Catalytic Asymmetric Formal [3+2] Cycloaddition of Azoalkenes with 3-Vinylindoles: Synthesis of 2,3-Dihydropyrroles

HIGHLIGHTS
Chiral phosphoric acid catalyzed formal [3 + 2] cycloaddition reaction
2,3-Dihydropyrroles were enantioselectively synthesized
Azoalkenes served as 3-atom synthons

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Mei et al., iScience 23, 100873
February 21, 2020 © 2020 The Authors.
https://doi.org/10.1016/j.isci.2020.100873
Catalytic Asymmetric Formal [3+2] Cycloaddition of Azoalkenes with 3-Vinylindoles: Synthesis of 2,3-Dihydropyrroles

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SUMMARY
Chiral phosphoric acid-catalyzed highly enantioselective formal [3 + 2] cycloaddition reaction of azoalkenes with 3-vinylindoles has been established. Under mild conditions, the projected cycloaddition proceeded smoothly, affording a variety of 2,3-dihydropyrroles in high yields and excellent enantioselectivities, and also in a diastereospecific manner. As opposed to the common 4-atom synthons in the previous literature reports, azoalkenes served as 3-atom synthons. Besides, the observed selectivity was supported by primary theoretical calculation. The unique chemistry of azoalkenes disclosed herein will empower asymmetric synthesis of nitrogen-containing ring structural motifs in a broader context.

INTRODUCTION
1,3-Dipolar cycloadditions are well-established synthetic strategies in organic chemistry for the preparation of five-membered heterocyclic ring systems (Coldham and Hufton, 2005; Fang and Wang, 2018; Gothelf and Jørgensen, 1998; Hashimoto and Maruoka, 2015; Kissane and Maguire, 2010; Stanley and Sibi, 2008). In a typical normal-electron-demand 1,3-dipolar cycloaddition, nucleophilic 1,3-dipoles and electron-deficient dipolarophiles are utilized. Asymmetric versions of such cycloadditions often rely on synthetic strategy that lowers the lowest unoccupied molecular orbital (LUMO) of dipolarophiles (Cheng et al., 2019; Hashimoto et al., 2007; Kano et al., 2005; Liu et al., 2008; Pascual-Escudero et al., 2016; Sibi et al., 2004; Tong et al., 2013; Wang et al., 2015; Xu et al., 2018; Yang et al., 2017). In stark contrast, inverse-electron-demand 1,3-dipolar cycloadditions utilizing electrophilic 1,3-dipoles and nucleophilic dipolarophiles are much less common. Among the reported catalytic asymmetric inverse-electron-demand 1,3-dipolar cycloadditions, nitrones and vinyl ethers are commonly employed reaction partners (Figure 1) (Ashizawa et al., 2006; Bayón et al., 2000a, 2000b; Hashimoto et al., 2011; Hon et al., 1998; Jensen et al., 1999, 2000; Jiao et al., 2008; Mikami et al., 2000; Sibi et al., 2007; Seerden et al., 1994, 1995, 1997; Simonsen et al., 1999a, 1999b; Suga et al., 2007, 2010; Yanagisawa et al., 2011) To date, there are only a handful of exceptions (Bartlett et al., 2017; Liu et al., 2016; Sohtome et al., 2017; Xu et al., 2015; Zhu et al., 2014). Sodeoka et al.’s employment of nitrile oxides as electrophilic 1,3-dipoles and Feng’s utilization of enecarbamates as nucleophilic dipolarophiles are interesting examples, among others. To design inverse-electron-demand 1,3-dipolar cycloaddition processes, we recognized the importance of introducing alternative electrophilic 1,3-dipole surrogates, which ideally could be easily combined with various dipolarophiles, thus allowing for ready creation of useful molecular architectures.

Azoalkenes, also known as 1,2-diaza-1,3-dienes, have proven to be versatile synthetic building blocks in organic chemistry (Attanasi et al., 2002a, 2002b, 2009; Attanasi and Filippone, 1997; Lopes et al., 2018; Wei et al., 2019). Their characteristic 1,3-conjugate systems have been utilized synthetically; azoalkenes were shown to be a valuable acceptor in 1,4-conjugate additions, displaying excellent reactivity toward a wide variety of nucleophiles (Attanasi et al., 2011a, 2011b, 2012, 2013a, 2013b; Ciccolini et al., 2019; Mantenuto et al., 2015; Miles et al., 2015; Preti et al., 2010). Another attractive synthetic application of azoalkenes is the cycloaddition reaction, which serves as a powerful strategy for the construction of nitrogen-containing heterocycles. In the currently available mode of cycloaddition, Wang and others employed azoalkenes as 4-atom (A4) synthons (Int-I), making use of C4 electrophilicity and N1 nucleophilicity of azoalkenes for various asymmetric formal [4 + n] cycloaddition processes (Chen et al., 2012; Gao et al., 2013; Huang et al., 2016; Tong et al., 2014; Wei et al., 2017, 2018; Wei and Wang, 2015; Zhang et al., 2018; Zhang and Song, 2018). Very recently, our group discovered an azoalkene-enabled enantioselective
dearomatization of indoles (Mei et al., 2020). Given the ubiquitous existence of nitrogen-containing cyclic structural motifs, we questioned whether it might be possible to utilize azoalkenes as a carbon-carbon-nitrogen (CCN) 1,3-dipole surrogate, a 3-atom (A3) synthon (Int-II) in asymmetric formal [3 + 2] cycloaddition reactions, and thereby to access a broad range of nitrogen-containing ring systems (Attanasi et al., 2002a, 2002b, 2005, 2013a, 2013b; Clarke et al., 1983; Karapetyan et al., 2008; Mari et al., 2017; Ran et al., 2017; Sommer, 1979). We reasoned the hydrazine-enamine tautomerization could play a key role, and fine-tuning of the system and judicious selection of potential reaction partners are of crucial importance to the successful implementation of synthetic plans (Figure 2). In particular, we believe that the current under-developed status of inverse-electron-demand 1,3-dipolar cycloadditions, in combination of rich chemistry of azoalkenes and anticipated broad applicability of the methodology, make the proposed strategy highly attractive and worthwhile investigating.

2,3-Dihydropyrroles are common structural motifs that are widely present in biologically significant molecules, and they are also valuable intermediates in organic synthesis (Augeri et al., 2005; Cantí et al., 1999; Hertel and Xu, 2002; Herzon and Myers, 2005; Kawase et al., 1999; Marti and Carreira, 2005; Petersen and Nielsen, 2013). Although approaches to access racemic 2,3-dihydropyrroles are well documented (El-Sepelgy et al., 2018; Jiang et al., 2017; Liang et al., 2017, 2018; Ma et al., 2018; Zhu et al., 2009, 2011), reports on catalytic asymmetric synthesis of 2,3-dihydropyrroles are scarce. In an early example, Gong et al. documented a catalytic asymmetric formal [3 + 2] cycloaddition reaction between isocyanates and nitroolefins for the synthesis of optically enriched 2,3-dihydropyrroles (Guo et al., 2008). More recently, Miura and Murakami, as well as the Fokin group, reported enantioselective preparation of 2,3-dihydropyrroles via RhII-catalyzed asymmetric annulations of triazoles with alkenes (Kwok et al., 2014; Miura et al., 2013). As part of our continuous interests in developing enantioselective cycloaddition reactions for the preparation various heterocyclic ring systems (Chan et al., 2019; Han et al., 2014, 2016; Li et al., 2019; Ni et al., 2017; Yao et al., 2016; Wu et al., 2019), we questioned the feasibility of establishing an effective asymmetric synthesis of 2,3-dihydropyrroles via a formal [3 + 2] cycloaddition reaction, by utilizing azoalkenes as an electrophilic CCN 1,3-dipole surrogate and employing simple 3-vinylindoles (Gioia et al., 2008; Li et al., 2018; Sun et al., 2016; Tan et al., 2011; Yang et al., 2019; Zhang et al., 2018; Zheng et al., 2015) as a C2 reaction partner (Figure 3). In this report, we document a formal

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**Figure 1.** Inverse-Electron-Demand 1,3-Dipolar Cycloadditions Utilizing Nitrones and Vinyl Ethers

**Figure 2.** Employment of Azoalkenes As a Reaction Partner in Enantioselective Formal Cycloaddition Reactions

---

FG

2

N

3

EWG

FG

3

N

4

EWG

azeoalkenes

FG

N

E

Nu

[4+n]

Int-I

[3+n]

Int-II

1,3-dipole A3-synthon

aza-diene A4-synthon

R

Nu

E

FG

R

EWG

Nu

E

FG

H

N

Nu

EWG
[3 + 2] cycloaddition reaction for enantioselective creation of 2,3-dihydropyrroles under the catalysis of chiral phosphoric acid (CPA) (Akiyama, 2007; Terada, 2008, 2010; Wu et al., 2015; Yu et al., 2011). The projected progress could be identified as a formal inverse-electron-demand 1,3-dipolar cycloaddition reaction, wherein azoalkene served as a CCN 1,3-dipole surrogate, a 3-atom synthon.

