Dabbling with air-stable organoaluminum species*

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Abstract: Highly stereoselective 1,2-additions of $AlMe_3$ or its air-stable analog DABCO-$(AlMe_3)_2$ to aldehydes are realized in the presence of a $Ni(acac)_2$-derived catalyst using phosphoramidite ligands giving *sec*-alcohols in up to 95 % ee. Very high turnover number (TON) (>1500) and turnover frequency (TOF) (>350 h^{-1}) values can be realized in these reactions. The substrate range, trials of various $(DABCO)_a(AlR_3)_b$ reagents ($a = 0.1$; $b = 1.2$; R = Me, Et, Bu^i), ligands, and molecular modeling studies are used to propose a working model for the catalytic cycle and the origin of the stereoselectivity. The phosphoramidite ligand is proposed to bind the nickel in an η^2 manner via the *P*-donor and one of the C=C aryl bonds of the CHAr amine group. Preliminary studies indicate that $DABCO(AlMe_3)_2$ can also be used as a methyl source in Pd-catalyzed cross-coupling reactions of ArX (X = Br, I) species.

Keywords: 1,2-additions; stereoselective; $DABCO(AlMe_3)_2$; trimethylaluminum; catalytic asymmetric synthesis; asymmetric synthesis.

INTRODUCTION

Our group has a long-term interest in the use of trimethylaluminum in catalytic asymmetric synthesis. Often, the reactivity of this intensely pyrophoric reagent is modified by the presence of oxo-containing by-products attained through accidental exposure of stock solutions to traces of air or moisture [1]. In looking for an alternative approach to preparing very pure $AlMe_3$ samples, we sought to use amine adducts ($R_3N \cdot AlMe_3$) first prepared by H. C. Brown and N. Davidson [2]. We screened a number of known, crystallographically characterized adducts [3] hoping that, if large enough crystals could be grown, this might allow limited handling of the reagent in air. We were amazed to discover that the DABCO (1,4-diazobicyclo[2.2.2]octane) adduct of $AlMe_3$ **1a** (Scheme 1) was stable for some hours in air under ambient laboratory conditions, even as a powder. Because these reagents are derived from DABCO and an aluminum species, we refer to them as "DABAL" reagents, which is alluded to in the title. Further investigation revealed the utility of DABAL-Me$_3$ in Ni-catalyzed methyl additions to aldehydes using ligands **L1–L3** (Scheme 1) [3]. These preliminary investigations raised many questions regarding the scope, utility, and mechanism of this reaction, and the relationship of the DABAL reagents **1** reactivities to their parent AlR_3 species. These are the topics of this present discussion.
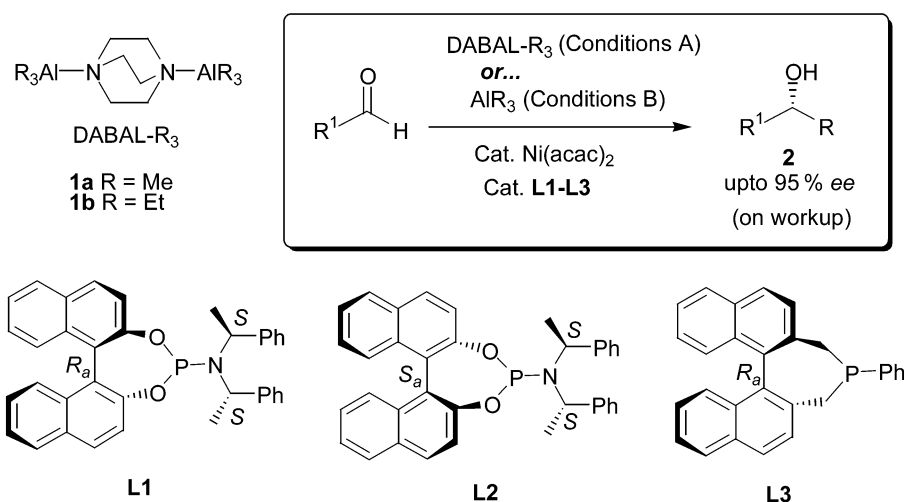
Scheme 1 Nickel-catalyzed 1,2-additions of AlR_3 reagents to aldehydes. Conditions A: DABAL-R_3 **1** (1.3 equiv), THF, 0 to 5 °C, 1–3 h. Conditions B: AlR_3 (2.0 equiv), THF, –25 to –20 °C, 4–6 h.

