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Asymmetric Synthesis of 1,3-Dioxolanes by Organocatalytic Formal [3 + 2] Cycloaddition via Hemiacetal Intermediates

Keisuke Asano* and Seijiro Matsubara*

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

keisuke.asano@t03kr913mk.mbox.media.kyoto-u.ac.jp; matsubar@orgrxn.mbox.media.kyoto-u.ac.jp

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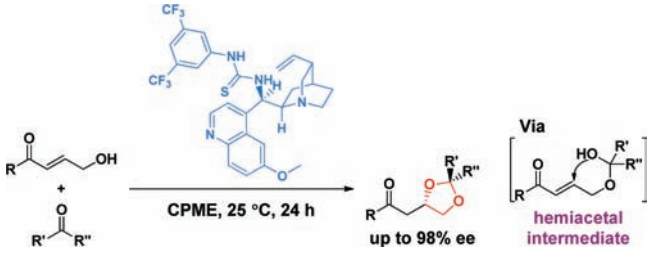
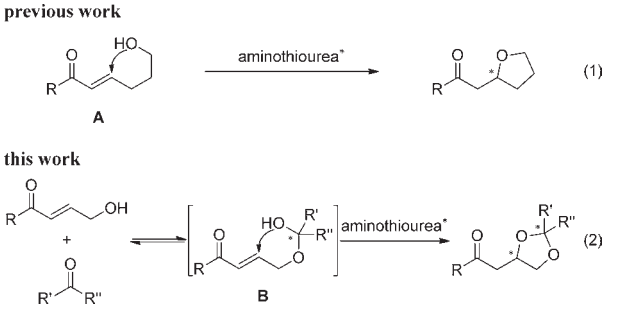
ABSTRACT



A novel asymmetric formal [3 + 2] cycloaddition reaction for the synthesis of 1,3-dioxolanes using cinchona-alkaloid-thiourea-based bifunctional organocatalysts is reported. The reaction proceeds via the formation of hemiacetal intermediates between γ-hydroxy-α,β-unsaturated ketones and aldehydes.

Optically active cyclic acetals are important in various biologically active agents and natural products.[1] They are also known as versatile intermediates for asymmetric synthesis:[2−4] they can be used as chiral auxiliaries to control the reaction of a proximal prochiral center[2,3] and can also be used as chiral templates for stereospecific cleavage of their ring in the presence of nucleophiles and Lewis acid reagents.[2,4] Therefore, asymmetric synthesis methods of chiral cyclic acetals would be particularly useful as approaches to various chiral building blocks. Nevertheless, optically active acetals are largely prepared from chiral starting materials or by the use of stoichiometric chiral reagents,[2−6] and there have been only a few examples of catalytic asymmetric syntheses.[7−9] Moreover, catalytic asymmetric cycloaddition has remained underdeveloped despite its advantage in terms of the ability to construct multiple bonds in a single step, thereby leading to divergent synthesis.

Scheme 1. Asymmetric Cycloetherification by Bifunctional Aminothiourea Catalyst



Recently, we reported an asymmetric cycloetherification reaction of ε-hydroxy-α,β-unsaturated ketones **A** mediated

(1) (a) Aho, J. E.; Pihko, P. M.; Rissa, T. K. *Chem. Rev.* **2005**, *105*, 4406. (b) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617. (c) Felix, W.; Rimbach, G.; Wengenroth, H. *Arzeim.-Forsch.* **1969**, *19*, 1860. (d) Mavragani, C. P.; Moutsopoulos, H. M. *Clinic Rev. Allerg. Immunol.* **2007**, *32*, 287.

(2) For reviews, see: (a) Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477. (b) Carreira, E. M.; Kvaerno, L. *Classics in Stereoselective Synthesis*; Wiley-VCH: Weinheim, 2009; Chapter 6.

