Published in final edited form as:

Org Biomol Chem. 2017 February 21; 15(7): 1718–1724. doi:10.1039/c6ob02801b.

Chiral GAP catalysts of phosphonylated imidazolidinones and their applications in asymmetrical Diels-Alder and Friedel-Craft reactions

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Abstract

The design and synthesis of recyclable imidazolidinone catalysts using GAP chemistry/technique was described. Their applications in asymmetric Diels-Alder and Friedel-Craft reactions with α,β -unsaturated aldehydes resulted in excellent yields and higher enantioselectivities than previous processes. As recyclable small molecular catalysts, the phosphonylated imidazolidinones can be recovered and reused for up to three runs without costing significant decrease in catalytic activity.

Graphical abstract

Chiral recoverable/re-usable GAP catalysts based on phosphonylated imidazolidinones have been designed, synthesized and applied for asymmetrical Diels-Alder and Friedel-Craft reactions.

Introduction

Among the most attractive and appealing synthetic strategies, organocatalysis has drawn a special attention due to its characteristics of foreseeable non-toxicity, invulnerability to moisture/air, convenience and less expense for modification and synthesis.¹ However, most of these successful applications showed higher catalyst loadings than corresponding transition metal catalytic systems besides the difficulty in catalyst separation.² Thus, these

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Electronic Supplementary Information (ESI) available. [details of any supplementary information available should be included here].
See DOI: 10.1039/x0xx00000x

drawbacks weaken the merits of organocatalyst and limit the application scope of organocatalysis for chemical and pharmaceutical industry. In view of this practical limit, the development of organocatalysts that can be recovered and recycled after reaction is highly desired but full of challenging task.³ Notably, MacMillan's group reported pioneering work on chiral imidazolidinone catalysts (Type I, Figure 1) depending on the iminium activation model,⁴ which has been proved to be an efficient organocatalyst in various asymmetrical reactions.⁵ Later on, several groups have contributed in this field using polymer-supported (Type II)^{6,7} or ionic-liquid immobilized (Type III) chiral imidazolidinone scaffold.⁸ However, in addition to complicated route for imidazolidinone preparation, these known catalysts may still suffer from either non-recovery or complex recovery process, thereby limiting their flexible potential.

Over the past few years, our group found when phosphonyl and phosphinyl groups were introduced into starting materials, the solubility of the desired products can be adjusted in various solvents, and their purification can be achieved simply by washing with combinational solvents of hexane and ethyl acetate. Based on these practical significant observations, we proposed the concept of group-assisted purification (GAP) chemistry so as to encourage synthetic community to perform synthesis by avoiding traditional purification methods such as chromatography and/or recrystallization.⁹ In our continuous effort on the GAP chemistry, we decided to install phosphonyl groups on the chiral imidazolidinone framework (Type IV and Type V) to explore their catalytic activities and the feasibility of recovery potential for asymmetric reactions such as Diels-Alder and Field-Craft reactions. After several attempts, we were pleased to find that the preformed diphenylphosphoryl (DPP) imidazolidinone (Type IV) showed high catalytic performance and can be recycled and recovered three times without loss of catalytic activity. Note that this is first example of small neutral and recoverable catalysts, which would find broad applications in asymmetrical synthesis based on the fact that the GAP catalysts can improve not only transformation efficiency and enantioselectivity but also lower production costs. Herein, we would like to report our preliminary results of this project.

Results and discussion

In an initial effort on installing phosphonyl group on the phenyl ring of imidazolidinone skeleton (MacMillan's catalyst), we designed two different synthetic pathways for their preparation with the use of diphenylphosphoryl (DPP) and 2-oxido-1,3-bis(1-naphthalenylmethyl)-1,3,2-diazaphospholidin-2-yl (DNP, 1-naphthalenyl (1-Np)) groups as GAP auxiliary functionality (Scheme 1). As shown in Scheme 1, the synthesis of imidazolidinone catalysts **1a–b** involved multiple steps consisted of nitration, amination, and cyclization as well as phosphinic amide formation using commercial available L-phenylalanine as starting materials (route *i*) whereas imidazolidinone catalysts **1c–d** were generated *via* an amidization/de-protection/ cyclization sequence (route *ii*). Notably, during the synthesis of catalysts **1a–b**, the last step did not require protection of the dialkyl amine group due to its bulky effect. Generally, these multi-step pathways toward catalysts **1** enable high conversion in almost each step except for the last step. Specifically, the pure catalyst **1a** could be obtained by washing with hexane/ether system in the last step without any column chromatography, which corresponds to the definition of our GAP chemistry. However, the

other types of catalysts (**1b–d**) require column chromatography at the final stage of their synthesis.

