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Cinchona Alkaloid Squaramide Catalyzed Enantioselective Hydrazination/Cyclization Cascade Reaction of α-Isocyanoacetates and Azodicarboxylates: Synthesis of Optically Active 1,2,4-Triazolines

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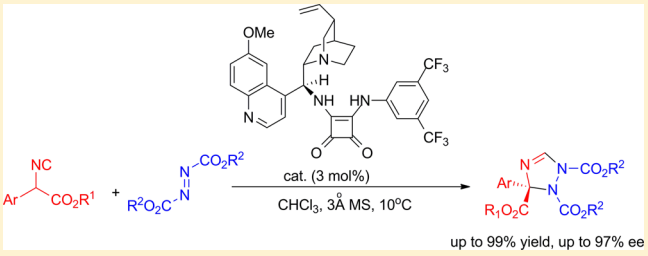
Supporting Information

ABSTRACT: An efficient enantioselective hydrazination/cyclization cascade reaction of α-substituted isocyanoacetates to azodicarboxylates catalyzed by *Cinchona* alkaloid derived squaramide catalysts has been investigated, affording the optically active 1,2,4-triazolines in excellent yields (up to 99%) and good to excellent enantioselectivities (up to 97% ee) under mild conditions.



INTRODUCTION

Nitrogen-containing heterocycles constitute a major family of pharmaceuticals and agrochemicals with a very long history, because they often exhibit interesting biological activities.[1] While the 1,2,4-triazole moiety is an important structural motifs and is present in a wide array of compounds that have antiviral, anticancer, anti-inflammatory, and anticonvulsant properties,[2] the saturated 1,2,4-trizaolines belong to an underutilized class of heterocycles and have received considerable attention only recently. Various synthetic approaches for the synthesis of 1,2,4-triazole derivatives using amino acids,[3] oxazoles,[4] imidazopyridines,[5] *N*-[(trimethylsilyl)methyl]iminium triflates,[6] oxazolones,[7] isocyanoacetates,[8] and azodicarboxylates have been developed during the past 20 years. Among them, the participation of α-substituted isocyanoacetates **1** in hydrazination/cyclization cascade reactions with azodicarboxylates has been shown to be a promising strategy, leading to 1,2,4-triazolines **3** bearing a quaternary C3 carbon atom containing a carboxylic acid functional group and a hydrogen atom substituent at C5 in excellent yields under mild conditions.[8] Although isocyanoacetates have been proven to be irreplaceable building blocks for the synthesis of numerous important classes of chiral nitrogen heterocyclic compounds by asymmetric addition with many electrophiles,[9] such as nitroolefins,[10] carbonyl compounds,[11] imines,[12] and α,β-unsaturated carbonyl compounds,[13] the enantioselective hydrazination/cyclization cascade reaction with azodicarboxylates has not been very successful, and excellent yields (>95%) and moderate enantioselectivities (up to 60% ee) were obtained by employing phase-transfer conditions (K_3PO_4–toluene) and a catalyst derived from cinchonine.[8] In light of this, the development of an efficient catalyst to improve the enantioselectivity of this hydrazination/cyclization cascade reaction was very necessary.

Over the past decades, hydrogen-bonding-promoted asymmetric organocatalysis has attracted intense research effort.[14] Especially, chiral thiourea or squaramide catalysts, incorporating the thiourea or squaramide moiety as powerful hydrogen bond donors in different chiral scaffolds, have been identified as goldmines in H-bonding-involved bifunctional activation processes to lead to high enantioselectivity and diastereoselectivity.[14] On the basis of the concept of bifunctional H-bonding catalysis and the earlier successes in the asymmetric additions of α-isocyanoacetates **1**,[10,11e,h,12,13e,f] we envisioned that the addition of α-isocyanoacetates to azodicarboxylates may be realized in the presence of bifunctional chiral tertiary amine–thiourea or –squaramide catalysts. α-Isocyanoacetates **1** with two electron-withdrawing substituents at the α-position (an isocyanide group and a carboxylic group) can be easily deprotonated by tertiary amine, and the azodicarboxylates may be activated by the H-bonding donor through double H bonds. Thus, the synergistic interactions of bifunctional catalysis would ensure high stereoselectivity in the hydrazination/cyclization cascade reactions (Scheme 1). While Feng et al. had reported very recently the catalytic asymmetric cyclization of α-alkyl-substituted isocyanoacetates with azodicarboxylates using a chiral iron(II) complex as the catalyst,[15] to the best of our knowledge, there is no example of a highly efficient

