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Divergent Amine-Catalyzed [4 + 2] Annulation of Morita–Baylis–Hillman Allylic Acetates with Electron-Deficient Alkenes

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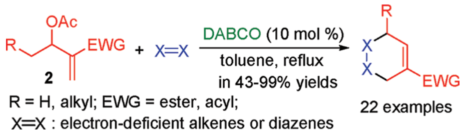
ABSTRACT



An amine-catalyzed [4 + 2] annulation of Morita–Baylis–Hillman allylic acetates 2 with electron-deficient alkenes or diazenes has been developed for efficient syntheses of highly functionalized cyclohexenes, tetrahydropyridazines, and important spirocycles. This reaction unveils a new reactivity pattern of the intensely studied allylic compounds 2 acting as a C_4 synthon in Lewis base catalyzed annulation reactions and also showcases divergent catalysis between tertiary amines and phosphines.

Lewis base catalysis[1] using phosphines and amines as catalysts is now established as a reliable platform for the construction of complex molecular architectures, as well as for diversity-oriented synthesis. In this context, phosphine-catalyzed annulation reactions of allenoates with activated alkenes, imines, or carbonyls provide a powerful synthetic toolbox for a series of carbo- and heterocycles.[2] For example, Lu's pioneering work[3] unveiled that, under the mediation of substoichiometric PPh$_3$, unsubstituted allenoates **1** (R = H) readily undergo [3 + 2] cycloaddition reactions with activated olefins or imines as a formal 1,3-dipole to generate cyclopentenes or pyrrolines (Scheme 1, top left). An innovative extension of this phosphine–allene chemistry reported by Kwon[4] disclosed that α-alkyl allenoates **1** (R = CH$_2$R′) undertake a distinct [4 + 2] annulation pattern as a formal 1,4-dipole with alkenes or imines to provide cyclohexenes or tetrahydropyridines (Scheme 1, top right). Owing to their high efficiency in the organic synthesis of ring structures, these two types of annulations have attracted intense research efforts.[5]

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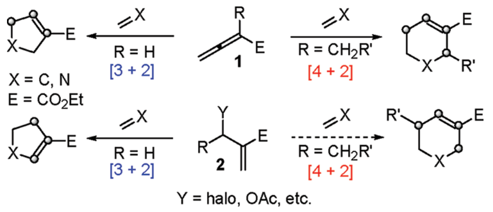
(6) In phosphine-catalyzed [3 + 2] annulations as a C$_3$ unit, see: (a) Du, Y.; Lu, X.; Zhang, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 1035. (b) Zheng, S.; Lu, X. *Org. Lett.* **2008**, *10*, 4481. (c) Feng, J.; Lu, X.; Kong, A.; Han, X. *Tetrahedron* **2007**, *63*, 6035. (d) Ye, L.-W.; Sun, X.-L.; Wang, Q.-G.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5951. (e) Wang, Q.-G.; Zhu, S.-F.; Ye, L.-W.; Zhou, C.-Y.; Sun, X.-L.; Tang, Y.; Zhou, Q.-L. *Adv. Synth. Catal.* **2010**, *352*, 1914. (f) Zhou, R.; Wang, J.; Song, H.; He, Z. *Org. Lett.* **2011**, *13*, 580. (g) Deng, H.-P.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 3348. (h) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672. (i) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837.

10.1021/ol2032569

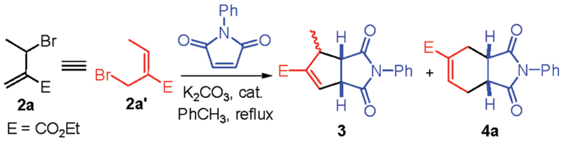
Scheme 1. Similar Annulation Patterns of Allenoates **1** and Allylic Compounds **2** under Lewis Base Catalysis