After the successful synthesis of catalysts, we set out to evaluate their catalytic capability and the recovery application in asymmetric Diels-Alder cycloaddition between cinnamaldehyde (**2a**) and cyclopentadiene (**3**), following the original protocol by MacMillan's group.¹⁰ The Diels-Alder reaction was conducted at room temperature for 24 h with loading of 20 mol % catalyst and acid as additive (Table 1), searching for the optimized conditions. As shown in Table 1, when HCl was used as an acid co-catalyst (Table 1, entry 1), the reaction employing catalyst **1a** proceeded readily to give the desired product **4a** with 90% *endo* ee and 84% yield, along with the maintenance of the catalyst recovery of 77%. The use of catalyst **1b** led to 92% *endo* ee and 77% yield, but lowered catalyst recovery (51%, entry 2). The latter two catalysts **1c–d** gave inferior outcomes with regard to enantioselectivity and yield of product **4a**, especially the recovery of these both catalysts. Next, five types of protic acids, including TfOH, (*D*)-10-camphorsulfonic acid (CSA), HBF₄, and trifluoroacetic acid (TFA), were investigated as the reaction co-catalysts by using catalyst **1a** (Table 1, entry 1 vs entries 5–8). In comparison to HCl, it was found that better yields and enantioselectivities were obtained when CSA, TfOH and TFA behaved as reaction co-catalysts whereas the use of HBF₄ completely suppressed the reaction process. Among all the acids screened, TFA was proven to be the most efficient one, delivering 98% *endo* ee and 98% yield of product **4a** under the reaction conditions (entry 8) with 92% catalyst recovery. Therefore, TFA was selected as a reaction co-catalyst in further transformations.

Next, the synthetic utility of this asymmetrical Diels-Alder reaction was investigated by the adoption of four examples of representative α,β -unsaturated aldehydes **2b–e** as the reaction partners. As described in Table 2, α,β -unsaturated aldehydes bearing both electron-donating (methoxy **2b** and methyl **2c**) and electron-withdrawing (nitro **2d**, **2e**) groups effectively underwent the Diels-Alder reaction with cyclopentadiene in the presence of phosphonylated imidazolidinone catalyst **1a** and acid co-catalyst TFA in MeOH-H₂O at 23 °C. The target bridged cyclic products **4b–e** were provided in good to excellent yields with excellent *endo* ee. Notably, in all cases, high catalyst recovery (87%–98%) was conducted without loss of catalytic activity.

With the success of the above reactions, we then explored the recyclability of chiral phosphonylated imidazolidinone catalyst **1a** in Diels-Alder reaction. As illustrated in Table 3, after reaction the remaining imidazolidinone catalyst **1a** was recovered and recycled in subsequent reactions with only a slight decrease in catalytic activity being observed. For instance, the recycling procedure involving cinnamaldehyde and cyclopentadiene was found to provide the product **4a** in 98% yield, 98% *endo* ee, 92% catalyst recovery (1st run), 97% yield, 96% *endo* ee, 90% catalyst recovery (2nd run), 98% yield, 95% *endo* ee, 95% catalyst recovery (3rd run).

To broaden the application of the preformed chiral GAP phosphonylated imidazolidinone catalyst, the Friedel-Craft alkylation of pyrrole was also studied under the previously reported conditions.¹¹ The reactions worked well to access the target products **6a–e** in 77%–

96% yields and 77%–99% ee determined by the corresponding alcohols through reduction (Table 4). Among them, Pr-substituted counterpart **2g** was converted into the corresponding product **6g** with 90% yield and 99% ee (Table 3, entry 5). The purification and recovery of the phosphonylated catalyst is different from the above Diels-Alder cycloaddition due to the target product containing nitrogen will be extracted along with the catalyst to the water phase. Nevertheless, the products **6** could be isolated from the catalyst when non-polar solvent was applied after neutralization. In addition, the first recovered catalyst **1a** could showed a highly catalytic activity in the Friedel-Craft alkylation, giving 88% ee of product **6a**.

Conclusions

In conclusion, we have designed and synthesized chiral GAP catalysts of phosphonylated imidazolidinones and applied to two asymmetric reactions. We found the GAP catalyst **1a** showed a highly catalytic activity in enantioselective Diels-Alder and Friedel-Craft reactions. Most importantly, the recovery and recycling of the phosphonylated imidazolidinone catalyst **1a** in further operations were successfully realized and the catalyst can be reused for at least three runs without significant dropping in both chemical yields and enantioselectivity. We believed that the present chiral GAP catalysts with easy recycling for re-usable characteristics would find great synthetic potential in asymmetric field. Further study on design and applications of new GAP catalysts for more asymmetric transformations is under study in our laboratory.

