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L-Valinol and L-phenylalaninol-derived 2-phenylamino-2-oxazolines as chiral auxiliaries in asymmetric alkylations

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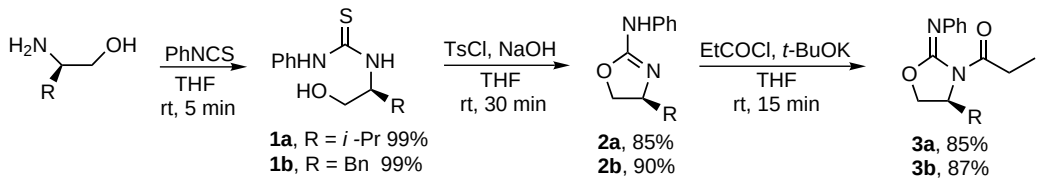
Abstract—Lithium enolates of *N*-acyl phenyliminooxazolidine auxiliaries reacted with alkyl halides to produce the α-alkylated products with very high diastereofacial selectivity (up to >99% d.e.). The products were readily cleaved by simple alkaline hydrolysis to give homochiral carboxylic acids and could also be directly converted to aldehydes and other acid derivatives such as esters and amides.

Chiral auxiliary-derived asymmetric alkylations have been studied extensively and are now important and general methods for asymmetric carbon–carbon bond formation.[1] In particular, metal enolates of *N*-acyl oxazolidinones, developed by Evans, are highly effective in controlling facial selectivity for the preparation of homochiral α-substituted carboxylic acid and their derivatives.[2] This auxiliary, however, undergoes endocyclic cleavage rather than the required exocyclic cleavage in removal of the auxiliary with alkaline hydrolysis.[3] To suppress the troublesome endocyclic cleavage, hazardous lithium hydroperoxide has been used in place of the hydroxide.[3a,3b] *N*-Acyl oxazolidinones are not directly converted to the corresponding aldehydes. The generation of aldehydes is possible via two-step processes involving reduction to the alcohol followed by oxidation[4] or conversion to either the *N*-methoxy-*N*-methyl amide (Weinreb amide) or the ester and subsequent reduction.[5]

We herein report that the use of metal enolates of new *N*-acyl phenyliminooxazolidine auxiliaries results in as high diastereoselectivity in alkylation reactions as *N*-acyl oxazolidinones. The alkylation products are easily hydrolyzed by simple alkaline hydrolysis (NaOH) without using hazardous lithium hydroperoxide to suppress the endocyclic cleavage[6] and can be directly converted to aldehydes[7] as well as to other functional groups.

The synthesis of 2-phenylamino-2-oxazoline auxiliaries **2** was readily performed by reaction of 1,2-aminoalcohol with phenyl isothiocyanate to give the corresponding *N*-(2-hydroxyethyl)thiourea, followed by cyclodesulfurization of the thiourea to the 2-phenylamino-2-oxazoline by a one-pot reaction using *p*-toluenesulfonyl chloride and NaOH according to our previous work (Scheme 1).[8] The auxiliary was then acylated with propionyl chloride in the presence of potassium *tert*-butoxide in THF (Scheme 1).[9] The acylation of



Scheme 1.

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2-phenylamino-2-oxazoline might afford the regioisomeric *N-endo*- and *N-exo*-acylated products. The obtained acyl derivative **3** was a regiocontrolled *N-endo* product which was confirmed by X-ray crystallographic analysis of the alkylation product **4e** (Fig. 1).[10]

Formation of the lithium enolate at −78°C using LiHMDS occurred within 1 h in THF and then subsequent addition of the alkyl halide led to the formation of α-alkylated product with excellent diastereoselectivity (Table 1).[11] The purified products **4** were identified by ^{1}H, ^{13}C NMR and MS analyses. The diastereomeric ratios were determined by HPLC. The absolute configurations of the alkylated products **4** were assigned by comparison of the $[\alpha]_D$ value reported in the literature after removal of auxiliary. As the results in Table 1 reveal, allyl bromide and benzyl bromides reacted with these enolates to give the respective alkylated products with excellent yields (runs 2–3 and 5–6). On the other hand, although a somewhat lower yield was observed with ethyl iodide, the diastereoselectivity was found to be virtually complete (runs 1 and 4). To enhance the reactivity to ethyl iodide the use of HMPA (5 V%) as cosolvent in NaHMDS was found to result in lower diastereoselectivity of 67:33 in HPLC.

