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Catalytic Asymmetric Five-Component Tandem Reaction: Diastereo- and Enantioselective Synthesis of Densely Functionalized Tetrahydropyridines with Biological Importance

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Abstract: The first catalytic asymmetric five-component tandem reactions of β-keto esters, aromatic aldehydes and anilines have been established in the presence of a chiral phosphoric acid, affording densely functionalized tetrahydropyridines with concomitant generation of five σ bonds and two stereogenic centers in high diastereo- and enantioselectivities (up to >99:1 *dr*, 95:5 *er*). In addition, the first isolation and preparation of a diene species as the key intermediate of the reaction has been successfully realized, leading to the formation of the desired tetrahydropyridine *via* further condensation with *in situ* generated imine, which supported the proposed tandem [4+2] reaction pathway to some extent. This protocol not only represents the first enantioselective example of this five-component tandem reaction, but also provides an unprecedented access to enantioenriched tetrahydropyridines with structural diversity, which holds great potential in medicinal chemistry.

Keywords: asymmetric catalysis; chirality; densely functionalized tetrahydropyridines; enantioselectivity; multicomponent reactions; organic catalysis

Introduction

The past decades have witnessed the great success of multicomponent reactions (MCRs) as a robust method to create molecules with structural diversity and complexity.[1] The tremendous advantages of MCRs[2] have made this protocol quite closely approach the realization of the ideal synthesis.[3] On the other hand, the increasing number of applications of optically pure compounds in the pharmaceutical industry has created a great demand for the development of asymmetric multicomponent reactions (AMCRs),[4] especially catalytic enantioselective MCRs, which assemble three or more achiral reagents in a single step to form two or more bonds and at least one stereogenic center in the presence of a chiral catalyst.[5] However, in sharp contrast to well-established non-enantioselective MCRs, the catalytic enantioselective MCR is still in its infancy.[1b,4c] Therefore, the development of catalytic asymmetric versions of existing MCRs has become a formidable challenge for the synthesis of optically pure compounds with structural diversity and complexity.

1,2,5,6-Tetrahydropyridines and piperidines are important heterocycles,[6] which constitute the core structures of a variety of natural products and pharmaceuticals (Figure 1).[7] In addition, recent studies have revealed that densely functionalized 1,2,5,6-tetrahydropyridines (compounds **I** and **II**, in Figure 1)

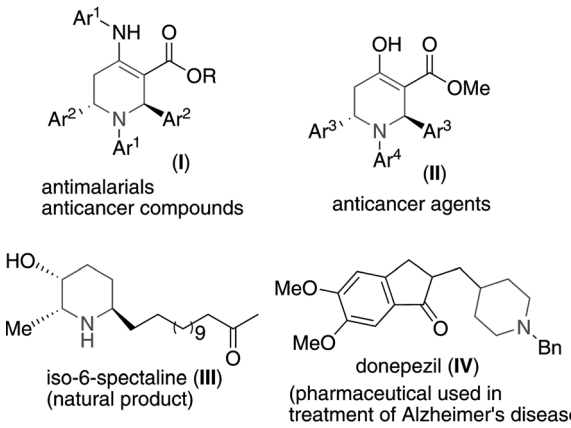


Figure 1. 1,2,5,6-Tetrahydropyridine and piperidine-related natural products and pharmaceuticals.

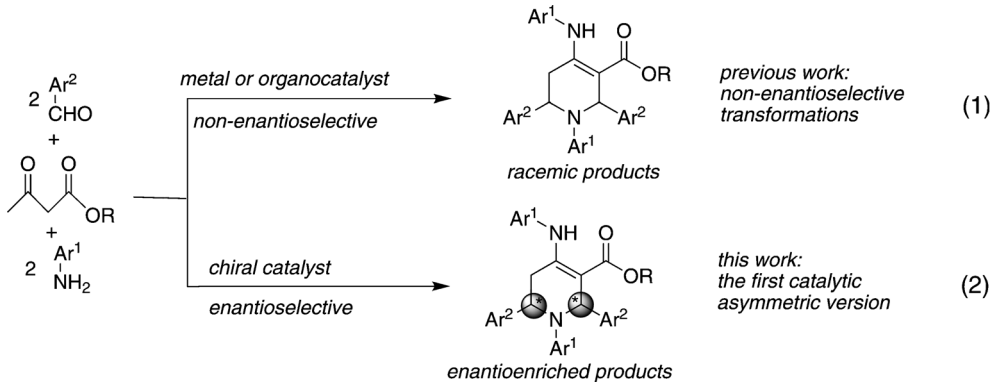


exhibit potent antimalarial[8] and anticancer[9] activities.

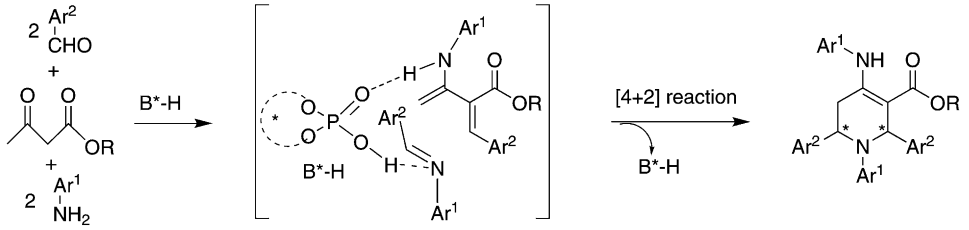
As a result, extensive attention has been paid to the synthesis of this series of heterocycles, and some developments have been achieved in the non-enantioselective MCRs which afford the racemic 1,2,5,6-tetrahydropyridines [Eq. (1)].[8–10] However, in contrast, no catalytic enantioselective versions of this MCR have been established in spite of the great demand for optically pure 1,2,5,6-tetrahydropyridines [Eq. (2)]. Thus, the development of this type of catalytic enantioselective MCR is highly desirable.

We have recently established a series of chiral phosphoric acid-catalyzed[11] MCRs for the preparation of enantioenriched heterocycles with potential bioactivities.[12] Inspired by these successes and in view of the fact that there is so far no enantioselective version of this five-component reaction together the importance of densely functionalized tetrahydropyridines, we decided to employ a chiral phosphoric acid to catalyze this five-component reaction, wherein the nitrogen-containing intermediates should be activated by this type of catalyst *via* hydrogen-bonding interactions (Scheme 1).

Herein, we report the first catalytic asymmetric five-component reaction, which directly assembles aldehydes, anilines and β-keto esters into densely functionalized tetrahydropyridines with concomitant generation of five σ bonds and two stereogenic centers in high diastereo- and enantioselectivities (up to 99:1 *dr*, 95:5 *er*). Besides, the key intermediate of the reaction has been firstly isolated or synthesized and subjected to further reaction, which strongly supported the proposed tandem [4+2] reaction pathway.

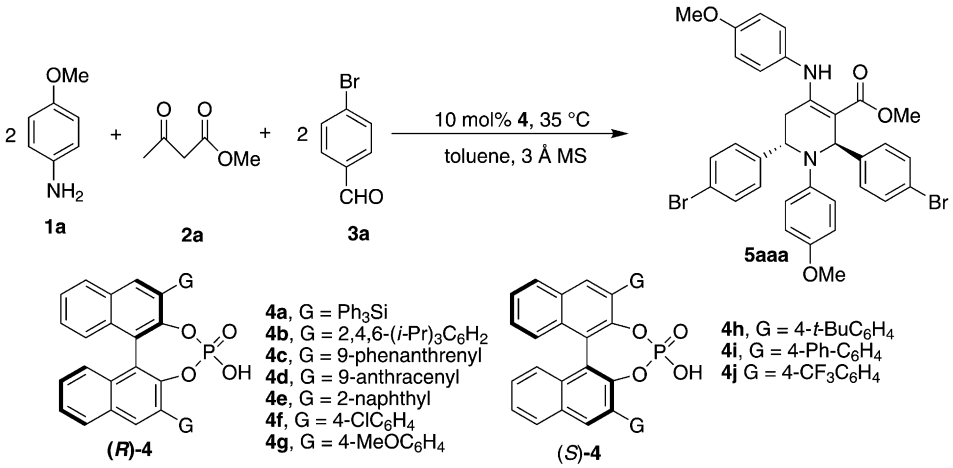
Results and Discussion

Our study commenced with a five-component reaction of two equivalents of 4-methoxyaniline **1a**, methyl acetoacetate **2a** and two equivalents of 4-bromobenzaldehyde **3a** in the presence of 10 mol% of chiral phosphoric acids (CPAs) **4** in toluene at 35 °C (Table 1). The initial results revealed that CPAs **4a**–**4e** with bulky groups at the 3,3′-positions of the BINOL backbone had inferior catalytic activity (entries 1–5), while CPA **4f** with 3,3′-*p*-chlorophenyl groups was much superior to other analogues, affording the desired tetrahydropyridine **5aaa** in 56% yield, 80:20 *dr* and 91:9 *er* (entry 6). Subsequent changing in the *para*-substituents of 3,3′-phenyl rings (entries 7–10) led to the finding that electron-donating substituents would decrease the yield and enantioselectivity (entries 7 and 8), while electron-withdrawing ones would increase the yield but still with reduced enantioselectivity (entries 9 and 10). Furthermore, there was no evident steric effect among these substituents and no other tested CPAs could deliver a higher *er* value than **4f**. Then, the model reaction in the presence of **4f** was performed in a wide range of solvents to find the optimal reaction medium. Several halogen-substituted benzenes were tentatively employed as solvents (entries 11–13), and bromobenzene afforded the product in the highest yield of 73% but with inferior enan-



Scheme 1. The designed activation mode of chiral catalyst to the intermediates.

Table 1. The screening of catalysts and solvents.[a]



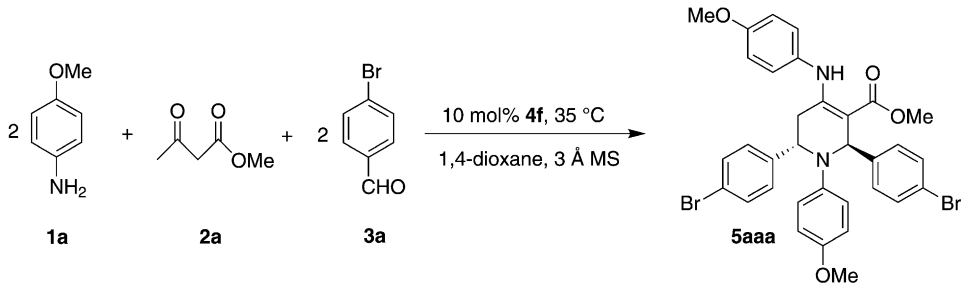
Entry	4	Solvent	Yield [%][b]	*dr*[c] (*trans*:*cis*)	*er*[d]
1[e]	**4a**	toluene	–	–	–
2	**4b**	toluene	34	89:11	61:39
3	**4c**	toluene	47	87:13	77:23
4	**4d**	toluene	19	76:24	78:22
5	**4e**	toluene	56	71:29	80:20
6	**4f**	**toluene**	**56**	**80:20**	**91:9**
7	**4g**	toluene	35	76:24	86:14
8	**4h**	toluene	48	73:27	16:84
9	**4i**	toluene	67	80:20	15:85
10	**4j**	toluene	68	84:16	13:87
11	**4f**	FPh	67	80:20	89:11
12	**4f**	ClPh	64	75:25	86:14
13	**4f**	BrPh	73	83:17	85:15
14	**4f**	CH_2Cl_2	59	67:33	87:13
15	**4f**	$CHCl_3$	69	67:33	89:11
16	**4f**	CCl_4	61	67:33	88:12
17	**4f**	THF	16	86:14	92:8
18	**4f**	**1,4-dioxane**	**47**	**92:8**	**93:7**
19[e]	**4f**	CH_3CN	–	–	–

[a] Unless indicated otherwise, the reaction was carried out on a 0.1-mmol scale in solvent (1 mL) with 3 Å MS (100 mg) for 48 h, and the ratio of **1a**:**2a**:**3a** was 2:1:2.
[b] Isolated yield.
[c] The diastereomeric ratio (*dr*) was determined by ^{1}H NMR.
[d] The enantiomeric ratio (*er*) value refers to the major *trans*-diastereomer and was determined by HPLC.
[e] No reaction.

tioselectivity (entry 13). Further utilization of chlorine-containing alkanes as solvents revealed that there was no significant difference among them and none of them provided a higher *er* value than toluene (entries 14–16). At last, ethers and acetonitrile were applied to the reaction (entries 17–19), which disclosed that 1,4-dioxane was the best solvent by offering the highest *er* value of 93:7 albeit with an unsatisfactory yield (entry 18). Surprisingly, acetonitrile as a polar non-protic solvent failed to facilitate the reaction under the current reaction conditions (entry 19), which was very different from its efficient performance in non-enantioselective tranformations.[8,10a–g,j] Thus, 1,4-dioxane was finally selected as the solvent of choice for further investigation.