Experiment

General Information

All commercially available chemicals were used as received without further purification. Flash chromatography was carried out using flash grade silica gel. Subsequent to elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-24061/F 254 nm. All reactions were carried out in flame dried flask under nitrogen atmosphere. The ¹H and ¹³C NMR spectra were recorded in CDCl₃ on a 400 MHz instrument with TMS as internal standard. Chemical shifts (δ) were reported in ppm with respect to TMS. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant (J, Hz) and integration. ³¹P NMR spectra were referenced to external H₃PO₄ (0.00 ppm). HRMS analyses were carried out using a TOF-MS instrument with an ESI source. For HPLC analysis of the enantioselectivity of the products, the corresponding racemic compounds were synthesized by using pyroline as catalyst in THF.

1. General Procedure for the Synthesis of Catalyst **1a**

1.1 Synthesis of (L)-p-Nitrophenylalanine (1–1): L-Phenylalanine (20.0 g, 0.12 mol) was dissolved in 96% sulfuric acid (50 mL) with vigorous stirring at 10 °C and concentrated nitric acid (6 mL) was added over a period of 35 min with vigorous stirring at 0–5 °C; the reaction mixture was then stirred for an additional 1 h. The reaction mixture was poured on 200 mL of ice cold water and neutralized with 30% ammonium hydroxide. During neutralization precipitation started; the reaction mixture was kept at room temperature for 45

min and then filtered to separate out the precipitate. The precipitate was washed with water until the washings were neutral to litmus. The solid product was recrystallized from hot water to yield (L)-*p*-nitrophenylalanine as white solid (22.4g, 88%).¹⁰

1.2 Synthesis of (S)-2-amino-N-methyl-3-(4-nitrophenyl)propan amide (1–2): A solution of (L)-*p*-Nitrophenylalanine (20.0 g, 95.5 mmol) in dry methanol (200 mL) under argon atmosphere was cooled to 0 °C and thionyl chloride (38.8 mL, 285 mmol) was added dropwise through an addition funnel. After the addition was complete, the cooling bath was removed and stirring was continued at room temperature overnight. The reaction mixture was concentrated under vacuum and the solid residue was stirred with acetone (2 × 150 mL) for one hour. Then it was concentrated in vacuum, and the process was repeated (dissolve in acetone, stir for 1 hour and evaporate). The solid was filtered off and washed with acetone (3 × 100 mL). The separated solid was dried under vacuum to afford (L)-*p*-Nitrophenylalanine methyl ester hydrochloride as a yellow solid. This above solid was treated with methylamine (60 mL, 60 %) and the resulting mixture was stirred at room temperature for 24 hours. After extracted with dichloromethane, the excess methylamine was removed by concentration in vacuo overnight and the product was directly used for the next step without further purification. (91%, 19 g) ¹H NMR (400 MHz, CDCl₃): δ 8.10 (d, *J* = 16.4 Hz, 2H), 7.38 (d, *J* = 16.4 Hz, 2H), 7.20 (s, 1H NH), 3.60 (t, *J* = 16.4 Hz, 1H), 3.31 (d, *J* = 4 Hz, 1H), 2.92–2.89 (m, 1H), 2.78 (d, *J* = 5.6 Hz, 3H), 1.23 (s, 2H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 173.9, 147.1, 145.9, 130.2, 130.1, 123.9, 123.8, 56.2, 40.9, 25.9 ppm

1.3 Synthesis of (S)-2,2,3-trimethyl-5-(4-nitrobenzyl)imidazolidin-4-one (1–3): (S)-2-amino-N-methyl-3-(4-nitrophenyl)propanamide (1–2) (10 g, 44.8 mmol) was dissolved in acetone (60 mL) followed by adding PTSA (2 mmol, 0.46 g). The reaction mixture was stirred under refluxing for overnight. After reaction, the solvent was removed under vacuo and the residue was dissolved in CH₂Cl₂, washed with saturated NaHCO₃ and brine, and dried over MgSO₄. After removal of organic solvent under vacuo, the product was directly used for the next step without further purification. (98%, 11 g) ¹H NMR (400 MHz, CDCl₃): δ 8.13 (d, *J* = 9.2 Hz, 2H), 7.42 (d, *J* = 9.2 Hz, 2H), 3.83 (t, *J* = 3.6 Hz, 1H), 3.22 (d, *J* = 4 Hz, 1H), 2.97–2.95 (m, 1H), 2.73 (s, 3H), 1.32 (s, 3H), 1.21 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 172.4, 146.9, 145.8, 130.5, 130.4, 123.6, 123.5, 75.7, 59.1, 38.1, 27.8, 25.5, 25.3 ppm

