Tandem Reactions

DOI: 10.1002/ange.201000609

Asymmetric Tandem Wittig Rearrangement/Mannich Reactions**

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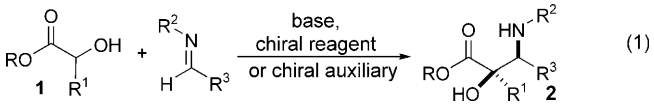
Asymmetric Mannich reactions provide a highly convergent and efficient method to access enantiomerically enriched β-amino acid derivatives.[1,2] In some instances these reactions have proven effective for the generation of biologically significant and synthetically useful β-amino acids that contain a quaternary stereocenter substituted with a nitrogen atom adjacent to the carbonyl group.[3] In principle, related asymmetric Mannich reactions of α-alkyl-α-hydroxy esters **1** could provide efficient access to α-alkyl-α-hydroxy-β-amino acids **2** [Eq. (1)], which have been used as intermediates in the synthesis of taxol analogues,[4] and are displayed in natural products such as leuhistin (a potent aminopeptidase inhibitor).[5] However, in practice, the transformation illustrated in Equation (1) is difficult to achieve, and the direct asymmetric synthesis of **2** by ester enolate Mannich reactions has not been described. This may be due to the fact that deprotonation of α-alkyl-α-hydroxy esters typically leads to formation of *E* and *Z* ester enolate mixtures,[6] which are transformed to stereoisomeric amino alcohol products in the Mannich reactions.



(1)

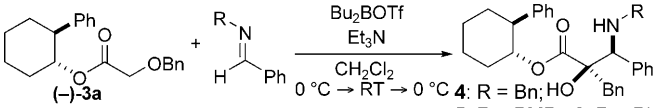
To avoid this problem, asymmetric Mannich reactions of chiral lactone enolates derived from enantiopure 1,3-dioxolan-4-ones have been developed.[7] Although these reactions do provide access to compounds related to **2**, formation of mixtures of *syn* and *anti* amino alcohol stereoisomers remains problematic. Several alternative approaches to the synthesis of α-alkyl-α-hydroxy-β-amino esters have also been explored, but they either lack the convergence of a Mannich-based strategy,[8] or suffer from limited stereocontrol.[9,10]

We recently reported a tandem asymmetric Wittig rearrangement/Aldol reaction between aldehydes and *O*-allyl or *O*-benzyl glycolate esters of *trans*-2-phenylcyclohexanol. The transformations proceed through *Z*-boron ester enolates, and afford *syn*-α-alkyl-α,β-dihydroxy esters with up to 95% *ee* and >20:1 *syn*:*anti* selectivity after cleavage of the 2-phenylcyclohexanol chiral auxiliary.[11] Based on these results, it seemed likely that a related Wittig rearrangement/Mannich reaction could provide an efficient means of preparing α-alkyl-α-hydroxy-β-amino esters with a high degree of stereocontrol. Herein we describe our preliminary studies in this area, which have led to the first asymmetric Mannich reactions of ester enolates that afford both *syn*- and *anti*-α-alkyl-α-hydroxy-β-amino esters with high d.r. and *ee*. These are also the first examples of asymmetric Mannich reactions that proceed through tetrasubstituted enolboronate intermediates.

In our initial efforts to effect tandem asymmetric Wittig rearrangement/Mannich reactions we examined the coupling of (−)-**3a** with several imines derived from benzaldehyde. As shown in Table 1, the nature of the N-substituents had a large effect on reactivity and selectivity. Imines bearing strongly electron-withdrawing N-substituents such as tosyl or phosphoryl failed to undergo the Mannich reaction with the boron enolate generated after the Wittig rearrangement (Table 1, entries 4 and 5). Improved reactivity was observed with *N*-aryl imines, but diastereoselectivity was modest (entries 2 and 3). However, use of the *N*-benzylimine provided satisfactory results (entry 1).[12]

