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# Ferrocenylphosphines as New Catalysts for Baylis−Hillman Reactions

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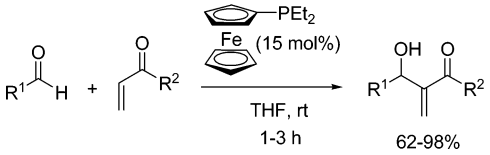


Readily available ferrocenyldialkylphosphines are effective air-stable catalysts for Baylis−Hillman reaction between aldehydes and acrylates, affording the corresponding adducts in high yields and short reaction times. A set of readily accessible planar chiral ferrocenyldialkylphosphines have been tested in asymmetric Baylis−Hillman reactions. The best enantioselectivities were obtained using Mandyphos as chiral catalyst (up to 65% ee).

The development of catalytic carbon−carbon bond-forming reactions leading to highly functionalized building blocks from simple starting materials is a fundamental challenge in organic chemistry. The Baylis−Hillman reaction,[1] which allows the direct preparation of α-methylene-β-hydroxycarbonyl products from Michael acceptors and aldehydes, is a clear example of this kind of outstanding process. This reaction is promoted by Lewis bases, among which nucleophilic nonhindered tertiary amines, such as diaza[2.2.2]bicyclooctane (DABCO), have been the most widely used. Nevertheless, the great synthetic potential of the Baylis−Hillman reaction is often hampered by low reaction rates (reactions lasting a week or more are common) and chemical yields highly sensitive to the substitution at both aldehyde and Michel acceptor partners. In attempts to overcome these limitations, a wide variety of chemical (more activated carbonyl compounds,[2] hydrogen bonds donors,[3] metal salts,[4] Lewis acids,[5] ionic liquids[6]) and physical methods (high pressure,[7] ultrasounds,[8] microwave irradiations[9]) have been described in recent years.

With the aim of developing more active Lewis base catalysts for Baylis−Hillman reaction, phosphines,[10] especially the highly nucleophilic trialkylphosphines,[11] constitute a very interesting alternative to the more basic tertiary amines. However, unlike tertiary amines, trialkylphosphines must be used under careful experimental conditions due to their high sensitivity to air oxidation and in some cases pyrophoric character.[12] Having in mind the idea of developing a phosphine catalyst enjoying simultaneously stability to air oxidation and high nucleophilicity, we envisaged that due to the electron-rich character of the ferrocene moiety, ferrocenyldialkylphosphines could be interesting catalysts in Baylis−Hillman reaction. Additionally, planar chiral ferrocenylphosphines, which have provided countless examples of excellent enantiocontrol in catalytic asymmetric metal-catalyzed reactions,[13] could offer a new alternative in asymmetric Baylis−Hillman reaction.

On the basis of these considerations, the ferrocenylphosphines **1a**−**c** were readily prepared according to literature procedures by reaction of ferrocenyllithium with the corresponding chlorophosphine.[14] Table 1 summarizes the results obtained in the model reaction between benzylacrylate and *p*-nitrobenzaldehyde (in THF at rt) in the presence of 15 mol % of the phosphine catalyst (ferrocenylphosphines **1a**−**c** and the commercially available $PPh_3$ and $PCy_3$).[15] For comparison purposes, all reactions were stopped after 1 h of reaction. To our delight, we observed that the diphenylphosphinoferrocene **1a** (entry 1) was not only much more reactive than $PPh_3$ (entry 4), but even more reactive than the aliphatic trialkylphosphine $PCy_3$ (entry 5, 24% conversion). Interestingly, in agreement with the increase in nucleophilicity with the alkyl substitution, ferrocenyldialkylphosphines **1b** and **1c** proved to be more effective.

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(15) The use of other solvents such as $CH_3CN$, DMF, MeOH, or mixtures of dioxane/$H_2O$, MeOH/$H_2O$ afforded lower yields.

