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# Synthetic Application and Structural Elucidation of Axially Chiral Dicarboxylic Acid: Asymmetric Mannich-type Reaction with Diazoacetate, (Diazomethyl)phosphonate, and (Diazomethyl)sulfone

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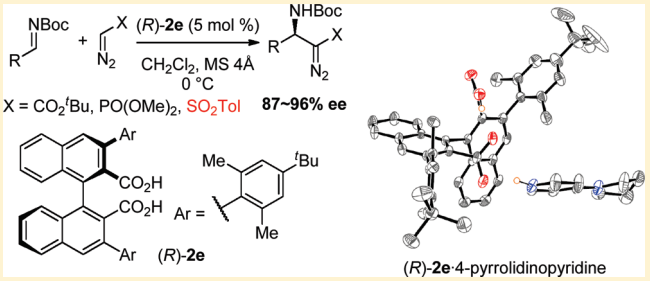
Supporting Information

**ABSTRACT:** The past decade has witnessed the burgeoning research fields of chiral Brønsted acid catalysis. However, carboxylic acids, arguably the most general acids in organic chemistry, have rarely been used as chiral Brønsted acid catalysts. In this context, we developed axially chiral dicarboxylic acid and evaluated its catalytic activity in asymmetric Mannich-type reaction of aromatic aldehyde-derived N-Boc imines and *tert*-butyl diazoacetate. To demonstrate the remarkable generality of this catalytic system, *tert*-butyl diazoacetate was replaced with its phosphorus and sulfur analogues, (diazomethyl) phosphonate and (diazomethyl)sulfone, by which synthetically valuable chiral $\beta$-amino phosphonates and $\beta$-amino sulfones could be obtained with high enantioselectivities under identical reaction conditions. X-ray crystallographic analysis of axially chiral dicarboxylic acid complexed with a pyridine derivative revealed its unique internal hydrogen bonding, a property that serves as a basis for its distinctive acidity and chiral scaffold.




## INTRODUCTION

In the wake of recent groundbreaking research revealing the utility of hydrogen bonding in asymmetric catalysis,[1] chiral Brønsted acid catalysis has now become an indispensable tool for environmentally benign access to a myriad of chiral building blocks.[2] Despite the possibility to employ various hydrogen-bond donors having different p$K_a$ values depending on the reaction systems, the relatively mild and very common Brønsted acids, carboxylic acids, have rarely been examined. The only exception published before we initiated our work was the use of mandelic acid derivative **1** in an asymmetric nitroso aldol reaction reported by Momiyama and Yamamoto in 2005[3] (Figure 1). In this context, we introduced axially chiral dicarboxylic acids (*R*)-**2**, having a binaphthyl backbone and two carboxylic acid moieties, as a new entry of chiral Brønsted acid catalysts in 2007,[4] and their high catalytic efficiency has been successfully demonstrated in several asymmetric transformations in the last couple of years.[5−7] These molecules were originally designed in anticipation of the internal hydrogen bonding among two carboxylic acid moieties, which would be beneficial to acquire sufficient acidity for catalysis and, more importantly, to fix the position of the hydrogen atom of otherwise freely rotating carboxylic acid. Thus fixed carboxylic acid is expected to act as an active hydrogen-bond donor. Modification of 3,3′-positions of a binaphthyl unit is conventionally applied as a general approach to efficiently impart the chiral information of the axial chirality to a remote substrate.

We report herein the detailed study of this axially chiral dicarboxylic acid-catalyzed Mannich-type reaction between N-Boc imines and diazoacetate, which could be successfully extended to other diazo compounds. Especially, tolyl (diazomethyl)sulfone was found to be a new viable option, giving chiral $\beta$-amino sulfones with high enantioselectivities. Elucidation of the X-ray structure of axially chiral dicarboxylic acid complexed with a pyridine derivative was carried out to confirm the formation of an internal hydrogen bond to give Brønsted acid-assisted Brønsted acid. Furthermore, this X-ray crystallographic analysis revealed the remarkably wide dihedral angle of the binaphthyl unit of this axially chiral dicarboxylic acid compared to the corresponding 1,1′-bi-2-naphthol (BINOL) derived monophosphoric acids, offering a distinctive chiral environment for asymmetric transformation.

## RESULTS AND DISCUSSION

At the initial stage of the development of axially chiral dicarboxylic acid, we were particularly keen to find out the reaction system that clearly shows the importance of the unique acidity of the catalyst. Toward this end, we became aware of BINOL-derived chiral monophosphoric acid catalyzed asymmetric Mannich-type reaction of *tert*-butyl diazoacetate, which was reported by Terada and co-workers in 2005.[8] As rather exotic *N*-(4-dimethylaminobenzoyl) imines were utilized in their report, we were interested in the outcome of the reaction using more conventional *N*-*tert*-butoxycarbonyl (N-Boc) imines.[9]

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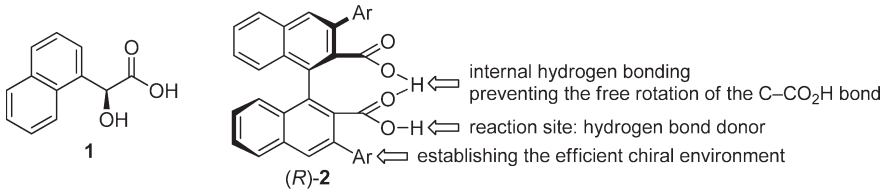
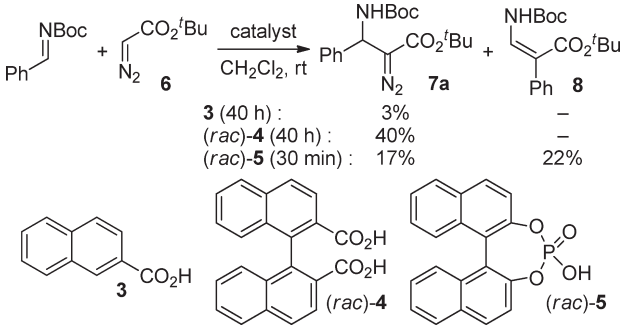
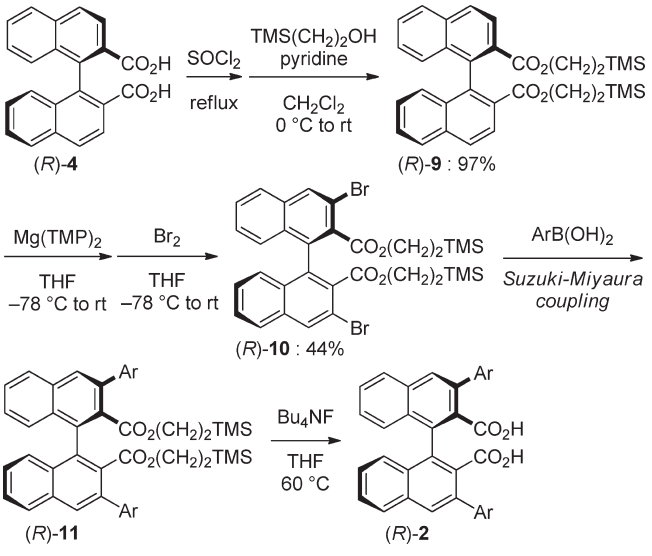



