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(Diisopinocampheyl)borane-Mediated Reductive Aldol Reactions of Acrylate Esters: Enantioselective Synthesis of *Anti*-Aldols

Christophe Allais,[†] Philippe Nuhant,[†] and William R. Roush*

Department of Chemistry, Scripps Florida, Jupiter, Florida 33458, United States

roush@scripps.edu

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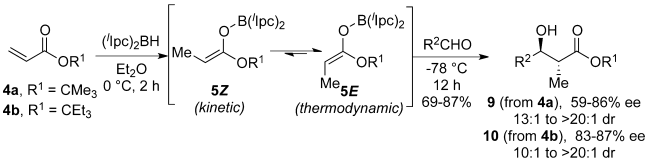
ABSTRACT



The (diisopinocampheyl)borane promoted reductive aldol reaction of acrylate esters 4 is described. Isomerization of the kinetically formed *Z*(O)-enolborinate 5*Z* to the thermodynamic *E*(O)-enolborinate 5*E* via 1,3-boratropic shifts, followed by treatment with representative achiral aldehydes, leads to *anti*-α-methyl-β-hydroxy esters 9 or 10 with excellent diastereo- (up to ≥20:1 dr) and enantioselectivity (up to 87% ee). The results of double asymmetric reactions of 5*E* with several chiral aldehydes are also presented.

The aldol reaction is a powerful method for the stereocontrolled construction of C−C bonds.[1,2] Although the formation of *syn*-aldols with exceptional stereoselectivity is well established, efficient means to access *anti*-aldols with synthetically useful diastereo- and enantioselectivity remains a significant challenge.[1] Noteworthy contributions toward the enantioselective *anti*-aldol reaction have emerged utilizing chiral auxiliary-based,[3] metal-promoted,[4] and organocatalytic procedures.[5] In 2005, Nishiyama reported an efficient Rh-catalyzed *anti*-selective reductive aldol reaction of acrylates predominantly with aromatic aldehydes.[6] To the best of our knowledge, this work represents the only boron-mediated reductive *anti*-aldol reaction originating from acyclic precursors.[7]

We recently reported the highly enantio- and diastereoselective reductive *syn*-aldol reaction[8] of *N*-acryloylmorpholine (**1**) with (diisopinocampheyl)borane [$(Ipc)_2BH$] as

[†] These authors contributed equally.

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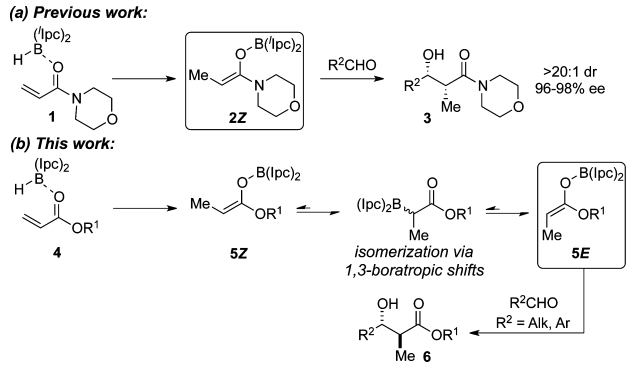
Scheme 1. Reductive Aldol Reactions of **1** and **4**

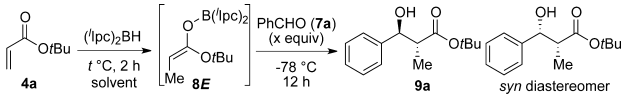


the reducing agent (Scheme 1a).[9] Isomerization of **2*Z*** to the corresponding *E*(O)-enolborinate did not occur evidently due to $A^{1,3}$ strain that develops between the morpholine unit and the enolborinate methyl substituent. Hence the reductive aldol reactions of *N*-acryloylmorpholine (**1**) were highly selective for the *syn*-aldol **3**.[9] We reasoned that replacing the morpholine amide of **1** with an ester unit in **4** would eliminate this interaction and that enolborinate **5*Z*** obtained from 1,4-reduction[8] of acrylate **4** would undergo a 1,3-boratropic shift to give the presumably more stable enolate **5*E***,[8c] thereby providing access to *anti*-aldols **6** (Scheme 1b).

