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Copper(I)-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with Fluorinated Imines: The Expanded Scope and Mechanism Insights

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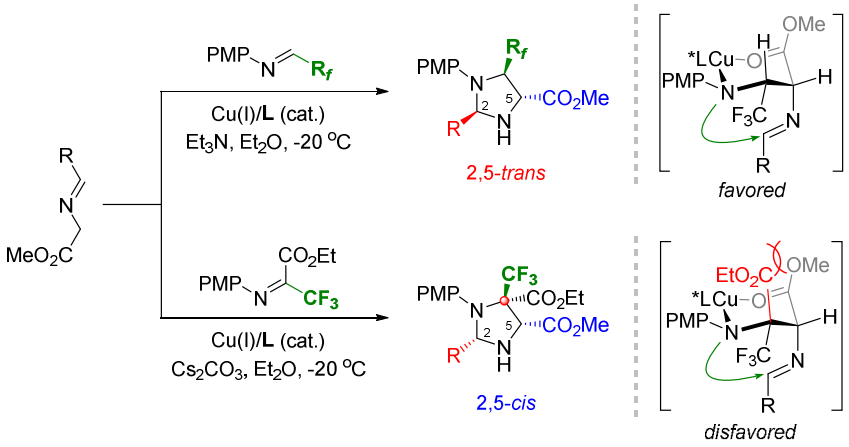
Graphic Abstract



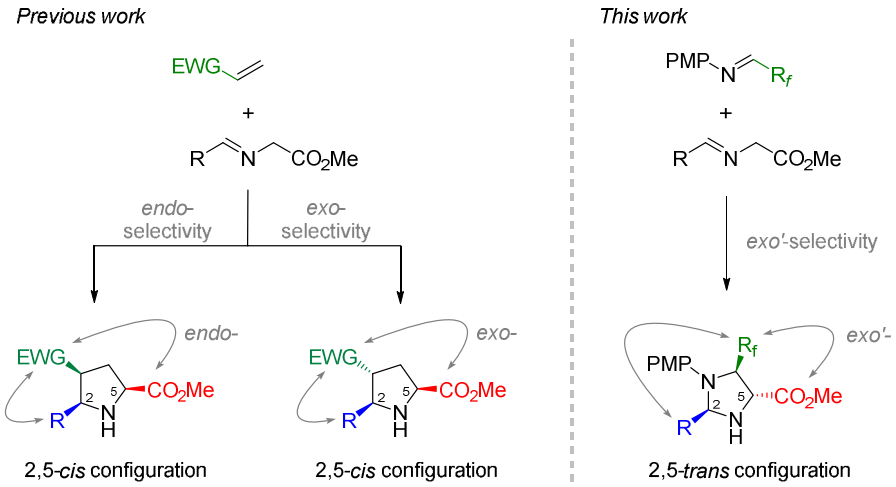
ABSTRACT: The mechanism of the Cu(I)/(S,R_p)-PPFOMe catalyzed 1,3-dipolar cycloaddition of azomethine ylides with fluorinated aldimines has been studied using labelling experiments, control experiments and linear effect experiments, which clearly ruled out the 1,3-DC/epimerization pathways and explained the unusal *exo*'-selective stereochemistry. This protocol allows for the preparation of a series of highly functionalized fluorinated imidazolidines in good yields with excellent stereoselectivities. Moreover, the current methods have been successfully extended to

synthesize more challenging imidazolidines bearing a CF_3-containing quaternary stereogenic center *via* the *endo*-selective 1,3-DC of azomethine ylides with trifluorinated ketimine under identical reaction conditions.

Introduction

The transition-metal-catalyzed asymmetric 1,3-dipolar cycloaddition (1,3-DC) reactions of azomethine ylides are one of the most efficient methods for the construction of enantiomerically enriched heterocyclic framework.[1] Various highly functionalized pyrrolidine[2] and piperidine[3] derivatives have been synthesized by the combination of azomethine ylides with diversified electron-deficient alkenes. The cross cycloaddition between azomethine ylides and azomethine imines has also been disclosed by us[4a] and others[4b] affording biologically important 1,2,4-triazinane derivatives in high enantiopurity. Nevertheless, it is surprising that limited progress has been made so far on employing imine as dipolarophile in catalytic asymmetric 1,3-DC reaction.[5] We believe this kind of 1,3-DC represents a significant challenge caused by various factors including the electronic nature of the C=N unsaturated double bond, competitive reactions and the stability of products. Considering the importance of the potential cycloadduct of imidazolidine,[6] developing a stereoselective 1,3-DC reaction with imine as dipolarophile is in highly desirable and be of great significance.

Scheme 1. Previous reports on the *endo*- or *exo*-selective asymmetric 1,3-DC of azomethine ylide with electron-deficient olefins (2,5-*cis* cycloadduct) and our work on the exo'-selective asymmetric 1,3-DC with fluorinated imines (2,5-*trans* cycloadduct)



In 2013, we reported the first example of catalytic asymmetric *exo*'-selective 1,3-DC of azomethine ylides with fluorinated aldimines, in which the C=N served as the efficient dipolarophilic moiety (Scheme 1, right side).[7] It is noteworthy that unusual *exo'*-selective cycloadducts[5a,8] (2,5-*trans*-configuration) were obtained in this reaction. Our curiosity was piqued by the unexpected stereochemistry outcome, and therefore we engaged on a study aiming at digging more details of this transformation. In this article, we describe the detailed mechanism investigation on the reaction mechanism and substrate scope. Considering that several different reaction pathways can be proposed, the experimental studies were designed to differentiate those pathways and to gain deep insight with the transformations. Moreover, the scope of the reaction has been extended to bulky trisubstituted fluorinated ketimine with reversed *endo*-selectivity (2,5-*cis*-configuration), which not only further validated the posulated mechanism, but also provided an unprecedented entry to chiral imidazolidines bearing a CF_3-containing quaternary stereogenic center. To our knowledge, only a few reports on constructing chiral trifluoromethylated quaternary stereocenters have been documented despite the fact that the study on the trifluoromethylated compounds has long been the hot topic.[9,10] The current method represents the

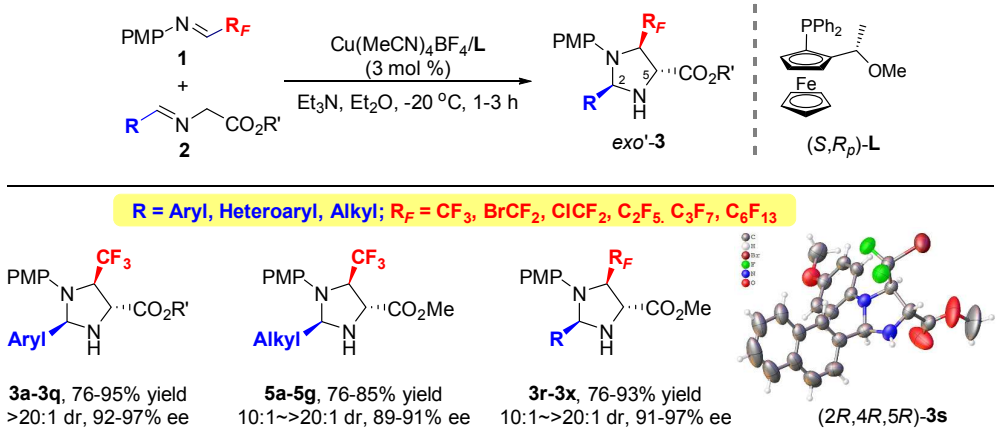
first example of the enantioselective preparation of imidazolidines bearing a trifluoromethylated quaternary stereocenter,[11] and we believe these compounds may exhibit some benefits to drug discovery and are expected to find valuable applications in medicinal chemistry.