**Figure 1.** Carboyxlic acid as a new entry to chiral Brønsted acids.

**Scheme 1. Comparison of Acidity Profile in Mannich-type Reaction of Benzaldehyde-Derived N-Boc Imine with *tert*-Butyl Diazoacetate**

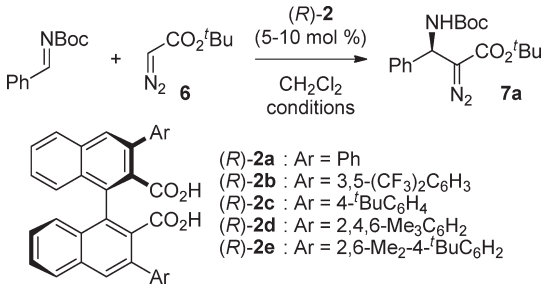



**Scheme 2. Preparation of Axially Chiral Dicaboxylic Acids**




In the initial experiment, three different Brønsted acids—2-naphthoic acid **3**, (*rac*)-1,1′-binaphthyl-2,2′-dicarboxylic acid (*rac*)-**4**, and (*rac*)-BINOL-derived monophosphoric acid (*rac*)-**5**—were compared in the reaction of *tert*-butyl diazoacetate **6** and benzaldehyde-derived N-Boc imine in $CH_2Cl_2$ at room temperature (Scheme 1). As a result, it became apparent that monophosphoric acid **5** exhibited quite high reactivity compared to the other two carboxylic acids. However, in conjunction with the desired Mannich-type adduct **7a**, a considerable amount of **8**,[10] which is assumed to be generated via migration of the phenyl group from the diazonium intermediate,[11] was obtained. On the other hand, use of (*rac*)-**4** furnished **7a** as an only isolable adduct in 41% yield after 40 h. The least acidic 2-naphthoic acid **3** was completely unproductive, giving **7a** only in 3% yield within the same time frame.

**Table 1. Screening of Axially Chiral Dicarboxylic Acids[a]**




| entry | catalyst (mol %) | conditions (temp, h) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | (*R*)-**2a** (10) | rt, 6 | 33 | 29 |
| 2 | (*R*)-**2b** (10) | rt, 20 | 25 | 17 |
| 3 | (*R*)-**2c** (10) | rt, 20 | 35 | 49 |
| 4 | (*R*)-**2d** (10) | rt, 16 | 38 | 69 |
| 5 | (*R*)-**2d** (5) | 0, 15 | 39 | 74 |
| 6 | (*R*)-**2e** (5) | 0, 38 | 38 | 95 |
| 7[d] | (*R*)-**2e** (5) + MS 4 Å | 0, 20 | 81 | 95 |

[a] Reactions were performed with benzaldehyde N-Boc imine (0.10 mmol) and *tert*-butyl diazoacetate (0.12 mmol) in the presence of (*R*)-**2** in $CH_2Cl_2$ (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] With MS 4 Å (100 mg).

As the acidity—reactivity relationship and advantage of using dicarboxylic acid as catalyst became clear in this Mannich-type reaction of N-Boc imines and diazoacetate, we stepped forward to the elaboration of the catalyst structure to create highly effective axially chiral dicarboxylic acid. According to the procedure developed in this laboratory for synthesis of phase-transfer catalysts,[12] 3,3′-positions of dicarboxylic acid (*R*)-**4**[13] were functionalized with aryl groups in anticipation of imparting the chiral environment of the binaphthyl moiety to substrates. (Trimethylsilyl)ethyl ester (*R*)-**9** was used as a substrate for ortho-magnesiation-bromination, taking its late-stage deprotection to the free carboxylic acid in mind, as normal alkyl esters arylated at 3,3′-positions were found not to be hydrolyzed even under harsh acidic or basic conditions. From the intermediate (*R*)-**10**, a variety of aryl groups could be incorporated into catalysts by Suzuki—Miyaura coupling to give (*R*)-**11**.[14] Subsequent deprotection of the (trimethylsilyl)ethyl group by the treatment with tetrabutylammonium fluoride provided a variety of axially chiral dicarboxylic acids (*R*)-**2** (Scheme 2).

As shown in Table 1, screening of catalysts identified a catalyst (*R*)-**2e** bearing a 4-(*tert*-butyl)-2,6-dimethylphenyl group as


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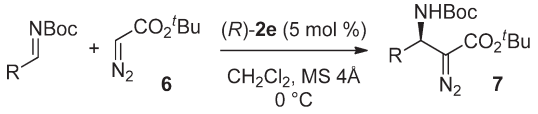
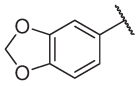
**Table 2. Use of *tert*-Butyl Diazoacetate**[a]



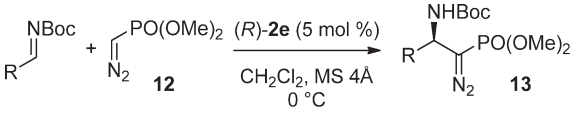

| entry | R | time (h) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | Ph | 24 | 80 (**7a**) | 95 (*R*) |
| 2 | 2-tolyl | 72 | 53 (**7b**) | 90 |
| 3 | 3-tolyl | 20 | 74 (**7c**) | 92 |
| 4 | 4-tolyl | 18 | 79 (**7d**) | 95 |
| 5 | 2-Np | 17 | 77 (**7e**) | 94 |
| 6 | 4-$FC_6H_4$ | 20 | 83 (**7f**) | 95 |
| 7 | 4-$ClC_6H_4$ | 26 | 89 (**7g**) | 96 |
| 8 | 4-$NO_2C_6H_4$ | 72 | 38 (**7h**) | 95 |
| 9 | 4-$MeOC_6H_4$ | 20 | 72 (**7i**) | 95 |
| 10 |  | 24 | 87 (**7j**) | 92 |
| 11 | 2-furyl | 5 | 84 (**7k**) | 85 |
| 12[d] | 2-furyl | 16 | 78 (**7k**) | 87 |
| 13[d] | 3-furyl | 20 | 77 (**7l**) | 94 |

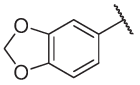
[a] Reactions were performed with aromatic aldehyde N-Boc imine (0.10 mmol) and *tert*-butyl diazoacetate **6** (0.15 mmol) in the presence of (*R*)-**2e** (0.005 mmol) and MS 4 Å (100 mg) in $CH_2Cl_2$ (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Performed at −20 °C.

