

Alkene Difunctionalization

Copper-Catalyzed Intramolecular Electrophilic Carbofunctionalization of Allylic Amides**

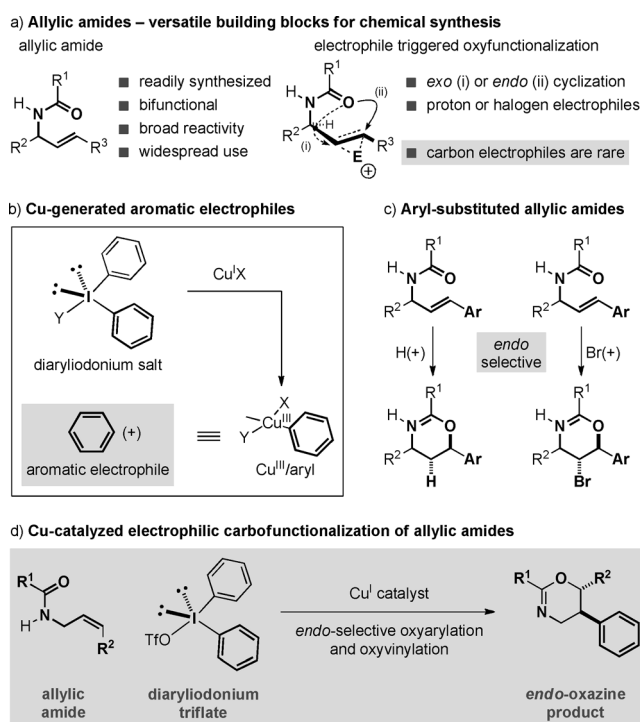
Elise Cahard, Nadine Bremeyer, and Matthew J. Gaunt*

Allylic amides and their derivatives represent a versatile class of nitrogen-containing building blocks, the bifunctional nature of which has enabled a diverse array of transformations and established them as strategically important molecules in chemical synthesis.^[1,2] Particularly useful are reactions where an electrophile activates the carbon–carbon double bond towards attack of the pendant oxygen atom of the amide carbonyl group to form either a five or six-membered ring heterocycle, depending on the mode of cyclization (Scheme 1a).^[3] Most of these reactions are triggered by heteroatom electrophiles, often activated by

a catalyst, and result in the formation of a carbon–oxygen and a carbon–heteroatom bond. It is, however, surprising that the related electrophilic carbofunctionalization process is rare. One possible reason for this is the lack of suitable carbon electrophiles that can activate the carbon–carbon double bond of the allylic amide. The development of Pd-catalyzed oxyarylation and aminoarylation reactions, in particular by Wolfe and co-workers,^[4] as well as related Pd,^[5] Cu,^[6] and Au-catalyzed^[7] processes have provided an alternative approach to related alkene difunctionalization^[8] and can be applied to derivatives of the generic allylic amine framework. Despite these advances, the development of novel methods that catalytically generate carbon electrophiles capable of activating alkenes to nucleophilic attack remains a challenge; the solution to this challenge would be of significant use in complex molecule synthesis.

As part of an overarching program aimed at the exploitation of high oxidation state metal species we,^[9] and others,^[10] have established that the combination of copper catalysts and diaryliodonium salts gives rise to a high oxidation state Cu^{III}/aryl^[11] intermediate that displays reactivity of an aromatic electrophile (Scheme 1b). We reasoned that this distinct catalytic activation strategy could be used to generate the aromatic electrophile equivalent that would be needed to affect an intramolecular oxyarylation of allylic amides, thus complementing the corresponding heteroatom electrophile triggered cyclizations that have become a mainstay in synthesis.

We selected aryl-substituted allylic amides with which to test our copper-catalyzed oxyarylation strategy as the products would generate a broadly useful class of diarylated amino alcohols. Furthermore, we noted that some aryl-substituted allylic amides have been utilized in other electrophile triggered cyclization reactions. For example, treatment with acid induces an intramolecular hydration-type reaction to form the 6-membered-ring oxazine product (Scheme 1c).^[13] Similarly, treatment with bromine gives rise to a bromocyclization, again forming the oxazine product, although this is dependent on the geometry of the starting alkene and the electronic nature of the aromatic ring.^[14,15] To the best of our knowledge, there are no examples of such a catalytic electrophilic carbofunctionalization of this class of molecules. Herein, we report the successful realization of this electrophilic carbofunctionalization hypothesis through the development of a new intramolecular copper-catalyzed oxyarylation and oxyvinylation of allylic amides that exclusively forms highly functionalized oxazine heterocycles (Scheme 1d). The new process is operationally simple, uses readily available reagents and catalysts and works for a wide range of substrates, and is complementary to existing methods for



Scheme 1.

