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Bisphosphine-Triggered One-Pot Sequential [3 + 2]/[3 + 2] Annulation of Allenoates with Cyclic Ketimines

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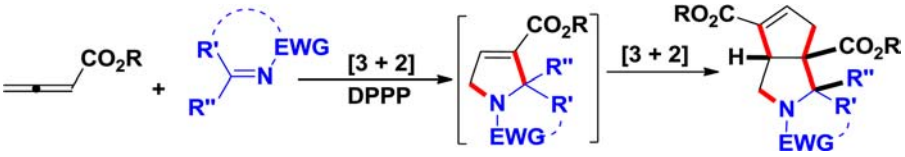
ABSTRACT



An efficient bisphosphine-triggered one-pot sequential [3 + 2]/[3 + 2] annulation of allenoates with cyclic ketimines was developed, in which the product of the first [3 + 2] annulation is the electron-deficient substrate for the second [3 + 2] annulation reaction. The reaction is exceptionally regioselective and diastereoselective. This novel and highly convergent strategy may open up a new viewpoint in utilizing allenoates to prepare *N*-fused polycyclic compounds.

Nucleophilic phosphine-promoted cycloaddition of activated alkenes and alkynes has emerged as a powerful tool for the construction of various carbo- and heterocyclic architectures from readily available starting materials.[1] In particular, much effort has been devoted to the [3 + 2] cycloadditions of allenoates with electron-deficient olefins and imines to form cyclopentenes and pyrrolidines, respectively (Figure 1a and b).[2,3] Furthermore, many annulation reactions have been successfully applied to the synthesis of natural products and compounds of pharmaceutical significance.[4] However, all such studies have focused on the use of a separate reaction system with different nucleophilic monophosphines. In sharp contrast, the integration of two individual [3 + 2] cycloaddition reactions of allenoates with imines and electron-deficient olefins into a one-pot sequential process still remains a formidable challenge and there has been no report in the literature, to date, of such a potentially useful transformation (Figure 1c). Here, we report a novel bisphosphine-triggered one-pot sequential [3 + 2]/[3 + 2] annulation process of allenoates with cyclic ketimines, in which the product of the first

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[3 + 2] annulation is the electron-deficient substrate for another [3 + 2] annulation reaction. The notable features of this transformation is the sequential formation of four new bonds and the creation of three contiguous stereogenic centers by using a single catalyst in one pot, without the need for isolation of the intermediates. Therefore, this protocol provides a novel and highly convergent synthetic approach to *N*-fused polycyclic compounds with excellent regio- and diastereoselectivity.

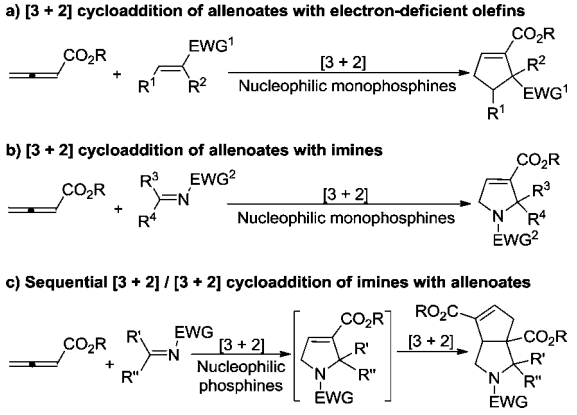


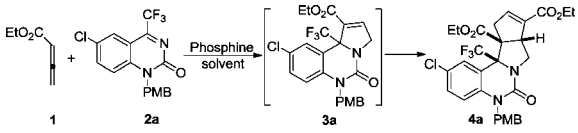
Figure 1. Phosphine-catalyzed cycloadditions of allenoates with electron-deficient olefins and imines.

