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Catalytic Asymmetric Synthesis of Atropisomeric Quinolines through the Friedländer Reaction

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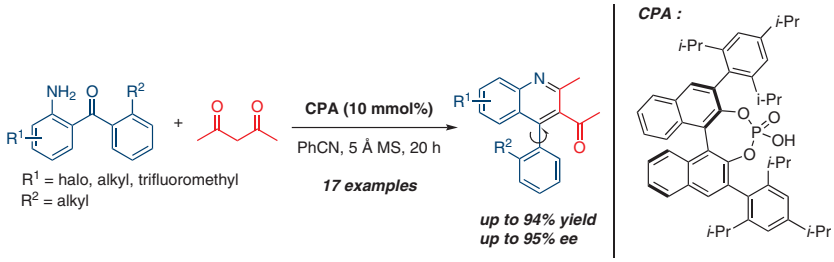

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Abstract A phosphoric acid catalyzed atroposelective Friedländer reaction was developed in which acetylacetone and a variety of 2′-substituted 2-aminobenzophenones were successfully employed to give optically active biaryl quinolines in good yields and with high enantioselectivities.

Key words Friedländer reaction, atroposelectivity, quinolines, phosphoric acids, acetylacetone

Since the first detection of atropisomerism by Christie and Kenner in 1922,[1] axially chiral scaffolds, especially biaryl ones, have been found in numerous natural products, bioactive compounds, functional materials, chiral catalysts, and ligands (Figure 1).[2–5] Inspired by these findings, many groups have since explored the asymmetric synthesis of axially chiral biaryl compounds.[6] In this context, asymmetric C–H functionalization reactions provide efficient strategies for constructing these molecules from prepared heteroaryls.[7] Furthermore, organocatalytic constructions of axially chiral biaryl compounds through transfer hydrogenation,[8] electrophilic halogenation,[9] or annulation[10] have also become well established. These reported examples provide various approaches for obtaining diverse axially chiral biaryl compounds with good outcomes. As part of our continuing interest in the catalytic asymmetric synthesis of heterocycles,[11] we are particularly interested in quinoline-type chiral biaryl moieties, not only because these represent important key structures of alkaloids and bioactive compounds, but also because of their unique properties, such as coordination and basic properties in catalytic transformations. Although many contributions have been made to the catalytic asymmetric syntheses of axially chiral biaryl compounds, the direct catalytic construction of a quinoline motif with simultaneous creation of atroposelectivity, which might provide versatile atropoisomeric quinolines from simple starting materials, is an attractive target that remains largely unexplored and unexploited.[12] We surmised that a Friedländer reaction, an efficient cascade approach to polysubstituted quinolines from 2-aminobenzophenones and 1,3-dicarbonyl compounds, might be an ideal way of achieving this goal.

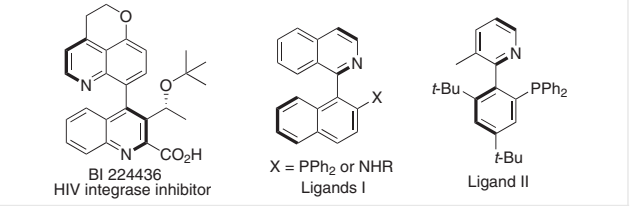

Figure 1 Bioactive compound and ligands with axially chiral biaryl structures

A simple retrosynthetic analysis clearly indicated that 2′-substituted 2-aminobenzophenones might be suitable reactants to provide restricted rotation of the two aromatic rings in the products of the Friedländer reaction. However, few examples exist of enantioselective Friedländer reactions, all of which were focused on breaking the symmetry of 4-substituted cyclohexanes.[12,13] Here, we report a chiral phosphoric acid catalyzed atroposelective Friedländer reaction of acetylacetone with a variety of 2-substituted benzophenones that affords enantioenriched biaryl quinolones in good yields and with high enantioselectivities.

