

Copper-Catalyzed Divergent Addition Reactions of Enoldiazoacetamides with Nitrones

Qing-Qing Cheng, Julietta Yedoyan, Hadi Arman, and Michael P. Doyle*

Department of Chemistry, The University of Texas at San Antonio, San Antonio, Texas 78249, United States

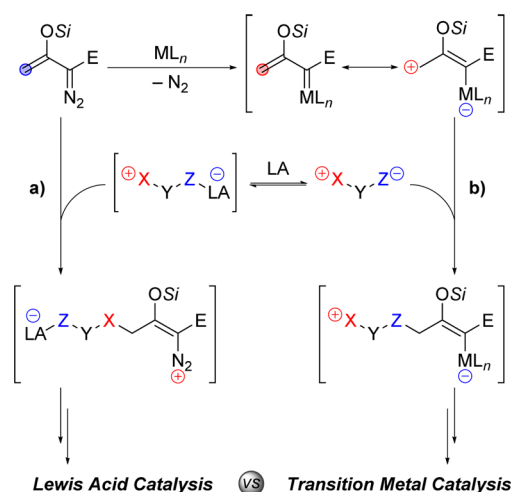
S Supporting Information

ABSTRACT: Catalyst-controlled divergent addition reactions of enoldiazoacetamides with nitrones have been developed. By using copper(I) tetrafluoroborate/bisoxazoline complex as the catalyst, a [3+3]-cycloaddition reaction was achieved with excellent yield and enantioselectivity under exceptionally mild conditions, which represents the first highly enantioselective base-metal-catalyzed vinyl-carbene transformation. When the catalyst was changed to copper(I) triflate, Mannich addition products were formed in high yields with near exclusivity under otherwise identical conditions.

Complete control over the product distribution of a catalytic reaction is a significant and long-standing goal in synthetic organic chemistry. Under similar reaction conditions divergent products can be obtained from identical reactants solely controlled by different catalysts.¹ In previous studies, vinyl diazoacetates have been successfully employed in several catalyst-dependent processes.^{2,3} For example, enoldiazoacetates and cinnamaldehydes underwent epoxide formation with dirhodium catalysts, whereas copper catalysts gave the Mukaiyama-aldol addition products.^{2c} In reactions of enoldiazoacetates with 1,3-dipoles, dirhodium catalysts directed the process to [3+3]-cycloaddition products,^{2d,f} while vinylogous addition or [3+2]-cycloaddition was achieved with Lewis acid catalysts in specific cases.^{2e,g} Compared to vinyl diazoacetates, vinyl diazoacetamides, another intriguing subclass of vinyl diazo compounds, have seldom been investigated, especially in intermolecular reactions.⁴ Inspired by recent advances in Lewis acid-catalyzed and dirhodium-catalyzed reactions of enoldiazoacetates,² we envisioned that catalyst-controlled divergence could be achieved with enoldiazoacetamides and stable dipoles. As illustrated in Scheme 1, with the promotion of Lewis acids, the electrophilic site of dipoles could attack the vinylogous position of enoldiazoacetamides (Scheme 1a). In contrast, after the formation of metallo-enolcarbenes, vinylogous association could take place at the dipole's nucleophilic site (Scheme 1b).

Copper salts can serve as Lewis acids and transition metal catalysts for various organic transformations, including addition reactions of silyl enol ethers⁵ and carbene transfer reactions.⁶ Their versatile catalytic activities, as well as their ready availability, low cost, and environmentally benign characteristics, make them ideal candidates for our proposed pathways. In the initial study, we conducted the reaction of *tert*-butyldimethylsilyl (TBS)-protected enoldiazoacetamide **1a** with *N*, α -diphenylnitronone **2a** in chloroform (CHCl₃) at room temperature, and a

Scheme 1. Catalyst-Controlled Divergence in Reactions of Enoldiazo Compounds with Stable Dipoles