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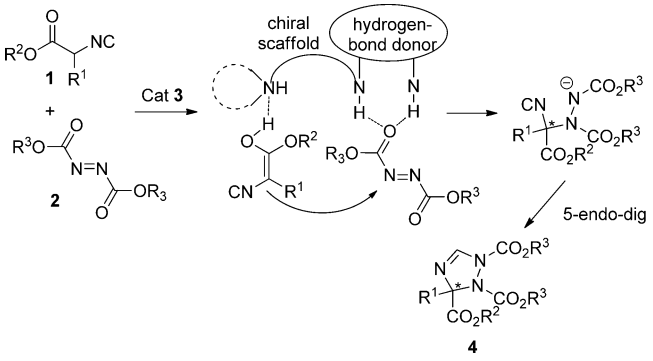
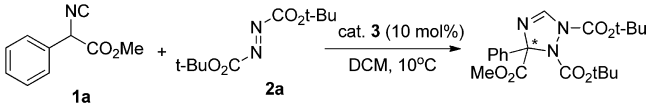
Scheme 1. Proposed Organocatalytic Reaction of α-Substituted Isocyanoacetate and Azodicarboxylate



organocatalytic system for this kind of reaction. As a part of our ongoing interest in enantioselective addition reactions of isocyanoacetates with unsaturated compounds for the synthesis of polysubstituted chiral heterocycles,[11h,13d] we describe herein the *Cinchona* alkaloid derived squaramide catalyzed enantioselective hydrazination/cyclization cascade reaction of a broad range of α-isocyanoacetates with azodicarboxylates, affording the chiral 1,2,4-triazolines in high yields and uniformly excellent enantioselectivities.

Table 1. Catalyst Screening for Enantioselective Hydrazination/Cyclization Cascade Reaction of Isocyanoacetate 1a with Azodicarboxylate 2a[a]



entry	cat. 3	time (h)	yield (%)	ee (%)[b]
1	**3a**	72	40	−21
2	**3b**	72	11	8
3	**3c**	66	15	−11
4	**3d**	66	44	−13
5	**3e**	12	98	−51
6	**3f**	12	98	89
7	**3g**	12	99	81
8	**3h**	12	99	81
9	**3i**	16	99	−79
10	**3j**	12	99	−61
11	**3k**	13	76	−65

[a]Unless noted otherwise, all reactions were carried out with isocyanoacetate **1a** (0.12 mmol), azodicarboxylate **2a** (0.10 mmol), and catalyst **3** (10 mol %) in CH_2Cl_2 (2.0 mL) at 10 °C. [b]Enantiomeric excesses were determined by chiral HPLC analysis.

RESULTS AND DISCUSSION

We initiated our study by examining the reaction between isocyanoacetate **1a** and azodicarboxylate **2a** in the presence of various tertiary amine−thiourea or −squaramide catalysts (Figure 1). As shown in Table 1, *Cinchona* alkaloid derived thiourea catalysts **3a,b** are not suitable catalysts for this reaction, affording 1,2,4-triazoline **4a** in low yields along with low enantioselectivities.[16] Squaramide catalysts **3c−e** with a chiral cyclohexane-1,2-diamine skeleton were then synthesized and evaluated (Table 1, entries 3−5). It was found that the substituents on the nitrogen atoms of the tertiary amine play an important role in determining the reaction outcome. Different from dimethyl- and pyrrolidine-substituted catalysts **3c,d**, which also gave **4a** in low yields and low enantioselectivities, the corresponding piperidine-substituted catalyst **3e** afforded the desired product **4a** in high yield and moderate enantioselectivity (Table 1, entries 3 and 4 vs entry 5). Further examination of *Cinchona* alkaloid derived squaramide catalysts **3f−k** revealed that the quinine-derived catalyst **3f** turned out to be an excellent catalyst for this hydrazination/cyclization cascade reaction, leading to the desired 1,2,4-triazoline **4a** in 98% yield along with 89% ee (Table 1, entry 6). Replacing the bis(trifluoromethyl)phenyl group on the squaramide moiety of **3f** with 4-(trifluoromethyl)phenyl and 4-fluorophenyl groups gave the desired product **4a** in relatively lower yields as well as lower enantioselectivities, probably due to the weak acidity of the N−H of the squaramide group of **3g,h** (Table 1, entries 7 and 8). Quinidine-derived squaramides **3i−k** also promoted this reaction but gave **4a** with opposite absolute configuration in much lower ee values in comparison to those of the corresponding quinine-derived catalysts **3f−h** (Table 1, entries 9−11).

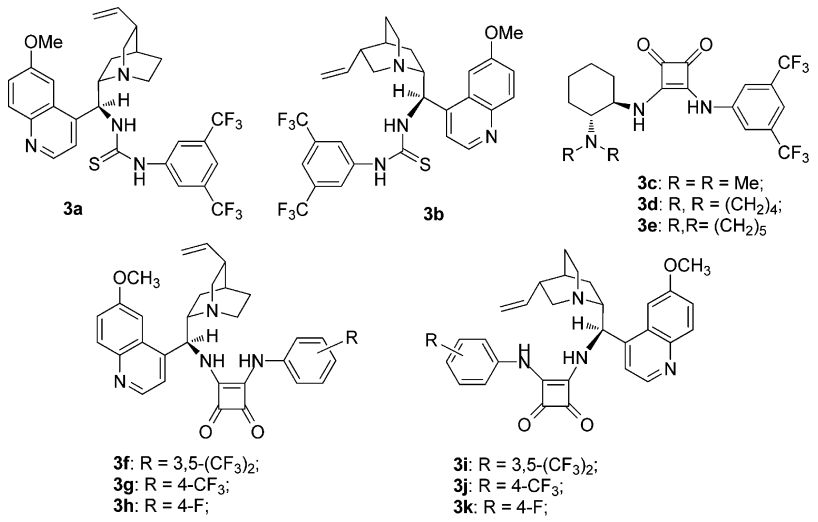


Figure 1. Evaluated catalysts.

