C–H Functionalization

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Redox-Neutral Copper(II) Carboxylate Catalyzed α-Alkynylation of Amines**

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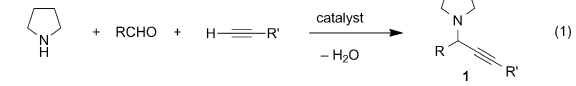
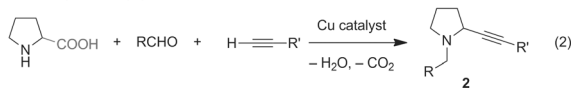
Propargylic amines represent important building blocks,[1] and compounds of this class (e.g., **1**) are readily assembled by three-component reactions of amines, aldehydes, and alkynes, frequently referred to as A^3 reactions [Eq. (1)].[2–4] Methods that enable direct access to the ring-substituted isomers **2** are much more limited [see Eq. (2)]. As part of a program to develop redox-neutral[5] reactions of broad utility,[6] we recently reported an α-amino acid based decarboxylative three-component coupling strategy to access ring-substituted propargylic amines such as **2** [Eq. (2)].[6e] A nearly identical approach was also reported by Li et al.[7–9] Replacement of the α-amino acid with a simple amine would represent a significant advance [Eq. (3)]. Herein we report the first examples of this elusive transformation.

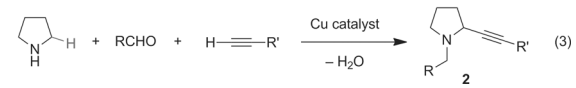
Typical A^3 reaction



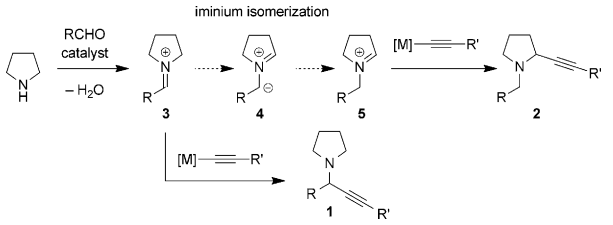
Decarboxylative alkynylation



Redox-neutral amine α-alkynylation (this work):



Direct α-alkynylation of tertiary amines has previously been accomplished by means of oxidative C–H functionalization,[10,11] including photoredox catalysis.[12] These methods require stoichiometric amounts of oxidant and are often limited to N-aryl tetrahydroisoquinolines and N,N-dialkylanilines.[13,14] As an attractive alternative, we envisioned a direct, redox-neutral, three-component coupling with concurrent amine α-alkynylation (Scheme 1). To realize such a process, reaction conditions must be identified so as to prevent the regular course of events in an A^3 reaction, namely addition of



Scheme 1. Competing reaction pathways in the formation of isomeric propargylic amines.

the metal acetylide to the initially formed iminium ion **3** to give the undesired isomer **1**. Access to **2** requires the isomerization of the iminium ion **3** into **5**, and must proceed in the presence of the metal acetylide. This isomerization could in principle be accomplished by iminium deprotonation/reprotonation via the azomethine ylide intermediate **4**. In fact, α-deprotonation of iminium ions as a means to form azomethine ylides has been reported in the context of pericyclic azomethine ylide chemistry.[15,16] We have previously developed powerful reactions of azomethine ylides leading to intramolecular C–N and C–C bond formation through nonpericyclic pathways.[6,17] Upon considering potential solutions to the added challenge of performing amine α-functionalizations in an intermolecular setting, we reasoned that an electron-withdrawing group (R) on **3** would serve to accelerate iminium isomerization through acidification of the amine α-proton. In addition, increasing the steric demand of R would be expected to slow down the rate of the formation of **1**.

