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Highly Diastereoselective Reaction of 2-Azanorbornyl Enolates with Electrophiles

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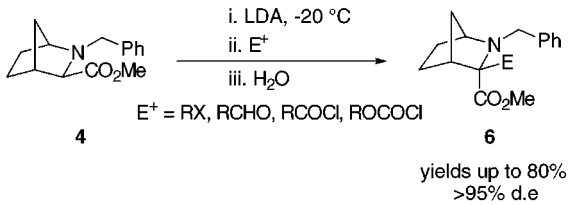
ABSTRACT



A highly diastereoselective reaction of 2-azanorbornyl enolates with electrophiles has been studied. Deprotonation of 4 with LDA at low temperature affords the corresponding exocyclic lithium enolate 5, which reacts with different electrophiles such as alkyl halides, aldehydes and acyl chlorides to give the corresponding *exo* addition products 6. The products are formed in good yields and with diastereoselectivities above 95%.

Proline and derivatives thereof have proven to be very useful precursors for chiral ligands in catalytic asymmetric synthesis.[1] During recent years we have had particular interest in the use of 2-azanorbornyl derivatives as chiral ligands due to their rigidity and equal availability of both enantiomeric forms.[2] These interesting bicyclic proline derivatives have successfully been used in the development of new routes toward multifunctionalized chiral cycloalkylamines[3] and new nonproteinogenic α-amino acid derivatives.[4] Their versatility as highly efficient chiral ligands in a wide variety of catalytic asymmetric transformations has also been demonstrated, i.e., diethylzinc additions to aldehydes,[5a] allylic oxidations of olefines to allylic alcohols,[5b] borane reduction of ketones,[5c] and rearrangement of *meso*-epoxides.[5d] Particularly good results were obtained using the bicyclic β-amino alcohol derivatives (Figure 1) for the ruthenium-catalyzed asymmetric transfer hydrogenation of aromatic ketones[6] (**1**, R^1 = R^2 = H) as well as in the nucleophilic addition of Et_2Zn to *N*-(diphenylphosphinoyl) imines[7] (**1**, R^1 = Bn; R^2 = H, Me, *i*-Pr, Ph). As part of our program focused on the synthesis of new chiral proline analogue ligands, we were interested

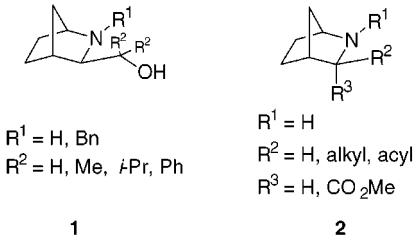


Figure 1. Chiral bicyclic ligands.

(1) (a) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111. (b) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5233. (c) Corey, E. J.; Yuen, P.; Hannon, F. J.; Wierda, D. A. *J. Org. Chem.* **1990**, *55*, 784. (d) Shi, M.; Satoh, Y.; Makihara, T.; Masaki, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2109.

(2) (a) Stella, L.; Abraham, H.; Feneu-Dupont, J.; Tinant, B.; Declercq, J. P. *Tetrahedron Lett.* **1990**, *31*, 2603. (b) Waldmann, H.; Braun, M. *Liebigs Ann. Chem.* **1991**, 1045. (c) Abraham, H.; Stella, L. *Tetrahedron* **1992**, *48*, 9707.

(3) Pinho, P.; Andersson, P. G. *Chem. Commun.* **1999**, 597.

(4) Alonso, D. A.; Bertilsson, S. K.; Johnsson, S. Y.; Nordin, S. J. M.; Södergren, M. J.; Andersson, P. G. *J. Org. Chem.* **1999**, *64*, 2276.

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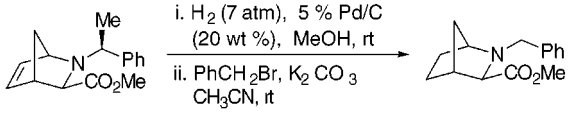
in developing methods for the stereoselective synthesis of 3,3-disubstituted 2-azanorbornyl derivatives **2** (Figure 1).

Recently, much interest has been directed toward the stereoselective alkylation of both *endo*- and *exo*-heterocyclic enolates[8] and in the origin of the high degrees of π-facial selectivity (>95%) usually observed in these reactions.[9] As a consequence, this research has found several applications in the synthesis of enantiomerically pure alkylated amino acid analogues[8] as well as in the preparation of naturally ocurring compounds.[10]

Here we report on the diastereoselective reaction of exocyclic enolate **5** with different electrophiles at low temperature which allows the synthesis of new 3,3-disubstituted bicyclic derivatives **6** which should be potential chiral ligands for a wide number of catalytic asymmetric reactions.

The starting bicyclic amino ester **4** was easily prepared in high yield as outlined in Scheme 1. Hydrogenation/hydrogenolysis of compound **3**[11] followed by alkylation with benzyl bromide in acetonitrile afforded **4** in a 80% overall yield from **3**.