Results and Discussion

1,3-Dipolar Cycloaddition of Imino esters and Fluorinated Aldimines

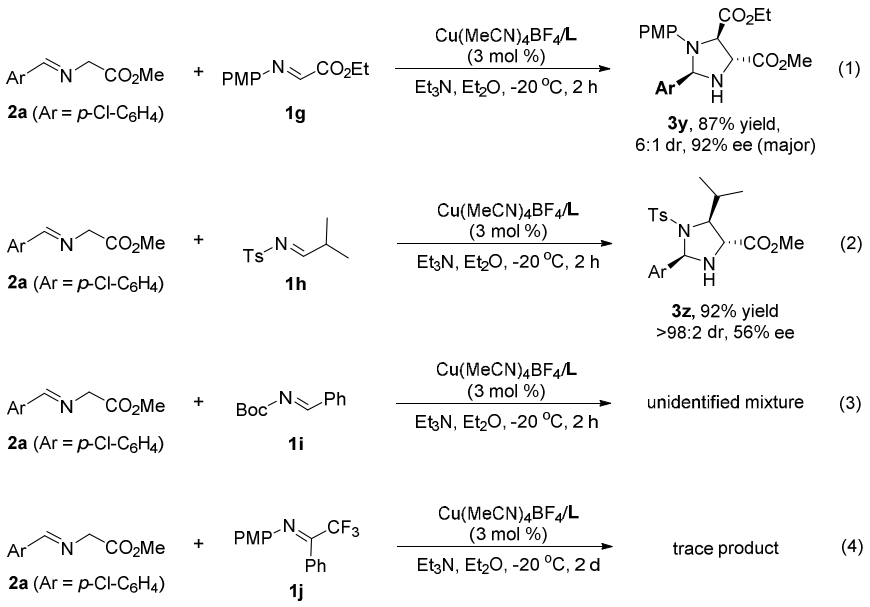
Our initial report[7] of the 1,3-DC reaction between imino esters **2** and fluoromethylated aldimine **1** catalyzed by 3 mol % of Cu(I)/(S,R_p)-PPFOMe[12] complex demonstrated that various functional groups are tolerated in this reaction, affording 2,5-*trans*-adduct **3** in high yields and excellent diastereo-/enantioselective control (Table 1, See Table S1-3 for the detail). The R group at 2-position, PMP group at 3-position, R_F group at 4-position and ester group at 5-position of the generated imidazolidine ring were controlled in an all *trans* relationship, corresponding to the *exo'*-adduct, which was further validated by the X-ray diffraction analysis of the enantiopure cycloadduct **3s** (Table 1) and **9** (Scheme 4) (*vide infra*).

Table 1: Subsrate Scope of Cu(I)/(S,R_p)-**L** Catalyzed 1,3-DCs of Azomethine Ylides with Fluorinated Aldimines[a]



[a] Each compound in Table 1 has been previously published.[7]

Non-fluorinated imines were further investigated for this transformation (Scheme 2, equations 1 and 2). Although no reaction occurred for non-activated imines, electron-deficient imine **1g** bearing ester group worked well in this catalytic system leading to product **3w** with 6:1 dr and 92% ee for the major isomer. Isobutyraldehyde derived *N*-tosyl imine **1h** was also tolerated affording adduct **3x** with excellent dr and moderate ee. However, unidentified mixture was observed for *N*-Boc imine **1i** (Scheme 2, equation 3). Only trace amount of [3+2] cycloadduct was observed when trifluoroacetophenone derived imine **1j** was employed even with prolonged reaction time, which probably caused by the disfavored steric congestion (Scheme 2, equation 4).



Scheme 2. The results of other electron-deficient imines.

Reaction Mechanism Investigations

Despite the fact that transition-metal-catalyzed 1,3-DCs of azomethine ylides have received significant attention in the recent years, examples on access to *exo'*-selective products are extremely rare.[8] Previous reports have demonstrated that cycloadducts with 2,5-*cis* configuration were usually

obtained in most cases no matter with *endo*- or *exo*-selectivity controlled 1,3-DCs of azomethine ylides (Scheme 1, left side).[2] With these prior observations in mind, we considered that the 2,5-*trans* products might formed *via* the epimerization of the first generated 2,5-*cis* imidazolidine. Give in to this view, we proposed two possible reaction pathways: the 1,3-DC of azomethine ylides with fluorinated aldimines gave the 2,5-*cis* configured **Int-I** (pathway a, *endo*-selectivity) or **Int-II** (pathway b, *exo*-selectivity) with the commonly-observed diastereoselectivity, then followed by the sequential base-promoted epimerization at 2- or 5-position to deliver the final *exo'*-selectivity (Figure 1).

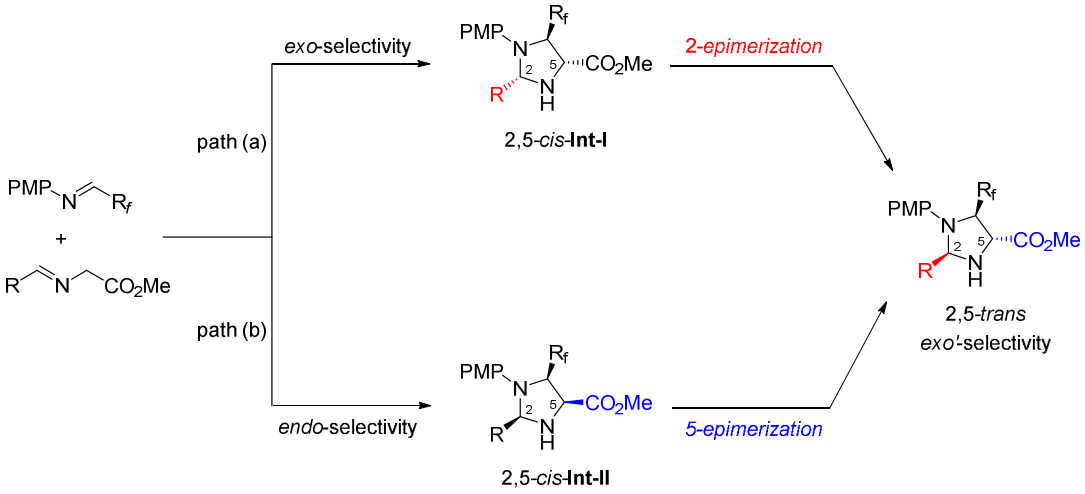
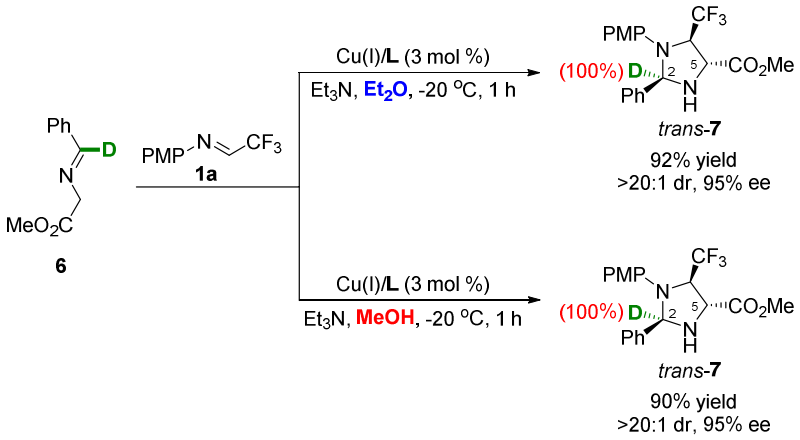


Figure 1. Possible epimerization reaction pathways for the exo'-1,3 dipolar cycloadditon.

Deuterium-labelled experiments were subsequently performed to validated the feasibility of the proposed 1,3-DC/epimerization mechanism. Deuterium-labelled *N*-benzylidene glycine methyl ester **6** was employed as the precursor of azomethine ylide under the optimized reaction condition with ether and methanol as the solvent, respectively (Scheme 3). No matter *non*-protic or protic solvent was used, only 2,5-*trans* imidazolidine **7** with 100% deuterium ration was obtained as single isomer in high yield and 95% ee, which revealed that no epimerization occurred at the

2-position of the imidazolidine ring in this annulation process under the reaction conditions and therefore ruled out the postulated reaction pathway (a) in Figure 1.

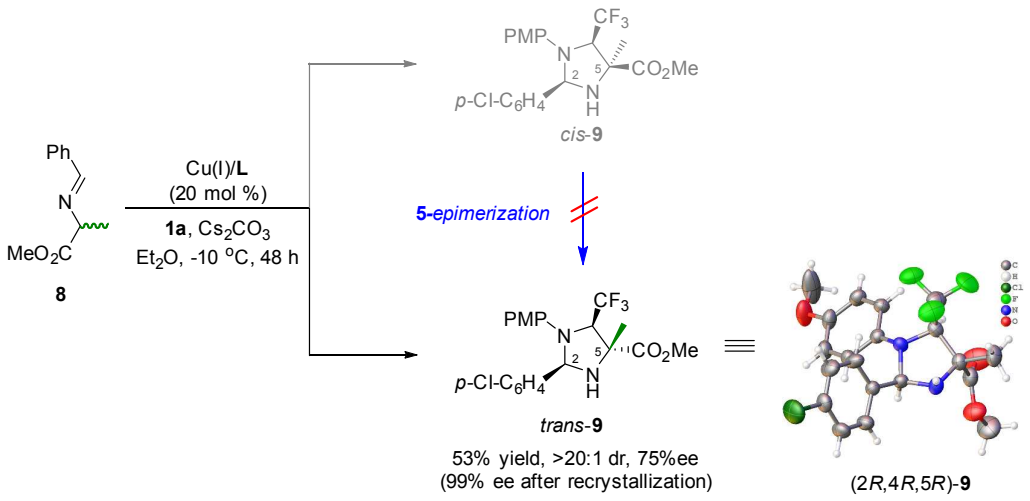
Scheme 3. Control experiment to investigate the possibility of epimerization at the 2-position of the imidazolidine ring with deuterium-labelled imino ester **6**



