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Enantioselective construction of 2,5-dihydropyrrole skeleton with quaternary stereogenic center *via* catalytic asymmetric 1,3-dipolar cycloaddition involving α-arylglycine esters†

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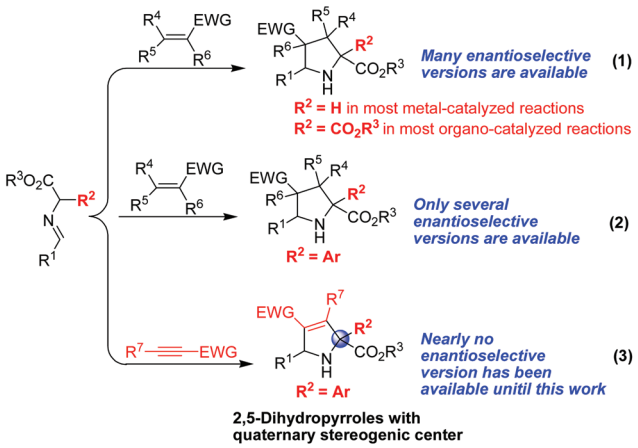
A catalytic asymmetric construction of synthetically and biologically important 2,5-dihydropyrrole scaffolds with concomitant creation of multiple chiral carbon centers including one quaternary stereogenic center in high yields (up to 99%) and excellent enantioselectivities (up to 99% ee) has been established *via* an organocatalytic 1,3-dipolar cycloaddition using α-arylglycine esters as azomethine precursors. Moreover, a detailed investigation has been performed on the catalytic asymmetric 1,3-dipolar cycloadditions of α-arylglycine ester-generated azomethine ylides with alkynes, providing an efficient way to simultaneously access both 2,5-dihydropyrrole diastereomers in good enantioselectivities.

Introduction

The 2,5-dihydropyrrole core represents a privileged heterocyclic skeleton which not only exists in a number of natural alkaloids (Fig. 1),[1] but also is able to serve as an important building block in organic synthesis by means of the rich chemistry in the functionalization of its carbon–carbon double bond.[2] Besides, this structural motif is featured in a large family of medicinally relevant compounds exhibiting important



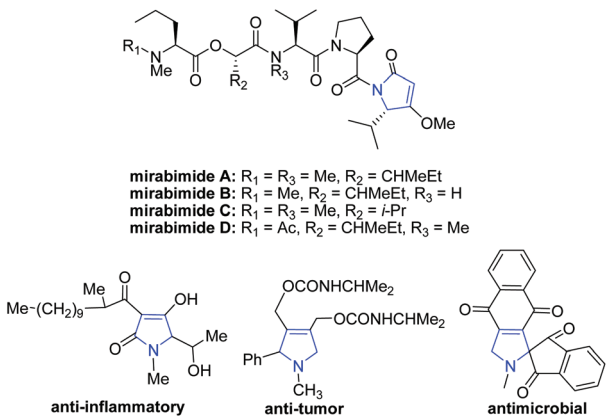


Fig. 1 Natural alkaloids and bioactive compounds containing a 2,5-dihydropyrrole core.

bioactivities such as antioxidant,[3] antimicrobial,[4] anti-tumor,[5] and anti-inflammatory[6] properties (Fig. 1). The importance of such a structural architecture has led to a great demand for efficient synthetic methods, especially those producing 2,5-dihydropyrroles in high optical purity.

The catalytic asymmetric 1,3-dipolar cycloadditions of azomethine ylides to electron-deficient olefins by either chiral metal-based catalysts[7] or organocatalysts[8] have achieved great success in the past decades. The azomethine ylides that participate in these reactions are mostly generated from glycine ester in metal-catalyzed transformations or highly reactive 2-aminomalonate in organocatalyzed versions (eqn (1)). In sharp contrast, α-arylglycine esters have been applied to far

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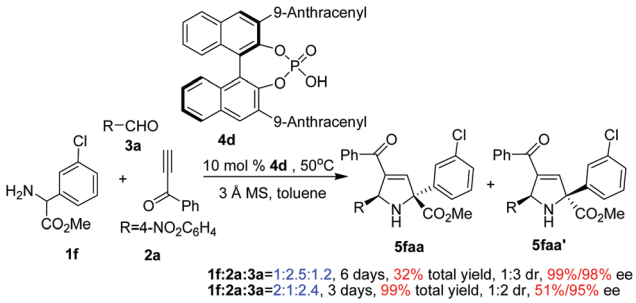
fewer 1,3-dipolar cycloadditions as azomethine ylide precursors, presumably due to the low reactivity inherent in both the α-arylglycine ester and the resultant azomethine ylide. So far, the catalytic asymmetric 1,3-dipolar cycloadditions involving α-arylglycine ester-based azomethine ylides have sporadically been found in a rather limited number of transformations with olefins (eqn (2)).[9] However, none of these protocols employed *alkynes* rather than olefins as dipolarophiles to react with α-arylglycine ester-derived azomethine ylides (eqn (3)). Nonetheless, the catalytic asymmetric 1,3-dipolar cycloadditions of α-arylglycine ester-derived azomethine ylides with alkynes would allow for the enantioselective access to synthetically and biologically important 2,5-dihydropyrroles with concomitant creation of quaternary chiral centers. In this regard, the protocol holds great synthetic importance, but remains a formidable challenge due to the low reactivity of α-arylglycine esters and the corresponding azomethine ylides.

Herein, we report a catalytic asymmetric construction of synthetically and biologically important 2,5-dihydropyrrole scaffolds with multiple chiral centers including one quaternary stereogenic center in high yields (up to 99%) and excellent enantioselectivities (up to 99% ee) *via* an organocatalytic 1,3-dipolar cycloaddition using α-arylglycine esters as azomethine precursors.

Results and discussion

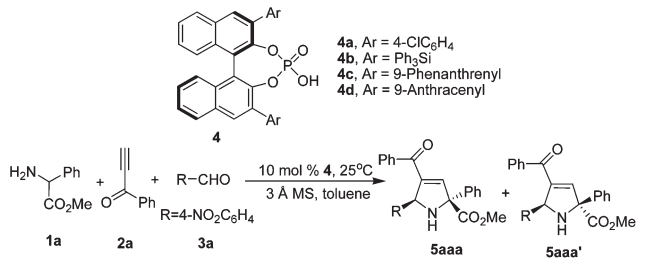
We have established the first catalytic enantioselective 1,3-dipolar cycloadditions between electron-deficient alkynes and azomethine ylides generated from 2-aminomalonate in the presence of chiral phosphoric acid.[10] However, the highly active diethyl 2-aminomalonate was selected as azomethine precursor in most cases and only one α-aryl amino-ester was tentatively employed in the reaction but with obviously inferior reactivity. Thereafter, further investigation on the reactions involving other α-arylglycine esters under the similar reaction conditions led to disappointing results with respect to yields (see ESI†). For example, the reaction temperature had to be lifted from rt to 50 °C, and the yields were only 32%–59% even with the considerably long reaction time of 6 days. These problems prompted us to carefully investigate the 1,3-dipolar cycloadditions of α-arylglycine ester-generated azomethine ylides with alkynes.