With the above considerations in mind and encouraged by our recent success in developing a redox-neutral amine α-cyanation,[6m] we selected 2,6-dichlorobenzaldehyde as the reaction partner in the proposed three-component reaction with pyrrolidine and phenylacetylene (Table 1). Different catalysts were evaluated as part of this survey, which was conducted under microwave conditions. Using CuBr and TMEDA, the catalyst combination that proved optimal in the decarboxylative alkynylation [Eq. (2)],[6e] a 1:3 mixture of **6a** and **7a** was obtained in 65% yield (entry 1). CuBr or $CuBr_2$ provided higher overall yields, but less favorable product ratios (entries 2 and 3). Interestingly, copper(II) triflate provided a favorable 5:1 ratio of regioisomers, albeit in moderate yield (entry 4). Gratifyingly, copper(II) acetate gave a 7:1 ratio of regioisomers but without improvement in

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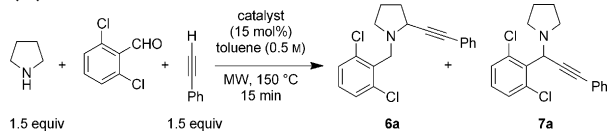
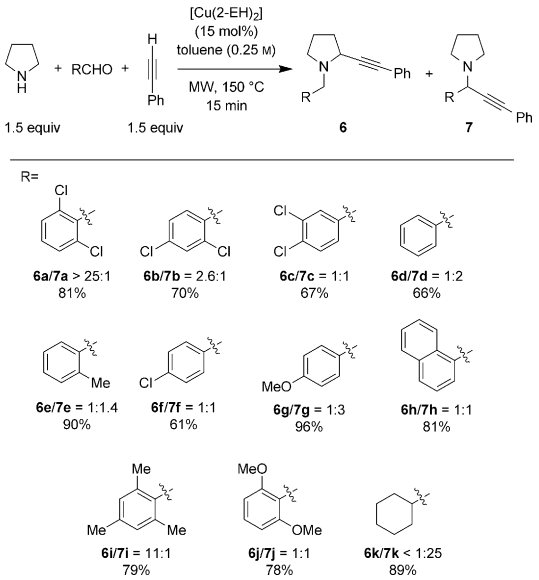
Table 1: Evaluation of catalysts for the direct three-component α-alkynylation.[a]



Entry	Catalyst	**6a**/**7a**	**6a**+**7a** Yield [%]
1	CuBr + TMEDA (30 mol%)	1:3	65
2	CuBr	1:5	94
3	$CuBr_2$	1:4	82
4	$Cu(OTf)_2$	5:1	45
5	$Cu(OAc)_2{\cdot}H_2O$	7:1	47
6	$Cu(HCOO)_2{\cdot}H_2O$	1:1	82
7	$Cu(OBz)_2{\cdot}H_2O$	7:1	74
8	copper(II) 2-ethylhexanoate	20:1	82
9	copper(II) cyclohexylbutanoate	14:1	76
10	copper(II) pivalate	15:1	82
11	$[Cu(acac)_2]$	1:4	67
12	$[Cu(hfacac)_2]{\cdot}H_2O$	3:1	76
13	$Cu(NO_2)_2{\cdot}H_2O$	1:1	67
14	2-ethylhexanoic acid	N/A	0
15	none	N/A	0

[a] Reactions were performed on a 0.5 mmol scale with anhydrous toluene. Yields are those of the isolated and chromatographically purified compounds. acac = acetylacetonate, hfacac = hexafluoroacetylacetonate, N/A = not applicable, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.



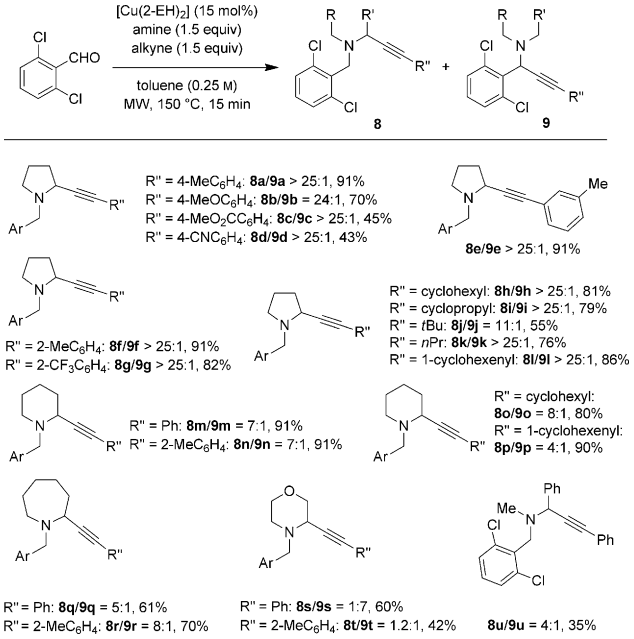
Scheme 2. Dependence of product ratios on the aldehyde. MW = microwave.