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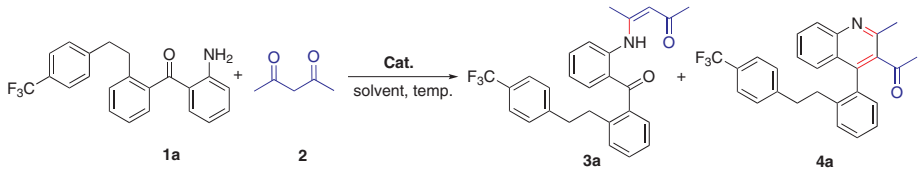
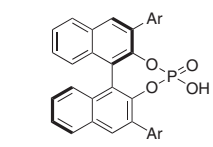
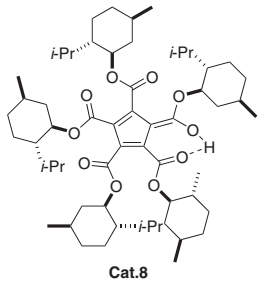
To test our hypothesis regarding the chiral-acid-catalyzed atroposelective Friedländer reaction, (2-aminophenyl)(2-{2-[4-(trifluoromethyl)phenyl]ethyl}phenyl)methanone (**1a**) and acetylacetone (**2**) were treated under various conditions (Table 1). First, the catalytic activity of various chiral phosphoric acids **Cat.1**–**Cat.7** was evaluated in $CHCl_3$. Most phosphoric acids promoted the target reaction well and afforded the desired product **4a** in moderate to good yields and enantioselectivities (Table 1, entries 1–7), accompanied by small amounts of the enamine intermediate **3a**. The 2,4,6-triisopropylphenyl-substituted catalyst **Cat.5** proved to be the catalyst of choice (entry 5; 65% yield, 84% ee). In addition, **Cat.8**,[14] a novel Brønsted acid with low pH, was also tested. However, this showed poor catalytic ability, and none of the Friedländer reaction product was obtained (entry 8). Subsequently, the effect of the solvent was studied and it was found that both the reactivity and enantioselectivity were improved by employing PhCN as the reaction medium. Finally, the best result was obtained when the reaction was carried out in the presence of 5 Å molecular sieves while heating from rt to 120 °C (Table 1, entry 15; 92% yield, 88% ee).

Table 1 Effects of Various Conditions on the Reaction of the 2-Aminobenzophenone **1a** and Acetylacetone (**2**)[a]





(*R*)-**Cat.1**: Ar = 1-naphthyl
(*R*)-**Cat.2**: Ar = 2,4,6-trimethylphenyl
(*R*)-**Cat.3**: Ar = 1-pyrenyl
(*R*)-**Cat.4**: Ar = 4-(2-naphthyl)phenyl
(*R*)-**Cat.5**: Ar = 2,4,6-triisopropylphenyl
(*R*)-**Cat.6**: Ar = triphenylsilyl
(*R*)-**Cat.7**: Ar = phenyl

