



**Trip Report for**

**“8<sup>th</sup> International conference on Heteroatom Chemistry”**

**Riverside, CA  
August 12-16, 2007**

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**Abstract:** *The 8<sup>th</sup> International Conference on Heteroatom Chemistry (ICHAC-8) was hold at Riverside, California on August 12-16, 2007. There were approximately 200 attendees representing about 20 countries. This report highlights selected material from information presented in seminars and poster session.*

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## “Highly Enantioselective Bi-functional Organocatalysis: New Powerful Methods and Synthetic Applications”

Darren J. Dixon, School of Chemistry, the University of Manchester, Oxford Road, Manchester M13 9PL, UK

Enantiomerically pure organic compounds with the capacity to activate simultaneously electrophilic substrates and pro-nucleophilic reagents towards one another, offer numerous opportunities for the discovery of powerful new asymmetric carbon-carbon and carbon-heteroatom bond forming reactions. When the catalyst has a well-defined chiral pocket combined with a fairly rigid skeleton and appropriate distances between the two activating groups, the templating of the two reagents via a ternary complex can lead to excellent levels of enantio- and diastereo-control in efficient reactions at relatively low loading and at reasonable reaction rates.

In pursuit of chemical efficiency, stereochemical control and synthetic utility, Dr. Dixon's group has been actively developing and applying new single-enantiomer bifunctional Lewis base/Bronsted acid catalysts to the discovery of new and powerful addition reactions. In Dr. Dixon's presentation, a new family of bi-functional organocatalysts derived from cinchona alkaloids and their use in highly enantioselective Michael addition reactions as well as Mannich reactions were described.

One family of heterocycles, the 1,3-dioxolan-4-ones, was particularly attractive owing to the simplicity of their structure combined with their ready synthesis (Scheme 1).

Scheme 1

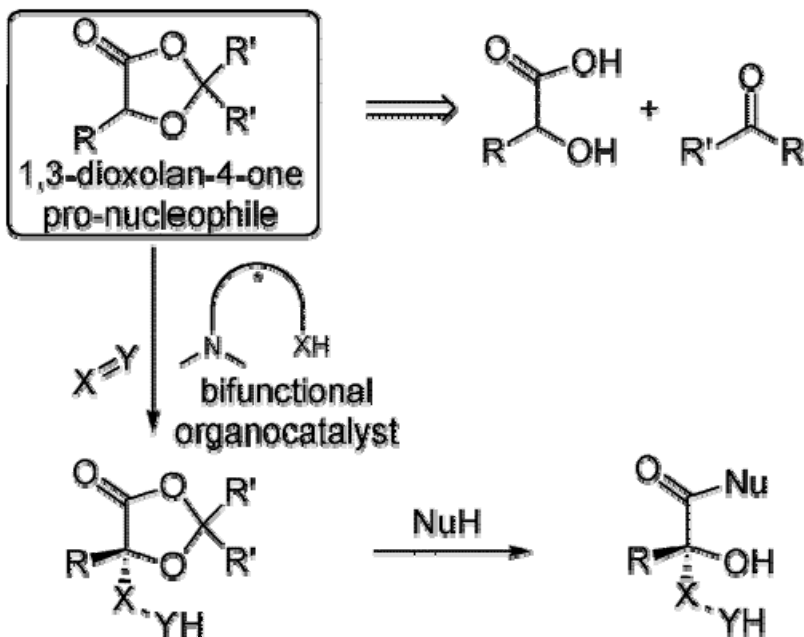
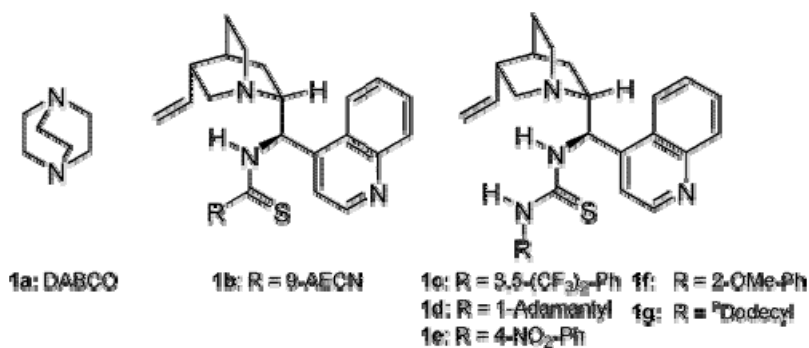
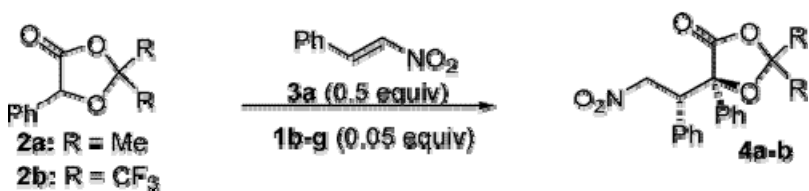