yield (entry 5). Other copper(II) carboxylate salts such as copper(II) benzoate also yielded **6a** as the major product. Copper(II) carboxylates with enhanced solubilities provided favorable product ratios and good product yields (entries 8–10). Readily available copper(II) 2-ethylhexanoate [Cu(2-EH)$_2$] was identified as an excellent catalyst, thus allowing for the isolation of **6a** and **7a** in a 20:1 ratio and 82% yield. Notably, $[Cu(acac)_2]$ provided product ratios vastly different from that of the corresponding perfluorinated catalyst (entries 11 and 12). The desired products were neither obtained with 2-ethylhexanoic acid (2-EHA) nor in the absence of a catalyst. In all copper(II)-catalyzed reactions, 1,4-diphenylbuta-1,3-diyne, the corresponding Glaser coupling product[18] of phenylacetylene was isolated as a byproduct.

Upon further examination of the parameters, we found that replacement of anhydrous toluene with HPLC grade toluene had no deleterious effect on the outcome of the reaction. Lowering the concentration from 0.5 M to 0.25 M was found to be beneficial. Under these reaction conditions, the reaction of 2,6-dichlorobenzaldehyde, pyrrolidine, and phenylacetylene gave products **6a** and **7a** in a greater than 25:1 ratio and 81% yield (Scheme 2).

To evaluate the impact of the aldehyde on the selectivity of the reaction, we tested a collection of electronically diverse aldehydes with varying steric demands (Scheme 2). Interestingly, replacement of 2,6-dichlorobenzaldehyde with the electronically similar 2,4-dichlorobenzaldehyde resulted in a dramatic reduction of the product ratio from greater than 25:1 to 2.6:1. Further reduction in the ratio to 1:1 was seen for 3,4-dichlorobenzaldehyde. Unsubstituted benzaldehyde gave rise to **6d** and **7d** in a 1:2 ratio, thus favoring the undesired regioisomer. 2-Methylbenzaldehyde performed slightly better, thus providing a 1:1.4 ratio of the products **6e** and **7e**. A comparison of the results obtained with benzaldehyde, 4-chlorobenzaldehyde, and 4-methoxybenzaldehyde (products **6d**, **6f**, and **6g**) clearly established the impact of electronic factors on the regioselectivity, with the more electron-poor aldehydes providing more favorable product ratios. However, upon inspection of all results, it can be concluded that steric factors outweigh electronics. The case in point is mesitaldehyde which provided an excellent product ratio of 11:1. Even the electron-rich 2,6-dimethoxybenzaldehyde provided a more favorable product ratio than benzaldehyde. In contrast, cyclohexane carbaldehyde gave rise to almost none of the desired product but rather underwent the standard A^3 reaction. As a side note, the reaction of 2,6-dichlorobenzaldehyde, pyrrolidine, and phenylacetylene can be performed under reflux using otherwise identical reaction conditions. In this instance, the products **6a** and **7a** were isolated in a 19:1 ratio (86% yield) after a reaction time of just 30 minutes.

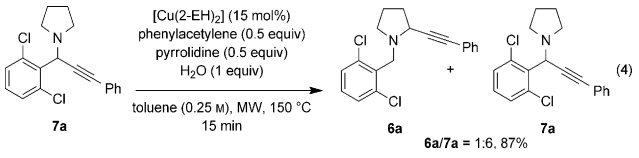
The scope of the three-component coupling reaction was explored under the optimized microwave conditions (Scheme 3). Reactions of 2,6-dichlorobenzaldehyde, pyrrolidine, and various terminal alkynes resulted in the formation of the desired products in generally good to excellent yields. Aromatic, alkenyl, and aliphatic substituents on the alkyne were readily accommodated. In the majority of cases, products were obtained with regioselectivities exceeding 25:1. Importantly, the α-alkynylation is not limited to pyrrolidine. Piperidine and azepane also underwent [Cu(2-EH)$_2$]-catalyzed couplings with various terminal alkynes to provide propargylic amines in good to excellent yields. While the observed regioselectivities for these more challenging substrates are lower than that for pyrrolidine, they are still in



Scheme 3. Scope of the direct α-alkynylation. Ar = 2,6-$Cl_2C_6H_3$.

