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Enantioselective Synthesis of β-Arylamines via Chiral Phosphoric Acid-Catalyzed Asymmetric Reductive Amination

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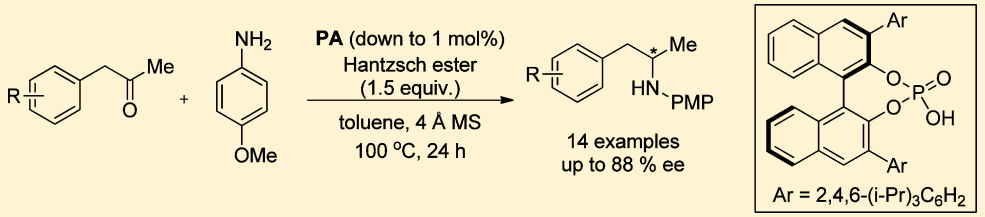
Supporting Information



ABSTRACT: A new method for the synthesis of chiral β-aryl amines via chiral phosphoric acid-catalyzed enantioselective reductive amination of benzyl methyl ketone derivatives with Hantzsch ester was developed. Various chiral β-aryl amines were obtained in high yields and with good to high enantioselectivities. This transformation is applicable to gram-scale reactions, and the catalyst loading can be reduced to 1 mol % without sacrificing any catalytic efficacy. Furthermore, the resulting β-aryl amine was successfully converted into a tetrahydroisoquinoline compound without any loss of enantioselectivity.

INTRODUCTION

Over the past decade, chiral phosphoric acid catalysis has become one of the most rapidly growing fields in asymmetric catalysis.[1,2] Specifically, the higher acidity of a chiral phosphoric acid compared to other chiral Brønsted acids provides an efficient route for enantioselective activation of imines through the protonation with the chiral phosphoric acid, and subsequent addition of nucleophiles to the activated imines affords a variety of chiral amines with excellent enantioselectivities. Among the various asymmetric reactions that involve chiral phosphoric acid catalysts, asymmetric reduction of ketimines with organic hydride sources,[3] such as Hantzsch esters, has been extensively studied and become one of the most popular reactions in asymmetric phosphoric acid catalysis.[4]

Chiral β-aryl amine moieties exist in many biologically important natural products and therapeutic agents (Figure 1).[5,6] For example, chiral β-aryl amine units are commonly found in numerous naphthylisoquinoline alkaloids, such as ancistrocladinium A and korupensamine A.[7] In addition, such structural scaffolds serve as important structural motifs in several active pharmaceutical ingredients. Thus, the development of efficient synthetic methods to access chiral β-aryl amine moieties is a subject of significant interest.[5,7] Although a number of examples of the synthesis of chiral amines through chiral phosphoric acid-catalyzed asymmetric reductions of imines have been reported,[4] these transformations have been limited to the synthesis of chiral α-aryl amines via enantioselective reduction of imines derived from alkyl aryl ketones, but the application of the chiral phosphoric acid-catalyzed asymmetric reductive amination to the synthesis of chiral β-aryl amines has been rarely explored.[8,9]

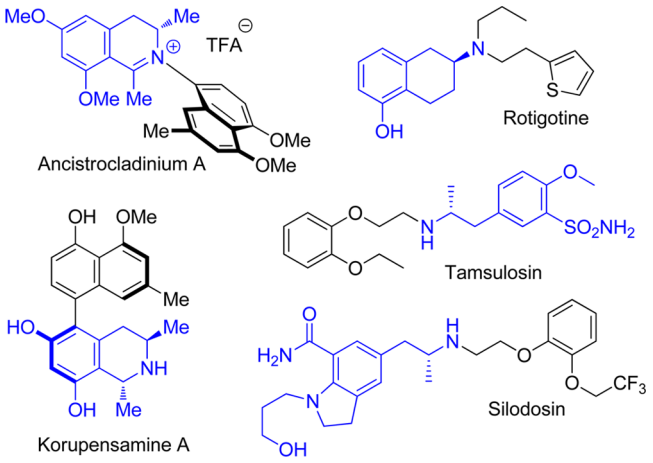


Figure 1. Selected natural products and therapeutic agents carrying chiral β-aryl amine moieties.

Herein, we describe a new method for the synthesis of chiral β-aryl amines via chiral phosphoric acid-catalyzed asymmetric reductive amination of benzyl methyl ketone derivatives using Hantzsch ester as an organic hydride source. Various benzyl methyl ketones were suitable for this protocol to generate the desired β-aryl amines in high yields and with good to high enantioselectivities. Moreover, this transformation was applied to gram-scale reactions with low catalyst loading (1 mol %) without sacrificing any efficacy. Furthermore, the resulting chiral β-aryl amine was successfully transformed to tetrahydroisoquinoline, which is one of the key building blocks in a

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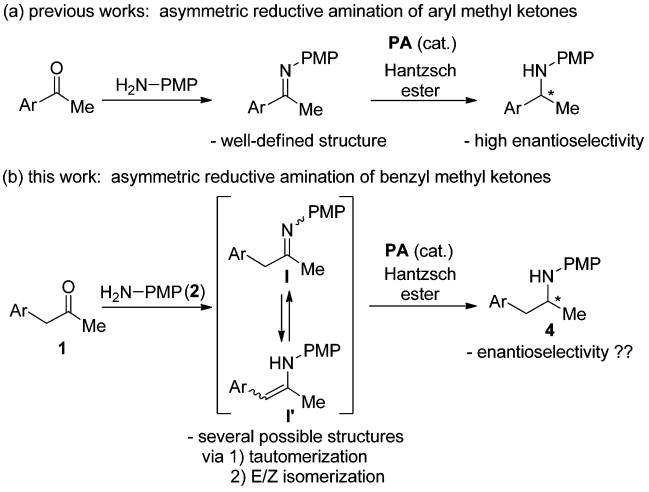
series of naphthylisoquinoline alkaloids, without any erosion of enantioselectivity.