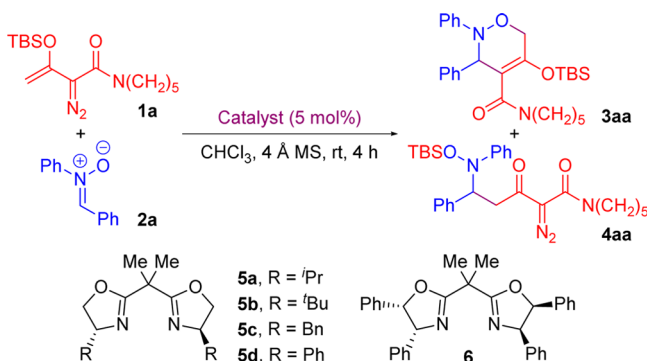


selection of copper salts⁷ were evaluated as catalysts (Table 1, entries 1–4). In the presence of 5 mol% of copper(II) triflate [Cu(OTf)₂], [3+3]-cycloaddition product **3aa** and Mukaiyama–Mannich addition product **4aa** were formed in 12% and 75% yields, respectively (entry 1). The retention of diazo functionality in **4aa** is quite surprising in view of the known ability of copper salts to facilitate dinitrogen extrusion from diazo compounds.⁶ Copper(I) triflate [Cu(OTf)₂·Tol_{1/2}] further improved chemoselectivity toward Mannich addition, affording **4aa** in 88% isolated yield (entry 2). Copper(I) hexafluorophosphate [Cu(MeCN)₄PF₆] provided a 1:1 ratio between **3aa** and **4aa** (entry 3). Remarkably, by changing the catalyst to copper(I) tetrafluoroborate [Cu(MeCN)₄BF₄], the reaction pathway was completely switched from Mannich addition to [3+3]-cycloaddition. However, 26% of nitronone **2a** was recovered after reaction, and the yield of **3aa** was only moderate (entry 4).⁸

In an attempt to improve the reactivity and selectivity of the annulation process, copper complexes of bisoxazoline ligands⁷ were tested in this reaction (Table 1, entries 5–9). A promising starting point was provided by the copper catalyst generated in situ from 5 mol% of Cu(MeCN)₄BF₄ and 6 mol% of (*R,R*)-*i*-Pr-BOX (**5a**), and **3aa** was obtained in 70% yield with 78% ee (entry 5). Ligand **5b**, which carries more bulky *tert*-butyl groups, was unfavorable in terms of reactivity and enantioselectivity (entry 6). Benzyl-substituted bisoxazoline ligand **5c** gave results similar

Received: October 16, 2015

Published: December 23, 2015

Table 1. Metal-Catalyzed Divergent Addition Reactions of Enoldiazoacetamide 1a with Nitron 2a: Screening of Catalysts^a

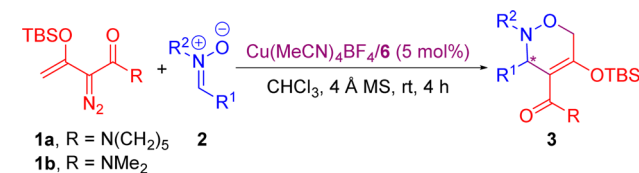
entry	catalyst	recovery of 2a (%) ^{b,c}	3aa yield (%) ^d	3aa ee (%) ^e	4aa yield (%) ^{c,d}
1	Cu(OTf) ₂	n.d.	12	—	75
2	CuOTf·Tol _{1/2}	n.d.	trace	—	88
3	Cu(MeCN) ₄ PF ₆	20	33	—	33
4	Cu(MeCN) ₄ BF ₄	26	61	—	n.d.
5 ^f	Cu(MeCN) ₄ BF ₄ / 5a	18	70	78	n.d.
6 ^f	Cu(MeCN) ₄ BF ₄ / 5b	81	10	rac.	n.d.
7 ^f	Cu(MeCN) ₄ BF ₄ / 5c	20	69	74	n.d.
8 ^f	Cu(MeCN) ₄ BF ₄ / 5d	n.d.	93	94	n.d.
9 ^f	Cu(MeCN) ₄ BF ₄ / 6	n.d.	96	98	n.d.
10	Rh ₂ (OAc) ₄	73	19	—	n.d.