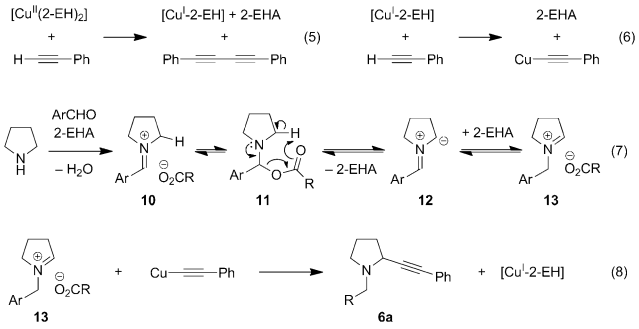
a synthetically useful range. Morpholine provided only small amounts of desired regioisomer in a reaction with phenylacetylene. Interestingly, the introduction of an *ortho*-methyl substituent to phenylacetylene allowed the isolation of **8t** and **9t** in a 1.2:1 ratio. Finally, although alkynylation products from acyclic amines are available by traditional A^3 chemistry, we decided to test *N*-methylbenzylamine under the standard reaction conditions. In the event, the products **8u** and **9u** were isolated in a 4:1 ratio, albeit in only 35% yield.

To establish whether the regioselectivity of the alkynylation could be affected by product isomerization, we exposed **7a** to the reaction conditions.[19] To best mimic the original reaction conditions, phenylacetylene, pyrrolidine and water were added [Eq. (4)]. Very little isomerization was observed



in addition to the formation of 1,4-diphenylbuta-1,3-diyne, and **6a** and **7a** were recovered in a 1:6 ratio (87% yield). While this study establishes the potential reversibility of the reaction, the degree of isomerization is insufficient to account for the observed regioselectivity of the parent reaction. Therefore, the product ratios likely reflect the intrinsic reactivities of the reaction intermediates. This is in stark contrast to our previous study on α-cyanation in which product isomerization is an important contributor to the overall selectivity.[6m]

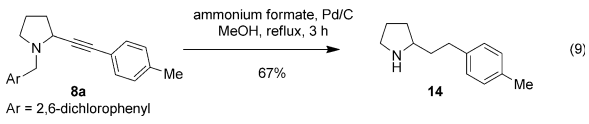
Outlined in Scheme 4 is a potential mechanism for the redox-neutral α-alkynylation. Reaction of $[Cu(2\text{-EH})_2]$ with phenylacetylene results in the formation of [Cu^I-2-EH], the

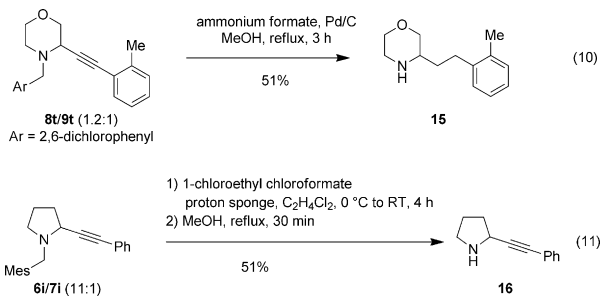


Scheme 4. Proposed mechanism for α-alkynylation.

Glaser product, and one equivalent of 2-EHA [Eq. (5)]. The active copper acetylide is formed upon reaction of [Cu^I-2-EH] with phenylacetylene, with concurrent release of another equivalent of 2-EHA [Eq. (6)]. 2-EHA is believed to play a crucial role in the overall reaction [Eq. (7)]. Firstly, it is expected to facilitate the formation of the iminium ion **10**. As indicated in Scheme 1, the carboxylate anion of **10** could bring about iminium isomerization by deprotonation/reprotonation. Alternatively, the N,O-acetal **11**, which should exist in equilibrium with **10**, could eliminate 2-EHA by a concerted pathway to form azomethine ylide **12**.[16,20] Regioselective protonation of the azomethine ylide **12** by 2-EHA results in the iminium ion **13**, which may exist in equilibrium with the corresponding N,O-acetal (not shown). In the final step, **13** engages the copper acetylide to form the propargylic amine **6a**, concomitant with the regeneration of [Cu^I-2-EH] [Eq. (8)]. Although $[Cu(2\text{-EH})_2]$ is the only additive, the two active catalysts [Cu^I-2-EH] and 2-EHA are formed in situ and activate both reaction partners separately in what may be considered an example of synergistic catalysis.[21]