RESULTS AND DISCUSSION

Reaction Development

Our investigation was initiated by identifying optimal conditions for the model reaction between azoalkene 1a and vinylindole 2a (Table 1). TRIP-CPA 4a effectively catalyzed the reaction, furnishing 2,3-dihydropyrrole 3a in excellent yield and moderate stereoselectivities (entry 1). The solvent screening was subsequently carried out, and chloroform was found to be the best solvent (entries 1–5). Next, the catalytic effects of different CPA catalysts (4b–f) were examined. Catalysts 4b and 4e had excellent controls on diastereoselectivities, but enantiomeric controls were less ideal (entries 6 and 9). Although 4c was less effective (entry 7), 4d was completely ineffective (entry 8). To our delight, the SiPh3-derived CPA 4f was found to be an excellent catalyst, leading to the formation of 2,3-dihydropyrrole 3a in excellent yield and excellent enantioselectivity and diastereoselectivity (entry 10). Lowering the reaction temperature or adding molecular sieves did not result in enhancement (entries 11 and 12). Under the optimized reaction conditions, the desired 2,3-dihydropyrrole 3a was obtained in 96% yield, and with 94% ee and >20:1 dr.

Scope

With the optimal reaction conditions in hand, the substrate scope with regard to azoalkenes was evaluated (Table 2). Azoalkenes bearing different R1 groups such as methyl (1a), ethyl (1b), and n-propyl (1c) were well tolerated. When azoalkenes containing different C=C double bond appended ester groups, e.g., CO2Et (1a), CO2Me (1d), CO2tBu (1e), CO2Bn (1f), and CO2iPr (1g) were utilized, consistently high chemical yields and enantio- and diastereoselectivities were attainable.

The reaction scope with regard to vinylindoles was subsequently investigated (Figure 4). Different substituted aryl groups could be installed at the terminal position of vinylindoles, regardless of electronic nature and substitution pattern (3h–3o). Moreover, vinylindoles bearing a dichloro-substituted phenyl ring (3p), a 2-naphthalenyl (3q), or a 2-thiophenyl substituent (3r) were found suitable for the reaction. In all the examples examined, the desired 2,3-dihydropyrrole products were obtained in high yields and with excellent ee values and all the reactions proceeded in a diastereospecific manner.
The indole moieties in the vinylindole structures could also be varied, and the results are summarized in Figure 5. A wide range of vinylindoles bearing various substituted indoles were employed, and the corresponding 2,3-dihydropyrrole products \( 3_s \) \((\text{Scheme } 1)\) were obtained in good to very good yields, and with consistently excellent enantioselectivities, as well as perfect diastereoselectivities. Notably, the electronic nature and position of the indole substituents did not appear to have much influence on the reaction, and this trend held true for 5,6-dichloro-substituted substrate \( 3_e \). The absolute configurations of 2,3-dihydropyrrole products were assigned based on X-ray crystallographic analysis of \( 3_y \).

### Mechanistic Investigations

We carried out a few further experiments to gain a better understanding of this reaction process. When methyl-substituted vinylindole \( 2_b \) was employed, only a moderate ee value of 64\% was obtained (Scheme 1 Equation 1), which suggested the importance of aryl moiety in vinylindole substrates for asymmetric induction. When 2-methyl-substituted vinylindole \( 2_c \) was utilized, a dearomatization of indole occurred, thus yielding 2,3-dihydropyrrole products in high yields and excellent ee values.

### Table 1. Optimization of the Reaction Conditions

| Entry | 4   | Solvent | Yield (%) | ee (%) | Dr |
|-------|-----|---------|-----------|--------|----|
| 1     | 4a  | CH\(_2\)Cl\(_2\) | 95  | 70 | 6:1 |
| 2     | 4a  | Toluene | 90  | 53 | 8:1 |
| 3     | 4a  | THF    | <5  | –  | –  |
| 4     | 4a  | DCE    | 85  | 70 | 7:1 |
| 5     | 4a  | CHCl\(_3\) | 86 | 72 | 11:1 |
| 6     | 4b  | CHCl\(_3\) | 80 | 28 | >20:1 |
| 7     | 4c  | CHCl\(_3\) | 92 | 62 | 7:1 |
| 8     | 4d  | CHCl\(_3\) | 95 | 0  | 2:1 |
| 9     | 4e  | CHCl\(_3\) | 88 | 54 | >20:1 |
| 10    | 4f  | CHCl\(_3\) | 96 | 94 | >20:1 |
| 11\(d\) | 4f  | CHCl\(_3\) | 94 | 92 | >20:1 |
| 12\(e\) | 4f  | CHCl\(_3\) | 92 | 91 | >20:1 |

*Yields refer to isolated yields.  
*The ee values were determined by HPLC analysis on a chiral stationary phase.  
*The dr values were determined by \(^1\)H NMR analysis of the crude mixture.  
*The reaction was carried out at 0°C.  
*Molecular sieves (4 Å) were added.
furnishing the pyrroloindoline product 5 in good yield and excellent enantioselectivity (Scheme 1 Equation 2). It is intriguing to note that such subtle difference in substrate structure could result in totally different chemoselectivity. The presence of a 2-methyl group may render indole higher nucleophilicity at the C3-position, thus favoring the dearomative process (Mei et al., 2020). Furthermore, no reaction was observed when N-methyl vinylindole 2d was employed (Scheme 1 Equation 3), indicating the indispensability of hydrogen bonding interactions between CPA and the substrates, not only in asymmetric induction but also in reaction activation.

On the basis of our experimental results, we have also constructed the models with the aid of computation using 1a and 2a as substrates to obtain some insights into the reaction selectivity. A plausible reaction pathway was proposed (Figure 6) where the asymmetric 1,4-addition of vinylindole 2a to azoalkene 1a is initiated via a hydrogen-bonding activation mode and both substrates can be activated simultaneously by the CPA catalyst within its chiral pockets. Vinylindole 2a adopts the s-cis geometry in order to reach the electrophilic site in 1a. The resulting intermediate A has its conformation locked for the 5-exo attack [3 + 2] of the iminic N to the spatially adjacent C=C bond (N1-C 3.98 Å, path a) to afford the experimentally observed product after proton transfer and tautomerization steps. Alternatively, hydrazone-enamine tautomerization may occur, furnishing intermediate B, which undergoes cyclization to afford the observed [3 + 2] product 3a via path c. In comparison, the 6-exo [4 + 2] attack was deemed difficult to occur. In intermediate A, path b is unfavorable, likely due to the ring strain under such a rigid structure (N2-C 5.32 Å), whereas in intermediate B, pathway d is unlikely because of the reduced nucleophilicity of the amide nitrogen. Indeed, the [4 + 2] products formed via path b or d were never observed in this reaction.

Conclusions
In conclusion, we have established a formal [3 + 2] cycloaddition reaction, utilizing azoalkenes as an electrophilic reaction component and simple alkenes as a nucleophilic partner. In the presence of chiral phosphoric acid, the reaction proceeded smoothly, furnishing a wide range of functionalized 2,3-dihydropyrroles in good yields and in a highly enantioselective and diastereoselective manner. It is noteworthy that the projected progress could be identified as a formal inverse-electron-demand 1,3-dipolar cycloaddition reaction, wherein azoalkenes served as CCN 1,3-dipole surrogates, 3-atom synths, as opposed to the common 4-atom synths in the previous literature reports. With the current successful demonstration of chiral 2,3-dihydropyrrole synthesis and theoretical understanding of the observed chemoselectivity,
we anticipate the unique chemistry of azoalkenes disclosed herein will empower asymmetric synthesis of nitrogen-containing ring structural motifs in a broader context. Our findings in this direction will be reported in due course.

**Figure 4. Reaction Scope of Vinylindoles**

Reaction conditions: 1 (0.1 mmol), 2 (0.12 mmol), and 4f (0.001 mmol) in CHCl₃ (1 mL) at room temperature for 0.5 h. Yields refer to isolated yields; the ee values were determined by HPLC analysis on a chiral stationary phase.
Figure 5. Further Reaction Scope of vinylindoles

Reaction conditions: 1a (0.1 mmol), 2 (0.12 mmol), and 4f (0.001 mmol) in CHCl₃ (1 mL) at room temperature for 0.5 h. Yields refer to isolated yields; the ee values were determined by HPLC analysis on a chiral stationary phase. The absolute configurations of the annulation products were assigned based on X-ray crystallographic analysis of 3y (CCDC 1957143).
Limitations of the Study

A brief examination showed that the present method is not compatible with N-methyl-substituted vinylindole and 2-methyl-substituted vinylindole for the construction of corresponding 2,3-dihydropyrroles.

Scheme 1. Control Experiments

Figure 6. A Plausible Reaction Mechanism Accounting for the Selectivity
METHODS
All methods can be found in the accompanying Transparent Methods supplemental file.

SUPPLEMENTAL INFORMATION
Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2020.100873.

ACKNOWLEDGMENTS
Y.L. thanks the Singapore National Research Foundation, Prime Minister’s Office for the NRF Investigatorship Award (R-143-000-A15-281). Financial supports from the National University of Singapore (R-143-000-695-114 & C-141-000-092-001) and the National Natural Science Foundation of China (21672158 & 21702077) are also gratefully acknowledged.

AUTHOR CONTRIBUTIONS
Methodology, G.-J.M., W.Z., and X.T.; Investigation, G.-J.M.; Calculation, T.P.G. and K.-W.H.; Writing – Original Draft & Review & Editing, G.-J.M. and Y.L.; Conceptualization & Project Administration, G.-J.M. and Y.L.; Supervision, Y.L.

DECLARATION OF INTERESTS
The authors declare no competing interests.