Subsequently, other reaction parameters such as molecular sieves (MS), temperature and reagent ratios were examined in the model reaction (Table 2). In the absence of MS, the reaction proceeded sluggishly in a low yield and poor diastereoselectivity (entry 2 *vs.* entries 1 and 3), which indicated that MS played an important role both in reactivity and in stereoselectivity. 3 Å MS exhibited a slight superiority over 4 Å MS in controlling the reactivity and the stereoselectivity (entry 1 *vs.* entry 3). Lowering or raising the reaction temperature could not improve the *er*

Table 2. Further screening of other reaction parameters.[a]



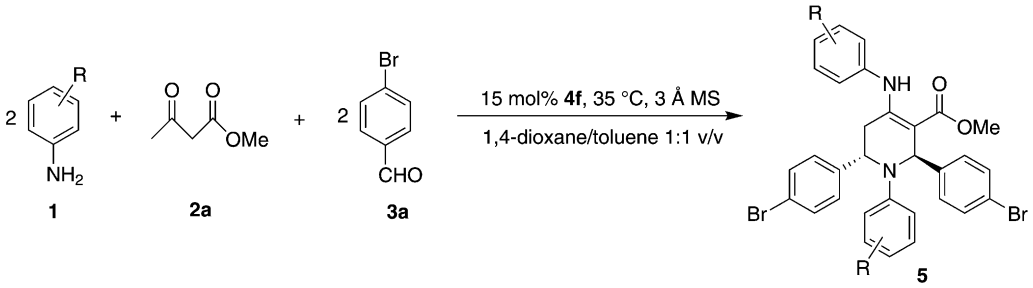
Entry	**1a**:**2a**:**3a**	Yield [%][b]	*dr*[c] (*trans*:*cis*)	*er*[d]
1	2:1:2	47	92:8	93:7
2[e]	2:1:2	23	50:50	89:11
3[f]	2:1:2	46	90:10	92:8
4[g]	2:1:2	21	67:33	93:7
5[h]	2:1:2	39	92:8	92:8
6	2:1:2.4	43	89:11	93:7
7	2:2.5:2	22	80:20	95:5
8	2:1.5:2.4	42	88:12	93:7
9	7.8:6:2	19	67:33	95:5
10	3.5:1:3.5	42	92:8	95:5
11[i]	**3.5:1:3.5**	**59**	**90:10**	**93:7**
12[j]	**2:1:2**	**73**	**88:12**	**88:12**

[a] Unless indicated otherwise, the reaction was carried out on a 0.1-mmol scale in 1,4-dioxane (1 mL) with 3 Å MS (100 mg) for 48 h.
[b] Isolated yield.
[c] The *dr* was determined by ^{1}H NMR.
[d] The *er* refers to the major *trans*-diastereomer and was determined by HPLC.
[e] In the absence of MS.
[f] 4 Å MS was used.
[g] Performed at 0 °C.
[h] Performed at 50 °C.
[i] Catalyzed by 15 mol% **4f** for 84 h.
[j] Catalyzed by 15 mol% **4f** in the mixed solvent of 1,4-dioxane and toluene (1:1 v/v) for 84 h.

value but would decrease the yield (entries 4 and 5 *vs* entry 1). Finally, the reagent ratio was carefully tuned in order to enhance the enantioselectivity as well as the yield (entries 6–10). The presence of excess **3a** had no obvious effect on the reaction (entry 6 *vs.* entry 1), while increasing the stoichiometry of **2a** led to an improved enantioselectivity but with a dramatically decreased yield (entries 7 *vs.* entry 1). And using an excess of **2a** and **3a** at the same time did not benefit the reaction (entry 8 *vs.* entry 1). When the stoichiometries of **1a** and **2a** were increased simultaneously, the enantioselectivity was improved but still with poor yield and decreased diastereoselectivity (entries 9 *vs.* entry 1). However, elevating the stoichiometry of **1a** and **3a** at the same time resulted in a better enantioselectivity and an acceptable yield (entry 10 *vs.* entry 1). So, the most suitable ratio of **1a**:**2a**:**3a** was set as 2:1:2 (entry 1) or 3.5:1:3.5 (entry 10). When the catalyst loading was increased to 15 mol% at the ratio of 3.5:1:3.5, the yield was enhanced from 42% to 59% albeit with a slightly reduced enantioselectivity of 93:7 *er* (entry 11 *vs.* entry 10). Notwithstanding, these conditions are relatively more suitable in terms of delivering a high stereoselectivity with a fair yield. In fact, it seemed that the two factors of yield and enantioselectivity were somewhat restricted by each other, thereby high yield accompanied with excellent enantioselectivity could hardly be achieved simultaneously and a compromise between them should be made. Thus, in an attempt to further increase the yield with minimally reduced enantioselectivity, a mixed solvent of 1,4-dioxane and toluene (1:1 v/v) was utilized at the ratio of 2:1:2, which rendered the reaction to proceed in a high yield of 73% with good enantioselectivity of 88:12 *er* (entry 12).

With the optimal conditions in hand, we then carried out an investigation on the substrate scope of anilines **1** by the reaction with methyl acetoacetate **2a** and 4-bromobenzaldehyde **3a** (Table 3). The results disclosed that a wide range of anilines including electronically poor, neutral and rich ones served as appro-

Table 3. The substrate scope of anilines.[a]



Entry	5	R	Yield [%][b]	*dr*[c]	*er*[d]
1	**5aaa**	4-OMe (**1a**)	59	90:10	93:7
2[e]	**5baa**	4-OEt (**1b**)	52	76:24	87:13
3	**5caa**	4-OPh (**1c**)	62	76:24	83:17
4	**5daa**	3,4-OCH_2CH_2O (**1d**)	47	79:21	88:12
5[e]	**5eaa**	4-CH_3 (**1e**)	58	84:16	90:10
6[e]	**5faa**	H (**1f**)	51	85:15	90:10
7	**5gaa**	4-F (**1g**)	59 (46[e])	79:21 (82:18[e])	84:16 (89:11[e])
8	**5haa**	3-F (**1h**)	58 (48[e])	89:11 (93:7[e])	89:11 (91:9[e])
9[f]	**5iaa**	4-CN (**1i**)	43	>99:1	87:13

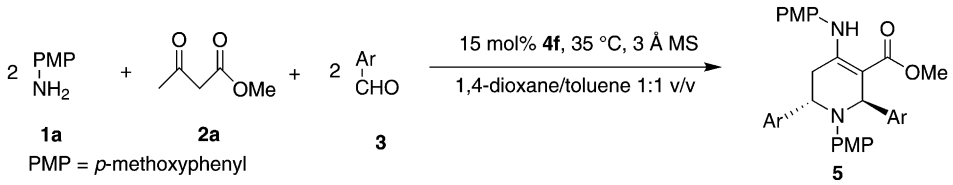
[a] Unless indicated otherwise, the reaction was carried out on a 0.1-mmol scale in the mixed solvent of 1,4-dioxane and toluene (1:1 v/v, 1 mL) with 3 Å MS (100 mg) for 84 h, and the ratio of **1**:**2a**:**3a** was 2:1:2.
[b] Isolated yield.
[c] The *dr* refers to the ratio of *trans*-diastereomer to *cis*-diastereomer and was determined by ^{1}H NMR.
[d] The *er* refers to the major *trans*-diastereomer and was determined by HPLC.
[e] Catalyzed by 12 mol% **4f**.
[f] Catalyzed by 18 mol% **4f**.

priate substrates, providing structurally diverse tetrahydropyridines **5** in good stereoselectivities (76:24 to >99:1 *dr,* 83:17 to 93:7 *er*). In general, the electronic nature of the substituents of the anilines had no significant influence on the enantioselectivity, but the size and position of the substituents had some delicate effect on the enantioselectivity in some cases. For instance, when increasing the size of an alkoxy group, the enantioselectivity was decreased from 93:7 to 83:17 *er* (entries 1–3). And *meta*-substituted fluoroaniline delivered higher *er* value than its *para*-substituted counterpart (entry 8 *vs.* entry 7). Besides, better diastereo- and enantioselectivities could be achieved when lowering the catalyst loading, albeit with decreased yields (entries 7 and 8, in parentheses). Importantly, even if an aniline bearing strong electron-withdrawing group was applied, excellent diastereoselectivity (>99:1 *dr*) and good enantioselectivity (87:13 *er*) could also be obtained as exemplified by 4-cyanoaniline (entry 9).

Next, the generality for aldehydes **3** was examined by the reaction with 4-methoxyaniline **1a** and methyl acetoacetate **2a**. As shown in Table 4, this protocol is applicable to a wide scope of aldehydes including benzaldehydes bearing either of an electronically poor, neutral, or rich substituent, and a heteroaromatic aldehyde in fair to good stereoselectivities (67:33 to 90:10 *dr*, 84:16 to 93:7 *er*). In general, there was no remarkable difference between electronically poor aldehydes and electronically rich ones with regard to enantioselectivity, but the former delivered higher yields than the latter in most cases (entries 1–7 *vs.* entries 9–12). In the cases of halogen-substituted benzaldehydes, the enantioselectivity was evidently enhanced from 89:11 to 93:7 *er* when increasing the atomic radius of the halogen (entries 1–3). As observed before, lowering the catalyst loading greatly improved the enantioselectivity albeit with a decreased yield (entry 1, in parentheses), while increasing the catalyst loading remarkably enhanced the yield but with an erosion of the enantioselectivity (entry 10, in parentheses). Moreover, benzaldehydes with strong electron-donating groups such as 4-methoxybenzaldehyde **3k** could also be employed to the reaction in spite of the low reactivity associated with such a aldehyde,[10a,c] delivering the desired tetrahydropyridine **5fak** in good stereoselectivity (86:14 *dr*, 90:10 *er*, entry 11). Notably, this protocol could also be applied to heteroaromatic aldehydes as exemplified by thiophene-2-carbaldehyde **3l** in a good stereoselectivity albeit with an unsatisfactory yield (entry 13).

Finally, the substrate scope with respect to β-keto esters **2** was explored by the reactions with 4-meth-

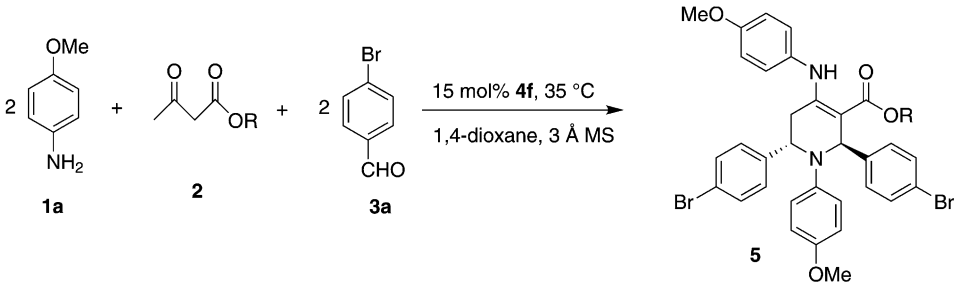
Table 4. The substrate scope of aldehydes.[a]



Entry	5	Ar	Yield [%][b]	*dr*[c]	*er*[d]
1	**5aab**	4-FC_6H_4 (**3b**)	58 (39[e])	79:21 (76:24[e])	89:11 (93:7[e])
2[e]	**5aac**	4-ClC_6H_4 (**3c**)	50	77:23	90:10
3	**5aaa**	4-BrC_6H_4 (**3a**)	59	90:10	93:7
4[e]	**5aad**	4-CNC_6H_4 (**3d**)	63	76:24	90:10
5	**5aae**	4-$MeO_2CC_6H_4$ (**3e**)	59	77:23	87:13
6[f]	**5aaf**	3,4-$F_2C_6H_3$ (**3f**)	65	67:33	84:16
7[e]	**5aag**	3-$NO_2C_6H_4$ (**3g**)	60	76:24	84:16
8	**5aah**	C_6H_5 (**3h**)	46	78:22	89:11
9[f]	**5aai**	4-MeC_6H_4 (**3i**)	51	82:18	87:13
10	**5aaj**	3-MeC_6H_4 (**3j**)	42 (64[f])	81:19 (82:18[f])	90:10 (86:14[f])
11[g]	**5fak**	4-$MeOC_6H_4$ (**3k**)	38	86:14	90:10
12[f,g]	**5fai**	4-MeC_6H_4 (**3i**)	68	86:14	86:14
13[h]	**5aal**	2-thiophenyl (**3l**)	38	76:24	87:13

[a] Unless indicated otherwise, the reaction was carried out on a 0.1 mmol scale in the mixed solvent of 1,4-dioxane and toluene (1:1 v/v, 1 mL) with 3 Å MS (100 mg) for 84 h, and the ratio of **1a**:**2a**:**3** was 2:1:2.
[b] Isolated yield.
[c] The *dr* refers to the ratio of *trans*-diastereomer to *cis*- diastereomer and was determined by ^{1}H NMR.
[d] The *er* refers to the major *trans*-diastereomer and was determined by HPLC.
[e] Catalyzed by 12 mol% **4f**.
[f] Catalyzed by 18 mol% **4f**.
[g] Aniline **1f** was employed as substrate instead of 4-methoxyaniline **1a**.
[h] Catalyzed by 20 mol% **4f**.

Table 5. The substrate scope of β-keto esters.[a]



Entry	5	R	Yield [%][b]	*dr*[c]	*er*[d]
1	**5aaa**	Me (**2a**)	59	90:10	93:7
2	**5aba**	Et (**2b**)	64	88:12	84:16
3[e]	**5aca**	allyl (**2c**)	59	77:23	90:10
4[e]	**5ada**	*i*-Pr (**2d**)	80	80:20	87:13
5	**5aea**	*t*-Bu (**2e**)	50	90:10	95:5
6[e]	**5afa**	Bn (**2f**)	64	76:24	88:12

[a] Unless indicated otherwise, the reaction was carried out on a 0.1-mmol scale in 1,4-dioxane (1 mL) with 3 Å MS (100 mg) for 84 h, and the ratio of **1a**:**2**:**3a** was 3.5:1:3.5.
[b] Isolated yield.
[c] The *dr* refers to the ratio of *trans*-diastereomer to *cis*-diastereomer and was determined by ^{1}H NMR.
[d] The *er* refers to the major *trans*-diastereomer and was determined by HPLC.
[e] Catalyzed by 18 mol% **4f** in the mixed solvent of 1,4-dioxane and toluene (1:1 v/v), and the ratio of **1a**:**2**:**3a** was 2:1:2.

