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Optically active palladium-catalyzed asymmetric amination of aryl halide

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Abstract—The asymmetric amination of aryl halides with racemic amines was examined in the presence of a transition metal complex having a chiral ligand. The yield and enantioselectivity of the products were strongly influenced by the kind of base, reaction temperature, solvent, and the additive. The best result was obtained from the reaction of 2-iodoanisole with 1-(1-naphthyl)ethylamine in the presence of sodium methoxide and 18-crown-6 by Pd–Tol–BINAP to afford the product in 70% yield with 80% ee.

1. Introduction

Substitution reactions of aryl halides using transition metal catalyst have been extensively developed in various fields.[1] Recently, palladium-catalyzed coupling of aryl halides with amines has been demonstrated to be a mild and efficient method for the synthesis of a variety of aniline derivatives.[2–5] Although this method is good for the preparation of such compounds, there is only one report of its application for the synthesis of optically active compounds, in which chiral amines were still used.[6] Such optically active aniline derivatives, such as BL-V8, hexahydro-carbazoles and Dynamics A, are known to have biological activities.[7] Herein, we report their preparation using a racemic amine by kinetic resolution catalyzed by palladium complex with chiral ligand.[8]

2. Results and discussion

First, the catalysts were examined for a reaction of 4-bromobiphenyl and racemic 1-phenylethylamine in the presence of sodium *tert*-butoxide in toluene at 70 °C (Table 1). The product, 4-phenyl-*N*-(1-phenylethyl)aniline **3a**, was obtained using $Pd_2(dba)_3{\cdot}CHCl_3$ and (*S*)-Tol–BINAP in 86% yield with 21% ee. $Pd(OAc)_2$ was not a good catalyst precursor for this reaction, while the Pt, Ni, and Cu precursors gave no reaction product. Various chiral ligands were then tested in combination with $Pd_2(dba)_3{\cdot}CHCl_3$. No reaction product was obtained using (*R*,*R*)-CHIRAPHOS and (*S*,*S*)-BPPM, while a racemic product was yielded by (*S*,*R*)-BPPFA and (*S*)-^{i}Pr-MOP. An optically active product was produced when (*R*,*R*)-MOD-DIOP, (*S*,*S*)-BDPP, (*R*)-MOP, and (*S*)-BINAP were used. Consequently, Tol–BINAP was the best ligand among those tested (see Scheme 1).

Even though no reaction product was obtained in acetonitrile and chloroform, the reaction proceeded smoothly in various solvents with yields over 80% (Table 2). Furthermore, the enantiomeric excesses of the products were about 20% in every solvent except cyclohexane. When 1-phenylethylamine was used as the solvent, a 30% enantiomeric excess of product was achieved.

Concerning the base that was added, little effect on selectivity was observed in different cations, while reactivity significantly changed when using potassium instead of sodium (Table 3, entries 1 and 4). On the other hand, the anion caused a difference in the reactivity and selectivity, that is, ethoxide and methoxide showed better selectivities than *tert*-butoxide. A reaction with carbonate, Na_2CO_3, K_2CO_3, or Cs_2CO_3, as a base yielded no product at all.

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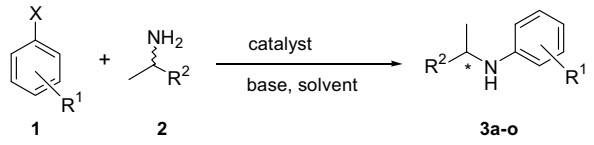
Table 1. Effect of ligand[a]

Entry	Metal source	Ligand	Yield[b] (%)	ee[c] (%)
1	$Pd_2(dba)_3{\cdot}CHCl_3$		86	21
2	$Pd(OAc)_2$		14	27
3	$Pt(dba)_2$	(*S*)-Tol–BINAP	Nr	—
4	$Ni(cod)_2$		5	Racemate
5	CuI		Nr	—
6		(*R*,*R*)-CHIRAPHOS	Nr	—
7		(*S*,*S*)-BPPM	Nr	—
8		(*S*,*R*)-BPPFA	27	Racemate
9	$Pd_2(dba)_3{\cdot}CHCl_3$	(*S*)-^{i}Pr–MOP	85	Racemate
10		(*R*,*R*)-MOD–DIOP	12	7
11		(*S*,*S*)-BDPP	63	7
12		(*R*)-MOP	71	7
13		(*S*)-BINAP	83	13

[a] Reaction condition: 4-bromobiphenyl 0.5 mmol, 1-phenylethylamine 1.2 mmol, metal source 4.0 mol % as a metal atom, ligand 0.02 mmol, NaO^{t}Bu 0.7 mmol, toluene 1 mL, 24 h, 70 °C, under Ar.
[b] Isolated yield.
[c] Determined by HPLC analysis using a Daicel Chiralcel OD-H column (eluent, hexane/2-propanol = 90/10, flow rate: 0.5 mL/min; detector UV 254 nm).



Scheme 1.