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In view of the high enantioselectivity, efforts were made to further optimize the reaction conditions by examining other parameters such as solvent, temperature, and reactant concentrations (Table 2). Of the various solvents screened, chloroform was found to be the best solvent for this cascade reaction, despite the high yields and similar levels of enantioselectivity in other chlorinated solvents (Table 2, entries 1−3). Other solvents, whether less polar solvents such as toluene, EA, ether, and THF or polar solvents, all gave the corresponding 1,2,4-triazoline **4a** in low to moderate yields and low ee values (Table 2, entries 4−9). The examination of reactant concentration revealed that increasing the concentration could significantly improve the enantioselectivity of **4a** without sacrificing the yield (Table 2, entries 10 and −11); the best enantioselectivity for **4a** was obtained with a 0.1 M solution of azodicarboxylate **2a** (Table 2, entry 11). The effect of temperature was also examined, and it was found that lowering or elevating the reaction temperature led to a decrease in yield or enantioselectivity, respectively (Table 2, entries 12 and 13). Studies on the effect of additives suggested that addition of 3 Å molecular sieves could slightly improve the enantioselectivity of **4a** (Table 2, entry 14).[17] To our delight, reducing the catalyst loading to 3 mol % still afforded **4a** in excellent yield with high enantioselectivity (Table 2, entry 15). Thus, the optimal reaction conditions have been identified as carrying out the reaction with 1.2 equiv of **1a** and 1.0 equiv of **2a** in chloroform (0.1 M for **2a**) at 10 °C using 3 mol % of **3f** as the catalyst.

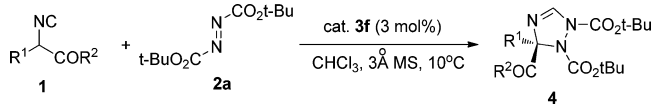
Table 2. Optimization of Reaction Conditions[a]

entry	solvent	temp (°C)	time (h)	yield (%)	ee (%)[b]
1	CH_2Cl_2	10	12	98	89
2	$CHCl_3$	10	12	98	91
3	$ClCH_2CH_2Cl$	10	12	98	85
4	toluene	10	12	76	71
5	EA	10	18	67	35
6	THF	10	18	29	−33
7	Et_2O	10	18	51	33
8	CH_3OH	10	12	28	−39
9	CH_3CN	10	12	72	5
10[c]	$CHCl_3$	10	12	97	89
11[d]	$CHCl_3$	10	12	98	93
12[d]	$CHCl_3$	0	12	85	93
13[d]	$CHCl_3$	20	12	99	89
14[d,e]	$CHCl_3$	10	12	99	93
15[d−f]	$CHCl_3$	10	12	99	93

[a]Unless noted otherwise, all reactions were carried out with isocyanoacetate **1a** (0.12 mmol), azodicarboxylate **2a** (0.10 mmol), and catalyst **3f** (10 mol %) in 2.0 mL of solvent. [b]Enantiomeric excesses were determined by chiral HPLC analysis. [c]4.0 mL of $CHCl_3$ was used. [d]1.0 mL of $CHCl_3$ was used. [e]30 mg of 3 Å molecular sieves was added. [f]3 mol % of catalyst **3f**.

Under the optimized conditions, the substrate scope of isocyanoacetates was investigated and the results of these experiments are summarized in Table 3. All of the tested α-aryl-substituted isocyanoacetates **3a−l** acted as excellent substrates to react with azodicarboxylate **2a**, affording the corresponding products **4a−l** in moderate to high yields (59−99% yield) along with good to excellent enantioselectivities (85−97% ee) (Table 3, entries 1−12). However, the electronic and steric properties of the substituent on the isocyanoacetate benzene ring played important roles in determining the reaction outcomes. Isocyanoacetates without a substituent or bearing an electron-donating group on the benzene ring yielded the desired products in slightly higher yields along with better enantioselectivities in comparison to the corresponding substrates with electron-withdrawing groups (Table 3, entries 1, 5, 6, 8, 10 vs entries 2−4, 7, 9). The presence of a substituent on the *ortho* position significantly slowed the reaction rate, as isocyanoacetates **1i,j** took a longer reaction time (65 h) to form **4i,j** in moderate to high yields along with excellent ee values. Variation on the ester moiety was then considered. In comparison with methyl isocyanoacetate **1a**, benzyl isocyanoacetate **1k** reacted smoothly with **2a** to afford the desired product **4k** in comparable yield and enantioselectivity; while *tert*-butyl isocyanoacetates **1l** afforded the product **4l** in moderate yield and similar stereoselectivity, even after prolonged reaction times (72 h), presumably owing to steric hindrance (Table 3, entries 11 and 12). Moreover, a limitation was observed with less reactive α-alkyl-substituted or non-substituted isocyanoacetates. For example, **1n,o** are not suitable for this reaction, affording the corresponding products **4n,o** in moderate yields and moderate to good enantioselectivities by prolonging the reaction time to 72 h (Table 3, entries 14 and 15). Using α-isopropyl-substituted isocyanoacetate **1m** as the reactant, no reaction occurred under the standard conditions (Table 3, entry 13).

