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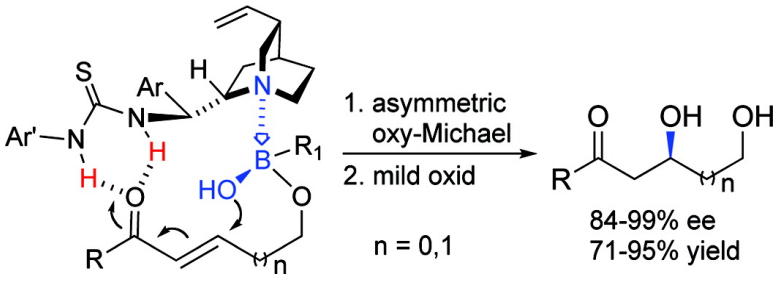

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Enantioselective, Organocatalytic Oxy-Michael Addition to γ/δ-Hydroxy-α,β-enones: Boronate-Amine Complexes as Chiral Hydroxide Synthons

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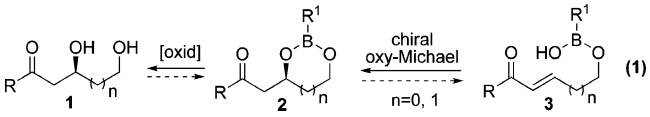
Structural motif **1** is present in a wide range of natural products and synthetic intermediates.[1] While Michael additions of hydroxide or synthetic equivalents to α,β-unsaturated carbonyls represent an attractive approach to this moiety,[2] the strong basicity of the former and generally poor nucleophilicity or lability of the latter often render this option problematic. In its place, the intramolecular oxy-Michael addition of hemiacetal/hemiketal-derived alkoxides has emerged as a popular alternative strategy,[3] although the resultant cyclic acetals/ketals can be difficult to remove. In some instances, satisfactory diastereoselectivity has been attained via exploitation of adjacent secondary hydroxy or amino stereocenters.[4,5] In 2001, Watanabe et al.[6] introduced an asymmetric version of the oxy-Michael addition utilizing chiral hemiketals derived from D-glucose and D-fructose in the more challenging case of achiral γ/δ-hydroxy-α,β-enones. Herein, we reported an unprecedented organocatalytic, enantioselective oxy-Michael addition to achiral γ/δ-hydroxy-α,β-enones and its use in the preparation of **1** (eq 1).[7] The key

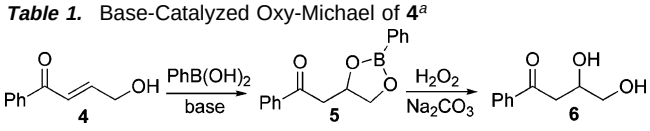


(1)

transformation is the asymmetric conjugate addition triggered by complexation between boronic acid hemiester **3**, generated in situ from γ/δ-hydroxy-α,β-enones, and a chiral amine catalyst. Functionally, the intermediate amine−boronate complex acts as a *chiral hydroxide surrogate or synthon*. Mild, oxidative removal of the boronate moiety from the dioxaborolane ($n = 0$) or dioxaborinane ($n = 1$) adduct **2** furnishes **1** in good to excellent overall yield and % ee.

Recently, this[8] and other laboratories[9] have highlighted the nucleophilic properties of organoboronic acids and the unique stereospecific reactions of their borate complexes. Despite expectations, when model compound (*E*)-4-hydroxy-1-phenyl-2-buten-1-one (**4**) was mixed with equimolar phenylboronic acid and activated 4 Å molecular sieves in CH_2Cl_2 (Table 1, entry 1), no intramolecular Michael addition was observed, even though the hemiester (**3**: R= Ph, $n = 0$) could be detected by ^1H and ^{13}C NMR. Inclusion of some common bases, namely, bicarbonate (entry 2), carbonate (entry 3), and pyridine (entry 4), likewise disappointed. However, a catalytic amount of Et_3N (20 mol %, entry 5) gave rise to the desired dioxaborolane **5** from which diol **6** was secured in 42% overall yield (50% recovered **4** after 48 h) following workup with basic H_2O_2. We attribute this dramatic difference to the in situ formation of a nucleophilic, pyramidized quaternary boronate complex.[10,11] 1,4-Diazabicyclo[2.2.2]octane (DABCO), under otherwise identical conditions, significantly improved the overall conversion (entry 6), whereas diisopropylamine (20 mol %, entry 7) worked even better and delivered **6** in 86% overall yield in just

