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MIB: an advantageous alternative to DAIB for the addition of organozinc reagents to aldehydes

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3-*exo*-Morpholinoisoborneol (MIB) catalyzes the addition of organozinc reagents to aldehydes in high enantiomeric excess and provides several advantages over the venerable amino alcohol ligand DAIB.

The addition of organozinc reagents to aldehydes catalyzed by enantiopure β-amino alcohols[1] represents the enantioselective counterpart of the Grignard addition reaction.[2] The extensive research on this transformation has been summarized in review articles.[3] The first ligand to provide high enantioselectivities in such reactions was 3-exo-dimethylaminoisoborneol (DAIB, **1b**) which was developed by Noyori and co-workers.[4] Despite the many alternative β-amino alcohol ligands[5] now available, interest in DAIB has remained remarkably high. Recent studies[6] provide detailed insight into the mechanism of DAIB-promoted additions and new applications of this venerable ligand continue to appear.[7]

While DAIB has enjoyed great success, three factors somewhat limit further extensions of this technology. (i) The most efficient synthesis, that developed by White and co-workers,[8] requires three steps for the conversion of parent amino alcohol **1a** to DAIB. (ii) DAIB is somewhat air-sensitive and slowly decomposes upon storage.[4] (iii) While DAIB-promoted addition of organozinc reagents to aromatic aldehydes proceeds in excellent enantiomeric excess, it has not yet proven possible to obtain similar ees in the case of α-branched aliphatic aldehydes.[4] Here we report that a simple structural modification circumvents these problems whilst retaining the desirable features of DAIB.

(2*R*)-(+)-3-*exo*-Aminoisoborneol (+)-**1a** was prepared by $LiAlH_4$ reduction of *anti*-(1*S*)-(−)-camphorquinone 3-oxime following the literature procedure.[8,9] Treatment of (+)-**1a** with commercial bis(2-bromoethyl) ether in the presence of excess Et_3N resulted in dialkylation of the amine nitrogen (Scheme 1).† Extractive work-up followed by crystallization from hexanes afforded (2*R*)-(+)-3-*exo*-morpholinoisoborneol **2** [(+)-MIB] as transparent crystals, mp 65–67 °C. The enantiomer (−)-MIB was prepared similarly from (−)-**1a**.

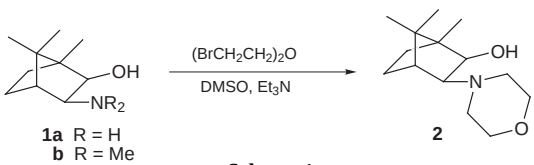
Like DAIB, MIB promotes the enantioselective addition of organozinc reagents to aldehydes (Scheme 2). The addition of Et_2Zn to a series of aldehydes under standard conditions (two-fold excess Et_2Zn in 2:1 hexane–toluene)‡ is summarized in Table 1. The reactions in Table 1 were quenched by addition of Ac_2O which quantitatively converts the intermediate zinc alkoxides to the corresponding acetate esters and allows direct analysis of the product mixture by chiral capillary column gas chromatography.[10] As exemplified by entries 1–4, addition of Et_2Zn to aromatic and heteroaromatic aldehydes proceeded cleanly with enantiomeric excesses similar to those reported using DAIB. Moreover, we were delighted to find that addition of Et_2Zn to several α-branched aliphatic aldehydes (entries 6–10) also proceeded in 97–99% enantiomeric excess. Only in the case of the straight-chain aliphatic aldehyde hexanal did the ee begin to erode. In all cases in Table 1 the major enantiomer of the product had the *R* absolute configuration, thus the sense of chirality obtained from (+)-MIB is the same as that obtained from (+)-DAIB.

Table 1 Enantioselective addition of Et_2Zn to aldehydes catalyzed by (+)-MIB[a]

Entry	Aldehyde	MIB/ mol%	*T*/°C	*t*/h	Yield (%)[b]	Ee (%)[b]
1	Benzaldehyde	2	0	3	98	98
2	*m*-Tolualdehyde	2	0	3	97	98
3	*p*-Fluorobenzaldehyde	5	0	3	98	98
4	3-Furaldehyde	5	0	6	91	97
5	Hexanal	5	0	3	96	91
6	Isobutyraldehyde	5	0	3	94	99
7	Cyclohexanecarboxaldehyde	5	0	3	94	99
8	2-Ethylbutyraldehyde	5	25	18	92	99
9	Cyclopropanecarboxaldehyde	5	0	3	91	98
10	Trimethylacetaldehyde	5	25	24	62	97

[a] All reactions contained aldehyde (3.0 mmol) and Et_2Zn (6.0 mmol) in 2:1 hexane–toluene (9 ml); for details see note ‡. [b] Determined by chiral capillary column gas chromatography on Cyclodex B stationary phase (J&W Scientific); in all cases (*R*)-enantiomer formed preferentially.

