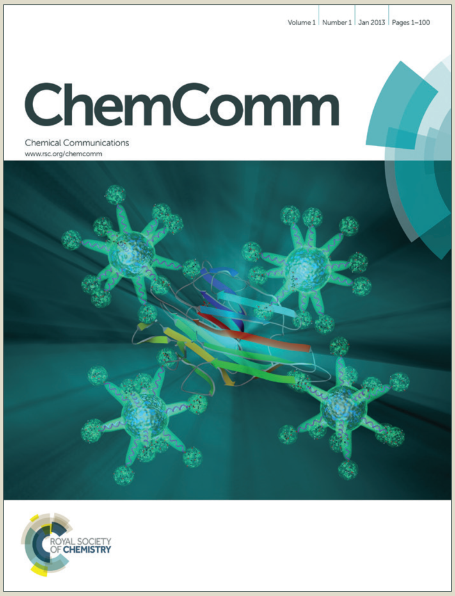
View Article Online
View Journal

ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: V. R. Gandi and Y. Lu, *Chem. Commun.*, 2015, DOI: 10.1039/C5CC06197K.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Journal Name

RSCPublishing

View Article Online
DOI: 10.1039/C5CC06197K

COMMUNICATION

Phosphine-catalyzed regioselective Michael addition to allenoates

Cite this: DOI: 10.1039/x0xx00000x

Vasudeva Rao Gandi and Yixin Lu[a]

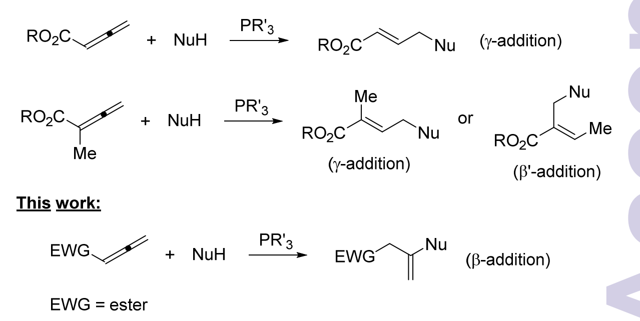
Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

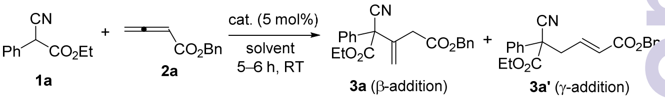
The first phosphine catalysed Michael addition of arylcyanoacetates to allenoates has been developed, and the β-selective products with a quaternary center were obtained in excellent yields. This unusual regioselectivity may open new opportunities to access interesting molecular structures.

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 allenoates 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 aza-Michael addition of hydrazones to allenoates.[8] Herein, we would like to document the first phosphine-catalyzed Michael additions of carbon nucleophiles to allenoates.



Scheme 1 Various types of additions to activated allenes.

Table 1 Michael addition of ethyl phenylcyanoacetate **1a** to allenoate **2a** catalyzed by phosphines[a]



Entry	Cat.	Solvent	Yield (%)[b]	β/γ[c]
1	PPh_3	CH_2Cl_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_3CN	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_2Cl_2	98	99/1
17	PCy_3	CH_2Cl_2	99	99/1
18	Me_2PPh	CH_2Cl_2	95	99/1
19	$P(tol)_3$	CH_2Cl_2	99	99/1
20	DBU	CH_2Cl_2	65	100/-
21	DABCO	CH_2Cl_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 ^{1}H 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 CH_2Cl_2 In the presence of PPh_3, 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, CH_2Cl_2 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 PPh_3 (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).

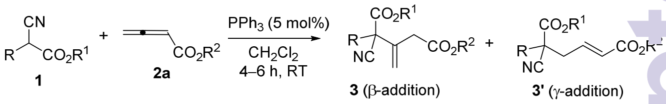
With the above optimized reaction conditions established, different allene esters were next utilized for the reaction (Table 2). When the ester moiety in phenylcyanoacetates was small, e.g. ethyl group, the β-selectivities of the products changed along with different allene esters employed, with *tert*-butyl 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.