We selected the inexpensive, commercially available *tert*-butyl acrylate **4a** as the initial substrate for this study.[4d,10]

The reductive aldol reaction of **4a**, with $(^{l}Ipc)_2BH$[11] and benzaldehyde (**7a**), was used to optimize reaction conditions (Table 1).

Table 1. Optimization of Reaction Parameters[a]



entry	solvent	t (°C)	x	yield[b]	dr (**9a**:syn)[c]	ee (**9a**)[d]
1	toluene	0	1.1	61	15:1	85
2	THF	0	1.1	92	11:1	76
3	CH_2Cl_2	0	1.1	84	11:1	80
4	Et_2O	0	1.1	76	16:1	85
5	toluene	0	0.85	81	16:1	85
6	toluene	−30	0.85	29	13:1	ND
7	**Et_2O**	**0**	**0.85**	**79**	**18:1**	**86**

[a] Reactions were performed by treating **4a** (0.275 mmol, 1.1 equiv) with $(^{l}Ipc)_2BH$ (0.25 mmol, 1 equiv) in solvent (1 mL) at the indicated temperature for 2 h, followed by addition of **7a** at −78 °C. After being stirred for 12 h at −78 °C, the reaction was subjected to oxidative hydrolysis (buffer/MeOH/H_2O_2) followed by product isolation. [b] Isolated yield of aldols following silica gel chromatography. [c] Diastereomer ratio (dr) determined by ^1H NMR analysis of crude reaction mixtures. [d] Enantiomeric excess (% ee) and absolute configuration were determined by using the Mosher ester analysis.[12]

Treatment of acrylate **4a** with $(^{l}Ipc)_2BH$ (1.1 equiv) in toluene at 0 °C for 2 h followed by addition of benzaldehyde at −78 °C provided a 15:1 mixture of **9a** and the *syn* diastereomer in 61% yield (entry 1). As indicated by the formation of *anti*-aldol **9a** as the major product, this initial experiment suggested that enolborinate **8*E*** is indeed the dominant species in this reaction. Reactions performed in toluene (entry 1) and Et_2O (entry 4) exhibited greater diastereo- and enantioselectivity than those in THF and CH_2Cl_2 (entries 2 and 3). Decreasing the amount of aldehyde to 0.85 equiv led to improved product yields (calculated based on aldehyde as the limiting reagent; entries 5, 7). Lowering the temperature of the hydroboration reaction had a dramatic effect on yield (entry 6), presumably due to incomplete reaction under these conditions. Ultimately, the best compromise between product yield and diastereo- and enantioselectivity was achieved by performing the hydroboration reaction at 0 °C in Et_2O (entry 7).

These conditions were applied to the reductive *anti*-aldol reactions of acrylate **4a** with a series of achiral aldehydes **7a**−**f** (Scheme 2). *anti*-α-Methyl-β-hydroxy *tert*-butyl esters **9a**−**f** were obtained in 69−87% yield with excellent diastereoselectivity (dr 13:1 to ≥20:1), and with moderate to good enantioselectivity (59−86% ee).[13] Interestingly, the sense of absolute stereochemical induction by the (diisopinocampheyl)boryl unit in these *anti*-selective aldol