^aReaction conditions: catalyst:**1a**:**2a** = 0.01:0.24:0.2 (mmol), with 4 Å molecular sieves (50 mg) in chloroform (2 mL) at room temperature for 4 h. ^bNitron **2a** was recovered after flash column chromatography. ^cn.d. = not detectable by ¹H NMR and TLC of the reaction mixture. ^dIsolated yields after flash column chromatography. ^eEnantiomeric excesses were determined by chiral HPLC analysis. ^fCatalysts were generated in situ from Cu(MeCN)₄BF₄ (0.01 mmol) and chiral ligands **5** or **6** (0.012 mmol).

to those obtained with **5a** (entry 7). However, (*R,R*)-Ph-BOX (**5d**) markedly increased the yield and enantiomeric excess of **3aa** (to 93% and 94%, respectively, entry 8). This excellent result spurred us to examine the cycloaddition process with ligand **6**, which has phenyl groups at both the 4- and 5-positions of the oxazoline rings, and using this ligand exceptional yield and enantioselectivity were achieved (96% yield and 98% ee, entry 9). It is worth mentioning that, although chiral base-metal complexes, such as copper, iron, and cobalt, are well-established catalysts for carbene transfer reactions,^{6,9} this study discloses their first employment for highly enantioselective vinylcarbene transformations.

Additionally, dirhodium(II) catalysts, which have proven to be successful in [3+3]-cycloadditions of enoldiazoacetates,^{2a} were also evaluated in this reaction. Surprisingly, when rhodium(II) acetate [Rh₂(OAc)₄] was used as the catalyst, most of nitron **2a** remained after all of the enoldiazoacetamide had been consumed (Table 1, entry 10), and a series of chiral dirhodium(II) catalysts exhibited even lower reactivities.^{8,10} These observations not only indicate the characteristic differences between enoldiazoacetamides and enoldiazoacetates, but also demonstrate the unique advantages of copper catalysts for carbene transfer reactions from enoldiazoacetamides.

After catalyst screening, we moved on to explore the substrate scope of these reactions. Initially, various *N,α*-diarylnitrones **2a–2i** were tested in the presence of copper(I) tetrafluoroborate/bisoxazoline catalyst (Table 2, entries 1–9). Neither electron-

Table 2. Copper-Catalyzed [3+3]-Cycloaddition of Enoldiazoacetamide 1 with Nitron 2: Substrate Scope^a

entry	2	R ¹ , R ²	3	yield (%) ^b	ee (%) ^c
1	2a	Ph, Ph	3aa	96	98
2	2b	4-ClC ₆ H ₄ , Ph	3ab	94	98 (S)
3	2c	4-MeC ₆ H ₄ , Ph	3ac	96	96
4	2d	4-MeOC ₆ H ₄ , Ph	3ad	95	96
5	2e	3-ClC ₆ H ₄ , Ph	3ae	90	96
6	2f	2-naphthyl, Ph	3af	94	97
7	2g	2-furyl, Ph	3ag	91	98
8	2h	Ph, 4-(EtO ₂ C)C ₆ H ₄	3ah	92	93
9	2i	Ph, 3-Br-4-MeC ₆ H ₃	3ai	96	94
10 ^d	2j	cyclohexyl, Bn	3aj	93	94
11 ^e	2a	Ph, Ph	3ba	96	96

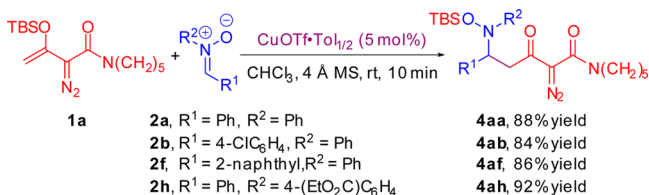
^aReaction conditions: Cu(MeCN)₄BF₄:**6**:**1a**:**2** = 0.01:0.012:0.24:0.2 (mmol), with 4 Å molecular sieves (50 mg) in chloroform (2 mL) at room temperature for 4 h. ^bIsolated yields after flash column chromatography. ^cEnantiomeric excesses were determined by chiral HPLC analysis. ^dThe reaction was conducted at -20 °C. ^eEnoldiazoacetamide **1b** was used instead of **1a**.