Table 3. Scope of Isocyanoacetates 1[a]



entry	1 (R^1/R^2)	4	t (h)	yield (%)	ee (%)[b]
1	**1a** (Ph/OMe)	**4a**	12	99	93
2	**1b** (4-FC_6H_4/OMe)	**4b**	12	98	94
3	**1c** (4-ClC_6H_4/OMe)	**4c**	12	88	87
4	**1d** (4-BrC_6H_4/OMe)	**4d**	12	98	89
5	**1e** (4-MeC_6H_4/OMe)	**4e**	18	98	97
6	**1f** (4-$MeOC_6H_4$/OMe)	**4f**	18	98	95
7	**1g** (3-FC_6H_4/OMe)	**4g**	12	76	85
8	**1h** (3-MeC_6H_4/OMe)	**4h**	12	90	95
9	**1i** (2-BrC_6H_4/OMe)	**4i**	65	59	93
10	**1j** (2-MeC_6H_4/OMe)	**4j**	65	99	96
11	**1k** (Ph/OBn)	**4k**	18	78	94
12	**1l** (Ph/O*t*-Bu)	**4l**	72	64	96
13	**1m** (*i*-Pr/OMe)	**4m**	72	n.r.	n.d.
14	**1n** (Bn/OMe)	**4n**	72	20	96
15	**1o** (H/OEt)	**4o**	72	43	54

[a]Unless noted otherwise, all reactions were carried out with isocyanoacetate **1** (0.18 mmol), azodicarboxylate **2a** (0.15 mmol), catalyst **3f** (3 mol %) and 3 Å MS (30 mg) in 1.5 mL of $CHCl_3$. [b]Enantiomeric excesses were determined by chiral HPLC analysis.

In order to investigate the substituent effect of azodicarboxylate on this reaction, several azodicarboxylates with different ester substituents were subjected to this reaction under the standard conditions, and the results are summarized in Table 4. Using DEAD (**2b**), DIAD (**2c**), and DBAD (**2d**) as the corresponding substrates, the reactions proceeded smoothly to afford the corresponding products **4p−r** in excellent yields along with good ee values (Table 4, entries 2−4). It should be also noted that the azodicarboxylate derivative 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD, **2e**) was not suitable for this

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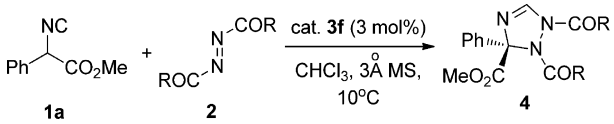
Table 4. Scope of Azodicarboxylates 2[a]



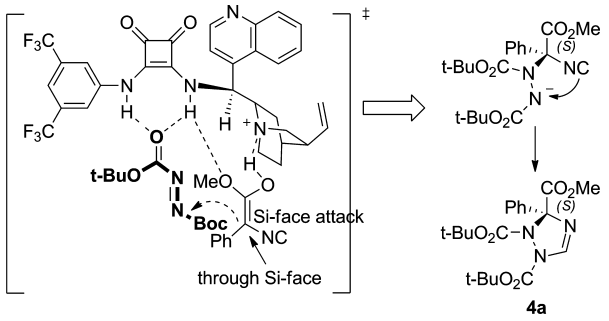
entry	2 (R)	4	t (h)	yield (%)	ee (%)[b]
1	**2a** (R = R = O-*t*-Bu)	**4a**	12	99	93
2	**2b**, DEAD (R = R = OEt)	**4p**	12	98	87
3	**2c**, DIAD (R = R = O-*i*-Pr)	**4q**	12	95	88
4	**2d**, DBAD (R = R = OBn)	**4r**	12	92	85
5	**2e**, PTAD (R, R = *N*-Ph)	**4s**	72	n.r.	n.d.

[a]Unless noted otherwise, all reactions were carried out with isocyanoacetate **1a** (0.18 mmol), azodicarboxylates **2** (0.15 mmol), catalyst **3g** (3 mol %), and 3 Å MS (30 mg) in 1.5 mL of $CHCl_3$. [b]Enantiomeric excesses were determined by chiral HPLC analysis.

reaction; no desired 1,2,4-triazoline derivative was detected under the optimized reaction conditions by prolonging the reaction time to 72 h, thus indicating that the presence of a bulky ester group is crucial for a satisfactory yield and stereochemical outcome (Table 4, entry 5).

