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N-Allylation of anilides with chiral palladium catalysts: the first catalytic asymmetric synthesis of axially chiral anilides

Jun Terauchi[†] and Dennis P. Curran*

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA, 15260, USA

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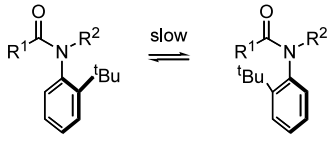
Abstract—The first catalytic asymmetric synthesis of axially chiral anilides has been carried out under palladium-catalyzed allylation reaction conditions with chiral phosphine ligands. Allylation of anilides bearing an *ortho tert*-butyl group with a palladium catalyst and (*S*)-BINAP as a chiral ligand gave axially chiral anilides in about 50% ee.

1. Introduction

In 1994, we reported that *N*-alkyl anilides **1** bearing a large *ortho* substituent (such as a *tert*-butyl group) are axially chiral and often exist as stable atropisomers at ambient temperatures.[1] Since then, work in our labs[2] and those of Simpkins[3] and Taguchi[4] has provided an understanding of some of the features controlling rotational barriers and shown that stereoselection is possible for an assortment of synthetically useful reactions including alkylations, cycloadditions and radical reactions, among others.



1 ent-**1**

The utility of axially chiral anilides in asymmetric synthesis is limited by the lack of methods for their synthesis in enantiopure form. To date, chiral chromatography and synthesis from chiral pool precursors have been used to obtain single enantiomers.[2–4] Uemura and co-workers have reported an elegant asymmetric synthesis of *o*-methyl-*o*-alkylanilides by enantioselective deprotonation of chromium carbene complexes,[5] but this cannot be used to prepare **1** and a number of other classes of axially chiral anilides. We have described the asymmetric synthesis of several axially chiral anilides by crystallization-induced asymmetric transformations and dynamic thermodynamic resolutions, but these methods may lack generality.[6]

The axial chirality of anilides of the type **1** requires that three substituents are present on the nitrogen. Accordingly, the construction of the third bond to nitrogen to form **1** has the potential for asymmetric synthesis (Fig. 1), and these anilides can be made by (1) asymmetric *N*-alkylation; (2) asymmetric acylation, or (3) asymmetric *N*-arylation. To date, our efforts at asymmetric acylation using methods introduced for the kinetic resolution of chiral secondary alcohols[7] have given only low ees (typically <20%).[8] We report herein the first catalytic asymmetric synthesis of axially chiral anilides; achiral anilides bearing an N–H group are allylated with chiral palladium catalysts in ees of up to about 50%. While this paper was in review, Taguchi and co-workers reported related asymmetric *N*-allylations of amides.[9] Taken together, our results and Taguchi's suggest that this approach has good potential for development into a highly enantioselective catalytic method to synthesise *N*-allylanilides.

2. Results and discussion

Palladium-catalyzed asymmetric allylations are often used to make new stereocenters[10] and *N*-allylations of 2°-amides at elevated temperatures to make achiral

* Corresponding author. Fax: 1-412-624-9861; e-mail: curran@pitt.edu

† Present address: Takeda Chemical Industries, Ltd., Osaka, Japan.

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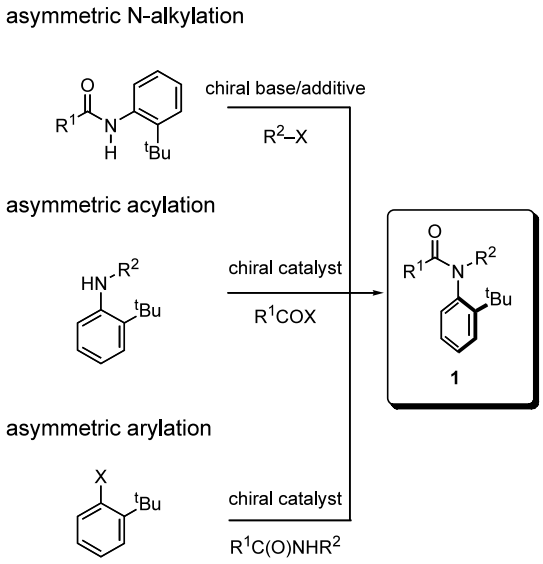
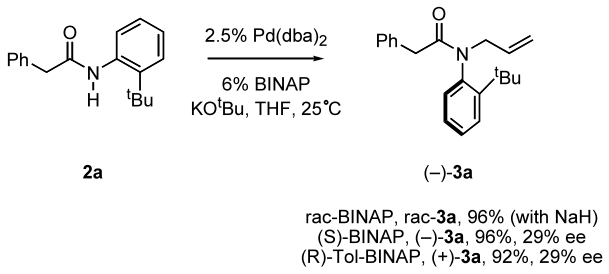


