Tetrahedron 67 (2011) 4103–4109

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

# Phosphonium ion tagged chiral phosphoric acids and their application in Friedel–Crafts reactions of indoles

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ARTICLE INFO

*Article history:*
Received 8 February 2011
Received in revised form 24 March 2011
Accepted 30 March 2011
Available online 8 April 2011

*Keywords:*
Organocatalysis
Asymmetric catalysis
Chiral phosphoric acid
Phosphonium salt
Friedel–Crafts reactions

ABSTRACT

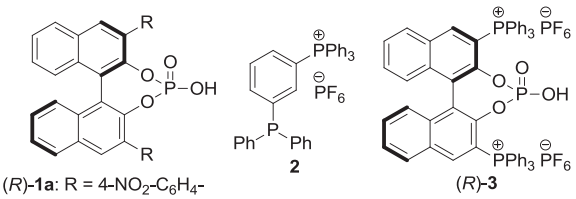
The attachment of phosphonium ion phase tags to chiral binapthyl-based phosphoric acid catalysts, and the use of these materials in a range of organocatalytic asymmetric Friedel–Crafts reactions of indoles has been studied. Placement of the tags at the 3 and 3′ positions of the phosphoric acid, so that they could serve as steric blocking groups, failed to produce an active catalyst. However, moving the phosphonium ion groups to the 6 and 6′ positions produced an efficient and enantioselective catalyst. Aided by the presence of the phase tags, the chiral catalyst was easily removed at the end of the reactions, and could be reused several times, albeit with somewhat decreased efficiency and enantioselectivity.



## 1. Introduction

Since the first publications regarding the concept of asymmetric Brønsted acid organocatalysis using chiral phosphoric acids by Akiyama[1] and Terada,[2] a large body of work has emerged in the organic chemistry literature examining various aspects and applications of such catalysis.[3] While this general field of asymmetric organocatalysis has been explored intensively, only a single report by Rueping describes the synthesis and utility of a chiral phosphoric acid catalyst, that is, easily recoverable, and readily reused without loss of reactivity or selectivity.[4] In this work, the chiral phosphoric acid was incorporated into a heterogeneous, cross-linked polystyrene framework so that it could be removed for re-use simply by filtration.

During a survey of this topic, we noted that all of the effective binapthyl-based chiral phosphoric acid organocatalysts reported in the literature were functionalized at the 3 and 3′ positions by sterically bulky groups. For example, (*R*)-**1a** (Akiyama's catalyst),[1] (*R*)-**1b** (Terada's catalyst),[2] and what is referred to as the TRIP catalyst (*R*)-**1c**,[3d] all possess substituted aryl groups at these positions (Fig. 1). Furthermore, MacMillan[5] and Gong[6] introduced (*R*)-**1d**, which bears triphenylsilyl groups at the 3 and 3′ positions. This later example caused us to consider if it might be possible to use Charette's phosphonium ion phase tag technology[7] to prepare a homogeneous chiral phosphoric acid organocatalyst in which the steric blocking groups also serve as handles to aid in its recovery from reaction mixtures. Illustrative of this methodology is the report that **2**[7a] can be used as a soluble reagent in triphenylphosphine mediated transformations, such as Mitsunobu reactions, and then it and its oxidized by-product can be separated from the desired reaction product by precipitation and filtration. Thus, we set out to synthesize (*R*)-**3** and examine its utility as a recyclable asymmetric organocatalyst. Herein we describe the results of our research regarding this concept.




(*R*)-**1a**: R = 4-$NO_2$-$C_6H_4$-
(*R*)-**1b**: R = 4-(β-napthyl-$C_6H_4$-
(*R*)-**1c**: R = 2,4,6-(i-Pr)$_3$-$C_6H_2$-
(*R*)-**1d**: R = $SiPh_3$-

**Fig. 1.** Chiral phosphoric acids and Charette's phosphonium ion tagged phosphine reagent.

## 2. Results and discussion

For the synthesis of (*R*)-**3**, diol (*R*)-**4** was prepared from (*R*)-BINOL according to literature procedures.[8–10] Phosphonium ions were then added to (*R*)-**4** in good yield using a $Pd_2(dba)_3$ mediated coupling reaction with $PPh_3$ in ethylene glycol at high

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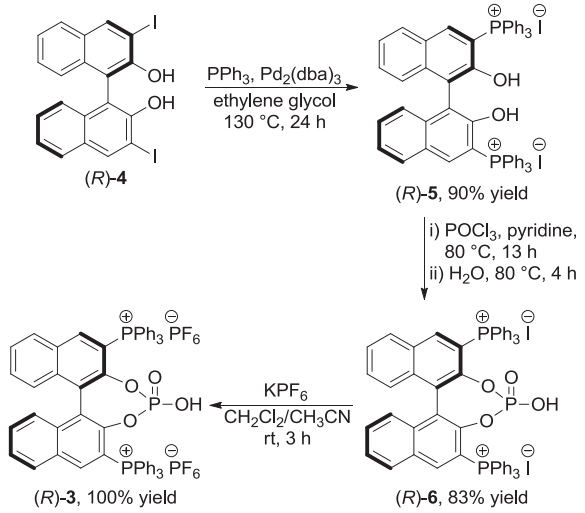
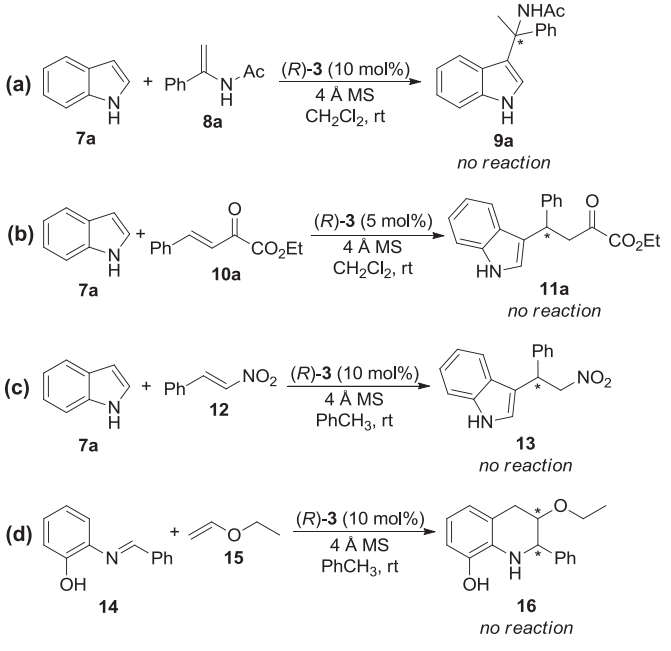
doi:10.1016/j.tet.2011.03.105

temperature, to afford tagged diol (*R*)-**5** (Scheme 1). Subsequent reaction of (*R*)-**5** with $POCl_3$ in pyridine at 80 °C, followed by treatment with water and acidification afforded phosphoric acid (*R*)-**6** in 83% overall yield. Finally, (*R*)-**6** was converted into (*R*)-**3** in quantitative yield by counter ion exchange using $KPF_6$.




**Scheme 1.** Synthesis of the phosphonium ion tagged chiral phosphoric acid (*R*)-**3**.

With the synthesis of phosphoric acid (*R*)-**3** completed, we moved on to examine its potential as an enantioselective organocatalyst in a range of asymmetric Friedel–Crafts and Diels–Alder reactions for which (*R*)-**1d** was previously reported to be an excellent catalyst (Scheme 2). In regards to the construction of carbon–carbon bonds, the catalytic asymmetric Friedel–Crafts reaction is a highly effective method that provides direct access to enantiomerically enriched arene derivatives.[11] This is especially true for indoles substrates,[12] due to their significant nucleophilic reactivity,[13] and chiral phosphoric acids have been reported to be a very efficient and highly stereoselective catalyst for such reactions.[14–16] First we set up a reaction with indole **7a** and α-aryl enamide **8a** using 0.1 equiv of (*R*)-**3** with molecular sieves in $CH_2Cl_2$ at room temperature (Scheme 2a).[14e] Unfortunately, none of the desired product **9a** was formed, even after 5 days. In the next reaction we changed the electrophilic reaction partner to α,β-unsaturated carbonyl compound **10a** using similar conditions (Scheme 2b).[17] However, once again, none of the desired product **11a** was formed. Acid (*R*)-**3** also failed to catalyze the reaction between **7a** and nitroalkene **12** to produce **13** (Scheme 2c).[14f] Finally, we attempted to use (*R*)-**3** to catalyze the Diels–Alder reaction between aldimine **14** and vinyl ether **15** in toluene at room temperature (Scheme 2d).[18] However, even after 7 days none of the expected product **16** was observed, and only the starting materials and catalyst were present in the reaction mixture.

