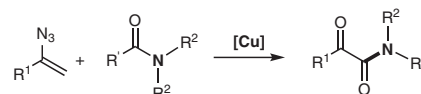


Copper-Catalyzed Amination of Vinyl Azides to α -Ketoamides

Yu Wang^aDongling Zhang^aKaining Zhang^bZhenhua Liu^{a,b}Jing Lin^aWei Cao^aZhongxue Fang^{*a, b}

- 20 examples, up to 93% yield
- good functional group tolerance
- novel C–N bond formation

● gram scale

^a School of Chemistry and Environmental Engineering,
Yancheng Teachers University, Yancheng224007,
P. R. of China
fangzhongxue120@163.com

^b College of Chemistry, Chemical Engineering and Materials
Science, Shandong Normal University, Jinan 250014,
P. R. of China
liuzhenhua2012@163.com

Received: 01.07.2019

Accepted after revision: 19.08.2019

Published online: 02.10.2019

DOI: 10.1055/s-0037-1611922; Art ID: so-2019-d0018-l

License terms:

© 2019. The Author(s). This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

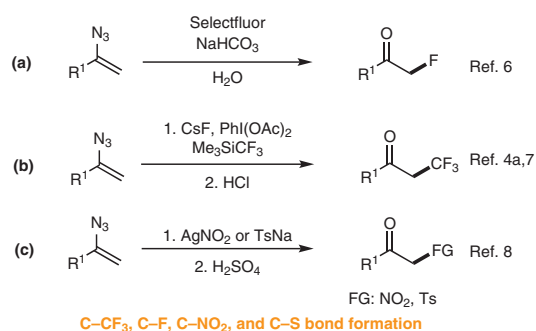
Abstract An efficient approach for the amination of vinyl azides with *N,N*-dialkylacylamides has been developed. By using this protocol, structurally important α -ketoamides can be easily synthesized. The key to success is not only the introduction of a Cu(I)/oxygen catalytic system but also the utilization of *t*-BuOCl and benzoic acid as additives. The reaction is operationally simple, scalable, and displays broad scope and functional group tolerance. A possible mechanism involving copper-catalyzed oxidative generation of peroxide radicals is proposed.

Key words amination, α -ketoamide, vinyl azide, copper-catalysis, *N,N*-dialkylacylamides

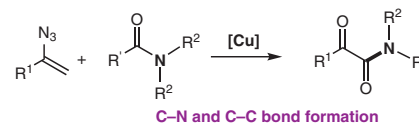
Vinyl azides are a class of unique functionalized alkenes with high intrinsic reactivity.¹ The numerous transformations of vinyl azides provide reliable synthetic approaches to diverse, structurally distinct molecular frameworks, including hetero/carbocycles,² amides,³ ketones,⁴ and 2*H*-azirines.⁵ Recently, Wu and Liu⁶ described an efficient and mild method for the synthesis of various α -fluoroketones from the corresponding vinyl azides by using Selectfluor[®] as the fluorine source (Scheme 1a). Additionally Chiba⁷ and Liu,^{4a} respectively, disclosed radical trifluoromethylation of vinyl azides with Me₃SiCF₃, to allow construction of α -trifluoromethyl azines, which could be further converted into α -trifluoromethyl ketones (Scheme 1b). Bi and co-workers presented a radical-induced enamination of vinyl azides that proceeded with electron-withdrawing substrates, and a variety of β -functionalized primary enamines, including β -nitro, acyl, and sulfonyl derivatives, could be prepared,

which were successfully transformed into a series of α -functionalized ketones (Scheme 1c).⁸ However, with respect to the construction of α -functionalized ketones, these methods usually suffer from disadvantages such as tedious multistep operations or harsh conditions. In a continuation of our efforts on the construction of C–N bond reactions,⁹ we herein report a novel radical amination of vinyl azides using a copper catalyst, to afford a series of α -ketoamides (Scheme 1). To our knowledge, this is the first example of the conversion of vinyl azides into α -ketoamides, which are important units in biologically active molecules, synthetic drugs, and drug candidates.¹⁰