Recently, a class of generally formulated allylic compounds **2** (Scheme 1, bottom), which could be conveniently prepared from Morita–Baylis–Hillman adducts, have also proven to be appealing and versatile substrates that can be used as a C_3 or C_1 synthon in phosphine-catalyzed [3 + *n*] and [1 + 4] annulations.[6–8] Interestingly, in [3 + 2] annulation reactions with activated olefins or imines, allylic compounds **2** act as a formal 1,3-dipole which undertakes a similar reactivity to that of allenoates **1** to furnish isomeric cyclopentenes or pyrrolines (Scheme 1, bottom left).[6] Intrigued by Kwon's [4 + 2] work,[4] and by the similar reactivity between allenoates **1** and allylic compounds **2**, we envisaged that allylic compounds **2** could be employed as a C_4 unit in Lewis base catalyzed [4 + 2] annulation reactions with activated alkenes if an alkyl group (R = CH_2R') is introduced, thereby providing new entries into six-membered ring structures (Scheme 1, bottom right). Herein, we wish to report the first example of a Lewis base catalyzed [4 + 2] annulation reaction of allylic compounds **2** bearing an extended alkyl group with activated alkenes and also showcase an example of divergent catalysis between amines and phosphines.

Due to its ease of preparation and equivalency in reactivity, ethyl 2-bromomethyl-2-butenoate **2a′** was chosen as an equivalent of allylic bromide **2a** (R = Me, Y = Br).[9] Our initial investigation started with the model reaction of allylic bromide **2a′** (0.6 mmol) and *N*-phenyl maleimide (0.5 mmol) with K_2CO_3 (0.75 mmol) in refluxing toluene (Scheme 2). Under the catalysis of PPh_3 (0.05 mmol), the reaction, however, still proceeded in the well-established [3 + 2] annulation mode,[6a] producing **3** in 57% yield. Gratifyingly, by employing 1,4-diazabicyclo[2.2.2]octane (DABCO) instead of PPh_3 under otherwise identical conditions, the reaction exclusively afforded the expected [4 + 2] annulation product **4a** in 95% yield, with a small amount (5%) of byproduct **D1**.[10] Further surveys on catalysts revealed that other nitrogen nucleophiles including NEt_3, DMAP, DBU, and imidazole all exclusively delivered **4a**, but in inferior yields. N-containing hexamethyl phosphorus triamide (HMPT) and 1,3,5-triaza-7-phosphaadamantane (PTA)[11] also effected the formation of **4a** in moderate yields, whereas PBu_3 resulted in a complex mixture and trimethyl phosphite was ineffective. In the absence of a catalyst, only a trace amount of **4a** was detected. Further optimizations on conditions confirmed that toluene was still the best solvent and a higher temperature was necessary for a fast transformation (for details, see Supporting Information).

Scheme 2. Divergent Annulation Induced by PPh_3 and DABCO



	3	4a
cat. = PPh_3	57%[a]	trace
= DABCO	none	95%

[a] *trans/cis* 7:1

Under the optimized conditions, the scope of allylic compounds **2** was investigated with *N*-phenyl maleimide as a model substrate (Table 1). Allylic carbonate **2b** readily afforded **4a** in 69% yield in the absence of K_2CO_3, since the in situ generated *tert*-butoxide anion acted as a base in the process[6a] (Table 1, entry 1). In the same manner, allylic acetate **2c** delivered **4a** in almost quantitative yield within 24 h (entry 2). Allylic acetates bearing different electron-withdrawing groups like *tert*-butoxycarbonyl (**2d**) and acetyl (**2e**) also smoothly produced the corresponding [4 + 2] annulation products in good yields (entries 3, 4). Impressively, allylic acetates (**2f–i**) with variable alkyl groups were all effective, delivering products **4d–g** in good to excellent yields and exclusive diastereoselectivity (entries 5–8). Regarding its high efficiency, broad scope, and homogeneous reaction media, allylic acetate **2** (Y = OAc) could be assessed as the preferred C_4 component over its carbonate and bromide analogues.

Various electron-deficient alkenes as C_2 components were also examined in DABCO-catalyzed [4 + 2] annulations with representative allylic acetates **2c**, **2g**, and **2h** (Table 2). Activated terminal alkenes were found to be good candidates. For example, doubly activated alkene **5** and monoactivated methyl vinyl ketone **7** and acrylates **9** all delivered their cyclohexenes in good yields, albeit with

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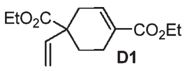
(7) In phosphine-catalyzed [3 + *n*] annulations (*n* = 3, 4, 6) as a C_3 unit, see: (a) Du, Y.; Feng, J.; Lu, X. *Org. Lett.* **2005**, *7*, 1987. (b) Zheng, S.; Lu, X. *Org. Lett.* **2009**, *11*, 3978. (c) Zheng, S.; Lu, X. *Tetrahedron Lett.* **2009**, *50*, 4532.