Table 2. Effect of solvent[a]

Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	Toluene	86	21
2	Cyclohexane	90	6
3	CH_3CN	Nr	—
4	$CHCl_3$	Nr	—
5	1,4-Dioxane	83	18
6	HMPA	93	15
7	DMSO	86	19
8	DMA	80[d]	22
9	DMF	57[d]	26
10	Pyridine	91	24
11	Et_3N	90	25
12	None[e]	87	30

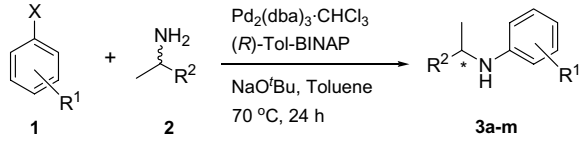
[a] Reaction condition: 4-bromobiphenyl 0.5 mmol, 1-phenylethylamine 1.2 mmol, $Pd_2(dba)_3{\cdot}CHCl_3$ 0.01 mmol (4.0 mol %), (*R*)-Tol–BINAP 0.02 mmol, NaO^{t}Bu 0.7 mmol, solvent 1 mL, 24 h, 70 °C, under Ar.
[b] Isolated yield.
[c] Determined by HPLC analysis using a Daicel Chiralcel OD-H column (eluent, hexane/2-propanol = 90/10, flow rate: 0.5 mL/min; detector UV 254 nm).
[d] By-product was observed.
[e] 1-Phenylethylamine (1.2 mL) was used as the reaction solvent.

Various aryl halides were subjected to this reaction (Scheme 2, Table 4). The yields of the products were slightly affected by the substituent on the bromobenzene. On the other hand, the stereoselectivities varied by changing the substrate. Substrates with an electron-donating substituent (–CH_3, –OCH_3) showed better enantioselectivities than those with an electron-withdrawing substituent (–CN).

Table 3. Effect of base[a]

Entry	Base	Yield[b] (%)	ee[c] (%)
1	NaO^{t}Bu	86	21
2	NaOMe	82	26
3	NaOEt	28	25
4	KO^{t}Bu	27	18
5	Cs_2CO_3	Nr	—
6	K_2CO_3	Nr	—
7	Na_2CO_3	Nr	—

[a] Reaction condition: 4-bromobiphenyl 0.5 mmol, 1-phenylethylamine 1.2 mmol, $Pd_2(dba)_3{\cdot}CHCl_3$ 0.01 mmol (4.0 mol %), (*R*)-Tol–BINAP 0.02 mmol, base 0.7 mmol, toluene 1 mL, 24 h, 70 °C, under Ar.
[b] Isolated yield.
[c] Determined by HPLC analysis using a Daicel Chiralcel OD-H column (eluent, hexane/2-propanol = 90/10, flow rate: 0.5 mL/min; detector UV 254 nm).



Scheme 2.

The structure of the amine affected the selectivity but not the reactivity. When the substituent on 1-C of ethylamine was changed to ethyl, phenyl, and 1-naphthyl, the yields of the products were almost the same but the stereoselectivity of the products increased using the substrates with a larger steric hindrance (Table 4, entries 1, 12, and 13).

The reaction temperature strongly affected the yield and enantiomeric excess of the product. At 70 °C, the reaction proceeded smoothly, and a higher enantioselectivity was obtained at room temperature, even though the yield was quite low (Table 4, entries 2 and 14). A prolonged reaction time did not improve the yield (Table 4, entries 15 and 16).

Table 4. Asymmetric amination of aryl halides[a]

Entry	Aryl halide **1**		Amine **2**	Product **3**		
	X =	R^1 =	R^2 =		Yield[b] (%)	ee[c] (%)
1	Br	4-Ph	Ph	**3a**	86	21
2[d]					31	39
3	Br	4-CH_3	Ph	**3b**	73	20
4		3-CH_3		**3c**	79	16
5		2-CH_3		**3d**	75	25
6	Br	4-OCH_3	Ph	**3e**	40	21
7		3-OCH_3		**3f**	68	19
8		2-OCH_3		**3g**	71	30
9	Br	4-CN	Ph	**3h**	86	10
10		3-CN		**3i**	80	16
11		2-CN		**3j**	82	5
12	Br	4-Ph	Et	**3k**	87	8
13	Br	4-Ph	1-Np	**3l**	84	37
14[d]					30	58
15[d,e]	Br	2-CH_3	1-Np	**3m**	Trace	72
16[d,e,f]	I				4	72

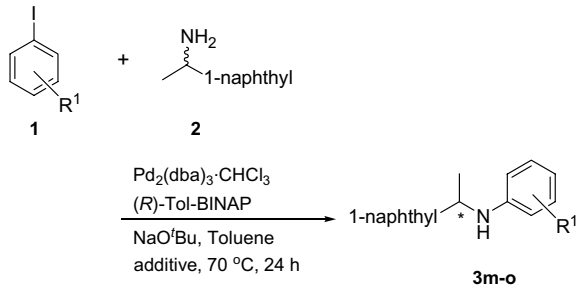
[a] Reaction condition: aryl halide 0.5 mmol, amine 1.2 mmol, $Pd_2(dba)_3{\cdot}CHCl_3$ 0.01 mmol (4.0 mol %), (*R*)-Tol–BINAP 0.02 mmol, NaO^{t}Bu 0.7 mmol, toluene 1 mL, 24 h, 70 °C, under Ar.
[b] Determined by ^{1}H NMR of the reaction mixture using an internal standard method.
[c] Determined by chiral HPLC analysis (see Section 4).
[d] At room temperature.
[e] NaOMe was used as the base, and amine (1.2 mL) was used as the reaction solvent.
[f] Reaction was performed for 72 h.