RESULTS AND DISCUSSION

Most of the previous examples of the chiral phosphoric acid-catalyzed enantioselective reductive amination have focused on the synthesis of chiral α-aryl amines. In these previous approaches, the imines derived from aryl methyl ketones are readily available and have well-defined structures. Thus, it was expected that the imine substrates could have rigid interactions with a chiral phosphoric acid at transition states, which is crucial in achieving high enantioselectivities of the resulting products (in these cases, α-aryl amines) (Scheme 1a). On the other hand, in the asymmetric synthesis of chiral β-aryl amines via the chiral phosphoric acid-catalyzed reductive amination, imines from benzyl methyl ketones might have several possible structures via tautomerization between imines **I** and enamines **I′** and/or possible *E*/*Z* isomerization in the resulting imines **I** and enamines **I′**.[10] As a result, it might be difficult to predict a well-defined structure between the substrate and a chiral phosphoric acid at transition state, which could lead to lower enantioselectivities of the resulting β-aryl amines (Scheme 1b).

Scheme 1. Comparison of Asymmetric Reductive Amination Reactions in Previous Works and This Work (PMP = *para*-Methoxyphenyl)

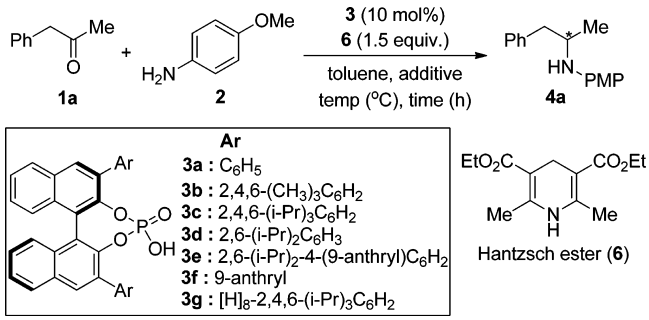


With this challenge in mind, we first attempted to prepare imine **I** from benzyl methyl ketone **1a** with *para*-anisidine **2**. However, the preparation of imine **I** from **1a** and **2** turned out to be challenging: no formation of **I** was observed even after several trials under conventional imine formation conditions.[11]

Although most of the previous reports on chiral phosphoric acid-catalyzed asymmetric reductive amination involved the use of pregenerated imines as substrates, there was one example of direct reductive amination from ketones without the isolation of imines; the MacMillan group developed chiral phosphoric acid-catalyzed direct enantioselective reductive amination of aryl methyl ketones without the isolation of the imine intermediates.[12]

Considering this previous report and the difficulty in preparing imines **I** from benzyl methyl ketones **1** with *para*-anisidine **2**, we attempted to synthesize chiral β-aryl amines via the direct asymmetric reductive amination of benzyl methyl ketone derivatives in the presence of a chiral phosphoric acid (Table 1). When benzyl methyl ketones **1a** and **2** were subjected to reductive amination conditions with Hantzsch ester **6** in the presence of chiral phosphoric acid **3c**, the reductive amination smoothly took place to afford the desired product **4a** with 69% ee and 80% yield (entry 1). Encouraged by this result, we systematically investigated various chiral phosphoric acids **3** derived from chiral BINOL derivatives. Substituents at the 3,3′-positions of the BINOL backbone turned out to play an important role in the enantioselectivity of the reaction (entries 1−7). Incorporation of an alkyl substituent at the 2,6-positions of the aryl substituent had a significant effect on enantioselectivity (entries 1−3). A substituent at the 4-position at the aryl substituent had an influence on the enantioselectivity of the transformation (entries 1, 4, and 5). The enantioselectivity initially increased with size of the substituent at the 4-position (entries 1 and 4); however, introduction of a too bulky substituent at the 4-position decreased the enantioselectivity (entry 5). Finally, the effect of dihedral angle along the chiral axis on the enantioselectivity was investigated. It turned out that increasing the dihedral angle along the chiral axis had a deleterious effect on the enantioselectivity. Phosphoric acid **3g** derived from an octahydro-BINOL derivative provided the desired product **4a** in a lower enantioselectivity than **3c** from a BINOL derivative did (entries 1 and 7). Since **3c** bearing a 2,4,6-isopropylphenyl substituent provided the best result, **3c** was selected for further investigation.

Table 1. Optimization of Reaction Conditions



entry	catalyst (**3**)	temp. (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	**3c**	80	50	80	69
2	**3a**	80	50	60	17 (−)[c]
3	**3b**	80	50	52	35
4	**3d**	80	50	50	53
5	**3e**	80	50	55	48
6	**3f**	80	50	40	40
7	**3g**	80	50	52	49
8[d]	**3c**	80	20	83	72
9[d]	**3c**	40	30	80	78
10[d]	**3c**	50	30	83	78
11[d]	**3c**	60	24	92	72
12[d]	**3c**	70	24	84	72
13[d]	**3c**	90	18	85	74
14[d]	**3c**	100	18	82	80

[a]Isolated yield of **4a**. [b]Enantiomeric excess (ee) was determined by a chiral HPLC analysis. [c]The opposite enantiomer was obtained as the major product. [d]In the presence of 4 Å molecular sieves.

The previous study[12] revealed that water, which is generated during imine formation, negatively affects both iminium formation and the reduction step; therefore, the effect of

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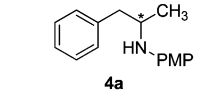
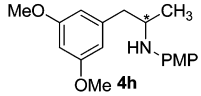
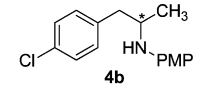
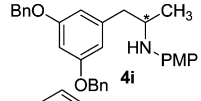
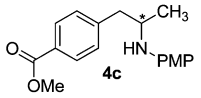
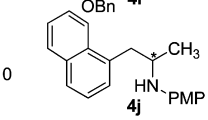
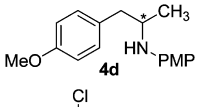
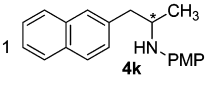
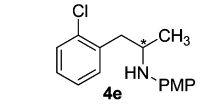
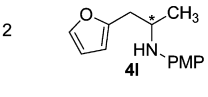
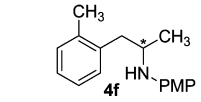
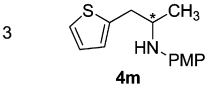
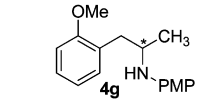
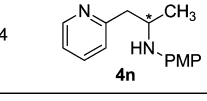
water, i.e., the effect of molecular sieves, on the efficiency of this transformation was examined (entries 1 and 8). Although the introduction of 4 Å molecular sieves increased the rate of reductive amination, rather disappointingly, enantioselectivity was only slightly improved. However, molecular sieves were found to play a critical role in achieving reproducibility of this protocol. Next, the reaction temperature was investigated (entries 8−14); the reaction rate increased with the reaction temperature, whereas the enantioselectivity was relatively unaffected with the reaction temperature. Although the desired product **4a** was obtained in similar enantioselectivity at 40 and 100 °C, 100 °C was selected as the optimal reaction temperature since the reaction time could be reduced at 100 °C (entry 14).

