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Diastereoselective alkylation of chiral 2-imidazolidinone glycolates: asymmetric synthesis of α-hydroxy carboxylic acids

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Abstract—Sodium enolates of chiral 2-imidazolidinone glycolates reacted with alkyl halides to produce α-alkylated products with high diastereoselectivities, which were readily removed by simple alkaline hydrolysis and were converted to the protected α-hydroxy carboxylic acids. The new stereogenic center was assigned the (*R*)-configuration by comparison with known compounds.

1. Introduction

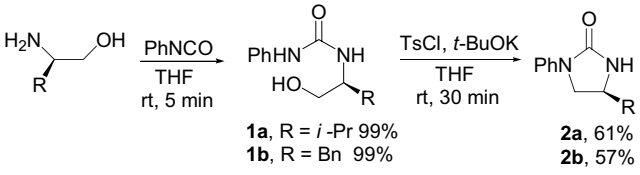
Chiral auxiliary-derived asymmetric alkylations have been studied extensively and are now important and general methods for asymmetric carbon–carbon bond formation.[1] The enantioselective synthesis of chiral α-hydroxy acids has been extensively studied because of their importance as synthetic building blocks.[2] Various methods including asymmetric dihydroxylations,[3] asymmetric enolate hydroxylation,[4] and asymmetric glycolate alkylation[5] have been used to prepare α-hydroxy acids.

Asymmetric glycolate alkylation is a straightforward approach because of the relative ease of changing the alkyl group and the protecting group of the glycolate hydroxyl. Chiral auxiliaries attached to the carbonyl group, the hydroxyl group, or to both have been used for the diastereoselective alkylation of chiral glycolates. The most notable of these reports employed a *trans*-2,5-disubstituted pyrrolidine,[5e] menthone,[5g] or camphorsulfonamide,[5i] D-fructose,[5l,m] or Evans's oxazolidinone[5k] as chiral auxiliaries. In particular, metal enolates of *N*-acyl oxazolidinones, as developed by Evans, are highly effective at controlling facial selectivity for the preparation of homochiral α-substituted carboxylic acids and their derivatives.[6] However, this auxiliary undergoes troublesome endocyclic cleavage rather than the required exocyclic cleavage during its removal of the auxiliary by alkaline hydrolysis.[7] Moreover, to suppress the undesired endocyclic cleavage, the hazardous agent lithium hydroperoxide has been used instead of the hydroxide.[7a,b]

During our efforts to prepare various 2-imidazolidinones, we previously developed **2a** and **2b** from L-valine and L-phenylalanine, respectively,[8,9] which contain the structural features of similar oxazolidinones. We now report on the utility and generality of the asymmetric alkylation of metal enolates of 2-imidazolidinone glycolates with high stereoselectivity for the preparation of α-hydroxy carboxylic acids as oxazolidinone glycolates. The auxiliaries are easily removed by simple alkaline hydrolysis (NaOH), without the need for lithium hydroperoxide to suppress the endocyclic cleavage.

2. Results and discussion

The 2-imidazolidinones **2a** and **2b** were easily prepared in two simple steps (addition to isocyanate, and cyclization)[8a] starting from readily available L-valinol and L-phenylalaninol, respectively (Scheme 1). The acylation of 2-imidazolidinones **2** with 1.0 equiv of benzyloxyacetyl



Scheme 1.

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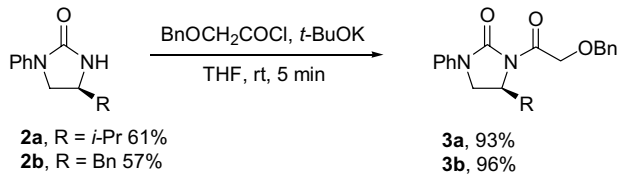
chloride in the presence of 1.0 equiv of *n*-BuLi at 0 °C furnished the required *N*-benzyloxyacetyl-2-imidazolidinones in high yield (Scheme 2) {**3a**: 93%, $[\alpha]_D^{20} = +17.0$ (*c* 4.16, $CHCl_3$), **3b**: 96%, $[\alpha]_D^{20} = +39.0$ (*c* 4.45, $CHCl_3$)}.[10] In initial experiments, the deprotonation of **3a** at −78 °C with LiHMDS and the subsequent alkylation of the lithium enolate with benzyl bromide did not provide the required product **4a** (Table 1, entry 1), instead deacylation occurred primarily. In nearly all enolate alkylations, the use of HMPA as an additive is believed to increase reactivity appreciably at the expense of selectivity.[5j,11] To improve the reactivity of **3a** with LiHMDS, 5% HMPA was added, and as expected the yield of **4a** increased by 72%, but HPLC analysis showed a poor diastereoselectivity of 56% de (Table 1, entry 2). with 1.5 equiv of LDA, the yield of **4a** was increased by 83% with high diastereoselectivity of 96% de (Table 1, entry 3). Another base NaHMDS provided slightly higher yields and proved more reactive than LiHMDS or LDA (Table 1, entry 5). The addition, of LDA or NaHMDS in 5% HMPA reduced the de values, and slightly lowered yields. In most cases, reaction rates were sluggish at −78 °C and warming to −40 to −45 °C appeared optimal in most cases.