SYSTEM IMPROVEMENTS, LIMITATIONS, AND MECHANISTIC INSIGHTS

Ni-phosphoramidite-catalyzed 1,2-alane aldehyde additions are remarkably active and high turn-over (TONs) numbers and frequencies (TOFs) can be attained. Effective catalysis at loadings as low as 0.5 mol % Ni is seen with DABAL-Me$_3$ **1a** (run 2). On further reduction to ligand loadings of 0.15 mol %, stereoslectivities of >15:1 are still realized, with TOFs of the order of 55 h^{-1}, but at poor conversion (run 3). Catalyst deactivation accounts for the loss of productivity (increasing the reaction run times leads to no further conversion). This deactivation can, however, be mitigated by using AlMe$_3$ instead with high purity PhCHO and THF leading to TON values in excess of 1000 at –25 °C. Catalyst stability is improved by the presence of excess nickel, without degrading the stereoselectivity, indicating very high ligand-accelerated catalysis (LAC) effects for **L1** ($k_{ML}/k_M > 20$) [4] (runs 4–9).

Table 1 Preparation of (R)-(+)-**2a** (R = Me, R^1 = Ph) at reduced catalyst loadings.[a]

Run	Method	L^1/mol %	Ni(acac)$_2$/mol %	Yield/%[b]	ee/%[b]	TOF/h^{-1} [c]	TON[c]
1	A	2	1	92	91	15	46
2	A	0.5	0.25	53	89	35	106
3	A	0.15	0.1	25	88	56	167
4	B	2.25	1	91	94	9	40
5	B	0.5	1	78	93	35	156
6	B	0.25	1	79	93	70	316
7	B	0.1	1	78	93	173	780
8	B	0.05	1	84	92	373	1680
9	B	0.02	1	38[d]	88	422	1900

[a]All reactions using PhCHO, and DABAL-Me$_3$ **1a** (1.3 equiv, THF 5 °C, 3 h) or AlMe$_3$ (2 M in heptanes, –25 °C, THF 4.5 h).
[b]Yields and ee values determined by GC against internal standards on LIPODEX-A.
[c]TOF/TON values based on amount of (R_{ax},S,S)-**L1** used.
[d]44 % starting material recovered.

While most aromatic aldehydes participate very well in DABAL-Me$_3$ **1a** 1,2-addition [3], very electron-rich 4-(MeO)C$_6$H$_4$CHO leads to an almost racemic product (**2b**, 2 % ee, Table 2, run 1). We