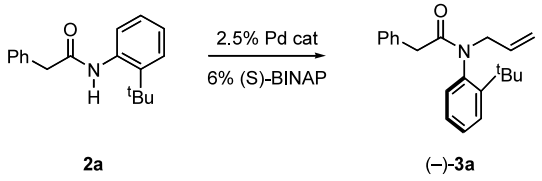
Figure 1. Bond disconnections for asymmetric synthesis of axially chiral anilides.

3°-amides have been reported,[11] so we felt that asymmetric allylation was a promising route to induce axial chirality. Our first goal was to identify conditions where the reaction proceeded rapidly at room temperature since heating could both lower the enantioselectivity of the reaction and begin to racemize the product. After a brief survey, we found that reaction of **2a** with NaH and allyl acetate in THF in the presence of $Pd_2(dba)_3$ and racemic BINAP produced the racemic anilide **3a** in 96% yield. Comparable yields were obtained with potassium *t*-butoxide and butyllithium as bases. With *t*-butoxide as the base, substituting (*S*)-BINAP gave (−)-**3a** in 29% ee and 96% yield, while (*R*)-Tol-BINAP gave (+)-**3a** in 29% ee and 92% yield. Other ligands including BPPFA, JOSIPHOS, Me-DUPHOS, Ph-PHOX and Trost's bis-phosphine[7] gave lower ees (0–10%) and sometimes lower yields.



We next varied the reaction conditions to improve the ee with (*S*)-BINAP as the chiral ligand. Results of these experiments are summarized in Table 1. In THF, variation of the base (entries 1–3) or temperature (entry 4) had little effect on the yield and enantioselectivity of the reaction. A brief survey of solvents (entries 5–7) identified slightly improved ee in toluene (32%, entry 5) and cooling the reaction to −30°C in this solvent improved the ee to 54% (entry 10) with a concomitant decrease in rate (30% of the starting material was recovered after 24 h). The use of $Pd_2(\pi\text{-allyl})_2Cl_2$ as precursor gave better conversion at lower temperatures, and ees settled at around 50% (entries 11–15). At

Table 1. Optimization of asymmetric allylation of **2a** with (*S*)-BINAP



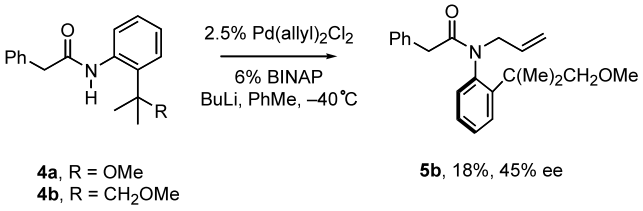
Entry	Pd cat.	Base	Solvent	Temp. (°C)	Time (h)	Yield **3a** (%)	ee (%)	Yield **2a** (%)[a]
1	$Pd_2(dba)_2$	NaH	THF	25	6	87	26	–
2	$Pd_2(dba)_2$	KO′Bu	THF	25	1.3	96	29	–
3	$Pd_2(dba)_2$	BuLi	THF	25	1.8	99	30	–
4	$Pd_2(dba)_2$	KO′Bu	THF	−78 to 25	18	95	36	–
5	$Pd_2(dba)_2$	KO′Bu	PhMe	25	24	72	32	26
6	$Pd_2(dba)_2$	KO′Bu	Et_2O	25	1	97	26	–
7	$Pd_2(dba)_2$	KO′Bu	CH_2Cl_2	25	1.6	89	24	–
8	$Pd_2(dba)_2$	BuLi	PhMe	0	17	91	45	–
9	$Pd_2(dba)_2$	BuLi	PhMe	−20	24	28	54	71
10[b]	$Pd_2(dba)_2$	BuLi	PhMe	−30	24	56	49	30
11[b]	$Pd_2(allyl)_2Cl_2$	BuLi	PhMe	−20	12	92	48	–
12[b]	$Pd_2(allyl)_2Cl_2$	BuLi	PhMe	−40	1	84	48	–
13[b]	$Pd_2(allyl)_2Cl_2$	BuLi	PhMe	−78	24	39	56	45
14	$Pd_2(allyl)_2Cl_2$	BuLi	PhMe	−40	7	76	53	24
15	$Pd_2(allyl)_2Cl_2$	BuLi	PhMe	−20	3	92	45	–
16[c]	$Pd_2(allyl)_2Cl_2$	BuLi	PhMe	25	2.5	92	41	–

