Practical Syntheses of *N*-Acetyl (*E*)-β-Arylenamides

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Abstract: A facile and practical method for the preparation of (*E*)-β-arylenamides [(*E*)-*N*-(1-arylprop-1-en-2-yl]acetamides] has been developed by reductive acetylation of the corresponding oximes with iron(II) acetate as the reducing reagent. Employment of hexamethylphosphoramide as the solvent was found to be critical for the high *E*/*Z* selectivity. The methodology has been applied in efficient syntheses of a key chiral intermediate of tamsulosin by asymmetric hydrogenation.

Key words: β-arylenamides, iron(II) acetate, reductive acylation, β-arylamines, tamsulosin

Chiral β-arylamines exist in numerous biologically interesting natural products and therapeutic agents.[1] For examples, such moieties commonly exist in a series of naphthylisoquinoline alkaloids[2] such as michellamine B and korupensamine A. They also serve as pivotal structural units for many active pharmaceutical ingredients such as MDA,[3a] tamsulosin,[3b] selegiline,[3c] arformoterol,[3d] rotigotine,[3e] and silodosin[3f] (Figure 1). The development of efficient asymmetric methods for the synthesis of chiral β-arylamines by asymmetric hydrogenation of *N*-acetyl (*E*)- or (*Z*)-β-arylenamides has gained significant interest.[4] Recent work led by Zhang,[5] Zhou,[6] and our group[7] have shown excellent enantioselectivities in the hydrogenation of *N*-acetyl (*E*)- or (*Z*)-β-arylenamides. Due to the different hydrogenation properties of (*E*)- and (*Z*)-β-arylenamides, it is imperative to access geometrically pure β-arylenamides for asymmetric hydrogenation. Unfortunately, there remains lack of methods for the practical synthesis of geometrically pure β-arylenamides, which has hampered the syntheses of chiral β-arylamines by asymmetric hydrogenation. Herein, we report a facile and practical method for the synthesis of (*E*)-β-arylenamides by reductive acylation of ketoximes mediated by iron(II) acetate.

A number of methods have been reported for the syntheses of β-arylenamides including: (1) the reduction of nitro alkenes;[8] (2) the direct condensation of a ketone with an amide;[5,9] (3) Beckmann rearrangement of ketoximes;[6,10] and (4) the palladium-catalyzed cross coupling between vinyl triflates and amides.[11] Unfortunately, most of them suffered from low yields or *E*/*Z* selectivities (Scheme 1). The palladium-catalyzed cross-coupling method is less cost effective, albeit providing high *E*/*Z* selectivities.[11] Thus, the development of a facile and practical synthesis of *N*-acetyl (*E*)- or (*Z*)-β-arylenamides remains a significant challenge. Reductive acylation of ketoximes have been frequently applied in the synthesis of α-arylenamides.[8,12] However, this method has not been successfully employed for stereoselective synthesis of β-arylenamides. We herein report the reductive acylation of

