Organic LETTERS

Letter

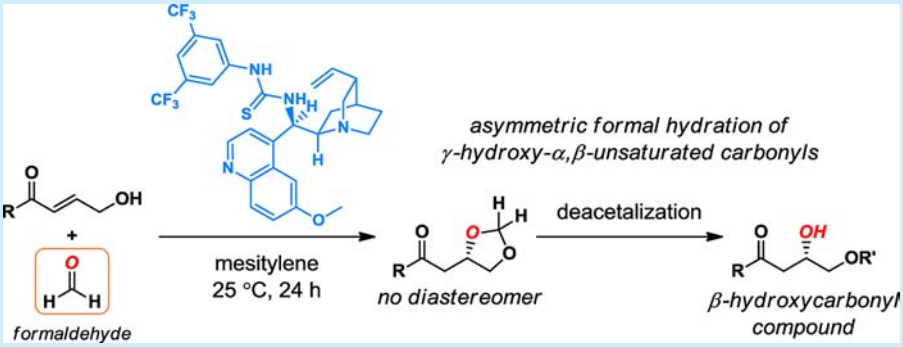
pubs.acs.org/OrgLett

Asymmetric Oxy-Michael Addition to γ-Hydroxy-α,β-Unsaturated Carbonyls Using Formaldehyde as an Oxygen-Centered Nucleophile

Naoki Yoneda, Ayano Hotta, Keisuke Asano,* and Seijiro Matsubara*

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyotodaigaku-Katsura, Nishikyo, Kyoto 615-8510, Japan

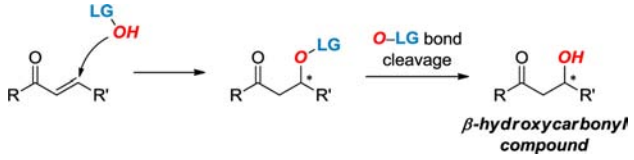
Supporting Information



ABSTRACT: Formaldehyde was utilized as an oxygen-centered nucleophile in an asymmetric oxy-Michael addition to γ-hydroxy-α,β-unsaturated carbonyl compounds using bifunctional organocatalysts through hemiacetal intermediates. The cyclic acetal product could be further transformed into β-hydroxycarbonyl compounds, useful synthetic intermediates leading to various important target molecules. As such, this method is an example of a novel formal asymmetric hydration of α,β-unsaturated carbonyl compounds.

The asymmetric hydration of α,β-unsaturated carbonyl compounds via oxy-Michael additions represents an attractive route toward chiral β-hydroxycarbonyl compounds, which are important synthetic intermediates and exist as structural motifs in a variety of natural products.[1] However, the Michael addition of water is challenging because of the low nucleophilicity of water, frequent reaction reversibility, and difficulties concerning stereochemical control.[2] Thus, a promising alternative is formal hydration utilizing the Michael addition of water surrogates, which are oxygen-centered nucleophiles bearing an easily removable group (Scheme 1).

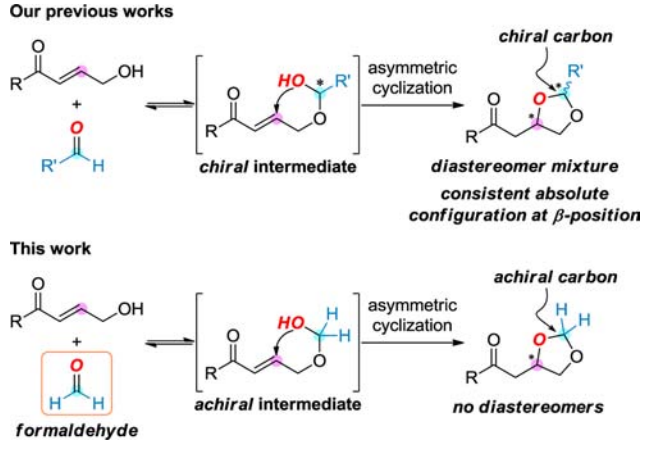
Scheme 1. Formal Hydration of α,β-Unsaturated Carbonyl Compounds



Among the oxygen-centered nucleophiles investigated thus far, oximes[3a−c] and hydrogen peroxide[3d] are advantageous because of their high nucleophilicity. On the other hand, intramolecularization[4] by a cleavable tether is also an efficient strategy to achieve high reactivity of oxy-Michael additions.[5]