3,3′-substituents,[15] with which Mannich-type adduct was obtained with 95% enantiomeric excess (ee) by carrying out the reaction in $CH_2Cl_2$ at 0 °C (entry 6). Addition of molecular sieves was found to be advantageous to increase the yield of the reaction, as they would scavenge adventitious water that caused hydrolysis of N-Boc imine (entry 7).

With these optimal reaction conditions in hand, we investigated the substrate scope of this Mannich-type reaction using various aromatic aldehyde-derived N-Boc imines as summarized in Table 2. As for the substitution pattern on the aromatic ring of N-Boc imines, use of 2-, 3-, and 4-tolualdehyde-derived N-Boc imines all provided the Mannich-type adducts **7b**−**d** with high enantioselectivities, although 2-substitution led to the requirement of a longer reaction time (entries 2−4). 2-Naphthaldehyde-derived N-Boc imine could be utilized as well (entry 5). Among the functionalities of a different electronic property (entries 6−10), attachment of a strongly electron-withdrawing substituent like a nitro group resulted in a considerable decrease of the yield (entry 8), presumably due to inefficient interaction of the less basic nitrogen lone pair of the imine to axially chiral dicarboxylic acid. In the case of reaction with 2-furaldehyde-derived imine, the enantioselectivity decreased slightly, although the reactivity was remarkably high (entry 11). Accordingly, the reaction temperature could be lowered to improve the selectivity to give **7k** in 78% yield with 87% ee (entry 12). These reaction conditions could be applied to 3-furaldehyde-derived imine, with which the product was obtained in 77% yield with 94% ee (entry 13).

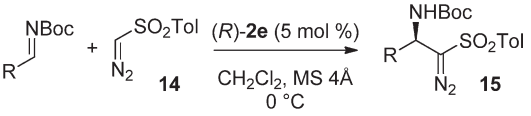
**Table 3. Use of Dimethyl (Diazomethyl)phosphonate**[a]

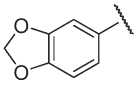



| entry | R | time (h) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | Ph | 85 | 68 (**13a**) | 96 |
| 2 | 4-tolyl | 68 | 68 (**13b**) | 96 |
| 3 | 4-$FC_6H_4$ | 52 | 85 (**13c**) | 96 |
| 4 | 4-$ClC_6H_4$ | 68 | 81 (**13d**) | 96 |
| 5 | 4-$MeOC_6H_4$ | 50 | 40 (**13e**) | 95 |
| 6 |  | 70 | 64 (**13f**) | 91 |
| 7 | 2-furyl | 46 | 89 (**13g**) | 92 |
| 8 | 3-furyl | 66 | 78 (**13h**) | 91 |

[a] Reactions were performed with aromatic aldehyde N-Boc imine (0.10 mmol) and dimethyl (diazomethyl)phosphonate **12** (0.15 mmol) in the presence of (*R*)-**2e** (0.005 mmol) and MS 4 Å (100 mg) in $CH_2Cl_2$ (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis.

**Table 4. Use of Tolyl (Diazomethyl)sulfone**[a]




| entry | R | time (h) | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | Ph | 70 | 70 (**15a**) | 92 |
| 2 | 3-tolyl | 109 | 60 (**15b**) | 90 |
| 3 | 4-tolyl | 46 | 61 (**15c**) | 94 |
| 4 | 2-Np | 85 | 77 (**15d**) | 93 |
| 5 | 4-$ClC_6H_4$ | 70 | 60 (**15e**) | 90 |
| 6[d] | 4-$MeOC_6H_4$ | 51 | 71 (**15f**) | 94 |
| 7 |  | 45 | 54 (**15g**) | 94 |
| 8[d] | 2-furyl | 91 | 80 (**15h**) | 90 |

[a] Reactions were performed with aromatic aldehyde N-Boc imine (0.10 mmol) and tolyl (diazomethyl)sulfone **14** (0.15 mmol) in the presence of (*R*)-**2e** (0.005 mmol) and MS 4 Å (100 mg) in $CH_2Cl_2$ (1.0 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Performed at −20 °C.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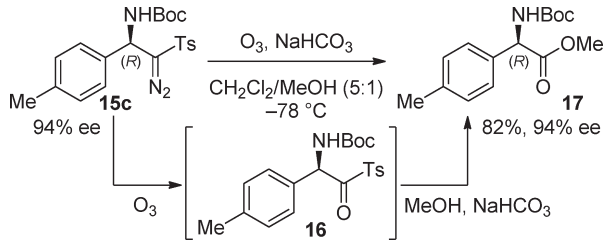
The noteworthy advantage of this procedure is its extension to other diazo compounds stabilized with an electron-withdrawing group. Namely, by simply applying the reaction conditions established as above, dimethyl (diazomethyl)phosphonate **12** could be utilized in place of *tert*-butyl diazoacetate to give chiral $\beta$-amino phosphonates **13** with excellent levels of enantioselectivity as summarized in Table 3.[16,17] In general, the reaction was slower compared to the reaction with diazoacetate, whereas the enantioselectivities were consistently high irrespective of the N-Boc imines employed (entries 1−6). Both 2- and 3-furaldehyde-derived N-Boc imines could be converted to α-diazo-$\beta$-amino phosphonates **13g** and **13h** with greater than 90% ee (entries 7 and 8).

To further extend the potential of this axially chiral dicarboxylic acid-catalyzed reaction, we then turned our attention to the use of tolyl (diazomethyl)sulfone **14** to give chiral $\beta$-amino sulfones,[18,19] in consideration of the attractive biological activities of the sulfonylated compounds[20] as well as the synthetic importance of sulfonyl groups acting as a key reactive functionality.[21] As anticipated, the reaction of tolyl (diazomethyl)sulfone **14** with benzaldehyde-derived N-Boc imine proceeded without difficulty, giving the corresponding $\beta$-amino sulfone **15a** in 70% yield with 92% ee (Table 4, entry 1). Due to the lower reactivity of (diazomethyl)sulfone compared to diazoacetate, the reaction of 2-tolualdehyde-derived N-Boc imine was too sluggish to provide the adduct (less than 10% yield). In other cases, this novel transformation had a broad generality, giving chiral $\beta$-amino sulfones with enantioselectivities ranging from 90% to 94% ee (entries 2−8).