Figure 1



Having established a good reactivity profile with **2b** and *trans*- $\beta$ -nitrostyrene (Table 1), a screen of a small library of cinchonine-derived bifunctional organocatalysts then followed. Other typical reaction parameters such as solvent and temperature were systematically varied and a selection of the findings are detailed in Table 1.

Table 1

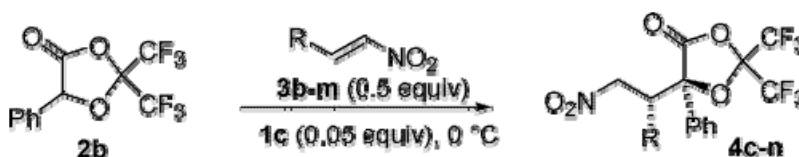


entry	cat.	R	solvent	temp (°C)	convn (%) <sup>b</sup>	de (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>1a<sup>d</sup></b>	Me	THF	30	<5 <sup>e</sup>		
2	<b>1a<sup>d</sup></b>	CF <sub>3</sub>	THF	30	>98 <sup>f</sup>	>98	
3	<b>1c</b>	CF <sub>3</sub>	DCM	0	>60 <sup>g</sup>	>80	65
4	<b>1c</b>	CF <sub>3</sub>	PhMe	0	>98 <sup>h</sup>	>98	76
5	<b>1c</b>	CF <sub>3</sub>	TBME	0	>98 <sup>g</sup>	>85	57
6	<b>1b</b>	CF <sub>3</sub>	DCM	0	>80 <sup>g</sup>	>98	43
7	<b>1d</b>	CF <sub>3</sub>	DCM	0	>98 <sup>g</sup>	>95	70
8	<b>1e</b>	CF <sub>3</sub>	DCM	0	>40 <sup>g</sup>	>90	51
9	<b>1f</b>	CF <sub>3</sub>	DCM	0	>40 <sup>g</sup>	>90	26
10	<b>1g</b>	CF <sub>3</sub>	DCM	0	>85 <sup>g</sup>	>80	56

<sup>a</sup> Reaction was carried out with **2** (1.0 equiv), **3a** (0.5 equiv), and **1b-g** (0.05 equiv) in solvent (1.0 M in **3**). <sup>b</sup> Determined by <sup>1</sup>H NMR. <sup>c</sup> Determined by HPLC analysis with a chiral column. <sup>d</sup> 0.1 equiv used. <sup>e</sup> After 14 days. <sup>f</sup> After 96 h. <sup>g</sup> After 72 h. <sup>h</sup> After 48 h.

With the optimal conditions established, the scope of the Michael addition reaction was surveyed by initially probing changes to the Michael acceptor. A range of heteroaromatic and aromatic nitro olefins bearing electron-donating or -accepting substituents in the *ortho*, *meta*, and *para* positions were treated with 5-phenyl-1,3-dioxolan-4-one **2b** in toluene at 0 °C in the presence of **1c**. Enantioselectivities ranged from 60% to 89% ee (Table 2).

