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Exo,Exo-2,3-Diaminoborneol-Derived Imidazolidinone as Chiral Auxiliary for Asymmetric Alkylations

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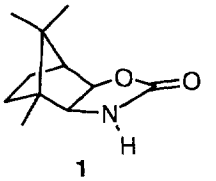
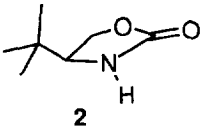
Abstract: A new camphor-derived imidazolidinone type auxiliary is described. Its acylated derivatives under Na enolate formation and treatment with primary halides give alkylated products in highly diastereoselective manner. Copyright © 1996 Elsevier Science Ltd

The use of the Evans α-amino acid-derived N-acyloxazolidinones for asymmetric C-C bond construction is one of the most straightforward and efficient strategies in modern organic synthesis.[1] Despite exhibiting high levels of diastereoselectivity in numerous transformations, the absolute stereochemical control in reactions of particularly poor diastereoface selection continues to be an important challenge. A recent report from this laboratory has addressed this issue and high levels of asymmetric induction were observed in reactions involving N-acylimides derived from exo,exo-2-amino-3-borneol **1**.[2] The design of **1** was inspired by the results achieved with the tert-leucine derived oxazolidinone **2**, and by the advantageous topological bias of camphor skeleton to form conformationally rigid derivatives.[3] Herein we wish to report on the preparation and synthetic utility of the imidazolidinone **5**, Scheme I, in asymmetric enolate alkylations.[4] The reagent **5**, which is closely related to **1**, has been delineated with the hope that the phenyl chromophore present in the imidazolidinone ring could facilitate reaction monitoring and/or product isolation.



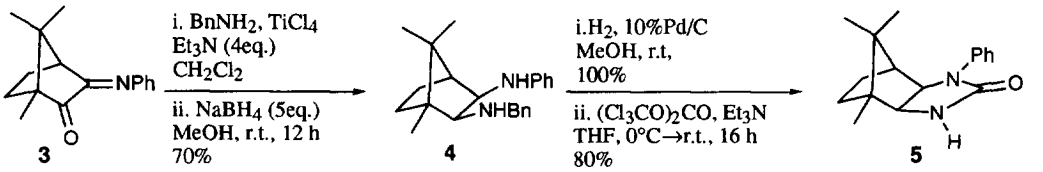
1



2

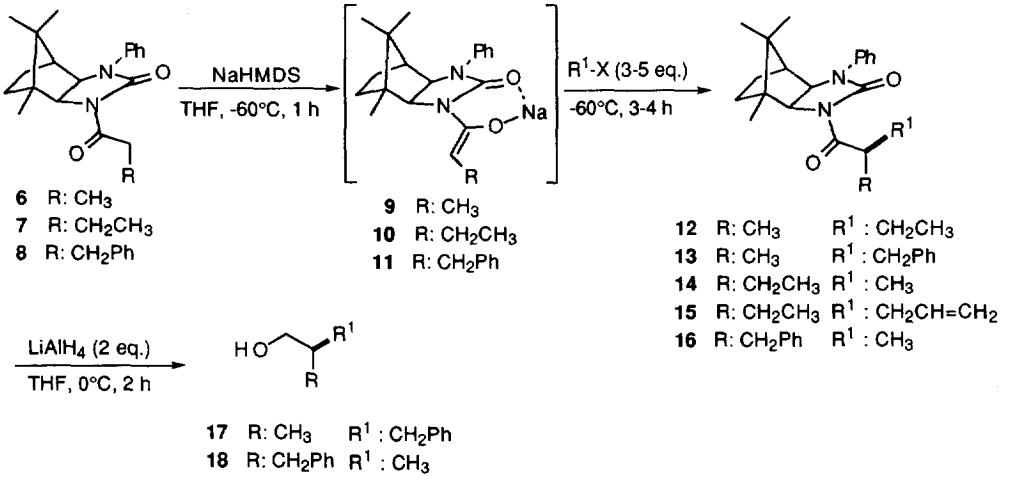
The imidazolidinone **5** was easily prepared in simple steps from the monoimine **3** derived from (1R)-(-)-camphorquinone.[5] When **3** was treated with benzylamine and $TiCl_4$ followed by reduction of the

resulting diimine with $NaBH_4$ the diamine **4** was obtained in 70% overall yield.[6] Subsequent N-debenzylation and further treatment with triphosgene produced the desired *exo,exo*-imidazolidinone **5** in 80% yield.[7]



Scheme I

To test the chemical and stereochemical behaviour of imidazolidinone **5** for asymmetric synthesis, we evaluated the alkylation of N-acylimides **6-8** with representative alkyl halides. The enolates **9-11** were generated by addition of NaHMDS to a solution of the corresponding N-acylimide under usual conditions[8] and after complete enolization, 1 h at -60°C, a threefold excess of the alkylating agent was added at the same temperature. After the disappearence of the starting material which could be checked by TLC (1-3 h), the mixture was quenched with saturated NH_4Cl and product isolated.



17 R: CH_3 R^1 : CH_2Ph
18 R: CH_2Ph R^1 : CH_3

Scheme II

As the results in Table 1 reveal methyl iodide, benzyl bromide and allyl bromide reacted with these enolates to give the respective alkylated products with excellent yields. In every case the analysis of the crude products by ^{13}C NMR showed an unique set of signals. This observation was confirmed by HPLC analysis, were absortion bands appeared well resolved and typically showed a retention time gap larger than 20 seconds. On the other hand, although a somewhat lower yield was produced in the alkylation of **9** (entry a) with ethyl iodide to give **12**, the diastereoselection level was found to be virtually complete. In an effort to enhance the reactivity of imide enolate **9** the use of HMPA as cosolvent (entry b) was found to be

effective albeit in lower diastereoselectivity.[9] Nevertheless, the most striking feature of the chiral auxiliary **5** is that the sterically undemanding methylations and ethylations, which often are difficult to control, proceeded with remarkable diastereoselectivity. From these results it is clear that auxiliary **5** gives rise to the same excelent level of diastereoselection than does **1** in alkylation reactions, including some monitoring advantages as mentioned before.