As a unique synthetic application of chiral α-diazo-$\beta$-amino sulfone, we implemented oxidative cleavage of the diazo moiety of **15c** to the oxo group by ozonolysis (Scheme 3). Thus-formed acylsulfone **16** acted as a chiral α-aminoacyl donor and could be trapped with methanol in situ to give α-amino acid ester **17** in good yield without deteriorating the enantioselectivity. By comparison of the optical rotation of **17** with the literature, the absolute configuration of **15c** was confirmed to be (*R*).[22]

**Scheme 3. Application of α-Diazo-$\beta$-aminosulfone as Chiral α-Aminoacyl Donor**




**X-ray Crystallographic Analysis.** Our attention was then moved to elucidation of the catalyst structure by X-ray crystallographic analysis to prove the existence of the postulated internal hydrogen bonding between two carboxylic acids and get insight about the chiral environment into which N-Boc imines fit while one prochiral face is exposed.[23] To this end, we succeeded in obtaining the crystal of the 1:1 complex of (*R*)-**2e** and 4-pyrrolidinopyridine grown in dichloromethane and hexane (Figure 2).[24]

The distance of two inward oxygen atoms belonging to each carboxylic acid [O(3)···O(2)] was determined to be remarkably short, 2.480(4) Å, and that of one outward oxygen and Lewis basic nitrogen atom of 4-pyrrolidinopyridine [O(1)···N(1)] was 2.676(5) Å. In addition, one hydrogen atom derived from the carboxylic acid was actually found between two carboxylic acids, as located in difference Fourier maps and refined isotropically. These facts clearly indicated the existence of an intra- and intermolecular hydrogen bonds as anticipated in our catalyst design.[25] The bond order of the carboxylic acid acting as a hydrogen-bond donor for internal hydrogen bonding was normal, as the single-bond character localized on the inward C(25)−O(3) bond. On the other hand, another carboxylic acid sharing its hydrogen with 4-pyrrolidinopyridine was highly delocalized, and the partial double-bond character resides on the outward C(5)−O(1) bond. As a whole, the hydrogen-bonding network of this complex is described as the donation of hydrogen from one carboxylic acid to another carboxylate anion, which is conjugated with protonated pyridinium salt [$CO_2$−H···(O−C=O)$^-$ ···H−$N^+$]. Importantly, this internal hydrogen bonding makes

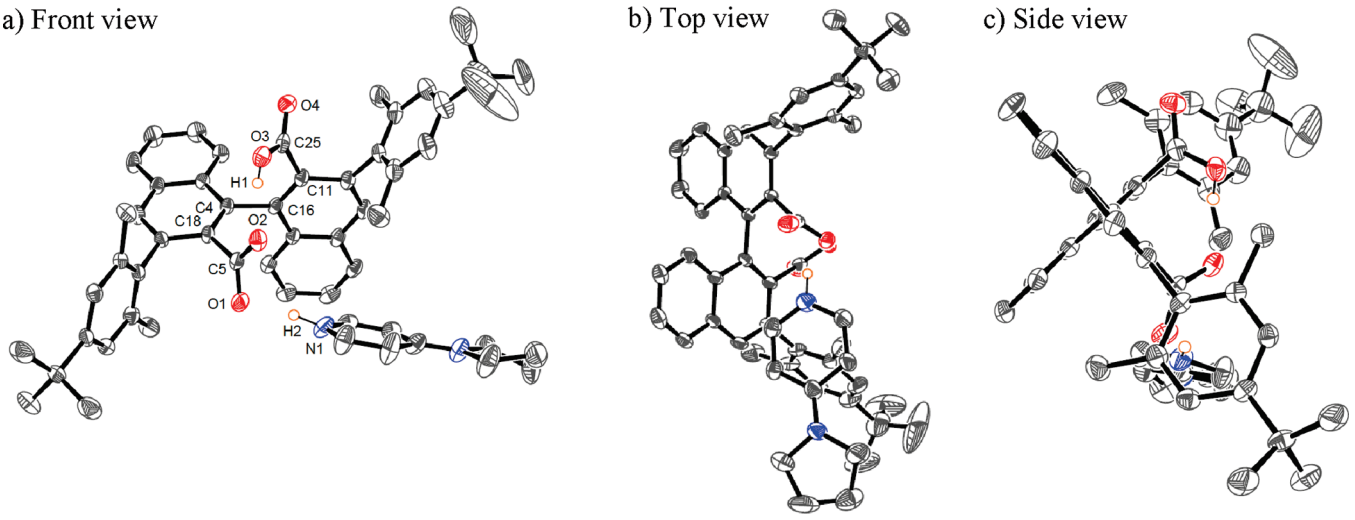



**Figure 2.** ORTEP diagrams of the 1:1 complex of (*R*)-**2e** and 4-pyrrolidinopyridine: (a) front view, (b) top view, and (c) side view. Hydrogen atoms, solvent, and disordered atoms are omitted for clarity. Selected bond lengths (in angstroms): C(5)−O(1) = 1.251(5), C(5)−O(2) = 1.273(5), C(25)−O(3) = 1.307(5), C(25)−O(4) = 1.221(5), O(3)···O(2) = 2.480(4), and O(1)···N(1) = 2.676(5).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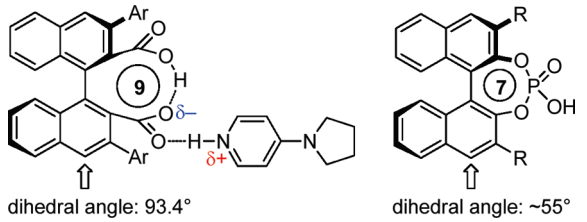


**Figure 3.** Comparison of dihedral angles between axially chiral dicarboxylic acid and BINOL-derived monophosphoric acid.