As shown in Table 2, tandem asymmetric Wittig rearrangement/Mannich reactions between *O*-alkyl-2-phenycyclohexyl glyclolate esters (−)-**3a**,**b** and a range of *N*-benzylimines derived from aromatic aldehydes proceed in good yield and with excellent stereoselectivity. In all cases products were formed with at least 20:1 d.r., and enantiomerically enriched aminodiols were obtained in 90–96% *ee*

Table 1: Imine substituent effects.[a]



Entry	R[b]	Yield [%][c]	d.r.[d]	*ee* after auxiliary cleavage[e]
1	Bn	71	>20:1	96%
2	PMP	85	4:1	58%
3	Ph	71	11:1	83%
4	Ts	0[f]	–	–
5	P(O)Ph$_2$	0[f]	–	–

[a] Conditions: 1.0 equiv (−)-**3a**, 3.2 equiv Bu_2BOTf, 4.0 equiv Et_3N, CH_2Cl_2 (0.1 M), 0°C, 5 min, warm to RT for 15 min, cool to 0°C, add imine. [b] Bn = benzyl, PMP = *p*-methoxyphenyl, Ts = *p*-toluenesulfonyl. [c] Yield of isolated product (average of two or more runs). [d] Diastereomeric ratio of isolated material (determined by ^{1}H NMR analysis). The d.r. value of the crude product could not be determined because of signal overlap with boron-containing by-products. [e] The enantiomeric excess was determined by HPLC or Mosher ester analysis after transesterification to the methyl ester or reduction to the aminodiol. [f] The imine failed to undergo Mannich reaction.

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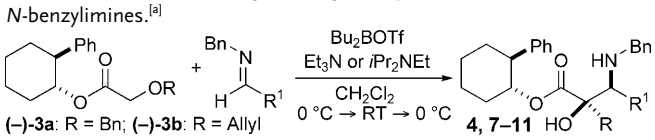
[**] We acknowledge the ACS Petroleum Research Fund for financial support of this work. Additional funding was provided by GlaxoSmithKline, Amgen, and Eli Lilly.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201000609.

Table 2: Asymmetric Wittig-rearrangement/Mannich reactions with *N*-benzylimines.[a]

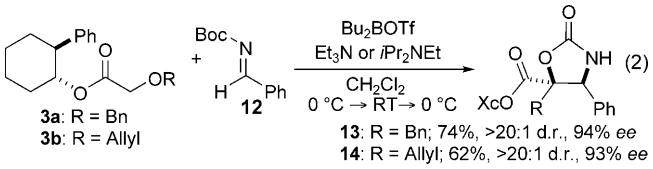


Entry	R	R^1	Product	Yield [%][b]	d.r.[c]	*ee* after auxiliary cleavage[d]
1	Bn	Ph	**4**	71	>20:1	96%
2	Bn	PMP	**7**	85	20:1	90%
3	Bn	2-furyl	**8**	70	20:1	90%
4	Bn	Cy	**9**	54	>20:1	93%
5	Allyl	Ph	**10**	63	>20:1	94%
6	Allyl	*p*-F-C_6H_4	**11**	69	>20:1	94%

[a] Conditions: 1.0 equiv (−)-**3a** or (−)-**3b**, 3.2 equiv Bu_2BOTf, 4.0 equiv Et_3N (R = Bn) or 4.0 equiv iPr_2NEt (R = allyl), CH_2Cl_2 (0.1 M), 0 °C, 5 min, warm to RT for 15–20 min, cool to 0 °C, add imine. [b] Yield of isolated product (average of two or more runs). [c] Diastereomeric ratio of isolated material (determined by ^1H NMR analysis). The d.r. value of the crude product could not be determined because of signal overlap with boron-containing by-products. [d] The enantiomeric excess was determined by HPLC or Mosher ester analysis after transesterification to the methyl ester or reduction to the aminodiol.

after reduction with $LiAlH_4$. The *N*-benzylimine prepared from cyclohexane carboxaldehyde was also transformed with high stereoselectivity, but in slightly lower yield (Table 2, entry 4). However, *N*-benzylimines derived from unbranched aliphatic aldehydes failed to undergo the Mannich reaction.

