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COMMUNICATION

Phosphine-catalyzed regioselective Michael addition to allenates

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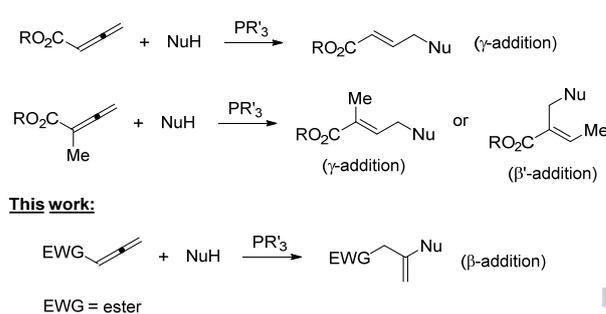
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The first phosphine catalysed Michael addition of arylcyanoacetates to allenates has been developed, and the β -selective products with a quaternary center were obtained in excellent yields. This unusual regioselectivity may open new opportunities to access interesting molecular structures.

Phosphine catalysis represents a powerful tool for constructing C–C bonds.¹ Most commonly, phosphines activate electron-deficient alkenes, alkynes and allenes by forming a zwitterionic intermediate, which then further reacts with suitable electrophiles to form new bonds.² Among numerous phosphine-mediated reactions, γ -addition reactions have been well investigated. The pioneering studies were independently reported by the groups of Trost and Lu in the 1990s, in which phosphine-promoted γ -additions to allenates or alkynoates were successfully developed.³ Subsequently, γ -umpolung additions attracted much attention from synthetic community, and many enantioselective γ -addition reactions have been developed over the years.⁴ Recently, the Kwon group reported a novel β' -umpolung addition of ethyl-2-alkyl-2,3-butadienoate.⁵ Almost at the same time, Shi et al. also independently described the synthesis of arylate derivatives via a β' -umpolung addition.⁶ On the other hand, β -addition (Michael) to activated allenes has been explored only to a very limited extent (Scheme 1). Brønsted base was shown to promote Michael addition to activated allenes,⁷ which was easy to understand as the α,β -double bond in the allene structures is more electron-deficient as compared with β,γ -double bond. However, Michael addition to activated allenes promoted by phosphines is a much more challenging task; the attack of phosphonium zwitterion intermediate generated from the phosphine to allenes will eventually direct the nucleophile to less electron-deficient

double bond in allenes, so-called γ -umpolung addition. To the best of our knowledge, there was only one report by Huang and workers, in which a phosphine was shown to catalyze azide-Michael addition of hydrazones to allenates.⁸ Herein, we would like to document the first phosphine-catalyzed Michael addition of carbon nucleophiles to allenates.



Scheme 1 Various types of additions to activated allenes.

Table 1 Michael addition of ethyl phenylcyanoacetate **1a** to allenate **2a** catalyzed by phosphines^a

Entry	Cat.	Solvent	Yield (%) ^b	β/γ ^c
1	PPh ₃	CH ₂ Cl ₂	99	99/1
2	PPh ₃	CHCl ₃	99	80/20
3	PPh ₃	THF	64	100/-
4	PPh ₃	MeOH	80	78/22

5	PPh ₃	CH ₃ CN	79	100/-
6	PPh ₃	ether	74	73/27
7	PPh ₃	DMF	69	99/1
8	PPh ₃	DMSO	99	99/1
9	PPh ₃	Toluene	99	66/33
10	PPh ₃	Acetone	99	99/1
11	PPh ₃	Xylene	99	76/24
12	PPh ₃	Mesitylene	99	72/28
13	PPh ₃	Dioxane	75	99/1
14	PPh ₃	Dimethoxyethane	81	99/1
15	PPh ₃	Dichloroethane	70	99/1
16	MePPh ₂	CH ₂ Cl ₂	98	99/1
17	PCy ₃	CH ₂ Cl ₂	99	99/1
18	Me ₂ PPh	CH ₂ Cl ₂	95	99/1
19	P(tol) ₃	CH ₂ Cl ₂	99	99/1
20	DBU	CH ₂ Cl ₂	65	100/-
21	DABCO	CH ₂ Cl ₂	33	100/-

^a Reactions were performed with **1a** (0.1 mmol), **2a** (0.15 mmol) and the catalyst (0.005 mmol) in the solvent specified (0.5 mL) at room temperature. ^b Isolated yield. ^c Determined by ¹H NMR analysis of the crude mixture.

We chose ethyl phenylcyanoacetate **1a** and allenoate **2a** as model compounds to start our investigation (Table 1). When the reaction was performed in CH₂Cl₂ in the presence of PPh₃, the β-addition took place almost exclusively, and the Michael product was obtained quantitatively (entry 1). Solvents were subsequently screened. While all the solvents favoured the formation of β-addition product over γ-adduct, CH₂Cl₂ remained to be the best solvent for the reaction (entries 2–14). The effects of different phosphines on the reaction were also examined, and all the phosphines investigated showed similar activities to that of PPh₃ (entries 15–18). Although DBU and DABCO led to the formation of only Michael adducts, the chemical yields were less satisfactory (entries 19 and 20).

