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Brief Communications

2-[1-(Dimethylamino)ethyl]ferrocenylphosphinic acid as an organocatalyst of Michael and Friedel—Crafts reactions*

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Racemic 2-[1-(dimethylamino)ethyl]ferrocenylphosphinic acid was tested as an organocatalyst in the Michael and Friedel—Crafts reactions. The use of this zwitterion provides 78% conversion in the Michael reaction between cyclohexanone and β-nitrostyrene, and 84% conversion in the Friedel—Crafts reaction between β-nitrostyrene and indole.

Key words: organocatalysis, ferrocenylphosphinic acid, Ugi's amine, Michael reaction, Friedel—Crafts reaction.

Asymmetric organocatalysis is a useful strategy for obtaining various chiral compounds. Of special interest are the addition reactions between nucleophiles and electron-deficient alkenes (Michael and Friedel—Crafts reactions), being among the most effective methods for the formation of the carbon—carbon and carbon—heteroatom bonds.[1,2] The Michael and related Friedel—Crafts reactions with activated arenes in the presence of chiral organocatalysts significantly enhanced the potential of enantioselective synthesis of analogs of natural and biologically active compounds.[3] This resulted in improved yields and/or enantiomeric excess of the products, and also opened access to compounds that could not be obtained by metal complex catalysis.

In recent years, a considerable interest of researchers has been drawn to zwitterions as to bifunctional organocatalysts for various practically relevant reactions.[4—7] Zwitterions are electroneutral molecules containing both negatively and positively charged moieties, where these ion pairs can function synergistically thus activating substrates. To move these studies forward and to develop new catalysts for organic reactions, it was of interest to study the catalytic activity of racemic 2-[1-(dimethylamino)ethyl]ferrocenylphosphinic acid (**1**)[8] based on the Ugi´s amine as a novel chemotype of zwitterionic organocatalysts with an element of axial chirality. Note that chiral ferrocenes relate to the so-called "privileged" universal ligands

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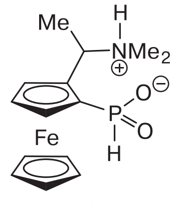
used in the design of chiral catalysts for asymmetric catalysis.[9,10]

Results and Discussion

The addition of *C*-nucleophiles (carbonyl compounds, derivatives of malonic or acetoacetic acids, *etc.*) to α-nitroalkenes is widely used in the synthesis of chiral nitro compounds[11—13] and several other useful chiral carbo- and heterocyclic compounds.[14,15] To test organocatalyst **1**, the catalytic Michael reaction of cyclohexanone and β-nitrostyrene **2** was chosen (Scheme 1, Table 1).



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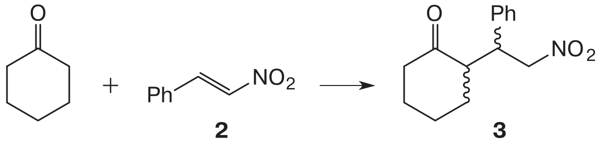
Scheme 1



Reaction conditions: catalyst **1** (15 mol.%), solvent.

It was found that the highest yields were achieved when carrying out the reaction in alcohols (EtOH and $\mathrm{Pr^iOH}$), while the reaction in THF, chloroform, and DMF failed. The use of organic acid (HCO_2H, AcOH, $PhCO_2H$) additives only decreases the conversion of the starting compounds (runs *6—8*). Probably, with an organic acid added, zwitterion **1** picks up a proton, thereby decreasing its basicity and catalytic activity. The best combination of the conversion value (78%) and the ratio of diastereomers, 86:14, was obtained in the course of heating in isopropyl alcohol at 75 °C in the absence of acid additives (run *5*).

Table 1. Optimization of conditions[a] for a model reaction between cyclohexanone and β-nitrostyrene **2**

Run	Acid (mol.%)	T/°C	τ/h	C (%)[b]	*d.r.*[c] (*syn-*/*anti-*)
1	—	60	48	45	85 : 15
2	—	60	48	54	88 : 12
3	—	50	72	52	90 : 10
4	—	60	72	64	84 : 16
5	—	75	72	78	86 : 14
6	HCOOH (15)	75	72	34	85 : 15
7	MeCOOH (15)	75	72	48	83 : 17
8	PhCOOH (15)	75	72	49	89 : 11

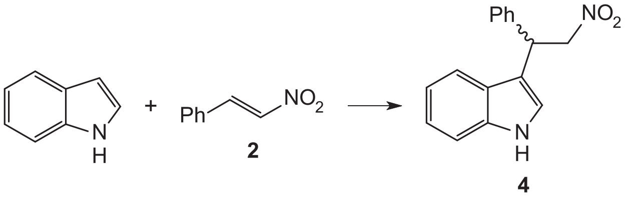
[a] Reaction conditions: cyclohexanone (0.25 mmol), **2** (0.25 mmol), catalyst **1** (15 mol.%), solvent $\mathrm{Pr^iOH}$ (2 mL).