were, therefore, anxious to fully define any electronic limitations on the substrate aldehyde ArCHO (Table 2) and to link these to a simple mechanistic proposal (Scheme 2). We speculated that the poor performance of **2b** was due to opening of a key intermediate **4a**, generating a stereochemically labile carbocation **4b** in the catalytic cycle (Scheme 2). Similar behavior is observed in S_N1 vs. S_N2 opening of epoxides [5]. In support of this hypothesis, changing the 4-MeO ether substituent to a less electron-releasing 4-AcO group resulted in recovery of the enantioselectivity (runs 4–5). The behavior of the 2- and 3-MeO substituted aldehydes is also in accord with this suggestion (runs 2 and 3). Other less (+I) electron-releasing groups (e.g., $4\text{-Bu}^t\text{C}_6\text{H}_4\text{CHO}$, runs 4 and 5) fortunately do not suffer from these problems. The intermediacy of a π-aldehyde complex **3** in the catalytic cycle was suggested to us by the seminal work of Walther, who crystallized $\text{Ni}(\eta^2\text{-O=CHAr})(\text{PCy}_3)_2$ (Ar=Ph, $2,4\text{-(MeO)}_2\text{C}_6\text{H}_3$) [6]. Consistent with this picture, substrates that are expected to enforce σ-binding of the aldehyde carbonyl lone pairs are poor substrates (e.g., 2-thiophene and 2-pyridyl carboxaldehydes give <15 % ee). Similarly, we believe the poor performance of cinamaldehyde (runs 8 and 9) in these reactions is due to complications in C=C vs. C=O π-bonding in the analog of **3** prior to the enantioface-determining ox-idative addition of **3** to **4a**. For this enone, a change of ligand to **L3** is required, together with very high purity DABAL-Me₃ **1a**, to attain even a 9:1 stereoselectivity. In additional support of competing C=C coordination, 2-vinyl-substituted **2h** (run 10) is also attained in poor ee compared to other 2-substituted aldehydes of similar or greater steric demand (runs 11 and 12). Finally, it is worth noting that the first-generation **L1**-based catalyst has apparently some steric limitations on the substrates that may be em-ployed; neither 1 or 2-naphthyl aldehydes afford acceptable results.

Table 2 Scope of methylation of ArCHO under nickel catalysis.[a]

Run	Ar in ArCHO	Product	Method	L	Yield/%[b]	ee/%[b]
1	$4\text{-(MeO)}C_6H_4$	**2b**	A	**L1**	70	2-(+)-(R)
2	$3\text{-(MeO)}C_6H_4$	**2c**	A	**L1**	58	89-(+)-(R)
3	$2\text{-(MeO)}C_6H_4$	**2d**	A	**L1**	32	2-(+)-(R)
4	$4\text{-(AcO)}C_6H_4$	**2e**	A	**L1**	80	91-(+)-(R)
5	$4\text{-(AcO)}C_6H_4$	**2e**	B	**L1**	78	90-(+)-(R)
6	$4\text{-Bu}^tC_6H_4$	**2f**	A	**L1**	91	94-(+)-(R)
7	$4\text{-Bu}^tC_6H_4$	**2f**	B	**L1**	84	92-(+)-(R)
8	(E)-PhCH=CH	**2g**	A	**L3**	53	80-(+)-(R)
9	(E)-PhCH=CH	**2g**	B	**L3**	73	77-(+)-(R)
10	$2\text{-(H}_2\text{C=CH)}C_6H_4$	**2h**	B	**L1**	22	58-(+)-(R)
11	2-ClC_6H_4	**2i**	A	**L1**	62	80-(+)-(R)
12	$2\text{-(CF}_3)C_6H_4$	**2f**	A	**L1**	48	86-(+)-(R)
13	Ph	**2a**	A	**L1**	91	91-(+)-(R)
14	Ph	**2a**	B	**L1**	60	85-(+)-(R)
15	Ph	**2j**	A	**L1**	95	86-(+)-(R)
16	Ph	**2j**	B[c]	**L1**	95	83-(+)-(R)