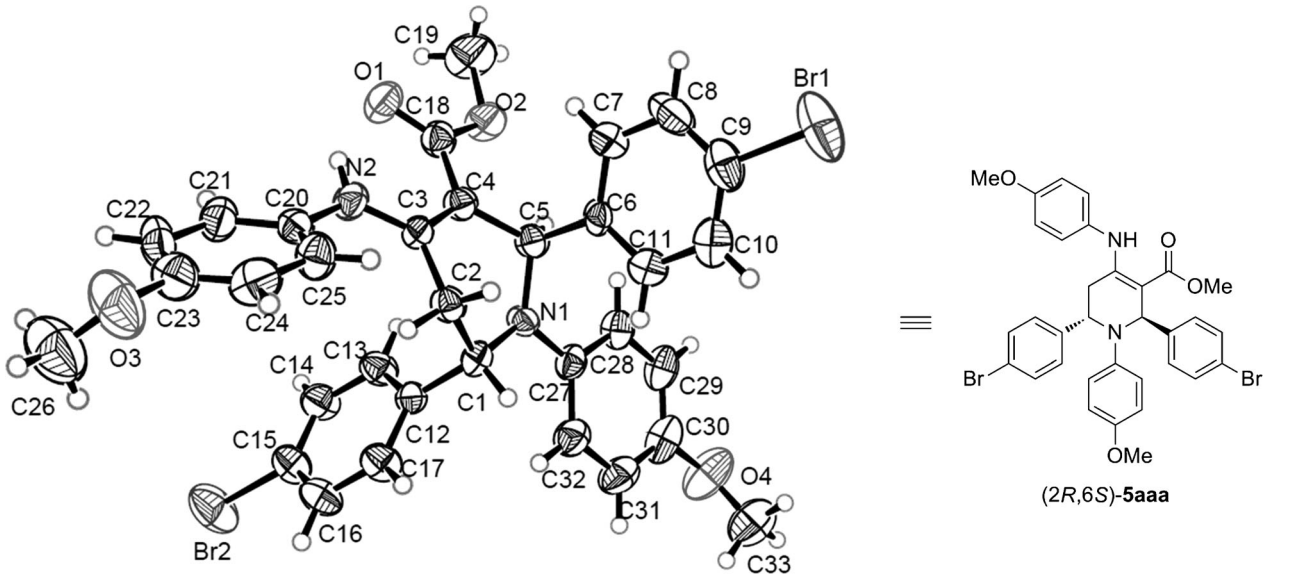
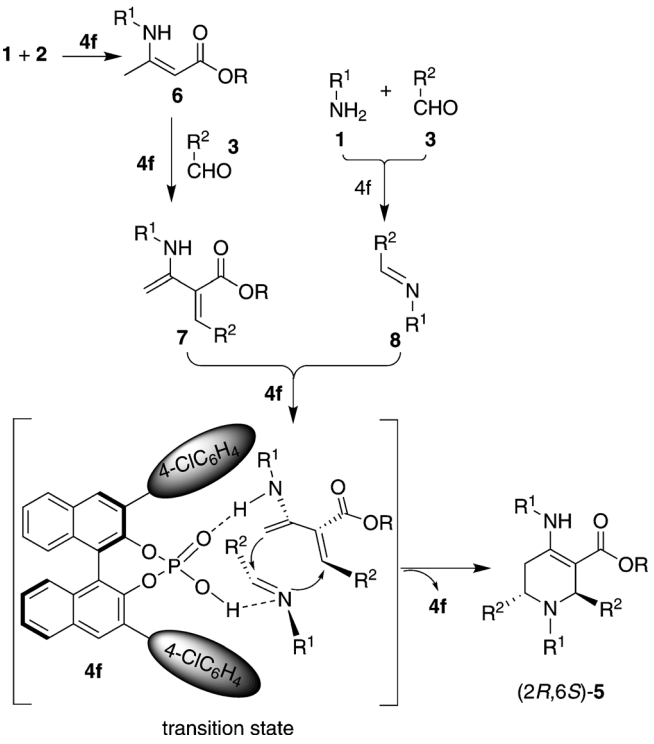


Figure 2. X-ray structure of tetrahydropyridine **5aaa**.

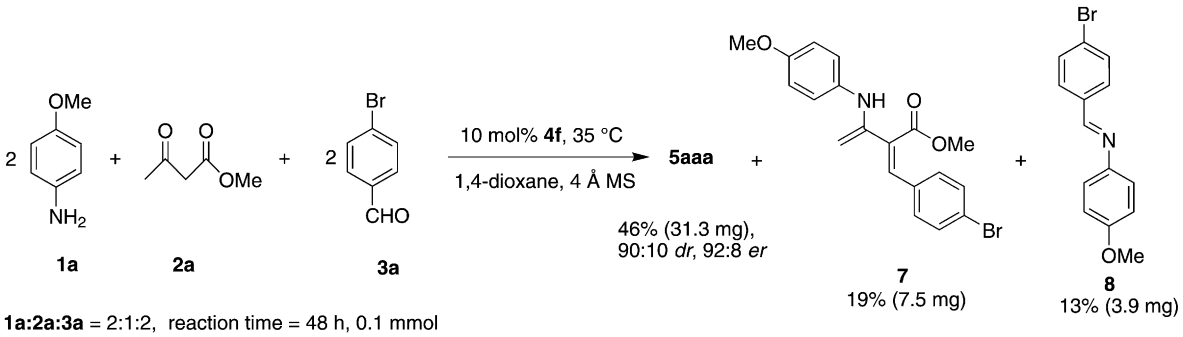
oxyaniline **1a** and 4-bromobenzaldehyde **3a**. As indicated in Table 5, this protocol is amenable to various β-keto esters with different ester groups including alkyl, allyl and benzyl ones, affording products **5** in good to high stereoselectivities (76:24 to 90:10 *dr*, 84:16 to 95:5 *er*). Among alkyl-substituted esters (entries 1, 2 and 4, 5), the *tert*-butyl ester delivered the highest stereoselectivity (90:10 *dr*, 95:5 *er*, entry 5), and the isopropyl ester was better than the ethyl ester with regard to enantioselectivity (entry 4 *vs.* entry 2). Apart from alkyl esters, allyl and benzyl ones could also participate in the reaction with good enantioselectivities (entries 3 and 6).

The absolute configuration of compound **5aaa** (98:2 *er* after recrystallization) was unambiguously determined to be (2*R*,6*S*) by single-crystal X-ray diffraction analysis (Figure 2).[13] Moreover, the relative configuration of compound **5aaa** was confirmed to be *trans* by its X-ray structure and comparison of its ^{1}H NMR spectrum with that of the racemic *trans*-product.[8,10f] The relative and absolute configurations of other functionalized tetrahydropyridines **5** were assigned by analogy.

Based on our experimental results and reports on non-enantioselective reactions,[8–10] we proposed a possible reaction pathway to explain the chemistry and the stereoselectivity of this catalytic asymmetric five-component reaction (Scheme 2). Initially, the reaction of anline **1** with β-keto ester **2** in the presence of chiral phosphoric acid **4f** generated enamine **6**, which then condensed with aldehyde **3** in a Knoevenagel-type reaction to produce a diene species **7**, a key intermediate in the tandem reaction. Simultaneously, **4f**-catalyzed condensation of aniline **1** with aldehyde **3** afforded the corresponding imine **8**, which subsequently underwent a [4+2] reaction with the intermediate **7** to provide the densely functionalized tetrahydropyridines **5**. In the proposed transition state of the [4+2] reaction, the 3,3′-bi(*p*-chlorophenyl)phosphoric acid **4f** acted as a bifunctional catalyst to activate both the diene **7** and the *E*-imine **8** by hydrogen-bonding interactions. Then a stereoselective [4+2] re-



Scheme 2. Proposed reaction mechanism and transition state.



Scheme 3. The isolation of intermediate **7**.

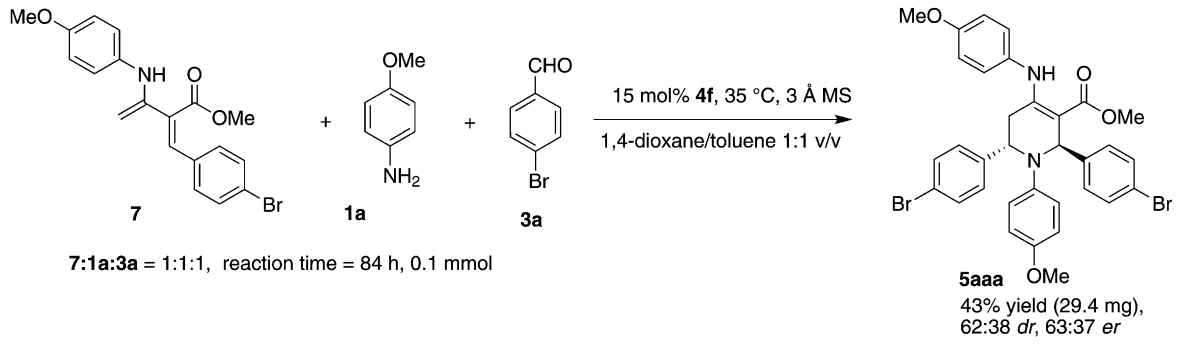
action occurred because of the chiral environment created by the (*R*)-BINOL backbone and the congested 3,3′-substitutents of the catalyst **4f**, thereby offering the experimentally observed (2*R*,6*S*)-configured product **5**.

However, in previous reports on non-enantioselective reactions,[8–10] the key intermediate **7** was not isolated or observed, which could hardly testify the proposed [4+2] process of the reaction. In an attempt to clarify the reaction pathway, we performed an in-depth study on the reaction mechanism. Fortunately, we observed and isolated the key intermediate **7** during the reaction process. As shown in Scheme 3, in the one-pot five-component model reaction, the desired product **5aaa** was afforded in 46% yield, accompanied by the isolation of intermediate **7** in 19% yield and imine **8** in 13% yield. The structure of intermediate **7** was unambiguously confirmed by ^{1}H and ^{13}C NMR, IR and HR-mass spectra. The isolation of this key intermediate demonstrated the high possibility of the [4+2] reaction pathway.

In order to further prove the proposed [4+2] reaction pathway, the intermediate **7** was subjected to the reaction with imine **8** generated *in situ* from aniline **1a** and aldehyde **3a** under the optimal reaction conditions (Scheme 4). As expected, the reaction proceeded smoothly to afford the desired product **5aaa** in 43% yield, which was a little lower than that of the five-component one-pot reaction. Although the stereoselectivity of the intermediate-involved reaction was inferior to that of the five-component one-pot reaction, the generation of tetrahydropyridine **5aaa** from intermediate **7** and *in situ* formed imine **8** supported the [4+2] reaction pathway to some extent.

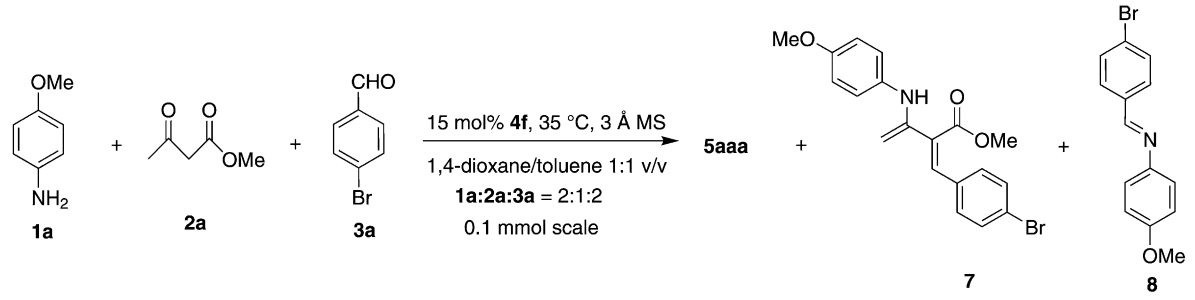
To explain the experimentally observed inferior stereoselectivity and reactivity of the reaction between intermediate **7** and *in situ* formed imine **8**, we monitored the mole ratio of intermediates **8** to **7** during the formation of **5aaa** in the five-component reaction. As illustrated in Table 6 and Figure 3, during the course of the five-component reaction (84 h), the amounts of intermediates **7** and **8** were constantly changing, which led to the remarkable variation in the mole ratio of intermediates **8** to **7**. The five-component reaction was a dynamic process, i.e., the formation of **5aaa** would consume intermediates **7** and **8**, which rendered the starting materials to continuously produce more amounts of the intermediates. While in the reaction of intermediate **7** with *in situ* formed imine **8** (Scheme 4), the starting concentration and mole ratio of the reactants were fixed and no more intermediate **7** could be generated during the reaction process. So, there existed a great difference in the concentrations and mole ratios of the two intermediates (**7** and **8**) between the five-component reaction and the intermediate-involved stepwise process.

Then, to investigate the influence of mole ratio on the intermediate-involved stepwise reaction, we car-



Scheme 4. The reaction between intermediate **7** and *in situ* formed imine.

Table 6. The mole ratio of intermediates **8** to **7** during the formation of **5aaa** in the five-component reaction.[a]



Entry	Time [h]	**8**:**7**[b]	**8**[c] (μmol)	**7**[c] (μmol)	**5aaa** Yield [%][d]	*dr*[e]	*er*[f]
1	12	22.2:1	71.0	3.2	38	86:14	91:9
2	24	21.9:1	56.9	2.6	38	89:11	90:10
3	36	7.5:1	61.7	8.2	41	90:10	90:10
4	48	5.5:1	55.2	10.1	56	87:13	89:11
5	60	7.4:1	68.3	9.2	59	85:15	89:11
6	72	5.6:1	62.1	11.1	60	85:15	88:12
7	84	4.2:1	43.1	10.3	73	88:12	88:12

[a] Unless indicated otherwise, the reaction was carried out on a 0.1-mmol scale in the mixed solvent of 1,4-dioxane and toluene (1:1 v/v, 1 mL) with 3 Å MS (100 mg) for a given time, and the ratio of **1a**:**2a**:**3a** was 2:1:2.
[b] The mole ratio of intermediates **7** to **8** at the specified time points.
[c] Determined by HPLC using an internal standard.
[d] Isolated yield.
[e] The *dr* refers to the ratio of *trans*-diastereomer to *cis*-diastereomer and was determined by ^{1}H NMR.
[f] The *er* refers to the major *trans*-diastereomer and was determined by HPLC.

ried out the reaction of intermediate **7** with *in situ* formed imine **8** under different mole ratios. As shown in Table 7, the mole ratio of the intermediates indeed imposed an obvious effect on the stereoselectivity and reactivity. Encouragingly, when the mole ratio of **1a**:**3a**:**7** was 2:2:1, the enantioselectivity of **5aaa** was improved to 72:28 *er* (entry 3), which was closer to the result of the five-component reaction (89:11 *er*, entry 7). But the intermediate-involved stepwise reaction could hardly imitate the real and continuously changeable concentrations and mole ratios of the intermediates *in situ* generated from the five-component reaction, thereby resulting in the observed inferior stereoselectivity and reactivity.