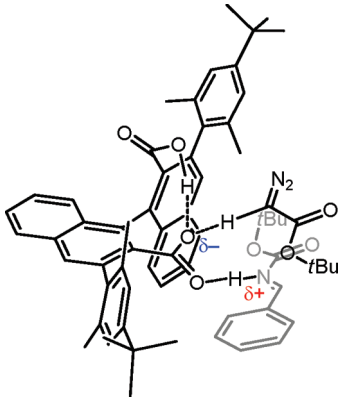


**Figure 4.** Plausible transition-state model of axially chiral dicarboxylic acid-catalyzed Mannich-type reaction of diazo compounds.

a large nine-membered ring in the catalyst, leading to significant broadening of the dihedral angle of the binaphthyl moiety to 93.4° [torsion angle of C(11)−C(16)−C(4)−C(18)] (Figure 3). This is in sharp contrast with BINOL-derived chiral monophosphoric acids having a rigid seven-membered ring with reported dihedral angles of around 55°,[26] thus underlining the distinctive chiral environment established by our axially chiral dicarboxylic acid.

From these observations, we delineated a plausible transition-state model of this Mannich-type reaction (Figure 4). N-Boc imines would coordinate to axially chiral dicarboxylic acid as 4-pyrrolidinopyridine did in crystal to give a reactive complex, while the steric bulk of 3,3′-aryl groups and the binaphthyl unit would harness the position of N-Boc imine by sterically preventing the formation of conformational isomers arising from the rotation of O···H−N hydrogen bond. Given the well-established fact in chiral phosphoric acid catalysis that phosphoric acid acts as a Brønsted acid/Lewis base bifunctional catalyst to activate electrophile and nucleophile simultaneously,[27] it is envisaged that nucleophilic diazo compound approaches from the side of the inward oxygen acting as a Lewis base while forming a hydrogen bond with the α-hydrogen of diazoacetate.

## CONCLUSIONS

In summary, we have developed axially chiral dicarboxylic acid as a new entry to chiral Brønsted acid catalysts and succeeded in evaluating its high catalytic performance and elucidating its unique structure. Highly enantioselective Mannich-type reaction between N-Boc imines and diazoacetate could be realized by use of axially chiral dicarboxylic acid having 4-(*tert*-butyl)-2,6-dimethylphenyl groups as 3,3′-substituents. As a notable feature of this catalysis, we extended this procedure to dimethyl (diazomethyl)phosphonate and tolyl (diazomethyl)sulfone, thus materializing a rare catalytic system giving β-amino esters, β-amino phosphonates, and β-amino sulfones under identical reaction conditions. X-ray crystallographic analysis of the catalyst complexed with a pyridine derivative confirmed the existence of internal hydrogen bonding between two carboxylic acid moieties and the wide dihedral angle of the binaphthyl unit, which are considered to be crucial for acquisition of sufficient reactivity and efficient chiral scaffold.

## EXPERIMENTAL SECTION

**General Information.** Infrared (IR) spectra were recorded on a Fourier transform infrared (FT-IR) spectrometer. $^1$H NMR spectra were measured at 400 MHz. Data were reported as follows: chemical shifts in parts per million (ppm) from tetramethylsilane as an internal standard, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double−doublet, m = multiplet, br = broad), coupling constants (in hertz), and assignment. $^{13}$C NMR spectra were measured at 100 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High-resolution mass spectra (HRMS) were performed on an electrospray ionization time-of-flight (ESI-TOF) mass spectrometer. Optical rotations were measured on a digital polarimeter. The products were purified by flash column chromatography on silica gel 60 (230−400 mesh). Dichloromethane was purchased from Kanto Chemical Co. Inc. as "dehydrated" and further purified by passing through neutral alumina under a nitrogen atmosphere. Spectral data for compounds (*R*)-**2a**−**2e**, **7a**−**7i**, **7k**, **13a**−**13e**, and **13g** were reported in our preliminary report.[4] Diazo compounds are potentially explosive and should be handled with care.[28]

**General Procedure for Axially Chiral Dicarboxylic Acid-Catalyzed Mannich-type Reaction of N-Boc Imines and Diazo Compounds.** The reaction flask containing powdered 4 Å molecular sieves (100 mg) was flame-dried under vacuum. To the flask were added (*R*)-**2e** (0.005 mmol, 3.3 mg), N-Boc imine (0.10 mmol), and dichloromethane (1.0 mL), and the solution was cooled to the temperature indicated in tables. Protection from light by aluminum foil was necessary in the reaction with tolyl (diazomethyl)sulfone. To the mixture was then added the corresponding diazo compound (0.15 mmol). After completion of the reaction, the solution was directly submitted to column chromatography on silica gel to give the corresponding product.

*tert-Butyl (R)-3-(tert-Butoxycarbonylamino)-2-diazo-3-[3,4-(methylenedioxy)phenyl]propanoate (**7j**).* Prepared according to the general procedure with (3,4-methylenedioxy)benzaldehyde N-Boc imine (0.10 mmol, 24.9 mg) and *tert*-butyl diazoacetate (0.15 mmol, 21.3 mg). The crude material was purified by column chromatography on silica gel (eluted with hexane/diethyl ether = 5:1) to give the title compound as a yellow amorphous solid [87% yield (34.1 mg), 92% ee]. Enantiomeric purity was determined by HPLC analysis [Daicel Chiralcel OD-H, hexane/2-propanol = 50:1, flow rate = 0.5 mL/min, retention time 16.1 min (minor) and 18.3 min (major)]. $^1$H NMR (400 MHz, $CDCl_3$) δ 6.83−6.76 (3H, m), 5.95 (2H, s), 5.52 (1H, d, *J* = 7.3 Hz), 5.30 (1H, br s), 1.451 (9H, s), 1.449 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.2, 154.8, 148.1, 147.2, 133.3, 108.3, 106.8, 101.2, 82.0, 80.2, 61.1, 51.1, 28.34, 28.29; IR (neat) 3358, 2978, 2091, 1690, 1489, 1368, 1246, 1163, 1040 cm$^{-1}$; HRMS (ESI) exact mass calcd for $C_{19}H_{25}N_3O_6$ *m*/*z* 414.1636 ([M + Na]$^+$), found *m*/*z* 414.1635 ([M + Na]$^+$); $[\alpha]_D^{27}$ = +22.1 (*c* = 1.0, $CHCl_3$, 92% ee).