[*] E. Cahard, Dr. N. Bremeyer, Prof. M. J. Gaunt
Department of Chemistry, University of Cambridge
Lensfield Road, Cambridge, CB2 1EW (UK)
E-mail: m.jg32@cam.ac.uk
Homepage: <http://www-gaunt.ch.cam.ac.uk/>

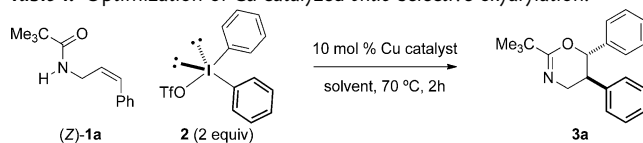
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intramolecular carbofunctionalization. The products are also precursors to useful substituted 1,3-amino alcohols, a class of molecule that displays versatile functionality and finds broad application in chemical synthesis.^[12]

At the outset of our investigations, we tested this hypothesis on a simple cinnamyl amide wherein the pendant carbonyl is derived from the pivaloyl group. Accordingly, allylic amide (*Z*)-**1a** was synthesized and treated with 10 mol % of copper (I) chloride and diphenyl iodonium triflate **2a**; after reaction for 2 h, the oxyarylation product **3a** was formed in 49 % yield (determined by ¹H NMR spectroscopy; Table 1, entry 1). Not only does this reaction proceed

Table 1: Optimization of Cu-catalyzed *endo*-selective oxyarylation.

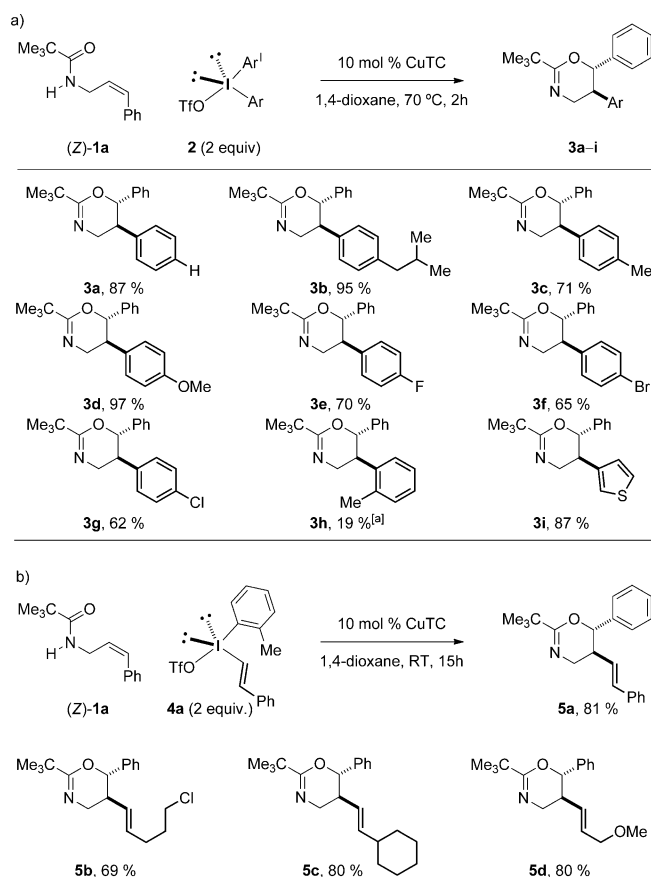


Entry	Catalyst	Solvent	Conc. [M]	Yield 3a [%] ^[a]
1	CuCl	CH ₂ Cl ₂	0.2	49
2	Cu(OTf) ₂	CH ₂ Cl ₂	0.2	51
3	CuI/AgOTf	CH ₂ Cl ₂	0.2	73
4	CuTC	CH ₂ Cl ₂	0.2	73
5	CuTC	PhMe	0.2	52
6	CuTC	EtOAc	0.2	56
7	CuTC	1,4-dioxane	0.1	81
8	CuTC	1,4-dioxane	0.05	94 (87) ^[b]
9	None	1,4-dioxane	0.05	0
10	None	1,4-dioxane ^[c]	0.05	4

