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Phosphine-Triggered Tandem Annulation between Morita–Baylis–Hillman Carbonates and Dinucleophiles: Facile Syntheses of Oxazepanes, Thiazepanes, and Diazepanes

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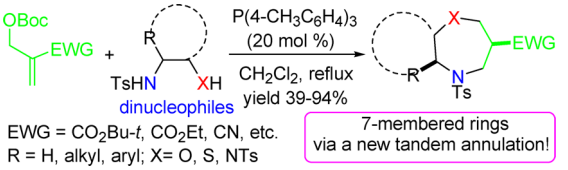
ABSTRACT



A new phosphine-triggered tandem [3 + 4] annulation reaction between Morita–Baylis–Hillman carbonates and 1,4-diheteroatom dinucleophiles has been developed, which provides a facile synthetic method for saturated seven-membered 1,4-heterocycles such as 1,4-oxazepanes, 1,4-thiazepanes, and 1,4-diazepanes. Mechanistic investigation implies that this reaction takes place through a phosphine-catalyzed allylic alkylation followed by a general base-catalyzed intramolecular Michael cyclization.

Saturated seven-membered 1,4-diheteroatom rings, such as 1,4-oxazepanes,[1] 1,4-thiazepanes,[2] and 1,4-diazepanes,[3] are frequently occurring substructures in natural and pharmaceutical compounds.[4] Syntheses of these biologically important frameworks are, however, somewhat challenging because the direct ring closures to medium-sized heterocycles are often slow and hampered by unfavorable enthalpies and entropies of the reactions.[5] Although several methods are available in the literature, syntheses of these 1,4-heterocycles are often troubled with either tedious manipulation or harsh conditions.[6] New and efficient synthetic approaches are therefore highly desirable.

Nucleophilic phosphine catalysis nowadays emerges as a rapidly growing area of research interest and has provided a reliable platform for efficient assembly of cyclic

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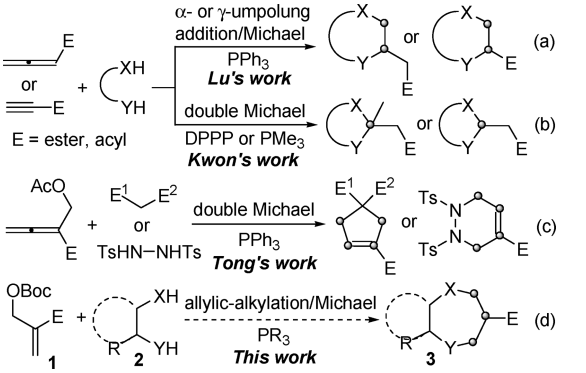
compounds.[7] In this context, phosphine-promoted tandem annulation reaction between dinucleophiles and unsaturated Michael acceptors represents an attractive protocol for synthesis of carbo- and heterocycles.[8] In 2002, Lu and co-workers[8a] first developed a PPh_3-catalyzed tandem umpolung addition/intramolecular Michael cyclization of electron-deficient allenes or alkynoates with dinucleophiles to readily generate functionalized dihydrofurans, piperazines, morpholines, and diazepanes in a $[2 + n]$ (n = 3, 4, 5) fashion (Scheme 1, eq a). Interestingly, with similar substrates, distinct tandem cyclization modes of $[1 + n]$ (n = 4, 5) via a double Michael sequence have been subsequently realized by Kwon[8b–d] through the catalysis of bisphosphines like 1,3-bis(diphenylphosphino)propane (DPPP) or electron-rich PMe_3, providing easy access to various five- and six-membered heterocycles (Scheme 1, eq b). Very recently, an elegant work from Tong's group[8e] unveiled that α-acetoxymethyl allenoates could undergo phosphine-catalyzed formal $[4 + n]$ (n = 1, 2) annulations with dinucleophiles to produce cyclopentenes and tetrahydropyridazines (Scheme 1, eq c). All of the above pioneering studies have unveiled the versatility of the electron-deficient allenes and alkynes in the phosphine-catalyzed tandem cyclizations with dinucleophiles.

