Organocatalytic Asymmetric Synthesis of 1,2,4-Trisubstituted Azetidines by Reductive Cyclization of Aza-Michael Adducts of Enones

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Abstract: An efficient and highly enantioselective organocatalytic aza-Michael addition of N-substituted phosphoramidates to enones generates aza-Michael adducts which undergo intramolecular reductive cyclization with (*R*)-alpine borane to afford 1,2,4-trisubstituted azetidines in a one-pot procedure. These optically active products are obtained in good to high yields (67–93%) with excellent stereocontrol (78–96% ee) from a vast variety of enones.

Key words: asymmetric organocatalysis, conjugate addition, enones, reductive cyclization, chiral azetidines, phosphoramidates

Over the years, functionalized aza-heterocycles, which are at the heart of many essential pharmaceuticals and physiologically active natural products, have attracted the attention of organic chemists in order to develop novel, synthetically useful, and elegant methodologies for the synthesis of such type of compounds as targets for design of new drugs and important intermediates in organic synthesis. Amongst chiral nitrogen heterocycles, azetidines[1,2] have received much attention during the last decade because of their utilization as ligands[3] and their biological and pharmaceutical activities.[4,5] For example, they are noticeably active against influenza A H_2N_2 virus[6] and have anti-HIV-I, anti-HSV-I, and HSV-2 potential.[7] Recently, 2-substituted *N*-tosylazetidines have been utilized as masked 1,4-dipoles for the construction of N-containing six-membered heterocycles.[8]

However, in terms of synthetic approaches and applications, azetidines have been comparatively less studied than their lower and higher homologous saturated aza-heterocycles, viz. aziridines, pyrrolidines, and piperidines. Several authors have pointed out the scarcity of general and efficient methods for the synthesis of enantiopure azetidines.[1b,2d,9] Most of the literature reports on optically active symmetrically disubstituted azetidines[10] are largely restricted to 1,3-disubstituted azetidines and azetidine-2,4-dicarboxylic acid derivatives and azetidine-2,4-dimethanol analogues derived from them (Figure 1). Furthermore, the low number of publications on optically active 2,4-disubstituted azetidines also reflects the need of new enantioselective approaches towards these heterocycles.[1b] Marinetti et al.[9b] conjectured that the reasons for the lack of progress in the development of the chemistry of optically active azetidines could be related to synthetic difficulties associated with the formation of the four-membered ring from acyclic precursors. This is a disfavored process compared to the analogous construction of slightly larger and even smaller rings. Recently, an excellent review by Couty et al.[1b] covered the synthesis of enantiopure azetidines.

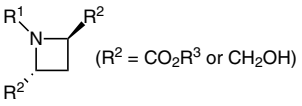

Figure 1 Optically active azetidine-2,4-dicarboxylic acid derivatives

The use of asymmetric aminocatalysis[11] has become a well-documented and powerful synthetic tool for the chemo- and enantioselective functionalization of carbonyl compounds. Recently, Bartoli and Melchiorre have developed primary amine salt catalyst **A**[12] which offers the advantages of both iminium ion catalysis and asymmetric counteranion-directed catalysis (ACDC) phenomenon,[13] and exhibits high reactivity and selectivity in the highly enantioselective conjugate addition of a series of different nucleophiles (C-, S-, O- and N-centered nucleophiles) to enones as both the cation and anion in the salt are chiral.[14] This led us to extend Melchiorre's method for the enantioselective aza-Michael addition to enones. The salt **A**, containing a chiral cation and anion, is obtained by combination of 9-amino-(9-deoxy)-*epi*-hydroquinine[15] and D-*N*-Boc-phenylglycine, which efficiently activates enones through iminium ion formation coupled with synergistic benefits of ACDC in enantioselective syntheses.

