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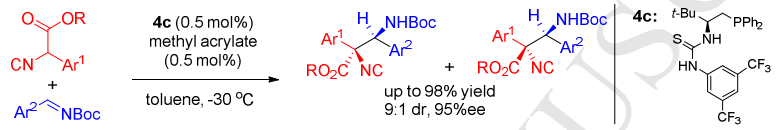

Dual-reagent Organophosphine Catalyzed Asymmetric Mannich Reactions of Isocyanoacetates with *N*-Boc-aldimines

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ABSTRACT

A combination of an amino-acid derived chiral phosphine catalyst and methyl acrylate has been employed to catalyze the direct Mannich reaction of α-aryl isocyanoacetate and *N*-Boc-aldimines efficiently. The loading of the catalyst could be as low as 0.5 mol% without compromise on the yield and enantioselectivity and the corresponding chiral adducts were obtained in excellent yields (up to 98%) and good enantioselectivities (up to 95%).

1. Introduction

Trivalent phosphine that possessed the characteristic of powerful nucleophilicity and Lewis base, is widely used in organocatalysis.[1] Over the past few decades, most of the organic phosphine-catalyzed asymmetric reactions essentially proceeded to combine phosphine with electron-deficient alkene, giving rise to a zwitterion which subsequently reacts with an appropriate reactant such as alkene (the Rauhut-Currier reaction),[2] allene (cycloaddition),[3] or aldehyde (the Mortia-Baylis-Hillman reaction).[4] To overcome the limitation of this general catalysis mode, our group has developed dual-reagent catalysis strategy, which utilized the oxygen anion of zwitterion formed from the phosphine catalyst and methyl acrylate as a Brønsted base or a Lewis base to catalyze related Mannich reactions[5] or Strecker reactions.[6] As a new catalytic strategy, exploring the applicability of this model becomes very important.

Isocyanide is a versatile reagent for heterocyclic synthesis.[7] Recently, the asymmetric additions of isocyanoacetates to carbon-carbon double bonds,[8] carbon-heteroatom multiple bonds[9] and other electrophiles such as azodicarboxylates[10] have provided efficient ways to prepare a wide range of optically active heterocyclic compounds. In addition, multicomponent reactions with isocyanoacetate derivatives have also been used for synthesis of varieties of peptides and peptide mimetics[11]. In the majority of the asymmetric addition reactions, chiral ligands and metals have cooperatively catalyzed the reaction of isocyanoacetates to afford excellent results. However, in the absence of metals, the reaction of α-phenylisocyanoacetates with aldimine still remains an unexplored area.[9b, 9e] Herein, we wish to report our preliminary findings on this reaction via the dual-reagent catalysis.

2. Results and discussion

In a model investigation, the reaction between α-phenylisocyanoacetate (**1a**) and *N*-Boc-benzaldimine (**2a**) was evaluated in the presence of dual-reagent catalysts in toluene at room temperature (table 1). The thiourea hydrogen-bonding vs amide N-H and urea (table 1, entries 1-3) gave better results with the catalyst **4c** used, which quickly afford the corresponding addition product **3a** and the diastereomers **3a′** in high yields and moderate enantioselectivity (97% yield, 75%, 76% ee, 79:21 dr, table 1, entry 3). Next, another chiral phosphine catalysts derived from isoleucine were evaluated. Unfortunately, catalyst **4d** afforded poor results on the enantioselectivity (table 1, entry 4). Based on our previous studies,[5, 6] the acidity of hydrogen bonding played an important role in the enantioselectivity control. Thus we then examined the electronic effect of phenyl group on thiourea moiety (table 1, entries 5-8), but no improved results were obtained. With catalyst **4c** as the optimal, the effect of solvents was investigated. It was notable that toluene was still the best (table 1, entries 9-14). Reactions run at lower temperature (i.e. -30 or -50 ˚C) delivered higher enantioselectivities (table 1, entries 15-17).

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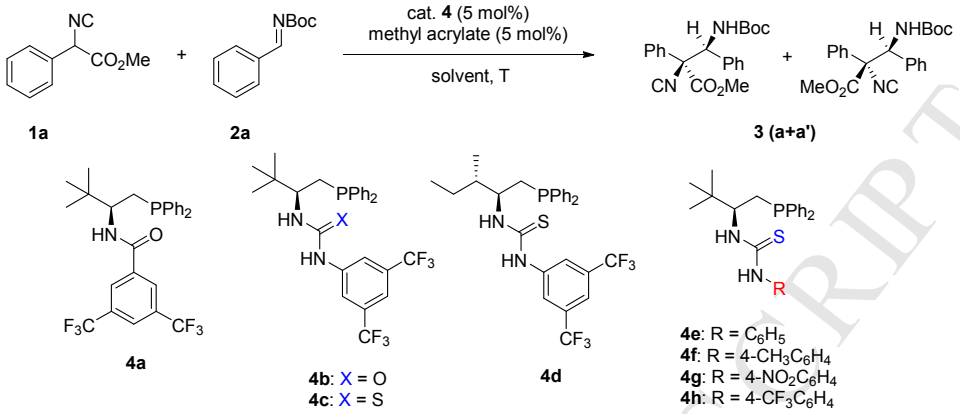
Given the dual-reagent catalysis is highly effective, we tried to lower the catalyst loading of **4c** from 5 mol% down to 0.5 mol% and 0.1%, and to our delight, the product could also be obtained in excellent enantioselectivity (83, 93%) although extension of reaction time is required (table 1, entries 18 and 19). Considering 2 hours are reasonable time for this reaction, we then use 0.5 mol% of catalyst **4c** in toluene at -30 □ as the optimal reaction condition for this Mannich reaction.

Table 1 Screening of the reaction conditions [a]

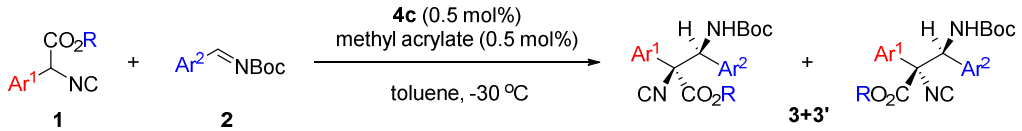


Entry	Catatlyst	Solvent	Temperature/(□)	Time	Yield [b] (%)	dr [c]	ee [c] (%)
1	**4a**	toluene	rt	3 h	95	2.8:1	18, -18
2	**4b**	toluene	rt	15 min	95	3.8:1	48, 60
3	**4c**	toluene	rt	5 min	97	3.8:1	75, 76
4	**4d**	toluene	rt	5 min	87	3.8:1	48, 34
5	**4e**	toluene	rt	30 min	97	2.7:1	45, 27
6	**4f**	toluene	rt	1 h	96	2.7:1	32, 73
7	**4g**	toluene	rt	5 min	92	5.2:1	75, 70
8	**4h**	toluene	rt	5 min	95	4.9:1	67, 61
9	**4c**	CH_2Cl_2	rt	5 min	89	1:1.3	18, 19
10	**4c**	THF	rt	1 h	68	1:1.8	Racemic
11	**4c**	acetonitrile	rt	20 min	84	1.4:1	0, -14
12	**4c**	ethyl acetate	rt	20 min	71	1:1	5, -10
13	**4c**	fluorobenzene	rt	10 min	82	1.5:1	56, 70
14	**4c**	mesitylene	rt	10 min	74	2.8:1	69, 72
15	**4c**	toluene	-10	15 min	92	2.4:1	72, 82
16	**4c**	toluene	-30	20 min	95	3.3:1	79, 92
17	**4c**	toluene	-50	30 min	92	3.3:1	77, 93
18[d]	**4c**	toluene	-30	2 h	98	3.3:1	83(93)[f], 93
19[e]	**4c**	toluene	-30	20 h	98	3.3:1	82, 93

[a] Unless otherwise specified, all reactions were carried out with α-phenylisocyanoacetates **1a** (0.1 mmol) and imines **2a** (0.20 mmol) in the presence of methyl acrylate (5 mol%) and catalyst **4** (5 mol%) in solvent (1.0 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] 0.5 mol% of methyl acrylate and catalyst **4c** were used.
[e] 0.1 mol% of methyl acrylate and catalyst **4c** were used.
[f] In brackets, enantiomeric excess after recrystallization from ethanol/*n*-pentane

With the optimized conditions established, the scope of the reaction with respect to isocyanoacetates was investigated. As summarized in table 2, isocyanoacetates **1b-1h** with *N*-Boc-benzaldimine **2a** could be smoothly converted into the corresponding products in good yields, moderate diastereoselectivities and good enantioselectivities (up to 98% yield, 2.5 : 1 dr, 93% ee; Table 2 entries 1-7). We found that α-phenylisocyanoacetates with an electron-donating group on the phenyl were better than that with electron-withdrawing groups on the enantioselectivity. Isocyanoacetates **1i-1k** with different ester substituents subjected to this reaction also gave the product **3i-3k** (table 2 entries 8-10), respectively, with good yields (up to 98%) and good ee values (up to 93%). An improved diastereoselectivity (dr 1 : 9, table 2, and entry 9) was obtained with *tert*-butyl 2-isocyano-2-phenylacetate (**1j**) probably due to the large steric resistance reasons and the reaction time was extended to 40 hours.

