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A One-Pot Asymmetric Sequential Amination-Alkylation of Aldehydes: Expedient Synthesis of Aliphatic Chiral Amines

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A one-pot asymmetric sequential amination-alkylation method has been developed for the synthesis of alkyl-alkyl′ α-chiral primary amines (aliphatic primary amines with a chiral center adjacent to the nitrogen atom) from aldehydes. In situ aldimine formation from non-branched, α-branched, and β-branched aliphatic aldehydes with (*R*)- or (*S*)-α-(methylbenzyl)amine [catalyzed by 5 mol-% Ti(O*i*Pr)$_4$] followed by reaction with a methyl, ethyl, or *n*-butyl cuprate complex in the presence of boron trifluoride or an allyl Grignard reagent provides good yield (77–88 %) and diastereomeric excess (77–92 %) for amines **2** or **5**. To further demonstrate the usefulness of this method, several of the secondary amine products (**2d**, **2e**, and **5**) were hydrogenolyzed, providing the corresponding enantioenriched alkyl-alkyl′ α-chiral primary amines **3d**, **3e**, and **6** (86–96 % yield).

Introduction

α-Chiral amine moieties are found in agrochemicals, natural products, and pharmaceutical drugs.[1] Despite their importance, asymmetric methods for their efficient synthesis have only recently begun to appear. For the synthesis of aliphatic amines, two main strategies have had significant impact: one employing "hydrogen" chemistry (molecular hydrogen,[2] transfer hydrogen,[3] hydrides,[4] or hydrosilylation[5]) and another based on carbanion[6–12] chemistry. Comparison of the literature pertaining to these two different approaches shows them to be generally complementary. For example, the carbanion methods are particularly good for the synthesis of α-chiral amines with two similarly sized aliphatic substituents at the α-chiral carbon atom in high *de* or *ee*. Presently, this is not possible when using the "hydrogen" based methods.

The aforementioned methods all rely on carbonyl compounds and amine starting materials, but flexibility regarding the amine is not possible yet.[13] Instead, specific sources of nitrogen (e.g. *tert*-butanesulfinamide, α-(methylbenzyl) amine, anisidine, and diphenylphosphinoylamide) are used and the supporting amine functionality is removed during the last step to provide an α-chiral aliphatic primary amine. Regarding the carbanion approaches to alkyl-alkyl′ α-chiral amines, the methods of Ellman[6] are precedent-setting, because they result in high overall yields and *ee* in three reaction steps starting from aliphatic aldehydes. Highly diastereoselective allyl anion additions to the chiral aldimines of (*R*)-phenylglycine amide have been achieved by Kellogg, Broxterman, and co-workers, again three reaction steps are required from aldehydes to produce the primary amine.[12e] More recently, the groups of Charette[8] and Hoveyda and Snapper[9] have independently developed enantioselective carbanion methods relying on in situ aldimine formation (enantioselective sequential amination-alkylation of aldehydes), thus decreasing the number of reaction steps starting from aliphatic aldehydes to two.

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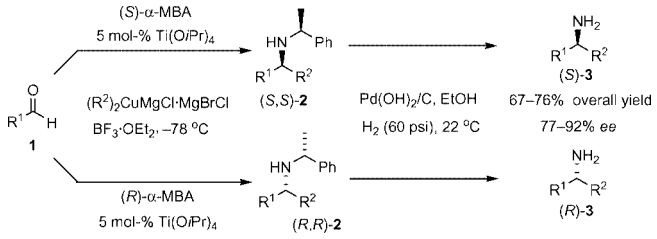
Results and Discussion