Moreover, we also tried the synthesis of the intermediate **7** *via* stepwise procedures according to the proposed mechanism (Scheme 5 and Scheme 6). As shown in Scheme 5, **4f**-catalyzed condensation of **1a**

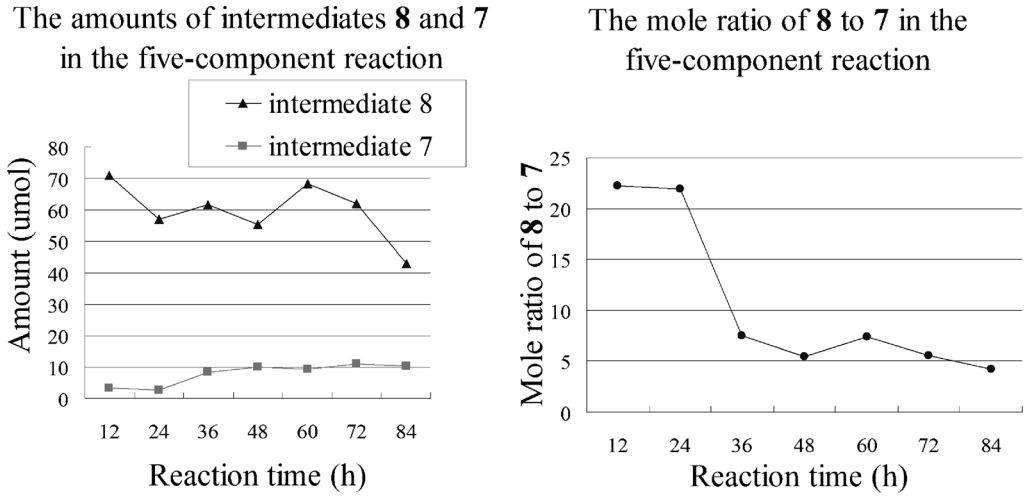
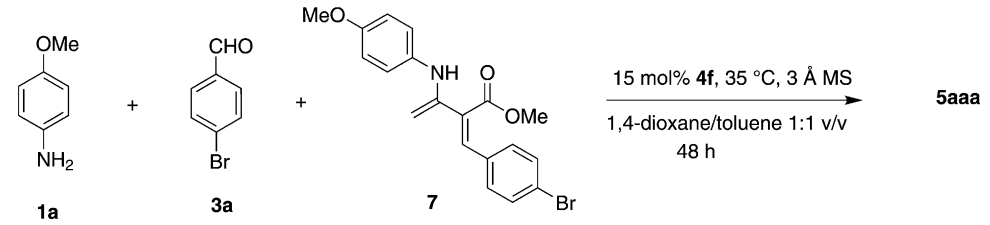


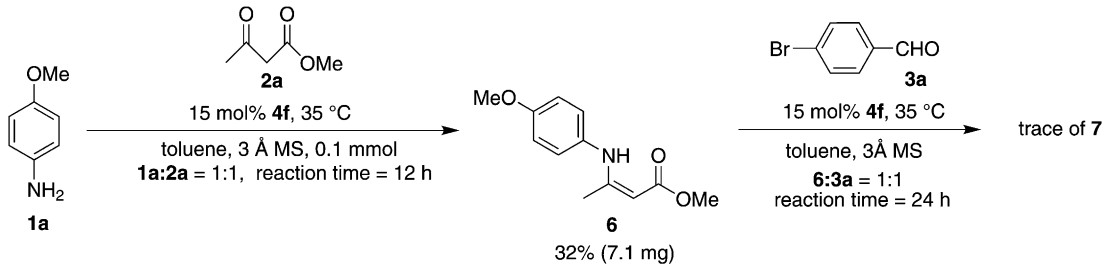
Figure 3. The amounts and the mole ratio of intermediates detected during the course of five-component reaction.

Table 7. The effect of mole ratios on the reaction between intermediate **7** and *in situ* formed imine.[a]

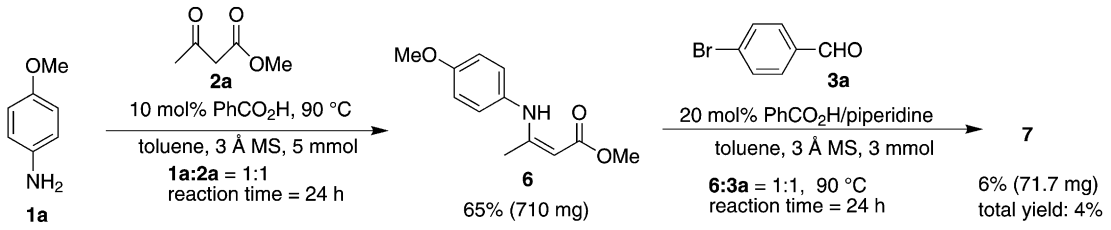


Entry	**1a**:**3a**:**7**	Yield [%][b]	*dr*[c] (*trans*:*cis*)	*er*[d]
1[e]	1:1:1	43	62:38	63:37
2	1.5:1.5:1	27	73:27	58:42
3	**2:2:1**	**37**	**66:34**	**72:28**
4	3:3:1	55	60:40	61:39
5	3.5:3.5:1	49	63:37	69:31
6	5:5:1	39	62:38	64:36
7	control[f]	56	87:13	89:11

[a] Unless indicated otherwise, the reaction was carried out on a 0.05-mmol scale in the mixed solvent of 1,4-dioxane and toluene (1:1 v/v, 0.5 mL) with 3 Å MS (50 mg) for 48 h.
[b] Isolated yield.
[c] The *dr* refers to the ratio of *trans*-diastereomer to *cis*-diastereomer and was determined by ^{1}H NMR.
[d] The *er* refers to the major *trans*-diastereomer and was determined by HPLC.
[e] The reaction was carried out on a 0.1-mmol scale for 84 h.
[f] The control experiment refers to the five-component reaction with the same reaction time of 48 h, which was illustrated in Table 6, entry 4.



Scheme 5. The synthesis of intermediate **7** *via* stepwise procedures at 35 °C.

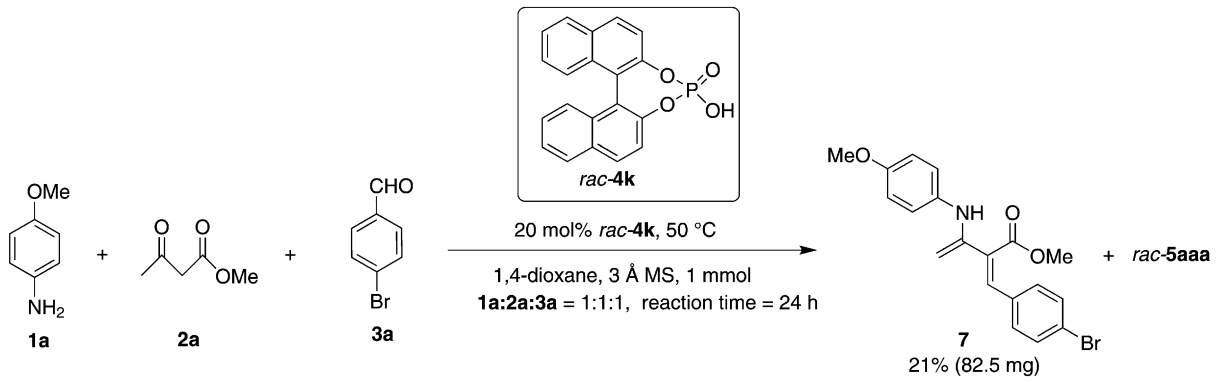


Scheme 6. The synthesis of intermediate **7** *via* stepwise procedures at 90 °C.

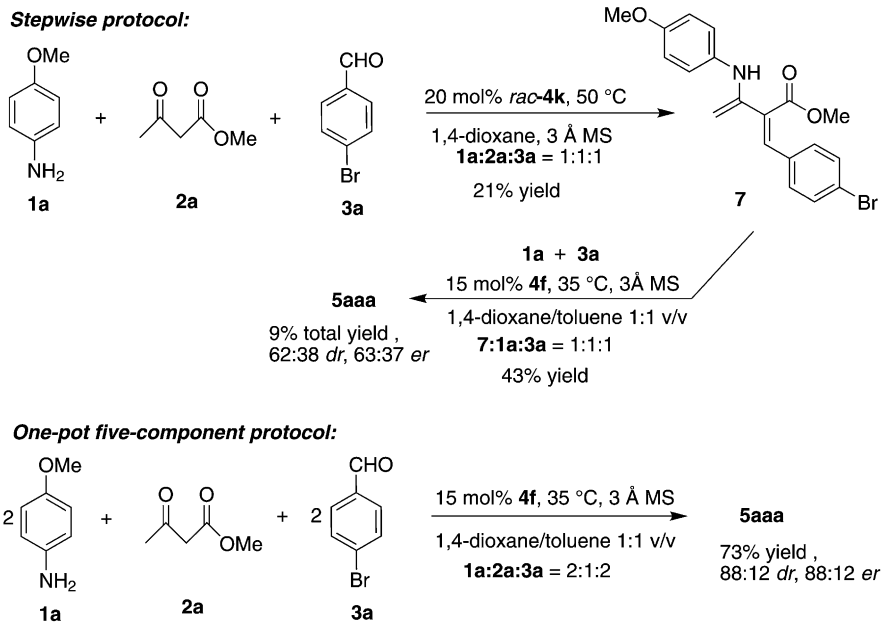
and **2a** at 35 °C afforded enamine **6** in 32% yield, but the subsequent treatment of enamine **6** with **3a** under the same reaction conditions could hardly offer the desired intermediate **7** after 24 h.

Then we tried the same stepwise procedures at an elevated temperature of 90 °C in the presence of benzoic acid (Scheme 6). At this reaction temperature, the enamine formation was more efficient (65% yield), but the second step was still very sluggish, affording the desired diene **7** in an extremely low yield of 6%.

On the contrary, the intermediate **7** was isolated in 19% yield *via* the one-pot reaction as mentioned above (Scheme 3). So, we further tried the one-pot protocol to prepare intermediate **7** at 50 °C in the presence of racemic phosphoric acid **4k** (Scheme 7).



Scheme 7. The synthesis of intermediate **7** *via* a one-pot protocol.



Scheme 8. The comparison between stepwise and one-pot protocols.

In the cases of Scheme 6 and Scheme 7, benzoic acid or racemic phosphoric acid **4k** was employed as catalyst in order to save up a large amount of CPA **4f**, since no chiral centers would be generated in intermediate **7**. As illustrated in Scheme 7, the one-pot reaction afforded the desired diene **7** in 21% yield accompanied with the formation of racemic **5aaa**. The yield of intermediate **7** in this one-pot protocol was much higher than those of the stepwise procedures, demonstrating the superiority of one-pot multicomponent reactions to multistep ones. The relatively higher efficiency of such a protocol may be attributed to the dynamic equilibrium existing in the multicomponent reaction: the formation of *rac*-**5aaa** would consume intermediate **7**, which rendered the reaction to continuously proceed toward the generation of more amounts of intermediate **7**.

On the basis of above investigations, we compared the efficiency of the stepwise protocol with that of the one-pot five-component protocol in the synthesis of chiral tetrahydropyridine **5aaa**. As demonstrated in Scheme 8, the one-pot five-component approach was much superior to stepwise procedures both in reactivity and in stereoselectivity. This comparison also strongly manifested the tremendous advantages of asymmetric multicomponent reactions over multistep ones.

Conclusions

In summary, we have established the first catalytic asymmetric five-component reactions of β-keto esters, aromatic aldehydes and anilines in the presence of a chiral phosphoric acid. This protocol combines the

merits of asymmetric organocatalysis and multicomponent reactions, tolerating a wide range of substrates to furnish densely functionalized tetrahydropyridines with concomitant generation of five σ bonds and two chiral centers in good to high diastereo- and enantioselectivities (up to >99:1 *dr*, 95:5 *er*). Besides, a diene species as the key intermediate of the reaction has been firstly isolated and synthesized. And this intermediate was subjected to further condensation with an *in situ* generated imine to afford the desired tetrahydropyridine, which supported the proposed tandem [4+2] reaction pathway to some extent. Moreover, the comparison between the stepwise protocol and the five-component one-pot approach has demonstrated the much higher efficiency of the latter over the former. This five-component approach not only provides an easy access to biologically relevant chiral tetrahydropyridines with structural diversity, but also greatly enriches the contents of catalytic enantioselective multicomponent reactions.

Experimental Section

General Remarks

NMR spectra were measured at 400 and 100 MHz, respectively. The solvent used for NMR spectroscopy was $CDCl_3$, using tetramethylsilane as the internal reference. HR-MS were recorded on a LTQ-Orbitrap mass spectrometer (ionization mode: ESI^+). The enantiomeric ratio (*er*) was determined by chiral high-performance liquid chromatography (chiral HPLC). The chiral columns used for the determination of enantiomeric ratios by chiral HPLC were Chiralpak AD-H, IA, OD-H and IC columns. Optical rotation values were measured with instruments operating at $\lambda = 589$ nm, corresponding to the sodium D line at the temperatures indicated. Analytical grade solvents for the column chromatography and commercially available reagents were used as received. Toluene was dried and distilled prior to use.

General Procedure for the Asymmetric Five-Component Reactions

After a solution of aniline **1** (0.2 mmol), β-keto ester **2** (0.1 mmol), the catalyst **4f** (0.015 mmol), and 3 Å molecular sieves (100 mg) in the mixed toluene/1,4-dioxane (1:1 v/v, 0.5 mL) had been stirred at 35 °C for 30 mins, the solution of aromatic aldehyde **3** (0.2 mmol) in the mixed toluene/1,4-dioxane (1:1 v/v, 0.5 mL) was added. In some cases as indicated in Table 3, toluene was used as solvent and the ratio of **1**:**2**:**3** was changed to 3.5:1:3.5. After being stirred at 35 °C for 84 h, the reaction mixture was filtered to remove molecular sieves and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under reduced pressure to give a residue, which was purified through flash column chromatography on silica gel to afford pure product **5**.