The alkylations of the sodium enolates derived from **3a** and **3b** with 1.5 equiv of NaHMDS were performed with alkyl halide (benzyl bromide, allyl iodide, and methyl iodide); results are summarized in Table 2.[12] α-Alkylated products with moderate to excellent diastereoselectivity were formed in good yields. The ratios of diastereomers were determined by HPLC. Benzyl bromide and allyl bromide reacted with these enolates to give the respective alkylated products in excellent yields (entries 1, 2, 4, and 5) and high de values. Alkylation with methyl iodide, as expected, was slow and mainly afforded the deacylation product and small amounts of the required product (10–18%). The addition of HMPA increased the alkylation yield from 10–18% to 72–75% and the diastereoselective level was found to be lower (entries 3 and 6). It was of interest to find that the valine-derived enolates were slightly more reactive and tended to give somewhat better yields than the phenylalanine derived auxiliaries (entries 1–3 vs entries 4–6).



Scheme 2.

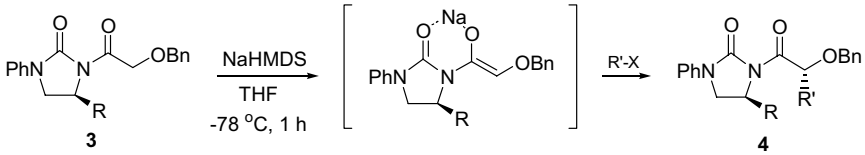
The alkylation products (**4a**, **4b**, and **4c**) were hydrolyzed by 2 M aqueous NaOH[13] in dioxane to furnish

Table 1. Diastereoselective benzylations of 2-phenyliminooxazolidine glycolate **3a**

Entry	Base (equiv)	Solvent (additive)	Time (h)[a]	Yield (%)[b]	dr[d]
1	LiHMDS	THF	24	0[c]	—
2	LiHMDS	THF (5% HMPA)	4	72	78:22
3	LDA	THF	8	83	98:2
4	LDA	THF (5% HMPA)	4	79	89:11
5	NaHMDS	THF	2	87	98:2
6	NaHMDS	THF (5% HMPA)	2	78	81:19

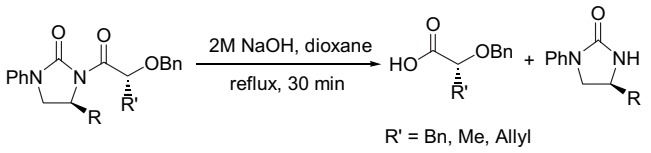
[a] After warming to −40 to −45 °C.
[b] Isolated yield after purification.
[c] Deacylation mainly occurred.
[d] Determined by HPLC (Spherisorb ODS column) after purification.

Table 2. Diastereoselective alkylations of *N*-acyl-2-phenyliminooxazolidines **3**



Entry	Substrate	R	R′	Product[a]	Yield (%)[b]	dr[c]
1	**3a**	*i*-Pr	$PhCH_2Br$	**4a**	87	>98:2
2	**3a**	*i*-Pr	$CH_2{=}CHCH_2I$	**4b**	87	>98:2
3[d]	**3a**	*i*-Pr	MeI	**4c**	75	87:13
4	**3b**	$PhCH_2$	$PhCH_2Br$	**4d**	85	>98:2
5	**3b**	$PhCH_2$	$CH_2{=}CHCH_2I$	**4e**	85	>98:2
6[d]	**3b**	$PhCH_2$	MeI	**4f**	72	82:18

[a] The configuration was verified by comparison with authentic samples after auxiliary removal.
[b] Isolated yields after purification.
[c] Determined by HPLC (Spherisorb ODS column) after purification.
[d] 5% HMPA was added to THF.