withdrawing nor electron-donating substituents at the *para*-position of the α -phenyl rings affected the efficiency of this process, and the corresponding annulation products **3ab–3ad** were formed in excellent yields and enantioselectivities (entries 2–4). The absolute configuration of the newly created stereocenter was confirmed to be *S* by X-ray crystallographic analysis of **3ab** (see Figure S1 in the Supporting Information). Nitrones bearing 2-naphthyl (**2f**) and 2-furyl (**2g**) groups at the α -position, as well as those with different substituents on the *N*-phenyl rings (**2h**, **2i**), all performed well in this reaction, furnishing their respective products **3af–3ai** with high yields and enantiomeric excesses (entries 6–9). Furthermore, for the first time, a *N,α*-dialkyl nitron (**2j**) was successfully employed in cycloadditions with vinyl diazo compounds (entry 10), albeit a lower reaction temperature was required to achieve high enantioselectivity in this case. In addition, both enoldiazoacetamides bearing cyclic amino (**1a**) and dimethylamino (**1b**) moieties were ideal substrates for this reaction (entries 1 and 11). In comparison with the previously reported dirhodium-catalyzed cycloaddition of enoldiazoacetates (53–96% yield, 77–93% ee),^{2d} the uniformly high yields and enantioselectivities achieved here (90–96% yield, 93–98% ee) are generally superior. Moreover, the use of easily accessible⁷ and highly efficient¹⁰ copper catalysts, the further expanded substrate scope, and the exceptionally mild reaction conditions are also advantages of this process.

Encouraged by the initial observation of the copper catalyst-controlled reversal in chemoselectivity (Table 1, entry 2 vs entry 9), we next performed the reaction under identical conditions except for changing the catalyst to copper(I) triflate. As

summarized in Scheme 2, all the tested nitrones **2a**, **2b**, **2f**, and **2h** reacted completely within 10 min, and the corresponding

Scheme 2. Copper-Catalyzed Mannich Addition of Enoldiazoacetamide **1** with Nitron **2**



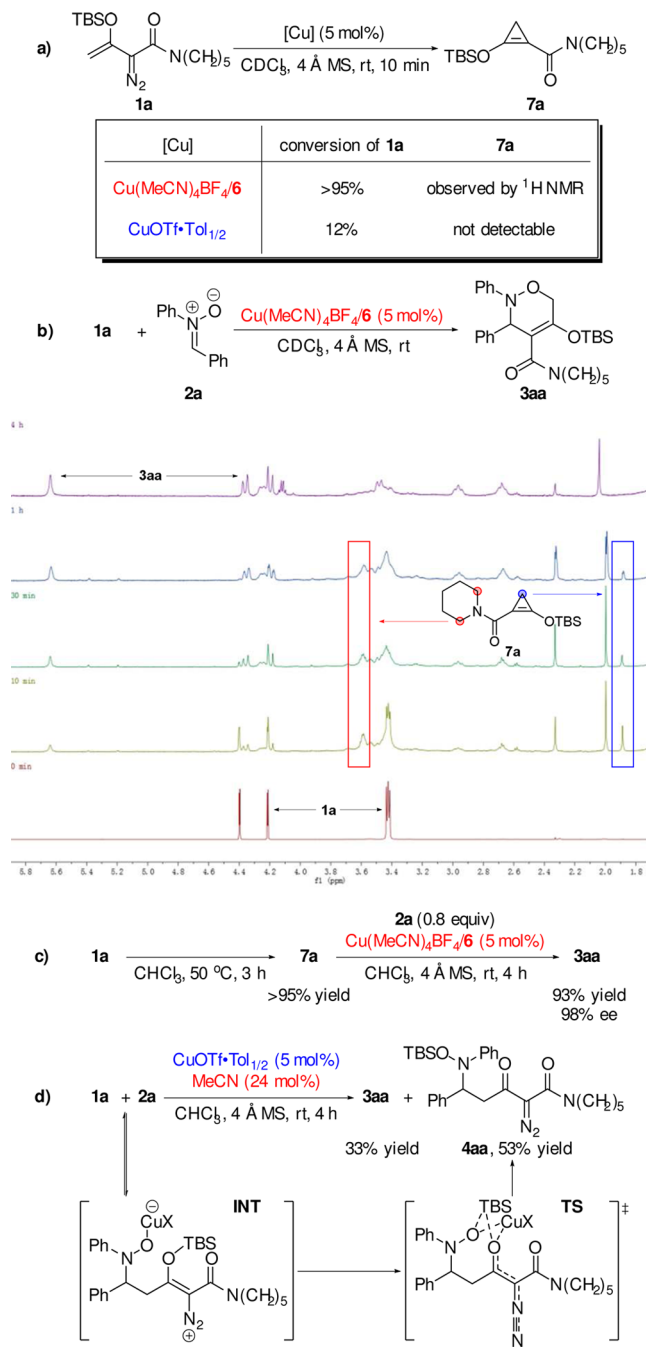
Mannich addition products **4aa**, **4ab**, **4af**, and **4ah** were obtained in high yields (84–92%). It should be noted that minor amounts of the cycloaddition products **3ab** and **3af** were also isolated from their respective reaction mixtures,¹¹ whereas Mannich addition process was totally excluded in all the cases shown in Table 2.