Previous Work



This Work



Scheme 1 Transformations of vinyl azides

For the optimization of the reaction conditions, we carried out the reaction of vinyl azide **1a** and *N,N*-dimethylformamide (DMF; **2a**), as model substrates for the amination

reaction, to screen different catalysts, solvents and additives (Table 1). Firstly, when CuI was used as the catalyst in DMF as the solvent at 100 °C for 5 h under an oxygen atmosphere, the corresponding α -ketoamide **3a** was obtained in 67% yield (entry 1). Using CuBr as the catalyst also gave a comparable yield under similar conditions (entry 2). Other metal catalysts, such as CuCl₂, NiCl₂, or Ag₂CO₃, gave either low yields or trace amounts of the desired product **3a** (entries 3–5). Subsequent solvent screening demonstrated that DMF was the best choice; solvents, such as toluene, ethylene glycol, and nitromethane resulted in no desired product (entries 6–8). The use of additives, such as *m*-CPBA, TBHP or BPO, did not improve the efficiency of the reaction (entries 9–11). However, the addition of acids (HBF₄ or benzoic acid) did improve the efficiency of the reaction, affording **3a** in 70% and 88% yields, respectively (entries 12 and 13). The reaction failed to occur in the absence of either the catalyst or additive (entries 14 and 15).

Table 1 Optimization of the Reaction Conditions^a

Entry	Catalyst	Solvent	Additive	Yield (%) ^b
1	CuI	DMF	<i>t</i> -BuOCl	67
2	CuBr	DMF	<i>t</i> -BuOCl	56
3	CuCl ₂	DMF	<i>t</i> -BuOCl	trace
4	NiCl ₂	DMF	<i>t</i> -BuOCl	19
5	Ag ₂ CO ₃	DMF	<i>t</i> -BuOCl	20
6	CuI	toluene	<i>t</i> -BuOCl	0
7	CuI	EG	<i>t</i> -BuOCl	0
8	CuI	MeNO ₂	<i>t</i> -BuOCl	0
9	CuI	DMF	<i>m</i> -CPBA	26
10	CuI	DMF	TBHP	53
11	CuI	DMF	BPO	38
12	CuI	DMF	<i>t</i> -BuOCl + HBF ₄ ^c	70
13	CuI	DMF	<i>t</i> -BuOCl + PhCO ₂ H ^c	88
14	–	DMF	<i>t</i> -BuOCl + PhCO ₂ H ^c	0
15	CuI	DMF	–	0

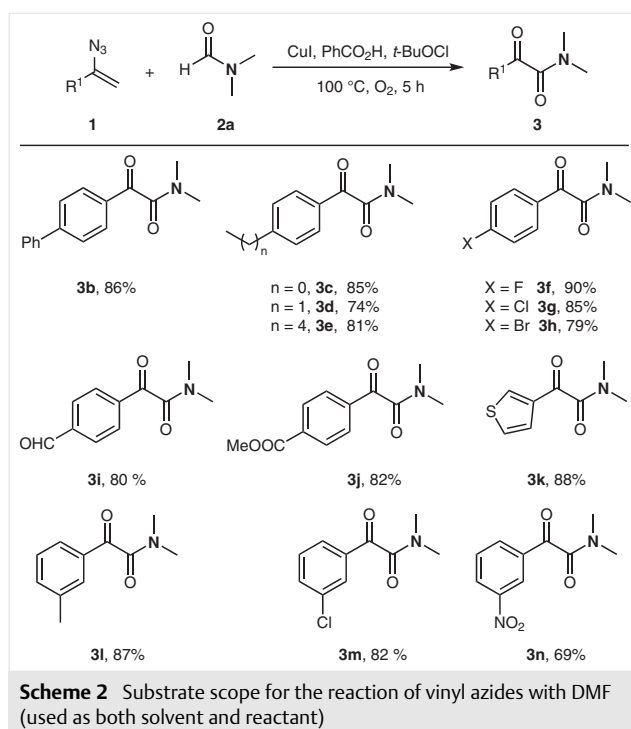
^a Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), catalyst (0.15 mmol), solvent (1.0 mL), additive (1.0 mmol), O₂ atmosphere, 100 °C, 5 h.