(2*R*,6*S*)-Methyl 2,6-bis(4-bromophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5aaa): Flash column chromatography eluent, petroleum ether/ethyl acetate = 18/1; reaction time = 84 h; yield: 40.0 mg (59%); 90:10 *dr*; white solid; mp 215–217 °C; $[\alpha]_D^{20}$: +43.0 (c 0.27, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 10.09$ (s, 1H), 7.41–7.36 (m, 4H), 7.15 (d, J = 8.3 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.70–6.64 (m, 4H), 6.40–6.32 (m, 4H), 6.19 (s, 1H), 4.96–4.94 (m, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.67 (s, 3H), 2.72 (dd, J = 15.3, 5.6 Hz, 1H), 2.61 (dd, J = 15.3, 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 168.3$, 158.0, 156.6, 151.4, 143.1, 141.9, 140.9, 131.6, 131.2, 130.4, 128.6, 128.3, 127.7, 120.8, 120.1, 114.6, 114.4, 114.1, 96.4, 57.3, 55.6, 55.6, 55.4, 51.0, 33.6; IR (KBr): ν = 3364, 3261, 3046, 2924, 2852, 1726, 1656, 1605, 1510, 1485, 1458, 1402, 1245, 1182, 1071, 1038, 1010, 979, 927, 883, 811, 736 cm^{-1}; ESI-FT-MS: m/z = 677.0652, calcd. for $(C_{33}H_{30}Br_2N_2O_4+H)^+$: 677.0651. Enantiomeric ratio: 93:7, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol = 90/10, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 9.488 min (major), t_R = 30.581 min (minor).

(2*R*,6*S*)-Methyl 2,6-bis(4-bromophenyl)-1-(4-ethoxyphenyl)-4-(4-ethoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5baa): Flash column chromatography eluent, petroleum ether/ethyl acetate = 25/1; reaction time = 84 h; yield: 36.7 mg (52%); 76:24 *dr*; white solid; mp 213–215 °C; $[\alpha]_D^{20}$: +38.7 (*c* 0.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 10.08 (s, 1H), 7.39–7.36 (m, 4H), 7.14 (d, J = 8.2 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.68–6.64 (m, 4H), 6.37–6.31 (m, 4H), 6.19 (s, 1H), 4.95–4.94 (m, 1H), 3.97 (q, J = 7.0 Hz, 2H), 3.90–3.85 (m, 5H), 2.71 (dd, J = 15.3, 5.6 Hz, 1H), 2.61 (dd, J = 15.3, 3.0 Hz, 1H), 1.40 (t, J = 7.0 Hz, 3H), 1.32 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 168.3$, 157.4, 156.7, 150.7, 143.2, 142.0, 140.9, 131.6, 131.2, 130.2, 128.6, 128.3, 127.7, 120.8, 120.1, 115.3, 114.6, 114.5, 96.4, 63.8, 63.6, 57.3, 55.6, 51.0, 33.5, 14.9, 14.7; IR (KBr): ν = 3362, 3241, 3166, 3046, 2978, 2854, 1727, 1656, 1605, 1510, 1481, 1454, 1397, 1242, 1186, 1113, 1070, 1048, 1009, 979, 808, 736 cm^{-1}; ESI-FT-MS: m/z = 705.0953, calcd. for $(C_{35}H_{34}Br_2N_2O_4+H)^+$: 705.0964. Enantiomeric ratio: 87:13, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 5.997 min (major), t_R = 14.421 min (minor).

(2*R*,6*S*)-Methyl 2,6-bis(4-bromophenyl)-1-(4-phenoxyphenyl)-4-(4-phenoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5caa): Flash column chromatography eluent, petroleum ether/ethyl acetate = 28/1; reaction time = 84 h; yield: 50.1 mg (62%); 76:24 *dr*; white solid; mp 99–101 °C; $[\alpha]_D^{20}$: +26.7 (*c* 0.3, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 10.16 (s, 1H), 7.40 (dd, J = 8.4, 1.7 Hz, 4H), 7.36–7.32 (m, 2H), 7.25–7.22 (m, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H), 7.04–6.96 (m, 5H), 6.88–6.86 (m, 2H), 6.80–6.76 (m, 4H), 6.40 (d, J = 9.2 Hz, 2H), 6.36 (d, J = 8.7 Hz, 2H), 6.27 (s, 1H), 5.04–5.03 (m, 1H), 3.91 (s, 3H), 2.79 (dd, J = 15.2, 5.6 Hz, 1H), 2.69 (dd, J = 15.2, 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.2, 157.5, 155.7, 155.1, 154.6, 146.4, 142.0, 141.7, 140.5, 131.61, 130.7, 130.3, 128.8, 128.4, 127.4, 127.1, 126.6, 122.6, 121.1, 120.0, 119.5, 119.3, 118.2, 117.9, 116.4, 112.9, 96.0, 56.5, 54.2, 50.1, 32.5; IR (KBr): ν = 3439, 3244, 3044, 2921, 2851, 1720, 1656, 1601, 1506, 1487, 1459, 1403, 1370, 1317, 1239, 1187, 1107, 1071, 1010, 978, 864, 817, 791, 750, 692 cm^{-1}; ESI- FT-MS: m/z = 801.0953, calcd. for $(C_{43}H_{34}Br_2N_2O_4+H)^+$: 801.0964. Enantiomeric ratio: 83:17, determined by HPLC (Daicel

Chirapak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 6.454 min (major), t_R = 13.696 min (minor).

(2*R*,6*S*)-Methyl 1-(benzo[*d*][1,3]dioxol-5-yl)-4-(benzo[*d*]-[1,3]dioxol-5-ylamino)-2,6-bis(4-bromophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (5daa): Flash column chromatography eluent, petroleum ether/ethyl acetate = 23/1; reaction time = 84 h; yield: 33.2 mg (47%); 79:21 *dr*; white solid; mp 222–224 °C; $[\alpha]_D^{20}$: +23.5 (*c* 0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.04 (s, 1H), 7.39 (t, J = 8.3 Hz, 4H), 7.13 (d, J = 8.3 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.55 (dd, J = 10.6, 8.3 Hz, 2H), 6.16 (s, 1H), 6.09 (d, J = 2.5 Hz, 1H), 5.94 (dd, J = 5.2, 1.4 Hz, 2H), 5.83–5.82 (m, 3H), 5.78 (dd, J = 5.5, 1.4 Hz, 2H), 4.95–4.94 (m, 1H), 3.89 (s, 3H), 2.73 (dd, J = 15.3, 5.6 Hz, 1H), 2.63 (dd, J = 15.3, 2.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.2, 156.4, 148.2, 147.8, 146.1, 142.8, 142.5, 141.6, 139.0, 131.7, 131.4, 131.2, 128.5, 128.2, 121.0, 120.2, 119.7, 108.3, 107.9, 107.8, 105.4, 101.5, 100.5, 96.7, 96.3, 57.7, 55.8, 51.0, 33.6; IR (KBr): ν = 3360, 3246, 3168, 3050, 2922, 2854, 1729, 1657, 1598, 1488, 1455, 1401, 1372, 1323, 1253, 1184, 1100, 1068, 1038, 1010, 976, 932, 894, 847, 814, 736 cm^{-1}; ESI-FT-MS: m/z = 705.0229, calcd. for $(C_{33}H_{26}Br_2N_2O_6+H)^+$: 705.0236. Enantiomeric ratio: 88:12, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 8.111 min (major), t_R = 16.123 min (minor).

(2*R*,6*S*)-Methyl 2,6-bis(4-bromophenyl)-1-*p*-tolyl-4-(*p*-tolylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5eaa): Flash column chromatography eluent, petroleum ether/ethyl acetate = 85/1; reaction time = 84 h; yield: 37.5 mg (58%); 84:16 *dr* (inseparable diastereomers); yellow solid; mp 207–209 °C; $[\alpha]_D^{20}$: +17.5 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.16 (s, 1H), 7.40–7.37 (m, 4H), 7.17 (d, J = 8.2 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 6.36 (d, J = 8.7 Hz, 2H), 6.29–6.27 (m, 3H), 5.04–5.03 (m, 1H), 3.91 (s, 3H), 2.77 (dd, J = 15.2, 5.5 Hz, 1H), 2.70 (dd, J = 15.2, 2.8 Hz, 1H), 2.29 (s, 3H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.3, 156.3, 144.3, 143.2, 141.7, 136.0, 134.9, 131.6, 131.3, 129.6, 128.4, 128.2, 125.9, 125.8, 123.0, 120.8, 120.1, 112.9, 96.9, 57.3, 54.9, 51.0, 33.5, 20.9, 20.1; IR (KBr): ν = 3358, 3243, 3169, 3051, 2955, 2924, 2853, 2219, 1728, 1658, 1599, 1511, 1487, 1457, 1403, 1372, 1325, 1178, 1104, 1070, 1033, 1010, 977, 885, 811, 736 cm^{-1}; ESI-FT-MS: m/z = 645.0757, calcd. for $(C_{33}H_{30}Br_2N_2O_2+H)^+$: 645.0752. Enantiomeric ratio: 90:10, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol = 85/15, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 4.789 min (major), t_R = 9.925 min (minor).

(2*R*,6*S*)-Methyl 2,6-bis(4-bromophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5faa): Flash column chromatography eluent, petroleum ether/ethyl acetate = 50/1; reaction time = 84 h; yield: 31.4 mg (51%); 85:15 *dr*; white solid; mp 236–237 °C; $[\alpha]_D^{20}$: +12.5 (*c* 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.24 (s, 1H), 7.40–7.38 (m, 4H), 7.19–7.13 (m, 5H), 7.10–7.06 (m, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.65 (t, J = 7.3 Hz, 1H), 6.45 (d, J = 8.1 Hz, 2H), 6.42–6.40 (m, 2H), 6.33 (s, 1H), 5.08–5.07 (m, 1H), 3.92 (s, 3H), 2.82 (dd, J = 15.2, 5.5 Hz, 1H), 2.74 (dd, J = 15.2, 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.2, 156.0, 146.4, 142.9, 141.4, 137.6, 131.7, 131.3, 129.0, 129.0, 128.4, 128.1, 126.0, 125.7, 120.9, 120.2, 116.8, 112.9, 97.4, 57.4, 54.8, 51.1, 33.6; IR (KBr): ν = 3437, 2972, 2918, 2877, 1654, 1609, 1504, 1437, 1408, 1317, 1256, 1182, 1022, 952, 881, 788, 741 cm^{-1}; ESI-FT-MS: m/z = 617.0434, calcd. for $(C_{31}H_{26}Br_2N_2O_2+H)^+$: 617.0439. Enantiomeric ratio: 90:10, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol = 95/5, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 7.655 min (major), t_R = 15.961 min (minor).

(2*R*,6*S*)-Methyl 2,6-bis(4-bromophenyl)-1-(4-fluorophenyl)-4-(4-fluorophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5gaa): Flash column chromatography eluent, petroleum ether/ethyl acetate = 50/1; reaction time = 84 h; yield: 38.3 mg (59%); 79:21 *dr*; pale yellow solid; mp 221–223 °C; $[\alpha]_D^{20}$: +33.4 (*c* 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.14 (s, 1H), 7.42–7.39 (m, 4H), 7.13 (d, J = 8.2 Hz, 2H), 6.99 (d, J = 8.2 Hz, 2H), 6.89–6.83 (m, 2H), 6.81–6.75 (m, 2H), 6.38–6.33 (m, 4H), 6.23 (s, 1H), 5.00–4.99 (m, 1H), 3.91 (s, 3H), 2.77 (dd, J = 15.3, 5.7 Hz, 1H), 2.61 (dd, J = 15.3, 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.2, 160.9 (J = 245.0 Hz), 155.9, 155.4 (J = 234.8 Hz), 154.2, 142.9, 142.5, 141.4, 133.5, 133.5, 131.8, 131.4, 128.4, 128.1, 128.0, 127.9, 121.1, 120.4, 116.0, 115.7, 115.5, 115.3, 113.9, 113.8, 97.3, 57.5, 55.4, 51.2, 33.5; IR (KBr): ν = 3361, 3241, 3167, 3052, 2951, 2923, 2852, 1721, 1658, 1610, 1509, 1457, 1402, 1370, 1319, 1258, 1186, 1071, 1010, 979, 953, 927, 887, 846, 809, 737 cm^{-1}; ESI-FT-MS: m/z = 653.0250, calcd. for $(C_{31}H_{24}Br_2F_2N_2O_2+H)^+$: 653.0251. Enantiomeric ratio: 84:16, determined by HPLC (Daicel Chirapak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 5.157 min (major), t_R = 10.597 min (minor).