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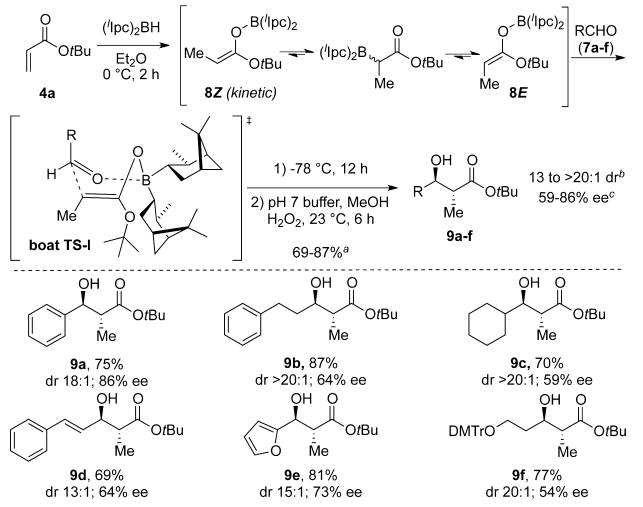
Scheme 2. Scope of the *Anti*-Reductive Aldol Reaction of **4a** with Achiral Aldehydes

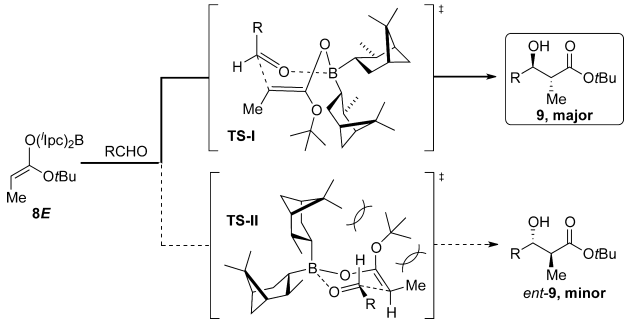


[a] Isolated yield after purification on silica gel. [b] Diastereomer ratio (dr) determined by ^{1}H NMR analysis of crude reaction mixture. [c] Enantiomeric excess (% ee) and absolute configuration determined by using the Mosher ester analysis.[12]

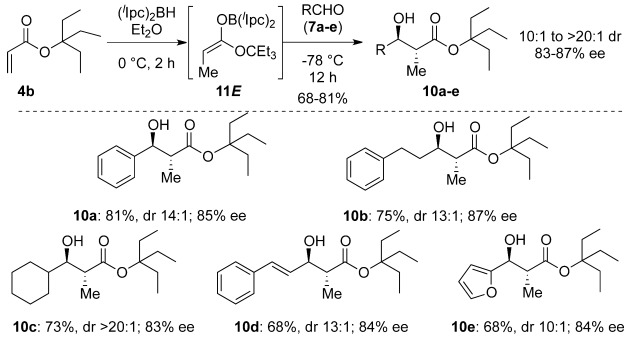
reactions is opposite to that determined in our studies of the *syn*-aldol reactions of acrylamide **1**.[9,14] This leads us to speculate that the major *anti*-aldol in each of the reactions summarized in Scheme 2 may possibly arise by way of the boat-like transition state **TS-I**. It is known that *anti*-selective boron-mediated aldol reactions proceed preferentially through boat-like transition states.[15] Indeed, ab initio calculations for the boron-mediated aldol reaction of ethyl methyl ketone with acetaldehyde showed not only that the lowest energy transition state for the *anti*-aldol reaction of the *E*-enolborinate is boat-like (analogous to **TS-I**) but also that a competitive chair-like and a second boat-like transition state are only 0.55 and 0.67 kcal/mmol higher in energy than the predominant boat-like transition structure.[15] Boat-like transition states also appear to dominate in the (diisopinocampheyl)borane-mediated aldol reactions of methyl ketones.[16] Thus, the impact of small structural changes in the substrates on the overall reaction enantioselectivity may not be surprising.

At present, we rationalize the good to excellent enantioselectivity data presented in Scheme 2 by a competition between the boat-like **TS-I** and the chairlike **TS-II** (Scheme 3). In an effort to improve the enantioselectivity of these reactions, especially with aliphatic aldehydes, we anticipated that increasing the size of the ester alkyl group might further destabilize chairlike **TS-II** relative to the major boat-like **TS-I**.

