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Mild Metal-Free Hydrosilylation of Secondary Amides to Amines

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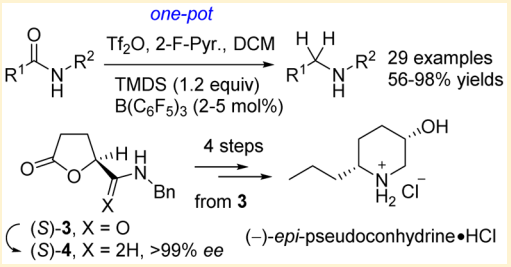
Supporting Information

ABSTRACT: The combination of amide activation by Tf_2O with $B(C_6F_5)_3$-catalyzed hydrosilylation with TMDS constitutes a method for the one-pot reduction of secondary amides to amines under mild conditions. The method displays a broad applicability for the reduction of many types of substrates, and shows good compatibility and excellent chemoselectivity for many sensitive functional groups. Reductions of a multifunctionalized α,β-unsaturated amide obtained from another synthetic methodology, and a C−H functionalization product produced the corresponding amines in good to excellent yield. Chemoselective reduction of enantiomeric pure (ee >99%) tetrahydro-5-oxo-2-furaneamides yielded 5-(aminomethyl)dihydrofuran-2(3*H*)-ones in a racemization-free manner. The latter were converted in one pot to *N*-protected 5-hydroxypiperidin-2-ones, which are building blocks for the synthesis of many natural products. Further elaboration of an intermediate led to a concise four-step synthesis of (−)-*epi*-pseudoconhydrine.



INTRODUCTION

The secondary amine is a structural motif found in numerous medicinal agents and bioactive alkaloids. In the list of top 200 brand-name drugs by total US prescriptions in 2012, 43 of those pharmaceuticals contain a secondary amino functional group,[1] from which, 19 are *N*-methyl, *N*-isopropyl, or *N*-*tert*-butylamines (cf. Figure 1). Because of the easy availability[2] and high stability of amides, their reduction constitutes an important entrance to amines.[3] The classical methods utilizing aluminum and boron-based strong reducing reagents[4] such as $LiAlH_4$, borane, and DIBAL-H present several drawbacks such as low functional group tolerance, production of large amounts of alumino residue and/or formation of borane-amine adducts. In fact, stepwise methods are being routinely used in organic synthesis, which require an extra step to convert an amide to a thioamide[2d] or an imide.[5]

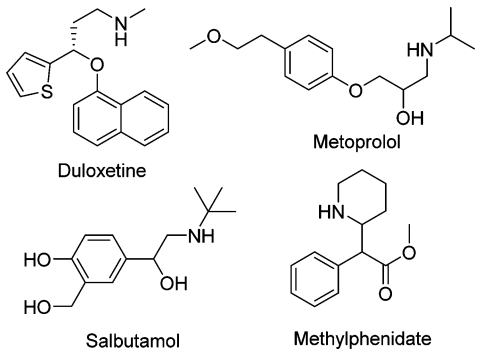


Figure 1. Selected examples of pharmaceuticals containing a secondary amino functional group (taken from the list of top 200 brand-name drugs by total US prescriptions in 2012).

In recent years, much efforts have been devoted to the direct reduction of secondary amide to amines, which cumulated in several chemoselective methods.[6] Those methods comprised (1) the metal-catalyzed hydrosilylation (Nagashima:[7] Ru and Pt; Beller:[8] Zn, Cu; Brookhart:[9] Ir; Reeves/Senanayake:[10] Ru; Sakai:[11] InI_3); (2) the metal-catalyzed hydrogenation (Breit:[12] Pd or Pt/Re/graphite; Luo:[13] Mg-$TiCl_4$); (3) the metal-free orgonocatalytic hydrosilylation {Beller:[14] boronic acid; Zhang,[15] Cantat[16] and Adronov:[17] tris(pentafluorophenyl) boron [$B(C_6F_5)_3$]}, and (4) the in situ triflic anhydride (Tf_2O)-activated reduction [Huang:[18] $NaBH_4$; Charette:[19] Hantzsch ester hydride (HEH)]. Among them, the $B(C_6F_5)_3$-catalyzed hydrosilylation with 1,1,3,3-tetramethyldisiloxane (TMDS)[16,17] is attractive because this system combines $B(C_6F_5)_3$,[20] a powerful Lewis acid with water, air, and functional group tolerance, with nontoxic, cheap, and easy-to-handle TMDS. Moreover, in Piers's seminal work on the $B(C_6F_5)_3$-catalyzed hydrosilylation of carbonyl compounds[21a,b] and imines,[21c] a Frustrated Lewis Pair (FLP)[22] consisted of silyliminium cation and a hydridoborate counterion has been postulated.[23] The FLP catalysis is a rapidly expanding field.[22] However, this class of metal-free organocatalysis, while powerful, is still at its infancy, much chemistry needs to be explored. Thus, development of complementary methods[16,17] that allow running the reduction reactions under milder conditions, display broader functional group tolerance, and suitable for more types of substrates, is highly desirable.

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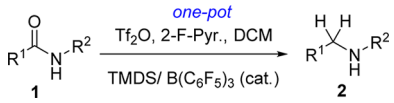
In a program of these laboratories aimed at the development of methods for the direct transformations of amides,[24] several reducing agents/systems including Et_3SiH,[24a−d] $LiAlH_4$,[24e,g] 10% Pd/C/H_2,[24f] Bu_3SnH,[24g] HEH,[24g] 20% $Pd(OH)_2$/ H_2,[24g] and $NaBH_4$[18,24g] have been employed. In particular, we have developed versatile and mild methods for the reduction of both tertiary and secondary amides with Tf_2O-$NaBH_4$ system,[18] and secondary lactams with Cp_2ZrHCl-$NaBH_4$ system, respectively.[18b] The former method employed Tf_2O[25] as an amide activating reagent and $NaBH_4$ as a reductant. With the aim to develop a mild and metal-free reduction of secondary amides, we opted for merging the Tf_2O activation with $B(C_6F_5)_3$ (cat.)/ TMDS reduction (Scheme 1), and the results are reported herein.

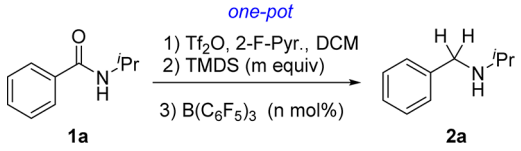
Scheme 1



RESULTS AND DISCUSSION

At the outset of our investigation, a one-stage protocol (Protocol A, Table 1) was first examined. In the event, *N*-*i*-propyl benzamide **1a** was treated successively with Tf_2O (1.1 equiv, 0 °C, 20 min), TMDS (1.2 equiv) and $B(C_6F_5)_3$ (5 mol %). To our delight, after been reacted at rt for 3 h, secondary amine **2a** was formed in 61% yield, along with 15% of the recovered starting material (Table 1, entry 1). To improve the yield of the reaction, 0.6 equiv of 2-fluoropyridine (2-F-Pyr.) was introduced as a base additive.[26] In this manner, the yield of **2a** was improved to 86%, and recovered starting material diminished to 6% (Table 1, entry 2). Increasing the amount of 2-F-Pyr. to 1.2 equiv led to an improved yield of 93% (entry 3). Lowering the catalyst loading from 5 mol % to 2 mol % resulted in a decrease of yield (87%) (entry 4). Considering the high price of $B(C_6F_5)_3$, efforts have been devoted to reduce catalyst loading. For this purpose, a two-stage one-pot protocol was investigated first at 5 mol % catalyst loading. Thus, amide **1a** was activated with Tf_2O (1.1 equiv, 0 °C, 20 min), partially reduced with TMDS (1.2 equiv, 0 °C, 30 min, rt, 3 h). At this stage, $B(C_6F_5)_3$ (5 mol %) was introduced at 0 °C, and the reaction was run at rt for 2−3 h. Similar to the results obtained via the protocol A, in the absence of 2-F-Pyr. or use of a lower amount of 2-F-Pyr. (0.6 equiv), amine **2a** was obtained in lower but respectable yield of 76% (entry 5) and 88% (entry 6), respectively. Further optimization by using 1.2 equiv of 2-F-Pyr. led to an improved yield to 94% (entry 7). The impact of amount of TMDS was next surveyed (entries 8 and 9), which showed that the use of 1.2 equiv of TMDS to be optimal (entry 7). After screening those reaction parameters, we were in a position to examine the feasibility to reduce the catalyst loading. To our satisfaction, when only 2 mol % of $B(C_6F_5)_3$ was used, amine **2a** was produced in 94% yield (entry 10). Further reducing the catalyst loading to 1 mol % resulted in a lower yield (83%, entry 11). On the basis of these results, the optimized conditions for Protocols A and B turned out to be those shown in entries 3 and 10 (Table 1), respectively.