1.4 Synthesis of (S)-5-(4-aminobenzyl)-2,2,3-trimethylimidazolidin-4-one (1–4): (S)-2,2,3-trimethyl-5-(4-nitrobenzyl)imidazolidin-4-one (1–3) (11 g, 40.8 mmol) was dissolved in methanol (50ml), followed by adding Pd/C (0.5g, 10%) and purged with H₂ three times, this mixture was stirred at room temperature for 24 h. The resulting mixture was filter through celite, and condensed to dryness as a colorless oil (96%, 9.5 g) for next step. ¹H NMR (400 MHz, CDCl₃): δ 6.95 (d, *J* = 20.0 Hz, 2H), 6.59 (d, *J* = 20.0 Hz, 2H), 3.68 (s, 1H), 2.94 (d, *J* = 8.0 Hz, 2H), 2.66 (s, 3H), 1.21 (s, 3H), 1.18 (s, 3H), ppm. ¹³C NMR (100 MHz, CDCl₃): δ 173.7, 145.2, 130.5, 130.4, 126.5, 115.4, 115.3, 75.5, 59.4, 35.9, 27.1, 25.3, 25.2 ppm.

1.5 Synthesis of (S)-P,P-diphenyl-N-(4-((1,2,2-trimethyl-5-oxoimidazolidin-4-yl)methyl)phenyl)phosphinic amide **1a:** A solution of (S)-5-(4-aminobenzyl)-2,2,3-trimethylimidazolidin-4-one (**1-4**) (9 g, 38 mmol) and triethyl amine (16 ml, 115 mmol) in dry CH₂Cl₂ (200 mL) under argon atmosphere was cooled to 0 °C, diphenyl phosphorite chloride (11 g, 46 mmol) was added dropwise through an addition funnel, and was stirred at room temperature for 72 h. The resulting solution was condensed to dryness after washed with H₂O twice and brine. The residue was added hexane and ether slurry until the product precipitated as white solid; the solid was collected as the title catalyst **1a**. (15.2 g, 68% overall yield) ³¹P NMR (CDCl₃ 162 MHz): δ 18.7 ¹H NMR (400 MHz, CDCl₃): δ 7.88-7.83 (m, 4H), 7.45-7.43 (m, 2H), 7.43-7.41 (m, 4H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8 Hz 2H), 5.26 (s, 1H), 3.68 (t, *J* = 5.2 Hz, 1H), 2.94 (d, *J* = 10.4 Hz, 2H), 2.70 (s, 3H), 1.21 (s, 3H), 1.11 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 173.4, 139.1, 132.5, 132.4, 132.3, 132.0, 131.9, 131.8, 131.7, 131.6, 131.3, 130.5, 130.4, 130.2, 128.9, 128.8, 118.8, 118.7, 75.5, 59.1, 36.0, 27.2, 25.3, 25.2 ppm. HRMS (TOF ES+) *m/z* calcd for C₂₅H₂₉N₃O₂P [(M + H)⁺], 434.1992; found, 434.1983.

2. Diels-Alder Reaction (Table 2)—The cinnamaldehydes (1.0 mmol) and pentadiene (0.36 ml, 5 mmol) were added sequentially to the catalyst **1a** (85 mg, 0.2 mmol, 20 mol %) and TFA (15 μL, 20 mol %) in the methanol (2 mL) and water (0.2 ml). After 12 h, the mixture was diluted with Et₂O and washed with H₂O and brine. The organic phases were dried (Na₂SO₄), concentrated, and then purified by flash chromatography. The enantioselectivity was determined by the corresponding alcoholic product after reduction with NaBH₄ (83 mg, 2.2 mmol). To recycle the catalyst **1a**, the resulting reaction mixture was extracted with HCl (1 M), and aqueous phase was added saturated NaHCO₃, and extracted with dichloromethane. The organic phase was condensed to dryness and treated with ether/hexane to get the cycled catalyst **1a** as white solid after filtration. The reaction was repeated three times using recycled catalyst **1a** as catalyst. The solid catalyst was used directly for the next run.

(1R,2S,3S,4S)-3-phenylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde and (1S,2S,3S,4R)-3-phenylbicyclo[2.2.1]hept-5-ene-2-carbaldehyde (4a**, Table 2, entry 1):** Pale yellow liquid, 190 mg, 98 % yield; ¹H NMR (400 MHz, CDCl₃): (endo isomer) δ 9.92 (d, *J* = 2.4 Hz, 1H), 7.29-7.16 (m, 5H), 6.33 (d, *J* = 2.8 Hz, 1H), 6.06 (d, *J* = 2.8 Hz, 1H), 3.74 (t, *J* = 4 Hz, 1H), 3.22 (t, *J* = 1.2 Hz, 1H), 3.10 (d, *J* = 2 Hz, 1H), 2.61 (t, *J* = 5.2 Hz, 1H), 1.64-1.55 (m, 2H) ppm. ¹³C NMR (100 MHz, CDCl₃): (endo isomer) δ 203.5, 143.6, 142.6, 139.3, 136.6, 133.9, 128.2, 127.4, 126.3, 59.5, 48.5, 48.1, 47.6, 45.7 ppm. Enantiomeric ratio was determined by HPLC using Chiracel IC column (× 2) after reduction with NaBH₄/MeOH (1:99 i-PrOH/hexane, 1 mL/min flow rate), endo isomers *t_r* = 87.9 min (minor enantiomer) and 116.2 min (major enantiomer) ee = 98%; exo isomers *t_r* = 73.1 min (minor enantiomer) and 103.6 min (major enantiomer) ee = 99%.