Good enantioselectivity (72% ee) was achieved from the reaction of 2-bromotoluene and 1-(1-naphthyl)ethylamine at room temperature in the presence of a base of sodium methoxide, but the yield was quite low. Therefore, 2-iodotoluene was employed for this reaction. However, the yield did not improve. The effect of additives was then studied to obtain the product in high yield, because the addition of crown ether or ammonium salt reportedly accelerates the reaction.[9] The addition of ammonium salts effectively yielded product **3a** in higher yields without any loss of enantioselectivity (Table 5). Use of tetrabutylammonium bromide increased the yield to 53%. Obtaining a higher yield by adding ammonium salt was difficult because of its low solubility. Crown ether (1.4 equiv) was then added to the reaction to provide a product in 27% yield. Interestingly, using 4.2 equiv of sodium methoxide and 4.2 equiv of crown ether increased the yield to 85% in 74% ee, although no improvement in the yield was observed using 4.2 equiv of sodium methoxide without crown ether. Although Buchwald et al. demonstrated a zero-order reaction in base,[10] our results indicate otherwise, when

Table 5. Asymmetric amination of aryl halides using 1-(1-naphthyl)ethylamine[a]

Entry	Aryl halide **1**	Additive[b] (equiv)	Product **3**		
	R^1 =			Yield[c] (%)	ee[d] (%)
1	2-CH_3	Me_4NCl (1.0)	**3m**	29	74
2		Bu_4NBr (1.0)		53	72
3		Bu_4NI (1.0)		6	71
4		18-Crown-6 (1.4)		27	71
5[e]		18-Crown-6 (4.2)		85	74
6[e]	H	18-Crown-6 (4.2)	**3n**	60	71
7[e]	2-OCH_3	18-Crown-6 (4.2)	**3o**	26	79
8[f]		18-Crown-6 (8.4)		70	80

[a] All reactions were performed using an aryl halide (0.5 mmol), 19 equiv of 1-(1-naphthyl)ethylamine, 1.4 equiv of $NaOCH_3$, 2 mol % $Pd_2(dba)_3{\cdot}CHCl_3$/4 mol % (*R*)-Tol–BINAP, and an additive at room temperature for 24 h.
[b] Equivalent to halide.
[c] Determined by ^{1}H NMR of the reaction mixture using an internal standard method.
[d] Determined by chiral HPLC analysis (see Section 4).
[e] 4.2 equiv of $NaOCH_3$ was used.
[f] 8.4 equiv of $NaOCH_3$ was used.



Scheme 3.

using a combination of base and 18-crown-6. 2-Iodoanisole, using 8.4 equiv of sodium methoxide and the same amount of crown ether, gave a satisfactory yield of 70%, while 4.2 equiv of them afforded product **3c** in only 26% yield (see Scheme 3).

As described above, better stereoselectivity was obtained from the reaction using a large amount of amine (Table 2, entry 12), suggesting that the reaction proceeded via a kinetic resolution of the amine. If the reaction proceeds in a kinetic resolution fashion, the remaining amine should also be optically active. Therefore, the remaining amine from the reaction of 4-bromobiphenyl and 2 equiv of 1-(1-naphthyl)ethylamine at 70 °C for 24 h was investigated. From this reaction, the product was obtained in 85% yield with 37% ee, while the remaining amine was isolated with 35% yield and 29% ee. Although the yield was low by column chromatography, stereoselectivity was close to the calculated value of 27% ee.

The optically active amines were then used for this reaction. When an equivalent of (*R*)-1-(1-naphthyl)ethylamine was employed using (*R*)-Tol–BINAP, the reaction at 55 °C proceeded in 90% yield after 5 h. On the other hand, the reaction of (*S*)-1-(1-naphthyl)ethylamine using (*R*)-Tol–BINAP resulted in a 68% yield after 5 h under the same reaction conditions. These results indicate that the reaction of (*R*)-1-(1-naphthyl)-ethylamine using (*R*)-Tol–BINAP is faster than (*S*)-isomer using (*R*)-Tol–BINAP, while the reaction of racemic amine proceeds with kinetic resolution (see Fig. 1).