The preliminary experiments revealed that the ratio of the reagents was crucial to this reaction in terms of delivering high yield. As indicated in Scheme 1, when the ratio of substrates **1f : 2a : 3a** was changed from 1 : 2.5 : 1.2 to 2 : 1 : 2.4, the yield was remarkably improved from 32% to 99% but with an obvious erosion of the enantioselectivity. Therefore, additional studies on the optimization of conditions were initially performed for the three-component reaction of methyl 2-amino-2-phenylacetate **1a**, 1-phenylprop-2-yn-1-one **2a** and 4-nitrobenzaldehyde **3a** with the molar ratio of 2 : 1 : 2.4 in toluene at 25 °C in the presence of 10 mol% of various chiral phosphoric acids **4**[11,12] (Table 1). The results revealed that the catalyst **4d** bearing bulky 9-anthracenyl substituents at the 3- and 3′-positions of the BINOL backbone was still much superior to other phosphoric acids, delivering 2,5-dihydropyrrole compounds **5aaa** and **5aaa′** in a high yield of 78% and with acceptable enantiomeric excess (entry 4 *vs.* 1–3). A survey of solvents found that toluene was a more suitable reaction media than dichloromethane and chloroform (entry 4 *vs.* 5–6). Screening of molecular sieves (MS) disclosed that the addition of 5 Å MS rendered a much more efficient and enantioselective reaction, providing 87% yield and 87%/98% ees (entry 8). On the contrary, both the yield and enantioselectivity decreased dramatically in the absence of MS (entry 9), which indicated that MS



Scheme 1 The impact of the ratio of reagents on the reaction.

Table 1 Screening of catalysts and optimization of conditions[a]



Entry	4	Solvent	Yield[b] (%)	dr[c] (**5aaa : 5aaa′**)	ee[d] (%) (**5aaa**/**5aaa′**)
1	**4a**	Toluene	60	6 : 1	7/26
2	**4b**	Toluene	52	5 : 1	<5/23
3	**4c**	Toluene	69	3 : 1	9/62
4	**4d**	Toluene	78	1 : 1	63/91
5	**4d**	CH_2Cl_2	56	5 : 1	<5/54
6	**4d**	$CHCl_3$	72	6 : 1	<5/45
7[e]	**4d**	Toluene	74	1 : 1	70/94
8[f]	**4d**	Toluene	87	1 : 1	87/98
9[g]	**4d**	Toluene	20	3 : 1	18/66
10[h]	**4d**	Toluene	55	3 : 1	10/50
11[i]	**4d**	Toluene	60	1.5 : 1	87/96
12[j]	**4d**	Toluene	91	1 : 1.5	84/97
13[k]	**4d**	Toluene	84	1 : 1.3	90/99
14[l]	**4d**	Toluene	95	1 : 1	72/94

[a] Unless indicated otherwise, the reaction was carried out on 0.1 mmol scale in solvent (1 mL) with 3 Å MS (100 mg) for 60 h, and the molar ratio of **1a : 2a : 3a** was 2 : 1 : 2.4. [b] Isolated yield. [c] The dr was determined by ^{1}H NMR. [d] The ee was determined by HPLC. [e] 4 Å MS (100 mg) was used. [f] 5 Å MS (100 mg) was used. [g] In the absence of MS. [h] Catalyzed by 5 mol% **4d**. [i] At 0 °C. [j] At 40 °C. [k] The molar ratio of **1a : 2a : 3a** was 1.5 : 1 : 1.8. [l] The molar ratio of **1a : 2a : 3a** was 2.5 : 1 : 3.

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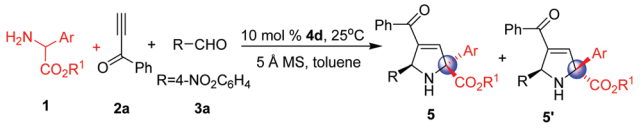
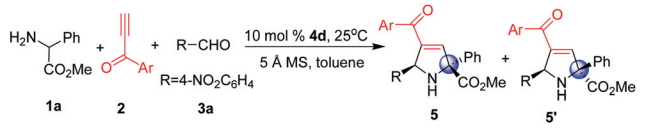
Table 2 Scope of α-arylglycine esters[a]



Entry	5 (5′)	Ar	R^1	Yield[b] (%)	dr[c] (5 : 5′)	ee[d] (%) (5/5′)
1	**5aaa** (**5aaa′**)	Ph (**1a**)	Me	84	1 : 1.3	90/99
2	**5baa** (**5baa′**)	4-$OMeC_6H_4$ (**1b**)	Me	66	1.8 : 1	92/92
3	**5caa** (**5caa′**)	4-FC_6H_4 (**1c**)	Me	79	1 : 1.4	89/97
4	**5daa** (**5daa′**)	3-FC_6H_4 (**1d**)	Me	95	1 : 2.8	86/99
5	**5eaa** (**5eaa′**)	4-ClC_6H_4 (**1e**)	Me	90	1 : 1.6	90/98
6	**5faa** (**5faa′**)	3-ClC_6H_4 (**1f**)	Me	83	1 : 2.4	87/96
7	**5ga** (**5ga′**)	2-ClC_6H_4 (**1g**)	Me	99	1 : 3	67/99
8	**5haa** (**5haa′**)	PhC_6H_4 (**1h**)	Et	81	1 : 1.3	93/93
9	**5iaa** (**5iaa′**)	4-ClC_6H_4 (**1i**)	Et	89	1 : 1.1	92/98
10	**5jaa** (**5jaa′**)	3-ClC_6H_4 (**1j**)	Et	77	1 : 2.4	89/97
11	**5kaa** (**5kaa′**)	2-ClC_6H_4 (**1k**)	Et	99	1 : 2	77/99

[a] Unless indicated otherwise, the reaction was carried out on 0.1 mmol scale in toluene (1 mL) with 5 Å MS (100 mg) for 60 h, and the molar ratio of **1 : 2a : 3a** was 1.5 : 1 : 1.8. [b] Isolated yield. [c] The dr was determined by ^{1}H NMR. [d] The ee was determined by HPLC.