Received: December 30, 2019
Revised: January 13, 2020
Accepted: January 27, 2020
Published: February 21, 2020

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Supplemental Information

Catalytic Asymmetric Formal

[3+2] Cycloaddition of Azoalkenes

with 3-Vinylindoles: Synthesis of 2,3-Dihydropyrroles

Guang-Jian Mei, Wenrui Zheng, Théo P. Gonçalves, Xiwen Tang, Kuo-Wei Huang, and Yixin Lu
Data S1. Spectra of Products: Related to Table 2, Figures 4, 5 and Scheme 1
**Data S2. Product Characterizations: Related to Table 2, Figures 4,5 and Scheme 1**

Ethyl (4R,5R)-5-((1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3a

A colorless oil; isolated yield = 96%, dr >20:1; \([\alpha]_D^{25} = -87\) (c 2.0, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) δ 8.34 (s, 1H), 7.51 (d, \(J = 6.7\) Hz, 1H), 7.38 (d, \(J = 8.2\) Hz, 1H), 7.31 – 7.13 (m, 6H), 7.11 – 7.08 (m, 1H), 6.96 (s, 1H), 6.48 (s, 1H), 4.88 (s, 1H), 4.33 (d, \(J = 7.9\) Hz, 1H), 4.07 – 3.99 (m, 1H), 3.95 – 3.85 (m, 1H), 3.70 (s, 3H), 2.37 (s, 3H), 0.95 (t, \(J = 7.1\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl₃) δ 166.8, 160.2, 156.2, 145.3, 137.1, 128.1, 128.0, 126.2, 125.6, 123.8, 122.5, 119.9, 114.2, 111.6, 102.1, 70.2, 58.9, 53.4, 52.8, 14.0, 12.2; HRMS (ESI) m/z calcd for C₂₄H₂₆N₃O₄ [M + H]⁺ = 420.1918, found = 420.1910; the ee value was 94%, \(t_R\) (major) = 7.0 min, \(t_R\) (minor) = 6.4 min (Chiralpak ID, \(\lambda = 254\) nm, 20% \(i\)-PrOH/Hexane, flow rate = 1.0 mL/min).
Ethyl (4R,5R)-2-ethyl-5-(1H-indol-3-yl)-1-((methoxycarbonyl)amino)-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3b

![Chemical Structure of 3b]

A yellowish oil; isolated yield = 90%, dr >20:1; $\left[\alpha\right]_{D}^{25} = -133$ (c 1.7, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.24 (s, 1H), 7.53 (d, $J = 7.7$ Hz, 1H), 7.39 (d, $J = 8.2$ Hz, 1H), 7.33 – 7.15 (m, 7H), 7.11 (t, $J = 7.5$ Hz, 1H), 6.99 (s, 1H), 6.36 (s, 1H), 4.89 (s, 1H), 4.31 (d, $J = 7.4$ Hz, 1H), 4.08 – 3.88 (m, 2H), 3.71 (s, 3H), 3.11 – 3.06 (m, 1H), 2.66 – 2.50 (m, 1H), 1.25 (t, $J = 7.4$ Hz, 3H), 0.96 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.3, 165.1, 156.3, 145.5, 137.1, 129.1, 128.2, 128.2, 127.9, 126.2, 125.5, 123.7, 122.6, 120.0, 114.5, 111.6, 101.0, 69.9, 58.8, 53.3, 52.9, 19.2, 14.0, 12.6; HRMS (ESI) m/z calcd for C$_{25}$H$_{28}$N$_3$O$_4$ [M + H]$^+$ = 434.2074, found =434.2067; the ee value was 90%, $t_R$ (major) = 5.0 min, $t_R$ (minor) = 6.2 min (Chiralpak IA, $\lambda = 254$ nm, 20% $i$-PrOH/Hexane, flow rate = 1.0 mL/min).

**Racemic 3b**

**Enantioenriched 3b**
Ethyl (4R,5R)-5-((1H-indol-3-yl)-1-((methoxycarbonyl)amino)-4-phenyl-2-propyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3c

![Chemical Structure](image)

A yellowish oil; isolated yield = 94%, dr >20:1; $[\alpha]_D^{25} = -110$ (c 2.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.24 (s, 1H), 7.53 (d, $J = 7.5$ Hz, 1H), 7.39 (d, $J = 8.2$ Hz, 1H), 7.34 – 7.15 (m, 6H), 7.13 – 7.09 (m, 1H), 6.98 (s, 1H), 6.34 (s, 1H), 4.89 (s, 1H), 4.33 (d, $J = 7.5$ Hz, 1H), 4.08 – 3.88 (m, 2H), 3.71 (s, 3H), 3.08 (d, $J = 12.0$ Hz, 1H), 2.63 – 2.41 (m, 1H), 1.71 – 1.66 (m, 2H), 1.06 (t, $J = 7.4$ Hz, 3H), 0.97 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.4, 163.6, 156.2, 145.5, 137.1, 128.1, 127.9, 126.2, 125.5, 123.8, 122.6, 119.9, 114.5, 111.6, 101.8, 69.8, 58.8, 53.3, 52.9, 27.6, 21.7, 14.2, 14.0; HRMS (ESI) m/z calcd for C$_{26}$H$_{30}$N$_{3}$O$_{4}$ [M + H]$^+$ = 448.2231, found = 448.2235; the ee value was 83%, $t_R$ (major) = 7.1 min, $t_R$ (minor) = 5.5 min (Chiralpak ID, $\lambda = 254$ nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

![Racemic Chromatogram](image)

Racemic 3c

![Enantioenriched Chromatogram](image)

Enantioenriched 3c
Methyl (4\(R\),5\(R\))-5-(1\(H\)-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-phenyl-4,5-dihydro-1\(H\)-pyrrole-3-carboxylate 3d

A yellowish oil; isolated yield = 85\%, dr >20:1; \([\alpha]_D^{25} = -92 \text{ (c 0.8, CHCl}_3\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.17 (s, 1H), 7.51 (d, \(J = 9.0 \text{ Hz}, 1\)H), 7.40 (d, \(J = 8.2 \text{ Hz}, 1\)H), 7.32 – 7.15 (m, 6H), 7.13 – 7.09 (m, 1H), 7.00 (s, 1H), 6.36 (s, 1H), 4.84 (s, 1H), 4.33 (d, \(J = 7.8 \text{ Hz}, 1\)H), 3.71 (s, 2H), 3.51 (s, 3H), 2.37 (d, \(J = 1.2 \text{ Hz}, 3\)H); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 167.1, 160.3, 156.1, 145.1, 137.0, 129.0, 128.2, 127.8, 126.3, 125.6, 123.7, 122.6, 120.0, 119.9, 114.3, 111.5, 101.7, 70.2, 53.2, 52.9, 50.4, 12.2; HRMS (ESI) m/z calcd for C\(_{23}\)H\(_{24}\)N\(_3\)O\(_4\) [M + H\(^+\)] = 406.1761, found = 406.1751; the ee value was 94\%, \(t_R\) (major) = 9.0 min, \(t_R\) (minor) = 5.5 min (Chirapak IA, \(\lambda = 254 \text{ nm}, 20\% \text{ i-PrOH/Hexane, flow rate = 1.0 mL/min}).
Tert-butyl \((4R,5R)-5-(1H-indol-3-yl)-1-((methoxycarbonyl)amino)-4-phenyl-4,5-dihydro-1H-pyrrole-3-
\text{carboxylate 3e}

A colorless oil; isolated yield = 86\%, \text{dr} >20:1; [\alpha]^{25}_{D} = -102 \text{ (c 1.0, CHCl}_3\text{)}; ^1H \text{ NMR (400 MHz, CDCl}_3\text{)} \delta 8.22 \text{ (s, 1H), 7.54 (s, 1H), 7.39 (d, } J = 8.2 \text{ Hz, 1H), 7.26 - 7.15 (m, 6H), 7.12 - 7.09 (m, 1H), 6.97 \text{ (s, 1H), 6.40 (s, 1H), 4.83 (s, 1H), 4.25 (d, } J = 8.4 \text{ Hz, 1H), 3.68 (s, 3H), 2.35 (d, } J = 1.4 \text{ Hz, 3H), 1.15 \text{ (s, 9H); }^{13}\text{C NMR (100 MHz, CDCl}_3\text{)} \delta 166.2, 159.8, 156.1, 145.4, 137.0, 128.2, 128.0, 126.1, 125.8, 123.7, 122.5, 120.0, 119.8, 114.4, 111.5, 103.9, 78.8, 70.4, 53.9, 52.8, 28.1, 12.1; \text{HRMS (ESI) } m/z \text{ calcd for } C_{26}H_{30}N_3O_4 [M + H]^+ = 448.2231, \text{ found } = 448.2219; \text{ the ee value was 92\%, } t_R \text{ (major) } = 8.2 \text{ min, } t_R \text{ (minor) } = 9.2 \text{ min (Chiralpak ID, } \lambda = 254 \text{ nm, 10\% } i\text{-PrOH/Hexane, flow rate } = 1.0 \text{ mL/min)}.
Benzyl (4R,5R)-5-(1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3f