To further evaluate the generality of the present method, enoldiazoacetamides bearing methyl (**1c**) and ethyl (**1d**) substituents at the vinylogous position were investigated (see Table S1 in the Supporting Information). Interestingly, both copper(I) tetrafluoroborate and copper(I) triflate gave the annulation products in excellent yields (90–96%) with exceptional diastereocontrol (dr >20:1), and moderate to good enantioselectivities were obtained in the presence of chiral ligand **6**. In addition, reactions with enoldiazoacetate **1e** showed the same product selectivity as those with enoldiazoacetamide **1a** (see Table S2 in the Supporting Information). Either [3+3]-cycloaddition or Mannich addition was achieved in high yield with absolute product exclusivity by the use of corresponding copper catalyst.

As depicted in Scheme 1, we envisioned that the opposite polarities at the vinylogous positions of enoldiazoacetamides and their derivative metallo-enolcarbenes could lead to divergent reaction pathways. Thus, differences in the ability of copper catalysts to facilitate metal carbene generation could be crucial for achieving the catalyst-controlled divergence. In order to gain some insight, control experiments were conducted in the absence of nitrones (Scheme 3a). Copper(I) tetrafluoroborate/bisoxazoline complex afforded complete conversion of enoldiazoacetamide **1a** within 10 min, whereas the enoldiazoacetamide was relatively inert in the presence of copper(I) triflate. Notably, cyclopropenes are not only effective carbene precursors¹² but also key intermediates in metal-catalyzed vinylcarbene transformations.^{2b,4} Therefore, in the reaction catalyzed by copper(I) tetrafluoroborate/bisoxazoline complex, the following results plausibly suggest a metal carbene pathway: cyclopropene **7a** was observed by ¹H NMR monitoring both in the control experiment (Scheme 3a) and under standard reaction conditions (Scheme 3b); additionally, the reactions of enoldiazoacetamide **1a** and thermal-generated cyclopropene **7a** exhibited identical enantioselectivity (98% ee, Scheme 3c).

During monitoring of the reactions, another noteworthy phenomenon was that, in the presence of nitron **2a**, the enoldiazoacetamide was fully consumed over a significantly prolonged time (1 h, Scheme 3b vs 10 min, Scheme 3a), which could be rationalized in terms of a reversible association between the copper catalyst and nitron. Moreover, by using the copper catalyst generated in situ from 5 mol% of copper(I) triflate and 24 mol% of acetonitrile (MeCN), the yield of Mannich addition product **4aa** dropped dramatically to 53%, and the cycloaddition

