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Highly Efficient Asymmetric Michael Addition of Diaryl Phosphine Oxides to α,β-Unsaturated N-Acylated Oxazolidin-2-ones

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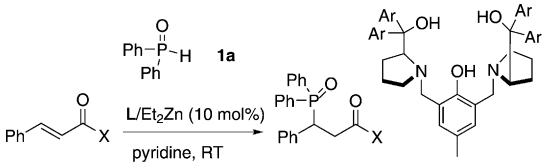
Organophosphorus compounds are an important class of compounds, which have been studied for more than 180 years. In recent years, organophosphorus chemistry has achieved its rapid development owing to its wide application in medical chemistry, agriculture, and industry.[1] Especially, the catalytic asymmetric construction of P–C bonds[2] is an intensively studied area in the past years and numerous studies have focused on asymmetric addition of nucleophiles such as dialkyl phosphites,[3] secondary phosphines,[4] and secondary phosphine oxides[5] to form P–C bonds with adjacent chiral centers. The conjugate addition of diaryl phosphine oxides to α,β-unsaturated carboxylic acid derivatives is one of the most practical approaches for asymmetric construction of P–C bonds. Nonetheless, present successful examples including asymmetric addition of diaryl phosphine oxides to α,β-unsaturated ketones[6] and aldehydes[7] are not efficent and require long reaction times of usually >12 h or several days. Therefore, there is still great demand to develop a new efficient approach towards these compounds. Herein, we report a highly efficient asymmetric reaction of diaryl phosphine oxides with α,β-unsaturated N-acylated oxazolidin-2-ones.

In connection with our continuous interest in phosphorus-containing nucleophiles[8] and previous success in asymmetric reactions of dialkyl phosphine oxides with enones,[9] we decided to investigate the reaction of diaryl phosphine oxides with α,β-unsaturated carboxylic acid derivatives. The preliminary attempts were unsuccessful, the reaction of α,β-unsaturated *N*-acylpyrrole **2** and diphenyl phosphine oxide **1a** gave only racemic products in the presence of the dinuclear catalyst[10] **L1**/Et_2Zn and pyridine (Table 1, entry 1). Considering the effect of the background reaction, the significantly less reactive α,β-unsaturated ester **3** was then employed as the acceptor. The low *ee* of the ester adduct suggested the origin of poor enantioselectivities was due to the steric hindrance imparted by diphenyl phosphine oxide (Table 1, entry 2).

Table 1. Optimization of the phospha-Michael reaction



Entry[a]	X	L	Solvent	Yield [%][b]	*ee* [%][c]
1		**L1**	THF	90	0
2	OMe **3**	**L1**	THF	85	2
3[d]		**L1**	THF	72	–
4		**L1**	THF	78	86
5		**L1**	THF	96	90
6	**6a**	**L2**	THF	97	75
7	**6a**	**L1**	THF	84	60[e]
8	**6a**	**L1**	DCM	82	89
9	**6a**	**L1**	diethyl ether	95	90
10	**6a**	**L1**	$PhCF_3$	96	89
11	**6a**	**L1**	toluene	96	99[f]

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.75 mmol, 1.5 equiv), **L**/Et_2Zn (10 mol%), α,β-unsaturated carbonyl compounds (0.5 mmol), and pyridine (0.5 mmol, 1 equiv) in solvent (5 mL) at RT for 12 h. [b] Yield of isolated product. [c] The enantiomeric excess was determined by chiral HPLC analysis. [d] Only the phospha-Brook rearrangement product was observed. [e] The reaction was performed without pyridine. [f] The reaction was completed within 10 min. THF = tetrahydrofuran.

Having failed to use these monodentate substrates in the asymmetric hydrophosphinylation reaction of diaryl phosphine oxides, we then tried some bidentate substrates, as we expected that these substrates might be helpful because the double binding could change the spatial conformation of the α,β-unsaturated carbonyl compounds. Interestingly, the use of ketoester **4** as the electrophile only led to 1,2-addition followed by a phospha-Brook rearrangement (Table 1, entry 3). Surprisingly, when pyrrolidinone **5** was employed as the electrophile, the enantioselectivity increased significantly to 86% (Table 1, entry 4). Further investigations suggest that oxazolidinone **6a** is a more advantageous substrate

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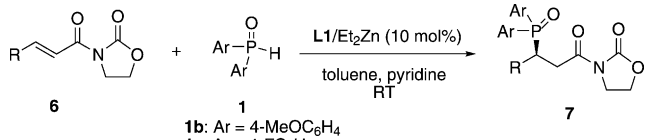
than **5** in terms of both yield and enantioselectivity (96%, 90% *ee*; Table 1, entry 5). In contrast, the phenyl ligand **L2** gave only 75% *ee* under the same reaction conditions. Then, the solvent test suggested that toluene was the best solvent and the reaction could be completed within 10 min (Table 1, entry 11).

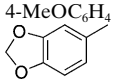
With optimized reaction conditions, we then screened a series of analogues **6a–q**, which bear various β-substituents. As shown in Table 2, oxazolidinones **6a–q** were well

Table 2. Substrate scope of the phospha-Michael reaction.



