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Chiral squaramides catalyzed diastereo- and enantioselective Michael addition of α-substituted isocyanoacetates to *N*-aryl maleimides

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ABSTRACT

An efficient diastereo- and enantioselective Michael addition of α-substituted isocyanoacetates to *N*-aryl maleimides catalyzed by quinine or cyclohexane-1,2-diamine derived squaramide catalysts has been disclosed, affording the corresponding adducts in good yields (up to 99%), high diastereoselectivities (up to >20:1 dr) and good to excellent enantioselectivities (up to 94% ee) under mild conditions.

1. Introduction

Hydrogen bonding promoted asymmetric organocatalysis has attracted intense research efforts in the past decade. Chiral ureas and thioureas, diols, and phosphoric acids dominated the field of hydrogen bonding, and the thiourea framework has been considered as a gold mine in *H*-bonding involved bifunctional activation processes.[1] However, chiral squaramide catalysts, pioneered by Rawal's group and later developed by other groups with incorporating the squaramide moiety as a powerful hydrogen bond donor in different chiral scaffolds, have been identified as another complementary or even superior *H*-bond donor catalyst in asymmetric organocatalysis in the past several years.[2] Squaramide's dual binding ability, structural rigidity, further apart *H*-bond spacing and lower p*K*a values of the *N*–H protons, may lead to a broader substrate scope, improved recognitions, better stereoinduction or rate-enhancement compared to the thiourea or urea analogues in some cases.

Isocyanides were found to be irreplaceable building blocks for the synthesis of numerous important classes of nitrogen heterocyclic compounds due to the unique divalent features of the isocyano group that make isocyanides react smoothly with both electrophiles and nucleophiles.[3] Isocyanoacetates **1**, which combined several potential reaction centers, such as an isocyano group, an acidic CH fragment, and a protected carboxylic acid, have shown exceptional reaction diversity and broad synthetic potential.[4] In light of the pioneering works by Ito and Hayashi,[5] Gong[6] et al., organo- and organometallic complex catalyzed asymmetric addition of isocyanoacetates to many carbon–carbon, carbon–heteroatom multiple bonds electrophiles, including nitroolefins,[6] carbonyl compounds,[7] imines,[8] azodicarboxylates,[9] and α,β-unsaturated carbonyl compounds,[10] have been intensively studied in recent years. In most cases, chiral cyclic compounds were obtained.

As part of our ongoing interest in the enantioselective addition reactions of α-aryl isocyanoacetates to unsaturated compounds,[7d,9b,10f] we have developed a highly diastereo- and enantioselective [3+2] cycloaddition reaction of α-aryl isocyanoacetates to maleimides cooperative catalyzed by bifunctional *cinchona* alkaloids-based squaramide/$AgSbF_6$ (Scheme 1).[10f] However, different from those organocatalyzed enantioselective addition reactions of isocyanoacetates to nitroolefin[6] or carbon–heteroatom multiple bonds electrophiles,[7a,d,8,9] Michael adducts **5** rather than

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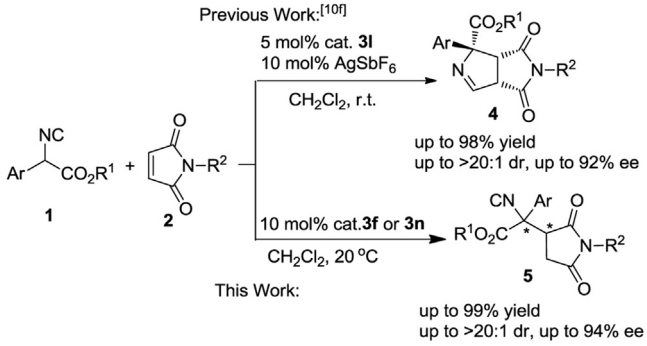
the expected [3+2] cycloaddition products **4** were obtained in the absence of silver salts. Considering that substituted maleimides are important structural motifs, which widely present in numerous biologically interesting molecules and pharmaceuticals[11] and the asymmetric Michael addition to maleimides is also an effective strategy for the construction of vicinal quaternary–tertiary stereocenters,[12] which are ubiquitous and structural moieties in complex natural products and pharmaceuticals, we described herein chiral squaramides catalyzed highly diastereo- and enantioselective Michael addition of α-aryl isocyanoacetates to maleimides. Despite Wang et al. have reported the chiral tertiary amine–thiourea catalyzed asymmetric Michael addition of isocyanoacetates to maleimdes,[10c] there are still several challenging issues, such as substrate generality, efficiency of catalyst, and reaction time, need to be addressed. Therefore, the development of other new, more efficient catalytic systems is still highly desirable.

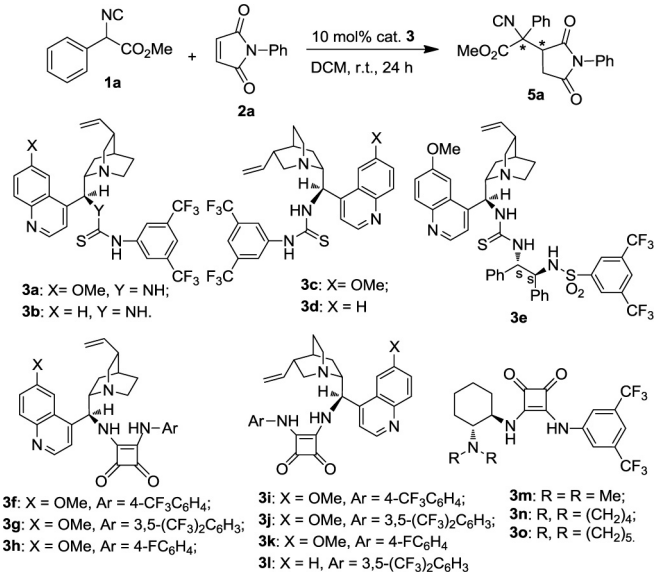


Scheme 1. Asymmetric reactions of α-aryl isocyanoacetates **1** with maleimides **2**.

2. Results and discussion

On the basis of the earlier successes of bifunctional catalysts possessing both *H*-bond donor and acceptor moieties in many maleimides involved enantioselective reactions[13] and *cinchona* alkaloids catalyzed asymmetric additions of α-aryl isocyanoacetates **1**,[6,7a,d,8,9b,10e] the initial studies were carried out using α-phenyl isocyanoacetate (**1a**) and *N*-phenyl maleimide (**2a**) as substrate and quinine derived thiourea **3a** as catalyst. When the reaction was carried out in dichloromethane at room temperature using 10 mol % of catalyst **3a**, the corresponding Michael adduct **5a**, rather than the expected [3+2] cycloaddition product, was obtained in moderate yield, diastereoselectivity, and enantioselectivity (50%, 8:1 dr, 56% ee) (Table 1, entry 1). Encouraged by this result, a series of *cinchona* alkaloid thioureas **3b–e** were used as catalysts to examine the reaction outcome (Table 1). Generally, most thiourea catalysts could effectively promote this reaction, giving the corresponding adduct **5a** in moderate yields and stereoselectivities (Table 1, entries 2–5). Among of these, quinine thiourea catalyst bearing sulfonamide as multiple *H*-bond donors **3e**, which has shown good catalytic activities in the enantioselective Michael addition of *N*-Boc-3-aryloxindoles to phenyl vinyl sulfone[14] and formal [3+2] cycloaddition of isocyanoacetates to isatins,[7d] was not effective catalyst for this reaction, providing **5a** in moderate yield along with low stereoselectivity (Table 1, entry 5). *Cinchona* alkaloid-based squaramides **3f–l** can serve as better bifunctional organocatalysts, and they showed much higher stereoselectivities than those of above mentioned thiourea catalysts (Table 1, entries 6–12). Of the *cinchona* alkaloid squaramides screened, quinine derived squaramide **3f** was the best catalyst, giving **5a** in high diastereo- and enantioselectivity, albeit with much lower yield (Table 1, entry 6).