Two-Step Strategy Leading to Aliphatic α-Chiral Primary Amines

Noting the beneficial qualities of the aforementioned methods, we developed an alternative approach by using the chiral ammonia equivalents (*R*)- or (*S*)-α-(methylbenzyl)amine (α-MBA) to achieve alkyl-alkyl′ α-chiral primary amine synthesis in two reaction steps from aliphatic aldehydes (Scheme 1). The first step in this one-pot sequence is the reaction of aliphatic aldehydes **1** with (*R*)- or (*S*)-α-MBA in the presence of 5 mol-% Ti(O*i*Pr)$_4$ for 30 min at room temperature. Addition of this mixture to a dialkyl cuprate complex in the presence of boron trifluoride at –78 °C provides α-chiral amines **2** as the major diastereomeric products. Previous approaches based on α-MBA[11] have always relied on forming and isolating the corresponding (*R*)- or (*S*)-*N*-α-(methylbenzyl) aldimine before adding the carbanion. Our method reduces this two-step procedure to a one-pot procedure. Finally, to show the

full potential of this method, we removed the chiral auxiliary from amines **2** to obtain the enantioenriched α-chiral primary amines **3** in high yield and unaffected *ee*.



Scheme 1. Two-step procedure for the synthesis of enantioenriched aliphatic primary amines.

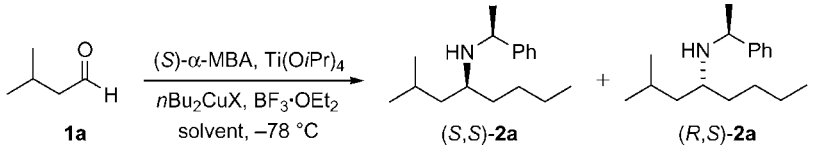
Proof of Concept

To investigate the feasibility of a one-pot sequential amination-alkylation reaction, we first had to establish that aliphatic aldehydes could be reliably and completely converted to aldimines. Isovaleraldehyde (**1a**) was chosen for this purpose and was used as the limiting reagent (5 mmol). The chiral ammonia equivalents (*R*)- or (*S*)-α-MBA (1.05 equiv.) were chosen, because they offer flexibility in producing either enantiomeric series of the desired amine product, are the least expensive amine auxiliaries available, and are routinely used in the pharmaceutical industry.[14] The choice of $Ti(OiPr)_4$ to catalyze aldimine formation was based on our experience with its use for ketimine formation.[15] GC analysis of a mixture of aldehyde **1a**, (*S*)-α-MBA, and $Ti(OiPr)_4$ (5 mol-%), prior to carbanion addition, showed the expected aldimine (>97 area%) before 30 min. After carbanion addition, >95 area% of **1a** and the corresponding aldimine was consumed. Failure to use $Ti(OiPr)_4$ resulted in significantly lower product yields (compound **2a**) due to unreacted starting materials and by-product formation.

After establishing that in situ aldimine formation was possible, the feasibility of efficient *n*-butyl carbanion addition had to be assessed. Addition to a Grignard reagent (*n*BuMgCl) alone or in the presence of stoichiometric quantities of a copper salt (CuI, CuBr, $CuBr{\cdot}SMe_2$, or CuCN) [16] did not provide the desired amine product **2a** (Table 1, entries 1 and 3–6). The use of $BF_3{\cdot}OEt_2$ has been previously reported to improve the yield and diastereoselectivity of cuprate additions.[11a,11c,17] Upon addition of the in situ formed aldimine to *n*BuMgCl in the presence $BF_3{\cdot}OEt_2$ and a catalytic amount of CuBr, we clearly observed amine **2a** as the major product, but in low diastereoselectivity (Table 1, entries 7 and 8).