[a]All reactions using PhCHO, and DABAL-Me₃ **1a** (1.3 equiv, THF 5 °C, 3 h) or AlMe₃ (2 M in heptanes, –25 °C, THF 4.5 h).
[b]Yields and ee values determined by GC against internal standards on LIPODEX-A or CYCLODEX-C. Using in situ prepared DABAL-Et₃ **1b**, 5 h run time.
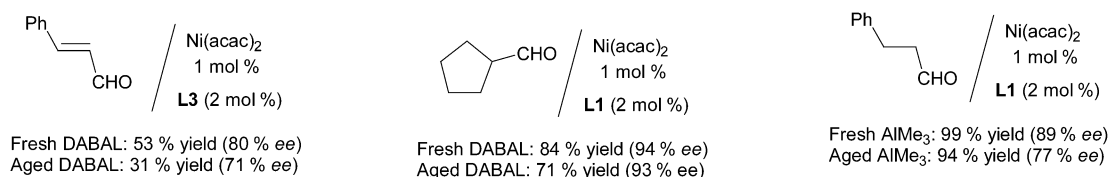
As both AlMe₃ and DABAL-Me₃ **1a** are viable sources of a methyl nucleophile, the strong pos-sibility exists that **1a** simply acts as a reservoir of AlMe₃, releasing it as the $\text{Ni}(L^*)_n$ catalyst requires it (Scheme 2, $a = 0$). If, however, the DABCO remains coordinated to the AlR_3 reagent in the enantio-selective step (Scheme 2, $a = 1$) different ee values should result due to modification of the nickel co-ordination sphere in the enantioselective step. It is difficult to run the required comparison reactions under identical conditions (DABAL-Me₃ **1a** is unreactive under conditions B, and using AlMe₃ under
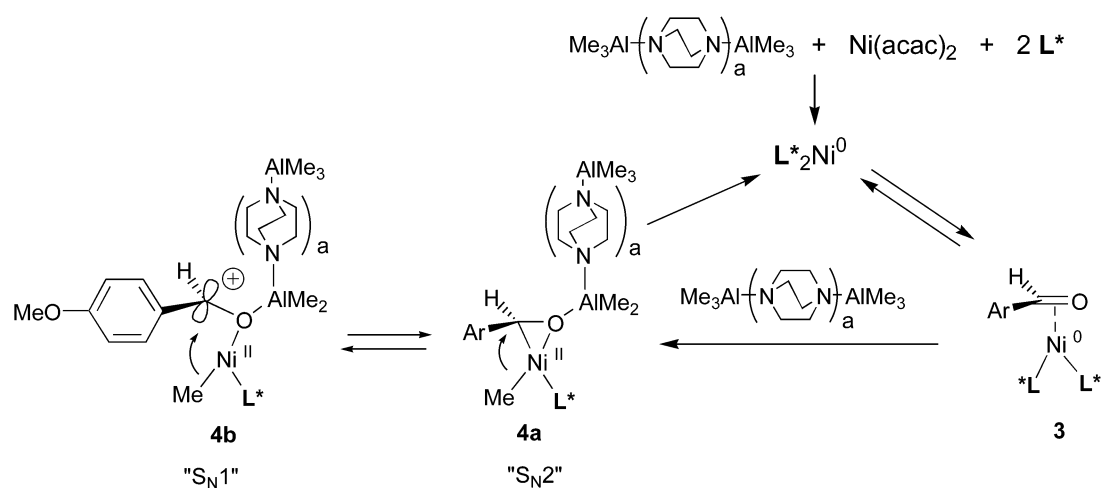
Scheme 2 Proposed catalytic cycle for the 1,2-addition of DABAL-Me$_3$ **1a** ($a = 1$) or AlMe$_3$ ($a = 0$) to aromatic aldehydes.

conditions A leads to secondary racemization reactions). In practice, the ee values attained by both methods A and B using both AlR$_3$ and their DABAL equivalents are very similar, but not identical (Table 2, runs 13 vs. 14 and 15 vs. 16). It is possible that both processes compete in the catalytic cycle.

Attempts to extend the scope of the reaction provided additional insights into the catalytic process. While both AlMe$_3$, AlEt$_3$, or their DABAL-R$_3$ analogs could be used (no β-elimination products are observed) attempts to employ AlBu$^i_3$ as an alkylating agent for PhCHO led to benzyl alcohol becoming the major product (59 %) while PhCH(OH)Bu^i (30 %) was isolated in trivial ee (8 %) using Ni(acac)$_2$ and **L1**. Similarly, it is also found that 1- and 2-naphthaldehyde do not participate in effective catalysis (poor conversion and <10 % ee under conditions A). These findings strongly suggest that excessive crowding in the enantioselective transition state leads to a catastrophic rearrangement in the nickel coordination geometry. Finally, on a practical level, we note that the best substrates (ArCHO) are rather forgiving of the quality of DABAL-R$_3$ **1** or AlR$_3$ reagents used. However, for the more challenging substrates (enones and aliphatic aldehydes), the enantioselectivities attained become a lot more sensitive to the purity of the organoaluminum species used (Scheme 3).