Table 2 Substrate Scope of Isocyanoacetates **1** and *N*-Boc-aldimines **2** in the Asymmetric Mannich Reaction [a]



Entry	**1** (Ar^1/R)	**2** (Ar^2)	**3/3′**	Time (h)	Yield [b] (%)	dr [c]	ee [d] (%)
1	**1b** (3-MeC_6H_4/Me)	**2a** (Phenyl)	**3b/3b′**	4	91	2.3:1	79, 92
2	**1c** (4-MeC_6H_4/Me)	**2a** (Phenyl)	**3c/3c′**	4	94	1.8:1	82, 93
3	**1d** (3-MeOC_6H_4/Me)	**2a** (Phenyl)	**3d/3d′**	2	92	2:1	80, 88
4	**1e** (4-MeOC_6H_4/Me)	**2a** (Phenyl)	**3e/3e′**	4	98	1.5:1	81, 92
5	**1f** (4-FC_6H_4/Me)	**2a** (Phenyl)	**3f/3f′**	1	95	2:1	82, 87
6	**1g** (4-ClC_6H_4/Me)	**2a** (Phenyl)	**3g/3g′**	1	98	2.3:1	72, 82
7	**1h** (4-BrC_6H_4/Me)	**2a** (Phenyl)	**3h/3h′**	1	98	2.5:1	79, 81
8 [d]	**1i** (Phenyl/Bn)	**2a** (Phenyl)	**3i/3i′**	3	95	4:1	93, 89
9 [d]	**1j** (Phenyl/*t*-Bu)	**2a** (Phenyl)	**3j/3j′**	40	98	9:1	91, 70
10 [d]	**1k** (Phenyl/*i*-Pr)	**2a** (Phenyl)	**3k/3k′**	35	96	3:1	92, 85
11	**1a** (Phenyl/Me)	**2b** (3-MeC_6H_4)	**3l/3l′**	2	98	1.3:1	72, 89
12	**1a** (Phenyl/Me)	**2c** (4-MeC_6H_4)	**3m/3m′**	2	85	2:1	81, 89
13	**1a** (Phenyl/Me)	**2d** (3-MeOC_6H_4)	**3n/3n′**	2	88	2:1	75, 91
14	**1a** (Phenyl/Me)	**2e** (4-MeOC_6H_4)	**3o/3o′**	2	94	1.8:1	82, 93
15	**1a** (Phenyl/Me)	**2f** (4-FC_6H_4)	**3p/3p′**	2	96	2:1	82, 93
16	**1a** (Phenyl/Me)	**2g** (4-ClC_6H_4)	**3q/3q′**	2	97	1.1:1	82, 93
17	**1a** (Phenyl/Me)	**2h** (4-BrC_6H_4)	**3r/3r′**	2	92	1.2:1	80, 94
18	**1a** (Phenyl/Me)	**2i** (4-$NO_2C_6H_4$)	**3s/3s′**	1.5	90	2:1	68, 95
19	**1a** (Phenyl/Me)	**2j** (3-BrC_6H_4)	**3t/3t′**	2	92	1.2:1	64, 90
20 [d]	**1a** (Phenyl/Me)	**2k** (2-furanyl)	**3u/3u′**	4	85	1.4:1	52, 80
21 [d]	**1a** (Phenyl/Me)	**2l** (2-thienyl)	**3v/3v′**	3	92	2:1	50, 79

[a] All reactions were carried out with isocyanoacetates **1** (0.10 mmol), imines **2** (0.20 mmol), methyl acrylate (0.5 mol%) and catalyst **4c** (0.5 mol%) in toluene (1.0 mL) at -30 □.

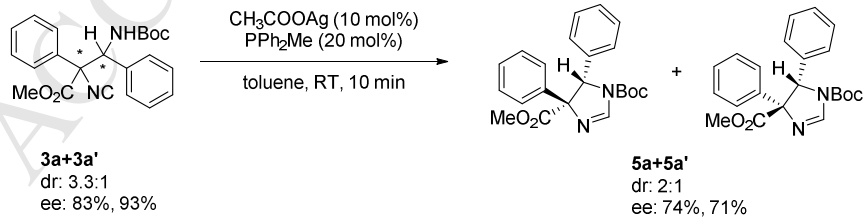
[b] Isolated yield.

[c] Unless otherwise noted, the diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product.

[d] The dr and ee value were determined by chiral HPLC analysis.

A variety of *N*-Boc-aldimines **2b-2l** were also tested for the Mannich reaction with α-phenylisocyanoacetate **1a**. As shown in table 2, the desired products **3′** (and **3**) were obtained in high yields and mostly high-to-excellent enantioselectivities (Table 2, entries 11-19). In the cases of heterocyclic aldimine substrates, the reactions proceeded to give moderate enantioselectivities, which afforded the product with 80% ee (**3u′**) and 79% ee (**3v′**) (Table 2, entries 20-21). The effect of *para*-substitution on the benzene ring is always better than that of the *meta*-substitution, irrespective of the imines moiety or the isocyanoacetate moiety.

Inspired by Dixon's work,[9d] we quickly obtained the adduct **5a** and **5a′** in good yield under the condition of acetoxysilver and methyldiphenylphosphane. Unfortunately, the enantioselectivity decreased to 74% and 71% (Scheme 1). We also tried to use a single diastereomer **3a** (or **3a′**) to turn off the ring. From the HPLC data (see supporting information), we found that each diastereomer had partial isomerization and converted to the other diastereomer.



Scheme 1. Transformation of **3a** and **3a′** to **5a** and **5a′**

The absolute configuration of compound **3a** and **3t′** were confirmed by single-crystal X-ray structural analysis (figure 1, see supporting information).[12] The structure enabled the (**2*R***,**3*S***) assignment of the newly formed stereogenic centers in **3t′** , and the (**2*S***,**3*S***) in **3a** , the configurations of other diastereomers were determined by analogy. Based on previous reports[5c, 9e] and on the known absolute stereochemical configuration of **3a** with **3t′**, a transition-state model rationalizing the stereochemical outcome of the Mannich reaction between **1a** and **2a** in the presence of dual-reagent catalyst is proposed in Scheme 2. In the transition-state II, the rotation of the enolate ion could play an important role on the presence of diastereomers.

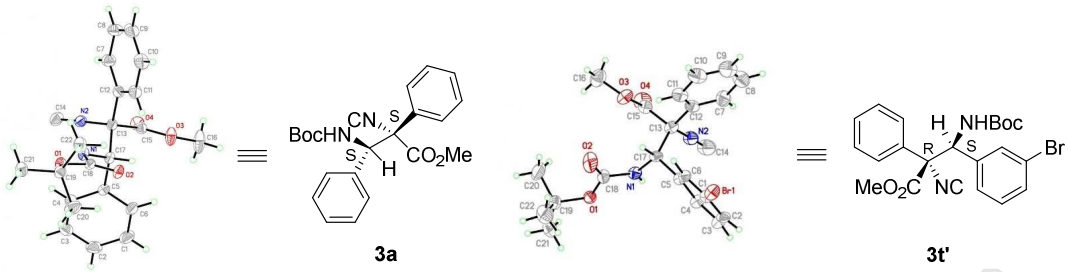
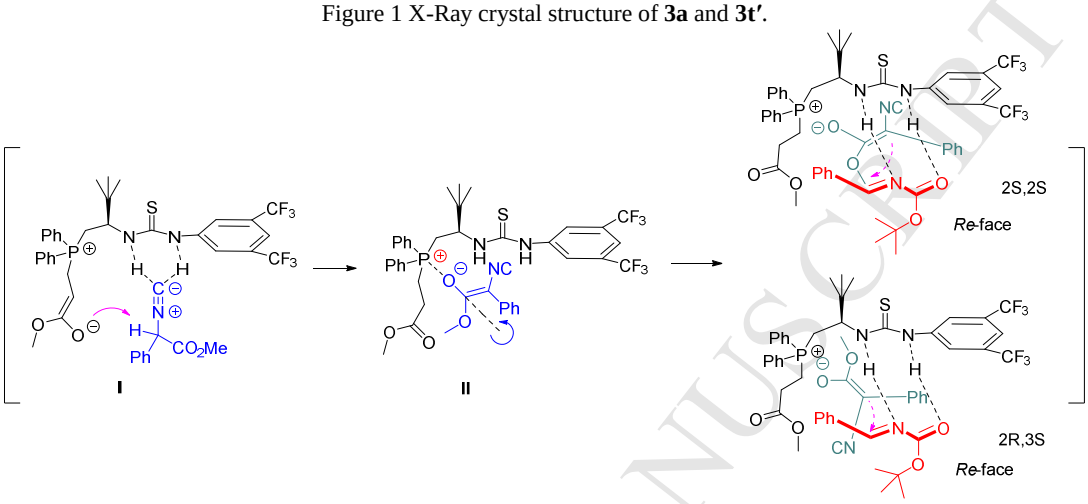


Figure 1 X-Ray crystal structure of **3a** and **3t′**.



Scheme 2. Proposed transition-state model

3. Conclusion

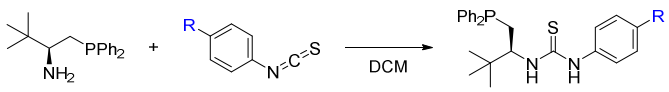
In summary, we have successfully developed a dual-reagent organophosphine catalyzed asymmetric Mannich reaction of α-phenylisocyanoacetates with *N*-Boc-aldimines. The corresponding products were obtained in excellent yields (up to 98%) and with moderate to good enantioselectivities (up to 95% *ee*) under mild reaction conditions with the catalyst as low as 0.5 mol%. Further studies on dual-reagent catalysis are underway in our group to broaden their applications in asymmetric reactions.

4. Experimental

4.1 General information

The ^{1}H NMR spectra were recorded on a Bruker (400 MHz). All chemical shifts (δ) were given in ppm. Data were reported as follows: chemical shift, multiplicity (s = single, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet) and coupling constants (Hz), intergration. ^{13}C NMR spectra were recorded on a DPX-400 (100 MHz). Flash column chromatography was performed using H silica gel. For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used and compounds were visualized by irradiation with UV light. Analytical high performance liquid chromatography (HPLC) was carried out on SHIMADZU equipment using chiral columns. Melting points were determined on a SGW X-4 melting point and were uncorrected. Optical rotations were measured on a JASCO P-1010 Polarimeter at λ =589 nm. IR spectra were recorded on a Perkin-Elmer 983G instrument. Mass spectra analysis was performed on API 200 LC/MS system (Applied Biosystems Co. Ltd.).