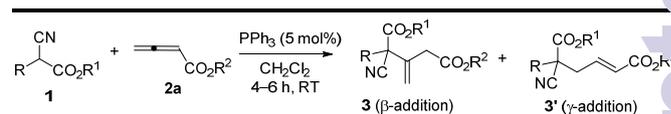
With the above optimized reaction conditions established, different allene esters were next utilized for the reaction (Table 2). When the ester moiety in phenylcyanoacetates was small, e.g. ethyl group, the β-selectivities of the products changed along with different allene esters employed, with *tert*-butyl ester giving the best β-selectivity (entries 1–3). By employing sterically hindered *tert*-butyl cyanoacetate, the high β-selectivity was constantly observed (entries 4 and 5). When phenylcyanoacetate was replaced by benzylcyanoacetate, β-

selectivity was lost and γ-adducts dominated (entries 6–8). In all the above cases, the β- and γ-adducts were easily separable by silica gel column chromatography.

By using the established synthetic protocol, we prepared a number of β-selective adducts by reacting the corresponding cyanoacetates and allenoates in the presence of either PPh₃ or MePPh₂, and the desired quaternary carbon-containing adducts were obtained in high to quantitative yields (Figure 1). Extending our current method to an asymmetric variant was unsuccessful. Phosphine catalysts **4**, **5** and **6** led to exclusive formation of β-adducts, however, no asymmetric induction was observed. On the other hand, employment of **7** yielded γ-addition products with low enantioselectivity (Figure 2). More extensive work needs to be carried out in the future for the development of a phosphine-catalyzed enantioselective β-selective addition reaction.

The mechanism for the formation of β-selective products is unclear, we propose that the steric hindrance of nucleophilic anion makes common γ-addition unfavourable, accounting for the formation of Michael adducts (Scheme 2).

Table 2 Examination of different allene esters^a



Entry	R	R ¹ /R ²	Yield (%) ^b	β/γ ^c
1	Ph	Et/Bn	99	99/1
2	Ph	Et/Et	92	75/25
3	Ph	Et/ <i>t</i> -Bu	96	66/33
4	Ph	<i>t</i> -Bu/Bn	98	90/10
5	Ph	<i>t</i> -Bu/Et	84	90/10
6	CH ₂ Ph	<i>t</i> -Bu/Bn	98	-/100
7	CH ₂ Ph	<i>t</i> -Bu/Et	95	40/60
8	CH ₂ Ph	<i>t</i> -Bu/ <i>t</i> -Bu	94	-/100
9	Me	Et/Bn	89	-/100

^a Reactions were performed with **1** (0.1 mmol), **2** (0.15 mmol) and PPh₃ (0.005 mmol) in CH₂Cl₂ (0.5 mL) at room temperature. ^b Isolated yield. ^c Determined by ¹H NMR analysis of the crude mixture.

In summary, we have developed the first phosphine-catalyzed β-selective addition of arylcyanoacetates to 2,3-butadienoates. The desired Michael adducts with a quaternary center were obtained in excellent yields. Currently, we are investigating the origin of such regioselectivity. Meanwhile, development of an asymmetric variant of such a β-addition to

activated allenes using our amino acid-derived chiral phosphines⁹ is underway.

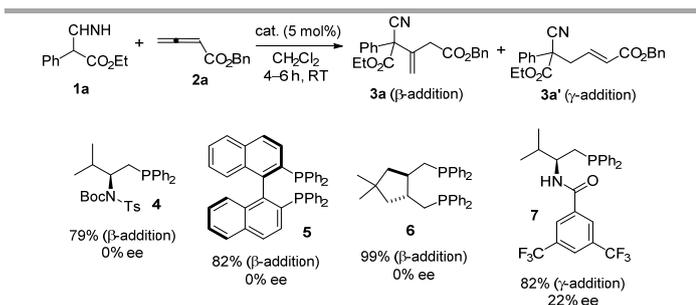


Figure 2: Preliminary studies employing chiral phosphines.

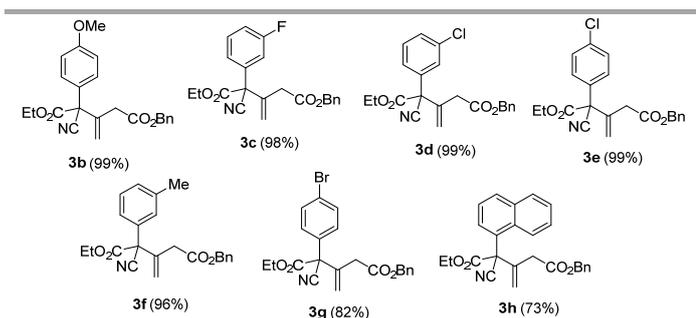
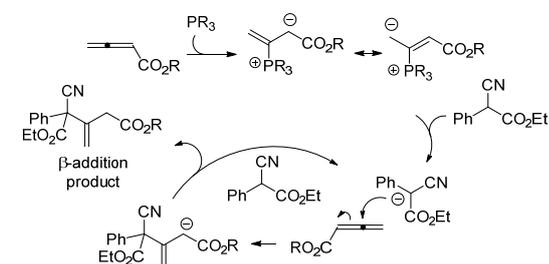


Figure 1: Selective β -adducts synthesized.



Scheme 2 Proposed mechanism.

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Notes and references

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