(2*R*,6*S*)-Methyl 2,6-bis(4-bromophenyl)-1-(3-fluorophenyl)-4-(3-fluorophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5haa): Flash column chromatography eluent, petroleum ether/ethyl acetate = 70/1; reaction time = 84 h; yield: 38.2 mg (58%); 89:11 *dr*; white solid; mp 199–201 °C; $[\alpha]_D^{20}$: +8.3 (*c* 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.25 (s, 1H), 7.41 (dd, J = 8.5, 2.8 Hz, 4H), 7.15–7.12 (m, 3H), 7.03–6.98 (m, 3H), 6.83 (td, J = 8.3, 2.1 Hz, 1H), 6.35 (td, J = 8.2, 2.0 Hz, 1H), 6.28 (s, 1H), 6.23–6.20 (m, 2H), 6.15 (dt, J = 12.8, 2.3 Hz, 1H), 6.09 (dt, J = 9.7, 2.2 Hz, 1H), 5.07 (d, J = 3.5 Hz, 1H), 3.94 (s, 3H), 2.85 (dd, J = 15.2, 5.6 Hz, 1H), 2.76 (dd, J = 15.3, 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.1, 164.5 (J = 109.7 Hz), 162.0 (J = 115.4 Hz), 155.0, 148.2, 148.1, 142.0, 140.7, 139.2, 139.1, 131.9, 131.5, 130.2, 130.1, 130.0, 128.2, 127.9, 121.3, 121.0, 121.0, 120.6, 113.0, 112.8, 112.7, 112.5, 108.6, 103.6, 103.4, 100.3, 100.0, 98.3, 57.6, 55.0, 51.3, 33.5; IR (KBr): ν = 3440, 2920, 2853, 1724, 1659, 1602, 1490, 1443, 1403, 1370, 1334, 1257, 1187, 1162, 1118, 1072, 1010, 978, 955, 846, 817, 790, 752 cm^{-1}; ESI-FT-MS: m/z = 653.0243, calcd. for $(C_{31}H_{24}Br_2F_2N_2O_2+H)^+$: 653.0251. Enantiomeric ratio: 89:11, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 4.715 min (major), t_R = 7.309 min (minor).

(2*R*,6*S*)-Methyl 2,6-bis(4-bromophenyl)-1-(4-cyanophenyl)-4-(4-cyanophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5iaa): Flash column chromatography eluent, petroleum ether/ethyl acetate = 6/1; reaction time = 84 h; yield: 28.5 mg (43%); > 99:1 *dr*; white solid; mp 248–250 °C; $[\alpha]_D^{20}$: −54.8 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.46 (s, 1H), 7.48–7.41 (m, 6H), 7.34 (d, J = 9.1 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 6.95 (d, J = 8.4 Hz, 2H), 6.50 (dd, J = 18.8, 8.8 Hz, 4H), 6.35 (s, 1H), 5.17–5.16 (m, 1H), 3.97 (s, 3H),

2.98 (dd, $J=15.3$, 5.6 Hz, 1H), 2.83 (dd, $J=15.3$, 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=167.8$, 153.4, 149.1, 141.7, 140.7, 139.4, 133.4, 133.2, 132.2, 131.8, 127.9, 127.7, 124.0, 121.8, 121.1, 119.8, 118.2, 113.0, 108.6, 100.5, 99.5, 57.5, 55.0, 51.8, 33.7; IR (KBr): $\nu=3356$, 3242, 3170, 3053, 2954, 2925, 2853, 2219, 1726, 1659, 1599, 1485, 1457, 1403, 1372, 1330, 1255, 1177, 1106, 1070, 1034, 1011, 976, 885, 813, 736 cm^{-1}; ESI-FT-MS: $m/z=667.0338$, calcd. for $(C_{33}H_{24}Br_2N_4O_2+H)^+$: 667.0344. Enantiomeric ratio: 87:13, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol=70/30, flow rate 1.0 mL min^{-1}, $T=30$ °C, 254 nm): $t_R=8.574$ min (major), $t_R=25.736$ min (minor).

(2*R*,6*S*)-Methyl 2,6-bis(4-fluorophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5aab): Flash column chromatography eluent, petroleum ether/ethyl acetate=17/1; reaction time=84 h; yield: 32.3 mg (58%); 79:21 *dr*; white solid; mp 224–226 °C; $[\alpha]_D^{20}$: +57.5 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=10.12$ (s, 1H), 7.23 (dd, $J=8.4$, 5.5 Hz, 2H), 7.11–7.08 (m, 2H), 7.00–6.93 (m, 4H), 6.68–6.65 (m, 4H), 6.41–6.33 (m, 2H), 6.35–6.33 (m, 2H), 6.23 (s, 1H), 5.00–4.98 (m, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 3.67 (s, 3H), 2.73 (dd, $J=15.3$, 5.6 Hz, 1H), 2.62 (dd, $J=15.3$, 3.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=168.4$, 162.9 ($J=44.6$ Hz), 160.5 ($J=43.7$ Hz), 157.9, 156.8, 151.3, 141.1, 139.6, 138.5, 130.5, 128.3, 128.2, 128.1, 128.0, 127.7, 115.5, 115.3, 114.9, 114.7, 114.5, 114.1, 96.7, 57.2, 55.6, 55.4, 55.4, 50.9, 33.7; IR (KBr): $\nu=3250$, 3048, 2996, 2924, 2851, 1732, 1654, 1605, 1509, 1457, 1415, 1373, 1243, 1182, 1158, 1070, 1036, 981, 830 cm^{-1}; ESI-FT-MS: $m/z=557.2256$, calcd. for $(C_{33}H_{30}F_2N_2O_4+H)^+$: 557.2252. Enantiomeric ratio: 89:11, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol=80/20, flow rate 1.0 mL min^{-1}, $T=30$ °C, 254 nm): $t_R=6.381$ min (major), $t_R=24.121$ min (minor).

(2*R*,6*S*)-Methyl 2,6-bis(4-chlorophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5aac): Flash column chromatography eluent, petroleum ether/ethyl acetate=23/1; reaction time=84 h; yield: 29.3 mg (50%); 77:23 *dr*; white solid; mp 206–208 °C; $[\alpha]_D^{20}$: +31.4 (*c* 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=10.10$ (s, 1H), 7.26–7.21 (m, 6H), 7.05 (d, $J=8.4$ Hz, 2H), 6.69–6.65 (m, 4H), 6.39–6.33 (m, 4H), 6.21 (s, 1H), 5.00–4.96 (m, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.67 (s, 3H), 2.73 (dd, $J=15.3$, 5.6 Hz, 1H), 2.62 (dd, $J=15.3$, 3.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=168.4$, 158.0, 156.6, 151.4, 142.6, 141.4, 140.9, 132.7, 132.0, 130.4, 128.7, 128.2, 128.2, 127.9, 127.7, 114.6, 114.5, 114.1, 96.5, 57.3, 55.6, 55.5, 55.4, 51.0, 33.6; IR (KBr): $\nu=3362$, 3244, 3168, 3047, 2993, 2922, 2850, 1726, 1656, 1603, 1510, 1487, 1459, 1405, 1371, 1245, 1183, 1070, 1037, 1012, 979, 888, 812, 736 cm^{-1}; ESI-FT-MS: $m/z=589.1657$, calcd. for $(C_{33}H_{30}Cl_2N_2O_4+H)^+$: 589.1661. Enantiomeric ratio: 90:10, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol=70/30, flow rate 1.0 mL min^{-1}, $T=30$ °C, 254 nm): $t_R=6.037$ min (major), $t_R=14.435$ min (minor).

(2*R*,6*S*)-Methyl 2,6-bis(4-cyanophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5aad): Flash column chromatography eluent, petroleum ether/ethyl acetate=6/1; reaction time=84 h; yield: 62.8 mg (63%); 76:24 *dr* (inseparable diastereomers); yellow solid; mp 123–125 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=10.51$ (s, 0.3H), 10.11 (s, 1H), 7.63–7.62 (m, 1H), 7.58–7.54 (m, 5H), 7.45 (d, $J=8.4$ Hz, 0.8H), 7.40 (d, $J=8.2$ Hz, 2H), 7.31 (d, $J=8.3$ Hz, 0.8H), 7.23 (d, $J=8.2$ Hz, 2H), 7.00–6.95 (m, 1H), 6.86–6.83 (m, 1H), 6.70–6.61 (m, 5.5H), 6.36–6.28 (m, 5H), 5.59 (s, 0.3H), 5.07–5.05 (m, 1H), 4.48 (dd, $J=11.7$, 3.0 Hz, 0.3H), 3.90 (s, 3H), 3.78 (s, 1H), 3.77 (s, 3H), 3.68 (s, 1H), 3.67 (s, 3H), 3.64 (s, 1H), 2.76–2.65 (m, 2H), 2.64–2.61 (m, 0.4H), 2.48–2.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=168.6$, 168.1, 158.2, 157.8, 157.7, 157.2, 157.1, 156.7, 156.2, 155.96, 154.8, 152.3, 152.1, 151.9, 149.9, 149.7, 148.7, 148.3, 148.1, 143.6, 141.9, 140.2, 133.0, 132.4, 132.4, 132.2, 132.1, 132.0, 131.2, 130.8, 130.1, 129.9, 129.2, 128.4, 128.1, 128.0, 127.9, 127.5, 127.5, 127.4, 126.8, 126.5, 123.6, 122.0, 120.6, 119.0, 118.9, 118.8, 118.7, 118.5, 118.5, 114.7, 114.6, 114.5, 114.3, 114.2, 111.3, 111.2, 110.4, 95.7, 94.8, 64.2, 61.9, 57.5, 56.0, 55.6, 55.4, 55.37, 51.2, 50.8, 36.4, 33.4; IR (KBr): $\nu=3358$, 3243, 3167, 3051, 2927, 2840, 2227, 1728, 1653, 1605, 1510, 1457, 1407, 1369, 1246, 1179, 1160, 1109, 1069, 1036, 979, 954, 893, 810, 736 cm^{-1}; ESI FT-MS: $m/z=571.2339$, calcd. for $(C_{35}H_{30}N_4O_4+H)^+$: 571.2345. Enantiomeric ratio: 90:10, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol=70/30, flow rate 1.0 mL min^{-1}, $T=30$ °C, 254 nm): $t_R=10.681$ min (major), $t_R=47.932$ min (minor).

Dimethyl 4,4′-[(2*S*,6*R*)-5-(methoxycarbonyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,3,6-tetrahydropyridine-2,6-diyl]dibenzoate (5aae): Flash column chromatography eluent, petroleum ether/ethyl acetate=6/1; reaction time=84 h; yield: 37.7 mg (59%); 77:23 *dr*; yellow solid; mp 207–209 °C; $[\alpha]_D^{20}$: +13.3 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=10.09$ (s, 1H), 7.95 (dd, $J=8.4$, 3.2 Hz, 4H), 7.37 (d, $J=8.2$ Hz, 2H), 7.22 (d, $J=8.3$ Hz, 2H), 6.64 (d, $J=8.3$ Hz, 4H), 6.37–6.27 (m, 5H), 5.09–5.08 (m, 1H), 3.92–3.90 (m, 9H), 3.75 (s, 3H), 3.65 (s, 3H), 2.77 (dd, $J=15.4$, 5.7 Hz, 1H), 2.68 (dd, $J=15.4$, 2.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=168.3$, 167.0, 166.9, 158.0, 156.5, 151.5, 149.7, 148.3, 140.9, 130.3, 129.9, 129.6, 129.1, 128.4, 127.7, 126.7, 126.6, 114.6, 114.4, 114.1, 96.2, 57.8, 56.1, 55.6, 55.4, 52.1, 52.0, 51.0, 33.4; IR (KBr): $\nu=3243$, 3166, 3049, 2995, 2950, 2845, 1721, 1656, 1605, 1511, 1437, 1412, 1373, 1280, 1246, 1185, 1108, 1071, 1036, 976, 931, 871, 838, 8167, 735, 707 cm^{-1}; ESI-FT-MS: $m/z=637.2550$, calcd. for $(C_{37}H_{36}N_2O_8+H)^+$: 637.255. Enantiomeric ratio: 87:13, determined by HPLC (Daicel Chirapak OD-H, hexane/2-propanol=85/15, flow rate 1.0 mL min^{-1}, $T=30$ °C, 254 nm): $t_R=14.164$ min (major), $t_R=17.111$ min (minor).

(2*R*,6*S*)-Methyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-bis(3-nitrophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (5aag): Flash column chromatography eluent, petroleum ether/ethyl acetate=7/1; reaction time=84 h; yield: 36.5 mg (60%); 76:24 *dr* (inseparable diastereomers); yellow solid; mp 98–100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=10.56$ (s, 0.3H), 10.16 (s, 1H), 8.28–8.27 (m, 0.3H), 8.17–8.16 (m, 1H), 8.12–8.07 (m, 3H), 7.95–7.94 (m, 1H), 7.76 (d, $J=7.7$ Hz, 0.3H), 7.62 (d, $J=7.7$ Hz, 1H), 7.56 (d, $J=7.8$ Hz, 0.3H), 7.50 (d, $J=7.9$ Hz, 0.3H), 7.47–7.42 (m, 3H), 7.32 (t, $J=7.9$ Hz, 0.3H), 7.03–7.01 (m, 1H), 6.87–6.84 (m, 1H), 6.76–6.72 (m, 1.5H), 6.68–6.62 (m, 5H), 6.41–6.35 (m, 4H), 6.31 (s, 1H), 5.59 (s, 0.3H), 5.18 (t, $J=4.3$ Hz, 1H), 4.56 (dd, $J=11.0$, 3.4 Hz, 0.3H), 3.92 (s, 3H), 3.78 (s, 1H), 3.75 (s, 3H), 3.74 (s, 1H), 3.67 (s, 3H), 3.64 (s, 1H), 2.82–2.72 (m, 2H), 2.70–2.54 (m, 0.8H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=168.6$, 168.2, 168.1, 158.3, 157.8, 157.0, 156.1,

155.2, 152.2, 148.9, 148.5, 148.3, 146.4, 144.8, 144.7, 143.4, 140.1, 139.9, 134.2, 133.4, 132.8, 130.8, 129.9, 129.5, 129.4, 129.1, 128.9, 127.6, 126.7, 123.0, 122.6, 122.5, 122.3, 121.7, 121.7, 121.6, 116.4, 115.3, 114.8, 114.8, 114.8, 114.6, 114.2, 95.6, 95.0, 94.6, 77.3, 77.2, 77.0, 76.7, 64.2, 61.7, 56.9, 56.3, 55.7, 55.7, 55.5, 55.4, 55.3, 55.3, 51.2, 51.0, 50.8, 36.2, 36.0, 33.7; IR (KBr): ν = 3359, 3243, 3166, 3067, 2998, 2925, 2851, 1725, 1658, 1607, 1512, 1460, 1348, 1245, 1185, 1129, 1072, 1035, 985, 946, 908, 809, 735 cm^{-1}; ESI-FT-MS: m/z = 611.2139, calcd. for $(C_{33}H_{30}N_4O_8+H)^+$: 611.2142. Enantiomeric ratio: 84:16, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 10.436 min (major), t_R = 33.810 min (minor).