Table 3 Scope of ethynyl arones[a]



Entry	5 (5′)	Ar	Yield[b] (%)	dr[c] (5 : 5′)	ee[d] (%) (5/5′)
1	**5aaa** (**5aaa′**)	Ph (**2a**)	84	1 : 1.3	90/99
2	**5aba** (**5aba′**)	2-Naphthyl (**2b**)	80	1.7 : 1	87/97
3	**5aca** (**5aca′**)	3-MeC_6H_4 (**2c**)	84	1 : 1.1	85/96
4	**5ada** (**5ada′**)	4-MeC_6H_4 (**2d**)	79	1 : 1.6	85/97
5	**5aea** (**5aea′**)	4-$MeOC_6H_4$ (**2e**)	66	1 : 1.4	79/95
6	**5afa** (**5afa′**)	4-$CF_3C_6H_4$ (**2f**)	86	1 : 1	78/94
7	**5aga** (**5aga′**)	4-FC_6H_4 (**2g**)	77	1 : 1.2	72/92
8	**5aha** (**5aha′**)	2-FC_6H_4 (**2h**)	77	1 : 1.5	83/93
9	**5aia** (**5aia′**)	3,4-$F_2C_6H_3$ (**2i**)	88	1 : 1.2	86/96
10	**5aja** (**5aja′**)	2-Thiophenyl (**2j**)	75	1 : 1.6	79/96

[a] Unless indicated otherwise, the reaction was carried out on 0.1 mmol scale in toluene (1 mL) with 5 Å MS (100 mg) for 60 h, and the molar ratio of **1a : 2 : 3a** was 1.5 : 1 : 1.8. [b] Isolated yield. [c] The dr was determined by ^{1}H NMR. [d] The ee was determined by HPLC.

played an important role both in reactivity and in enantioselectivity control. Lowering the catalyst loading to 5 mol% led to an inferior yield and enantioselectivity albeit with an improved diastereoselectivity (entry 10), which demonstrated that 10 mol% of **4d** was necessary to this reaction. Variation of the reaction temperature could not give better results with regard to enantioselectivity (entries 11–12). Finally, fine-tuning the molar ratio of **1a : 2a : 3a** to 1.5 : 1 : 1.8 gave a high yield of 84% and excellent enantioselectivities of 90%/99% ees (entry 13).

With the optimal conditions in hand, the generality of the reaction for α-arylglycine esters **1** was explored in the reaction with 1-phenylprop-2-yn-1-one **2a** and 4-nitrobenzaldehyde **3a**. As shown in Table 2, this protocol was amenable to a wide scope of α-arylglycine esters bearing either an electronically poor, neutral, or rich substituent on their aromatic ring, offering 2,5-dihydropyrroles **5** and **5′** in high yields (up to 99%) and with good to excellent enantioselectivities (up to 93% ee for *trans*-**5** and up to 99% ee for *cis*-**5′**). α-Arylglycine esters substituted with electron-withdrawing groups were seemingly more reactive than their counterparts substituted with electron-donating groups in terms of yield (entries 3–7 *vs.* 2), but the latter (**1b**) was capable of affording two diastereomers, both with high enantioselectivity of 92% ee (entry 2). In most cases, the *cis*-diastereomers **5′** were obtained with higher enantioselectivities (92–99% ees) than their *trans*-counterparts **5** (67–93% ees). The position of the substituents of benzene ring appeared to exert some impact on the diastereoselectivity of the reaction as well as the enantioselectivity of the *trans*-product **5** (entries 5–7). Among chlorine-substituted α-arylglycine esters **1e–1g**, the *ortho*-substituted α-arylglycine ester **1g** provided the highest diastereoselectivity of 1 : 3 (entry 7), while the *para*-substituted α-arylglycine ester **1e** delivered the *trans*-product **5eaa** with the best enantioselectivity of 90% ee (entry 5). Moreover, the use of ethyl 2-amino-2-arylacetates (**1h–1k**) as azomethine precursors also enabled the reactions to proceed smoothly in high yields (77–99%) and good to excellent enantioselectivities (77–93% ees for *trans*-**5** and 93–99% ees for *cis*-**5′**, entries 8–11).

Next, the substrate scope with respect to ethynyl arones **2** was explored by the reactions of 2-amino-2-phenylacetate **1a**, 4-nitrobenzaldehyde **3a** with a variety of ethynyl arones **2** under the optimized reaction conditions (Table 3). In general, this protocol was not only applicable to various ethynyl arones **2** with electronically different substituents on their aromatic rings (entries 1–9), but also amenable to ethynyl heteroaromatic ketones such as **2j** (entry 10) in high yields (66–88%) and good to excellent enantioselectivities (72–90% ees for *trans*-**5** and 92–99% ees for *cis*-**5′**). It seemed that ethynyl arone **2e** with strong electron-donating group exhibited lower reactivity than others (entry 5), while ethynyl arones with electron-neutral or weakly electron-donating groups delivered higher yields and retained good enantioselectivities (entries 1–4). Among ethynyl arones bearing electron-withdrawing substituents, disubstituted ethynyl arone **2i** appeared to be a superior substrate, offering a high yield of 88% and good enantioselectivities of 86%/96% ees (entry 9 *vs.* 6–8).

We also investigated the generality of the reaction for different aromatic aldehydes. When aldehyde **3b** was employed as a substrate to react with amino-ester **1a** and ethynyl arone **2a** under the optimized reaction conditions, the desired products **5aab** and **5aab′** were afforded in acceptable yield and diastereoselectivity but with unsatisfactory enantioselectivities (Table 4, entry 1). Thus, the reaction parameters such as solvent and ratio of reagents were further optimized to improve the enantioselectivity. When increasing the stoichiometry of the azomethine ylide generated *in situ* from **1a** and **3b**, the yield and diastereoselectivity were significantly

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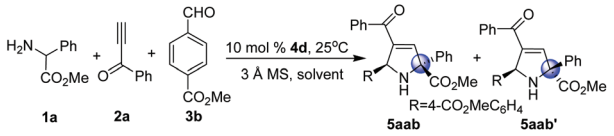
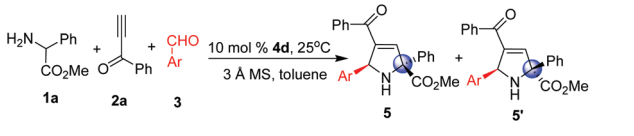
Table 4 Further optimization of reaction conditions[a]



Entry	Molar ratio of **1a** : **2a** : **3b**	Solvent	Yield[b] (%)	dr[c] (**5aab** : **5aab′**)	ee[d] (%) (**5aab**/**5aab′**)
1	2 : 1 : 2.4	Toluene	61	2.7 : 1	33/69
2	3 : 1 : 3.6	Toluene	64	3.3 : 1	25/59
3	4 : 1 : 4.8	Toluene	99	11 : 1	13/50
4	1 : 1.2 : 1.2	Toluene	58	2.2 : 1	53/80
5	1 : 2.4 : 1.2	Toluene	56	2.5 : 1	55/77
6	1 : 3.6 : 1.2	Toluene	27	2.6 : 1	69/82
7	1 : 4.8 : 1.2	Toluene	42	2.5 : 1	74/81
8	1 : 2.4 : 2.4	Toluene	44	1.2 : 1	79/91
9	1 : 2.4 : 2.4	PhF	40	1.5 : 1	36/60
10	1 : 2.4 : 2.4	PhCl	42	2.5 : 1	73/80
11	1 : 2.4 : 2.4	PhBr	35	2 : 1	82/88
12	1 : 2.4 : 2.4	1,2-$Cl_2C_6H_4$	42	4 : 1	67/70
13	1 : 2.4 : 2.4	1,3-$Cl_2C_6H_4$	33	4 : 1	72/73

[a] Unless indicated otherwise, the reaction was carried out on 0.1 mmol scale in solvent (1 mL) with 3 Å MS (100 mg) for 60 h. [b] Isolated yield. [c] The dr was determined by ^{1}H NMR. [d] The ee was determined by HPLC.