*tert-Butyl (R)-3-(tert-Butoxycarbonylamino)-2-diazo-3-(3-furyl)-propanoate (**7l**).* Prepared according to the general procedure with 3-furaldehyde N-Boc imine (0.10 mmol, 19.5 mg) and *tert*-butyl diazoacetate (0.15 mmol, 21.3 mg). The crude material was purified by column chromatography on silica gel (eluted with hexane/diethyl ether = 5:1) to give the title compound as a yellow oil [77% yield


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(26.0 mg), 94% ee]. Enantiomeric purity was determined by HPLC analysis [Daicel Chiralpak AD-H, hexane/2-propanol = 50:1, flow rate = 0.5 mL/min, retention time 33.4 min (major) and 38.0 min (minor)]. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.39 (2H, m), 6.37 (1H, m), 5.51 (1H, d, $J$ = 8.0 Hz), 5.29 (1H, br s), 1.47 (9H, s), 1.46 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 165.1, 154.8, 143.7, 139.6, 124.7, 109.1, 81.9, 80.3, 60.7, 44.7, 28.34, 28.29; IR (neat) 3350, 2978, 2093, 1690, 1506, 1368, 1252, 1163 cm$^{-1}$; HRMS (ESI) exact mass calcd for $C_{16}H_{23}N_3O_5$ $m/z$ 360.1530 ([M + Na]$^+$), found $m/z$ 360.1533 ([M + Na]$^+$); $[\alpha]_D^{28}$ = +23.7 ($c$ = 1.0, $CHCl_3$, 94% ee).

*Dimethyl (R)-2-(tert-Butoxycarbonylamino)-1-diazo-2-[3,4-(methylenedioxy)phenyl]ethylphosphonate (**13f**).* Prepared according to the general procedure with (3,4-methylenedioxy)benzaldehyde N-Boc imine (0.10 mmol, 24.9 mg) and dimethyl (diazomethyl)phosphonate (0.15 mmol, 22.5 mg). The crude material was purified by column chromatography on silica gel (eluted with hexane/ethyl acetate = 1:1) to give the title compound as a yellow oil [64% yield (25.7 mg), 91% ee]. Enantiomeric purity was determined by HPLC analysis [Daicel Chiralcel OD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time 16.8 min (minor) and 20.0 min (major)]. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.86−6.78 (3H, m), 5.97 (2H, s), 5.37 (2H, br s), 3.76 [3H, d, $^2J(^1H, ^{31}P)$ = 11.8 Hz], 3.68 [3H, d, $^2J(^1H, ^{31}P)$ = 11.8 Hz], 1.45 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.6, 148.1, 147.4, 133.0 [d, $^3J(^{13}C, ^{31}P)$ = 3.3 Hz], 119.6, 108.4, 106.9, 101.3, 80.3, 53.1 [d, $^2J(^{13}C, ^{31}P)$ = 5.7 Hz], 51.8, 46.0 [d, $^1J(^{13}C, ^{31}P)$ = 229.4 Hz], 28.2; IR (neat) 3287, 2980, 2091, 1709, 1489, 1244, 1167, 1024 cm$^{-1}$; HRMS (ESI) exact mass calcd for $C_{16}H_{22}N_3O_7P$ $m/z$ 422.1088 ([M + Na]$^+$), found $m/z$ 422.1092 ([M + Na]$^+$); $[\alpha]_D^{26}$ = +55.7 ($c$ = 1.0, $CHCl_3$, 91% ee).

*Dimethyl (R)-2-(tert-Butoxycarbonylamino)-1-diazo-2-(3-furyl)-ethylphosphonate (**13h**).* Prepared according to the general procedure with 3-furaldehyde N-Boc imine (0.10 mmol, 19.5 mg) and dimethyl (diazomethyl)phosphonate (0.15 mmol, 22.5 mg). The crude material was purified by column chromatography on silica gel (eluted with hexane/ethyl acetate = 1:1) to give the title compound as a yellow oil [78% yield (27.1 mg), 91% ee]. Enantiomeric purity was determined by HPLC analysis [Daicel Chiralcel OJ-H, hexane/2-propanol = 20:1, flow rate = 0.5 mL/min, retention time 24.8 min (minor) and 30.7 min (major)]. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.45−7.41 (2H, m), 6.41 (1H, s), 5.40 (1H, m), 5.31 (1H, br s), 3.77 [3H, d, $^2J(^1H, ^{31}P)$ = 11.8 Hz], 3.73 [3H, d, $^2J(^1H, ^{31}P)$ = 11.6 Hz], 1.46 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.7, 143.9, 139.8, 124.4 [d, $^3J(^{13}C, ^{31}P)$ = 3.3 Hz], 109.0, 80.3, 53.1 [d, $^2J(^{13}C, ^{31}P)$ = 5.7 Hz], 53.0 [d, $^2J(^{13}C, ^{31}P)$ = 4.9 Hz], 45.5, 45.4 [d, $^1J(^{13}C, ^{31}P)$ = 230.2 Hz], 28.2; IR (neat) 3273, 2978, 2091, 1709, 1524, 1524, 1248, 1165, 1024 cm$^{-1}$; HRMS (ESI) exact mass calcd for $C_{13}H_{20}N_3O_6P$ $m/z$ 368.0982 ([M + Na]$^+$), found $m/z$ 368.0983 ([M + Na]$^+$); $[\alpha]_D^{23}$ = +67.1 ($c$ = 1.0, $CHCl_3$, 91% ee).

*Tolyl (R)-2-(tert-Butoxycarbonylamino)-1-diazo-2-phenylethylsulfone (**15a**).* Prepared according to the general procedure with benzaldehyde N-Boc imine (0.10 mmol, 20.5 mg) and tolyl (diazomethyl)sulfone (0.15 mmol, 29.4 mg). The crude material was purified by column chromatography on silica gel (eluted with toluene/EtOAc = 60:1) to give the title compound [70% (28.1 mg), 92% ee]. Enantiomeric purity was determined by HPLC analysis [Daicel Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time 43.1 min (minor), 48.6 min (major)]. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.57 (2H, d, $J$ = 8.4 Hz), 7.29−7.21 (5H, m), 7.18 (2H, m), 5.73 (1H, d, $J$ = 6.8 Hz), 5.35 (1H, br s), 2.41 (3H, s), 1.40 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.5, 144.2, 139.9, 136.9, 129.8, 128.8, 128.2, 126.8, 126.1, 80.5, 70.9, 51.9, 28.2, 21.5; IR (neat) 2085, 1711, 1597, 1495, 1452, 1367, 1325, 1238, 1145, 1088 cm$^{-1}$; HRMS (ESI) exact mass calcd for $C_{20}H_{23}N_3O_4S$ $m/z$ 424.1301 ([M + Na]$^+$), found $m/z$ 424.1301 ([M + Na]$^+$); $[\alpha]_D^{30}$ = +9.7 ($c$ = 1.0, $CHCl_3$, 92% ee).