Scheme 3. Postulated TS for the Formation of *Anti*-Aldols **9**



Scheme 4. Reductive *Anti*-Aldol Reactions of Acrylate **4b**[a–c]



[a] Isolated yield after purification on silica gel. [b] Diastereomer ratio (dr) determined by ^{1}H NMR analysis of crude reaction mixture. [c] Enantiomeric excess (% ee) and absolute configuration determined using Mosher ester analysis.[12]

Based on this analysis we examined the more hindered acrylate **4b** as the substrate for the *anti*-selective aldol reactions.[17] Gratifyingly, markedly enhanced levels of enantioselectivity (83–87% ee) were obtained for *anti*-aldols **10a**–**e**, in comparison to the results summarized in Scheme 2 for aldols **9a**–**e**.

In order to investigate the potential for application of this methodology to the synthesis of more complex polyketide structures, we turned our attention to double asymmetric[19] reductive aldol reactions (Scheme 5).

(13) Ramachandran and Pratihar have previously reported the synthesis of *anti*-aldols with ≥98:2 dr and 50–66% ee from the Ipc_2-BOTf mediated aldol reactions of **4a** (Ramachandran, P. V.; Pratihar, D. *Org. Lett.* **2009**, *11*, 1467–1470). We repeated Ramachandran's procedure with $(^{\prime}Ipc)_2BH$ and cinnamaldehyde as the substrates and obtained **9b** with 15:1 dr and 58% ee. However, we also determined that the absolute stereochemistry of the *anti*-aldols described by Ramachandran have been misassigned, as Mosher ester analysis[12] clearly indicated that **9b** so obtained was identical to **9b** obtained by the reductive aldol reaction presented in Scheme 2.

(14) This conclusion derives from the fact that the absolute configuration of the hydroxyl groups of the *syn*-aldols deriving from **1** (see ref 9) and the *anti*-aldol reactions deriving from **4**, both using $(^{\prime}Ipc)_2BH$ as the reducing agent, are opposite.

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(17) Use of the substantially bulkier 2,6-di-*tert*-butyl-4-methylphenyl acrylate ester led to diminished reaction diastereoselectivity (see Supporting Information).

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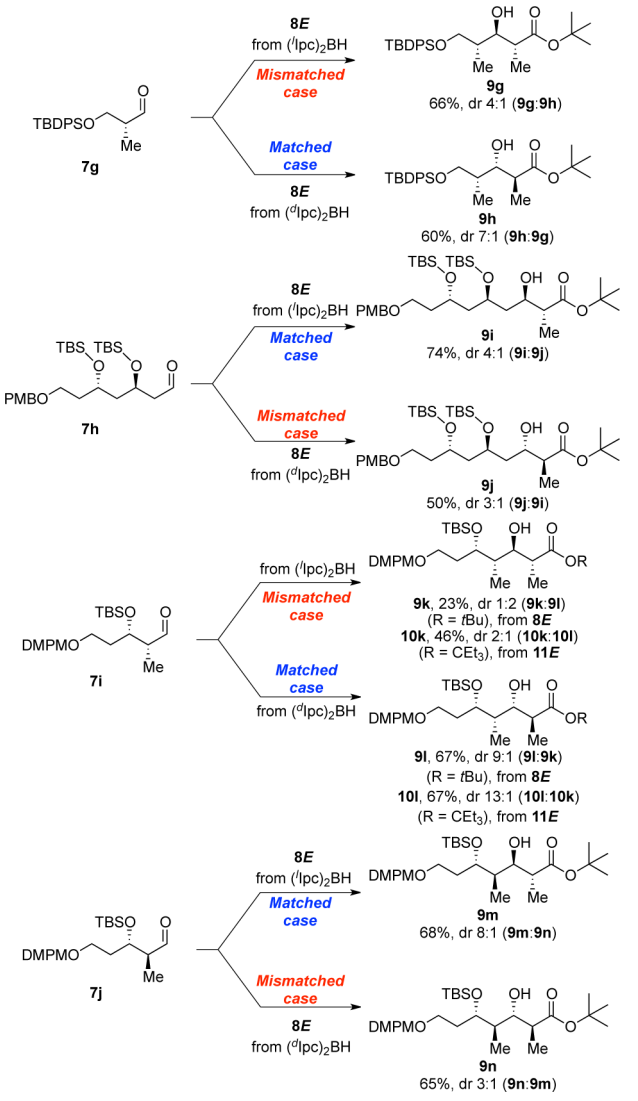
Scheme 5. Double Asymmetric Aldol Reactions of Chiral Aldehydes and the Chiral *E*-Enolborinate Generated from **4a,b**[a–d]