The mechanism of the coupling of aryl halides and amines catalyzed by a palladium complex has been extensively studied. Buchwald et al. demonstrated that the coordination of an amine to a palladium center accelerates the oxidative addition of aryl halides to a metal center.[10] They also showed that the reaction rate depended on the concentration of the aryl halide and amine instead of the concentration of the additive base. Hartwig suggested that the reaction rate depends on the concentration of the catalyst.[11] In our reaction system, the enantioselectivity was influenced either by the kind of aryl halide, amine, or base. Furthermore, the yield of the product depended on the amount of a combination of crown ether and sodium methoxide as base; while the amount of sodium

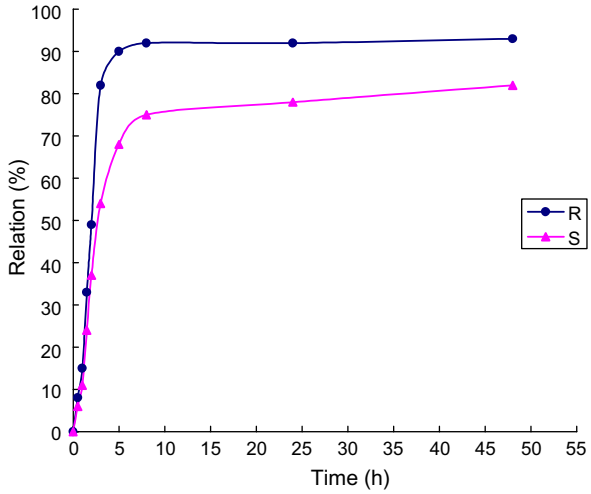


Figure 1. Comparison of the reaction yields of 4-bromobiphenyl with (*R*)- or (*S*)-1-(1-naphthyl)ethylamine in the presence of (*R*)-Tol–BINAP–Pd catalyst.

methoxide as a base did not affect the yield of the product.

To investigate the reaction sequence, bromoaryl–palladium species, prepared in situ by the reaction of $Pd_2(dba)_3{\cdot}CHCl_3$, (*S*)-BINAP, and 4-bromobiphenyl in toluene, was allowed to react with 1-phenylethylamine. Reaction at 70 °C and at 100 °C did not proceed at all. These results indicate that, without crown ether, the reaction proceeds through the coordination of the amine to the palladium center, and then this intermediate reacts with the aryl halide, as already demonstrated by Buchwald et al. This mechanism explains the effect on the stereoselectivity of the structures of aryl halide, amine, and base. That is, the intermediates coordinated with the amine are diastereomeric, and that these diastereomers should show a different reactivity to the aryl halide and to the base. Therefore, a different enantioselectivity was detected.

On the other hand, the reaction was accelerated using crown ether. This phenomenon could be explained as follows: the same intermediate from the palladium and amine reacted with a strong base, a cation-free methoxide, which is prepared using sodium methoxide with crown ether, to give the anionic palladium species. This anionic species might have reacted with an aryl halide faster than the intermediate coordinated by the amine. At the same time, the steric energies (MM2 calculation) of both anionic diastereomers of (*S*)-Tol–BINAP–Pd having (*R*)- or (*S*)-1-phenylethylamine and (*R*)- or (*S*)-1-(1-naphthyl)ethylamine as the covalent bond between the palladium atom and nitrogen atom were conferred. Modeling results correlated with the conclusion that the (*S*)-isomer of the aniline derivatives are dominant when using (*S*)-Tol–BINAP as a ligand, and that 1-(1-naphthyl)ethylamine shows better stereoselectivity than 1-phenylethylamine. These results might demonstrate the role of crown ether on catalytic cycles (see Fig. 2).

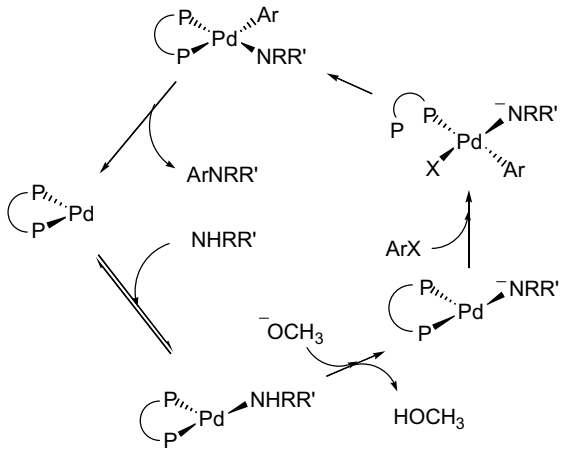


Figure 2. Plausible mechanism.

3. Conclusion

In conclusion, asymmetric amination was examined using aryl halides and racemic amines in the presence of a transition metal complex with a chiral ligand. $Pd_2(dba)_3{\cdot}CHCl_3$ combined with Tol–BINAP was demonstrated to be the best catalyst. The best results (70% yield, 80% enantiomeric excess of the product) were obtained from the reaction of 2-iodoanisole with excess and racemic 1-(1-naphthyl)ethylamine without solvent at room temperature for 24 h in the presence of 18-crown-6 as the additive, $NaOCH_3$ as the base, and LnPd (Ln = (*R*) or (*S*)-Tol–BINAP) as the catalyst. Obtaining optically active aniline derivatives from racemic amines increases the utility of aryl amination reactions.

4. Experimental

4.1. General

Nuclear magnetic resonance spectra were measured using a JEOL JNM A-400 (^{1}H NMR: 400 MHz, ^{13}C NMR: 100 MHz) spectrometer with tetramethylsilane as the internal standard for the ^{1}H NMR and $CDCl_3$ at 77 ppm for the ^{13}C NMR. IR spectra were measured on a Shimadzu IR-408 spectrometer. Mass spectral (GC–MS) data were recorded on a Shimadzu GP2000A instrument. High resolution mass spectra (FAB) were measured using a JEOL JMS-700 with *meta*-nitrobenzyl alcohol as the matrix and PEG-200 as the calibration standard. The enantiomeric excesses were determined by HPLC analyses using a Hitachi series L-7100 HPLC with a detection system using a Chiralcel OD or OJ column. Optical rotations were measured using a Horiba SEPA-200 spectrometer.