A yellowish oil; isolated yield = 95%; dr >20:1; \([\alpha]_D^{25} = -101\) (c 2.3, CHCl3); \(^1\)H NMR (400 MHz, CDCl3) \(\delta 8.22\) (s, 1H), 7.51 (d, \(J = 7.6\) Hz, 1H), 7.38 (d, \(J = 8.2\) Hz, 1H), 7.30 – 7.06 (m, 10H), 6.96 (s, 1H), 6.88 – 6.81 (m, 2H), 6.43 (s, 1H), 5.12 – 4.85 (m, 3H), 4.37 (d, \(J = 7.9\) Hz, 1H), 3.70 (s, 3H), 2.39 (d, \(J = 1.3\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl3) \(\delta 166.5, 161.2, 156.1, 145.2, 137.0, 136.8, 128.3, 128.1, 127.3, 126.3, 125.6, 123.8, 122.6, 120.0, 119.8, 114.1, 111.6, 101.4, 70.4, 64.8, 53.3, 52.9, 12.3; HRMS (ESI) m/z calcd for C\(_{29}\)H\(_{28}\)N\(_3\)O\(_4\) [M + H]\(^+\) = 482.2074, found = 482.2065; the ee value was 91%, \(t_R\) (major) = 17.0 min, \(t_R\) (minor) = 14.7 min (Chiralpak IC, \(\lambda = 254\) nm, 10% \(i\)-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3f

Enantioenriched 3f
Isopropyl (4R,5R)-5-(1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3g

A yellowish oil; isolated yield = 92%; dr >20:1; [α]_D^{25} = −106 (c 1.5, CHCl₃); 'H NMR (400 MHz, CDCl₃) δ 8.27 (s, 1H), 7.52 (s, 1H), 7.39 (d, J = 8.2 Hz, 1H), 7.32 – 7.05 (m, 7H), 6.99 (s, 1H), 6.43 (s, 1H), 4.90 – 4.82 (m, 2H), 4.30 (d, J = 8.3 Hz, 1H), 3.70 (s, 3H), 2.37 (d, J = 1.4 Hz, 3H), 1.07 (d, J = 6.2 Hz, 3H), 0.75 (d, J = 6.2 Hz, 3H); ^13C NMR (100 MHz, CDCl₃) δ 166.2, 160.0, 156.1, 145.4, 137.0, 128.0, 126.1, 125.7, 123.7, 122.5, 119.9, 119.9, 114.3, 111.5, 102.7, 70.3, 65.9, 53.5, 52.8, 22.0, 21.4, 12.1; HRMS (ESI) m/z calcd for C₂₅H₂₈N₃O₄ [M + H]^+ = 434.2074, found = 434.2063; the ee value was 91%, t_R (major) = 6.3 min, t_R (minor) = 5.7 min (Chiralpak ID, λ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
Ethyl (4R,5R)-5-(1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-(o-tolyl)-4,5-dihydro-1H-pyrrole-3-carboxylate 3h

A yellowish oil; isolated yield = 99%; dr >20:1; $\left[\alpha\right]_D^{25} = -94$ (c 2.4, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.26 (s, 1H), 7.52 (d, $J = 3.6$ Hz, 2H), 7.38 (d, $J = 8.2$ Hz, 1H), 7.24 – 7.16 (m, 2H), 7.13 – 7.02 (m, 2H), 6.98 (s, 2H), 6.41 (s, 1H), 4.87 (s, 1H), 4.70 (d, $J = 7.8$ Hz, 1H), 4.03 – 3.85 (m, 2H), 3.69 (s, 3H), 2.37 (d, $J = 0.9$ Hz, 3H), 1.94 (s, 3H), 0.91 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.6, 160.0, 156.1, 143.8, 137.0, 135.8, 129.4, 127.7, 126.4, 125.9, 125.6, 123.6, 122.5, 119.9, 119.8, 114.5, 111.5, 102.5, 70.3, 58.9, 52.8, 48.3, 19.6, 13.9, 12.1; HRMS (ESI) m/z calcd for C$_{25}$H$_{28}$N$_3$O$_4$ [M + H]$^+$ = 434.2074, found = 434.2070; the ee value was 90%, $t_R$ (major) = 6.1 min, $t_R$ (minor) = 5.0 min (Chiralpak IA, $\lambda = 254$ nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
Ethyl (4R,5R)-5-([1H-indol-3-yl]-1-((methoxycarbonyl)amino)-2-methyl-4-(m-tolyl)-4,5-dihydro-1H-pyrrole-3-carboxylate 3i

A colorless oil; isolated yield = 75%; dr >20:1; [α]₂⁵\(^D\) = –93 (c 0.6, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) δ 8.27 (s, 1H), 7.58 – 7.48 (m, 1H), 7.38 (d, \(J = 8.2\) Hz, 1H), 7.23 (dd, \(J = 11.3, 3.9\) Hz, 1H), 7.16 – 7.02 (m, 4H), 6.98 (s, 2H), 6.40 (s, 1H), 4.87 (s, 1H), 4.30 (d, \(J = 8.0\) Hz, 1H), 4.09 – 4.01 (m, 1H), 3.96 – 3.88 (m, 1H), 3.70 (s, 2H), 2.36 (d, \(J = 1.1\) Hz, 3H), 2.28 (s, 3H), 0.97 (t, \(J = 7.1\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl₃) δ 166.8, 159.9, 156.2, 145.1, 137.5, 137.0, 128.8, 128.0, 127.0, 125.6, 125.0, 123.8, 122.5, 119.9, 114.3, 111.6, 102.2, 70.2, 58.9, 53.2, 21.4, 14.1, 12.2; HRMS (ESI) m/z calcd for C₂₅H₂₈N₃O₄ [M + H]\(^+\) = 434.2074, found = 434.2068; the ee value was 92%, \(t_R\) (major) = 7.5 min, \(t_R\) (minor) = 6.4 min (Chiralpak IC, \(\lambda = 254\) nm, 20% \(-\)PrOH/Hexane, flow rate = 1.0 mL/min).
Ethyl (4R,5R)-4-(3-chlorophenyl)-5-(1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3j

A yellowish oil; isolated yield = 80%; dr >20:1; [α]D25 = -109 (c 1.7, CHCl3); 1H NMR (400 MHz, CDCl3) δ 8.24 (s, 1H), 7.51 (d, J = 8.2 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.29 – 7.08 (m, 6H), 7.01 (s, 1H), 6.41 (s, 1H), 4.85 (s, 1H), 4.30 (d, J = 8.1 Hz, 1H), 4.08 – 4.01 (m, 1H), 3.95 – 3.87 (m, 1H), 3.71 (s, 3H), 2.37 (d, J = 1.2 Hz, 3H), 0.98 (t, J = 7.1 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 166.4, 160.6, 154.4, 147.4, 137.1, 133.8, 129.4, 128.3, 126.4, 126.2, 125.4, 123.8, 122.7, 120.1, 119.8, 113.9, 111.6, 101.6, 69.9, 58.9, 53.1, 52.9, 14.1, 12.2; HRMS (ESI) m/z calcd for C24H25ClN3O4 [M + H]+ = 454.1528, found = 454.1521; the ee value was 94%, tR (major) = 5.0 min, tR (minor) = 7.3 min (Chiralpak IA, λ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
Ethyl (4R,5R)-5-(1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-(p-tolyl)-4,5-dihydro-1H-pyrrole-3-carboxylate 3k

A yellowish oil; isolated yield = 99%; dr > 20:1; [α]$_D^{25}$ = −130 (c 2.2, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.24 (s, 1H), 7.52 (d, $J$ = 7.2 Hz, 1H), 7.38 (d, $J$ = 8.2 Hz, 1H), 7.23 (dd, $J$ = 11.3, 3.9 Hz, 1H), 7.18 – 7.03 (m, 5H), 6.98 (s, 1H), 6.41 (s, 1H), 4.84 (s, 1H), 4.30 (d, $J$ = 7.6 Hz, 1H), 4.06 – 3.88 (m, 2H), 3.70 (s, 3H), 2.36 (d, $J$ = 0.9 Hz, 3H), 2.30 (s, 3H), 0.99 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.8, 159.8, 156.1, 142.3, 137.0, 135.6, 128.8, 127.8, 125.6, 123.7, 122.5, 119.9, 114.4, 111.5, 102.2, 70.3, 58.9, 52.9, 21.1, 14.1, 12.2; HRMS (ESI) m/z calcd for C$_{25}$H$_{28}$N$_3$O$_4$ [M + H]$^+$ = 434.2074, found = 434.2062; the ee value was 90%, t$_R$ (major) = 6.8 min, t$_R$ (minor) = 5.5 min (Chiralpak IA, λ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
Ethyl (4R,5R)-4-(4-fluorophenyl)-5-(1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4,5-dihydro-1H-pyrrole-3-carboxylate 31

A yellowish oil; isolated yield = 92%; dr >20:1; $\left[\alpha\right]_{D}^{25} = -124$ (c 1.8, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.28 (s, 1H), 7.49 (d, $J = 7.3$ Hz, 1H), 7.39 (d, $J = 8.2$ Hz, 1H), 7.26 – 7.16 (m, 3H), 7.10 (t, $J = 7.5$ Hz, 1H), 7.00 (s, 1H), 6.93 (t, $J = 8.7$ Hz, 2H), 6.45 (s, 1H), 4.83 (s, 1H), 4.30 (d, $J = 8.1$ Hz, 1H), 4.07 – 3.99 (m, 1H), 3.95 – 3.86 (m, 1H), 3.71 (s, 3H), 2.36 (d, $J = 1.1$ Hz, 3H), 0.98 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.6, 161.5 (d, $J = 242$ Hz), 160.3, 156.1, 141.1, 137.1, 129.4, 125.6, 123.6, 122.6, 119.9 (d, $J = 19$ Hz), 114.8 (d, $J = 21$ Hz), 114.1, 111.6, 102.0, 70.2, 58.9, 52.9, 52.8, 14.1, 12.2; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -117.4; HRMS (ESI) m/z calcd for C$_{24}$H$_{25}$FN$_{3}$O$_{4}$ [M + H]$^+$ = 438.1824, found = 438.1815; the ee value was 94%, $t_R$ (major) = 5.2 min, $t_R$ (minor) = 7.9 min (Chiralpak IA, $\lambda = 254$ nm, 20% $i$-PrOH/Hexane, flow rate = 1.0 mL/min).