[a] Yield determined by ¹H NMR spectroscopy with 1,3,5-(MeO₂C)₃C₆H₃ as internal standard. [b] Yield of isolated product. [c] Reaction at 90 °C for 24 h. TC = thiophenecarboxylate, Tf = trifluoromethanesulfonyl.

with exclusive *endo* regioselectivity, thus representing a rare example of a metal-catalyzed *endo*-selective alkene carbofunctionalization, it is also completely diastereoselective with respect to the formation of carbon–carbon and carbon–oxygen bonds within the newly formed oxazine product. A brief survey of the reaction parameters revealed that optimal conditions were 10 mol % of CuTC as catalyst, 2 equivalents of **2a** in a 0.05 M solution of dioxane at 70 °C, and gave oxazine **3a** in 87 % yield upon isolation. At 70 °C, no reaction occurred in the absence of copper catalysts. A small amount of product (4 %) was obtained when the control reaction was conducted at 90 °C, although we cannot rule out that this comes from a reaction catalyzed by trace copper impurities at the higher temperature.

With optimal conditions established, we first examined the scope of the new copper-catalyzed *endo*-selective oxyarylation process by assessing the capacity of the aryl-transfer component (Scheme 2).^[16] We were pleased to find that a range of substituted diaryliodonium triflates worked well in the reaction to provide access to aryl-substituted oxazines. Aromatic groups displaying electron-donating substituents (**3a–d**) are transferred in particularly good yields from the corresponding diaryliodonium triflates. Useful halogenated arenes are also accommodated (**3e–g**), thereby providing



Scheme 2. Cu-catalyzed oxyarylation (a) and oxyvinylation (b) of allylic amides. [a] Yield determined by ¹H NMR spectroscopy with 1,3,5-(MeO₂C)₃C₆H₃ as internal standard.

possibilities for subsequent chemical transformations. *Ortho*-substituted aryl groups could also be transferred through this protocol although reduced yields were observed (**3h**), presumably as a result of increased steric hindrance attenuating the reactivity of the di(*o*-tolyl)iodonium triflate. Also, diaryliodonium triflates displaying electron-withdrawing groups performed poorly in the reaction, and none of the desired product was obtained. However, we were pleased that the coupling of a heterocyclic thiophene motif was possible and proceeded in excellent yield (**3i**), thus enhancing the scope of our reaction. In all cases, only the *anti-endo*-oxyarylation products were observed.

An important extension of this reaction was realized when we tested the *endo*-selective carbofunctionalization with vinyl(aryl)iodonium triflates^[17] and found that the corresponding oxyvinylation provides the respective vinyl-substituted products in excellent yield as a single diastereomer (Scheme 2). Interestingly, the oxyvinylation operates at room temperature in contrast to the reaction with diaryliodonium triflates, which occurred at 70 °C, thus reflecting the increased reactivity of this class of hypervalent iodine reagent. Styrenyl, simple alkyl-substituted vinyl, alkyl-substituted vinyl motifs displaying remote functionality, and allyl ethers can be transferred. This simple extension in substrate scope signifi-