In order to examine the possibility of the 2,5-*trans* cycloadduct caused by the epimerization of the firstly formed 2,5-*cis*-imidazolidine at its 5-position, the second control experiment was designed with the α-substituted imino ester **8** derived from (±)-alanine as the precursor of azomethine ylide. In this case, if the 2,5-*cis*-imidazolidine **9** was formed as the intermediate via reaction pathway (b), no epimerization would occur due to the generated nitrogen-substituted quaternary stereogenic center at the 5-position (Scheme 4, the upside). Initial experiment revealed that the reaction proceeded smoothly with 20 mol % Cu(I)/(S,R_p)-PPFOMe complex catalyst loading and the Cs_2CO_3 as the base because of the less reactive nature of imino ester **8**, producing the cycloadduct imidazolidine **9** as single isomer in moderate ylide with excellent diastereoselectivity and moderate enantioselectivity (Scheme 4, the downside). The X-ray crystallographic analysis validated the configuration of **9** is still in 2,5-*trans* configuration, which further ruled out the possible epimerization at the 5-position of the imidazolidine ring in the

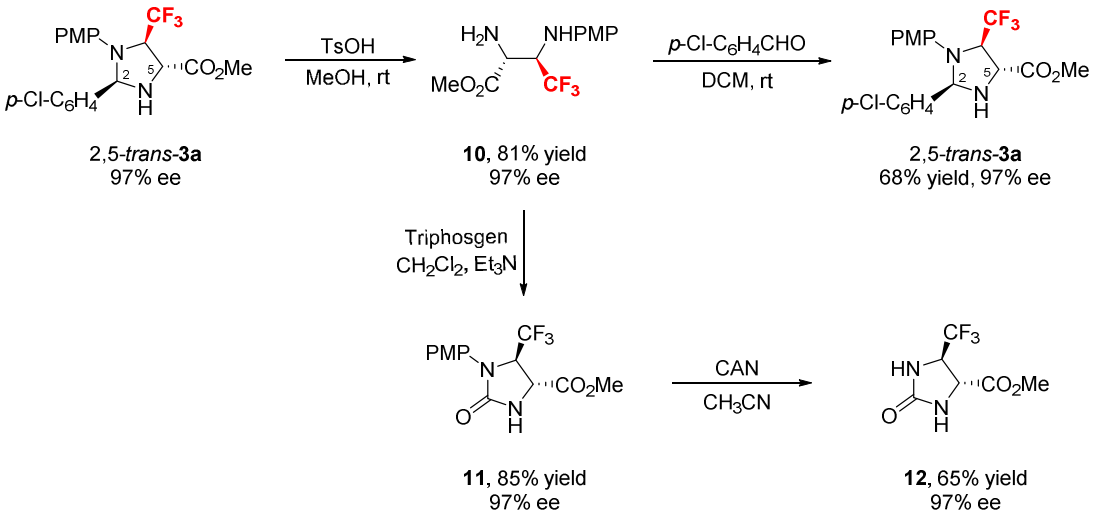
postulated reaction pathway (b) in Figure 1.

Scheme 4. Control experiment to investigate the possibility of epimerization at the 5-position of the imidazolidine ring with *rac*-alanine derived **8**



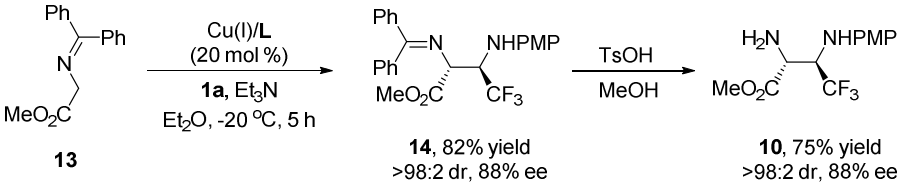
The optically active imidazolidine derivative **3a** was readily converted into other related chiral molecules as depicted in Scheme 5.[7] The *p*-TsOH mediated hydrolysis of the adduct **3a** targeted the diamine (2*R*,3*R*)-**10**, a trifluoromethylated analogue of the synthetically useful (2*R*,3*R*)-2,3-diaminobutanoic acid[13] in 81% yield with maintained enantioselectivity. Interestingly, imidazolidine **3a** could also be alternatively achieved by the condensation of *p*-chloro benzaldehyde and enantiomerically enriched (2*R*,3*R*)-**10** (Scheme 5). That the predominantly 2,5-*trans* isomer is more thermodynamically stable than other epimers can thus be verified both in the asymmetric catalytic process and the simple condensation. Diamine **10** then transformed to cyclic urea **11** using triphosgen as the cyclization reagent under basic condition. The deprotection of the PMP group in the presence of $Ce(NH_4)_2(NO_3)_6$ give corresponding hetereocycles **12** in 65% yield without any erosion of the stereoselectivity.

Scheme 5. Thermodynamical stablility of 2,5-*trans* isomer and synthetic transformations of the cycloadduct



Furthermore, only asymmetric Mannich addition occurred with the consistent stereoselectivity when glycine ketimine **13** was employed under standard reaction conditions, and no annulation adduct was observed. The subsequent intramolecular cyclization was totally suppressed probably due to the disfavored steric hindrance of benzophenone moiety (Scheme 6). Hydrolysis of the adduct **14** under acid condition gave rise to the compound (2*R*,3*R*)-**10**, which confirmed the stereochemistry of the Mannich addition step.

Scheme 6. Asymmetric Mannich addition of benzophenone Schiff base **13** with fluorinated imine **1a** and the determination of the stereochemistry



The linear effect experiment for this reaction was also examined (see SI for more details). As shown in Figure 2, with (S,R_p)-PPFOMe as the chiral ligand, we observed a clear linear effect in the asymmetric 1,3-DCs of azomethine ylide **2a** with trifluoromethylated imine **1a**. Such a linear

correlation indicates that the possible active species in this Cu(I)/(S,R_p)-PPFOMe-catalyzed cycloaddition reaction is a monomeric Cu(I) complex having (S,R_p)-PPFOMe as a bidentate chiral ligand [Cu(I):**L** = 1:1].[14]

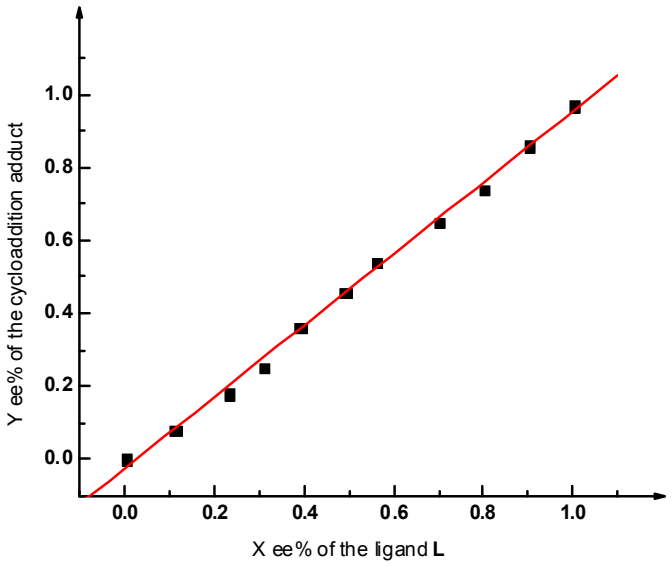


Figure 2. Linear Effect for the Asymmetric 1,3-Dipolar Cycloaddition of Trifluoromethylated Imine **1a** with Imino Ester **2a** Catalyzed by $Cu(CH_3CN)_4BF_4$/(S,R_p)-PPFOMe Complex.

On the basis of deuterium-labelled experiments, thermodynamic stability of the cycloadduct and the linear correlation results, a plausible stepwise mechanism was proposed to rationalize the observed *exo*-selectivity for this 1,3-DC (Figure 3). The *in situ*-formed azomethine ylide is coordinated to the Cu(I) complex leading to the catalytically active species (**A**) based on the linear correlation results. Initial Mannich addition of the chiral metallated azomethine ylide (**A**) to the *Re* face (C=N) of the fluorinated imine **1a** through the gauche conformation generates the zwitterionic intermediate (**B**), which could be facilitated by the possible coordination interaction between the imino group of **1a** and the Cu(I) center. After the Mannich reaction, the copper atom spontaneously switches from imino ester to NPMP for forming the six-membered chair-like species (**C**). Before

the subsequent intramolecular cyclization, the C-N single bond must rotate into the species (**D**) hence the amino unit approaches the *Re* face of the imine moiety to give the *exo'*-diastereomer, in which the substituents at 2 and 5 position of imidazolidine ring are arranged at *trans* configuration.

