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Practical Synthesis of α-Amino Acids using *cis*-Aminoindanol Derived Hippuric Acid Amide as a Glycine Enolate Equivalent

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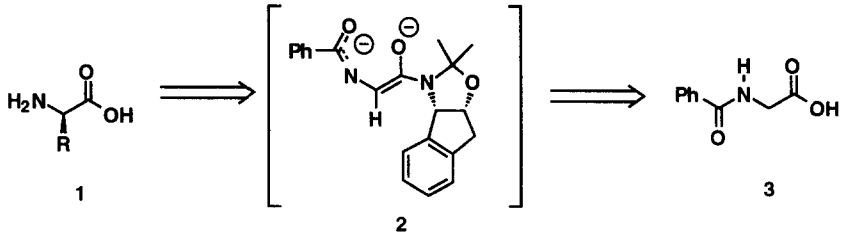
Abstract: The use of *cis*-aminoindanol as a chiral auxiliary for asymmetric synthesis of α-amino acids is described. Alkylation of the chirally modified glycine enolate **2** with a number of alkyl halides in the presence of lithium chloride gave the corresponding alkylated product in 90 ~ 99% diastereoselectivity.

Synthetic, unnatural α-amino acids have attracted increasing interest as synthetic targets because of emerging therapeutic and biological possibilities.[1] Various methods have been developed to access natural and unnatural α-amino acid through methods such as alkylation,[2] electrophilic amination,[3] and hydrogenation, etc.[4] Of the various methods explored, the stereoselective formation of a carbon-carbon bond to a glycine enolate synthon has an advantage in that a variety of amino acids could be prepared from a common intermediate. However, certain α-amino acids are inaccessible by stereoselective glycine enolate alkylation due to the low reactivity of some alkyl halides such as unactivated 2° iodides. Additionally, oxazolidinone or *N*-acylmorpholinone-derived enolates react efficiently only with reactive halides.[5]



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At the outset of our investigation, we envisioned that the acetonide derived dianion **2** might show increased reactivity and stability as an enolate nucleophile. In the literature, the corresponding asymmetric C-alkylation of hippurate often gave only moderate diastereoselectivity and chemical yield.[2a, 6] Recently, Myers and coworkers have elegantly addressed these problems using a pseudoephidrine-derived chiral auxiliary.[2b,c] We report herein our use of (*1S,2R*)-1-amino-indan-2-ol as an alternative readily available

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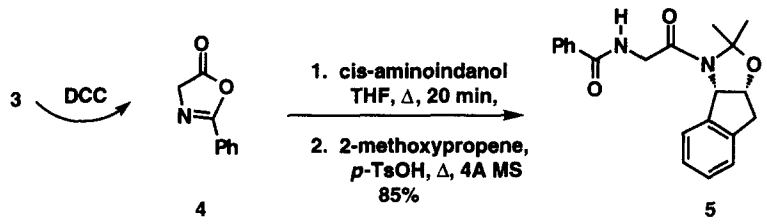
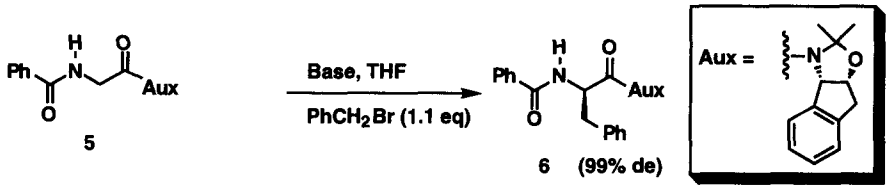
chiral auxiliary[7] for the enantioselective synthesis of α-amino acids derived from hippuric acid amide **5** as shown below.



Scheme 1. Preparation of Substrate for Alkylation Reaction

Substrate **5** for the alkylation reaction was readily available from commercially available azlactone **4**[8] (Lancaster synthesis Inc.) via a one-pot, 2 step operation. Treatment of azlactone **4** with 1.1 equiv of (*1S,2R*)-1-amino-indan-2-ol in THF (60 °C, 20 min) gave the corresponding amide and subsequent treatment with 2-methoxypropene and 0.15 equiv of *p*-TsOH in THF at reflux gave acetonide **5**. After extractive work up, addition of pentane-THF precipitated the desired amide-acetonide **5** as a non-hygroscopic solid in 85% yield.