4.2 Preparation of catalysts [5]



To a stirred solution of α-amino acid-derives phosphine (1.0 mmol) in CH_2Cl_2 (10 mL), isothiocyanatobenzene (2.0 mmol) was added. Then the reaction was vigorously stirred for 4 h. After removal of the solvent, direct purification by silica gel chromatography (15% EtOAc-petroleum ether) provided products.

4.2.1 (S)-1-(1-(diphenylphosphanyl)-3,3-dimethylbutan-2-yl)-3-phenylthiourea ***(4e)***

Yield:82%; White solid; m.p. 51-52 °C, $[\alpha]_D^{23.6}$ = +42.1 (*c* 0.5, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.71-8.56 (br, 1H), 7.51-7.43 (m, 4H), 7.35-7.20 (m, 9H), 7.09-7.07 (m, 2H), 5.98 (m, 1H), 4.81-4.74 (m, 1H), 2.51-2.47 (m, 1H), 2.00 (t, *J* =12.0 Hz, 1H), 0.91 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz)) δ 180.7, 139.2 (d, $J_{C\text{-}P}$ = 12.6 Hz), 138.7 (d, $J_{C\text{-}P}$ = 12.5 Hz), 136.2, 133.1 (d, $J_{C\text{-}P}$ = 18.9 Hz), 132.7 (d, $J_{C\text{-}P}$ = 19.2 Hz), 129.9, 128.6, 128.6 (d, $J_{C\text{-}P}$ = 6.7 Hz), 128.4 (d, $J_{C\text{-}P}$ = 6.7 Hz), 126.9, 125.3, 60.9 (d, $J_{C\text{-}P}$ = 14.5 Hz), 36.4 (d, $J_{C\text{-}P}$ = 6.7 Hz), 31.3 (d, $J_{C\text{-}P}$ =

14.2 Hz), 26.5; **^{31}P NMR** (400 MHz, $CDCl_3$) δ -23.4 (s); **IR** (Neat): 3379, 3247, 3051, 2961, 1596, 1531, 1497, 1433, 1367, 1253, 1181, 1092, 738, 696; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{25}H_{30}N_2PS)^+$ requires 421.1862; found 421.1862.

*4.2.2 (S)-1-(1-(diphenylphosphanyl)-3,3-dimethylbutan-2-yl)-3-(p-tolyl)thiourea **(4f)***

Yield:81%; White solid; m.p. 52-53 °C, $[\alpha]_D^{23.5}$ = +46.4 (*c* 0.5, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.39-8.32 (br, 1H), 7.51-7.30 (m, 10H), 7.14-7.12 (m, 2H), 6.96-6.94 (m, 2H), 5.89 (d, *J* =6.4 Hz, 1H), 4.76-4.73 (m, 1H), 2.49-2.46 (m, 1H), 1.97 (t, *J* =12.0 Hz, 1H), 0.89 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 180.9, 139.3 (d, $J_{C\text{-}P}$ = 13.4 Hz), 138.0 (d, $J_{C\text{-}P}$ = 14.0 Hz), 133.1 (d, $J_{C\text{-}P}$ = 19.1 Hz), 132.7 (d, $J_{C\text{-}P}$ = 19.2 Hz), 130.5, 128.6, 128.6, 128.5, 128.3 (d, $J_{C\text{-}P}$ = 6.8 Hz), 125.6, 60.8 (d, $J_{C\text{-}P}$ = 14.0 Hz), 36.4 (d, $J_{C\text{-}P}$ = 6.6 Hz), 31.4 (d, $J_{C\text{-}P}$ = 15.0 Hz), 26.5, 21.1; **^{31}P NMR** (400 MHz, $CDCl_3$) δ -23.3 (s); **IR** (Neat): 3378, 3200, 3051, 2961, 2867, 1584, 1531, 1478, 1433, 1367, 1329, 1260, 1184, 1092, 817, 740, 696; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{26}H_{30}N_2PS)^+$ requires 433.1873; found 433.1872.

*4.2.3 (S)-1-(1-(diphenylphosphanyl)-3,3-dimethylbutan-2-yl)-3-(4-(trifluoromethyl)phenyl)thiourea **(4h)***

Yield:85%; White solid; m.p. 64-65 °C, $[\alpha]_D^{23.7}$ = +16.6 (*c* 2.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.26 (br, 1H), 7.55-7.47 (m, 6H), 7.33-7.29 (m, 7H), 6.32 (m, 1H), 4.87-4.85 (m, 1H), 2.58-2.54 (m, 1H), 2.18 (t, *J* =12.0 Hz 1H), 0.99 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz)) δ 180.4, 140.2, 138.8 (d, $J_{C\text{-}P}$ = 12.4 Hz), 138.3 (d, $J_{C\text{-}P}$ = 13.3 Hz), 133.1 (d, $J_{C\text{-}P}$ = 18.8 Hz), 128.8, 128.7 (d, $J_{C\text{-}P}$ = 6.6 Hz), 128.5 (d, $J_{C\text{-}P}$ = 6.7 Hz), 127.4 (q, $J_{C\text{-}F}$ = 32.7 Hz), 126.8, 123.9 (q, $J_{C\text{-}F}$ = 270.5 Hz), 123.7, 61.0 (d, $J_{C\text{-}P}$ = 13.7 Hz), 36.5 (d, $J_{C\text{-}P}$ = 6.5 Hz), 31.1 (d, $J_{C\text{-}P}$ = 13.7 Hz), 26.6; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ -62.2 (s); **^{31}P NMR** (400 MHz, $CDCl_3$) δ -23.3 (s); **IR** (Neat): 3264, 3052, 2962, 1615, 1532, 1478, 1433, 1368, 1324, 1266, 1123, 1067, 1015, 840, 746, 696; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{26}H_{29}N_2F_3PS)^+$ requires 489.1736; found 489.1735.

*4.3 Preparation of isocyanoacetates **1d** and **1k**[8]*

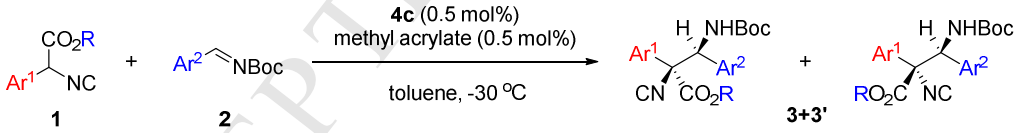
*4.3.1 Methyl 2-isocyano-2-(3-methoxyphenyl)acetate **(1d)***

Yield:42%; light yellow oil; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.34-7.30 (m, 1H), 7.05-7.03 (m, 1H), 7.01-7.00 (m, 1H), 6.94-6.91 (m, 1H), 5.34 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.0, 161.4, 160.1, 133.0, 130.2, 118.9, 115.1, 112.2, 60.1, 55.4, 53.8; **IR** (Neat): 3008, 2956, 2839, 2150, 1758, 1603, 1589, 1492, 1455, 1436, 1265, 1208, 1265, 1208, 1035, 781, 746, 691; **HRMS** (ESI): calcd for $[M-H]^-$ $(C_{11}H_{10}O_3N)^-$ requires 204.0666; found 204.0667.

*4.3.2 Isopropyl 2-isocyano-2-phenylacetate **(1k)***

Yield:32%; light yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48-7.45 (m, 2H), 7.40-7.39 (m, 3H), 5.32 (s, 1H), 5.07-4.98 (m, 1H), 1.25 (d, *J* = 6.0 Hz, 3H), 1.16 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 161.0, 132.0, 129.4, 129.1, 71.1, 60.5, 21.5, 21.3; IR (Neat): 2984, 2938, 2149, 1750, 1496, 1455, 1377, 1254, 1209, 1174, 1104, 1020, 960, 733, 696; HRMS (ESI): calcd for $[M-H]^-$ $(C_{12}H_{12}O_4N)^-$ requires 202.0874; found 202.0872.

4.4 Asymmetric dual-reagent catalyzed Mannich-type reactions



The reactions were carried out in a dry round-bottom flask reactor (5 mL). To a solution of catalyst **4c** (0.005 mmol) in toluene (1.0 mL) at room temperature were added methyl acrylate (0.005 mmol), stirring 5 minutes, then lowered temperature to -30□, added isocyanoacetates **1a** (0.1 mmol), and finally *N*-Boc-aldimines **2a** (0.2 mmol), the resulting mixture was stirred vigorously. When the reaction was finished (determined by TLC analysis), the crude mixture was warmed to the room temperature and purified by flash column chromatography (silica gel: petroleum ether/AcOEt = 10 : 1) to afford the products.

*4.5 Characterization data of products **3a, 3a'-3v, 3v'***

*4.5.1 Methyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2,3-diphenylpropanoate **(3a)***

Yield:98% (**3a** and **3a'**); White solid; m.p. 125-126 °C, $[\alpha]_D^{25.1}$ = -38.7 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.82-7.80 (m, 2H), 7.49-7.35 (m, 8H), 5.92 (d, *J* = 9.2 Hz, 1H), 5.22 (d, *J* = 8.8 Hz, 1H), 3.60 (s, 3H), 1.21 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.4, 164.1, 154.3, 136.1, 132.4, 129.3, 128.8, 128.7, 128.5, 128.2, 126.2, 80.3, 58.7, 53.8, 28.0; **IR** (Neat): 3341, 2978, 2137, 1745, 1703, 1513, 1499, 1451, 1367, 1247,1168, 1009; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{25}O_4N_2)^+$ requires 381.1809; found 381.1811; enantiomeric excess: 83%, determined by HPLC (Chiralpak AD-H+AS-H, hexane/*i*-PrOH 93/7, flow rate 0.9 mL/min; t_{major} = 22.3 min, t_{minor} = 16.6 min, λ = 220 nm);

*Methyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2,3-diphenylpropanoate **(3a')***

White solid; m.p. 178-180 °C, $[\alpha]_D^{25.1}$ = -69.4 (*c* 0.5, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48 (m, 2H), 7.30-7.29 (m, 3H), 7.20-7.11 (m, 3H), 7.04-7.03, 5.71 (m, 2H), 3.85 (s, 3H), 1.40(s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.8, 164.2, 154.2, 135.0, 131.8, 129.3, 128.7, 128.3, 128.0, 127.9, 125.9, 80.5, 76.6, 60.2, 54.1, 28.2; **IR** (Neat): 3341, 2979, 2137, 1754, 1720, 1495, 1451, 1367, 1247,1167; **HRMS** (ESI):

calcd for $[M+H]^+$ $(C_{22}H_{25}O_4N_2)^+$ requires 381.1809; found 381.1812; enantiomeric excess: 93%, determined by HPLC (Chiralpak AD-H and AS-H, hexane/*i*-PrOH 93/7, flow rate 0.9 mL/min; t_{major} = 30.4 min, t_{minor} = 18.6 min, λ = 220 nm).