The best results (yield and diastereoselectivity) were obtained when using *n*BuMgCl with stoichiometric amounts of CuBr, which was preferred over CuI, which, in turn, was preferred over $CuBr{\cdot}SMe_2$ or CuCN (Table 1, compare entries 11, 13, 16, and 17). For example, when CuI was the source of copper, only 2.0 equiv. of cuprate was required, and amine **2a** was obtained in 77% yield and 89% diastereoselectivity (Table 1, entry 16). Adding more than 2.0 equiv. of a CuI based cuprate did not improve the yield or *de*. Slightly improved results (85% yield and 90% dia-

Table 1. Reaction parameter optimization for the one-pot asymmetric sequential amination-alkylation of isovaleraldehyde.[a]



Entry	Cu salt	*n*BuMgCl (equiv.)	*n*BuLi (equiv.)	$BF_3{\cdot}OEt_2$ (equiv.)	Solvent	Yield (%)[b]	*de* (%)[c]
1	none	5	–	–	THF	0	–
2	none	5	–	2	THF	0	–
3	CuI	4	–	–	THF	0	–
4	CuBr	6	–	–	THF	0	–
5	$CuBr{\cdot}SMe_2$	6	–	–	THF	0	–
6	CuCN	–	9	–	THF	0	–
7[d]	CuBr	5	–	2	THF	–[g]	44
8[e]	CuBr	6	–	2	THF	–[g]	52
9[f]	CuBr	–	6	3	THF	–[g]	80
10	CuBr	6	–	2	THF	88	88
11	CuBr	6	–	2	Et_2O	85	90
12	CuBr	6	–	2	CH_2Cl_2	80	85
13	$CuBr{\cdot}SMe_2$	6	–	2	THF	–[g]	88
14	CuI	–	6	3	THF	–[g]	65
15	CuI	4	–	2	THF	78	85
16	CuI	4	–	2	Et_2O	77	89
17[f]	CuCN	6	–	3	THF	–[g]	71
18	CuCN	–	10	5	THF	81	84

[a] Isovaleraldehyde (5.0 mmol, 1 equiv.), (*S*)-α-MBA (1.05 equiv.), $Ti(OiPr)_4$ (5 mol-%), solvent (0.08–0.10 M). [b] Isolated yield of both diastereomers after flash chromatography. [c] Determined by GC analysis; the major diastereomer is (*S*,*S*)-**2a**. [d] 5 mol-% CuBr was used. [e] 25 mol-% CuBr was used. [f] 25% of the starting material remained unreacted (GC area%). [g] The isolated yield was not recorded, because of the low *de* and/or the presence of unreacted starting material (>15% by GC).

stereoselectivity) were observed when using CuBr, albeit 3.0 equiv. of cuprate were required (Table 1, entry 11). As we examined more aldehyde substrates, higher yields and diastereoselectivity were observed for CuBr cuprates than for CuI cuprates. The counterion of the Grignard reagent had no effect on reactivity or diastereoselectivity when comparing *n*BuMgCl to its analogous bromide. Finally, the diastereoselectivity was found to be higher in Et_2O than in THF or CH_2Cl_2 (Table 1, entries 10–12, 15, and 16).

Satisfactory results were also observed when *n*BuMgCl was replaced with *n*BuLi (Table 1, entry 18); however, unlike a Grignard reagent, *n*BuLi required CuCN (preferred over CuBr or CuI) in the presence of $BF_3{\cdot}OEt_2$ (Table 1, entries 9 and 14). This method could not be extended to the use of other Gilman reagents (e.g. methyl- or ethyllithium in THF or Et_2O).

Compared with other in situ methods,[8,9] which require a minimum of 5 or 6 equiv. of $ZnEt_2$ (the standard source of carbanion in these studies), our method requires 2 or 3 equiv. of nBu_2CuX. Compared to methods based on preformed (*R*)- or (*S*)-*N*-α-(methylbenzyl) aldimines, our method requires the same number of equivalents of $nBu_2Cu{\cdot}MgI$, or one additional equivalent of $nBu_2Cu{\cdot}MgBr$.[11c]

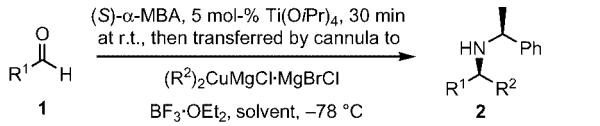
Examination of Various Normal and Branched Aliphatic Aldehydes with Methyl, Ethyl, and *n*-Butyl Carbanions

