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L-Valinol and L-phenylalaninol-derived 2-imidazolidinones as chiral auxiliaries in asymmetric aldol reactions

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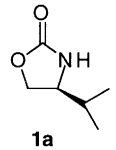
Abstract

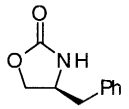
The chiral *N*-propionyl-2-imidazolidinones were synthesized in three steps from L-valinol and L-phenylalaninol and the aldol reaction of their boron enolate with aldehydes proceeded with high diastereoselectivity.

Keywords: chiral *N*-propionyl-2-imidazolidinones; asymmetric aldol reaction; L-valinol; L-phenylalaninol.

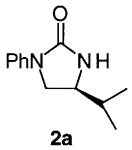
The asymmetric aldol reaction has become a major tool for the asymmetric C–C bond construction.[1] Among the developments of highly stereoregulated aldol reactions, the use of the Evans' α-amino acid-derived oxazolidinones **1** as the chiral auxiliaries is one of the most straightforward and efficient strategies in organic synthesis.[2] In connection with our effort to prepare various 2-imidazolidinones,[3] we have previously developed interesting 2-imidazolidinones **2a** and **2b** from L-valine and L-phenylalanine, which combine structural features of similar oxazolidinones **1a** and **1b**.[3a] This letter reports the utility of **2** as the chiral auxiliaries in highly diastereoselective aldol reactions, which is proven to be efficient for boron enolates.



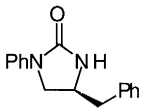
1a



1b



2a



2b

Evans' 2-oxazolidinone methodology in aldol reactions has some limitations suffering from nucleophilic ring opening of the oxazolidinone ring in the sterically congested aldol adduct such as α,α-disubstituted β-hydroxycabonyl units to lead to the corresponding oxazinedione.[4] The 2-imidazolidinone, (4*R*,5*S*)-1,5-dimethyl-4-phenyl-2-imidazolidinone, was reported to be a successful chiral auxiliary avoiding such a nucleophilic ring opening in aldol reactions.[5] Therefore, we expected the related 2-imidazolidinone **2** to have the similar resistance to nucleophilic ring opening.[6] In addition, the compound **2**, which is closely related to **1**, has been used with the hope that the phenyl chromophore present in the 2-imidazolidinone ring could facilitate reaction monitoring and product isolation.

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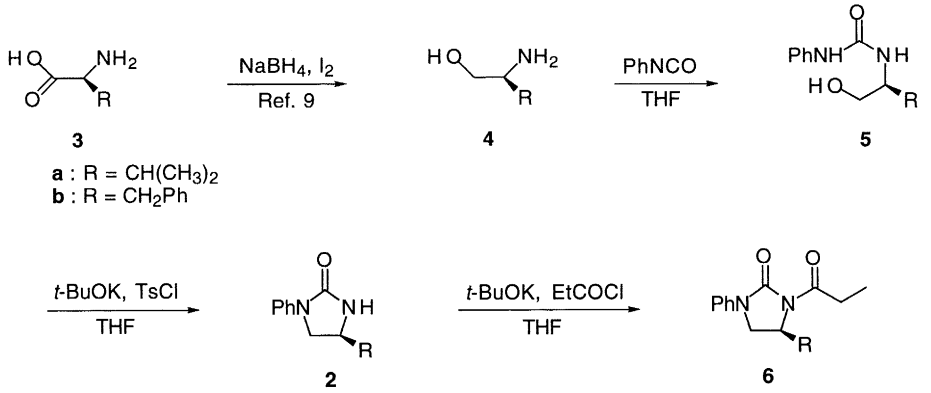
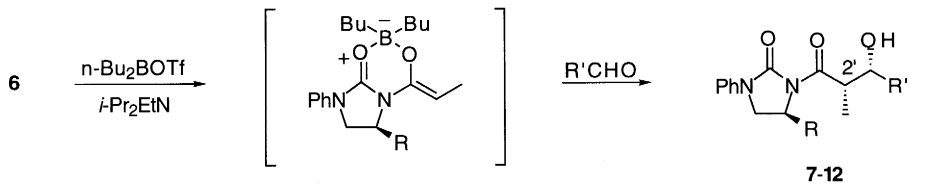
In general, 2-imidazolidinones are prepared from the cyclization of the corresponding 1,2-diamines with phosgene[7] or its derivatives.[8] This reaction, however, causes the side reaction such as polymerization, and an access to an appropriate range of optically pure diamines is restricted. As a result, the diversity of the synthetically useful 2-imidazolidinones has remained severely limited.