Table 1. Optimization of the Reduction Reaction



entry	TMDS (equiv)	2-F-Pyr. (equiv)	$B(C_6F_5)_3$ (mol %)	yield (%)[c]
1[a]	1.2	0	5	61 (15)[d]
2[a]	1.2	0.6	5	86 (6)[d]
3[a]	**1.2**	**1.2**	**5**	**93**
4[a]	1.2	1.2	2	87
5[b]	1.2	0	5	76
6[b]	1.2	0.6	5	88
7[b]	1.2	1.2	5	94
8[b]	1.1	1.2	5	91
9[b]	1.5	1.2	5	93
10[b]	**1.2**	**1.2**	**2**	**94**
11[b]	1.2	1.2	1	83

[a]Protocol A: Tf_2O (1.1 equiv), 2-F-Pyr. (1.2 equiv), DCM, 0 °C, 20 min; TMDS (*m* equiv), 10 min; $B(C_6F_5)_3$ (*n* mol %), 0 °C to rt, 3 h. [b]Protocol B: Tf_2O (1.1 equiv), 2-F-Pyr. (1.2 equiv), DCM, 0 °C, 20 min; TMDS (*m* equiv), rt, 3 h; $B(C_6F_5)_3$ (*n* mol %), rt, 2−3 h. [c]Isolated yield. [d]Recovered starting material.

After optimizing the reaction conditions, we turned our attention to examine the scope of the reaction by Protocol B (using 2 mol % catalyst loading). A series of benzamide derivatives bearing either electron-donating groups (Me, OMe, Table 2, entries 2 and 3) or electron-withdrawing groups (Br, CF_3, NO_2, CO_2Me, OAc, and CN, Table 2, entries 4−9) reacted smoothly to give the corresponding secondary amines **2b−i** in good to excellent yields (86−98%). Naphthane-2-carboxamide **1j** and heteroaromatic amide thiophene-2-carboxamide **1k** reacted similarly to give the corresponding amines **2j** and **2k** in 98% (entry 10) and 88% yield (entry 11), respectively.

On the other hand, similar to the amides [(*i*-Pr (**1a−k**)] bearing a secondary *N*-alkyl group, *N*-cyclohexylamides (**1l**) and **1m** were reduced to give **2l** and **2m** in excellent yields (95%, entry 12; 96%, entry 13). The reductions of *β*-branched *N*-alkyl amide **1n** and *δ*-branched *N*-alkyl amide **1o** also gave the corresponding amines **2n** and **2o** in similar excellent yields (94% and 97%, entries 14 and 15), and unbranched *N*-alkyl and *N*-alkynyl amides **1p** and **1q** produced amines **2p** and **2q** in 87% and 88% yields (entries 16 and 17). As two exceptions, the reduction reactions of *N*-cyclopropyl and *N*-allyl amides **1r** and **1s** are less efficient giving the corresponding amines **2r** and **2s** in 76% (entry 18) and 73% yield (entry 19), respectively. The lowest yield (34%) was obtained with the least hindered *N*-methylbenzamide **1t**, which was improved to 58% by performing the amide activation at −78 °C (entry 20). Interestingly, *N*-*tert*-butyl benzamide reacted to give amine **2u** in 58% yield along with 14% of benzonitrile. The yield of amine **2u** was improved to 74% with the use of 2.0 equiv of TMDS and 10 mol % of $B(C_6F_5)_3$ (entry 21).

Besides aromatic and heteroaromatic amides, reactions of aliphatic amides were examined. The reduction of cyclohexanecarboxamide **1v** gave amine **2v** in excellent yield (90%, entry 22), while less hindered 2-methylpropanamide **1w** and acetamide **1x** produced amines **2w** and **2x** in only 74% and 58% yield, respectively (entries 23 and 24). Reduction of *α*,*β*-unsaturated amide **1y** by protocol A produced the fully reduced saturated amine **2y−a** as the major product (56%), while by employing protocol B, allylic amine **2y** and saturated amine

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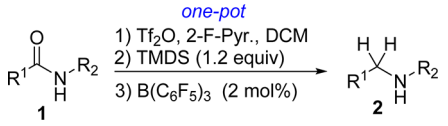
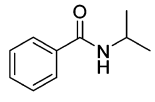
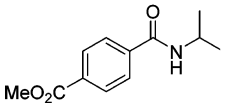
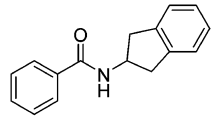
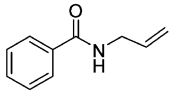
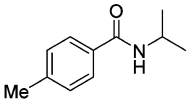
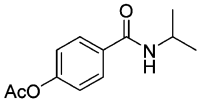
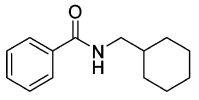
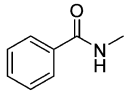
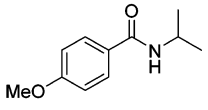
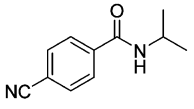
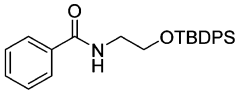
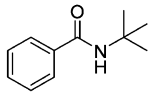
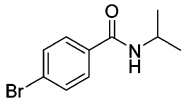
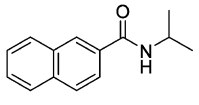
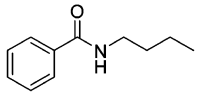
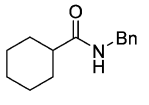
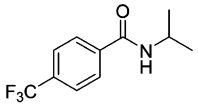
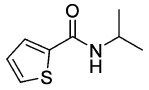
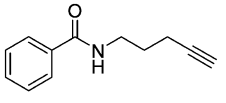
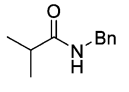
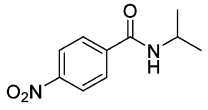
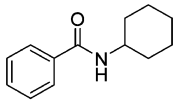
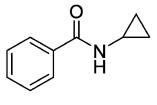
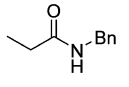
Table 2. Scope of the Reduction Reaction[a]



Entry	Amide (Yield of amine)[b]	Entry	Amide (Yield of amine)[b]	Entry	Amide (Yield of amine)[b]	Entry	Amide (Yield of amine)[b]
1	 **1a** (**2a**: 94%)	7	 **1g** (**2g**: 98%)	13	 **1m** (**2m**: 96%)	19	 **1s** (**2s**: 73%)
2	 **1b** (**2b**: 91%)	8	 **1h** (**2h**: 87%)	14	 **1n** (**2n**: 94%)	20	 **1t** (**2t**: 58%)[c]
3	 **1c** (**2c**: 94%)	9	 **1i** (**2i**: 88%)	15	 **1o** (**2o**: 97%)	21	 **1u** (**2u**: 74%)[d]
4	 **1d** (**2d**: 94%)	10	 **1j** (**2j**: 98%)	16	 **1p** (**2p**:87%)	22	 **1v** (**2v**: 90%)
5	 **1e** (**2e**: 86%)	11	 **1k** (**2k**: 88%)	17	 **1q** (**2q**: 88%)	23	 **1w** (**2w**: 74%)
6	 **1f** (**2f**: 96%)	12	 **1l** (**2l**: 95%)	18	 **1r** (**2r**: 76%)	24	 **1x** (**2x**: 58%)

[a]Protocol B was used unless otherwise specified. [b]Isolated yield. [c]Protocol B, amide activation was undertaken at −78 °C for 40 min. [d]Amide activation was undertaken at −78 °C for 40 min, TMDS (2.0 equiv) was added and stirred for 10 min at −78 °C, and then $B(C_6F_5)_3$ (10 mol %) was added, the mixture was warmed up to rt slowly, and stirred for another 3 h.