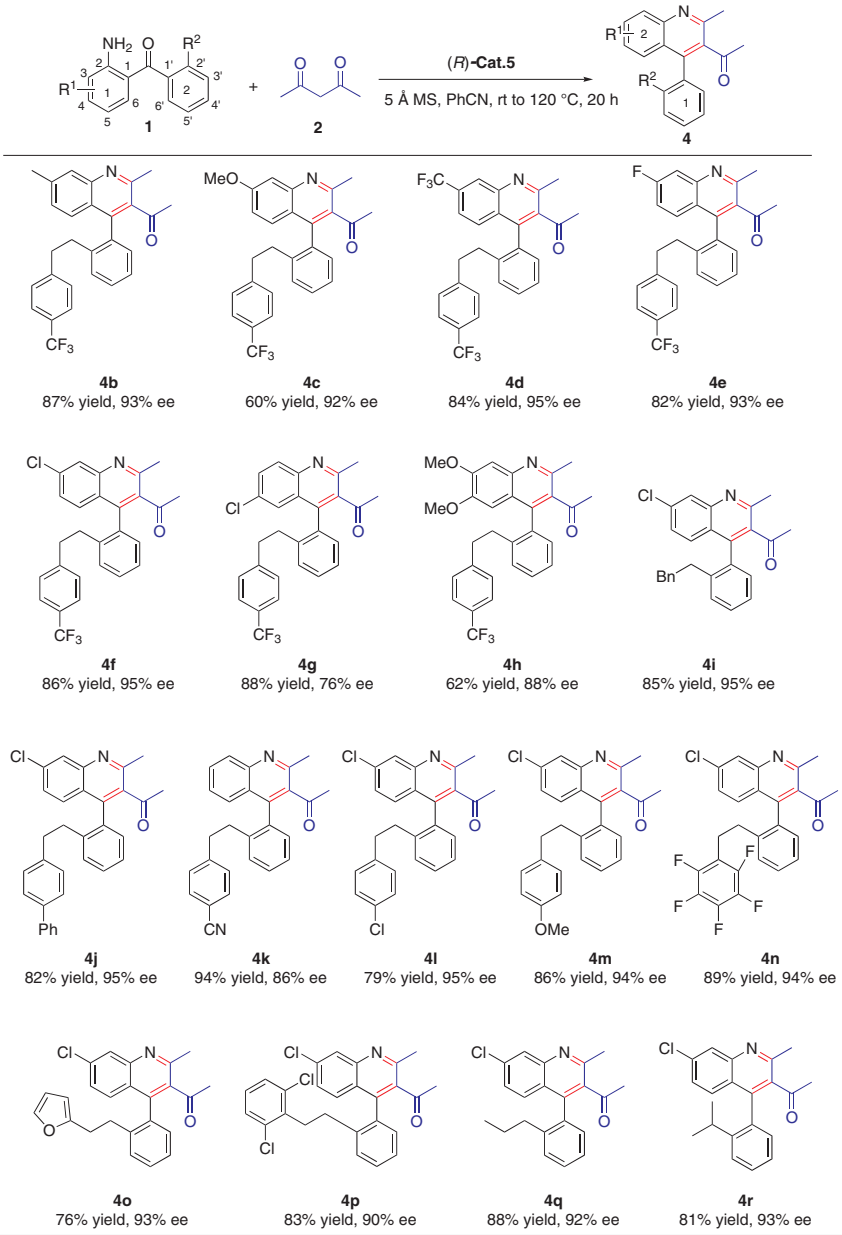


Cat.8

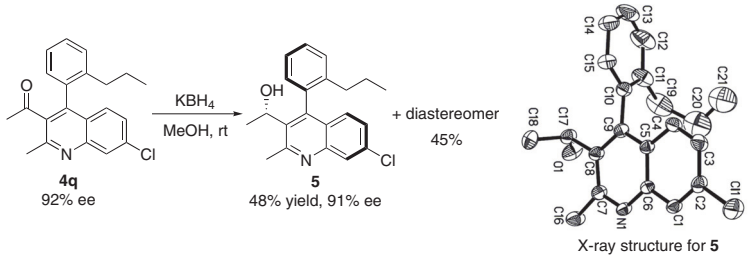
Entry	Catalyst	Solvent	Yield[b] (%) of **3**	Yield[b] (%) of **4**	ee[c] (%)
1	(*R*)-**Cat.1**	$CHCl_3$	8	45	5
2	(*R*)-**Cat.2**	$CHCl_3$	trace	72	26
3	(*R*)-**Cat.3**	$CHCl_3$	11	31	13
4	(*R*)-**Cat.4**	$CHCl_3$	8	60	16
5	(*R*)-**Cat.5**	$CHCl_3$	trace	65	84
6	(*R*)-**Cat.6**	$CHCl_3$	12	trace	–
7	(*R*)-**Cat.7**	$CHCl_3$	6	46	18
8	**Cat.8**	$CHCl_3$	18	–	–
9	(*R*)-**Cat.5**	CH_2Cl_2	5	56	84
10	(*R*)-**Cat.5**	toluene	trace	60	82
11	(*R*)-**Cat.5**	THF	–	52	75
12	(*R*)-**Cat.5**	CPME[d]	–	46	70
13	(*R*)-**Cat.5**	PhCN	–	68	88
14[e]	(*R*)-**Cat.5**	PhCN	–	83	88
15[e,f]	(*R*)-**Cat.5**	PhCN	–	92	88

[a] Unless otherwise noted, the reactions were carried out with **1a** (0.1 mmol), **2** (0.5 mmol), and catalyst (10 mol%) in solvent (0.5 mL) at 80 °C for 1 d.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Cyclopentyl methyl ether.
[e] At rt for 12 h then 120 °C for 8 h.
[f] 5Å MS (50 mg) was added.