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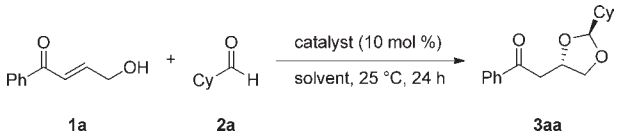
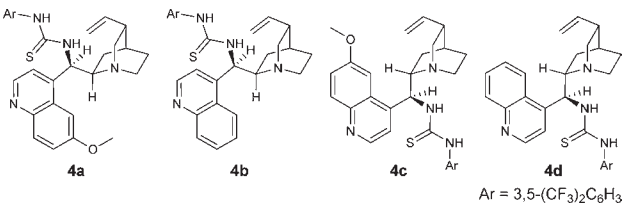
by cinchona-alkaloid-thiourea-based bifunctional organocatalysts (Scheme 1, eq 1).[10] In this reaction, concerted catalysis due to the bifunctional nature of the catalyst led to highly enantioselective cyclization, which afforded chiral oxacyclic compounds. The results of our previous work motivated us to exploit this efficient cyclization route in the development of a formal cycloaddition reaction starting from γ-hydroxy-α,β-unsaturated ketones with aldehydes or ketones via hemiacetal intermediates **B** (Scheme 1, eq 2).[5,11] Herein we present a novel catalytic asymmetric formal [3 + 2] cycloaddition reaction for the synthesis of chiral 1,3-dioxolanes using bifunctional organocatalysts derived from cinchona alkaloids.[12,13]

Table 1. Optimization of Conditions[a]



entry	catalyst	solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	**4a**	CH_2Cl_2	83	2.9:1	93
2	**4a**	benzene	89	2.3:1	94
3	**4a**	THF	56	3.7:1	96
4	**4a**	Et_2O	85	2.4:1	95
5	**4a**	TBME[f]	81	2.9:1	96
6	**4a**	CPME[g]	86	3.0:1	96
7[e]	**4a**	CPME[g]	95	3.0:1	96
8[e]	**4b**	CPME[g]	88	2.7:1	95
9[e]	**4c**	CPME[g]	91	4.0:1	−93
10[e]	**4d**	CPME[g]	87	3.4:1	−93

[a] Reactions were run using **1a** (0.25 mmol), **2a** (0.25 mmol), and the catalyst (0.025 mmol) in the solvent (0.5 mL). [b] Isolated yields. [c] Diastereomeric ratios were determined by ^{1}H NMR. [d] Values are for the major diastereomer of **3aa**. [e] Reactions were run using 0.3 mmol of **2a**. [f] TBME = *tert*-butyl methyl ether. [g] CPME = cyclopentyl methyl ether.



We initiated our investigations using (*E*)-4-hydroxy-1-phenylbut-2-en-1-one (**1a**) and cyclohexanecarboxaldehyde (**2a**) with 10 mol % of quinidine-derived bifunctional catalyst **4a** in CH_2Cl_2 at 25 °C. As expected, 1,3-dioxolane **3aa** was obtained stereoselectively in 83% yield (Table 1, entry 1). Through a process of solvent optimization, ethereal solvents were identified as being efficient for stereoselectivity, and cyclopentyl methyl ether (CPME) was identified as the most suitable solvent from the viewpoints of both yield and enantioselectivity (Table 1, entries 1−6). The use of 1.2 equiv of **2a** further improved the yield without decreasing the stereoselectivity (Table 1, entry 7). Catalyst screening identified **4c** also as an efficient catalyst for obtaining the opposite enantiomer of **3aa** in good yield with high enantioselectivity (Table 1, entry 9).

With the optimized conditions and using **4a** as a catalyst, we next explored the substrate scope. γ-Hydroxy-α,β-unsaturated ketones **1** could be readily prepared from commercially available materials by our reported procedure.[14] Good to excellent yields and enantioselectivities were obtained with both electron-rich and -poor enones

(4) For selected examples, see: (a) Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 5279. (b) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2088. (c) Johnson, W. S.; Elliott, R.; Elliott, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2904. (d) McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7371. (e) Sekizaki, H.; Jung, M.; McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7372. (f) Mori, A.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 4421. (g) Mori, A.; Ishihara, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 987. (h) Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 7074. (i) Ghribi, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 3083. (j) Alexakis, A.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 4197. (k) Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 3143. (l) Matsutani, H.; Ichikawa, S.; Yaruva, J.; Kusumoto, T.; Hiyama, T. *J. Am. Chem. Soc.* **1997**, *119*, 4541. (m) Fukuzawa, S.; Tsuchimoto, T.; Hotaka, T.; Hiyama, T. *Synlett* **1995**, 1077. (n) Zhao, Y.-J.; Chng, S.-S.; Loh, T.-P. *J. Am. Chem. Soc.* **2007**, *129*, 492. (o) Li, H.; Loh, T.-P. *Org. Lett.* **2010**, *12*, 2679. (p) Richter, W. J. *J. Org. Chem.* **1981**, *46*, 5119. (q) Mashraqui, S. H.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 2513. (r) Yamamoto, Y.; Nishi, S.; Yamada, J. *J. Am. Chem. Soc.* **1986**, *108*, 7116. (s) Yamamoto, K.; Ando, H.; Chikamatsu, H. *J. Chem. Soc., Chem. Commun.* **1987**, 334. (t) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Chem. Lett.* **1987**, *16*, 1531. (u) Kato, K.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1993**, *34*, 4979. (v) Sugimura, T.; Fujiwara, Y.; Tai, A. *Tetrahedron Lett.* **1997**, *38*, 6019. (w) Takayama, Y.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3559. (x) Fujioka, H.; Kitagawa, H.; Matsunaga, N.; Nagatomi, Y.; Kita, Y. *Tetrahedron Lett.* **1996**, *37*, 2245. (y) Andrus, M. B.; Lepore, S. D. *Tetrahedron Lett.* **1995**, *36*, 9149.