2y−**a** were obtained in 31% and 37% yield, respectively (Scheme 2, eq 1).

Because amides are products of a number of synthetic methodologies,[2] their further transformation is, in most case, imperative. In this context, Jiang and co-workers have developed a method for the synthesis of multifunctionalized secondary amides such as **1z**.[2a] Subjection of this amide to our reduction produced **2z** in 93% yield (Scheme 2, eq 2). Interestingly, reduction of C−H functionalization product **1aa**[2c] afforded amine **2aa** in a respectable yield of 78% (Scheme 2, eq 3). Comparing this result with that obtained from amide **1t** which lacks an *o*-butyl group (**2t**, yield: 58%) allowed confirming the beneficial effect of steric hindrance for the reaction.

To further demonstrate the synthetic utility of the method, the synthesis of amino lactones **4a** and **4b**,[27] protected forms of 5-hydroxypiperidin-2-one (**6a** and **6b**), as well as their further elaboration were envisioned (Scheme 3). 5-Hydroxypiperidin-2-one is a structural feature found in peptidal nucleoside antibiotics streptothricins,[28] and has been converted into the 5-amino-4-hydroxypentanoic acid, a molecule possessing anxiolytic and sedative activities.[27a] In addition, several protected forms of 5-hydroxypiperidin-2-one have served as intermediates in the synthesis of several drugs and alkaloids, which include immunosuppressant agents tofacitinib (CP-690,550)[29a] and FR901483 (**9**),[29b] xestocyclamine A,[29c] fasicularin,[29d] (−)-deoxoprosophylline, (+)-*cis*-195A,[29e] streptolutine stereoisomers,[29f] (2*R*,5*R*)-5-chloropipecolic acid,[29g] and (2*S*,5*S*)-5-hydroxypipecolic acids.[29h] Thus, chemoselective reduction of the known amido lactones **3a** and **3b**, easily available in two steps from (*S*) or (*R*)-glutamic acid,[29b] were investigated. Reduction of (*S*)-**3a** by protocol A produced **4a** in 69% yield (Scheme 3). HPLC analysis of the resultant amino lactone **4a** on a chiral stationary phase[30] showed that its enantiomeric

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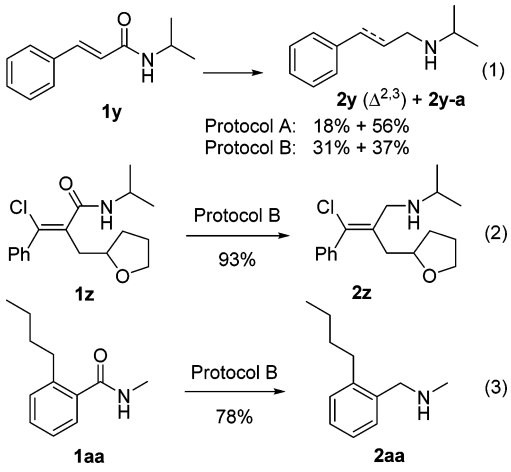
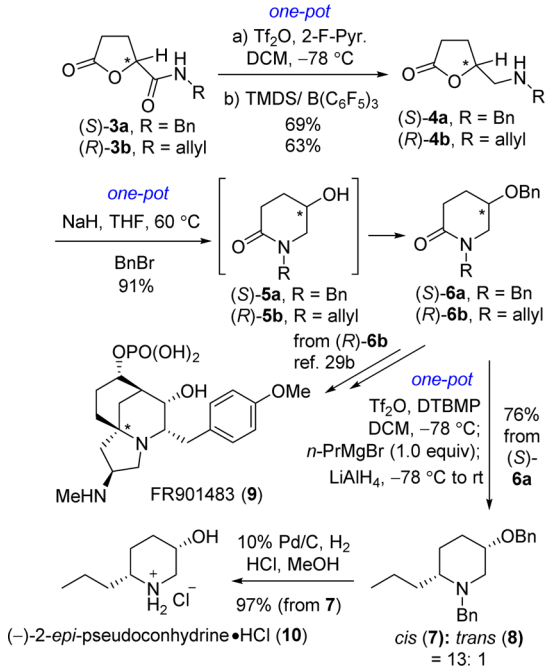
Scheme 2



Scheme 3

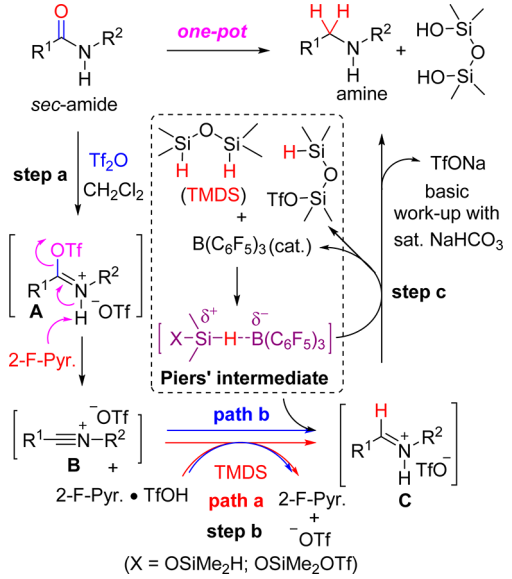


excess is >99% (cf. SI). Treatment of amino lactone **4a** with NaH in THF at 60 °C yielded the ring expanded hydroxylactam **5a**, which was *O*-benzylated in situ with BnBr to give directly lactam **6a** in 91% yield. Employing the method developed from these laboratories,[24g] one-pot reductive alkylation of (*R*)-**6a** produced **7** and diastereomer **8** in a 13:1 ratio with a combined yield of 76%. The stereochemistry of the major diastereomer **7** was deduced from the final product (−)-*epi*-pseudoconhydrine[31] hydrochloride salt (**10**), which was obtained in 97% yield via catalytic hydrogenolysis. Thus, starting from the known **3a**, (−)-*epi*-pseudoconhydrine·HCl (**10**) was synthesized in four steps with an overall yield of 43%.

Following the same two-step sequence described for the transformation of (*S*)-**3a**, the known amido lactone (*R*)-**3b** was converted into 5-benzyloxypiperidin-2-one (*R*)-**6b** in an overall yield of 57%. **6b** has served as the key chiral building block in the total synthesis of the potent immunosuppressant agent FR901483 (**9**) where it was prepared from (*R*)-**3b** by a four-step procedure.[29b]

Mechanistic Considerations. Plausible mechanisms for the reduction of secondary amides by two protocols are depicted in Scheme 4, which differ from each other only in the step b. Thus, for both protocols A and B, the first step involves amide activation with Tf_2O to generate the iminium triflate **A**, which upon treatment with 2-F-Pyr. generates the nitrilium ion intermediate **B** and 2-F-Pyr. triflic acid salt.[24a−c,32] Movassaghi has detected nitrilium ion **B** by IR.[26] Previously we have observed that the amide activation-based C−C bond forming reaction failed with secondary lactams, which also implicated the intermediacy of a nitrilium ion intermediate.[32]

Scheme 4. Plausible Mechanisms for the Reduction of Secondary Amides by Protocols A and B



For Protocol B, the nitrilium ion **B** is reduced by TMDS to give, after protonation, the iminium ion **C** (step b, path a). The latter was further reduced by the Piers' intermediate (step c), in situ generated from $B(C_6F_5)_3$ (cat.) and TMDS, to produce, after basic workup, a free amine. For the reduction employing Protocol A, nitrilium ion intermediate **B** was reduced by the Piers' intermediate (Piers' hydride) to give intermediates **C** (the regeneration of $B(C_6F_5)_3$ not shown in the Scheme 4), that is further reduced by the Piers' hydride (step c) to give an amine.

