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Highly Enantioselective Organocatalyzed Vinylogous Michael-Type Reaction for the Construction of Trifluoromethylated All-Carbon Quaternary Stereocenters

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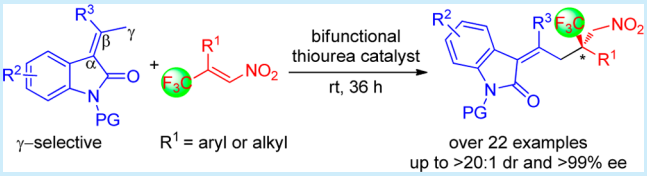
Supporting Information

ABSTRACT: The first example of a highly enantioselective vinylogous Michael-type reaction of β,β-disubstituted nitroalkenes is disclosed. A series of biologically important chiral oxindoles, featuring a trifluoromethylated all-carbon quaternary chiral center, were obtained in good yields with excellent enantioselectivities (up to >99% ee).



Optically active organofluorine compounds are fundamentally used in the realm of pharmaceutical and agricultural chemistry.[1] Particularly, those bearing a trifluoromethyl group are fascinating building blocks for new drug candidates.[2] Thus, tremendous efforts have been devoted toward the development of effective and reliable methods for the easy construction of trifluoromethylated compounds.[3] Although a variety of processes have been reported to generate CF_3-substituted tertiary or heteroquaternary stereogenic centers, the enantioselective construction of trifluoromethylated all-carbon quaternary stereocenters remains not only a demand for biochemists and medicinal chemists but also a great challenge for synthetic organic chemists.[4] In 2012, the groups of Shibata developed a highly enantioselective cyanation of β,β-CF_3 enones to provide addition adducts having trifluoromethylated all-carbon quaternary stereocenters; they next succeeded in the enantioselective conjugate addition of nitromethane to β-aryl-β-CF_3 enones.[5] Gade and co-workers reported a copper-catalyzed electrophilic trifluoromethylation of β-ketoesters.[6] Very recently, Jia et al. demonstrated that the construction of trifluoromethylated all-carbon quaternary stereocenters could be achieved via a Ni-catalzyed Fridel–Craft reaction.[7] Despite these notable advances, the development of efficient methodologies is still highly desirable.

The vinylogous Michael-type reaction has been demonstrated as an effective protocol for the enantioselective carbon–carbon bond formation at the γ-position and was intensively studied in recent years.[8−12] However, much to our surprise, the application of this methodology for the synthesis of all-carbon quaternary stereocenters has remained elusive until now. To the best of our knowledge, only one single example with good ee and moderate yield was disclosed by the group of Melchiorre.[10] Recently, Cashiraghi and co-workers reported the first example of an organocatalyzed vinylogous Michael-type reaction of 3-alkylidene oxindoles to β-monosubstituted nitroolefins, with outstanding levels of yields and enantioselectivity.[11] We wondered whether β-CF_3-β-disubstituted nitroolefins would be proper vinylogous Michael acceptors and lead to the construction of all-carbon quaternary stereocenters featuring a trifluoromethyl group. The intrinsic steric hindrance and poor reactivity of the β,β-disubstituted α,β-unsaturated compounds, and the difficulty in the stereocontrol are underlying challenges. Moreover, it is clear that methods established for nonfluorinated substrates are often not appropriate for CF_3-containing molecules. Thus, application of trifluoromethylated nitroalkenes to a vinylogous Michael-type reaction is also a big challenge since they have never been tested in this type of reaction.

On the basis of our continuing interest in the stereocontrolled γ functionalization of α,β-unsaturated carbonyl compounds[12] and asymmetric modification of oxindoles,[13] we disclose herein the first asymmetric vinylogous Michael-type addition of olefinic oxindoles to β,β-disubstituted nitroalkenes for the construction of trifluoromethylated all-carbon quaternary stereocenters. The reaction proceeded smoothly at room temperature and gave the desired products with uniformly excellent enantioselectivities and high yields. It is known that 3-alkylidene oxindoles can react in the α- or γ-position with electrophilic reagents and increase the complexity of the reaction's pathway. What is more, the geometry of the double bond in the substrate is lost during the dienolation process, which may lead to an inseparable mixture of the products with *Z*- and *E*-isomers. Notably, under our optimized conditions, 3-alkylidene oxindoles exhibited complete γ-selectivity and the alkene geometries in the products were excellently controlled (in most cases, $Z/E > 20/1$).