In our endeavors to synthesize enantiopure azetidines, we advanced this organocatalytic activation strategy to document an operationally trivial procedure for the aza-Michael addition of *N*-arylphosphoramidates **2** to α,β-unsaturated ketones **1** catalyzed by the chiral salt **A** to give aza-Michael adducts **3** followed by the intramolecular reductive cyclization via (*R*)-alpine borane to give 1,2,4-trisubstituted azetidines **4** (in 67–93% yield with 85–95% diastereoselectivity and 78–96% enantioselectivity) in a one-pot procedure as outlined in Scheme 1. We herein report the first organocatalytic addition of phosphoramidates (a weak nitrogen nucleophile) to enones using catalyst salt **A** ultimately leading to azetidines **4**.

The organocatalytic asymmetric aza-Michael addition is an excellent way of forming C–N bonds and is of tremendous significance in asymmetric synthesis.[16] Specifically,

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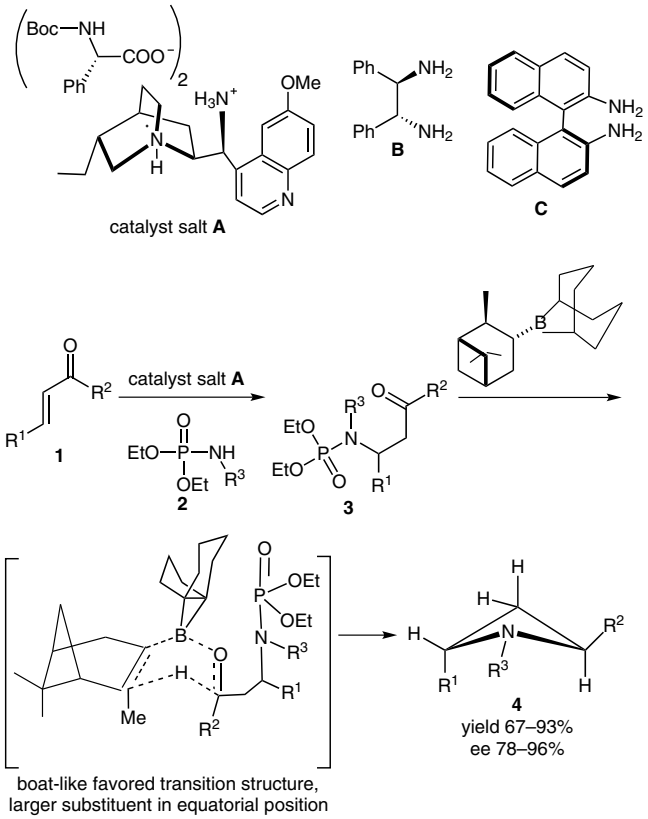
the asymmetric aza-Michael addition of enones by iminium ion catalysis has received considerable attention in recent years.[14d,17] Michael adducts formed during the course of reaction have potential for broad utility as synthetic building blocks in the preparation of natural and biologically active products. These aza-Michael adducts have been used for the synthesis of various aza-heterocyclic scaffolds including azetidines through heterocyclization in our laboratory on several occasions.[18]

