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Enantioselective phospha-Michael addition of diarylphosphines to β,γ-unsaturated α-ketoesters and amides†

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An enantioselective hydrophosphination of β,γ-unsaturated α-ketoesters and amides has been developed using a chiral palladacycle catalyst. Adducts can be obtained in excellent yields and enantioselectivities, providing direct access to chiral tertiary phosphines which are synthetically useful intermediates in the preparation of bidentate ligands.

The ability to fine-tune chiral phosphines to achieve varying steric and electronic properties has resulted in their widespread utilization as ligands in metal-mediated asymmetric transformations[1] as well as in organocatalysis.[2] Despite their importance, the preparation of chiral phosphines has traditionally been a cumbersome and wasteful affair.[3] Since Glueck pioneered the Pt(0)-catalyzed addition of secondary phosphines to alkenes,[4] it has sparked interest as a powerful method for the direct generation of chiral phosphines from prochiral reactants.[5] Up to this date, there have been a considerable number of reports involving the enantioselective addition of secondary phosphines to Michael acceptors.[6]

In spite of these reports, the majority of the protocols usually require the protection of the phosphine products for ease of handling and characterization. However, in the context of *in situ* complexation or direct organocatalyst preparation, such protocols render the phosphine dysfunctional since the electron pair on phosphorus, which is critical for its purported function, is no longer available. Furthermore, deprotection protocols are usually plagued with problems such as racemisation.[7]

Literature review revealed that over the past decade, β,γ-unsaturated α-ketoesters have served as excellent substrates for a myriad of reactions due to their superior reactivities *versus* typical α,β-unsaturated carbonyls. They are valuable electrophiles in conjugate additions,[8] including less commonly reported sulfa-,[9] oxy-[10] and aza-Michael additions.[11] Other than 1,4-additions, they also participate readily in other classes of reactions.[12] It should be noted that the resultant products can be further converted into other synthetically and biologically useful compounds.[13]

To the best of our knowledge, there have been no known reports on the enantioselective addition of phosphorus nucleophiles amongst the diverse reactions associated with β,γ-unsaturated α-ketoesters. An added advantage is that desired adducts can be readily transformed into corresponding alkoxyphosphines[14a]/phosphine-amino acid esters,[14b] providing rapid access to a library of versatile chiral P,O and P,N-ligands. Inspired by the potential of the targeted phospha-Michael adducts, we hereby disclose the first enantioselective addition of diarylphosphines to β,γ-unsaturated α-ketoesters and amides.

Using (*E*)-2-methyl-2-oxo-4-phenylbut-3-enoate **1a** as the model substrate, we attempted the hydrophosphination with diphenylphosphine (Ph_2PH). While it was expected for **1a** to have an improved reactivity over chalcones and their analogues, we were intrigued to find that the reaction proceeded even in the absence of any catalyst at room temperature (Table 1, entry 1). It should be highlighted that the uncatalyzed hydrophosphination of Michael acceptors under mild conditions is rare in recent literature. As such, this finding made our desired asymmetric transformation considerably more challenging. In order to circumvent the problem at hand, it was imperative to suppress the uncatalyzed pathway in the hope of achieving enantioselectivity control. It was fortuitous to find that when a temperature of −80 °C was utilized, the rate of the uncatalyzed reaction was significantly suppressed (Table 1, entry 2). To our delight, the use of (*R*)-**4** as the catalyst produced commendable results when coupled with reduced temperature and base loading (Table 1, entry 3). It should be highlighted that few catalysts are able to achieve a fine balance between reactivity and stereoselectivity when subjected to low operating temperatures. The choice of catalyst here was based on reports demonstrating the effectiveness and versatility of (*R*)-**4** and its analogues as catalysts in cycloaddition,[15] hydroamination[16] and hydrophosphination[6e–g] reactions.

Encouraged by the results, we performed a systematic screening of reaction conditions (Table 1). A mixture of chloroform and dichloromethane turned out to be the ideal solvent system (Table 1, entry 9). In addition, our studies also revealed

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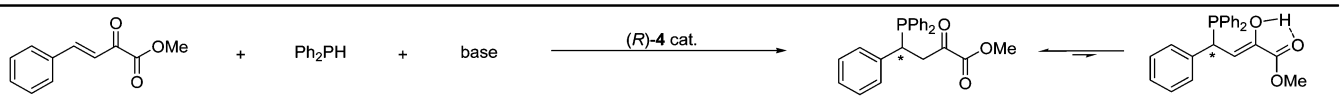
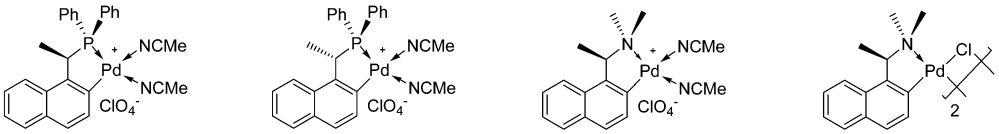
Table 1 Optimization of reaction conditions for the asymmetric hydrophosphination of (*E*)-2-methyl-2-oxo-4-phenylbut-3-enoate **1a** with diphenylphosphine[a]