We initiated our study by examining the reaction of 3-alkylidene oxindole **2a** with trifluoromethylated nitroalkene **3a** in the presence of 10 mol % organocatalyst **1** in toluene, and at room temperature (Table 1). To our delight, the quinine-derived bifunctional catalyst **1a** gave the desired product **4aa**

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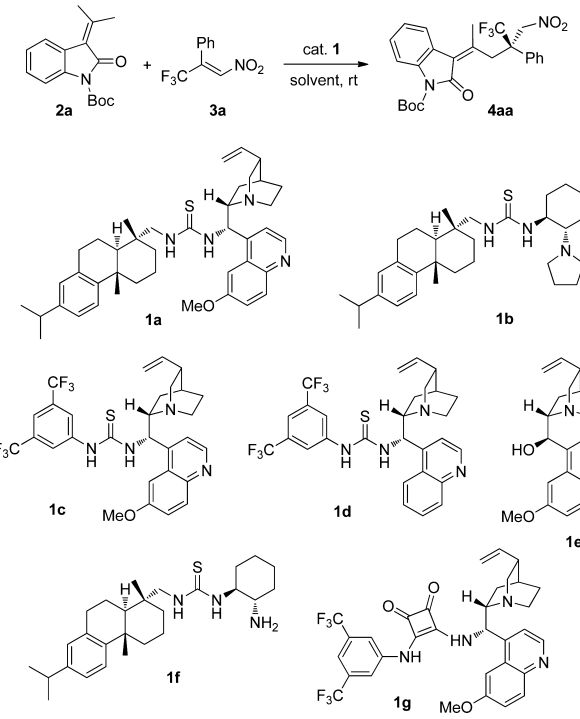
Table 1. Optimization of the Reaction Conditions[a]



entry	cat.	solvent	conv (%)[b]	dr (*Z*:*E*)[b]	ee (%)[c]
1	**1a**	toluene	56	>20:1	95
2	**1b**	toluene	0	–	–
3	**1c**	toluene	78	>20:1	99
4	**1d**	toluene	64	>20:1	98
5	**1e**	toluene	0	–	–
6	**1f**	toluene	0	–	–
7	**1g**	toluene	37	>20:1	98
8	**1c**	CH_2Cl_2	72	>20:1	98
9	**1c**	THF	52	>20:1	97
10	**1c**	MeOH	trace	–	–
11	**1c**	MeCN	trace	–	–
12	**1c**	$CHCl_3$	70	>20:1	98
13[d]	**1c**	toluene	89	>20:1	99
14[e]	**1c**	toluene	84	>20:1	99
15[f]	**1c**	toluene	98	>20:1	99

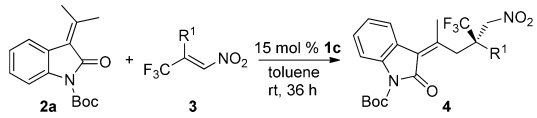
[a]Unless otherwise noted, the reactions were carried out by using 0.1 mmol of **3a**, 1.2 equiv of **2a**, 10 mol % of the catalyst, and 1 mL of solvent; stirred for 24 h. [b]Conversions and diastereomeric ratios were determined by ^{19}F NMR analysis of the crude reaction mixtures. [c]Determined by chiral HPLC analysis. [d]1.5 equiv of **2a** was used. [e]15 mol % of **1c** was used. [f]0.15 mmol of **3a**, 1.5 equiv of **2a**, 15 mol % of **1c**, 0.75 mL of toluene, and 36 h.

with high enantioselectivity and moderate yield (entry 1). In contrast, thiourea catalyst **1b** was proven to be inactive for this transformation (entry 2). Under the same conditions, quinine derivative **1c** and cinchonidine derivative **1d** showed relatively higher catalytic activities in comparison with **1a**, affording the product **4aa** in excellent diastereoselectivities and promising yields (entries 3 and 4). The reaction did not proceed in the presence of quinine **1e** or primary amine-thiourea catalyst **1f** (entries 5 and 6), while quinine-derived squaramide **1g** gave the product **4aa** with almost the same ee values as that obtained with **1c**, albeit with poor yield (entry 7). The above results suggested that both the cinchona group and the thiourea moiety are essential for reaction progress and the high degree of enantioselectivity. The quinine-derived thiourea catalyst **1c** was found to be the most promising catalyst and was selected for further investigation.