[a] The starting material was re-isolated when TLC analysis showed that the reaction was incomplete.
[b] 25% of catalyst was used.
[c] (*E*)-Cinnamyl acetate was used and the product is the cinnamyl analog of **3a** ($PhCH_2CON(o\text{-}^tBuC_6H_4)CH_2CH{=}CHPh$.

–78°C, the ee reached 56%, though the conversion was only 55%. We also conducted a trial with cinnamyl acetate (entry 16), which gave comparable results to allyl acetate (compare entries 3 and 16).

Selecting the conditions of entry 14 ($Pd_2(\pi\text{-allyl})_2Cl_2$, BuLi, PhMe, –40°C) as optimal, we then reacted a series of secondary *o*-*tert*-butylanilides **2b–e** with allyl acetate, and the results of these experiments are shown in Table 2. The *t*-butyl amide **2d** gave low yield and ee, but the others gave ees in the range of **2a** (36–53%). The absolute configuration of **2a** was assigned as (P) by comparison of the specific rotation value and retention time in chiral chromatography to the reported sample,[4,6] and the configurations of the others was assigned by analogy.

We also briefly explored the possibility that a chelating group on the *ortho* position of the aryl ring might improve the stereoselectivity. The obvious candidate **4a** was not investigated since we have already learned that this molecule has a low rotational barrier and racemizes at a reasonable rate at room temperature.[2c] Instead, we prepared homolog **4b** (see Section 4) and submitted it to the standard conditions. This produced **5b** in 18% yield (75% recovered starting material) and 45% ee. Apparently, the presence of the chelating group does not increase the selectivity.



4a, R = OMe
4b, R = CH_2OMe

5b, 18%, 45% ee

3. Conclusions

In conclusion, we have described the first catalytic asymmetric synthesis of axially chiral *o*-*tert*-butyl anilides through Pd(0)-mediated allylic alkylation. This preliminary survey has reliably attained ees in the range of 50%, and we suggest that with further catalyst and ligand variation, the chiral allylation approach could be developed into a practical method to make enantioenriched *N*-allylanilides.

4. Experimental

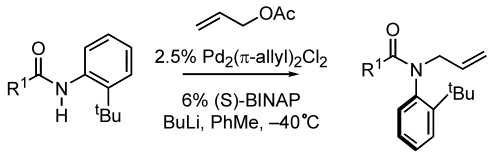
4.1. General methods

All experiments were conducted under an atmosphere of argon or nitrogen. Solvents were dried as follows: methylene chloride was distilled from CaH_2; tetrahydrofuran (THF), toluene, and ether were distilled from sodium/benzophenone. HPLC separation were done using a Regis (*S*,*S*)Whelk-O 1 column with 5 micron packing (25 cm×4.6 mm).

4.2. Synthesis of anilides 2

4.2.1. *N*-(2-*tert*-Butylphenyl)phenylacetamide, 2a. To a stirred mixture of 2-*tert*-butylaniline (1.59 g, 10 mmol) in ethyl acetate (20 ml) and 2 M Na_2CO_3 was added a solution of phenylacetyl chloride (1.498 g, 10 mmol) in ethyl acetate (10 ml) at room temperature. The mixture was stirred for 5 h at room temperature. Water (50 ml) and ethyl acetate (50 ml) were then added, and the organic layer was separated. The organic layer was washed with 50 ml of brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to give white crystals, which were washed with Et_2O to give 2.090 g (78%) of **2a** as white crystals: mp = 152–154°C; IR (thin film/NaCl/cm^{-1}) 3257.6, 2962.0, 1644.2, 1522.5, 1493.4, 1441.7; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.05 (s, 9H), 3.81 (s, 2H), 7.04 (br, 1H),7.08 (dt, 1H, J = 1.4, 7.6 Hz), 7.20 (dt, 1H, J = 1.5, 7.6 Hz), 7.28 (dd, 1H, J = 1.5, 7.9 Hz), 7.31–7.45 (m, 5H), 7.72 (dd, 1H, J = 1.4, 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 30.0, 33.9, 44.9, 125.7, 126.3, 126.5, 126.6, 127.9, 129.4, 130.0, 134.1, 135.1, 141.5, 168.8; LRMS (EI, 70 eV) m/z (rel. intens.) 267 (M^+, 25), 210 (77), 160 (20), 149 (32),

