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Synthesis of Functionalized Epoxides by Copper-Catalyzed Alkylative Epoxidation of Allylic Alcohols with Alkyl Nitriles

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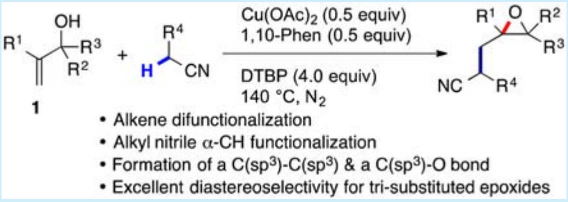
Supporting Information

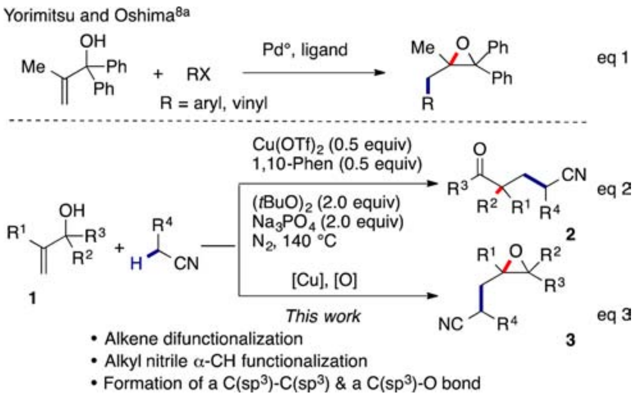
ABSTRACT: A copper-catalyzed oxyalkylation of allylic alcohols using nonactivated alkyl nitriles as reaction partners was developed. A sequence involving generation of an alkyl nitrile radical followed by its addition to a double bond and a copper-mediated formation of $C(sp^3)-O$ bond was proposed to account for the reaction outcome. The protocol provided an efficient route to functionalized tri- and tetrasubstituted epoxides via formation of a $C(sp^3)-C(sp^3)$ and a $C(sp^3)-O$ bond with moderate to excellent diastereoselectivity.



The epoxides are highly important motifs in organic synthesis due to their versatility as synthetic intermediates[1] and their occurrence in many natural and synthetic molecules.[2,3] Among many efficient synthetic strategies, epoxidation of olefins[4] and reaction of carbonyl compounds with sulfur ylides[5] or α-haloenolate (Darzens reactions)[6] have been extensively investigated. While the Sharpless epoxidation of allylic alcohols has become an invaluable tool in organic synthesis,[7] the carboetherifcation of allylic alcohols remains largely unexplored. Yorimitsu, Oshima, and co-workers reported an elegant palladium-catalyzed oxypalladation/arylation (vinylation) sequence for the synthesis of tetrasubstituted epoxides (eq 1, Scheme 1).[8] This sequence was nevertheless difficult to apply to alkylative epoxidation (R = alkyl) due to the nature of the reaction intermediates.[9,10]

The metal-catalyzed difunctionalization of readily accessible alkenes represents a domain of main interest in organic synthesis.[11] Despite the significant progress realized in the field of copper catalyzed olefin difunctionalization,[12−14] examples of copper-mediated/catalyzed difunctionalization of alkenes with generation of a $C(sp^3)-C(sp^3)$ bond remain scarce.[9,15,16] In connection with our ongoing project on metal-catalyzed functionalization of carbon−carbon multiple bonds,[17,18] we have recently developed a copper-catalyzed coupling/rearrangement sequence to convert allylic alcohols to homologated δ-oxo alkyl nitriles (eq 2, Scheme 1).[19] In this transformation, the alkylating reagent was generated from alkyl nitriles through a selective α-$C(sp^3)-H$ functionalization process.[20−22] We report herein that the reaction pathway can be diverted to polysubstituted epoxides **3** from the same allylic alcohols by simply changing the catalytic conditions (eq 3, Scheme 1).[23] This represents a rare example of alkylative epoxidation of allylic alcohols.