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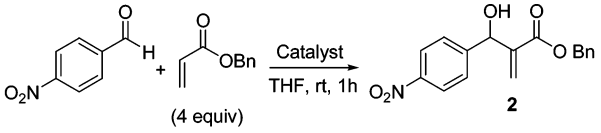
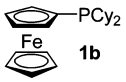
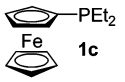
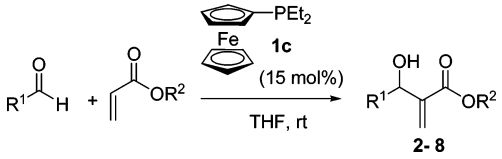
**TABLE 1. Ferrocenylphosphines as Catalysts in the Baylis–Hillman Reaction between Benzylacrylate and *p*-Nitrobenzaldehyde**




| entry | catalyst | Conv.(%)[a] | Yield(%)[b] |
|---|---|---|---|
| 1 |  **1a** | 50 | 42 |
| 2 |  **1b** | 95 | 74 |
| 3 |  **1c** | 100 | 98 |
| 4 | $PPh_3$ | 0 | 0 |
| 5 | $PCy_3$ | 24 | 8 |

[a] Determined by $^1H$ NMR analysis of the crude reaction mixture. [b] Isolated yield after flash chromatography.

**TABLE 2. Baylis–Hillman Reaction Catalyzed by Ferrocenyldiethylphosphine 1c**




| entry | $R^1$ | $R^2$ | compd | *t* (h) | yield[a] (%) |
|---|---|---|---|---|---|
| 1 | *p*-$NO_2C_6H_4$ | Bn | **2** | 1 | 98 |
| 2 | *p*-$NO_2C_6H_4$ | Me | **3** | 1 | 84 |
| 3 | *p*-$FC_6H_4$ | Bn | **4** | 3 | 85 |
| 4 | $C_6H_5$ | Bn | **5** | 3 | 76 |
| 5 | 2-Py | Bn | **6** | 1.5 | 62 |
| 6 | Cy | Bn | **7** | 3 | 72 |
| 7 | Me | Bn | **8** | 3 | 69 |

[a] Isolated yield after flash chromatography.

In particular, the least hindered diethylphosphine **1c** promoted a complete conversion within 1 h, providing the Baylis–Hillman adduct **2** in an excellent 98% yield (entry 3). Ferrocenylphosphines **1a**–**c** are perfectly stable compounds that can be handled in air, affording very similar results in the Baylis–Hillman reaction either under inert atmosphere or in open-air flasks.

With the optimized catalyst **1c** in hand, we next explored the scope of the process by studying a variety of aldehydes. As shown in Table 2, several aromatic aldehydes with varied subtitution provided good yields (76–98%, entries 1–5) in short reaction times (1–3 h). Because aliphatic aldehydes are very prone to suffer aldolic condensation, most of the reported Baylis–Hillman reactions involve the use of aromatic aldehydes, especially those promoted by basic tertiary amines. Remarkably, ferrocenylphosphine **1c** catalyzed the Baylis–Hillman reaction with both branched and linear aliphatic aldehydes (entries 6 and 7), providing the corresponding alcohols in satisfactory yields after chromatographic purification (69–72%).

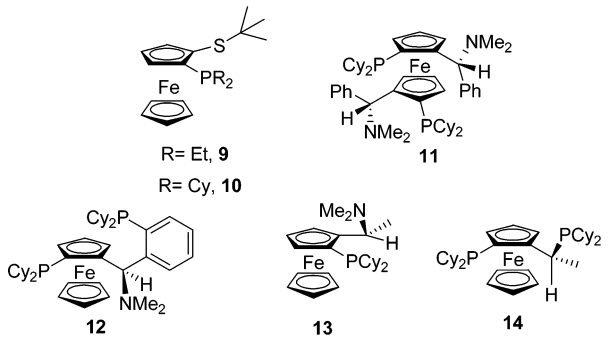



**FIGURE 1.** Tested chiral nonracemic ferrocenylphosphines.

In the past few years, great progresses toward the development of a enantioselective version of the Baylis–Hillman reaction,[16] including the use of chiral auxiliaries,[17] chiral Lewis bases,[18] and chiral Lewis[5c] or Brønsted[19] acids, have been described. Despite all these improvements, the identification of a broad scope, asymmetric version of this reaction remains an unsolved problem. Until now, concerning the use of chiral phosphines in asymmetric Baylis–Hillman reaction with aldehydes, only moderate enantioselectivities have been reported (up to 44% ee with BINAP).[20,21]