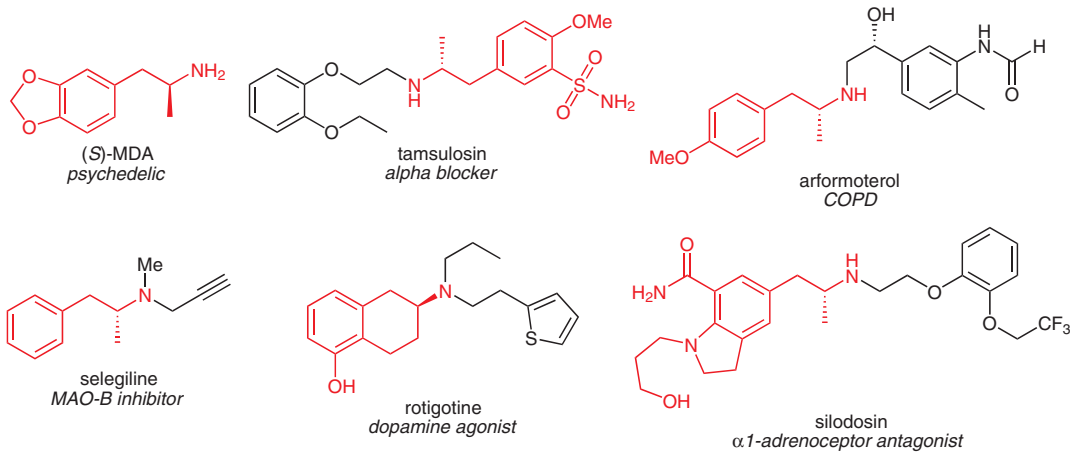

Figure 1 Several therapeutic agents containing chiral β-arylamine moieties

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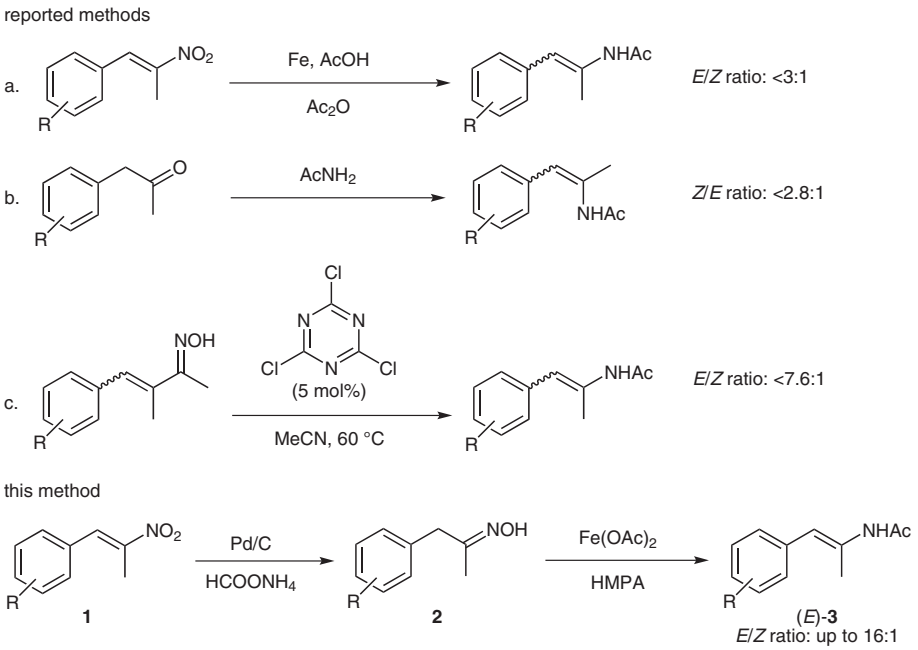


Scheme 1 New synthetic strategy of (*E*)-β-arylenamides

ketoximes **2**, which can be easily prepared from nitroalkenes **1**, to form (*E*)-β-arylenamides stereoselectively with up to 16:1 *E*/*Z* ratios.

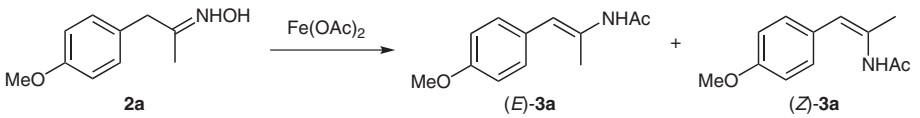
We have developed a facile and practical method for the syntheses of *N*-acetyl α-arylenamides by reductive acylation of corresponding oximes with iron(II) acetate as the reagent.[13] We envision this mild condition could also be applied to the stereoselective syntheses of (*E*)-β-arylenamides. Thus, the reductive acylation of 1-(4-methoxyphenyl)propan-2-one oxime (**2a**, *E*/*Z* 2.8:1) was chosen for study (Table 1). Initial work with toluene as the solvent provided a nonselective *E*/*Z* ratio (~1:1, entry 1). Further screening of various solvents such as acetic acid, acetonitrile, ethyl acetate, dichloromethane, dioxane, and tetrahydrofuran all provided <3:1 *E*/*Z* ratio (entries 2–7). When dipolar aprotic solvents were applied, a significant increase in *E*/*Z* ratio was observed. Thus, *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide, and DMPU all provided 3~4:1 *E*/*Z* ratios (entries 8–10). When hexamethylphosphoramide was employed as the solvent, an excellent *E*/*Z* ratio (10:1) was achieved with 80% isolated yield of (*E*)-β-arylenamides **3a** (entry 11). Further screening of mixed solvents with hexamethylphosphoramide all provided diminished *E*/*Z* ratios. A high reaction temperature (~80 °C) also led to a lower *E*/*Z* ratio. We reasoned that the dramatic hexamethylphosphoramide effect on the *E*/*Z* ratio could be largely due to the large dipole moment of hexamethylphosphoramide in stabilizing the (*E*)-β-arylenamides product.