Scheme 1. Oxyalkylation of Allylic Alcohols



Using 2-methyl-3-phenylbut-3-en-2-ol (**1a**) and acetonitrile as test substrates, conditions were surveyed by varying the copper salts, ligands, and bases (Table 1). Applying the conditions optimized for the coupling/migration[19] to **1a** afforded a mixture of epoxide **3a** and ketone **2a** in 37% yield (**3a**/**2a** = 1/1.2 entry 1). Employing stoichiometric conditions developed earlier for phthalide synthesis [$Cu(OTf)_2$ (2.0 equiv), BiPy (1.0 equiv), DTBP (2.0 equiv), K_3PO_4 (2.0 equiv), H_2O (11.0 equiv), air, 140 °C, CH_3CN (0.1 M)],[18a] the desired epoxide **3a** was formed together with ketone **2a** in 61% yield (**3a**/**2a** = 1/1.9) (entry 2). Interestingly, using cesium pivalate (CsOPiv, 2.0 equiv) and substoichiometric amount of copper triflate, the desired epoxide was isolated as a single product in 45% yield (entry 3). Similar results were obtained using KOPiv and potassium acetate (KOAc) as bases (entries 4 and 5). Only degradation of **1a** was observed in the absence of base under these conditions (entry 6). Copper acetate outperformed copper triflate and a combination of $Cu(OAc)_2$/1,10-Phen/KOAc afforded **3a** in 71% isolated yield (entry 9). It was subsequently found that base was not needed when $Cu(OAc)_2$/1,10-Phen was used as a catalyst (entry

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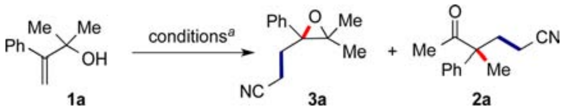
Table 1. Carboetherification of Allylic Alcohols: A Survey of Reaction Conditions[a]



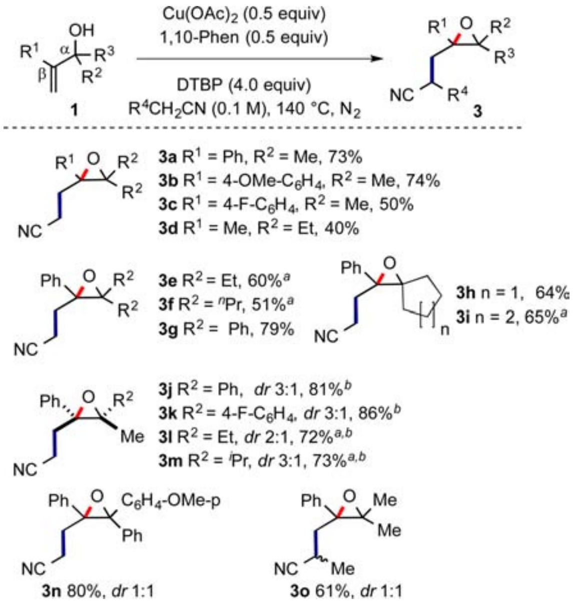
entry	[Cu]	ligand	base[b]	yield of 3a[c] (%)
1	Cu(OTf)$_2$	1,10-Phen	Na$_3$PO$_4$	37[e]
2[d]	Cu(OTf)$_2$	2,2′-BiPy	K$_3$PO$_4$	61[f]
3	Cu(OTf)$_2$	2,2′-BiPy	CsOPiv	45 (53), no **2a**
4	Cu(OTf)$_2$	2,2′-BiPy	KOPiv	51, no **2a**
5	Cu(OTf)$_2$	2,2′-BiPy	KOAc	(64), no **2a**
6	Cu(OTf)$_2$	2,2′-BiPy		degradation
7	Cu(OTf)$_2$	Bpym	CsOPiv	(53), no **2a**
8	Cu(OTf)$_2$	Phen	CsOPiv	57, no **2a**
9	Cu(OAc)$_2$	Phen	KOAc	71, no **2a**
10	Cu(OAc)$_2$	Phen		73, no **2a**
11	Cu(OAc)$_2$			(61), no **2a**
12	Cu(OAc)$_2$[g]	Phen[g]		(55), no **2a**