Table 5 Scope of aromatic aldehydes[a]



Entry	**5** (**5′**)	Ar	Yield[b] (%)	dr[c] (**5** : **5′**)	ee[d] (%) (**5**/**5′**)
1	**5aab** (**5aab′**)	4-$CO_2MeC_6H_4$ (**3b**)	44 (99[e])	1.2 : 1 (11 : 1[e])	79/91 (13/50[e])
2	**5aac** (**5aac′**)	4-CNC_6H_4 (**3c**)	52	1 : 1.3	77/89
3	**5aad** (**5aad′**)	4-$CF_3C_6H_4$ (**3d**)	33	2.5 : 1	68/72
4[f]	**5aaa** (**5aaa′**)	4-$NO_2C_6H_4$ (**3a**)	84	1 : 1.3	90/99
5	**5aae** (**5aae′**)	3-$NO_2C_6H_4$ (**3e**)	37	1.8 : 1	77/74
6	**5aaf**	2-$NO_2C_6H_4$ (**3f**)	40	>20 : 1	66[g]
7	**5aag**	4-$CH_3C_6H_4$ (**3g**)	36	5 : 1	24[g]

[a] Unless indicated otherwise, the reaction was carried out on 0.1 mmol scale in toluene (1 mL) with 3 Å MS (100 mg) for 60 h, and the molar ratio of **1a** : **2a** : **3** was 1 : 2.4 : 2.4. [b] Isolated yield. [c] The dr was determined by ^{1}H NMR. [d] The ee was determined by HPLC. [e] The molar ratio of **1a** : **2a** : **3b** was 4 : 1 : 4.8. [f] The molar ratio of **1a** : **2a** : **3a** was 1.5 : 1 : 1.8, and 5 Å MS was used instead of 3 Å MS. [g] The ee value of major *trans*-diastereomer **5**.

enhanced to 99% and 11 : 1 dr, but the enantioselectivity sharply decreased (entries 1–3). On the contrary, increasing the stoichiometry of ethynyl arone **2a** led to the improvement of enantioselectivity but with inferior yield (entries 4–7). Ultimately, the highest enantioselectivities of 79% ee for **5aab** and 91% ee for **5aab′** were achieved with an acceptable yield by tuning the ratio of **1a** : **2a** : **3b** to 1 : 2.4 : 2.4 (entry 8). During the course of fine-tuning the ratio of reagents, the two factors of yield and enantioselectivity were obviously restricted by each other, thereby excellent enantioselectivity accompanied by high yield could rarely be simultaneously obtained in this case and a compromise between them should be made. So, the molar ratio of 1 : 2.4 : 2.4 was utilized as the optimal ratio of reagents to further screen other benzene-related solvents. The results revealed that no other tested solvents were better than toluene with regard to yield and enantioselectivity (entries 9–13 *vs.* 8).

Under the newly optimized reaction conditions, a number of aromatic aldehydes were examined (Table 5). The electronic nature of the aromatic aldehydes had an evident effect on the reaction. Generally, this protocol is amenable to aromatic aldehydes substituted with electron-withdrawing groups, delivering good or acceptable enantioselectivities albeit with unsatisfactory yields in some cases (entries 1–6). However, quantitative yield could be obtained at the mole ratio of 4 : 1 : 4.8 but with low enantioselectivities as exemplified by **3b** (entry 1, in parentheses). Besides, the substituent position of aromatic aldehydes seemed to impose some impact on the reactivity and stereoselectivity as illustrated by the examples of nitro-substituted benzaldehydes **3a**, **3e** and **3f** (entries 4–6). Among the three aldehydes, *para*-nitrobenzaldehyde was the best one to deliver high yield and enantioselectivity (entry 4), and *meta*-nitrobenzaldehyde was better than *ortho*-nitrobenzaldehyde in terms of enantioselectivity (entry 5), while *ortho*-nitrobenzaldehyde offered the highest diastereoselectivity (>20 : 1 dr, entry 6). Moreover, electronically rich benzaldehydes such as *para*-methyl benzaldehyde **3g** could also be applied to this reaction with high diastereoselectivity but in low yield and with inferior enantioselectivity (entry 8). These results could largely be ascribed to the low reactivity associated with azomethine ylides generated from amino-esters, especially from α-arylglycine esters with electronically rich benzaldehydes.[9c,10]

In spite of the fact that the electronic features of the aldehydes had some delicate effect on the reaction, this protocol could be applied to a wide range of α-arylglycine esters and ethynyl arones, affording synthetically and biologically important 2,5-dihydropyrroles with quaternary stereogenic centers in high yields and with good to excellent enantioselectivities. Although the diastereoselectivity was not satisfactory, this protocol could provide an easy access to both of the diastereomers in good enantioselectivities simultaneously.

The structures of the synthesized 2,5-dihydropyrroles **5** and **5′** were unambiguously characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS (ESI). The relative configuration of compound **5caa** was assigned to be *trans* by comparison of its ^{1}H NMR proton shift with the same known compound, whose configuration was confirmed by the single crystal of its derivative.[10] Consequently, the relative configuration of compound **5caa′** was assigned to be *cis* accordingly. In simple terms, the chemical shift of the proton linked to the C=C bond in *trans*-2,5-dihydropyrrole ring is higher (6.90 in **5caa**) than its *cis*-counterpart (6.77 in **5caa′**), while the chemical shift of the tertiary CH proton in *trans*-**5** (5.69 in **5caa**) is lower than *cis*-**5** (5.87 in **5caa**). The absolute configurations of compounds **5caa** and

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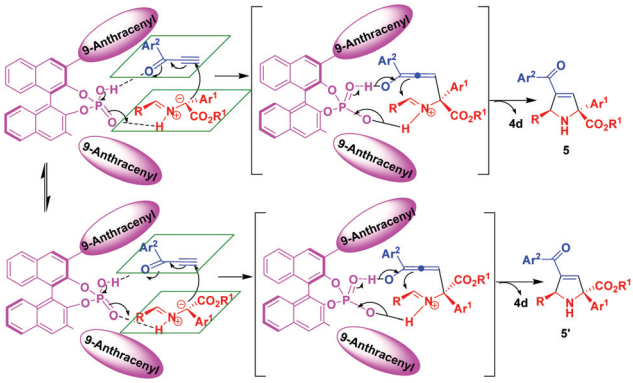
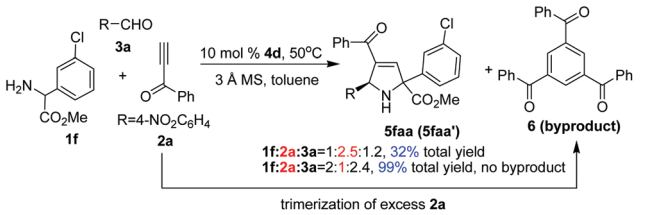


Scheme 2 Possible reaction pathway and transition states.