We then investigated the substrate scope of this methodology. As can be seen in Table 2, the ketoximes **2** (*E*/*Z* 0.8~2.8:1) could be easily prepared from corresponding nitroalkenes **1**[14] via transfer hydrogenation in 57–80% unoptimized yields.[15] By using iron(II) acetate as the reducing reagent and hexamethylphosphoramide as the solvent, **2a**–**f** were preferentially converted into (*E*)-β-arylenamides (*E*)-**3a**–**f** with high *E*/*Z* ratios (*E*/*Z* 5:1 to 16:1) in good to excellent yields. Both electron-donating and electron-withdrawing substituents were well tolerated (entries 1–4). Naphthyl and 2-thiophenyl groups were also compatible (entries 5 and 6). The high *E*/*Z* ratios allow the separation of pure (*E*)-β-arylenamides (*E*)-**3a**–**f** by simple crystallization, providing a practical method for the synthesis of (*E*)-β-arylenamides that could be scaled up.

To demonstrate the synthetic utilities of this methodology, pure (*E*)-β-arylenamide (*E*)-**3a** was isolated from the crude reaction mixture without column chromatography in 73% isolated yield on an 18 gram scale by simple crystallization (EtOAc–hexanes). Asymmetric hydrogenation of pure (*E*)-**3a** in the presence of 0.01 mol% [Rh(NBD)((*S*,*S*,*S*,*S*)-WingPhos)]BF_4 as the catalyst provided the hydrogenation product **4** in 99% ee and 98% yield (Scheme 2).[7] Installation of the aminosulfonyl group[16] on amide **4** by chlorosulfonylation followed by amination led to the key chiral intermediate of tamsulosin **5** in 69% yield and 99% ee.

In summary, a facile and practical preparation of (*E*)-β-arylenamides has been developed by reductive acetylation of corresponding oximes with iron(II) acetate as the reducing reagent. Employment of hexamethylphosphoramide as the solvent is crucial for the high *E*/*Z* selectivity. The methodology has been applied to the synthesis of enamide (*E*)-**3a** without column chromatography, which was successfully transformed into a key chiral intermediate of tamsulosin **5** by asymmetric hydrogenation. Further applications of this methodology in conjunction with asymmetric hydrogenation technology for the synthesis of various chiral β-aryl amides are currently ongoing in our laboratory.

Table 1 Reductive Acylation of 1-Phenylpropan-2-one Oxime (**2a**)

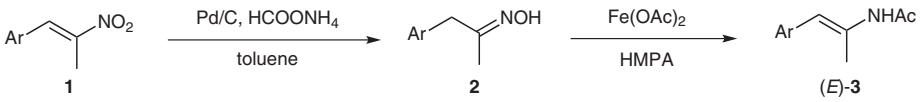


2a (*E*)-**3a** (*Z*)-**3a**

Entry[a]	Solvent	Temp (°C)	Ketone (%)	Yield (%)[b] (*E*)-**3a**	(*Z*)-**3a**	Ratio[c] *E*/*Z*
1	toluene	60	–	48	52	0.9
2	AcOH	60	–	48	52	0.9
3	MeCN	60	–	56	44	1.3
4	EtOAc	60	–	59	41	1.4
5	CH_2Cl_2	40	10	58	32	1.8
6	dioxane	60	–	54	25	2.2
7	THF	60	–	75	25	3.0
8	DMAc	60	–	79	21	3.8
9	NMP	60	9	73	17	4.3
10	DMF	60	–	77	23	3.5
11	DMPU	60	–	81	19	4.2
12	HMPA	60	–	82	8	10
13	DMF–HMPA (10:1)	60	–	78	22	3.6
14	DMPU–HMPA (4:1)	60	–	70	22	3.2
15	HMPA	80	–	75	15	5.1

[a] The reactions were carried out under N_2 for 5 h, $Fe(OAc)_2$ was prepared in situ by refluxing Fe powder in AcOH for 4 h.
[b] Isolated yield.
[c] Determined by RP-HPLC on a C18 column.