CONCLUSIONS

In conclusion, we have demonstrated that by in situ activation with Tf_2O/2-F-Pyr., secondary amides can be efficiently reduced to amines by the $B(C_6F_5)_3$ (2 mol %)−TMDS combination under very mild conditions. The reaction displays a broad applicability for many types of substrates, including those been excluded by other methods such as *N*-alkyl (in particular *N*-methyl, *N*-isopropyl, *N*-*c*-hexylCH$_2$, *N*-*tert*-butyl, and *N*-allyl) amides. The reaction also shows good functional group tolerance and excellent chemoselectivity for several functional groups including MeO, CF_3, Br, NO_2, CO_2Me, AcO, CN, alkenyl, alkynyl, cyclopropyl, and OTBDPS groups. The mildness, chemoselectivity, and synthetic utility of the method were further demonstrated by the smooth reduction of the Jiang's multifunctionalized α,β-unsaturated secondary amide **1z**, the C−H activation product **1aa**, and enantiomeric amido

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lactones **3a** and **3b**. The latter were directly transformed to lactams (*S*)-**6a** and (*R*)-**6b**, respectively, which are building blocks for the synthesis several natural products such as the potent immunosuppressant agent FR901483 (**9**). Moreover, direct reductive alkylation of (*S*)-**6a** resulted in a concise four-step synthesis of (−)-*epi*-pseudoconhydrine·HCl (**10**) from the known **3a** with an overall yield of 43%.

EXPERIMENTAL SECTION

For general experimental methods, see refs 24b, g.

General Procedure for Reduction of Secondary Amides 1 to Secondary Amines 2. *Protocol A.* Into a dry 10 mL round-bottom flask equipped with a stirring bar were added successively an amide (1.0 mmol), 4 mL of anhydrous dichloromethane and 2-fluoropyridine (117 mg, 103 μL, 1.2 mmol). After being cooled to 0 °C, trifluoromethanesulfonic anhydride (Tf_2O) (310 mg, 185 μL, 1.1 mmol) was added dropwise via a syringe at 0 °C and the mixture was stirred for 20 min. To the resulting mixture, 1,1,3,3-tetramethyldisiloxane (TMDS) (161 mg, 212 μL, 1.2 mmol) was added dropwise at 0 °C and the resulting mixture was stirred for 10 min. A solution of $B(C_6F_5)_3$ (25.6 mg, 5 mol %) in 1 mL of dichloromethane was added at 0 °C and allowed to warm-up to room temperature slowly, then stirred at room temperature for 3 h. The reaction was quenched by addition of 5 mL of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$) at 0 °C and diluted with 30 mL of dichloromethane. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate (Na_2SO_4), filtered and concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel (300−400 mesh) to give the corresponding amine.

Protocol B. Into a dry 10 mL round-bottom flask equipped with a stirring bar were added successively an amide (1.0 mmol), 4 mL of anhydrous dichloromethane and 2-fluoropyridine (117 mg, 103 μL, 1.2 mmol). After being cooled to 0 °C, trifluoromethanesulfonic anhydride (Tf_2O) (310 mg, 185 μL, 1.1 mmol) was added dropwise via a syringe at 0 °C and the reaction was stirred for 20 min. To the resulting mixture, 1,1,3,3-tetramethyldisiloxane (TMDS) (161 mg, 212 μL, 1.2 mmol) was added dropwise at 0 °C and the mixture was stirred for 10 min. The mixture was allowed to warm-up to room temperature and stirred for 3 h before addition of a solution of $B(C_6F_5)_3$ (10.2 mg, 2 mol %) in 1 mL of dichloromethane at 0 °C. The resulting mixture was stirred at room temperature for 2−3 h. The reaction was quenched with 5 mL of a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$) at 0 °C, and mixture diluted with 30 mL of dichloromethane. The aqueous layer was extracted with dichloromethane (2 × 5 mL). The organic layers were dried over anhydrous sodium sulfate (Na_2SO_4), filtered and concentrated under reduced pressure, the residue was purified by flash chromatography on silica gel (300−400 mesh) to give the corresponding amine.

***N*-Benzyl-isopropylamine (2a).** Following the general procedure (Protocol B), the reduction of amide **1a** (163 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/2/0.01), the known amine **2a**[18b] (140 mg, yield: 94%) as a colorless oil. IR (film) ν_{max} 3448, 2934, 2856, 1615, 1470, 1367, 1113, 707 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (d, J = 6.3 Hz, 6H), 1.86 (br s, 1H), 2.85 (septet, J = 6.3 Hz, 1H), 3.77 (s, 2H), 7.20−7.26 (m, 1H), 7.28−7.34 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.7 (2C), 48.0, 51.5, 126.8, 128.0 (2C), 128.3 (2C), 140.4 ppm; MS (ESI, m/z) 150 ($M + H^+$).

***N*-(4-Methylbenzyl)isopropylamine (2b).** Following the general procedure (Protocol B), the reduction of amide **1b** (177 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/2/0.01), the known amine **2b**[18b] (147 mg, yield: 90%) as a colorless oil. IR (film) ν_{max} 3326, 2963, 2920, 2850, 1577, 1541, 1515, 1467, 1383, 1337, 1259, 1174, 1121, 1073, 1021, 805, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (d, J = 6.3 Hz, 6H), 1.40 (br s, 1H), 2.32 (s, 3H), 2.84 (septet, J = 6.3 Hz, 1H), 3.73 (s, 2H), 7.12 (d, J = 7.8 Hz, 2H), 7.20 (d, J = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0, 22.8 (2C), 47.9, 51.3, 128.0 (2C), 129.0 (2C), 136.3, 137.6 ppm; MS (ESI, m/z) 164 ($M + H^+$).

***N*-(4-Methoxybenzyl)isopropylamine (2c).** Following the general procedure (Protocol B), the reduction of amide **1c** (193 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/1/0.01), the known amine **2c**[18b] (169 mg, yield: 94%) as a colorless oil. IR (film) ν_{max} 3316, 2962, 2930, 2835, 1612, 1585, 1512, 1465, 1379, 1300, 1247, 1172, 1070, 1037, 823, 750, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (d, J = 6.3 Hz, 6H), 1.50 (br s, 1H), 2.84 (septet, J = 6.3 Hz, 1H), 3.71 (s, 2H), 3.78 (s, 3H), 6.83−6.87 (m, 2H), 7.21−7.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.8 (2C), 47.9, 50.9, 55.2, 113.7 (2C), 129.2 (2C), 132.8, 158.5 ppm; MS (ESI, m/z) 180 ($M + H^+$).

***N*-(4-Bromobenzyl)isopropylamine (2d).** Following the general procedure (Protocol B), the reduction of amide **1d** (242 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/2/0.01), amine **2d** (215 mg, yield: 94%) as a colorless oil. IR (film) ν_{max} 3315, 2963, 2928, 2867, 2829, 1591, 1487, 1469, 1403, 1380, 1367, 1337, 1173, 1125, 1070, 1012, 812, 800, 739 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.08 (d, J = 6.3 Hz, 6H), 1.36 (br s, 1H,), 2.82 (septet, J = 6.3 Hz, 1H), 3.72 (s, 2H), 7.19 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9 (2C), 48.0, 50.8, 120.5, 129.7 (2C), 131.4 (2C), 139.8 ppm; HRMS-ESI calcd for $[C_{10}H_{14}BrN + H]^+$ ($M + H)^+$ 228.0382, found 228.0380.

***N*-[4-(Trifluoromethyl)benzyl]isopropylamine (2e).** Following the general procedure (Protocol B), the reduction of amide **1e** (231 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/2/0.01), the known amine **2e**[33] (188 mg, yield: 86%) as a pale yellow oil. IR (film) ν_{max} 3311, 2966, 2930, 2866, 1620, 1469, 1418, 1382, 1326, 1165, 1126, 1066, 1019, 829, 757, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.11 (d, J = 6.3 Hz, 6H), 1.41 (br s, 1H), 2.84 (septet, J = 6.3 Hz, 1H), 3.84 (s, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9 (2C), 48.2, 51.0, 124.2 (q, $J_{C,F}$ = 272.2 Hz), 125.2 (q, $J_{C,F}$ = 3.7 Hz, 2C), 128.2 (2C), 129.1 (q, $J_{C,F}$ = 32.1 Hz), 145.0 ppm; MS (ESI, m/z) 218 ($M + H^+$).