5caa′ were respectively determined to be (2*R*, 5*S*) and (2*S*, 5*S*) by comparing their optical rotations with those of the same known compounds.[10] The relative and absolute configurations of other new 2,5-dihydropyrroles **5** and **5′** were assigned by analogy.

On the basis of our experimental results and previous studies on the reaction mechanism,[9f,10] we proposed the possible pathway and transition states of the reaction to explain the stereochemistry experimentally observed (Scheme 2). The 1,3-dipolar cycloaddition might also proceed *via* a sequential Michael addition and Mannich-type cyclization rather than a concerted pathway.[10] The chiral phosphoric acid **4d** served as a Brønsted acid/Lewis base bifunctional catalyst to simultaneously activate both the α-arylglycine ester-derived azomethine ylide and ethynyl arone by H-bonding interactions. The enantioselective [3+2] reaction occurred because of the chiral environment created by the (*R*)-BINOL backbone and the congested 3,3′-substituents of the catalyst **4d**, thereby leading to the formation of the experimentally observed (2*R*, 5*S*)- and (2*S*, 5*S*)-configured products **5** and **5′**. The two stable configurations of α-arylglycine ester-generated azomethine ylide had little difference in steric hindrance and could isomerize to each other easily, thereby resulting in the low diastereoselectivities.

As mentioned above, the ratio of the reagents was crucial to the yield of the 1,3-dipolar cycloadditions. We also investigated the possible reasons. As illustrated in Scheme 3, when the molar ratio of **1f** : **2a** : **3a** was 1 : 2.5 : 1.2, the excess amount of **2a** would undergo self-trimerization under the amine catalysis to give 1,3,5-tribenzoylbenzene **6**.[13] Due to the low reactivity and small amount of azomethine ylide generated from α-arylglycine ester **1f** and aldehyde **3a**, ethynyl arone **2a** might undergo self-trimerization more easily than 1,3-dipolar cycloaddition. Therefore, the low yields of products **5faa** and **5faa′** were mainly ascribed to the formation of byproduct **6**, which consumed a large amount of reagent **2a**. However, when the molar ratio of **1f** : **2a** : **3a** was 2 : 1 : 2.4, the amount of azomethine ylide was much greater than that of dipolarophile **2a**, thus facilitating the 1,3-dipolar cycloaddition and avoiding the self-trimerization of **2a**. As a result, the yields of products **5faa** and **5faa′** were greatly improved at this ratio of reagents.



Scheme 3 The formation of byproduct.

Conclusions

In summary, we have established a catalytic enantioselective construction of synthetically and biologically important 2,5-dihydropyrrole scaffolds with multiple chiral centers including one quaternary stereogenic center in high yields (up to 99%) and with excellent enantioselectivities (up to 99% ee) in most cases. More importantly, this work has realized the first in-depth study on catalytic asymmetric 1,3-dipolar cycloadditions of α-arylglycine ester-generated azomethine ylides with alkynes, providing an efficient way to access both of the 2,5-dihydropyrrole diastereomers in good enantioselectivities simultaneously. This protocol also combines the merits of organocatalysis and multicomponent reactions, furnishing structurally diverse 2,5-dihydropyrroles with quaternary chiral center.

Experimental

General information

NMR spectra were measured at 400 and 100 MHz on a Brucker-400 MHz spectrometer. The solvent used for NMR spectroscopy was $CDCl_3$, using tetramethylsilane as the internal reference. HRMS (Bio TOF Q) spectra were recorded with an ESI resource on P-SIMS-Gly of Bruker Daltonics Inc. Infrared spectra were recorded on a Nicolet MX-1E FT-IR spectrometer. HPLC analysis was performed on Waters-Breeze (2487 Dual Absorbance Detector and 1525 Binary HPLC Pump) or Agilent 1200. Chiralpak IC, IA, and AD columns were purchased from Daicel Chemical Industries, Ltd. Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line at the temperatures indicated.

Analytical grade solvents for column chromatography and commercially available reagents were used as received. Toluene was dried over Na and distilled prior to use. All commercially available starting materials were used directly. Catalysts **4a–4d** were prepared according to previously described procedures[11a,b,14] and **4d** was acidified with 4 N HCl before use. α-Arylglycine esters **1a–1k** were prepared using previously reported methods.[9f] Substrates **2a–2j** were obtained according to the literature methods.[10,15]

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General procedure for asymmetric 1,3-dipolar cycloadditions of alkynes with azomethine ylides generated from α-arylglycine esters and 4-nitrobenzaldehyde 3a

The solution of α-arylglycine esters **1** (0.15 mmol), 4-nitrobenzaldehyde **3a** (0.18 mmol), the catalyst **4d** (0.01 mmol), and 5 Å molecular sieves (100 mg) in toluene (0.5 mL) was stirred at 25 °C for 20 min. Then to this resultant mixture was added the solution of ethynyl arones **2** (0.1 mmol) in toluene (0.5 mL). The reaction mixture was stirred at 25 °C for 60 h. Then the reaction mixture was filtered to remove molecular sieves, and the solid powder was washed with ethyl acetate. The resultant solution was evaporated under reduced pressure, and the residue was purified through flash column chromatography on silica gel to yield pure products **5** and **5′**.

Selected examples of characterization of new compounds 5

Methyl 4-benzoyl-2-(3-fluorophenyl)-5-(4-nitrophenyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylate (5daa and 5daa′). Reaction time = 60 h; dr (**5daa : 5daa′**) = 1 : 2.8; total yield: 95%.

5daa: yellow oil; $[\alpha]_D^{20}$ = +43.6 (*c* 0.2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.18 (d, *J* = 8.4 Hz, 2H), 7.77–7.72 (m, 2H), 7.61–7.54 (m, 3H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.38–7.26 (m, 3H), 7.06–6.98 (m, 1H), 6.89 (d, *J* = 2.0 Hz, 1H), 5.70 (d, *J* = 1.6 Hz, 1H), 3.88 (s, 3H), 3.19 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.8, 172.8, 163.1 (*J* = 245.9 Hz), 148.7, 147.7, 143.6, 141.2, 137.2, 133.3, 130.5, 128.9, 128.7, 128.4, 124.1, 121.3, 115.3 (*J* = 20.0 Hz), 113.2, 113.0, 78.6, 68.3, 53.5; IR (KBr): 3380, 3075, 2954, 2925, 2859, 1735, 1651, 1597, 1447, 1345, 1232, 854, 693; enantiomeric excess: 86%, determined by HPLC (Daicel Chirapak IA, hexane–isopropanol = 70 : 30, flow rate 1.0 mL min^{-1}, *T* = 30 °C, 254 nm): t_R = 11.90 min (major), t_R = 16.91 min (minor).

