

Published on Web 12/13/2007

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

De Run Li, Andiappan Murugan, and J. R. Falck*

Departments of Biochemistry and Pharmacology, University of Texas Southwestern Medical Center, Dallas, Texas 75390

Received September 8, 2007; E-mail: j.falck@utsouthwestern.edu

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

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, this⁸ and other laboratories⁹ 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-1one (4) was mixed with equimolar phenylboronic acid and activated 4 Å molecular sieves in CH₂Cl₂ (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 ¹³C NMR. Inclusion of some common bases, namely, bicarbonate (entry 2), carbonate (entry 3), and pyridine (entry 4), likewise disappointed. However, a catalytic amount of Et₃N (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 H₂O₂. 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

	Ph					
h 4	OH PhB(OH) ₂ base		$\frac{H_2O_2}{Na_2CO_3}$ Ph			
entry	base	solvent	time (h)	yield ^b (%)		
1	none	CH ₂ Cl ₂	48	0		
2	NaHCO ₃	CH_2Cl_2	48	0		
3	Na ₂ CO ₃	CH_2Cl_2	48	0		
4	pyridine	CH_2Cl_2	48	0		
5	Et ₃ N	CH_2Cl_2	48	42		
6	DABCO	CH_2Cl_2	48	70		
7	iPr ₂ NH	CH_2Cl_2	16	86		
8	iPr ₂ NH	PhCH ₃	8	87		
9	iPr ₂ NH	DME	48	70		
10	DBU	CH_2Cl_2	48	30		
11	PMP^{c}	PhCH ₃	80	82		

Table 1. Base-Catalyzed Oxy-Michael of 4^a

^{*a*} Reaction conditions: (i) PhB(OH)₂ (1.2 equiv), base (20 mol %), 4 Å MS, room temp; (ii) H₂O₂, Na₂CO₃, 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 CH₂Cl₂ mediated by catalyst **7**^{12b} was complete in 16 h (Table 2, entry 1), > 3 times faster than a similar Et₃N catalyzed addition. More significantly, **12** was obtained in 91% yield and 91% ee after basic H₂O₂ 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

entry	enone	diol	solvent	time (h)	yield ^a (%)	ee ^b (%)
1	4	O OH H OH 12	CH ₂ Cl ₂ ^c PhCH ₃ ^c DME ^c DME ^d	16 8 24 24	91 87 89 90	91 65 94 95
2	4	O OH 13	DME ^e DME ^f	40 48	84 84	89 91
3 O ₂ N´	0 ОН	0 OH O2N 15	DME ^d	14	92	90
4 MeO [^]	0 ОН	MeO OH OH	DME ^d	27	85	97
5	о —О 18	О ОН О 19	DME ^d	22	83	97
6	О ОН 20	O OH L OH 21	CH₂Cl₂ ^d	72	78	89
7 [/] B	о и 22	^O OH ′Bu 23 OH	CH ₂ Cl ₂ d	72	95	87
8 TESC	О И 4 24 ОН	TESO O OH 4 25 OH	CH₂Cl₂ ^d	27	94	92
9 F	о радовновно 26	о он Ph 27	PhCH3 ^d	36	78	98
10				20	71	00

^{*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) H₂O₂, Na₂CO₃, room temp, 15 min. ^{*d*} Catalyst **8** (10 mol %) was used. ^{*e*} Catalyst **9** (10 mol %) was used.

29

28

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*Pr₂NH, catalyst 11, which also contains a secondary amine, proved surprisingly sluggish and was not pursued further.



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



^{*a*} Reagents and conditions: (a) $H_3CP(O)(OMe)_2$, LDA, THF, $-78 \degree C$, 2 h, 90%; (b) [HC(O)CH₂OH]₂, LiCl, DIPEA, room temp, CH₃CN, 2 h, 51%; (c) (i) PhB(OH)₂ (1.2 equiv), **8** (10 mol %), 4 Å MS, CH₂Cl₂, room temp, 56 h; (ii) H₂O₂, Na₂CO₃, room temp, 15 min; (d) AcCl (1.2 equiv), collidine, CH₂Cl₂, $-78 \degree C$, 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% ee¹⁴) 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



^{*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) H₂O₂, Na₂CO₃, room temp, 15 min. ^{*d*} Catalyst **9** (20 mol %) was used. ^{*e*} Catalyst **10** (20 mol %)

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. ¹¹B 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.

References

 Recent review: Schetter, B.; Mahrwald, R. Angew. Chem., Int. Ed. 2006, 45, 7506-7525.