In order to obviate unproductive reaction pathways and to further improve the yield, we therefore examined a series of solvents (entries 8–12). However, other solvents did not show any positive effect on the reaction reactivity. A trace amount or even no desired product was obtained when methanol or acetonitrile was used as solvent (entries 10 and 11). Using an excess of oxindole **2a** or 15 mol % catalyst gave a sharp increase of the reaction yield[14] (entries 13 and 14). Finally, the best result was obtained when the reaction was performed with 1.5 equiv of **2a**, using 15 mol % of **1c** in 0.5 M toluene, and stirred at room temperature for 36 h (98% conversion, >20:1 dr, 99% ee; entry 15).

Under the optimized reaction conditions outlined above, a wide range of trifluoromethylated nitroalkenes (**3a**–**3n**) were investigated (Table 2). Both electron-donating and -withdrawing substituents at different positions on the aryl ring of the nitroalkenes (entries 2–9) afforded the products in high yields and excellent stereoselectivities. Notably, 3,5-disubstituted product **4aj** (entry 10) and heteroaromatic-substituted product **4ak** (entry 11) were also isolated with unexceptionable yields and stereoselectivities. Moreover, the sterically demanding naphthyl-substituted nitroalkene **3l** and the 2-phenylethyl substituted nitroalkene **3m** were well tolerated substrates for this transformation. It is very interesting that substrate **3n** bearing an aliphatic side chain still gave the desired product with the same remarkable enantioselectivity, albeit with a decrease in diastereoselectivity and yield. It is worth noting that the corresponding opposite enantiomers of the products were also obtained with uniformly excellent enantioselectivities, which are displayed in the parentheses in the last column of Table 2.

Table 2. Scope of Trifluoromethylated Nitroalkene 3[a]



entry	R^1 (**3**)	product	yield (%)[b]	dr (*Z*/*E*)[c]	ee (%)[d]
1	Ph (**3a**)	**4aa**	92	>20:1	99 (99)
2	4-MePh (**3b**)	**4ab**	87	>20:1	99 (99)
3	4-ClPh (**3c**)	**4ac**	91	>20:1	99 (99)
4	4-FPh (**3d**)	**4ad**	84	>20:1	99 (99)
5	4-CF_3Ph (**3e**)	**4ae**	90	>20:1	99 (98)
6	3-ClPh (**3f**)	**4af**	88	>20:1	99 (99)
7	3-MeOPh (**3g**)	**4ag**	82	>20:1	99 (99)
8	3-MePh (**3h**)	**4ah**	90	>20:1	99 (99)
9	2-FPh (**3i**)	**4ai**	83	20:1	99 (99)
10	3,5-Me_2Ph (**3j**)	**4aj**	92	>20:1	99 (99)
11	2-thienyl (**3k**)	**4ak**	91	>20:1	98 (98)
12	2-naphthyl (**3l**)	**4al**	82	>20:1	99 (98)
13	2-phenylethyl (**3m**)	**4am**	93	>20:1	99 (99)
14	1-octyl (**3n**)	**4an**	60	15:1	99 (99)

[a]All reactions were carried out by using 0.15 mmol of **3**, 1.5 equiv of **2a**, 15 mol % of **1c**, and 0.75 mL of toluene. [b]Isolated yield. [c]Determined by ^{19}F NMR analysis. [d]Determined by chiral HPLC analysis. Values in parentheses refer to reactions catalyzed by the corresponding opposite enantiomer of **1c** (derived from quinidine).