Encouraged by the results illustrated in Tables 1 and 2, we decided to explore the potential of planar chiral ferrocenylphophines in asymmetric Baylis–Hillman reactions (Figure 1).[22] To this end, we tested sulfenylphosphinoferrocenes **9** and **10** developed by our group as bidentate planar chiral P,S-ligands in enantioselective metal-catalyzed reactions,[23] as well as the commercially available aminophosphinoferrocenes **11**–**13** and the diphosphinoferrocene **14**, combining both planar and central chirality (Table 3).

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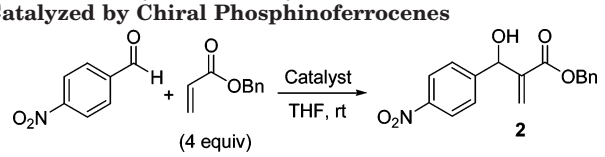
**TABLE 3. Asymmetric Baylis–Hillman Reaction Catalyzed by Chiral Phosphinoferrocenes**




| entry | catalyst | *t* (h) | yield[a] (%) | ee[b] (%) |
|---|---|---|---|---|
| 1 | **9** | 22 | 84 | 4 (*S*) |
| 2 | **10** | 16 | 74 | 29 (*R*) |
| 3 | **11** | 22 | 78 | 65 (*R*) |
| 4 | **12** | 22 | 40 | 55 (*R*) |
| 5 | **13** | 22 | 28 | 55 (*R*) |
| 6 | **14** | 22 | 51 | 24 (*R*) |

[a] Isolated yield after flash chromatography. [b] Determined by Chiral HPLC analysis (Daicel Chiralcel AD column, hexane/$^i$PrOH 91/9, 0.5 mL/min.). [c] Absolute configuration determined by comparison with previously described data.[5c]

According to the bulkier character of these catalysts, compared to the parent ferrocene **1c**, the reaction with *p*-nitrobenzaldehyde was slower (16–22 h), giving rise to the product **2** in yields highly depending on the catalyst used (28–84% yield). Disappointingly, from a stereochemical point of view, the enantioselectivities were low to moderate. The Mandyphos-type ferrocenylphosphine **11**, with two pendant dicyclohexylphosphine and dimethylamino groups, proved to be the best catalyst providing the Baylis–Hillman adduct **2** in 78% yield and 65% ee[24] (entry 3). No improvement in the enantioselectivity was observed when this reaction was performed at 0 °C instead of room temperature.

In summary, the readily available and air-stable ferrocenyldiethylphosphine is a highly active catalyst in the Baylis–Hillman reaction between acrylates and aldehydes. Good to excellent yields have been obtained with a range of aldehydes within low reaction times. Enantioselectivities up to 65% ee were obtained in the asymmetric Baylis–Hillman reaction using planar chiral ferrocenylphosphines.

## Experimental Section

The Baylis–Hillman adducts **2**, **3**, **5**, and **8** have been previously reported.[5c]