View Article Online
DOI: 10.1039/C5CC06197K

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 PPh_3 or $MePPh_2$, 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/*t*-Bu	96	66/33
4	Ph	*t*-Bu/Bn	98	90/10
5	Ph	*t*-Bu/Et	84	90/10
6	CH_2Ph	*t*-Bu/Bn	98	-/100
7	CH_2Ph	*t*-Bu/Et	95	40/60
8	CH_2Ph	*t*-Bu/*t*-Bu	94	-/100
9	Me	Et/Bn	89	-/100

[a] Reactions were performed with **1** (0.1 mmol), **2** (0.15 mmol) and PPh_3 (0.005 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. [b] Isolated yield. [c] Determined by ^{1}H 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

View Article Online
DOI: 10.1039/C5CC06197K

activated allenes using our amino acid-derived chiral phosphines[9] is underway.

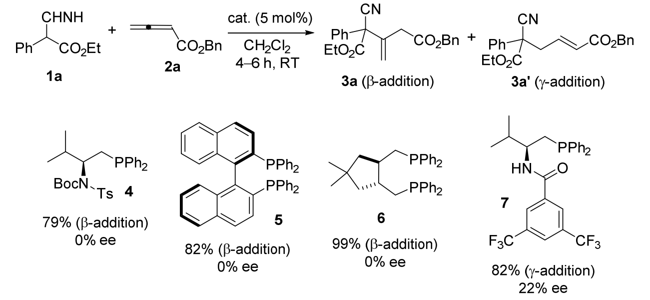


Figure 2: Preliminary studies employing chiral phosphines.

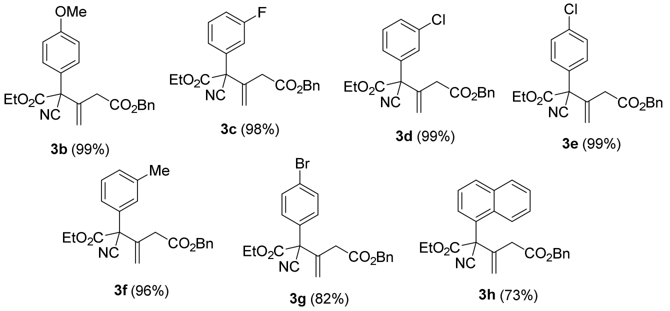
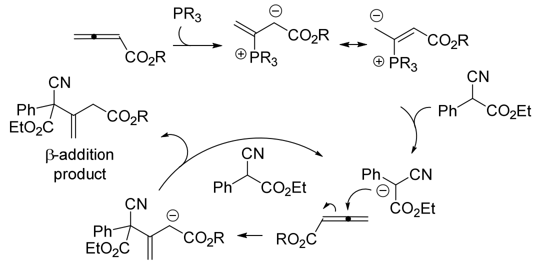


Figure 1: Selective β-adducts synthesized.



Scheme 2 Proposed mechanism.

We thank National University of Singapore (R-143-000-599-112), Ministry of Education of Singapore (R-143-000-494-112) and GSK-EDB (R-143-000-491-592) for financial support.

Notes and references

[a] Department of Chemistry, National University of Singapore, 3 Science Drive 3, Republic of Singapore 117543.
Email: chmlyx@nus.edu.sg

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

1 For reviews, see: (a) X. Lu, C. Zhang and Z. Xu, *Acc. Chem. Res*. 2001, **34**, 535; (b) D. H. Valentine and J. H. Hillhouse, *Synthesis* 2003, 317; (c) J. L. Methot and W. R. Roush, *Adv. Synth. Catal*. 2004, **346**, 1035; (d) X. Lu, Y. Du and C. *Pure Appl. Chem*. 2005, **77**, 1985; (e) V. Nair, R. S. Menon, A. R. Sreekanth, N. Abhilash and A. T. Biju, *Acc. Chem. Re* 2006, **39**, 520; (f) S. E. Denmark and G. L. Beutner, *Angew. Chem. Int. Ed*. 2008, **47**, 1560; (g) L.-W. Ye, J. Zhou and . Tang, *Chem. Soc. Rev*. 2008, **37**, 1140; (h) C. K.-W. Kwon, M. Y. Fu, C. S.-L. Lam and P. H. Toy, *Synthesis* 2008, 230 , (i) C. E. Aroyan, A. Dermenci and S. J. Miller, *Tetrahedro* 2009, **65**, 4069; (j) B. J. Cowen and S. J. Miller, *Chem. So . Rev*. 2009, **38**, 3102; (k) A. Marinetti and A. Voituriez, *Synle* 2010, 174.

