoline) (**8**) (Figure S30) that is inactive in the C-H amidation of ethylbenzene with BzN_3, even at elevated temperatures (60 °C).

To probe the pathway for catalytic C-H amidation, we employed (2-methylcyclopropyl)benzene as R-H substrate with BzN_3 that provided the ring-opened product **9** in 23% yield along with $PhC(O)NH_2$ and some unreacted starting material (Scheme 1). The absence of any amidation product with the cyclopropane ring intact suggests a HAA pathway to generate the 1° cyclopropylmethyl radical that rapidly ring opens ($k = 4 \times 10^{11}$ s^{-1})[11] followed by capture by a copper(II) benzamide intermediate [Cu^{II}]-NHC(O)Ph. We identified a kinetic isotope effect (*KIE*) of 3.4 ± 0.3 for cyclohexane, and 5.5 ± 0.3 for *tert*-butylbenzene (See Supporting Information section 7). These KIE values are



Scheme 1. Radical clock: C-H amidation occurs solely with ring opening.

similar to that identified for C-H amination of ethylbenzene, adamantane and cumene via *N*-adamantyl (5.3), *N*-tosyl (4.9 and 4.1) and *N*-nosyl (3.1 and 3.2) copper nitrene intermediates, respectively,[7b,12] a bit lower than observed in the C-H amination of cyclohexane via β-diketiminato copper *N*-adamantyl nitrene intermediates (6.6).[7c]

Employing theory at the uBP86/mixed basis set level of theory (see Section 10 of Supporting Information for details),[7b,13] κ^1-*N*, κ^1-*O*, and κ^2-*N*,*O* binding modes of the highly reactive intermediates were evaluated for copper nitrenes [IPr*$_2$NN]Cu(NC(O)Ph) (Figure 3) and [Cl$_2$NN]Cu(NC(O)Ph) (Supporting Information Figure S35). Geometry optimizations indicate the κ^1-*N* and κ^1-*O* isomers were higher in energy (>13 kcal/mol) than the κ^2-*N*,*O* isomer and are not considered further. The ground state computed for nitrene [IPr*$_2$NN]Cu(κ^2-*N*,*O*-NC(O)Ph) (**10**) is a singlet that is 21.1 kcal/mol lower than the triplet. Moreover, MCSCF (multi-configuration self-consistent-field) calculations at the DFT-optimized geometries also predict the ground state is a singlet, but this structure has significant multi-configuration character as evidenced by deviation of natural orbital occupation numbers (NOONs) from single-determinant values (1.6 and 0.4 e$^-$ in Supporting Information Figure S37). Therefore, like reported Cu-alkynitrenes, copper acylnitrenes have significant multi-reference (singlet biradical) character.[7a,7c,13]

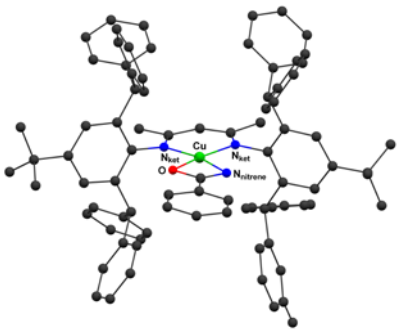
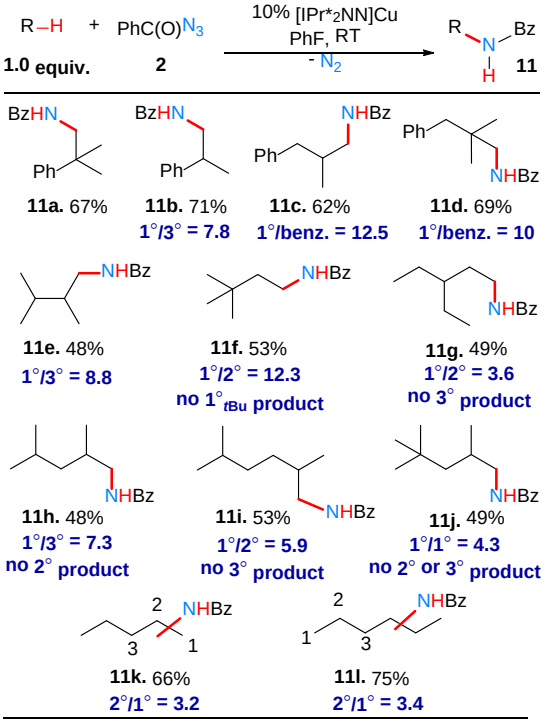


Figure 3. DFT calculated structure of [Cu](κ^2-NC(O)Ph) (**10**).