[a] The reactions were carried out on a 0.05 mmol scale in sealed tubes. [b] Standard conditions: copper salt (0.5 equiv), ligand (0.5 equiv), DTBP (4.0 equiv), base (2.0 equiv), N_2, 140 °C, CH_3CN (0.1 M). [c] Yield in parentheses was calculated on the basis of the ^1H NMR spectra using CH_3NO_2 as an internal standard. [d] Cu(OTf)$_2$ (2.0 equiv), BiPy (1.0 equiv), DTBP (2.0 equiv), H_2O (11.0 equiv), air. [e] **3a**/**2a** = 1/1.2. [f] **3a**/**2a** = 1/1.9. [g] 0.1 equiv.

10) and the reaction took place even in the absence of 1,10-phen although in a lower yield (entry 11). Finally, attempts to reduce catalyst loading resulted in a drop of the reaction efficiency (entry 12).

With the optimized conditions in hand, the generality of the oxyalkylation process was next investigated (Scheme 2). First, the effect of the substituents at the β-position of allylic alcohols was examined. Electron-rich (R^1 = 4-MeOC$_6$H$_4$) and electron-poor (R^1 = 4-FC$_6$H$_4$) aromatic groups were well tolerated leading to the desired epoxides **3b** and **3c** in yields of 74% and 50%, respectively. The methyl group was also tolerated producing tetraalkyl substituted oxirane **3d**, albeit with a diminished yield. Next, we varied the nature of groups R^2 and R^3. In addition to methyl group, ethyl, propyl, and phenyl substituents at the α position are well tolerated (**3e**−**g**), and the spirooxiranes were accessible without event (**3h**, **3i**). In the case of asymmetrically α,α-disubstituted alcohols, two diastereomers were obtained with low to moderate diastereoselectivity (**3j**−**n**). Finally, reaction of **1a** with propionitrile afforded **3o** in 61% yield (dr = 1/1).

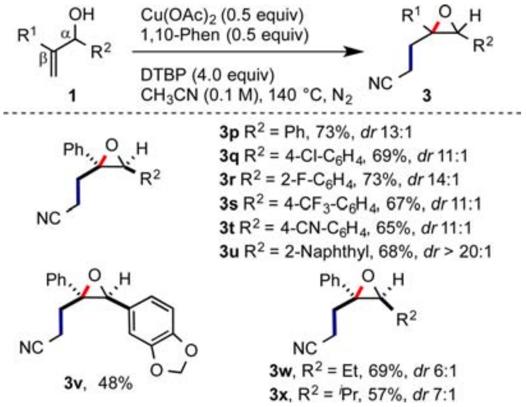
Scheme 2. Scope of Carboetherification Reaction of Tertiary Allylic Alcohols



[a] Additional DTBP (2.0 equiv) was added after 2 h and the mixture stirred for an additional 1 h. [b] Major diastereoisomer is represented.

Secondary allylic alcohols were next examined (Scheme 3). Reaction of 1,2-diphenylprop-2-en-1-ol with MeCN furnished epoxide **3p** in 73% yield with excellent diastereoselectivity (dr = 13:1). This trend was maintained regardless of the electronic nature and the position of substitution on the aromatic ring (4-Cl, 2-F, 4-CF$_3$, 4-CN, 2-naphthyl) to afford the corresponding epoxides (**3q**−**u**) in good yields with excellent diastereoselectivities. Interestingly, when 1-(benzo[*d*][1,3]dioxol-5-yl)-2-phenylprop-2-en-1-ol was subjected to the reaction conditions a single isomer of **3v** was obtained in 48% yield. The reaction of the α-alkyl substituted allylic alcohol with MeCN proceeded equally well to furnish the desired epoxides in good yields, albeit with slightly diminished diastereoselectivities (**3w**−**x**). The structure of the major diastereoisomer of epodxide **3t** was determined unambiguously by X-ray crystallographic analysis (Figure 1).