(2*R*,6*S*)-Methyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (5aah): Flash column chromatography eluent, petroleum ether/ethyl acetate = 23/1; reaction time = 84 h; yield: 24 mg (46%); 78:22 *dr*; yellow solid; mp 228–229 °C; $[\alpha]_D^{20}$: +103.5 (*c* 0.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.09 (s, 1H), 7.29–7.25 (m, 6H), 7.17–7.15 (m, 4H), 6.66–6.59 (m, 4H), 6.44–6.42 (m, 2H), 6.33 (s, 1H), 6.21–6.18 (m, 2H), 5.05–5.04 (m, 1H), 3.90 (s, 3H), 3.74 (s, 3H), 3.65 (s, 3H), 2.79 (dd, J = 15.2, 5.8 Hz, 1H), 2.63 (dd, J = 15.2, 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.6, 157.8, 157.0, 150.9, 144.2, 143.2, 141.5, 130.6, 128.6, 128.1, 127.8, 127.0, 126.7, 126.5, 126.2, 114.5, 114.0, 113.9, 97.0, 58.2, 55.7, 55.6, 55.3, 50.8, 33.5; IR (KBr): ν = 3244, 3057, 3028, 2996, 2922, 2851, 1736, 1653, 1597, 1508, 1455, 1374, 1319, 1245, 1178, 1106, 1070, 1034, 980, 833, 808, 746 cm^{-1}; ESI-FT-MS: m/z = 521.2437, calcd. for $(C_{33}H_{32}N_2O_4+H)^+$:521.244. Enantiomeric ratio: 89:11, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 6.405 min (major), t_R = 29.936 min (minor).

(2*R*,6*S*)-Methyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-di-*p*-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (5aai): Flash column chromatography eluent, petroleum ether/ethyl acetate = 21/1; reaction time = 84 h; yield: 28.1 mg (51%); 82:18 *dr*; yellow solid; mp 197–198 °C; $[\alpha]_D^{20}$: +80.9 (*c* 0.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.09 (s, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.09–7.03 (m, 6H), 6.67–6.59 (m, 4H), 6.45–6.43 (m, 2H), 6.27 (s, 1H), 6.22 (d, J = 8.7 Hz, 2H), 5.01–5.00 (m, 1H), 3.89 (s, 3H), 3.75 (s, 3H), 3.66 (s, 3H), 2.78 (dd, J = 15.1, 5.7 Hz, 1H), 2.63 (d, J = 15.1, 2.8 Hz, 1H), 2.34 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.7, 157.7, 157.0, 150.8, 141.7, 141.29, 140.1, 136.5, 135.6, 130.8, 129.2, 128.8, 127.8, 126.7, 126.4, 114.5, 114.0, 113.9, 97.1, 57.9, 55.7, 55.5, 55.4, 50.8, 33.6, 21.1, 21.0; IR (KBr): ν = 3366, 3248, 3045, 2922, 2851, 1729, 1654, 1606, 1510, 1458, 1411, 1372, 1245, 1182, 1108, 1070, 1036, 980, 928, 810, 736 cm^{-1}; ESI-FT-MS: m/z = 549.2751, calcd. for $(C_{35}H_{36}N_2O_4+H)^+$: 549.2753. Enantiomeric ratio: 87:13, determined by HPLC (Daicel Chirapak IA, hexane/2-propanol = 85/15, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 8.004 min (major), t_R = 18.534 min (minor).

(2*R*,6*S*)-Methyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-di-*m*-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (5aaj): Flash column chromatography eluent, petroleum ether/ethyl acetate = 23/1; reaction time = 84 h; yield: 23.1 mg (42%); 81:19 *dr*; yellow solid; mp 189–191 °C; $[\alpha]_D^{20}$: +115.3 (*c* 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.06 (s, 1H), 7.18–7.11 (m, 3H), 7.06 (d, J = 7.6 Hz, 2H), 7.01 (d, J = 7.3 Hz, 1H), 6.97–6.94 (m, 2H), 6.67–6.60 (m, 4H), 6.46–6.42 (m, 2H), 6.29 (s, 1H), 6.21–6.17 (m, 2H), 5.01–5.00 (m, 1H), 3.91 (s, 3H), 3.75 (s, 3H), 3.66 (s, 3H), 2.80 (dd, J = 15.1, 5.8 Hz, 1H), 2.61 (dd, J = 15.1, 2.7 Hz, 1H), 2.32 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.6, 157.8, 157.1, 150.8, 144.3, 143.2, 141.7, 138.0, 137.7, 130.7, 128.4, 128.0, 127.9, 127.8, 127.4, 127.1, 127.0, 123.8, 123.7, 114.4, 114.0, 113.8, 97.0, 58.2, 55.7, 55.7, 55.3, 50.8, 33.6, 21.8, 21.5; IR (KBr): ν = 3244, 3168, 3043, 2993, 2921, 2852, 1730, 1653, 1605, 1511, 1459, 1371, 1243, 1183, 1071, 1037, 838, 810, 778, 735 cm^{-1}; ESI-FT-MS: m/z = 549.2749, calcd. for $(C_{35}H_{36}N_2O_4+H)^+$: 549.2753. Enantiomeric ratio: 90:10, determined by HPLC (Daicel Chirapak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 4.569 min (major), t_R = 6.521 min (minor).

(2*R*,6*S*)-Methyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5fak): Flash column chromatography eluent, petroleum ether/ethyl acetate = 20/1; reaction time = 84 h; yield: 19.8 mg (38%); 86:14 *dr*; white solid; mp 163–165 °C; $[\alpha]_D^{20}$: +102.6 (*c* 0.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.26 (s, 1H), 7.21 (d, J = 8.5 Hz, 2H), 7.14–7.04 (m, 7H), 6.81 (dd, J = 8.7, 1.2 Hz, 4H), 6.60 (t, J = 7.2 Hz, 1H), 6.52 (d, J = 8.1 Hz, 2H), 6.37–6.35 (m, 3H), 5.08–5.07 (m, 1H), 3.92 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 2.85 (dd, J = 15.0, 5.5 Hz, 1H), 2.75 (dd, J = 15.0, 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.6, 158.7, 158.0, 156.3, 147.0, 137.9, 135.8, 134.6, 128.8, 128.8, 127.7, 127.5, 125.8, 125.6, 116.0, 114.0, 113.5, 112.9, 98.1, 57.5, 55.3, 55.2, 54.5, 50.9, 33.7; IR (KBr): ν = 3244, 3058, 3031, 2997, 2949, 2850, 1732, 1654, 1593, 1503, 1447, 1373, 1323, 1249, 1174, 1110, 1071, 1033, 981, 951, 852, 828, 793, 746, 694 cm^{-1}; ESI-FT-MS: m/z = 521.2441, calcd. for $(C_{33}H_{32}N_2O_4+H)^+$: 521.244. Enantiomeric ratio: 90:10, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 5.124 min (major), t_R = 14.636 min (minor).

(2*R*,6*S*)-Methyl 1-phenyl-4-(phenylamino)-2,6-di-*p*-tolyl-1,2,5,6-tetrahydropyridine-3-carboxylate (5fai): Flash column chromatography eluent, petroleum ether/ethyl acetate = 70/1; reaction time = 84 h; yield: 33.3 mg (68%); 86:14 *dr* (inseparable diastereomers); yellow solid; mp 183–185 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.54 (s, 0.2H), 10.17 (s, 1H), 7.44 (d, J = 7.7 Hz, 0.4H), 7.22–7.18 (m, 1H), 7.15–7.10 (m, 3H), 7.06–6.88 (m, 12H), 6.77 (d, J = 8.1 Hz, 0.4H), 6.63 (t, J = 7.2 Hz, 0.2H), 6.51 (t, J = 7.2 Hz, 1H), 6.45 (d, J = 8.1 Hz, 2H), 6.32 (s, 1H), 6.24–6.21 (m, 2H), 6.07 (s, 0.2H), 5.03–5.02 (m, 1H), 4.45 (dd, J = 12.6, 3.5 Hz, 0.2H), 3.84 (s, 3H), 3.65 (s, 0.5H), 2.79 (dd, J = 15.1, 5.6 Hz, 1H), 2.68 (dd, J = 15.1, 2.5 Hz, 1H), 2.43–2.34 (m, 0.3H), 2.31 (s, 0.5H), 2.26 (s, 3H), 2.24 (s, 3H), 2.16 (s, 0.5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.5, 155.2, 146.0, 139.9, 138.6, 136.9, 135.5, 134.7, 128.2, 127.9, 127.8, 127.7, 125.5, 125.2, 124.7, 124.5, 114.9, 111.8, 97.1, 56.8, 53.9, 49.9, 32.6, 20.0, 19.9; IR (KBr): ν = 3244, 3170, 3089, 3024, 2922, 2854, 1729, 1656, 1594, 1500, 1444, 1372, 1319, 1255, 1186, 1119, 1073, 1037, 982, 950, 924, 852, 813, 788, 743, 695 cm^{-1}; ESI-FT-MS: m/z = 489.2534, calcd. for $(C_{33}H_{32}N_2O_2+H)^+$: 489.2542. Enantiomeric ratio: 86:14, determined by HPLC (Daicel Chirapak IA, hexane/2-propanol = 85/15, flow rate

1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 5.888 min (major), t_R = 9.910 min (minor).

(2*R*,6*S*)-Methyl 2,6-bis(3,4-difluorophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5aaf): Flash column chromatography eluent, petroleum ether/ethyl acetate = 18/1; reaction time = 84 h; yield: 38.4 mg (65%); 67:33 *dr*; white solid; mp 142–143 °C; $[\alpha]_D^{20}$: +15.3 (*c* 0.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.14 (s, 1H), 7.11–6.99 (m, 3H), 6.96–6.88 (m, 2H), 6.85–6.82 (m, 1H), 6.72–6.65 (m, 4H), 6.43–6.37 (m, 4H), 6.17 (s, 1H), 4.96–4.94 (m, 1H), 3.89 (s, 3H), 3.77 (s, 3H), 3.68 (s, 3H), 2.73 (dd, J = 15.4, 5.5 Hz, 1H), 2.64 (dd, J = 15.4, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.2, 157.6 (J = 110.4 Hz), 151.7, 140.5, 140.4 (J = 130.2 Hz), 130.3, 127.7, 117.1 (J = 17.1 Hz), 115.7 (J = 17.4 Hz), 114.7, 114.6, 114.2, 96.0, 56.8, 55.6, 55.4, 51.1, 33.5; IR (KBr): ν = 3243, 3169, 3050, 2994, 2918, 2845, 1730, 1656, 1607, 1511, 1455, 1430, 1370, 1275, 1186, 1106, 1070, 1037, 986, 934, 883, 800, 776, 737 cm^{-1}; ESI-FT-MS: m/z = 593.2049, calcd. for $(C_{33}H_{28}F_4N_2O_4+H)^+$: 593.2063. Enantiomeric ratio: 84:16, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 5.439 min (major), t_R = 10.193 min (minor).

(2*S*,6*S*)-Methyl 1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-2,6-di(thiophen-2-yl)-1,2,5,6-tetrahydropyridine-3-carboxylate (5aal): Flash column chromatography eluent, petroleum ether/ethyl acetate = 20/1; reaction time = 84 h; yield: 20.0 mg (38%); 76:24 *dr* (inseparable diastereomers); yellow solid; mp 226–228 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.42 (s, 0.3H), 10.28 (s, 1H), 7.23 (d, J = 5.1 Hz, 0.4H), 7.13–7.11 (m, 2H), 7.07 (dd, J = 5.0, 1.1 Hz, 0.4H), 7.02–7.00 (m, 0.4H), 6.96–6.91 (m, 1.5H), 6.89–6.72 (m, 11.6H), 6.68–6.55 (m, 2H), 6.25 (s, 1H), 5.94 (s, 0.3H), 5.25 (t, J = 4.5 Hz, 1H), 4.78 (t, J = 7.7 Hz, 0.3H), 3.86 (s, 3H), 3.78 (s, 1H), 3.77 (s, 3H), 3.74 (s, 1H), 3.71 (s, 1H), 3.69 (s, 3H), 2.97 (dd, J = 15.6, 5.2 Hz, 1H), 2.80–2.75 (m, 1.6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.2, 157.8, 156.7, 153.8, 152.0, 149.6, 147.5, 130.8, 127.7, 126.4, 126.3, 126.1, 124.1, 123.4, 119.0, 115.8, 114.2, 114.1, 96.1, 55.5, 55.4, 53.5, 50.8, 34.0, 29.7; IR (KBr): ν = 3247, 3173, 3103, 3068, 2922, 2851, 1727, 1657, 1607, 1510, 1460, 1379, 1244, 1184, 1106, 1068, 1035, 973, 801, 702 cm^{-1}; ESI-FT-MS: m/z = 533.1568, calcd. for $(C_{29}H_{28}N_2O_4S_2+H)^+$: 533.1569. Enantiomeric ratio: 87:13, determined by HPLC (Daicel Chirapak IC, hexane/2-propanol = 80/20, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 7.304 min (major), t_R = 8.573 min (minor).

(2*R*,6*S*)-Ethyl 2,6-bis(4-bromophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5aba): Flash column chromatography eluent, petroleum ether/ethyl acetate = 18/1; reaction time = 84 h; yield: 44.3 mg (64%); 88:12 *dr*; white solid; mp 177–179 °C; $[\alpha]_D^{20}$: +23.0 (*c* 0.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.13 (s, 1H), 7.40–7.37 (m, 4H), 7.16 (d, J = 8.2 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.69–6.65 (m, 4H), 6.39–6.34 (m, 4H), 6.19 (s, 1H), 4.96–4.94 (s, 1H), 4.42–4.38 (m, 1H), 4.31–4.26 (m, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 2.72 (dd, J = 15.3, 5.6 Hz, 1H), 2.62 (dd, J = 15.4, 3.1 Hz, 1H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.0, 157.9, 156.4, 151.5, 143.2, 141.9, 140.9, 131.6, 131.2, 130.5, 128.6, 128.3, 127.7, 120.8, 120.1, 114.6, 114.6, 114.1, 96.6, 59.6, 57.3, 55.7, 55.6, 55.4, 33.6, 14.7; IR (KBr): ν = 3438, 2972, 2919, 2854, 1652, 1610, 1511, 1483, 1438, 1406, 1371, 1315, 1244, 1176, 1029, 953, 880, 797, 734, 706, 669 cm^{-1}; ESI-FT-MS: m/z = 691.0808, calcd. for $(C_{34}H_{32}Br_2N_2O_4+H)^+$: 691.0807. Enantiomeric ratio: 84:16, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 5.988 min (major), t_R = 18.179 min (minor).