[a] Isolated yield of the indicated aldol products (major product in all cases except **9k** from **7i**) after purification by silica gel chromatography. [b] Diastereomer ratio (dr) determined by ^{1}H NMR analysis of crude reaction mixture. [c] Absolute and relative configuration of **9g**–**9n** determined using Mosher ester analysis[12] and the Rychnovsky acetonide method[18] (see Supporting Information). [d] Relative configuration of **10k, l** determined by analogy with **9k,l**.

Four chiral aldehydes **7g**–**j** were used in aldol reactions with the *E*(O)-enolborinates generated by reduction of **4a** with both (^{l}Ipc)$_2$BH and (^{d}Ipc)$_2$BH. Reductive aldol reactions of β-alkoxy aldehydes **7g, 7h**,[20] and **7j**[9] furnished *anti*-aldols **9g**–**j,m,n** (50–74% isolated yield of major aldol isomer) with moderate to good diastereoselectivity (dr 3:1 to 8:1, as determined by analysis of crude product mixtures). However, when the double stereodifferentiating reactions were carried out with *syn*-α-methyl-β-alkoxy aldehyde **7i**,[21] it was not possible to achieve the synthesis of *anti,anti* stereotriad **9k** with acceptable mismatched stereoselectivity (when acrylate **4a** (via **8*E***) was used as the starting material). However, when these reactions were performed by using the more sterically demanding acrylate **4b** (via enolborinate **11*E***), the *anti,anti* stereotriad **10k** was obtained with 2:1 dr in the mismatched case, and the diastereomer **10l** was obtained with 13:1 dr in the matched double aymmetric reaction using **11*E*** generated from the hydroboration of **4b** with (^{d}Ipc)$_2$BH. These results confirm the conclusion from Scheme 4 that the enolborinate **11*E*** generated from hindered acrylate **4b** exhibits a higher level of enantioselectivity than **8*E*** deriving from **4a** and that **11*E*** should be used in the most stereochemically demanding applications of this methodology.

In summary, we have developed an enantio- and diastereoselective synthesis of *anti*-α-methyl-β-hydroxy propionate esters from achiral and chiral aldehydes, *via* the hydroboration of *tert*-butyl acrylate **4a** or **4b** with (diisopinocampheyl)borane. This highly cost-effective[9] methodology takes advantage of the *in situ* formation of enolborinates **8*E*** (from **4a**) or **11*E*** (from **4b**) under neutral reaction conditions that is compatible with various protecting groups. As an example, the highly acid sensitive dimethoxytrityl -ODMTr ether **9f** (Scheme 2) is well tolerated under standard reaction conditions. Hydroboration of acrylate **4a** directly produces the (diisopinocampheyl)-enolborinate **8*Z*** which presumably isomerizes to **8*E*** via 1,3-boratropic shifts. The latter then undergoes aldol reactions with achiral aldehydes (dr 13:1 to >20:1; 59–86% ee, Scheme 2). Higher levels of enantioselectivity were reached when the reaction was performed with bulkier acrylate **4b** (Scheme 4). The study of double asymmetric reactions with chiral aldehydes demonstrated that this methodology can be applied to the synthesis of polyketide fragments of natural products (Scheme 5). Synthetic applications of this methodology are in progress and will be reported in due course.

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

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The authors declare no competing financial interest.