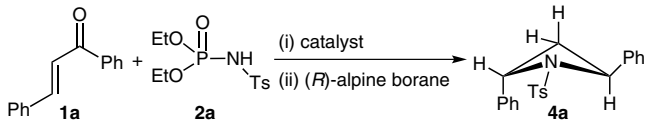


Scheme 1 Enantioselective synthesis of azetidines **4**

Initially, enantioselective conjugate addition of *N*-arylphosphoramidates **2** to α,β-unsaturated ketones **1** with a stoichiometric amount of secondary amines (proline or imidazolidinone) was undertaken which furnished poor results, most probably due to the inherent difficulties in generating covalent intermediates from enones and chiral secondary amines owing to steric constraints. The steric constraints are reduced in primary amine catalysis using chiral salt **A**, the cornerstone for the present organo aminocatalytic protocol, which has already provided a platform for the development of a large range of asymmetric transformations involving α,β-unsaturated ketones[21] via the formation of iminium ion intermediates from enones availing the benefits of ACDC strategy as well. Attracted by the chemistry of primary amino catalysis we then performed the reaction with chiral salt **A** (20 mol%) and α,β-unsaturated ketones **1** in toluene at 60 °C to generate iminium ion intermediates in situ to which the aza-Michael addition of *N*-arylphosphoramidates **2** took place efficiently to afford the representative adducts **3h** ($R^1 = R^2 =$ Et, $R^3 = o$-tolyl, yield 85%, ee 80%) and **3j** (R^1 = Bn, R^2 = Et, R^3 = Ts, yield 92%, ee 82%).[19] Diastereoselective reduction of these adducts with (*R*)-alpine borane furnished the corresponding azetidines **4h** (yield 69%, ee 82%) and **4j** (yield 73%, ee 80%).[20] In place of the primary amine chiral salt **A**, TFA salts of primary amines **B** and **C** were also able to promote the reaction but with lower levels of yield and diastereo- and enantioselectivity. Lowering the catalyst loading (20 mol% to 15 mol%) exhibited significant decrease in the yield and enantioselectivity of Michael adducts **3h**,**j**. Moreover, increasing the catalyst loading from 20 mol% to 25 mol% neither improved the yield nor the enantioselectivity. On carrying out the reaction at room temperature instead of at 60 °C, there was a marginal increase in the enantiomeric excess but at the expense of a drastic reduction in the yield of **3h**,**j**. In view of the advantages of one-pot syntheses, we combined the above two steps in a one-pot procedure, and it worked well for the asymmetric synthesis of azetidines **4**.

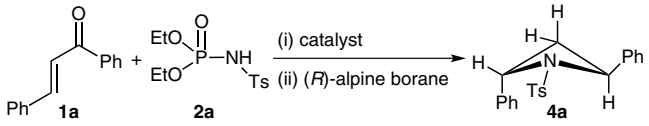
From among the investigated solvents (toluene, dichloromethane, and diethyl ether), toluene was the best solvent in terms of yield as well as enantioselectivity (Table 1).

Table 1 Optimization of Reaction Conditions for the Synthesis of **4a** in a One-Pot Procedure[a]



Entry	Catalyst[b]	Solvent[c]	Time (h)[d]	Yield (%)[e]	*trans*/*cis*[f]	ee (%)[g]
1	A	toluene	54	87	95:5	96
		CH_2Cl_2	60	62	91:9	93
		Et_2O	59	65	92:8	90
2	B	toluene	62	49	81:19	62
		CH_2Cl_2	66	40	80:20	62
		Et_2O	64	44	84:14	65

Table 1 Optimization of Reaction Conditions for the Synthesis of **4a** in a One-Pot Procedure[a]



Entry	Catalyst[b]	Solvent[c]	Time (h)[d]	Yield (%)[e]	*trans*/*cis*[f]	ee (%)[g]
3	C	toluene	60	57	90:10	72
		CH_2Cl_2	66	50	85:15	65
		Et_2O	64	46	87:13	68

[a] For the experimental procedure, see ref. 21.

[b] Catalyst load used was 20 mol%.

[c] The reaction was performed in toluene at 60 °C, whereas in CH_2Cl_2 and Et_2O at reflux.

[d] Total time for the completion of steps (i) and (ii) as indicated by TLC.

[e] Yields of isolated and purified product.

