Asymmetric Synthesis

Remarkably Stable $(Me_3Al)_2$·DABCO and Stereoselective Nickel-Catalyzed AlR_3 (R = Me, Et) Additions to Aldehydes**

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The attainment of a largely air-stable, low-molecular-weight equivalent of "chiral Me^-" for addition to prochiral aldehydes is reported herein together with complementary additions of AlR_3 (R = Me, Et). Although there has been considerable interest recently in air-stable boron, silicon, and tin reagents for the catalytic delivery of $C(sp^2)$ nucleophiles,[1,2] the equivalent alkyl ($C(sp^3)$) chemistry, including methyl transfer, remains quite underdeveloped; however, a notable exception is the stabilization of a methylaluminum species by formation of a Lewis acid/base pair, whose use has been pioneered by Blum, Schumann, and co-workers.[3] Despite this development, asymmetric addition to carbonyl compounds using such reagents has not been realized.

The reports of X-ray crystallographic studies of several $Me_3Al{\cdot}NR_3$ species encouraged us to test their synthetic utility. Although Me_3Al·pyridine and $(Me_3Al)_2$·TMEDA (TMEDA = tetramethylethylenediamine) proved far too reactive to handle under normal laboratory conditions, we were astonished to find that $(Me_3Al)_2$·DABCO (DABCO = 1,4-diazabicyclo[2.2.2]octane; **1a**),[5] which we call DABAL-Me_3, is surprisingly robust and can be readily used in the

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DABCO = 1,4-diazabicyclo[2.2.2]octane.

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laboratory. Compound **1a** has a hydrolytic stability comparable to $LiBH_4$ as it is moisture sensitive but can be weighed out easily on the bench without the need for an inert air atmosphere and stored in standard glassware. DABAL-Me_3 (**1a**), unlike the Schumann–Blum reagent **2**, is prepared in a single step from commercially available materials and is obtained directly from the reaction mixture as a free-flowing, white powder. The analogous DABAL-Et_3 species (**1b**) proved too reactive to isolate (possibly because of weaker Al–C bonds) but it can be generated and used in situ.

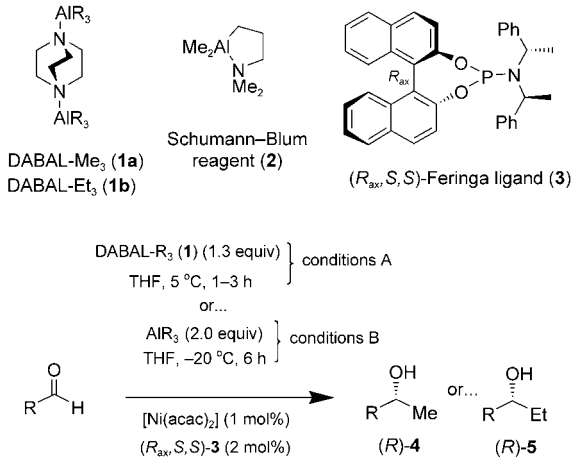
We initially concentrated on the addition DABAL-Me_3 to prochiral aldehydes to fashion secondary alcohols to demonstrate the utility of this reaction. Approaches based on [L*$AlMe_n$] (L* = chiral ligand) Lewis acids seemed unlikely to be very successful as the Lewis acidity of the aluminum center in **1** is rather compromised by the coordination of DABCO to it, and so an alternative strategy based on transmetalation was sought. In 1997, Fujisawa and coworkers demonstrated that phosphanes cause dramatic rate acceleration in the nickel-catalyzed additions of (neat) $AlMe_3$ to aldehydes.[6] To the best of our knowledge, no asymmetric version of this reaction has appeared despite the enormous recent interest in selective nickel catalysis.[7] Pleasingly, when DABAL-Me_3 (**1a**; 1.0–1.5 equiv) is added to PhCHO in THF in the presence of [$Ni(acac)_2$] (acac = acetylacetone; 1 mol%) and (R_{ax},*S*,*S*)-Feringa ligand **3** (2 mol%) at 5 °C, the resulting alcohol **4** (R = Ph) is isolated in high yield and enantiomeric excess (Scheme 1). We were further gratified to find that the range of substrates for this reaction using DABAL-Me_3 **1** was rather wider than that of the original Fujisawa reaction (Table 1), which had a rather narrow substrate range as only electron-rich aldehydes reacted quickly. Furthermore, the scope of the reaction could be extended by the use of DABAL-Et_3 (**1b**). Remarkably, byproduct formation arising from β elimination of any [$L_nNi(Et)$] intermediate amounted to less than 1 mol%, which is in accordance with the findings of Fujisawa and coworkers.[6]