^b Isolated yield.

^c Acid (1.0 mmol).

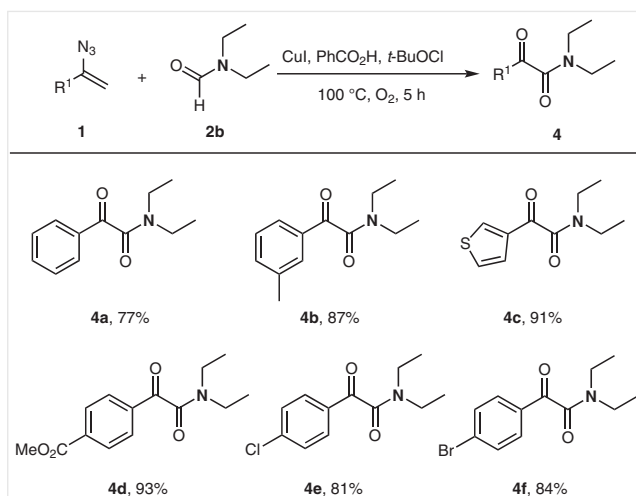
With the optimized reaction conditions in hand (Table 1, entry 13), the generality of this α -ketoamide synthesis was examined by using a series of vinyl azides to react with DMF (Scheme 2). α -Aryl-substituted vinyl azides were readily transformed into the corresponding α -ketoamides **3a–n** in moderate to excellent yields. Electron-donating groups in

the *para*-position of the aromatic ring were well tolerated, leading to the corresponding products **3a–e** in good to excellent yields. Likewise, vinyl azides possessing aryl substituents bearing electron-withdrawing groups, such as -F, -Cl, -Br, -CHO, and -CO₂Me, afforded the desired α -ketoamides **3f–j** in 79–90% yield. Note that vinyl azides bearing heteroaromatic substituents such as thienyl could be smoothly incorporated onto α -ketoamide **3k** in 88% yield. Moreover, vinyl azide derivatives bearing a variety of substitutions in the *meta*-position of the aryl ring, including both electron-donating and electron-withdrawing groups, were well tolerated; thereby affording the functionalized α -ketoamides **3l–n** in 69–87% yields.



To investigate the applicability of this protocol further, *N,N*-diethyl- α -ketoamide products **4a–f** were prepared using vinyl azides **1** and *N,N*-diethylformamide (**2b**) as the substrates under the optimized conditions (Scheme 3). Vinyl azides **1a–f** with aromatic substituents, including aryl and heteroaryl groups, underwent the reaction smoothly to give the desired products **4a–f** in 77–93% yield.

Encouraged by these results, we next turned our attention to other representative nitrogen sources (Table 2). Indeed, not only DMF (**2a**) and *N,N*-diethylformamide (**2b**) but also *N,N*-dimethylacetamide (DMA) and *N,N*-dimethylpropylamide (DMP) were tolerated under the standard conditions, with the resultant α -ketoamide products being obtained in slightly lower yields (entries 1–4). In addition, the long chain *N,N*-dimethylbutylamide (DMB) was also examined, although no desired product was detected (entry 5).



Scheme 3 Substrate scope for the reaction of vinyl azides with *N,N*-diethylformamide. Reaction conditions: **1** (0.5 mmol), **2** (1.0 mL), CuI (0.15 mmol), PhCO₂H (1.0 mmol), *t*-BuOCl (1.0 mmol), O₂ atmosphere, 100 °C, 5 h.