Table 1
Catalysts screening[a]



Entry	Cat. **3**	Yield[b] (%)	dr[c]	ee (%)[d]
1	**3a**	50	8:1	56
2	**3b**	61	6:1	52
3	**3c**	62	8:1	−61
4	**3d**	58	6:1	−50
5	**3e**	57	2.4:1	15
6	**3f**	36	>20:1	82
7	**3g**	72	>20:1	73
8	**3h**	54	>20:1	61
9	**3i**	74	>20:1	−56
10	**3j**	73	>20:1	−81
11	**3k**	56	>20:1	−70
12	**3l**	34	>20:1	−75

[a] All of reactions were carried out with **1a** (0.24 mmol), **2a** (0.20 mmol), and cat. **3** (0.02 mmol) in DCM (2.0 mL) at rt for 24 h.
[b] Isolated yield.
[c] The dr value of the purified product was determined by ^{1}H NMR spectroscopy.
[d] The ee value was determined by chiral HPLC analysis.

In view of the higher yield and enantioselectivity, efforts were taken to further optimize the reaction conditions by examining other parameters, such as solvent, temperature, reactant concentrations, and additives (Table 2; For more details see Table S1 in the Supplementary data). It was found that the ratio of **1a**/**2a** was crucial for the yield and enantioselectivity; higher yield was obtained by using 2:1 of **1a**/**2a** without impairing the enantioselectivity (Table 2, entries 1 vs 2 and Table 1, entry 6). Of the various solvents screened, dichloromethane was the best solvent for this Michael addition, despite that high dr values, similar level of enantioselectivities in other chlorinated solvents (Table 2, entries 3 and 4). Moderate ee values and low yields were obtained in toluene and xylene (Table 2, entries 5 and 6). Ethers and polar solvents, such as acetone, methanol, and acetonitrile were not suitable for this reaction, giving **5a** with low enantioselectivities (Table 2, entries 7–11). Prolonging the reaction time can significantly improve the yield and ee value, and the lower concentration led to the formation of **5a** in a similar ee value but in lower yield (Table 2, entries 12–14). Further examination of temperature effect revealed that lowering the reaction temperature produced **5a** in lower yield and ee value (Table 2, entry 15); elevating the reaction temperature could improve the yield of **5a**, but decreased the enantioselectivity (Table 2, entry 16). Moreover, the addition of 4 Å molecular sieves could further improve the enantioselectivity, affording **5a** in good yield with up to 90% ee (Table 2, entry 17); Reducing the catalyst loading from 10 mol % to 5 mol %, leads to similar yield and much lower ee values (Table 2, entry 18).

Table 2
Optimization of the reaction conditions for the asymmetric Michael addition of α-phenyl isocyanoacetate **1a** with *N*-phenyl maleimide **2a** catalyzed by **3f**[a]

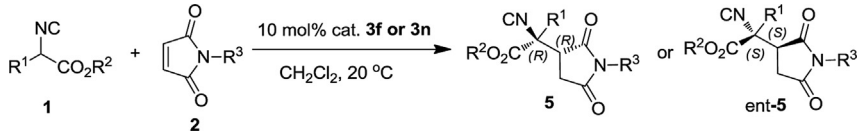
Entry	Solvent	*T* (°C)	Time (h)	Yield[b] (%)	dr[c]	ee (%)[d]
1	CH_2Cl_2	20	24	51	>20:1	83
2[e]	CH_2Cl_2	20	24	63	>20:1	67
3	$CHCl_3$	20	24	51	>20:1	81
4	DCE	20	24	67	>20:1	73
5	Toluene	20	24	33	>20:1	53
6	Xylene	20	24	27	>20:1	57
7	THF	20	24	69	>20:1	17
8	Et_2O	20	24	33	>20:1	55
9	Acetone	20	24	69	>20:1	4
10	CH_3OH	20	24	53	>20:1	0
11	CH_3CN	20	24	36	>20:1	5
12	CH_2Cl_2	20	72	74	>20:1	86
13[f]	CH_2Cl_2	20	72	85	>20:1	86
14[g]	CH_2Cl_2	20	72	55	>20:1	86
15[f]	CH_2Cl_2	0	72	45	>20:1	84
16[f]	CH_2Cl_2	30	30	95	>20:1	81
17[f,h]	CH_2Cl_2	20	72	88	>20:1	90
18[f,h,i]	CH_2Cl_2	20	72	91	>20:1	88

[a] Unless otherwise noted, all of reactions were carried out with isocyanoacetate **1a** (0.30 mmol), maleimide **2a** (0.15 mmol), and cat. **3f** (0.015 mmol) in DCM (1.5 mL).
[b] Isolated yield.
[c] The dr value of the purified product was determined by ^{1}H NMR spectroscopy.
[d] The ee value was determined by chiral HPLC analysis.
[e] The ratio of **1a**/**2a** was 1:2.
[f] CH_2Cl_2 (1.0 mL) was used.
[g] CH_2Cl_2 (3.0 mL) was used.
[h] MS (30 mg of 4 Å) was added.
[i] Cat. **3f** (5 mol %) was used.

With the optimal conditions in hand, we explored the substrate scope of this Michael addition. As shown in Table 3, with respect to 3-phenyl isocyanoacetate (**1a**), a variety of *N*-aryl maleimides worked well and the corresponding adducts were obtained in good yields (70–94%), high diastereoselectivities (up to >20:1) and good enantioselectivities (85–92% ee) (Table 3, entries 1–7). However, low yield and moderate enantioselectivity was afforded for *N*-alkyl substituted maleimide **2h** (Table 3, entries 8). Further examination of substituent effect of isocyanoacetates revealed that most α-aryl isocyanoacetates, whether bearing electron-donating or electron-withdrawing group on *para*- or *meta*-position of the phenyl group, could give the desired adducts in good to excellent yields (60–95%), excellent stereoselectivities (up to >20:1 dr and 94% ee) (Table 3, entries 9–16), albeit isocyanoacetates with an electron-withdrawing group gave the desired products with slightly higher enantioselectivities than those of isocyanoacetates without substituent or with electron-donating groups (Table 3, entries 9–12 and 15 vs 1, 13, 14 and 16). It should be also noted that as for more sterically hindered substrate, such as *ortho*-tolyl derived isocyanoacetate (**1i**), the reaction became sluggish and no desired adduct was detected under the optimal conditions (Table 3, entry 17). Different from benzyl α-phenyl isocyanoacetate (**1j**), which afforded the similar result to methyl isocyanoacetate (**1a**), *tert*-butyl isocyanoacetate (**1k**) led to the formation of the desired product **5s** in low yield (41%) and diastereoselectivity (1:1 dr) as well as comparable ee value (86% ee) even with prolonged reaction time to 7 days, presumably due to steric effect (Table 3, entries 18 and 19). Moreover, α-alkyl isocyanoacetate **1l** is not suitable for this reaction; trace product **5t** was detected due to its low reactivity (Table 3, entry 20).

It is not surprising that the above Michael addition catalyzed by **3f** proceeded slowly and was not applicable to less reactive alkyl-substituted maleimides and isocyanoacetates probably due to the inefficient basicity of *cinchona* alkaloid derivatives. Recently, Wang et al. reported chiral cyclohexane-1,2-diamine derived bifunctional tertiary-amine thiourea can efficiently catalyze this enantioselective Michael addition[10c] and chiral cyclohexane-1,2-diamine derived bifunctional tertiary amine–squaramides have found

Table 3
Enantioselective asymmetric Michael addition of isocyanoacetate **1** with *N*-substituted maleimides **2** catalyzed by squaramides **3f** or **3n**[a]