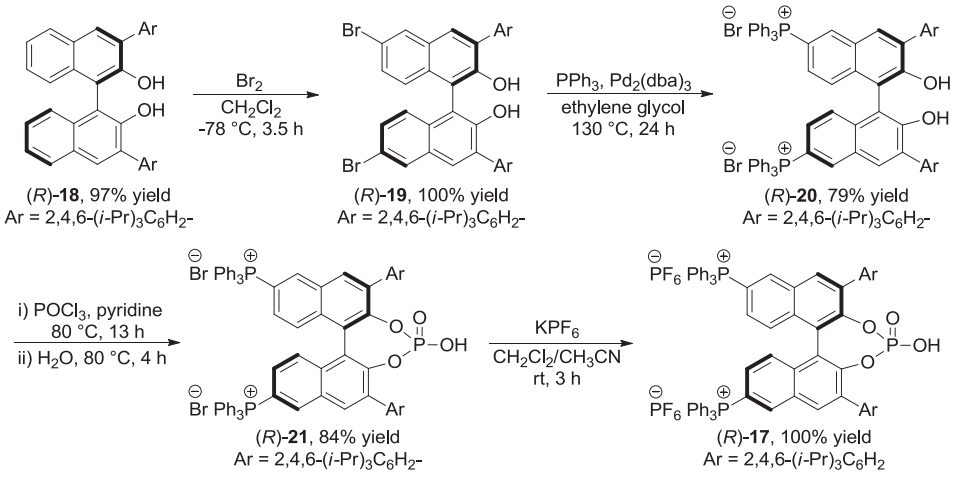



**Scheme 2.** Attempts to use (*R*)-**3** as an asymmetric organocatalyst.

We believed that there were two possible explanations for our disappointing results; that the phosphonium groups were too bulky, and thereby sterically inhibited (*R*)-**3** from interacting with the substrates in the necessary way for catalysis to occur, or that their cationic nature electronically affected the ability of the phosphoric acid groups to activate the substrates in the desired manner. In order to determine which of these possibilities was responsible for the failure of (*R*)-**3** to catalyze the reactions studied in Scheme 2, we felt that moving the phosphonium ion phase tags from the 3 and 3′ positions of the BINOL skeleton to the 6 and 6′ positions might be informative. Thus, we designed and synthesized (*R*)-**17** as outlined in Scheme 3. For (*R*)-**17** we chose to install 2,4,6-triisopropylphenyl groups at the 3 and 3′ positions since they are the basis for the TRIP catalyst (*R*)-**1c**, which has been shown to be an excellent catalyst for asymmetric transfer hydrogenation,[19,20] and Friedel–Crafts reactions.[21]

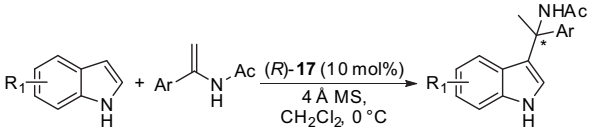
To begin with, diol (*R*)-**18** was synthesized from (*R*)-BINOL according to literature procedures[8,9,22] and was subsequently brominated in $CH_2Cl_2$ at −78 °C to afford (*R*)-**19** in quantitative yield (Scheme 3). It should be noted that this reaction is very sensitive to both the quantity of $Br_2$ used, and the time allowed for the reaction to occur, since over-bromination at 4 and 4′ positions occurred if the reaction was not carefully controlled and monitored. The phosphonium ion groups were then added to (*R*)-**19** as before, using a palladium-catalyzed coupling reaction with $PPh_3$ in hot ethylene glycol, to afford diol (*R*)-**20** in 79% yield. Conversion of (*R*)-**20** into the corresponding phosphoric acid (*R*)-**21** in 84% yield was achieved by treating it with $POCl_3$ in pyridine at 80 °C, followed by water and acidification. Finally, exchange of the counter ion of (*R*)-**21** was accomplished by treatment with $KPF_6$ to afford phosphoric acid (*R*)-**17** in quantitative yield. It should be noted that purification of (*R*)-**17**, (*R*)-**20** and (*R*)-**21** was accomplished simply by precipitation and filtration. These products were found to be soluble in solvents, such as $CH_2Cl_2$, acetonitrile, dimethyl sulfoxide, dimethylformamide, but insoluble in solvents, such as diethyl ether and *n*-hexane. Thus, addition of one of these later solvents to the reaction mixture caused the phosphonium ion tagged species to precipitate, so that it could be isolated by filtration and purified by washing with additional solvent.

Once the phosphonium ion tagged phosphoric acid (*R*)-**17** was synthesized, we tested its catalytic utility in asymmetric Friedel–Crafts reactions. Gratifyingly, when we attempted to use (*R*)-**17** to catalyze the same reaction that (*R*)-**3** failed to promote between **7a** and **8a** (Scheme 2a), we obtained the desired product **9a** in excellent yield with moderate enantioselectivity using molecular sieves in $CH_2Cl_2$ at 0 °C (Table 1, entry 1). Encouraged by this result, we next used (*R*)-**17** to catalyze a series of similar reactions, using indoles **7a**–**c** and enamides **8a**–**d**. The reactions between unsubstituted **7a** and enamides bearing an electron-withdrawing group in the *para*-position (**8b**–**c**) also proceeded to afford excellent yield of the products **9b** and **9c**, respectively, but with slightly higher enantioselectivity than before (Table 1, entries 2 and 3). When an electron-donating group was placed in the *para*-position, as in **8d**, the yield of the alkylated indole **9d** was somewhat lower, as was the enantioselectivity (Table 1, entry 4). The use of substituted indoles **7b** and **7c** as the reacting partner with unsubstituted enamide **8a** afforded products **9e** and **9f**, respectively, in yields and enantioselectivities similar to the other products (Table 1, entries 5 and 6). Overall, these




**Scheme 3.** Synthesis of phosphonium ion tagged chiral phosphoric acid (*R*)-**17**.

**Table 1**
Enantioselective Friedel–Crafts reactions of indoles with enamides[a]




**7a**: $R_1$ = H-
**7b**: $R_1$ = 5-Br-
**7c**: $R_1$ = 5-F-

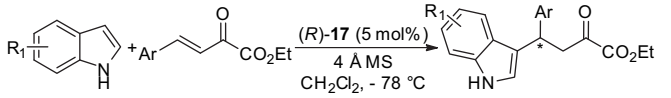
**8a**: Ar = $C_6H_5$-
**8b**: Ar = 4-Br-$C_6H_4$-
**8c**: Ar = 4-F-$C_6H_4$-
**8d**: Ar = 4-OMe-$C_6H_4$-

**9a**: $R_1$ = H-, Ar = $C_6H_5$-
**9b**: $R_1$ = H-, Ar = 4-Br-$C_6H_4$-
**9c**: $R_1$ = H-, Ar = 4-F-$C_6H_4$-
**9d**: $R_1$ = H-, Ar = 4-OMe-$C_6H_4$-
**9e**: $R_1$ = 5-Br-, Ar = $C_6H_5$-
**9f**: $R_1$ = 5-F-, Ar = $C_6H_5$-

| Entry | Substrates | Products | Reaction time (h) | Yield[b] (%) | er[c] |
|---|---|---|---|---|---|
| 1 | **7a**+**8a** | **9a** | 24 | 95 | 87:13 |
| 2 | **7a**+**8b** | **9b** | 24 | 98 | 95:5 |
| 3 | **7a**+**8c** | **9c** | 24 | 98 | 91:9 |
| 4 | **7a**+**8d** | **9d** | 48 | 81 | 85:15 |
| 5 | **7b**+**8a** | **9e** | 24 | 95 | 93:7 |
| 6 | **7c**+**8a** | **9f** | 24 | 82 | 87:13 |

[a] Reactions were conducted using 0.14 mmol of **7a**–**c**, 0.1 mmol of **8a**–**d** and 0.01 mmol of (*R*)-**17**.
[b] Isolated yields.
[c] Enantiomer ratios were determined by HPLC using a chiral stationary phase column.