Scheme 3. Scope of Carboetherification Reaction of Secondary Allylic Alcohols[a]



[a] Only the major diastereoisomer is represented.

Control experiments were performed to gain insights on the reaction mechanism (Scheme 4). The reaction of **1a** with MeCN in the presence of TEMPO under standard conditions for 30 min afforded **4** and **5** in yields of 15% and 8%, respectively (exp 1). No epoxide **3a** was detected at this stage of the reaction. However, continuing the reaction after the total consumption of

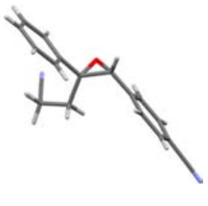
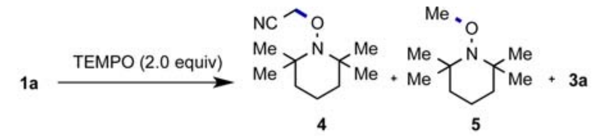


Figure 1. X-ray structure of **3t**.

Scheme 4. Radical-Trapping Experiment

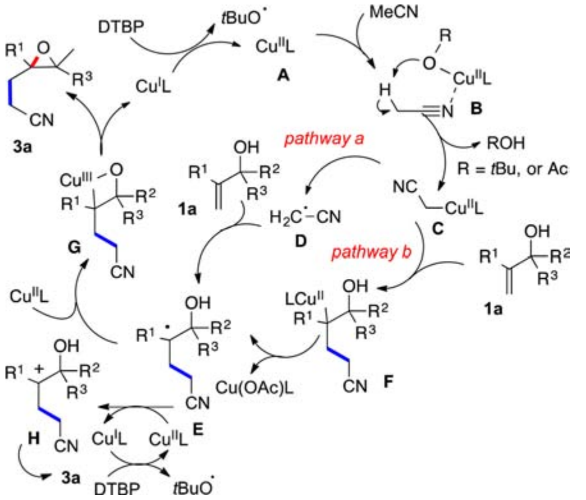


	4	5	3a
expt 1: Standard conditions, 30 min[a]	15%	8%	–
expt 2: Standard conditions, 2 h	19%	15%	36%
expt 3: Without $Cu(OAc)_2$, 2 h	5%	31%	–
expt 4: Without DTB, 2 h	68%	–	–

[a] Reaction was quenched before the total consumption of TEMPO.

TEMPO (2 h) afforded **3a** in 36% yield (exp 2). Performing the same trapping experiment in the absence of $Cu(OAc)_2$ afforded **4** in only 5% yield with **5** being a major product (31%, exp 3). The same trapping experiment in the absence of DTBP afforded **4** in 68% yield (exp 4). The results of these control experiments suggested the following:(a) the cyanomethyl radical might be involved in the formation of product **3a**; (b) a small amount of cyanomethyl radical could be generated through hydrogen atom abstraction by *t*-BuO$^\bullet$ or Me$^\bullet$ generated in situ by decomposition of DTBP (however, this way of generation was not the main path by which the reaction was initiated); (c) $Cu(OAc)_2$ was responsible for the activation of acetonitrile. Indeed, the reaction of **1a** with MeCN took place in the absence of DTBP to afford **3a**, albeit with low conversion. However, no epoxide was detected when the same reaction was performed in the absence of $Cu(OAc)_2$ and 1,10-Phen.