We also recently reported enantioselective oxy-Michael addition reactions to γ-hydroxy-α,β-unsaturated carbonyl compounds, which go through hemiacetal intermediates to give 1,3-dioxolanes, which contain an easily removable acetal functionality (Scheme 2).[6] Although this reaction proceeded

Scheme 2. Asymmetric Oxy-Michael Addition Using Formaldehyde as Oxygen-Centered Nucleophile



Received: October 23, 2014
Published: November 10, 2014

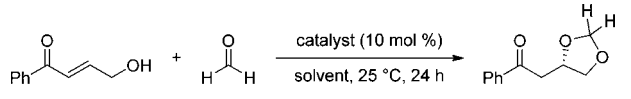
dx.doi.org/10.1021/ol503104b | Org. Lett. 2014, 16, 6264–6266

with high enantioselectivity, the products consisted of a mixture of diastereomers in a modest ratio. However, fortunately, the β-positions of the carbonyl groups in both diastereomers proved to have the same absolute configuration, indicating that the step comprising the intramolecular oxy-Michael addition from the hemiacetal intermediates can proceed enantioselectively, regardless of the stereochemistry of the hemiacetal.[7] Thus, in order to avoid the generation of diastereomers, we attempted to use formaldehyde as an oxygen-centered nucleophile that could provide an achiral hemiacetal intermediate (Scheme 2). Here, we present an asymmetric oxy-Michael addition to γ-hydroxy-α,β-unsaturated carbonyl compounds using formaldehyde as an oxygen source and demonstrate further transformations of the product.

We initially investigated the reaction between (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**1a**) and formaldehyde (**2**) with 10 mol % of quinidine-derived bifunctional aminothiourea catalyst **4a** in various solvents at 25 °C (Table 1, entries 1−9).[8,9] The enantioselectivity was superior in aromatic hydrocarbon-based solvents (Table 1, entries 1 and 5−8); mesitylene gave the best enantioselectivity (Table 1, entry 8). The presence of water did not affect the enantioselectivity of the reaction in mesitylene (Table 1, entries 8 and 9). Other catalysts were also investigated,[10,11] and the quinidine-derived catalyst **4a** led to higher enantioselectivity, among the cinchona-derived thiourea catalysts and Takemoto catalyst (Table 1, entries 8 and 10−13). In addition, the bifunctionality of the catalyst, including the thiourea moiety, proved to be significant for enantioselectivity (Table 1, entries 8, 14, and 15).

Other substrates were also investigated by using **4a** as the catalyst in mesitylene at 25 °C (Table 2). An electron-rich enone resulted in slightly higher stereoselectivity, although an electron-poor substrate was also tolerated (Table 2, entries 2 and 3). In addition, a substrate bearing a *p*-bromophenyl moiety afforded the corresponding product in comparable yield and enantioselectivity (Table 2, entry 4). Unfortunately, the stereoselectivity was sensitive to *ortho*-substituents on the aryl

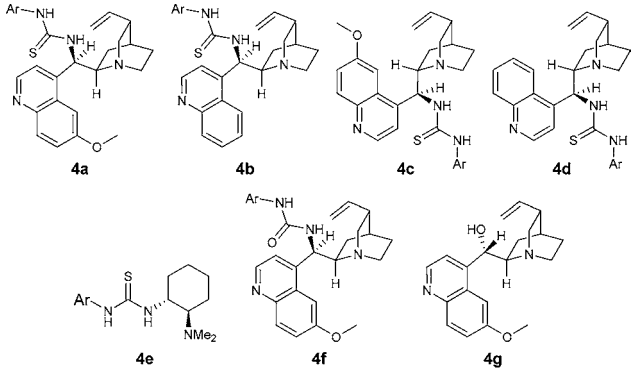
Table 1. Optimization of Conditions[a]



1a 2 3a

entry	catalyst	solvent	yield (%)[b]	ee (%)
1	**4a**	CPME[c]	91	62
2[d]	**4a**	CPME[c]	54	72
3	**4a**	CH_2Cl_2	76	61
4	**4a**	hexane	94	43
5	**4a**	benzene	65	69
6	**4a**	toluene	82	72
7	**4a**	xylene	84	73
8	**4a**	mesitylene	92	75
9[d]	**4a**	mesitylene	51	75
10	**4b**	mesitylene	92	73
11	**4c**	mesitylene	76	−57
12	**4d**	mesitylene	89	−58
13	**4e**	mesitylene	76	57
14	**4f**	mesitylene	75	71
15	**4g**	mesitylene	84	4