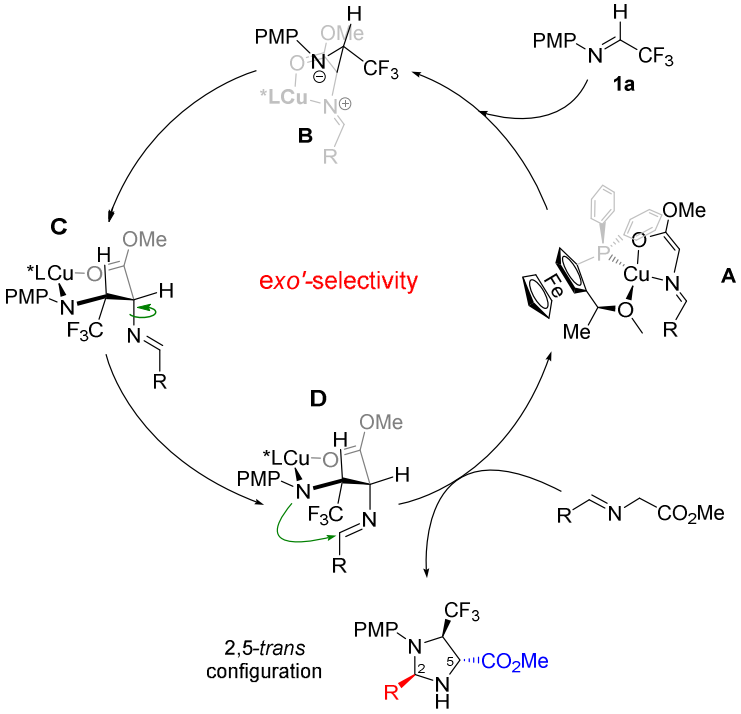
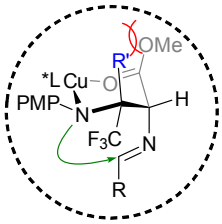


Figure 3. Postulated catalytic cycle for the Cu(I)-catalyzed *exo*-selective 1,3-DC of azomethine ylide with fluorinated aldimine and computational investigations.

The key intermediate **C** (**Int-C**) was studied by configuration analysis and further understood by the reaction of azomethine ylide with trisubstituted ketamine. As shown in Figure 4, both the OMe group and the hydrogen atom are arranged in the 1,3-axial positions of the six-membered chair-like **Int-C**. We envisioned that if the H atom in axial position was replaced by a more bulky group such as CO_2Et, the steric congestion between the CO_2Et group of the ketimine and the OMe group would lead to energy disfavored intermediate **G**, which may result in a different reaction pathway and therefore in a change in selectivity (Figure 4).

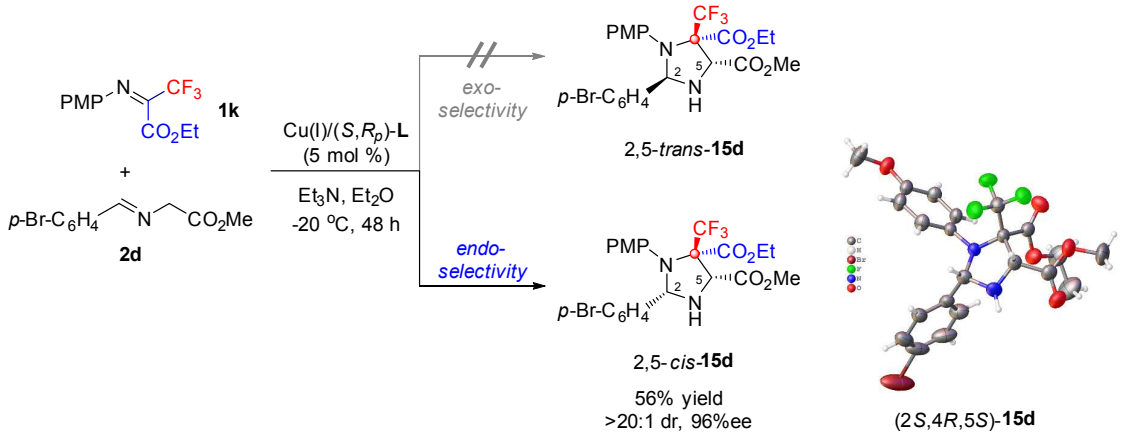


R = H (**D**, favored): MeO_{ax} and H_{ax}
R = CO_2Et (**G**, disfavored): MeO_{ax} and CO_2Et_{ax}

Figure 4. Conformation analysis based on the six-memebered chair-like intermediates.

To verify this postulate, *N*-(4-chlorobenzylidene)-glycine methyl ester **2a** and trisubstituted α-CF_3-ketimine ester **1k** were subjected to the standard reaction conditions, and the cycloadduct imidazolidine **15d** was obtained indeed as a single isomer with exclusive diastereoselectivity and excellent enantioselectivity in moderate yield (Scheme 7). The relative configuration of **15d** was finally identified as 2,5-*cis* configuration, and its absolute configuration was further confirmed by X-ray structure analysis as (2*S*,4*R*,5*S*), which validates the above configuration analysis of the postulated intermediates in the catalytic cycle (Figure 3 and 4).

Scheme 7. Initial test on the Cu(I)-catalyzed asymmetric 1,3-dipolar cycloaddition of α-CF_3-ketimine ester **1g** with imino ester **2a**



Based on the experiment result, the mechanism for the Cu(I)-catalyzed *endo*-selective 1,3-DC of azomethine ylide with trisubstituted ketimine was then postulated (Figure 5). The similar

six-membered chair-like intermediate (**G**) leading to *exo*'-selectivity was inhibited due to the disfavored 1,3-axial interaction between -OMe and -CO_2Et group and instead the cyclization step takes place through intermediate **F** providing 2,5-*cis* imidazolidine **15**. The postulated catalytic cycle is fully consistent with the observed stereochemical outcome.

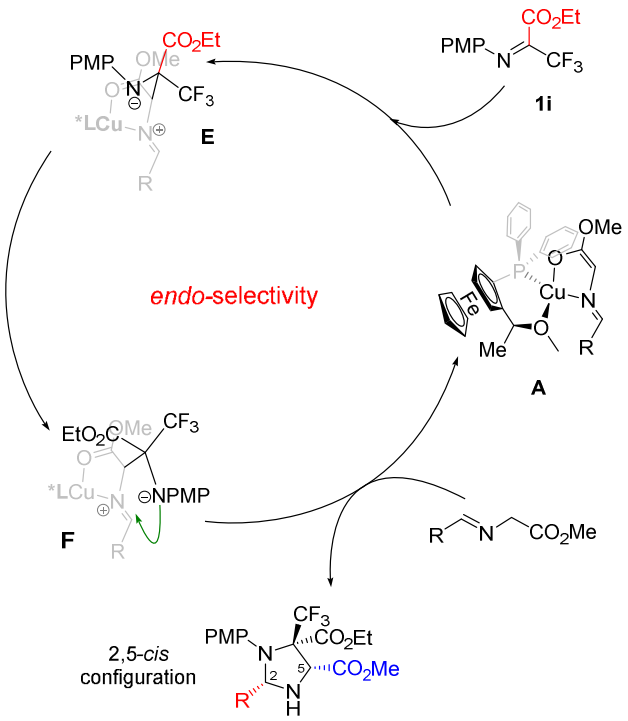
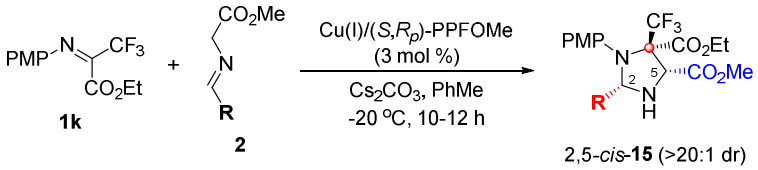


Figure 5. Postulated catalytic cycle for the Cu(I)-catalyzed *endo*-selective 1,3-DC of azomethine ylide with trisubstituted fluorinated ketimine and computational investigations.