*4.5.2 Methyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-3-phenyl-2-(m-tolyl)propanoate **(3b)***

Yield:91% (**3b** and **3b′**); colorless oil; $[\alpha]_D^{28.5}$ = -51.3 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.58-7.57 (m, 2H), 7.48-7.45 (m, 2H), 7.40-7.30 (m, 4H), 7.21-7.19 (m, 1H), 5.91 (d, *J* = 8.4 Hz, 1H), 5.17 (d, *J* = 7.6 Hz, 1H), 3.60 (s, 3H), 2.41 (s, 3H), 1.22 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.4, 163.9, 154.3, 138.5, 136.2, 132.4, 130.0, 128.7, 128.6, 128.4, 128.2, 128.4, 128.2, 126.8, 123.3, 80.2, 58.4, 53.8, 28.0, 21.5; **IR** (Neat): 3328, 2958, 2925, 2135, 1754, 1720, 1493, 1367, 1248, 1166, 1085, 1022; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_4N_2)^+$ requires 395.1965; found 395.1970; enantiomeric excess: 79%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min; t_{major} = 16.9 min, t_{minor} = 7.6 min, λ = 220 nm);

*Methyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-3-phenyl-2-(m-tolyl)propanoate **(3b′)***

White solid; m.p. 171-173 °C, $[\alpha]_D^{28.5}$ = -77.1 (*c* 0.28, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.28-7.25 (m, 2H), 7.20-7.10 (m, 5H), 7.04-7.02 (m, 2H), 5.68 (dd, J_1 = 9.6 Hz, J_2 = 24.0 Hz, 2H), 3.86 (s, 3H), 2.30 (s, 3H), 1.40 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.8, 163.9, 154.2, 138.5, 135.1, 131.7, 130.0, 128.5, 128.3, 128.0, 127.9, 126.4, 123.0, 80.5, 60.0, 54.1, 28.2, 21.5; **IR** (Neat): 3329, 2956, 2925, 2134, 1747, 1704, 1498, 1391, 1367, 1248, 1167, 1034, 1009, **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_4N_2)^+$ requires 395.1965; found 395.1964; enantiomeric excess: 92%, determined by HPLC (Chiralpak AS-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min; t_{major} = 5.3 min, t_{minor} = 7.9 min, λ = 220 nm).

*4.5.3 Methyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-3-phenyl-2-(p-tolyl)propanoate **(3c)***

Yield:94% (**3c** and **3c′**); colorless oil; $[\alpha]_D^{25.7}$ = -35.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.67-7.65 (m, 2H), 7.47-7.45 (m, 2H), 7.39-7.34 (m, 3H), 7.25-7.23 (m, 2H), 5.88 (d, *J* = 10.0 Hz, 1H), 5.17 (d, *J* = 8.4 Hz, 1H), 3.60 (s, 3H), 2.36 (s, 3H), 1.21 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.1, 165.3, 154.3, 148.1, 143.4, 131.8, 129.8, 129.5, 129.1, 126.0, 123.6, 81.0, 76.1, 58.3, 54.2, 28.0; **IR** (Neat): 3358, 2977, 2927, 2135, 1746, 1704, 1513, 1392, 1367, 1249, 1168, 1009; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_4N_2)^+$ requires 395.1965; found 395.1972; enantiomeric excess: 82%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min; t_{major} = 10.6 min, t_{minor} = 8.6 min, λ = 220 nm);

*Methyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-3-phenyl-2-(p-tolyl)propanoate **(3c′)***

White solid; m.p. 171-173 °C, $[\alpha]_D^{25.5}$ = -83.2 (*c* 0.5, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.37-7.35 (m, 2H), 7.21-7.09 (m, 5H), 7.05-7.04 (m, 2H), 5.67 (dd, J_1 = 10.0 Hz, J_2 = 25.2 Hz, 2H), 3.85 (s, 3H), 2.30 (s, 3H), 1.40(s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.3, 165.3, 154.1, 147.8, 142.4, 131.1, 129.9, 129.1, 129.1, 129.7, 123.1, 81.2, 75.9, 59.8, 54.4, 28.2; **IR** (Neat): 3359, 2923, 2133, 1754, 1722, 1499, 1368, 1275, 1260, 1165; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_4N_2)^+$ requires 395.1965; found 395.1970; enantiomeric excess: 92%, determined by HPLC (Chiralpak AS-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min; t_{major} = 5.5 min, t_{minor} = 8.4 min, λ = 220 nm).

*4.5.4 Methyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2-(3-methoxyphenyl)-3-phenylpropanoate **(3d)***

Yield:92% (**3d** and **3d′**); colorless oil; $[\alpha]_D^{24.1}$ = -40.8 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.47-7.44 (m, 2H), 7.40-7.33 (m, 6H), 6.95-6.92 (m, 1H), 5.92 (d, *J* = 9.2 Hz, 1H), 5.20 (d, *J* = 8.4 Hz, 1H), 3.86 (s, 3H), 3.61 (s, 3H), 1.23 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.3, 164.1, 159.8, 154.3, 136.1, 134.0, 129.7, 128.8, 128.4, 128.2, 118.5, 115.2, 111.8, 80.3, 58.5, 55.4, 53.8, 28.0; **IR** (Neat): 3361, 3193, 2955, 2923, 2852, 2135, 1747, 1720, 1659, 1632, 1495, 1468, 1257, 1166, 1015; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_5N_2)^+$ requires 411.1914; found 411.1917; enantiomeric excess: 80%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min; t_{major} = 26.5 min, t_{minor} = 11.5 min, λ = 220 nm);

*Methyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2-(3-methoxyphenyl)-3-phenylpropanoate **(3d′)***

colorless oil; $[\alpha]_D^{24.3}$ = -87.2 (*c* 0.5, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.23-7.15 (m, 4H), 7.07-7.05 (m, 3H), 6.99 (m, 1H), 6.85-6.82 (m, 1H), 5.68 (dd, J_1 = 8.0 Hz, J_2 = 20.0 Hz, 2H), 3.86 (s, 3H), 3.73 (s, 3H), 1.40(s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.7, 164.1, 159.7, 154.2, 135.1, 133.3, 129.7, 128.3, 128.0, 127.9, 118.2, 114.9, 111.7, 80.5, 76.5, 60.1, 55.3, 54.1, 28.2; **IR** (Neat): 3340, 2956, 2927, 2854, 2136, 1755, 1720, 1603, 1586, 1494, 1454, 1368, 1250, 1165, 1045; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_5N_2)^+$ requires 411.1914; found 411.1921; enantiomeric excess: 88%, determined by HPLC (Chiralpak IC, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min; t_{major} = 10.5 min, t_{minor} = 11.5 min, λ = 220 nm).

*4.5.5 Methyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2-(4-methoxyphenyl)-3-phenylpropanoate **(3e)***

Yield:98% (**3e** and **3e′**); White solid; m.p. 70-71 °C, $[\alpha]_D^{27.7}$ = -37.8 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.70-7.68 (m, 2H), 7.46-7.44 (m, 2H), 7.38-7.36 (m, 3H), 6.96-6.93 (m, 2H), 5.85 (d, *J* = 10.0 Hz, 1H), 5.18 (d, *J* = 9.2 Hz, 1H), 3.82 (s, 3H), 3.60 (s, 3H), 1.23 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.6, 163.8, 160.3, 154.3, 136.1, 128.7, 128.4, 128.1, 127.6, 124.4, 114.0, 80.3, 58.6, 55.4, 53.7, 28.0; **IR** (Neat): 3358, 2977, 2929, 2136, 1745, 1717, 1609, 1456, 1295, 1186, 1033, 1009; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_5N_2)^+$ requires 411.1914; found 411.1917; enantiomeric excess: 81%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min; t_{major} = 14.5 min, t_{minor} = 12.1 min, λ = 220 nm);

*Methyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2-(4-methoxyphenyl)-3-phenylpropanoate **(3e′)***

White solid; m.p. 78-80 °C, $[\alpha]_D^{26.5}$ = -64.0 (*c* 1.5, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.40-7.38 (m, 2H), 7.19-7.15 (m, 3H), 7.05-7.03 (m, 2H), 6.82-6.80 (m 2H), 5.67-5.66(m, 2H), 3.85 (s, 3H), 3.77 (s, 3H), 1.40(s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 167.0, 163.8, 160.1, 154.2, 135.1, 128.3, 128.0, 127.9, 127.3, 123.8, 113.9, 80.5, 76.2, 60.1, 54.0, 28.2; **IR** (Neat): 3356, 2977, 2932, 2137, 1754, 1718, 1610, 1513, 1456, 1255, 1184, 1166, 1033; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_5N_2)^+$ requires 411.1914; found 411.1919; enantiomeric excess: 92%, determined by HPLC (Chiralpak AS-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min; t_{major} = 8.4 min, t_{minor} = 14.5 min, λ = 220 nm).