**Typical Procedure for the Baylis–Hillman Reaction. Synthesis of Benzyl 3-Hydroxy-3-(4-nitrophenyl)-2-methylenepropanoate (2).** To a solution of diethylferrocenylphosphine (25 mg, 0.0912 mmol) and *p*-nitrobenzaldehyde (91.9 mg, 0.608 mmol) in dry THF (1,8 mL) was added benzyl acrylate (394.1 mg, 2.43 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was stirred for 1 h, after which time the solvent was removed under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, Hex/EtOAc 3:1) to afford **2** (195 mg, 98%) as a colorless oil. $^1$H NMR ($CDCl_3$): $\delta$ 8.15 (d, $J$ = 8.8 Hz, 2H), 7.53 (d, $J$ = 8.4 Hz, 2H), 7.36–7.23 (m, 5H), 6.45 (s, 1H), 5.91 (s, 1H), 5.63 (s, 1H), 5.15 (s, 2H), 3.38 (br, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 165.6, 148.5, 147.5, 141.0, 135.1, 128.6 (×2), 128.5, 128.3 (×2), 127.5, 127.3 (×2), 123.6 (×2), 72.8, 67.0.

**Benzyl 3-Hydroxy-3-(4-fluorophenyl)-2-methylenepropanoate (4).** Colorless oil. Yield: 85%. $^1$H NMR ($CDCl_3$): $\delta$ 7.37–7.23 (m, 7H), 7.05–6.96 (m, 2H), 6.40 (s, 1H), 5.91 (s, 1H), 5.55 (s, 1H), 5.13 (s, 2H), 3.45 (br, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 166.0, 142.0, 137.1, 135.4, 128.6 (×2), 128.6, 128.4, 128.4, 128.1 (×2), 126.3 (×2), 115.4 (×2), 72.5, 66.7. IR: 3431.1, 3035.1, 2953.8, 1716.5, 1508.8, 1267.2, 1155.3, 1097.5, 837.4, 737.2. MS (EI+) *m/z*: 195 ($M^+$ − Bn, 49), 177 (56), 134 (25), 123 (67), 91 (100). HRMS ($EI^+$): calcd for ($C_{10}H_8O_3F$) [$M^+$ − Bn] 195.0457, found 195.0456.

**Benzyl 3-Hydroxy-3-(2-pyridyl)-2-methylenepropanoate (6).** Colorless oil. Yield: 62%. $^1$H NMR ($CDCl_3$): $\delta$ 8.42–8.40 (m, 1H), 7.53 (dt, $J$ 7.6, 1.7 Hz, 1H), 7.30–7.06 (m, 8H), 6.33 (s, 1H), 5.90 (s, 1H), 5.56 (s, 1H), 5.07 (s, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 165.9, 159.5, 148.3 (×2), 141.8, 136.8 (×2), 135.6 128.5, 128.2, 128.1, 127.2, 122.6, 121.2, 72.2, 66.5. IR: 3445, 3064.6, 1956.40, 1715.8, 1437.5, 1046.8, 952.5, 736.4. MS ($FAB^+$) *m/z*: 270 ($M^+$ + 1, 49), 162 (56), 91 (100). HRMS (electrospray$^+$): calcd for ($C_{16}H_{16}NO_3$) [$M^+$ + 1] 270.1124, found 270.1123.

**Benzyl 3-Cyclohexyl-3-hydroxy-2-methylenepropanoate (7).** Colorless oil. Yield: 72%. $^1$H NMR ($CDCl_3$): $\delta$ 7.39–7.34 (m, 5H), 6.30 (d, $J$ 0.8 Hz, 1H), 5.75 (d, $J$ 0.8 Hz, 1H), 5.22 (s, 2H), 2.49 (d, $J$ 8.1 Hz, 1H), 1.9–0.88 (m, 11H). $^{13}$C NMR ($CDCl_3$): $\delta$ 165.5, 141.2, 135.7, 128.6 (×2), 128.3, 128.1 (×2), 126.4, 66.5, 42.5, 29.9, 28.2, 26.3, 26.1, 25.9. IR: 3493.0, 3035.2, 2929.4, 2853.4, 1718.4, 1627.9, 1498.5, 819.9, 737.1. MS ($EI^+$) *m/z*: 274 ($M^+$ + 1, 0.4), 256 (1), 222 (0.1), 91 (100). HRMS ($EI^+$): calcd for ($C_{17}H_{22}O_3$) [$M^+$] 274.1568, found 274.1563.

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**Supporting Information Available:** Copies of $^1$H and $^{13}$C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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