Entry	**1** (R^1/R^2)	**2** (R^3)	*t* (h)	**5** (*ent*-**5**)	Yield[b] (%)	dr[c]	ee (%)[d]
1	**1a** (Ph/Me)	**2a** (Ph)	72 (4)	**5a** (*ent*-**5a**)	88 (99)	>20:1 (>20:1)	90 (90)
2	**1a** (Ph/Me)	**2b** (4-FC_6H_4)	72 (9)	**5b** (*ent*-**5b**)	70 (92)	>20:1 (>20:1)	86 (85)
3	**1a** (Ph/Me)	**2c** (4-BrC_6H_4)	72 (4)	**5c** (*ent*-**5c**)	82 (98)	20:1 (20:1)	87 (91)
4	**1a** (Ph/Me)	**2d** (4-MeC_6H_4)	72 (4)	**5d** (*ent*-**5d**)	86 (98)	>20:1 (>20:1)	88 (86)
5	**1a** (Ph/Me)	**2e** (4-$MeOC_6H_4$)	72 (4)	**5e** (*ent*-**5e**)	81 (99)	20:1 (20:1)	85 (88)
6	**1a** (Ph/Me)	**2f** (3-ClC_6H_4)	72 (4)	**5f** (*ent*-**5f**)	81 (99)	>20:1 (>20:1)	87 (88)
7	**1a** (Ph/Me)	**2g** (3-$MeOC_6H_4$)	72 (4)	**5g** (*ent*-**5g**)	94 (99)	>20:1 (>20:1)	92 (90)
8	**1a** (Ph/Me)	**2h** (Bn)	72 (4)	**5h** (*ent*-**5h**)	25 (71)	>20:1 (>20:1)	76 (65)
9	**1b** (4-FC_6H_4/Me)	**2a** (Ph)	72 (4)	**5i** (*ent*-**5i**)	71 (99)	>20:1 (>20:1)	94 (89)
10	**1c** (4-ClC_6H_4/Me)	**2a** (Ph)	72 (4)	**5j** (*ent*-**5j**)	90 (99)	>20:1 (>20:1)	92 (90)
11	**1d** (4-BrC_6H_4/Me)	**2a** (Ph)	72 (4)	**5k** (*ent*-**5k**)	77 (99)	>20:1 (>20:1)	90 (91)
12	**1d** (4-BrC_6H_4/Me)	**2g** (3-$MeOC_6H_4$)	72	**5l**	95	>20:1	91
13	**1e** (4-MeC_6H_4/Me)	**2a** (Ph)	72 (4)	**5m** (*ent*-**5m**)	66 (98)	>20:1 (>20:1)	90 (86)
14	**1f** (4-$MeOC_6H_4$/Me)	**2a** (Ph)	72 (4)	**5n** (*ent*-**5n**)	60 (92)	20:1 (>20:1)	88 (88)
15	**1g** (3-FC_6H_4/Me)	**2a** (Ph)	72 (4)	**5o** (*ent*-**5o**)	95 (98)	>20:1 (>20:1)	93 (84)
16	**1h** (3-MeC_6H_4/Me)	**2a** (Ph)	72 (7)	**5p** (*ent*-**5p**)	85 (99)	>20:1 (>20:1)	86 (86)
17	**1i** (2-MeC_6H_4/Me)	**2a** (Ph)	72	**5q**	n.r.	n.d.	n.d.
18	**1j** (Ph/Bn)	**2a** (Ph)	72	**5r**	95	10:1	90
19	**1k** (Ph/*t*-Bu)	**2a** (Ph)	168 (24)	**5s** (*ent*-**5s**)	41 (93)	1:1 (3:1)	86, 0 (85, 51)[e]
20	**1l** (Bn/Me)	**2a** (Ph)	120 (72)	**5t** (*ent*-**5t**)	Trace (20)	n.d. (2.4:1)	n.d. (46, 33)[e]
21	**1m** (H/Et)	**2a** (Ph)	(72)	(*ent*-**5u**)	(15)	(1.4:1)	(20, 15)[e]

[a] All of reactions were carried out with isocyanoacetates **1** (0.30 mmol), maleimides **2** (0.15 mmol), catalyst **3f** or **3n** (10 mol %), and 30 mg of 4 Å MS in DCM (1.0 mL) at 20 °C, the data in parenthesis was obtained by using the catalyst **3n**.
[b] Isolated yield.
[c] The dr value of the purified product was determined by ^{1}H NMR spectroscopy.
[d] The ee value was determined by chiral HPLC analysis.
[e] The second data was the ee value for minor isomer.

wide applications in organocatalyzed asymmetric reactions.[2i–l] Inspired by these new results and to further expand the use of bifunctional squaramide catalysts in this asymmetric Michael addition, we synthesized the 1,2-diaminocyclohexane derived squaramide catalysts **3m**–**o** to evaluate their catalytic activity for this reaction. It was found that the substituent on nitrogen atoms of the tertiary amine has played an important role in determining the reaction outcome. Under the above optimal conditions, pyrrolidine substituted catalyst **3n** showed better catalytic activity than those of the corresponding dimethyl and piperidine substituted catalysts **3m** and **3o**, affording **5a** in almost quantitative yield, excellent diastereoselectivity and up to 90% ee value after just 4 h (Table 3, entry 1).[15] Although the result is comparable to those of quinine-derived squaramide **3f** (3 d, 88%, >20:1 dr, 90% ee) and cyclohexane-1,2-diamine derived thiourea catalyst of Wang (18 h, 93%, 99:1 dr and 94% ee),[10c] the yield was improved and the reaction time was greatly shortened. Further examination of the substrate scope revealed that this conjugate addition mediated by catalyst **3n** is applicable to a variety of *N*-aryl maleimides and α-aryl-substituted isocyanoacetates, excellent yields as well as good to excellent stereoselectivities were generally attainable (Table 3, entries 2–11 and 13–16). For sterically bulky *tert*-butyl isocyanoacetate (**1k**), excellent yield, moderate diastereoselectivity and good ee value were obtained (Table 3, entry 19). However, to our disappointment, less reactive alkyl-substituted isocyanoacetates and *N*-alkyl substituted maleimide still could not give satisfactory results. *N*-Benzyl maleimide **2h** reacted smoothly with isocyanoacetate **1a** to give the desired product in moderate yield, high diastereoselectivity and moderate ee value (Table 3, entry 8); whereas α-benzyl or hydrogen atom substituted isocyanoacetates **1l** and **1m** gave only low yields and low stereoselectivities (Table 3, entries 20 and 21).

The absolute configuration of **5** and *ent*-**5** has been assigned as (*R*,*R*) and (*S*,*S*) by comparing the specific rotation with the reported ones[10c] and X-ray crystal analysis of product *ent*-**5c** (Fig. 1),[16] respectively. The absolute configurations of the other products were assigned as well.

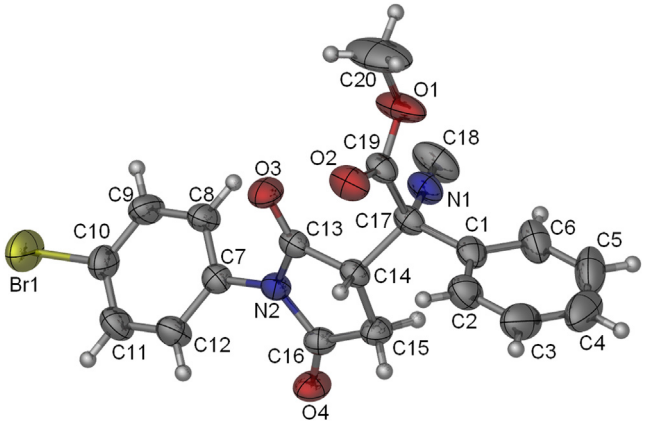


Fig. 1. X-ray crystallography of compound *ent*-**5c**.

A plausible transition-state model is proposed based on the above results and general accepted mechanism for squaramides catalyst (Scheme 2). The carbonyl of maleimide is *H*-bonded to the squaramide motif, while isocyanoacetate is deprotonated and resulted in a single *H*-bonding interaction between the OH group of the enolized isocyanoacetate and the tertiary amine. Additionally, a weak *H*-bonding interaction might be formed concurrently between the OMe group of the enolized isocyanoacetate and the NH in the squaramide moiety, which forcing the enolized isocyanoacetate through *si*-face to attack the maleimide from the *si*-face or *re*-face, affording the adduct **5a** and *ent*-**5a** with (*R*,*R*)- and (*S*,*S*)-configuration, respectively.

3. Conclusion

In conclusion, we have developed quinine- or cyclohexane-1,2-diamine derived squaramides catalyzed highly diastereo- and enantioselective Michael addition of α-aryl isocyanoacetates to *N*-aryl maleimides under mild conditions. A variety of α-aryl substituted isocyanoacetates, as well as *N*-aryl maleimides, with different electron property of substituent were tolerated in this catalytic enantioselective Michael addition, affording the corresponding adducts in good yields (up to 99%), high diastereoselectivities (up to >20:1 dr), and good to excellent enantioselectivities (up to 94% ee). Compared with quinine derived squaramide catalyst **3f**, cyclohexane-1,2-diamine derived squaramide catalyst **3n** exhibited the higher catalytic reactivity; the yields were improved, and the reaction times were greatly shortened. Investigations on the asymmetric addition of α-aryl isocyanoacetates to other electrophiles are currently ongoing in our laboratory.