**Table 2**

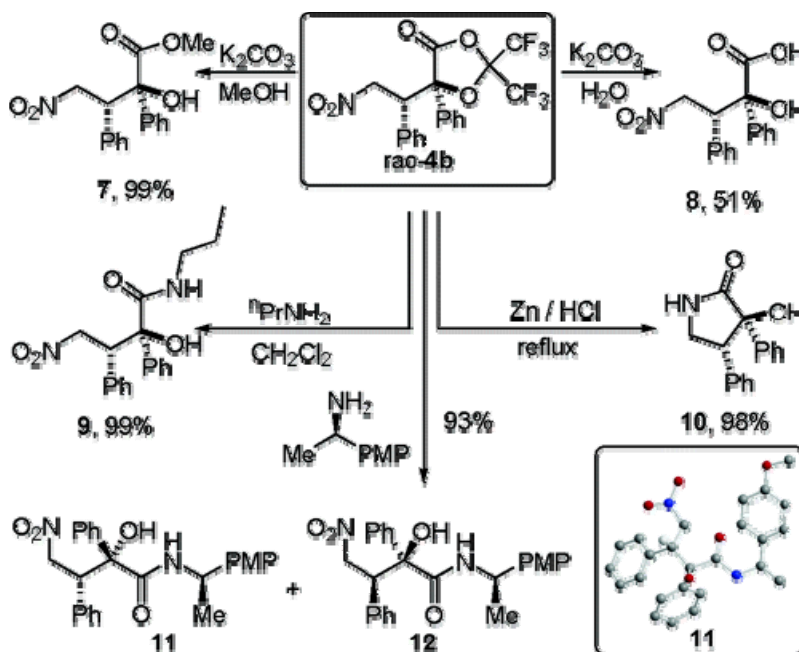


entry		R	solvent	time (h)	yield (%) <sup>b</sup>	de (%) <sup>c</sup>	ee (%) <sup>d</sup>
1	<b>4c</b>	<i>o</i> -Br-Ph	PhMe	336	58	>98	89
2	<b>4c</b>	<i>o</i> -Br-Ph	DCM	288	72	>98	79
3	<b>4d</b>	<i>m</i> -Br-Ph	PhMe	30	71	>98	68
4	<b>4e</b>	<i>p</i> -Br-Ph	PhMe	72	59	>98	73
5	<b>4e</b>	<i>p</i> -Br-Ph	DCM	48	85	>97	68
6	<b>4f</b>	<i>o</i> -OMe-Ph	PhMe	72	65	>97	74
7	<b>4g</b>	<i>m</i> -OMe-Ph	PhMe	24	50	>97	71
8	<b>4g</b>	<i>m</i> -OMe-Ph	DCM	48	70	>98	68
9	<b>4h</b>	<i>p</i> -OMe-Ph	PhMe	72	81	>97	73
10	<b>4i</b>	<i>m</i> -Me-Ph	PhMe	40	70	>98	69
11	<b>4j</b>	<i>p</i> -Me-Ph	PhMe	40	67	>97	70
12	<b>4k</b>	<i>o</i> -Cl-Ph	PhMe	264	52	>97	82
13	<b>4l</b>	2-naphth	PhMe	72	62	>97	75
14	<b>4m</b>	2-furyl	PhMe	24	69	>93	60
15	<b>4n</b>	2-thienyl	PhMe	48	88	>98	66

<sup>a</sup> Reaction was carried out with **2b** (1.0 equiv), **3b-n** (0.5 equiv), and **1c** (0.05 equiv) in solvent (1.0 M in **3**). <sup>b</sup> Isolated yield. <sup>c</sup> Determined by <sup>1</sup>H NMR. <sup>d</sup> Determined by HPLC analysis with a chiral column.

With the scope of the reaction established, the synthetic utility of the Michael adducts was investigated. A selected adduct *rac*-**4b** was synthesized on a gram scale and subjected to routine alcoholysis, hydrolysis, and aminolysis conditions (Scheme 2).