The absolute configuration of **4** was unambiguously assigned as *S* by X-ray crystal analysis of product **4d**.[18] The absolute configurations of the other products were assigned as well. On the basis of the above results and the commonly accepted mechanism for squaramide catalysts, a plausible transition-state model is proposed as shown in Scheme 2. The carbonyl of

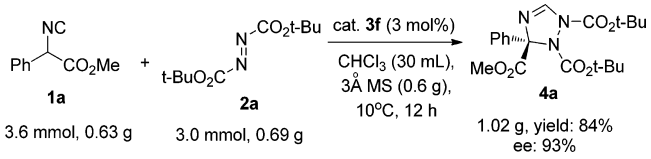
Scheme 2. Proposed Transition State Model



azodicarboxylate is H-bonded to the squaramide motif, while isocyanoacetate is deprotonated, resulting in a single H-bonding interaction between the OH group of the enolized isocyanoacetate and the tertiary amine. Additionally, a weak H-bonding interaction might be formed concurrently between the OMe group of the enolized isocyanoacetate and the NH in the squaramide moiety, which forces the enolized isocyanoacetate through the *Si* face to attack the azodicarboxylate from the *Si* face, affording the adduct **4a** with an *S* configuration. Subsequently, a 5-*endo-dig* cyclization would take place by an intramolecular reaction between the amine group of the resulting hydrazine intermediate and the isocyano group to afford the observed 1,2,4-triazoline **4a**.

To further explore the synthetic utility of the current catalyst system, a gram-scale reaction was also evaluated. The enantioselective hydrazination/cyclization cascade reaction of **1a** with **2a** was performed on 3.0 mmol of **2a** and 3.6 mmol of **1a** with 3 mol % of catalyst **3f**. The desired product **4a** could be obtained smoothly in 84% yield and 93% ee after 12 h, without significant deleterious effect on the reactivity and stereoselectivity (Scheme 3).

Scheme 3. Enantioselective Hydrazination/Cyclization Cascade Reaction of 1a with 2a on a Gram Scale



CONCLUSION

In conclusion, we have developed an efficient *Cinchona* alkaloid squaramide catalyzed enantioselective hydrazination/cyclization cascade reaction between α-aryl isocyanoacetates and azodicarboxylates. A wide variety of α-aryl isocyanoacetates and azodicarboxylates, with different electronic and steric properties, were tolerated in this catalytic enantioselective cascade reaction, leading to optically active 1,2,4-triazolines bearing a quaternary C3 stereogenic center in good to excellent yields along with good to excellent enantioselectivities (up to 97% ee). Investigations aimed at fully understanding the reaction mechanism and developing more effective enantioselective addition reactions of isocyanoacetates with other electrophiles are currently ongoing in our laboratory.

EXPERIMENTAL SECTION

General Procedure for the Enantioselective Hydrazination/Cyclization Cascade Reaction of Isocyanoacetates 1 with Various Azodicarboxylates 2 Catalyzed by 3f. To a solution of azodicarboxylates **2** (0.15 mmol), catalyst **3f** (2.8 mg, 3 mol %), and 3 Å MS (30 mg) in $CHCl_3$ (1.5 mL) was added isocyanoacetates **1** (0.18 mmol). The resulting mixture was stirred at 10 °C for 12−72 h until the reaction was complete (monitored by TLC). After concentration, the residue was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate 12/1 as eluent) to furnish the corresponding adducts **4**.

*(3S)-1,2-Di-tert-butyl 3-methyl 3-phenyl-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4a**):*[8] yellow solid; yield 60.0 mg (99%); mp 138.0−138.3 °C; $[\alpha]_D^{20}$ +69.7 (c 1.00, CH_2Cl_2) (93% ee); the ee was determined by HPLC analysis with a Chiralpak AS-H column (90/10 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 9.92 min; t_{minor} = 11.59 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 9H), 1.51 (s, 9H), 3.75 (s, 3H), 7.37−7.40 (m, 3H), 7.637 (s, 1H), 7.644 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 28.0, 53.3, 83.6, 84.7, 96.5, 127.2, 128.0, 128.6, 137.6, 146.6, 148.7, 154.1, 168.0; IR (film) ν 1763, 1758, 1718, 1620, 1450, 1370, 1351, 1290, 1258, 1236, 1153, 1125 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{28}N_3O_6$ 406.1978, found 406.1951.

*(3S)-1,2-Di-tert-butyl 3-methyl 3-(4-fluorophenyl)-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4b**):* white solid; yield 62.0 mg (98%); mp 115.8−116.2 °C; $[\alpha]_D^{20}$ +71.2 (c 1.00, CH_2Cl_2) (94% ee); the ee was determined by HPLC analysis with a Chiralpak AS-H column (90/10 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 9.30 min; t_{minor} = 10.34 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 9H), 1.51 (s, 9H), 3.75 (s, 3H), 7.07 (t, J = 8.4 Hz, 2H), 7.62 (dd, J = 8.8, 5.6 Hz, 2H), 7.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 28.0, 53.4, 83.8, 84.9, 96.0, 114.9 (d, J = 21.3 Hz), 129.1 (d, J = 8.4 Hz), 133.5 (J = 2.8 Hz), 146.7, 148.6, 154.1, 162.8 (d, J = 246.0 Hz), 167.9; ^{19}F NMR ($CDCl_3$, 376 MHz) δ −118.4; IR (film) ν 1759, 1717, 1509, 1370, 1291, 1232, 1152, 1124 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{27}FN_3O_6$ 424.1884, found 424.1879.