To demonstrate the utility of the propargylic amines derived from the redox-neutral α-alkynylation, a number of products were selectively transformed. Debenzylation of **8a** with simultaneous reduction of the triple bond was accomplished by transfer hydrogenation to provide the product **14** [Eq. (9)]. This approach can also be employed to remove the undesired regioisomer in cases where the alkynylation is less regioselective. For instance, exposure of a 1.2:1 mixture of **8t** and **9t** to the transfer hydrogenation conditions led to clean formation of morpholine **15** [Eq. (10)]. An alternative two-step debenzylation strategy designed to preserve the alkyne functionality allowed the synthesis of the propargylamine **16** [Eq. (11)].





In summary, we have developed an unprecedented approach for the one-step synthesis of ring-substituted propargylic amines. The combination of a reductive amine N-alkylation with an oxidative α-functionalization effectively renders this process redox-neutral. We anticipate wide adoption of this concept as a means to rapidly access α-functionalized amines from simple precursors.

Experimental Section

General procedure: A 10 mL microwave reaction tube was charged with a 10 × 8 mm SiC passive heating element, copper(II) 2-ethylhexanoate (0.038 mmol, 0.15 equiv), toluene (1 mL), alkyne (0.375 mmol, 1.5 equiv), amine (0.375 mmol, 1.5 equiv) and aldehyde (0.25 mmol). The reaction tube was sealed with a Teflon-lined snap cap, and heated in a microwave reactor at 150 °C (200 W, 30–80 psi) for 15 min. [**Note:** SiC passive heating elements must not be used in conjunction with stir bars for they may score glass and cause vessel failure.] After cooling with compressed air flow, the reaction mixture was directly loaded onto a column and purified by silica gel chromatography.

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[1] See: P. de Armas, D. Tejedor, F. Garcia-Tellado, *Angew. Chem.* **2010**, *122*, 1029; *Angew. Chem. Int. Ed.* **2010**, *49*, 1013, and references therein.

[2] A^3 reactions: selected key contributions: a) A. B. Dyatkin, R. A. Rivero, *Tetrahedron Lett.* **1998**, *39*, 3647; b) G. W. Kabalka, L. Wang, R. M. Pagni, *Synlett* **2001**, 676; c) C.-J. Li, C. M. Wei, *Chem. Commun.* **2002**, 268; d) C. M. Wei, C.-J. Li, *J. Am. Chem. Soc.* **2003**, *125*, 9584; e) N. Gommermann, C. Koradin, K. Polborn, P. Knochel, *Angew. Chem.* **2003**, *115*, 5941; *Angew. Chem. Int. Ed.* **2003**, *42*, 5763.

[3] A^3 reactions: selected reviews: a) C. Wei, Z. Li, C.-J. Li, *Synlett* **2004**, 1472; b) L. Zani, C. Bolm, *Chem. Commun.* **2006**, 4263; c) V. V. Kouznetsov, L. Y. V. Mendez, *Synthesis* **2008**, 491; d) W. J. Yoo, L. Zhao, C.-J. Li, *Aldrichimica Acta* **2011**, *44*, 43; e) V. A. Peshkov, O. P. Pereshivko, E. V. Van der Eycken, *Chem. Soc. Rev.* **2012**, *41*, 3790.