Scheme 3.

the corresponding benzyl protected α-hydroxyl carboxylic acids in yields of 87%, 95%, and 95%, respectively.[14] The absolute configurations of these acids were assigned (*R*) by comparing specific rotations with those previously reported (Scheme 3).[15]

3. Conclusion

In summary, the asymmetric alkylation of 2-phenyliminooxazolidine glycolates can be used for the enantioselective synthesis of highly useful protected α-hydroxy carboxylic acids by auxiliary removal. In addition the 2-imidazolidineone auxiliaries can be easily removed by aqueous base, without the need for hydroperoxide, and can be readily recovered.

Acknowledgement

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10. *General procedure for the preparation of 2-imidazolidinone glycolates*: To a stirred solution of *n*-BuLi (0.16 g, 1.43 mmol) and **2** (10 mmol) in anhydrous THF (20 mL) under nitrogen at 0 °C, benzyloxyacetyl chloride (1.84 g, 10 mmol) was added dropwise. The solution was stirred for 60 min, and then quenched with saturated ammonium chloride, and extracted with dichloromethane. Combined extracts were dried over magnesium sulfate, filtered, and concentrated. Purification by flash chromatography afforded the desired compounds **3** in good yield.
Compound **3a**: Yield 93%; oil; $[\alpha]_D^{20} = +17.0$ (*c* 4.16, $CHCl_3$); $R_f = 0.33$ (*n*-hexane/ethyl acetate 7/3); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.51–7.15 (m, 10H), 4.85–4.71 (m, 2H), 4.68 (s, 2H), 4.46–4.41 (m, 1H), 3.94 (t, 1H, $J = 9.5$ Hz), 3.58 (dd, 1H $J = 9.7$, 2.6 Hz), 2.52–2.47 (m, 1H), 0.97 (d, 3H, $J = 7.0$), 0.84 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 153.4, 138.7, 137.5, 129.5, 128.9, 128.5, 128.3, 125.1, 119.6, 73.8, 70.5, 54.9, 44.3, 28.2, 18.5, 15.0; HRMS calcd for $C_{21}H_{24}N_2O_3$: 352.1787. Found 352.1784. Compound **3b**: Yield 96%; oil; $[\alpha]_D^{20} = +39.0$ (*c* 4.45, $CHCl_3$); $R_f = 0.4$ (*n*-hexane/ethyl acetate 7/3); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42–7.12 (m, 15), 4.86–4.85 (m, 2H), 4.72 (s, 2H), 4.72–4.65 (m, 1H), 3.88 (t, 1H, $J = 9.3$ Hz), 3.55 (dd, 1H, $J = 9.7$, 2.1 Hz), 3.33 (dd, 1H, $J = 13.3$, 3.1 Hz), 2.82 (dd, 1H, $J = 13.3$, 6.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 170.4, 152.3, 138.2, 137.5, 135.7, 129.4, 128.9, 128.8, 128.4, 127.9, 127.8, 127.1, 124.6, 119.1, 73.3, 70.0, 51.1, 47.1, 38.4; HRMS calcd for $C_{25}H_{24}N_2O_3$: 400.1787. Found 400.1785.
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12. *Typical procedure for the alkylation of 2-imidazolidinone glycolates*: A solution of 2-imidazolidinone glycolate (1 mmol) in anhydrous THF (4 mL) was added to a dry round-bottomed flask under nitrogen and cooled to −78 °C. A solution of sodium bistrimethylsilylamide (1.0 M in THF, 1.5 mmol) was then added dropwise over 5 min, stirred at −78 °C for 60 min, and then a solution of benzyl bromide (3 mmol or 5 mmol) in THF (2 mL) was added dropwise. This solution was stirred at −78 °C for 60 min, allowed to warm to −40 to −45 °C, and stirred for a further 2 h. The reaction was monitored by TLC. After the reaction had gone to completion, saturated aqueous ammonium chloride was added. It was then warmed to room temperature and extracted with dichloromethane. Combined extracts were dried over magnesium sulfate, filtered, and concentrated. Purification by flash

chromatography (hexane/EtOAc 7:3) afforded the alkylation product **4**.