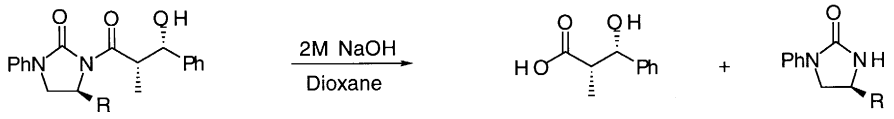
Scheme 1.

However, the 2-imidazolidinones **2a** (mp: 80–82°C, $[\alpha]_D^{18}$ −26.9 (c 0.85, $CHCl_3$)) and **2b** (mp: 115–117°C, $[\alpha]_D^{18}$ −43.3 (c 0.55, $CHCl_3$)) were easily prepared in two simple steps (addition to isocyanate, and cyclization)[3a] starting from readily available L-valinol and L-phenylalaninol, respectively (Scheme 1). We chose the *N*-propionyl derivatives for examination of the auxiliary in aldol reactions. Thus, acylation of 2-imidazolidinones **2** with 4.0 equiv. of propionyl chloride under 2.0 equiv. of *t*-BuOK at room temperature furnished the *N*-propionyl-2-imidazolidinones in high yield (**6a**: 89%, $[\alpha]_D^{18}$ +35.1 (c 1.2, $CHCl_3$), **6b**: 91%, $[\alpha]_D^{18}$ +37.7 (c 1.9, $CHCl_3$)).[10] Aldol reaction of **6** with a representative series of aldehydes (1.2 equiv.) was initially examined. The *Z*-enolate of **6** was generated upon treatment with *n*-Bu_2BOTf (1.1 equiv.) followed by diisopropylethylamine (1.2 equiv.) in CH_2Cl_2 in an ice bath. Treatment of the enolate with the appropriate aldehydes provided the desired aldol adducts **7**–**12** in good yields (Scheme 2).[11] The *syn*/*anti* relative stereochemistry of aldol adducts may be assigned on the basis of ^1H NMR vicinal coupling constants.[12] For the compounds **7**–**12**, the $J(2',3')$ values were in the range of 2.1–3.3 Hz, consistent with the *syn* stereochemistry. The absolute stereochemistry of the aldol product was confirmed by NaOH hydrolysis of **10** to furnish the enantiomer of the known carboxylic acid **13** along with the chiral auxiliary which could be recycled (Scheme 3).[2d] The results summarized in Table 1 illustrate the excellent diastereofacial selection in these reactions. This was the expected stereochemistry and shows that **2** gives the same aldol product as the corresponding Evans' *N*-acyl oxazolidinone. From the observed diastereoselectivities, we propose that this reaction should be complete via a kinetic *Z*-boron enolate generation and the similar coordinated transition state model between boron enolate and aldehyde as in Evans' system.[2,13]



Scheme 2.

In conclusion, we have successfully shown that the reagent **2a** and **2b** are highly diastereoselective chiral enolate equivalents for the aldol reactions. Also, we have developed the direct synthetic route



10 13 2

Scheme 3.

Table 1
Aldol reaction of *N*-propionyl-2-imidazolidinones **6**

entry	R	R'	product	*syn:anti* [a]	yield (%) [b]	de [c]	$[\alpha]_D^{18}$ (c) [d]
1	$CH(CH_3)_2$	Ph	**7**	>98:2	78 [e]	>99	+24.5° (1.2)
2	$CH(CH_3)_2$	CH_3	**8**	>98:2	58	>99	+25.4° (0.98)
3	$CH(CH_3)_2$	$CH(CH_3)_2$	**9**	>98:2	68	>99	+7.7° (0.7)
4	CH_2Ph	Ph	**10**	>98:2	85	>99	+38.0° (3.8)
5	CH_2Ph	CH_3	**11**	>98:2	53	>99	+26.3° (1.2)
6	CH_2Ph	$CH(CH_3)_2$	**12**	>98:2	67	>99	+21.0° (1.2)

[a]Ratios determined by ^1H NMR of the reaction crudes.
[b]Isolated yields by column chromatography.
[c]Determined by ^1H NMR and HPLC after purification.
[d]Concentration (g/100 mL) in $CHCl_3$.
[e]Mp: 145-147 °C.

of *N*-acyl-2-imidazolidinones in three steps from chiral 1,2-aminoalcohols.[14] The extension to other asymmetric reaction will be reported in due course.[15]