[4] A^3 reactions: selected recent contributions: a) T. A. Graf, T. K. Anderson, N. B. Bowden, *Adv. Synth. Catal.* **2011**, *353*, 1033; b) M. Cheng, Q. Zhang, X. Y. Hu, B. G. Li, J. X. Ji, A. S. C. Chan, *Adv. Synth. Catal.* **2011**, *353*, 1274; c) S. S. Patil, S. V. Patil, V. D. Bobade, *Synlett* **2011**, 1157; d) M. Saifuddin, P. K. Agarwal, B. Kundu, *J. Org. Chem.* **2011**, *76*, 10122; e) M. T. Chen, B. Landers, O. Navarro, *Org. Biomol. Chem.* **2012**, *10*, 2206; f) C. E. Meyet, C. J. Pierce, C. H. Larsen, *Org. Lett.* **2012**, *14*, 964; g) B. R. Buckley, A. N. Khan, H. Heaney, *Chem. Eur. J.* **2012**, *18*, 3855; h) C. J. Pierce, M. Nguyen, C. H. Larsen, *Angew. Chem.* **2012**, *124*, 12455; *Angew. Chem. Int. Ed.* **2012**, *51*, 12289.

[5] a) N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem.* **2009**, *121*, 2896; *Angew. Chem. Int. Ed.* **2009**, *48*, 2854; b) T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*, 3010.

[6] a) C. Zhang, C. K. De, R. Mal, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 416; b) S. Murarka, C. Zhang, M. D. Konieczynska, D. Seidel, *Org. Lett.* **2009**, *11*, 129; c) C. Zhang, S. Murarka, D. Seidel, *J. Org. Chem.* **2009**, *74*, 419; d) S. Murarka, I. Deb, C. Zhang, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 13226; e) C. Zhang, D. Seidel, *J. Am. Chem. Soc.* **2010**, *132*, 1798; f) I. Deb, D. Seidel, *Tetrahedron Lett.* **2010**, *51*, 2945; g) C. Zhang, D. Das, D. Seidel, *Chem. Sci.* **2011**, *2*, 233; h) I. Deb, D. Das, D. Seidel, *Org. Lett.* **2011**, *13*, 812; i) M. C. Haibach, I. Deb, C. K. De, D. Seidel, *J. Am. Chem. Soc.* **2011**, *133*, 2100; j) I. Deb, D. Coiro, D. Seidel, *Chem. Commun.* **2011**, *47*, 6473; k) M. K. Vecchione, A. X. Sun, D. Seidel, *Chem. Sci.* **2011**, *2*, 2178; l) D. Das, M. T. Richers, L. Ma, D. Seidel, *Org. Lett.* **2011**, *13*, 6584; m) L. Ma, W. Chen, D. Seidel, *J. Am. Chem. Soc.* **2012**, *134*, 15305.

[7] H.-P. Bi, Q. Teng, M. Guan, W.-W. Chen, Y.-M. Liang, X. Yao, C.-J. Li, *J. Org. Chem.* **2010**, *75*, 783.

[8] For an oxidative variant, see: H.-P. Bi, L. Zhao, Y.-M. Liang, C.-J. Li, *Angew. Chem.* **2009**, *121*, 806; *Angew. Chem. Int. Ed.* **2009**, *48*, 792.

[9] Decarboxylative A^3 reactions: a) H. Feng, D. S. Ermolat'ev, G. Song, E. V. Van der Eycken, *J. Org. Chem.* **2011**, *76*, 7608; b) H. Feng, D. S. Ermolat'ev, G. Song, E. V. Van der Eycken, *Org. Lett.* **2012**, *14*, 1942; c) H. Feng, D. S. Ermolat'ev, G. Song, E. V. Van der Eycken, *J. Org. Chem.* **2012**, *77*, 5149.

[10] Selected reviews on amine α-functionalization: a) S. I. Murahashi, *Angew. Chem.* **1995**, *107*, 2670; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2443; b) S. Doye, *Angew. Chem.* **2001**, *113*, 3455; *Angew. Chem. Int. Ed.* **2001**, *40*, 3351; c) K. R. Campos, *Chem. Soc. Rev.* **2007**, *36*, 1069; d) S. I. Murahashi, D. Zhang, *Chem. Soc. Rev.* **2008**, *37*, 1490; e) C.-J. Li, *Acc. Chem. Res.* **2009**, *42*, 335; f) W. J. Yoo, C.-J. Li, *Top. Curr. Chem.* **2010**, *292*, 281; g) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654; h) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; i) C. L. Sun, B. J. Li, Z. J. Shi, *Chem. Rev.* **2011**, *111*, 1293; j) C. Liu, H. Zhang, W. Shi, A. W. Lei, *Chem. Rev.* **2011**, *111*, 1780; k) A. E. Wendlandt, A. M. Suess, S. S. Stahl, *Angew. Chem.* **2011**, *123*, 11256; *Angew. Chem. Int. Ed.* **2011**, *50*, 11062; l) K. M. Jones, M. Klussmann, *Synlett* **2012**, 159; m) C. Zhang, C. H. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464; n) E. A. Mitchell, A. Peschiulli, N. Lefevre, L. Meerpoel, B. U. W. Maes, *Chem. Eur. J.* **2012**, *18*, 10092; o) L. Shi, W. Xia, *Chem. Soc. Rev.* **2012**, *41*, 7687.