Under these optimized reaction conditions, the substrate scope of this transformation was investigated (Table 2).

Table 2. Substrate Scope

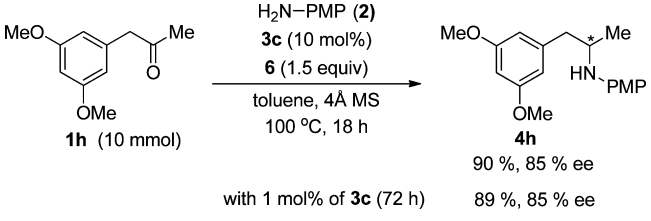
entry	product (**4**)	yield (%)[a] ee (%)[b]	entry	product (**4**)	yield (%)[a] ee (%)[b]
1	 **4a**	83 % 80 % ee	8	 **4h**	82 % 88 % ee
2	 **4b**	82 % 81 % ee	9	 **4i**	83 % 81 % ee
3	 **4c**	81 % 78 % ee	10	 **4j**	82 % 85 % ee
4	 **4d**	84 % 80 % ee	11	 **4k**	84 % 81 % ee
5	 **4e**	80 % 79 % ee	12	 **4l**	75 % 78 % ee
6	 **4f**	83 % 82 % ee	13	 **4m**	74 % 70 % ee
7	 **4g**	81 % 78 % ee	14	 **4n**	78 % 74 % ee

[a]Isolated yield of **4**. [b]Ee was determined by a chiral HPLC analysis.

Various benzyl methyl ketone derivatives **1** bearing different aryl groups could be amenable to this protocol and the desired *β*-aryl amines **4** were obtained in high yields and with good to high enantioselectivities. The electronic and steric nature of the substituent on the aryl group had little impact on both the enantioselectivity and reactivity (entries 1−9), and the desired products **4** were obtained with similar enantioselectivities (around 80% ee) regardless of the stereoelectronic natures of aryl groups. Benzyl methyl ketone derivatives bearing fused aromatic moieties were also applicable for this protocol, and the desired *β*-aryl amines were obtained with similar efficiencies (entries 10 and 11). In addition, this protocol could be extended to ketones bearing heteroaromatic moieties; however, the resulting *β*-aryl amines from these ketones were obtained with slightly lower enantioselectivities than those of simple benzyl methyl ketone derivatives (entries 12−14). When this protocol could not be extended to other benzyl alkyl ketones other than benzyl methyl ketones, it was found that the reactivity in this transformation dramatically decreased with the size of the alkyl group.[13] When benzyl ketones bearing a different alkyl group were subjected to the standard conditions, no formation of the desired product was observed and the ketones remained unreacted even after long reaction times.[14]

To demonstrate the practicality of this method, a gram-scale reaction was carried out. Delightfully, this transformation was successfully performed on a 10 mmol scale to produce the desired *β*-aryl amine **4h** with a similar efficiency. Furthermore, the catalyst loading could be reduced to 1 mol % without sacrificing the efficacy of this transformation (Scheme 2).

Scheme 2. Gram-Scale Reaction



We further attempted to demonstrate the synthetic utility of this protocol by converting the resulting *β*-aryl amine **4h** into tetrahydroisoquinoline **7**,[15] which is a key building block in a series of naphthylisoquinoline natural products.[7]

Since amine **8** was utilized as the key intermediate in the previous synthesis of tetrahydroisoquinoline **7**,[15] our initial plan was to prepare amine **8** by removing the PMP moiety in **4h** (Scheme 3). However, the deprotection of the PMP moiety in **4h** gave rather unexpected result. When **4h** was treated with cerium ammonium nitrate (CAN), the expected product **8** was not observed at all;[16,17] instead, spiro compound **9** was obtained as the major product (Scheme 4).

With this result in hand, we attempted to rationalize the unexpected formation of the spiro compound **9** (Scheme 5). It is generally believed that the deprotection of PMP group under oxidative conditions proceeds through a two-step sequence: oxidation of an electron-rich *para*-methoxyaniline ring with an oxidant produces iminium intermediate **10** and subsequent hydrolysis of intermediate **10** affords free amine **8** and benzoquinone.[14] However, since another electron-rich arene ring is located nearby to the iminium moiety in intermediate **10**, intramolecular Friedel−Crafts reaction might take place predominantly over the hydrolysis, leading to spiro compound **9**, not the expected amine **8**.

Since this result strongly suggested that tetrahydroisoquinoline **7** could not be prepared according to the synthetic route shown in Scheme 3, we attempted an alternative approach (Scheme 6). The acetylated amine **11**, prepared by the reaction of **4h** with acetic anhydride, was subjected to Bischler−Napieralski reaction to afford a dihydroisoquinolinium salt, and subsequent reduction of the resulting dihydroisoquinolinium salt with $NaBH_4$ provided the PMP-protected tetrahydroisoquinoline **12** in ca. 1:1 ratio of *cis* and *trans* isomers as an