**Table 2**
Enantioselective Friedel–Crafts reactions of indoles with β,γ-unsaturated α-keto esters[a]




**7a**: $R_1$ = H-
**7b**: $R_1$ = 5-Br-
**7c**: $R_1$ = 5-F-

**10a**: Ar = $C_6H_5$-
**10b**: Ar = 4-Me-$C_6H_4$-
**10c**: Ar = 4-Br-$C_6H_4$-
**10d**: Ar = 4-OMe-$C_6H_4$-

**11a**: $R_1$ = H, Ar = $C_6H_5$-
**11b**: $R_1$ = H, Ar = 4-Br-$C_6H_4$-
**11c**: $R_1$ = H, Ar = 4-F-$C_6H_4$-
**11d**: $R_1$ = H, Ar = 4-OMe-$C_6H_4$-
**11e**: $R_1$ = 5-Br, Ar = $C_6H_5$-
**11f**: $R_1$ = 5-F, Ar = $C_6H_5$-

| Entry | Substrates | Product | Reaction time (h) | Yield[b] (%) | er[c] |
|---|---|---|---|---|---|
| 1 | **7a**+**10a** | **11a** | 24 | 98 | 80:20 |
| 2 | **7a**+**10b** | **11b** | 24 | 94 | 75:25 |
| 3 | **7a**+**10c** | **11c** | 24 | 92 | 80:20 |
| 4 | **7a**+**10d** | **11d** | 48 | 89 | 75:25 |
| 5 | **7b**+**10a** | **11e** | 24 | 90 | 73:27 |
| 6 | **7c**+**10a** | **11f** | 24 | 92 | 77:23 |

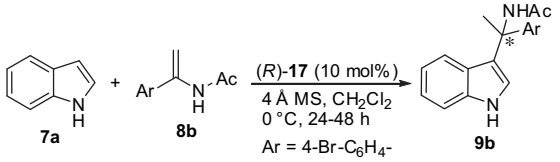
[a] Reactions were conducted using 0.21 mmol **7a**–**c**, 0.1 mmol **10a**–**d** and 0.005 mmol of (*R*)-**17**.
[b] Isolated yields.
[c] Enantiomer ratios were determined by HPLC using a chiral stationary phase column.

results are generally similar, albeit with slightly lower selectivity, to what was reported by Zhou in his related pioneering work.[14e]

In order to further demonstrate the utility of (*R*)-**17** as a catalyst in asymmetric Friedel–Crafts reactions, we examined another reaction that (*R*)-**3** failed to promote, specifically that between **7a** and β,γ-unsaturated α-keto ester **10a** (Scheme 2b). Such reactions were previously studied by Desimoni using a scandium(III) triflate catalyst.[23] The only use of an organocatalysts in such reactions with *N*-methylindole substrates was described by Rueping, and these were catalyzed by a chiral *N*-triflylphosphoramide.[17] Satisfyingly, in the reaction between **7a** and **10a**, using molecular sieves in $CH_2Cl_2$ at −78 °C, product **11a** was formed in nearly quantitative yield and with moderate enantioselectivity (Table 2, entry 1). We then reacted **7a** with substituted substrates **10b**–**d**, and obtained similar results for products **11b**–**d** (Table 2, entries 2-4). When substituted indoles **7b** and **7c** were reacted with **10a**, both **11e** and **11f** were obtained in excellent yield, respectively. However, the enantioselectivities of these reactions were only moderate (Table 2, entries 5 and 6).

As described above, the impetus for incorporating phosphonium ion groups into both (*R*)-**3** and (*R*)-**17** was to allow them to serve as recyclable homogeneous catalysts that could be easily separated from reaction mixtures by precipitation and filtration operations. Thus, since we demonstrated the catalytic activity of (*R*)-**17**, we next examined its recyclability. The reaction arbitrarily chosen for this exercise was the Friedel–Crafts reaction between **7a** with enamide **8b** to form **9b**. As can be seen in Table 3, **9b** was isolated in similar

**Table 3**
Recyclability of phosphoric acid (*R*)-**17**[a]




**7a** **8b** **9b**

| Cycle | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Reaction time (h) | 24 | 30 | 48 | 48 |
| Yield (%) | 76 | 73 | 74 | 72 |
| er[b] | 96:4 | 93:8 | 85:15 | 87:13 |
| Recovered catalyst (%)[c] | 98 | 95 | 93 | 93 |

[a] Reactions were conducted using 2.8 mmol of **7a**, 2.0 mmol of **8b** and 0.2 mmol of (*R*)-**17**. At the end of each reaction, (*R*)-**17** was precipitated by the addition of diethyl ether to the reaction mixture, washed and then reused in the next cycle.
[b] Enantiomer ratios were determined by HPLC using a chiral stationary phase column.
[c] Catalyst recovery was calculated based on the previous experiment.

yield (76–72% yield) in reactions that took progressively longer to complete, and with decreased enantioselectivity (Table 3). Thus, it is clear that (*R*)-**17** has limited reusability.

## 3. Conclusion

In summary, we used the phosphonium ion phase tag technology to prepare a pair of phase tagged chiral binapthyl-based phosphoric acids, (*R*)-**3** and (*R*)-**17** and studied their catalytic activity in a range of asymmetric Friedel–Crafts reactions with indoles substrates. Unfortunately, our attempt to use the phase tags as steric blocking groups at the 3 and 3′ positions of the binapthyl skeleton in (*R*)-**3** failed to produce an active catalyst. On the other hand, when we placed the phosphonium ion phase tags at the 6 and 6′ positions of the binapthyl skeleton and used conventional 2,4,6-triisopropylphenyl steric blocking substituents at the 3 and 3′ positions, (*R*)-**17** proved to be an active and stereoselective catalyst. These contrasting sets of results lead us to believe that the lack of catalytic activity exhibited by (*R*)-**3** can be ascribed to steric hindrance by the phosphonium ion groups, which should be larger than the previously studied triphenylsilyl groups, and is not due to any electronic effect that the phase tags impart on the phosphoric acid group. As for the less than optimal results in the recycling experiments, perhaps the decreased enantioselectivity observed with recovered (*R*)-**17** was due to an undetected impurity that co-precipitated with it during the recycling process, and that inhibited enantioselective catalysis by (*R*)-**17**, allowing the non-selective background reaction to occur to a greater extent.[24,25] However, we cannot rule out the possibility that the electronic properties of the phosphonium groups play a role in limiting the recyclability of (*R*)-**17**. Regardless, we hope that our observations in this study can aid others as they work to develop more stereoselective and recyclable versions of these important organocatalysts.

## 4. Experimental

### 4.1. General

All reagents were obtained from the Acros, Aldrich, International Laboratory or Lancaster chemical companies and were used as received. Diethyl ether and $CH_2Cl_2$ were dried using a Solv-Tek purification system employing activated $Al_2O_3$. All reactions were carried out in dry glassware under $N_2$ atmosphere, and monitored by TLC analysis using $GF_{254}$ silica gel coated plates. Merck silica gel 60 (230–400 mesh) was used for chromatography. $^1H$, $^{13}C$, $^{31}P$ and $^{19}F$ NMR spectra were recorded in $CDCl_3$ on a Bruker DRX-300, DRX-400 or DRX-500 spectrometer operating at 300/400/500 MHz for $^1H$, 75/100/125 MHz for $^{13}C$, 162 MHz for $^{31}P$, and 376 MHz for $^{19}F$ analysis. Chemical shift data is expressed in parts per million with reference to TMS. HR EI-MS data was recorded on a Finnigan MAT 96 mass spectrometer and HR ESI-MS data was recorded on a ABI Q-STAR Pulsar i mass spectrometer. HPLC analyses were performed using a Waters 2998 chromatography system.

### 4.2. Synthesis of (*R*)-3 and (*R*)-17

*4.2.1. Diol (R)-**5**.* Starting material (*R*)-**4** was prepared according to literature procedures.[8–10] (*R*)-**4** (0.80 g, 1.49 mmol), $Pd_2(dba)_3$ (0.08 g, 6 mol %, 0.09 mmol) and $PPh_3$ (1.17 g, 4.46 mmol) were added to a 2-necked flask under a $N_2$ atmosphere, followed by ethylene glycol (0.57 g, 0.51 mL). The reaction mixture was then heated at 130 °C for 24 h. At this time $CH_2Cl_2$ was added, and then the mixture was filtered through Celite, and the filtrate was concentrated to afford the crude product. This was purified by dissolving it in $CH_2Cl_2$ (3.0 mL) and precipitating it by the addition of cold $Et_2O$ (60 mL). Filtration and washing of the precipitate afforded pure phosphonium salt (*R*)-**5** (1.50 g, 95%) as a yellow solid. $^1H$ NMR (400 MHz, $CD_3Cl$): $\delta$ 7.83–7.53 (m, *ArH*, 32H), 7.40–7.36 (m, *ArH*, 4H), 7.34–7.26 (m, *ArH*, 4H), 7.23–7.19 (m, *ArH*, 2H); $^{13}C$ NMR (126 MHz, $CD_3Cl$): $\delta$ 162.0 (d, $J$=9.0 Hz, 2C), 138.9 (d, $J$=8.0 Hz, 2C), 138.6 (s, 2C), 134.2 (d, $J$=10.4 Hz, 18C), 129.8 (d, $J$=12.9 Hz, 12C), 129.6 (s, 2C), 128.9 (s, 2C), 126.6 (s, 2C), 122.8 (s, 2C), 120.8 (d, $J$=11.5 Hz, 2C), 120.7 (d, $J$=7.3 Hz, 2C), 118.6 (d, $J$=86.6 Hz, 6C), 111.1 (d, $J$=95.8 Hz, 2C); $^{31}P$ NMR (162 MHz, $CD_3Cl$): $\delta$ 23.0; HRMS for $C_{56}H_{41}O_2P_2$: calcd 807.2571, found 807.2555.