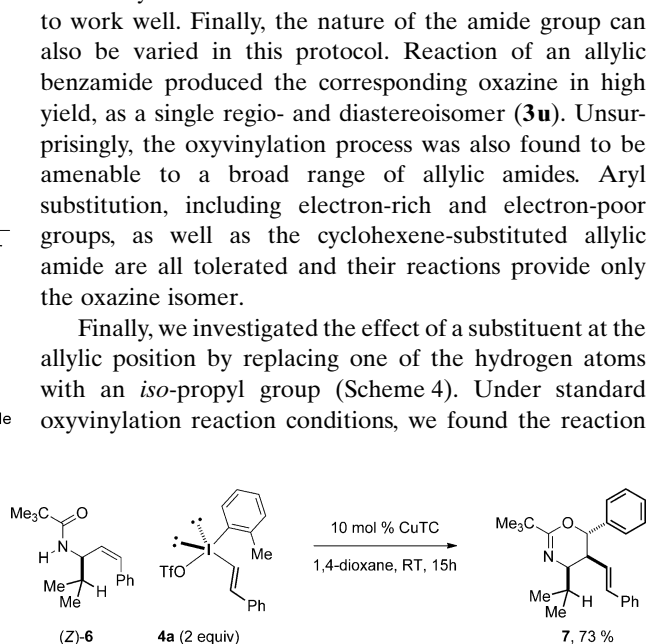
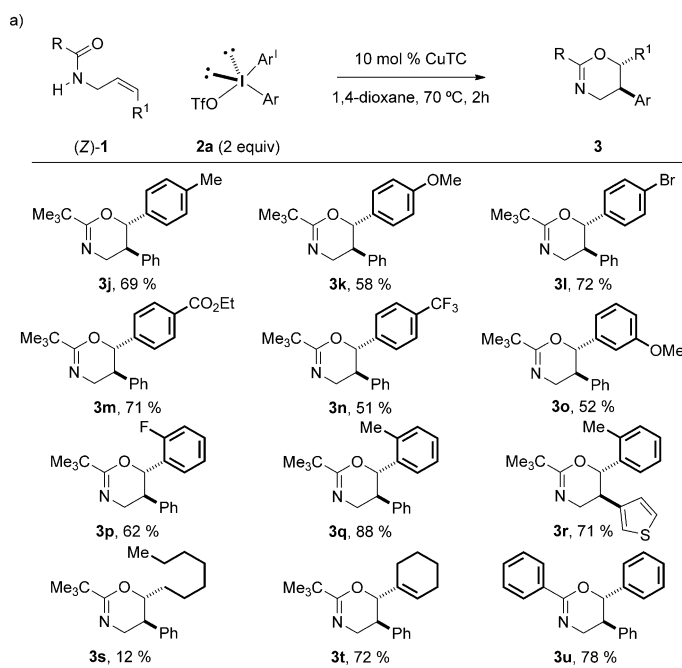
cantly expands the synthetic versatility of the products derived from the new copper-catalyzed reaction.

Next, we turned our attention to the substituent on the carbon–carbon double bond of the allylic amide (Scheme 3). As well as the original phenyl substituent, a broad range of aromatic groups were tolerated and *endo*-oxazine products with electron-donating substituents (**3j–k**), halogens (**3l**), and electron withdrawing-substituents (**3m–o**) on the aromatic ring were produced in good yield as a single diastereoisomer. We also found that *ortho*-substituents on the aromatic group are also tolerated and produced the desired products in

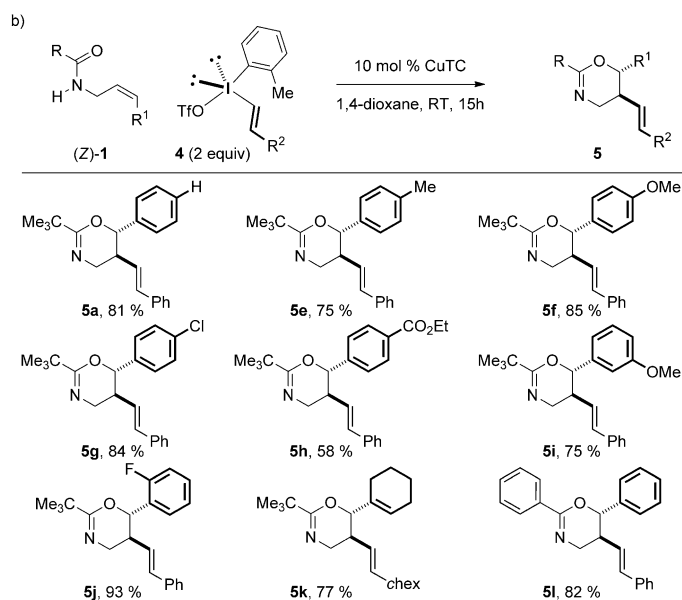
excellent yields (**3p–r**). When the aromatic group was replaced with an alkyl chain the reactivity of the substrate was greatly diminished, and gave a 1:1 mixture of *endo* and *exo* isomers (**3s**). Despite this apparent limitation, the reaction is not restricted to aromatic substituents; we were delighted that dienyl substrates undergo the copper-catalyzed oxyarylation in very good yield (see **3t**), thus expanding the scope of the reaction beyond the generic aryl-substituted allylic amides. These results do, however, point to the requirement for a group with an sp^2 -hybridized carbon atom to be directly attached to the alkene in order for the reaction