4. Experimental section

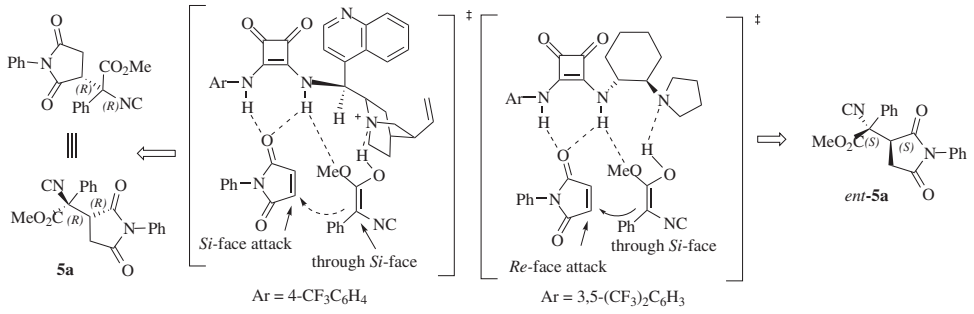
4.1. General method

NMR spectra were recorded on a Bruker AVANCE III 400 MHz spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as an internal standard; *J*-values are in Hertz. Infrared spectra were recorded on a Bio-Rad FTS-185. Chiral HPLC was performed on a SHIMADZU SPD-10A series with chiral columns. Mass spectra were recorded by EI and HRMS (EI, ESI) was measured on a Finnigan MA^+ instrument. Optical rotations were determined at 589 nm (sodium D line) using a Perkin–Elmer-341 MC digital polarimeter; $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}. Melting points were measured with a digital melting point apparatus. Flash column chromatography was performed using silica gel (300–400 mesh). Unless otherwise noted, all commercially obtained reagents were used without further purification. All reactions were carried out under an atmosphere of air in a closed system. α-Aryl isocyanoacetate **1**,[17] *N*-substituted maleimides **2**,[18] and catalyst **3**[19] were prepared using literature method. Racemic Michael adducts for chiral HPLC analysis were prepared from the corresponding isocyanoacetates **1** (0.24 mmol) and maleimides **2** (0.20 mmol) in the presence of DABCO (20 mol %) in 2.0 mL of DCM at room temperature for 2 h.

4.2. General procedure for the asymmetric Michael addition of α-isocyanoacetates 1 with *N*-substituted maleimides 2 catalyzed by 3f

A solution of isocyanoacetates **1** (0.30 mmol), *N*-substituted maleimides **2** (0.15 mmol), cat. **3f** (8.9 mg, 0.015 mmol), and 4 Å MS (30 mg) in DCM (1.0 mL) was stirred at 20 °C for 3 d. And then the reaction mixture was concentrated and the residue was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate=4:1) to furnish the corresponding products **5**.

*4.2.1. (R)-Methyl 2-((R)-2,5-dioxo-1-phenyl pyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**5a**).*[10c] Yellow solid (45.3 mg, 88%); mp 172.9–174.7 °C. >20:1 dr. $[\alpha]_D^{25}$ −41.4 (*c* 1.01, CH_2Cl_2); 90% ee (Chiralpak OD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{major}=18.84 min, t_{minor}=31.05 min). ^1H NMR (400 MHz, $CDCl_3$): δ=7.65 (dd, *J*=8.0, 1.6 Hz, 2H, ArH), 7.52–7.40 (m, 6H, ArH), 7.31 (d, *J*=8.4 Hz, 2H, ArH), 4.44 (dd, *J*=9.6, 6.0 Hz, 1H, CH), 3.88 (s, 3H,



Scheme 2. Proposed transition state model.

OCH_3), 2.80 (dd, J=18.4, 9.6 Hz, 1H, CH), 2.53 (dd, J=18.8, 6.4 Hz, 1H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.6, 173.1, 166.6, 164.3, 131.8, 131.1, 129.9, 129.4, 129.2, 129.0, 126.5, 125.4, 71.0, 54.4, 48.2, 30.6 ppm. IR (film): ν=2131, 1751, 1713, 1499, 1384, 1245, 1182, 1038, 1018 cm^{-1}.

*4.2.2. (R)-Methyl 2-((R)-1-(4-fluorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**5b**).*[10c] Pale-yellow solid (38.6 mg, 70%); mp 163.7–165.8 °C. >20:1 dr. $[\alpha]_D^{25}$ −37.0 (c 0.8, CH_2Cl_2); 86% ee (Chiralcel OD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{major}=17.88 min, t_{minor}=34.64 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.65–7.62 (m, 2H, ArH), 7.52–7.45 (m, 3H, ArH), 7.33–7.28 (m, 2H, ArH), 7.20–7.14 (m, 2H, ArH), 4.43 (dd, J=9.6, 6.0 Hz, 1H, CH), 3.89 (s, 3H, OCH_3), 2.81 (dd, J=18.4, 9.6 Hz, 1H, CH), 2.52 (dd, J=18.4, 6.4 Hz, 1H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.5, 173.0, 166.5, 164.4, 162.5 (d, J=247.7 Hz), 131.8, 130.0, 129.6, 128.5 (d, J=8.6 Hz), 127.0 (d, J=3.4 Hz), 125.4, 116.4 (d, J=22.1 Hz), 71.1, 54.5, 48.3, 30.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ=−111.5 ppm. IR (film): ν=2132, 1752, 1716, 1509, 1391, 1238, 1190 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{20}H_{16}FN_2O_4$ $[M+H]^+$ 367.1094; found 367.1096.

*4.2.3. (R)-Methyl 2-((R)-1-(4-bromophenyl)-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**5c**).*[10c] Pale-yellow solid (53.2 mg, 82%); mp 187.0–190.3 °C. 20:1 dr. $[\alpha]_D^{25}$ −41.4 (c 1.0, CH_2Cl_2); 87% ee (Chiralcel OD-H; hexane/2-propanol, 60:40; 1.0 mL/min; 230 nm; t_{major}=10.76 min, t_{minor}=19.57 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.64–7.59 (m, 4H, ArH), 7.55–7.47 (m, 3H, ArH), 7.24–7.20 (m, 2H, ArH), 4.43 (dd, J=9.6, 6.0 Hz, 1H, CH), 3.88 (s, 3H, OCH_3), 2.80 (dd, J=18.8, 9.6 Hz, 1H, CH), 2.52 (dd, J=18.8, 6.0 Hz, 1H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.2, 172.7, 166.5, 164.4, 132.5, 131.8, 130.1, 130.0, 129.6, 128.0, 125.4, 123.0, 71.0, 54.6, 48.3, 30.6 ppm. IR (film): ν=2361, 2342, 2131, 1751, 1716, 1489, 1384, 1245, 1177, 1035 cm^{-1}.

*4.2.4. (R)-Methyl 2-((R)-2,5-dioxo-1-(p-tolyl)pyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**5d**).*[10c] Yellow solid (46.6 mg, 86%); mp 166.6–168.7 °C. >20:1 dr. $[\alpha]_D^{25}$ −45.3 (c 1.02, CH_2Cl_2); 88% ee (Chiralcel OD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{major}=16.77 min, t_{minor}=29.27 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.64 (dd, J=8.0, 2.0 Hz, 2H, ArH), 7.52–7.46 (m, 3H, ArH), 7.28 (d, J=8.0 Hz, 2H, ArH), 7.18 (d, J=8.4 Hz, 2H, ArH), 4.42 (dd, J=9.2, 6.0 Hz, 1H, CH), 3.88 (s, 3H, OCH_3), 2.79 (dd, J=18.8, 9.6 Hz, 1H, CH), 2.52 (dd, J=18.8, 6.0 Hz, 1H, CH), 2.38 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.6, 173.2, 166.6, 164.3, 139.2, 131.9, 129.9, 129.5, 128.5, 126.3, 125.4, 71.1, 54.5, 48.3, 30.6, 21.2 ppm. IR (film): ν=2132, 1754, 1717, 1514, 1389, 1246, 1193 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{21}H_{19}N_2O_4$ $[M+H]^+$ 363.1345; found 363.1343.