Table 1. Base-Catalyzed Oxy-Michael of **4**[a]



entry	base	solvent	time (h)	yield[b] (%)
1	none	CH_2Cl_2	48	0
2	$NaHCO_3$	CH_2Cl_2	48	0
3	Na_2CO_3	CH_2Cl_2	48	0
4	pyridine	CH_2Cl_2	48	0
5	Et_3N	CH_2Cl_2	48	42
6	DABCO	CH_2Cl_2	48	70
7	iPr_2NH	CH_2Cl_2	16	86
8	iPr_2NH	$PhCH_3$	8	87
9	iPr_2NH	DME	48	70
10	DBU	CH_2Cl_2	48	30
11	PMP[c]	$PhCH_3$	80	82

[a] Reaction conditions: (i) $PhB(OH)_2$ (1.2 equiv), base (20 mol %), 4 Å MS, room temp; (ii) H_2O_2, Na_2CO_3, room temp, 15 min. [b] Overall for two steps from enone **4** to diol **6**. [c] PMP = 1,2,2,6,6-pentamethylpiperidine.

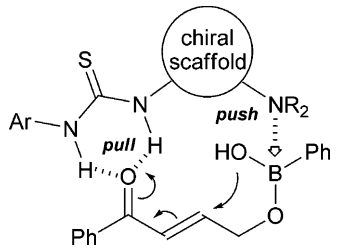


Figure 1. Proposed asymmetric catalysis.

16 h. The reaction rate for the latter was enhanced even further in toluene (entry 8), but not in 1,2-dimethoxyethane (DME) (entry 9); the yield showed only a modest solvent dependency. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (entry 10) and the highly hindered 1,2,2,6,6-pentamethylpiperidine (entry 11) offered no advantage.

Inspired by the pronounced success of push/pull-type bifunctional organocatalysts,[12] we pursued an asymmetric version of this intramolecular oxy-Michael addition (Figure 1). Coordination of the carbonyl by the thiourea (the pull) and complexation of the tertiary nitrogen to boron (the push) were expected to simultaneously enhance the nucleophilicity of the boronate oxygen as well as envelope the enone in a chiral environment.[13] Indeed, Michael addition to **4** in CH_2Cl_2 mediated by catalyst **7**[12b] was complete in 16 h (Table 2, entry 1), > 3 times faster than a similar Et_3N catalyzed addition. More significantly, **12** was obtained in 91% yield and 91% ee after basic H_2O_2 workup.[14,15] A comparable reaction in toluene proceeded still faster (8 h), but with significantly reduced enantioselectivity (65% ee), whereas in DME the rate was slower (24 h) and the % ee improved modestly to 94%. The less expensive

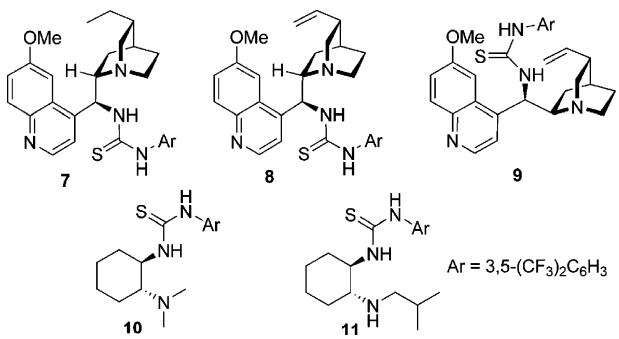
10.1021/ja076802c CCC: $40.75

Table 2. Asymmetric Oxy-Michael of γ-Hydroxy-α,β-enones

entry	enone	diol	solvent	time (h)	yield[a] (%)	ee[b] (%)
1	**4**	**12**	CH_2Cl_2[c]	16	91	91
			$PhCH_3$[c]	8	87	65
			DME[c]	24	89	94
			DME[d]	24	90	95
2	**4**	**13**	DME[e]	40	84	89
			DME[f]	48	84	91
3	**14**	**15**	DME[d]	14	92	90
4	**16**	**17**	DME[d]	27	85	97
5	**18**	**19**	DME[d]	22	83	97
6	**20**	**21**	CH_2Cl_2[d]	72	78	89
7	**22**	**23**	CH_2Cl_2[d]	72	95	87
8	**24**	**25**	CH_2Cl_2[d]	27	94	92
9	**26**	**27**	$PhCH_3$[d]	36	78	98
10	**28**	**29**	DME[d]	28	71	99