Table 1. Diatereoselective Alkylations of Chiral Enolates **9-11**[a]

Entry	Enolate	R	R^1X	Product	d.r.[b]	Yield, %[c]	mp °C	$[\alpha]_D^{25}$ [d]
a	**9**	CH_3	**EtI**	**12**	>99:1	41	120-122	+20.4
b	**9**		**EtI(HMPA)**	**12**	92:8	73		
c	**9**		**$PhCH_2Br$**	**13**	>99:1	88	oil	+11.8
d	**10**	CH_2CH_3	**MeI**	**14**	>99:1	90	73-75	+74.5
e	**10**		**CH_2=$CHCH_2Br$**	**15**	>99:1	79	98-100	+50.4
f	**11**	CH_2Ph	**MeI**	**16**	>99:1	78	oil	+32.1

[a] Reactions conducted on a 1 mmol scale. Enolate formation at -60°C in THF as solvent during 1 h and alkylations performed at -60°C using 3 equiv. of alkyl halide, except for MeI (5 equiv.). [b]Diastereomeric ratio determined by HPLC using a Shimadzu LC-8A instrument (column Hibar Lichrosorb Si 60 7μm, Supelco). [c]Yields of isolated pure products, after flash-column chromatography (Silica gel, Hex:EtOAc 4:1). [d]Measured in $CHCl_3$ at c 1.0 .

The sense of asymmetric induction can be interpreted by assuming alkylations occur predominantly at the relatively unhindered α-face of the corresponding chelated enolates. The stereochemical course of these reactions was unambiguosly confirmed by lithium aluminium hydride reduction of both **13** and **16** to afford carbinols **17** {$[\alpha]_D^{25}$ +11.1° (c=1.15, C_6H_6); lit.[10] $[\alpha]_D^{25}$ +11.0° (c=1.15, C_6H_6)} and **18** {$[\alpha]_D^{25}$ -10.6° (c=1.15, C_6H_6)} in 87% and 85% yield respectively, along with the imidazolidinone **5** which could be separated by column chromatography and recycled.

ACKNOWLEDGEMENTS

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6. Spectroscopic data for compound **4** ($CDCl_3$, δ ppm): ^1H NMR 7.41-6.50 (m, 10H, arom), 5.48 (s_b, 1H, NH), 3.73 (s, 2H, CH_2Ph), 3.29 (dd, 1H, J=8.4Hz, J'=3.8Hz, CHN), 2.88 (d, 1H, J=8.4Hz, CHN), 1.90 (d, 1H, J=4.5Hz, CH bridgehead), 1.80-1.70 (m, 1H, CHaHb), 1.79-1.55 (m, 1H, CHaHb), 1.42 (s_b, 1H, NH), 1.40-1.15 (m, 2H,.CHaHb), 1.09, 0.96 and 0.79 (s, 3H, CH_3). ^{13}C NMR 148.2, 140.4, 129.2, 128.5, 128.1, 127.0, 115.7, 112.4, 69.4, 60.2, 55.8, 48.9, 48.8, 47.0, 36.7, 25.6, 21.8, 21.0, 12.1
7. Preparation of **5**: H_2 was supplied by balloon for 12 h to a solution of **4** (18.3 g, 54 mmol) in MeOH (150 mL) in the presence of 10% Pd/C (1.83 g, 10% w/w). After filtration of the catalyst and evaporation of the solvent, to the oily residue dissolved in dry THF (350 mL) and cooled at 0°C were added successively under a N_2 atmosphere Et_3N (37.8 mL, 270 mmol) and dropwise during 1 h a solution of $(Cl_3CO)_2CO$ (8.02 g, 27 mmol) in THF (50 mL). The resulting solution was stirred at r.t. for 1h, solvent evaporated, the residue dissolved in CH_2Cl_2 (300 mL), washed with H_2O (2 x 100 mL) and brine (100 mL), dried over $MgSO_4$, and solvent removed. The pale yellow solid thus obtained was purified by flash column chromatography (EtOAc/Hex 1:3) to afford pure compound **5** (8.37 g, 80%) which recrystallized from Et_2O/Hex: mp 184-185°C; $[\alpha]_D^{25}$ -9.9° (CH_2Cl_2, c 1.0); ^1H NMR ($CDCl_3$, δ ppm) 7.51-7.00 (m, 5H, arom), 5.73 (s, 1H, NH), 4.31 (d, 1H, J=9.3Hz, CH), 3.59 (dd, 1H, J=9.3Hz, J'=2.2Hz, CH), 2.10 (d, 1H, J=4.9Hz, CH bridgehead), 1.84-1.71 (m, 1H, CH), 1.61-1.50 (m, 1H, CH), 1.17-1.03 (m, 2H, CHaHb), 1.07, 0.96 and 0.81 (s, 3H, CH_3); ^{13}C NMR 159.3, 139.1, 128.8, 122.6, 119.0, 65.0, 62.3, 48.2, 46.7, 45.9, 33.4, 25.0, 23.3, 18.8, 10.9. Anal. Calcd. for $C_{17}H_{22}N_2O$: C, 75.52%; H, 8.20%; N, 10.36%. Found: C, 75.47%; H, 8.67%; N, 10.20%.
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