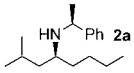
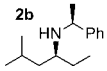
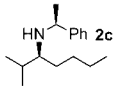
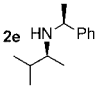
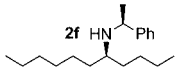
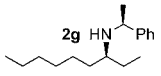
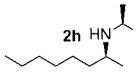
After determination of the basic reaction parameters, we turned our attention to diversifying the starting aliphatic aldehyde and investigating the effect of adding carbanions with different chain lengths to those aldehydes. Addition of *n*-butyl cuprate to isobutyraldehyde or heptaldehyde proceeded in good yield and diastereoselectivity (Table 2, entries 3 and 6). It is significant to note the high *de* (86%) of **2f**, which has two very similarly sized α-substituents (*n*-hexyl and *n*-butyl). In the case of methyl and ethyl cuprates, THF was not only preferred over Et_2O, but essential for allowing complete reaction to occur. This was readily explained by the low observed solubility of both methyl and ethyl cuprates in Et_2O, whereas the more lipophilic *n*-butyl cuprate was readily soluble in Et_2O.

Comparing the addition of ethyl cuprate to progressively more hindered aldehydes (heptaldehyde, isovaleraldehyde, and finally isobutyraldehyde), we noted that the resulting amine products **2** showed very little difference in *de*: 81%, 83%, and 86%, respectively (Table 2, entries 7, 2, 4). This strongly implies that the aliphatic chain of the aldehyde does not reside in the crucial diastereotopic space of the transition state responsible for carbanion facial selectivity. It should be noted that ethyl cuprate addition to isobutyraldehyde and heptaldehyde required the presence of 3 equiv. of ethyl cuprate and $BF_3{\cdot}OEt_2$ for complete reaction, while isovaleraldehyde required 4 equiv.

Nucleophilic addition of dimethyl cuprates is known to be slow in comparison with other simple types of dialkyl cuprates, e.g. *n*-butyl.[17,18] Even under optimal reaction conditions, the addition of dimethyl cuprates to isobutyraldehyde or heptaldehyde resulted in less than 80% conversion. Only after addition of 5 and 6 equiv. of methyl cuprate, respectively, was complete consumption of the starting material possible (Table 2, entries 5 and 8). For the synthesis of methyl-alkyl α-chiral amines, e.g. **2e** and **2h**, the previously outlined hydrogen methods[2–4a,5] provide superior results. For all of the cuprate nucleophilic additions, the (*S*,*S*)-**2** amine is the major diastereomer formed when (*S*)-α-MBA is used as the chiral ammonia equivalent.[19,20]

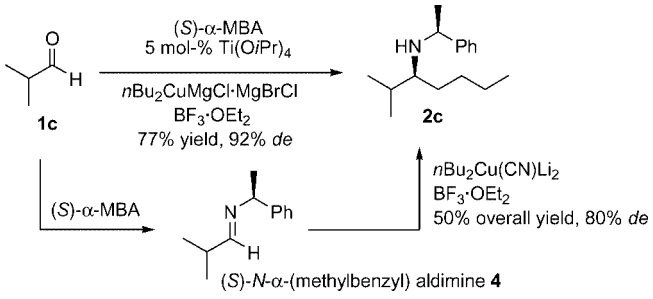
Table 2. Scope of aliphatic aldehyde and carbanion substrates.[a]



Entry	Product	Solvent	Yield (%)[b]	*de* (%)[c]
1		THF	88	88
		Et_2O	85	90
2[d]		THF	84	83
		Et_2O[e]	–[f]	80
3		THF	79	84
		Et_2O	77	92
4[g,h]		THF	85	86
		Et_2O	80	80
5[i]		THF	78	87
6		THF	87	82
		Et_2O	85	86
7[g]		THF	86	78
		Et_2O	81	81
8[j]		THF	79	77