(3) For selected examples, see: (a) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031. (c) Lu, X. *Tetrahedron Lett.* **1999**, *40*, 549. (d) Zhu, X.-F.; Henry, C. E.; Kwon, O. *Tetrahedron* **2005**, *61*, 6276. (e) Shi, Y.-L.; Shi, M. *Org. Lett.* **2005**, *7*, 3057. (f) Zhao, G.-L.; Shi, M. *J. Org. Chem.* **2005**, *70*, 9975. (g) Jean, L.; Marinetti, A. *Tetrahedron Lett.* **2006**, *47*, 2141. (h) Scherer, A.; Gladysz, J. A. *Tetrahedron Lett.* **2006**, *47*, 6335. (i) Tang, X.; Zhang, B.; He, Z.; Gao, R.; He, Z. *Adv. Synth. Catal.* **2007**, *349*, 2007. (j) Fleury-Brégeot, N.; Jean, L.; Retailleau, P.; Marinetti, A. *Tetrahedron* **2007**, *63*, 11920. (k) Panossian, A.; Fleury-Brégeot, N.; Marinetti, A. *Eur. J. Org. Chem.* **2008**, 3826. (l) Fang, Y.-Q.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 5660. (m) Meng, L.-G.; Cai, P.; Guo, Q.; Xue, S. *J. Org. Chem.* **2008**, *73*, 8491. (n) Zhang, B.; He, Z.; Xu, S.; Wu, G.; He, Z. *Tetrahedron* **2008**, *64*, 9471. (o) Pinto, N.; Fleury-Brégeot, N.; Marinetti, A. *Eur. J. Org. Chem.* **2009**, 146. (p) Guan, X.-Y.; Shi, M. *J. Org. Chem.* **2009**, *74*, 1977. (q) Schuler, M.; Duvvuru, D.; Retailleau, P.; Betzer, J.-F.; Marinetti, A. *Org. Lett.* **2009**, *11*, 4406. (r) Han, X.; Zhong, F.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 767. (s) Chen, X.-Y.; Lin, R.-C.; Ye, S. *Chem. Commun.* **2012**, *48*, 1317. (t) Wang, Y.-Q.; Zhang, Y.; Dong, H.; Zhang, J.; Zhao, J. *Eur. J. Org. Chem.* **2013**, 3764.

(4) For selected examples, see: (a) Ung, A. T.; Schafer, K.; Lindsay, K. B.; Pyne, S. G.; Amornraksa, K.; Wouters, R.; Van der Linden, I.; Biesmans, I.; Lesage, A. S. J.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2002**, *67*, 227. (b) Du, Y.; Lu, L. *J. Org. Chem.* **2003**, *68*, 6463. (c) Wang, J.-C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855. (d) Pham, T. Q.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2005**, *70*, 6369. (e) Yong, S. R.; Williams, M. C.; Pyne, S. G.; Ung, A. T.; Skelton, B. W.; White, A. H.; Turner, P. *Tetrahedron* **2005**, *61*, 8120. (f) Henry, C. E.; Kwon, O. *Org. Lett.* **2007**, *9*, 3069. (g) Wu, H.; Zhang, H.; Zhao, G. *Tetrahedron Lett.* **2007**, *63*, 6454. (h) Tamanoi, F.; Kwon, O.; Watanabe, M.; Fiji, H. PCT Int. Appl. WO 2007111948 (2007). (i) Castellano, S.; Fiji, H. D. G.; Kinderman, S. S.; Watanabe, M.; De Leon, P.; Tamanoi, F.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 5843. (j) Watanabe, M.; Fiji, H. D. G.; Guo, L.; Chan, L.; Kinderman, S. S.; Slamon, D. J.; Kwon, O.; Tamanoi, F. *J. Biol. Chem.* **2008**, *283*, 9571. (k) Jones, R. A.; Krische, M. J. *Org. Lett.* **2009**, *11*, 1849. (l) Lu, J.; Chan, L.; Fiji, H. D. G.; Dahl, R.; Kwon, O.; Tamanoi, F. *Mol. Cancer Ther.* **2009**, *8*, 1218. (m) Kwon, O.; Tamanoi, F.; Fiji, H.; Watanabe, M. PCT Int. Appl. WO 2010014054 (2010). (n) Wang, Z.; Castellano, S.; Kinderman, S. S.; Argueta, C. E.; Beshir, A. B.; Fenteany, G.; Kwon, O. *Chem.—Eur. J.* **2011**, *17*, 649. (o) Sampath, M.; Lee, P.-Y. B.; Loh, T.-P. *Chem. Sci.* **2011**, *2*, 1988. (p) Andrews, I. P.; Kwon, O. *Chem. Sci.* **2012**, *3*, 2510.