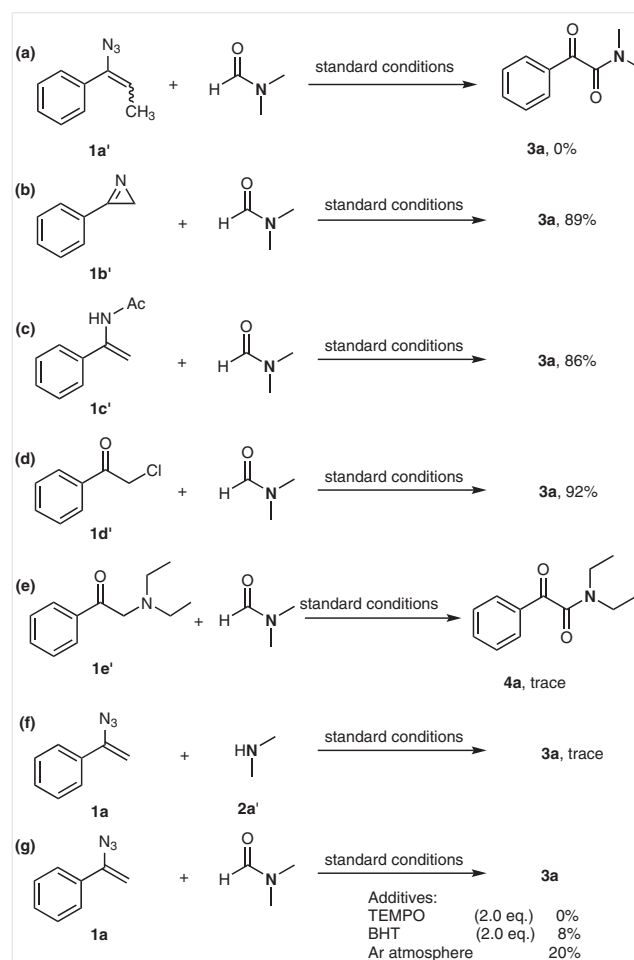
Table 2 Substrate Scope for the Reaction of Vinyl Azides with *N,N*-Dimethyl Substrates^a

Entry	Substrate	Product	Yield (%) ^b
1			51
2			44
3			55
4	 DMPA		20
5	 DMB		0

^a Reaction conditions: **1** (0.5 mmol), **2** (1.0 mL), CuI (0.15 mmol), PhCO₂H (1.0 mmol), *t*-BuOCl (1.0 mmol), O₂ atmosphere, 100 °C, 5 h.

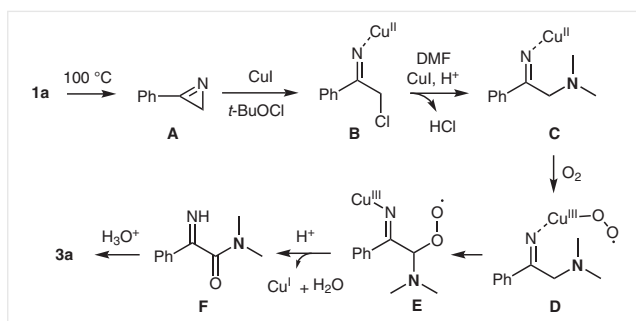
^b Isolated yield.

To elucidate a plausible reaction mechanism for this transformation, some potential intermediates were prepared and tested under the standard conditions (Table 1, entry 13). Vinyl azide **1a'** did not afford benzamide **3a** under the standard conditions (Scheme 4a), although 3-phenyl-2*H*-azirine (**1b'**), *N*-(1-phenylvinyl)acetamide (**1c'**), and 2-chloro-1-phenylethan-1-one (**1d'**) all afforded **3a** in good yields (Scheme 4b–d). 2-(Diethylamino)-1-phenylethan-1-one (**1e'**) did not react under the standard conditions (Scheme 4e),¹¹ nor did dimethylamine (**2a'**; Scheme 4f). Interestingly, the addition of the radical scavengers 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or 2,6-di-*tert*-butyl-*p*-cresol (BHT) suppressed the reaction, which indicates that free radical intermediates could be involved in this transformation (Scheme 4g). Notably, only 20% yield of **3a** was observed under an argon atmosphere, suggesting that oxygen is required to oxidize the catalyst in preparation for another cycle (Scheme 4g). These control experiments indicate that the vinyl azide substrate possibly reacts with the *t*-BuOCl as the electrophile and then undergoes oxidation catalyzed by the Cu/O₂ system.