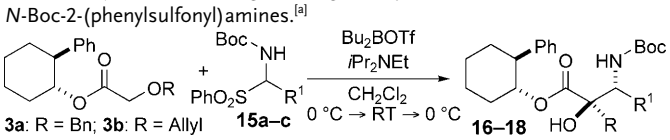
Although imines bearing strong electron-withdrawing groups failed to undergo Mannich reaction (Table 1, entries 4 and 5), use of *N*-Boc imine **12** as an electrophile in the tandem reaction with **3a** generated isoxazolidin-2-one **13** (derived from the corresponding *syn*-amino alcohol) in 74% yield and >20:1 d.r. (94% *ee* after reduction) [Eq. (2)]. A similar result was obtained for the coupling of **12** with *O*-allyl glycolate ester (−)-**3b** to give **14**.



Reactions of *N*-Boc imines or enamides derived from aliphatic aldehydes failed to afford the desired amino alcohol products. However, we were pleased to discover that transformations of *N*-Boc-2-(phenylsulfonyl)amines **15a–c** bearing either aliphatic or aromatic R^1 groups proceeded in moderate to good yields with excellent stereocontrol (Table 3). In contrast to reactions of imine electrophiles, which afforded *syn*-amino alcohols (or oxazolidinones), use of **15** led to the formation of *anti*-amino alcohol products **16–18**.

Cleavage of the chiral auxiliary from the amino alcohol products was accomplished either through methanolysis or reduction. For example, treatment of **4** with NaOMe/MeOH provided methyl ester **19** in 62% yield [Eq. (3)]. Alternatively, reduction of **11** with $LiAlH_4$ generated amino-diol **20** in 97% yield [Eq. (4)]. Selective reduction of cyclic carbamate

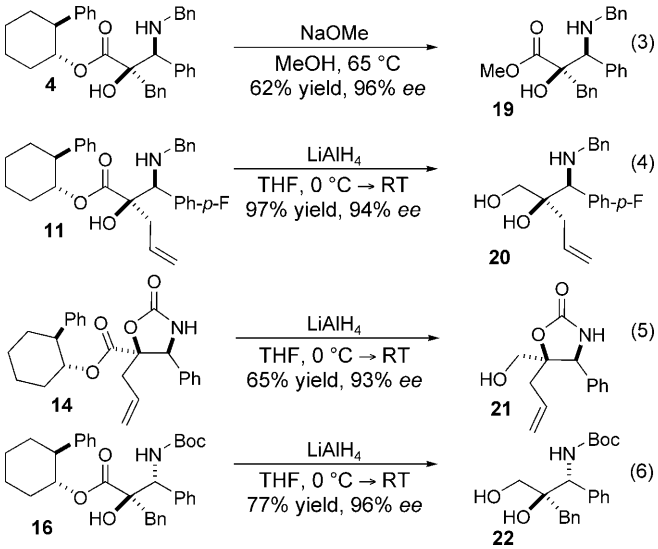
Table 3: Asymmetric Wittig-rearrangement/Mannich reactions with *N*-Boc-2-(phenylsulfonyl)amines.[a]



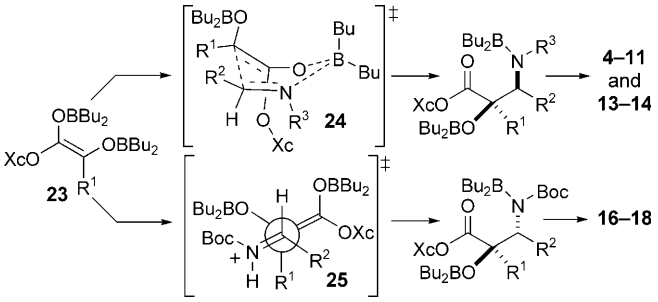
Entry	R	R^1	Product	Yield [%][b]	d.r.[c]	*ee* after auxiliary cleavage[d]
1	Bn	Ph (**15a**)	**16**	58	>20:1	96%
2	Bn	*i*Bu (**15b**)	**17**	75	20:1	91%
3	Allyl	Cy (**15c**)	**18**	60	20:1	90%

[a] Conditions: 1.0 equiv (−)-**3a** or (−)-**3b**, 3.2 equiv Bu_2BOTf, 4.0 equiv iPr_2NEt, CH_2Cl_2 (0.1 M), 0 °C, 5 min, warm to RT for 20 min, cool to 0 °C, add **15**. [b] Yield of isolated products (average of two or more runs). [c] Diastereomeric ratio of isolated material (determined by ^1H NMR analysis). The d.r. value of the crude product could not be determined because of signal overlap with boron-containing by-products. [d] The enantiomeric excess was determined by HPLC or Mosher ester analysis after reduction to the corresponding aminodiol.