*4.2.5. (R)-Methyl 2-isocyano-2-((R)-1-(4-methoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-2-phenylacetate (**5e**).*[10c] Yellow solid (46.1 mg, 81%); mp 179.5–181.9 °C. 20:1 dr. $[\alpha]_D^{25}$ −46.7 (c 1.0, CH_2Cl_2); 85% ee (Chiralpak AD-H; hexane/2-propanol, 60:40; 1.0 mL/min; 230 nm; t_{major}=30.90 min, t_{minor}=17.81 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.64 (d, J=6.8 Hz, 2H, ArH), 7.52–7.45 (m, 3H, ArH), 7.22 (d, J=8.8 Hz, 2H, ArH), 6.98 (d, J=8.8 Hz, 2H, ArH), 4.42 (dd, J=9.6, 6.0 Hz, 1H, CH), 3.88 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 2.78 (dd, J=18.8, 9.6 Hz, 1H, CH), 2.51 (dd, J=18.8, 6.0 Hz, 1H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.8, 173.4, 166.7, 164.4, 159.9, 132.0, 130.0, 129.6, 127.8, 125.5, 123.8, 114.6, 71.2, 55.5, 54.5, 48.3, 30.6 ppm. IR (film): ν=2358, 2132, 1752, 1712, 1511, 1391, 1247, 1166, 1023 cm^{-1}.

*4.2.6. (R)-Methyl 2-((R)-1-(3-chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**5f**).* White solid (46.5 mg, 81%); mp 125.3–127.1 °C. >20:1 dr. $[\alpha]_D^{25}$ −46.0 (c 0.75, CH_2Cl_2); 87% ee (Chiralcel OD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{major}=15.68 min, t_{minor}=28.32 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.64 (dd, J=8.0, 1.6 Hz, 2H, ArH), 7.52–7.45 (m, 3H, ArH), 7.43–7.41 (m, 2H, ArH), 7.36 (d, J=1.6 Hz, 1H, ArH), 7.25–7.23 (m, 1H, ArH), 4.44 (dd, J=9.6, 6.0 Hz, 1H, CH), 3.89 (s, 3H, OCH_3), 2.81 (dd, J=18.8, 9.6 Hz, 1H, CH), 2.53 (dd, J=18.8, 6.0 Hz, 1H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.1, 172.6, 166.5, 164.5, 134.8, 132.2, 131.8, 130.2, 130.0, 129.5, 129.3, 126.7, 125.4, 124.7, 71.0, 54.5, 48.3, 30.6 ppm. IR (film): ν=2133, 1752, 1717, 1478, 1450, 1383, 1247, 1186 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{20}H_{16}ClN_2O_4$ $[M+H]^+$ 383.0799; found 383.0801.

*4.2.7. (R)-Methyl 2-isocyano-2-((R)-1-(3-methoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-2-phenylacetate (**5g**).* Yellow solid (53.4 mg, 94%); mp 140.6–143.2 °C. >20:1 dr. $[\alpha]_D^{25}$ −43.9 (c 1.0, CH_2Cl_2); 92% ee (Chiralpak OD-H; hexane/2-propanol, 70:30; 0.8 mL/min; 230 nm; t_{major}=17.28 min, t_{minor}=25.94 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.64 (dd, J=8.0, 1.6 Hz, 2H, ArH), 7.52–7.46 (m, 3H), 7.39 (t, J=7.6 Hz, 1H, ArH), 6.96 (dd, J=8.0, 2.0 Hz, 1H, ArH), 6.89 (d, J=7.6 Hz, 1H, ArH), 6.83 (d, J=2.0 Hz, 1H, ArH), 4.43 (dd, J=7.2, 6.0 Hz, 1H, CH), 3.88 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.79 (dd, J=18.8, 9.6 Hz, 1H, CH), 2.52 (dd, J=18.8, 6.0 Hz, 1H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.4, 173.0, 166.6, 164.4, 160.1, 132.1, 131.9, 130.0, 129.9, 129.5, 125.4, 118.7, 115.1, 112.2, 71.0, 55.4, 54.5, 48.3, 30.6 ppm. IR (film): ν=2133, 1752, 1717, 1478, 1450, 1383, 1247, 1186 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{21}H_{19}N_2O_5$ $[M+H]^+$ 379.1294; found 379.1293.

*4.2.8. (R)-methyl 2-((R)-1-benzyl-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**5h**).*[10c] Yellow solid (13.4 mg, 25%); mp 71.6–73.8 °C. >20:1 dr. $[\alpha]_D^{25}$ −9.5 (c 0.5, CH_2Cl_2); 76% ee (Chiralpak OD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{major}=16.19 min, t_{minor}=19.17 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.57 (d, J=8.0 Hz, 2H, ArH), 7.48–7.43 (m, 5H, ArH), 7.39 (d, J=6.8 Hz, 1H, ArH), 7.34–7.28 (m, 2H, ArH), 4.71 (dd, J=30.0, 14.0 Hz, 2H, CH_2), 4.25 (dd, J=9.2, 6.4 Hz, 1H, CH), 3.90 (s, 3H, OCH_3), 2.60

(dd, J=18.4, 9.6 Hz, 1H, CH), 2.35 (dd, J=18.4, 6.4 Hz, 1H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.9, 173.6, 166.7, 164.3, 135.1, 132.0, 129.9, 129.5, 128.8, 128.7, 128.2, 125.3, 70.6, 54.5, 48.3, 42.9, 30.5 ppm. IR (film): ν=2133, 1751, 1717, 1504, 1389, 1253, 1200, 1022 cm^{-1}.

*4.2.9. (R)-Methyl 2-((R)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-(4-fluorophenyl)-2-isocyanoacetate (**5i**).* White solid (39.1 mg, 71%); mp 185.5–186.9 °C. >20:1 dr. $[\alpha]_D^{25}$ −40.7 (c 0.77, CH_2Cl_2); 94% ee (Chiralcel OD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{major}=17.69 min, t_{minor}=31.46 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.66–7.62 (m, 2H, ArH), 7.51–7.43 (m, 3H, ArH), 7.31 (d, J=8.0 Hz, 2H, ArH), 7.19 (td, J=8.0, 2.0 Hz, 2H, ArH), 4.39 (dd, J=9.6, 6.0 Hz, 1H, CH), 3.89 (s, 3H, OCH_3), 2.81 (dd, J=18.4, 9.6 Hz, 1H, CH), 2.53 (dd, J=18.4, 6.0 Hz, 1H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.3, 172.9, 166.5, 164.8, 163.4 (d, J=250.1 Hz), 130.1, 129.3, 129.1, 127.8 (d, J=3.6 Hz), 127.6 (d, J=9.2 Hz), 126.5, 116.6 (d, J=21.7 Hz), 70.5, 54.6, 48.3, 30.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$, non-decoupled): δ=−111.1 (m) ppm. IR (film): ν=2360, 2341, 2132, 1751, 1705, 1450, 1432, 1398, 1344, 1244, 1168 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{20}H_{16}FN_2O_4$ $[M+H]^+$ 367.1094; found 367.1091.

*4.2.10. (R)-Methyl 2-(4-chlorophenyl)-2-((R)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyanoacetate (**5j**).* Yellow solid (51.6 mg, 90%); mp 187.6–191.0 °C. >20:1 dr. $[\alpha]_D^{25}$ −53.1 (c 1.01, CH_2Cl_2); 92% ee (Chiralpak AD-H; hexane/2-propanol, 70:30; 1.0 mL/min; 230 nm; t_{major}=23.97 min, t_{minor}=15.45 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.59 (d, J=8.8 Hz, 2H, ArH), 7.50–7.42 (m, 5H, ArH), 7.30 (d, J=7.6 Hz, 1H, ArH), 4.38 (dd, J=9.6, 6.0 Hz, 1H, CH), 3.88 (s, 3H, OCH_3), 2.80 (dd, J=18.8, 9.6 Hz, 1H, CH), 2.51 (dd, J=18.4, 6.0 Hz, 1H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.2, 172.7, 166.3, 165.1, 136.4, 131.1, 130.5, 130.0, 129.7, 129.2, 127.0, 126.4, 70.6, 54.6, 48.3, 30.6 ppm. IR (film): ν=2131, 1749, 1713, 1598, 1508, 1500, 1386, 1238, 1188, 1165, 1015 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{20}H_{16}ClN_2O_4$ $[M+H]^+$ 383.0799; found 383.0797.