[a] Aldehyde (5.0 mmol, 1 equiv.), (*S*)-α-MBA (1.05 equiv.), $Ti(OiPr)_4$ (5 mol-%), solvent (0.08–0.10 M), CuBr (3 equiv.), MeMgCl, EtMgCl, or *n*BuMgCl (6 equiv.), and $BF_3{\cdot}OEt_2$ (2 equiv.). [b] Isolated yield of both diastereomers after chromatography. [c] Determined by GC analysis. [d] CuBr (4 equiv.), EtMgCl (8 equiv.), $BF_3{\cdot}OEt_2$ (4 equiv.). [e] 15% starting material remained unreacted (GC area%). [f] The isolated yield was not recorded. [g] $BF_3{\cdot}OEt_2$ (3 equiv.). [h] After removal of chiral auxiliary, the *ee* was determined by chiral GC analysis of the trifluoroacetyl derivative of the primary amine. [i] CuBr (5 equiv.), MeMgCl (10 equiv.), $BF_3{\cdot}OEt_2$ (5 equiv.). [j] CuBr (6 equiv.), MeMgCl (12 equiv.), $BF_3{\cdot}OEt_2$ (6 equiv.).

The stepwise approach relying on α-MBA (chiral imine formation, isolation, and subsequent carbanion addition) has been previously examined and can be compared to our work in one instance. nBu$_2$Cu(CN)Li$_2$ (2 equiv.) was the cuprate of choice for the addition of an *n*-butyl carbanion to (*S*)-α-(methylbenzyl) aldimine **4** in the presence of BF_3·OEt_2, and this provided a 50% overall yield of amine **2c** (from **1c**) in 80% *de* (Scheme 2).[11b,11c] Our one-pot method eliminates the need for isolation of the aldimine intermediate and provides amine **2c** in higher yield (77%) and diastereoselectivity (92%).



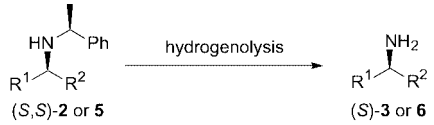
Scheme 2. Preformed imine vs. in situ method.

Regarding the addition of allyl carbanions, allylmagnesium chloride was found to be optimal and required no BF_3·OEt_2 when examining isobutyraldehyde. The reaction was performed by using substoichiometric amounts of Ti(O*i*Pr)$_4$ (5 mol-% to 50 mol-%) followed by the addition of allylmagnesium chloride at –78 °C. Addition of diallyl cuprates did not improve upon this result. This reaction, which represents a reverse sense of addition[21] relative to the methyl, ethyl, or butyl additions, provided the homoallylic amine **5** (not shown). The hydrogenolysis of this amine afforded primary amine **6** in very good overall yield (84%), but with mediocre enantioselectivity (76%). The stereochemistry of **5** was confirmed by chemical correlation with the known compound **6**.[20] In general, cleavage of the auxiliary compounds proceeded smoothly with a Pd-based hydrogenolysis catalyst (Table 3) and provided the enantioenriched aliphatic α-chiral primary amines **3d**, **3e**, and **6** in good overall yield (67–84%) with *ee* (chiral GC analysis) values that corresponded to the *de* values of the starting material **2** (achiral GC analysis) (compare Table 2 and Table 3).

Conclusions

We have developed a one-pot two-step procedure for the synthesis of enantioenriched alkyl-alkyl′ α-chiral primary amines from aliphatic aldehydes. The usefulness of (*S*)-α-MBA as a chiral ammonia equivalent during the nucleophilic addition of methyl, ethyl, allyl, and *n*-butyl carbanions to non-branched, α-branched, and β-branched aliphatic aldehydes has been demonstrated in good yield and *de*. We have significantly reduced the amount of carbanion required relative to current in situ methods and have shown that one isolation step can be removed in comparison with the methods using preformed α-MBA aldimines. Hydrogenolysis formed alkyl-alkyl′ α-chiral primary amines in very good overall yield and in the corresponding *ee*. Furthermore, the ease of preparation makes our new asymmetric sequential amination-alkylation method a competitive alternative to the existing methodologies and should be applicable to aromatic aldehydes and aryl cuprates. We focused on the synthesis of aliphatic chiral amines in this paper, because in the past they have been difficult to achieve in high yield and *ee*.