In the past decade, another class of so-called modified allylic derivatives such as halides, acetates, and *tert*-butyl carbonates, which could be easily prepared from Morita–Baylis–Hillman (MBH) adducts, have proven to be appealing substrates in an array of phosphine-catalyzed annulations.[9] The pioneering and important reports by Lu and others have disclosed that such modified allylic derivatives could be readily used as C_3 and C_1 synthons in a number of phosphine-catalyzed $[3 + 2]$ and $[1 + 4]$ annulations with various *electrophiles* including electron-deficient alkenes and imines. Apart from their uses in the annulation reactions, the allylic derivatives were also reported by Krische et al. to undertake allylic alkylation reactions with different *nucleophiles* under the phosphine catalysis, producing functionalized products bearing an electrophilic terminal alkene subunit.[10]

Scheme 1. Phosphine-Catalyzed Tandem Annulations with Dinucleophiles



Considering the above diverse reactivity of the allylic derivatives and the fact that nucleophilic phosphines are capable of triggering Michael addition reactions between activated alkenes and pronucleophiles,[11] we envisaged that, under the mediation of phosphines, dinucleophiles and the modified allylic derivatives such as *tert*-butyl MBH carbonates could undertake a tandem allylic alkylation–intramolecular Michael cyclization process, thereby leading to new entries for carbo- and heterocycles.[12] Following this strategy, we investigated a phosphine-triggered tandem $[3 + 4]$ annulation reaction between MBH carbonates **1** and 1,4-diheteroatom dinucleophiles **2** to generate saturated seven-membered 1,4-heterocycles (Scheme 1, eq d). Herein we report the preliminary results.

Enantiopure β-amino alcohol **2a** derived from L-valine was chosen as a dinucleophile to evaluate our proposal. To our delight, a model reaction of MBH carbonate **1a** (0.6 mmol) and dinucleophile **2a** (0.5 mmol) under the catalysis of PPh_3 (20 mol %) in refluxing acetonitrile produced the expected 1,4-oxazepane **3a** in 46% isolated yield and 7:1 dr after 48 h (Table 1, entry 1). A brief survey on the model reaction conditions was further carried out to improve the annulation efficiency.

A series of nucleophilic phosphines were examined (Table 1, entries 1–10). Triarylphosphines bearing electron-donating groups on phenyl rings showed relatively better catalytic activity with $P(4\text{-}CH_3C_6H_4)_3$ offering the best yield of **3a** (entry 2). Relatively electron-poor triarylphosphines such as $P(4\text{-}FC_6H_4)_3$ and $P(4\text{-}CF_3C_6H_4)_3$ were, however, completely ineffective for the annulation reaction. Electron-richer alkylarylphosphines such as Ph_2PMe, $PhPMe_2$, and tributylphosphine were less effective, only giving **3a** in modest

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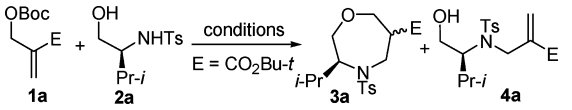
Table 1. Surveying on the Model Reaction Conditions[a]



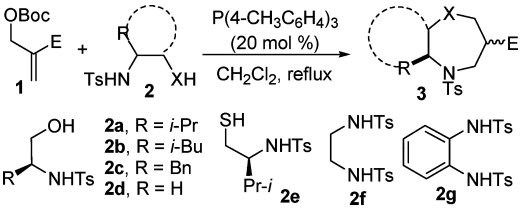
entry	phosphine	solvent	yield of **3a** (%)[b], dr[c]	yield of **4a** (%)[b]
1	PPh_3	CH_3CN	46, 7:1	/
2	$P(4\text{-}CH_3C_6H_4)_3$	CH_3CN	55, 8:1	/
3	$P(4\text{-}CH_3OC_6H_4)_3$	CH_3CN	44, 7:1	/
4	$P(4\text{-}FC_6H_4)_3$	CH_3CN	/	17
5	$P(4\text{-}CF_3C_6H_4)_3$	CH_3CN	/	/
6	Ph_2PMe	CH_3CN	32, 8:1	/
7	$PhPMe_2$	CH_3CN	24, 7:1	/
8	PBu_3	CH_3CN	39, 6:1	/
9	DPPE	CH_3CN	23, 6:1	/
10	(*S*)-BINAP	CH_3CN	24, 10:1	39
11	$P(4\text{-}CH_3C_6H_4)_3$	CH_2Cl_2	76, 11:1	/
12	$P(4\text{-}CH_3C_6H_4)_3$	DMF	43, 6:1	/
13	$P(4\text{-}CH_3C_6H_4)_3$	$CHCl_3$	40, 8:1	14
14	$P(4\text{-}CH_3C_6H_4)_3$	THF	53, 6:1	/
15	$P(4\text{-}CH_3C_6H_4)_3$	toluene	47, 9:1	/
16[d]	$P(4\text{-}CH_3C_6H_4)_3$	CH_2Cl_2	91, 11:1	/

[a] Typical conditions: under a N_2 atmosphere, a mixture of **1a** (0.6 mmol), **2a** (0.5 mmol), and phosphine (0.1 mmol) in solvent (2.0 mL) was stirred under reflux or at 60 °C for 48 h. [b] Isolated yield based on **2a**. [c] Determined by ^{1}H NMR assay and referring to the ratio of *cis*-**3a**/*trans*-**3a**. [d] Carbonate **1a** (1.0 mmol) was used.