*4.2.11. (R)-Methyl 2-(4-bromophenyl)-2-((R)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyanoacetate (**5k**).* Yellow solid (49.0 mg, 77%); mp 189.6–193.0 °C. >20:1 dr. $[\alpha]_D^{25}$ −48.5 (c 1.02, CH_2Cl_2); 90% ee (Chiralpak AD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{major}=42.01 min, t_{minor}=25.66 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.63 (d, J=8.4 Hz, 2H, ArH), 7.54–7.41 (m, 5H, ArH), 7.31 (d, J=8.0 Hz, 1H, ArH), 4.38 (dd, J=9.2, 6.0 Hz, 1H, CH), 3.89 (s, 3H, OCH_3), 2.81 (dd, J=18.8, 9.6 Hz, 1H, CH), 2.51 (dd, J=18.4, 6.0 Hz, 1H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.2, 172.8, 166.2, 165.1, 132.7, 131.1, 131.0, 129.3, 129.2, 127.2, 126.5, 124.6, 70.7, 54.7, 48.2, 30.5 ppm. IR (film): ν=2134, 1752, 1716, 1499, 1489, 1388, 1246, 1183, 1010 cm^{-1}. MS (EI) m/z: 428 [$(M+2)^+$, 27%], 426 (M^+, 27), 386 (17), 384 (19), 222 (44), 196 (30), 194 (26), 141 (100), 140 (48), 119 (41), 115 (39), 114 (34), 91 (33), 59 (30); HRMS (EI-TOF): calcd for $C_{20}H_{16}BrN_2O_4$ $[M]^+$ 426.0215; found 426.0216.

*4.2.12. (R)-Methyl 2-(4-bromophenyl)-2-isocyano-2-((R)-1-(3-methoxyphenyl)-2,5-dioxopyrrolidin-3-yl)acetate (**5l**).* Yellow solid (65.3 mg, 95%); mp 164.1–166.6 °C. >20:1 dr. $[\alpha]_D^{25}$ −46.1 (c 1.04, CH_2Cl_2); 91% ee (Chiralpak AD-H; hexane/2-propanol, 70:30; 1.0 mL/min; 230 nm; t_{major}=41.40 min, t_{minor}=23.80 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.63 (d, J=8.4 Hz, 2H, ArH), 7.52 (d, J=8.8 Hz, 2H, ArH), 7.39 (t, J=8.0 Hz, 1H, ArH), 6.97 (dd, J=8.4, 2.0 Hz, 1H, ArH), 6.88 (d, J=8.8 Hz, 1H, ArH), 6.82 (t, J=2.0 Hz, 1H, ArH), 4.37 (dd, J=9.6, 6.0 Hz, 1H, ArH), 3.89 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.80 (dd, J=18.8, 9.6 Hz, 1H, CH), 2.51 (dd, J=18.4, 6.0 Hz, 1H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.2, 172.7, 166.3, 165.0, 160.2, 132.7, 132.0, 131.0, 130.1, 127.2, 124.6, 118.7, 115.1, 112.2, 70.6, 55.4, 54.7, 48.2, 30.5 ppm. IR (film): ν=2132, 1752, 1717, 1606, 1491, 1387, 1257, 1196, 1077, 1094, 1010 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{21}H_{18}BrN_2O_5$ $[M+H]^+$ 457.0399; found 457.0396.

*4.2.13. (R)-Methyl 2-((R)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyano-2-(p-tolyl)acetate (**5m**).* White solid (35.8 mg, 66%); mp 208.5–211.3 °C. >20:1 dr. $[\alpha]_D^{25}$ −50.5 (c 0.9, CH_2Cl_2); 90% ee (Chiralcel OD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{major}=16.52 min, t_{minor}=41.30 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.52–7.42 (m, 5H, ArH), 7.32–7.27 (m, 4H, ArH), 4.42 (dd, J=9.6, 6.0 Hz, 1H, CH), 3.87 (s, 3H, OCH_3), 2.81 (dd, J=18.4, 9.6 Hz, 1H, CH), 2.53 (dd, J=18.8, 6.0 Hz, 1H, CH), 2.39 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.6, 173.1, 166.7, 164.1, 140.1, 131.2, 130.1, 129.3, 129.1, 129.0, 126.5, 125.3, 70.9, 54.4, 48.2, 30.7, 21.0 ppm. IR (film): ν=2132, 1751, 1716, 1500, 1388, 1247, 1189, 1040, 1020 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{21}H_{19}N_2O_4$ $[M+H]^+$ 363.1345; found 363.1342.

*4.2.14. (R)-Methyl 2-((R)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyano-2-(4-methoxyphenyl)acetate (**5n**).* Pale-yellow solid (34.2 mg, 60%); mp 201.3–202.8 °C. 20:1 dr. $[\alpha]_D^{25}$ −45.3 (c 0.45, CH_2Cl_2); 88% ee (Chiralcel OD-H; hexane/2-propanol, 70:30; 1.0 mL/min; 230 nm; t_{major}=18.38 min, t_{minor}=43.58 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.54 (dd, J=6.8, 2.0 Hz, 2H, ArH), 7.50–7.41 (m, 3H, ArH), 7.31 (d, J=8.4 Hz, 2H, ArH), 6.98 (dd, J=7.2, 2.0 Hz, 2H, ArH), 4.39 (dd, J=9.6, 6.0 Hz, 1H, CH), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 2.81 (dd, J=18.8, 9.2 Hz, 1H, CH), 2.54 (dd, J=18.8, 6.0 Hz, 1H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.6, 173.1, 166.8, 164.0, 160.6, 131.2, 129.3, 129.1, 126.8, 126.5, 123.7, 114.7, 70.7, 55.4, 54.4, 48.2, 30.7 ppm. IR (film): ν=2132, 1750, 1713, 1511, 1500, 1386, 1257, 1182, 1029 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{21}H_{19}N_2O_5$ $[M+H]^+$ 379.1294; found 379.1292.

*4.2.15. (R)-Methyl 2-((R)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-(3-fluoro-phenyl)-2-isocyanoacetate (**5o**).* Pale-yellow solid (52.4 mg, 95%); mp 158.3–160.2 °C. >20:1 dr. $[\alpha]_D^{25}$ −36.1 (c 1.1, CH_2Cl_2); 93% ee (Chiralpak AD-H; hexane/2-propanol, 70:30; 1.0 mL/min; 230 nm; t_{major}=22.76 min, t_{minor}=16.70 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.51–7.37 (m, 6H, ArH), 7.31 (d, J=7.2 Hz, 2H, ArH), 7.20–7.16 (m, 1H, ArH), 4.38 (dd, J=9.6, 6.0 Hz, 1H, CH), 3.90 (s, 3H, OCH_3), 2.82 (dd, J=18.8, 9.6 Hz, 1H, CH), 2.53 (dd, J=18.8, 6.0 Hz, 1H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.2, 172.8, 166.2, 165.1, 163.0 (d, J=247.1 Hz), 134.3 (d, J=7.5 Hz), 131.3 (d, J=8.8 Hz), 131.1, 129.3, 129.2, 126.5, 121.2 (d, J=2.7 Hz), 117.2 (d, J=21.6 Hz), 113.2 (d, J=25.1 Hz), 70.6, 54.7, 48.4, 30.5 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ=−109.5 ppm. IR (film): ν=2360, 2131, 1752, 1713, 1593, 1500, 1489, 1437, 1386, 1246, 1189, 1069, 1017 cm^{-1}. HRMS (EI-TOF): calcd for $C_{20}H_{15}FN_2O_4$ $[M]^+$ 366.1016; found 366.1013.

*4.2.16. (R)-Methyl 2-((R)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyano-2-(m-tolyl)acetate (**5p**).* Pale-yellow solid (46.2 mg, 85%); mp 180.7–184.3 °C. >20:1 dr. $[\alpha]_D^{25}$ −33.7 (c 1.0, CH_2Cl_2); 86% ee (Chiralpak AD-H; hexane/2-propanol, 70:30; 1.0 mL/min; 230 nm; t_{major}=35.22 min, t_{minor}=14.87 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.51–7.44 (m, 5H, ArH), 7.42–7.31 (m, 3H, ArH), 7.27–7.26 (m, 1H, ArH), 4.43 (dd, J=9.6, 6.0 Hz, 1H, CH), 3.88 (s, 3H, OCH_3), 2.81 (dd, J=18.4, 9.6 Hz, 1H, CH), 2.54 (dd, J=18.8, 6.0 Hz, 1H, CH), 2.43 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.5, 173.1, 166.6, 164.2, 139.6, 131.8, 131.2, 130.7, 129.4, 129.3, 129.1, 126.5, 126.0, 122.5, 71.0, 54.5, 48.3, 30.7, 21.6 ppm. IR (film): ν=2133, 1752, 1716, 1500, 1388, 1247, 1191 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{21}H_{19}N_2O_4$ $[M+H]^+$ 363.1345; found 363.1342.