Scheme 5. Possible Reaction Pathway



Taking into consideration the above results, possible reaction pathways for this oxyalkylation of alkene are depicted in Scheme 5. Coordination of a ligated copper(II) species to the cyano group followed by deprotonation by acetate[21a,b] would produce the organocopper species **C**[24] that, after homolytic cleavage of C–Cu(II) bond, would deliver the cyanomethyl radical **D**. Radical addition across the double bond in **1a** would produce the radical **E** (pathway a) that could recombine with Cu(II) to produce the Cu(III) intermediate **G**. The latter underwent reductive elimination to afford product **3a**. Alternatively, radical **E** could also be oxidized by Cu(II) to tertiary cation **H** that upon cyclization would produce **3a**. Oxidation of Cu(I) species with DTBP would regenerate the Cu(II) salt.[25] However, an alternative carbocupration of alkene **1a**[26] by **C** followed by homolytic cleavage of **F** to **E**[13] could not be discarded at the present stage of development. We note that intermediate **H** is susceptible to the Wagner–Meerwein rearrangement,[27] while **E** could undergo the neophyl migration (if R^2 or R^3 is an aromatic ring)[28] to provide ketone **2** (cf. entries 1 and 2, Table 1) as observed in our previous studies.[19] However, this reaction pathway was suppressed under the present conditions. Therefore, we hypothesized that the carbocation intermediate **H** may not be produced and that the epoxide was formed most probably by reductive elimination of the Cu(III) intermediate **G**. While the reaction conditions played a key role in the divergence of the reaction pathway, we noticed that the nature of R^1 could also influence the product distribution. When R^1 was an aryl group, epoxide formation was favored due probably to the increased stability of the radical **E**, while rearrangement[19] became competitive if R^1 was an alkyl group.

In summary, we developed a simple Cu-catalyzed carboetherification of allylic alcohols by alkyl nitriles affording an efficient access to epoxides via formation of a $C(sp^3)-C(sp^3)$ and a $C(sp^3)-O$ bond. The reaction allowed a ready access to diversely functionalized epoxides including the tetrasubstituted ones that are otherwise difficult to access.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, product characterization data, ^1H and ^{13}C NMR spectra for new compounds, and X-ray crystallographic data (CIF) of compound **3t**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) He, J.; Ling, J.; Chiu, P. *Chem. Rev.* **2014**, *114*, 8037. (b) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K. Ed.; Wiley–VCH Verlag: Weinheim, 2006. (c) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.

(2) Drahl, C.; Cravatt, B. F.; Sorensen, E. J. *Angerw. Chem. Int. Ed.* **2005**, *44*, 5788.

(3) Kim, K. B.; Crews, C. M. *Nat. Prod. Rep.* **2013**, *30*, 600.

(4) (a) Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. *Chem. Rev.* **2014**, *114*, 8199. (b) Yang, D. *Acc. Chem. Res.* **2004**, *37*, 497. (c) Lane, B. S.; Burgess, K. *Chem. Rev.* **2003**, *103*, 2457.

(5) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611.

(6) Ballester, M. *Chem. Rev.* **1955**, *55*, 283.

(7) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; p 103.

(8) (a) Hayashi, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2009**, *131*, 2052. For a review on Pd-catalyzed carboetherification, see: Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571.

(9) Trifluoromethylation–epoxidation: (a) Kim, E.; Choi, S.; Kim, H.; Cho, E. J. *Chem.—Eur. J.* **2013**, *19*, 6209. (b) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 12462. (c) Laurent, P.; Blancou, H.; Commeyras, A. *J. Fluor. Chem.* **1993**, *64*, 125. (d) Fuchikami, T.; Shibata, Y.; Urata, H. *Chem. Lett.* **1987**, *16*, 521.

(10) From allyl peroxides, see: (a) Maillard, B.; Kharrat, A.; Rakotomanana, F.; Montaudon, E.; Gardrat, C. *Tetrahedron* **1985**, *41*, 4047. (b) Cramay, C.; Ferdinando, R.; Degueil-Castaing, M.; Maillard, B. *Chem. Commun.* **1998**, 1855. (c) Colombani, D.; Maillard, B. *J. Chem. Soc., Chem. Commun.* **1994**, 1259.

(11) (a) Zhu, Y.; Cornwall, R. G.; Du, H.; Zhao, B.; Shi, Y. *Acc. Chem. Res.* **2014**, *47*, 3665. (b) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *3*, 351. (c) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (d) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083. (e) Minatti, A.; Muniz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142.