Considering the great significance of developing new methods on accessing CF_3-containing quaternary stereocenters, we decided to extend the generality of the 1,3-DCof azomethine ylides with ketimine **1k**. To improve the reaction yield, Et_3N was replaced with a stronger inorganic base Cs_2CO_3 and toluene was chosen to be the reaction solvent instead of ethyl ether according to the solvent re-screening. To our delight, the less reactive ketimine **1k** was consumed completely based on the TLC monitoring and the desired product was isolated in 77% yield with excellent stereoselectivity at -20 ^oC with toluene as the solvent. Under the re-optimized reaction conditions,

the substrate scope with respect to the imino esters was evaluated and the results were summarized in Table 4. Imino esters with electron-withdrawing, -donating or -neutral substituted phenyl group were all well tolerated delivering the desired products in good yield and good to excellent enantioselectivity (up to 83% yield, 96% ee, Table 2, entries 1-7). Notably, fused 2-naphthyl imine **15i** and heteroaromatic substituted 2-thienyl imino ester **15j** gave the comparable results. (entries 8 and 9). The alkyl-substituted imino esters are not viable substrates in this reaction, only trace amount of desired products were isolated. α-Substituted amino acids derived imino esters also failed to reaction with **1k** probably due to the disfavored steric hindrance.

Table 2. Substrate scope of Cu**(I)/L**-catalyzed asymmetric 1,3-dipolar cycloaddition of α-CF_3-ketimine ester **1k** with various imino ester **2**[a]



entry	R	2	15	yield (%)[b]	ee (%)[c]
1	*p*-Cl-C_6H_4	**2a**	**15a**	77	96
2	*m*-Cl-C_6H_4	**2b**	**15b**	79	83
3	*o*-Cl-C_6H_4	**2c**	**15c**	62	94
4	*p*-Br-C_6H_4	**2d**	**15d**	75	96
5	Ph	**2e**	**15e**	68	95
6	*p*-Me-C_6H_4	**2f**	**15f**	77	96
7	*o*-Me-C_6H_4	**2h**	**15g**	75	95
8	1-Naphthyl	**2l**	**15h**	83	92
9	2-Thienyl	**2n**	**15i**	52	96

[a] All reactions were carried out with 0.23 mmol of **1k** and 0.35 mmol of **2** in 2 mL of toluene. [b] Isolated yield. [c] Dr was determined by the crude ^{1}H NMR and HPLC analysis, and ee was determined by HPLC analysis.

Conclusion

The copper(I)-catalyzed 1,3-dipolar cycloaddition between azomethine ylide and fluorinated aldimine has been studied with different tools with the goal of refining the reaction mechanism. The elaborated control experiments successfully rule out the possible sequential 1,3-DCs/epimerization

pathways and demonstrated that the generated exo′-cycloadducts are the thermodynamically stable diastereoisomers. Combination the results of the control experiments and linear effect experiments, we proposed that the current 1,3-dipolar cycloaddition might proceeded stereospecifically in a stepwise Mannich/cyclization process. In addition, we have applied the Cu(I)/(S,R_p)-PPFOMe catalyzed asymmetric 1,3-dipolar cycloaddition to a range of disubstituted fluorinated aldimines and trisubstituted fluorinated ketimine. This methodology provides a direct entry to biologically important imidazolidines bearing a fluoroalkyl-containing tertiary or quaternary stereogenic center in high yield with excellent stereoselectivity, and further transformations provide useful chiral fluorinated compounds.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR spectra were recorded on a VARIAN Mercury 300 MHz or Bruker 400 MHz spectrometer in $CDCl_3$. Chemical shifts are reported in ppm with the internal TMS signal at 0.0 ppm as a standard. The data are reported as (s = single, d = double, t = triple, q = quartet, m = multiple or unresolved, and brs = broad single). ^{13}C NMR spectra were recorded on a Bruker 100 MHz or 75 MHz spectrometer in $CDCl_3$ or DMSO-d_6. Chemical shifts are reported in ppm with the internal chloroform signal at 77.0 ppm as a standard. Commercially available reagents were used without further purification. All reactions were monitored by TLC with silica gel-coated plates. Diastereomeric ratios were determined from crude ^{1}H NMR or HPLC analysis. Enantiomeric ratios were determined by HPLC, using a chiralpak AD-H column, a chiralpak AS-H column or a chiralcel OD-H column with hexane and *i*-PrOH as solvents, or determined by GC using β-dex 325 column. Chiral ligand (S,R_p)-PPFOMe[12] and fluorinated imines[15] was prepared according to the literature procedure. The racemic adducts were obtained by using AgOAc/PPh_3 as the catalyst. The absolute configuration of (2*R*,4*R*,5*R*)-**3s**, (2*R*,4*R*,5*R*)-**9** and (2*S*,4*R*,5*S*)-**15d** was determined unequivocally according to the X-ray diffraction analysis, and those of other adducts were deduced on the basis of these results.

Procedure for the Synthesis of ketimine 1k. This compound is prepared according to reported procedure[15c]: To a solution of the iminophosphorane (5 mmol) in dry toluene (20 mL) was added dropwise the trifluorinated keto ester (5 mmol), and the reaction mixture was stirred at 80 °C for 18 h. Then the reaction mixture was cooled to room temperature, and the solvents were eliminated under reduced pressure. Et_2O (20 mL) was added and the reaction mixture cooled to 0 °C. The white precipitate was filtered through a pad of Celite and washed with cold Et_2O (3 × 10 mL). The filtrate was concentrated under reduced pressure and purified by flash column chromatography.

General Procedure for the Synthesis of Racemic Cycloadducts. Under argon atmosphere, PPh_3 (6.6 mg, 0.025 mmol) and AgOAc (3.8 mg, 0.023 mmol) were dissolved in 2 mL of DCM, and stirred at room temperature for about 0.5 h. Then, imine substrate (0.35 mmol), base (0.03 mmol) and imines (0.23 mmol) were added sequentially. Once starting material was consumed (monitored by TLC), the organic solvent was removed and the residue was purified by column chromatography to give the cycloaddition product, which was used as the racemic sample for the HPLC analysis.

General Procedure for Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with Aldimines. Under argon atmosphere, (S,R_p)-PPFOMe (3.3 mg, 0.0077 mmol) and $Cu(CH_3CN)_4BF_4$ (2.2 mg, 0.007 mmol) were dissolved in 2 mL of ethyl ether, and stirred at room temperature for about 0.5 h. After imino ester (0.35 mmol) was added, the mixture was dropped to -20 ^oC. Then, Aldimine (0.23 mmol) and Et_3N (0.03 mmol) were added sequentially. Once starting material was consumed (monitored by TLC), the mixture was filtered through celite and the filtrate was concentrated to dryness. The residue was purified by column chromatography to give the corresponding cycloaddition product, which was then directly analyzed by HPLC analysis to determine the enantiomeric excess.

(2*R*,4*R*,5*R*)-5-ethyl 4-methyl 2-(4-chlorophenyl)-1-(4-methoxyphenyl)imidazo-lidine-4,5-dicarboxylate (3y). The title compound was prepared according to the general procedure as described above in 87% yield (83.8 mg). d.r. = 6:1; $[\alpha]^{25}_D$ = +15.4 (*c* 0.59, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.61 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 9.2 Hz, 2H), 6.45 (d, *J* = 9.2 Hz, 2H), 5.50 (s, 1H), 4.50 (d, *J* = 2.8 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.26 (d, *J* = 2.8 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 172.4, 170.9, 152.6, 139.3, 138.6, 134.3, 128.9, 128.6, 114.7, 114.5, 79.2, 66.4, 63.0, 61.8, 55.6, 52.8, 14.2; IR (KBr) ν 2927, 2337, 1743, 1513, 1445, 1247, 1209, 1037, 816cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For

$C_{21}H_{24}ClN_2O_5$: 419.1361, found: 419.1368. The product was analyzed by HPLC to determine the enantiomeric excess: 92% ee (Chiralpak AD-H, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 220 nm); t_r = 10.07 and 19.09 min.

(2*R*,4*R*,5*S*)-methyl 2-(4-chlorophenyl)-5-isopropyl-1-tosylimidazolidine-4-car-boxylate (3z). The title compound was prepared according to the general procedure as described above in 92% yield (92.5 mg). $[\alpha]^{25}_D$ = -7.7 (*c* 0.45, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.36-7.29 (m, 4H), 5.80 (s, 1H), 3.65-3.61 (m, 2H), 3.57 (s, 3H), 2.46 (s, 3H), 1.48-1.44 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 172.7, 144.3, 138.1, 134.8, 134.0, 130.0, 128.5, 128.4, 128.0, 77.9, 69.8, 63.2, 52.5, 33.7, 21.6, 20.4, 18.8; IR (KBr) ν 2927, 2332, 1741, 1597, 1489, 1349, 1163, 1089, 1014, 755, 665 cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For $C_{21}H_{26}ClN_2O_4S$: 437.1290, found: 437.1296. The product was analyzed by HPLC to determine the enantiomeric excess: 56% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 16.52 and 23.51 min.