Electron-deficient aromatic aldehydes gave the highest enantioselectivities in our reaction, while the electron-rich substrate 4-MePh gave the poorest (compare entries 15 versus 5, 7–12, and 14). Control reactions showed that electronic effects do not contribute to any competing reactions (4-XPhCHO (X = MeO, H, NO_2) did not react with **1a** alone within 3 h at 5 °C). The enantioselectivity and reactivity of the reaction is also influenced significantly by steric factors (compare entries 1 and 2 versus 8–10; 1, 2 versus 18 and 21; 15 versus 17; and 21 versus 23). The activities displayed outperform other reported data given for addition reactions of AlR_3 to an aldehyde, which normally require catalyst

Table 1: Alkylation of aldehydes (RCHO) with A) DABAL-R_3 **1** or B) AlR_3 reagents.

Entry	R in RCHO	Method (R)	*t* [h]	Yield [%][a]	Product *ee* (antipode) [%][b]
1	Ph (**a**)	A (Me)	1	92	91 (*R*)-(+)-**4a**
2	Ph (**a**)	B (Me)	3	60	85 (*R*)-(+)-**4a**
3	Ph (**a**)	A (Et)	5	95	86 (*R*)-(+)-**5a**
4	Ph (**a**)	B (Et)	5	95	83 (*R*)-(+)-**5a**
5	4-BrC_6H_4 (**b**)	A (Me)	1	98	93 (*R*)-(+)-**4b**
6	4-BrC_6H_4 (**b**)	A (Et)	1	91	89 (*R*)-(+)-**5d**
7	4-ClC_6H_4 (**c**)	A (Me)	1	79	93 (*R*)-(+)-**4c**
8	4-FC_6H_4 (**d**)	A (Me)	3	84	94 (*R*)-(+)-**4d**
9	3-FC_6H_4 (**e**)	A (Me)	1	77	94 (*R*)-(+)-**4e**
10	2-FC_6H_4 (**f**)	A (Me)	1	81	87 (*R*)-(+)-**4f**
11	4-$(CN)C_6H_4$ (**g**)	A (Me)	1	69	94 (*R*)-(+)-**4g**
12	4-$(CF_3)C_6H_4$ (**h**)	A (Me)	1	58	94 (*R*)-(+)-**4h**
13	4-$(CF_3)C_6H_4$ (**h**)	A (Et)	1	90	95 (*R*)-(+)-**5h**
14	3-$(CF_3)C_6H_4$ (**i**)	A (Me)	1	93	93 (*R*)-(+)-**4i**
15	4-MeC_6H_4 (**j**)	A (Me)	3	90	81 (*R*)-(+)-**4j**
16	3-MeC_6H_4 (**k**)	A (Me)	1	82	93 (*R*)-(+)-**4k**
17	2-MeC_6H_4 (**l**)	A (Me)	1	78	90 (*R*)-(+)-**4l**
18	*c*-C_6H_{11}[c] (**m**)	A (Me)	1	80	94 (*R*)-(−)-**4m**
19	*c*-C_6H_{11}[c] (**m**)	A (Et)	10	60[d]	91 (*R*)-(+)-**5m**
20	*c*-C_6H_{11}[c] (**m**)	B (Et)	1.5	55	7 (*R*)-(+)-**5m**
21	*i*Bu (**n**)	B (Me)	6	60	95 (*R*)-(−)-**4n**
22	*i*Bu (**n**)	B (Et)	6	72	48 (*R*)-(−)-**5n**
23	*t*$BuCH_2$ (**o**)	B (Me)	7	95	67 (*R*)-(−)-**4o**
24	*n*-C_6H_{13} (**p**)	B (Me)	6	91	61 (*R*)-(−)-**4p**
25	$PhCH_2CH_2$ (**q**)	B (Me)	6	94	77 (*R*)-(−)-**4q**
26	(*E*)-PhCH=CH (**r**)	A (Me)	1	94	66 (*R*)-(+)-**4r**

[a] Yield determined from isolated product or by GC analysis: GC versus the internal standard on 0.25 mmol (RCHO) scale reaction and yields of isolated product were within 2–5% of these obtained on 1.0 mmol scale duplicate reactions. Compounds **4** and **5** were authenticated against genuine samples prepared either by reactions catalyzed with achiral Ph_3P (2 mol%)/[$Ni(acac)_2$] (1 mol%) and **1** and/or $NaBH_4$ reduction of the parent ketones. [b] Determined by GC analysis on a cyclodex-B column in all cases except **4a** and **5a** (GC analysis on lipodex-A); **4q** and **4r** (GC analysis on 2,6-me-3-pe-γ-CD[9]); and **4m**–**p**, **5m**, and **5n** (determined by GC analysis of the acetate of isolated secondary alcohol as described before).[8] Stereochemical correlations were assigned on the basis of the sign of the optical rotation or by comparison with the GC data of authentic samples of known configuration. [c] 1.0 equivalents of DABAL-R_3 **1** were used. [d] Mass balance was accounted for from by-products derived from α deprotonation.