(12) For reviews on copper-catalyzed difunctionalization of olefins, see: (a) Chemler, S. R.; Fuller, P. H. *Chem. Soc. Rev.* **2007**, *36*, 1153. (b) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11062. (c) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (d) Shimizu, Y.; Kanai, M. *Tetrahedron Lett.* **2014**, *55*, 3727.

(13) For examples of copper-catalyzed difunctionalization of alkenes initiated by aminocupration, see: (a) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250. (b) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948. (c) Fuller, P. H.; Kim, J.-W.; Chemler, S. R. *J. Am. Chem. Soc.* **2008**, *130*, 17638. (d) Paderes, M. C.; Chemler, S. R. *Eur. J. Org. Chem.* **2011**, *2011*, 3679. (e) Liwosz, T. W.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 2020. Oxycupration: (f) Miller, Y.; Miao, L.; Hosseini, A. S.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 12149.

(14) For examples of copper-catalyzed diamination of alkenes, see: (a) Zhao, B.; Peng, X.; Cui, S.; Shi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 11009. (b) Zhao, B.; Peng, X.; Zhu, Y.; Ramirez, T. A.; Cornwall, R. G.; Shi, Y. *J. Am. Chem. Soc.* **2011**, *133*, 20890. (c) Wang, Y.-F.; Zhu, X.; Chiba, S. *J. Am. Chem. Soc.* **2012**, *134*, 3679.

(15) For recent examples of Cu-peroxide mediated functionalization of *activated* alkenes by (cyclo)alkanes, see: (a) Zhou, M.-B.; Song, R.-J.; Ouyang, X.-H.; Liu, Y.; Wei, W.-T.; Deng, G.-B.; Li, J.-H. *Chem. Sci.* **2013**, *4*, 2690. (b) Zhou, S.-L.; Guo, L.-N.; Wang, H.; Duan, X.-H. *Chem.—Eur. J.* **2013**, *19*, 12970. (c) Li, Z.; Zhang, Y.; Zhang, L.; Liu, Z.-Q. *Org. Lett.* **2014**, *16*, 382. See also: (d) Huang, L.; Jiang, H.; Qi, C.; Liu, X. *J. Am. Chem. Soc.* **2010**, *132*, 17652.

(16) For copper-catalyzed trifluoromethylation-initiated functionalization of alkenes, see: (a) Parsons, A. T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9120. (b) Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 15300. (c) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410. (d) Chu, L.; Qing, F.-L. *Org. Lett.* **2012**, *14*, 2106. (e) Janson, P. G.; Ghoneim, I.; Ilchenko, N. O.; Szabó, K. *Org. Lett.* **2012**, *14*, 2882. (f) Zhu, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2013**, *52*, 12655. (g) Egami, H.; Shimizu, R.; Kawamura, S.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4000. (h) Egami, H.; Kawamura, S.; Miyazaki, A.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7841. (i) Egami, H.; Shimizu, R.; Kawamura, S.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4000. (j) For a highlight, see: Studer, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8950.

(17) Difunctionalization of alkynes: (a) Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5170. (b) Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 12311. (c) Yao, B.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12992.

(18) (a) Bunescu, A.; Wang, Q.; Zhu, J. *Chem.—Eur. J.* **2014**, *20*, 14633. (b) Chatalova-Sazepin, C.; Wang, Q.; Sammis, G. M.; Zhu, J. *Angew. Chem., Int. Ed.* **2015**, DOI: 10.1002/anie.201412357.

(19) Bunescu, A.; Wang, Q.; Zhu, J. *Angew. Chem., Int. Ed.* **2015**, *54*, 3132.