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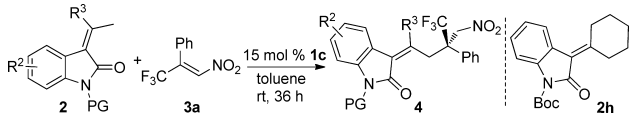
With positive results obtained for the alkene **3** as the Michael acceptors, our attention was turned to the reactivity of different oxindole donors (Table 3). Variation of the substituents on the benzene ring of the oxindole had little influence on the stereoselectivities or yields of the products (entries 1−4). Even the benzylidene oxindole **2f** was well tolerated, and a high level of yield and enantioselectivity were observed (entry 5). 3-Alkylidene oxindole **2g** also proved to be efficient for this progress, providing the addition product **4ga** in admirable diastereo- and enantioselectivities with a moderate yield (entry 6), whereas oxindole **2h** was relatively unreactive and only trace amounts of **4ha** were detected (entry 7). Additionally, as expected, oxindole **2i**, protected by a methoxy carbonyl (Moc) group, was a competent donor in the reaction (entry 8). In sharp contrast, protection-free oxindole, as well as a methyl protected derivative, did not demonstrate any sign of reactivity, thus highlighting the importance of a proper *N*-substituent for this organocatalytic progress[15] (for details, see Figure S2 in the Supporting Information). Significantly, the Boc group of the product could be easily removed via a single step under acidic conditions, and the corresponding *N*-unprotected oxindole ring **5** was formed with unexceptionable yield and stereoselectivities (Scheme 1). This makes up for the sluggishness of unprotected oxindole, and the NH of **5** could be further modified. The relative and absolute configurations of the products were determined by X-ray crystal structure analysis of **5**[16] (see Supporting Information).

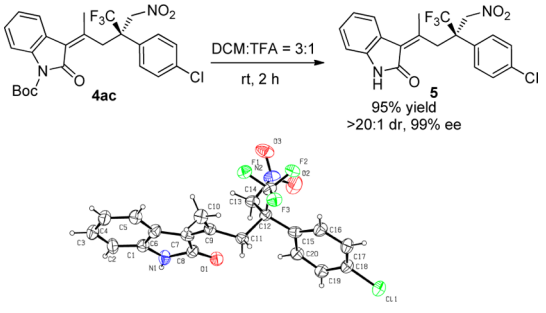
Table 3. Scope of 3-Alkylidene Oxindole 2[a]



entry	R^2, R^3 (**2**)	PG	product	yield (%)[b]	dr (*Z*:*E*)[c]	ee (%)[d]
1	5-F, H (**2b**)	Boc	**4ba**	86	>20:1	99 (>99)
2	5-Br, H (**2c**)	Boc	**4ca**	81	>20:1	98 (99)
3	5-Me, H (**2d**)	Boc	**4da**	81	>20:1	99 (99)
4	6-Cl, H (**2e**)	Boc	**4ea**	87	>20:1	99 (99)
5	H, Ph (**2f**)	Boc	**4fa**	91	>20:1	99 (99)
6	H, ethyl (**2g**)	Boc	**4ga**	72	>20:1	99 (99)
7	H, − (**2h**)	Boc	**4ha**	<10	N. D.	N. D.
8	H, H (**2i**)	Moc	**4ia**	81	>20:1	99 (99)

[a]All reactions were carried out by using 0.15 mmol of **3a**, 1.5 equiv of **2**, 15 mol % of **1c**, and 0.75 mL of toluene. [b]Isolated yield. [c]Determined by ^{19}F NMR analysis. [d]Determined by chiral HPLC analysis. Values in parentheses refer to reactions catalyzed by the corresponding opposite enantiomer of **1c** (derived from quinidine).

Scheme 1. Removal of the Boc Group on 4ac and the X-ray Structure of 5



In summary, an unprecedented organocatalytic enantioselective vinylogous Michael-type reaction between 3-alkylidene oxindoles and trifluoromethylated nitroalkenes under mild reaction conditions has been developed. The reaction proceeded with a very high level of site selectivity and excellent enantioselectivities (up to 93% yield, >20:1 dr, and >99% ee), providing a mild and efficient method for the construction of trifluoromethylated all-carbon quaternary stereocenters. Moreover, this is the first application of β,β-disubstituted α,β-unsaturated compounds in a vinylogous Michael-type reaction. Since the oxindole enjoys a privileged role in the realm of medicinal chemistry, and the CF_3 modification often enhances the efficacy of the drug, the compounds prepared herein will be potential candidates for new drug discovery. Further applications of this methodology as well as the biological evaluation of the products are underway.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of the products. CCDC 986456 and the CIF data are available in the Supporting Information. 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) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013. (b) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (c) *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Wiley-Blackwell: Chichester, 2009.