***N*-(4-Nitrobenzyl)isopropylamine (2f).** Following the general procedure (Protocol B), the reduction of amide **1f** (208 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/2/0.01), the known amine **2f**[18b] (186 mg, yield: 96%) as a pale yellow oil. IR (film) ν_{max} 3321, 3103, 3078, 2964, 2929, 2867, 1604, 1519, 1468, 1380, 1347, 1174, 1126, 1109, 1080, 1015, 854, 799, 737 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.11(d, J = 6.3 Hz, 6H), 1.48 (br s, 1H), 2.85 (septet, J = 6.3 Hz, 1H), 3.90 (s, 2H), 7.51 (d, J = 8.7 Hz, 2H), 8.17 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9 (2C), 48.4, 50.7, 123.5 (2C), 128.5 (2C), 146.8, 148.7 ppm; MS (ESI, m/z) 195 ($M + H^+$).

Methyl 4-[(isopropylamino)methyl]benzoate (2g). Following the general procedure (Protocol B), the reduction of amide **1g** (221 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/1/0.01), the known amine **2g**[18b] (203 mg, yield: 98%) as a pale yellow oil. IR (film) ν_{max} 3322, 2962, 2920, 2866, 1722, 1611, 1435, 1380, 1278, 1176, 1109, 1020, 967, 848, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.10 (d, J = 6.3 Hz, 6H), 1.53 (br s, 1H), 2.84 (septet, J = 6.3 Hz, 1H), 3.84 (s, 2H), 3.90 (s, 3H), 7.40 (d, J = 8.1 Hz, 2H), 7.99 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.8 (2C), 48.2, 51.2, 51.9, 127.9 (2C), 128.7, 129.7 (2C), 146.1, 167.0 ppm; MS (ESI, m/z) 208 ($M + H^+$).

4-[(Isopropylamino)methyl]phenyl acetate (2h). Following the general procedure (Protocol B), the reduction of amide **1h** (221 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/1/0.01), amine **2h** (180 mg, yield: 87%) as a pale yellow oil. IR (film) ν_{max} 3298, 2964, 2921, 2850, 1762, 1610, 1560, 1507, 1467, 1370, 1216, 1195, 1165, 1017, 911, 834 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (d, J = 6.3 Hz, 6H), 1.61 (br s, 1H), 2.29 (s, 3H), 2.85 (septet, J = 6.3 Hz, 1H), 3.77 (s, 2H), 7.01−7.05 (m, 2H), 7.31−7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.1, 22.8 (2C), 48.1, 50.9, 121.4 (2C), 129.1 (2C), 138.3, 149.5,

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169.6 ppm; HRMS-ESI calcd for $[C_{12}H_{17}NO_2 + H]^+$ $(M + H)^+$ 208.1332, found 208.1337.

4-[(Isopropylamino)methyl]benzonitrile (2i). Following the general procedure (Protocol B), the reduction of amide **1i** (188 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/2/0.01), the known amine **2i**[18b] (153 mg, yield: 88%) as a pale yellow oil. IR (film) ν_{max} 3318, 3055, 2964, 2929, 2869, 2834, 2227, 1608, 1504, 1467, 1412, 1380, 1337, 1174, 1127, 1078, 1220, 824, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.10 (d, J = 6.3 Hz, 6H), 1.36 (br s, 1H), 2.84 (septet, J = 6.3 Hz, 1H), 3.85 (s, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.8 (2C), 48.3, 51.0, 110.5, 118.9, 128.5 (2C), 132.1 (2C), 146.5 ppm; MS (ESI, m/z) 175 $(M + H^+)$.

***N*-(Naphthalen-2-ylmethyl)isopropylamine (2j).** Following the general procedure (Protocol B), the reduction of amide**1j** (213 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/1/0.01), amine **2j** (196 mg, yield: 98%) as a pale yellow oil. IR (film) ν_{max} 3313, 3054, 2963, 2928, 2868, 2821, 1601, 1508, 1467, 1379, 1363, 1325, 1173, 1124, 1067, 949, 891, 855, 815, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.11 (d, J = 6.3 Hz, 6H), 1.47 (br s, 1H), 2.88 (septet, J = 6.3 Hz, 1H), 3.93 (s, 2H), 7.39–7.46 (m, 3H), 7.74 (s, 1H), 7.77–7.82 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9 (2C), 48.1, 51.7, 125.4, 125.9, 126.3, 126.6, 127.6 (2C), 128.0, 132.5, 133.4, 138.2 ppm; HRMS-ESI calcd for $[C_{14}H_{17}N + H]^+$ $(M + H)^+$ 200.1434, found 200.1438.

***N*-(Thiophen-2-ylmethyl)isopropylamine (2k).** Following the general procedure (Protocol B), the reduction of amide **1k** (169 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/2/0.01), the known amine **2k**[34] (137 mg, yield: 88%) as a colorless oil. IR (film) ν_{max} 3312, 3070, 2963, 2930, 2869, 2826, 1467, 1440, 1380, 1338, 1309, 1259, 1220, 1175, 1123, 1069, 1039, 854, 824, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (d, J = 6.3 Hz, 6H), 1.42 (br s, 1H), 2.89 (septet, J = 6.3 Hz, 1H), 3.98 (s, 2H), 6.90–6.96 (m, 2H), 7.19 (dd, J = 5.0, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.8 (2C), 45.9, 47.6, 124.1, 124.6, 126.5, 144.4 ppm; MS (ESI, m/z) 156 $(M + H^+)$.

***N*-Benzyl-cyclohexylamine (2l).** Following the general procedure (Protocol B), the reduction of amide **1l** (203 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/2/0.01), the known amine **2l**[18b] (180 mg, yield: 95%) as a colorless oil. IR (film) ν_{max} 3311, 3084, 3062, 3026, 2926, 2852, 1601, 1495, 1451, 1361, 1259, 1124, 1074, 1028, 889, 733, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06–1.31 (m, 5H), 1.36 (br s, 1H), 1.57–1.65 (m, 1H), 1.69–1.77 (m, 2H), 1.88–1.95 (m, 2H), 2.44–2.52 (m, 1H), 3.80 (s, 2H), 7.20–7.26 (m, 1H), 7.30–7.32 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.9 (2C), 26.1, 33.5 (2C), 51.0, 56.1, 126.7, 128.0 (2C), 128.3 (2C), 140.9 ppm; MS (ESI, m/z) 190 $(M + H^+)$.

***N*-Benzyl-2,3-dihydro-1*H*-inden-2-amine (2m).** Following the general procedure (Protocol B), the reduction of amide **1m** (237 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/5/0.01), the known amine **2m**[35] (215 mg, yield: 96%) as a colorless oil. IR (film) ν_{max} 3307, 3063, 3023, 2934, 2897, 2836, 1604, 1584, 1494, 1483, 1457, 1343, 1253, 1216, 1194, 1126, 1026, 972, 907, 741, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.59 (br s, 1H), 2.81 (dd, J = 15.6, 7.0 Hz, 2H), 3.17 (dd, J = 15.6, 7.0 Hz, 2H), 3.67 (quintet, J = 6.8 Hz, 1H), 3.85 (s, 2H), 7.10–715 (m, 2H), 7.16–7.20 (m, 2H), 7.21–7.26 (m, 1H), 7.28–7.36 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 40.0 (2C), 52.3, 58.9, 124.6 (2C), 126.4 (2C), 126.9, 128.2 (2C), 128.4 (2C), 140.3, 141.7 (2C) ppm; MS (ESI, m/z) 224 $(M + H^+)$.