- (2) For examples of asymmetric Michael additions of oxygen-centered nucleophiles, see, (a) alcohols: Kano, T.; Tanaka, Y.; Maruoka, K. *Tetrahedron* 2007, 63, 8658–8664. (b) Oximes: Bertelsen, S.; Diner, P.; Johansen, R. L.; Jorgensen, K. A. J. Am. Chem. Soc. 2007, 129, 1536–1537. Vanderwal, C. D.; Jacobsen, E. N. J. Am. Chem. Soc. 2004, 126, 14724–14725. (c) Phenols: Govender, T.; Hojabri, L.; Moghaddam, F. M.; Arvidsson, P. I. Tetrahedron: Asymmetry 2006, 17, 1763–1767.
- (3) Chandrasekhar, S.; Rambabu, C.; Shyamsunder, T. Tetrahedron Lett. 2007, 48, 4683–4685.
- (4) Evans, D. A.; Gauchet-Prunet, J. A. J. Org. Chem. 1993, 58, 2446-2453.
- (5) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. J. Am. Chem. Soc. 2006, 128, 9328–9329.
- (6) Watanabe, H.; Machida, K.; Itoh, D.; Nagatsuka, H.; Kitahara, T. Chirality 2001, 13, 379–385.
- (7) For a review of asymmetric organocatalytic oxy-Michael additions, see: Berkessel, A.; Groerger, H. Asymmetric Organocatalysis; Wiley-VCH: Weinheim, Germany, 2005; Chapter 4.
- (8) Falck, J. R.; Bondlela, M.; Venkataraman, S. K.; Srinivas, D. J. Org. Chem. 2001, 66, 7148–7150.
- (9) (a) Yamaoka, Y.; Miyabe, H.; Takemoto, Y. J. Am. Chem. Soc. 2007, 129, 6686–6687. (b) Oshima, K.; Aoyama, Y. J. Am. Chem. Soc. 1999, 121, 2315–2316. (c) Matteson, D. S. Pure Appl. Chem. 2003, 75, 1249– 1253.
- (10) Amine-borate complexes are well-known: Gillis, E. P.; Burke, M. D. J. Am. Chem. Soc. 2007, 129, 6716–6717.
- (11) Rehybridization of the boron center from sp² to sp³ via coordination with trivalent nitrogen was unambiguously supported by the upfield chemical shift in the ¹¹B NMR as described in Supporting Information section and ref 9b.
- (12) (a) Okino, T.; Hoashi, Y.; Takemoto, Y. J. Am. Chem. Soc. 2003, 125, 12672–12673. (b) Vakulya, B.; Varga, S.; Csámpai, A.; Soos, T. Org. Lett. 2005, 7, 1967–1969.
- (13) The critical role played by thiourea hydrogen bonding in the activation of the enone is evident from a control experiment in which the thiourea catalyst 8 was replaced with 20 mol% *O*-benzoylquinine (Shi, M.; Lei, Z.-Y.; Zhao, M.-X.; Shi, J.-W. *Tetrahedron Lett.* 2007, 48, 5743–5746). Diol 12 was obtained in <5% yield and the majority of starting 4 was recovered unchanged.
- (14) Enantiomeric ratio measured by chiral HPLC.
- (15) Absolute configuration assigned by comparison with literature optical rotation data: Ticozzi, C.; Zanarotti, A. *Tetrahedron Lett.* **1994**, *35*, 7421– 7424.
- (16) Synthesis: MacLeod, J. K.; Schäffeler, L. J. Nat. Prod. 1995, 58, 1270– 1273. Interestingly, the (S)-enantiomer is inactive.
- (17) Ishihara, K.; Kurihara, H.; Yamamoto, H. J. Org. Chem. 1993, 58, 3791– 3793.
- (18) Selective primary silylation of 40 (TBDPSCI, DCM, DMAP, room temp, 10 h) followed by *p*-methoxybenzylation (PMB-O(NH)CCl₃) gave compound (i): [α]²⁰_D = +5.9 (*c* 0.85, CHCl₃); lit. [α]²⁰_D = +4.8 (*c* 1.49, CHCl₃). See, Li, D. R.; Zhang, D.-H.; Sun, C.-Y.; Zhang, J.-W.; Yang, L.; Chen, J.; Liu, B.; Su, C.; Zhou, W.-S.; Lin, G.-Q. *Chem. Eur. J.* 2006, *12*, 1185–1204.



- (19) Dollt, H.; Hammann, P.; Blechert, S. *Helv. Chim. Acta* **1999**, 82, 1111–1122 and references cited therein.
- (20) A similar diastereoselective addition of allenylboronic acid to β-hydoxy ketones has been reported: Ikeda, N.; Omori, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 1175–1178.
- (21) The absolute configuration of **46** was confirmed by X-ray analysis (see Supporting Information).

JA076802C