(1R,2S,3S,4S)-3-(4-Methoxyphenyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and (1S,2S,3S,4R)-3-(4-methoxyphenyl)bicycle [2.2.1]hept-5-ene-2-carbaldehyde (4b**, Table 2, entry 2):** Pale yellow liquid, 184 mg, 81 % yield; ¹H NMR (400 MHz, CDCl₃): (endo isomer) δ 9.89 (d, *J* = 2.4 Hz, 1H), 7.18-6.79 (m, 4H), 6.31 (d, *J* = 2.8 Hz, 1H), 6.04 (d, *J* =

2.8 Hz, 1H), 3.77 (s, 3H), 3.64 (t, J = 3.6 Hz, 1H), 3.18 (d, J = 1.6 Hz, 2H), 2.52-2.51 (m, 1H), 1.57-1.54 (m, 2H) ppm. ^{13}C NMR (100 MHz, CDCl_3): (endo isomer) δ 203.8, 158.1, 139.3, 136.6, 136.3, 128.8, 128.3, 114.1, 113.6, 61.1, 59.7, 55.4, 48.6, 47.1, 45.1 ppm. Enantiomeric ratio was determined by HPLC using Chiracel IC column after reduction with $\text{NaBH}_4/\text{MeOH}$ (1:99 i-PrOH/hexane, 1 mL/min flow rate), endo isomers t_r = 34.7 min (major enantiomer) and 36.3 min (minor enantiomer) ee = 91 %; exo isomers t_r = 38.8 min (major enantiomer) and 40.6 min (minor enantiomer) ee = 75 %.

(1R,2S,3S,4S)-3-(p-Tolyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and (1S,2S,3S,4R)-3-(p-tolyl)bicyclo[2.2.1] hept-5-ene-2-carbaldehyde (4c, Table 2, entry 3): Pale yellow liquid, 184 mg, 87 % yield; ^1H NMR (400 MHz, CDCl_3): (endo isomer) δ 9.92 (d, J = 1.6 Hz, 1H), 7.18-7.06 (m, 4H), 6.33 (d, J = 2.8 Hz, 1H), 6.07 (d, J = 2.8 Hz, 1H), 3.69 (t, J = 2 Hz, 1H), 3.21 (dd, J = 2 Hz, 1H), 3.09 (d, J = 2 Hz, 1H), 2.57 (d, J = 2 Hz, 1H), 2.31 (s, 3H), 1.64-1.54 (m, 2H) ppm. ^{13}C NMR (100 MHz, CDCl_3): (endo isomer) δ 202.9, 139.6, 139.3, 136.3, 135.9, 133.8, 129.3, 128.9, 127.3, 59.6, 48.6, 48.5, 45.5, 45.2 21.2 ppm. Enantiomeric ratio was determined by HPLC using Chiracel IC column after reduction with $\text{NaBH}_4/\text{MeOH}$ (1:99 i-PrOH/hexane, 1 mL/min flow rate), endo isomers t_r = 59.1 min (major enantiomer) and 73.6 min (minor enantiomer) ee = 92 %; exo isomers t_r = 47.1 min (major enantiomer) and 64.2 min (minor enantiomer) ee = 90 %.

(1R,2S,3S,4S)-3-(2-Nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and (1S,2S,3S,4R)-3-(2-nitrophenyl) bicyclo[2.2.1] hept-5-ene-2-carbaldehyde (4d, Table 2, entry 4): Yellow liquid, 223 mg, 92 % yield, ^1H NMR (400 MHz, CDCl_3): (endo isomer) δ 9.39 (d, J = 2.4 Hz, 1H), 7.81-7.24 (m, 4H), 6.48 (d, J = 3.6 Hz, 1H), 6.21 (d, J = 3.6 Hz, 1H), 3.42 (t, J = 5.2 Hz, 1H), 3.31 (dd, J = 3.6 Hz, 1H), 3.10 (t, J = 4.8 Hz, 1H), 2.94 (d, J = 3.8 Hz, 1H), 1.84-1.81 (m, 1H), 1.65-1.61 (m, 1H) ppm. ^{13}C NMR (100 MHz, CDCl_3): (endo isomer) δ 203.6, 150.4, 139.2, 137.3, 134.2, 132.9, 127.9, 127.4, 124.8, 59.1, 49.8, 47.3, 46.6, 41.7 ppm. Enantiomeric ratio was determined by HPLC using Chiral IC column after reduction with $\text{NaBH}_4/\text{MeOH}$ (1:99 i-PrOH/hexane, 1 mL/min flow rate), endo isomers t_r = 101.6 min (minor enantiomer) and 113.5 min (major enantiomer) ee = 97 %.