*4.5.6 Methyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-(4-fluorophenyl)-2-isocyano-3-phenylpropanoate **(3f)***

Yield:95% (**3f** and **3f′**); colorless oil; $[\alpha]_D^{25.4}$ = -39.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.81-7.78 (m, 2H), 7.46-7.43 (m, 2H), 7.39-7.37 (m, 3H), 7.15-7.10 (m, 2H), 5.87 (d, *J* = 10.4 Hz, 1H), 5.19 (d, *J* = 9.6 Hz, 1H), 3.61 (s, 3H), 1.23 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.3, 164.6, 163.3 (d, $J_{C\text{-}F}$ = 251.6 Hz), 154.3, 135.8, 128.9, 128.6, 128.4, 128.3, 128.3, 128.1, 115.6 (d, $J_{C\text{-}F}$ = 21.8 Hz), 80.5, 76.4, 58.9, 53.9, 28.0; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ -112.6 (s); **IR** (Neat): 3355, 2979, 2136, 1746, 1704, 1510, 1242, 1168, 1010;.**HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_4N_2F)^+$ requires 399.1715; found 399.1717; enantiomeric excess: 82%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 97/3, flow rate 0.9 mL/min; t_{major} = 14.9 min, t_{minor} = 11.8 min, λ = 220 nm);

*Methyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-(4-fluorophenyl)-2-isocyano-3-phenylpropanoate **(3f′)***

White solid; m.p. 169-170 °C, $[\alpha]_D^{25.4}$ = -48.7 (*c* 0.5, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.49-7.46 (m, 2H), 7.22-7.17 (m, 3H), 7.04-6.97 (m, 5H), 5.65 (dd, J_1 = 10.8 Hz, J_2 = 13.2 Hz, 2H), 3.87 (s, 3H), 1.40(s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.7, 164.7, 163.1 (d, $J_{C\text{-}F}$ = 248.3 Hz), 154.2, 134.9, 128.5, 128.1, 128.0, 128.0, 127.8, 127.8, 115.7 (d, $J_{C\text{-}F}$ = 21.8 Hz), 80.7, 76.0, 60.4, 54.2, 28.2; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ -112.1 (s); **IR** (Neat): 3357, 2920, 2850, 2136, 1753, 1718, 1509, 1275, 1259, 1166, 1048; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_4N_2F)^+$ requires 399.1715; found 399.1720; enantiomeric excess: 87%, determined by HPLC (Chiralpak AS-H, hexane/*i*-PrOH 97/3, flow rate 0.9 mL/min; t_{major} = 14.5 min, t_{minor} = 12.1 min, λ = 220 nm).

*4.5.7 Methyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-(4-chlorophenyl)-2-isocyano-3-phenylpropanoate **(3g)***

Yield:98% (**3g** and **3g′**); colorless oil; $[\alpha]_D^{27.3}$ = -29.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.76-7.74 (m, 2H), 7.46-7.42 (m, 3H), 7.40-7.36 (m, 4H), 5.87 (d, *J* = 10.0 Hz, 1H), 5.20 (d, *J* = 10.0 Hz, 1H), 3.61 (s, 3H), 1.23 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.2, 164.5, 154.2, 135.2, 132.1, 131.6, 130.0, 129.5, 128.8, 126.1, 123.0, 80.5, 76.4, 58.2, 54.0, 28.0; **IR** (Neat): 3358, 2922, 2851, 2135, 1746, 1704, 1494, 1275, 1260, 1167, 1014; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_4N_2Cl)^+$ requires 415.1419; found 415.1423; enantiomeric excess: 72%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 97/3, flow rate 0.9 mL/min; t_{major} = 14.4 min, t_{minor} = 12.5 min, λ = 220 nm);

*Methyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-(4-chlorophenyl)-2-isocyano-3-phenylpropanoate **(3g′)***

White solid; m.p. 120-122 °C, $[\alpha]_D^{25.5}$ = -34.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.45-7.43 (m, 2H), 7.30-7.27 (m, 2H), 7.21-7.15 (m, 3H), 7.06-7.04 (m, 2H), 5.68 (m, 2H), 3.86 (s, 3H), 1.40(s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.5, 164.5, 154.1, 134.2, 131.5, 131.1, 129.6, 129.5, 128.9, 125.8, 122.6, 80.8, 76.3, 59.7, 54.2, 28.2; **IR** (Neat): 3358, 2924, 2136, 1755, 1721, 1493, 1275, 1260, 1166, 1097; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_4N_2Cl)^+$ requires 415.1419; found 415.1422; enantiomeric excess: 82%, determined by HPLC (Chiralpak AS-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min; t_{major} = 5.4 min, t_{minor} = 7.8 min, λ = 220 nm).

*4.5.8 Methyl (2S,3S)-2-(4-bromophenyl)-3-((tert-butoxycarbonyl)amino)-2-isocyano-3-phenylpropanoate **(3h)***

Yield:98% (**3h** and **3h′**); colorless oil; $[\alpha]_D^{28.7}$ = -26.7 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.69-7.67 (m, 2H), 7.58-7.56 (m, 2H), 7.45-7.37 (m, 5H), 5.86 (d, *J* = 10.4 Hz, 1H), 5.19 (d, *J* = 10.4 Hz, 1H), 3.61 (s, 3H), 1.23 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.1, 164.8, 154.3, 135.7, 131.8, 131.6, 129.0, 128.6, 128.1, 123.9, 80.6, 76.6, 58.8, 54.0, 28.0; **IR** (Neat): 3358, 2922, 2851, 2135, 1747, 1491, 1457, 1275, 1260, 1168, 1010; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_4N_2Br)^+$ requires 459.0914; found 459.0915; enantiomeric excess: 79%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 97/3, flow rate 0.9 mL/min; t_{major} = 15.4 min, t_{minor} = 13.9 min, λ = 220 nm);

*Methyl (2R,3S)-2-(4-bromophenyl)-3-((tert-butoxycarbonyl)amino)-2-isocyano-3-phenylpropanoate **(3h′)***

White solid; m.p. 145-146 °C, $[\alpha]_D^{23.4}$ = -79.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.45-7.43 (m, 2H), 7.38-7.36 (m, 2H), 7.22-7.15 (m, 3H), 7.06-7.04 (m 2H), 5.65 (dd, J_1 = 9.2 Hz, J_2 = 16.0 Hz, 2H), 2.86 (s, 3H), 1.40(s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.5, 165.0, 154.1, 134.8, 131.8, 131.1, 128.6,128.2, 128.0, 127.8, 123.8, 80.7, 76.2, 60.2, 54.3, 28.2; **IR** (Neat): 3356, 2978, 2135, 1747, 1703, 1491, 1249, 1166, 1079; 1010; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_4N_2Br)^+$ requires 459.0914; found 459.0919; enantiomeric excess: 81%, determined by HPLC (Chiralpak AS-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min; t_{major} = 5.6 min, t_{minor} = 7.8 min, λ = 220 nm).

*4.5.9 Benzyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2,3-diphenylpropanoate **(3i)** and Benzyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2,3-diphenylpropanoate **(3i′)***

Yield:95%; white solid; m.p. 74-75 °C, $[\alpha]_D^{27.6}$ = -56.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz δ 7.80-7.79 (m, 2H), 7.42-7.24 (m, major 11H, minor 3H, dr = 4:1), 7.04-7.03 (m, 2H), 5.90 (d, *J* = 8.8 Hz, 1H), 5.21-5.17 (m, 1H), 5.00 (dd, *J* = 12.4 Hz, 2H, AB), 1.37 (s, 2.4H minor), 1.19 (s, 9H major); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.6 (166.1 minor), 164.3, 154.3, 136.0, 134.1, 132.4 (131.8 minor), 131.8, 129.3

(129.2 minor), 128.7, 128.6, 128.6, 128.4 (128.5 minor), 128.2, 128.0, 127.9, 126.3, 80.3, 68.6 (69.0 minor), 58.5 (60.2 minor), 28.0 (28.2 minor); **IR** (Neat): 3356, 2978, 2136, 1749, 1717, 1498, 1451, 1367, 1234, 1167; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{28}H_{29}O_4N_2)^+$ requires 457.2122; found 457.2126; major diastereoisomer enantiomeric excess: 89%, t_{major} = 25.2 min, t_{minor} = 12.4 min; minor diastereoisomer enantiomeric excess: 93%, t_{major} = 59.4 min, t_{minor} = 10.9 min, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 93/7, flow rate 0.85 mL/min, λ = 220 nm).

Tert-butyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2,3-diphenylpropanoate ***(3j)*** *and Tert-butyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2,3-diphenylpropanoate* ***(3j')***

Yield:98%; white solid; m.p. 123-125 °C, $[\alpha]_D^{27.1}$ = -46.3 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.80-7.78 (m, 2H), 7.56-7.54 (m, 2H), 7.43-7.36 (m, 6H), 5.83 (d, *J* = 9.2 Hz, 1H), 5.18 (d, *J* = 9.2 Hz, 1H), 1.24 (s, 9H), 1.21 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 164.3, 163.4, 154.3, 136.5, 133.1, 129.1, 128.7, 128.5, 128.5, 128.3, 128.0, 126.1, 84.8, 80.2, 58.3, 28.0 (28.4 minor), 27.4 (27.6 minor); **IR** (Neat): 3357, 2979, 2932, 2136, 1718, 1498, 1450, 1394, 1370, 1258, 1049; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{25}H_{31}O_4N_2)^+$ requires 423.2278; found 423.2283; major diastereoisomer enantiomeric excess: 91%, t_{major} = 30.5 min, t_{minor} = 17.4 min; minor diastereoisomer enantiomeric excess: 70%, t_{major} = 28.3 min, t_{minor} = 24.3 min, determined by HPLC (Chiralpak IC+AD-H, hexane/*i*-PrOH 97/3, flow rate 0.85 mL/min, λ = 220 nm).