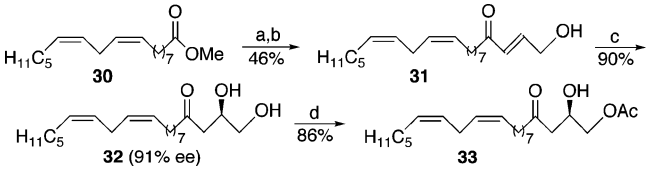
[a] Isolated yield. [b] Determined by chiral HPLC; absolute configuration assigned in analogy with **12** and **33**. [c] Reaction conditions: (i) $PhB(OH)_2$ (1.2 equiv), **7** (10 mol %), 4 Å MS, room temp; (ii) H_2O_2, Na_2CO_3, room temp, 15 min. [d] Catalyst **8** (10 mol %) was used. [e] Catalyst **9** (10 mol %) was used. [f] Catalyst **10** (10 mol %) was used.

quinine-based catalyst **8**[12b] was virtually equivalent to **7** in all respects (24 h, 95% ee). Notably, catalysts **9**[12b] and **10**[12a] in DME (entry 2) provided access to the opposite enantiomeric diol, **13**, in synthetically useful yields and enantioselectivities (40 h/89% ee and 48 h/91% ee, respectively). In sharp contrast to the accelerated rate seen with *i*Pr_2NH, catalyst **11**, which also contains a secondary amine, proved surprisingly sluggish and was not pursued further.



7 **8** **9** **10** **11**

Scheme 1. Biomimetic Synthesis of Antifungal/Hepatic Protective Agent from Avocado[a]



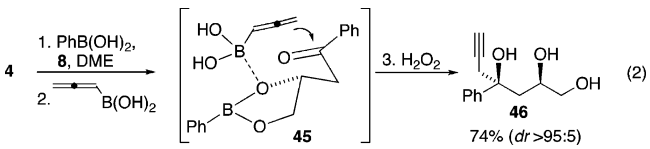
[a] Reagents and conditions: (a) $H_3CP(O)(OMe)_2$, LDA, THF, −78 °C, 2 h, 90%; (b) $[HC(O)CH_2OH]_2$, LiCl, DIPEA, room temp, CH_3CN, 2 h, 51%; (c) (i) $PhB(OH)_2$ (1.2 equiv), **8** (10 mol %), 4 Å MS, CH_2Cl_2, room temp, 56 h; (ii) H_2O_2, Na_2CO_3, room temp, 15 min; (d) AcCl (1.2 equiv), collidine, CH_2Cl_2, −78 °C, 10 h.

The scope of the oxy-Michael was further explored using catalyst **8** and a representative sampling of γ-hydroxy-α,β-enones (Table 2). Predictably, arylketones bearing strong electron withdrawing substituents (entry 3) reacted faster than electron-rich systems (entries 4 and 5), although the enantioselectivities of the latter were better.

Aliphatic ketones (entries 6 and 7), regardless of steric congestion adjacent to the carbonyl (**20** vs **22**), had retarded reaction rates, yet still afforded excellent overall yields. The conversion of **24** into **25** (entry 8) thus appears anomalous for its comparatively rapid rate and may reflect an unanticipated coordination by the terminal oxygen substituent. The survival of the labile silyl (TES) ether also testifies to the mildness of the reaction conditions. Importantly, additional substitution at the olefin (entry 9) or carbinol (entry 10) was well tolerated and adds to the level of structural complexity that can be achieved.