yields (entries 6−8). In sharp contrast with Kwon's results that bisphosphines are superior catalysts for the tandem double Michael annulation reaction of alkynoates with dinucleophiles,[8b,c] bisphosphines such as DPPE [1,2-bis-(diphenyphosphino)ethane] and BINAP only delivered inferior yields of the cyclic product **3a** (entries 9, 10), although BINAP brought about the acyclic *N*-allylation product **4a** in a substantial yield (entry 10). By choosing $P(4\text{-}CH_3C_6H_4)_3$ as the catalyst, several common solvents were screened (entries 11−15). Dichloromethane emerged as a preferred solvent, affording **3a** in 76% yield (entry 11). Gratifyingly, the yield of **3a** could be further upgraded to 91% by adjusting the molar ratio of **1a**/**2a** to 2:1 (entry 16). Thus, the preferable conditions for the annulation reaction were established.

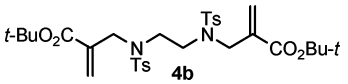
Under the optimized conditions, the substrate scope of the tandem annulation reaction was investigated. A couple of β-amino alcohols **2** prepared from natural amino acids were examined with MBH carbonate **1a**, and the corresponding 1,4-oxazepanes **3** were readily obtained in good yields with good diastereoselectivity (*cis*-**3**/*trans*-**3** = 5:1−11:1) (Table 2, entries 1−4). MBH carbonates **1** with varying alkyl groups were also tested in the reactions with representative β-amino alcohols **2**: the change of the alkyl group did not significantly interfere with the annulation reaction concerning the yield and stereoselectivity (entries 5−9). Cyano substituted allylic carbonate **1e** was also effective in the annulation with β-amino alcohol **2a**, albeit giving the cyclic product **3j** in modest yield and low diastereoselectivity (entry 10). Other 1,4-dinucleophiles

Table 2. Synthesis of 1,4-Heterocycles **3** from Carbonates **1** and Dinucleophiles **2**[a]



entry	E in **1**	**2**	time (h)	yield of **3** (%),[b] dr[c]
1	CO_2Bu-*t*, **1a**	**2a**	48	**3a**, 91, 11:1
2	CO_2Bu-*t*, **1a**	**2b**	48	**3b**, 87, 10:1
3	CO_2Bu-*t*, **1a**	**2c**	48	**3c**, 70, 5:1
4	CO_2Bu-*t*, **1a**	**2d**	48	**3d**, 74
5	CO_2Bu-*n*, **1b**	**2a**	24	**3e**, 72, 14:1
6	CO_2Bu-*n*, **1b**	**2d**	48	**3f**, 81
7	CO_2Et, **1c**	**2a**	36	**3g**, 86, 13:1
8	CO_2Et, **1c**	**2c**	48	**3h**, 85, 20:1
9	CO_2Me, **1d**	**2a**	24	**3i**, 80, 20:1
10[d]	CN, **1e**	**2a**	48	**3j**, 39, 1.5:1
11	CO_2Et, **1c**	**2e**	24	**3k**, 94, 7:1
12[e]	CO_2Bu-*t*, **1a**	**2f**	36	**3l**, 68
13	CO_2Et, **1c**	**2f**	36	**3m**, 90
14	CO_2Et, **1c**	**2g**	24	**3n**, 67

[a] For details, see Supporting Information. [b] Isolated yield. [c] Ratio of *cis*-**3**/*trans*-**3** and determined by ^{1}H NMR assay of the isolated **3**. [d] *cis*-**3j** and *trans*-**3j** were separable by column chromatography and obtained in 23% and 16% yields, respectively. [e] A double allylic alkylation byprodcut **4b** was isolated in 20% yield.



than β-amino alcohols were also found to be effective in this tandem annulation reaction. Under standard conditions, β-amino thiol **2e** and MBH carbonate **1c** readily afforded 1,4-thiazepane **3k** in 94% yield and 7:1 dr (entry 11). Furthermore, both aliphatic and aromatic 1,2-diamines **2f** and **2g** were good dinucleophiles in the annulation reaction, furnishing the corresponding 1,4-diazepanes **3l**−**m** and benzo[*b*][1,4]diazepine **3n** in good yields, respectively (entries 12−14). Both [1,4]diazepanes and benzo[1,4]diazepines are privileged skeletons in the biologically active molecules and drugs.[13]

The structures and stereochemistry of the annulation products **3** were identified by ^{1}H, ^{13}C NMR and HRMS-ESI measurements, as well as by HMQC, NOESY, and X-ray crystallographic analyses for representative compounds (for details, see Supporting Information).[14]