*Tolyl (R)-2-(tert-Butoxycarbonylamino)-1-diazo-2-(3-tolyl)ethylsulfone (**15b**).* Prepared according to the general procedure with 3-tolualdehyde N-Boc imine (0.10 mmol, 21.9 mg) and tolyl (diazomethyl)sulfone (0.15 mmol, 29.4 mg). The crude material was purified by column chromatography on silica gel (eluted with toluene/EtOAc = 60:1) to give the title compound [60% (25.1 mg), 90% ee]. Enantiomeric purity was determined by HPLC analysis [Daicel Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time 35.0 min (minor), 40.0 min (major)]. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.55 (2H, d, $J$ = 8.4 Hz), 7.23 (2H, d, $J$ = 8.4 Hz), 7.16 (1H, dd, $J$ = 8.0, 7.6 Hz), 7.04 (1H, d, $J$ = 7.6 Hz), 6.98 (1H, d, $J$ = 8.0 Hz), 6.90 (1H, s), 5.70 (1H, d, $J$ = 8.0 Hz), 5.30 (1H, br s), 2.42 (3H, s), 2.23 (3H, s), 1.41 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.5, 144.1, 140.0, 138.6, 136.8, 129.7, 128.9, 128.8, 126.9, 126.8, 123.2, 80.5, 70.9, 52.0, 28.2, 21.6, 21.3; IR (neat) 2085, 1710, 1495, 1367, 1327, 1244, 1147, 1088 cm$^{-1}$; HRMS (ESI) exact mass calcd for $C_{21}H_{25}N_3O_4S$ $m/z$ 438.1458 ([M + Na]$^+$), found $m/z$ 438.1461 ([M + Na]$^+$); $[\alpha]_D^{29}$ = +19.0 ($c$ = 1.0, $CHCl_3$, 90% ee).

*Tolyl (R)-2-(tert-Butoxycarbonylamino)-1-diazo-2-(4-tolyl)ethylsulfone (**15c**).* Prepared according to the general procedure with 4-tolualdehyde N-Boc imine (0.10 mmol, 21.9 mg) and tolyl (diazomethyl)sulfone (0.15 mmol, 29.4 mg). The crude material was purified by column chromatography on silica gel (eluted with toluene/EtOAc = 60:1) to give the title compound [61% (25.4 mg), 94% ee]. Enantiomeric purity was determined by HPLC analysis [Daicel Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time 34.1 min (minor), 40.9 min (major)]. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59 (2H, d, $J$ = 8.0 Hz), 7.24 (2H, d, $J$ = 8.0 Hz), 7.07−7.03 (4H, m), 5.69 (1H, d, $J$ = 8.0 Hz), 5.29 (1H, br s), 2.42 (3H, s), 2.30 (3H, s), 1.40 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.5, 144.1, 139.9, 138.0, 134.0, 129.7, 129.5, 126.8, 126.0, 80.4, 70.9, 51.8, 28.2, 21.6, 21.0; IR (neat) 2085, 1711, 1510, 1327, 1165, 1149, 1087 cm$^{-1}$; HRMS (ESI) exact mass calcd for $C_{21}H_{25}N_3O_4S$ $m/z$ 438.1458 ([M + Na]$^+$), found $m/z$ 438.1462 ([M + Na]$^+$); $[\alpha]_D^{28}$ = +28.9 ($c$ = 1.0, $CHCl_3$, 94% ee).

*Tolyl (R)-2-(tert-Butoxycarbonylamino)-1-diazo-2-(2-naphthyl)ethylsulfone (**15d**).* Prepared according to the general procedure with 2-naphthaldehyde N-Boc imine (0.10 mmol, 25.5 mg) and tolyl (diazomethyl)sulfone (0.15 mmol, 29.4 mg). The crude material was purified by column chromatography on silica gel (eluted with toluene/EtOAc = 50:1) to give the title compound [77% (34.6 mg), 93% ee]. Enantiomeric purity was determined by HPLC analysis [Daicel Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 1.0 mL/min, retention time 20.0 min (minor), 24.7 min (major)]. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.76 (1H, m), 7.72−7.68 (2H, m), 7.61 (1H, s), 7.52−7.44 (4H, m), 7.18 (1H, dd, $J$ = 8.8, 1.6 Hz), 7.06 (2H, d, $J$ = 8.0 Hz), 5.91 (1H, d, $J$ = 6.8 Hz), 5.54 (1H, br s), 2.32 (3H, s), 1.43 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.6, 144.1, 139.8, 134.1, 133.0, 132.9, 129.6, 128.8, 128.0, 127.5, 126.7, 126.44, 126.42, 125.2, 123.9, 80.6, 70.8, 52.2, 28.2, 21.4; IR (neat) 2360, 2340, 2083, 1710, 1495, 1368, 1323, 1306, 1244, 1146 cm$^{-1}$; HRMS (ESI) exact mass calcd for $C_{24}H_{25}N_3O_4S$ $m/z$ 474.1458 ([M + Na]$^+$), found $m/z$ 474.1463 ([M + Na]$^+$); $[\alpha]_D^{31}$ = +26.2 ($c$ = 1.0, $CHCl_3$, 93% ee).

*Tolyl (R)-2-(tert-Butoxycarbonylamino)-1-diazo-2-(4-chlorophenyl)ethylsulfone (**15e**).* Prepared according to the general procedure with 4-chlorobenzaldehyde N-Boc imine (0.10 mmol, 24.0 mg) and tolyl (diazomethyl)sulfone (0.15 mmol, 29.4 mg). The crude material was purified by column chromatography on silica gel (eluted with toluene/EtOAc = 60:1) to give the title compound [60% (25.3 mg), 90% ee]. Enantiomeric purity was determined by HPLC analysis [Daicel Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time 29.7 min (minor), 35.8 min (major)]. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.53 (2H, d, $J$ = 8.4 Hz), 7.27−7.15 (4H, m), 7.09 (2H, d, $J$ = 8.4 Hz), 5.70 (1H, d, $J$ = 8.0 Hz), 5.40 (1H, br s), 2.43 (3H, s), 1.41 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.5, 144.4, 139.8, 135.5, 134.1, 129.8, 128.9, 127.6, 126.7, 80.7, 70.6, 51.7, 28.2, 21.6; IR (neat) 2360, 2340, 2085, 1710, 1595, 1490, 1454, 1393, 1367, 1325, 1242, 1147 cm$^{-1}$; HRMS (ESI) exact mass calcd for $C_{20}H_{22}ClN_3O_4S$ $m/z$

458.0912 ([M + Na]$^+$), found $m/z$ 458.0919 ([M + Na]$^+$); $[\alpha]_D^{30}$ = +11.9 ($c$ = 1.0, $CHCl_3$, 90% ee).