Table 2. Asymmetric allylation of **2b–e** with allyl acetate and (*S*)-BINAP



2b-e **3b-e**

Entry	Anilide	R^1	Time (h)	Product	Yield (%)	%ee
1	**2b**	$CH{=}CH_2$	21	**3b**	27[a]	43
2	**2c**	Ph	13	**3c**	89	36
3[b]	**2d**	^{t}Bu	6	**3d**	53[c]	12
4	**2e**	Me	5	**3e**	97	53

[a] 43% **2b** was recovered.
[b] This reaction was conducted at 0°C due to low conversion at –40°C.
[c] 34% **2d** was recovered.

134 (80), 91 (100); HRMS (EI) m/z calcd for $C_{18}H_{21}NO$ (M^+): 267.1623, found: 267.1627.

4.2.2. *N*-(2-*tert*-Butylphenyl)acrylamide, 2b. Mp = 140–142°C; IR (thin film/NaCl/cm^{-1}) 3207.4, 2963.3, 1652.1; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.43 (s, 9H), 5.81 (d, 1H, J = 9.5 Hz), 6.23–6.50 (m, 2H), 7.13–7.33 (m, 3H), 7.43 (d, 1H, J = 7.1 Hz), 7.65–7.73 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 30.63, 34.58, 126.39, 126.54, 126.72, 127.73, 128.28, 131.43, 134.86, 143.13, 164.03; LRMS (EI, 70 eV) m/z (rel. intens.) (M^+) 203 (28), 146 (100), 134 (55); HRMS m/z calcd for $C_{13}H_{17}NO$ (M^+): 203.1310, found: 203.1307.

4.2.3. *N*-(2-*tert*-Butylphenyl)benzamide, 2c. Mp = 189–191°C; IR (thin film/NaCl/cm^{-1}) 3339.5, 1646.0, 1516.5, 1481.6, 1290.7, 759.1, 710.2; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.47 (s, 9H), 7.17–7.33 (m, 2H), 7.45 (d, 1H, J = 7.8 Hz), 7.49–7.67 (m, 3H), 7.76 (d, 1H, J = 7.8 Hz), 7.91 (br s, 1H), 7.92 (d, 2H, J = 7.7 Hz)); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 30.71, 34.60, 126.28, 126.58, 126.84, 126.94, 128.06, 128.80, 131.73, 134.83, 135.24, 142.86, 165.67; LRMS (EI, 70 eV) m/z (rel. intens.) (M^+) 253 (15), 196 (100), 105 (65), 91 (12), 77 (69); HRMS (M+1) = 206 (5), ($M^{+\bullet}$–t-Bu$^\bullet$) = 148 (100), calcd mass for: ($M^\bullet$) $C_{17}H_{19}NO$: 253.1467, found: 253.1465.

4.2.4. *N*-(2-*tert*-Butylphenyl)pivalamide, 2d. Mp = 122–123°C; IR (thin film/NaCl/cm–^{1}) 3289.0, 2955.5, 1650.2, 1503.4, 755.2; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.47 (s, 9H), 1.54 (s, 9H), 7.26 (dt, 1H, J = 1.5, 7.6 Hz), 7.34 (dt, 1H, J = 1.7, 7.6 Hz), 7.50 (dd, 1H, J = 1.6, 7.9 Hz), 7.52 (br s, 1H), 7.76 (dd, 1H, J = 1.6, 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 27.78, 30.71, 34.63, 36.56, 125.90, 126.55, 126.86, 127.79, 135.70, 142.24, 176.39; LRMS (EI, 70 eV) m/z (rel. intens.) (M^+) 233 (24), 176 (100); HRMS m/z calcd for $C_{15}H_{23}NO$ ($M^{+\cdot}$): 233.1780, found: 233.1779.