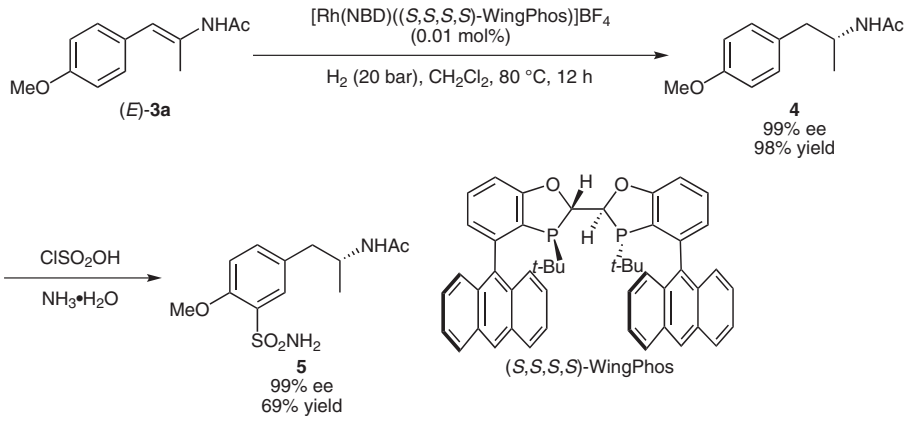
Table 2 Syntheses of (*E*)-β-Arylenamides



1 **2** (*E*)-**3**

Entry[a]	**1**	Ar	Yield[b] (%) of **2** (ratio *E*/*Z*)	Yield[c] of (*E*)-**3** (%)	Ratio[d] *E*/*Z*
1	**1a**	4-$MeOC_6H_4$	60 (**2a**, 2.8:1)	82 [(*E*)-**3a**]	10
2	**1b**	2-$MeOC_6H_4$	57 (**2b**, 1.4:1)	60 [(*E*)-**3b**]	14
3	**1c**	Ph	72 (**2c**, 2.1:1)	75 [(*E*)-**3c**]	13
4	**1d**	4-FC_6H_4	74 (**2d**, 2.8:1)	60 [(*E*)-**3d**]	11
5	**1e**	2-naphthyl	63 (**2e**, 0.8:1)	74 [(*E*)-**3e**]	16
6	**1f**	2-thienyl	80 (**2f**, 2.4:1)	60 [(*E*)-**3f**]	5

[a] The preparation of oximes were performed according to a reported procedure.[15] The reductive acylations were run under N_2 for 5 h. $Fe(OAc)_2$ was prepared in situ by refluxing Fe powder in AcOH for 4 h.
[b] Isolated yield, the *E*/*Z* ratios were determined by ^1H NMR.
[c] Isolated yield.
[d] The *E*/*Z* ratios observed during the reductive acylation step were determined by HPLC on a C18 column.



Scheme 2 Synthesis of a key chiral intermediate **5** of tamsulosin

Unless otherwise indicated, all reactions were conducted under a N_2 atmosphere in oven-dried glassware with a magnetic stirrer bar or mechanical stirring. THF, CH_2Cl_2, dioxane, toluene, and HMPA were purchased from China Reagents and used after standard purifications. All reagents were purchased from either China Reagents or J & K Chemicals Inc. and used directly without further purification. ^1H and ^{13}C NMR spectra were recorded on Bruker-Biospin DRX500 and DRX400 NMR spectrometers with $CDCl_3$ or DMSO-d_6 as the solvent. ^1H shifts were referenced to $CDCl_3$ at δ = 7.26 as external standard and obtained with ^1H decoupling. ^{13}C shifts were referenced to $CDCl_3$ at δ = 77 and obtained with ^1H decoupling. MS was measured on an Agilent 1100 Series LC/MSD mass spectrometer. Column chromatography was performed with silica gel (300–400 mesh).

Reduction of Nitroalkenes to Oximes 2; General Procedure[15]
To a dry three-necked flask was charged nitroalkene (80 mmol), dry ammonium formate (25.2 g, 400 mmol) and MeOH–toluene (1:1, 200 mL). Pd/C (9.5 g, 5 mol%, wet) was added to the solution under stirring. The resulting mixture was stirred at r.t. until the complete disappearance of the starting material. The mixture was filtered and the filter cake was washed with CH_2Cl_2 (50 mL). The combined filtrates were concentrated, retreated with CH_2Cl_2 (50 mL), filtered to remove the insoluble salt, and concentrated. The residue was purified by column chromatography (silica gel, hexanes–EtOAc, 15:1) to afford the desired product as a mixture of *E*/*Z* isomers (*E*/*Z* 0.8:1 to 2.8:1).