*4.2.2. Phosphoric acid (R)-**6**.* To a solution of (*R*)-**5** (1.2 g, 1.41 mmol) in pyridine (19.0 mL) was added $POCl_3$ (1.05 mL, 11.3 mmol) at room temperature under a $N_2$ atmosphere. The reaction mixture was then heated at 80 °C and stirred at this temperature for 13 h. At this time water (9.5 mL) was added and stirring was continued for an additional 4 h at 80 °C. The reaction mixture was then cooled using an ice bath and 3 M HCl was slowly added to the reaction mixture. Extraction with $CH_2Cl_2$ was followed by additional washing with 3 M HCl, drying over anhydrous $MgSO_4$, filtration and solvent removal. The crude product was purified by dissolving it in $CH_2Cl_2$ (3 mL) and precipitating it with chilled $Et_2O$ (60 mL) to afford (*R*)-**6** (1.06 g, 85%) as a yellow solid. $^1H$ NMR (400 MHz, $CD_3Cl$): $\delta$ 8.03 (d, $J$=16.3 Hz, *ArH*, 2H), 7.90 (d, $J$=7.9 Hz, *ArH*, 2H), 7.80–7.74 (m, *ArH*, 18H), 7.69–7.64 (m, *ArH*, 12H), 7.59–7.53 (m, *ArH*, 4H), 7.30 (d, $J$=7.9 Hz, *ArH*, 2H); $^{13}C$ NMR (126 MHz, $CD_3Cl$): $\delta$ 150.8 (d, $J$=9.4 Hz, 2C), 141.1 (d, $J$=8.3 Hz, 2C), 136.3 (s, 2C), 135.1 (d, $J$=10.8 Hz, 12C), 135.1 (d, $J$=3.2 Hz, 6C), 131.1 (s, 2C), 130.1 (d, $J$=13.3 Hz, 12C), 129.9 (s, 2C), 129.3 (d, $J$=14.3 Hz, 2C), 127.1 (s, 2C), 126.6 (s, 2C), 124.6 (d, $J$=6.6 Hz, 2C), 118.9 (d, $J$=91.2 Hz, 6C), 110.8 (d, $J$=91.7 Hz, 2C); $^{31}P$ NMR (162 MHz, $CD_3Cl$): $\delta$ 23.0, 0.5; HRMS for $C_{56}H_{40}O_4P_3$: calcd 869.2128, found 869.2113.

*4.2.3. Phosphoric acid (R)-**3**.* A solution of $KPF_6$ (0.66 g, 3.56 mmol) in $CH_3CN$ (64 mL) was added dropwise to a solution of (*R*)-**6** (1.00 g, 0.89 mmol) in $CH_2Cl_2$ (64 mL) and the resulting reaction mixture was stirred at room temperature for 3 h. Afterwards, the mixture was washed with water and 3 M HCl, dried over anhydrous $MgSO_4$, filtered and evaporated to dryness to afford (*R*)-**3** (0.68 g, 100%) as a yellow solid. If necessary, the product could be purified by dissolving it in $CH_2Cl_2$ and precipitating it with $Et_2O$. $^1H$ NMR (400 MHz, $CD_3Cl$): $\delta$ 8.01 (d, $J$=16.3 Hz, *ArH*, 2H), 7.86–7.84 (m, *ArH*, 2H), 7.78–7.73 (m, *ArH*, 18H), 7.66–7.61 (m, *ArH*, 12H), 7.56–7.48 (m, *ArH*, 4H), 7.27–7.30 (m, *ArH*, 2H); $^{13}C$ NMR (126 MHz, $CD_3Cl$): $\delta$ 150.7 (d, $J$=9.1 Hz, 2C), 141.1 (d, $J$=7.3 Hz, 2C), 136.4 (s, 2C), 135.0 (d, $J$=10.2 Hz, 12C), 135.0 (d, $J$=3.2 Hz, 6C), 131.1 (s, 2C), 130.1 (d, $J$=15.5 Hz, 12C), 129.8 (s, 2C), 129.3 (d, $J$=14.5 Hz, 2C), 127.0 (s, 2C), 126.6 (s, 2C), 124.5 (d, $J$=7.5 Hz, 2C), 119.0 (d, $J$=91.1 Hz, 6C), 110.7 (d, $J$=90.9 Hz, 2C); $^{31}P$ NMR (162 MHz, $CD_3Cl$): $\delta$ 23.0, 0.9, −144.3 (septet, $J$=713 Hz, $PF_6$); $^{19}F$ NMR (376 MHz, $CD_3Cl$): $\delta$ −73.4 (d, $J$=712 Hz, $PF_6$); HRMS for $C_{56}H_{40}O_4P_3$: calcd 869.2128, found 869.2117.

*4.2.4. (R)-6,6′-Dibromo-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diol (**19**).* The synthesis of (*R*)-**19** was based on literature procedures.[26] A solution of (*R*)-**18** (1.0 g, 1.45 mmol)[8,9,22] in dry $CH_2Cl_2$ (10 mL) was cooled to −78 °C and a solution of $Br_2$ (0.51 g, 3.18 mmol) in $CH_2Cl_2$ (5.0 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 2.5 h and then at room temperature for 1 h. If the reaction was not complete, it was cooled to −78 °C and an additional 0.3 equiv of $Br_2$ (0.07 g, 0.43 mmol) in $CH_2Cl_2$ (0.7 mL) was added to the reaction mixture. After confirming the completeness of the reaction by $^1H$ NMR, the reaction mixture was quenched by an aqueous solution of sodium bisulfate to destroy the excess $Br_2$, extracted with $CH_2Cl_2$ (3×20 mL), washed

with brine, dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by chromatography (2% ethyl acetate/hexane) to obtain (*R*)-**19** (1.23 g, 100%) as a yellow solid. $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 8.00 (s, *ArH*, 2H), 7.66 (s, *ArH*, 2H), 7.39–7.36 (m, *ArH*, 2H), 7.15–7.11 (m, *ArH*, 6H), 4.90 (s, *OH*, 2H), 2.98–2.94 (m, *CH*($CH_3$)$_2$, 2H), 2.79–2.75 (m, *CH*($CH_3$)$_2$, 2H), 2.65–2.61 (m, *CH*($CH_3$)$_2$, 2H), 1.31 (d, *J*=8.0 Hz, ArCH(*CH*$_3$)$_2$, 12H), 1.20 (d, *J*=4.0 Hz, ArCH(*CH*$_3$)$_2$, 6H), 1.12–1.08 (m, ArCH(*CH*$_3$)$_2$, 12H), 1.03 (d, ArCH(*CH*$_3$)$_2$, 6H); $^{13}$C NMR (100 MHz, $CD_3Cl$): $\delta$ 150.8, 149.8, 148.1, 148.0, 132.2, 130.4, 130.3, 130.3, 130.0, 129.6, 129.4, 126.4, 121.6, 121.6, 117.7, 113.7, 34.5, 31.1, 31.0, 24.5, 24.2, 24.2, 24.1, 23.9; HRMS for $C_{50}H_{56}Br_2O_2$: calcd 846.2647, found 846.2628.