(5) For examples of diastereoselective cyclic acetal syntheses by intramolecular oxy-Michael addition via hemiacetal formation, see: (a) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446. (b) Evans, P. A.; Grisin, A.; Lawler, M. J. *J. Am. Chem. Soc.* **2012**, *134*, 2856. (c) Watanabe, H.; Machida, K.; Itoh, D.; Nagatsuka, H.; Kitahara, T. *Chirality* **2001**, *13*, 379.

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(10) Asano, K.; Matsubara, S. *J. Am. Chem. Soc.* **2011**, *133*, 16711.

(11) Reactions between γ-hydroxy-α,β-unsaturated ketones and boronic acids via boronic acid hemiester intermediates have been previously reported; see: Li, D. R.; Murugan, A.; Falck, J. R. *J. Am. Chem. Soc.* **2008**, *130*, 46.

(12) (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.

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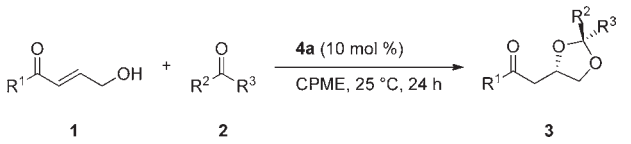
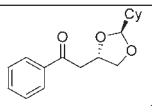
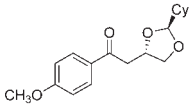
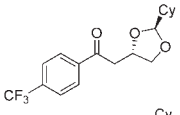
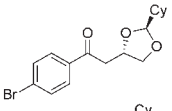
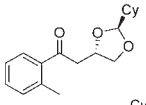
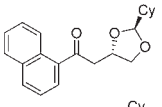
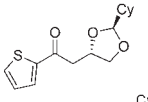
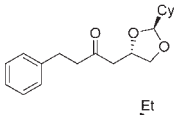
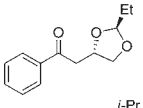
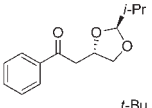
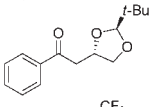
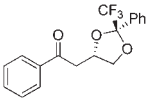
Table 2. Scope of Substrates[a,b]



1 2 3

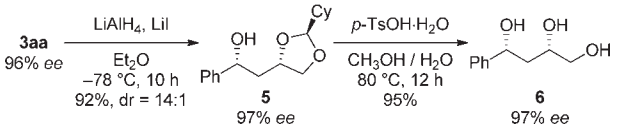
entry	product (3)		yield (%)[c]	dr[d]	ee (%)[e]
1		**3aa**	95	3.0:1	96
2[f]		**3ba**	93	3.4:1	96
3		**3ca**	83	2.5:1	95
4		**3da**	88	4.7:1	96
5		**3ea**	71	3.3:1	91
6		**3fa**	82	2.9:1	90
7		**3ga**	84	3.3:1	98
8[g]		**3ha**	82	3.3:1	96
9		**3ab**	94	3.0:1	94
10		**3ac**	92	2.7:1	93
11[h]		**3ad**	84	2.6:1	94
12		**3ae**	99	1.2:1	70

[a] Reactions were run using **1** (0.25 mmol), **2** (0.3 mmol), and **4a** (0.025 mmol) in CPME (0.5 mL). [b] CPME = cyclopentyl methyl ether. [c] Isolated yields. [d] Diastereomeric ratios were determined by ^{1}H NMR. [e] Values are for the major diastereomers of **3**. See Supporting Information for minor diastereomers. [f] Reaction was run for 48 h. [g] Reaction was run for 96 h. [h] Reaction was run for 120 h.