(2) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(3) For recent reviews, see: (a) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (b) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455. (c) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (d) Roy, S.; Gregg, B. T.; Gribble, G. W.; Le, V.-D.; Roy, S. *Tetrahedron* **2011**, *67*, 2161. (e) Qing, F.-L.; Zheng, F. *Synlett* **2011**, 1052. (f) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem.* **2012**, *124*, 5134; *Angew. Chem., Int. Ed.* **2012**, *51*, 5048. (g) Ye, Y.; Sanford, M. S. *Synlett* **2012**, 2005. (h) Qing, F. L. *Chin. J. Org. Chem.* **2012**, *32*, 815. (i) Studer, A. *Angew. Chem.* **2012**, *124*, 9082; *Angew. Chem., Int. Ed.* **2012**, *51*, 8950. (j) He, Z.; Huang, Y.; Verpoort, F. *Acta Chim. Sin.* **2013**, *71*, 700. (k) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem.* **2013**, *125*, 8372; *Angew. Chem., Int. Ed.* **2013**, *52*, 8214.

(4) For reviews on the asymmetric construction of all-carbon quaternary stereocenters, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem.* **1998**, *110*, 402; *Angew. Chem., Int. Ed.* **1998**, *37*, 388.

(b) Christoffers, J.; Mann, A. *Angew. Chem.* **2001**, *113*, 4725; *Angew. Chem., Int. Ed.* **2001**, *40*, 4591. (c) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (d) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (e) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (f) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (g) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. *Eur. J. Org. Chem.* **2007**, 5969. (h) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583. (i) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295. (j) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593. (k) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247.

(5) (a) Kawai, H.; Okusu, S.; Tokunaga, E.; Sato, H.; Shiro, M.; Shibata, N. *Angew. Chem.* **2012**, *124*, 5043; *Angew. Chem., Int. Ed.* **2012**, *51*, 4959. (b) Kawai, H.; Yuan, Z.; Kitayama, T.; Tokunaga, E.; Shibata, N. *Angew. Chem.* **2013**, *125*, 5685; *Angew. Chem., Int. Ed.* **2013**, *52*, 5575.

(6) Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2012**, *134*, 10769.

(7) Gao, J.-R.; Wu, H.; Xiang, B.; Yu, W.-B.; Han, L.; Jia, Y.-X. *J. Am. Chem. Soc.* **2013**, *135*, 2983.

(8) For reviews on vinylogous addition reactions, see: (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (b) Kalesse, M. *Top. Curr. Chem.* **2005**, *244*, 43. (c) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem.* **2005**, *117*, 4760; *Angew. Chem., Int. Ed.* **2005**, *44*, 4682. (d) Casiraghi, G.; Zanardi, F.; Battistini, L.; Rassu, G. *Synlett* **2009**, 1525. (e) Brodmann, T.; Lorenz, M.; Schäckel, R.; Simsek, S.; Kalesse, M. *Synlett* **2009**, 174. (f) Cui, H.-L.; Chen, Y.-C. *Chem. Commun.* **2009**, 4479. (g) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076. (h) Pansare, S. V.; Paul, E. K. *Chem.—Eur. J.* **2011**, *17*, 8770. (i) Bisai, V. *Synthesis* **2012**, *44*, 1453.

(9) For selected examples on organocatalyed vinylogous Michael-type reactions: (a) Zhang, Y.; Shao, Y.-L.; Xu, H.-S.; Wang, W. *J. Org. Chem.* **2011**, *76*, 1472. (b) Quintard, A.; Lefranc, A.; Alexakis, A. *Org. Lett.* **2011**, *13*, 1540. (c) Terada, M.; Ando, K. *Org. Lett.* **2011**, *13*, 2026. (d) Yang, Y.; Dong, S.; Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2012**, *48*, 5040. (e) Gupta, V.; Sudhir, V. S.; Mandal, T.; Schneider, C. *Angew. Chem.* **2012**, *124*, 12778; *Angew. Chem., Int. Ed.* **2012**, *51*, 12609. (f) Zhong, F.; Luo, J.; Chen, G.-Y.; Dou, X.; Lu, Y. *J. Am. Chem. Soc.* **2012**, *134*, 10222. (g) Manna, M. S.; Kumar, V.; Mukherjee, S. *Chem. Commun.* **2012**, *48*, 5193. (h) Dell'Amico, L.; Albrecht, Ł.; Naicker, T.; Poulsen, P. H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2013**, *135*, 8063.