Initially, we examined the annulation of ethyl 2,3-butadienoate **1** with cyclic ketimine **2a** by using PBu_3 (20 mol %) as a nucleophilic catalyst at room temperature (Table 1, entry 1). The reaction proceeded smoothly to give the sequential [3 + 2]/[3 + 2] annulation product **4a** along with the single [3 + 2] cycloadduct **3a** in a combined yield of 87% in a 2:1 ratio. The other monophosphines tested gave similar results (entries 2−5). Considering that this sequential annulation reaction involves two molecules of ethyl 2,3-butadienoate, we hypothesized that the use of bisphosphines could facilitate the formation of biszwitterionic intermediate and enable the second annulation to proceed well in an intramolecular-like fashion. Next, we employed several commercially available bisphosphines as nucleophilic catalysts. To our delight, we isolated the sequential cycloadduct **4a** in good yield with excellent regio- and diastereoselectivity (entries 6−8). In addition, the yield of **4a** can be improved from 82% to 88% with a prolonged reaction time (entry 9). The subsequent change of the reaction temperature and solvent did not have a significant effect on the ratio of **4a** to **3a** (entries 10−15). The use of excess ethyl 2,3-butadienoate was found to significantly

Table 1. Screening of Nucleophilic Phosphines and Optimization of the Reaction Conditions[a]

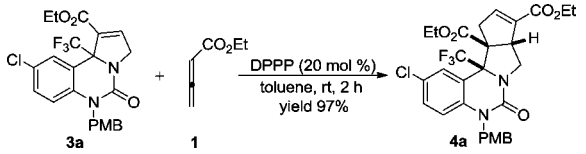


entry	phosphine (mol %)	solvent	temp (°C)/ time (h)	yield (%)[b] 3a	4a[c]
1	PBu_3 (20)	toluene	25/12	28	59
2	PCy_3 (20)	toluene	25/12	20	42
3	PPh_3 (20)	toluene	25/12	44	54
4	$P(NMe_2)_3$ (20)	toluene	25/12	31	35
5	$P(NEt_2)_3$ (20)	toluene	25/12	34	43
6	DPPE (20)	toluene	25/2	14	77
7	DPPP (20)	toluene	25/2	13	82
8	DPPB (20)	toluene	25/2	14	81
9	DPPP (20)	toluene	25/24	8	88
10	DPPP (20)	toluene	40/2	8	89
11	DPPP (20)	toluene	0/24	17	80
12	DPPP (20)	THF	25/2	17	78
13	DPPP (20)	Et_2O	25/2	18	73
14	DPPP (20)	CH_2Cl_2	25/2	19	79
15	DPPP (20)	CH_3CN	25/12	11	21
16[d]	DPPP (20)	toluene	25/2	3	96
17[e]	DPPP (20)	toluene	25/2	0	97
18[d]	DPPP (10)	toluene	25/12	5	92

[a] Reactions were conducted with 2.0 equiv of ethyl 2,3-butadienoate (**1**), 1.0 equiv of **2a**, and the phosphine catalyst (10−20 mol %) in solvent for the stated time. PMB = *p*-methoxybenzyl. DPPE = 1,2-bis(diphenylphosphino)ethane. DPPB = 1,4-bis(diphenylphosphino)-butane. [b] Isolated yield. [c] > 99:1 dr (determined by ^{19}F NMR analysis of crude product **4a**), and the relative configuration was determined by X-ray crystal structure analysis (vide infra). [d] 2.5 equiv of **1** were used. [e] 3.0 equiv of **1** were used.