Scheme 2



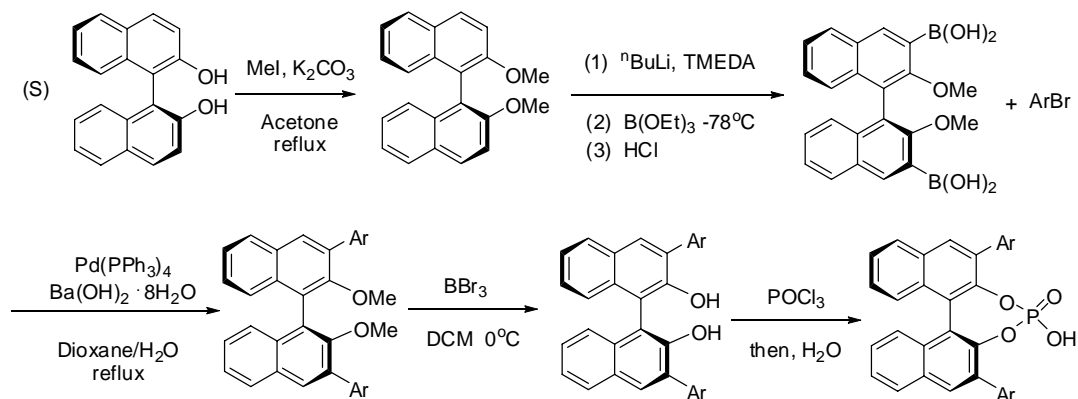
### “Chiral Phosphoric Acids for Highly Enantioselective Friedel-Crafts Reactions”

Shu-Li You, Qiang Kang and Zhuo-An Zhao, Shanghai Institute of Organic Chemistry, 354 Fenglin Lu, Shanghai 200032, China

The asymmetric Friedel-Crafts reaction of indoles with imines provides easy access to the synthesis of enantiopure 3-indolyl methanamine derivatives. The latter exist in numerous natural and unnatural products with significant biological activities. In recent study, Prof. You’s group found chiral phosphoric acids are efficient organocatalysts for the Friedel-Crafts reaction of indoles with imines, affording the 3-indolyl methanamine derivatives with up to >99% ee. The reaction features high efficiency of the catalyst, mild reaction conditions, high yield and enantioselectivities, providing a practical method to synthesize highly enantiopure 3-indolyl methanamine derivatives.