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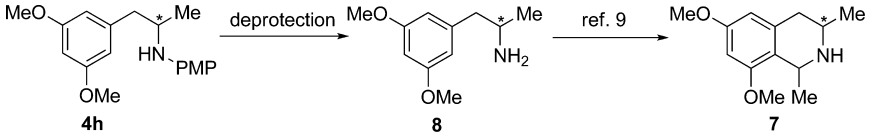
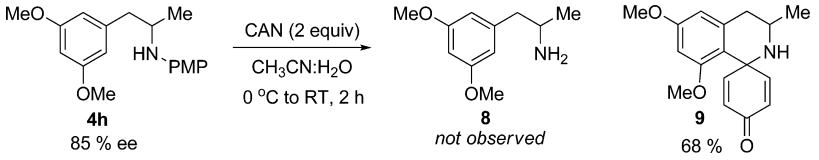
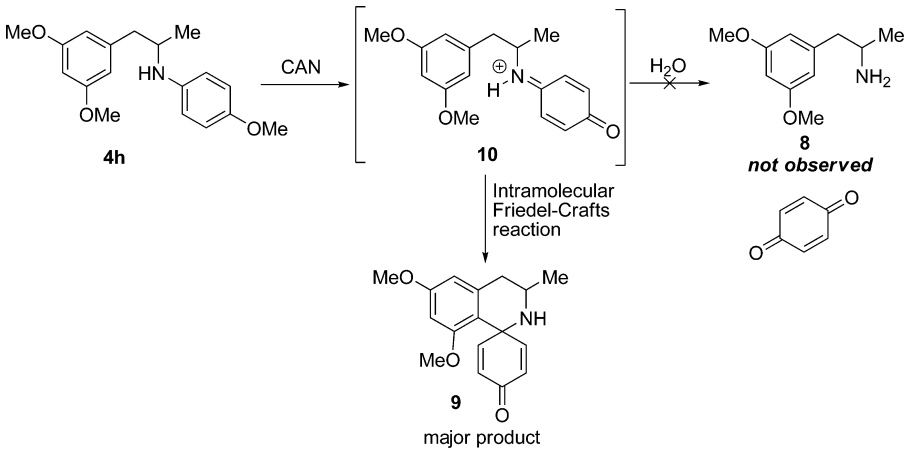
Scheme 3. Initial Plan for the Synthesis of Tetrahydroisoquinoline 7 from Amine 4h



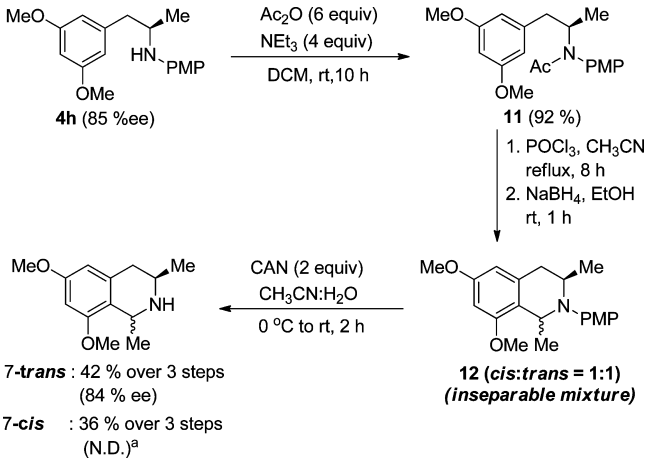
Scheme 4. Unexpected Formation of Spiro Compound 9 during the Attempt To Remove the PMP Group with CAN



Scheme 5. Rationale for Unexpected Formation of Spiro Compound 9



Scheme 6. Synthesis of Tetrahydroisoquinoline 7



[a]N.D. means not determined.[16]

inseparable mixture. Finally, the PMP group in **12** was successfully removed with CAN under oxidative conditions to afford *cis*- and *trans*-tetrahydroisoquinoline (7-*cis* and 7-*trans*), which was readily separable by column chromatography, in 42 and 36% yields over three steps, respectively. It should be noted that this transformation was achieved without any significant loss of enantioselectivity.[18] Furthermore, the absolute configuration at the C-3 position of tetrahydroisoquinoline **7** was successfully assigned as (*R*)-configuration by comparing the optical rotations of the *cis* and *trans* products **7** with their literature values, respectively.[19]

CONCLUSIONS

In conclusion, we developed a new method for the synthesis of chiral *β*-aryl amines via chiral phosphoric acid-catalyzed enantioselective reductive amination of benzyl methyl ketone derivatives with Hantzsch ester. Various benzyl methyl ketones carrying different aryl groups were applicable to this protocol, and the desired *β*-aryl amines were obtained in good yields and with good to high enantioselectivities. Furthermore, this protocol was successfully performed on a gram scale with low catalyst loading (1 mol %) without any loss of efficiency. The resulting amine compound was successfully converted into the tetrahydroisoquinoline moiety, a key building block in a series of naphthylisoquinoline natural products, through the formation of the tetrahydroisoquinoline ring followed by the removal of the PMP moiety without any loss of enantioselectivity.

Furthermore, during the deprotection of the PMP moiety in a PMP-protected amine with CAN, we also found unexpected formation of a spiro compound **9** via intramolecular Friedel–Crafts reaction of iminium ion with a nearby electron-rich aryl group. The direct conversion of the PMP moiety in a PMP-protected amine into a spiro compound will provide a new opportunity of a PMP protecting group in the synthesis of natural products bearing a spiro ring scaffold.[20] Further application of this new finding is underway in our laboratory and will be reported in due course.

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EXPERIMENT SECTION

General. All reactions were carried out in oven- or flame-dried glassware under an argon atmosphere unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using precoated silica gel glass plates (0.25 mm) with F254 indicator. Visualization was accomplished by UV light (254 nm), with combination of potassium permanganate and/or phosphomolybdic acid solution as an indicator. Flash column chromatography was performed according to the method of Still using silica gel 60 (230−400 mesh). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. Commercial grade reagents and solvents were used without further purification. Benzyl methyl ketone **1a** was purchased from Aldrich and other benzyl methyl ketone derivatives **1** except **1a** were prepared according to the literature procedure.[21] ^{1}H NMR and ^{13}C NMR spectra were recorded on 300/400 and 75/100 MHz, respectively. Tetramethylsilane and $CDCl_3$ were used as internal standards for ^{1}H NMR (δ: 0.0 ppm) and ^{13}C NMR (δ: 77.0 ppm), respectively. The proton spectra are reported as follows δ (position of proton, multiplicity, coupling constant J, number of protons). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet), and br (broad). High-performance liquid chromatography (HPLC) was performed by using chiral columns with a mixture of 2-propanol and hexanes as the eluent. High-resolution mass spectra (HRMS) were recorded on quadrupole time-of-flight mass spectrometer (QTOF-MS) using electrospray ionization (ESI).