Acknowledgements

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10. General procedure for the preparation of the *N*-propionyl-2-imidazolidinones **6**: To a stirred solution 2-imidazolidinone **2** (0.5 mmol, 100 M%) in THF (7 mL) under nitrogen at 0°C was added *t*-BuOK (0.11 g, 1.0 mmol, 200 M%) and propionyl chloride (0.21 mL, 2.0 mmol, 400 M%) dropwise for 5 min with a syringe. The reaction mixture was stirred for 10 min, added to water (20 mL), and extracted with ether (30 mL×2). The organic layer was dried, filtered, evaporated, and purified by flash column chromatography to give **6**. Compound **6a**: IR ($CDCl_3$, cm^{-1}) 1687, 1587; ^{1}H NMR (300 MHz, $CDCl_3$) 7.56–7.15 (5H, m), 4.45–4.40 (1H, m), 3.89 (1H, t, *J*=9.3), 3.55 (1H, dd, *J*=9.3, 2.3), 3.13–2.89 (2H, m), 2.43 (1H, m, *J*=6.8, 3.9), 1.19 (3H, t, *J*=7.2). 0.96 (3H, d, *J*=6.9), 0.84 (3H, d, *J*=6.9); ^{13}C NMR (75 MHz, $CDCl_3$) 174.6, 153.1, 138.7, 129.0, 124.4, 119.1, 54.7, 43.2, 29.6, 28.9, 18.1, 14.6, 8.9. Compound **6b**: ^{1}H NMR (300 MHz, $CDCl_3$) 7.41–7.10 (10H, m), 4.72–4.64 (1H, m), 3.84 (1H, t, *J*=9.3), 3.53 (1H, dd, *J*=9.3, 1.8), 3.30 (1H, dd, *J*=13.2, 3.3). 3.13–2.94 (2H, m), 2.77 (1H, dd, *J*=13.2, 9.3), 1.19 (3H, t, *J*=7.2); ^{13}C NMR (75 MHz, $CDCl_3$) 174.8, 152.8, 139.0, 136.4, 129.7, 129.2, 129.0, 127.3, 124.7, 119.5, 51.9, 46.7, 38.9, 29.8, 9.0.
11. General procedure of the aldol reactions: To a stirred solution of the *N*-acyl-2-imidazolidinone **6** (0.3 mmol, 100 M%) in dichloromethane (4 mL) under nitrogen at 0°C was added dibutylboron triflate (0.33 mL, 0.33 mmol, 110 M%) and diisopropylethylamine (0.36 mmol, 120 M%) dropwise for 5 min with a syringe. The reaction mixture was stirred for 60 min, cooled to −78°C, and the appropriate aldehyde (0.36 mmol, 120 M%) was added. After 60 min at −78°C, the reaction temperature was allowed to rise to 0°C and maintained at this temperature for 60 min. The reaction mixture was quenched with aqueous pH 7 phosphate buffer (2 mL), MeOH (3 mL), and 28% H_2O_2 (2 mL). After 60 min at 0°C methanol was removed. The aqueous layer was extracted with dichloromethane (30 mL) and the organic layer was washed with water, dried, and evaporated. The crude product was purified by flash chromatography to give **7**–**12**. Compound **7**: IR ($CDCl_3$, cm^{-1}) 3485, 1728, 1671; ^{1}H NMR (300 MHz, $CDCl_3$) 7.54–7.15 (10H, m), 5.13 (1H, d, *J*=3.3), 4.44–4.39 (1H, m), 4.27 (1H, dq, *J*=7.2, 3.3), 3.83 (1H, t, *J*=9.3), 3.53 (1H, dd, *J*=9.3, 2.7), 2.39 (1H, m, *J*=6.9, 3.9), 1.21 (3H, d, *J*=6.9), 0.96 (3H, d, *J*=6.9), 0.85 (3H, d, *J*=7.2); ^{13}C NMR (75 MHz, $CDCl_3$) 