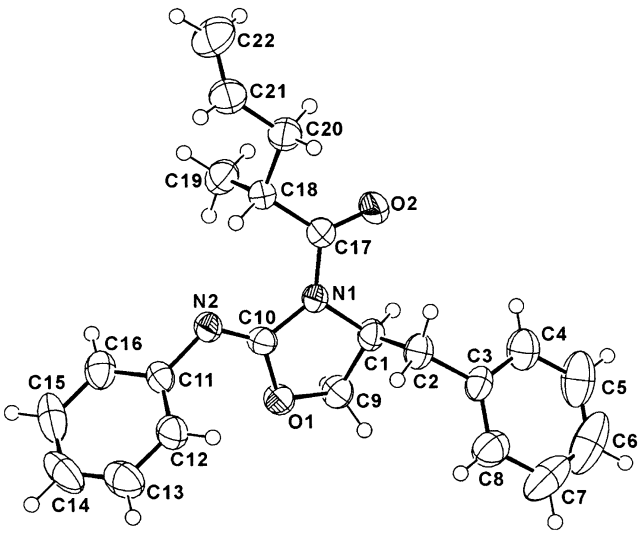
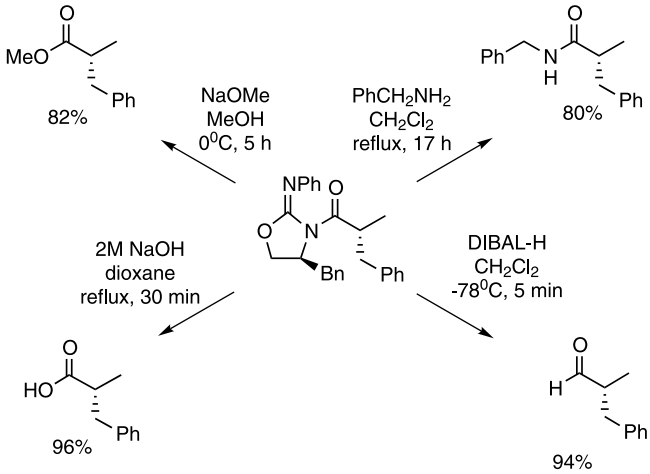


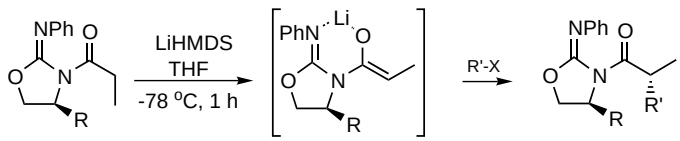
Figure 1. X-Ray structure of **4e**. Thermal ellipsoids are drawn at the 30% probability level. Selected bond lengths (Å) and angles (°): N(1)–C(10) 1.408(6), N(2)–C(10) 1.252(6); N(2)–C(10)–O(1) 125.1(5), N(2)–C(10)–N(1) 126.4(5), O(1)–C(10)–N(1) 108.4(4).



Scheme 2.

The alkylation product can be converted to a variety of derivatives (Scheme 2). Treatment with NaOH yielded the α-alkylated carboxylic acid.[12] Conversion to the chiral amide via simple substitution[14] using benzylamine also proceeded cleanly in the presence of two drops of acetic acid.[15] Formation of the methyl ester was also possible by treatment with sodium methoxide. Most significantly, direct conversion to aldehydes using *i*-Bu_2AlH (DIBAL-H) was achievable. In all cases, recovery of deacylated auxiliary was performed successfully.

Table 1. Diastereoselective alkylations of *N*-acyl-2-phenyliminooxazolidines **3**



3 **4**

Run	Substrate	R	R′	Product[a]	Yield (%)[b]	D.e.[c,d]
1	**3a**	*i*-Pr	Et	**4a**	55	98 (98:2)
2	**3a**	*i*-Pr	Allyl	**4b**	82	>99 (95:5)
3	**3a**	*i*-Pr	$PhCH_2$	**4c**	88	>99 (97:3)
4	**3b**	$PhCH_2$	Et	**4d**	53	>99 (100:0)
5	**3b**	$PhCH_2$	Allyl	**4e**	80	>99 (98:2)
6	**3b**	$PhCH_2$	$PhCH_2$	**4f**	81	>99 (95:5)

[a] The configuration was verified by correlation to authentic samples after removal of the auxiliary.
[b] Isolated yields after purification.
[c] Determined by HPLC (Spherisorb ODS column) after purification.
[d] Parenthesis is the ratios of the unpurified diastereomeric mixture.