5daa′: yellow oil; $[\alpha]_D^{20}$ = +103.1 (*c* 0.5, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.10 (d, *J* = 8.8 Hz, 2H), 7.71–7.66 (m, 2H), 7.60–7.54 (m, 3H), 7.46–7.39 (m, 5H), 7.13–7.07 (m, 1H), 6.75 (d, *J* = 2.0 Hz, 1H), 5.88 (s, 1H), 3.94 (s, 1H), 3.77 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.0, 171.8, 162.1 (*J* = 242.0 Hz), 148.5, 146.4, 142.8, 142.7, 138.5, 136.1, 132.4, 129.6, 129.5, 128.0, 127.7, 122.6, 120.7, 114.3 (*J* = 21.0 Hz), 112.6, 112.4, 76.9, 66.3, 52.5; IR (KBr): 3357, 3076, 2953, 2925, 2855, 1733, 1651, 1519, 1344, 1232, 850, 721; enantiomeric excess: 99%, determined by HPLC (Daicel Chirapak IA, hexane–isopropanol = 70 : 30, flow rate 1.0 mL min^{-1}, *T* = 30 °C, 254 nm): t_R = 9.47 min (minor), t_R = 13.22 min (major).

Methyl-4-benzoyl-2-(3-chlorophenyl)-5-(4-nitrophenyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylate (5faa and 5faa′). Reaction time = 60 h; dr (**5faa : 5faa′**) = 1 : 2.4; total yield: 83%.

5faa: yellow oil; $[\alpha]_D^{20}$ = +47.0 (*c* 0.1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.19 (dt, *J* = 2.4 Hz, 4.3 Hz, 2H), 7.76–7.73 (m, 2H), 7.59–7.54 (m, 4H), 7.48–7.44 (m, 2H), 7.42–7.38 (m, 1H), 7.32–7.30 (m, 2H), 6.89 (d, *J* = 2.0 Hz, 1H), 5.70 (d, *J* = 2.0 Hz, 1H), 3.88 (s, 3H), 3.19 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.8, 172.7, 148.6, 147.7, 143.7, 143.0, 141.1, 137.2, 135.0, 133.3, 130.2, 129.0, 128.7, 128.5, 128.4, 126.1, 124.1, 123.9, 78.6, 68.3, 53.5; IR (KBr): 3381, 3074, 2924, 2853, 1734, 1648, 1596, 1520, 1450, 1344, 1236, 1185, 1106, 1079, 1024, 851, 782, 722, 695; ESI FTMS exact mass calcd for $(C_{25}H_{19}ClN_2O_5 + H)^+$ requires *m*/*z* 463.1061, found *m*/*z* 463.1061; enantiomeric excess: 87%, determined by HPLC (Daicel Chirapak IA, hexane–isopropanol = 70 : 30, flow rate 1.0 mL min^{-1}, *T* = 30 °C, 254 nm): t_R = 10.91 min (major), t_R = 16.37 min (minor).

5faa′: yellow oil; $[\alpha]_D^{20}$ = +89.6 (*c* 0.2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.11 (dt, *J* = 2.3 Hz, 4.2 Hz, 2H), 7.69–7.67 (m, 3H), 7.58–7.54 (m, 4H), 7.45–7.39 (m, 4H), 6.76 (d, *J* = 2.1 Hz, 1H), 5.88 (d, *J* = 1.9 Hz, 1H), 3.95 (s, 1H), 3.77 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.0, 172.8, 149.4, 147.4, 144.5, 143.2, 139.3, 137.1, 135.0, 133.4, 130.2, 129.0, 128.7, 128.5, 126.5, 124.3, 123.6, 78.2, 67.7, 53.8; IR (KBr): 3356, 3072, 2924, 2855, 1733, 1651, 1596, 1520, 1450, 1342, 1237, 1077, 1016, 853, 791, 712; ESI FTMS exact mass calcd for $(C_{25}H_{19}ClN_2O_5 + H)^+$ requires *m*/*z* 463.1061, found *m*/*z* 463.1062; enantiomeric excess: 96%, determined by HPLC (Daicel Chirapak IC, hexane–isopropanol = 70 : 30, flow rate 1.0 mL min^{-1}, *T* = 30 °C, 254 nm): t_R = 9.31 min (minor), t_R = 11.17 min (major).

Ethyl 4-benzoyl-2-(4-chlorophenyl)-5-(4-nitrophenyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylate (5ia and 5ia′). Reaction time = 60 h; dr (**5iaa : 5iaa′**) = 1 : 1.1; total yield: 89%.

5iaa: yellow oil; $[\alpha]_D^{20}$ = +74.0 (*c* 0.2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.18 (dt, *J* = 2.4 Hz, 4.3 Hz, 2H), 7.75–7.72 (m, 2H), 7.59–7.56 (m, 3H), 7.50–7.44 (m, 4H), 7.36–7.33 (m, 2H), 6.89 (d, *J* = 2.0 Hz, 1H), 5.69 (d, *J* = 2.0 Hz, 1H), 4.39–4.28 (m, 2H), 3.19 (s, 1H), 1.31 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.0, 172.7, 148.9, 147.9, 143.7, 141.9, 139.9, 137.7, 134.6, 133.6, 129.4, 129.3, 129.0, 128.4, 127.2, 124.1, 78.5, 68.3, 62.6, 14.2; IR (KBr): 3381, 3077, 2924, 2853, 1730, 1649, 1598, 1520, 1488, 1448, 1344, 1232, 1092, 1014, 956, 850, 720, 696; ESI FTMS exact mass calcd for $(C_{26}H_{21}ClN_2O_5 + H)^+$ requires *m*/*z* 477.1217, found *m*/*z* 477.1216; enantiomeric excess: 92%, determined by HPLC (Daicel Chirapak IA, hexane–isopropanol = 70 : 30, flow rate 1.0 mL min^{-1}, *T* = 30 °C, 254 nm): t_R = 13.84 min (major), t_R = 20.81 min (minor).

5iaa′: yellow oil; $[\alpha]_D^{20}$ = +104.9 (*c* 0.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.10 (dt, *J* = 2.3 Hz, 4.0 Hz, 2H), 7.69–7.67 (m, 2H), 7.65–7.62 (m, 2H), 7.58–7.54 (m, 3H), 7.46–7.40 (m, 4H), 6.75 (d, *J* = 2.1 Hz, 1H), 5.88 (d, *J* = 1.8 Hz, 1H), 4.28–4.15 (m, 2H), 3.96 (s, 1H), 1.23 (t, *J* = 7.2 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.3, 172.6, 149.9, 147.6, 144.5, 140.2, 139.9, 137.4, 134.5, 133.6, 129.3, 129.0, 128.9, 127.8, 123.8, 78.1, 67.6, 63.0, 14.3; IR (KBr): 3356, 3075, 2924, 2855, 1729, 1651, 1599, 1520, 1485, 1450, 1401, 1341, 1230, 1095, 1019, 838, 718, 698; ESI FTMS exact mass calcd for $(C_{26}H_{21}ClN_2O_5 + H)^+$ requires *m*/*z* 477.1217, found *m*/*z* 477.1216; enantiomeric excess: 98%, determined by HPLC (Daicel Chirapak IA, hexane–isopropanol = 70 : 30, flow rate 1.0 mL min^{-1}, *T* = 30 °C, 254 nm): t_R = 12.95 min (major), t_R = 14.97 min (minor).