Fresh DABAL: 53 % yield (80 % *ee*)
Aged DABAL: 31 % yield (71 % *ee*)

Fresh DABAL: 84 % yield (94 % *ee*)
Aged DABAL: 71 % yield (93 % ee)

Fresh AlMe$_3$: 99 % yield (89 % *ee*)
Aged AlMe$_3$: 94 % yield (77 % *ee*)

Scheme 3 Precautionary note: always use fresh reagents for the more challenging substrates ['Fresh' reagents are as purchased (Aldrich) or as prepared (DABAL-Me$_3$); 'aged' reagents are after ca. 2 months using non-vacuum line approaches to avoid accidental air inclusion.

TOWARD A WORKING MODEL FOR THE ENANTIOSELECTIVE STEP

The need for monodentate phosphorus ligands (chelate diphosphines afford very low ee values) and the variable amounts of β-elimination observed in the use of AlEt$_3$ (<2 %) to AlBu$^i_3$ (~60 %) are pertinent facts that have to be explained by any mechanism accounting 1,2-alane addition to aldehydes by

these catalysts. The optimal Ni:L* ratio could not be determined by the method of Job as the ee value is independent of the Ni:L ratio in the range 20:1 to 1:3 (e.g., AlMe$_3$ addition to PhCHO gives a linear plot at 93 ± 1 % ee, see Table 1). Inspired by the work of Leitner [7], we turned to a low-level computational approach to identifying key intermediates. We selected semi-empirical PM3 methods [8] to form the basis of our search, as these are computationally inexpensive and allow rapid screening/optimization of fully functionalized catalytic intermediates without the need for specialist computers. The results of some of these searches are summarized in Scheme 4. Calculations were carried out on DABCO free alanes to simplify the computational situation.
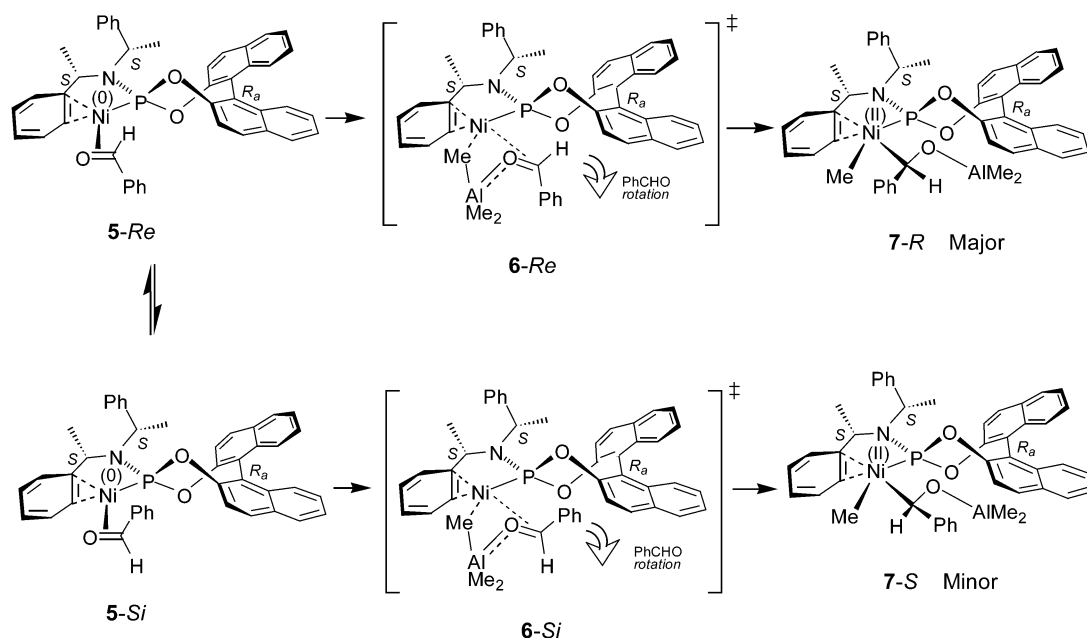
Scheme 4 A mechanistic proposal for the formation of (*R*)-PhCH(OH)Me from PhCHO and AlMe$_3$ under Ni(acac)$_2$/**L1** catalysis.