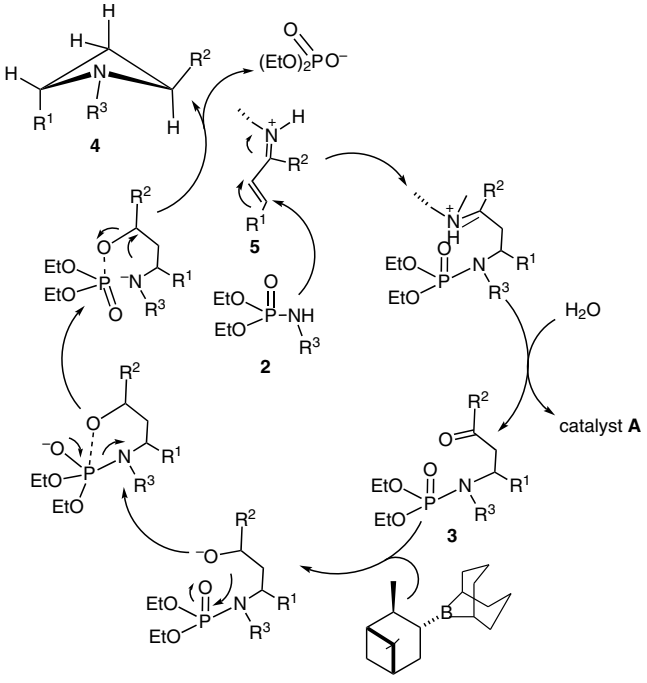
[f] As determined by ^{1}H NMR integration of *trans* and *cis* isomers in the crude product.

[g] The ee of the *trans* isomer **4a** was checked by chiral HPLC with a 250 × 4.6 mm, 5μ chiral Eurocel column. HPLC traces were compared to racemic samples prepared by our previously reported method.[18a]

In order to investigate the substrate scope for the present synthetic strategy, different α,β-unsaturated ketones were reacted with differently substituted phosphoramidates under the optimized reaction conditions, and it was found that in all the cases azetidines **4** could be isolated in good to excellent yields along with high optical purity by harmonizing the catalyst loading and the reaction time (Table 2). Our aforementioned organocatalytic protocol is also worthwhile in activating aromatic ketones such as (*E*)-chalcone (**1**, $R^1 = R^2 = Ph$), a class of substrates which is not generally suitable for iminium ion activation.[21]

The synthesis of azetidines may be tentatively rationalized by the enantioselective formation of adducts through iminium ion catalysis with chiral salt **A** as outlined in Scheme 2. These adducts underwent intramolecular reductive cyclization with (*R*)-alpine borane to give the desired products **4** in high yields and with high diastereo- and enantioselectivity. The high affinity of phosphorus for oxygen is the main driving force for the present heterocyclization reaction. The crude isolates of **4** were found to be diastereomeric mixtures containing 85–95% of the 2,4-*trans* isomer (Table 2). The ^{1}H NMR spectra of azetidines **4a**–**i** and **4m**,**n** show common signals for H_b and H_c resonances, which is a direct proof for their 2,4-*trans* configuration. If 1,2,4-trisubstituted azetidines **4a**–**i** and **4m**,**n** would have 2,4-*cis* stereochemistry, the H_b and H_c resonances should appear as inequivalent signals. The stereochemistry of 1,2,4-trisubstituted azetidines **4** was further confirmed by NOE measurements between the H_e and H_f protons (Figure 2). The absolute configurations of azetidines **4d**–**f** and **4i**–**n** are known and were elucidated by comparison of the measured specific rotations with those reported in the literature.[2a,9b] The absolute configurations of **4a**–**c** and **4g**,**h** were assumed by analogy based on the uniform reaction mechanism and elution order in the chiral HPLC.[2a,9b]

In summary we have developed a highly enantio- and diastereoselective synthesis of 1,2,4-trisubstituted azetidines.



Scheme 2 A tentative reaction pathway leading to azetidines **4**

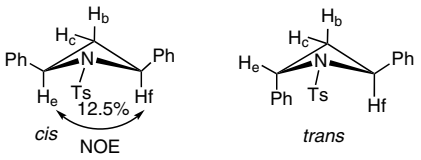
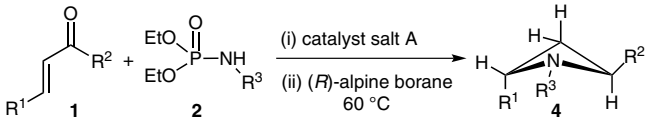