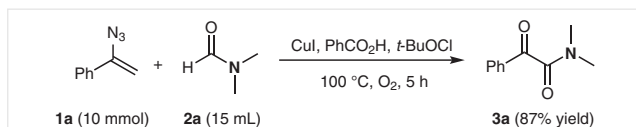
Scheme 4 Control experiments

According to previous reports and considering the above results,^{2e,12} a possible mechanism for this amination reaction is proposed in Scheme 5. Initially, the vinyl azide **1a** undergoes thermal decomposition into a highly strained three-membered cyclic imine (*2H*-azirine **A**) that reacts with the Cu(I) catalyst and *t*-BuOCl to form Cu(II) imine **B**, which is then converted into Cu(II) imine **C**.^{2e,13} Radical intermediate **E** would be formed via Cu(III) peroxide radical **D**, which could be generated by a combination of molecular oxygen with Cu(II) imine **C**. Subsequent reductive elimination of radical intermediate **E** gives intermediate **F** and regenerates the active Cu(I) species. Finally, α -ketoamide **3a** is obtained through acid hydrolysis of intermediate **F**.



Scheme 5 Proposed mechanism

The potential synthetic applicability of this method was investigated on a gram scale by using the model reaction. As shown in Scheme 6, 1.54 g of α -ketoamide **3a** was isolated in 87% yield without any significant loss of efficiency, demonstrating the potential of this methodology for large-scale synthesis of α -ketoamide derivatives.



Scheme 6 Gram-scale experiment

In conclusion, we have developed a general and efficient method for the synthesis of α -ketoamides from vinyl azides with *N,N*-dialkylaclylamide as the nitrogen source.¹⁴ The key to success is not only the introduction of a Cu/O₂ catalytic system but also the use of *t*-BuOCl and benzoic acid as additives. This method features readily accessible substrates, commercially available and inexpensive reagents, and mild conditions. This mild catalytic reaction demonstrates a broad substrate scope and high functional group tolerance. A possible mechanism involving copper-catalyzed oxidative generation of peroxide radicals is proposed. The reaction can be effectively scaled up and the product conveniently obtained in a one-pot process. Efforts to further clarify the mechanism and to expand the application of vinyl azides are under way in our laboratory.

Funding Information

The authors wish to thank the National Natural Science Foundation of China (21605097), the Natural Science Foundation of Shandong Province of China (ZR2016BQ01), the China Postdoctoral Science Foundation (2017M610442), and The Natural Science Foundation of the Jiangsu Higher Education Institutions of China (18KJB610021).