***N*-(Cyclohexylmethyl)benzylamine (2n/ 2v).** Following the general procedure (Protocol B), the reduction of amides **1*n*/1v** (217 mg, 1.0 mmol) and gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/4/0.01), the known amine **2n**[35] (191 mg, yield: 94%)/ **2v** (183 mg, yield: 90%) as a colorless oil. IR (film) ν_{max} 3333, 3062, 3026, 2920, 2850, 2805, 1494, 1449, 1357, 1258, 1200, 1124, 1072, 1031, 973, 733, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.85–0.96 (m, 2H), 1.09–1.30 (m, 3H), 1.40–1.54 (m, 2H), 1.63–1.78 (m, 5H), 2.46 (d, J = 6.7 Hz, 2H), 3.77 (s, 2H), 7.20–7.26 (m, 1H), 7.28–7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.0 (2C), 26.7, 31.4 (2C), 38.0, 54.1, 56.2, 126.7, 128.0 (2C), 128.3 (2C), 140.7 ppm; MS (ESI, m/z) 204 $(M + H^+)$.

***N*-Benzyl-2-[(*t*-butyldiphenylsilyl)oxy]ethylamine (2o).** Following the general procedure (Protocol B), the reduction of amide **1o** (404 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/6/0.01), amine **2o** (376 mg, yield: 97%) as a colorless oil. IR (film) ν_{max} 3324, 3069, 3045, 3027, 2929, 2857, 1661, 1494, 1471, 1453, 1428, 1390, 1361, 1259, 1190, 1111, 1028, 938, 823, 737, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.05 (s, 9H), 1.87 (br s, 1H), 2.77 (t, J = 5.2 Hz, 2H), 3.78–3.82 (m, 4H), 7.22–7.27 (m, 1H), 7.28–7.33 (m, 4H), 7.34–7.38 (m, 4H), 7.39–7.43 (m, 2H), 7.63–7.69 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.2, 26.8, 50.9, 53.6, 63.1, 126.8, 127.7, 128.0, 128.4, 129.6, 133.6, 135.5, 140.5 ppm; HRMS-ESI calcd for $[C_{25}H_{31}NOSi + H]^+$ $(M + H)^+$ 390.2248, found 390.2247.

***N*-Benzyl-*n*-butylamine (2p).** Following the general procedure (Protocol B), the reduction of amide **1p** (177 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/2/0.01), the known amine **2p**[18b] (142 mg, yield: 87%) as a colorless oil. IR (film) ν_{max} 3309, 3085, 3063, 3027, 2957, 2927, 2871, 2812, 1604, 1495, 1454, 1377, 1359, 1260, 1200, 1122, 1075, 1028, 905, 732, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.91 (t, J = 7.3 Hz, 3H), 1.30–1.39 (m, 2H), 1.46–1.54 (m, 3H), 2.63 (t, J = 7.3 Hz, 2H), 3.78 (s, 2H), 7.21–7.27 (m, 1H), 7.29–7.34 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 20.4, 32.2, 49.1, 54.1, 126.8, 128.1 (2C), 128.3 (2C), 140.5 ppm; MS (ESI, m/z) 164 $(M + H^+)$.

***N*-Benzylpent-4-yn-1-ylamine (2q).** Following the general procedure (Protocol B), the reduction of amide **1q** (187 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/2/0.01), the known amine **2q**[36] (152 mg, yield: 88%) as a pale yellow oil. IR (film) ν_{max} 3299, 3084, 3062, 3027, 2932, 2820, 2116, 1603, 1495, 1453, 1354, 1259, 1121, 1073, 1028, 906, 806, 735, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.43 (br s, 1H), 1.73 (quintet, J = 7.1 Hz, 2H), 1.94 (t, J = 2.6 Hz, 1H), 2.27 (td, J = 7.1, 2.6 Hz, 2H), 2.74 (t, J = 7.0 Hz, 2H), 3.79 (s, 2H), 7.22–7.27 (m, 1H), 7.29–7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 16.3, 28.7, 48.1, 53.9, 68.5, 84.1, 126.9, 128.0 (2C), 128.3 (2C), 140.4 ppm; MS (ESI, m/z) 174 $(M + H^+)$.

***N*-Benzyl-cyclopropylamine (2r).** Following the general procedure (Protocol B), the reduction of amide **1r** (161 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/5/0.01), the known amine **2r**[37] (111 mg, yield: 76%) as a pale yellow oil. IR (film) ν_{max} 3320, 3085, 3063, 3026, 3006, 2923, 2850, 2819, 1604, 1495, 1452, 1373, 1347, 1213, 1160, 1089, 1014, 928, 827, 730, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.36–0.41 (m, 2H), 0.42–0.46 (m, 2H), 1.80 (br s, 1H), 2.13–2.18 (m, 1H), 3.83 (s, 2H), 7.22–7.27 (m, 1H), 7.29–7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 6.4 (2C), 30.0, 53.7, 126.8, 128.2 (2C), 128.3 (2C), 140.6 ppm; MS (ESI, m/z) 148 $(M + H^+)$.

***N*-Benzyl-allylamine (2s).** Following the general procedure (Protocol B), the reduction of amide **1s** (161 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/3/0.01), the known amine **2s**[38] (107 mg, yield: 73%) as a colorless oil. IR (film) ν_{max} 3332, 3084, 3062, 3026, 2920, 2850, 2805, 1601, 1494, 1450, 1358, 1260, 1201, 1124, 1073, 1028, 977, 893, 843, 733, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.54 (br s, 1H), 3.27 (d, J = 6.0 Hz, 2H), 3.79 (s, 2H), 5.09–5.13 (m, 1H), 5.16–5.23 (m, 1H), 5.88–5.98 (m, 1H), 7.22–7.27 (m, 1H), 7.30–7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 51.7, 53.2, 116.0, 126.9, 128.1 (2C), 128.3 (2C), 136.7, 140.2 ppm; MS (ESI, m/z) 148 $(M + H^+)$.

***N*-Benzyl-methylamine (2t).** Following the general procedure (Protocol B, activation at −78 °C), the reduction of amide **1t** (135 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/1/0.01), the commercially available amine **2t** (70 mg, yield: 58%) as a colorless oil. IR (film) ν_{max} 3311, 3058, 3026, 2920, 2844, 2789, 1601, 1494, 1452, 1382, 1263, 1027, 736, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.43 (br s, 1H), 2.45 (s, 3H), 3.74 (s, 2H), 7.22–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 125

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MHz) δ 36.0, 56.0, 126.9, 128.1 (2C), 128.3 (2C), 140.1 ppm; MS (ESI, m/z) 122 ($M + H^+$).

***N*-Benzyl-*t*-butylamine (2u).** Following the general procedure [Protocol A, activation at −78 °C, TMDS (2.0 equiv), $B(C_6F_5)_3$ (10 mol %)], the reduction of amide **1u** (177 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/4/0.01), the known amine **2u**[38] (121 mg, yield: 74%) as a colorless oil. IR (film) ν_{max} 3309, 3086, 3063, 3027, 2964, 2901, 2861, 1605, 1495, 1478, 1452, 1387, 1361, 1230, 1214, 1095, 1073, 1027, 902, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.18 (s, 9H), 3.72 (s, 2H), 7.20−7.25 (m, 1H), 7.28−7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 29.1 (3C), 47.2, 50.6, 126.7, 128.2 (2C), 128.4 (2C), 141.4 ppm; MS (ESI, m/z) 164 ($M + H^+$).

***N*-Benzyl-isobutylamine (2w).** Following the general procedure (Protocol B), the reduction of amide **1w** (177 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/2/0.01), the known amine **2w**[39] (121 mg, yield: 74%) as a colorless oil. IR (film) ν_{max} 3334, 3085, 3063, 3027, 2954, 2920, 2870, 2809, 1604, 1494, 1454, 1385, 1365, 1207, 1116, 1075, 1028, 977, 903, 800, 735, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.91 (d, J = 6.7 Hz, 6H), 1.41 (br s, 1H), 1.72−1.83 (m, 1H), 2.44 (d, J = 6.8 Hz, 2H), 3.78 (s, 2H), 7.21−7.26 (m, 1H), 7.27−7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.6 (2C), 28.3, 54.1, 57.5, 126.8, 128.0 (2C), 128.3 (2C), 140.7 ppm; MS (ESI, m/z) 164 ($M + H^+$).