[11] Selected articles on oxidative amine α-alkynylation: a) Z. Li, C.-J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 11810; b) Z. Li, C.-J. Li, *Org. Lett.* **2004**, *6*, 4997; c) Z. Li, P. D. MacLeod, C.-J. Li, *Tetrahedron: Asymmetry* **2006**, *17*, 590; d) S. Turcaud, E. Sierecki, T. Martens, J. Royer, *J. Org. Chem.* **2007**, *72*, 4882; e) M. Niu, Z. Yin, H. Fu, Y. Jiang, Y. Zhao, *J. Org. Chem.* **2008**, *73*, 3961; f) L. Zhao, C.-J. Li, *Angew. Chem.* **2008**, *120*, 7183; *Angew. Chem. Int. Ed.* **2008**, *47*, 7075; g) X. L. Xu, X. N. Li, *Org. Lett.* **2009**, *11*, 1027; h) C. M. R. Volla, P. Vogel, *Org. Lett.* **2009**, *11*, 1701; i) P. Liu, C. Y. Zhou, S. Xiang, C. M. Che, *Chem. Commun.* **2010**, *46*, 2739; j) W. K. Su, J. B. Yu, Z. H. Li, Z. J. Jiang, *J. Org. Chem.* **2011**, *76*, 9144; k) E. Boess, C. Schmitz, M. Klussmann, *J. Am. Chem. Soc.* **2012**, *134*, 5317; l) K. N. Singh, P. Singh, A. Kaur, *Synlett* **2012**, 760.

[12] Photoredox approaches to amine α-alkynylation: a) D. B. Freeman, L. Furst, A. G. Condie, C. R. Stephenson, *Org. Lett.* **2012**,

14, 94; b) M. Rueping, R. M. Koenigs, K. Poscharny, D. C. Fabry, D. Leonori, C. Vila, *Chem. Eur. J.* **2012**, *18*, 5170.

[13] For conceptually different α-alkynylations of tertiary amines, see: T. Sugiishi, H. Nakamura, *J. Am. Chem. Soc.* **2012**, *134*, 2504.

[14] For iridium-catalyzed α-alkenylations of imines with alkynes, see: S. Sakaguchi, T. Kubo, Y. Ishii, *Angew. Chem.* **2001**, *113*, 2602; *Angew. Chem. Int. Ed.* **2001**, *40*, 2534.

[15] R. Huisgen, R. Grashey, E. Steingruber, *Tetrahedron Lett.* **1963**, *4*, 1441.

[16] Selected reviews on azomethine ylides: a) A. Padwa, W. H. Pearson, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*, *Vol. 59*, Wiley, Chichester, **2002**; b) C. Najera, J. M. Sansano, *Curr. Org. Chem.* **2003**, *7*, 1105; c) I. Coldham, R. Hufton, *Chem. Rev.* **2005**, *105*, 2765; d) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484; e) T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.* **2006**, 2873; f) C. Nájera, J. M. Sansano, *Top. Heterocycl. Chem.* **2008**, *12*, 117; g) M. Nyerges, J. Toth, P. W. Groundwater, *Synlett* **2008**, 1269; h) J. Adrio, J. C. Carretero, *Chem. Commun.* **2011**, *47*, 6784.