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Ethyl 4-benzoyl-2-(3-chlorophenyl)-5-(4-nitrophenyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylate (5jaa and 5jaa′). Reaction time = 60 h; dr (**5jaa** : **5jaa′**) = 1 : 2.4; total yield: 77%.

5jaa: yellow oil; $[\alpha]_D^{20}$ = +46.8 (*c* 0.2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.19 (dt, *J* = 2.4 Hz, 4.2 Hz, 2H), 7.75–7.72 (m, 2H), 7.60–7.52 (m, 4H), 7.48–7.44 (m, 2H), 7.43–7.40 (m, 1H), 7.31–7.30 (m, 2H), 6.88 (d, *J* = 2.0, 1H), 5.71 (d, *J* = 1.9 Hz, 1H), 4.39–4.31 (m, 2H), 3.19 (s, 1H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.8, 172.2, 148.7, 147.6, 143.8, 143.4, 141.7, 137.6, 135.3, 133.6, 130.5, 129.3, 129.1, 128.8, 128.6, 126.1, 124.1, 123.9, 78.6, 68.3, 62.7, 14.2; IR (KBr): 3379, 2924, 2854, 1730, 1650, 1597, 1521, 1452, 1405, 1343, 1234, 1104, 1025, 853, 786, 720, 696; ESI FTMS exact mass calcd for $(C_{26}H_{21}ClN_2O_5 + H)^+$ requires *m*/*z* 477.1217, found *m*/*z* 477.1218; enantiomeric excess: 89%, determined by HPLC (Daicel Chirapak IA, hexane–isopropanol = 70 : 30, flow rate 1.0 mL min^{-1}, *T* = 30 °C, 254 nm): t_R = 10.13 min (major), t_R = 13.10 min (minor).

5jaa′: yellow oil; $[\alpha]_D^{20}$ = +142.0 (*c* 0.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.11 (dt, *J* = 2.3 Hz, 2.0 Hz, 2H), 7.70–7.68 (m, 3H), 7.60–7.54 (m, 4H), 7.45–7.38 (m, 4H), 6.75 (d, *J* = 2.1 Hz, 1H), 5.88 (d, *J* = 1.8 Hz, 1H), 4.29–4.16 (m, 2H), 3.96 (s, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 191.0, 172.2, 149.5, 147.4, 144.3, 143.3, 139.4, 137.1, 134.9, 133.3, 130.1, 129.0, 128.7, 128.4, 126.5, 124.3, 123.6, 77.9, 67.3, 62.9, 14.0; IR (KBr): 3353, 3069, 2923, 2853, 1729, 1651, 1597, 1520, 1451, 1415, 1342, 1229, 1166, 1102, 1022, 855, 793, 719, 694; ESI FTMS exact mass calcd for $(C_{26}H_{21}ClN_2O_5 + H)^+$ requires *m*/*z* 477.1217, found *m*/*z* 477.1216; enantiomeric excess: 97%, determined by HPLC (Daicel Chirapak IC, hexane–isopropanol = 70 : 30, flow rate 1.0 mL min^{-1}, *T* = 30 °C, 254 nm): t_R = 9.19 min (minor), *t* = 10.36 min (major).

Methyl 5-(4-nitrophenyl)-2-phenyl-4-(4-(trifluoromethyl)-benzoyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylate (5af and 5af′). Reaction time = 60 h; dr (**5afa** : **5afa′**) = 1 : 1; total yield: 86%.

5afa: yellow oil; $[\alpha]_D^{20}$ = +64.4 (*c* 0.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.2 (dt, *J* = 2.3 Hz, 1.9 Hz, 2H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.59 (dt, *J* = 2.3 Hz, 1.8 Hz, 2H), 7.5–7.47 (m, 2H), 7.41–7.34 (m, 3H), 6.95 (d, *J* = 2.0 Hz, 1H), 5.73 (d, *J* = 1.8 Hz, 1H), 3.87 (s, 3H), 3.21 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.9, 172.9, 148.7, 147.7, 143.3, 143.2, 141.0, 140.5, 134.8 (*J* = 32.7 Hz), 129.5, 129.4, 128.8, 128.7, 126.1 (*J* = 3.7 Hz), 125.5, 124.0, 79.0, 68.0, 53.4; IR (KBr): 3380, 3068, 2924, 2853, 1735, 1656, 1603, 1522, 1442, 1409, 1324, 1237, 1169, 1130, 1068, 1018, 964, 853, 822, 738, 699; ESI FTMS exact mass calcd for $(C_{26}H_{19}F_3N_2O_5 + H)^+$ requires *m*/*z* 497.1324, found *m*/*z* 497.1324; enantiomeric excess: 78%, determined by HPLC (Daicel Chirapak IA, hexane–isopropanol = 70 : 30, flow rate 1.0 mL min^{-1}, *T* = 30 °C, 254 nm): t_R = 12.92 min (major), t_R = 26.84 min (minor).

5afa′: yellow oil; $[\alpha]_D^{20}$ = +117.7 (*c* 0.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.11 (dt, *J* = 2.4 Hz, 1.9 Hz, 2H), 7.79 (d, *J* = 8.1 Hz, 2H), 7.7 (d, *J* = 8.1 Hz, 2H), 7.67–7.63 (m, 2H), 7.6 (dt, *J* = 2.3 Hz, 1.9 Hz, 2H), 7.5–7.46 (m, 2H), 7.44–7.40 (m, 1H), 6.84 (d, *J* = 2.1 Hz, 1H), 5.87 (d, *J* = 1.9 Hz, 1H), 3.93 (s, 1H), 3.76 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 190.0, 173.3, 149.4, 147.4, 143.9, 141.6, 141.0, 140.0, 134.9 (*J* = 32.6 Hz), 129.6, 129.4, 129.1, 128.6, 126.3, 126.1 (*J* = 3.7 Hz), 125.7, 123.6, 78.3, 67.2, 53.4; IR (KBr): 3356, 3200, 2924, 2855, 1731, 1655, 1519, 1449, 1402, 1325, 1254, 1169, 1125, 1066, 853, 810, 703; ESI FTMS exact mass calcd for $(C_{26}H_{19}F_3N_2O_5 + H)^+$ requires *m*/*z* 497.1324, found *m*/*z* 497.1327; enantiomeric excess: 94%, determined by HPLC (Daicel Chirapak IA, hexane–isopropanol = 70 : 30, flow rate 1.0 mL min^{-1}, *T* = 30 °C, 254 nm): t_R = 9.76 min (minor), t_R = 12.69 min (major).