4.3. General method for asymmetric allylation of anilides 2

A mixture of [Pd(π-allyl)Cl]$_2$ (1.8 mg, 4.9 μmol) and (*S*)-BINAP (6.8 mg, 10.9 μmol) in toluene (1 ml) was stirred for 30 min at room temperature. Allyl acetate (33 μl, 0.306 mmol) was added to the solution. After 10 min, the solution was added to a suspension of anilide **2** (0.2 mmol) and BuLi (1.6 M in hexane, 0.15 ml, 0.24 mmol) in toluene (2 ml) at –40°C. The reaction was quenched by water after the complete consumption of **2** or 24 h. The mixture was extracted with ether (2×50 ml). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane), giving **5**.

4.3.1. *N*-Allyl-*N*-(2-*tert*-butylphenyl)phenylacetamide, 3a. The enantiomeric excess was determined to be 53% by HPLC analysis (hexane/2-propanol = 90/10), 1.0 ml/min, 0.84 kpsi, retention times: 17.6 and 21.9 min (dominant): IR (thin film/NaCl/cm^{-1}) 2961.3, 1657.3, 1486.9, 1438.1, 1389.2, 1256.5; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.46 (s, 9H), 3.31–3.45 (m, 3H), 4.86–5.12 (m, 2H), 5.15 (d, 1H, J = 10.0 Hz), 5.92–6.06 (m, 1H), 6.85 (dd, 1H, J = 1.5, 7.8 Hz), 7.10–7.32 (m, 6H), 7.38 (dt, 1H, J = 1.6, 7.7 Hz), 7.64 (dd, 1H, J = 1.5, 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 32.25, 36.16, 41.80, 54.21, 118.65, 126.56, 126.66, 128.20, 128.68, 129.37, 129.89, 132.41, 132.60, 135.04, 139.65, 146.28, 171.05; LRMS (EI, 70 eV) m/z (rel. intens.) (M+1) 308 (4), 251 (91), 216 (25), 132 (100), 117 (45), 91 (57), 65 (68), 57 (97); HRMS m/z calcd for $C_{21}H_{25}NO$ ($M^{+\bullet}$): 307.1936, found: 307.1933; $[\alpha]_D^{23}$ = +73.4 (c 1.11, $CHCl_3$).

4.3.2. *N*-Allyl-*N*-(2-*tert*-butylphenyl)acrylamide, 3b. The enantiomeric excess was determined to be 43% by HPLC analysis (hexane/2-propanol = 90/10), 0.5 ml/min, 0.40 kpsi, retention times: 17.2 min (dominant) and 18.6 min. IR (thin film/NaCl/cm^{-1}) 2962.9, 1659.4, 1406.0, 1255.0, 982.9, 759.1; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.37 (s, 9H), 3.43 (dd, 1H, J = 8.1, 14.1 Hz), 5.01 (dd, 1H, J = 5.1, 14.1 Hz), 5.12 (dd, 1H, J = 1.0, 17.1 Hz), 5.18 (d, 1H, J = 9.9 Hz), 5.49 (dd, 1H, J = 2.0, 10.2 Hz), 5.92 (dd, 1H, J = 10.3, 16.8 Hz), 5.99–6.12 (m, 1H), 6.39 (dd, 1H, J = 2.0, 16.8 Hz), 6.95 (d, 1H, J = 7.7 Hz), 7.20 (t, 1H, J = 7.5 Hz), 7.34 (t, 1H, J = 7.6 Hz), 7.58 (d, 1H, J = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 32.26, 36.19, 54.42, 118.93, 126.93, 127.65, 128.76, 129.10, 129.82, 132.35, 132.65, 139.47, 146.99, 165.82; LRMS (EI, 70 eV) m/z (rel. intens.) (M+) 243 (3), 186 (100), 132 (54), 55 (78); HRMS m/z calcd for $C_{16}H_{21}NO$ (M^+): 243.1623, found: 243.1626; $[\alpha]_D^{23}$ = +54.5 (c 0.415, $CHCl_3$).