We propose that a single **L1** binds a Ni(0) center in *P,C=C* mode **5** and that this species incorporates the aldehydes in the η^2 manner observed by Walther [6]. Ni-arene contacts are known [9], but are weak interactions easily displaced by phosphanes, other "strong" ligands, and even other arenes. Interaction of **5** with AlMe$_3$ leads to an oxidative addition (via **6**) promoted by the formation of an extremely strong Al–O bond. Related processes in the oxidative addition of TMSOTf to Ni-coordinated aldehydes has been observed by Ogoshi and coworkers [10]. Reductive elimination from **7** releases the kinetic aluminum alkoxide product and regenerates **5**. Consistent with our proposal, increasing the size of the alane to AlBu$^i_3$ is expected to displace the Ni-arene contact leading β-elimination via the vacant site generated. As such a process also results in Ni-phosphoramidite free rotation, a collapse in the enantioselectivity is observed. If **6**-*Re* is the favored transition state, then the observed asymmetric induction should be mostly dependent on the chirality of the 1,1'-binaphthyl fragment rather than the amine. This is the case as ligand **L2** (with S_{ax} configuration) leads to (*S*)-**2a** in 68 % ee using DABAL-Me$_3$ **1a**. Transition-state **6**-*Re* is expected to put the aldehydic C–H in very close proximity to the 3-position of the binaphthyl core. In support of this idea, all the 3,3'-binaphthyl-based ligands we have tried in this chemistry thus far have delivered far lower enantioselectivities. To provide further evidence of the viability of an η^2-arene contact in intermediates **5–7**, four ligands differing in electronic properties were compared in DABAL-Me$_3$ **1a** alkylations of cinnamaldehyde (Scheme 5).
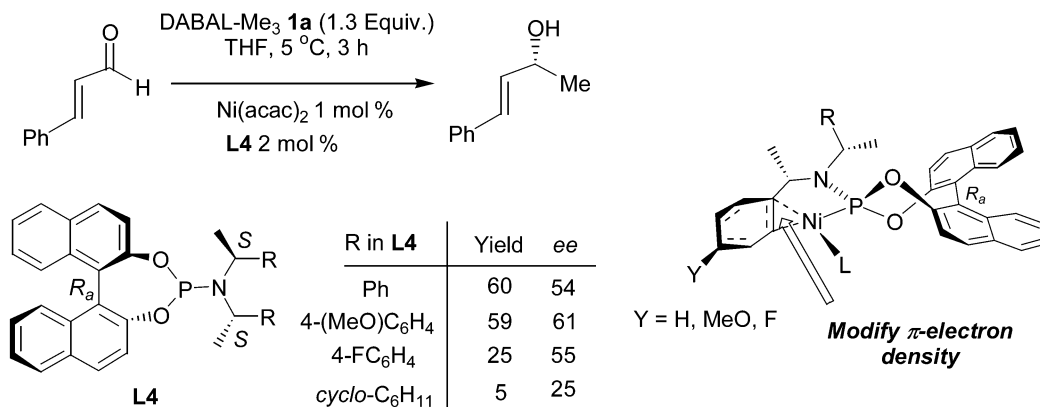
Scheme 5 Experiments designed to perturb a putative ligand π-contact in catalytic DABAL chemistry.