[b] Conversion by GC-MS.

[c] Diastereomeric ratio by ^{1}H NMR.

The indole derivatives can act as nucleophiles in the reactions with α-nitroalkenes. Catalysts for these reactions are chiral thioureas[16,17] and phosphates[18], activating the nitroalkene by hydrogen bonding. To test organocatalyst **1**, the Friedel—Crafts reaction of indole with β-nitrostyrene **2** was chosen (Scheme 2, Table 2).

Scheme 2



Reaction conditions: catalyst **1** (15 mol.%), solvent.

The reactions were carried out in isopropyl alcohol. The best results (84% conversion) were achieved in the course of heating at 75 °C for 48 h in the presence of 15 mol.% of organocatalyst **1** and 15 mol.% of diethylamine additive (run *6*). Probably, upon the addition of organic bases, zwitterion **1** releases a hydrogen ion into the solution, thereby accelerating the acid-catalyzed reaction between indole and β-nitrostyrene.

To conclude, racemic 2-[1-(dimethylamino)ethyl]ferrocenylphosphinic acid (**1**), which is the first representative of the novel class of axially chiral zwitterionic organocatalysts, has been tested as an organocatalyst in Michael and Friedel—Crafts reactions. Its use ensures the organocatalytic Michael reaction between cyclohexanone and β-nitrostyrene **2** to proceed with 78% conversion. The use of compound **1** in the Friedel—Crafts reaction between indole and β-nitrostyrene **2** leads to the formation of the corresponding product **4** of the catalytic reaction with 84% conversion.

Table 2. Optimization of conditions[a] for a model reaction between indole and β-nitrostyrene **2**

Run	Base (mol.%)	τ/h	C (%)[b]
1	—	48	59
2	Na_2CO_3 (15)	48	—
3	Et_2NH (30)	48	62
4	Et_2NH (45)	48	72
5	Et_3N (15)	72	57
6	Et_2NH (15)	48	84
7	$PhNH_2$ (15)	48	61

[a] Reaction conditions: indole (0.25 mmol), **2** (0.25 mmol), catalyst **1** (15 mol.%), solvent $\mathrm{Pr^iOH}$ (2 mL), 75 °C.

[b] Conversion by GC-MS.

Experimental

All manipulations connected with the preparation of the reactants, synthesis, and isolation of the products were performed under an inert atmosphere by using the standard Schlenk-tube techniques. All solvents were distilled from Na/benzophenone or P_2O_5 just before use. ^1H NMR spectra were recorded on a Bruker MSL-400 (^1H 400 MHz) spectrometer using $SiMe_4$ as an internal standard. To record the spectra, 10—20% solutions in $CDCl_3$ were used. 2-[1-(Dimethylamino)ethyl]ferrocenylphosphinic acid (**1**) was obtained according to the previously reported procedure.[8] Commercial cyclohexanone, β-nitrostyrene **2**, and indole were used after distillation, recrystallization or without any preliminary purification.

The catalytic reaction conditions. A Schlenk tube was loaded with 0.25 mmol of both substrates (cyclohexanone and β-nitrostyrene **2** or indole and β-nitrostyrene **2**), 2-[1-(dimethylamino)ethyl]ferrocenylphosphinic acid (0.0375 mmol), and the corresponding amount of organic acid or base, and isopropyl alcohol or another solvent (5 mL) were added. The mixture was kept at the specified temperature (50—75 °C) in an oil bath under vigorous stirring. The analysis of the reaction mixture was carried out without isolation of the products. Before injection, the test sample was dissolved in chromatographically pure ethyl acetate (1 mL). The conversion of the reaction products was assessed by gas chromatography-mass spectrometry (GC-MS) on a DFS ThermoElectronCorporation apparatus (Germany), ionization method: electron impact, the energy of the ionizing electrons was 70 eV, ion source temperature was 250 °C, capillary column ID-BP5X, helium as a carrier gas. Mass spectral data were converted using Xcalibur software.

The diastereomeric ratio (*d.r.*, see Table 1) for the reaction between cyclohexanone and β-nitrostyrene (**2**) was estimated from the ^1H NMR data of the reaction mixture. Upon completion of the catalytic experiment, the reaction mixture was supplemented with 0.25 *M* aqueous solution of acetic acid (2 mL) and toluene (2 mL). The aqueous layer was additionally extracted with toluene (2×2 mL). Then, the organic phases were combined, the solvent was evaporated to dryness under reduced pressure. The reaction mixture was analyzed by ^1H NMR spectroscopy in $CDCl_3$ to determine the diastereoselectivity of the catalytic reaction (for *syn*-**3**, δ_H = 3.76 (m, 1 H, $C\underline{H}$—Ph); for *anti*-**3**, δ_H = 4.01 (m, 1 H, $C\underline{H}$—Ph)).[19—21]

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The authors declare no competing interests.

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