4.3.3. *N*-Allyl-*N*-(2-*tert*-butylphenyl)benzamide, 3c. The enantiomeric excess was determined to be 36% by HPLC analysis (hexane/2-propanol = 90/10), 2.0 ml/min, 1.95 kpsi, retention times: 6.9 and 13.2 min (dominant). IR (thin film/NaCl/cm^{-1}) 2955.1, 1636.8, 1488.0, 1438.8, 1384.1, 1302.8; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.26 (s, 9H (maj)), 1.50 (s, 9H (min)), 3.56 (dd, 1H (maj), J = 8.0, 14.0 Hz), 3.76 (dd, 1H (min), J = 7.6, 15.2 Hz), 4.13 (q, 1H (min), J = 7.1 Hz), 4.52 (dd, 1H (min), J = 5.8, 15.9 Hz), 4.80 (d, 1H (min), J = 16.9 Hz), 5.00–5.27 (m, 3H (maj)), 5.75–5.89 (m, 1H (min)), 6.07–6.24 (m, 1H (maj)), 7.06–7.17 (m, 4H), 7.18–7.34 (m, 4H), 7.43–7.49 (m, 2H), 7.56–7.62 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 31.94, 32.37, 36.31, 56.08, 118.79, 126.33, 126.83, 127.52, 128.30, 128.64, 129.40, 129.74, 130.72, 132.58, 132.90, 136.00, 140.08, 146.13, 168.88; LRMS (EI, 70 eV) m/z (rel. intens.) (M+1) 293 (3), 236 (90), 195 (19), 132 (28), 105 (100), 91 (20), 77 (87), 69 (25), 57(33); HRMS m/z calcd for $C_{20}H_{23}NO$ (M^+): 293.1780, found: 293.1784; $[\alpha]_D^{23}$ = +12.4 (c 0.41, $CHCl_3$).

4.3.4. *N*-Allyl-*N*-(2-*tert*-butylphenyl)pivamide, 3d. The enantiomeric excess was determined to 9% by HPLC analysis (hexane/2-propanol = 90/10), 0.5 ml/min, 0.40 kpsi, retention times: 9.9 min (dominant) and 11.0 min. mp = 77–80°C; IR (thin film/NaCl/cm^{-1}) 2961.4, 1630.3, 1481.7, 1364.4, 1198.7; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.02 (s, 9H), 1.41 (s, 9H), 3.12 (dd, 1H, J = 7.9, 13.9 Hz), 5.02 (d, 1H, J = 15.9 Hz), 5.14 (d, 1H, J = 10.2 Hz), 5.89–6.07 (m, 1H), 6.97 (d, 1H, J = 7.4 Hz), 7.13 (t, 1H, J = 7.5 Hz), 7.31 (t, 1H, J = 7.2 Hz), 7.55 (d, 1H, J = 8.1

Hz); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 29.58, 32.65, 36.35, 41.15, 57.36, 118.30, 125.73, 128.33, 130.60, 132.10, 132.57, 140.28, 145.77, 176.65; LRMS (EI, 70 eV) m/z (rel. intens.) (M+1) 274 (5), 217 (100), 174 (40), 160 (49), 132 (90), 124 (58), 117 (60), 91 (65), 77 (54), 68 (57), 57 (77); HRMS m/z calcd for $C_{18}H_{28}NO$ ($M^{+\bullet}$): 274.2171, found: 274.2171; $[\alpha]_D^{23}=+14.6$ (c 0.705, $CHCl_3$).

4.3.5. *N*-Allyl-*N*-(2-*tert*-butylphenyl)acetamide, 3e. The enantiomeric excess was determined to be 53% by HPLC analysis (hexane/2-propanol = 90/10), 1.5 ml/min, 1.42 kpsi, retention times: 7.8 min (dominant) and 8.8 min; IR (thin film/NaCl/cm^{-1}) 3065.3, 2963.1, 2914.9, 2874.4, 1659.4, 1486.8, 1439.6, 1383.7, 1295.9, 1280.5, 1228.4, 760.8; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.39 (s, 9H), 1.80 (s, 3H), 3.33 (dd, 1H, $J=14.2$, 8.2 Hz), 4.95 (dd, 1H, $J=14.2$, 5.0 Hz), 5.10 (d, 1H, $J=17.3$ Hz), 5.15 (d, 1H, $J=10.0$ Hz), 6.09–5.94 (m, 1H), 6.95 (dd, 1H, $J=7.72$, 1.3 Hz), 7.19 (td, 1H, $J=7.6$, $J=1.5$ Hz), 7.37–7.28 (m, 1H), 7.57 (dd, 1H, $J=8.15$, 1.41 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, ppm) 23.3, 31.9, 35.9, 53.8, 118.5, 126.7, 128.4, 129.7, 131.7, 132.6, 140.3, 146.1, 170.7; LRMS (EI, 70 eV) m/z (rel. intens) (M^+) 231 (0), (M^+–$CH_3^\bullet$) 216 (20), ($M^{+\bullet}$–t-$Bu^\bullet$) 174 (100), 132 (25), 91 (22); HRMS (M^+) = 231 (0), (M^+–t-$Bu^\bullet$) = 174 (100), calcd mass for: (M^+–t-$Bu^\bullet$) $C_{15}H_{21}NO$: 174.0918, found: 174.0918; $[\alpha]_D^{24}=+70.6$ (c 0.565, $CHCl_3$).