*4.2.17. (R)-Benzyl 2-((R)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**5r**).* White solid (60.5 mg, 95%); mp

161.8–164.2 °C. 10:1 dr. $[\alpha]_D^{25}$ −21.8 (*c* 1.0, CH_2Cl_2); 90% ee (Chiralpak AD-H; hexane/2-propanol, 70:30; 1.0 mL/min; 230 nm; t_{major}=52.98 min, t_{minor}=29.16 min). ^1H NMR (400 MHz, $CDCl_3$): δ=7.63–7.61 (m, 2H, ArH), 7.52–7.43 (m, 6H, ArH), 7.34–7.31 (m, 5H, ArH), 7.28–7.25 (m, 2H, ArH), 5.27 (s, 2H, CH_2), 4.45 (dd, *J*=9.6, 6.0 Hz, 1H, CH), 2.81 (dd, *J*=18.8, 9.6 Hz, 1H, CH), 2.54 (dd, *J*=18.8, 6.0 Hz, 1H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.3, 173.0, 165.7, 164.3, 134.2, 131.8, 131.2, 129.9, 129.5, 129.3, 129.2, 129.07, 129.06, 128.9, 128.7, 128.5, 128.1, 128.0, 126.53, 126.47, 125.5, 125.4, 71.3, 69.3, 48.0, 30.7 ppm. IR (film): ν=2132, 1752, 1714, 1499, 1450, 1383, 1182 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{26}H_{21}N_2O_4$ $[M+H]^+$ 425.1501; found 425.1500.

*4.2.18. (R)-tert-Butyl 2-((R)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyano-2-phenylacetate (**5s**).* Pale-yellow solid (24.2 mg, 41%); mp 126.2–130.2 °C. 1:1 dr. $[\alpha]_D^{25}$ −10.0 (*c* 1.0, CH_2Cl_2); 86% ee for major isomer (Chiralpak AD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{major}=41.08 min, t_{minor}=35.01 min). ^1H NMR (400 MHz, $CDCl_3$): δ=7.62 (d, *J*=6.8 Hz, 1H, ArH), 7.58 (d, *J*=6.8 Hz, 1H, ArH), 7.52–7.35 (m, 6H, ArH), 7.32 (d, *J*=7.6 Hz, 1H, ArH), 7.23 (d, *J*=7.2 Hz, 1H, ArH), 4.41 (dd, *J*=9.6, 6.0 Hz, 0.5H, CH), 4.09 (dd, *J*=8.8, 6.0 Hz, 0.5H, CH), 3.18 (dd, *J*=18.8, 9.6 Hz, 0.5H, CH), 2.88 (dd, *J*=18.8, 4.8 Hz, 0.5H, CH), 2.79 (dd, *J*=18.8, 9.6 Hz, 0.5H, CH), 2.50 (dd, *J*=18.8, 6.0 Hz, 0.5H, CH), 1.48 (s, 4.5H, 3× CH_3), 1.47 (s, 4.5H, 3× CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.5, 173.32, 173.28, 172.6, 164.7, 164.4, 163.5, 163.3, 132.54, 132.46, 131.3, 129.7, 129.4, 129.34, 129.29, 129.1, 129.0, 128.93, 128.88, 126.7, 126.5, 125.29, 125.26, 85.9, 85.3, 72.3, 71.7, 47.8, 32.6, 30.9, 29.6, 27.5 ppm. IR (film): ν=2360, 2342, 2131, 1717, 1450, 1383, 1371, 1259, 1186, 1149 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{23}H_{23}N_2O_4$ $[M+H]^+$ 391.1658; found 391.1656.

4.3. General procedure for the asymmetric Michael addition of α-isocyanoacetates 1 with *N*-substituted maleimides 2 catalyzed by 3n

To a solution of isocyanoacetates **1** (0.30 mmol), cat. **3n** (7.1 mg, 0.015 mmol), and 4 Å MS (30 mg) in DCM (1.0 mL) was added *N*-substituted maleimides **2** (0.15 mmol). The resulting mixture was stirred at 20 °C for 4–72 h. Then the reaction mixture was concentrated and the residue was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate=4:1) to furnish the corresponding products *ent*-**5**.

*4.3.1. (S)-Methyl 2-((S)-2,5-dioxo-1-phenyl pyrrolidin-3-yl)-2-isocyano-2-phenylacetate (ent-**5a**).* Yellow solid (52.1 mg, 99%); >20:1 dr. $[\alpha]_D^{25}$ +44.4 (*c* 0.4, CH_2Cl_2); 90% ee (Chiralpak OD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{minor}=16.55 min, t_{major}=27.68 min).

*4.3.2. (S)-Methyl 2-((S)-1-(4-fluorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (ent-**5b**).* Pale-yellow solid (50.5 mg, 92%); >20:1 dr. $[\alpha]_D^{25}$ +43.9 (*c* 0.3, CH_2Cl_2); 85% ee (Chiralcel OD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{minor}=15.41 min, t_{major}=27.13 min).

*4.3.3. (S)-Methyl 2-((S)-1-(4-bromophenyl)-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (ent-**5c**).* Pale-yellow solid (63.0 mg, 98%); >20:1 dr. $[\alpha]_D^{25}$ +43.7 (*c* 0.3, CH_2Cl_2); 91% ee (Chiralcel OD-H; hexane/2-propanol, 60:40; 1.0 mL/min; 230 nm; t_{minor}=8.91 min, t_{major}=13.60 min).

*4.3.4. (S)-Methyl 2-((S)-2,5-dioxo-1-(p-tolyl)pyrrolidin-3-yl)-2-isocyano-2-phenylacetate (ent-**5d**).* Yellow solid (53.3 mg, 98%); >20:1 dr. $[\alpha]_D^{25}$ +39.7 (*c* 0.35, CH_2Cl_2); 86% ee (Chiralcel OD-H; hexane/2-propanol, 60:40; 1.0 mL/min; 230 nm; t_{minor}=8.05 min, t_{major}=11.47 min).

*4.3.5. (S)-Methyl 2-isocyano-2-((S)-1-(4-methoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-2-phenylacetate (ent-**5e**).* Yellow solid (63.4 mg, 99%); 20:1 dr. $[\alpha]_D^{25}$ +42.9 (*c* 0.5, CH_2Cl_2); 88% ee (Chiralpak AD-H; hexane/2-propanol, 60:40; 1.0 mL/min; 230 nm; t_{major}=14.37 min, t_{minor}=23.15 min).

*4.3.6. (S)-Methyl 2-((S)-1-(3-chlorophenyl)-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (ent-**5f**).* White solid (60.0 mg, 99%); >20:1 dr. $[\alpha]_D^{25}$ +46.6 (*c* 0.35, CH_2Cl_2); 88% ee (Chiralcel OD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{minor}=14.12 min, t_{major}=23.19 min).

*4.3.7. (S)-Methyl 2-isocyano-2-((S)-1-(3-methoxyphenyl)-2,5-dioxopyrrolidin-3-yl)-2-phenylacetate (ent-**5g**).* Yellow solid (57.4 mg, 99%); >20:1 dr. $[\alpha]_D^{25}$ +48.7 (*c* 2.7, CH_2Cl_2); 90% ee (Chiralpak OD-H; hexane/2-propanol, 70:30; 0.8 mL/min; 230 nm; t_{minor}=17.85 min, t_{major}=24.67 min).

*4.3.8. (S)-Methyl 2-((S)-1-benzyl-2,5-dioxopyrrolidin-3-yl)-2-isocyano-2-phenylacetate (ent-**5h**).* Yellow solid (38.5 mg, 71%); >20:1 dr. $[\alpha]_D^{25}$ +105.0 (*c* 0.2, CH_2Cl_2); 65% ee (Chiralpak OD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{minor}=15.12 min, t_{major}=18.16 min).