(1R,2S,3S,4S)-3-(4-Nitrophenyl)bicyclo[2.2.1]hept-5-ene-2-carbaldehyde and (1S,2S,3S,4R)-3-(4-nitrophenyl) bicyclo[2.2.1] hept-5-ene-2-carbaldehyde (4e, Table 2, entry 5): Yellow liquid, 231 mg, 95 % yield; ^1H NMR (400 MHz, CDCl_3): (endo isomer) δ 9.89 (d, J = 1.6 Hz, 1H), 8.14-7.28 (m, 4H), 6.39 (d, J = 3.2 Hz, 1H), 6.01 (d, J = 3.8 Hz, 1H), 3.87 (t, J = 4.4 Hz, 1H), 3.28 (m, 1H), 2.93 (t, J = 2.8 Hz, 1H), 2.61-2.60 (m, 1H), 1.69-1.61 (m, 2H) ppm. ^{13}C NMR (100 MHz, CDCl_3): (endo isomer) δ 202.2, 151.6, 146.6, 139.1, 137.0, 136.0, 134.0, 128.7, 123.8, 61.25, 59.6, 48.4, 45.6, 45.2 ppm. Enantiomeric ratio was determined by HPLC using Chiral IC column after reduction with $\text{NaBH}_4/\text{MeOH}$ (1:99 i-PrOH/hexane, 1 mL/min flow rate), endo isomers t_r = 81.5 min, and 176.1 min (major enantiomer) ee = 92 %; exo isomers t_r = 115.9 min (minor enantiomer) and 176.1 min (major enantiomer) ee = 92 %.

3 Friedel–Crafts Alkylation (Table 4)

Catalyst **1a** (43 mg, 0.1 mmol, 20 mol %) was dissolved in THF (5 mL), H₂O (0.5 mL) and aqueous TFA solution (1 M, 0.1 mL, 0.1 mmol, 20 mol %) was added. The mixture was stirred for 10 min, and then N-methylpyrrole (0.2 mL, 2.5 mmol) was added. Next, trans-cinnamaldehyde derivatives (0.5 mmol) was added dropwise to the reaction vial. The suspension was stirred at –30 °C, and the reaction was monitored by thin layer chromatography (TLC). After 48 h, NaBH₄ (84 g, 2.2 mmol) was added, the reaction proceed for 2 h at room temperature, followed by washing with H₂O, brine and purification with gel column chromatography to get the alcoholic product for HPLC. To recycle the catalyst **1a**, the resulting reaction mixture before reduction was extracted with HCl (1 M), and aqueous phase was added saturated NaHCO₃, and extracted with dichloromethane. The organic phase was condensed to dryness and treated with ether/hexane to get the cycled catalyst **1a** as white solid after filtration. The solid catalyst was used directly for the next run. The filtrate was condensed to dryness and purified with gel column chromatography to get the product which was used for reduction.

(S)-3-(1-Methyl-1H-pyrrol-2-yl)-3-phenylpropan-1-ol (**7a**, Table 4, entry 1)—

Colorless liquid, 93 mg, 89 % yield; ¹H NMR (400 MHz, CDCl₃): δ 7.27–7.12 (m, 5H), 6.52 (s, 1H), 6.13 (s, 1H), 6.11 (d, *J* = 3.6 Hz, 1H), 4.12 (t, *J* = 7.6 Hz, 1H), 3.70–3.68 (m, 1H), 3.67–3.62 (m, 1H), 3.29 (s, 3H), 2.37–2.32 (m, 1H), 2.08–2.04 (m, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 143.5, 134.9, 128.6, 128.4, 128.1, 127.9, 126.4, 121.9, 106.3, 105.8, 60.8, 39.6, 39.1, 33.9 ppm. Enantiomeric ratio was determined by HPLC using Chiracel IC column after reduction with NaBH₄/MeOH (5:95 i-PrOH/hexane, 1 mL/min flow rate), isomers *t*_r = 9.0 min (minor enantiomer) and 10.4 min (major enantiomer) ee = 87 %.

(S)-3-(1-Methyl-1H-pyrrol-2-yl)-3-phenylpropan-1-ol (**7b**, Table 4, entry 2)—

Colorless liquid, yield 94 mg, 77 %, ¹H NMR (400 MHz, CDCl₃): δ 7.05 (m, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.51 (s, 1H), 6.11 (t, *J* = 3.2 Hz, 2H), 4.07 (t, *J* = 7.2 Hz, 1H), 3.75 (s, 3H), 3.67–3.61 (m, 1H), 3.59–3.51 (m, 1H), 2.28 (s, 3H), 2.31–2.29 (m, 1H), 2.06–2.01 (m, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 158.1, 135.5, 135.3, 128.9, 121.8, 114.2, 114.1, 106.4, 106.3, 105.6, 60.8, 55.3, 39.1, 38.7, 33.9 ppm. Enantiomeric ratio was determined by HPLC using Chiracel IC column after reduction with NaBH₄/MeOH (5:95 i-PrOH/hexane, 1 mL/min flow rate), isomers *t*_r = 26.6 min (minor enantiomer) and 30.7 min (major enantiomer) ee = 80 %.