In summary, *N*-acyl 2-phenyliminooxazolidines have been shown to perform highly diastereoselective alkylations similarly to the corresponding oxazolidinones when using LiHMDS. The products are easily isolated and can be converted directly to aldehydes as well as various other functional groups. Clean removal of the auxiliary with aqueous base is also possible without using hydroperoxide.

Acknowledgements

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9. **Procedure for synthesis of 3**. To a stirred solution of potassium *tert*-butoxide (0.16 g, 1.43 mmol) and **2** (1.19 mmol) in anhydrous THF (15 mL) under nitrogen at room temperature, propionyl chloride (1.13 mL, 1.55 mmol) was added dropwise. The solution was allowed to stir for 15 min, then was quenched with water (30 mL) and extracted with ether. The combined extracts were dried over magnesium sulfate, filtered, and concentrated. Purification by flash chromatography (hexane/EtOAc, 8:2, $R_f = 0.6$) afforded the desired compounds **3** in good yields.
10. Crystal data for **4e**: $C_{22}H_{24}N_2O_2$: $M = 348.43$, monoclinic, $a = 13.137(5)$, $b = 7.546(3)$, $c = 9.835(4)$ Å, $\beta = 100.40(4)$, $U = 958.9(7)$ Å^3, $T = 298(2)$ K, space group $P21$, $Z = 2$, $D_{calcd} = 1.207$ g cm^{-3}, $F(000) = 372$, μ(Mo–Kα) = 0.078 mm^{-1}, crystal size 0.3×0.4×0.6 mm, 2356 reflections collected, 2356 unique ($R_{int} = 0.0000$), which were used in all calculations. Final R indices [$I > 2\sigma(I)$]: $R_1 = 0.0711$, $wR_2 = 0.1074$, R indices (all data) $R_1 = 0.1510$, $wR_2 = 0.1408$. The reflection data were collected on a Stoe Stadi4 diffractometer using combination of ω and 2θ scans. The structure was solved using direct methods techniques (SHELXS-86, Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467) and refined using full-matrix least-squares based on F^2 (SHELXL-97-2, Sheldrick, G. M. University of Göttingen, Germany, **1997**). (Note that two independent molecules which have the same configuration are contained in the unit cell of the crystal of **4e**.) The absolute configuration could not be determined. Further details of the structural investigations of **4e** are available on request from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (Deposit number CCDC 171612).
11. **Procedure for alkylation of 3b**. To a dry round-bottomed flask under nitrogen was added **3b** (0.1 g, 0.32 mmol) in anhydrous THF (4 mL). The solution was cooled to −78°C. A solution of lithium bis(trimethylsilylamide) (LiHMDS) in THF (1.0 M, 0.39 mL 120 mol%) was added dropwise, and the solution was allowed to stir for 1 h. The mixture was treated with allyl bromide (0.03 mL, 120 mol%). After stirring for 30 min at −78°C and 1 h at 0°C, the reaction mixture was quenched with saturated ammonium chloride (4 mL) and water (20 mL), extracted with ether. The combined extracts were dried over magnesium sulfate, filtered, and concentrated. HPLC analysis of the crude product revealed the isomer ratios. Purification by flash chromatography (hexane/EtOAc, 8:2) afforded the major diastereomer **4e**. Yield 80%; mp 92–93°C; $[\alpha]_D^{20} = +94.8$ ($c = 3.4$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–6.96 (m, 10H), 5.96–5.83 (m, 1H), 5.16–5.04 (m, 2H), 4.82–4.77 (m, 1H), 4.31 (m, 1H), 4.15–4.13 (m, 2H), 3.22 (dd, 1H, $J = 13.2$, 3.3 Hz), 2.80 (dd, 1H, $J = 13.2$, 9.6 Hz), 2.72–2.62 (m, 1H), 2.30–2.17 (m, 1H), 1.22 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.3, 145.8, 145.6, 136.1, 136.0, 129.6, 128.8, 128.7, 127.1, 123.5, 122.8, 116.8, 67.7, 56.2, 37.9, 37.8,

37.0, 16.3; HRMS calcd for $C_{22}H_{24}N_2O_2$: 348.1838. Found 348.1841; anal. calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.36; H, 6.86; N, 7.93%.

12. In the case of acid the auxiliary was recovered by extraction of the reaction mixture with CH_2Cl_2. The chiral acid was almost quantitatively isolated by extraction with EtOAc after acidification to pH 2. The absolute configuration and enantiomeric purity were assigned by comparison of the measured optical rotation ($[\alpha]_D^{20} = -23.6$ ($c = 0.8$, $CHCl_3$)] with the published values[13] ($[\alpha]_D^{20} = -23.1$ ($c = 1$, $CHCl_3$)].
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