*4.2.5. Diol (R)-**20**.* (*R*)-**19** (0.90 g, 1.06 mmol), $Pd_2(dba)_3$ (0.06 g, 6 mol %, 0.06 mmol) and $PPh_3$ (0.83 g, 3.18 mmol) were added to a 2-necked flask under a $N_2$ atmosphere, followed by ethylene glycol (0.40 g, 0.36 mL). The reaction mixture was heated at 130 °C for 24 h. At this time $CH_2Cl_2$ was added, the mixture was filtered through Celite and the filtrate was concentrated to afford the crude product. This was purified by dissolving it in $CH_2Cl_2$ (2.3 mL) and precipitating it by the addition of cold $Et_2O$ (45 mL). Filtration and washing of the precipitate afforded pure phosphonium salt (*R*)-**20** (1.15 g, 79%) as a yellow solid. $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 7.92–7.88 (m, *ArH*, 8H), 7.82–7.80 (m, *ArH*, 15H), 7.75–7.63 (m, *ArH*, 15H), 7.12 (d, *J*=7.3 Hz, *ArH*, 4H), 3.64 (s, *OH*, 2H), 2.96–2.90 (m, *CH*($CH_3$)$_2$, 2H), 2.72–2.70 (m, *CH*($CH_3$)$_2$, 2H), 2.61–2.59 (m, *CH*($CH_3$)$_2$, 2H), 1.28 (d, *J*=6.9 Hz, ArCH(*CH*$_3$)$_2$, 12H), 1.16 (d, *J*=6.3 Hz, ArCH(*CH*$_3$)$_2$, 6H), 1.11–0.90 (m, ArCH(*CH*$_3$)$_2$, 18H); $^{13}$C NMR (126 MHz, $CD_3Cl$): $\delta$ 154.6 (s, 2C), 150.7 (s, 2C), 148.3 (s, 2C), 148.2 (s, 2C), 137.7 (d, *J*=12.1 Hz, 2C), 136.6 (s, 2C), 135.8 (d, *J*=2.4 Hz, 6C), 134.5 (d, *J*=10.5 Hz, 12C), 132.1 (d, *J*=10.2 Hz, 2C), 132.0.0 (s, 2C), 131.6 (s, 2C), 130.9 (d, *J*=12.8 Hz, 12C), 128.6 (d, *J*=8.5 Hz, 2C), 128.5 (d, *J*=12.2 Hz, 2C),127.4 (s, 2C), 121.8 (s, 2C), 121.8 (s, 2C), 117.9 (d, *J*=89.9 Hz, 6C), 117.5 (d, *J*=89.6 Hz, 2C), 114.2 (s, 2C), 34.4 (s, 2C), 31.0 (s, 2C), 30.9 (s, 2C), 24.3 (s, 2C), 24.3 (s, 2C), 24.1 (s, 2C), 24.0 (s, 2C), 24.0 (s, 2C), 23.9 (s, 2C); $^{31}$P NMR (162 MHz, $CD_3Cl$): $\delta$ 23.2; HRMS for $C_{86}H_{86}O_2P_2^{2+}$: calcd 606.3046, found 606.3067.

*4.2.6. Phosphoric acid (R)-**21**.* To a solution of (*R*)-**20** (0.4 g, 0.29 mmol) in pyridine (4.0 mL) was added $POCl_3$ (0.08 mL, 0.87 mmol) at room temperature under a $N_2$ atmosphere. The reaction mixture was heated at 80 °C and stirred at this temperature for 13 h. At this time water (1.9 mL) was added and stirring was continued for 4 h more at 80 °C. The reaction mixture was then cooled using an ice bath and 3 M HCl was slowly added to the reaction mixture. Extraction with $CH_2Cl_2$ was followed by additional washing with 3 M HCl, drying over anhydrous $MgSO_4$, filtration and solvent removal. The crude product was purified by dissolving it in $CH_2Cl_2$ (1.5 mL) and precipitating it with chilled $Et_2O$ (30 mL) to afford (*R*)-**21** (0.31 g, 84%) as a yellow solid. $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 7.92–7.88 (m, *ArH*, 8H), 7.80–7.70 (m, *ArH*, 26H), 7.55–7.54 (m, *ArH*, 2H), 7.40 (t, *ArH*, 2H), 7.09 (s, *ArH*, 2H), 6.94 (s, *ArH*, 2H), 3.04–3.01 (m, *CH*($CH_3$)$_2$, 2H), 2.89–2.86 (m, *CH*($CH_3$)$_2$, 2H), 2.51 (m, *CH*($CH_3$)$_2$, 2H), 1.32–1.26 (m, ArCH(*CH*$_3$)$_2$, 18H), 1.11 (d, *J*=6.7 Hz, ArCH(*CH*$_3$)$_2$, 6H), 1.06 (d, *J*=6.7 Hz, ArCH(*CH*$_3$)$_2$, 6H), 0.88 (d, *J*=6.4 Hz, ArCH(*CH*$_3$)$_2$, 6H); $^{13}$C NMR (126 MHz, $CD_3Cl$): $\delta$ 153.5 (s, 2C), 148.3 (s, 2C), 148.0 (s, 2C), 146.6 (s, 2C), 137.9 (s, 2C), 137.5 (d, *J*=10.7 Hz, 2C), 135.8 (d, *J*=2.3 Hz, 6C), 135.3 (s, 2C), 134.7 (d, *J*=9.9 Hz, 2C), 134.5 (d, *J*=10.4 Hz, 12C), 132.9 (s, 2C), 131.4 (s, 2C), 130.9 (d, *J*=12.3 Hz, 2C), 130.9 (d, *J*=12.7 Hz, 12C), 129.6 (d, *J*=10.7 Hz, 2C), 122.2 (s, 2C), 121.3 (s, 2C), 120.0 (s, 2C), 117.8 (d, *J*=89.9 Hz, 6C), 117.5(d, *J*=89.6 Hz, 2C), 34.3 (s, 2C), 31.2 (s, 2C), 30.9 (s, 2C), 26.6 (s, 2C), 25.1 (s, 2C), 24.1 (s, 2C), 24.1 (s, 2C), 23.7 (s, 2C), 23.3 (s, 2C); $^{31}$P NMR (162 MHz, $CD_3Cl$): $\delta$ 23.1, 2.0; HRMS for $C_{86}H_{85}O_4P_3^{2+}$: calcd 637.2825, found 637.2873; HRMS for $C_{86}H_{84}O_4P_3^{+}$: calcd 1273.5577, found 1273.5535.

*4.2.7. Phosphoric acid (R)-**17**.* A solution of $KPF_6$ (0.29 g, 1.59 mmol) in $CH_3CN$ (28 mL) was added dropwise to a solution of (*R*)-**21** (0.57 g, 0.40 mmol) in $CH_2Cl_2$ (28 mL) and the resulting reaction mixture was stirred at room temperature for 3 h. Afterwards, the mixture was washed with 3 M HCl, dried over anhydrous $MgSO_4$, filtered and evaporated to dryness to afford (*R*)-**17** (0.32 g, 100%). If necessary, the product could be purified by dissolving it in $CH_2Cl_2$ and precipitating it with $Et_2O$. $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 8.00 (d, *J*=14.9 Hz, *ArH*, 2H), 7.87–7.83 (m, *ArH*, 8H), 7.75–7.67 (m, *ArH*, 28H), 6.98 (d, *J*=7.0 Hz, *ArH*, 4H), 2.87–2.86 (m, *CH*($CH_3$)$_2$, 2H), 2.54–2.50 (m, *CH*($CH_3$)$_2$, 4H), 1.22 (d, *J*=6.9 Hz, ArCH(*CH*$_3$)$_2$, 12H), 1.06 (d, *J*=6.8 Hz, ArCH(*CH*$_3$)$_2$, 6H), 1.00 (d, *J*=6.7 Hz, ArCH(*CH*$_3$)$_2$, 6H), 0.94 (d, *J*=6.7 Hz, ArCH(*CH*$_3$)$_2$, 6H), 0.90 (d, *J*=6.4 Hz, ArCH(*CH*$_3$)$_2$, 6H); $^{13}$C NMR (126 MHz, $CD_3Cl$): $\delta$ 151.7 (s, 2C), 148.7 (s, 2C), 147.8 (s, 2C), 147.0 (s, 2C), 137.6 (d, *J*=2.0 Hz, 6C), 136.8 (s, 2C), 135.6 (s, 2C), 134.9 (d, *J*=9.0 Hz, 12C), 134.6 (d, *J*=10.3 Hz, 2C), 132.1 (d, *J*=9.9 Hz, 2C), 130.9 (d, *J*=12.1 Hz, 12C), 130.7 (s, 2C), 130.2 (s, 2C), 130.0 (d, *J*=13.1 Hz, 2C), 128.6 (d, *J*=12.4 Hz, 2C), 122.0 (s, 2C), 121.2 (s, 2C), 120.3 (s, 2C), 117.9 (d, *J*=89.6 Hz, 8C), 34.3 (s, 2C), 31.1 (s, 2C), 31.1 (s, 2C), 29.7 (s, 2C), 26.6 (s, 2C), 25.3 (s, 2C), 24.1 (s, 2C), 23.6 (s, 2C), 23.2 (s, 2C); $^{31}$P NMR (162 MHz, $CD_3Cl$): $\delta$ 23.2, 1.5, −144.5 (septet, *J*=713 Hz, *P*$F_6$) $^{19}$F NMR (376 MHz, $CD_3Cl$): $\delta$ −73.4 (d, *J*=713 Hz, P*F*$_6$); HRMS for $C_{86}H_{85}O_4P_3^{2+}$: calcd 637.2825, found 637.2779; HRMS for $C_{86}H_{84}O_4P_3^{+}$: calcd 1273.5577, found 1273.5518.