General Procedure for Asymmetric 1,3-Dipolar Cycloaddition of Azomethine Ylides with Fluorinated Ketimine 1k. Under argon atmosphere, (*S*,R_p)-PPFOMe (3.3 mg, 0.0077 mmol) and $Cu(CH_3CN)_4BF_4$ (2.2 mg, 0.007 mmol) were dissolved in 2 mL of toluene, and stirred at room temperature for about 0.5 h. After imino ester (0.35 mmol) was added, the mixture was dropped to -20 ^{o}C. Then, fluorinated imine **1k** (0.23 mmol) and Cs_2CO_3 (0.03 mmol) were added sequentially. Once starting material was consumed (monitored by TLC), the mixture was filtered through celite and the filtrate was concentrated to dryness. The residue was purified by column chromatography to give the corresponding cycloaddition product, which was then directly analyzed by HPLC analysis to determine the enantiomeric excess.

(2*S*,4*R*,5*S*)-5-ethyl 4-methyl 2-(4-chlorophenyl)-1-(4-methoxyphenyl)-5-(trifluoromethyl)imidazolidine-4,5-dicarboxylate (15a). The title compound was prepared according to the general procedure as described above in 77% yield (86.1 mg); $[\alpha]^{25}_D$ = -99.4 (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.48 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.1 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.64 (d, *J* = 8.7 Hz, 2H), 5.66 (d, *J* = 12.0 Hz, 1H), 4.48-4.32 (m, 3H), 3.81 (s, 3H), 3.87 (s, 3H), 2.93 (dd, J_1 = J_2 = 12.0 Hz, 1H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 168.4, 167.8, 155.6, 136.3, 134.7, 134.1, 129.1, 128.9, 124.7 (q, *J* = 289.4 Hz), 123.8, 113.9, 79.8, 75.3 (q, *J* = 26.0 Hz), 66.6, 62.8,

55.1, 53.0, 14.0; IR (KBr) ν 2950, 2424, 1745, 1710, 1515, 1468, 1421, 1215, 1135, 1037, 929, 664, 626 cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For $C_{22}H_{24}ClF_3N_2O_5$: 487.1242, found: 487.1249. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.65 and 8.40 min.

(2*S*,4*R*,5*S*)-5-ethyl 4-methyl 2-(3-chlorophenyl)-1-(4-methoxyphenyl)-5-(trifluoromethyl) imidazolidine-4,5-dicarboxylate (15b). The title compound was prepared according to the general procedure as described above in 79% yield (88.4 mg); $[\alpha]^{25}_D$ = -92.3 (*c* 1.46, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.56 (s, 1H), 7.43-7.41 (m, 1H), 7.23-7.21 (m, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 5.65 (d, *J* = 11.7 Hz, 1H), 4.48-4.34 (m, 3H), 3.80 (s, 3H), 3.67 (s, 3H), 2.96 (dd, $J_1 = J_2$ = 12.3 Hz, 1H), 1.45 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 168.3, 167.7, 155.6, 140.0, 134.5, 133.9, 129.9, 129.2, 127.8, 126.0, 124.6 (q, *J* = 288.8 Hz), 123.7, 113.9, 79.8, 75.3 (q, *J* = 25.5 Hz), 66.6, 62.8, 55.0, 53.0, 13.9; IR (KBr) ν 2947, 2420, 1743, 1707, 1512, 1458, 1421, 1225, 1130, 1032, 933, 668, 625 cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For $C_{22}H_{23}ClF_3N_2O_5$: 487.1242, found: 487.1251. The product was analyzed by HPLC to determine the enantiomeric excess: 83% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.20 and 10.23 min.

(2*S*,4*R*,5*S*)-5-ethyl 4-methyl 2-(2-chlorophenyl)-1-(4-methoxyphenyl)-5-(trifluoromethyl) imidazolidine-4,5-dicarboxylate (15c). The title compound was prepared according to the general procedure as described above in 62% yield (69.3 mg); $[\alpha]^{25}_D$ = -182.5 (*c* 0.90, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.78 (m, 1H), 7.30-7.29 (m, 1H), 7.18-7.16 (m, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 6.64 (d, *J* = 8.7 Hz, 2H), 6.18 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 12.9 Hz, 1H), 4.39-4.35 (m, 2H), 3.78 (s, 3H), 3.63 (s, 3H), 2.90 (dd, $J_1 = J_2$ = 12.3 Hz, 1H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 168.3, 167.8, 155.3, 135.0, 134.4, 134.2, 130.0, 129.4, 128.5, 127.6, 124.7 (q, *J* = 289.1 Hz), 123.0, 113.9, 75.8, 75.1 (q, *J* = 25.3 Hz), 66.8, 62.8, 55.0, 53.0, 13.9; IR (KBr) ν 2957, 2418, 1739, 1714, 1517, 1463, 1425, 1230, 1038, 936, 659, 618 cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For $C_{22}H_{23}ClF_3N_2O_5$: 487.1242, found: 487.1248. The product was analyzed by HPLC to determine the enantiomeric excess: 94% ee (Chiralpak AD-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.73 and 7.64 min.

(2*S*,4*R*,5*S*)-5-ethyl 4-methyl 2-(4-bromophenyl)-1-(4-methoxyphenyl)-5-(trifluoromethyl) imidazolidine-4,5-dicarboxylate (15d). The title compound was prepared according to the general procedure as described above in 75% yield (91.5 mg); $[\alpha]^{25}_D$ = -84.3 (*c* 1.48, $CHCl_3$); ^1H NMR

($CDCl_3$, TMS, 300 MHz) δ 7.41 (m, 4H), 6.78 (d, J = 8.7 Hz, 2H), 6.64 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 12.0 Hz, 1H), 4.48-4.34 (m, 3H), 3.79 (s, 3H), 3.66 (s, 3H), 2.94 (dd, $J_1 = J_2$ = 12.0 Hz, 1H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 168.3, 167.7, 155.5, 136.8, 134.0, 131.8, 129.4, 124.7 (q, J = 289.1 Hz), 123.7, 122.9, 113.8, 79.7, 75.3 (q, J = 24.9 Hz), 66.5, 62.7, 55.0, 52.9, 13.9; IR (KBr) ν 2948, 2433, 1745, 1722, 1560, 1517, 1473, 1422, 1235, 1037, 927, 679, 622 cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For $C_{22}H_{23}BrF_3N_2O_5$: 531.0742, found: 531.0732. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 7.18 and 9.01 min.

(2*S*,4*R*,5*S*)-5-ethyl 4-methyl 1-(4-methoxyphenyl)-2-phenyl-5-(trifluoromethyl) imidazolidine-4,5-dicarboxylate (15e). The title compound was prepared according to the general procedure as described above in 68% yield (70.7 mg); $[\alpha]^{25}_D$ = -100.6 (*c* 1.30, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.54-7.52 (m, 2H), 7.29-7.26 (m, 3H), 6.79 (d, J = 8.7 Hz, 2H), 6.62 (d, J = 8.7 Hz, 2H), 5.68 (d, J = 11.7 Hz, 1H), 4.50-4.35 (m, 3H), 3.80 (s, 3H), 3.65 (s, 3H), 2.99 (dd, $J_1 = J_2$ = 12.3 Hz, 1H), 1.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 168.4, 167.9, 155.3, 137.7, 134.4, 128.9, 128.6, 127.7, 124.8 (q, J = 289.4 Hz), 123.7, 113.8, 80.4, 75.3 (q, J = 25.3 Hz), 66.7, 62.7, 55.0, 53.0, 14.0; IR (KBr) ν 2944, 2401, 1745, 1718, 1523, 1507, 1428, 1219, 1027, 935, 679, 616 cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For $C_{22}H_{24}F_3N_2O_5$: 453.1632, found: 453.1632. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.47 and 8.52 min.

(2*S*,4*R*,5*S*)-5-ethyl 4-methyl 1-(4-methoxyphenyl)-2-(*p*-tolyl)-5-(trifluoromethyl) imidazolidine-4,5-dicarboxylate (15f). The title compound was prepared according to the general procedure as described above in 77% yield (82.6 mg); $[\alpha]^{25}_D$ = -103.0 (*c* 1.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.41 (d, J = 7.5 Hz, 2H), 7.08 (d, J = 7.5 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.62 (d, J = 8.7 Hz, 2H), 5.65 (d, J = 11.7 Hz, 1H), 4.48-4.34 (m, 3H), 3.79 (s, 3H), 3.65 (s, 3H), 2.97 (dd, $J_1 = J_2$ = 12.3 Hz, 1H), 2.27 (s, 3H), 1.42 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 168.5, 168.0, 155.3, 138.2, 137.7, 134.5, 129.7, 128.5, 128.4, 124.8 (q, J = 289.3 Hz), 124.7, 123.7, 113.8, 80.5, 75.4 (q, J = 25.1 Hz), 66.7, 62.7, 55.1, 53.0, 21.4, 14.0; IR (KBr) ν 2955, 2421, 1748, 1730, 1516, 1507, 1458, 1225, 1028, 935, 669, 619 cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For $C_{23}H_{26}F_3N_2O_5$: 467.1788, found: 467.1793. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate

1.0 mL/min, λ = 220 nm); t_r = 6.05 and 7.66 min.