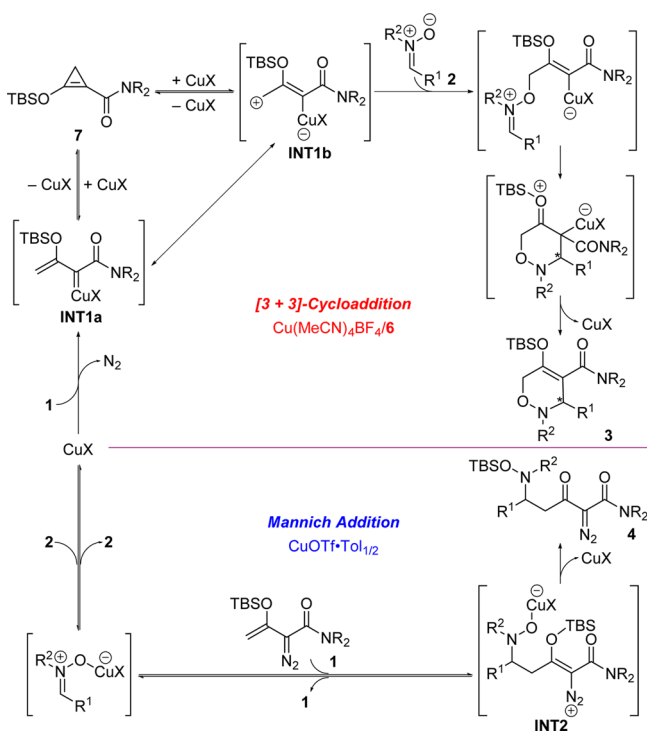
Scheme 3. Experimental Studies of Mechanism



product **3aa** was obtained in 33% yield (Scheme 3d). Compared with the reaction catalyzed merely by copper(I) triflate, these observations raise the possibility that the formation of a diazonium ion intermediate is also reversible (Scheme 3d, INT), and the copper catalyst with more open coordination sites is favorable to promote subsequent TBS migration to furnish the Mannich addition product (Scheme 3d, TS), which could be another important factor for achieving the catalyst-controlled divergence.

On the basis of the aforementioned results and previous reports,² plausible pathways of the divergent addition reactions are proposed (Scheme 4). Copper(I) tetrafluoroborate/bisoxazoline complex facilitates dinitrogen extrusion from enoldiazoacetamide **1** to form metallo-enolcarbene INT₁,

Scheme 4. Proposed Mechanism of Copper-Catalyzed Divergent Addition Reactions



which is in equilibrium with donor–acceptor cyclopropene **7**. Subsequent nucleophilic attack by nitrone **2** at the vinylogous position of INT1 followed by intramolecular cyclization with elimination of the copper catalyst produces cycloaddition product **3**. In contrast, activated by copper(I) triflate, the nitrone undergoes electrophilic addition at the vinylogous position of the enoldiazoacetamide to generate diazonium ion INT2, and the following migration of the *tert*-butyldimethylsilyl group completes the transformation.

In summary, catalyst-controlled divergent addition reactions of enoldiazoacetamides with nitrones have been realized with high yields and excellent selectivities under exceptionally mild conditions. Easily accessible and highly efficient copper catalysts exhibit their unique advantages by switching the reaction pathway between Mannich addition and [3+3]-cycloaddition. This study not only furnishes the first example of intermolecular reaction with vinyldiazoacetamides, but also represents the first highly enantioselective base-metal-catalyzed vinylcarbene transformation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10860.

Experimental procedures and characterization data, Tables S1–S3, Figure S1, and Scheme S1 (PDF)
Crystallographic data for **3ab** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*michael.doyle@utsa.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support for this research from the National Science Foundation (CHE-1464690) is gratefully acknowledged. The HRMS used in this research was supported by a grant from the National Institutes of Health (G12MD007591).