*(3S)-1,2-Di-tert-butyl 3-methyl 3-(4-chlorophenyl)-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4c**):* yellow viscous solid; yield 58.0 mg (88%); $[\alpha]_D^{20}$ +34.4 (c 1.00, CH_2Cl_2) (87% ee); the ee was

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determined by HPLC analysis with a Chiralpak AS-H column (90/10 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 9.12 min; t_{minor} = 10.36 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 9H), 1.51 (s, 9H), 3.75 (s, 3H), 7.36 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.65 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 28.0, 53.4, 83.8, 84.9, 96.0, 128.2, 128.7, 134.6, 136.3, 146.9, 148.6, 154.1, 167.7; IR (film) ν 1762, 1719, 1618, 1370, 1290, 1259, 1242, 1154, 1127 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{27}ClN_3O_6$ 440.1588, found 440.1583.

*(3S)-1,2-Di-tert-butyl 3-methyl 3-(4-bromophenyl)-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4d**):* white solid; yield 70.9 mg (98%); mp 140.8−142.2 °C; $[\alpha]_D^{20}$ +31.5 (c 1.00, CH_2Cl_2) (89% ee); the ee was determined by HPLC analysis with a Chiralpak AS-H column (90/10 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 9.28 min; t_{minor} = 10.76 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 9H), 1.51 (s, 9H), 3.75 (s, 3H), 7.51 (s, 4H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.88, 27.93, 53.4, 83.8, 84.9, 96.0, 122.9, 129.0, 131.1, 136.8, 146.8, 148.6, 154.0, 167.6; IR (film) ν 1760, 1718, 1618, 1370, 1290, 1259, 1241, 1154, 1127 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{27}BrN_3O_6$ 484.1083, found 484.1087.

*(3S)-1,2-Di-tert-butyl 3-methyl 3-(p-tolyl)-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4e**):* yellow viscous solid; yield 61.6 mg (98%); $[\alpha]_D^{20}$ +41.7 (c 1.00, CH_2Cl_2) (97% ee); the ee was determined by HPLC analysis with a Chiralpak AS-H column (90/10 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 9.28 min; t_{minor} = 10.25 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 9H), 1.51 (s, 9H), 2.36 (s, 3H), 3.75 (s, 3H), 7.21 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 27.9, 28.0, 53.3, 83.5, 84.6, 96.5, 127.0, 128.7, 134.7, 138.4, 146.5, 148.7, 154.1, 168.1; IR (film) ν 1763, 1718, 1620, 1370, 1291, 1238, 1154, 1129 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{30}N_3O_6$ 420.2135, found 420.2133.

*(3S)-1,2-Di-tert-butyl 3-methyl 3-(4-methoxyphenyl)-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4f**):* white solid; yield 63.9 mg (98%); mp 116.9−118.1 °C; $[\alpha]_D^{20}$ +40.7 (c 1.00, CH_2Cl_2) (95% ee); the ee was determined by HPLC analysis with a Chiralpak AS-H column (90/10 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 12.18 min; t_{minor} = 15.00 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 1.51 (s, 9H), 3.75 (s, 3H), 3.81 (s, 3H), 6.92 (d, J = 8.8 Hz, 2H), 7.56 (d, J = 9.2 Hz, 2H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 28.0, 53.3, 55.3, 83.5, 84.7, 96.3, 113.4, 128.5, 129.8, 146.5, 148.7, 154.1, 159.7, 168.2; IR (film) ν 1762, 1717, 1613, 1514, 1370, 1292, 1240, 1154, 1127 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{30}N_3O_7$ 436.2084, found 436.2082.

*(3S)-1,2-Di-tert-butyl 3-methyl 3-(3-fluorophenyl)-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4g**):* white solid; yield 48.2 mg (76%); mp 102.1−102.5 °C; $[\alpha]_D^{20}$ +60.6 (c 1.00, CH_2Cl_2) (85% ee); the ee was determined by HPLC analysis with a Chiralpak AS-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 14.67 min; t_{minor} = 16.73 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 9H), 1.51 (s, 9H), 3.75 (s, 3H), 7.03 (tdd, J = 8.0, 2.4, 0.8 Hz, 1H), 7.32−7.38 (m, 2H), 7.44 (dt, J = 8.0, 1.2 Hz, 1H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.89, 27.94, 53.4, 83.8, 84.9, 95.9, 114.6 (d, J = 23.9 Hz), 115.5 (d, J = 21.3 Hz), 122.9 (d, J = 2.3 Hz), 129.5 (d, J = 7.6 Hz), 140.3 (d, J = 7.5 Hz), 147.0, 148.6, 154.1, 162.4 (d, J = 244.0 Hz), 167.6; ^{19}F NMR ($CDCl_3$, 376 MHz, not-decoupled) δ −113.1 (m); IR (film) ν 1762, 1719, 1616, 1592, 1371, 12921, 1255, 1153, 1120 cm^{-1}; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{20}H_{26}FN_3O_6Na$ 446.1703, found 446.1705.