![Chromatogram](Racemic 31)

![Chromatogram](Enantioenriched 31)
Ethyl (4\(R,5R\))-4-(4-chlorophenyl)-5-(1\(H\)-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4,5-dihydro-1\(H\)-pyrrole-3-carboxylate 3m

A yellowish oil; isolated yield = 99%; dr >20:1; \([\alpha]_D^{25} = -120\) (c 2.3, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.27 (s, 1H), 7.50 (d, \(J = 7.4\) Hz, 1H), 7.39 (d, \(J = 8.2\) Hz, 1H), 7.26 – 7.14 (m, 5H), 7.11 (t, \(J = 7.5\) Hz, 1H), 7.00 (s, 1H), 6.45 (s, 1H), 4.81 (s, 1H), 4.30 (d, \(J = 8.0\) Hz, 1H), 4.08 – 3.88 (m, 2H), 3.71 (s, 3H), 2.36 (d, \(J = 0.9\) Hz, 3H), 0.99 (t, \(J = 7.1\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 166.5, 160.5, 156.0, 143.8, 137.1, 131.9, 129.4, 128.3, 125.5, 123.7, 122.7, 120.0, 119.8, 114.0, 111.6, 101.8, 70.1, 59.0, 52.9, 14.1, 12.2; HRMS (ESI) m/z calcd for C\(_{24}\)H\(_{25}\)ClN\(_3\)O\(_4\) [M + H]\(^+\) = 454.1528, found = 454.1518; the ee value was 94%, \(t_R\) (major) = 5.5 min, \(t_R\) (minor) = 7.4 min (Chiralpak IA, \(\lambda\) = 254 nm, 20% \(i\)-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3m  Enantioenriched 3m
Ethyl (4R,5R)-5-(1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-(4-nitrophenyl)-4,5-dihydro-1H-pyrrole-3-carboxylate 3n

A yellowish oil; isolated yield = 91%; dr >20:1; $[\alpha]_D^{25} = -119$ (c 2.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.26 (s, 1H), 8.12 (d, $J = 8.7$ Hz, 2H), 7.58 – 7.37 (m, 4H), 7.28 – 7.08 (m, 2H), 7.01 (d, $J = 1.7$ Hz, 1H), 6.47 (s, 1H), 4.84 (s, 1H), 4.46 (d, $J = 8.5$ Hz, 1H), 4.05 – 3.90 (m, 2H), 3.73 (s, 3H), 2.39 (d, $J = 1.3$ Hz, 3H), 0.98 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.1, 161.2, 156.0, 152.9, 146.6, 137.1, 129.0, 128.9, 128.2, 125.3, 123.8, 123.6, 122.9, 120.2, 119.6, 113.5, 111.7, 101.1, 69.6, 59.1, 53.4, 53.0, 14.1, 12.3; HRMS (ESI) m/z calcd for C$_{24}$H$_{25}$N$_4$O$_6$ [M + H]$^+$ = 465.1769, found = 465.1753; the ee value was 95%, $t_R$ (major) = 6.3 min, $t_R$ (minor) = 9.9 min (Chiralpak IA, $\lambda = 254$ nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
Ethyl (4R,5R)-5-((1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrrole-3-carboxylate 3o

A yellowish oil; isolated yield = 95%; dr >20:1; $[\alpha]_D^{25} = -116$ (c 2.2, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.27 (s, 1H), 7.50 (d, $J$ = 8.0 Hz, 3H), 7.39 (dd, $J$ = 12.8, 7.5 Hz, 3H), 7.28 – 7.22 (m, 1H), 7.14 – 7.10 (m, 1H), 7.00 (s, 1H), 6.45 (s, 1H), 4.84 (s, 1H), 4.40 (d, $J$ = 8.3 Hz, 1H), 4.08 – 3.88 (m, 2H), 3.71 (s, 3H), 2.38 (d, $J$ = 0.7 Hz, 3H), 0.96 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.4, 160.8, 156.0, 149.3, 137.1, 128.7, 128.3, 125.8 (t, $J$ = 270 Hz), 125.5, 125.1 (d, $J$ = 4 Hz), 123.8, 123.1, 122.7, 120.1, 119.7, 113.8, 111.7, 101.4, 69.9, 59.0, 53.2, 52.9, 14.0, 12.2; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -62.2; HRMS (ESI) m/z calcd for C$_{25}$H$_{25}$F$_3$N$_3$O$_4$ [M + H]$^+$ = 488.1792, found = 488.1773; the ee value was 93%, $t_R$ (major) = 4.6 min, $t_R$ (minor) = 6.9 min (Chiralpak IA, $\lambda$ = 254 nm, 20% $i$-PrOH/Hexane, flow rate = 1.0 mL/min).
Ethyl (4R,5R)-4-(3,4-dichlorophenyl)-5-(1H-indol-3-yl)-1-(((methoxycarbonyl)amino)-2-methyl-4,5-
dihydro-1H-pyrrole-3-carboxylate 3p

A yellowish oil; isolated yield = 99%; dr >20:1; [α]$^D_{25}$ = -154 (c 2.4, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.29 (s, 1H), 7.50 (d, $J$ = 7.8 Hz, 1H), 7.40 (d, $J$ = 8.2 Hz, 1H), 7.35 (s, 1H), 7.32 (d, $J$ = 8.2 Hz, 1H), 7.26 – 7.21 (m, 1H), 7.14 – 7.10 (m, 2H), 7.01 (s, 1H), 6.46 (s, 1H), 4.81 (s, 1H), 4.28 (d, $J$ = 8.1 Hz, 1H), 4.10 – 3.90 (m, 2H), 3.71 (s, 3H), 2.36 (d, $J$ = 1.0 Hz, 3H), 1.02 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.3, 160.8, 156.1, 145.7, 137.1, 131.9, 130.1, 127.5, 125.4, 123.8, 122.8, 120.1, 119.7, 113.7, 111.7, 101.1, 69.8, 59.1, 53.0, 52.7, 14.1, 12.2; HRMS (ESI) m/z calcd for C$_{24}$H$_{24}$Cl$_2$N$_3$O$_4$ [M + H]$^+$ = 488.1138, found = 488.1120; the ee value was 95%, $t_R$ (major) = 5.0 min, $t_R$ (minor) = 7.1 min (Chiralpak IA, λ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

![Chromatogram](image1)

**Racemic 3p**

![Chromatogram](image2)

**Enantioenriched 3p**
Ethyl (4R,5R)-5-(1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-(naphthalen-2-yl)-4,5-dihydro-1H-pyrrole-3-carboxylate 3q

A yellowish solid; isolated yield = 98%; dr > 20:1; $[\alpha]_{D}^{25} = -150$ (c 2.5, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.22 (s, 1H), 7.78 (dd, $J = 9.8$, 5.9 Hz, 2H), 7.71 (dd, $J = 6.1$, 3.4 Hz, 1H), 7.62 (s, 1H), 7.59 – 7.46 (m, 2H), 7.43 – 7.34 (m, 3H), 7.28 – 7.21 (m, 1H), 7.11 (t, $J = 7.4$ Hz, 1H), 6.93 (s, 1H), 6.44 (s, 1H), 4.96 (s, 1H), 4.52 (d, $J = 8.2$ Hz, 1H), 4.00 – 3.84 (m, 2H), 3.71 (s, 3H), 2.41 (d, $J = 1.2$ Hz, 3H), 0.89 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.7, 160.3, 156.1, 142.5, 137.1, 133.4, 132.4, 127.9, 127.8, 127.6, 126.5, 125.6, 125.1, 123.8, 122.6, 120.0, 114.2, 111.6, 102.1, 70.1, 58.9, 53.5, 52.9, 14.1, 12.3; HRMS (ESI) m/z calcd for C$_{28}$H$_{28}$N$_3$O$_4$ [M + H]$^+$ = 470.2074, found = 470.2074; the ee value was 95%, $t_R$ (major) = 7.0 min, $t_R$ (minor) = 8.6 min (Chiralpak IA, $\lambda = 254$ nm, 20% i-PrOH.Hexane, flow rate = 1.0 mL/min).