(20) For formation of organometallic complexes of acetonitrile using a stoichiometric amount of metals (Ln, Rh, Fe, Ru), see: (a) Ittel, S. D.; Tolman, C. A.; English, A. D.; Jesson, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 7577. (b) Heeres, H. J.; Meetsma, A.; Teuben, J. H. *Angew. Chem., Int. Ed.* **1990**, *29*, 420. (c) Churchill, D.; Shin, J. H.; Hascall, T.; Hahn, J. M.; Bridgewater, B. M.; Parkin, G. *Organometallics* **1999**, *18*, 2403. (d) Evans, M. E.; Li, T.; Vetter, A. J.; Rieth, R. D.; Jones, W. D. *J. Org. Chem.* **2009**, *74*, 6907.

(21) Addition to aldehydes, Cu-catalyzed: (a) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3147. (b) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 3757. (c) Wang, G.-W.; Zhou, A.-X.; Wang, J.-J.; Hu, R.-B.; Yang, S.-D. *Org. Lett.* **2013**, *15*, 5270. (d) Shen, J.; Yang, D.; Liu, Y.; Qin, S.; Zhang, J.; Sun, J.; Liu, C.; Liu, C.; Zhao, X.; Chu, C.; Liu, R. *Org. Lett.* **2014**, *16*, 350. Ru-catalyzed: (e) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 13632. (f) Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 8598. Ni-catalyzed: (g) Chakraborty, S.; Patel, Y. J.; Krause, J. A.; Guan, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7523.

(22) Difunctionalization of *activated* alkenes with acetonitrile, Pd-catalyzed: (a) Wu, T.; Mu, X.; Liu, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 12578. Cu-catalyzed: (b) Li, J.; Wang, Z.; Wu, N.; Gao, G.; You, J. *Chem. Commun.* **2014**, *50*, 15049.

(23) Synthesis of epoxide from iodoacetonitriles: (a) Peralta-Hernández, E.; Cortezano-Arellano, O.; Cordero-Vargas, A. *Tetrahedron Lett.* **2011**, *52*, 6899. For recent work on carbooxygenation of olefins by haloacetonitriles, see: (b) Yi, H.; Zhang, X.; Qin, C.; Liao, Z.; Liu, J.; Lei, A. *Adv. Synth. Catal.* **2014**, *356*, 2873. (c) Liao, Z.; Hong, Y.; Zheng, L.; Fan, C.; Zhang, X.; Liu, J.; Deng, Z.; Lei, A. *Chem.—Asian J.* **2015**, *10*, 96. For a review on radical alkenylation, see: (d) Tang, S.; Liu, K.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2015**, *44*, 1070.

(24) Cu prefers C-metalation with alkyl nitriles; see: (a) Purzycki, M.; Liu, W.; Hilmersson, G.; Fleming, F. F. *Chem. Commun.* **2013**, *49*, 4700. For the synthesis of $CuCH_2CN$ from $LiCH_2CN$, see: (b) Corey, E. J.; Kuwajima, I. *Tetrahedron Lett.* **1972**, 487.

(25) (a) Morris, G. E.; Oakley, D.; Pippard, D. A.; Smith, D. J. H. *J. Chem. Soc., Chem. Commun.* **1987**, 411. (b) Gephart, R. T., III; McMullin, C. L.; Sapiezynski, N. G.; Jang, E. S.; Aguila, M. J. B.; Cundari, T. R.; Warren, T. H. *J. Am. Chem. Soc.* **2012**, *134*, 17350.

(26) (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841. (b) Nakamura, E.; Isaka, M.; Mstsuzawa, S. *J. Am. Chem. Soc.* **1988**, *110*, 1297. (c) Toh, K.-K.; Wang, Y.-F.; Ng, S. E. P.; Chiba, J. *J. Am. Chem. Soc.* **2011**, *133*, 13942.

(27) For reviews on pinacol/semipinacol rearrangements, see: (a) Umland, K.-D.; Kirsch, S. F. *Synlett* **2013**, *24*, 1471. (b) Wang, B.; Tu, Y. *Acc. Chem. Res.* **2011**, *44*, 1207. (c) Snape, T. J. *Chem. Soc. Rev.* **2007**, *36*, 1823.

(28) For a review, see: Studer, A.; Bossart, M. *Tetrahedron* **2001**, *57*, 9649.