[17] Selected recent articles on redox-neutral amine functionalization: a) S. J. Pastine, K. M. McQuaid, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 12180; b) M. Tobisu, N. Chatani, *Angew. Chem.* **2006**, *118*, 1713; *Angew. Chem. Int. Ed.* **2006**, *45*, 1683; c) P. Mátyus, O. Éliás, P. Tapolcsányi, A. Polonka-Bálint, B. Halász-Dajka, *Synthesis* **2006**, 2625; d) M. Oda, Y. Fukuchi, S. Ito, N. C. Thanh, S. Kuroda, *Tetrahedron Lett.* **2007**, *48*, 9159; e) L. Zheng, F. Yang, Q. Dang, X. Bai, *Org. Lett.* **2008**, *10*, 889; f) J. Barluenga, M. Fananas-Mastral, F. Aznar, C. Valdes, *Angew. Chem.* **2008**, *120*, 6696; *Angew. Chem. Int. Ed.* **2008**, *47*, 6594; g) K. Mori, Y. Ohshima, K. Ehara, T. Akiyama, *Chem. Lett.* **2009**, *38*, 524; h) L. Cui, Y. Peng, L. Zhang, *J. Am. Chem. Soc.* **2009**, *131*, 8394; i) P. A. Vadola, D. Sames, *J. Am. Chem. Soc.* **2009**, *131*, 16525; j) N. K. Pahadi, M. Paley, R. Jana, S. R. Waetzig, J. A. Tunge, *J. Am. Chem. Soc.* **2009**, *131*, 16626; k) V. K.-Y. Lo, C.-Y. Zhou, M.-K. Wong, C.-M. Che, *Chem. Commun.* **2010**, *46*, 213; l) J. Kuang, S. Ma, *J. Am. Chem. Soc.* **2010**, *132*, 1786; m) Y. K. Kang, S. M. Kim, D. Y. Kim, *J. Am. Chem. Soc.* **2010**, *132*, 11847; n) P. Dunkel, G. Turos, A. Benyei, K. Ludanyi, P. Matyus, *Tetrahedron* **2010**, *66*, 2331; o) G. Zhou, J. Zhang, *Chem. Commun.* **2010**, *46*, 6593; p) H. Mao, R. Xu, J. Wan, Z. Jiang, C. Sun, Y. Pan, *Chem. Eur. J.* **2010**, *16*, 13352; q) W. D. Cao, X. H. Liu, W. T. Wang, L. L. Lin, X. M. Feng, *Org. Lett.* **2011**, *13*, 600; r) G. H. Zhou, F. Liu, J. L. Zhang, *Chem. Eur. J.* **2011**, *17*, 3101; s) N. Ghavtadze, R. Narayan, B. Wibbeling, E. U. Wuerthwein, *J. Org. Chem.* **2011**, *76*, 5185; t) K. Mori, K. Ehara, K. Kurihara, T. Akiyama, *J. Am. Chem. Soc.* **2011**, *133*, 6166; u) Y. P. He, Y. L. Du, S. W. Luo, L. Z. Gong, *Tetrahedron Lett.* **2011**, *52*, 7064; v) S. J. Mahoney, E. Fillion, *Chem. Eur. J.* **2012**, *18*, 68; w) I. D. Jurberg, B. Peng, E. Woestefeld, M. Wasserloos, N. Maulide, *Angew. Chem.* **2012**, *124*, 1986; *Angew. Chem. Int. Ed.* **2012**, *51*, 1950; x) Y. Y. Han, W. Y. Han, X. Hou, X. M. Zhang, W. C. Yuan, *Org. Lett.* **2012**, *14*, 4054; y) L. J. Chen, L. Zhang, J. Lv, J. P. Cheng, S. Z. Luo, *Chem. Eur. J.* **2012**, *18*, 8891.

[18] a) C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422; b) P. Siemsen, R. C. Livingston, F. Diederich, *Angew. Chem.* **2000**, *112*, 2740; *Angew. Chem. Int. Ed.* **2000**, *39*, 2632.

[19] Reversibility in an iminium alkynylation has previously been demonstrated: T. Sugiishi, A. Kimura, H. Nakamura, *J. Am. Chem. Soc.* **2010**, *132*, 5332.

[20] This mode of azomethine ylide formation from a carboxylic acid derived N,O-acetal was proposed by Yu et al. as part of a computational investigation of Tunge's benzoic acid catalyzed synthesis of N-alkyl pyrroles from 3-pyrroline: X. S. Xue, A. Yu, Y. Cai, J. P. Cheng, *Org. Lett.* **2011**, *13*, 6054. See also reference [17j].

[21] A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633.