This catalytic system can efficiently functionalize 1° C-H bonds as illustrated in the reaction of BzN$_3$ with *tert*-butylbenzene (BDE ~ 99 kcal/mol)[10] to furnish the 1° C-H amidation product in 67% isolated yield (Table 2, entry **11a**). Remarkably, amidation of the 1° sp^3 C-H bond of cumene (BDE ~ 101 kcal/mol)[10] occurs with synthetically useful selectivity over the more hindered, yet weaker 3° benzylic C-H bond (BDE ~ 85 kcal/mol)[10] to give a 71% yield (Table 2, entry **11b**). A small amount of 3° amidation product is observed to give a (regiomeric ratio (r.r.) of 7.8:1. Indeed, synthetically useful 1° selectivity also occurs in the presence of benzylic and methine C-H bonds in isobutylbenzene and neopentylbenzene (entries **11c** and **11d**) to give 1° amidation products in 62% and 69% isolated yields, respectively, with r.r. ≥10:1 in each case.

Table 2. Catalyst-dictated site selectivities in C–H amidation of diverse straight-chain hydrocarbon substrates.



Conditions: RT, slow addition of BzN$_3$ solution (4.1 M in PhF, 0.01 mL/min). Isolated yields.

This catalyst system also differentiates between the 1°, 2°, and 3° C-H bonds present in branched hydrocarbons (Table 2, entries **11e** – **11j**) to deliver the 1° functionalized benzamide as the major product. Amidation of 2,3-dimethylbutane and 2,2-dimethylbutane (entries **11e** and **11f**) occur in 48% and 53% yield with 1°/3° and 1°/2° selectivities of 8.8 and 12.3, respectively. 2,4-dimethylpentane (entry **11h**) led to amidation principally at the 1° C−H bonds with small amount of the 3° product (r.r. = 7.3), reversing the site-selectivity reported for other related C-H functionalization reactions.[4-5,14-16]

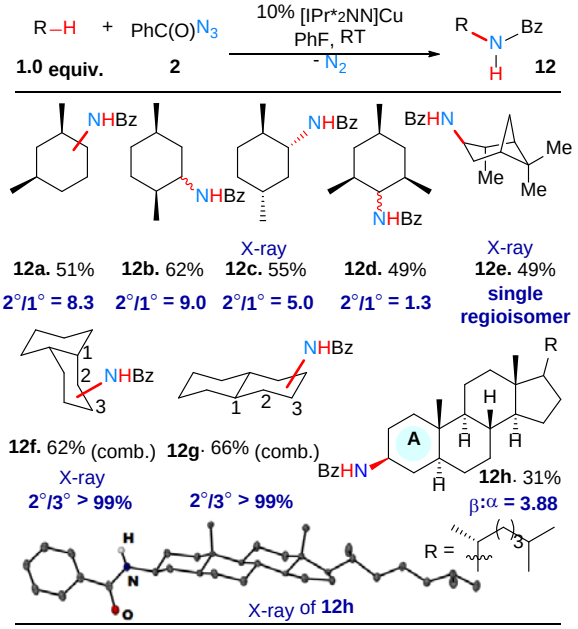
Surprisingly, **4** is capable of differentiating more hindered methyl C-H bonds from less hindered ones. For instance, amidation of isooctane proceeds with exclusive 1° selectivity that targets the slightly less hindered Me C-H bonds in the *i*-Pr vs. the *t*-Bu ends of the molecule (r.r = 4.3; entry **11j**). While 1° over 2° C-H amidation occurs when 2° sites are hindered (entries **11c, d, f-j**), straight chain alkanes lead to a preference for CH$_2$ sites (entries **11k, l**). The C−H amidation of *n*-pentane and *n*-hexane principally furnished C2-products with overall $k_{2°}/k_{1°}$ = 6.3 and $k_{2°}/k_{1°}$ = 9.4 in combined yields of 66% and 75%, respectively.