1-(4-Methoxyphenyl)propan-2-one Oxime (2a)
White solid; yield: 8.6 g (60%); ratio *E*/*Z* 2.8:1.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.10 (m, 2 H), 6.87–6.80 (m, 2 H), 3.78 (s, 3 H), 3.68, 3.44 (2 s, 2 H), 1.80, 1.79 (2 s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5, 157.9, 130.2, 130.0, 128.7, 114.0, 55.3, 41.2, 33.9, 19.6, 13.2.

1-(2-Methoxyphenyl)propan-2-one Oxime (2b)
Oil; yield: 8.2 g (57%); ratio *E*/*Z* 1.4:1.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.10 (m, 2 H), 6.94–6.82 (m, 2 H), 3.81 (d, *J* = 1.1 Hz, 3 H), 3.75, 3.53 (2 s, 2 H), 1.83, 1.75 (2 s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.5 (d, *J* = 2.5 Hz), 157.4, 130.7, 130.5, 128.0, 127.8, 125.2, 125.0, 120.6, 120.5, 110.5, 110.3, 55.4, 55.3, 35.6, 29.2, 19.5, 13.3.

1-Phenylpropan-2-one Oxime (2c)
Oil; yield: 8.6 g (72%); ratio *E*/*Z* 2.1:1.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.26 (m, 2 H), 7.25–7.20 (m, 3 H), 3.75, 3.50 (2 s, 2 H), 1.82, 1.81 (2 s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.7, 157.0, 136.7, 129.2, 129.0, 128.6, 126.8, 126.5, 42.1, 34.8, 19.7, 13.3.

1-(4-Fluorophenyl)propan-2-one Oxime (2d)
Oil; yield: 9.9 g (74%); ratio *E*/*Z* 2.8:1.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.22–7.16 (m, 2 H), 7.03–6.95 (m, 2 H), 3.70, 3.47 (2 s, 2 H), 1.81, 1.80 (2 s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.8 (d, *J* = 243.7 Hz), 161.7 (d, *J* = 243.7 Hz), 157.5, 156.8, 132.2 (d, *J* = 3.7 Hz), 130.6 (d, *J* = 8.7 Hz), 130.4 (d, *J* = 7.5 Hz), 115.5 (d, *J* = 21.2 Hz), 115.4 (d, *J* = 21.2 Hz), 41.3, 34.0, 19.6, 13.2.

1-(Naphthalen-2-yl)propan-2-one Oxime (2e)
White solid; yield: 10.0 g (63%); ratio *E*/*Z* 0.8:1.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.74 (m, 3 H), 7.67 (s, 1 H), 7.48–7.41 (m, 2 H), 7.40–7.33 (m, 1 H), 3.92, 3.67 (2 s, 2 H), 1.85, 1.84 (2 s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.8, 157.0, 134.1, 133.6, 132.3, 128.3, 127.7, 127.6, 127.2, 126.1, 125.6, 42.3, 35.0, 19.8, 13.4.

1-(Thiophen-2-yl)propan-2-one Oxime (2f)
Oil; yield: 9.9 g (80%); ratio *E*/*Z* 2.4:1.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.14 (m, 1 H), 6.97–6.91 (m, 1 H), 6.90–6.86 (m, 1 H), 3.91, 3.69 (2 s, 2 H), 1.89, 1.88 (2 s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.9, 156.1, 138.9, 137.9, 127.0, 126.9, 126.4, 126.2, 124.6, 124.4, 36.2, 28.9, 19.4, 13.1.

(*E*)-β-Arylenamides (*E*)-3; General Procedure
To a 50-mL three-necked flask equipped with a dropping funnel, thermometer, and reflux condenser was charged iron powder (1.0 g, 18 mmol), AcOH (2.2 mL, 36 mmol), and Ac_2O (1.7 mL, 18 mmol). The mixture was stirred under N_2 at 130 °C for 5 h and then cooled to 60 °C. Oxime (6 mmol) in HMPA (5 mL) was added dropwise through a dropping funnel over 5 min. The mixture was stirred at 60 °C for 6–12 h until complete disappearance of the oxime monitored by HPLC. The mixture was diluted with EtOAc (50 mL) and then filtered through celite. The filtrate was washed with H_2O (2 × 20 mL), dried (Na_2SO_4), concentrated, and purified by column chromatography (silica gel, petroleum ether–EtOAc, 4:1) to afford the target product.

(*E*)-*N*-[1-(4-Methoxyphenyl)prop-1-en-2-yl]acetamide [(*E*)-3a]
White solid; yield: 1.0 g (82%).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.6 Hz, 2 H), 6.90 (s, 1 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 6.83 (br s, 1 H), 3.80 (s, 3 H), 2.09 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 157.8, 132.0, 130.0, 129.5, 116.4, 113.6, 55.2, 24.4, 17.8.