Table 3. Hydrogenolysis of secondary amines **2** and **5**.



Entry	Product	Source of Pd	Overall yield (%)[b]	*ee* (%)[c]
1[a]	**3d** 	$Pd(OH)_2$/C	76	86
2[a]	**3e** 	$Pd(OH)_2$/C	67	87
3[d]	**6** 	Pd/C	84	76

[a] Diastereomeric amine (2.0 mmol, 1 equiv.), $Pd(OH)_2$/C (5 mol-%), AcOH (2 equiv.), EtOH (0.4 M), H_2 (60 psi), room temperature. [b] Isolated yield of analytically pure material starting from the aldehyde. [c] Determined by chiral GC analysis of the trifluoroacetyl derivative of primary amine **3** or **6** with the racemate (see Supporting Information). [d] Homoallylic amine (2.0 mmol, 1 equiv.), Pd/C (4 mol-%), MeOH (0.4 M), H_2 (50 psi), room temperature.

Experimental Section

Representative experimental procedures for the one-pot asymmetric sequential amination-alkylation preparation of amine (*S*,*S*)-**2a** by using di-nBu$_2$CuX (Table 1).

Synthesis of 2a with CuCN in THF: A round-bottom flask containing anhydrous CuCN (2.24 g, 25.0 mmol, 5.0 equiv.) was gently heated (< 80 °C) with a heat gun under high vacuum for 5 min, flushed with nitrogen, and cooled to room temperature before the addition of THF (30.0 mL, in a total volume of 39.0 mL, 0.08 M). This solution was cooled to –78 °C and added to *n*BuLi in hexanes (20.0 mL, 2.5 M, 50.0 mmol, 10.0 equiv.) over 5 min. The mixture was then warmed to –45 °C, stirred for 15 min, and cooled back to –78 °C. BF_3·OEt_2 (3.13 mL, 25.0 mmol, 5.0 equiv.) was added over 2 min and the solution was stirred for another 5 min. A prestirred (0.5 h at room temp.) solution of isovaleraldehyde (0.54 mL, 5.0 mmol, 1.0 equiv.), THF (7.0 mL), Ti(O*i*Pr)$_4$ (73 μL, 0.25 mmol, 0.05 equiv.) and (*S*)-α-MBA (0.68 mL, 5.25 mmol, 1.05 equiv.) was then added by cannula over 20–25 min. Additional THF (2.0 mL) was added to the residual imine, and the resulting solution was added by cannula to the reaction flask. The reaction solution was stirred at –78 °C for 2 h, then at –45 °C for 1 h. The reaction was quenched by the addition of a 7:3 mixture (total volume 30 mL) of

saturated NH_4Cl and NH_4OH (25%) at –45 °C and was stirred for 5 min. The cooling bath was removed, and the stirring was continued for another 90 min at room temp. Et_2O (20 mL) was added, and the biphasic solution was stirred for 5 min. The reaction mixture was then filtered through a bed of Celite, and the Celite subsequently washed with Et_2O (3 × 25 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with saturated NH_4Cl (2 × 25 mL), then with brine (2 × 20 mL), dried with Na_2SO_4, filtered, and the solvents were evaporated to dryness to obtain the crude product (85% *de*). Purification by silica gel flash chromatography (hexanes/EtOAc/NH_4OH, 93.5:3.5:3) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with ethereal HCl to yield the hydrochloride salt (1.15 g, 81% yield). The major (*S*,*S*) diastereomer was isolated in pure form after recrystallization (EtOAc/hexanes, 4:6) of the HBr salt. GC (program A, see General Experimental Details in the Supporting Information): retention time [min]: major (*S*,*S*)-**2a** isomer, 30.28; minor (*R*,*S*)-**2a** isomer, 29.35.