1a **2a** **3a**

Entry	Catalyst/loading [mol%]	Solvent	Temperature [°C]	Base [equiv.]	Time [h]	Yield[b] [%]	ee[c] [%]
1	—/0%	$CHCl_3$	21 (rt)	Et_3N (1.0 eq.)	>2	99	0
2	—/0%	DCM	−80	Et_3N (0.2 eq.)	>15	16	0
3	(*R*)-**4**/5%	DCM	−80	Et_3N (0.5 eq.)	2	99	70
4	(*R*)-**4**/5%	DCM	−80	Et_3N (0.2 eq.)	>1.5	99	80
5	(*R*)-**4**/5%	Acetone	−80	Et_3N (0.2 eq.)	<2.5	99	70
6	(*R*)-**4**/5%	THF	−80	Et_3N (0.2 eq.)	2	99	71
7	(*R*)-**4**/5%	$CHCl_3$	−50	Et_3N (0.2 eq.)	2	99	70
8	(*R*)-**4**/5%	$CHCl_3$–DCM (5%)	−80	Et_3N (0.2 eq.)	4	98	76
9	(*R*)-**4**/5%	$CHCl_3$–DCM (10%)	−80	Et_3N (0.2 eq.)	2.5	98	81
10	(*S*)-**4**/5%	$CHCl_3$–DCM (10%)	−80	Et_3N (0.2 eq.)	2.5	98	−77
11	(*R*)-**4**/5%	DCE–DCM (25%)	−80	Et_3N (0.2 eq.)	>3	99	68
12	(*R*)-**4**/5%	$CHCl_3$–DCM (10%)	−80	Piperidine (0.2 eq.)	2.5	55	52
13	(*R*)-**5**/5%	$CHCl_3$–DCM (10%)	−80	Et_3N (0.2 eq.)	31	20	29

[a] Reaction was carried out with Ph_2PH (0.1–0.15 mmol) and **1a** (0.1–0.15 mmol) in 4 mL of degassed solvent(s). [b] Yield is derived from the $^{31}P\{^1H\}$ NMR spectrum of the crude product. [c] Enantiomeric excess (ee) is calculated from the $^{31}P\{^1H\}$ NMR integration of signals of diastereomers arising from the treatment of **2a** and **3a** with (*R*)-**6**.



(*R*)-**4** (*S*)-**4** (*R*)-**5** (*R*)-**6**

that while the amount of base employed did not significantly impact yields, a reduction in base loading did produce better selectivities (Table 1, entries 3 and 4). Triethylamine was the base of choice due to its suitable basicity as well as its ease of removal. Nevertheless, we attempted the reaction with a weaker amine but unfortunately this gave poor results (Table 1, entry 12). Lastly, we employed an amine analog of (*R*)-**4**, (*R*)-**5**, as the catalyst but it was disappointing as it produced poor results even with prolonged reaction times (Table 1, entry 13).

The enantiomeric excess (ee) of the adducts was determined from the integration of $^{31}P\{^1H\}$ NMR signals arising from diastereomers formed upon treatment of **2a** and **3a** with (*R*)-**6**, an effective resolving agent for both phosphines and arsines.[17] Enantioselectivities were readily established with adducts showing signals at δ 49.22 (*R*,*S*)-**7a**, 45.78 (*R*,*S*)-**8a** and 44.04 (*R*,*R*)-**7a**.[18] Single crystal X-ray diffraction analysis of **9a**, a phosphine–enolate chelate, revealed that the absolute configuration of the newly generated chiral centre was *S*.[18,19] A subsequent reaction carried out using (*S*)-**4** as the catalyst generated the *R* isomer with comparable results (Table 1, entry 10).

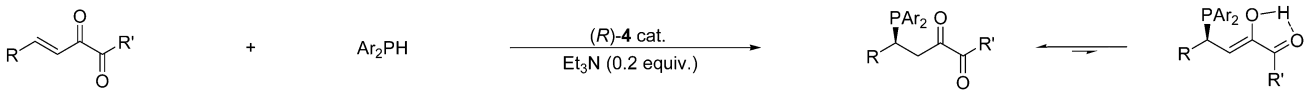
With the optimal conditions thus established, the substrate scope for the asymmetric phospha-Michael addition of β,γ-unsaturated α-ketoesters was examined and our findings are summarised in Table 2. Our protocol can tolerate a wide range of functional groups including halo, nitro, alkyl, and alkoxy chains as well as heterocycles. Generally, reactions proceeded smoothly to give excellent yields of up to >99%. However, it should be noted that when an electronically richer and bulkier isopropyl ester was employed, the ee improved slightly (Table 2, entry 2). Excellent results were also obtained by changing the substitution from the *para* to the *meta* position (Table 2, entries 4 and 5). However, for heterocycles, substandard results were observed for *ortho*-substituted moieties as compared to *meta*-substituted ones (Table 2, entries 11 and 12).