*4.3.9. (S)-Methyl 2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-(4-fluorophenyl)-2-isocyanoacetate (ent-**5i**).* White solid (54.2 mg, 99%); >20:1 dr. $[\alpha]_D^{25}$ +37.0 (*c* 0.25, CH_2Cl_2); 89% ee (Chiralcel OD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{minor}=17.65 min, t_{major}=28.57 min).

*4.3.10. (S)-Methyl 2-(4-chlorophenyl)-2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyanoacetate (ent-**5j**).* Yellow solid (52.8 mg, 99%); >20:1 dr. $[\alpha]_D^{25}$ +53.8 (*c* 0.6, CH_2Cl_2); 90% ee (Chiralpak AD-H; hexane/2-propanol, 70:30; 1.0 mL/min; 230 nm; t_{major}=15.46 min, t_{minor}=23.72 min).

*4.3.11. (S)-Methyl 2-(4-bromophenyl)-2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyanoacetate (ent-**5k**).* Yellow solid (71.2 mg, 99%); >20:1 dr. $[\alpha]_D^{25}$ +32.2 (*c* 0.35, CH_2Cl_2); 91% ee (Chiralpak AD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{major}=24.39 min, t_{minor}=40.37 min).

*4.3.12. (S)-Methyl 2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyano-2-(p-tolyl)acetate (ent-**5m**).* White solid (53.4 mg, 98%); >20:1 dr. $[\alpha]_D^{25}$ +52.2 (*c* 0.40, CH_2Cl_2); 86% ee (Chiralcel OD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; t_{minor}=16.86 min, t_{major}=38.42 min).

*4.3.13. (S)-Methyl 2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyano-2-(4-methoxyphenyl)acetate (ent-**5n**).* Pale-yellow solid (52.2 mg, 92%); >20:1 dr. $[\alpha]_D^{25}$ +45.5 (*c* 0.25, CH_2Cl_2); 88% ee (Chiralcel OD-H; hexane/2-propanol, 70:30; 1.0 mL/min; 230 nm; t_{minor}=18.60 min, t_{major}=42.10 min).

*4.3.14. (S)-Methyl 2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-(3-fluoro-phenyl)-2-isocyanoacetate (ent-**5o**).* Pale-yellow solid (54.0 mg, 98%); >20:1 dr. $[\alpha]_D^{25}$ +37.3 (*c* 0.25, CH_2Cl_2); 84% ee (Chiralpak AD-H; hexane/2-propanol, 70:30; 1.0 mL/min; 230 nm; t_{major}=18.68 min, t_{minor}=25.87 min).

*4.3.15. (S)-Methyl 2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyano-2-(m-tolyl)acetate (ent-**5p**).* Pale-yellow solid (59.0 mg, 99%); >20:1 dr. $[\alpha]_D^{25}$ +49.8 (*c* 1.0, CH_2Cl_2); 86% ee (Chiralpak AD-H;

hexane/2-propanol, 70:30; 1.0 mL/min; 230 nm; t_{major}=16.68 min, t_{minor}=41.41 min).

*4.3.16. (S)-tert-Butyl 2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyano-2-phenylacetate (ent-**5s**).* Pale-yellow solid (54.2 mg, 93%); 3:1 dr. $[\alpha]_D^{25}$ +24.8 (*c* 0.25, CH_2Cl_2); 85% ee and 51% ee (Chiralpak AD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; $t_{minor-minor}$=13.49 min, $t_{minor-major}$=14.65 min $t_{major-major}$=28.85 min, $t_{major-minor}$=35.08 min).

*4.3.17. (R)-Methyl 2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyano-3-phenylpropanoate (ent-**5t**).*[10c] Pale-yellow solid (10.7 mg, 20%); mp 122.8–124.6 °C. 2.4:1 dr. $[\alpha]_D^{25}$ +12.4 (*c* 0.15, CH_2Cl_2); 46% and 33% ee (Chiralpak AD-H; hexane/2-propanol, 80:20; 1.0 mL/min; 230 nm; $t_{major-major}$=21.43 min, $t_{major-minor}$=31.35 min, $t_{minor-major}$=29.70 min, $t_{minor-minor}$=16.63 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.54–7.47 (m, 3H, ArH), 7.45–7.40 (m, 1.5H, ArH), 7.38–7.29 (m, 10H, ArH), 3.89 (d, *J*=13.6 Hz, 0.45H, CH), 3.78 (s, 3H, OCH_3), 3.74 (s, 1.4H, OCH_3), 3.69 (dd, *J*=9.6, 6.4 Hz, 1H, CH), 3.65–3.57 (m, 0.9H, 2× CH), 3.34 (dd, *J*=20.8, 9.6 Hz, 2H, 2× CH), 3.12 (dd, *J*=18.4, 9.2 Hz, 1H, CH), 3.08 (dd, *J*=18.4, 9.2 Hz, 0.45H, CH), 2.93 (dd, *J*=18.4, 6.0 Hz, 1H, CH), 2.72 (dd, *J*=18.4, 4.8 Hz, 0.45H, CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.4, 173.2, 173.03, 172.97, 167.1, 166.7, 163.6, 163.4, 132.8, 132.0, 131.3, 130.2, 130.0, 129.3, 129.2, 129.1, 129.0, 128.70, 128.65, 128.4, 128.2, 126.7, 126.5, 70.3, 69.4, 53.9, 53.8, 46.0, 45.1, 42.60, 42.58, 32.0, 31.2 ppm. IR (film): ν=2140, 1715, 1497, 1393, 1260, 1089, 1018 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{21}H_{18}N_2O_4Na$ $[M+Na]^+$ 385.1164; found 385.1143.

*4.3.18. (R)-Methyl 2-((S)-2,5-dioxo-1-phenylpyrrolidin-3-yl)-2-isocyanoacetate (ent-**5u**).* White viscous solid (6.5 mg, 15%); 1.4:1 dr. $[\alpha]_D^{25}$ +4.5 (*c* 0.4, CH_2Cl_2); 20% and 15% ee (Chiralpak AD-H; hexane/2-propanol, 70:30; 1.0 mL/min; 234 nm; $t_{major-minor}$=11.49 min, $t_{major-major}$=14.89 min, $t_{minor-minor}$ =23.48 min, $t_{minor-major}$=25.00 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.52–7.40 (m, 5H, ArH), 7.31–7.27 (m, 3.5H, ArH), 5.08 (d, *J*=3.2 Hz, 1H, CH), 4.90 (d, *J*=3.6 Hz, 0.7H, CH), 4.36 (q, *J*=7.2 Hz, 2H, OCH_2), 4.35 (q, *J*=7.2 Hz, 1.4H, OCH_2), 3.70–3.63 (m, 1H+0.7H, CH), 3.16 (dd, *J*=16.4, 9.6 Hz, 0.7H, CH), 3.05 (dd, *J*=16.4, 9.6 Hz, 1H, CH), 2.92 (dd, *J*=16.4, 5.6 Hz, 1H, CH), 2.83 (dd, *J*=16.4, 5.6 Hz, 0.7H, CH), 1.37 (t, *J*=7.2 Hz, 3H, CH_3), 1.35 (t, *J*=7.2 Hz, 2.1H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=173.8, 173.42, 173.36, 173.2, 164.2, 163.9, 163.8, 163.1, 131.3, 131.2, 129.3, 129.2, 129.1, 129.0, 126.4, 126.3, 63.8, 55.9, 42.3, 42.1, 31.2, 29.5, 13.92, 13.86 ppm. IR (film): ν=2147, 1715, 1501, 1390, 1187, 1031 cm^{-1}. MS (EI): *m*/*z* (%)=286 (86) $[M]^+$, 259 (37), 213 (100), 174 (92), 119 (22), 91 (12). HRMS (EI-TOF): calcd for $C_{15}H_{14}N_2O_4$ $[M]^+$ 286.0954; found 286.0955.

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Supplementary data

Detailed optimization reaction conditions, copies of NMR spectra of new compounds, HPLC traces for the determination of the enantiomeric excess for compounds **5** and X-ray crystal data of product *ent*-**5c** (CCDC 932205) have been provided. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.09.084.

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