4.5.10 Isopropyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2,3-diphenylpropanoate ***(3k)*** and *Isopropyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2,3-diphenylpropanoate* ***(3k')***

Yield:91%; White solid; m.p. 119-120 °C, $[\alpha]_D^{24.2}$ = -39.9 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz)) dr = 1.2:1 δ 7.82-7.80 (m, 2H), 7.52-751 (m, 4H), 7.45-7.35 (m, 6H), 7.31-7.29 (m, 3.6H major), 7.17-7.11 (m, 3.8H major), 7.04-7.02 (m, 2.6H major), 5.93(d, *J* = 10.4 Hz, 1H), 5.70 (dd, J_1 = 15.2 Hz, J_2 = 10.4 Hz, 2H major), 5.19 (d, *J* = 11.6 Hz, 1H), 5.16-5.01 (m, 1H), 4.87-4.81 (m, 1H), 1.39 (s, 10H major), 1.32-1.30 (m, 6H major), 1.20 (s, 9H minor), 1.10 (d, *J* = 6 Hz, 3H minor), 0.94 (d, *J* = 6 Hz, 3H minor); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 165.6 (165.2 minor), 163.9, 154.1, 135.3 (136.2 minor), 132.7 (132.0 minor), 128.7 (129.1 minor), 128.6 (128.4 minor), 128.2, 127.8 (128.0 minor), 126.2 (126.0 minor), 80.4 (80.2 minor), 72.0 (71.6 minor), 60.0 (58.5 minor), 28.0 (28.2 minor), 21.3 (21.4 minor), 21.1 (21.1 minor); **IR** (Neat): 3355, 2981, 2134, 2136, 1721, 1498, 1451, 1391, 1367, 1248, 116, 1103; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{24}H_{29}O_4N_2)^+$ requires 409.2122; found 409.2126; major diastereoisomer enantiomeric excess: 92%, t_{major} = 21.1 min, t_{minor} = 23.1 min; minor diastereoisomer enantiomeric excess: 85%, t_{major} = 19.9 min, t_{minor} = 37.7 min, determined by HPLC (Chiralpak OD-H+AS-H, hexane/*i*-PrOH 98/2, flow rate 0.5 mL/min, λ = 220 nm).

4.5.11 Methyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2-phenyl-3-(m-tolyl)propanoate ***(3l)***

Yield:98% (**3l** and **3l'**); White solid; m.p. 97-98 °C, $[\alpha]_D^{25.7}$ = -34.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.81-7.79 (m, 2H), 7.46-7.40 (m, 3H), 7.27 (m, 3H), 7.18-7.15 (m, 1H), 5.88 (d, *J* = 10.0 Hz, 1H), 5.18 (d, *J* = 9.6 Hz, 1H), 3.62 (s, 3H), 2.38 (s, 3H), 1.21 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.4, 164.0, 154.3, 138.1, 136.0, 132.5, 129.5, 129.2, 128.8, 128.6, 128.3, 126.3, 125.2, 80.2, 58.6, 53.7, 28.0, 21.5; **IR** (Neat): 3355, 2954, 2926, 2854, 2136, 1747, 1703, 1499, 1367, 1248, 1164, 1010; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_4N_2)^+$ requires 395.1965; found 395.1968; enantiomeric excess: 72%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min, t_{major} = 11.0 min, t_{minor} = 7.8 min, λ = 220 nm);

Methyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2-phenyl-3-(m-tolyl)propanoate ***(3l')***

White solid; m.p. 135-136 °C, $[\alpha]_D^{25.8}$ = -66.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48 (m, 2H), 7.31-7.29 (m, 3H), 7.04-6.97 (m, 2H), 6.84-6.80 (m, 2H), 5.67 (m, 2H), 3.85 (s, 3H), 2.18 (s, 3H), 1.40(s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.8, 164.0, 154.2, 137.5, 134.8, 131.9, 129.2, 129.0, 128.8, 128.6, 128.6, 127.7, 126.0, 125.0, 80.4, 60.2, 54.1, 28.2, 21.2; **IR** (Neat): 3356, 2977, 2927, 2136, 1754, 1720, 1497, 1450, 1367, 1247, 1163, 1048; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_4N_2)^+$ requires 395.1965; found 395.1971; enantiomeric excess: 89%, determined by HPLC (Chiralpak AS-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min, t_{major} = 5.0 min, t_{minor} = 7.4 min, λ = 220 nm).

4.5.12 Methyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2-phenyl-3-(p-tolyl)propanoate ***(3m)***

Yield:85% (**3m** and **3m'**); colorless oil; $[\alpha]_D^{20.9}$ = -23.9 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.80-7.78 (m, 2H), 7.45-7.36 (m, 5H), 7.19-7.17 (m, 2H), 5.88 (d, *J* = 10.0 Hz, 1H), 5.16 (d, *J* = 9.2 Hz, 1H), 3.61 (s, 3H), 2.35 (s, 3H), 1.20 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.4, 164.2, 154.3, 138.6, 133.2, 132.6, 129.3, 129.2, 128.7, 128.0, 126.3, 80.2, 58.5, 53.8, 28.0, 21.2; **IR** (Neat): 3353, 2978, 2928, 2136, 1747, 1717, 1498, 1450, 1367, 1250, 1167, 1010; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_4N_2)^+$ requires 395.1965; found 395.1969; enantiomeric excess: 81%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min, t_{major} = 19.9 min, t_{minor} = 10.2 min, λ = 220 nm);

Methyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2-phenyl-3-(p-tolyl)propanoate ***(3m')***

White solid; m.p. 120-122 °C, $[\alpha]_D^{23.8}$ = -69.4 (*c* 0.5, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.50 (m, 2H), 7.31-7.30 (m, 3H), 6.95-6.91 (m, 4H), 5.67 (dd, J_1 = 9.6 Hz, J_2 = 19.2 Hz, 2H), 3.85 (s, 3H), 2.23 (s, 3H), 1.39 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.8, 164.0, 154.2, 138.1, 132.1, 131.9, 129.2, 128.6, 127.8, 126.0, 80.4, 60.0, 54.0, 28.2, 21.0; **IR** (Neat): 3356, 2926, 2136, 1755, 1721, 1497, 1450, 1367, 1247,

1166; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_4N_2)^+$ requires 395.1965; found 395.1970; enantiomeric excess: 89%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min, t_{major} = 34.4 min, t_{minor} = 9.2 min, λ = 220 nm);

4.5.13 Methyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-3-(3-methoxyphenyl)-2-phenylpropanoate ***(3n)***

Yield:88% (**3n** and **3n′**); White solid; m.p. 94-96 °C, $[\alpha]_D^{25.1}$ = -31.4 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.75-7.74 (m, 2H), 7.41-7.35 (m, 3H), 7.24-7.22 (m, 1H), 7.01-6.97 (m, 2H),6.86-6.84 (m, 1H), 5.84 (d, *J* = 9.6 Hz, 1H), 5.12 (d, *J* = 9.6 Hz, 1H), 3.78 (s, 3H), 3.58 (s, 3H), 1.17 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.3, 164.2, 159.5, 154.3, 137.5, 132.4, 129.5, 129.3, 128.7, 126.2, 120.4, 114.4, 113.8, 80.3, 58.6, 55.3, 53.8, 28.0; **IR** (Neat): 3357, 2137, 1746, 1710, 1602, 1493, 1450, 1368, 1258, 1164, 1044, 1010; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_5N_2)^+$ requires 411.1914; found 411.1918; enantiomeric excess: 75%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min, t_{major} = 18.1 min, t_{minor} = 10.9 min, λ = 220 nm);

Methyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-3-(3-methoxyphenyl)-2-phenylpropanoate ***(3n′)***

White solid; m.p. 143-144 °C, $[\alpha]_D^{25.2}$ = -69.7 (*c* 0.5, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.50 (m, 2H), 7.33-7.31 (m, 3H), 7.09-7.05 (m, 1H), 6.73-6.71 (m, 1H), 6.68-6.66 (m, 1H), 6.49-6.48 (m, 1H), 5.66 (dd, J_1 = 9.6 Hz, J_2 = 25.2 Hz, 2H), 3.87 (s, 3H), 3.60 (s, 3H), 1.41 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.7, 164.2, 158.9, 154.2, 136.4, 131.9, 129.3, 128.9, 128.7, 126.0, 120.2, 114.4, 113.5, 80.5, 60.2, 55.1, 54.1, 28.2; **IR** (Neat): 3356, 2137, 1754, 1722, 1602, 1494, 1451, 1368, 1246, 1163, 1047; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_5N_2)^+$ requires 411.1914; found 411.1917; enantiomeric excess: 91%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min, t_{major} = 21.4 min, t_{minor} = 11.4 min, λ = 220 nm).

4.5.14 Methyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-3-(4-methoxyphenyl)-2-phenylpropanoate ***(3o)***

Yield:94% (**3o** and **3o′**); White solid; m.p. 50-52 °C, $[\alpha]_D^{25.4}$ = -25.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.79-7.78 (m, 2H), 7.45-7.38 (m, 5H), 6.91-6.89 (m, 2H), 5.86 (d, *J* = 8.4 Hz, 1H), 5.15 (d, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 3.61 (s, 3H), 1.20 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.5, 164.1, 159.8, 154.3, 132.5, 129.4, 129.3, 128.7, 128.3, 126.3, 113.8, 80.2, 58.3, 55.3, 53.8, 28.0; **IR** (Neat): 3356, 2977, 2933, 2137, 1746, 1715, 1612, 1513, 1450, 1367, 1251, 1167, 1033, 1009; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_5N_2)^+$ requires 411.1914; found 411.1917; enantiomeric excess: 82%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min, t_{major} = 23.7 min, t_{minor} = 13.5 min, λ = 220 nm);

Methyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-3-(4-methoxyphenyl)-2-phenylpropanoate ***(3o′)***

White solid; m.p. 56-58 °C, $[\alpha]_D^{25.5}$ = -62.5 (*c* 0.5, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.49 (m, 2H), 7.32-7.30 (m, 3H), 6.97-6.95 (m, 2H), 6.67-6.65 (m, 2H), 5.66-5.63(m, 2H), 3.85 (s, 3H), 3.71 (s, 3H), 1.40(s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.9, 164.1, 159.4, 154.2, 132.0, 129.2, 129.1, 128.7, 127.3, 126.0, 113.3, 80.5, 59.8, 55.1, 54.1, 28.2; **IR** (Neat): 3357, 2922, 2137, 1721, 1714, 1367, 1248, 1166, 1035; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{23}H_{27}O_5N_2)^+$ requires 411.1914; found 411.1917; enantiomeric excess: 93%, determined by HPLC (Chiralpak AS-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min, t_{major} = 16.6 min, t_{minor} = 8.9 min, λ = 220 nm).