General Procedure for the Asymmetric Reductive Amination of Benzyl Methyl Ketones 1 (Table 2). To a test tube equipped with a stirring bar were added a benzyl methyl ketone derivative **1** (0.20 mmol; 1.0 equiv), *p*-anisidine **2** (0.24 mmol; 1.2 equiv), Hantzsch ester (0.30 mmol; 1.5 equiv), catalyst **3c** (0.020 mmol; 10 mol %) and 4 Å molecular sieves (100 mg). Then, toluene was added to the above mixture. The reaction mixture was allowed to stir at 100 °C under an argon atmosphere and monitored by TLC. After complete consumption of ketone **1**, the reaction mixture was cooled to room temperature and filtered to remove molecular sieves. The filtrate was purified by column chromatography on silica gel using hexanes/ethyl acetate (7:1) as an eluent to provide the desired product **4**.

*4-Methoxy-N-(1-phenylpropan-2-yl)aniline (**4a**).*[22] The product was obtained as yellow oil in 83% (40 mg) yield and 80% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.32−7.17 (m, 5H), 6.80 (d, J = 9.1 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H), 3.71−3.65 (m, 1H), 2.93 (dd, J = 13.5, 4.7 Hz, 1H), 2.67 (dd, J = 13.3, 7.3 Hz, 1 H), 1.14 (d, J = 6.3 Hz, 3H). Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OJ-H column (hexanes/2-propanol = 95:5, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 22.7 min, t_r(minor) = 27.6 min. $[\alpha]_D^{20}$ = +4.7 (c = 1.0, $CHCl_3$).

*N-(1-(4-Chlorophenyl)propan-2-yl)-4-methoxyaniline (**4b**).* The product was obtained as colorless oil in 82% (45 mg) yield and 81% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.25 (d, J = 9.1 Hz, 2H), 7.09 (d, J = 8.2 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 6.58 (d, J = 9.0 Hz, 2H), 3.75 (s, 3H), 3.69−3.63 (m, 1H), 2.86 (dd, J = 13.5, 4.7 Hz, 1H), 2.66 (dd, J = 13.3, 7.0 Hz, 1H), 1.11 (d, J = 6.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 152.3, 141.4, 137.3, 132.3, 131.1, 128.6, 115.2 (2C), 56.0, 50.5, 41.8, 20.4. HRMS (ESI) calcd for $C_{16}H_{19}ClNO$ 276.1155, found 276.1149. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OJ-H column (hexanes/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 22.6 min, t_r(minor) = 29.3 min. $[\alpha]_D^{20}$= +21.0 (c = 1.0, $CHCl_3$).

*4-Methoxy-N-(1-(4-methoxycarbonylphenyl)propan-2-yl)aniline (**4c**).* The product was obtained as brown oil in 81% (49 mg) yield and 78% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.97 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 6.80 (d, J = 9.1 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 3.91 (s, 3H), 3.76 (s, 3H), 3.72−3.66 (m, 1H), 2.98 (dd, J = 13.5, 4.7 Hz, 1H), 2.74 (dd, J = 13.2, 7.1 Hz, 1H), 1.13 (d, J = 6.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 167.3, 152.4, 144.5, 141.3, 129.8, 129.7, 128.4, 115.2, 56.0, 52.3, 50.5, 42.5, 20.5. HRMS (ESI) calcd for $C_{18}H_{22}NO_3$ 300.1600, found 300.1594. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel AD-H column (hexanes/2-propanol = 99:1, flow rate = 1.5 mL/min, λ = 250 nm), t_r(major) = 43.6 min, t_r(minor) = 31.6 min. $[\alpha]_D^{20}$= +14.0 (c = 1.0, $CHCl_3$).

*4-Methoxy-N-(1-(4-methoxyphenyl)propan-2-yl)aniline (**4d**).* The product was obtained as colorless oil in 84% (45 mg) yield and 80% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.09 (d, J = 8.2 Hz, 2H), 6.84 (d, J = 8.5 Hz, 1H), 6.79 (d, J = 8.8 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.69−3.61 (m, 1H), 2.85 (dd, J = 13.6, 4.8 Hz, 1H), 2.64 (dd, J = 13.5, 7.1 Hz, 1H), 1.12 (d, J = 6.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 158.3, 152.2, 141.7, 130.9, 130.7, 115.2, 114.0, 56.0, 55.5, 50.7, 41.6, 20.4. HRMS (ESI) calcd for $C_{17}H_{22}NO_2$ 272.1651, found 272.1644. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OJ-H column (hexanes/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 48.7 min, t_r(minor) = 43.4 min. $[\alpha]_D^{20}$ = +11.1 (c = 1.0, $CHCl_3$).

*N-(1-(2-Chlorophenyl)t,propan-2-yl)-4-methoxyaniline (**4e**).* The product was obtained as brown oil in 80% (44 mg) yield and 79% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.36−7.34 (m, 1H), 7.23−7.20 (m, 1H), 7.18−7.15 (m, 2H), 6.79 (d, J = 8.2 Hz, 2H), 6.71 (d, J = 8.2 Hz, 2H), 3.81−3.78 (m, 1H), 3.75 (s, 3H), 3.18 (dd, J = 13.5, 5.7 Hz, 1H), 2.75 (dd, J = 13.3, 7.8 Hz, 1H), 1.18 (d, J = 6.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 152.2, 141.6, 137.1, 134.5, 131.8, 129.8, 127.9, 126.9, 115.2, 56.0, 50.0, 40.7, 20.8. HRMS (ESI) calcd for $C_{16}H_{19}ClNO$ 276.1155, found 276.1147. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OJ-H column (hexanes/2-propanol = 65:35, flow rate = 0.75 mL/min, = 254 nm), t_r(major) = 16.2 min, t_r(minor) = 18.0 min. $[\alpha]_D^{20}$= +24.6 (c = 1.0, $CHCl_3$).