(*E*)-*N*-[1-(2-Methoxyphenyl)prop-1-en-2-yl]acetamide [(*E*)-3b]
White solid; yield: 0.74 g (60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 7.6 Hz, 2 H), 6.92 (t, *J* = 7.4 Hz, 1 H), 6.87 (s, 1 H), 6.85 (s, 1 H), 6.73 (br s, 1 H), 3.82 (s, 3 H), 2.09 (s, 3 H), 2.07 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5, 157.0, 133.1, 130.3, 127.7, 125.7, 120.1, 111.7, 110.2, 55.4, 24.7, 17.8.

(*E*)-*N*-(1-Phenylprop-1-en-2-yl)acetamide [(*E*)-3c]
White solid; yield: 0.79 g (75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (t, *J* = 7.7 Hz, 2 H), 7.24–7.15 (m, 3 H), 7.01 (s, 1 H), 6.64 (br s, 1 H), 2.10 (s, 3 H), 2.08 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 137.1, 133.1, 128.9, 128.1, 126.0, 116.4, 24.6, 17.8.

(*E*)-*N*-[1-(4-Fluorophenyl)prop-1-en-2-yl]acetamide [(*E*)-3d]
White solid; yield: 0.70 g (60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.10 (m, 3 H), 7.05–6.88 (m, 3 H), 2.10 (s, 3 H), 2.03 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0, 161.2 (d, *J* = 224.0 Hz), 132.9 (d, *J* = 22.0 Hz), 130.5, 130.4, 115.2, 115.0 (d, *J* = 21.0 Hz), 24.65, 17.82.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{12}FNONa$: 216.0795; found: 216.0793.

(*E*)-*N*-[1-(Naphthalen-2-yl)prop-1-en-2-yl]acetamide [(*E*)-3e]
White solid; yield: 1.0 g (74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84–7.75 (m, 3 H), 7.66 (s, 1 H), 7.50–7.40 (m, 2 H), 7.36 (d, *J* = 8.3 Hz, 1 H), 7.18 (s, 1 H), 6.60 (br s, 1 H), 2.16 (s, 3 H), 2.13 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.9, 134.6, 133.4, 133.3, 131.9, 127.8, 127.6, 127.5, 127.3, 126.0, 125.5, 116.3, 24.7, 18.1.

(*E*)-*N*-[1-(Thiophen-2-yl)prop-1-en-2-yl]acetamide [(*E*)-3f]
Pale yellow solid; yield: 0.65 g (60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 5.0 Hz, 1 H), 7.00 (t, *J* = 3.7 Hz, 1 H), 6.92 (d, *J* = 3.2 Hz, 1 H), 6.52 (br s, 1 H), 2.20 (s, 3 H), 2.10 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4, 139.8, 131.6, 127.0, 126.4, 124.2, 109.8, 24.8, 18.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{11}NOSNa$: 204.0454; found: 204.0445.

Large-Scale Preparation of (*E*)-*N*-[1-(4-Methoxyphenyl)prop-1-en-2-yl]acetamide [(*E*)-3a]
To a 250-mL three-necked flask equipped with a dropping funnel, mechanical stirring bar, and reflux condenser was charged iron powder (20.0 g, 0.36 mol), AcOH (42 mL, 0.72 mol), and Ac_2O (34 mL, 0.36 mol). The mixture was stirred under N_2 at 130 °C for 7 h, and then cooled to 60 °C. 1-(4-Methoxyphenyl)propan-2-one oxime (21.5 g, 0.12 mol) in HMPA (100 mL) was added dropwise over 10 min through a dropping funnel. The mixture was stirred at 60 °C for ~12 h, then diluted with EtOAc (200 mL), and filtered through celite. The filtrate was washed repeatedly with H_2O (2 × 100 mL), dried (Na_2SO_4), concentrated, and crystallized (EtOAc–hexanes, 2:1, 90 mL) to afford (*E*)-**3a** (18.0 g, 88 mmol, 73%) as a white solid.