### 4.3. Friedel–Crafts reaction procedures

*4.3.1. General procedure for Friedel–Crafts reaction of indoles with enamides (Table 1).* Phosphoric acid catalyst (*R*)-**17** (15.6 mg, 0.01 mmol, 10 mol %), enamide **8** (0.1 mmol, 1.0 equiv) and 4 Å MS (90 mg) were added to a flame dried Schlenck tube under a $N_2$ atmosphere, followed by dry $CH_2Cl_2$ (1.5 mL). The reaction mixture was then cooled to 0 °C and indole **7** (0.14 mmol, 1.4 equiv) was added. After TLC analysis indicated that the reaction was completed, the reaction mixture was purified directly by chromatography (50% ethyl acetate/hexane) to afford product **9**.

*4.3.1.1. N-(1-(3-Indolyl)-1-phenylethyl)acetamide (**9a**).* This was obtained in 91% yield and 75% ee. $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 8.19 (s, *NH*, 1H), 7.48 (d, *J*=8.0 Hz, *ArH*, 1H), 7.41 (d, *J*=8.1 Hz, *ArH*, 2H), 7.36–7.31 (m, *ArH*, 3H), 7.27–7.23 (m, *ArH*, 1H), 7.18 (dt, *J*=7.3, 1.0 Hz, *ArH*, 1H), 7.06 (dt, *J*=7.4, 0.9 Hz, *ArH*, 1H), 6.69 (d, *J*=2.3 Hz, *ArH*, 1H), 6.31 (s, *NH*, 1H), 2.34 (s, *CH*$_3$, 3H), 2.02 (s, *CH*$_3$, 3H); $^{13}$C NMR (126 MHz, $CD_3Cl$): $\delta$ 169.3, 145.4, 137.1, 128.2, 126.8, 126.2, 124.8, 123.1, 122.7, 122.2, 120.2, 119.8, 111.7, 59.3, 26.7, 24.5; HRMS for $C_{18}H_{18}N_2O$: calcd 278.1419, found 278.1416; HPLC conditions: IPA/hexane=10:90, flow rate=1.0 mL/min, AD-H column, minor 21.0 min, major 33.2 min.

*4.3.1.2. N-(1-(4-Bromophenyl)-1-(3-indolyl)ethyl)acetamide (**9b**).* This was obtained in 94% yield and 91% ee. $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 8.41 (s, *NH*, 1H), 7.49 (d, *J*=8.0 Hz, *ArH*, 1H), 7.43 (d, *J*=8.6 Hz, *ArH*, 2H), 7.34–7.28 (m, *ArH*, 3H), 7.19 (t, *J*=7.6 Hz, *ArH*, 1H), 7.08 (t, *J*=7.5 Hz, *ArH*, 1H), 6.61 (d, *J*=2.6 Hz, *ArH*, 1H), 6.36 (s, *NH*, 1H), 2.30 (s, *CH*$_3$, 3H), 2.01 (s, *CH*$_3$, 3H); $^{13}$C NMR (101 MHz, $CD_3Cl$): $\delta$ 169.6, 144.5, 137.3, 131.4, 128.3, 124.6, 123.1, 122.5, 122.2, 120.9, 120.1, 120.0, 112.0, 59.1, 26.6, 24.5; HRMS for $C_{18}H_{17}BrN_2O$: calcd 356.0524, found 356.0502; HPLC condition: IPA/hexane=10:90, flow rate=1.0 mL/min, AD-H column, minor 20.0 min, major 25.3 min.

*4.3.1.3. N-(1-(4-Flourophenyl)-1-(3-indolyl)ethyl)acetamide (**9c**).* This was obtained in 71% yield and 80% ee. $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 8.19 (s, *NH*, 1H), 7.49 (d, *J*=8.0 Hz, *ArH*, 1H), 7.40–7.35 (m, *ArH*, 3H), 7.20 (t, *J*=7.6 Hz, *ArH*, 1H), 7.10 (t, *J*=7.6 Hz, *ArH*, 1H), 7.00

(t, *J*=8.7 Hz, *ArH*, 2H), 6.67 (d, *J*=2.3 Hz, *ArH*, 1H), 6.31 (s, *NH*, 1H), 2.32 (s, *CH*$_3$, 3H), 2.02 (s, *CH*$_3$, 3H); $^{13}$C NMR (126 MHz, $CD_3Cl$): $\delta$ 169.3 (s, 1C), 161.7 (d, *J*=246 Hz, 1C), 141.0 (d, *J*=2.9 Hz, 1C), 137.1 (s, 1C), 128.0 (s, 1C), 127.9 (s, 1C), 124.6 (s, 1C), 122.9 (d, *J*=11.8 Hz, 2C), 122.4 (s, 1C), 120.2 (s, 1C), 120.0 (s, 1C), 114.9 (d, *J*=21.4 Hz, 2C), 111.8 (s, 1C), 58.9 (s, 1C), 26.7 (s, 1C), 24.4 (s, 1C); HRMS for $C_{18}H_{17}FN_2O$: calcd 296.1325, found 296.1319; HPLC condition: IPA/hexane=10:90, flow rate=1.0 mL/min, AD-H column, minor 18.7 min, major 23.7 min.

*4.3.1.4. N-(1-(3-Indolyl)-1-(4-methoxyphenyl)ethyl)acetamide (**9d**).* This was obtained in 65% yield and 61% ee. $^1$H NMR (300 MHz, $CD_3Cl$): $\delta$ 8.08 (s, *NH*, 1H), 7.49 (d, *J*=8.1 Hz, *ArH*, 1H), 7.38–7.32 (m, *ArH*, 3H), 7.19 (t, *J*=7.5 Hz, *ArH*, 1H), 7.06 (t, *J*=7.4 Hz, *ArH*, 1H), 6.86 (d, *J*=8.8 Hz, *ArH*, 2H), 6.74 (d, *J*=2.4 Hz, *ArH*, 1H), 6.27 (s, *NH*, 1H), 3.80 (s, MeO, 3H), 2.31 (s, *CH*$_3$, 3H), 2.01 (s, *CH*$_3$, 3H); $^{13}$C NMR (126 MHz, $CD_3Cl$): $\delta$ 169.3, 158.3, 137.7, 137.1, 129.2, 127.4, 124.8, 123.1, 122.7, 122.1, 120.3, 119.7, 113.5, 113.5, 111.7, 58.9, 55.3, 26.8, 24.5; HRMS for $C_{19}H_{20}N_2O_2$: calcd 308.1525, found 308.1524; HPLC condition: IPA/hexane=17:83, flow rate=1.0 mL/min, AS-H column, major 14.7 min, minor 20.3 min.

*4.3.1.5. N-(1-(5-Bromo-3-indolyl)-1-phenylethyl)acetamide (**9e**).* This was obtained in 83% yield and 89% ee. $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 8.29 (s, *NH*, 1H), 7.53 (s, *ArH*, 1H), 7.38–7.31 (m, *ArH*, 4H), 7.29–7.28 (m, *ArH*, 1H), 7.24 (dd, *J*=8.6, 1.8 Hz, *ArH*, 1H), 7.17 (d, *J*=8.6 Hz, *ArH*, 1H), 6.78 (d, *J*=2.6 Hz, *ArH*, 1H), 6.21 (s, *NH*, 1H), 2.28 (s, *CH*$_3$, 3H), 2.04 (s, *CH*$_3$, 3H); $^{13}$C NMR (126 MHz, $CD_3Cl$): $\delta$ 169.4, 145.2, 135.7, 128.4, 127.2, 126.7, 126.1, 125.0, 124.5, 122.7, 121.5, 113.1, 112.9, 59.1, 27.2, 24.5; HRMS for $C_{18}H_{17}BrN_2O$: calcd 356.0524, found 356.0502; HPLC condition: IPA/hexane=10:90, flow rate=1.0 mL/min, AD-H column, minor 17.3 min, major 35.4 min.

*4.3.1.6. N-(1-(5-Flouro-3-indolyl)-1-phenylethyl)acetamide (**9f**).* This was obtained in 80% yield and 58% ee. $^1$H NMR (500 MHz, $CD_3Cl$): $\delta$ 8.07 (s, *NH*, 1H), 7.39–7.36 (m, *ArH*, 2H), 7.33 (t, *J*=7.6 Hz, *ArH*, 3H), 7.30–7.28 (m, *ArH*, 1H), 7.04 (dd, *J*=2.0, 9.0 Hz, *ArH*, 1H), 6.93 (dt, *J*=2.5, 9.0 Hz, *ArH*, 1H), 6.87 (d, *J*=2.5 Hz, *ArH*, 1H), 6.19 (s, *NH*, 1H), 2.30 (s, *CH*$_3$, 3H), 2.03 (s, *CH*$_3$, 3H); $^{13}$C NMR (126 MHz, $CD_3Cl$): $\delta$ 169.3 (s, 1C), 157.6 (d, *J*=230 Hz, 1C), 145.2 (s, 1C), 133.5 (s, 1C), 130.9 (d, *J*=3.0 Hz, 1C), 128.8 (s, 1C), 128.4 (s, 2C), 127.1 (s, 1C), 126.1 (s, 1C), 124.8 (s, 2C), 112.3 (d, *J*=9.7 Hz, 1C), 110.6 (d, *J*=26.6 Hz, 1C), 105.3 (d, *J*=24.2 Hz, 1C), 59.2 (s, 1C), 26.8 (s, 1C), 24.5 (s, 1C); HRMS for $C_{18}H_{17}FN_2O$: calcd 296.1325, found 296.1320; HPLC condition: IPA/hexane=10:90, flow rate=1.0 mL/min, AD-H column minor 18.5 min, major 30.6 min.