increase the sequential annulation yield (entries 16 and 17). When the amount of catalyst was reduced to 10 mol %, the sequential annulation performed equally well in high yield (entry 18). It is noteworthy that, under the catalysis of 1,3-bis(diphenylphosphino)propane (DPPP), further annulation of **3a** with ethyl 2,3-butadienoate worked well to give the cycloadduct **4a** in 97% yield (Scheme 1). These results provide further evidence that a sequential process could be involved in the catalytic cycle.

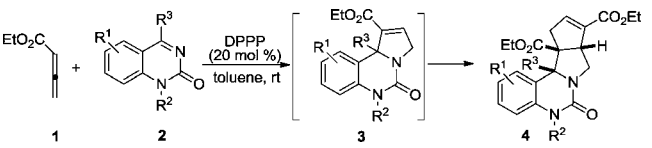
Scheme 1. Further Annulation of **3a** with Ethyl Allenoate under the Catalysis of DPPP



With the optimized reaction conditions in hand, we next investigated the substrate scope of this DPPP-catalyzed sequential annulation of ethyl 2,3-butadienoate with a variety of cyclic ketimines, and the results are summarized in Table 2. Four cyclic ketimines bearing electron-withdrawing groups on the aromatic ring participate in the reaction, affording the annulation products **4a**–**d** in excellent yields and diastereoselectivities within 2 h (entries 1–4). The substrates bearing two halogen, electron-neutral, or electron-donating groups on the aromatic ring participate in the slower transformation, delivering the sequential products **4e**–**j** in good yields after 12 h, together with a small amount of the cycloadducts **3e**–**j** (entries 5–10). The change of *N*-protecting groups at the cyclic ketimine substrates did not have a significant effect on the reaction activity, and the annulation products **4k**–**n** were obtained in 91–97% yields (entries 11–14). The cyclic ketimine without a protecting group on the nitrogen atom could also proceed under similar conditions in good yield although a prolonged reaction time was required (entry 15). In addition, when the trifluoromethyl group on the cyclic ketimines was replaced with a difluoromethyl group, the sequential adduct **4p** was also obtained in 91% yield (entry 16). However, when the trifluoromethyl group was replaced with a methyl or phenyl group, no annulation products were observed (entries 17 and 18). These results indicated that the strong electron-withdrawing di- and trifluoromethyl groups are critical for the annulations to occur.

In order to gain more insight into this one-pot sequential [3 + 2]/[3 + 2] annulation, an NMR study was carried out to detect potential intermediates. The ^{31}P NMR spectrum of a 2.5:0.2 mixture of ethyl 2,3-butadienoate **1** and DPPP in toluene-D_8 exhibits two new broad signals at 29.5 and 28.1 ppm that could correspond to mono- and biszwitterions. When 1 equiv of cyclic ketimine **2a** was added into the NMR tube, the broad signal (at −17.7 ppm) of DPPP became weaker, and other broad signals at 29.5 and 28.1 ppm were also observed (see the Supporting Information).

Table 2. Sequential [3 + 2]/[3 + 2] Annulation of Ethyl Allenoate **1** with Cyclic Ketimines **2**