6 + **1** → **7**

1b: Ar = 4-$MeOC_6H_4$
1c: Ar = 4-FC_6H_4

Entry[a]	R	1	7	*t* [min]	Yield [%][b]	*ee* [%][c]
1	Ph	**1a**	**7a**	10	96	99
2	4-MeC_6H_4	**1a**	**7b**	15	95	>99
3	4-$MeOC_6H_4$	**1a**	**7c**	30	98	>99[e]
4		**1a**	**7d**	60	95	96
5	4-ClC_6H_4	**1a**	**7e**	15	98	99[d]
6	4-BrC_6H_4	**1a**	**7f**	15	99	98
7	4-FC_6H_4	**1a**	**7g**	15	93	94
8	2-FC_6H_4	**1a**	**7h**	90	94	90[e]
9	3-ClC_6H_4	**1a**	**7i**	30	97	94
10	4-$CF_3C_6H_4$	**1a**	**7j**	15	97	93
11	2-furyl	**1a**	**7k**	90	92	95
12	2-thienyl	**1a**	**7l**	90	96	99
13	2-naphthyl	**1a**	**7m**	45	95	98
14	Me	**1a**	**7n**	30	98	99
15	*i*Pr	**1a**	**7o**	90	97	96[e]
16	*i*Bu	**1a**	**7p**	15	95	93
17	*n*Hex	**1a**	**7q**	60	98	99[e]
18	Ph	**1b**	**7r**	60	95	93[e]
19	Ph	**1c**	**7s**	30	99	95[e]

[a] Unless otherwise noted, reactions were carried out with **1** (0.75 mmol, 1.5 equiv), **6** (0.5 mmol), **L1**/Et_2Zn (10 mol%), and pyridine (0.5 mmol, 1 equiv) in toluene (5 mL) at RT. [b] Yield of isolated product. [c] The enantiomeric excess was determined by chiral HPLC analysis. [d] The absolute configuration of **7e** was determined as *S* by X-ray analysis. [e] 15 mol% of the catalyst was employed.

applicable to the present catalysis; the products can be efficiently synthesized in high yield and high enantioselectivities. In comparison, the rate of the reaction was lower for electron-rich substrate **7c** (R = *para*-methoxyphenyl) and *ortho*-substituted substrate **7h** and higher catalyst loading was required to achieve good results (Table 2, entries 3 and 8). Interestingly, we found, in many cases, the products formed in the reaction were poorly soluble in toluene and precipitated from the solution. As a result, the reaction rates of the reactions with insoluble products such as **7a** and **7b** are much faster than those dissolved in the solution such as **7k** and **7l** (Table 2, entries 1, 2, 11, and 12). In addition, two other diaryl phosphine oxides **1b** and **1c** bearing electron-withdrawing substituents or electron-donating substituents were also tested and proved to be excellent substrates for the present method (Table 2, entries 18 and 19).

The absolute configuration of the Michael adduct **7e** was determined to be *S* by X-ray crystallographic analysis (Figure 1).[11] According to this result, a plausible transition

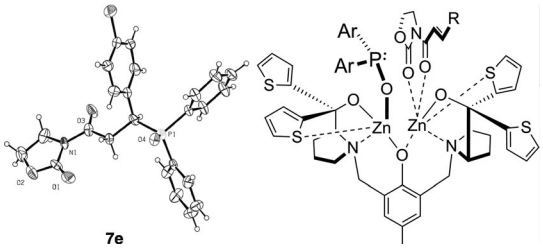


Figure 1. X-ray crystal structure of **7e** and proposed reaction mechanism.

state that explains the absolute stereochemistry of the products can be proposed. As shown in Figure 1, the diaryl phosphine oxides can be readily deprontonated by the zinc complex, and the bidentate oxazolidinones are believed to bind to one zinc atom of the catalyst. The mechanism is similar to the reaction of dialkyl phosphine oxides with enones.[9b] However, in the current case, the spatial conformation of the α,β-unsaturated carbonyl compounds was changed by the bindings of the two carbonyl groups, thus making the chiral pocket more compatible with more sterically hindered diaryl phosphine oxides.

In summary, we have developed a highly efficient asymmetric Michael reaction of diaryl phosphine oxides with α,β-unsaturated N-acylated oxazolidinones. This is a significant improvement over previous methods in which long reaction times are required, typically >12 hours or more. Excellent enantioselectivities (up to >99% *ee*) and chemical yields (up to 99%) were achieved with a broad substrate scope of the oxazolidinones. The bidentate property of oxazolidinones was found to be critical for high enantioselectivities. We have found that the precipitation of the products from the reaction solution greatly accelerated the reaction rate. Further investigations of the detailed mechanism and applications of the products are in progress.

Acknowledgements

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Keywords: asymmetric catalysis · C–P bonds · Michael addition · phosphine oxides · synthetic methods

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[11] CCDC 842933 contains the supplementary crystallographic data for **7e**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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