Scheme 1. Synthesis of Amino Ester **4**

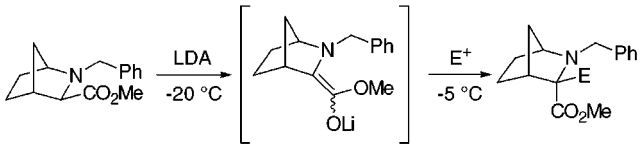


3 **4** (80%)

At first, we attempted to alkylate **3**[12] using LDA as base and benzyl bromide as electrophile. However, this only led to very low conversions even when high reaction temperatures or large excess of base and/or electrophile were used. This is probably due to a very slow deprotonation of the sterically encumbered ester.

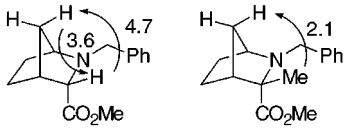
On the other hand, compound **4** was readily deprotonated when treated with freshly prepared LDA at −20 °C in THF for 1 h.[13] The intermediate enolate **5** (Scheme 2) was then reacted with a number of different electrophiles. The results are summarized in Table 1.

Scheme 2. Reaction of Enolate **5** with Electrophiles



4 **5** **6**

Treatment of **5** with water afforded a 70/30 mixture of *endo*/*exo* diastereoisomers due to the protonation from the less hindered *exo* face of the enolate[14] (Table 1, entry 1). The absolute configuration of the major isomer *endo*-**4** was confirmed by NOE experiments which clearly showed the new *endo* arrangement for the methyl ester substituent (Figure 2).



endo-**4** **6a**

Figure 2. Selected NOE (%) observed for *endo*-**4** and **6a**.

On the other hand, enolate **5** reacted with very high levels of diastereoselectivity at the less hindered *exo* face,[15] with a wide range of different electrophiles (alkyl halides, aldehydes, acid derivatives, and Michael aceptors) to afford the bicyclic *exo*-addition products **6** with good yields and >95% d.e. in all cases (Table 1). Absolute configurations at C3 for all new compounds **6a**−**j** were confirmed by NOE experi-

(5) (a) Nakano, H.; Kumagai, N.; Kabuto, Ch.; Matsuzaki, H.; Hongo, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1391. (b) Södergren, M. J.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 7577. (c) Pinho, P.; Guijarro, D.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 7897. (d) Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10760.

(6) (a) Alonso, D. A.; Guijarro, D.; Pinho, P.; Temme, O.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 2749. (b) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, in press.

(7) (a) Guijarro, D.; Pinho, P.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 3, 2530. (b) Brandt, P.; Hedberg, C.; Lawonn, K.; Pinho, P.; Andersson, P. G. *Chem. Eur. J.* **1999**, *5*, 1692.

(8) (a) Zhang, R.; Brownewell, F.; Madalengoitia, J. S. *Tetrahedron Lett.* **1999**, *40*, 2707. (b) Nagumo, Sh.; Mizukami, M.; Akutsu, N.; Nishida, A.; Kawahara, N. *Tetrahedron Lett.* **1999**, *40*, 3209.

(9) (a) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 4565. (b) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A.; Blake, J. F.; Williard, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 7429. (c) Ando, K.; Green, N. S.; Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 5334 and references therein.

(10) Arrington, M. P.; Meyers, A. I. *Chem. Commun.* **1999**, 1371.

(11) Compound **3** is obtained in high yield via a highly *exo*-selective and diastereoselective aza-Diels−Alder reaction between cyclopentadiene and the iminium ion derived from ethyl glyoxylate and (*S*)-1-phenylethylamine. See ref 2a.

(12) For methylation of the racemic *N*-benzyl derivative of **3** and its use in the synthesis of cyclopentyl glycine derivatives, see: Bourgeois-Cury, A.; Doan, D.; Gore, J. *Tetrahedron Lett.* **1992**, *33*, 1277.

(13) **Typical Experimental Procedure.** A solution of compound **4** (100 mg, 0.41 mmol) in dry THF (1 mL) was slowly added to a solution of freshly prepared LDA (0.45 mmol) in dry THF (5 mL) at −20 °C. After 40 min of stirring the corresponding electrophile was added (0.43 mmol) at −5 °C, and the mixture was allowed to reach room-temperature overnight. The reaction was quenched with a saturated aqueous solution of NaCl and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated, and the residue was purified by flash chromatography (silica gel, pentane/ether) to afford compounds **6**. Yields and physical data are included in Table 1. Spectral and analytical data for compound **6j** are as follows: $[\alpha]^{21}_D = -4.5$ ($c = 0.11$, CH_2Cl_2); ^{1}H NMR (400 MHz/$CDCl_3$) δ 1.27−1.40, 1.48−1.59, 1.90−1.98 (6H, 3m), 3.03 (1H, br s), 3.09 (1H, s), 3.73 (3H, s), 3.76 (3H, s), 4.20 (2H, s), and 7.19−7.32 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 25.1, 38.4, 45.8, 49.7, 51.9, 52.0, 57.7, 126.5, 127.9, 128.1, 141.6, 170.2, and 171.7; IR (neat, cm^{-1}) 2949, 1738, 1264, 1213, 1161, and 1105; MS (EI) *m*/*z* (rel intensity) 304 ($M^+ + 1$, <1%), 303 (M^+, 2), 245 (20), 244 (100), 216 (65), 184 (11), and 91 (54). Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.25; H, 7.04; N, 4.71.