4.5.15 Methyl (2S,3S) -3-((tert-butoxycarbonyl)amino)-3-(4-fluorophenyl)-2-isocyano-2-phenylpropanoate ***(3p)***

Yield:96% (**3p** and **3p′**); white solid; m.p. 58-59 °C, $[\alpha]_D^{23.3}$ = -27.7 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.78-7.76 (m, 2H), 7.48-7.40 (m, 5H), 7.09-7.04 (m, 2H), 5.90 (d, *J* = 8.0 Hz, 1H), 5.15 (d, *J* = 8.8 Hz, 1H), 3.62 (s, 3H), 1.21 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.3, 164.6, 162.9 (d, $J_{C\text{-}F}$ = 246.5 Hz), 154.2, 132.3, 132.1, 130.1(d, $J_{C\text{-}F}$ =82.0 Hz), 129.4, 128.8, 126.2, 115.5 (d, $J_{C\text{-}F}$ = 21.4 Hz), 80.5, 58.1, 53.9, 28.0; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ -112.9 (s); **IR** (Neat): 3355, 2979, 2931, 2136, 1747, 1704, 1606, 1510, 1450, 1368, 1249, 1165, 1009; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_4N_2F)^+$ requires 399.1715; found 399.1710; enantiomeric excess: 82%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 95/5, flow rate 0.9 mL/min, t_{major} = 20.0 min, t_{minor} = 11.3 min, λ = 220 nm);

Methyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-3-(4-fluorophenyl)-2-isocyano-2-phenylpropanoate ***(3p′)***

White solid; m.p. 144-146 °C, $[\alpha]_D^{23.4}$ = -79.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.46 (m, 2H), 7.32-7.30 (m, 3H), 7.02-6.99 (m, 2H), 6.83-6.79 (m 2H), 5.69 (m, 2H), 1.39 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.6, 164.4, 162.5 (d, $J_{C\text{-}F}$ = 246.3 Hz), 154.2, 131.7, 131.0, 129.7 (d, $J_{C\text{-}F}$ = 82.0 Hz), 129.4, 128.8, 125.8, 114. (d, $J_{C\text{-}F}$ = 21.5 Hz), 80.6, 76.5 59.6, 54.2, 28.2; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ -113.4 (s); **IR** (Neat): 3357, 2979, 2931, 2137, 1755, 1720, 1606, 1511, 1451, 1368, 1247, 1164, 1049; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_4N_2F)^+$ requires 399.1715; found 399.1705; enantiomeric excess: 93%, determined by HPLC (Chiralpak AS-H, hexane/*i*-PrOH 95/5, flow rate 0.9 mL/min, t_{major} = 14.4 min, t_{minor} = 7.6 min, λ = 220 nm).

4.5.16 Methyl (2S,3S) -3-((tert-butoxycarbonyl)amino)-3-(4-chlorophenyl)-2-isocyano-2-phenylpropanoate ***(3q)***

Yield:97% (**3q** and **3q′**); colorless oil; $[\alpha]_D^{24.6}$ = -31.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.77-7.75 (m, 2H), 7.46-7.40 (m, 5H), 7.36-7.34 (m, 2H), 5.89 (d, *J* = 8.0Hz, 1H), 5.13 (d, *J* = 8.8 Hz, 1H), 3.63 (s, 3H), 1.21 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.3, 164.6, 154.2, 134.8, 134.8, 132.2, 129.6, 129.5, 128.8, 128.7, 126.4, 80.6, 58.2, 54.0, 28.0; **IR** (Neat): 3358, 2955, 2926, 2854, 2135, 1717, 1494, 1450, 1368, 1250, 1167, 1093, 1014; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_4N_2Cl)^+$ requires 415.1419; found 415.1422; enantiomeric excess: 82%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 97/3, flow rate 0.8 mL/min, t_{major} = 32.2 min, t_{minor} = 17.7 min, λ = 220 nm);

*Methyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-3-(4-chlorophenyl)-2-isocyano-2-phenylpropanoate **(3q′)***

White solid; m.p. 54-56 °C, $[\alpha]_D^{24.8}$ = -67.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.48-7.46 (m, 2H), 7.34-7.32 (m, 3H), 7.12-7.10 (m, 2H), 6.96-6.74 (m, 2H), 5.65(dd, J_1 = 8.8 Hz, J_2 = 30 Hz, 2H), 3.86 (s, 3H), 1.40 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.6, 164.5, 154.1, 134.3, 133.7, 131.5, 129.5, 129.3, 128.8, 128.1, 125.8, 80.8, 76.3, 59.7, 54.2, 28.2; **IR** (Neat): 3357, 2955, 2926, 2854, 2136, 1755, 1718, 1493, 1451, 1368, 1248, 1165, 1092, 1015; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_4N_2Cl)^+$ requires 415.1419; found 415.1422; enantiomeric excess: 93%, determined by HPLC (Chiralpak AS-H, hexane/*i*-PrOH 95/5, flow rate 0.8 mL/min, t_{major} = 7.1 min, t_{minor} = 12.1 min, λ = 220 nm).

*4.5.17 Methyl (2R,3S)-3-(4-bromophenyl)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2-phenylpropanoate **(3r)***

Yield:92% (**3r** and **3r′**); colorless oil; $[\alpha]_D^{26.0}$ = -23.2 (*c* 2.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.77-7.75 (m, 2H), 7.52-7.50 (m, 3H), 7.45-7.53 (m, 3H), 7.36-7.34 (m, 2H), 5.87 (d, *J* = 8.4 Hz, 1H), 5.13 (d, *J* = 8.8 Hz, 1H), 3.63 (s, 3H), 1.21 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.2, 164.5, 154.2, 135.2, 132.1, 131.6, 130.0, 129.5, 128.8, 126.1, 123.0, 80.5, 76.4, 58.2, 54.0, 28.0; **IR** (Neat): 3358, 2923, 2135, 1747, 1704, 1491, 1450, 1367, 1259, 1167, 1011; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_4N_2Br)^+$ requires 459.0914; found 459.0917; enantiomeric excess: 80%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min, t_{major} = 19.3 min, t_{minor} = 10.7 min, λ = 220 nm);

*Methyl (2R,3S)-3-(4-bromophenyl)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2-phenylpropanoate **(3r′)***

White solid; m.p. 51-53 °C, $[\alpha]_D^{25.8}$ = -57.5 (*c* 0.25, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.47 (m, 2H), 7.34-7.32 (m, 3H), 7.28-7.26 (m, 2H), 6.90-6.88 (m, 2H), 5.67-5.64 (m, 2H), 3.86 (s, 3H), 1.40 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.5, 164.5, 154.1, 134.2, 131.5, 131.1, 129.6, 129.5, 128.9, 125.8, 122.6, 80.8, 76.3, 59.7, 54.2, 28.2; **IR** (Neat): 3356, 2979, 2136, 1755, 1721, 1490, 1451, 1367, 1250, 1165, 1010; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_4N_2Br)^+$ requires 459.0914; found 459.0915; enantiomeric excess: 84%, determined by HPLC (Chiralpak AS-H, hexane/*i*-PrOH 95/5, flow rate 1.0 mL/min, t_{major} = 6.9 min, t_{minor} = 13.4 min, λ = 220 nm).

*4.5.18 Methyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-3-(4-nitrophenyl)-2-phenylpropanoate **(3s)***

Yield:90% (**3s** and **3s′**); White solid; m.p. 70-71 °C, $[\alpha]_D^{26.2}$ = -28.8 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.24-8.22 (m, 2H), 7.76-7.66 (m, 4H), 7.47-7.45 (m, 3H), 6.01 (d, *J* = 8.8 Hz, 1H), 5.23 (d, *J* = 9.6 Hz, 1H), 3.64 (s, 3H), 1.20 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.1, 165.3, 154.3, 148.1, 143.4, 131.8, 129.8, 129.5, 129.1, 126.0, 123.6, 81.0, 76.1, 58.3, 54.2, 28.0; **IR** (Neat): 3357, 2979, 2918, 2135, 1747, 1720, 1608, 1526, 1450, 1368, 1349, 1275, 1259, 1165, 1111, 1069, 1010; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_6N_3)^+$ requires 426.1660; found 426.1662; enantiomeric excess: 68%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 90/10, flow rate 1.0 mL/min, t_{major} = 13.4 min, t_{minor} = 8.7 min, λ = 220 nm);

*Methyl (2R,3S)-3-((tert-butoxycarbonyl)amino)-2-isocyano-3-(4-nitrophenyl)-2-phenylpropanoate **(3s′)***

White solid; m.p. 61-62 °C, $[\alpha]_D^{26.3}$ = -57.5 (*c* 2.6, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.00-7.98 (m, 2H), 7.45 (m, 2H), 7.35-7.33 (m, 3H), 7.20-7.18 (m, 2H), 5.76 (dd, J_1 = 9.6 Hz, J_2 = 40.4 Hz, 2H), 3.89 (s, 3H), 1.40(s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.3, 165.3, 154.1, 147.8, 142.4, 131.1, 129.9, 129.1, 129.1, 129.7, 123.1, 81.2, 75.9, 59.8, 54.4, 28.2; **IR** (Neat): 3357, 2978, 2929, 2854, 2135, 1757, 1720, 1608, 1525, 1497, 1367, 1349, 1248, 1164; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_6N_3)^+$ requires 426.1660; found 426.1662; enantiomeric excess: 95%, determined by HPLC (Chiralpak AS-H, hexane/*i*-PrOH 90/10, flow rate 1.0 mL/min, t_{major} = 9.6 min, t_{minor} = 15.7 min, λ = 220 nm).