Compound **4a**: Yield 87%; oil; $[\alpha]_D^{20} = +35.1$ (*c* 1.49, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.56–7.11 (m, 15H), 5.47 (dd, 1H, $J = 9.3$, 3.3 Hz), 4.52 (d, 1H, $J = 11.7$ Hz), 4.42–4.36 (m, 1H), 4.34 (d, 1H, $J = 11.7$ Hz), 3.86 (t, 1H, $J = 9.6$ Hz), 3.54 (dd, 1H, $J = 9.6$, 2.7 Hz), 3.27 (dd, 1H, $J = 13.6$, 3.3 Hz), 2.96 (dd, 1H, $J = 13.6$, 9.3 Hz), 2.41–2.27 (m, 1H), 0.94 (d, 3H, $J = 6.9$ Hz), 0.76 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 173.0, 152.6, 138.4, 137.8, 137.8, 129.8, 129.1, 128.1, 128.0, 127.9, 127.4, 126.4, 124.7, 119.4, 79.1, 72.6, 54.4, 43.7, 39.9, 28.9, 17.9, 14.7; HRMS calcd for $C_{28}H_{30}N_2O_3$: 442.2256. Found 442.2255.

Compound **4b**: Yield 87%; oil; $[\alpha]_D^{20} = +47.0$ (*c* 5.57, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55–7.26 (m, 10H), 6.05–5.91 (m, 1H), 5.36 (dd, 1H, $J = 7.2$, 4.4 Hz) 5.22–5.09 (m, 2H), 4.62 (d, 1H, $J = 11.6$ Hz), 4.47 (d, 1H, $J = 11.6$ Hz), 4.43–4.37 (m, 1H), 3.86 (t, 1H, $J = 9.5$ Hz), 3.55 (dd, 1H, $J = 9.6$, 2.6 Hz), 2.75–2.69 (m, 1H), 2.65–2.57 (m, 1H), 2.39–2.33 (m, 1H), 0.94 (d, 3H, $J = 7.0$ Hz), 0.83 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.8, 152.5, 138.4, 137.9, 133.6, 129.1, 128.2, 128.1, 127.6, 124.7, 119.3, 117.7, 77.5, 72.4, 54.3, 43.5, 37.9, 28.9, 17.9, 14.7; HRMS calcd for $C_{24}H_{28}N_2O_3$: 392.2100. Found 392.2104.

Compound **4c**: Yield 75%; white solid; $[\alpha]_D^{20} = +39.0$ (*c* 0.73, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.56–7.18 (m, 10H), 5.33 (q, 1H, $J = 6.6$ Hz), 4.62 (d, 1H, $J = 11.3$ Hz), 4.48 (d, 1H, $J = 11.3$ Hz), 4.48–4.43 (m, 1H), 3.91 (t, 1H, $J = 9.5$ Hz), 3.58 (dd, 1H, $J = 9.6$, 2.8 Hz), 2.44–2.38 (m, 1H), 1.57 (d, 3H, $J = 6.6$ Hz), 0.96 (d, 1H, $J = 7.0$ Hz), 0.85 (d, 3H, $J = 6.9$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.1, 152.5, 138.4, 137.9, 129.1, 128.3, 128.1, 127.6, 124.6, 119.2, 74.4, 72.1, 54.3, 43.7, 28.9, 19.4, 17.9, 14.7; HRMS calcd for $C_{22}H_{26}N_2O_3$: 366.1943. Found 366.1938.

Compound **4d**: Yield 82%; oil; $[\alpha]_D^{20} = +32.0$ (*c* 2.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.46–7.12 (m, 20H), 5.44 (dd, 2H, $J = 9.2$, 3.5 Hz), 4.66–4.60 (m, 1H), 4.55 (d, 1H, $J = 11.9$ Hz), 4.38 (d, 1H, $J = 11.9$ Hz), 3.82 (t, 1H, $J = 9.3$ Hz), 3.53 (dd, 1H, $J = 9.5$, 2.3 Hz), 3.29 (dd, 1H, $J = 13.4$, 3.5 Hz), 3.18 (dd, 1H, $J = 13.4$, 3.2 Hz), 3.02 (dd, 1H, $J = 13.4$, 9.2 Hz), 2.71 (dd, 1H, $J = 13.4$, 9.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 172.8, 151.9, 138.3, 137.8, 137.7, 135.7, 129.9, 129.4, 129.0, 128.7, 128.1, 128.0, 127.8, 127.4, 127.1, 126.4, 124.7, 119.5, 78.9, 72.6, 60.3, 51.2, 46.8, 39.5, 38.4; HRMS calcd for $C_{32}H_{30}N_2O_3$: 490.2256. Found 490.2250.