(*R*)-*N*-[1-(4-Methoxyphenyl)propan-2-yl]acetamide (4) by Asymmetric Hydrogenation[7]
To a 150-mL conical flask equipped with a magnetic stirrer bar was charged with β-aryl-*N*-acetylenamide (*E*)-**3a** (4.1 g, 20 mmol), [Rh(NBD)((*S*,*S*,*S*,*S*)-WingPhos)]BF_4 (2 mg, 0.002 mmol, 0.01 mol%) and CH_2Cl_2 (50 mL) under N_2. The mixture was stirred for 5 min at r.t., and then it was transferred to an autoclave. The autoclave was purged with H_2 (3 ×) and charged to 50 bar. The mixture was stirred at 50 °C for 12 h, then cooled to r.t., and depressurized carefully in a well-ventilated hood. A reaction sample was filtered through celite to remove metal species and directly analyzed by chiral HPLC to determine the conversion and ee value. Concentration of the mixture and crystallization (EtOAc–hexanes, 1:2, 20 mL) provided **4** (4.12 g, 98%, 99% ee) as a white solid.

Chiral HPLC (Chiralcel AD-H, 25 °C, flow rate: 1 mL/min; *n*-hexane–*i*-PrOH, 95:5, 210 nm): t_R = 19.05 (*R*), 20.17 min (*S*).

$[\alpha]_D^{20}$ +45.8 (*c* 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14–7.03 (m, 2 H), 6.87–6.78 (m, 2 H), 5.66 (br, 1 H), 4.20 (dp, *J* = 13.7, 6.7 Hz, 1 H), 3.78 (s, 3 H), 2.77 (dd, *J* = 13.6, 5.7 Hz, 1 H), 2.64 (dd, *J* = 13.6, 7.2 Hz, 1 H), 1.92 (s, 3 H), 1.09 (d, *J* = 6.7 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3, 158.3, 130.4, 129.9, 113.8, 55.2, 46.2, 41.4, 23.5, 19.9.

(*R*)-*N*-[1-(4-Methoxy-3-sulfamoylphenyl]propan-2-yl)acetamide (5)[16]
To acetamide **4** (4.0 g, 19.2 mmol) held in an oven-dried Schlenk tube at 0–5 °C was charged dropwise with chlorosulfonic acid (40.4 g, 342 mmol) over 5 min. The mixture was stirred at 0–5 °C for 3 h, and then carefully added to cold H_2O (100 mL). The resulting mixture was extracted with EtOAc (3 × 30 mL), and the organic phase was washed sequentially with sat. $NaHCO_3$ (20 mL) and H_2O (20 mL), dried (anhyd Na_2SO_4), concentrated, and re-dissolved in MeCN (60 mL) and concd aq NH_3 solution (15 N, 120 mL). The mixture was stirred at r.t. for 3 h, and it was concentrated and extracted with EtOAc (40 mL). The EtOAc layer was washed with H_2O (20 mL), concentrated, and crystallized (MeOH) to afford **5** (3.8 g, 13.3 mmol, 69%, 99% ee) as a white solid.

Chiral HPLC (Chiralcel AD-H, 25 °C, flow rate: 1 mL/min, *n*-hexane–*i*-PrOH, 80:20, 210 nm): t_R = 7.717 min (*R*), 9.433 min (*S*).

$[\alpha]_D^{28}$ +9.8 (*c* 0.5, MeOH) {Lit.[15] $[\alpha]_D^{20}$ +13.3}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.78 (d, *J* = 8.0 Hz, 1 H), 7.55 (d, *J* = 2.0 Hz, 1 H), 7.37 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.11 (d, *J* = 8.5 Hz, 1 H), 7.01 (s, 2 H), 3.95–3.80 (m, 4 H), 2.68 (dd, *J* = 13.4, 7.1 Hz, 1 H), 2.58 (dd, *J* = 13.4, 6.7 Hz, 1 H), 1.75 (s, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.8, 154.8, 134.6, 131.2, 131.1, 128.4, 112.8, 56.5, 46.4, 41.2, 23.2, 20.4.

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Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) Bentley, K. W. *Nat. Prod. Rep.* **2001**, *18*, 148.
(2) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. *Chem. Rev.* **2011**, *111*, 563.
(3) (a) Snyder, H. S.; Tayler, K. M. *Science* **1970**, *168*, 1487. (b) Roehrbom, C. G.; Siami, P.; Barkin, J.; Damião, R.; Major-Walker, K.; Morrill, B.; Montorsi, F. *J. Urol. (N. Y., NY, U. S.)* **2008**, *179*, 616. (c) Sano, M.; Ernesto, C.; Thomas, R. C.; Klauber, M. R. N. *N. Engl. J. Med.* **1997**, *336*, 1216. (d) Barnes, B. *Formoterol, A New Generation of Beta-2-agonist*; Hogrefe and Huber Pub: Toronto, **1991**.