*4.5.19 Methyl (2S,3S)-3-(3-bromophenyl)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2-phenylpropanoate **(3t)***

Yield:92% (**3t** and **3t′**); White solid; m.p. 55-56 °C $[\alpha]_D^{23.0}$ = -34.2 (*c* 2.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.75-7.73 (m, 2H), 7.58 (m, 1H), 7.48-7.39 (m, 5H), 7.24-7.22 (m, 2H), 5.86 (d, *J* = 8.8 Hz, 1H), 5.12 (d, *J* = 8.8 Hz, 1H), 3.63 (s, 3H), 1.19 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.2, 164.6, 154.2, 138.3, 132.1, 131.9, 131.4, 130.0, 129.5, 128.8, 126.8, 126.1, 122.5, 80.6, 58.1, 54.0, 28.0; **IR** (Neat): 3350, 2978, 2136, 1721, 1572, 1498, 1450, 1368, 1248, 1165, 1050; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_6N_3)^+$ requires 459.0914; found 459.0912; enantiomeric excess: 64%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 95/15, flow rate 0.8 mL/min, t_{major} = 17.2 min, t_{minor} = 11.9 min, λ = 220 nm);

*Methyl (2R,3S)-3-(3-bromophenyl)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2-phenylpropanoate **(3t′)***

White solid; m.p. 57-58 °C, $[\alpha]_D^{23.1}$ = -74.4 (*c* 2.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.46 (m, 2H), 7.35-7.30 (m, 4H), 7.12 (m, 1H), 7.03-6.95 (m, 2H), 5.65 (m, 2H), 3.87 (s, 3H), 1.40(s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.5, 164.6, 154.1, 137.3, 131.5, 131.1, 129.6, 129.4, 128.9, 126.6, 125.8, 122.0, 80.8, 76.2, 59.7, 54.2, 28.2; **IR** (Neat): 3350, 2956, 2925, 2852, 2136, 1755, 1703, 1572, 1497, 1477, 1450, 1367, 1248, 1164, 1048, 855, 745; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_{24}O_4N_2Br)^+$ requires 459.0914; found 429.0915; enantiomeric excess: 90%, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 96/4, flow rate 0.9 mL/min, t_{major} = 7.4 min, t_{minor} = 12.7 min, λ = 220 nm).

*4.5.20 Methyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-3-(furan-2-yl)-2-isocyano-2-phenylpropanoate **(3u)** and Methyl (2R,3R)-3-((tert-butoxycarbonyl)amino)-3-(furan-2-yl)-2-isocyano-2-phenylpropanoate **(3u′)***

Yield:85%; White solid; m.p. 106-107 °C, $[\alpha]_D^{23.1}$ = +3.2 (*c* 2.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) dr = 1:1, δ 7.74-7.72 (m, 2H), 7.56-7.55 (m, 2H), 7.42-7.36 (m, 7H), 7.24 (m, 1H), 6.41-6.40 (m, 1H), 6.38-6.37 (m, 1H), 6.14 (m, 1H), 6.05 (d, *J* = 10.4 Hz, 1H), 5.94 (m, 1H), 5.87 (d, *J* = 10.4 Hz, 1H), 5.60 (d, *J* = 9.6 Hz, 1H), 5.13 (d, *J* = 10.4 Hz, 1H), 3.83 (s, 3.1H major), 3.77 (s, 3H minor), 1.42 (s, 9.5H major), 1.21 (s, 9H minor); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.3, 164.0 (163.6 minor), 154.2, 149.5 (148.3 minor), 142.5 (143.0 minor), 131.7 (131.5 minor), 129.3, 128.7, 128.6, 126.2, 125.8, 80.4 (80.7 minor), 75.6 (75.3 minor), 54.6 (55.2 minor), 54.1 (54.0 minor), 27.9 (28.2 minor); **IR** (Neat): 3356, 2979, 2137, 1750, 1720, 1499, 1450, 1435, 1392, 1368, 1248, 1160, 1010; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{20}H_{23}O_5N_2)^+$ requires 371.1601; found 371.1599; major diastereoisomer enantiomeric excess: 52%, t_{major} = 14.5 min, t_{minor} = 8.9 min; minor diastereoisomer enantiomeric excess: 80%, t_{major} = 33.4 min, t_{minor} = 10.3 min, determined by HPLC (Chiralpak AD-H, hexane/*i*-PrOH 93/7, flow rate 1.0 mL/min, λ = 220 nm).

*4.5.21 Methyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2-phenyl-3-(thiophen-2-yl)propanoate **(3v)** and Methyl (2R,3R)-3-((tert-butoxycarbonyl)amino)-2-isocyano-2-phenyl-3-(thiophen-2-yl)propanoate **(3v′)***

Yield:92%; White solid; m.p. 75-76 °C, $[\alpha]_D^{23.3}$ = -18.4 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) dr = 1.3:1, δ 7.76-7.74 (m, 2H), 7.59-7.58 (m, 1.7H minor), 7.45-7.37 (m, 5H), 7.30 (dd, J_1 = 1.2 Hz, J_2 = 5.2 Hz, 1H), 7.17 (d, *J* = 3.2 Hz, 1H), 7.11 (dd, J_1 = 1.2 Hz, J_2 = 5.2 Hz, 0.8H minor), 7.01 (dd, J_1 = 4.8 Hz, J_2 = 3.6 Hz, 1H), 6.81-6.79 (m, 1H), 6.75-6.74 (m, 1H), 6.20 (d, *J* = 10.4Hz, 1H), 6.05 (d, *J* = 10.4 Hz, 1H), 5.53 (d, *J* = 10.4 Hz, 1H), 5.08 (d, *J* = 10.0 Hz, 1H), 3.85 (s, 2.4H minor), 3.72 (s, 3H), 1.42 (s, 7.2H minor), 1.21 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 166.5 (166.3 minor), 164.8 (164.7 minor), 154.1, 139.2 (138.2 minor), 131.8 (132.1 minor), 129.5 (129.4 minor), 128.9, 128.8, 126.9, 126.9, 126.8, 126.4, 126.1, 125.8, 125.6, 80.7 (80.4 minor), 76.6, 55.8 (57.0 minor), 54.0 (54.1 minor), 28.0 (28.2 minor); **IR** (Neat): 3354, 2978, 2136, 1754, 1718, 1498, 1450, 1434, 1367, 1248, 1161, 1009; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{20}H_{23}O_4N_2S)^+$ requires 387.1373; found 387.1369; major diastereoisomer enantiomeric excess: 50%, t_{major} = 13.5 min, t_{minor} = 16.3 min; minor diastereoisomer enantiomeric excess: 79%, t_{major} = 11.8 min, t_{minor} = 21.3 min, determined by HPLC (Chiralpak AS-H, hexane/*i*-PrOH 97/3, flow rate 0.8 mL/min, λ = 220 nm).

*4.6 Characterization data of products **5a+5a′***

1-(Tert-butyl) 4-methyl (4S,5S)-4,5-diphenyl-4,5-dihydro-1H-imidazole-1,4-dicarboxylate (**5a**) and *1-(Tert-butyl) 4-methyl (4R,5S)-4,5-diphenyl-4,5-dihydro-1H-imidazole-1,4-dicarboxylate **(5a′)***

Yield:94%; White solid; m.p. 175-176 °C, $[\alpha]_D^{27.1}$ = -109.9 (*c* 1.0, $CHCl_3$); **^{1}H NMR** ($CDCl_3$, 400 MHz) dr = 1.2:1, δ 8.09 (s, 1H), 8.04 (s, 1H), 7.76-7.74 (m, 2H), 7.44-7.40 (m, 2H), 7.36-7.29 (m, 6H), 7.04-6.98 (m, 6H), 6.85 (m, 2H), 6.01 (s, 1H), 5.38 (s, 1H), 3.77 (s, 2.4H minor), 3.16 (s, 3H major), 1.22 (s, major 9H, minor 7H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 169.6 (173.0 minor), 150.4 (149.6 minor), 141.9 (136.7 minor), 128.4, 128.4, 128.2, 127.7, 127.3 (127.3 minor), 126.8, 126.7, 132.1 (131.8 minor), 129.5 (129.4 minor), 82.8, 66.4, 52.1 (53.4 minor), 27.7; **IR** (Neat): 2980, 2923, 2852, 1732, 1707, 1612, 1446, 1382, 1278, 1257, 1222, 1129, 1081, 742, 699; **HRMS** (ESI): calcd for $[M+H]^+$ $(C_{22}H_5O_4N_2)^+$ requires 381.1809; found 381.1811; major diastereoisomer enantiomeric excess: 74%, t_{major} = 24.3 min, t_{minor} = 18.3 min; minor diastereoisomer enantiomeric excess: 71%, t_{major} = 20.0 min, t_{minor} = 16.4 min, determined by HPLC (Chiralpak PC-II, hexane/*i*-PrOH 90/10, flow rate 0.8 mL/min, λ = 220 nm).

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Supplementary data

Supplementary data (details of condition optimization, NMR spectra, HPLC datas and X-ray crystal data of compounds **3a** and **3t′**) associated with this article can be found in the online version, at http://

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