(2*S*,4*R*,5*S*)-5-ethyl 4-methyl 1-(4-methoxyphenyl)-2-(o-tolyl)-5-(trifluoromethyl) imidazolidine-4,5-dicarboxylate (15g). The title compound was prepared according to the general procedure as described above in 75% yield (80.4 mg); $[\alpha]^{25}_D$ = -132.9 (*c* 1.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.63 (d, *J* = 7.2 Hz, 1H), 7.11-7.09 (m, 3H), 6.72 (d, *J* = 8.7 Hz, 2H), 6.63 (d, *J* = 8.7 Hz, 2H), 5.90 (d, *J* = 11.7 Hz, 1H), 4.51-4.30 (m, 3H), 3.80 (s, 3H), 3.66 (s, 3H), 2.91-2.83 (m, 1H), 2.51 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 168.5, 168.0, 155.2, 136.8, 135.5, 134.7, 130.3, 128.4, 126.6, 124.8 (q, *J* = 291.3 Hz), 123.1, 113.8, 76.3, 75.1 (q, *J* = 25.7 Hz), 66.8, 62.7, 55.1, 53.0, 18.9, 14.0; IR (KBr) ν 2932, 2433, 2401, 1741, 1723, 1523, 1510, 1422, 1215, 1036, 930, 671, 628 cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For $C_{23}H_{26}F_3N_2O_5$: 467.1788, found: 467.1791. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak AD-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 6.64 and 7.64 min.

(2*S*,4*R*,5*S*)-5-ethyl 4-methyl 1-(4-methoxyphenyl)-2-(naphthalen-2-yl)-5-(trifluoromethyl) imidazolidine-4,5-dicarboxylate (15h). The title compound was prepared according to the general procedure as described above in 83% yield (95.9 mg); $[\alpha]^{25}_D$ = -109.4 (*c* 1.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.98 (s, 1H), 7.78-7.69 (m, 4H), 7.44-7.41 (m, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.58 (d, *J* = 8.7 Hz, 2H), 5.86 (d, *J* = 11.7 Hz, 1H), 4.56-4.37 (m, 3H), 3.79 (s, 3H), 3.57 (s, 3H), 3.12 (dd, $J_1 = J_2$ = 12.3 Hz, 1H), 1.46 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 168.5, 167.9, 155.4, 135.2, 134.3, 133.6, 133.0, 128.7, 128.0, 127.6, 126.3, 126.1, 124.8 (q, *J* = 289.7 Hz), 124.4, 123.8, 113.8, 80.6, 75.5 (q, *J* = 25.5 Hz), 66.7, 62.7, 55.0, 53.0, 14.0; IR (KBr) ν 2952, 2430, 2410, 1748, 1713, 1517, 1502, 1424, 1362, 1211, 1040, 925, 673, 626 cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For $C_{26}H_{26}F_3N_2O_5$: 503.1788, found: 503.1788. The product was analyzed by HPLC to determine the enantiomeric excess: 92% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 8.46 and 11.78 min.

(2*S*,4*R*,5*S*)-5-ethyl 4-methyl 1-(4-methoxyphenyl)-2-(thiophen-2-yl)-5-(trifluoromethyl) imidazolidine-4,5-dicarboxylate (15i). The title compound was prepared according to the general procedure as described above in 52% yield (54.8 mg); $[\alpha]^{25}_D$ = -110.2 (*c* 0.32, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.18 (m, 2H), 6.87-6.85 (m, 3H), 6.67 (d, *J* = 8.4 Hz, 2H), 5.99 (d, *J* = 11.7 Hz, 1H), 4.48-4.31 (m, 3H), 3.79 (s, 3H), 3.67 (s, 3H), 3.15 (dd, $J_1 = J_2$ = 12.3 Hz, 1H), 1.42 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 168.2, 167.5, 155.9, 141.8, 134.1, 127.5,

126.5, 126.4, 124.5 (q, J = 289.3 Hz), 124.4, 113.8, 76.0, 75.0 (q, J = 25.3 Hz), 66.1, 62.6, 55.0, 53.0, 13.9; IR (KBr) ν 2938, 2428, 2405, 1742, 1712, 1574, 1513, 1432, 1220, 1039, 925, 665, 621 cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For $C_{20}H_{22}F_3N_2O_5S$: 459.1196, found: 459.1199. The product was analyzed by HPLC to determine the enantiomeric excess: 96% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 7.71 and 11.42 min.

(2*R*,3*R*)-methyl 2-amino-4,4,4-trifluoro-3-((4-methoxyphenyl)amino)butanoate (10). 3a (207 mg, 0.5 mmol) was dissolved in 3 mL of methanol at room temperature followed by the addition of $TsOH{\cdot}H_2O$ (380 mg, 2 mmol). The reaction mixture was stirred until starting material was consumed (monitored by TLC) and neutralized the mixture by Na_2CO_3. Then the mixture was partitioned between ethyl acetate and water, then the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo then the organic solvent was removed and the residue was purified by column chromatography to give compound **10** in 81% yield (118.3 mg). $[\alpha]^{25}_D$ = -41.2 (*c* 0.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.76 (d, J = 8.7 Hz, 2H), 6.66 (d, J = 8.7 Hz, 2H), 4.54-4.51 (m, 1H), 4.43-4.36 (m, 1H), 4.12 (s, 1H), 3.73 (s, 3H), 3.59 (s, 3H), 1.78 (brs, 2H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 171.7, 153.1, 139.9, 125.6 (q, J = 283.1 Hz), 116.0, 114.7, 58.4 (q, J = 27.9 Hz), 55.6, 52.7, 52.6; IR (KBr) ν 3368, 2951, 1746, 1516, 1453, 1218, 1035, 929, 669 cm^{-1}. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 11.07 and 20.46 min.

(4*R*,5*R*)-methyl 1-(4-methoxyphenyl)-2-oxo-5-(trifluoromethyl)imidazolidine-4-Carboxylate (11). To a solution of **10** (100 mg, 0.34 mmol) and triethylamine (141 μL, 1.02 mmol) in dry CH_2Cl_2(15.0 mL) under nitrogen at 0 °C was added a solution of triphosgene (100 mg, 0.34 mmol) in dry CH_2Cl_2 dropwise. The reaction mixture was warmed to room temperature and stirred until the starting material was consumed completely as indicated by TLC.Then the reaction was quenched and purified by column chromatography to give the cyclic urea **11** in 85% yield (92.0 mg). $[\alpha]^{25}_D$ = +18.8 (*c* 0.16, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 7.24 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 5.85 (s, 1H), 4.91-4.88 (m, 1H), 4.33 (d, J = 2.4 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) δ 169.7, 158.9, 158.2, 129.3, 126.9, 123.8 (q, J = 281.5 Hz), 114.3, 61.1 (q, J = 32.4 Hz), 55.3, 53.3, 52.0; IR (KBr) ν 2917, 2846, 2335, 1722, 1515, 1423, 1241, 1166cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For $C_{13}H_{14}F_3N_2O_4$: 319.0897, found: 319.0900. The product was analyzed by

HPLC to determine the enantiomeric excess: 97% ee (Chiralpak AD-H, *i*-propanol/hexane = 40/60, flow rate 1.0 mL/min, λ = 220 nm); t_r = 14.87 and 16.88 min.

(4*R*,5*R*)-methyl 2-oxo-5-(trifluoromethyl)imidazolidine-4-carboxylate (12). To a solution of **11** (92 mg, 0.29 mmol) in dry acetonitrile (2.0 mL) was added dropwise a solution of CAN (477 mg, 0.87 mmol) in H_2O (1.0 mL) at 0 °C. The reaction was completed immediately and quenched by the addition of saturated NH_4Cl aqueous solution. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated under vacuum. The residue was purified by chromatography to give **12** as a white soild (40.0 mg, 65%). $[\alpha]^{25}_D$ = -35.0 (*c* 0.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 300 MHz) δ 6.92 (s, 1H), 6.41 (s, 1H), 4.46 (m, 1H), 4.33 (d, *J* = 3.2 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (DMSO-d_6, TMS, 100 MHz) δ 170.7, 161.1, 124.7 (q, *J* = 279.4 Hz), 55.2 (q, *J* = 32.2 Hz), 53.4, 52.9; IR (KBr) ν 3243, 2922, 2360, 2341, 1724, 1443, 1240, 1176, 1145cm^{-1}. HRMS (ESI+) m/z: ($[M+Na]^+$) Calcd. For $C_6H_7F_3N_2O_3Na$: 235.0296, found: 235.0301. The product was analyzed by GC to determine the enantiomeric excess: 97% ee (β-dex 325 column, 30 m x 0.25 mm x 0.25 μm, column temperature: 170 ^{o}C, carrier gas: N_2, 1 mL/min); t_r = 9.84 and 14.29 min.