(14) Attempts to increase this selectivity by the use of lower temperatures, different bulkier proton sources such as *i*-PrOH, *t*-BuOH, PhOH, or via acidic workup with 1 M HCl only led to lower or similar levels of diastereoselection.

(15) Meyers and Houk have explain the observed π-facial stereoselectivity in the alkylations of some particular heterocyclic enolates based on electronic and steric effects or torsional strain and steric effects. See ref 9.

Table 1. Reaction of Enolate **5** with Electrophiles

		product				
entry	E^+	no.	E	yield (%)[a]	selectivity (% *exo* addition)[b]	$[\alpha]_D^{21}$ ($c = 0.11$, CH_2Cl_2)
1	H_2O	*endo*-**4**	H	90	70[c]	−71.8
2	CH_3I	**6a**	CH_3	80 (78)[d]	>98	−30.9
3	CH_3CH_2Br	**6b**	CH_3CH_2	62	>98	−22.7
4	$CH_3CH_2CH_2Br$	**6c**	$CH_3CH_2CH_2$	67	>98	−12.7
5	CH_2CHCH_2Br	**6d**	CH_2CHCH_2	60[e]	>98	−85.4
6	$C_6H_5CH_2Br$	**6e**	$C_6H_5CH_2$	50[e]	95	−140.9
7	$CH_3CH_2CHICH_3$	**6f**	$CH_3CH_2CHCH_3$	40[e]	>98[f]	-
8	C_6H_5CHO	**6 g**	C_6H_5CHOH	68	>98	−49
9	CH_2=$CHCOCH_3$	**6h**	$CH_2CH_2COCH_3$	20	>98	−21
10	C_6H_5COCl	**6i**	C_6H_5CO	56	>98	+59
11	CH_3OCOCl	**6j**	CH_3OCO	75	>98	−4.5

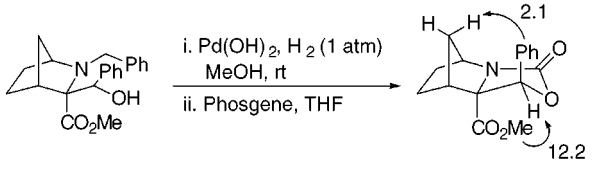
[a] Isolated yield after flash chromatography (silica gel, pentane/ether). [b] Determined by ^1H NMR. [c] See ref 14. [d] Yield when DMPU was used as cosolvent. [e] Two equivalents of LDA and electrophile were used. [f] A 1/1 mixture of *exo* diastereoisomers was obtained.

ments and a representative example for the *exo*-methyl-substituted **6a** is shown in Figure 2. It should be mentioned that in no case was the diastereoselectivity found to be dependent on the alkylation reagent.[16]

Reaction with both activated and nonactivated primary alkyl halides led to higher conversions than when using secondary halides (Table 1, compare entries 2, 5, and 7). In the case of using 2-iodobutane as electrophile, a 1/1 mixture of diastereoisomers was obtained. The addition of chelating cosolvents such as *N*,*N*-dimethylpropyleneurea (DMPU) to the reaction mixture did not improved the yields (entry 2).

When benzaldehyde was used as an electrophile, the reaction afforded amino alcohol **6g** as the only diastereoisomer and in good isolated yield. The absolute configurations of C3 and the new stereocenter were found to be (*S*) as determined by NOE experiments for the rigid carbamate **7** which was prepared as outlined in Scheme 3.

Scheme 3. Synthesis and Selected NOE (%) Observed on **7**



6g **7**

The α,β-unsaturated ketone reacted with high regio- and chemoselectivity to give exclusively the Michael addition product albeit with low yield (Table 1, entry 9). Finally, good yields were obtained using acid chlorides and chloroformates as shown in entries 10 and 11.

In conclusion, a highly diastereoselective bicyclic enolate alkylation has been described. The reaction takes place with a wide range of electrophiles and in most cases the diastereoselectivity is >98%. The potential of the 3,3-disubstituted 2-azanorbornyl derivatives as chiral ligands in catalytic asymmetric reactions is now under investigation.

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Supporting Information Available: Physical and analytical data for products **4** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Recently it has been found that the stereoselectivity of some 4-hydroxyproline derivatives is dependent on the alkylating agent. See ref 8b.