References and Notes

- (1) For recent progress in the synthesis of vinyl azides, see: (a) Liu, Z.; Liu, J.; Zhang, L.; Liao, P.; Song, J.; Bi, X. *Angew. Chem. Int. Ed.* **2014**, *53*, 5305. (b) Liu, Z.; Liao, P.; Bi, X. *Org. Lett.* **2014**, *16*, 3668.
- (2) (a) Lopez, E.; Lopez, L. *Angew. Chem. Int. Ed.* **2017**, *56*, 5121. (b) Shu, W.; Lorente, A.; Gómez-Bengoa, E.; Nevado, C. *Nat. Commun.* **2017**, *8*, 13832. (c) Wang, Y.-F.; Toh, K. K.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 6411. (d) Wang, Y.-F.; Chiba, S. *J. Am. Chem. Soc.* **2009**, *131*, 12570. (e) Wang, Y.-F.; Toh, K. K.; Lee, J.-Y.; Chiba, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 5927.
- (3) (a) Lin, C.; Shen, Y.; Huang, B.; Liu, Y.; Cui, S. *J. Org. Chem.* **2017**, *82*, 3950. (b) Zhang, Z.; Kumar, R. K.; Li, G.; Wu, D.; Bi, X. *Org. Lett.* **2015**, *17*, 6190. (c) Zhang, F.-L.; Wang, Y.-F.; Lonca, G. H.; Zhu, X.; Chiba, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 4390. (d) Qin, C.; Feng, P.; Ou, Y.; Shen, T.; Wang, T.; Jiao, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 7850.
- (4) (a) Qin, H.-T.; Wu, S.-W.; Liu, J.-L.; Liu, F. *Chem. Commun.* **2017**, *53*, 1696. (b) Chen, W.; Liu, X.; Chen, E.; Chen, B.; Shao, J.; Yu, Y. *Org. Chem. Front.* **2017**, *4*, 1162.
- (5) (a) Xu, H.-D.; Zhou, H.; Pan, Y.-P.; Ren, X.-T.; Wu, H.; Han, M.; Han, R.-Z.; Shen, M.-H. *Angew. Chem. Int. Ed.* **2016**, *55*, 2540. (b) Farney, E. P.; Yoon, T. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 793.
- (6) Wu, S.-W.; Liu, F. *Org. Lett.* **2016**, *18*, 3642.
- (7) Wang, Y.-F.; Lonca, G. H.; Chiba, S. *Angew. Chem. Int. Ed.* **2014**, *53*, 1067.
- (8) Ning, Y.; Zhao, X.-F.; Wu, Y.-B.; Bi, X. *Org. Lett.* **2017**, *19*, 6240.
- (9) (a) Wang, Y.; Wei, C.; Tang, R.; Zhan, H.; Lin, J.; Liu, Z.; Tao, W.; Fang, Z. *Org. Biomol. Chem.* **2018**, *16*, 6191. (b) Fang, Z.; Feng, Y.; Dong, H.; Li, D.; Tang, T. *Chem. Commun.* **2016**, *52*, 11120. (c) Liu, J.; Fang, Z.; Zhang, Q.; Liu, Q.; Bi, X. *Angew. Chem. Int. Ed.* **2013**, *125*, 7091. (d) Fang, Z.; Yuan, H.; Liu, Y.; Tong, Z.; Li, H.; Yang, J.; Barry, B.-D.; Liu, J.; Liao, P.; Zhang, J.; Liu, Q.; Bi, X. *Chem. Commun.* **2012**, *48*, 8802. (e) Wang, K.; Bi, X.; Xing, S.; Liao, P.; Fang, Z.; Meng, X.; Zhang, Q.; Liu, Q.; Ji, Y. *Green Chem.* **2011**, *13*, 562.
- (10) (a) Blackburn, E. A.; Walkinshaw, M. D. *Curr. Opin. Pharmacol.* **2011**, *11*, 365. (b) Álvarez, S.; Álvarez, R.; Khanwalkar, H.; Germain, P.; Lemaire, G.; Rodríguez-Barrios, F.; Gronemeyer, H.; de Lera, A. R. *Bioorg. Med. Chem.* **2009**, *17*, 4345. (c) Avolio, S.; Robertson, K.; Hernando, J. I. M.; DiMuzio, J.; Summa, V. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2295. (d) Knust, H.; Nettekoven, M.; Pinard, E.; Roche, O.; Rogers-Evans, M. PCT Int. Appl. WO 2009016087, **2009**. (e) Njoroge, F.; Chen, K. X.; Shih, N.-Y.; Piwinski, J. J. *Acc. Chem. Res.* **2008**, *41*, 50. (f) De Clercq, E. *Nat. Rev. Drug Discovery* **2007**, *6*, 1001.
- (11) Liang, S.; Zeng, C.-C.; Tian, H.-Y.; Sun, B.-G.; Luo, X.-G.; Ren, F.-Z. *J. Org. Chem.* **2016**, *81*, 11565.
- (12) (a) Hayashi, H.; Kaga, A.; Chiba, S. *J. Org. Chem.* **2017**, *82*, 11981. (b) Liu, H.; Feng, M.; Jiang, X. *Chem. Asian J.* **2014**, *9*, 3360. (c) Ding, S.; Jiao, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 9226. (d) Liu, Z.-Q.; Zhao, L.; Shang, X.; Cui, Z. *Org. Lett.* **2012**, *14*, 3218. (e) Rolff, M.; Schottenheim, J.; Decker, H.; Tuzcek, F. *Chem. Soc.*