178.0, 152.4, 141.5, 138.4, 129.1, 128.1, 127.1, 126.1, 124.7, 119.4, 73.3, 54.7, 44.4, 43.2, 29.0, 18.0, 14.7, 11.1. Compound **8**: IR ($CDCl_3$, cm^{-1}) 3501, 1732, 1677; ^{1}H NMR (300 MHz, $CDCl_3$) 7.56–7.15 (5H, m), 4.51–4.46 (1H, m), 4.18 (1H, dq, *J*=6.6, 2.4), 3.92 (1H, t, *J*=9.3), 3.90 (1H, dq, *J*=7.2, 2.4), 3.57 (1H, dd, *J*=9.3, 2.7), 2.45–2.35 (1H, m), 1.30 (3H, d, *J*=7.2), 1.18 (3H, d, *J*=6.6), 0.97 (3H, d, *J*=6.9), 0.86 (3H, d, *J*=6.9); ^{13}C NMR (75 MHz, $CDCl_3$) 178.4, 152.6, 138.4, 129.1, 124.7, 119.4, 67.4, 54.5, 43.2, 43.1, 28.9, 19.4, 18.0, 14.6, 10.8. Compound **9**: IR ($CDCl_3$, cm^{-1}) 3509, 1731, 1664; ^{1}H NMR (300 MHz, $CDCl_3$) 7.55–7.15 (5H, m), 4.50–4.45 (1H, m), 4.15 (1H, dq, *J*=6.6, 2.1), 3.93 (1H, t, *J*=9.3), 3.58–3.51 (1H+1H, m), 2.40 (1H, m, *J*=7.2, 3.9), 1.73 (1H, m, *J*=6.9, 2.1), 1.28 (3H, d, *J*=7.2), 1.03 (3H, d, *J*=6.6), 0.97 (3H, d, *J*=7.2), 0.89 (3H, d, *J*=6.9), 0.86 (3H, d, *J*=6.9); ^{13}C NMR (75 MHz, $CDCl_3$) 179.0, 152.4, 138.4, 129.1, 124.7, 119.5, 76.6, 54.5, 43.1, 39.4, 30.5, 28.8, 19.5, 18.9, 18.0, 14.6, 10.6. Compound **10**: IR ($CDCl_3$, cm^{-1}) 3483, 1732, 1676; ^{1}H NMR (300 MHz, $CDCl_3$) 7.42–7.14 (15H, m), 5.14 (1H, d, *J*=3.3), 4.70–4.63 (1H, m), 4.25 (1H, dq, *J*=7.2, 3.3), 3.78 (1H, t, *J*=9.0), 3.51 (1H, dd, *J*=9.6, 1.8), 3.24 (1H, dd, *J*=13.2, 3.0), 2.80 (1H, dd, *J*=13.2, 9.0), 1.24 (3H, d, *J*=7.2); ^{13}C NMR (75 MHz, $CDCl_3$) 177.6, 151.9, 141.5, 138.4, 135.8, 129.4, 129.0, 128.8, 127.1, 126.1, 124.8, 119.5, 73.7, 51.6, 46.4, 44.5, 38.5, 10.8. Compound **11**: IR ($CDCl_3$, cm^{-1}) 3502, 1731, 1675; ^{1}H NMR (300 MHz, $CDCl_3$) 7.39–7.15 (10H, m), 4.77–4.70 (1H, m), 4.19 (1H, dq, *J*=6.3, 2.4), 3.94–3.86 (1H+1H, m), 3.56 (1H, dd, *J*=9.6, 2.1), 3.25 (1H, dd, *J*=13.2, 3.3), 2.81 (1H, dd, *J*=13.2, 9.0), 1.32 (3H, d, *J*=7.2), 1.20 (3H, d, *J*=6.3); ^{13}C NMR (75 MHz, $CDCl_3$) 177.9, 152.2, 138.4, 135.8, 129.4, 129.0, 128.8, 127.2, 124.8, 119.6, 67.8, 51.5, 46.4, 43.2, 38.5, 19.5, 10.6. Compound **12**: IR ($CDCl_3$, cm^{-1}) 3500, 1732, 1670; ^{1}H NMR (300 MHz, $CDCl_3$) 7.39–7.12 (10H, m), 4.76–4.69 (1H, m), 4.12 (1H, dq, *J*=7.2, 2.1), 3.89 (1H, t, *J*=8.4), 3.57–3.53 (1H+1H, m), 3.23 (1H, dd, *J*=13.5, 3.3), 2.82 (1H, dd, *J*=13.5, 9.0), 1.75 (1H, m, *J*=6.6, 2.1), 1.30 (3H, d, *J*=7.2), 1.04 (3H, d, *J*=6.6), 0.89 (3H, d, *J*=6.6); ^{13}C NMR (75 MHz, $CDCl_3$) 178.7, 151.9, 138.4, 135.8, 129.4, 129.0, 128.8, 127.2, 124.7, 119.6, 76.8, 51.5, 46.4, 39.5, 38.5, 30.6, 19.5, 18.9, 10.2.
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15. For the use of **2** as a chiral auxiliary so far; see Refs. 6 and 14.