(10) Bencivenni, G.; Galzerano, P.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20642.

(11) (a) Curti, C.; Rassu, G.; Zambrano, V.; Pinna, L.; Pelosi, G.; Sartori, A.; Battistini, L.; Zanardi, F.; Casiraghi, G. *Angew. Chem.* **2012**, *124*, 6304; *Angew. Chem., Int. Ed.* **2012**, *51*, 6200. (b) Rassu, G.; Zambrano, V.; Pinna, L.; Curti, C.; Battistini, L.; Sartori, A.; Pelosi, G.; Zanardi, F.; Casiraghi, G. *Adv. Synth. Catal.* **2013**, *355*, 1881.

(12) (a) Lin, L.; Zhang, J.; Ma, X.; Fu, X.; Wang, R. *Org. Lett.* **2011**, *13*, 6410. (b) Zhang, J.; Liu, X.; Ma, X.; Wang, R. *Chem. Commun.* **2013**, *49*, 9329. (c) Yang, D.; Wang, L.; Han, F.; Zhao, D.; Zhang, B.; Wang, R. *Angew. Chem.* **2013**, *125*, 6871; *Angew. Chem., Int. Ed.* **2013**, *52*, 6739. (d) Jiang, X.; Liu, L.; Zhang, P.; Zhong, Y.; Wang, R. *Angew. Chem.* **2013**, *125*, 11539; *Angew. Chem., Int. Ed.* **2013**, *52*, 11329. (e) Shi, X.-M.; Dong, W.-P.; Zhu, L.-P.; Jiang, X.-X.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 3119.

(13) For selected examples of our related works, see: (a) Jiang, X.; Cao, Y.; Wang, Y.; Liu, L.; Shen, F.; Wang, R. *J. Am. Chem. Soc.* **2010**, *132*, 15328. (b) Cao, Y.; Jiang, X.; Liu, L.; Shen, F.; Zhang, F.; Wang, R. *Angew. Chem.* **2011**, *123*, 9290; *Angew. Chem., Int. Ed.* **2011**, *50*, 9124. (c) Chen, Q.; Liang, J.; Wang, S.; Wang, D.; Wang, R. *Chem. Commun.* **2013**, *49*, 1657. (d) Hong, L.; Kai, M.; Wu, C.; Sun, W.; Zhu, G.; Li, G.; Yao, X.; Wang, R. *Chem. Commun.* **2013**, *49*, 6713. (e) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023. (f) Sun, W.; Zhu, G.; Wu, C.; Li, G.; Hong, L.; Wang, R. *Angew. Chem.* **2013**, *125*, 8795; *Angew. Chem., Int. Ed.* **2013**, *52*, 8633.

(14) Using an excess of oxindole **2a** could offset the deprotection of **2a**, and 15 mol % catalyst can increase the conversion of trifluoromethylated nitroalkene **3** since they were hard to activate.

(15) The *N*-Boc/Moc protecting groups may enhance the acidity of the γ-methylene protons in **2**, thereby promoting the enolization of the substrates. For *N*-carbamoyl group participation in organocatalytic enantioselective reactions involving *N*-protected 3-methylene oxindoles, see examples: (a) Shi, Y.; Lin, A.; Mao, H.; Mao, Z.; Li, W.; Hu, H.; Zhu, C.; Cheng, Y. *Chem.—Eur. J.* **2013**, *19*, 1914. (b) Pesciaioli, F.; Righi, P.; Mazzanti, A.; Bartoli, G.; Bencivenni, G. *Chem.—Eur. J.* **2011**, *17*, 2842. (c) Tan, B.; Hernández-Torres, G.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 12354.

(16) CCDC 986456 (**5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data_request/cif.