The scope of the protocol was fully evaluated by employing a variety of 2′-substituted 2-aminobenzophenones under the optimized reaction conditions.[15] As shown in Scheme 1, we first studied the influence of substituents on ring 1. We found that benzophenones with an electron-withdrawing or electron-donating group on the 4-position of ring 1 afforded the desired products **4b–f** in good yields and 92–95% ee (Scheme 1), whereas substitution at the 5-position of ring 1 resulted in an obvious decrease in the enantioselectivity (**4g** and **4h**). Next, the effect of substituents on the 2′-position of ring 2 was evaluated. Benzophenones bearing various arylethyl groups on the 2′-position reacted smoothly with acetylacetone to give biarylquinolones **4l–p** containing four aromatic rings in high yields (76–94%) and high optical purities (86–95% ee). Additionally, propyl- or isopropyl-substituted benzophenones proved to be good participants in this transformation and were converted into the corresponding products **4q** and **4r** with good results. Subsequently, other 1,3-dicarbonyl compounds were also examined under the standard reaction condition, but no satisfactory results were obtained.



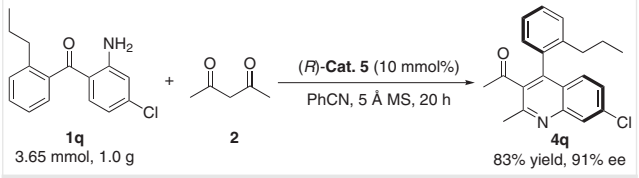
Scheme 1 Chiral phosphoric acid catalyzed asymmetric Friedländer reaction of 2′-substituted 2-aminobenzophenones **1** with acetylacetone (**2**). *Reagents and conditions*: **1** (0.1 mmol), **2** (0.5 mmol), (*R*)-**cat.5** (10 mol%), PhCN (0.5 mL), rt, 12 h then 120 °C, 8 h. Isolated yields are reported; enantioselectivities were determined by chiral HPLC.



Scheme 2 Simple transformation of Friedländer reaction product

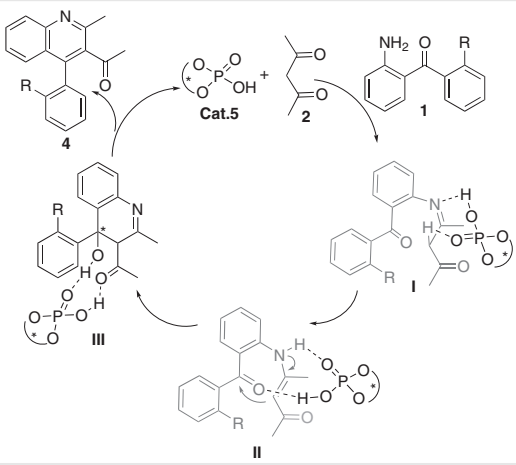
To demonstrate the synthetic utility of our method, a simple transformation of a Friedländer reaction product was carried out (Scheme 2). Product **4q** was reduced by KBH_4 in MeOH at room temperature, to give the corresponding biarylquinoline-type alcohol **5** in 93% yield and with high enantioselectivity (49:51 dr; 91% ee). The stereochemistry of **5** was assigned as (*S*,*R*) by X-ray crystal structure analysis (see Supporting Information).[16]

Next, a gram-scale asymmetric Friedländer reaction was also performed. As shown in Scheme 3, treatment of **1q** (1 g, 3.65 mmol) with **2** under the optimal reaction conditions gave the desired product **4q** in good yield (83%) with maintained enantioselectivity (91% ee).



Scheme 3 A gram-scale Friedländer reaction

On the basis of the results obtained above, we proposed the mechanism shown in Scheme 4 for the chiral phosphoric acid catalyzed atroposelective Friedländer reaction. In the promotion by the phosphoric acid **Cat. 5**, the 2-aminobenzophenone **1** condenses with acetylacetone (**2**) to afford an imine intermediate **I**, which is then converted into the nucleophilic enamine intermediate **II**. Subsequently, a phosphoric-acid-catalyzed intramolecular aldol reaction gives a dihydroquinoline bearing a tertiary alcohol in enantioenriched form. Finally, the resulting dihydroquinoline eliminates a molecule of H_2O to produce the desired atropoisomeric quinolines **4** in good yield and with high enantioselectivity.



Scheme 4 Proposed mechanism of the chiral-phosphoric-acid-catalyzed asymmetric Friedländer reaction between 2-aminobenzophenones **1** and acetylacetone (**2**).