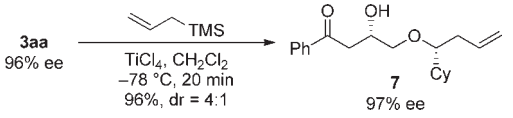
(Table 2, entries 2 and 3). Substrates bearing *p*-bromophenyl, *o*-tolyl, and 1-naphthyl groups were tolerated (Table 2, entries 4–6). Further, enones substituted by a heterocycle or an alkyl group also gave 1,3-dioxolanes in good yields and high enantioselectivities (Table 2, entries 7 and 8). In addition, we could replace **2a** with propionaldehyde (**2b**), isobutyraldehyde (**2c**), and pivalaldehyde (**2d**) to obtain the corresponding cycloadducts in excellent enantioselectivities (Table 2, entries 9–11).[15] Instead of an aldehyde, electron-deficient ketone **2e** could also be employed to furnish the cyclic acetal **3ae** with a chiral quaternary acetal carbon (Table 2, entry 12). The absolute configurations of **3da** were determined by X-ray analysis for both diastereomers (see Supporting Information for details),[16] and the configurations of all other examples were assigned analogously.

To demonstrate the utility of our products as synthetic intermediates, we performed the transformation of **3aa**. Reduction with lithium aluminum hydride in the presence of lithium iodide afforded the corresponding alcohol **5** in high diastereoselectivity, and subsequent deacetalization gave optically active triol **6** (Scheme 2). In addition, treatment of **3aa** with allyltrimethylsilane in the presence of titanium tetrachloride led to allylative ring cleavage to provide **7** in regio- and diastereoselective fashion while maintaining the optical purity (Scheme 3).[4b]

Scheme 2. Synthesis of Chiral Triol **6**



Scheme 3. Stereospecific Ring Cleavage of **3aa**

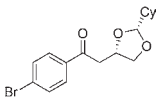


To gain insight into the enantiodetermining step, we further investigated formal [3 + 2] cycloaddition reactions

(14) Sada, M.; Ueno, S.; Asano, K.; Nomura, K.; Matsubara, S. *Synlett* **2009**, 724.

(15) Aryl and alkenyl aldehydes proved to be much less reactive: reactions using benzaldehyde or cinnamaldehyde with **1a** gave the corresponding products in less than 10% yields, while electron-poor 4-(trifluoromethyl)benzaldehyde gave the acetal product in 70% yield with moderate stereoselectivities (dr = 0.9:1, 79% *ee* and 82% *ee*, respectively). Similar observations were also recently reported; see ref 5b. For quantification of the electrophilic reactivity of aldehydes, see: Appel, R.; Mayr, H. *J. Am. Chem. Soc.* **2011**, *133*, 8240.

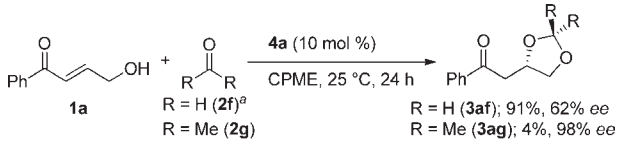
(16) The absolute configuration of the minor diastereomer of **3da** was determined by X-ray analysis to be as follows:



(17) Although not confirmed directly, we believe the catalyst might also be responsible for the enatioselective formation of acetal carbon, and the diastereoselectivity might be determined kinetically.

using formaldehyde (**2f**) and acetone (**2g**) with **1a** (Scheme 4). We found that products **3af** and **3ag** were obtained enantioselectively regardless of the fact that the forming acetal carbon was achiral. Although a precise understanding of the mechanism requires additional studies, from these results, the enantioselectivity of this reaction can be attributed largely to the step comprising oxy-Michael addition from the hemiacetal intermediates.[17] This is in accordance with the consistent absolute configuration (the same (*S*)-configuration) at the β-position of the carbonyl group in both diastereomers of **3da**.[16]

Scheme 4. Formal [3 + 2] Cycloaddition with Formaldehyde (**2f**) and Acetone (**2g**)[a]



[a] Reaction was run using 37% aqueous solution of formaldehyde.

In summary, we developed a novel organocatalytic formal [3 + 2] cycloaddition reaction leading to optically active 1,3-dioxolanes. Bifunctional organocatalysts allowed cyclization from hemiacetals in high enantioselectivity. This synthetic route provides efficient access to a range of chiral cyclic acetals. In addition, the novel potential of bifunctional organocatalysts in chiral heterocycle synthesis was demonstrated. Further studies on the application of this methodology to other related transformations are currently underway in our laboratory and will be reported in due course.

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

The authors declare no competing financial interest.