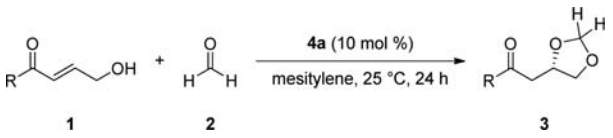
[a]Reactions were run using **1a** (0.15 mmol), **2** (37% aqueous solution, 0.18 mmol), and the catalyst (0.015 mmol) in the solvent (0.3 mL). [b]Isolated yields. [c]CPME = cyclopentyl methyl ether. [d]Reaction was run using paraformaldehyde (0.18 mmol).



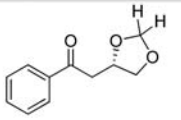
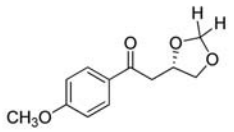
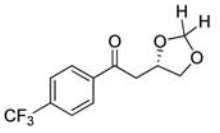
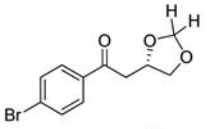
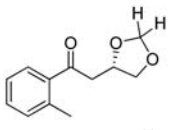
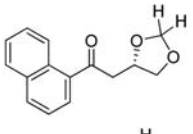
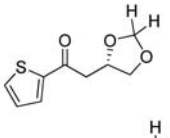
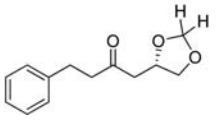
4a 4b 4c 4d 4e 4f 4g

Ar = 3,5-$(CF_3)_2C_6H_3$

Table 2. Substrate Scope[a]



1 2 3

entry	product (**3**)		yield (%)[b]	ee (%)
1		**3a**	95	75
2		**3b**	85	79
3		**3c**	88	74
4		**3d**	91	73
5		**3e**	76	49
6		**3f**	67	61
7		**3g**	79	67
8		**3h**	82	65

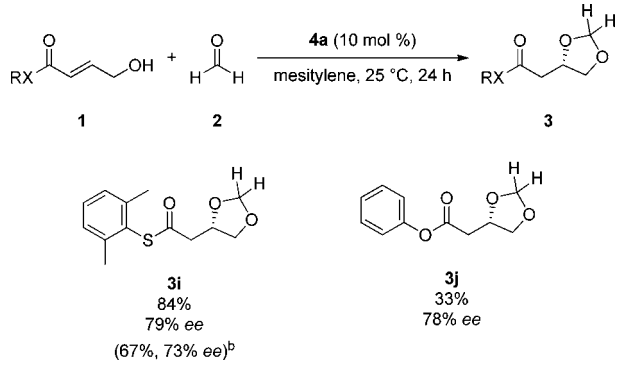
[a]Reactions were run using **1** (0.15 mmol), **2** (37% aqueous solution, 0.18 mmol), and **4a** (0.015 mmol) in mesitylene (0.3 mL). [b]Isolated yields.

dx.doi.org/10.1021/ol503104b | *Org. Lett.* 2014, 16, 6264−6266

groups of the α,β-unsaturated ketones (Table 2, entries 5 and 6). Substrates with heterocyclic and aliphatic substituents also gave the corresponding products in moderate enantioselectivity (Table 2, entries 7 and 8).

In addition, α,β-unsaturated carboxylic acid derivatives proved to be useful substrates in this reaction (Scheme 3).

Scheme 3. Reactions from α,β-Unsaturated Thioester and Ester[a]

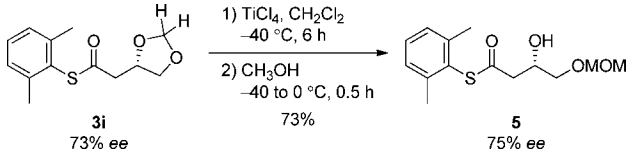


[a]Reactions were run using **1** (0.15 mmol), **2** (37% aqueous solution, 0.18 mmol), and **4a** (0.015 mmol) in mesitylene (0.3 mL). [b]Reactions were run using **1** (5.0 mmol), **2** (37% aqueous solution, 6.0 mmol), and **4a** (0.5 mmol) in mesitylene (10 mL) for 48 h.