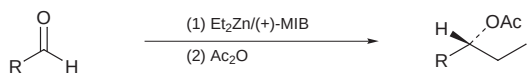
The reduced yield observed for addition of Et_2Zn to the tertiary aliphatic aldehyde trimethylacetaldehyde requires some comment. The limited yield can be traced to competing reduction of the the aldehyde to the zinc alkoxide of neopentyl alcohol which is subsequently acetylated under our reaction conditions (Scheme 3). The formation of minor amounts of BnOH as a side-product of DAIB-catalyzed addition of Et_2Zn to benzaldehyde has been noted by Noyori and co-workers.[11] In our experience, detectable amounts of primary alcohol are invariably formed during addition of organozinc reagents to aldehydes in the presence of β-amino alcohols. This side-reaction is most severe in the case of sterically bulky aldehydes bearing tertiary alkyl substituents. In contrast, for the other aldehydes in Table 1, this reductive pathway occurs to the extent of 2% or less for aromatic and primary aliphatic aldehydes (entries 1–5) and 5% or less for secondary aliphatic aldehydes (entries 6–9).



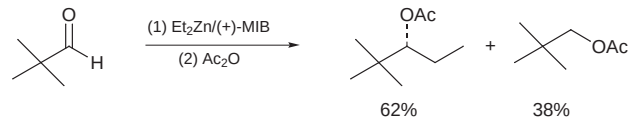
1a R = H
b R = Me

2

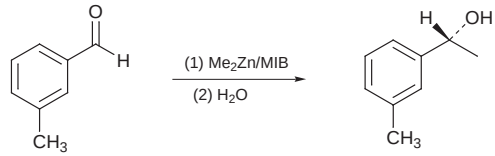
Scheme 1



Scheme 2



Scheme 3



Scheme 4

MIB can also be used to effect the addition of Me_2Zn to aldehydes although longer reaction times are required to compensate for the lower reactivity of this organozinc reagent. Addition of Me_2Zn to *m*-tolualdehyde [18 h, room temperature, 5% (+)-MIB] afforded (*R*)-(+)-1-(*m*-tolyl)ethanol§ in 95% ee and 88% isolated yield after flash chromatography (Scheme 4).

It is also noteworthy that the crystalline nature of MIB imparts greater air-stability as compared with DAIB. A sample of MIB stored under air at ambient conditions for three months showed no degradation of spectroscopic properties nor catalytic performance when compared with freshly prepared material. Given the several advantages of MIB, we suggest that it should be considered as an alternative ligand for reactions where DAIB has previously been utilized.

Notes and references

† *Preparation* of (+)-**2**: Amino alcohol (+)-**1a** (4.53 g, 26.8 mmol) was dissolved in DMSO (25 ml) and Et_3N (10 ml). A solution of di(2-bromoethyl) ether (8.07 g, 90% pure, 31.3 mmol) in DMSO (20 ml) was added dropwise. After 72 h the mixture was added to 250 ml water and 60 ml 1 M NaOH and was extracted into Et_2O (3 × 100 ml). After removal of solvent at reduced pressure the product was taken up in Et_2O, extracted into 1 M HCl (50 ml), released with NaOH, and again extracted into Et_2O. After removal of volatiles, the residue was dissolved in hexanes (4 ml per g of crude product), filtered and cooled to −30 °C to produce **2** (2.95 g, 46%) as a white crystalline solid, mp 65–67 °C. ($C_{14}H_{25}NO_2$: Calc: C, 70.25; H, 10.53; N, 5.85; found: C, 70.18; H, 10.83, N, 5.94%). $\delta_H(C_6D_6)$ 0.69 (s, 3 H), 0.73 (m, 1 H), 0.88 (m, 1 H), 1.04 (s, 3 H), 1.15 (s, 3 H), 1.31 (td, 1 H), 1.52 (m, 1 H), 1.67 (d, 1 H), 1.99 (d, 1 H), 2.13 (br, 2 H), 2.31 (br, 2 H), 3.32–3.42 (m, 5 H total), 3.92 (br d, 1 H); $\delta_c(C_6D_6)$ 11.88, 21.10, 22.19, 27.99, 32.56, 45.35, 46.64, 49.52, 66.82, 73.37, 79.03 (as in the case of **1b**, one ^{13}C resonance is too broad to observe at room temperature); $[\alpha]_D^{25}$ +4.4, (*c* = 2.03, MeOH).

‡ *Typical procedure*: A solution of freshly distilled aldehyde (3.00 mmol), toluene (3.0 ml), internal standard (chlorobenzene or *tert*-butybenzene) and (+)-**2** (14.4 mg, 0.060 mmol) was cooled to 0 °C. After dropwise addition of 1.0 M Et_2Zn in hexane solution (6.0 ml, 6.0 mmol), the mixture was maintained at 0 °C for 3 h. Ac_2O (1.2 ml, 13 mmol) was added and the mixture was allowed to stand overnight prior to capillary column GC analysis on a Cyclodex B stationary phase (J&W Scientific).

§ *Optical rotation* data: $[\alpha]_D^{25}$ +40.5 (*c* = 1.48, EtOH), lit.[12] for (*R*)-enantiomer, $[\alpha]_D^{21}$ +40.4 (*c* 0.530, EtOH), lit.[12] for (*S*)-enantiomer, $[\alpha]_D^{21}$ −41.9 (*c* = 0.500, EtOH).

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