To glean mechanistic clues about this tandem annulation, the following experiments were deliberately conducted

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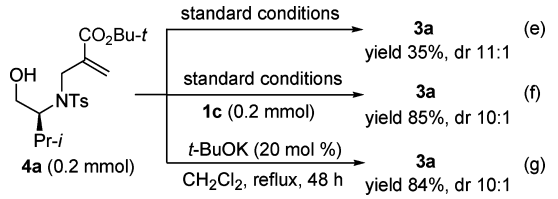
(14) A similar NMR method was applied to determine the stereochemistry of seven- and eight-membered heterocycles. See ref 5.

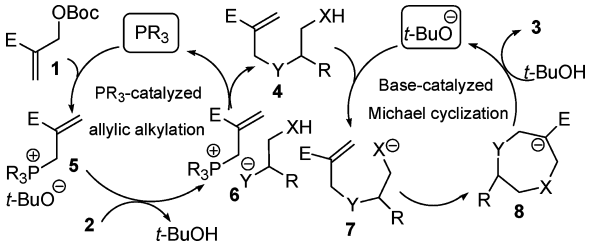
Scheme 2. Mechanistic Experiments



(Scheme 2). The allylic alkylation product **4a**, which was collected from the model reaction experiments (Table 1), was first subjected to the standard phosphine-triggered annulation reaction conditions, the expected cyclization product **3a** was uneventfully obtained, but in a fair yield (Scheme 2, eq e). Interestingly, when equimolar MBH carbonate **1c** was introduced into the above reaction under otherwise identical conditions, the yield of **3a** was significantly increased to 85% (Scheme 2, eq f). This result clearly confirms that addition of the carbonate **1c** facilitates the phosphine-triggered intramolecular Michael cyclization of **4a**. Furthermore, when acyclic **4a** was treated under the general base catalysis of *t*-BuOK, the Michael cyclization product **3a** was also smoothly obtained in 84% yield with comparable stereoselectivity (eq g). The above results strongly imply that the phosphine-mediated Michael cyclization of **4a** is most likely a general base-catalyzed process. The in situ generated *tert*-butoxide anion from nucleophilic attack of the phosphine at the allylic carbonate subunit of **4a** or carbonate **1c** acts as the base catalyst.[8d,9f,10a] Extra addition of carbonate **1c** guaranteed a sufficient supply of the base *tert*-butoxide anion for the Michael cyclization of **4a** so that the yield of **3a** was significantly improved (eq f). The yield increase of **3a** in the model reaction by increasing the loading of carbonate **1a** could be well interpreted by this assumption (Table 1, entry 14).

Based on above mechanistic insights and previous reports on the phosphine-triggered allylic alkylation[10a] and Michael cyclization,[8d] a proposed mechanism was depicted in Scheme 3 to account for the formation of heterocycles **3**. Initially, nucleophilic attack of the catalyst phosphine at allylic carbonate **1** in an S_N2' fashion results in a phosphonium *tert*-butoxide **5**, which in turn deprotonates dinucleophile **2** to bring about an ion pair of phosphonium-nucleophile anion **6**. Ion pair **6** then undergoes another S_N2' substitution to afford allylic alkylation

Scheme 3. Proposed Mechanism for the Phosphine-Triggered Tandem Annulation Reaction



intermediate **4** and regenerate the catalyst phosphine. Under the influence of the in situ generated *tert*-butoxide anion base, intermediate **4** finally undertakes a 7-*endo*-*trig* cyclization to accomplish the tandem assembly of cyclic product **3**.

In summary, a new phosphine-triggered tandem [3 + 4] annulation reaction between Morita–Baylis–Hillman carbonates **1** and 1,4-diheteroatom dinucleophiles **2** has been developed, which provides a facile synthetic method for saturated seven-membered 1,4-heterocycles such as 1,4-oxazepanes, 1,4-thiazepanes, and 1,4-diazepanes. Based on mechanistic investigations in this study and closely related reports[8d,10a] in the literature, this tandem annulation reaction is supposed to proceed through a phosphine-catalyzed allylic alkylation followed by a general base-promoted intramolecular Michael cyclization. With regard to other established phosphine-catalyzed tandem annulations of electron-deficient allenes or alkynes with dinucleophiles, this reaction particularly provides a complementary route to medium-sized heterocycles. Our future efforts will be directed toward further expanding the reaction scope and exploring its application in the synthesis of biologically important compounds.

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Supporting Information Available. Experimental details, characterization data and NMR spectra for new compounds **3** and **4**, and the X-ray crystallographic data (CIF files) for **3n** and **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.