***N*-Benzyl-*n*-propylamine (2x).** Following the general procedure (Protocol B), the reduction of amide **1x** (163 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/1/0.01), the known amine **2x**[40] (86 mg, yield: 58%) as a colorless oil. IR (film) ν_{max} 3305, 3085, 3063, 3027, 2958, 2930, 2873, 2812, 1601, 1494, 1454, 1378, 1198, 1122, 1074, 1028, 970, 906, 820, 733, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, J = 7.4 Hz, 3H), 1.49−1.57 (m, 3H), 2.60 (t, J = 7.3 Hz, 2H), 3.78 (s, 2H), 7.22−7.27 (m, 1H), 7.29−7.36 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 11.7, 23.2, 51.3, 54.0, 126.8, 128.1 (2C), 128.3 (2C), 140.5 ppm; MS (ESI, m/z) 150 ($M + H^+$).

***(E)*-*N*-(3-Phenylprop-2-en-1-yl)isopropylamine (2y) and *N*-(3-Phenylpropyl)isopropylamine (2y−a).** Following the general procedure (Protocol B), the reduction of amide **1y** (177 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/2/0.01), the inseparable known amine **2y**[18b] and **2y−a**[18b] (120 mg, combined yield: 68%, **2y**:**2y−a** = 1:1.2, determined by ^1H NMR of crude product) as a pale yellow oil. **2y** (data read from the spectrum of the mixture): ^1H NMR ($CDCl_3$, 500 MHz) δ 1.09 (d, J = 6.3 Hz, 6H), 2.89 (septet, J = 6.3 Hz, 1H), 3.41 (d, J = 6.4 Hz, 2H), 6.31 (dt, J = 15.8, 6.4 Hz, 1H), 6.52 (d, J = 15.8 Hz, 1H), 7.15−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9 (2C), 48.1, 49.5, 126.2 (2C), 127.2, 128.5 (2C), 128.7, 131.0, 137.1 ppm; MS (ESI, m/z) 176 ($M + H^+$). **2y−a** (data read from the spectrum of the mixture): ^1H NMR ($CDCl_3$, 500 MHz) δ 1.04 (d, J = 6.3 Hz, 6H), 1.77−1.85 (m, 2H), 2.60−2.68 (m, 4H), 2.77 (septet, J = 6.3 Hz, 1H), 7.18−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9 (2C), 32.0, 33.8, 47.0, 48.6, 125.7, 128.30 (2C), 128.25 (2C), 142.1 ppm; MS (ESI, m/z) 178 ($M + H^+$).

***(Z)*-3-Chloro-*N*-isopropyl-3-phenyl-2-[(tetrahydrofuran-2-yl)methyl)]prop-2-en-1-ylamine (2z).** Following the general procedure (Protocol B, activation at −78 °C), the reduction of amide **1z**[2a] (46 mg, 0.15 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 1/3/0.01), amine **2z** (41 mg, yield: 93%) as a colorless oil. IR (film) ν_{max} 3324, 3056, 2964, 2927, 2867, 1640, 1597, 1489, 1467, 1444, 1379, 1336, 1261, 1228, 1173, 1063, 1016, 920, 890, 810, 761, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.12 (d, J = 6.3 Hz, 6H), 1.28−1.36 (m, 1H), 1.70−1.81 (m, 3H), 1.83−1.91 (m, 1H), 2.34 (d, J = 6.5 Hz, 2H), 2.85 (septet, J = 6.3 Hz, 1H), 3.59 (d, J = 12.8 Hz, 1H), 3.65 (d, J = 12.8 Hz, 1H), 3.68 (dd, J = 14.4, 7.4 Hz, 1H), 3.74 (dd, J = 14.4, 7.4 Hz, 1H), 3.91−3.98 (m, 1H), 7.28−7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.9, 23.0, 25.4, 31.3, 37.5, 48.3, 48.4, 67.7, 77.9, 128.1, 128.2 (2C), 129.2 (2C), 129.8, 135.0, 139.1 ppm; HRMS-ESI calcd for $[C_{17}H_{24}ClNO + H]^+$ ($M + H)^+$ 294.1619, found 294.1617.

***N*-(2-Butylbenzyl)methylamine (2aa).** Following the general procedure (Protocol B, activation at −78 °C), the reduction of amide **1aa**[2c] (96 mg, 0.5 mmol) gave, after flash column chromatography on silica gel (eluent: EtOAc/Hexane/Et_3N = 2/1/0.01), amine **2aa** (69 mg, yield: 78%) as a colorless oil. IR (film) ν_{max} 3324, 2956, 2930, 2871, 2788, 1604, 1450, 1378, 1353, 1131, 1103, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.95 (t, J = 7.3 Hz, 3H), 1.36−1.43 (m, 2H), 1.45 (br s, 1H), 1.53−1.61 (m, 2H), 2.50 (s, 3H), 2.66 (t, J = 8.0 Hz, 2H), 3.75 (s, 2H), 7.13−7.22 (m, 3H), 7.28−7.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.0, 22.8, 32.1, 33.5, 36.4, 53.1, 125.8, 127.0, 128.7, 129.3, 137.6, 141.0 ppm; HRMS-ESI calcd for $[C_{12}H_{19}N + H]^+$ ($M + H)^+$ 178.1590, found 178.1593.

***(S)*-5-[(Benzylamino)methyl]dihydrofuran-2(3*H*)-one (4a).** Following the general procedure [Protocol A, activation at −78 °C, TMDS (1.1 equiv), $B(C_6F_5)_3$ (5 mol %)], the reduction of amide **3a**[29b] (219 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: MeOH/CH_2Cl_2 = 1/30), amine **4a** (141 mg, yield: 69%) as a colorless oil. $[\alpha]_D^{20}$ = +27.7 (c 1.0, $CHCl_3$). IR (film) ν_{max} 3332, 3027, 2921, 2850, 1770, 1453, 1352, 1261, 1181, 1026, 915, 801, 738, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.68 (br s, 1H), 1.96−2.06 (m, 1H), 2.22−2.32 (m, 1H), 2.48−2.62 (m, 2H), 2.78 (dd, J = 12.9, 6.8 Hz, 1H), 2.89 (dd, J = 12.9, 3.5 Hz, 1H), 3.82 (d, J = 13.4 Hz, 1H), 3.84 (d, J = 13.4 Hz, 1H), 4.62−4.69 (m, 1H), 7.23−7.28 (m, 1H), 7.29−7.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.2, 28.6, 52.8, 53.8, 80.2, 127.1, 128.0 (2C), 128.4 (2C), 139.7, 177.1 ppm; HRMS-ESI calcd for $[C_{12}H_{15}NO_2 + Na]^+$ ($M + Na)^+$ 228.0995, found 228.0996.

***(S)*-5-[(Allylamino)methyl]dihydrofuran-2(3*H*)-one (4b).** Following the general procedure [Protocol A, activation at −78 °C, TMDS (1.1 equiv), $B(C_6F_5)_3$ (5 mol %)], the reduction of amide **3b**[29b] (169 mg, 1.0 mmol) gave, after flash column chromatography on silica gel (eluent: MeOH/CH_2Cl_2 = 1/30), amine **4b** (98 mg, yield: 63%) as a colorless oil. $[\alpha]_D^{20}$ = −36.8 (c 1.0, $CHCl_3$). IR (film) ν_{max} 3324, 3078, 2923, 2850, 1775, 1643, 1461, 1261, 1184, 1020, 916, 802 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.71 (br s, 1H), 1.96−2.06 (m, 1H), 2.27−2.34 (m, 1H), 2.52−1.61 (m, 2H), 2.79 (dd, J = 12.9, 7.2 Hz, 1H), 2.88 (dd, J = 12.9, 3.6 Hz, 1H), 3.29 (d, J = 6.2 Hz, 2H), 4.66 (ddd, J = 10.8, 7.2, 3.6 Hz, 1H), 5.12 (dq, J = 10.2, 1.4 Hz, 1H), 5.19 (dq, J = 17.1, 1.6 Hz, 1H), 5.87 (ddt, J = 17.1, 10.2, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.3, 28.6, 52.3, 52.9, 80.1, 116.4, 136.2, 177.1 ppm; HRMS-ESI calcd for $[C_8H_{13}NO_2 + Na]^+$ ($M + Na)^+$ 178.0839, found 178.0839.