Figure 2 NOE observation in azetidine **4a**

The protocol features an efficient and highly enantioselective organocatalytic aza-Michael addition of N-substituted phosphoramidates to enones followed by intramolecular reductive cyclization with (*R*)-alpine borane to afford 1,2,4-trisubstituted azetidines in a one-pot procedure. Operational simplicity, good to excellent

Table 2 One-Pot Organocatalytic Asymmetric Synthesis of Azetidines **4**[a]



Entry	Azetidine **4**	R^1	R^2	R^3	Time (h)[b]	Yield (%)[c,d]	*trans*/*cis*[e]	ee (%)[f]
1	**4a**	Ph	Ph	Ts	54	87	95:5	96
2	**4b**	Ph	Ph	Ph	56	90	94:6	93
3	**4c**	Ph	Ph	4-$MeOC_6H_4$	55	93	95:5	94
4	**4d**	Me	Me	Ph	66	75	90:10	82
5	**4e**	Me	Me	*o*-tolyl	57	84	89:11	80
6	**4f**	Bn	Bn	Bn	62	71	94:6	92
7	**4g**	4-ClC_6H_4	4-ClC_6H_4	Ph	58	92	93:7	94
8	**4h**	Et	Et	*o*-tolyl	70	67	85:15	81
9	**4i**	Et	Et	Bn	68	75	91:9	85
10	**4j**	Bn	Et	Ts	67	70	89:11	78
11	**4k**	Ph	Et	Ts	61	73	91:9	85
12	**4l**	Ph	*n*-Pr	Ts	64	76	87:13	79
13	**4m**	Me	Me	2-BrC_6H_4	68	72	88:12	84
14	**4n**	Me	Me	Bn	67	76	85:15	83

[a] For the experimental procedure, see ref. 21.
[b] Total time for the completion of steps (i) and (ii) as indicated by TLC.
[c] Yields of pure isolated products **4** after column chromatography.
[d] All compounds gave C, H, N analyses within ±0.36% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.
[e] As determined by ^{1}H NMR integration of *trans* and *cis* isomers in the crude products.
[f] The ee of the *trans* isomers **4** was checked by chiral HPLC with a 250 × 4.6 mm, 5µ chiral Eurocel column. HPLC traces were compared to racemic samples prepared by our previously reported method.[18a]

chemical yields, and the first application of organocatalysis via iminium ion formation coupled with synergistic benefits of ACDC to enantioselective aza-Michael addition of phosphoramidates (weak nitrogen nucleophiles) to enones are additional interesting aspects of the present methodology.

Acknowledgment

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(19) **General Procedure for the Synthesis of Representative Diethyl N,N-Disubstituted Phosphoramidates 3h,j**

Reactions were carried out in undistilled toluene without any precaution to exclude water. The aforementioned catalytic salt **A** (0.04 mmol) was prepared from 9-amino-(9-deoxy)-*epi*-hydroquinine (0.04 mmol, 13.0 mg) and 0.08 mmol (20 mg) of D-*N*-Boc-phenylglycine in toluene (2 mL) as reported in the literature.[14a] After addition of α,β-unsaturated ketone **1** (0.2 mmol) to it, the mixture was stirred at 60 °C for 10 min. Then a solution of phosphoramidate **2** (0.2 mmol) was added to the reaction mixture slowly with stirring at 60 °C, and stirring was continued for 12–24 h which resulted in the formation of aza-Michael adduct **3h**,**j** as monitored by TLC. The resulting mixture was diluted with toluene and filtered on neutral Al_2O_3. The solvent was evaporated under reduced pressure, and the product was purified by flash chromatography on neutral Al_2O_3 (PE–CH_2Cl_2 = 6:4) to obtain pure phosphoramidates **3h**,**j** as white solids. Enantiomeric purity of adducts were checked by chiral HPLC with a 250 × 4.6 mm, 5μ chiral Eurocel column.