to work well. Finally, the nature of the amide group can also be varied in this protocol. Reaction of an allylic benzamide produced the corresponding oxazine in high yield, as a single regio- and diastereoisomer (**3u**). Unsurprisingly, the oxyvinilation process was also found to be amenable to a broad range of allylic amides. Aryl substitution, including electron-rich and electron-poor groups, as well as the cyclohexene-substituted allylic amide are all tolerated and their reactions provide only the oxazine isomer.

Finally, we investigated the effect of a substituent at the allylic position by replacing one of the hydrogen atoms with an *iso*-propyl group (Scheme 4). Under standard oxyvinilation reaction conditions, we found the reaction



Scheme 4. Diastereoselectivity in the Cu-catalyzed oxyvinilation.

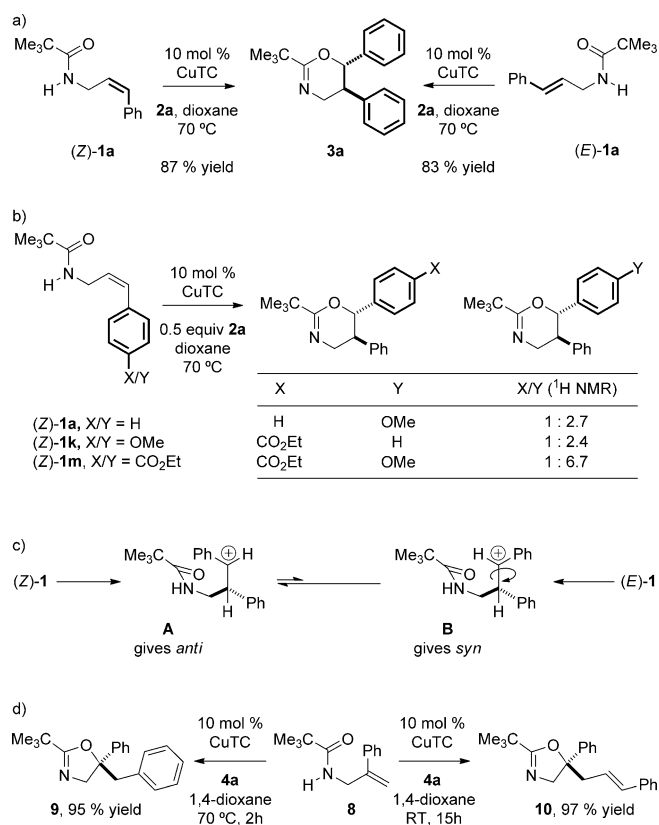


Scheme 3. Scope of alkene substituent in oxyarylation (a) and oxyvinilation (b).

produced a single isomer **7** in 73 % yield. Interestingly, the vinylation takes place from the same face as the *iso*-propyl group to give the *syn* relationship, whereas the diastereoselectivity of the oxyvinilation remains *anti*. This reaction affords a product that displays a high density of stereogenic centers and functional groups and such a transformation will likely find broad utility in synthesis applications given the plethora of methods available to make chiral allylic amides.

We conducted a number of simple experiments to probe the mechanism of this reaction. Firstly, only copper salts catalyze this reaction and use of other classical metal and non-metal Lewis acids resulted in no reaction ($\text{Bi}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$, $\text{Zn}(\text{OTf})_2$, $\text{BF}_3 \cdot \text{OEt}_2$). Given that the *Z* alkene (*Z*)-**1a** produces the *anti*-substituted oxazine **3a**, we expected that the *E* alkene (*E*)-**1a** would form the corresponding *syn* product. However, we were surprised to find that (*E*)-**1a** formed the same product (**3a**), with identical selectivity to that from the reaction of (*Z*)-**1a** (Scheme 5a).