(S)-3-(1-methyl-1H-pyrrol-2-yl)-3-(4-nitrophenyl)propan-1-ol (**7c**, Table 4, entry 3)—

Colorless liquid, yield 124 mg, 96 %, ¹H NMR (400 MHz, CDCl₃): δ 8.13 (d, *J* = 2 Hz, 2H), 7.32 (m, *J* = 2 Hz, 2H), 6.55 (s, 1H), 6.16 (d, *J* = 2.8 Hz, 2H), 4.32 (t, *J* = 8 Hz, 1H), 3.74–3.72 (m, 1H), 3.71–3.67 (m, 1H), 3.29 (s, 3H), 2.34–2.30 (m, 1H), 2.07–2.02 (m, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 151.5, 146.6, 133.2, 128.8, 128.7, 123.9, 122.5, 106.8, 106.4, 106.3, 60.1, 39.1, 38.6, 33.9 ppm. Enantiomeric ratio was determined by HPLC using Chiracel IC column after reduction with NaBH₄/MeOH (5:95 i-PrOH/hexane, 1 mL/min flow rate), isomers *t*_r = 39.7 min (minor enantiomer) and 51.1 min (major enantiomer) ee = 77 %.

(R)-Ethyl 4-hydroxy-2-(1-methyl-1H-pyrrol-2-yl)butanoate (7d, Table 4, entry 4)

—Colorless liquid, yield 91 mg, 87 %, ¹H NMR (400 MHz, CDCl₃): δ, 6.62 (s, 1H), 6.07 (t, *J* = 2.4 Hz, 1H), 6.04 (d, *J* = 2 Hz, 1H), 4.51-4.48 (m, 1H), 4.37-4.35 (m, 1H), 3.85 (t, *J* = 6.5 Hz, 1H), 3.68 (s, 3H), 3.45-3.42 (m, 2H), 2.63-2.53 (m, 2H), 1.21 (t, *J* = 6.8 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 175.9, 126.7, 123.5, 107.1, 106.4, 66.8, 65.9, 37.8, 34.3, 29.2, 15.3 ppm. Enantiomeric ratio was determined by HPLC using Chiracel IC column after reduction with NaBH₄/MeOH (5:95 i-PrOH/hexane, 1 mL/min flow rate), isomers *t_r* = 34.9 min (minor enantiomer) and 44.7 min (major enantiomer) ee = 85 %.

(R)-3-(1-Methyl-1H-pyrrol-2-yl)hexan-1-ol (7e, Table 4, entry 5)

—Colorless liquid, yield 86 mg, 90 %, ¹H NMR (400 MHz, CDCl₃): δ 6.48 (d, *J* = 2.4 Hz, 1H), 6.06 (t, *J* = 3.2 Hz, 1H), 5.85 (t, *J* = 2 Hz, 1H), 3.62-3.59 (m, 1H), 3.55 (s, 3H), 3.54-3.53 (m, 1H), 2.85-2.82 (m, 1H), 1.90-1.76 (m, 2H), 1.59-1.53 (m, 2H), 1.29-1.21 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ 136.8, 121.1, 106.7, 104.3, 61.1, 38.6, 33.8, 33.7, 32.9, 20.5, 14.2 ppm. Enantiomeric ratio was determined by HPLC using Chiracel IC column after reduction with NaBH₄/MeOH (5:95 i-PrOH/hexane, 1 mL/min flow rate), isomers *t_r* = 19.5 min (major enantiomer) and 23.7 min (minor enantiomer).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful for financial support from the NSFC (Nos. 21332005 and 21672100), NSF of Jiangsu Province (BK20151163), PAPD of Jiangsu Higher Education Institutions, Robert A. Welch Foundation (D-1361, USA) and NIH (R33DA031860, USA)

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Previous works

Our design

FG = DPP and DNP

Scheme 1.

Design of chiral phosphonylated imidazolidinone catalysts

Scheme 1.