14 and Boc-protected amino alcohol **16** also proceeded smoothly [Eqs. (5) and (6)].



The mechanism of the tandem reactions likely occurs through an initial ester enolate Wittig-rearrangement followed by a second enolization to yield **23**.[11,13,14] The relative stereochemical configuration of the amino-alcohol product is set during the subsequent Mannich reaction, and is dependent on the nature of the electrophile. In reactions involving *N*-benzyl- or *N*-Boc-imine electrophiles the Mannich reactions occur through boat-like transition state **24** to afford the *syn*-amino alcohol products **4–11** and oxazolidin-2-ones **13** and **14**.[15] In contrast, reactions of *N*-Boc-2-(phenylsulfonyl)-amines **15a–c** likely involve intermediate *N*-Boc iminium ions. The Mannich reactions between **23** and the electrophilic iminium ions occur through open transition states **25** in which R^2 is positioned away from the two bulky boron groups. This gives rise to the observed *anti*-amino alcohol products **16–18** (Scheme 1).



Scheme 1. Stereochemical hypothesis.

In conclusion, we have developed a new, highly stereoselective synthesis of enantiomerically enriched α-alkyl-α-hydroxy-β-amino esters through tandem asymmetric Wittig rearrangement/Mannich reactions. This method provides access to a range of *syn*- and *anti*-amino alcohol products from simple starting materials, and further illustrates the utility of Wittig rearrangements for stereoselective generation of enolates derived from α-alkyl-α-hydroxy esters.

Experimental Section

Representative procedure for tandem Wittig rearrangement/Mannich reactions: A flame-dried flask was cooled under a stream of nitrogen and charged with a 1M solution of dibutylboron triflate in dichloromethane (0.56 mL, 0.56 mmol). The pale yellow solution was cooled to 0°C, and triethylamine (62 μL, 0.45 mmol) was added dropwise to afford a colorless solution. A solution of ester **3a** (47 mg, 0.14 mmol) in CH_2Cl_2 (0.14 mL) was then added dropwise, and the reaction mixture was warmed to room temperature, stirred for 15 min, and then cooled to 0°C. A solution of *N*-(benzylidene)benzylamine (42 mg, 0.22 mmol) in CH_2Cl_2 (0.22 mL) was added dropwise, and the reaction mixture was warmed to room temperature and stirred for 3 h. The reaction vessel was then opened to air, and pH 7 buffer (1.4 mL), and methanol (2.8 mL) were added. The resulting mixture was cooled to 0°C, 30% aqueous H_2O_2 (2.8 mL) was added slowly, and the reaction mixture was warmed to room temperature and stirred for 1 h. The mixture was diluted with ether (14 mL) and water (7 mL), then was transferred to a separatory funnel. The layers were separated, and the organic layer was washed with a saturated aqueous solution of $FeSO_4$ (4×7 mL) until a red-orange aqueous phase no longer persisted in order to quench any remaining peroxide. *Caution! This procedure is exothermic. The $FeSO_4$ solution should be added through a glass pipette SLOWLY DROPWISE.* The organic layer was then washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel to afford 54 mg (72%) of (−)-(1*R*,2*S*,2′*R*,3′*S*)-2-phenylcyclohexyl-2′-benzyl-3′-benzylamino-2′-hydroxy-3′-phenylpropanoate (**4**) as a white foam.

Received: February 1, 2010
Published online: March 15, 2010

Keywords: asymmetric synthesis · imines · Mannich reaction · rearrangements · stereoselectivity

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