This system shows a high degree of methylene selectivity in methylated cycloalkanes. Amidation of *cis*-1,3-dimethylcyclohexane principally targets the two methylene sites C4 and C5 with $k_{2°}/k_{1°}$ = 8.3 (Table 3, entry **12a**) while *cis*-1,4-dimethylcyclohexane gives a 2:1 ratio of 2° products with $k_{2°}/k_{1°}$ = 10 (entry **12b**). In contrast, *trans*-1,4-dimethylcyclohexane furnishes a single 2° product in 55% yield with $k_{2°}/k_{1°}$ = 10 (entry **12c**). Heavily methylated *cis*-1,3,5-trimethylcyclohexane produces a single 2° isomer along with the 1° product ($k_{2°}/k_{1°}$ = 2.5; entry **12d**).

We were profoundly interested in establishing the potential for site-selective amidation of more complex molecules. The amidation of *trans*-pinane occurred at a single methylene site (C-3) in 49% yield (Table 3, entry **12e**). Exclusive methylene

10.1002/anie.201810556

Table 3. Methylene selectivity in the C–H amidation of cyclic substrates.



Conditions: RT, slow addition of BzN_3 solution (4.1 M in PhF, 0.01 mL/min). Isolated yields.

functionalization occurs with *cis*-and *trans*-decalin with C3/C2 selectivities of 2.1 and 1.3, respectively (Table 3, entries **12f,g**). Selective C-H amidation of 5*α*-cholestane (entry **12h**, 48 sp^3 C-H bonds; 7 3° C−H bonds and 13 unique 2° sites) takes place at the steroidal A-ring at the sterically most accessible, most electron-rich methylene site (C3) to give the *β*-C-3 benzamide product **12h** in 31% yield, along with 8% of the *α*-C-3 product (β/α = 3.88) with no evidence of functionalization at other sites. Previous C-H chlorination of this substrate with a *N*-chloroamide reagent or under Mn catalysis showed significantly lower selectivities (k_{C3}/k_{C2} = 2[17a] and 1.5,[17b] respectively). These examples further outline the unique capabilities of this catalyst system to differentiate among closely related C−H bonds within substrates.

In summary, the high reactivity of the Cu-nitrene intermediate [Cu](NC(O)Ph) along with the tremendous steric influence of the supporting β-diketiminate ligand leads to site-selectivities that favor stronger, yet more exposed 1° C-H bonds over weaker, more hindered 3° C-H bonds. Rigid cyclic substrates demonstrate a preference for amidation of 2° C-H bonds over 1° and 3° sites, allowing for selective functionalization of cycloalkanes. As such, this Cu-acylnitrene system provides a credible starting point for the further development of *catalyst-controlled site-selectivity* to introduce *N*-based functionalities into 1° and 2° sites in more complex molecules for applications in late-stage C-H functionalization and diversification.

Acknowledgements

This work has been supported by the US National Science Foundation under awards CHE-1300774 and CHE-1665348 (T.H.W.). Q.J. and T.R.C. thank the U.S. Department of Energy, Office of Basic Energy Sciences (Division of Chemical Sciences, Geosciences, and Biosciences) for partial support of this research via grant DE-FG02-03ER15387. Calculations employed the UNT Chemistry high-performance computing facility, supported by a grant from the NSF (CHE-1531468).

Keywords: Site-selectivity • Copper • Nitrene • C-H functionalization • Catalysis

[1] a) J. F. Hartwig, *Acc. Chem. Res*. **2017**, *50*, 549; b) T. Cernak, K. D. Dykstra, S. Tyagarajan, P. Vachal, S. W. Krska *Chem. Soc. Rev.* **2016**, *45*, 546. c) Hartwig, M. A. Larsen, *ACS Cent. Sci.* **2016**, *2*, 281; d) M. C. White, *Science* **2012**, *335*, 807; e) T. Newhouse, P. S. Baran *Angew. Chem. Int. Ed.* **2011**, *50*, 3362; *Angew Chem.* **2011**, *123*, 3422; f) C. M. Che, V. K. Y. Lo, C. Y. Zhoua, J. S. Huang, *Chem. Soc. Rev*. **2011**, *40*, 1950.