*Tolyl (R)-2-(tert-Butoxycarbonylamino)-1-diazo-2-(4-methoxyphenyl)ethylsulfone (**15f**).* Prepared according to the general procedure with 4-methoxybenzaldehyde N-Boc imine (0.10 mmol, 23.5 mg) and tolyl (diazomethyl)sulfone (0.15 mmol, 29.4 mg). The crude material was purified by column chromatography on silica gel (eluted with toluene/EtOAc = 60:1) to give the title compound [71% (30.8 mg), 95% ee]. Enantiomeric purity was determined by HPLC analysis [Daicel Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time 54.1 min (minor), 65.1 min (major)]. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.58 (2H, d, $J$ = 8.4 Hz), 7.24 (2H, d, $J$ = 8.4 Hz), 7.08 (2H, d, $J$ = 8.8 Hz), 6.78 (2H, m), 5.67 (1H, d, $J$ = 7.6 Hz), 5.28 (1H, br s), 3.77 (3H, s), 2.42 (3H, s), 1.40 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.4, 154.5, 144.1, 140.0, 129.8, 129.0, 127.4, 126.8, 114.2, 80.4, 71.0, 55.2, 51.5, 28.2, 21.6; IR (neat) 2083, 1710, 1610, 1510, 1325, 1247, 1145, 1085, 812 cm$^{-1}$; HRMS (ESI) exact mass calcd for $C_{21}H_{25}N_3O_5S$ $m/z$ 454.1407 ([M + Na]$^+$), found $m/z$ 454.1411 ([M + Na]$^+$); $[\alpha]_D^{30}$ = +17.2 ($c$ = 1.0, $CHCl_3$, 95% ee).

*Tolyl (R)-2-(tert-Butoxycarbonylamino)-1-diazo-2-[3,4-(methylenedioxy)phenyl]ethylsulfone (**15g**).* Prepared according to the general procedure with 3,4-(methylenedioxy)benzaldehyde N-Boc imine (0.10 mmol, 24.9 mg) and tolyl (diazomethyl)sulfone (0.15 mmol, 29.4 mg). The crude material was purified by column chromatography on silica gel (eluted with toluene/EtOAc = 50:1) to give the title compound [54% (23.9 mg), 94% ee]. Enantiomeric purity was determined by HPLC analysis [Daicel Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time 62.7 min (minor), 92.2 min (major)]. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.60 (2H, d, $J$ = 8.4 Hz), 7.26 (2H, d, $J$ = 8.4 Hz), 6.70−6.64 (2H, m), 6.59 (1H, d, $J$ = 1.6 Hz), 5.92 (2H, m), 5.62 (1H, d, $J$ = 8.0 Hz), 5.28 (1H, br s), 2.43 (3H, s), 1.41 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.4, 148.1, 147.5, 144.2, 139.8, 130.9, 129.8, 126.8, 119.6, 108.3, 106.7, 101.3, 80.6, 70.9, 51.8, 28.2, 21.5; IR (neat) 2083, 1711, 1503, 1487, 1323, 1238, 1148 cm$^{-1}$; HRMS (ESI) exact mass calcd for $C_{21}H_{23}N_3O_6S$ $m/z$ 468.1200 ([M + Na]$^+$), found $m/z$ 468.1182 ([M + Na]$^+$); $[\alpha]_D^{29}$ = +27.4 ($c$ = 1.0, $CHCl_3$, 94% ee).

*Tolyl (R)-2-(tert-Butoxycarbonylamino)-1-diazo-2-(2-furyl)ethylsulfone (**15h**).* Prepared according to the general procedure with 2-furaldehyde N-Boc imine (0.10 mmol, 19.5 mg) and tolyl (diazomethyl)sulfone (0.15 mmol, 29.4 mg). The crude material was purified by column chromatography on silica gel (eluted with toluene/EtOAc = 60:1) to give the title compound [80% (31.2 mg), 90% ee]. Enantiomeric purity was determined by HPLC analysis [Daicel Chiralpak AD-H, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, retention time 42.3 min (major), 51.1 min (minor)]. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59 (2H, d, $J$ = 8.4 Hz), 7.25 (2H, d, $J$ = 8.4 Hz), 7.17 (1H, m), 6.28−6.24 (2H, m), 5.77 (1H, d, $J$ = 6.8 Hz), 5.44 (1H, br s), 2.41 (3H, s), 1.41 (9H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 154.3, 149.5, 144.1, 142.6, 139.9, 129.7, 126.7, 110.4, 107.8, 80.7, 69.5, 47.1, 28.1, 21.5; IR (neat) 2085, 1714, 1597 1497, 1454, 1368, 1327, 1306, 1233, 1148 cm$^{-1}$; HRMS (ESI) exact mass calcd for $C_{18}H_{21}N_3O_5S$ $m/z$ 414.1094 ([M + Na]$^+$), found $m/z$ 414.1096 ([M + Na]$^+$); $[\alpha]_D^{30}$ = −20.2 ($c$ = 1.0, $CHCl_3$, 90% ee).

**Preparation of (*R*)-Methyl 2-(*tert*-Butoxycarbonylamino)-2-(4-tolyl)acetate (17).** Ozone was bubbled through the solution of tolyl (*R*)-2-(*tert*-butoxycarbonylamino)-1-diazo-2-(4-tolyl)ethylsulfone **15c** (0.046 mmol, 19.2 mg) and $NaHCO_3$ (0.23 mmol, 19.4 mg) in $CH_2Cl_2$/MeOH (1.2 mL, v/v = 5:1) at −78 °C for 1 h. After addition of excess $Me_2S$, the mixture was allowed to warm to room temperature, treated with saturated $NH_4Cl$, and extracted with $CH_2Cl_2$. The combined organic layers were washed with brine, dried over $Na_2SO_4$, and concentrated under vacuum. The residue was then purified by column chromatography on silica gel (eluted with hexane/ethyl acetate = 5:1) to give the title compound [82% yield (10.5 mg), 94% ee]. Enantiomeric purity was determined by HPLC analysis [Daicel Chiralcel OJ-H, hexane/ethanol = 200:1, flow rate = 0.5 mL/min, retention time 25.7 min (minor), 30.9 min (major)]. $[\alpha]_D^{29}$ = −122.2 ($c$ = 1.0, $CHCl_3$, 94% ee). Absolute configuration of the title compound was determined by the comparison of its optical rotation with the same compound reported in the literature.[22]

## ■ ASSOCIATED CONTENT

**Ⓢ Supporting Information.** $^1$H and $^{13}$C NMR for all new compounds (PDF) and crystallographic information for the complex of (*R*)-**2e** and 4-pyrrolidinopyridine (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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