Synthesis of phosphonylated imidazolidinone catalysts

Table 1

Optimization of reaction conditions for Diels-Alder reaction

Entry	Cat. (mol %)	Acid	endo:exo ^b %	endo (ee %) ^c	Yield (%) ^d	Recycle yield (%) ^e
1	1a (20)	HCl	1.1:1	90	84	77
2	1b (20)	HCl	1.0:1	92	77	51
3	2a (20)	HCl	1.3:1	83	78	trace
4	2b (20)	HCl	1.2:1	78	61	trace
5	1a (20)	HBF ₄	-	-	trace	-
6	1a (20)	TfOH	1.0:1	91	85	90
7	1a (20)	CSA ^f	1.0:1	94	88	87
8	1a (20)	TFA	1.9:1	98	98	92
9	I (20, Lit.) ^g	HCl	1.3:1	93	99	-

^aThe reactions were carried out at 23 °C for 12 h using catalyst (0.2 mmol, 20 mol %), HX (0.2 mmol, 20 mol %), cinnamaldehyde (**2a**, 1.0 mmol), cyclopentadiene (**3**, 5.0 mmol), MeOH (2.0 mL), and H₂O (0.1 mL).

^bEndo/exo ratio was determined by ¹H NMR analysis of crude reaction mixture.

^cProduct enantiomer excesses was determined by HPLC using chiral IC column after reduction of the aldehyde to alcohol with NaBH₄.

^dIsolated yield based on substrate **2**.

^eResult of first recycling experiment with catalyst **1a**.

$f_{\text{CSA}} = \text{D-}(+)\text{-10-camphorsulfonic acid.}$

$g_{\text{Ref.4.}}$

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Table 2

The synthetic utility of asymmetrical Diels-Alder reaction

Entry	4	Ar	endo: exo ^b	Endo ee (%) ^c	Exo ee (%) ^c	Yield ^d /%	Cat. Recovery (%) ^e
1	4a	C ₆ H ₅ (2a)	1.9:1	98	99	98	92
2	4b	<i>p</i> -MeOC ₆ H ₄ (2b)	1.6:1	91	75	81	88
3	4c	<i>p</i> -MeC ₆ H ₄ (2c)	1.7:1	92	90	87	91
4	4d	<i>o</i> -NO ₂ C ₆ H ₄ (2d)	13:1	97	-	92	87
5	4e	<i>p</i> -NO ₂ C ₆ H ₄ (2e)	1.1:1	92	90	95	83

^aThe reactions were carried out at 23 °C for 12 h using catalyst **1a** (0.2 mmol, 20 mol %), TFA (0.2 mmol, 20 mol %), aldehydes **2** (1.0 mmol), cyclopentadiene **3** (5.0 mmol), MeOH (2.0 mL) and H₂O (0.1 mL).

^bEndo/exo ratio was determined by ¹H NMR analysis of crude reaction mixture.

^cProduct enantiomer excesses was determined by HPLC using chiral IC column after reduction of the aldehyde to alcohol with NaBH₄.

^dIsolated yield based on substrate **2**.

^eResult of first recycling experiment with catalyst **1a**.

Table 3Recycling of catalyst **1a** in Diels-Alder reaction

Time	Yield (%) ^d	<i>endo</i> : <i>exo</i> ^b	ee (%) ^c	Cat. Recovery (%) ^e
1	98	1.9:1	98	92
2	97	1.8:1	96	90
3	98	1.9:1	95	95

^a The reactions were carried out at 23 °C for 12 h using catalyst **1a** (reused from last run), TFA (0.2 mmol, 20 mol %), aldehydes **2** (1.0 mmol), cyclopentadiene **3** (5.0 mmol), MeOH (2.0 mL) and H₂O (0.1 mL).

^b Endo/exo ratio was determined by ¹H NMR analysis of crude reaction mixture.

^c Product enantiomer excesses was determined by HPLC using chiral IC column after reduction of the aldehyde to alcohol with NaBH₄.

^d Isolated yield based on substrate **2**.

^e Recovery of catalyst **1a** with method 1 in the supporting information.

Table 4Substrate scope of Friedel-Craft alkylation of *N*-methyl pyrrole

entry	6	R	Yield(%) ^b	ee (%) ^c
1	6a	C ₆ H ₅ (2a)	89	87
2	6b	<i>p</i> -OMeC ₆ H ₄ (2b)	77	80
3	6c	<i>p</i> -NO ₂ C ₆ H ₄ (2e)	96	77
4	6d	CO ₂ Et (2f)	83	85 ^d
5	6e	Pr (2g)	90	99
6 ^e	6a	C ₆ H ₅ (2a)	77	88

^aReaction conditions: aldehyde (0.5 mmol, 1.0 equiv), *N*-methylpyrrole (2.50 mmol, 5.0 equiv), catalyst 1a (20 mol %), aq TFA (1 M; 20 mol %), -30 °C, 48 hours.

^bIsolated yield based on substrate 2.

^cProduct enantiomer excesses were determined by HPLC using chiral IC column after reduction of aldehydes to alcohols with NaBH₄.

^dUsing cyanoacetic acid as co-catalyst.

^eResult with recycled catalyst with method 2.