*4-Methoxy-N-(1-(2-methylphenyl)propan-2-yl)aniline (**4f**).* The product was obtained as brown oil in 83% (42 mg) yield and 82% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.14 (s, 4H), 6.78 (d, J = 8.8 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 3.75 (s, 3H), 3.72−3.65 (m, 1H), 3.00 (dd, J = 13.7, 5.2 Hz, 1 H), 2.62 (dd, J = 13.7, 8.0 Hz, 1 H), 2.34 (s, 3H), 1.16 (d, J = 6.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 152.3, 141.7, 137.5, 136.7, 130.6, 130.2, 126.5, 126.1, 115.3, 115.2, 56.0, 50.3, 40.5, 20.8, 20.1. HRMS (ESI) calcd for $C_{17}H_{22}NO$ 56.1701, found 256.1696. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OJ-H column (hexanes/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 247 nm), t_r(major) = 15.2 min, t_r(minor) = 19.8 min. $[\alpha]_D^{20}$= +36.8 (c = 1.0, $CHCl_3$).

*4-Methoxy-N-(1-(2-methoxyphenyl)propan-2-yl)aniline (**4g**).* The product was obtained as colorless oil in 81% (44 mg) yield and 78% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.20 (m, 1H), 7.12 (d, J = 7.4 Hz, 1H), 6.88 (m, 2H), 6.78 (d, J = 8.6 Hz, 2H), 6.64 (d, J = 9.0 Hz, 2H), 3.86 (s, 3H), 3.75 (s, 3H), 3.71−3.66 (m, 1H), 3.12 (dd, J = 13.1, 5.3 Hz, 1H), 2.50 (dd, J = 13.3, 7.4 Hz, 1H), 1.13 (d, J = 6.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 157.9, 151.9, 142.1, 131.5, 127.9, 127.8, 120.7, 115.2, 114.8, 110.6, 56.1, 55.5, 49.9, 37.9, 20.9. HRMS (ESI) calcd for $C_{17}H_{22}NO_2$ 272.1651, found 272.1644. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OD-H column (hexanes/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 314 nm), t_r(minor) = 6.3 min, t_r(major) = 7.5 min. $[\alpha]_D^{20}$ = +65.7 (c = 0.5, $CHCl_3$).

*N-(1-(3,5-Dimethoxyphenyl)propan-2-yl)-4-methoxyaniline (**4h**).* The product was obtained as yellow oil in 82% (49 mg) yield and 88% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 6.79 (d, J = 9.1 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H), 6.63 (s, 3H), 3.77 (s, 6H), 3.75 (s, 3H), 3.71−3.65 (m, 1H), 2.86 (dd, J = 13.3, 4.8 Hz, 1H), 2.62 (dd, J = 13.2, 7.1 Hz, 1 H), 1.15 (d, J = 6.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 160.9, 152.3, 141.6, 141.2, 115.3, 115.2, 107.8, 98.3, 56.0, 55.5, 50.5, 42.7, 20.6. HRMS (ESI) calcd for $C_{18}H_{24}NO_3$ 302.1756, found 302.1751. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OJ-H column (hexanes/2-propanol = 90:10, flow rate = 1.0 mL/min, = 254 nm), t_r(major) = 46.8 min, t_r(minor) = 61.3 min. $[\alpha]_D^{20}$ = +8.3 (c = 1.0, $CHCl_3$).

*N-(1-(3,5-Bis(benzyloxy)phenyl)propan-2-yl)-4-methoxyaniline (**4i**).* The product was obtained as yellow oil in 83% (75 mg) yield and 81% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.43−7.33 (m, 10H), 6.78 (d, J = 8.6 Hz, 2H), 6.57 (d, J = 8.6 Hz, 2H), 6.50 (s, 1H), 6.42

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(d, J = 2.0 Hz, 2H), 5.01 (s, 4H), 3.74 (s, 3H), 3.65−3.62 (m, 1H), 2.84 (dd, J = 13.3, 4.7 Hz, 1H), 2.59 (dd, J = 13.3, 7.0 Hz, 1H), 1.11 (d, J = 6.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 160.0, 152.3, 141.6, 141.3, 137.1, 128.8, 128.2, 127.8, 115.3, 115.2, 109.0, 100.1, 70.3, 56.0, 50.5, 42.8, 20.6. HRMS (ESI) calcd for $C_{30}H_{32}NO_3$ 454.2382, found 454.2377. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OD-H column (hexanes/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 230 nm), t_r(major) = 21.0 min, t_r(minor) = 50.5 min. $[\alpha]_D^{20}$ = +9.8 (c = 0.4, $CHCl_3$).

*4-Methoxy-N-(1-(naphthalen-1-yl)propan-2-yl)aniline (**4j**).* The product was obtained as brown oil in 82% (48 mg) yield and 85% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.08 (d, J = 8.0 Hz, 1H), 7.88 (d, J = 7.1 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.55−7.47 (m, 2H), 5.45−7.35 (m, 2H), 6.81 (d, J = 8.5 Hz, 2H), 6.65 (d, J = 8.8 Hz, 2H), 3.92−3.83 (m, 1H), 3.77 (s, 3H), 3.48 (dd, J = 13.7, 5.2 Hz, 1H), 3.08 (dd, J = 13.7, 7.7 Hz, 1H), 1.18 (d, J = 6.0 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 152.4, 141.7, 135.4, 134.2, 132.6, 129.1, 127.7, 127.3, 126.1, 125.8, 125.6, 124.2, 115.5, 115.2, 56.0, 50.6, 40.4, 21.1. HRMS (ESI) calcd for $C_{20}H_{22}NO$ 292.1701, found 292.1697. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OB-H column (hexanes/2-propanol = 95:5, flow rate = 1.0 mL/min, λ = 220 nm), t_r(major) = 49.4 min, t_r(minor) = 35.6 min. $[\alpha]_D^{20}$ = +33.6 (c = 0.5, $CHCl_3$).