All reactions were performed under an argon atmosphere using standard Schlenk techniques. All solvents were dried by standard methods and distilled under argon. Commercially available compounds were used without further purification.

4.2. Pd-catalyzed coupling of α-substituted amines with aryl bromides

The aryl bromide (0.5 mmol), amine (1.2 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (11 mg, 0.01 mmol, 4 mol % Pd), NaO^{t}Bu (67 mg, 0.7 mmol, 1.4 equiv) and toluene (1 mL) were added to a dried sealable Schlenk tube which was capped with a septum, purged with argon, and then heated to 70 °C for 24 h. The reaction mixture was then allowed to cool to room temperature, diluted with Et_2O (10 mL), and filtered through Celite. The Celite was then rinsed with Et_2O. The filtrate was concentrated to give the crude product. Purification by column chromatography (10% EtOAc/hexane) afforded the pure product.

4.3. (*S*)-4-Phenyl-*N*-(1-phenylethyl)aniline 3a[6]

$[\alpha]_D^{25} = -11.9$ (*c* 0.5, $CHCl_3$) {lit.[6] $[\alpha]_D^{25} = +54$ for (*R*)-4-phenyl-1-phenylethylaniline in >99% ee}, 21% ee [(*R*)-Tol–BINAP] by HPLC (Chiralcel OD, hexane/2-propanol = 1:9, 0.5 mL/min, t_R = 16.3 min (major), t_R = 19.5 min (minor)); ^{1}H NMR ($CDCl_3$): δ 1.54 (d, 3H, *J* = 6.7 Hz), 4.13 (s, 1H), 4.52 (q, *J* = 6.7 Hz, 1H), 6.56–6.60 (m, 2H), 7.20–7.25 (m, 2H), 7.31–7.40 (m, 8H), 7.48 (d, 2H, *J* = 5.2 Hz); GC–MS (*m*/*z*) 273.

4.4. 4-Methyl-*N*-(1-phenylethyl)aniline 3b[12]

$[\alpha]_D^{25} = +26$ (*c* 0.5, $CHCl_3$); 20% ee [(*R*)-Tol–BINAP] by HPLC (column: Daicel Chiralcel OD-H; eluent: hexane/2-propanol = 9/1, 0.5 mL/min, t_R = 11.1 min (major), t_R = 12.2 min (minor)); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.52 (d, 3H, *J* = 6.7 Hz), 2.18 (s, 3H), 4.45 (q, 1H, *J* = 6.7 Hz), 6.46 (d, *J* = 8.4 Hz, 2H, *Ar*), 6.90 (d, *J* = 8.4, 2H, *Ar*), 7.20–737 (5H, m, *Ar*); GC–MS (*m*/*z*) 211.

4.5. 3-Methyl-*N*-(1-phenylethyl)aniline 3c[13]

$[\alpha]_D^{25} = +16$ (*c* 0.5, $CHCl_3$); 16% ee [(*R*)-Tol–BINAP] by HPLC (column: Daicel Chiralcel OD-H; eluent: hexane/2-propanol = 9/1, 0.5 mL/min, t_R = 10.1 min (minor), t_R = 12.8 min (major)); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.51 (d, *J* = 6.8, 3H, CHC*H*$_3$), 2.20 (s, 3H, $C_6H_4CH_3$), 4.47 (q, *J* = 6.8, 1H, C*H*NH), 6.30–6.32 (m, 1H, *Ar*), 6.37 (m, 1H, *Ar*), 6.47 (d, *J* = 7.2, 1H, *Ar*), 6.95–6.99 (m, 1H, *Ar*), 7.20–7.24 (m, 1H, *Ar*), 7.29–7.39 (m, 4H, *Ar*); GC–MS (*m*/*z*) 211.

4.6. 2-Methyl-*N*-(1-phenylethyl)aniline 3d[12]

$[\alpha]_D^{25} = +14$ (*c* 0.5, $CHCl_3$), 25% ee [(*R*)-Tol–BINAP] by HPLC (column: Daicel Chiralcel OD-H; eluent: hexane/2-propanol = 9/1, 0.5 mL/min, t_R = 10.3 min (minor), t_R = 18.8 min (major)); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.55 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 2.21 (s, 3H, $C_6H_4CH_3$), 3.85 (s, 1H, N*H*), 4.52 (q, *J* = 6.8 Hz, 1H, C*H*NH), 6.36 (d, *J* = 6.8 Hz, 1H, *Ar*), 6.59 (t, *J* = 7.2 Hz, 1H, *Ar*), 6.94 (t, *J* = 7.6 Hz, 1H, *Ar*), 7.04 (d, *J* = 7.6 Hz, 1H, *Ar*), 7.19–7.23 (m, 1H, *Ar*), 7.28–7.36 (m, 4H, *Ar*); GC–MS (*m*/*z*) 211.