(2*R*,6*S*)-Allyl 2,6-bis(4-bromophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5aca): Flash column chromatography eluent, petroleum ether/ethyl acetate = 18/1; reaction time = 84 h; yield: 41.6 mg (59%); 77:23 *dr*; white solid; mp 83–85 °C; $[\alpha]_D^{20}$: +32.4 (*c* 0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.13 (s, 1H), 7.40–7.36 (m, 4H), 7.17 (d, J = 8.3 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.70–6.65 (m, 4H), 6.39–6.35 (m, 4H), 6.23 (s, 1H), 6.10–6.03 (m, 1H), 5.42–5.28 (m, 2H), 5.00–4.95 (m, 1H), 4.83–4.77 (m, 2H), 3.77 (s, 3H), 3.67 (s, 3H), 2.74 (dd, J = 15.3, 5.6 Hz, 1H), 2.63 (dd, J = 15.4, 3.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.5, 158.0, 156.9, 151.5, 143.1, 141.9, 140.9, 133.0, 131.6, 131.2, 130.4, 128.6, 128.3, 127.7, 120.8, 120.1, 117.7, 114.6, 114.6, 114.1, 96.3, 64.4, 57.3, 55.6, 55.6, 55.4, 33.7; IR (KBr): ν = 3364, 3243, 3165, 3047, 2959, 2924, 2853, 1729, 1653, 1603, 1510, 1483, 1460, 1403, 1370, 1242, 1176, 1065, 1036, 980, 937, 799, 738, 702 cm^{-1}; ESI-FT-MS: m/z = 703.0796, calcd. for $(C_{35}H_{32}Br_2N_2O_4+H)^+$: 703.0807. Enantiomeric ratio: 90:10, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol = 85/15, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 8.659 min (major), t_R = 26.563 min (minor).

(2*R*,6*S*)-Isopropyl 2,6-bis(4-bromophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5ada): Flash column chromatography eluent, petroleum ether/ethyl acetate = 18/1; reaction time = 84 h; yield: 56.4 mg (80%); 80:20 *dr*; white solid; mp 184–186 °C; $[\alpha]_D^{20}$: +26.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.19 (s, 1H), 7.38 (d, J = 8.0 Hz, 4H), 7.17 (d, J = 8.3 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.70–6.66 (m, 4H), 6.40–6.37 (m, 4H), 6.16 (s, 1H), 5.25–5.19 (m, 1H), 4.95–4.93 (m, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 2.72 (dd, J = 15.4, 5.5 Hz, 1H), 2.62 (dd, J = 15.4, 3.3 Hz, 1H), 1.37 (dd, J = 6.2, 4.3 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.6, 157.9, 156.2, 151.5, 143.3, 141.9, 141.0, 131.6, 131.1, 130.6, 128.6, 128.4, 127.6, 120.8, 120.1, 114.9, 114.5, 114.1, 96.9, 66.9, 57.3, 55.9, 55.6, 55.4, 33.7, 22.4, 22.2; IR (KBr): ν = 3444, 3244, 3049, 2958, 2924, 2853, 1733, 1648, 1605, 1511, 1483, 1459, 1401, 1372, 1243, 1176, 1105, 1063, 1036, 957, 891, 804 cm^{-1}; ESI-FT-MS: m/z = 705.0958, exact mass calcd. for $(C_{35}H_{34}Br_2N_2O_4+H)^+$: 705.0964. Enantiomeric ratio: 87:13, determined by HPLC (Daicel Chirapak IA, hexane/2-propanol = 70/30, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 5.206 min (major), t_R = 19.283 min (minor).

(2*R*,6*S*)-*tert*-Butyl 2,6-bis(4-bromophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5aea): Flash column chromatography eluent, petroleum ether/ethyl acetate = 24/1; reaction time = 84 h; yield: 36.0 mg (50%); 90:10 *dr* (inseparable diastereomers); yellow solid; mp 100–102 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.47 (s, 0.1H), 10.14 (s, 1H), 7.44–7.42 (m, 0.3H), 7.40–7.37 (m, 4H), 7.32–7.28 (m, 0.5H), 7.17 (d, J = 8.3 Hz, 2H), 7.08 (d, J = 8.5 Hz, 0.3H), 7.00 (d, J = 8.4 Hz, 2H), 6.97–6.95 (m, 0.3H), 6.83–6.81 (m, 0.3H), 6.69–6.65 (m, 5H), 6.40–6.37 (m, 4H), 6.11 (s, 1H), 5.50 (s, 0.1H), 4.91–4.89 (m, 1H), 4.37 (dd, J = 11.7, 3.3 Hz, 0.1H), 3.77 (s,

0.4H), 3.77 (s, 3H), 3.69 (s, 0.4H), 3.68 (s, 3H), 2.69 (dd, J = 15.4, 5.4 Hz, 1H), 2.60 (dd, J = 15.4, 3.6 Hz, 1H), 1.59 (s, 9H), 1.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 168.0, 157.7, 155.6, 151.6, 143.3, 142.0, 141.0, 131.5, 131.1, 130.8, 128.7, 128.5, 128.4, 127.6, 120.7, 120.0, 115.3, 114.5, 114.0, 97.9, 80.0, 57.2, 56.5, 55.6, 55.4, 33.6, 28.7, 28.4; IR (KBr): ν = 3360, 3247, 3046, 2966, 2928, 2835, 1726, 1648, 1605, 1510, 1483, 1456, 1400, 1366, 1245, 1156, 1106, 1066, 1037, 1101, 953, 898, 810, 737 cm^{-1}; ESI-FT-MS: m/z = 719.1113, calcd. for $(C_{36}H_{36}Br_2N_2O_4+H)^+$: 719.112. Enantiomeric ratio: 95:5, determined by HPLC (Daicel Chirapak IA, hexane/2-propanol = 95/5, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 5.065 min (major), t_R = 10.266 min (minor).

(2*R*,6*S*)-Benzyl 2,6-bis(4-bromophenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (5afa): Flash column chromatography eluent, petroleum ether/ethyl acetate = 6/1; reaction time = 84 h; yield: 48.6 mg (64%); 76:24 *dr*; white solid; mp 105–108 °C; $[\alpha]_D^{20}$: +39.3 (c 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.18 (s, 1H), 7.40–7.30 (m, 7H), 7.32 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 6.71–6.64 (m, 4H), 6.40–6.36 (m, 4H), 6.21 (s, 1H), 5.46 (d, J = 12.5 Hz, 1H), 5.22 (d, J = 12.5 Hz, 1H), 4.94–4.92 (m, 1H), 3.77 (s, 3H), 3.67 (s, 3H), 2.72 (dd, J = 15.5, 5.4 Hz, 1H), 2.63 (dd, J = 15.5, 3.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 167.6, 158.0, 157.0, 151.7, 143.0, 141.8, 140.9, 136.8, 131.6, 131.1, 130.4, 128.8, 128.6, 128.4, 128.1, 127.9, 127.7, 120.8, 120.1, 115.2, 114.5, 114.1, 96.1, 65.3, 57.1, 56.1, 55.6, 55.4, 33.7; IR (KBr): ν = 3361, 3251, 3062, 2955, 2925, 2853, 1728, 1651, 1603, 1510, 1484, 1455, 1403, 1370, 1241, 1175, 1105, 1063, 1036, 809, 737, 699 cm^{-1}; ESI-FT-MS: m/z = 753.0966, calcd. for $(C_{39}H_{34}Br_2N_2O_4+H)^+$:753.0964. Enantiomeric ratio: 88:12, determined by HPLC (Daicel Chirapak AD-H, hexane/2-propanol = 70/30, flow rate 1.0 mL min^{-1}, T = 30 °C, 254 nm): t_R = 6.696 min (major), t_R = 19.372 min (minor).

Procedure for the Asymmetric Five-Component Reaction to Isolate Intermediate 7 (Scheme 3)

After a solution of 4-methoxyaniline **1a** (0.2 mmol), methyl acetoacetate **2a** (0.1 mmol), the catalyst **4f** (0.01 mmol), and 4 Å molecular sieves (100 mg) in 1,4-dioxane (0.5 mL) had been stirred at 35 °C for 30 min, the solution of 4-bromobenzaldehyde **3a** (0.2 mmol) in 1,4-dioxane (0.5 mL) was added. After being stirred at 35 °C for 48 h, the reaction mixture was filtered to remove molecular sieves and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford pure product **5aaa** and intermediates **7** and **8**.

Procedure for the Asymmetric Reaction of Intermediate 7 and *in situ* Formed Imine (Scheme 4)

After a solution of 4-methoxyaniline **1a** (0.1 mmol), 4-bromobenzaldehyde **3a** (0.1 mmol), the catalyst **4f** (0.015 mmol), and 3 Å molecular sieves (100 mg) in the mixed toluene/1,4-dioxane (1:1 v/v, 0.5 mL) had been stirred at 35 °C for 30 min, the solution of the intermediate **7** (0.1 mmol) in the mixed toluene/1,4-dioxane (1:1 v/v, 0.5 mL) was added. After being stirred at 35 °C for 84 h, the reaction mixture was filtered to remove molecular sieves and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford pure product **5aaa**.

Procedure for the Synthesis of Intermediate 7 *via* stepwise Procedures at 35 °C (Scheme 5)

After a solution of 4-methoxyaniline **1a** (0.1 mmol), methyl acetoacetate **2a** (0.1 mmol), the catalyst **4f** (0.015 mmol), and 3 Å molecular sieves (100 mg) in toluene (1 mL) had been stirred at 35 °C for 12 h, the reaction mixture was filtered to remove molecular sieves and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford the intermediate **6**. Then, the solution of intermediate **6** (0.1 mmol) in toluene (0.5 mL) was added to the mixture of 4-bromobenzaldehyde **3a** (0.1 mmol), the catalyst **4f** (0.015 mmol), 3 Å molecular sieves (100 mg) in toluene (0.5 mL). After stirring at 35 °C for 24 h, TLC of the reaction mixture indicated that a trace of intermediate **7** had been generated.

Procedure for the Synthesis of Intermediate 7 *via* Stepwise Procedures at 90 °C (Scheme 6)

After a solution of 4-methoxyaniline **1a** (5 mmol), methyl acetoacetate **2a** (5 mmol), benzoic acid (0.5 mmol), and 3 Å molecular sieves (1.5 g) in toluene (20 mL) had been stirred at 90 °C for 24 h, the reaction mixture was filtered to remove molecular sieves and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford the intermediate **6**. Then, the solution of intermediate **6** (3 mmol) in toluene (2 mL) was added to the mixture of 4-bromobenzaldehyde **3a** (3 mmol), benzoic acid (0.6 mmol), piperidine (0.6 mmol), 3 Å molecular sieves (1.5 g) in toluene (3 mL). After stirred at 90 °C for 24 h, the reaction mixture was filtered to remove molecular sieves and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford the intermediate **7**.

Procedure for the Synthesis of Intermediate 7 *via* the One-Pot Protocol (Scheme 7)

After a solution of 4-methoxyaniline **1a** (1 mmol), methyl acetoacetate **2a** (1 mmol), 4-bromobenzaldehyde **3a** (1 mmol), racemic phosphoric acid **4k** (0.2 mmol), and 3 Å molecular sieves (600 mg) in 1,4-dioxane (4 mL) had been stirred at 50 °C for 24 h, the reaction mixture was filtered to remove molecular sieves and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford the intermediate **7**.

(*Z*)-Methyl 3-(4-methoxyphenylamino)but-2-enoate (6): Flash column chromatography eluent, petroleum ether/ethyl acetate = 30/1; colorless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.12 (s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.65 (s, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 1.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.8, 160.1, 157.5, 132.1, 126.8, 114.2, 84.3, 55.4, 50.1, 20.1; IR (KBr): ν = 3264, 3189, 2996, 2947, 2835, 1654, 1614, 1513, 1490, 1438, 1385, 1357, 1273, 1247, 1164, 1107, 1057, 1034, 1007, 952, 916, 845, 816, 786, 681 cm^{-1}; ESI-FT-MS: m/z 222.1122, calcd. for $(C_{12}H_{15}NO_3+H)^+$: 222.113.

(*Z*)-Methyl 2-(4-bromobenzylidene)-3-(4-methoxyphenylamino)but-3-enoate (7): Flash column chromatography eluent, petroleum ether/ethyl acetate = 40/1; yellow solid; mp 99–101 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 10.11 (s, 1H), 7.44 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 7.07 (d, J = 16.1 Hz, 1H), 7.01–6.98 (m, 2H), 6.87–6.82 (m, 2H), 6.58 (d, J = 16.1 Hz, 1H), 5.08 (s, 1H), 3.79 (s, 3H), 3.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.8, 156.9, 156.8, 134.7, 133.5, 132.4, 132.0, 128.6, 125.1, 123.9, 122.9, 114.3, 83.6, 55.4, 50.5; IR (KBr): ν = 3269, 2946, 2835, 1731, 1652, 1599, 1511, 1487, 1372, 1272, 1163, 1107, 1044, 1010, 970, 813, 788, 734 cm^{-1}; ESI-FT-MS: m/z = 388.0537, calcd. for $(C_{19}H_{18}BrNO_3+H)^+$: 388.0548, found .

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[13] CCDC 912036 (**5aaa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif See the Supporting Information for details.