![Chromatogram](image1.png)  
Racemic 3q

![Chromatogram](image2.png)  
Enantioenriched 3q
Ethyl (4'R,5'R)-5-(1'H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-(thiophen-2-yl)-4,5-dihydro-1'H-pyrrole-3-carboxylate 3r

A yellowish oil; isolated yield = 91%; dr >20:1; [α]D25 = -106 (c 1.8, CHCl3); 1H NMR (400 MHz, CDCl3) δ 8.32 (s, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.40 (d, J = 8.2 Hz, 1H), 7.23 (dd, J = 11.2, 3.9 Hz, 1H), 7.16 – 7.02 (m, 3H), 6.91 – 6.75 (m, 2H), 6.44 (s, 1H), 4.92 (s, 1H), 4.60 (d, J = 7.2 Hz, 1H), 4.16 – 4.07 (m, 1H), 4.02 – 3.94 (m, 1H), 3.70 (s, 3H), 2.35 (d, J = 1.1 Hz, 3H), 1.04 (t, J = 7.1 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 166.6, 160.2, 155.8, 149.1, 137.0, 126.6, 125.6, 124.1, 123.9, 123.5, 122.6, 120.0, 119.7, 113.9, 111.6, 101.9, 70.6, 59.0, 52.9, 48.4, 14.1, 12.2; HRMS (ESI) m/z calcd for C22H24N3O4S [M + H]+ = 426.1482, found = 426.1489; the ee value was 95%, tR (major) = 9.0 min, tR (minor) = 7.2 min (Chiralpak IC, λ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
Ethyl (4R,5R)-5-(4-methoxy-1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3s

A colorless oil; isolated yield= 98%; dr >20:1; \([\alpha]_{D}^{25} = -126\) (c 2.4, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) \(\delta\) 8.36 (s, 1H), 7.32 (s, 2H), 7.27 – 7.21 (m, 2H), 7.19 – 7.06 (m, 2H), 7.02 – 6.90 (m, 2H), 6.45 (d, \(J = 7.7\) Hz, 2H), 5.19 (s, 1H), 4.27 (d, \(J = 6.4\) Hz, 1H), 4.05 – 3.87 (m, 2H), 3.82 – 3.42 (m, 6H), 2.31 (s, 3H), 0.98 (t, \(J = 7.1\) Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) \(\delta\) 166.9, 159.7, 156.4, 154.2, 145.6, 138.3, 128.1, 127.9, 125.9, 123.2, 121.8, 116.6, 115.2, 104.5, 99.8, 69.4, 58.7, 54.8, 52.7, 14.2, 12.2; HRMS (ESI) m/z calcd for C$_{25}$H$_{28}$N$_3$O$_5$ [M + H]$^+$ = 450.2023, found = 450.2020; the ee value was 92%, \(t_R\) (major) = 7.8 min, \(t_R\) (minor) = 7.1 min (Chiralpak IC, \(\lambda = 254\) nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3s

Enantioenriched 3s
Ethyl (4R,5R)-1-((methoxycarbonyl)amino)-2-methyl-5-(5-methyl-1H-indol-3-yl)-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3t

A colorless oil; isolated yield = 88%; dr >20:1; [α]_D^{25} = −105 (c 1.8, CHCl₃); ^1H NMR (400 MHz, CDCl₃) δ 8.12 (s, 1H), 7.34 – 7.12 (m, 7H), 7.05 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 6.40 (s, 1H), 4.86 (s, 1H), 4.32 (d, J = 8.4 Hz, 1H), 4.07 – 4.00 (m, 1H), 3.94 – 3.87 (m, 1H), 3.71 (s, 3H), 2.42 (s, 3H), 2.37 (d, J = 1.2 Hz, 3H), 0.95 (t, J = 7.1 Hz, 3H); ^13C NMR (100 MHz, CDCl₃) δ 166.7, 160.2, 156.1, 145.2, 135.3, 129.2, 128.1, 126.2, 125.9, 124.1, 123.8, 119.5, 113.6, 111.2, 102.3, 70.3, 58.8, 53.2, 52.8, 21.57, 14.0, 12.2; HRMS (ESI) m/z calcd for C₂₅H₂₈N₃O₄ [M + H]^+ = 434.2074, found = 434.2068; the ee value was 90%, t_R (major) = 6.5 min, t_R (minor) = 5.8 min (Chiralpak ID, λ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
Ethyl (4R,5R)-5-(5-methoxy-1H-indol-3-yl)-1-(((methoxycarbonyl)amino)-2-methyl-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3u

A yellow oil; isolated yield = 85%; δr >20:1; [α]D25 = -116 (c 1.8, CHCl3); 1H NMR (400 MHz, CDCl3) δ 8.15 (s, 1H), 7.36 – 7.22 (m, 5H), 7.19 – 7.16 (m, 1H), 7.00 (s, 1H), 6.88 – 6.85 (m, 2H), 6.44 (s, 1H), 4.88 (s, 1H), 4.27 (d, J = 7.4 Hz, 1H), 4.07 – 3.98 (m, 1H), 3.95 – 3.87 (m, 1H), 3.73 (s, 6H), 2.36 (d, J = 1.1 Hz, 3H), 0.95 (t, J = 7.1 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 166.6, 160.1, 154.1, 145.2, 132.0, 128.2, 128.0, 126.3, 126.1, 124.0, 114.3, 112.6, 112.2, 109.5, 102.4, 101.6, 70.2, 58.9, 55.7, 53.4, 52.9, 14.1, 12.1; HRMS (ESI) m/z calcd for C25H28N3O5 [M + H]+ = 450.2023, found = 450.2015; the ee value was 90%, tR (major) = 14.0 min, tR (minor) = 6.2 min (Chiralpak IA, λ = 254 nm, 10% i-PrOH/Hexane, flow rate = 1.0 mL/min).
Ethyl (4R,5R)-5-(5-fluoro-1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3v

A yellow oil; isolated yield = 83%; dr >20:1; $\left[a\right]^{25}_D = -98$ (c 1.7, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.33 (s, 1H), 7.32 – 7.10 (m, 7H), 7.03 – 6.93 (m, 2H), 6.44 (s, 1H), 4.83 (s, 1H), 4.26 (d, $J = 8.2$ Hz, 1H), 4.08 – 3.98 (m, 1H), 3.95 – 3.86 (m, 1H), 3.70 (s, 3H), 2.36 (d, $J = 1.3$ Hz, 3H), 0.95 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.5, 160.2, 157.7 (d, $J = 233$ Hz), 156.0, 145.0, 133.5, 128.1, 128.0, 126.3, 125.4, 114.34, 112.2 (d, $J = 8$ Hz), 110.9 (d, $J = 27$ Hz), 104.7 (d, $J = 23$ Hz), 70.1, 59.0, 53.4, 52.9, 14.0, 12.2; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -123.6; HRMS (ESI) m/z calcd for C$_{24}$H$_{25}$FN$_3$O$_4$ [M + H]$^+$ = 438.1824, found = 438.1813; the ee value was 93%, $t_R$ (major) = 6.1 min, $t_R$ (minor) = 5.4 min (Chiralpak ID, $\lambda = 254$ nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

![Chromatogram](Image)

Racemic 3v  Enantioenriched 3v
Ethyl (4R,5R)-5-(5-chloro-1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3w

A yellow oil; isolated yield = 76%; dr > 20:1; [α]$_D^{25}$ = -107 (c 1.6, CHCl$_3$); 1H NMR (400 MHz, CDCl$_3$) δ 8.36 (s, 1H), 7.43 (s, 1H), 7.29 (d, J = 8.6 Hz, 1H), 7.26 – 7.12 (m, 6H), 6.98 (s, 1H), 6.44 (s, 1H), 4.84 (s, 1H), 4.25 (d, J = 9.2 Hz, 1H), 4.06 – 3.99 (m, 1H), 3.94 – 3.86 (m, 1H), 3.70 (s, 3H), 2.36 (d, J = 1.4 Hz, 3H), 0.94 (t, J = 7.1 Hz, 3H); 13C NMR (100 MHz, CDCl$_3$) δ 166.5, 160.3, 156.0, 144.7, 135.3, 128.1, 128.0, 126.8, 126.3, 125.6, 125.0, 122.9, 119.3, 113.9, 112.6, 102.6, 70.2, 59.0, 53.4, 52.9, 14.0, 12.3; HRMS (ESI) m/z calcd for C$_{24}$H$_{25}$ClN$_3$O$_4$ [M + H]$^+$ = 454.1528, found = 454.1535; the ee value was 94%, t$_R$ (major) = 5.7 min, t$_R$ (minor) = 5.0 min (Chiralpak ID, λ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3w

Enantioenriched 3w
Ethyl (4R,5R)-5-(5-chloro-1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3x

A yellowish solid; isolated yield = 70%; dr >20:1; [α]$_D^{25}$ = -109 (c 1.5, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.41 (s, 1H), 7.57 (s, 1H), 7.33 – 7.14 (m, 7H), 6.96 (s, 1H), 6.46 (s, 1H), 4.84 (s, 1H), 4.25 (d, $J$ = 8.9 Hz, 1H), 4.08 – 4.00 (m, 1H), 3.95 – 3.87 (m, 1H), 3.70 (s, 3H), 2.36 (d, $J$ = 1.3 Hz, 3H), 0.94 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 166.6, 160.4, 156.0, 144.7, 135.6, 128.1, 128.0, 127.5, 126.3, 125.4, 124.8, 122.3, 113.7, 113.0, 102.6, 70.2 59.0, 53.4, 52.9, 14.0, 12.3; HRMS (ESI) m/z calcd for C$_{24}$H$_{25}$BrN$_3$O$_4$ [M + H]$^+$ = 498.1023, found = 498.1011; the ee value was 94%, $t_R$ (major) = 7.6 min, $t_R$ (minor) = 4.9 min (Chiralpak IC, $\lambda$ = 254 nm, 10% i-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3x  Enantioenriched 3x
Ethyl (4R,5R)-5-(5-cyano-1H-indol-3-yl)-1-(((methoxycarbonyl)amino)-2-methyl-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3y