(*S*,*S*)-2a major isomer (free base): R_f = 0.48 (hexanes/EtOAc/NH_4OH, 83:15:2). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.19 (m, 5 H), 3.86 (q, J = 6.4 Hz, 1 H), 2.38–2.32 (m, 1 H), 1.63–1.55 (m, 1 H), 1.33–1.12 (m, 12 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.84 (t, J = 6.8 Hz, 3 H), 0.77 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.6, 128.2, 126.7, 126.6, 55.1, 52.4, 44.4, 34.8, 27.7, 24.9, 24.6, 23.5, 22.8, 22.6, 14.0 ppm. HRMS (70 eV): calcd. for $C_{17}H_{29}N$ [M^+] 247.2300; found 247.2295. LRMS (EI): *m*/*z* (%): 247 (2) [M^+], 232 (4), 190 (100), 106 (10), 105 (82), 86 (48). IR (KBr): $\tilde{\nu}_{max}$ = 3441, 3026, 2956, 2930, 2628, 1467, 1367, 1154, 1118, 700, 558 cm^{-1}.

Synthesis of 2a with CuBr or CuI in THF, Et_2O, or CH_2Cl_2 (Table 1): A round-bottom flask containing anhydrous CuBr or CuI (2.0–3.0 equiv.) was gently heated (< 80 °C) with a heat gun under high vacuum for 5 min, flushed with nitrogen, and cooled to room temperature before the addition of THF, Et_2O, or CH_2Cl_2 (30.0–35.0 mL, in a total volume of 39.0–44.0 mL, 0.10–0.08 M). This solution was cooled to –45 °C and added to *n*-BuMgCl in THF (4.0–6.0 equiv.) over 5 min. The mixture was then further stirred at –45 °C for 15 min, and then cooled to –78 °C. $BF_3{\cdot}OEt_2$ (2.0 equiv.) was added over 2 min, and the solution was stirred for 5 min. A prestirred (0.5 h at room temp.) solution of isovaleraldehyde (0.54 mL, 5.0 mmol, 1.0 equiv.) in THF, Et_2O, or CH_2Cl_2 (7.0 mL), with $Ti(OiPr)_4$ (73 μL, 0.25 mmol, 0.05 equiv.) and (*S*)-α-MBA (0.68 mL, 5.25 mmol, 1.05 equiv.) was added by cannula over 20–25 min. Additional THF, Et_2O, or CH_2Cl_2 (2.0 mL) was added to the residual imine, and the resulting solution was added by cannula to the reaction flask. The reaction solution was stirred at –78 °C for 2 h, then at –45 °C for 1 h. The reaction was quenched by the addition of a 7:3 mixture (total volume 30 mL) of saturated NH_4Cl and NH_4OH (25%) at –45 °C and was stirred for 5 min. The cooling bath was removed, and the stirring was continued for another 90 min at room temp. Et_2O (20 mL) was added, and the biphasic solution was stirred for 5 min. The reaction mixture was then filtered through a bed of Celite, and the Celite was subsequently washed with Et_2O (3 × 25 mL). The aqueous phase was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with saturated NH_4Cl (2 × 25 mL), then with brine (2 × 20 mL), dried with Na_2SO_4, filtered, and evaporated to dryness to obtain the crude product (*de* was measured with unpurified material). Purification by silica gel flash chromatography provided the mixture of diastereomers as a colorless viscous liquid, which was treated with ethereal HCl to obtain the hydrochloride salt [note that amine products are considered semivolatile and converted into the HCl salts, then kept under high vacuum (defined as 0.5 Torr) for at least 24 h.]. The major (*S*,*S*) diastereomer was isolated in pure form either through further flash chromatography or by the recrystallization of the HBr or HCl salt.