(8) In phosphine-catalyzed [4 + 1] annulations as a C_1 unit, see: (a) Chen, Z.; Zhang, J. *Chem.—Asian J.* **2010**, *5*, 1542. (b) Xie, P.; Huang, Y.; Chen, R. *Org. Lett.* **2010**, *12*, 3768. (c) Tian, J.; Zhou, R.; Sun, H.; Song, H.; He, Z. *J. Org. Chem.* **2011**, *76*, 2374.

(9) Bromination of Morita–Baylis–Hillman adduct ethyl 3-hydroxy-2-methylenebutanoate with PBr_3 exclusively produced allylic bormide **2a′** rather than **2a**. In treatment with nucleophilic phosphines or amines, both allylic bromides **2a** and **2a′** gave the same allylic phosphonium or ammonium salt and stood chemically equivalent. Also see ref 6a.

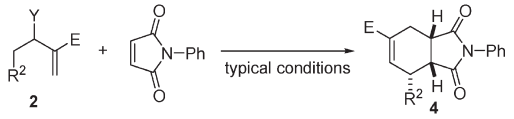
(10) Presumably, **D1** resulted from dimerization of 2-carboethoxy-1,3-diene which was derived from **2a′**. (a) Spino, C.; Crawford, J.; Gugelchuk, M.; Cui, Y. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1499. (b) Spino, C.; Pesant, M.; Dory, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 3262.



D1

(11) An air-stable and water-soluble cage-like phosphine, often used as a nucleophilic trialkylphosphine. Tang, X.; Zhang, B.; He, Z.; Gao, R.; He, Z. *Adv. Synth. Catal.* **2007**, *349*, 2007 and references cited therein.

Table 1. C_4 Scope for the [4 + 2] Annulation Reaction[a]



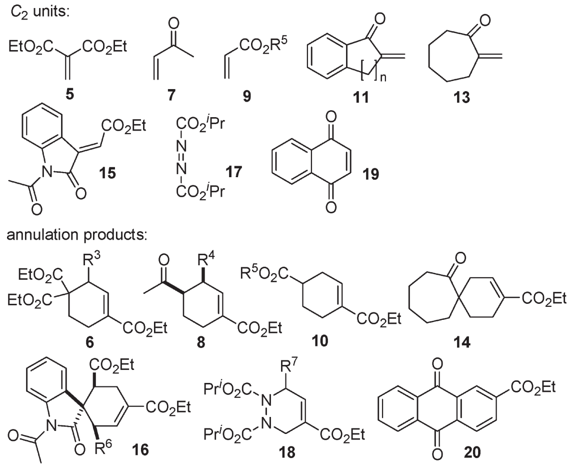
entry	C_4 units	time (h)	4	yield (%)[b]
1	**2b**: Y = OBoc; E = CO_2Et; R^2 = H	17	**4a**	69
2	**2c**: Y = OAc; E = CO_2Et; R^2 = H	24	**4a**	99
3	**2d**: Y = OAc; E = $CO_2{}^tBu$; R^2 = H	10	**4b**	86
4	**2e**: Y = OAc; E = COMe; R^2 = H	17	**4c**	53
5	**2f**: Y = OAc; E = CO_2Et; R^2 = Me	5.5	**4d**	77
6	**2g**: Y = OAc; E = CO_2Et; R^2 = Et	4	**4e**	78
7	**2h**: Y = OAc; E = CO_2Et; R^2 = ${}^iPr$	12	**4f**	96
8	**2i**: Y = OAc; E = CO_2Et; R^2 = ${}^nBu$	12	**4g**	93

[a] Typical conditions: a mixture of **2** (0.6 mmol), maleimide (0.5 mmol), and DABCO (0.05 mmol) was refluxed in toluene (3 mL) under a N_2 atmosphere. [b] Isolated yield based on maleimide.

modest regioselectivity in some cases (entries 1–6). Cyclic enones **11** and **13** also worked well in the cyclization with allylic acetate **2c**, efficiently constructing spirocycles in moderate yields with good regioselectivity (> 8:1) (entries 7–9). Spirooxindole scaffolds exist in a number of natural products and biologically active compounds.[12] Isatin-derived alkene **15** proved to be effective in the [4 + 2] annulation reactions with allylic acetates **2c** and **2h** to readily generate such complex structures. In a single step, spirohexeneoxindoles **16** with two or three stereogenic centers were formed stereoselectively and efficiently (entries 10, 11).