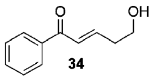
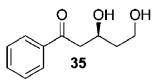
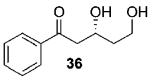
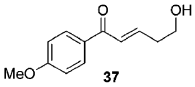
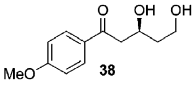
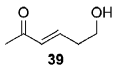
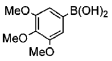
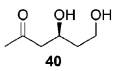
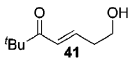
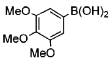
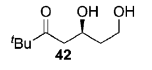
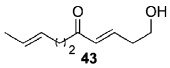
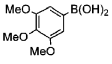
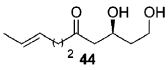
To validate the applicability of the foregoing methodology in natural products total synthesis, acetate **33**,[16] an extraordinarily potent antifungal/hepatic protective agent isolated from avocado, was prepared by a biomimetic route (Scheme 1). Addition of lithium dimethyl methylphosphonate to methyl linoleate (**30**) and condensation of the adduct with glycoaldehyde furnished enone **31** which was subjected to oxy-Michael addition catalyzed by **8**. The product (*R*)-diol **32** (90% yield, 91% ee[14]) was selectively acetylated to give **33**.[17]

With δ-hydroxy-α,β-enones, oxy-Michael addition proceeded quite slowly in all solvents, although toluene was generally the best. Increasing the catalyst loading to 20 mol % and the temperature to 50 °C, however, allowed the reaction to proceed at an acceptable rate and enantioselectivity for aromatic enones (Table 3: entries 1−3). For the more recalcitrant aliphatic enones (entries 4−6), these conditions were not sufficient. We, thus, screened a panel of commercial arylboronic acids to identify 3,4,5-trimethoxyphenylboronic acid as a more efficacious nucleophilic partner, which furnished aliphatic diols in good to excellent enantioselectivities at suitable rates. Diol **44** was identical in all respects with (+)-(*S*)-streptenol A, one of four known streptenols produced by *Streptomyces luteogriseus* that has attracted attention as an immunostimulant as well as an inhibitor of cholesterol biosynthesis and tumor cells.[19]



In contrast to carboxylic acids, boronic acids and their chiral complexes have not been well explored as nucleophilic reagents in organic synthesis. Furthermore, the often idiosyncratic reactivity

Table 3. Oxy-Michael of δ-Hydroxy-α,β-enones

entry	enone	$ArB(OH)_2$	diol	time (h)	yield[a] (%)	ee[b] (%)
1	 **34**		 **35**	12[c]	80	91
2	**34**		 **36**	26[d] 27[e]	72 71	83 86
3	 **37**		 **38**	18[c]	86	87
4	 **39**		 **40**	24[c]	73	84
5	 **41**		 **42**	50[c]	82	96
6	 **43**		 **44**	37[c]	75	88

[a] Isolated yield. [b] Determined by chiral HPLC; absolute configuration assigned in analogy with natural **44** and chemical correlation of **40** with a known intermediate (see ref 18). [c] Reaction conditions: (i) $ArB(OH)_2$ (1.2 equiv), **8** (20 mol %), 4 Å MS, toluene, 50 °C; (ii) H_2O_2, Na_2CO_3, room temp, 15 min. [d] Catalyst **9** (20 mol %) was used. [e] Catalyst **10** (20 mol %) was used.

of boronates offers unique opportunities for stereoselective manipulations. As an illustration, the oxy-Michael adduct formed in situ from **4** and phenylboronic acid under catalysis by **8** acted as a template for the stereoselective addition of allenylboronic acid to the carbonyl, possibly via intermediate **45** (eq 2). Diol **46** was generated, without isolation of intermediates, in good overall yield and diastereoselectivity.[20,21] Further developments including diastereoselective and intermolecular oxy-Michael additions are under investigation.

Acknowledgment. ^{11}B NMR was measured by Dr. RenSheng Luo (UMSL), X-ray analysis was performed by Radha Akella (UTSW), and financial support was provide by the Robert A. Welch Foundation and NIH (Grant GM31278, DK38226).

Supporting Information Available: Synthetic procedures, analytical data, X-ray, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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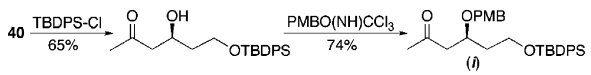

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JA076802C