4.7. 4-Methoxy-*N*-(1-phenylethyl)aniline 3e[14]

$[\alpha]_D^{25} = +6.0$ (*c* 0.3, $CHCl_3$) {lit.[14] $[\alpha]_{365}^{20} = +27.1$ (*c* 1.21, EtOH) 59% ee, (*R*)}; 21% ee [(*S*)-Tol–BINAP] by HPLC (column: Daicel Chiralcel OD-H; eluent: hexane/2-propanol = 99/1, 0.5 mL/min, t_R = 24.4 min (major), t_R = 25.6 min (minor)); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.49 (d, *J* = 6.8, 3H, $CHCH_3$), 3.68 (s, 3H, OCH_3), 4.40 (q, *J* = 6.8, 1H, C*H*NH), 6.46 (d, *J* = 9.2, 2H, *Ar*), 6.68 (d, *J* = 9.2, 2H, *Ar*), 7.19–7.37 (m, 5H, *Ar*); GC–MS (*m*/*z*) 227.

4.8. 3-Methoxy-*N*-(1-phenylethyl)aniline 3f[15]

$[\alpha]_D^{25} = +8.0$ (*c* 0.5, $CHCl_3$); 19% ee [(*S*)-Tol–BINAP] by HPLC (column: Daicel Chiralcel OJ; eluent: hexane/2-propanol = 9/1, 0.5 mL/min, t_R = 36.9 min (minor), t_R = 19.5 min (major)); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.48 (d, *J* = 6.4, 3H, $CHCH_3$), 3.66 (s, 3H, OCH_3), 4.06 (br, 1H, N*H*), 4.46 (q, *J* = 6.4 Hz, 1H, C*H*NH), 6.05 (t, *J* = 4.8, 1H, *Ar*), 6.13 (dd, *J* = 2.0, 7.6 Hz, 1H, *Ar*), 6.20 (dd, *J* = 2.0, 7.6, 1H, *Ar*), 6.98 (t, *J* = 8.4 Hz, 1H, *Ar*), 7.18–7.22 (m, 1H, *Ar*), 7.28–7.36 (m, 4H, *Ar*); GC–MS (*m*/*z*) 227.

4.9. (*S*)-2-Methoxy-*N*-(1-phenylethyl)aniline 3g[16]

$[\alpha]_D^{25} = +14$ (*c* 0.5, $CHCl_3$) {lit.[16] $[\alpha]_D^{25} = +38.5$ (*c* 10.3, $CHCl_3$) for 88% ee of (*S*)-**3g**}; 30% ee ((*S*)-Tol–BINAP) by HPLC (column: Daicel Chiralcel OD-H; eluent: hexane/2-propanol = 9/1, 0.5 mL/min, t_R = 9.3 min (major), t_R = 11.8 min (minor)); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.54 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 3.87 (s, 3H, OCH_3), 4.46 (q, *J* = 6.8 Hz, 1H, C*H*NH), 4.63 (br, 1H, N*H*), 6.30–6.35 (m, 1H, *Ar*), 6.59–6.62 (m, 1H, *Ar*), 6.67–6.89 (m, 2H, *Ar*), 7.18–7.37 (m, 5H, *Ar*); GC–MS (*m*/*z*) 227.

4.10. 4-(1-Phenylethylamino)benzonitrile 3h[17]

$[\alpha]_D^{25} = +6.1$ (*c* 0.5, $CHCl_3$); 10% ee [(*R*)-Tol–BINAP] by HPLC (column: Daicel Chiralcel OD-H; eluent: hexane/2-propanol = 8/2, 0.5 mL/min, t_R = 10.7 min (major), t_R = 12.5 min (minor)); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.54 (d, *J* = 6.4, 3H, $CHCH_3$), 4.51 (quintet, *J* = 6.4, 1H, C*H*NH), 4.68 (br, 1H, N*H*), 6.47 (d, *J* = 8.8, 2H, *Ar*), 7.22–7.27 (m, 2H, *Ar*), 7.29–7.35 (m, 5H, *Ar*). GC–MS (*m*/*z*) 222.

4.11. 3-(1-Phenylethylamino)benzonitrile 3i

$[\alpha]_D^{25} = -5.9$ (*c* 0.5, $CHCl_3$); 16% ee ((*R*)-Tol–BINAP) by HPLC (column: Daicel Chiralcel OD-H; eluent: hexane/2-propanol = 8/2, 0.5 mL/min, t_R = 10.2 min (minor), t_R = 13.3 min (major); IR (KBr) *v* 3368, 2966, 2228, 1603, 1522, 1479, 1433, 1335, 1299, 1269, 1200, 1165, 843, 781, 765, 704, 677, 548 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.53 (d, *J* = 6.8, 3H, $CHCH_3$), 4.31 (br, 1H, N*H*), 4.46 (q, *J* = 6.8, 1H, C*H*NH), 6.68–6.71 (m, 2H, *Ar*), 6.87–6.90 (m, 1H, *Ar*), 7.10–7.14 (m, 1H, *Ar*), 7.22–7.28 (m, 1H, *Ar*), 7.30–7.34 (m, 4H, *Ar*); ^{13}C NMR (100 MHz): δ 24.9, 53.3, 112.6, 115.5, 117.6, 119.5, 120.7, 125.6, 127.3, 128.9, 129.7, 143.8, 147.3; GC–MS (*m*/*z*) 222. HR-MS (FAB, PEG-200) calcd for $C_{15}H_{14}N_2$ 222.1157. Found 222.1166.