2 (a) Y. Xia, Y. Liang, Y. Chen, M. Wang, L. Jiao, F. Huang, Liu, Y. Li and Z. Yu, *J. Am. Chem. Soc*. 2007, **129**, 3470; (X. Meng, Y. Huang and R. Chen, *Org. Lett***.** 2009, **11**, 137; (X. Meng, Y. Huang, H. Zhao, P. Xie, J. Ma and R. Chen, *Org. Lett*. 2009, **11**, 991; (d) H. Guo, Q. Xu and O. Kwon, *J. A . Chem. Soc*. 2009, **131**, 6318; (e) Y. Sun, X. Guan and M. Shi. *Org. Lett*. 2010, **12**, 5664; (f) T. Wang and S. Ye, *Org.* 2010, **12**, 4168; (g) X. Zhang, L. Yang and X. Tong, *J. Chem. Soc*. 2010, **132**, 2550; (h) X. Chen, M. Wen, S. Ye and Z. Wang, *Org. Lett*. 2011, **13**, 1138.

3 (a) B. M. Trost and C. Li, *J. Am. Chem. Soc*. 1994, **116**, 316 ; (b) B. M. Trost and C. Li, *J. Am. Chem. Soc*. 1994, **116**, 10819; (c) B. M. Trost and G. R. Drake, *J. Org. Chem*. 199 , **62**, 5670; (d) C. Zhang and X. Lu, *Synlett* 1995, 645.

4 (a) Z. Chen, G. Zhu, Q. Jiang, D. Xiao, P. Cao and X. Zha *J. Org. Chem*., 1998, **63**, 5631; (b) Y. K. Chung and G. C. F *Angew. Chem*. 2009, **48**, 2225; (c) S. W. Smith and G. C. F *J. Am. Chem. Soc*. 2009, **131**, 14231; (d) R. Sinisi, J. Sun and G. C. Fu, *Proc. Natl. Acad. Sci. USA*, 2010, **107**, 20652; (e) Sun and G. C. Fu, *J. Am. Chem. Soc*. 2010, **132**, 4568; (f) R. Lundgren, A. Wilsily, N. Marion, C. Ma, Y. K. Chung and C. Fu, *Angew. Chem. Int. Ed*. 2013, **52**, 2525; (g) T. Wang, W Yao, F. Zhong, G. H. Pang and Y. Lu, *Angew. Chem. Int. E* 2014, **53**, 2964.

5 T. J. Martin, V. G. Vakhshori, Y. S. Tran and O. Kwon, *Lett*. 2011, **13**, 2586.

6 X. Guan, Y. Wei and M. Shi, *Eur. J. Org. Chem*. 2011, 2673.

7 (a) A. Padwa and P. E. Yeske, *J. Org. Chem*., 1991, **56**, 638 (b) X. Huang and R.-W. Shen, *Synthesis*, 2006, 2731.

8 E. Li, P. Xie, L. Yang, L. Liang and Y. Huang, *Chem. Asian* 2013, **8**, 603.

9 For selected examples, see: (a) F. Zhong, Y. Wang, X. Han, K-W. Huang and Y. Lu, *Org. Lett*. 2011, **13**, 1310; (b) F. Zhong, . Han, Y. Wang and Y. Lu, *Angew. Chem. Int. Ed*. 2011, **50**, 783 (c) X. Han, Y. Wang, F. Zhong and Y. Lu, *J. Am. Chem. Soc* 2011, **133**, 1726; (d) X. Han, F. Zhong, Y. Wang and Y. L *Angew. Chem. Int. Ed*. 2012, **51**, 767; (e) F. Zhong, X. Han, Y. Wang and Y. Lu, *Chem. Sci*. 2012, **3**, 1231; (f) F. Zhong, C Y. Chen, X. Han, W. Yao and Y. Lu, *Org. Lett*. 2012, **14**, 3764 (g) Q. Zhao, X. Han, Y. Wei, M. Shi, Y. Lu, *Chem. Commun*. 2012, **48**, 970; (h) F. Zhong, X. Dou, X. Han, W. Yao, Q. Zhu, . Meng, and Y. Lu, *Angew. Chem. Int. Ed*. 2013, **52**, 943; (i) Han, W. Yao, T. Wang, Y. R. Tan, Z. Yan, J. Kwiskowski, and Lu, *Angew. Chem. Int. Ed*. 2014, **53**, 5643; (j) W. Yao, X. Dou and Y. Lu, *J. Am. Chem. Soc*. 2015, **137**, 54.