[2] a) A. M. Carestia, D. Ravelli, E. J. Alexanian, *Chem. Sci*., **2018**, *9*, 5360; b) C. Le, Y. Liang, R. W. Evan, X. Li, D. W. C. MacMillan *Nature* **2017**, *547*, 79; c) N. D. Chiappini, J. B. C. Mack, J. Du Bois, *Angew. Chem. Int. Ed.* **2018**, *57*, 4956; *Angew Chem.* **2018**, *130*, 5050; d) M. Milan, M. Bietti, M. Costas, *ACS Cent. Sci.* **2017**, *3*, 196; e) D. Font, M. Canta, M. Milan, O. Cussó, X. Ribas, R. J. M. Klein Gebbink, M. Costas, *Angew. Chem. Int. Ed*. **2016**, *55*, 5776; *Angew. Chem.* **2016**, *128*, 5870. f) A. Sharma, J. F. Hartwig *Nature* **2015**, *517*, 600; g) P. E. Gormisky, M. C. White, *J. Am. Chem. Soc*. **2013**, *135*, 14052; h) V. Kar-Yan Lo, Z. Guo, M. Kwok-Wai Choi, W. Y. Yu, J. S. Huang, C. M. Che, *J. Am. Chem. Soc*. **2012**, *134*, 7588; i) M. S. Chen, M. C. White, *Science* **2010**, *327*, 566. j) M. S. Chen, M. C. White, *Science* **2007**, *318*, 783.

[3] H. J. Callot, F. Metz, *Tetrahedron Lett*. **1982**, *23*, 4321.

[4] H. Y. Thu, G. S. M. Tong, J. S. Huang, S. L. F. Chan, Q. H. Deng, C. M. Che, *Angew. Chem. Int. Ed*. **2008**, *47*, 9747; *Angew. Chem.* **2008**, *120*, 9893.

[5] a) K. Liao, Y.F. Yang, Y. Li, J. N. Sanders, K. N. Houk, D. G. Musaev, H. M. L. Davies, *Nat. Chem*. **2018** DOI:10.1038/s41557-018-0087-7; b) K. Liao, T. C. Pickel, V. Boyarskikh, J. Bacsa, D. G. Musaev, H. M. L. Davies, *Nature* **2017**, *551*, 609; c) K. Liao, S. Negretti, D. G. Musaev, J. Bacsa, H. M. L. Davies, *Nature* **2016**, *533*, 230.

[6] M. R. Fructos, S. Trofimenko, M. M. Díaz-Requejo, P. J. Pérez, *J. Am. Chem. Soc*. **2006**, *128*, 11784.

[7] a) A. Bakhoda, Q. Jiang, J. A. Bertke, T. R. Cundari, T. H. Warren *Angew. Chem. Int. Ed.* **2017**, *56*, 6426; *Angew. Chem.* **2017**, *129*, 6526; b) M. J. B. Aguila, Y. M. Badiei, T. H. Warren, *J. Am. Chem. Soc.* **2013**, *135*, 9399; c) Y. M. Badiei, A. Dinescu, X. Dai, R. M. Palomino, F. W. Heinemann, T. R. Cundari, T. H. Warren, *Angew. Chem. Int. Ed*. **2008**, *47*, 9961; *Angew. Chem.* **2008**, *120*, 10109.

[8] a) K. Shin, J. Ryu, S. Chang, *Org. Lett*. **2014**, *16*, 2022; b) J. Peng, Z. Xie, M. Chen, J. Wang, Qiang Zhu, *Org. Lett*. **2014**, *16*, 4702; c) J. Ryu, J. Kwak, K. Shin, D. Lee, S. Chang, *J. Am. Chem. Soc.* **2013**, *135*, 12861.