4.12. 2-(1-Phenylethylamino)benzonitrile 3j[18]

$[\alpha]_D^{25} = -6.0$ (*c* 0.5, $CHCl_3$); 5% ee [(*R*)-Tol–BINAP] by HPLC (column: Daicel Chiralcel OD-H; eluent: hexane/2-propanol = 8/2, 0.5 mL/min, t_R = 8.7 min (minor), t_R = 11.5 min (major)); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.58 (d, *J* = 6.8, 3H, $CHCH_3$), 4.57 (quintet, *J* = 6.8 Hz, 1H, C*H*NH), 4.90 (br, 1H, N*H*), 6.42 (d, *J* = 8.4, 1H, *Ar*), 6.62 (t, *J* = 7.6, 1H, *Ar*), 7.16–7.28 (m, 2H, *Ar*), 7.32–7.35 (m, 4H, *Ar*), 7.36–7.40 (m, 1H, *Ar*); GC–MS (*m*/*z*) 222.

4.13. *N*-(2-Butyl)-4-phenylaniline 3k

$[\alpha]_D^{25} = +10$ (*c* 0.5, $CHCl_3$); 8% ee [(*S*)-Tol–BINAP] by HPLC (column: Daicel Chiralcel OD-H; eluent: hexane/2-propanol = 99/1, 0.5 mL/min), t_R = 26.2 min (major), t_R = 28.7 min (minor); IR (NaCl) *v* 3400, 3000, 2950, 1600, 1520, 1480, 1450, 1400, 1370, 1320, 1290, 1270, 1240, 1190, 1160, 820, 760, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.97 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.20 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 1.45–1.66 (m, 2H, $CHCH_2CH_3$), 3.44 (sextet, *J* = 6.4, 1H, C*H*NH), 6.65 (d, *J* = 8.8, 2H, *Ar*), 7.22–7.26 (m, 1H, *Ar*), 7.36–7.44 (m, 4H, *Ar*), 7.52–7.54 (m, 2H, *Ar*); ^{13}C NMR (100 MHz): δ 10.4, 20.2, 29.5, 49.7, 113.1, 125.8, 126.1, 127.9, 128.6, 129.4, 141.2, 147.0; GC–MS (*m*/*z*) 225. HR-MS (FAB, PEG-200) calcd for $C_{16}H_{19}N$ 225.1518. Found 225.1539.

4.14. *N*-(1-(1-Naphthyl)ethyl)-4-phenylaniline 3l

$[\alpha]_D^{25} = +86$ (*c* 0.5, $CHCl_3$); 37% ee [(*S*)-Tol–BINAP] by HPLC (column: Daicel Chiralcel OD-H; eluent: hexane/2-propanol = 9/1, 0.5 mL/min) t_R = 27.0 min (minor), t_R = 32.9 min (major); IR (KBr) *v* 3400, 3020, 1620, 1600, 1520, 1480, 1440, 1370, 1320, 1300, 1270, 1250, 1230, 1190, 1140, 820, 800, 770, 760, 690 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.70 (d, *J* = 6.8 Hz, 3H, $CHCH_3$), 5.33 (q, *J* = 6.8 Hz, 1H, C*H*NH), 6.57 (d, *J* = 8.8 Hz, 2H, *Ar*), 7.19–7.59 (m, 10H, *Ar*), 7.68 (d, *J* = 6.8 Hz, 1H, *Ar*), 7.76 (d, *J* = 8.4 Hz, 1H, *Ar*), 7.91 (d, *J* = 8.0 Hz, 1H, *Ar*), 8.17 (d, *J* = 8.0 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz): δ 23.6, 49.5, 113.3, 122.2, 122.5, 125.5, 125.9, 125.9, 126.1, 126.2, 127.5, 127.8, 128.6, 129.1, 130.0, 130.6, 134.0, 139.7, 141.1, 146.4; GC–MS (*m*/*z*) 323. HR-MS (FAB, PEG-200) calcd for $C_{24}H_{21}N$ 323.1674. Found 323.1686.