*4.3.2. General procedure for Friedel–Crafts Reaction of indoles with β,γ-unsaturated α-keto esters (Table 2).* Phosphoric acid catalyst (*R*)-**17** (5.5 mg, 0.005 mmol, 5 mol %), β,γ-unsaturated α-keto ester **10** (0.07 mmol, 1.0 equiv) and 4 Å MS (90 mg) were added to a flame dried Schlenk tube under a $N_2$ atmosphere, followed by dry $CH_2Cl_2$ (1.0 mL). The reaction mixture was then cooled to −78 °C and indole **7** (0.15 mmol, 2.1 equiv) was added. After TLC analysis indicated that the reaction was completed, the reaction mixture was purified directly by chromatography (20% ethyl acetate/hexane) to afford product **11**.

*4.3.2.1. 4-(1H-Indol-3-yl)-2-oxo-4-phenylbutyric acid ethyl ester (**11a**).* This was obtained in 98% yield and 61% ee. $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 8.01 (s, *NH*, 1H), 7.42 (d, *J*=8.0 Hz, *ArH*, 1H), 7.32 (t, *J*=6.8 Hz, *ArH*, 3H), 7.26 (t, *J*=7.5 Hz, *ArH*, 2H), 7.15 (q, *J*=6.0 Hz, *ArH*, 2H), 7.02 (t, *J*=7.5 Hz, *ArH*, 2H), 4.91 (t, *J*=7.5 Hz, *CH*, 1H), 4.20 (dq, *J*=1.2, 5.6 Hz, *CH*$_2$, 2H), 3.67 (dd, *J*=7.4, 16.9 Hz, *CH*$_a$*H*$_b$, 1H), 3.59 (dd, *J*=7.4, 16.9 Hz, *CH*$_a$*H*$_b$, 1H), 1.26 (t, *J*=7.1 Hz, *CH*$_3$, 3H); $^{13}$C NMR (126 MHz, $CD_3Cl$): $\delta$ 193.2, 161.1, 143.4, 136.7, 128.7, 127.9, 126.7, 126.6, 122.4, 121.7, 119.7, 119.5, 118.5, 111.3, 62.6, 45.7, 37.9, 14.0; HRMS for $C_{20}H_{19}NO_3$: calcd 321.1365, found 321.1356; HPLC condition: IPA/hexane=10:90, flow rate=1.0 mL/min, AD-H column, major 22.5 min, minor 28.4 min.

*4.3.2.2. 4-(1H-Indol-3-yl)-2-oxo-4-(4-methylphenyl)butyric acid ethyl ester (**11b**).* This was obtained in 94% yield and 50% ee. $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 8.01 (s, *NH*, 1H), 7.43 (d, *J*=7.9 Hz, *ArH*, 1H), 7.30 (d, *J*=8.1 Hz, *ArH*, 1H), 7.20 (d, *J*=8.0 Hz, *ArH*, 2H), 7.15 (t, *J*=7.8 Hz, *ArH*, 1H), 7.07–7.00 (m, *ArH*, 4H), 4.88 (t, *J*=7.5 Hz, *CH*, 1H), 4.20 (dq, *J*=1.1, 4.1 Hz, *CH*$_2$, 2H), 3.63 (dd, *J*=7.3, 18.9 Hz, *CH*$_a$*H*$_b$, 1H), 3.59 (dd, *J*=7.3, 18.9 Hz, *CH*$_a$*H*$_b$, 1H), 2.27 (s, *CH*$_3$, 3H), 1.26 (t, *J*=7.1 Hz, *CH*$_3$, 3H); $^{13}$C NMR (126 MHz, $CD_3Cl$): $\delta$ 193.3, 161.2, 140.3, 136.7, 136.2, 129.4, 127.8, 126.6, 122.4, 121.6, 119.6, 119.6, 118.7, 111.3, 62.6, 45.9, 37.6, 21.1, 14.0; HRMS for $C_{21}H_{21}NO_3$: calcd 335.1521, found 335.1521; HPLC condition: IPA/hexane=10:90, flow rate=1.0 mL/min, AD-H column, major 22.2 min, minor 30.3 min.

*4.3.2.3. 4-(1H-Indol-3-yl)-2-oxo-4-(4-bromophenyl)butyric acid ethyl ester (**11c**).* This was obtained in 92% yield and 60% ee. $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 8.04 (s, *NH*, 1H), 7.40–7.32 (m, *ArH*, 4H), 7.21–7.15 (m, *ArH*, 3H), 7.05–7.01 (m, *ArH*, 2H), 4.87 (t, *J*=7.5 Hz, *CH*, 1H), 4.24 (dq, *J*=0.6, 7.1 Hz, *CH*$_2$, 2H), 3.65 (dd, *J*=7.0, 12.1 Hz, *CH*$_a$*H*$_b$, 1H), 3.56 (dd, *J*=8.0, 12.6 Hz, *CH*$_a$*H*$_b$, 1H), 1.29 (t, *J*=7.1 Hz, *CH*$_3$, 3H); $^{13}$C NMR (126 MHz, $CD_3Cl$): $\delta$ 192.7, 160.9, 142.3, 136.6, 131.6, 129.6, 126.2, 122.5, 121.5, 120.4, 119.7, 119.3, 117.9, 111.2, 62.6, 45.3, 37.2, 13.9; HRMS for $C_{20}H_{18}BrNO_3$: calcd 399.0470, found 399.0464; HPLC condition: IPA/hexane=10:90, flow rate=1.0 mL/min, AD-H column, major 23.2 min, minor 38.4 min.

*4.3.2.4. 4-(1H-Indol-3-yl)-2-oxo-4-(4-methoxyphenyl)butyric acid ethyl ester (**11d**).* This was obtained in 89% yield and 50% ee. $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 8.02 (s, *NH*, 1H), 7.41 (d, *J*=7.9 Hz, *ArH*, 1H), 7.31 (d, *J*=8.1 Hz, *ArH*, 1H), 7.20 (d, *J*=8.5 Hz, *ArH*, 2H), 7.15 (t, *J*=7.5 Hz, *ArH*, 1H), 7.07–7.01 (m, *ArH*, 2H), 6.79 (d, *J*=8.5 Hz, *ArH*, 2H), 4.86 (t, *J*=7.5 Hz, *CH*, 1H), 4.24 (q, *J*=6.9 Hz, *CH*$_2$, 2H), 3.75 (s, −*OCH*$_3$, 3H), 3.64 (dd, *J*=7.2, 16.7 Hz, *CH*$_a$*H*$_b$, 1H), 3.57 (dd, *J*=8.0, 16.7 Hz, *CH*$_a$*H*$_b$, 1H), 1.27 (t, *J*=7.0 Hz, *CH*$_3$, 3H); $^{13}$C NMR (101 MHz, $CD_3Cl$): $\delta$ 193.4, 161.1, 158.3, 136.7, 135.5, 135.5, 128.9, 126.6, 122.4, 121.5, 119.6, 119.6, 118.9, 114.0, 111.3, 62.6, 55.6, 45.9, 37.2, 14.0; HRMS for $C_{21}H_{21}NO_4$: calcd 351.1471, found 351.1467; HPLC condition: IPA/hexane=17:83, flow rate=1.0 mL/min, AS-H column, major 15.3 min, minor 17.9 min.

*4.3.2.5. 4-(1H-5-Bromoindol-3-yl)-2-oxo-4-phenylbutyric acid ethyl ester (**11e**).* This was obtained in 90% yield and 46% ee. $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 8.08 (s, *NH*, 1H), 7.53 (s, *ArH*, 1H), 7.31–7.24 (m, *ArH*, 4H), 7.22–7.17 (m, *ArH*, 3H), 7.05 (d, *J*=2.0 Hz, *ArH*, 1H), 4.85 (t, *J*=7.5 Hz, *CH*, 1H), 4.23 (dq, *J*=1.0, 8.4 Hz, *CH*$_2$, 2H), 3.64 (dd, *J*=7.6, 17.1 Hz, *CH*$_a$*H*$_b$, 1H), 3.56 (dd, *J*=7.6, 17.0 Hz, *CH*$_a$*H*$_b$, 1H), 1.28 (t, *J*=7.1 Hz, *CH*$_3$, 3H); $^{13}$C NMR (101 MHz, $CD_3Cl$): 193.0, 161.0, 142.9, 135.3, 128.8, 128.3, 127.8, 126.9, 125.4, 122.9, 122.0, 118.1, 113.0, 112.8, 62.7, 45.7, 37.7, 14.1; HRMS for $C_{20}H_{18}BrNO_3$: calcd 399.0470, found 399.0464; HPLC condition: IPA/hexane=10:90, flow rate=1.0 mL/min, AD-H column, major 16.8 min, minor 20.6 min.