***(S)*-1-Benzyl-5-(benzyloxy)piperidin-2-one (6a).** To a suspension of NaH (60% dispersion in mineral oil, 272 mg, 6.8 mmol) in THF (20 mL) was added a solution of **4a** (700 mg, 3.4 mmol) in THF (4 mL) at room temperature and the reaction mixture was heated to the 60 °C and stirred for 4 h. Benzyl bromide was added dropwise and the reaction stirred at 60 °C for 15 h. The reaction was quenched by addition of H_2O at 0 °C and extracted with Et_2O (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/1) to give the known compound **6a**[41] (914 mg, yield: 91%) as a colorless oil. $[\alpha]_D^{20}$ = +22.1 (c 1.0, $CHCl_3$) {lit.[41] $[\alpha]_D^{25}$ = +29.8 (c 1.68, CH_2Cl_2)}. IR (film) ν_{max} 3029, 2922, 1644, 1495, 1453, 1416, 1359, 1265, 1205, 1181, 1089, 737, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.90−2.00 (m, 1H), 2.01−2.09 (m, 1H), 2.44 (dt, J = 17.7, 5.8 Hz, 1H), 2.71 (ddd, J = 17.7, 9.5, 6.3 Hz, 1H), 3.26−3.35 (m, 2H), 3.77−3.82 (m, 1H), 4.41 (d, J = 11.8 Hz, 1H), 4.48 (d, J = 11.8 Hz, 1H), 4.52 (d, J = 14.8 Hz, 1H), 4.64 (d, J = 14.8 Hz, 1H), 7.22−7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.8, 28.1, 49.8, 50.6, 70.2, 70.4, 127.30, 127.34 (2C), 127.7, 127.9 (2C), 128.4 (2C), 128.5 (2C), 136.8, 137.9, 169.3 ppm; HRMS-ESI calcd for $[C_{19}H_{21}NO_2 + Na]^+$ ($M + Na)^+$ 318.1465, found 318.1464.

***(R)*-1-Allyl-5-(benzyloxy)piperidin-2-one (6b).** To a suspension of NaH (60% dispersion in mineral oil, 186 mg, 4.6 mmol) in THF (10 mL) was added a solution of **4b** (360 mg, 2.3 mmol) in THF (2 mL) at room temperature and the reaction mixture was heated to the 60 °C and stirred for 4 h. Benzyl bromide was added dropwise and the reaction stirred at 60 °C for 15 h. The reaction was quenched by

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addition of H_2O at 0 °C and extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/hexane = 2/1) to give compound **6b** (508 mg, yield: 90%) as a colorless oil. $[\alpha]_D^{20}$ = −10.6 (*c* 1.0, $CHCl_3$) {lit.[29b] $[\alpha]_D^{20}$ = −6.4 (*c* 1.0, $CHCl_3$)}. IR (film) ν_{max} 3029, 2919, 1641, 1490, 1454, 1415, 1359, 1270, 1193, 1099, 924, 738, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.90−2.09 (m, 2H), 2.37 (dt, *J* = 17.6, 5.9 Hz, 1H), 2.63 (ddd, *J* = 17.6, 9.4, 6.3 Hz, 1H), 3.33 (dd, *J* = 12.7, 4.6 Hz, 1H), 3.37 (dd, *J* = 12.7, 4.1 Hz, 1H), 3.80−3.86 (m, 1H), 3.94 (dd, *J* = 15.2, 5.8 Hz, 1H), 4.01 (dd, *J* = 15.2, 5.8 Hz, 1H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.59 (d, *J* = 11.9 Hz, 1H), 5.14−5.16 (m, 1H), 5.17−5.20 (m, 1H), 5.74 (ddt, *J* = 17.6, 9.8, 5.9 Hz, 1H), 7.27−7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 28.1, 49.1, 50.9, 70.3, 70.5, 117.3, 127.4 (2C), 127.7, 128.4 (2C), 132.5, 137.9, 169.0; MS (ESI, *m*/*z*) 268 (M + Na^+).

(2*R*,5*S*)-1-Benzyl-5-(benzyloxy)-2-propylpiperidine (7). Tf_2O (217 mg, 130 uL, 1.1 equiv) was added dropwise to a cooled (−78 °C) solution of **6a** (207 mg, 1.0 equiv) and DTBMP (172 mg, 1.2 equiv) in CH_2Cl_2 (10 mL) and stirred at −78 °C for 2 h. A solution of *n*-PrMgBr (0.41 M, 1.7 mL, 1.0 equiv) in THF was added dropwise to the resultant mixture. Then the mixture was allowed to warm slowly to rt and was stirred for 1 h. Then $LiAlH_4$ (80 mg, 3.0 equiv) was added in one portion at −78 °C, and the mixture was allowed to warm slowly to rt and stirred for 1 h. The resulting mixture was quenched by successive addition of H_2O: 15% NaOH (aq.): H_2O (80 μL/80 μL/240 μL, 1/1/3). After filtration, the filtrate was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent: EtOAc/hexane = 1/20) to give pure compound **7** and its diastereomeric mixture with **8** (172 mg in total, yield: 76%) as a colorless oil (*dr* = 13:1, determined by ^1H NMR of a crude product). $[\alpha]_D^{20}$ = +1.7 (*c* 1.0, $CHCl_3$). IR (film) ν_{max} 3028, 2931, 2869, 1494, 1453, 1368, 1096, 1028, 734, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, *J* = 7.3 Hz, 3H), 1.15−1.27 (m, 1H), 1.28−1.40 (m, 1H), 1.46−1.83 (m, 6H), 2.52−2.60 (m, 3H), 3.45−3.53 (m, 1H), 3.57 (d, *J* = 13.6 Hz, 1H), 3.75 (d, *J* = 13.6 Hz, 1H), 4.46 (s, 2H), 7.20−7.35 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.4, 19.9, 25.7, 26.7, 28.4, 51.6, 57.5, 58.2, 70.0, 73.6, 126.7, 127.3, 127.5 (2C), 128.1 (2C), 128.2 (2C), 128.6 (2C), 138.9, 139.9 ppm; HRMS-ESI calcd for $[C_{22}H_{29}NO + H]^+$ $(M + H)^+$ 324.2322, found 324.2321.

(2*R*,5*S*)-*epi*-Pseudoconhydrine hydrochloride salt (10). A suspension of **7** (53 mg, 0.16 mmol) and 10% Pd/C (20 mg) in MeOH (5 mL, mixed with 2−3 drops of concentrated HCl) was stirred under an atmosphere of H_2 for 20 h. The catalyst was filtered, and the filtrate was concentrated under reduced pressure. The residue was crystallized from MeOH/Et_2O to afford **10** (23 mg, yield: 97%) as white crystals. mp 145−146 °C (MeOH/Et_2O) [lit.[31e] 148−148.5 °C]; $[\alpha]_D^{20}$ = −12.6 (*c* 1.0, EtOH) {lit.[31e] $[\alpha]_D^{20}$ = −10.2 (*c* 1.0, EtOH)}; IR (film) ν_{max} 3331, 2955, 2926, 2870, 1589, 1446, 1384, 1258, 1087, 1038, 983 cm; ^1H NMR (D_2O, 500 MHz) δ 0. 81 (t, *J* = 7.3 Hz, 3H), 1.22−1.37 (m, 2H), 1.45−1.57 (m, 2H), 1.58−1.70 (m, 2H), 1.72−1.86 (m, 2H), 3.00−3.09 (m, 2H), 3.13−3.20 (m, 1H), 4.10 (s, 1H); ^{13}C NMR (D_2O, 125 MHz) δ 12.8, 17.7, 22.7, 27.6, 35.0, 49.1, 56.5, 61.4; HRMS-ESI calcd for $[C_8H_{17}NO + H]^+$ $(M + H)^+$ 144.1383, found 144.1385.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00572.

HPLC chromatograms of (±)-**3a**/**4a** and (*S*)-**3a**/**4a**; ^1H and ^{13}C NMR spectra of all products. (PDF)

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Notes

The authors declare no competing financial interest.

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