Characterization Data of Representative Compounds

Compound **3h** ($R^1 = R^2 = Et$, $R^3 = o$-tolyl): white solid; yield 85%; mp 195–197 °C. IR (KBr): ν_{max} = 3060, 2889, 1690, 1609, 1565, 1455, 1353, 1272, 1115, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.4 Hz, 3 H), 1.14 (q, *J* = 7.4 Hz, 2 H), 1.20 (t, *J* = 7.5 Hz, 6 H), 1.52 (m, 2 H), 2.35 (s, 3 H), 2.50 (t, *J* = 7.2 Hz, 3 H), 2.96 (dd, *J* = 12.9, 8.5 Hz, 1 H), 3.16 (dd, *J* = 12.9, 3.5 Hz, 1 H), 4.06 (q, *J* = 7.5 Hz, 4 H), 4.09 (m, 1 H), 6.61 (d, *J* = 8.1 Hz, 1 H_{ortho}), 6.68–7.06 (m, 3 H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.4, 10.4, 14.5, 16.0, 30.0, 40.1, 46.2, 54.0, 62.6, 113.4, 117.5, 126.9, 127.8, 130.5, 144.0, 219.5 ppm. MS (EI): *m*/*z* = 355 [M^+]. Anal. Calcd for $C_{18}H_{30}NO_4P$: C, 60.83; H, 8.51; N, 3.94. Found: C, 60.57; H, 8.63; N, 4.27. $[\alpha]_D^{25}$ –115 (*c* 1, $CHCl_3$). The ee was determined to be 80% by HPLC on a chiral Eurocel column [(250 × 4.6 mm, 5μ), λ = 225 nm, (*i*-PrOH–hexane = 10:90), 1 mL/min]; t_R (minor) = 12.4 min, t_R (major) = 14.2 min.

Compound **3j** (R^1 = Bn, R^2 = Et, R^3 = Ts): white solid; yield 92%; mp 178–179 °C. IR (KBr): ν_{max} = 3054, 2992, 1692, 1605, 1580, 1455, 1372, 1337, 1263, 1154, 1130, 855 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.78 (t, *J* = 7.4 Hz, 3 H), 1.23 (t, *J* = 7.5 Hz, 6 H), 2.37 (s, 3 H), 2.05 (q, *J* = 7.4 Hz, 2 H), 2.49 (dd, *J* = 12.9, 8.5 Hz, 1 H), 2.58 (dd, *J* = 12.9, 3.5 Hz, 1 H), 2.75 (dd, *J* = 13.4, 10.5 Hz, 1 H), 2.83 (dd, *J* = 13.4, 3.9 Hz, 1 H), 3.24 (m, 1 H), 4.16 (q, *J* = 7.5 Hz, 4 H), 7.08–7.43 (m, 9 H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.4, 15.6, 23.3, 28.4, 35.8, 42.6, 44.7, 62.9, 124.4, 126.3, 128.2, 129.0, 129.9, 136.7, 138.0, 143.9, 218.9 ppm. MS (EI): *m*/*z* = 481 [M^+]. Anal. Calcd for $C_{23}H_{32}NO_6PS$: C, 57.37; H, 6.70; N, 2.91. Found: C, 57.57; H, 6.97; N, 3.25. $[a]_D^{25}$ –120 (*c* 1, $CHCl_3$). The ee was determined to be 82% by HPLC on a chiral Eurocel column [(250 × 4.6 mm, 5μ), λ = 225 nm, (*i*-PrOH–hexane = 10:90), 1 mL/min]; t_R (minor) = 10.9 min, t_R (major) = 13.4 min.