In a competition experiment, the allylic amide with the electron-donating substituent reacted faster than that with either neutral or electron-deficient aromatic substituents (Scheme 5b). These results clearly demonstrate that the



Scheme 5. Mechanistic investigations. a) The effect of alkene geometry. b) Competition experiments to investigate the effect of the electronic properties of the alkene. One equivalent of a 1:1 mixture of two allylic amides were treated with **2a** under the standard reaction conditions. c) A possible carbocation mechanism. d) Location of cation-stabilizing groups can affect the selectivity of the cyclization.

mechanistic pathway operating in this reaction is not straightforward. There are a number of scenarios that could explain these observations. Firstly, the reactions of the *E* and *Z* isomers may proceed through different pathways, but arrive at the same product. However, it is possible that the reaction proceeds through a mechanism involving a carbocation and there is an equilibration of the conformations of the carbocation prior to carbon–oxygen bond formation (Scheme 5c).^[13,14,18] To further probe the validity of a carbocation mechanism we synthesized allylic amide **8**, where the phenyl group was on the internal position of the alkene and should move the position of the most stable positive charge. Under the standard arylation and vinylation reaction conditions, **8** exclusively forms the *exo*-products **9** and **10** in excellent yield, further supporting the importance of the cationic intermediate and extending the scope of the Cu-catalyzed process (Scheme 5d).

In summary, we have developed a new copper-catalyzed *endo*-selective oxyarylation and oxyvinylation of allylic amides with a range of diaryl- and vinyl(aryl)iodonium triflates. This transformation is tolerant to a wide range of functional groups and provides ready access to a broad selection of oxazine products in high yield and excellent diastereoselectivity. Allylic stereogenic centers are capable of controlling the diastereoselectivity of the process resulting in

the formation of stereochemically complex oxazine products. The heterocyclic products can be further manipulated into 1,3-amino alcohol derivatives that will find widespread use in synthesis.^[12,19]