4.4. Synthesis of anilides 4b

4.4.1. 2-(2-Methoxy-1,1-dimethylethyl)-1-nitrobenzene. To a cooled (0°C) mixture of 2-(2-hydroxy-1,1-dimethyl-ethyl)-1-nitrobenzene (1.945 g, 9.96 mmol) and iodomethane (0.94 ml, 15.1 mmol) in tetrahydrofuran (20 ml) was added 60% sodium hydride (463 mg, 11.6 mmol) portionwise. The mixture was stirred for 2 h. Water (50 ml) was then added, and the mixture was extracted with ether (2×100 ml). The extracts were washed with 100 ml of brine and dried over $MgSO_4$. The residue was purified by column chromatography on silica gel (AcOEt:hexane, 1:4), yield 1.962 g (94%): IR (thin film/NaCl/cm^{-1}) 2974.7, 2895.9, 1528.8, 1369.9, 1108.7, 774.1, 750.7; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.39 (s, 6H), 3.29 (s, 3H), 3.51 (s, 2H), 7.26–7.36 (m, 2H), 7.45 (dt, 1H, $J=2.1$, 6.6 Hz), 7.54 (dd, 1H, $J=0.9$, 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 26.18, 40.06, 59.04, 81.08, 123.90, 127.04, 129.85, 130.65, 137.94, 151.46; LRMS (EI, 70 eV) m/z (rel. intens.) (M+1) 210 (5), 178 (55), 165 (63), 148 (76), 133 (89), 130 (80), 117 (92), 105 (100); HRMS (M+1) = 206 (5), ($M^{+\bullet}$–t-$Bu^\bullet$) = 148 (100), calcd mass for: (M+H) $C_{11}H_{16}NO_3$: 210.1130, found: 210.1123.

4.4.2. 2-(2-Methoxy-1,1-dimethylethyl)phenylamine. 2-(2-Methoxy-1,1-dimethylethyl)-1-nitrobenzene (1.962 g, 9.38 mmol) in methanol (20 ml) was hydrogenated in the presence of 10% Pd–C (53 mg) under a hydrogen atmosphere at room temperature for 3 days. The catalyst was removed by filtration and the filtrate was condensed in vacuo. The residue was purified by column chromatography on silica gel (AcOEt:hexane, 1:10), yield 1.618 g (96%): IR (thin film/NaCl/cm^{-1}) 3341.6, 2974.4, 2933.3, 2875.2, 1623.0, 1495.7, 1445.4, 1301.2, 1099.4, 961.7, 747.8; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.45 (s, 6H), 3.36 (s, 3H), 3.51 (s, 2H), 4.49 (br s, 2H), 6.66 (d, 1H, $J=7.8$ Hz), 6.73 (t, 1H, $J=7.1$ Hz), 7.04 (t, 1H, $J=7.4$ Hz), 7.22 (d, 1H, $J=7.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 25.37, 38.96, 58.98, 83.17, 117.91, 118.13, 121.19, 127.36, 131.45, 146.07; LRMS (EI, 70 eV) m/z (rel. intens.) (M^+) 179 (16), 134 (100), 117 (12), 106 (30), 91 (15), 77 (12), 69 (14); HRMS calcd mass for: (M^+) $C_{11}H_{17}NO$: 179.1310, found: 179.1314.