Methyl (2*R*,4*R*,5*R*)-1-(4-methoxyphenyl)-2-phenyl-5-(trifluoromethyl)imidazolidine-4-carboxylate-2-*d* (7). Under argon atmosphere, (S,R_p)-PPFOMe (3.3 mg, 0.0077 mmol) and $Cu(CH_3CN)_4BF_4$ (2.2 mg, 0.007 mmol) were dissolved in 2 mL of ether or methanol, and stirred at room temperature for about 0.5 h. After deuterium-labelled *N*-benzylidene glycine methyl ester **6** (0.35 mmol) was added, the mixture was dropped to -20 ^{o}C. Then, fluorinated imine **1a** (0.23 mmol) and Et_3N (0.03 mmol) was added sequentially. Once starting material was consumed (monitored by TLC), the mixture was filtered through celite and the filtrate was concentrated to dryness. The residue was purified by column chromatography to give the cycloaddition product **7**, which was then directly analyzed by HPLC analysis to determine the enantiomeric excess. In Et_2O: 80.6 mg, 92%; In MeOH: 78.9 mg, 90%. $[\alpha]^{25}_D$ = -37.3 (*c* 0.71, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.54 (d, *J* = 7.6 Hz, 2H), 7.39-7.35 (m, 3H), 6.74 (d, *J* = 9.2 Hz, 2H), 6.69 (d, *J* = 9.2 Hz, 2H), 4.63 (q, *J* = 6.8 Hz, 1H), 4.31 (s, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 2.69 (brs, 1H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 170.5, 153.8, 139.8, 138.9, 128.94, 128.88, 126.6, 125.9 (q, *J* = 280.9 Hz), 117.0, 114.5, 81.4 (t, *J* = 23.3 Hz), 65.5 (q, *J* = 30.6 Hz), 60.6, 55.4, 52.9; IR (KBr) ν 3365, 2951, 2845, 1755, 1515, 1420, 1362, 1243, 1136, 1030, 930, 823, 699 cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For $C_{19}H_{19}DF_3N_2O_3$:

382.1483, found: 382.1477. The product was analyzed by HPLC to determine the enantiomeric excess: 95% ee (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 7.66 and 10.95 min.

(2*R*,4*R*,5*R*)-methyl 2-(4-chlorophenyl)-1-(4-methoxyphenyl)-4-methyl-5-(trifluoromethyl) imidazolidine-4-carboxylate (9). Under argon atmosphere, (*S*,R_p)-PPFOMe (21.8 mg, 0.051 mmol) and $Cu(CH_3CN)_4BF_4$ (14.5 mg, 0.046 mmol) were dissolved in 2 mL of ether or methanol, and stirred at room temperature for about 0.5 h. After (±)-alanine-derived imino ester **8** (78.8 mg, 0.35 mmol) was added, the mixture was dropped to -10 ^oC. Then, fluorinated imine **1a** (46.7 mg, 0.23 mmol) and Cs_2CO_3 (22.8 mg, 0.07 mmol) was added sequentially. Once starting material was consumed (monitored by TLC), the mixture was filtered through celite and the filtrate was concentrated to dryness. The residue was purified by column chromatography to give the cycloaddition product **9**, which was then directly analyzed by HPLC analysis to determine the enantiomeric excess. 52.2 mg, 53%. $[\alpha]^{25}_D$ = -86.0 (*c* 0.13, $CHCl_3$); ^1H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 9.2 Hz, 2H), 6.58 (d, *J* = 9.2 Hz, 2H), 5.21 (s, 1H), 4.88 (q, *J* = 7.6 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 1.64 (s, 3H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 173.1, 153.5, 139.6, 137.7, 134.6, 129.2, 128.0, 125.7 (q, *J* = 282.1 Hz), 115.9, 114.6, 79.2, 67.8, 65.8 (q, *J* = 29.0 Hz), 55.5, 53.4, 18.9; IR (KBr) ν 3318, 2945, 2420, 1741, 1515, 1470, 1423, 1210, 1134, 1026, 929, 849, 788, 670 cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For $C_{20}H_{21}ClF_3N_2O_3$: 429.1187, found: 429.1179. The product was analyzed by HPLC to determine the enantiomeric excess: 75% ee for the cycloadduct and 99% ee was achieved after simple recrystallization (Chiralpak AS-H, *i*-propanol/hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm); t_r = 7.24 and 13.67 min.

(2*R*,3*R*)-methyl 2-((diphenylmethylene)amino)-4,4,4-trifluoro-3-((4-methoxy-phenyl)amino)butanoate (14). Under argon atmosphere, (*S*,R_p)-PPFOMe (3.3 mg, 0.0077 mmol) and $Cu(CH_3CN)_4BF_4$ (2.2 mg, 0.007 mmol) were dissolved in 2 mL of ether, and stirred at room temperature for about 0.5 h. After glycine ethyl ester benzophenone Schiff Base **13** (0.35 mmol) was added, the mixture was dropped to -20 ^oC. Then, fluorinated imine **1a** (0.23 mmol) and Et_3N (0.03 mmol) was added sequentially. Once starting material was consumed (monitored by TLC), the mixture was filtered through celite and the filtrate was concentrated to dryness. The residue was purified by column chromatography to give the product **14**, which was then directly analyzed by HPLC analysis to determine the

enantiomeric excess. In order to determine the relative and absolute configuration of the corresponding Mannich adduct, compound **14** was hydrolyzed to compound **10** as below: **14** (78 mg, 0.19 mmol) was dissolved in 3 mL of methanol at room temperature followed by the addition of $TsOH{\cdot}H_2O$ (144 mg, 0.76 mmol). The reaction mixture was stirred until starting material was consumed (monitored by TLC) and then neutralized the mixture with Na_2CO_3. Then the mixture was partitioned between ethyl acetate and water, then the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo then the organic solvent was removed and the residue was purified by column chromatography to give compound **10** in 75% yield without loss of the diastereo-/enantiomeric excess. 86 mg, 82% yield. $[\alpha]^{25}_D$ = +10.3 (*c* 0.61, $CHCl_3$); ^{1}H NMR ($CDCl_3$, TMS, 400 MHz) δ 7.69-7.67 (m, 2H), 7.46-7.36 (m, 6H), 7.16-7.14 (m, 2H), 6.78-6.75 (m, 4H), 5.02 (d, *J* = 9.6 Hz, 1H), 4.57 (q, *J* = 7.6 Hz, 1H), 4.53 (s, 1H), 3.75 (s, 3H), 3.55 (s, 3H); ^{13}C NMR ($CDCl_3$, TMS, 100 MHz) δ 173.4, 169.3, 153.0, 140.2, 139.0, 135.9, 130.9, 129.0, 128.7, 128.2, 127.3, 125.3 (q, *J* = 283.3 Hz), 115.9, 114.7, 63.9, 59.4 (q, *J* = 28.5 Hz), 55.6, 52.7; IR (KBr) ν 2927, 2354, 1744, 1512, 1446, 1238, 1125, 1025, 916, 695, 665 cm^{-1}. HRMS (ESI+) m/z: ($[M+H]^+$) Calcd. For $C_{25}H_{24}F_3N_2O_3$: 457.1726, found: 457.1734. The product was analyzed by HPLC to determine the enantiomeric excess: 88% ee (Chiralpak AD-H, *i*-propanol/hexane = 5/95, flow rate 1.0 mL/min, λ = 220 nm); t_r = 10.58 and 16.20 min.

General procedure for the synthesis of 3a from 10 and *p*-chloro benzaldehyde: A solution of enantiomerically enriched compound 10 (117 mg, 0.4 mmol, 97% ee) and *p*-chlorobenzaldehyde (84 mg, 0.6 mmol) was stirred at room temperature. The reaction mixture was stirred until starting material was consumed (monitored by TLC), then the organic solvent was removed and the residue was purified by column chromatography to give compound 3a in 68% yield. The product was analyzed by HPLC to determine the enantiomeric excess: 97% ee (Chiralpak AD-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 220 nm); t_r = 9.75 and 11.05 min.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge *via* the Internet at http://pubs.acs.org.

Table S1-S3, Data characterization for **3a-x** and **5a-g**, Figure S1-S3, Crystallographic data for **3s**, **9**, **15d**, copies of NMR spectra and HPLC spectra supplied as the Supporting Information.

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Notes

The authors declare no competing financial interest.

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