4.15. 2-Methyl-*N*-(1-(1-naphthyl)ethyl)aniline 3m

$[\alpha]_D^{25} = +226$ (*c* 0.5, $CHCl_3$); 100% ee (product from the reaction using enantiomerically pure amine) by HPLC (column: Daicel Chiralcel OD-H; eluent: hexane/2-propanol = 9/1, 0.5 mL/min, t_R = 11.5 min (major), t_R = 12.4 min (minor)); IR (KBr) *v* 3400, 2950, 1600, 1580, 1500, 1470, 1460, 1380, 1310, 1300, 1250, 1220, 1170, 800, 770, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.72 (d, *J* = 6.4 Hz, 3H, $CHCH_3$), 2.28 (s, 3H, $PhCH_3$), 5.33 (q, *J* = 6.4 Hz,

1H, C*H*NH), 6.26 (s, 1H, *Ar*), 6.60 (t, $J = 7.6$ Hz, 1H, *Ar*), 6.87 (t, $J = 8.0$ Hz, 1H, *Ar*), 7.07 (d, $J = 7.6$ Hz, 1H, *Ar*), 7.40 (t, $J = 7.6$ Hz, 1H, *Ar*), 7.50–7.62 (m, 3H, *Ar*), 7.75 (d, $J = 7.6$, 1H, *Ar*), 7.91 (d, $J = 8.0$ Hz, 1H, *Ar*), 8.17 (d, $J = 8.0$ Hz, 1H, *Ar*); ^{13}C NMR (100 MHz): δ 17.7, 23.8, 49.3, 110.8, 116.7, 121.5, 122.1, 122.5, 125.4, 125.9, 126.0, 127.0, 127.4, 129.1, 129.9, 130.6, 134.0, 139.8, 144.8; GC–MS (*m*/*z*) 261. HR-MS (FAB, PEG-200) calcd for $C_{19}H_{19}N$ 261.1517. Found 261.1533.

4.16. (*R*)-*N*-(1-(1-Naphthyl)ethyl)aniline 3n[19]

$[\alpha]_D^{25} = +142$ (*c* 0.5, $CHCl_3$) {lit.[19] $[\alpha]_D^{25} = +249$ (*c* 1.9, CH_3OH) for (*R*)-**3n**}; 75% ee [(*S*)-Tol–BINAP] by HPLC (column: Daicel Chiralcel OD-H; eluent: hexane/2-propanol = 9/1, 0.5 mL/min, $t_R = 30.8$ min (minor), $t_R = 67.7$ min (major)); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.66 (d, $J = 6.8$ Hz, 3H, CHC*H*$_3$), 4.26 (br, 1H, N*H*), 5.28 (t, 1H, $J = 6.8$ Hz, C*H*NH), 6.49 (d, 2H, $J = 8.0$ Hz, Ar), 6.64 (t, 1H, $J = 7.2$ Hz, Ar), 7.04–7.08 (m, 2H, Ar), 7.41 (t, 1H, $J = 7.8$ Hz, Ar), 7.50–7.58 (m, 2H, Ar), 7.66 (d, 1H, $J = 6.8$ Hz, Ar), 7.75 (d, 1H, $J = 8.0$ Hz, Ar), 7.91 (d, 1H, $J = 7.6$ Hz, Ar), 8.16 (d, 1H, $J = 8.4$ Hz, Ar); GC–MS (*m*/*z*) 224.

4.17. (*S*)-2-Methoxy-*N*-(1-(1-naphthyl)ethyl)aniline 3o[19]

$[\alpha]_D^{25} = +170$ (*c* 0.3, $CHCl_3$) {lit.[19] $[\alpha]_D^{25} = -249$ (*c* 1.9, CH_3OH) for (*R*)-**3o**}; 80% ee [(*S*)-Tol–BINAP] by HPLC (column: Daicel Chiralcel OD-H; eluent: hexane/2-propanol = 9/1, 0.5 mL/min, $t_R = 11.3$ min (minor), $t_R = 20.4$ min (major)); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.65 (d, 3H, $J = 6.8$ Hz, CHC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 4.76 (br, 1H, N*H*), 5.25 (q, 1H, $J = 6.8$ Hz, C*H*NH), 6.19–6.21 (m, 1H, *Ar*), 6.55–6.61 (m, 2H, *Ar*), 6.72–6.76 (m, 1H, *Ar*), 7.35 (t, 1H, $J = 8.0$ Hz, *Ar*), 7.44–7.54 (m, 2H, *Ar*), 7.61 (d, 1H, $J = 7.6$ Hz, *Ar*), 7.69 (d, 1H, $J = 8.4$ Hz, *Ar*), 7.86 (d, 1H, $J = 8.0$ Hz, *Ar*), 8.14 (d, 1H, $J = 8.4$ Hz, *Ar*); GC–MS (*m*/*z*) 277.

4.18. Modeling study of the plausible anionic intermediates of (*S*)-Tol–BINAP-Pd with chiral amine

Based on a modeling study, the steric energies (MM2 calculation) of both anionic diastereomers of (*S*)-Tol–BINAP–Pd having (*R*)-1-phenylethylamine or (*S*)-1-phenylethylamine as the covalent bond between the palladium atom and nitrogen atom were conferred. (*S*)-Tol–BINAP–Pd–(*S*)-1-phenylethylamine (−71.22 kcal/mol) is more stable than (*S*)-Tol–BINAP–Pd–(*R*)-1-phenylethylamine (−70.72 kcal/mol). In the case of 1-(1-naphthyl)ethylamine, (*S*)-Tol–BINAP–Pd–(*S*)-1-(1-naphthyl)ethylamine (−80.71 kcal/mol) is more stable than (*S*)-Tol–BINAP-Pd–(*R*)-1-(1-naphthyl)ethylamine (−79.42 kcal/mol).

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