Funding Information

We are grateful for financial support from the National Natural Science Foundation of China (NSFC, Grant Nos. 21573161 and 21571144), the Natural Science Foundation of Zhejiang Province (Grant Nos. LY18B020011 and LQ19B020004), and the Foundation of Wenzhou Basic Scientific Research Project (G20180015).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690228.

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(15) **Phosphoric-Acid-Catalyzed Asymmetric Friedländer Reaction; General Procedure**

A Schlenk tube was charged with the appropriate 2-aminobenzophenone **1** (1 equiv, 0.1 mmol), acetylacetone (**2**; 5 equiv, 0.5 mmol), catalyst **Cat.5** (0.1 equiv, 10% mmol), powdered 5 Å MS (50 mg), and anhyd PhCN (0.5 mL). The resulting mixture was stirred at rt for 12 h and then at 120 °C for an additional 8 h. When the reaction was complete, the mixture was purified by flash column chromatography [silica gel, PE–EtOAc (8:1 to 6:1)].

1-[2-Methyl-5-(3-{2-[4-(trifluoromethyl)phenyl]ethyl}phenyl)quinolin-3-yl]ethanone (4a)

Yellow liquid; yield: 39.9 mg (92%; ee 88%); $[\alpha]_D^{27}$ +5.6 (*c* 0.01, EtOAc). HPCL [Daicel Chiralpak AD-H, hexane–*i*-PrOH (98:2), flow rate: 0.7 mL/min, λ = 254 nm, 25°C]: t_R (major) = 11.40 min; t_R (minor) = 12.42 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.4 Hz, 1 H), 7.76–7.68 (m, 1 H), 7.46 (t, *J* = 7.3 Hz, 1 H), 7.42–7.32 (m, 5 H), 7.25 (d, *J* = 9.4 Hz, 1 H), 7.19 (d, *J* = 7.4 Hz, 1 H), 6.89 (d, *J* = 8.0 Hz, 2 H), 2.81–2.60 (m, 2 H), 2.71 (s, 3 H), 2.66–2.60 (m, 1 H), 2.56–2.49 (m, 1 H), 2.08 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 205.01, 153.54, 147.37, 145.26, 143.11, 139.86, 135.16, 134.42, 130.22, 130.08, 129.38, 129.28, 128.93, 128.53, 126.62, 126.23, 125.98, 125.46, 125.20, 125.17, 125.14, 125.11, 36.10, 34.64, 31.90, 23.85. HRMS (Bruker micrOTOF-QII): *m/z* [M + H]$^+$ calcd for $C_{27}H_{23}F_3NO$: 434.1726; found: 434.1743.

1-[2,7-Dimethyl-5-(3-{2-[4-(trifluoromethyl)phenyl]ethyl}phenyl)quinolin-3-yl]ethanone (4b)

Yellow liquid; yield: 38.9 mg (87%; ee 93%); $[\alpha]_D^{27}$ +16.4 (*c* 0.01, EtOAc); HPLC [Daicel Chiralpak AD-H, hexane–*i*-PrOH (98:2), flow rate 0.7 mL/min, λ = 254 nm, 25 °C]: t_R (major) = 9.18 min, t_R (minor) = 11.06 min. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (s, 1 H), 7.45 (t, *J* = 7.5 Hz, 1 H), 7.40 (d, *J* = 7.4 Hz, 1 H), 7.35–7.31 (m, 3 H), 7.18 (t, *J* = 7.6 Hz, 2 H), 7.12 (d, *J* = 8.5 Hz, 1 H), 6.89 (d, *J* = 8.0 Hz, 2 H), 2.81–2.71 (m, 2 H), 2.69 (s, 3 H), 2.66–2.60 (m, 1 H), 2.58–2.51 (m, 1 H), 2.54 (s, 3 H), 2.07 (s, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 205.21, 153.48, 147.61, 145.30, 142.95, 140.73, 139.81, 134.64, 134.42, 130.06, 129.38, 129.19, 128.84, 128.56, 127.98, 126.19, 125.66, 125.17, 125.14, 125.11, 125.08, 123.42, 36.13, 34.62, 31.96, 23.85, 21.71. HRMS (Bruker micrOTOF-QII): *m/z* [M + H]$^+$ calcd for $C_{28}H_{25}F_3NO$: 448.1883; found: 448.1879.

(16) CCDC 1957624 contains the supplementary crystallographic data for compound (*S*,*R*)-**5**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.