			yield (%)[a]	
entry	**2** (R^1, R^2, R^3)	time (h)	**3**	**4**[b]
1	**2a** (6-Cl, PMB, CF_3)	2	**3a**: 3	**4a**: 96
2	**2b** (6-F, PMB, CF_3)	2	**3b**: 4	**4b**: 94
3	**2c** (6-Br, PMB, CF_3)	2	**3c**: 2	**4c**: 97
4	**2d** (6-CF_3, PMB, CF_3)	2	**3d**: 3	**4d**: 95
5	**2e** (5,6-F_2, PMB, CF_3)	12	**3e**: 26	**4e**: 68
6	**2f** (5-F-6-Cl, PMB, CF_3)	12	**3f**: 30	**4f**: 65
7	**2g** (H, PMB, CF_3)	12	**3g**: 12	**4g**: 80
8	**2h** (6-Me, PMB, CF_3)	12	**3h**: 30	**4h**: 64
9	**2i** (6-^{i}Pr, PMB, CF_3)	12	**3i**: 21	**4i**: 75
10	**2j** (6-MeO, PMB, CF_3)	12	**3j**: 19	**4j**: 68
11[c]	**2k** (6-Cl, TMB, CF_3)	2	**3k**: 2	**4k**: 97
12	**2l** (6-Cl, 1-naphthylmethyl, CF_3)	2	**3l**: 2	**4l**: 96
13	**2m** (6-Cl, 9-anthracenylmethyl, CF_3)	2	**3m**: 2	**4m**: 96
14	**2n** (6-Cl, 1-pyrenylmethyl, CF_3)	2	**3n**: 0	**4n**: 95
15	**2o** (6-Cl, H, CF_3)	12	**3o**: 10	**4o**: 82
16	**2p** (6-Cl, PMB, CHF_2)	2	**3p**: 7	**4p**: 91
17	**2q** (6-Cl, PMB, Me)	24	**3q**: 0	**4q**: 0
18	**2r** (6-Cl, PMB,Ph)	24	**3r**: 0	**4r**: 0

[a] Isolated yield. [b] >99:1 dr (determined by ^{19}F NMR analysis of crude products **4**). [c] TMB = 2,4,6-trimethylbenzyl.

On the basis of our experimental results and some related literature,[5] a possible mechanism for this one-pot sequential [3 + 2]/[3 + 2] annulation, which could involve two catalytic cycles, is outlined in Figure 2. In the first cycle, the nucleophilic bisphosphine DPPP initially attacks the *β*-carbon atom of ethyl 2,3-butadienoate (**1**) to yield monozwitterion **A** and biszwitterion **B**. The α-carbon atom of anionic allylic **B** may add to the C=N group of cyclic ketimines **2** to give the intermediate **C**, and then an intramolecular Michael addition reaction of **C** affords the cycloadduct **D**. Subsequently, the proton shift of **D** brings about the zwitterionic intermediates **E** and **F**, which dissociate to give the products **3** and **4**, and regenerates the bisphosphine DPPP and monozwitterion **A**. In the second cycle, an intermolecular Michael addition of anionic allylic **A** to the cycloadduct **3** leads to the addition intermediate **G**, which undergoes an intramolecular Michael addition to form **H**. Proton transfer of the most acidic proton yields the zwitterionic intermediates **I** and **J**. Finally, expulsion of the biphosphine DPPP from **J** produces the sequential product **4**.

(5) For mechanistic studies of phosphine-mediated annulations of allenoates, see: (a) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470. (b) Mercier, E.; Fonovic, B.; Henry, C.; Kwon, O.; Dudding, T. *Tetrahedron Lett.* **2007**, *48*, 3617. (c) Liang, Y.; Liu, S.; Yu, Z.-X. *Synlett* **2009**, 905.