CuBr with Et_2O as a Solvent: Isovaleraldehyde (0.54 mL, 5.0 mmol, 1.0 equiv.), CuBr (2.15 g, 15.0 mmol, 3.0 equiv.), *n*BuMgCl in THF (15.0 mL, 2.0 M, 30.0 mmol, 6.0 equiv.), $BF_3{\cdot}OEt_2$ (1.27 mL, 10.0 mmol, 2.0 equiv.), Et_2O (44.0 mL, 0.08 M); 90% *de*. Purification by silica gel flash chromatography (hexanes/EtOAc/NH_4OH, 93.5:3.5:3) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with ethereal HCl to obtain the hydrochloride salt (1.21 g, 85% yield).

CuBr with THF as a Solvent: Isovaleraldehyde (0.54 mL, 5.0 mmol, 1.0 equiv.), CuBr (2.15 g, 15.0 mmol, 3.0 equiv.), *n*BuMgCl in THF (15.0 mL, 2.0 M, 30.0 mmol, 6.0 equiv.), $BF_3{\cdot}OEt_2$ (1.27 mL, 10.0 mmol, 2.0 equiv.), THF (39.0 mL, 0.09 M); 88% *de*. Purification by silica gel flash chromatography (hexanes/EtOAc/NH_4OH, 93.5:3.5:3) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with ethereal HCl to obtain the hydrochloride salt (1.25 g, 88% yield).

CuBr with CH_2Cl_2 as a Solvent: Isovaleraldehyde (0.54 mL, 5.0 mmol, 1.0 equiv.), CuBr (2.15 g, 15.0 mmol, 3.0 equiv.), *n*BuMgCl in THF (15.0 mL, 2.0 M, 30.0 mmol, 6.0 equiv.), $BF_3{\cdot}OEt_2$ (1.27 mL, 10.0 mmol, 2.0 equiv.), CH_2Cl_2 (39.0 mL, 0.09 M); 85% *de*. Purification by silica gel flash chromatography (hexanes/EtOAc/NH_4OH, 93.5:3.5:3) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with ethereal HCl to obtain the hydrochloride salt (1.13 g, 80% yield).

CuI with Et_2O as a Solvent: Isovaleraldehyde (0.54 mL, 5.0 mmol, 1.0 equiv.), CuI (1.9 g, 10.0 mmol, 2.0 equiv.), *n*BuMgCl in THF (10.0 mL, 2.0 M, 20.0 mmol, 4.0 equiv.), $BF_3{\cdot}OEt_2$ (1.27 mL, 10.0 mmol, 2.0 equiv.), Et_2O (44.0 mL, 0.09 M); 89% *de*. Purification by silica gel flash chromatography (hexanes/EtOAc/NH_4OH, 93.5:3.5:3) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with ethereal HCl to obtain the hydrochloride salt (1.09 g, 77% yield).

CuI with THF as a Solvent: Isovaleraldehyde (0.54 mL, 5.0 mmol, 1.0 equiv.), CuI (1.9 g, 10.0 mmol, 2.0 equiv.), *n*BuMgCl in THF (10.0 mL, 2.0 M, 20.0 mmol, 4.0 equiv.), $BF_3{\cdot}OEt_2$ (1.27 mL, 10.0 mmol, 2.0 equiv.), THF (39.0 mL, 0.10 M); 85% *de*. Purification by silica gel flash chromatography (hexanes/EtOAc/NH_4OH, 93.5:3.5:3) gave the mixture of diastereomers as a colorless viscous liquid, which was then treated with ethereal HCl to obtain the hydrochloride salt (1.12 g, 78% yield).

Supporting Information (see footnote on the first page of this article): A summary of general experimental practices and detailed procedures for all remaining compounds (**2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, **3d**, **3e**, **5**, and **6**) and all ^1H and ^{13}C NMR spectra and GC chromatograms (*de* and *ee*) are provided for all new compounds.

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