A yellowish solid; isolated yield = 73%; dr >20:1; \([\alpha]_D^{25} = -82\) (c 1.5, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) δ 8.87 (s, 1H), 7.76 (s, 1H), 7.41 (s, 2H), 7.25 – 7.04 (m, 6H), 6.56 (s, 1H), 4.86 (s, 1H), 4.20 (d, J = 9.2 Hz, 1H), 4.08 – 4.00 (m, 1H), 3.94 – 3.86 (m, 1H), 3.70 (s, 3H), 2.37 (d, J = 1.3 Hz, 3H), 0.96 (t, J = 7.1 Hz, 3H); \(^1\)C NMR (100 MHz, CDCl₃) δ 166.4, 160.3, 155.9, 144.3, 138.7, 128.7, 128.2, 128.0, 126.5, 125.7, 125.6, 125.3, 120.6, 115.2, 112.5, 102.9, 70.2, 59.2, 53.9, 52.9, 14.0, 12.4; HRMS (ESI) m/z calcd for C₂₅H₂₅N₄O₄ [M + H]⁺ = 445.1870, found = 445.1870; the ee value was 91%, \(t_R\) (major) = 8.1 min, \(t_R\) (minor) = 6.1 min (Chiralpak ID, \(\lambda = 254\) nm, 20% \(i\)-PrOH/Hexane, flow rate = 1.0 mL/min).
Ethyl (3aS,8aR)-3a-(3-methoxy-3-oxopropyl)-1-((methoxycarbonyl)amino)-2-methyl-1,3a,8a-tetrahydropyrrolo[2,3-b]indole-3-carboxylate 3z

A colorless oil; isolated yield = 70%; dr > 20:1; [α]D25 = -10 (c 1.2, CHCl3); 1H NMR (400 MHz, CDCl3) δ 8.57 (s, 1H), 8.19 (s, 1H), 7.91 (dd, J = 8.6, 1.2 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.25 – 7.13 (m, 5H), 7.07 (s, 1H), 6.51 (s, 1H), 4.94 (s, 1H), 4.27 (d, J = 8.4 Hz, 1H), 4.05 – 3.99 (m, 1H), 3.95 – 3.84 (m, 4H), 3.70 (s, 3H), 2.37 (s, 3H), 0.94 (t, J = 7.1 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 168.0, 166.5, 160.3, 156.0, 144.4, 139.5, 128.1, 128.1, 126.3, 124.8, 123.9, 122.7, 122.0, 115.6, 111.2, 100.0, 70.1, 58.9, 53.70, 52.9, 51.9, 14.0, 12.3; HRMS (ESI) m/z calcd for C26H28N3O6 [M + H]+ = 478.1973, found = 478.1960; the ee value was 91%, tR (major) = 5.6 min, tR (minor) = 7.7 min (Chiralpak IA, λ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3z

Enantioenriched 3z
Ethyl (4R,5R)-5-(6-fluoro-1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3a'

A colorless oil; isolated yield = 87%; dr >20:1; [α]_D^{25} = -99 (c 1.8, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.30 (s, 1H), 7.37 (s, 1H), 7.26 – 7.13 (m, 5H), 7.05 (dd, J = 9.5, 2.2 Hz, 1H), 6.95 (s, 1H), 6.85 (t, J = 9.1 Hz, 1H), 6.44 (s, 1H), 4.83 (s, 1H), 4.26 (d, J = 8.2 Hz, 1H), 4.06 – 3.99 (m, 1H), 3.94 – 3.86 (m, 1H), 3.70 (s, 3H), 2.36 (d, J = 1.3 Hz, 3H), 0.94 (t, J = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.62, 160.1, 160.1 (d, J = 238 Hz), 156.1, 145.0, 137.0 (d, J = 13 Hz), 128.2, 127.9, 126.3, 123.9, 122.2, 120.6 (d, J = 10 Hz), 114.4, 108.7 (d, J = 26 Hz), 97.8 (d, J = 26 Hz), 70.3, 58.9, 53.5, 52.9, 14.0, 12.2; ¹⁹F NMR (376 MHz, CDCl₃) δ -120.3; HRMS (ESI) m/z calcd for C₂₄H₂₅FN₃O₄ [M + H]⁺ = 438.1824, found = 438.1815; the ee value was 94%, t_R (major) = 5.9 min, t_R (minor) = 5.3 min (Chiralpak ID, λ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3a'

Enantioenriched 3a'
Ethyl (4R,5R)-5-(6-chloro-1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3b'

A yellowish solid; isolated yield = 97%; dr >20:1; \([\alpha]_D^{25} = -121\) (c 2.1, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 8.38 (s, 1H), 7.36 (d, \(J = 1.6\) Hz, 2H), 7.26 – 7.12 (m, 5H), 7.05 (d, \(J = 8.3\) Hz, 1H), 6.97 (s, 1H), 6.46 (s, 1H), 4.84 (s, 1H), 4.24 (d, \(J = 8.3\) Hz, 1H), 4.07 – 3.99 (m, 1H), 3.94 – 3.85 (m, 1H), 2.36 (d, \(J = 1.2\) Hz, 3H), 0.94 (t, \(J = 7.1\) Hz, 3H); \(^13\)C NMR (100 MHz, CDCl₃) \(\delta\) 166.6, 160.2, 156.1, 144.9, 137.4, 128.5, 128.2, 127.9, 126.3, 124.2, 120.6, 114.5, 111.5, 102.4, 70.3, 58.9, 53.6, 52.9, 14.0, 12.2; HRMS (ESI) m/z calcld for C₂₄H₂₅ClN₃O₄ [M + H]\(^{+}\) = 454.1528, found = 454.1516; the ee value was 91\%, \(t_R\) (major) = 6.0 min, \(t_R\) (minor) = 5.5 min (Chiralpak ID, \(\lambda = 254\) nm, 20\% i-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3b'  Enantioenriched 3b'
Ethyl (4R,5R)-5-(7-fluoro-1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3c'

A colorless oil; isolated yield = 78%; dr >2:1; \([\alpha]_D^{25} = -116\) (c 1.6, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.45 (s, 1H), 7.31 – 7.13 (m, 6H), 7.04 – 6.86 (m, 3H), 6.43 (s, 1H), 4.87 (s, 1H), 4.28 (d, J = 8.3 Hz, 1H), 4.07 – 3.99 (m, 1H), 3.94 – 3.86 (m, 1H), 3.71 (s, 3H), 2.36 (d, J = 1.4 Hz, 3H), 0.94 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 166.6, 160.1, 155.9, 149.7 (d, J = 243 Hz), 144.9, 129.3, 128.1, 128.0, 126.3, 125.4 (d, J = 14 Hz), 124.3, 120.2, 115.7, 115.3, 107.3 (d, J = 16 Hz), 102.4, 70.2, 58.9, 53.6, 52.9, 14.0, 12.2; ¹⁹F NMR (376 MHz, CDCl₃) δ -134.7; HRMS (ESI) m/z calcd for C₂₄H₂₅FN₃O₄ [M + H]⁺ = 438.1824, found = 438.1813; the ee value was 92%, \(t_R\) (major) = 12.1 min, \(t_R\) (minor) = 13.9 min (Chiralpak IC, λ = 254 nm, 10% i-PrOH/Hexane, flow rate = 1.0 mL/min).

![Chromatogram](image)

| Peak Table | Detection A 254nm | Detection A 204nm |
|------------|------------------|------------------|
| Masses     |                  |                  |
| 1           | 13.18            | 13.18            |
| 2           | 13.91            | 13.91            |
| Total       | 100.00           | 100.00           |

| Peak Table | Detection A 254nm | Detection A 204nm |
|------------|------------------|------------------|
| Masses     |                  |                  |
| 1           | 13.18            | 13.18            |
| 2           | 13.91            | 13.91            |
| Total       | 100.00           | 100.00           |

Racemic 3c'  Enantioenriched 3c'
Ethyl (4R,5R)-1-((methoxycarbonyl)amino)-2-methyl-5-(7-methyl-1H-indol-3-yl)-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3d'

A yellowish solid; isolated yield = 97%; dr >20:1; [\alpha]_D^{25} = -107 (c 2.1, CHCl_3); \textsuperscript{1}H NMR (400 MHz, CDCl_3) \(\delta\) 8.15 (s, 1H), 7.37 (s, 1H), 7.30 – 7.21 (m, 4H), 7.17 (d, \(J = 5.7\) Hz, 1H), 7.04 – 7.01 (m, 3H), 6.39 (s, 1H), 4.88 (s, 1H), 4.32 (d, \(J = 8.0\) Hz, 1H), 4.07 – 3.99 (m, 1H), 3.94 – 3.86 (m, 1H), 3.70 (s, 3H), 2.50 (s, 3H), 2.37 (d, \(J = 1.2\) Hz, 3H), 0.94 (t, \(J = 7.1\) Hz, 3H); \textsuperscript{13}C NMR (100 MHz, CDCl_3) \(\delta\) 166.7, 160.1, 156.4, 145.2, 136.6, 128.1, 126.2, 125.2, 123.4, 123.1, 120.8, 120.2, 117.6, 114.8, 102.2, 70.3, 58.8, 53.4, 52.8, 16.6, 14.0, 12.2; HRMS (ESI) m/z calcd for C\textsubscript{25}H\textsubscript{28}N\textsubscript{3}O\textsubscript{4} [M + H]+ = 434.2074, found = 434.2058; the ee value was 90%, \(t_R\) (major) = 6.6 min, \(t_R\) (minor) = 5.8 min (Chiralpak ID, \(\lambda = 254\) nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
Ethyl (4R,5R)-5-(5,6-dichloro-1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2-methyl-4-phenyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3e'  