(e) Pharm, D. Q.; Nogid, A. *Clin. Ther.* **2008**, *30*, 813. (f) Yoshida, M.; Homma, Y.; Kawabe, K. *Expert Opin. Invest. Drugs* **2007**, *16*, 1955.

(4) For selected reviews of transition-metal-catalyzed asymmetric hydrogenation, see: (a) Xie, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *Chem. Rev.* **2011**, *111*, 1713. (b) Gopalaiah, K.; Kagan, H. B. *Chem. Rev.* **2011**, *111*, 4599. (c) Nugent, T. C.; El-Shazly, M. *Adv. Synth. Catal.* **2010**, *352*, 753. (d) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(5) Chen, J.; Zhang, W.; Geng, H.; Li, W.; Hou, G.; Lei, A.; Zhang, X. *Angew. Chem. Int. Ed.* **2009**, *48*, 800.

(6) Zhu, S.-F.; Liu, T.; Yang, S.; Song, S.; Zhou, Q.-L. *Tetrahedron* **2012**, *68*, 7685.

(7) Liu, G.; Liu, X.; Cai, Z.; Jiao, G.; Xu, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 4235.

(8) Laso, N. M.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 1605.

(9) Tschaen, D. M.; Abramson, L.; Cai, D.; Desmond, R.; Dolling, U.-H.; Frey, L.; Karady, S.; Shi, Y.-J.; Verhoeven, T. R. *J. Org. Chem.* **1995**, *60*, 4324.

(10) Brettle, R.; Shibib, S. M.; Wheeler, K. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 831.

(11) Wallace, D. J.; Klauber, D. J.; Chen, C.-Y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749.

(12) (a) Burk, M. J.; Casey, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084. (b) Zhu, G.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 9590. (c) Le, J. C.-D.; Pagenkopf, B. L. *J. Org. Chem.* **2004**, *69*, 4177. (d) Allwein, S. P.; McWilliams, J. C.; Secord, E. A.; Mowrey, D. R.; Nelson, T. D.; Kress, M. H. *Tetrahedron Lett.* **2006**, *47*, 6409. (e) Zhao, H.; Vandenbossche, C. P.; Koenig, S. G.; Singh, S. P.; Bakale, R. P. *Org. Lett.* **2008**, *10*, 505. (f) Guan, Z.-H.; Huang, K.; Yu, S.; Zhang, X. *Org. Lett.* **2009**, *11*, 481. (g) Guang, Z.-H.; Zhang, Z.-Y.; Ren, Z.-Y.; Wang, Y.-Y.; Zhang, X.-M. *J. Org. Chem.* **2011**, *76*, 339. (h) Reeves, J. T.; Tan, Z.; Han, Z. S.; Li, G.; Zhang, Y.; Xu, Y.; Reeves, D. C.; Gonnella, N. C.; Ma, S.; Lee, H.; Lu, B. Z.; Senanayake, C. H. *Angew. Chem. Int. Ed.* **2012**, *51*, 1400.

(13) (a) Tang, W.; Capacci, A.; Sarvestani, M.; Wei, X.; Yee, N. K.; Senanayake, C. H. *J. Org. Chem.* **2009**, *74*, 9528. (b) Tang, W.; Patel, N. P.; Capacci, A.; Wei, X.; Yee, N. K.; Senanayake, C. H. *Org. Synth.* **2013**, *90*, 62. (c) Li, W.; Rodriguez, S.; Duran, A.; Sun, X.; Tang, W.; Premasiri, A.; Wang, J.; Sidhu, K.; Patel, N. D.; Savoie, J.; Qu, B.; Lee, H.; Haddad, N.; Lorenz, J. C.; Nummy, L.; Hossain, A.; Yee, N.; Lu, B.; Senanayake, C. H. *Org. Process Res. Dev.* **2013**, *17*, 1061.

(14) Abdolhamid, A.; Khodaei, M.; Eshghi, A. *J. Org. Chem.* **2010**, *75*, 8295.

(15) Kabalka, G.; Pace, R.; Wadgaonkar, P. *Synth. Commun.* **1990**, *20*, 2453.

(16) Hwu, J.; Balaachary, M.; Subhasish, C.; Asish, D.; Shwu, T.; Sheu, K.; Shu, C.; Lu, C.; Chang, W. EP 1,734,036, **2006**.