*4-Methoxy-N-(1-(naphthalen-2-yl)HRMSpropan-2-yl)aniline (**4k**).* The product was obtained as brown oil in 84% (49 mg) yield and 81% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.84−7.77 (m, 3H), 7.62 (s, 1H), 7.49−7.42 (m, 2H), 7.33 (d, J = 8.2 Hz, 1H), 3.83−3.80 (m, 1H), 3.77 (s, 3H), 3.10 (dd, J = 13.3, 4.5 Hz, 1H), 2.85 (dd, J = 13.2, 7.4 Hz, 1H), 1.17 (d, J = 6.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 152.5, 141.3, 136.4, 133.7, 132.4, 128.3, 128.1, 127.9, 127.7, 126.2, 125.6, 115.6, 115.3, 56.0, 50.9, 42.6, 20.5. HRMS (ESI) calcd for $C_{20}H_{22}NO$ 292.1701, found 292.1697. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OJ-H column (hexanes/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 82.0 min, t_r(minor) = 98.6 min. $[\alpha]_D^{20}$ = +18.7 (c = 0.5, $CHCl_3$)

*N-(1-(Furan-2-yl)propan-2-yl)-4-methoxyaniline (**4l**).* The product was obtained as light brown oil in 75% (35 mg) yield and 78% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.34 (s, 1H), 6.79 (d, J = 9.1 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 6.30 (d, J = 1.9 Hz, 1H), 6.06 (d, J = 3.0 Hz, 1H) 3.75 (s, 3H), 3.71−3.69 (m, 1H), 2.92 (dd, J = 14.8, 4.9 Hz, 1H), 2.72 (dd, J = 14.8, 6.9 Hz, 1H), 1.18 (d, J = 6.6 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 153.3, 152.4, 141.6, 141.5, 115.3, 115.2, 110.4, 107.2, 56.0, 49.1, 34.9, 20.7. HRMS (ESI) calcd for $C_{14}H_{18}NO_2$ 232.1338, found 232.1331. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OJ-H column (hexanes/2-propanol = 90:10, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 17.4 min, t_r(minor) = 20.1 min. $[\alpha]_D^{20}$ = +9.3 (c = 0.5, $CHCl_3$)

*4-Methoxy-N-(1-(thiophen-2-yl)propan-2-yl)aniline (**4m**).* The product was obtained as an yellow oil in 74% (37 mg) yield and 70% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.16 (d, J = 4.9 Hz, 1H), 6.95 (dd, J = 4.9, 3.6 Hz, 1H), 6.81−6.78 (m, 3H), 6.61 (d, J = 8.8 Hz, 2H), 3.76 (s, 3H), 3.73−3.67 (m, 1H), 3.07 (m, 1H), 2.97 (m, 1H), 1.19 (d, J = 6.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 152.4, 141.3, 140.8, 127.0, 126.2, 124.1, 115.3, 115.2, 56.0, 50.6, 36.4, 20.6. HRMS (ESI) calcd for $C_{14}H_{18}NOS$ 248.1109, found 248.1105. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OJ-H column (hexanes/2-propanol = 95:5, flow rate = 0.75 mL/min, λ = 254 nm), t_r(major) = 36.6 min, t_r(minor) = 41.4 min. $[\alpha]_D^{20}$ = +4.5 (c = 0.5, $CHCl_3$).

*4-Methoxy-N-(1-(pyridin-2-yl)propan-2-yl)aniline (**4n**).* The product was obtained as dark brown oil in 78% yield (38 mg) and 74% ee. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.56 (d, J = 4.4 Hz, 1H), 7.59 (t, J = 6.9 Hz, 1H), 7.14 (m, 2H), 6.77 (d, J = 8.8 Hz, 2H), 6.62 (d, J = 8.5 Hz, 2H), 3.86−3.81 (m, 1H), 3.74 (s, 3H), 3.07 (dd, J = 13.3, 5.9 Hz, 1H), 2.85 (dd, J = 13.3, 6.5 Hz, 1H), 1.19 (d, J = 6.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 159.7, 152.2, 149.4, 141.8, 136.6, 124.1, 121.6, 115.2, 115.1, 56.0, 50.3, 45.0, 20.9. HRMS (ESI) calcd for $C_{15}H_{18}N_2ONa$ 265.1317, found 265.1311. Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OB-H column (hexanes/2-propanol = 97:3, flow rate = 1.0 mL/min, λ = 254 nm), t_r(major) = 67.6 min, t_r(minor) = 87.7 min. $[\alpha]_D^{20}$ = +11.4 (c = 1.0, $CHCl_3$).

Synthesis of Spiro Compound 9 (Scheme 4). A solution of CAN (3.6 mmol; 2.0 equiv) in H_2O (8.0 mL) was added to a stirred solution of amine **4h** (542 mg; 1.8 mmol, 1.0 equiv) in acetonitrile (6.0 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. Afterward ether was added to the reaction mixture and the organic phase was separated. A solution of NaOH (1.0 N) was added to the above biphase solution, and then the reaction mixture was extracted with ether. The combined organic layer was dried $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using hexanes/ethyl acetate (2:1) as an eluent to provide the desired product spiro compound **9** as a dark green solid. Yield: 68% (349 mg). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.12 (dd, J = 9.9, 2.7 Hz, 1H), 6.69 (dd, J = 10, 2.5 Hz, 1H), 6.30 (s, 1H), 6.25 (s, 1H), 6.19 (d, J = 9.8 Hz, 1H), 6.14 (d, J = 10.2 Hz, 1H), 3.79 (s, 1H), 3.58 (s, 1H), 3.35−3.30 (m, 1H), 2.73−2.60 (m, 2H), 1.21 (d, J = 6.3 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 187.0, 160.1, 158.7, 154.4, 150.7, 138.9, 127.0, 126.0, 114.2, 105.7, 97.3, 55.5, 55.4, 44.1, 38.9, 22.5. HRMS (ESI) calcd for $C_{17}H_{20}NO_3$ 286.1443, found 286.1442.

Synthesis of Tetrahydroisoquinoline 7 (Scheme 6). *Synthesis of Compound **11**.* To a solution of amine **4h** (2.0 mmol; 1.0 equiv) in dichloromethane (DCM) (20 mL) were added triethylamine (8.0 mmol; 4.0 equiv) and acetic anhydride (12 mmol; 6.0 equiv). The reaction mixture was stirred at room temperature under an argon atmosphere and monitored by TLC. On completion of reaction, the reaction mixture was quenched with saturated NH_4Cl aqueous solution and extracted with DCM. The organic layer was collected, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel using hexanes/ethyl acetate (1:1) as an eluent to provide the desired product **11** as yellow oil. Yield: 92% (632 mg). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.95−6.88 (m, 4H), 6.39 (s, 2H), 6.33 (s, 1H), 5.10−5.05 (m, 1H), 3.84 (s, 3H), 3.77 (s, 6H), 2.91 (dd, J = 13.7, 6.3 Hz, 1H), 2.43 (dd, J = 13.5, 8.8 Hz, 1H), 1.74 (s, 3H), 1.03 (d, J = 6.7 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$, ppm) δ 171.0, 160.9, 159.4, 141.5, 132.5, 131.0, 114.6, 107.1, 98.8, 55.7, 55.5, 51.5, 41.7, 23.8, 18.6. HRMS (ESI) calcd for $C_{20}H_{25}NO_4Na$ 366.1681, found 366.1674.