■ REFERENCES

- (1) For an excellent review, see: (a) Mahatthananchai, J.; Dumas, A. M.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 10954. For recent examples, see: (b) Dooley, J. D.; Chidipudi, S. R.; Lam, H. W. *J. Am. Chem. Soc.* **2013**, *135*, 10829. (c) Sun, X.; Lee, H.; Lee, S.; Tan, K. L. *Nat. Chem.* **2013**, *5*, 790. (d) Daniels, D. S. B.; Jones, A. S.; Thompson, A. L.; Paton, R. S.; Anderson, E. A. *Angew. Chem., Int. Ed.* **2014**, *53*, 1915. (e) Liao, J.-Y.; Shao, P.-L.; Zhao, Y. *J. Am. Chem. Soc.* **2015**, *137*, 628. (f) Donets, P. A.; Cramer, N. *Angew. Chem., Int. Ed.* **2015**, *54*, 633.
- (2) For reviews, see: (a) Xu, X.; Doyle, M. P. *Acc. Chem. Res.* **2014**, *47*, 1396. (b) Xu, X.; Doyle, M. P. *Chin. Chem. Lett.* **2015**, *26*, 227. For selected examples of enoldiazoacetates, see: (c) Xu, X.; Hu, W.; Zavalij, P. Y.; Doyle, M. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 11152. (d) Wang, X.; Xu, X.; Zavalij, P. Y.; Doyle, M. P. *J. Am. Chem. Soc.* **2011**, *133*, 16402. (e) Xu, X.; Ratnikov, M. O.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2011**, *13*, 6122. (f) Qian, Y.; Zavalij, P. J.; Hu, W.; Doyle, M. P. *Org. Lett.* **2013**, *15*, 1564. (g) Xu, X.; Qian, Y.; Zavalij, P. Y.; Doyle, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 1244. (h) Xu, X.; Zavalij, P. Y.; Doyle, M. P. *Chem. Commun.* **2013**, *49*, 10287.
- (3) For selected examples of other vinyldiazoacetates, see: (a) Doyle, M. P.; Yan, M.; Hu, W.; Gronenberg, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 4692. (b) Yue, Y.; Wang, Y.; Hu, W. *Tetrahedron Lett.* **2007**, *48*, 3975. (c) Sevryugina, Y.; Weaver, B.; Hansen, J.; Thompson, J.; Davies, H. M. L.; Petrukhina, M. A. *Organometallics* **2008**, *27*, 1750. (d) Hansen, J.; Davies, H. M. L. *Chem. Sci.* **2011**, *2*, 457.
- (4) For intramolecular reactions, see: Xu, X.; Deng, Y.; Yim, D. N.; Zavalij, P. Y.; Doyle, M. P. *Chem. Sci.* **2015**, *6*, 2196.
- (5) For reviews, see: (a) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095. (b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325. (c) Sibi, M. P.; Cook, G. R. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 2, Chapter 12.
- (6) For reviews, see: (a) Kirmse, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 1088. (b) Zhu, S.-F.; Zhou, Q.-L. *Acc. Chem. Res.* **2012**, *45*, 1365. (c) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981.
- (7) All the copper salts and ligands are commercially available and were used as received. Chiral copper complexes were generated in situ from copper(I) tetrafluoroborate and ligands.
- (8) Enoldiazoacetamide **1a** was completely consumed, and unidentified products generated from **1a** were observed by ¹H NMR analysis of the reaction mixture.
- (9) For recent examples, see: (a) Li, J.; Liao, S.-H.; Xiong, H.; Zhou, Y.-Y.; Sun, X.-L.; Zhang, Y.; Zhou, X.-G.; Tang, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 8838. (b) Coelho, P. S.; Brustad, E. M.; Kannan, A.; Arnold, F. H. *Science* **2013**, *339*, 307. (c) Wu, X.-P.; Su, Y.; Gu, P. *Org. Lett.* **2014**, *16*, 5339. (d) Tang, Y.; Chen, Q.; Liu, X.; Wang, G.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 9512.
- (10) All the tested chiral dirhodium(II) catalysts, including Rh₂(S-PTA)₄, Rh₂(S-PTTL)₄, and Rh₂(S-DOSP)₄, afforded less than 10% conversion of nitrone **2a**.
- (11) The [3+3]-cycloaddition products **3ab** and **3af** were isolated in 8% and 6% yields, respectively.
- (12) For reviews, see: (a) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (b) Zhu, Z.-B.; Wei, Y.; Shi, M. *Chem. Soc. Rev.* **2011**, *40*, 5534. (c) Archambeau, A.; Miege, F.; Meyer, C.; Cossy, J. *Acc. Chem. Res.* **2015**, *48*, 1021.