## Preparation of the Chiral Phosphoric Acids

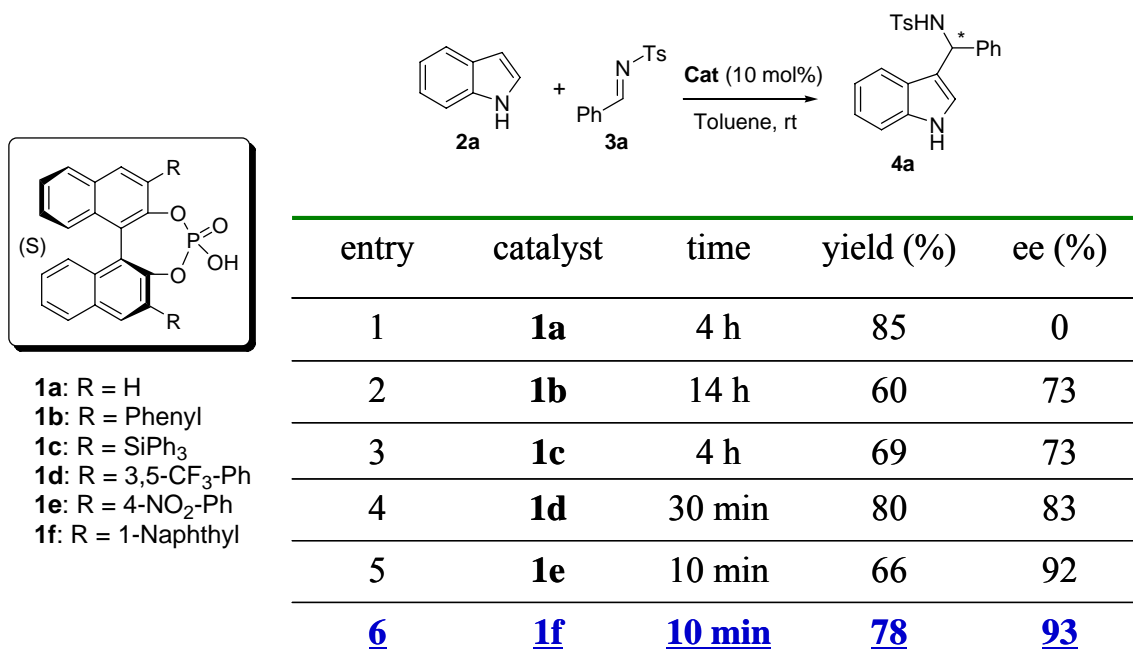
Scheme 1



## Screening of the Phosphoric Acid Catalysts

Several phosphoric acids with varying substituents at the 3- and 3'-positions of the binaphthyl scaffold were tested, and the results are listed in Scheme 2.

Scheme 2

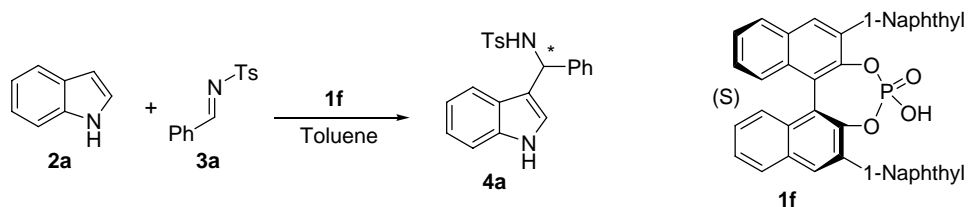


<sup>a</sup> Reaction conditions: 10 mol % of catalyst, 5 equiv of **2a**, 0.25 mol/L of **3a** in toluene at room temperature. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by chiral HPLC analysis (Chiralcel OD-H).

### Investigation of the Reaction Temperature and Catalyst Loading

Next the effect of the reaction temperature and catalyst loading were investigated using catalyst **1f**. The results are summarized in Scheme 3.

Scheme 3

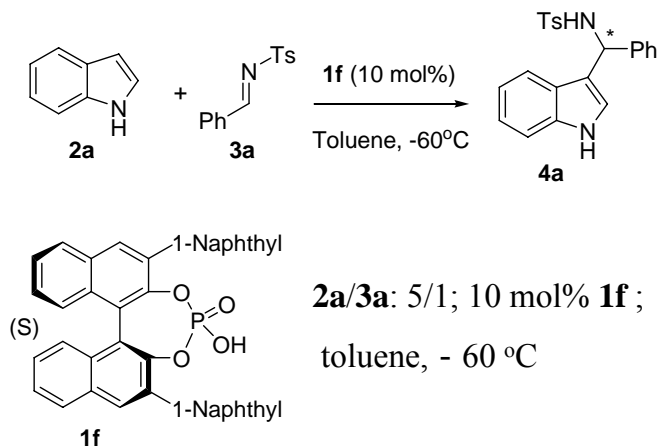


entry	<b>1f</b> (mol %)	temp	time	yield (%)	ee (%)
1	10	r.t.	10 min	78	93
2	10	0 °C	10 min	80	95
3	10	-40 °C	10 min	75	97
<b>4</b>	<b>10</b>	<b>-60 °C</b>	<b>30 min</b>	<b>83</b>	<b>98</b>
5	10	-78 °C	2 h	81	98
6	5	-60 °C	1.5 h	83	96
7	2	-60 °C	10 h	72	75

<sup>a</sup> Reaction conditions: 5 equiv of **2a**, 0.25 mol/L of **3a** in toluene. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by chiral HPLC analysis (Chiralcel OD-H).