A colorless oil; isolated yield = 94%; dr >20:1; $[\alpha]_{D}^{25} = -82$ (c 2.3, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.43 (s, 1H), 7.47 (s, 2H), 7.25 – 7.13 (m, 5H), 6.99 (s, 1H), 6.47 (s, 1H), 4.82 (s, 1H), 4.20 (d, $J = 9.2$ Hz, 1H), 4.08 – 3.98 (m, 1H), 3.95 – 3.84 (m, 1H), 3.70 (s, 3H), 2.36 (d, $J = 1.2$ Hz, 3H), 0.94 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 166.5, 160.3, 155.9, 144.4, 135.7, 128.2, 128.0, 126.5, 125.4, 123.9, 120.8, 113.9, 113.0, 102.8, 77.3, 77.0, 76.7, 70.1, 59.1, 53.6, 52.9, 14.0, 12.3; HRMS (ESI) m/z calcd for C$_{24}$H$_{24}$Cl$_2$N$_3$O$_4$ [M + H]$^+$ = 488.1138, found = 488.1114; the ee value was 92%, $t_R$ (major) = 5.2 min, $t_R$ (minor) = 4.5 min (Chiralpak ID, $\lambda$ = 254 nm, 20% $i$-PrOH/Hexane, flow rate = 1.0 mL/min).
Ethyl (4R,5R)-5-(1H-indol-3-yl)-1-((methoxycarbonyl)amino)-2,4-dimethyl-4,5-dihydro-1H-pyrrole-3-carboxylate 3f'

A colorless oil; isolated yield = 84%; dr >20:1; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.31 (s, 1H), 7.59 (d, \(J = 7.6\) Hz, 1H), 7.39 (d, \(J = 8.1\) Hz, 1H), 7.24 – 7.06 (m, 3H), 6.31 (s, 1H), 4.52 (s, 1H), 4.30 – 4.10 (m, 2H), 3.69 (s, 3H), 3.27 (s, 1H), 2.24 (s, 3H), 1.37 – 1.22 (m, 6H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 167.2, 159.7, 156.1, 144.3, 136.9, 125.9, 123.7, 122.5, 119.9, 119.8, 114.5, 111.5, 103.6, 68.6, 58.9, 52.8, 41.7, 19.7, 14.5, 12.3; HRMS (ESI) m/z calcd for C\(_{19}\)H\(_{24}\)N\(_3\)O\(_4\) [M + H]\(^+\) = 358.1761, found = 358.1755; the ee value was 64\%, \(t_R\) (major) = 6.4 min, \(t_R\) (minor) = 5.7 min (Chiralpak ID, \(\lambda = 254\) nm, 20\% \(i\)-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3f'

Enantioenriched 3f'
Ethyl (3S,8R)-1-((methoxycarbonyl)amino)-2,8-dimethyl-3-((E)-styryl)-1,3,8,8-tetrahydropyrrolo[2,3-b]indole-3-carboxylate 5

A colorless oil; isolated yield = 88%; $[\alpha]_D^{25} = -98$ (c 1.6, CHCl$_3$); dr >20:1; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.55 (d, $J = 4$ Hz, 1H), 7.37 (d, $J = 7.3$ Hz, 2H), 7.31 – 7.28 (m, 2H), 7.23 – 7.20 (m, 1H), 7.13 – 7.08 (m, 1H), 6.90 – 6.86 (m, 1H), 6.72 – 6.70 (m, 2H), 6.47 – 6.30 (m, 2H), 4.21 – 4.06 (m, 2H), 3.79 (s, 3H), 2.26 (s, 3H), 1.40 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.6, 159.8, 156.8, 147.8, 137.3, 132.4, 132.0, 130.4, 128.5, 127.9, 127.4, 126.5, 120.5, 110.4, 104.7, 94.1, 62.9, 59.2, 53.1, 21.6, 14.5, 12.6; HRMS (ESI) m/z calcd for C$_{25}$H$_{28}$N$_3$O$_4$ [M + H]$^+$ = 434.2074, found = 434.2083; the ee value was 95%, $t_R$ (major) = 6.9 min, $t_R$ (minor) = 12.4 min (Chiralpak IC, $\lambda$ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
X-Ray Crystallographic Analysis

Determination of the Absolute Configurations of the Product 3y

Table S1. Crystal data and structure refinement for j518. Related to Figure 5.

| Identification code | j518          |
|--------------------|---------------|
| Empirical formula  | C25 H24 N4 O4 |
| Formula weight     | 444.48        |
| Temperature        | 100(2) K      |
| Wavelength         | 1.54178 Å     |
| Crystal system     | Triclinic     |
| Space group        | P1            |
| Unit cell dimensions | a = 9.6507(9) Å , b = 10.4976(10) Å |
Volume \( 1136.32(19) \, \text{Å}^3 \)

Z \( 2 \)

Density (calculated) \( 1.299 \, \text{Mg/m}^3 \)

Absorption coefficient \( 0.734 \, \text{mm}^{-1} \)

\( c = 13.0255(12) \, \text{Å} \)

\( \beta = 62.679(3)^\circ \).

\( F(000) \) \( 468 \)

Crystal size \( 0.312 \times 0.107 \times 0.098 \, \text{mm}^3 \)

Theta range for data collection \( 3.501 \) to \( 72.253^\circ \).

Index ranges -11≤h≤11, -12≤k≤12, -16≤l≤16

Reflections collected \( 80402 \)

Independent reflections \( 8646 \) \([R(\text{int}) = 0.0508]\)

Completeness to theta = 67.679\(^\circ\) \( 99.3\% \)

Absorption correction Semi-empirical from equivalents

Max. and min. transmission \( 0.7533 \) and \( 0.6811 \)

Refinement method Full-matrix least-squares on \( F^2 \)

Data / restraints / parameters \( 8646 / 3 / 617 \)

Goodness-of-fit on \( F^2 \) \( 1.034 \)

Final R indices \([I>2\sigma(I)]\) \( R1 = 0.0289, \, wR2 = 0.0741 \)

R indices (all data) \( R1 = 0.0298, \, wR2 = 0.0747 \)

Absolute structure parameter \( 0.07(4) \)

Extinction coefficient \( \text{n/a} \)

Largest diff. peak and hole \( 0.259 \) and \(-0.194 \, \text{e.Å}^{-3} \)
Preliminary Modeling Approach

The distance N1-C is 3.98 Å and N2-C is 5.32 Å.

Figure S2. Distances between key atoms in intermediate A. Related to Figure 6.

Figure S3. 5-exo attack from intermediate A. Related to Figure 6.
TS1 (Favored)

Figure S4. Plausible Transition states. Related to Figure 6.

Figure S5. TS1’ (6.2 kcal/mol higher). Related to Figure 6.
Transparent Methods

A. General Information

Unless otherwise specified, all reactions were conducted under an inert atmosphere and anhydrous conditions. All the solvents were purified according to the standard procedures. All chemicals which are commercially available were employed without further purification. Thin-layer chromatography (TLC) was performed on silica gel plates (60F-254) using UV-light (254 and 365 nm). Flash chromatography was conducted on silica gel (200–300 mesh). $^1$H and $^{13}$C NMR spectra were recorded at ambient temperature in CDCl$_3$ on a Bruker AMX500 (500 MHz) or AMX400 (400 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm). The data are reported as follows: for $^1$H NMR, chemical shift in ppm from tetramethylsilane with the solvent as internal standard (CDCl$_3$ δ 7.26 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances), integration; for $^{13}$C NMR, chemical shift in ppm from tetramethylsilane with the solvent as internal indicator (CDCl$_3$ δ 77.1 ppm), multiplicity with respect to protons. All high-resolution mass spectra were performed by the MS service at the chemistry department, National University of Singapore, and were obtained on a Finnigan/MAT 95XL-T spectrometer to be given in m/z. Optical rotations were measured using an Anton Paar MCP-100 digital polarimeter using a 1 cm glass cell. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase using CHIRALPAK® columns (IA and ID) eluting with hexane/isopropanol mixtures as indicated.
B. Representative Procedures

General Procedure for synthesis of 3:

To a stirring anhydrous CHCl₃ solution (1 ml) of azoalkenes 1 (0.12 mmol) and olefins 2 (0.1 mmol) was added CPA 4f (1 mol%) at rt. The reaction mixture was stirred until completion of reaction (0.5 h, as monitored by TLC). The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (PE:EtOAc = 4:1) to afford cycloadducts 3.

Synthesis of 3a at a gram-scale:

To a stirring anhydrous CHCl₃ solution (15 ml) of azoalkenes 1a (4.8 mmol) and indoles 2a (4 mmol) was added CPA 4f (1 mol%) at rt. The reaction mixture was stirred until completion of reaction (1.5 h, as monitored by TLC). Water was added and the mixture was extracted with AcOEt (2 × 20 mL). The combined organic layer was washed with brine, separated, dried over Na₂SO₄ and filtered. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (PE:EtOAc = 4:1) to afford product 3a (1.5 g) in 90% yield with 92% ee.

C. Calculations

Because the system contains large and flexible binaphthol backbone and SiPh₃ groups, selected geometries of the plausible transition states and intermediate were pre-modeled at the HF/STO-3G level of theory to provide visual guidance. The computed energies are thus for providing qualitative insights but subjected to errors. (Frisch et al. 2016) Post-processing visualization was carried out with the ChemCraft program. (Zhurko, http://www.chemcraftprog.com.)
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