4.4.3. *N*-[(2-Methoxymethyl-2-methylethyl)phenyl]-phenylacetamide, 4b. This was prepared in similar manner as **2a**; mp = 88–90°C; IR (thin film/NaCl/cm^{-1}) 3290.9, 2942.5, 1680.7, 1516.2, 1443.2, 1302.9, 1100.0; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.34 (s, 6H), 3.12 (s, 2H), 3.74 (s, 2H), 7.09 (t, 1H, $J=7.6$ Hz), 7.21–7.42 (m, 7H), 7.76 (d, 1H, $J=8.1$ Hz), 9.53 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 25.97, 38.90, 45.20, 58.90, 84.48, 124.91, 126.25, 126.85, 127.06, 128.63, 128.70, 128.77, 128.80, 129.45, 129.52, 134.86, 136.69, 138.19, 168.65; LRMS (EI, 70 eV) m/z (rel. intens.) (M^+) 297 (5), 252 (52), 206 (31), 134 (59), 91 (100); HRMS m/z calcd for $C_{19}H_{23}NO_2$ (M^+): 297.1729, found: 297.1736.

4.5. Allylation of anilide 4b

4.5.1. *N*-Allyl-*N*-[2-(2-methoxy-1,1-dimethylethyl)-phenyl]-2-phenylacetamide, 5b. The enantiomeric excess was determined to be 45% by HPLC analysis (hexane/2-propanol = 90/10), 1.0 ml/min, 0.84 kpsi, retention times: 19.8 and 22.5 min (dominant). IR (thin film/NaCl/cm^{-1}) 2878.6, 1657.3, 1390.9, 1107.9; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.40 (s, 3H), 1.43 (s, 3H), 3.28 (s, 3H), 3.34–3.58 (m, 5H), 4.93–5.08 (m, 2H), 5.11 (d, 1H, $J=10.2$ Hz), 5.88–6.04 (m, 1H), 6.79 (dd, 1H, $J=1.5$, 7.8 Hz), 7.08–7.28 (m, 6H), 7.35 (dt, 1H, $J=1.6$, 7.7 Hz), 7.59 (dd, 1H, $J=1.5$, 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 27.52, 27.72, 40.81, 41.77, 54.00, 59.28, 83.58, 118.75, 126.60, 126.95, 128.29, 128.70, 129.55, 130.39, 132.70, 132.87, 135.44, 140.42, 143.43, 171.37; LRMS (EI, 70 eV) m/z (rel. intens.) (M^+) 337 (2), 292 (25), 266 (72), 250 (88), 218 (44), 174 (54), 155 (50), 132 (39), 91 (100), 65 (30); HRMS m/z calcd for $C_{22}H_{27}NO_2$ (M^+): 337.2042, found: 337.2045. $[\alpha]_D^{24}=+51.7$ (c 0.41 $CHCl_3$).

4.6. Reaction of anilide 2a with cinnamate

4.6.1. *N*-(2-*tert*-Butylphenyl)-2-phenyl-*N*-(3-phenyl-2-propenyl)acetamide. (Table 1, entry 16). The enantiomeric excess was determined to be 41% by HPLC analysis (hexane/2-propanol = 70/30), 2.0 ml/min, 2.07 kpsi, retention times: 9.6 min (dominant) and 26.8 min. IR (thin film/NaCl/cm^{-1}) 2957.0, 1655.3, 1486.3, 1393.6, 1249.2, 967.9, 733.5, 694.1; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 1.45 (s, 9H), 3.36 (dd, 2H, $J=15.0$, 22.9 Hz), 3.44–3.52 (m, 3H), 5.14 (dd, 1H, $J=3.5$, 14.0 Hz), 6.30–6.44 (m, 2H), 6.81 (dd, 1H, $J=1.3$, 7.8 Hz), 7.07–7.14 (m, 2H), 7.18–7.37 (m, 8H), 7.61 (dd, 1H,

$J=1.5$, 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 32.29, 36.20, 41.85, 53.68, 123.77, 126.47, 126.60, 126.77, 127.62, 128.24, 128.47, 128.71, 129.40, 129.93, 132.49, 133.85, 135.01, 136.71, 139.57, 146.31, 171.19; LRMS (EI, 70 eV) m/z (rel. intens.) (M^+) 383 (45), 292 (40), 160 (40), 117 (58), 91 (100); HRMS m/z calcd for $C_{27}H_{29}NO$ (M^+): 383.2249, found: 383.2254. $[\alpha]_D^{24}=+8.9$ (c 0.76, $CHCl_3$).

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