*(3S)-1,2-Di-tert-butyl 3-methyl 3-(m-tolyl)-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4h**):* white viscous solid; yield 56.8 mg (90%); $[\alpha]_D^{20}$ +55.0 (c 1.00, CH_2Cl_2) (95% ee); the ee was determined by HPLC analysis with a Chiralpak AS-H column (90/10 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 9.41 min; t_{minor} = 13.63 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 9H), 1.51 (s, 9H), 2.38 (s, 3H), 3.75 (s, 3H), 7.16 (d, J = 7.2 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.45 (s, 1H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 27.89, 27.93, 53.2, 83.5, 84.6, 96.5, 124.1, 127.8, 127.9, 129.4, 137.5, 146.5, 148.6, 154.1, 168.0; IR (film) ν 1763, 1718, 1620, 1370, 1290, 1252, 1154, 1124 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{30}N_3O_6$ 420.2135, found 420.2130.

*(3S)-1,2-Di-tert-butyl 3-methyl 3-(2-bromophenyl)-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4i**):* white solid; yield 43.1 mg (59%); mp 103.3−104.8 °C; $[\alpha]_D^{20}$ −7.7 (c 1.00, CH_2Cl_2) (93% ee); the ee was determined by HPLC analysis with a Chiralpak AS-H column (90/10 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 10.80 min; t_{minor} = 12.96 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (s, 9H), 1.52 (s, 9H), 3.80 (s, 3H), 7.21 (td, J = 8.0, 1.6 Hz, 1H), 7.35 (td, J = 7.6, 1.2 Hz, 1H), 7.66 (dd, J = 7.6, 0.8 Hz, 1H), 7.67 (s, 1H), 7.71 (dd, J = 8.0, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.8, 27.9, 53.3, 83.9, 84.8, 97.0, 122.4, 127.3, 128.5, 130.1, 134.8, 136.0, 146.7, 148.5, 153.6, 166.3; IR (film) ν 1752, 1724, 1617, 1463, 1370, 1291, 1259, 1153, 1134, 1112 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{27}BrN_3O_6$ 484.1083, found 484.1088.

*(3S)-1,2-Di-tert-butyl 3-methyl 3-(o-tolyl)-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4j**):* white solid; yield 62.2 mg (99%); mp 126.0−126.6 °C; $[\alpha]_D^{20}$ +15.4 (c 1.00, CH_2Cl_2) (96% ee); the ee was determined by HPLC analysis with a Chiralpak AS-H column (90/10 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 8.51 min; t_{minor} = 9.61 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 9H), 1.52 (s, 9H), 2.50 (s, 3H), 3.77 (s, 3H), 7.20−7.26 (m, 3H), 7.61 (s,1H), 7.62 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 27.9, 28.0, 53.2, 83.6, 84.6, 97.5, 125.6, 126.5, 128.7, 131.8, 134.9, 137.4, 146.0, 148.8, 153.9, 167.3; IR (film) ν 1764, 1756, 1720, 1622, 1457, 1394, 1370, 1291, 1258, 1227, 1155, 1107 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{30}N_3O_6$ 420.2135, found 420.2137.

*(3S)-3-Benzyl 1,2-di-tert-butyl 3-phenyl-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4k**):* white solid; yield 56.4 mg (78%); mp 116.2−117.4 °C; $[\alpha]_D^{20}$ +70.9 (c 1.00, CH_2Cl_2) (94% ee); the ee was determined by HPLC analysis with a Chiralpak AS-H column (90/10 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 11.21 min; t_{minor} = 13.16 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 1.49 (s, 9H), 5.08 (d, J = 12.4 Hz, 1H), 5.29 (d, J = 12.8 Hz, 1H), 7.24−7.40 (m, 8H), 7.63−7.65 (m, 2H), 7.64 (s,1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.87, 27.94, 67.9, 83.5, 84.7, 96.5, 127.2, 127.7, 127.9, 128.1, 128.4, 128.5, 134.9, 137.5, 146.7, 148.7, 154.0, 167.4; IR (film) ν 1759, 1717, 1619, 1456, 1370, 1290, 1259, 1233, 1153, 1126 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{26}H_{32}N_3O_6$ 482.2291, found 482.2286.

*(3S)-Tri-tert-butyl 3-phenyl-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4l**):* white solid; yield 43.3 mg (64%); mp 89.2−91.0 °C; $[\alpha]_D^{20}$ +92.5 (c 1.00, CH_2Cl_2) (96% ee); the ee was determined by HPLC analysis with a Chiralpak AD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 26.12 min; t_{minor} = 22.61 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 1.51 (s, 9H), 1.53 (s, 9H), 7.31−7.39 (m, 3H), 7.60 (s, 1H), 7.64 (d, J = 7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.6, 28.0, 28.1, 83.2, 83.6, 84.5, 97.0, 127.3, 127.7, 128.2, 138.0, 146.2, 148.9, 154.3, 166.3; IR (film) ν 1759, 1717, 1621, 1478, 1369, 1292, 1250, 1147 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{34}N_3O_6$ 448.2448, found 448.2447.