Scheme 1. The asymmetric synthesis of chiral secondary alcohols from benzaldehyde using either A) DABAL-R_3 or B) AlR_3 reagents (R = Me, Et).

loadings of 10–15 mol%.[8] Further lowering of the ligand loading was possible: methylation of PhCHO with 1 mol% of **3** proceeded in identical enantiomeric excess but in a slightly lower yield (78%). PhCHO was converted into **4a** even when undried THF was used as the solvent (89% *ee*, 96% yield). An enal also participated in the reaction with **1a** but at lower selectivity (**4r**, entry 26). In two cases, the use of **1a** and **1b** allowed the isolation of secondary alcohols that are not available from classical Noyori-type transfer hydrogenations (**4m** and **5m**).[10] However, reagents **1a** and **1b** can cause the α deprotonation of some aliphatic aldehydes, thus resulting in aldol/Knovenagel derived by-products. This problem can be overcome by carrying out the reaction with these substrates at −20°C in the absence of DABCO.

The enantioselectivities attained in reactions using AlR_3 reagents are low to excellent (entries 4 and 20–25), thus indicating that the structure of **3** requires modification for each substrate.[11] Again β elimination by-products are only present at trace levels in all addition reactions using the $AlEt_3$ reagent under DABCO-free conditions. The use of DABCO is critical with some substrates, for example, **5m** is attained in only 7% *ee* in its absence (entry 20).[12] Although detailed discussion of the mechanism of the catalytic cycle is premature at this point, we strongly suspect that Lewis acid activation of an nickel/η^2-aldehyde complex by the aluminum reagent, in a manner related to the work of Ogoshi et al., is involved.[13] Extensive work to further delineate the reactivity of other DABAL-reagents and to explore their substrate range, both in the present reaction and other metal-catalyzed processes, is underway.

Experimental Section

1a: Neat $AlMe_3$ (4.5 g, 62.5 mmol) was added to a solution of freshly sublimed DABCO (3.4 g, 34.7 mmol) in toluene (30 mL) at 0°C. The resulting white precipitate was allowed to settle, and the supernatant toluene was removed by cannula. Dry diethyl ether (20 mL) was added and swirled with the solid. The solid was again allowed to settle and the supernatant liquid removed by cannula. Washing with diethyl ether was repeated four times before the residual slurry was evaporated to dryness under vacuum to obtain **1a** directly (4.5–6.1 g; 60–81%); its spectroscopic properties were as described previously.[5] DABAL-Me_3 (**1a**) that had been stored in screw-top vials under an argon blanket was still active after at least 4 months. (**Warning**: while we have encountered no problems using this reagent on scales of up to 25 g, we recommend caution on its initial handling. For example, if washing with diethyl ether, as outlined above, is not carried out properly traces of free $AlMe_3$ can lead to very reactive samples of **1a**. Deliberate addition of water to **1a** causes a strong exothermic reaction and methane liberation. Furthermore, **1a** ignites on tissue paper especially on "damp" days.)

Catalytic addition to aldehydes: $[Ni(acac)_2]$ (0.6 mg, 2.33 μmol, 1 mol%) and (R_{ax},*S*,*S*)-**3** (2.7 mg, 0.005 mmol, 2 mol%) were stirred in dry THF (2 mL) under an argon atmosphere at 5°C for 10–30 min. Neat aldehyde (0.25 mmol) was then added and DABAL-Me_3 (**1a**) (84 mg, 0.325 mmol, 1.3 equiv) was added after a further 10 min. The yellow reaction mixture was stirred (1–3 h) before being quenched with aqueous NH_4Cl. The yields of the obtained secondary alcohols were determined either by isolation or by GC analysis after addition of dodecane as the internal standard. DABAL-Et_3 (**1b**) was prepared by mixing 2:1 molar quantities of $AlEt_3$ and DABCO in THF. The use of **1b** or an uncoordinated AlR_3 species was carried out in an equivalent manner to that for **1a**. Screening reactions using AlR_3 (R = Me, Et) were carried out in 2.0 M hexanes solutions.

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[11] Individual ligand optimization is underway in our laboratory for both alkyl aldehyde and enal substrates (on the basis of PM3 studies of the selective step in the reaction).

[12] The presence of *c*-$C_6H_{11}C(=O)Et$ (c = cyclo) can be detected, which indicates product racemization by Meerwin–Pondorf–Varley–Oppenauer reactions. Related ketones were not detected in the products **4**.

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