## The Optimal Reaction Conditions

Scheme 4

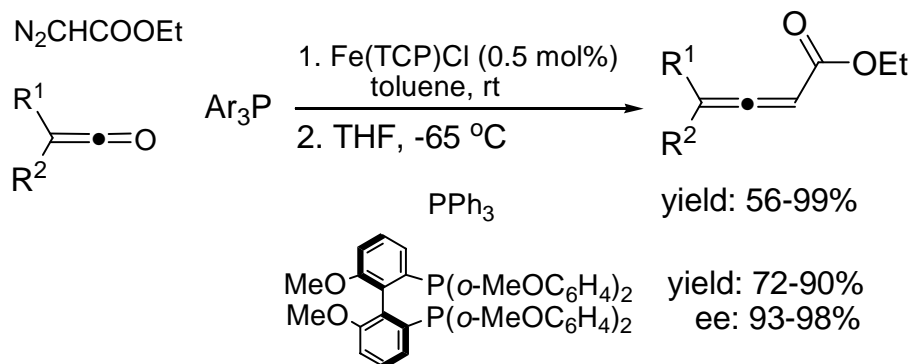


### “Catalytic Wittig-Type Olefination of Carbonyl Compounds”

Peng Cao, Chuan-Ying Li, Xiu-Li Sun, and Yong Tang, *Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China*

Highly efficient catalysis has become one of the most important frontiers in exploratory organic synthetic research. Prof. Tang's group reported the reaction of ketenes with diazoacetate in the presence of Fe(TCP)Cl (0.5 mol%) (TCP = tetra(*p*-chlorophenyl)porphyrinate) and chiral phosphine in high yields with up to 98% ee, providing an useful method for the enantioselective synthesis of allenes under neutral conditions. However, a stoichiometric chiral phosphine was required (Scheme 1).

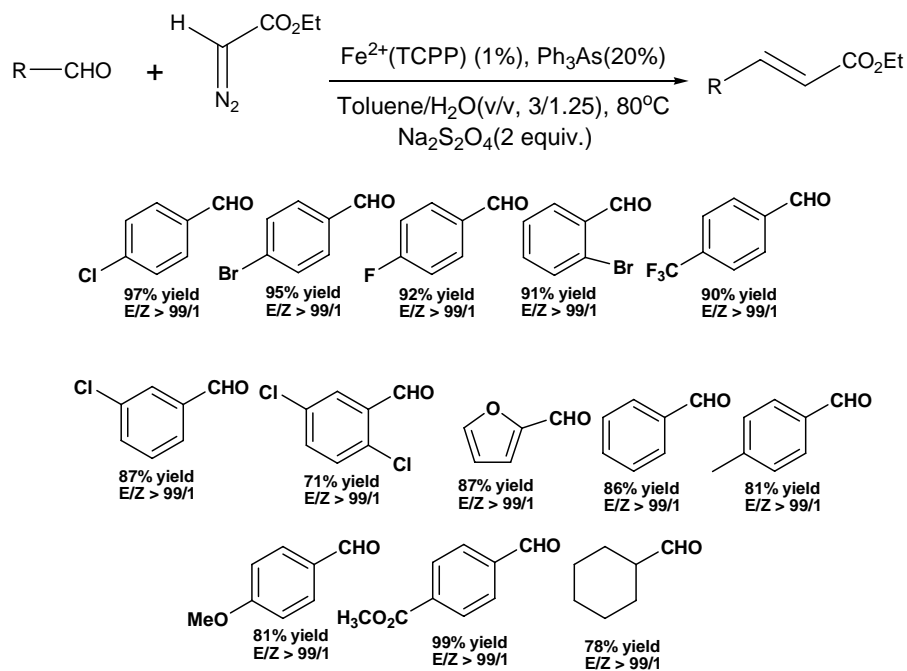
Scheme 1



On the basis of this finding, Prof. Tang's group developed a catalytic olefination with ethyl diazoacetate (EDA) to give the olefin product in up to 99 % yield with excellent stereoselectivity ( $E/Z > 99/1$  in most cases) in the presence of catalytic amount of  $\text{AsPh}_3$

(20 mol%) and Fe(TCP)Cl (0.5-1.0 mol%) using Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> as a reducing reagent (Scheme 2).

**Scheme 2**



A mechanism involved in biphasic system is proposed. (Scheme 3)

**Scheme 3**