[9] a) K. Liao, T. C. Pickel, V. Boyarskikh, J. Bacsa, D. G. Musaev, H. M. L. Davies, *Nature* **2017**, *551*, 609; b) K. Liao, S. Negretti, D. G. Musaev, J. Bacsa, H. M. L. Davies, *Nature* **2016**, *533*, 230; c) K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc*. **2007**, *129*, 562.

[10] Y. R. Luo in *Handbook of Bond Dissociation Energies in Organic Compounds*, CRC Press, Boca Raton, FL. **2007**.

[11] K. E. Liu, C. C. Johnson, M. Newcomb, S. J. Lippard, *J. Am. Chem. Soc.* **1993**, *115*, 939.

[12] V. Bagchi, P. Paraskevopoulou, P. Das, L. Chi, Q. Wang, A. Choudhury, J. S. Mathieson, L. Cronin, D. B. Pardue, T. R. Cundari, G. Mitrikas, Y. Sanakis, P. Stavropoulos, *J. Am. Chem. Soc*. **2014**, *136*, 11362.

[13] a) T. R. Cundari, A. Dinescu, A. B. Kazi, *Inorg. Chem*. **2008**, *47*, 10067.

[14] a) B. L. Tran, B. Li, M. Driess, J. F. Hartwig, *J. Am. Chem. Soc*. **2014**, *136*, 2555; b) Á. Beltrán, C. Lescot, M. Mar Díaz-Requejo, P. J. Pérez, P. Dauban, *Tetrahedron* **2013**, *69*, 4488; c) M. Ochiai, K. Miyamoto, T. Kaneaki, S. Hayashi, W. Nakanishi, *Science* **2011**, *332*, 448; d) M. Inagaki, T. Shingaki, T. Nagai, *Chem. Lett*. **1982**, 9; e) C. Walling, B. B. Jacknow, *J. Am. Chem. Soc.* **1960**, *82*, 6108; f) C. Walling in *Free Radicals in Solution*, Wiley, New York, **1957**.

[15] a) M. R. Fructos, P. de Frémont, S. P. Nolan, M. Mar Díaz-Requejo, P. J. Pérez, *Organometallics* **2006**, *25*, 2237; b) A. Caballero, M. Mar Díaz-Requejo, T. R. Belderraín, M. C. Nicasio, S. Trofimenko, P. J. Pérez, *Organometallics* **2003**, *22*, 4145.

[16] X. Huang, T. M. Bergsten, J. T. Groves, *J. Am. Chem. Soc*. **2015**, *137*, 5300.

[17] a) R. K. Quinn, Z. A. Könst, S. E. Michalak, Y. Schmidt, A. R. Szklarski, A. R. Flores, S. Nam, D. A. Horne, C. D. Vanderwal, E. J. Alexanian, *J. Am. Chem. Soc.* **2016**, *138*, 696; b) W. Liu, J. T. Groves, *J. Am. Chem. Soc.* **2010**, *132*, 12847.

10.1002/anie.201810556

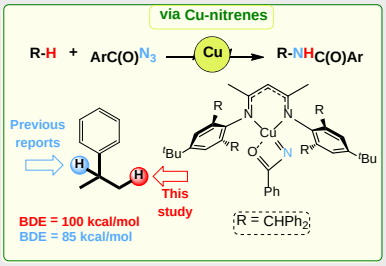
WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Catalyst-controlled, undirected site-selectivity that overcomes a substrate's innate C-H bond reactivity represents a crucial challenge for C-H functionalization. We report a new β-diketiminate Cu(I) catalyst system for C-H amidation with aroyl azides via copper nitrene intermediates whose steric bulk targets stronger, more accessible 1° and 2° C-H bonds in the presence weaker, hindered 3° C-H bonds.



Abolghasem (Gus) Bakhoda,[a] Quan Jian,[b] Yosra M. Badiei,[a] Jeffery A. Bertke,[a] Thomas R. Cundari,[b] and Timothy H. Warren[a]**

Page No. – Page No.

Copper Catalyzed sp^3 C-H Amidation: Sterically Driven Primary and Secondary C-H Site-selectivity