*4.3.2.6. 4-(1H-5-Flouroindol-3-yl)-2-oxo-4-phenylbutyric acid ethyl ester (**11f**).* This was obtained in 92% yield and 54% ee. $^1$H NMR (400 MHz, $CD_3Cl$): $\delta$ 8.07 (s, *NH*, 1H), 7.29–7.19 (m, *ArH*, 6H), 7.07–7.02 (m, *ArH*, 2H), 6.88 (t, *J*=7.5 Hz, *ArH*, 1H), 4.83 (t, *J*=7.3 Hz, *CH*, 1H), 4.22 (q, *J*=6.8 Hz, *CH*$_2$, 2H), 3.65 (dd, *J*=7.5, 16.9 Hz, *CH*$_a$*H*$_b$, 1H), 3.56 (dd, *J*=7.5, 16.9 Hz, *CH*$_a$*H*$_b$, 1H), 1.28 (t, *J*=7.1 Hz, *CH*$_3$, 3H); $^{13}$C NMR (101 MHz, $CD_3Cl$): $\delta$ 193.1 (s, 1C), 161.1 (s, 1C), 157.7 (d, *J*=230 Hz, 1C), 143.0 (s, 1C), 133.2 (s, 1C), 128.8 (s, 2C), 127.8 (s, 2C), 127.0 (s, 1C), 126.9 (s, 1C), 123.4 (s, 1C), 118.6 (d, *J*=3.5 Hz, 1C), 111.9

(d, $J$=9.7 Hz, 1C), 110.9 (d, $J$=26.3 Hz, 1C), 104.5 (d, $J$=23.5 Hz, 1C), 62.7 (s, 1C), 45.6 (s, 1C), 37.8 (s, 1C), 14.0 (s, 1C); HRMS for $C_{20}H_{18}FNO_3$: calcd 339.1271, found 339.1266; HPLC condition: IPA/hexane=10:90, flow rate=1.0 mL/min, AD-H column, minor 18.0 min, major 22.9 min.

*4.3.3. Recycling experiments (Table 3).* These reactions were performed using **7a** (2.8 mmol), **8b** (2.0 mmol) and (*R*)-**17** (0.2 mmol) as described above using catalyst recovered from the previous experiment. Recovery of the catalyst was achieved by precipitation from the reaction mixture using diethyl ether, and the morphology and $^1$H NMR spectra of the recovered material was essentially identical to that of newly synthesized (*R*)-**17**.

## Acknowledgements

This research was supported financially by the University of Hong Kong and the Research Grants Council of the Hong Kong SAR, PR of China (Project No. HKU 705209P), and Mr. Jun Ou performed some preliminary experiments.

## Supplementary data

Supplementary data associated with this article, including $^1$H, $^{13}$C, $^{19}$F and $^{31}$P NMR spectra and HPLC graphs. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.03.105.

## References and notes

1. Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566.
2. Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356.
3. For reviews regarding chiral phosphoric acid organocatalysis, see: (a) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909; (b) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744; (c) Terada, M. *Chem. Commun.* **2008**, 4097; (d) Adair, G.; Mukherjee, S.; List, B. *Aldrichimica Acta* **2008**, *41*, 31; (e) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2010**, *8*, 5262.
4. Rueping, M.; Sugiono, E.; Steck, A.; Theissmann, T. *Adv. Synth. Catal.* **2010**, *352*, 281.
5. Storer, R. I.; Carrera, D. E.; Ni, Y.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 84.
6. Liu, H.; Cun, L. F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Org. Lett.* **2006**, *8*, 6023.
7. (a) Poupon, J. C.; Boezio, A. A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1415; (b) Stazi, F.; Marcoux, D.; Poupon, J. C.; Latassa, D.; Charette, A. B. *Angew. Chem., Int. Ed.* **2007**, *46*, 5011; (c) Poupon, J. C.; Marcoux, D.; Cloarec, J. M.; Charette, A. B. *Org. Lett.* **2007**, *9*, 3591; (d) Marcoux, D.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 590; (e) Ginisty, M.; Roy, M. N.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 2542; (f) Marcoux, D.; Charette, A. B. *Adv. Synth. Catal.* **2008**, *350*, 2967; (g) Roy, M. N.; Poupon, J. C.; Charette, A. B. *J. Org. Chem.* **2009**, *74*, 8510.
8. Periasamy, M.; Nagaraju, M.; Kishorebabu, N. *Synthesis* **2007**, *24*, 3821.
9. Tsang, W. C. P.; Schrock, R. R.; Hoveyda, A. H. *Organometallics* **2001**, *20*, 5658.
10. Hua, J.; Lin, W. *Org. Lett.* **2004**, *6*, 861.
11. For reviews of asymmetric Friedel–Crafts reactions in general, see: (a) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199; (b) Poulsen, T.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903; (c) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190; (d) Terrasson, V.; de Figueiredo, R. M.; Campagne, J. M. *Eur. J. Org. Chem.* **2010**, 2635.
12. For reviews of asymmetric Friedel–Crafts reactions of indole substrates, see: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550; (b) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608; (c) Zeng, M.; You, S. L. *Synlett* **2010**, 1289.
13. (a) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1; (b) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278; (c) Agarwal, S.; Caemmerer, S.; Filali, S.; Froehner, W.; Knoell, J.; Krahl, M. P.; Reddy, K. R.; Knölker, H.-J. *Curr. Org. Chem.* **2005**, *9*, 1601; (d) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873; (e) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532; (f) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875.
14. For selected examples of asymmetric Friedel–Crafts reactions catalyzed by chiral phosphoric acids, see: (a) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292; (b) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484; (c) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609; (d) Terada, M.; Yokoyama, S.; Sorimachi, K.; Uraguchi, D. *Adv. Synth. Catal.* **2007**, *349*, 1863; (e) Jia, Y. X.; Zhong, J.; Zhu, S. F.; Zhang, C. M.; Zhou, Q. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5565; (f) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 4016; (g) Sun, F. L.; Zheng, X. J.; Gu, Q.; He, Q. L.; You, S. L. *Eur. J. Org. Chem.* **2010**, *47*, 8.
15. For selected examples of chiral metal-complex catalysis, see: (a) Johannsen, M. *Chem. Commun.* **1999**, 2233; (b) Gathergood, N.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 12517; (c) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030; (d) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780; (e) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942; (f) Jia, Y. X.; Xie, J. H.; Duan, H. F.; Wang, L. X.; Zhou, Q. L. *Org. Lett.* **2006**, *8*, 1621; (g) Blay, G.; Fernández, I.; Pedro, J. R.; Vila, C. *Org. Lett.* **2007**, *9*, 2601; (h) Liu, Z.; Shi, M. *Tetrahedron: Asymmetry* **2009**, *20*, 119; (i) Wang, W.; Liu, X.; Cao, W.; Wang, J.; Lin, L.; Feng, X. *Chem.—Eur. J.* **2010**, *16*, 1664.
16. For selected examples of enantioselective organocatalysis, see: (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172; (b) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156; (c) Wang, Z.-J.; Yang, J.-G.; Jin, J.; Lv, X.; Bao, W. *Synthesis* **2009**, *23*, 3994; (d) Qian, Y.; Ma, G.; Lv, A.; Zhu, H. L.; Zhao, J.; Rawal, V. H. *Chem. Commun.* **2010**, 3004.
17. Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593.
18. Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070.
19. (a) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424; (b) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074; (c) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368.
20. Zhu, C.; Akiyama, T. *Org. Lett.* **2009**, *11*, 4180.
21. Zhang, G. W.; Wang, L.; Nie, J.; Ma, J. A. *Adv. Synth. Catal.* **2008**, *350*, 1457.
22. Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251.
23. Desimoni, G.; Faita, G.; Toscanini, M.; Boiocchi, M. *Chem.—Eur. J.* **2008**, *14*, 3630.
24. Klussmann, M.; Ratjen, L.; Hoffmann, S.; Wakchaure, V.; Goddard, R.; List, B. *Synlett* **2010**, 2189.
25. It should be noted that NMR analysis of the recovered and recycled (*R*)-**17** afforded spectra that matched that of newly prepared material. Thus, if such an impurity was present, its concentration was below the limit of detection of NMR analysis.
26. (a) Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3035; (b) Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2008**, *350*, 399.