The results of these experiments are consistent with the proposed η^2-contact of the amine aryl group with the Ni center. Of course, an alternative explanation involving through bond effects to the *P*-donor cannot be discounted, but it is harder to rationalize the observed trend. Additional support for the idea of a π-contact from **L1** and related ligands to nickel comes from the observation that addition of 10 mol % 4-fluorostyrene to the catalyst formed from **L1**/Ni(acac)$_2$ leads to a distinct reduction in the catalyst selectivity (e.g., PhCHO/AlMe$_3$ under conditions B gives **2a** in 79 % ee, **45 % *cy***). It is known that 4-FC$_6$H$_4$CH=CH$_2$ is a strong promoter in Ni-catalyzed cross-coupling reactions [11]. Presently, its exact role is not known, but it is popularly thought to act as a π-donor and as such it could effect a displacement of the Feringa ligand chelate binding mode suggested in Scheme 5.

CROSS-COUPLING

Finally, DABAL-Me$_3$ **1a** is also of utility in other C–C bond-forming reactions, of which we choose to highlight here group 10 catalyzed cross-coupling reactions. In the presence of 3 mol % Pd(PPh$_3$)$_4$ in THF at reflux, preliminary trials revealed that synthetically useful yields of methylated products are attained (Table 3). Between 0.5–0.8 equiv of DABAL-Me$_3$ **1a** are required to ensure complete conversion of aryl bromides and iodides. Control experiments revealed that only one methyl group is transferred per AlMe$_3$ unit. Nitro groups were only partial tolerated in the reaction, for example, GC–MS studies of the reaction of 1-bromo-2-nitrobenzene revealed the presence of significant amounts of PhNO by-product through deoxygenation events. Additional functional groups were not tolerated by the reaction: NH$_2$, CHO, C(O)Me, OAc. Selective methylation of aryl-iodide bonds in the presence of aryl chlorides was possible. Overall, the behavior of the DABAL-Me$_3$ reagent is comparable in this chemistry to the stabilized aluminum–methyl compounds introduced by Schumann and Blum [12].

Table 3 Cross-coupling of aryl halides with DABAL-Me$_3$ **1a**.[a]

Starting material	Product	Amount DABAL-Me$_3$ **1a**/equiv	Yield/%[b]
1-Bromonaphthalene	1-methylnaphthalene	0.8	71 (71)
2-Bromonaphthalene	2-methylnaphthalene	0.8	84 (71)
2-Bromonaphthalene	2-methylnaphthalene	0.5	97
1-Chloro-3-iodobenzene	1-chloro-3-methylbenzene	0.8	96 (74)
1-Bromo-2-nitrobenzene	2-nitrotoluene	0.8	50

[a]Conditions: Ratio of DABAL-Me$_3$/ArX/Pd(PPh$_3$)$_4$ 0.5–0.8 mmol/1.0 mmol/3 mol %, 4 h reflux in THF (3 mL).
[b]By GC vs. internal standard (phenyldecane), isolated yields in parentheses.

CONCLUSIONS

The introduction of the DABAL-Me$_3$ **1a** reagent has afforded a number of opportunities for the preparation of fine chemicals through efficient transition-metal catalysis. Ni-phosphoramidite-promoted catalysis allows the enantioselective preparation of secondary alcohols in high ee. Extension of this reaction to encompass aliphatic substrates is possible by the use of AlMe$_3$. This area is of significance as such species are not always accessible via traditional asymmetric hydrogenation approaches. A working model of the selective catalytic cycle has been proposed, and it is hoped that this will allow rational design of second-generation ligands for this process. Clear potential exists for the use of DABAL-R$_3$ **1** reagents in other transition-metal-catalyzed processes—preliminary cross-coupling studies have been reported, details of this and other applications will follow in the near future.

ACKNOWLEDGMENTS

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