An α,β-unsaturated thioester, which is amenable to further transformations, gave the product **3i** in high yield and enantioselectivity. Furthermore, the reaction of **1i** was scalable; the reaction with 5.0 mmol of **1i** gave **3i** in similar, good enantioselectivity. Moreover, even though α,β-unsaturated esters rarely serve as viable substrates for oxy-Michael additions,[3] α,β-unsaturated ester **1j** gave the corresponding product in comparable enantioselectivity.

To demonstrate the utility of the developed reaction as a formal hydration method, we carried out the deacetalization of **3i**. The treatment of **3i** with titanium tetrachloride afforded free β-hydroxy thioester **5**, in which the γ-hydroxy group was protected by a methoxymethyl group (Scheme 4). The absolute

Scheme 4. Deacetalization of the Product



configuration of **5** was assigned as (*S*) after further transformations to a known compound, (*S*)-4-(benzyloxy)butane-1,2-diol, by comparing the optical rotation with the literature value[12] (see the Supporting Information (SI) for details). The configurations of all other products were assigned analogously.

In summary, we have demonstrated the utility of formaldehyde as an oxygen-centered nucleophile for the formal hydration of γ-hydroxy-α,β-unsaturated carbonyl compounds. The reaction proceeded in high yield and acceptable enantioselectivity, and the subsequent deacetalization yielded a valuable chiral β-hydroxycarbonyl compound. Further studies regarding expanding the scope of substrates to other α,β-unsaturated carbonyls and the application of this methodology to the asymmetric syntheses of various chiral molecules including natural products are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: asano.keisuke.5w@kyoto-u.ac.jp.
*E-mail: matsubara.seijiro.2e@kyoto-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported financially by the Japanese Ministry of Education, Culture, Sports, Science and Technology. K.A. also acknowledges the Asahi Glass Foundation.

■ REFERENCES

(1) For reviews on oxy-Michael addition reactions, see: (a) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2008**, *37*, 1218. (b) Hartmann, E.; Vyas, D. J.; Oestreich, M. *Chem. Commun.* **2011**, *47*, 7917. (c) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* **2012**, *41*, 988.

(2) Boersma, A. J.; Coquière, D.; Geerdink, D.; Rosati, F.; Feringa, B. L.; Roelfes, G. *Nat. Chem.* **2010**, *2*, 991.

(3) (a) Vanderwal, C. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 14724. (b) Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536. (c) Carlone, A.; Bartoli, G.; Bosco, M.; Pesciaioli, F.; Ricci, P.; Sambri, L.; Melchiorre, P. *Eur. J. Org. Chem.* **2007**, 5492. (d) Reisinger, C. M.; Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 8112.

(4) Ho, T.-L. *Tactics of Organic Synthesis*; Wiley: New York, 1994.

(5) Li, D. R.; Murugan, A.; Falck, J. R. *J. Am. Chem. Soc.* **2008**, *130*, 46.

(6) (a) Asano, K.; Matsubara, S. *Org. Lett.* **2012**, *14*, 1620. (b) Okamura, T.; Asano, K.; Matsubara, S. *Chem. Commun.* **2012**, *48*, 5076. (c) Fukata, Y.; Miyaji, R.; Okamura, T.; Asano, K.; Matsubara, S. *Synthesis* **2013**, *45*, 1627.

(7) For our related works on intramolecular hetero-Michael addition by bifunctional organocatalysts, see: (a) Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* **2011**, *133*, 16711. (b) Fukata, Y.; Asano, K.; Matsubara, S. *Chem. Lett.* **2013**, *42*, 355. (c) Miyaji, R.; Asano, K.; Matsubara, S. *Org. Lett.* **2013**, *15*, 3658. (d) Fukata, Y.; Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* **2013**, *135*, 12160. (e) Miyaji, R.; Asano, K.; Matsubara, S. *Org. Biomol. Chem.* **2014**, *12*, 119.

(8) For seminal works on aminothiourea catalysts, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (c) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (d) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151. (e) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418. (f) Zhu, J.-L.; Zhang, Y.; Liu, C.; Zheng, A.-M.; Wang, W. *J. Org. Chem.* **2012**, *77*, 9813.

(9) Results of further solvent screening are described in the SI (Table S1).

(10) Results of further catalyst screening are described in the SI (Table S2).

(11) Further details on screening of reaction conditions are described in the SI (Table S3).

(12) Beuerle, T.; Engelhard, S.; Bicchi, C.; Schwab, W. *J. Nat. Prod.* **1999**, *62*, 35.