Table 1. Alkylation Studies I



Entry	Base	Temp-Time (Deprotonation-Alkylation)	Additive	Isolated Yield (%)
1	*n*-BuLi (2.1 eq.)	-70 to -60 °C, 20 min; -78 to 0°C, 1.5h	--	60
2	*n*-BuLi (2.1 eq.)	-70 to -60 °C, 20 min; -78 to 0°C, 2 h	DMPU	63
3	LiHMDS (2.15 eq)	-30 °C, 0.5h; 0 °C, 10h	--	62
4	LiHMDS (2.15 eq)	-30 °C, 0.5h; 0 °C, 14h	LiCl (4 equiv.)	85

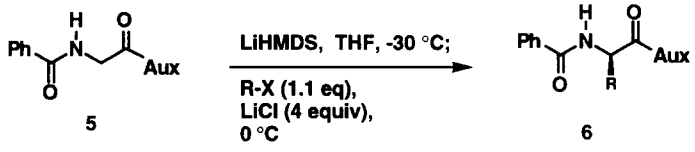
Gratifyingly, our initial attempt at alkylation of the lithium enolate of amide-acetonide **5** with benzyl bromide met with encouraging results, providing greater than 99% de of **6** (see entry 1 in Table 1).

However, the chemical yield was only 60%. Subsequently a variety of reaction conditions were screened in order to optimize the yield of the alkylation reaction. Our initial assumption was that the recovery of starting material might be due to aggregation of the unreacted amide enolate. However, the addition of DMPU or the use of LiHMDS had no effect on the conversion.[9]

We assumed that lithium halide might then enhance the reactivity of the amide enolate by facilitating its dissociation from the aggregated state.[2c, 10] Thus, by employing 4 equiv. of lithium chloride as an additive, the alkylation was realized with a 25% increase in yield.

With operationally simple alkylation conditions in hand, the reaction was extended to a variety of electrophiles as shown in Table 2.

Table 2. Alkylation Reactions of Hippuric acid amide 5 with Alkyl halides



Entry	R-X	isolated Yield (%)	de (%) [a]
1	$PhCH_2Br$	85	99[b]
2	2-Nap-CH_2Br	84	99[c]
3	allyl-Br	88	96[b]
4	$C_{10}H_{12}$-I	88	98.5[b]
5	CH_3-I	80	95[d]
6	$(CH_3)_2CH$-I	92	90.5[b] (86[e], 99[f])
7	cyclopentyl-I	37	95[b]

a) Diastereoselectivites were determined by HPLC analysis,[11] b) Zorbax, Rx- C-18 column, 4.6 mm x 25 cm, c) Zorbax, Rx-C-8 column, 4.6 mm x 25 cm, d) Chiralcel OD column, e) without LiCl, f) after recrystallization (*n*-hexanes).

Treatment of **5** with benzylic or naphthyl bromide under our standard conditions gave alkylated product with excellent diastereoselectivity.[11] Electrophiles such as allylic or 1° alkyl halides typically gave 95 to 98% de . In the case of an acyclic 2° iodide (entry 6 in table 2), the desired product was obtained in good chemical yield albeit with slightly lower diastereoselectivity. It is interesting to note that the diastereo-selectivity was slightly lower without lithium chloride as an additive, even though a good chemical yield was obtained (entry 6). Reaction with 5 or 6 membered cyclic 2° iodides or homobenzylic iodide gave products in moderate yield due to a competing elimination reaction.

In a typical experiment, the amide-acetonide (**5**, 820 mg, 2.34 mmol) was treated with LiHMDS (5.0 mL, 5 mmol, 1 M in THF) in 16 mL of THF at -30 °C under nitrogen. After 20 min at this temperature, benzyl bromide (0.45 mL, 3.50 mmol) and LiCl (400 mg, 9.4 mmol) were added sequentially. The reaction was warmed to 0 °C over a period of 30 min. The mixture was stirred for 10 h (or left to stand

overnight at 0 °C), and the reaction was quenched by addition of aq. NH_4Cl solution. After extractive workup, **6** was isolated as a single diastereomer by simple flash chromatography.
The auxiliary and benzoyl amide were effectively removed using known epimerization-free conditions[3a] and the auxiliary was recovered by basic (pH 11) extraction.

References and Notes

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2. Glycine enolate approach; see a) McIntosh, J. M.; Leavitt, R. K. *Tetrahedron Lett.* **1986**, *27*, 3839. b) Myers, A. G.; Gleason, J. L.;Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488. c) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc*, **1997**, *119*, 656 and references cited therein.
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9. LiHMDS is known to exist as a dimer in THF. As a consequence, it normally doesn't require the use of TMEDA or lithium halide for dissociation of this aggregated state of the base itself. see: Collum, D, B. *Accounts of Chemical Research*, **1993**, 227 and references cited therein.
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11. Diastereoselectivities were measured by HPLC by comparison with racemic authentic compounds. Authentic racemic compounds were prepared as follows: i) C-alkylation of trianion derived from hippuric acid with corresponding electrophile in THF using modified Krapcho's procedure (*Tetrahedron Lett.* **1976**, *17*, 2205), ii) amide formation with DCC followed by acetonide formation as described previously.