The C_2 scope could be further extended to heteroatom double bonds. Diisopropyl azodicarboxylate **17** was found to be an excellent partner in the annulations with all selected allylic acetates, providing tetrahydropyridazines **18** in good to excellent yields (entries 12–14). Finally, when 1,4-naphthaquinone **19** was tested, an interesting cascade [4 + 2] annulation–oxidation process occurred, leading to the functional anthraquinone **20**[13] in one step (entry 15). In the reaction, the naphthaquinone acts as both an annulation partner and oxidant for the subsequent aromatization.

Table 2. C_2 Scope for the [4 + 2] Annulation Reaction[a]



entry	C_4 units	C_2 units	time (h)	products	yield (%)[b]
1[c]	**2c**	**5**	6	**6a**: R^3 = H, major	64
2	**2h**	**5**	12	**6b**: R^3 = ${}^iPr$	76
3[c]	**2c**	**7**	15	**8a**: R^4 = H, major	88
4	**2h**	**7**	15	**8b**: R^4 = ${}^iPr$	51
5[c]	**2c**	**9a**: R^5 = Me	15	**10a**: R^5 = Me, major	83
6[c]	**2c**	**9b**: R^5 = ${}^tBu$	15	**10b**: R^5 = ${}^tBu$, major	75
7[c]	**2c**	**11a**: n = 1	16	**12a**: n = 1, major	66
8	**2c**	**11b**: n = 2	12	**12b**: n = 2	53
9	**2c**	**13**	24	**14**	49
10	**2c**	**15**	12	**16a**: R^6 = H	79
11	**2h**	**15**	7	**16b**: R^6 = ${}^iPr$	76
12	**2c**	**17**	12	**18a**: R^7 = H	83
13	**2g**	**17**	13	**18b**: R^7 = Et	92
14	**2h**	**17**	12	**18c**: R^7 = ${}^iPr$	94
15	**2c**	**19**	12	**20**	43

[a] For details, see Supporting Information. [b] Isolated yield. [c] Product was isolated as a regioisomeric mixture with a ratio of 2:1–8:1.

The above results indicate that this amine-catalyzed [4 + 2] annulation features a broad substrate scope with respect to both the C_4 and C_2 components. Also, most of the reactions were clean and afforded the cyclization products in good to excellent yields with complete diastereocontrol and good regioselectivity. These merits guarantee the annulation reaction significant potential in the construction of six-membered carbo-, hetero-, and spirocycles. It is worthy to mention that, under the catalysis of phosphines, a series of structurally similar allylic compounds and

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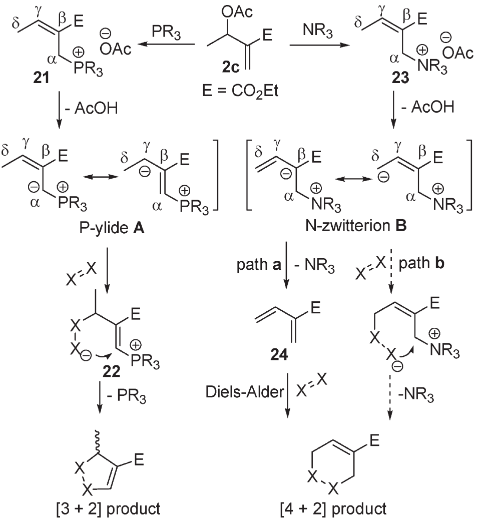
(12) (a) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. (b) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (c) Nandy, J. P.; Prakesch, M.; Khadem, S.; Reddy, P. T.; Sharma, U.; Arya, P. *Chem. Rev.* **2009**, *109*, 1999.

(13) Anthraquinone **20** could provide easy access to some efficient photoinitiators ("photonucleases") for oxidative DNA cleavage. See: (a) Armitage, B.; Yu, C.; Devadoss, C.; Schuster, G. B. *J. Am. Chem. Soc.* **1994**, *116*, 9847. (b) Schuster, G. B. *Acc. Chem. Res.* **2000**, *33*, 253.