Methyl 4-(4-fluorobenzoyl)-5-(4-nitrophenyl)-2-phenyl-2,5-dihydro-1*H*-pyrrole-2-carboxylate (5ag and 5ag′). Reaction time = 60 h; dr (**5aga** : **5aga′**) = 1 : 1.2; total yield: 77%.

5aga: yellow oil; $[\alpha]_D^{20}$ = +54.2 (*c* 0.1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.18 (dt, *J* = 1.9 Hz, 4.3 Hz, 2H), 7.82–7.77 (m, 2H), 7.60–7.57 (m, 2H), 7.49–7.46 (m, 2H), 7.41–7.33 (m, 3H), 7.16–7.10 (m, 2H), 6.89 (d, *J* = 2.0 Hz, 1H), 5.73 (d, *J* = 1.8 Hz, 1H), 3.87 (s, 3H), 3.18 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.3, 173.5, 166.2 (*J* = 254.0 Hz), 149.2, 147.9, 143.4, 142.0, 141.2, 133.9, 132.0, 131.9, 129.4, 128.8, 125.9, 124.3, 116.0 (*J* = 21.9 Hz), 79.0, 68.2, 53.3; IR (KBr): 3380, 3073, 2951, 2924, 2854, 1733, 1651, 1598, 1520, 1442, 1410, 1343, 1235, 1154, 1107, 1073, 1022, 965, 852, 752, 698; ESI FTMS exact mass calcd for $(C_{25}H_{19}FN_2O_5 + H)^+$ requires *m*/*z* 447.1356, found *m*/*z* 447.1358; enantiomeric excess: 72%, determined by HPLC (Daicel Chirapak IA, hexane–isopropanol = 70 : 30, flow rate 1.0 mL min^{-1}, *T* = 30 °C, 254 nm): t_R = 15.76 min (major), t_R = 36.28 min (minor).

5aga′: yellow oil; $[\alpha]_D^{20}$ = +119.1 (*c* 0.2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.09 (dt, *J* = 1.9 Hz, 4.2 Hz, 2H), 7.77–7.72 (m, 2H), 7.67–7.64 (m, 2H), 7.60–7.57 (m, 2H), 7.50–7.46 (m, 2H), 7.43–7.39 (m, 1H), 7.12–7.08 (m, 2H), 6.79 (d, *J* = 2.1 Hz, 1H), 5.87 (s, 1H), 3.91 (s, 1H), 3.76 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 189.6, 173.2, 166.2 (*J* = 254.2 Hz), 149.6, 147.4, 144.1, 141.3, 140.1, 133.8, 131.9, 129.0, 128.7, 126.1, 123.6, 115.9 (*J* = 21.9 Hz), 78.3, 67.3, 53.4; IR (KBr):3357, 3071, 2923, 2853, 1733, 1651, 1597, 1519, 1447, 1410, 1343, 1234, 1156, 1105, 1068, 1014, 977, 853, 738, 699; ESI FTMS exact mass calcd for $(C_{25}H_{19}FN_2O_5 + H)^+$ requires *m*/*z* 447.1356, found *m*/*z* 447.1358; enantiomeric excess: 92%, determined by HPLC (Daicel Chirapak IA, hexane–isopropanol = 85 : 15, flow rate 1.0 mL min^{-1}, *T* = 30 °C, 254 nm): t_R = 18.87 min (minor), t_R = 20.91 min (major).

Methyl 4-(3,4-difluorobenzoyl)-5-(4-nitrophenyl)-2-phenyl-2,5-dihydro-1*H*-pyrrole-2-carboxylate (5ai and 5ai′). Reaction time = 60 h; dr (**5aia** : **5aia′**) = 1 : 1.2; total yield: 88%.

5aia: yellow oil; $[\alpha]_D^{20}$ = +56.7 (*c* 0.1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.19 (dt, *J* = 2.3 Hz, 1.9 Hz, 2H), 7.62–7.56 (m, 4H), 7.52–7.46 (m, 2H), 7.42–7.33 (m, 2H), 7.28–7.22 (m, 1H), 6.92 (d, *J* = 2.0 Hz, 1H), 5.72 (d, *J* = 1.9 Hz, 1H), 3.88 (s, 3H), 3.22 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 188.3, 173.3, 148.0 (*J* = 98.5 Hz), 142.6, 142.4, 140.7, 129.1, 128.5, 128.4, 125.5, 124.0, 118.3 (*J* = 16.6 Hz), 117.7 (*J* = 17.6 Hz), 79.0, 68.2, 53.4; IR (KBr): 3436, 3385, 3074, 2922,

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2854, 1733, 1653, 1604, 1517, 1427, 1343, 1279, 1234, 1109, 1063, 1023, 957, 852, 818, 761, 698; ESI FTMS exact mass calcd for $(C_{25}H_{18}F_2N_2O_5 + H)^+$ requires *m*/*z* 465.1262, found *m*/*z* 465.1262; enantiomeric excess: 86%, determined by HPLC (Daicel Chirapak IA, hexane–isopropanol = 70 : 30, flow rate 1.0 mL min^{-1}, *T* = 30 °C, 254 nm): t_R = 15.25 min (major), t_R = 33.92 min (minor).

5aia′: yellow oil; $[\alpha]_D^{20}$ = +126.7 (*c* 0.2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.1 (dt, *J* = 2.3 Hz, 1.9 Hz, 2H), 7.66–7.63 (m, 2H), 7.6–7.56 (m, 3H), 7.5–7.46 (m, 4H), 7.44–7.40 (m, 1H), 6.81 (d, *J* = 2.1 Hz, 1H), 5.85 (d, *J* = 1.9 Hz, 1H), 3.95 (s, 1H), 3.77 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (ppm): 188.3, 173.8, 148.7 (*J* = 190.3 Hz), 142.7 (*J* = 260.1 Hz), 140.9, 134.3, 129.4, 129.1, 128.7, 126.3, 123.9, 118.1 (*J* = 18.3 Hz), 117.6 (*J* = 17.9 Hz), 78.3, 67.3, 53.4; IR (KBr): 3437, 2922, 2854, 1732, 1668, 1644, 1609, 1554, 1515, 1449, 1342, 1279, 1021, 952, 702; ESI FTMS exact mass calcd for $(C_{25}H_{18}F_2N_2O_5 + H)^+$ requires *m*/*z* 465.1262, found *m*/*z* 465.1262; enantiomeric excess: 96%, determined by HPLC (Daicel Chirapak IC, hexane–isopropanol = 70 : 30, flow rate 1.0 mL min^{-1}, *T* = 30 °C, 254 nm): t_R = 9.51 min (minor), t_R = 10.46 min (major).

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