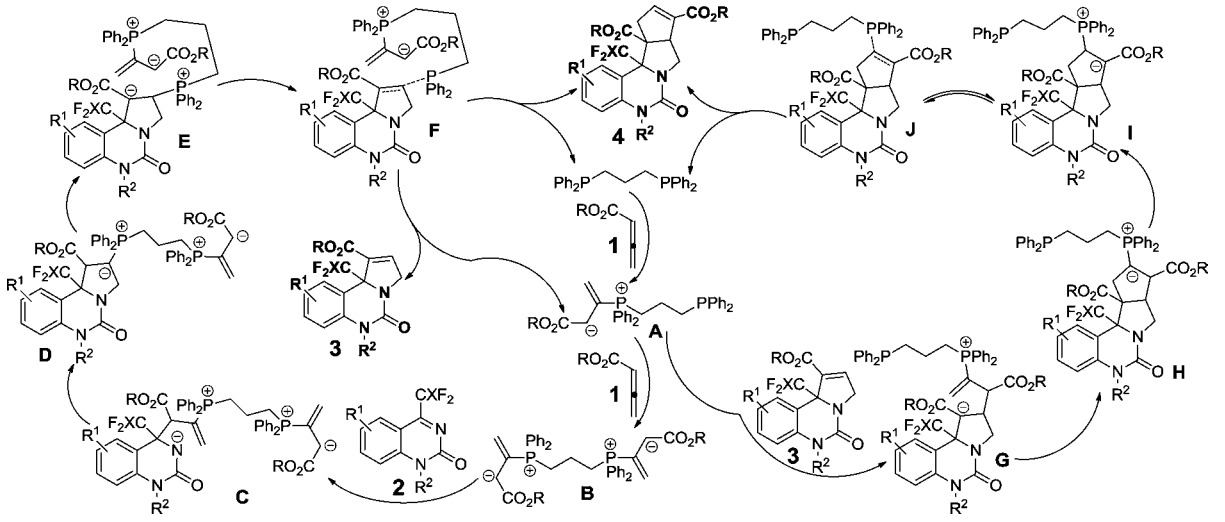
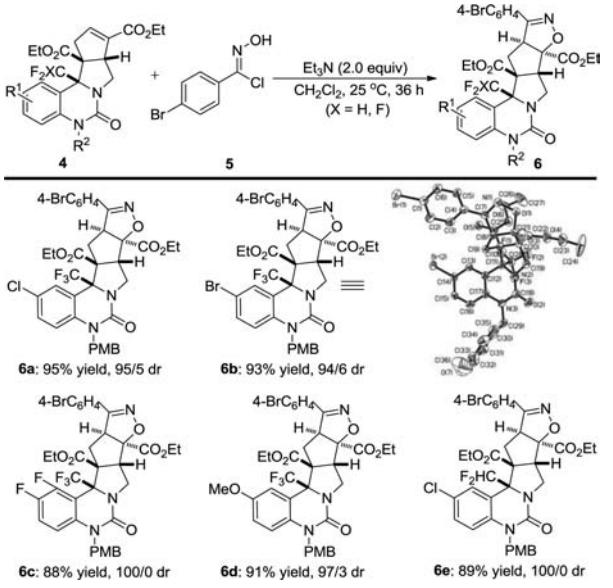


Figure 2. Proposed mechanism for the DPPP-catalyzed annulation of allenoates with cyclic ketimines to form the products **3** and **4**.

Scheme 2. Further Transformation of the Sequential Products **4** with Chlorinated Aldoxime **5** into the Polycycles **6**



In the presence of one or more molar equivalents of ethyl 2,3-butadienoate **1**, the sequential annulation products **4** cannot be further converted using the present protocol, even when the reaction temperature is increased to 110 °C. Interestingly, the [3 + 2] annulation of the sequential cycloadducts **4** with the chlorinated aldoxime **5** could be achieved to afford the polycyclic compounds **6** in 88−95% isolated yields with high diastereoselectivities (Scheme 2). Furthermore, the single stereoisomer of **6b** proved to be crystalline, thus allowing the determination of the relative configuration of five adjacent stereogenic centers by means of X-ray crystallographic analysis.

In summary, we have developed a novel and efficient bisphosphine-triggered sequential [3 + 2]/[3 + 2] annulation reaction of allenoates with cyclic ketimines. During this transformation, four new bonds (one C−N bond and three C−C bonds) were constructed and three contiguous stereogenic centers were created in one pot. The reaction is exceptionally regio- and diastereoselective. The present finding expands the reach of nucleophilic phosphine-based catalysis in new ways and could have implications for other annulation reactions of allenoates. Detailed mechanistic investigations and the development of enantioselective variants of this sequential annulation are currently ongoing in our laboratory.

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Supporting Information Available. Experimental details, spectral data of all the new compounds, and the CIF information for **3a** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.