Rev. **2011**, *40*, 4077. (f) Too, P. C.; Chua, S. H.; Wong, S. H.; Chiba, S. *J. Org. Chem.* **2011**, *76*, 6159. (g) Chiba, S.; Zhang, L.; Ang, G. Y.; Hui, B. W.-Q. *Org. Lett.* **2010**, *12*, 2052. (h) Que, L. J.; Tolman, W. B. *Nature* **2008**, *455*, 333. (i) Cramer, C. J.; Tolman, W. B. *Acc. Chem. Res.* **2007**, *40*, 601. (j) Arends, I.; Gamez, P.; Sheldon, R. A. *Adv. Inorg. Chem.* **2006**, *58*, 235. (k) Mirica, L. M.; Vance, M.; Rudd, D. J.; Hedman, B.; Hodgson, K. O.; Solomon, E. I.; Stack, T. D. P. *Science* **2005**, *308*, 1890. (l) Prigge, S. T.; Eipper, B. A.; Mains, R. E.; Amzel, L. M. *Science* **2004**, *304*, 864. (m) Wang, Y.; DuBios, J. L.; Hedman, B.; Hodgson, K. O.; Stack, T. D. P. *Science* **1998**, *279*, 537. (n) Manis, P. A.; Rathke, M. W. *J. Org. Chem.* **1980**, *45*, 4952.

(13) Fu, J.; Zaroni, G.; Anderson, E. A.; Bi, X. *Chem. Soc. Rev.* **2017**, *46*, 7208.

(14) **Synthesis of 4a; Typical Procedure:** To a solution of α -azido styrene (**1a**; 72.5 mg, 0.5 mmol), *tert*-butyl hypochlorite (113.1 μ L, 1.0 mmol), and benzoic acid (122.1 mg, 1.0 mmol) in *N,N*-diethylformamide (**2b**; 1 mL) at room temperature, CuI (28.6

mg, 0.15 mmol) was added. The reaction mixture was heated at 100 °C and stirred for 5 h under an oxygen atmosphere, when TLC analysis confirmed that substrate **1a** had been consumed. The resulting reaction mixture was cooled to room temperature and K₂CO₃ was added. The mixture was extracted with dichloromethane (3 \times 15 mL), and the combined organic extracts were washed with brine (3 \times 40 mL), dried over MgSO₄, filtered and concentrated. Purification of the crude product by flash column chromatography (silica gel; petroleum ether) afforded **4a** (77% yield) as a yellow oil.

***N,N*-Diethyl-2-oxo-2-phenylacetamide (4a):** ¹H NMR (400 MHz, CDCl₃): δ = 7.93 (d, *J* = 7.1 Hz, 2 H), 7.64 (t, *J* = 7.4 Hz, 1 H), 7.51 (t, *J* = 7.7 Hz, 2 H), 3.61–3.53 (m, 2 H), 3.29–3.20 (m, 2 H), 1.29 (t, *J* = 7.2 Hz, 3 H), 1.16 (t, *J* = 7.1 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): δ = 191.5, 166.7, 134.5, 133.2, 129.6, 128.9, 42.0, 38.7, 14.0, 12.8. HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₂H₁₅NO₂: 206.1181; found: 206.1142.