(20) **General Procedure for the Synthesis of Azetidines 4h,j**

To a solution of adduct **3h** or **3j** (0.2 mmol) in THF was added (*R*)-alpine borane (0.2 mmol), and the reaction mixture was stirred at 60 °C for 42–48 h. A sat. aq NH_4Cl solution (4 mL) was added, and the resulting mixture was extracted once with Et_2O (5 mL) and then with CH_2Cl_2 (2 × 5 mL), dried over anhyd $MgSO_4$, filtered, and evaporated to dryness. The crude product thus obtained was purified by flash chromatography using a gradient mixture of EtOAc–hexane as eluent to afford an analytically pure sample of **4h**

(yield 69%) or **4j** (yield 73%). Characterization data were in good agreement with those given in ref. 21.

(21) **General Procedure for the One-Pot Synthesis of Azetidines 4**

Reactions were carried out in undistilled toluene without any precaution to exclude water. The catalytic salt **A** (0.04 mmol) was prepared as described above (ref. 19) following the literature method.[14a] After addition of α,β-unsaturated ketone **1** (0.2 mmol) to it, the mixture was stirred at 60 °C for 10 min. Then a solution of phosphoramidate **2** (0.2 mmol) was added to the reaction mixture slowly with stirring at 60 °C, and stirring was continued for next 12–24 h which resulted in the formation of aza-Michael adduct **3** as monitored by TLC. The reaction mixture was cooled to r.t. followed by addition of (*R*)-alpine borane (0.2 mmol), and stirring at r.t. for another 42–48 h. A sat. aq NH_4Cl solution (4 mL) was added, and the resulting mixture was extracted once with Et_2O (5 mL) and then with CH_2Cl_2 (2 × 5 mL), dried over anhyd $MgSO_4$, filtered, and evaporated to dryness. The crude product thus obtained was purified by flash chromatography using a gradient mixture of EtOAc–hexane as eluent to afford an analytically pure sample of **4**.

Characterization Data for Representative Compounds

Compound **4h**: colorless oil; yield 67%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.4 Hz, 6 H), 1.33–1.52 (m, 4 H), 2.02 (t, *J* = 6.1 Hz, 2 H), 2.12 (s, 3 H), 4.07 (m, 2 H), 6.62 (d, *J* = 8.1 Hz, 1 H_{ortho}), 6.76–7.11 (m, 3 H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.0, 19.2, 26.0, 27.8, 61.8, 114.0, 119.4, 126.1, 130.8 ppm. MS (EI): *m*/*z* = 203 [M^+]. Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 83.06; H, 10.49; N, 6.82. $[\alpha]_D^{25}$ –193 (*c* 1, $CHCl_3$). The ee was determined to be 81% by HPLC on a chiral Eurocel column [(250 × 4.6 mm, 5μ), λ = 225 nm, (*i*-PrOH–hexane = 10:90), 1 mL/min]; t_R (minor) = 19.4 min, t_R (major) = 20.5 min.

Compound **4j**: colorless oil; yield 70%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.67 (t, *J* = 7.6 Hz, 3 H), 1.35–1.43 (m, 1 H), 1.66–1.72 (m, 1 H), 1.86–1.97 (m, 2 H), 2.35 (s, 3 H), 2.70 (dd, *J* = 13.4, 10.5 Hz, 1 H), 3.29 (dd, *J* = 13.4, 3.9 Hz, 1 H), 4.04–4.08 (m, 1 H), 4.30–4.33 (m, 1 H), 7.06–7.25 (m, 7 H), 7.69 (d, *J* = 8.3 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.3, 21.5, 26.5, 27.2, 40.2, 62.8, 63.6, 126.6, 127.4, 128.5, 129.3, 129.6, 136.7, 137.9, 143.1 ppm. MS (EI): *m*/*z* = 329 [M^+]. Anal. Calcd for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04; N, 4.25. Found: C, 69.35; H, 7.40; N, 4.50. $[\alpha]_D^{25}$ +79 (*c* 1, $CHCl_3$). The ee was determined to be 78% by HPLC on a chiral Eurocel column [(250 × 4.6 mm, 5μ), λ = 225 nm, (*i*-PrOH–hexane = 10:90), 1 mL/min]; t_R (minor) = 21.3 min, t_R (major) = 22.4 min.