*Synthesis of Tetrahydroisoquinoline **12**.* To solution of amide **11** (618 mg; 1.8 mmol; 1.0 equiv) in acetonitrile (15 mL) was added $POCl_3$ (2.7 mmol; 1.5 equiv). The reaction mixture was refluxed under an argon atmosphere for 10 h. On completion of reaction, the reaction mixture was cooled, solvent was removed and the residue was dried in vacuo to give the crude mixture of the desired iminium salt. (HRMS (ESI) calcd for $C_{20}H_{24}NO_3$ 326.1751, found 326.1761).

To a solution of a crude mixture of the iminium salt in EtOH (15 mL) was added sodium borohydride (5.4 mmol; 3.0 equiv). The reaction mixture was stirred at room temperature in an open flask and monitored by TLC. On completion of reaction, the reaction mixture was quenched with 1 N NaOH and extracted with DCM. The organic layer was combined, dried over $MgSO_4$, and concentrated to provide the crude product as an inseparable mixture in ca. 1:1 ratio (**12**-*cis*/**12**-*trans* ≈ 1:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.24 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.36 (s, 1H), 6.33−6.30 (m, 3H), 4.84−4,79 (m, 1H), 4.16−4.13 (m, 1H), 3.81 (s, 12H), 3.77 (s, 6H), 3.09−3.02 (m, 1H), 2.89−2.82 (m, 1H), 2.63 (dd, J = 16.2, 7.1 Hz, 2H), 1.53 (d, J = 8.5 Hz, 3H), 1.49 (d, J = 6.3 Hz, 3H), 1.24 (d, J = 6.0 Hz, 3H), 1.11 (d, J = 6.3 Hz, 3H). HRMS (ESI) calcd for $C_{20}H_{26}NO_3$ 328.1913, found 328.1907.

*Synthesis of Tetrahydroisoquinoline **7**.* A solution of CAN (3.6 mmol; 2.0 equiv) in H_2O (8.0 mL) was added to a stirred solution of a crude mixture of PMP-protected tetrahydroisoquinoline **12** (a mixture of **12**-*cis*/**12**-*trans*) from the above reaction in acetonitrile (6.0 mL). The reaction mixture was stirred at room temperature for 2 h. Afterward, ether was added to the reaction mixture to generate a biphase solution. A solution of NaOH (1.0 N) was added to the above biphase solution, and then the crude mixture was extracted with ether. The combined organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column

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chromatography on silica gel using NEt_3/hexanes/ethyl acetate (0.05:2:1) as an eluent to provide the desired product 7-*cis* and 7-*trans*, respectively.

7-cis. The product was obtained as yellow oil in 36% (143.3 mg) yield over three steps. The spectroscopic data were in good agreement with the literature.[15] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.31 (s, 1H), 6.21 (s, 1H), 4.25−4.20 (m, 1H), 3.78 (s, 6H), 2.90−2.84 (m, 1H), 2.64−2.61 (m, 1H), 2.47−2.40 (m, 1H), 1.44 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.3 Hz, 3H). $[\alpha]_D^{20}$ = −145.0 (c = 1.0, MeOH) {Lit.[15] $[\alpha]_D^{20}$ = −130.0 (c = 1.0, MeOH)}.

7-trans. The product was obtained as yellow oil in 42% (167.2 mg) yield over three steps in 84% ee. The spectroscopic data were in good agreement with the literature.[13] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 6.28 (s, 1H), 6.20 (s, 1H), 4.30−4.25 (m, 1H), 3.78 (s, 6H), 3.30−3.24 (m, 1H), 2.71 (dd, J = 16.5, 3.8 Hz, 1H), 2.40 (dd, J = 16.3, 11.1 Hz, 1H), 1.38 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 6.0 Hz, 3H). Enantiomeric excess (ee) was determined by HPLC with a Chiralcel OD-H column (hexanes/2-propanol = 95:5, flow rate = 1.2 mL/min, λ = 277 nm), t_r(major) = 10.2 min, t_r(minor) = 6.9 min. $[\alpha]_D^{20}$ = −18.7 (c = 1.0, MeOH) {Lit.[15] $[\alpha]_D^{20}$ = −7.4 (c = 0.9, MeOH)}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00812.

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Notes

The authors declare no competing financial interest.

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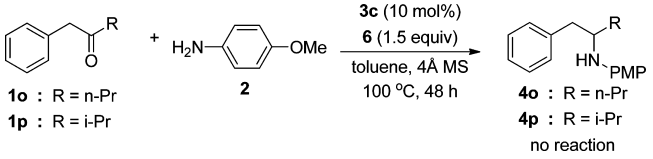
(14) Benzyl propyl ketone **1o** and benzyl isoproply ketone **1p** were subjected to the standard conditions. Unfortunately, however, no formation of the desired products **4o** and **4p** was observed and ketones and anisidine remained intact even after long reaction times.



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(18) Unfortunately, the enantiopurity of **7**-*cis* was not able to be determined by chiral HPLC analysis.

(19) Optical rotation ($[\alpha]_D^{20}$) values of **7**-*cis* and **7**-*trans* were −145.0 (c = 1.0, CH_3OH), and −18.7 (c = 1.0, CH_3OH), respectively. Since these values have the same signs with the reference values of (1*S*,3*R*)-**7**-*cis* {−130.0 (c = 1.0, CH_3OH)}, and (1*R*,3*R*)-**7**-*trans* {−7.4 (c = 0.9, CH_3OH)}, respectively, we assigned the absolute stereochemistry at the C-3 in tetrahydroisoquinoline **7** as (*R*)-configuration from the sign of the optical rotations, although there were some differences in $[\alpha]_D^{20}$ values between the measured ones and ones in literature. For reported $[\alpha]_D^{20}$ values in literature, see: ref 15a.

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