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- a) M. Johannsen, K. A. Jørgensen, *Chem. Rev.* **1998**, 98, 1689–1708; b) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, 99, 1069–1094; c) B. M. Trost, M. L. Crawley, *Chem. Rev.* **2003**, 103, 2921–2943; d) E. Skucas, M.-Y. Ngai, V. Komanduri, M. J. Krische, *Acc. Chem. Res.* **2007**, 40, 1394–1401; e) J. F. Hartwig, L. M. Stanley, *Acc. Chem. Res.* **2010**, 43, 1461–1475; f) B. M. Trost, T. Zhang, J. D. Sieber, *Chem. Sci.* **2010**, 1, 427–440.
- Reactions of allylic amides. Cyclopropanation, see a) K. Csatayová, S. G. Davies, J. A. Lee, K. B. Ling, P. M. Roberts, A. J. Russell, J. E. Thomson, *Tetrahedron* **2010**, 66, 8420–8440; Dihydroxylation, see b) T. J. Donohoe, K. Blades, P. R. Moore, M. J. Waring, J. J. G. Winter, M. Helliwell, N. J. Newcombe, G. Stemp, *J. Org. Chem.* **2002**, 67, 7946–7956; Epoxidation, see c) W. R. Roush, J. A. Straub, R. J. Brown, *J. Org. Chem.* **1987**, 52, 5127–5136.
- Asymmetric halo-cyclizations, see S. E. Denmark, W. E. Kuester, M. T. Burk, *Angew. Chem.* **2012**, 124, 11098–11113; *Angew. Chem. Int. Ed.* **2012**, 51, 10938–10953.
- a) J. E. Ney, J. P. Wolfe, *Angew. Chem.* **2004**, 116, 3689–3692; *Angew. Chem. Int. Ed.* **2004**, 43, 3605–3608; b) D. M. Schultz, J. P. Wolfe, *Synthesis* **2012**, 351–361; c) A. Minatti, K. Muñoz, *Chem. Soc. Rev.* **2007**, 36, 1142–1152.
- Pd-catalyzed carbonylfunctionalization, see a) E. J. Alexanian, C. B. Lee, E. J. Sorensen, *J. Am. Chem. Soc.* **2005**, 127, 7690–7691; b) D. Kalyani, M. S. Sanford, *J. Am. Chem. Soc.* **2008**, 130, 2150–2151; c) C. F. Rosewall, P. A. Sibbald, D. V. Liskin, F. E. Michael, *J. Am. Chem. Soc.* **2009**, 131, 9488–9489; d) T. P. Pathak, K. M. Gligorich, B. E. Welm, M. S. Sigman, *J. Am. Chem. Soc.* **2010**, 132, 7870–7871; e) S. Kirchberg, R. Froehlich, A. Studer, *Angew. Chem.* **2010**, 122, 7029–7032; *Angew. Chem. Int. Ed.* **2010**, 49, 6877–6880; f) S. Nicolai, C. Piemontesi, J. Waser, *Angew. Chem.* **2011**, 123, 4776–4779; *Angew. Chem. Int. Ed.* **2011**, 50, 4680–4683; g) A. B. Weinstein, S. S. Stahl, *Angew. Chem.* **2012**, 124, 11673–11677; *Angew. Chem. Int. Ed.* **2012**, 51, 11505–11509.
- Cu-catalyzed carbonylfunctionalization, see a) W. Zeng, S. Chemler, *J. Am. Chem. Soc.* **2007**, 129, 12948–12949; b) E. S. Sherman, P. H. Fuller, D. Kasi, S. R. Chemler, *J. Org. Chem.* **2007**, 72, 3896–3905; c) L. Miao, I. Haque, M. R. Manzoni, W. S. Tham, S. R. Chemler, *Org. Lett.* **2010**, 12, 4739–4741; d) Y. Miller, L. Miao, A. Hosseini, S. R. Chemler, *J. Am. Chem. Soc.* **2012**, 134, 12149–12156; e) T. W. Liwosz, S. R. Chemler, *J. Am. Chem. Soc.* **2012**, 134, 2020–2023.
- Au-catalyzed carbonylfunctionalization, see a) G. Zhang, L. Cui, Y. Wang, L. Zhang, *J. Am. Chem. Soc.* **2010**, 132, 1474–1475; b) W. E. Brenzovich, D. Benitez, A. D. Lackner, H. P. Shunatona, E. Tkatchouk, W. A. Goddard, F. D. Toste, *Angew. Chem.* **2010**, 122, 5651–5654; *Angew. Chem. Int. Ed.* **2010**, 49, 5519–5522; c) A. D. Melhado, W. E. Brenzovich, A. D. Lackner, F. D. Toste, *J. Am. Chem. Soc.* **2010**, 132, 8885–8887; d) L. T. Ball, M. Green, G. C. Lloyd-Jones, C. A. Russell, *Org. Lett.* **2010**, 12, 4724–4727; e) E. Tkatchouk, N. P. Mankad, D. Benitez, W. A. Goddard, F. D. Toste, *J. Am. Chem. Soc.* **2011**, 133, 14293–