Compound **4e**: Yield 85%; oil; $[\alpha]_D^{20} = +28.6$ (*c* 0.71, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.24 (m, 15H), 6.05–5.97 (m, 1H), 5.31 (dd, 1H, $J = 7.1$, 4.5 Hz), 5.24–5.12 (m, 2H), 4.65 (d, 1H, $J = 11.6$ Hz), 4.64–4.61 (m, 1H), 4.51 (d, 1H, $J = 11.6$ Hz), 3.80 (t, 1H, $J = 9.3$ Hz), 3.55 (dd, 1H, $J = 9.6$, 2.3 Hz), 3.28 (dd, 1H, $J = 13.3$, 3.2 Hz), 2.75–2.61 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) 172.6, 151.9, 138.4, 137.9, 135.8, 133.6, 129.4, 129.0, 128.8, 128.2, 128.1, 127.2, 124.7, 119.3, 117.8, 77.3, 72.4, 51.8, 46.7 38.5, 37.5; HRMS calcd for $C_{28}H_{28}N_2O_3$: 440.2100. Found 440.2104.

Compound **4f**: Yield 72%; white solid; $[\alpha]_D^{20} = +48.2$ (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$,300 MHz) δ 7.38–7.14 (m, 15H), 5.29 (q, 1H, $J = 6.6$ Hz), 4.68–4.66 (m, 1H), 4.65 (d, 1H, $J = 11.4$ Hz), 4.47 (d, 1H, $J = 11.4$ Hz), 3.87 (t, 1H, $J = 9.4$ Hz), 3.58 (dd, 1H, $J = 9.6$, 2.3 Hz), 3.25 (dd, 1H, $J = 13.4$, 3.2 Hz), 2.82 (dd, 1H, $J = 13.4$, 9.0 Hz), 1.58 (d, 3H, $J = 6.6$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) 173.9, 151.9, 138.4, 137.9, 135.7, 129.5, 129.0, 128.8, 128.3, 128.1, 127.7, 127.2, 124.8, 119.4, 74.3, 72.1, 51.2, 46.9, 38.5, 19.0; HRMS calcd for $C_{26}H_{26}N_2O_3$: 414.1943. Found 414.1950.

13. Prasad et al. reported that chiral *N*-acylated 2-imidazolidinones have been demonstrated to undergo highly diastereoselective benzylations and methylations via their sodium enolates and the chiral auxiliaries can be readily recycled with refluxing 2 M NaOH/dioxane (1:1) (30 min) without racemization; see: Konigsberger, K.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron: Asymmetry* **1997**, *8*, 2347–2354.

14. The crude auxiliary was recovered by extracting the reaction mixture with CH_2Cl_2 and purified by column chromatography in 87% yield. The required carboxylic acid was isolated almost quantitatively by extracting with EtOAc after acidifying the aqueous layer to pH 2. Specific rotation: **4a**: $[\alpha]_D^{19} = +76.1$ (*c* 0.73, EtOH), lit.[15a] $[\alpha]_D^{25} = +79.1$ (*c* 2.37, EtOH); **4b**: $[\alpha]_D^{19} = +53.0$ (*c* 0.81, EtOH), lit.[15b] $[\alpha]_D^{18} = +54.0$ (*c* 2.3, benzene); **4c**: $[\alpha]_D^{19} = +97.0$ (*c* 0.71, EtOH).

15. For (2*R*)-2-benzyloxy-3-phenylpropionic acid, see: (a) Siraja, V.; Deshmukh, A. R. A. S.; Puranik, V. G.; Bhawal, B. M. *Tetrahedron: Asymmetry* **1996**, *7*, 2733–2738; For (2*R*)-2-benzyloxypropionic acid, see: (b) Nakata, M.; Arai, M.; Tomooka, K.; Ohsawa, N.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2618–2635.