*(3S)-1,2-Di-tert-butyl 3-methyl 3-benzyl-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4n**):*[8] white viscous solid; yield 13.0 mg (20%); $[\alpha]_D^{20}$ +42.9 (c 1.00, CH_2Cl_2) (96% ee); the ee was determined by HPLC analysis with a Chiralpak AD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 21.12 min; t_{minor} = 28.60 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (s, 9H), 1.46 (s, 9H), 3.33 (d, J = 14.0 Hz, 1H), 3.45 (d, J = 14.0 Hz, 1H), 3.75 (s, 3H), 7.11−7.20 (m, 5H), 7.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.6, 27.8, 41.1, 52.8, 82.8, 83.8, 94.9, 126.6, 127.5, 131.1, 133.8, 147.6, 148.1, 153.2, 168.1; IR (film) ν 1760, 1716, 1618, 1457, 1369, 1290, 1259, 1155, 1103 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{21}H_{30}N_3O_6$ 420.2135, found 420.2135.

*(3S)-1,2-Di-tert-butyl 3-ethyl 1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4o**):* pale yellow oil; yield 22.3 mg (43%); $[\alpha]_D^{20}$ +34.0 (c 1.00, CH_2Cl_2) (54% ee); the ee was determined by HPLC analysis with a Chiralpak AS-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 18.47 min; t_{minor} = 20.52 min); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, J = 7.2 Hz, 3H), 1.50 (s, 9H), 1.53 (s, 9H), 4.21 (q, J = 7.2 Hz, 2H), 6.07 (s, 1H), 7.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 100

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MHz) δ 13.9, 27.9, 28.0, 62.0, 83.8, 84.3, 84.6, 148.1, 154.1, 155.5, 166.4; IR (film) ν 1760, 1723, 1609, 1458, 1393, 1369, 1327, 1255, 1145 cm^{-1}; HRMS (ESI-TOF) m/z $[M + K]^+$ calcd for $C_{15}H_{25}N_3O_6K$ 382.1380, found 382.1385.

*(3S)-1,2-Diethyl 3-methyl 3-phenyl-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4p**):* pale yellow viscous solid; yield 51.3 mg (98%); $[\alpha]_D^{20}$ +70.8 (*c* 1.00, CH_2Cl_2) (87% ee); the ee was determined by HPLC analysis with a Chiralpak AS-H column (90/10 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 25.14 min; t_{minor} = 27.65 min); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.28 (t, *J* = 7.2 Hz, 3H), 1.32 (t, *J* = 7.2 Hz, 3H), 3.76 (s, 3H), 4.20−4.37 (m, 4H), 7.38−7.40 (m, 3H), 7.64−7.66 (m, 2H), 7.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 53.6, 63.5, 64.1, 96.9, 127.1, 128.0, 128.8, 137.0, 146.1, 150.1, 155.4, 167.7; IR (film) ν 1762, 1750, 1721, 1621, 1398, 1372, 1328, 1270, 1232, 1012 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{20}N_3O_6$ 350.1352, found 350.1348.

*(3S)-1,2-Diisopropyl 3-methyl 3-phenyl-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4q**):*[3] white viscous solid; yield 53.9 mg (95%); $[\alpha]_D^{20}$ +75.6 (*c* 1.00, CH_2Cl_2) (88% ee); the ee was determined by HPLC analysis with a Chiralcel OD-H column (98/2 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 34.68 min; t_{minor} = 30.24 min); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.26−1.34 (m, 12H), 3.76 (s, 3H), 5.02−5.06 (m, 2H), 7.36−7.40 (m, 3H), 7.65 (dt, *J* = 6.4, 1.6 Hz, 2H), 7.71 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 21.73, 21.74, 21.9, 53.4, 71.8, 72.5, 96.7, 127.2, 128.0, 128.7, 137.2, 146.2, 149.8, 154.9, 167.7; IR (film) ν 1762, 1750, 1719, 1621, 1450, 1375, 1315, 1275, 1234, 1180, 1102, 1015 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{18}H_{24}N_3O_6$ 378.1665, found 378.1656.

*(3S)-1,2-Dibenzyl 3-methyl 3-phenyl-1H-1,2,4-triazole-1,2,3(3H)-tricarboxylate (**4r**):* yellow viscous solid; yield 65.4 mg (92%); $[\alpha]_D^{20}$ +49.0 (*c* 1.00, CH_2Cl_2) (85% ee); the ee was determined by HPLC analysis with a Chiralpak AD-H column (60/40 hexane/*i*-PrOH; 0.5 mL/min; λ 214 nm; t_{major} = 21.81 min; t_{minor} = 26.56 min); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.45 (s, 3H), 5.18 (d, *J* = 12.0 Hz, 1H), 5.23 (d, *J* = 12.4 Hz, 1H), 5.27 (d, *J* = 12.0 Hz, 1H), 5.31 (d, *J* = 12.0 Hz, 1H), 7.33−7.40 (m, 13H), 7.64−7.67 (m, 2H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.3, 68.9, 69.4, 96.9, 127.1, 128.0, 128.3, 128.47, 125.50, 128.6, 128.79, 128.82, 134.2, 134.8, 136.8, 145.9, 150.2, 155.3, 167.3; IR (film) ν 1758, 1749, 1724, 1622, 1456, 1385, 1328, 1268, 1233, 1213, 1155, 1013 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{26}H_{24}N_3O_6$ 474.1665, found 474.1662.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures, a table, and a CIF files giving NMR spectra and HPLC analysis spectra of compounds **4** and X-ray structural data of compound **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) CCDC 948689 (for **4d**) contains supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.