(14) Other important observations on divergent catalysis from amines and phosphines were also reported. (a) Evans, C. A.; Miller, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 12394. (b) Shi, Y.-L.; Shi, M. *Org. Lett.* **2005**, *7*, 3057. (c) Saunders, L. B.; Miller, S. J. *ACS Catal.* **2011**, *1*, 1347.

electron-deficient alkenes were previously reported by Lu to undergo a distinct [3 + 2] annulation.[6a−c] Hence this study showcases a divergent catalytic reactivity between tertiary amines and phosphines.[14]

Scheme 3. Rationale for the Divergent Annulation Modes Induced by Phosphines and Amines



The different annulation modes of allylic acetates **2** induced by phosphines and amines are tentatively rationalized in Scheme 3 according to the stimulating work of Aggarwal[15] and Miller.[14a] As commonly proposed in literatures,[6−8] under the catalysis of phosphines, an allylic P-ylide intermediate **A**[16] is preferentially formed through an addition−elimination−deprotonation process, which serves as a surrogate of a 1,3-dipole to undergo the [3 + 2] cycloaddition with electron-deficient alkenes.[6] This annulation mode takes advantage of the decent ability of phosphorus to stabilize an ylide structure.[15] In sharp contrast, the amine-catalyzed annulation of allylic compounds **2** with alkenes could not adopt the same [3 + 2] mode since the N-atom lacks the suitable ability to stabilize its corresponding *N*-ylide intermediate.[15] Consequently, the zwitterionic intermediate **B** is alternatively formed, presumably by deprotonation at the δ-carbon of ammonium salt **23**. Theoretically, the putative intermediate **B** could be fairly stabilized by the right-positioned ester group. Such a resonance-stabilized species **B** is well poised to undergo 1,2-elimination of the amine catalyst to produce a highly reactive diene **24**,[10b] which subsequently undergoes a Diels−Alder reaction with alkenes to form the [4 + 2] products (Scheme 3, path a). From the outset, we are also aware that the [4 + 2] annulation might proceed via a stepwise mechanism, in which **B** acts as a formal 1,4-dipole to couple with the electrophilic alkene (path b). Formations of regioisomeric [4 + 2] products in our experiments (Table 2, entries 1, 3, 5−7), however, argue against such a stepwise scenario.[17] Conversely, the high diastereoselectivity observed in the [4 + 2] annulation is well in agreement with the *endo* stereochemistry of a Diels−Alder reaction.[18]

In conclusion, we have developed a novel amine-catalyzed [4 + 2] annulation reaction of Morita−Baylis−Hillman allylic acetates **2** with electron-deficient alkenes, which provides easy access to highly functionalized cyclohexenes, tetrahydropyridazines, and important spirocycles from simple, readily available starting materials. This reaction represents a new reactivity pattern of the intensely studied allylic compounds **2** acting as a C_4 unit in Lewis base catalyzed annulation reactions. This amine-induced annulation mode is certainly complementary to the previously well-established phosphine-induced annulation modes as C_3 and C_1 units.[6−8] Furthermore, this study showcases divergent catalysis between tertiary amines and phosphines, which could be attributed to their subtle difference in intrinsic properties such as the stabilizing ability of ylides.[14a,c] Future efforts will focus on exploring the application of the amine-induced reactivity mode in the development of new synthetic reactions.

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Supporting Information Available. Experimental details, characterization data, and NMR spectra for new compounds, as well as the X-ray crystallographic data (CIF files) for **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Riches, S. L.; Saha, C.; Filgueira, N. F.; Grange, E.; McGarrigle, E. M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 7626.

(16) P-ylide intermediates like **A** were observed by ^{31}P NMR and were successfully entrapped with aldehydes via a Wittig reaction in our prior work. Zhou, R.; Wang, C.; Song, H.; He, Z. *Org. Lett.* **2010**, *12*, 976.

(17) Our preliminary attempt to explore an asymmetric version of the [4 + 2] annulation by using chiral amine catalysts (quinine, cinchonine, *O*-methylated quinine) rendered no enantioselectivity. This result implies that the amine catalyst might be eliminated before the annulation and also supports the Diels−Alder pathway.

(18) (a) Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1928**, *460*, 98. (b) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741.

The authors declare no competing financial interest.