- 14300; f) B. Sahoo, M. Hopkinson, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 5505–5508.
- [8] For selected reviews, see: a) J. P. Wolfe, *Eur. J. Org. Chem.* **2007**, 571–582; b) V. Kotov, C. C. Scarborough, S. S. Stahl, *Inorg. Chem.* **2007**, *46*, 1910–1923; c) J. P. Wolfe, *Synlett* **2008**, 2913–2937; d) S. R. Chemler, *Org. Biomol. Chem.* **2009**, *7*, 3009–3019; e) R. I. McDonald, G. Liu, S. S. Stahl, *Chem. Rev.* **2011**, *111*, 2981–3019.
- [9] a) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172–8174; b) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593–1597; c) C.-L. Ciana, R. J. Phipps, J. R. Brandt, F. M. Meyer, M. J. Gaunt, *Angew. Chem.* **2011**, *123*, 478–482; *Angew. Chem. Int. Ed.* **2011**, *50*, 458–462; d) H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps, M. J. Gaunt, *Angew. Chem.* **2011**, *123*, 483–486; *Angew. Chem. Int. Ed.* **2011**, *50*, 463–466; e) A. Bigot, A. E. Williamson, M. J. Gaunt, *J. Am. Chem. Soc.* **2011**, *133*, 13778–13781; f) R. J. Phipps, L. McMurray, S. Ritter, H. A. Duong, M. J. Gaunt, *J. Am. Chem. Soc.* **2012**, *134*, 10773–10776.
- [10] a) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 4260–4263; b) J. S. Harvey, S. P. Simonovich, C. R. Jamison, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 13782–13785; c) S. Zhu, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2012**, *134*, 10815–10818; d) E. Skucas, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2012**, *134*, 9090–9093; e) C. Liu, W. Zhang, L.-X. Dai, S.-L. You, *Org. Lett.* **2012**, *14*, 4525–4527; f) M. E. Kieffer, K. V. Chuang, S. E. Reisman, *Chem. Sci.* **2012**, *3*, 3170–3174.
- [11] a) F. M. Beringer, E. J. Geering, I. Kuntz, M. Mausner, *J. Phys. Chem.* **1956**, *60*, 141–150; b) T. P. Lockhart, *J. Am. Chem. Soc.* **1983**, *105*, 1940–1946; c) A. E. King, T. C. Brunold, S. S. Stahl, *J. Am. Chem. Soc.* **2009**, *131*, 5044–5045; d) A. Casitas, A. E. King, T. Parella, M. Costas, S. S. Stahl, X. Ribas, *Chem. Sci.* **2010**, *1*, 326–330; e) A. J. Hickman, M. S. Sanford, *Nature* **2012**, *484*, 177–185.
- [12] a) J. P. Yardley, G. E. Morris Husbands, G. Stack, J. Butch, J. Bicksler, J. A. Moyer, E. A. Muth, T. Andree, H. Fletcher III, M. N. G. James, A. R. Sielecki, *J. Med. Chem.* **1990**, *33*, 2899–2905; b) T. M. Koenig, D. Mitchell, *Tetrahedron Lett.* **1994**, *35*, 1339–1342; c) S. M. Lait, D. A. Rankic, B. A. Keay, *Chem. Rev.* **2007**, *107*, 767–796.
- [13] a) L. Engman, *J. Org. Chem.* **1991**, *56*, 3425–3430; b) Y.-M. Wang, J. Wu, C. Hoong, V. Rauniyar, F. D. Toste, *J. Am. Chem. Soc.* **2012**, *134*, 12928–12931.
- [14] a) S. P. McManus, D. W. Ware, R. A. Hames, *J. Org. Chem.* **1978**, *43*, 4288–4294; b) K. A. Parker, R. O'Fee, *J. Am. Chem. Soc.* **1983**, *105*, 654–655; c) A. Commerçon, G. Ponsinet, *Tetrahedron Lett.* **1990**, *31*, 3871–3874.
- [15] Hypervalent iodine reagents yield *endo*-selective cyclizations of alkenyl amines, see a) J. Barluenga, M. Trincado, E. Rubio, J. M. González, *J. Am. Chem. Soc.* **2004**, *126*, 3416–3417; b) H. M. Lovick, F. E. Michael, *J. Am. Chem. Soc.* **2010**, *132*, 1249–1251; c) D. J. Wardrop, E. G. Bowen, R. E. Forslund, A. D. Sussman, S. L. Weerasekera, *J. Am. Chem. Soc.* **2010**, *132*, 1188–1189; d) U. Farid, T. Wirth, *Angew. Chem.* **2012**, *124*, 3518–3522; *Angew. Chem. Int. Ed.* **2012**, *51*, 3462–3465; for a related cyclization reaction, see: e) J. Streuff, C. H. Hovelmann, M. Nieger, K. Muniz, *J. Am. Chem. Soc.* **2005**, *127*, 14586–14587.
- [16] a) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331; b) M. Bielawski, B. Olofsson, *Chem. Commun.* **2007**, 2521–2523; c) M. Bielawski, M. Zhu, B. Olofsson, *Adv. Synth. Catal.* **2007**, *349*, 2610–2618.
- [17] a) M. Ochiai, K. Sumi, Y. Takaoka, M. Kunishima, Y. Nagao, M. Shiro, E. Fujita, *Tetrahedron* **1988**, *44*, 4095–4112; b) M. Ochiai, T. Shu, T. Nagaoka, Y. Kitagawa, *J. Org. Chem.* **1997**, *62*, 2130–2138.
- [18] For a related trifluoromethylation reaction, see: R. Zhu, S. L. Buchwald, *J. Am. Chem. Soc.* **2012**, *134*, 12462–12465.
- [19] The oxazine is cleaved to the 1,3-amino alcohol through acid hydrolysis.