In addition to Ph_2PH, we also examined di(*p*-tolyl)phosphine ($(p\text{-Tol})_2PH$) to study the applicability of various secondary phosphines in our protocol. While $(p\text{-Tol})_2PH$ also afforded excellent yields, only moderate ee values were obtained, with comparatively longer reaction times (Table 2, entries 13–16). We believe that the reduced reactivity of $(p\text{-Tol})_2PH$ ensured that the uncatalyzed reaction was marginally more dominant, thus accounting for the reduced selectivities. In general, regardless of the phosphinating agents employed, electron-deficient substrates produced superior enantioselectivities compared to more electron-rich moieties (Table 2, entries 3–10 and 13–15).

In addition to β,γ-unsaturated α-ketoesters, we were curious as to whether the protocol would also be pertinent for β,γ-unsaturated α-ketoamides **1aa**. Owing to the Lewis basicity of nitrogen, the ketone carbonyl was activated to a lesser extent, thus accounting for the longer reaction time required (Table 2, entry 17).

Drawing upon previously reported experimental results,[6e] a catalytic cycle for the asymmetric phospha-Michael addition of **1** is proposed. Relative to the phosphorus atom in metallacycle **4**, the naphthyl ring exerts a stronger *trans* effect, thereby labilizing the bound diarylphosphine *trans* to the aromatic ring. Its departure generates a vacant site, allowing **1** to bind *via* its keto oxygen due to the pronounced oxophilicity of that particular site.[20] The remaining bound phosphine then undergoes deprotonation in the presence of base to give a phosphido species, which attacks the electrophilic

Table 2 Substrate scope for the (*R*)-**4** catalyzed enantioselective phospha-Michael addition of β,γ-unsaturated α-ketoesters and amides **1** with diarylphosphines[a]



1 **2** **3**

Entry	Substrate	R	R′	Ar	Time [h]	Product	Yield[b,c] [%]	ee[d] [%]
1	**1a**	Ph	OMe	Ph	2.5	**2a**	98 (93)	81
2	**1b**	Ph	O^{i}Pr	Ph	4	**2b**	98 (94)	83
3	**1c**	*p*-FC_6H_4	OMe	Ph	2.5	**2c**	98 (93)	83
4	**1d**	*p*-ClC_6H_4	OMe	Ph	2.5	**2d**	98 (94)	85
5	**1e**	*m*-ClC_6H_4	OMe	Ph	2.5	**2e**	98 (90)	85
6	**1f**	*p*-BrC_6H_4	OMe	Ph	2.5	**2f**	99 (95)	87
7	**1g**	*p*-$CF_3C_6H_4$	OMe	Ph	2.5	**2g**	98 (90)	90
8	**1h**	*p*-$NO_2C_6H_4$	OMe	Ph	4	**2h**	98 (94)	89
9	**1i**	*p*-MeC_6H_4	OMe	Ph	5	**2i**	98 (91)	71
10	**1j**	*p*-$MeOC_6H_4$	OMe	Ph	5	**2j**	93 (95)	78
11	**1k**	*m*-Pyridyl	OMe	Ph	2	**2k**	90 (93)	84
12	**1l**	2-Thienyl	OMe	Ph	4	**2l**	94 (95)	65
13	**1a**	Ph	OMe	*p*-Tolyl	3.5	**2a′**	98 (96)	66
14	**1d**	*p*-ClC_6H_4	OMe	*p*-Tolyl	3.5	**2d′**	>99 (96)	71
15	**1i**	*p*-MeC_6H_4	OMe	*p*-Tolyl	6	**2i′**	98 (94)	70
16	**1k**	*m*-Pyridyl	OMe	*p*-Tolyl	3.5	**2k′**	>99 (90)	75
17	**1aa**	Ph	NEt_2	Ph	23	**2aa**	95 (>99)	70

[a] Reaction was carried out with Ar_2PH (0.1 mmol) and **1** (0.1 mmol) in 3.6 mL of chloroform and 0.4 mL of dichloromethane. Solvents were degassed prior to use. [b] Yield is derived from the $^{31}P\{^1H\}$ NMR spectrum of the product. [c] Values in parentheses indicate the abundance of keto tautomer **2** which is determined from the $^{31}P\{^1H\}$ NMR spectrum of the product. [d] Enantiomeric excess (ee) is calculated from the $^{31}P\{^1H\}$ NMR integration signals of diastereomers arising from the treatment of **2** and **3** with (*R*)-**6**.

centre in **1**. Proton exchange followed by dissociation of the desired product from the catalyst then completes the catalytic cycle. It should be highlighted that **4** behaves purely as a Lewis acid catalyst and thus palladium does not undergo any change in oxidation state throughout the cycle. It is noteworthy that similar catalytic cycles have recently been reported, resembling our proposed system.[5]

In conclusion, we have developed the first protocol involving the catalytic enantioselective phospha-Michael addition of β,γ-unsaturated α-ketoesters and amides. Excellent yields of up to >99% and enantioselectivities of up to 90% can be achieved when coupled with low temperatures, which suppress the undesired uncatalyzed pathway. The ease of access to such synthetically important chiral tertiary phosphines greatly facilitates the preparation of catalytically versatile P,O and P,N bidentate ligands.

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