Published in final edited form as:
J Am Chem Soc. 2007 October 24; 129(42): 12632–12633. doi:10.1021/ja0752181.

Phosphine-Catalyzed [4 + 2] Annulation: Synthesis of Cyclohexenes

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Abstract

Phosphine-catalyzed [4 + 2] annulations of α-alkylallenoates with activated olefins allow the efficient syntheses of cyclohexenes. Hexamethylphosphorous triamide (HMPT)-catalyzed [4 + 2] annulations of α-alkylallenoates with arylidenemalononitriles provided highly functionalized 5,5-dicyano-4,6-disubstituted cyclohex-1-enecarboxylates in excellent yields (77–98%) and moderate to high diastereoselectivities (1:2–12:1). Remarkably, the corresponding triarylphosphine-catalyzed [4 + 2] annulations of α-methylallenoate with arylidenemalononitriles manifested a polarity inversion of the 1,4-dipole synthon, providing 4,4-dicyano-5-substituted cyclohex-1-enecarboxylates in excellent yields (80–93%). The polarity inversion of α-alkylallenoates from one 1,4-dipole to another under phosphine catalysis presumably resulted from a change in the balance of the equilibrium between the phosphonium dienolate and the vinylogous phosphonium ylide intermediate.

The construction of suitably functionalized cyclohexene frameworks plays a central role in many natural product synthesis.[1] Although the Diels–Alder reaction is among the most powerful tools for generating such carbocycles,[2] it is often difficult to form systems that are highly congested or possess substituent arrays that are incompatible with the reaction.[3] A number of alternative methods for synthesizing cyclohexenes have arisen from catalytic approaches, such as the phosphine-catalyzed Rauhut–Currier reaction,[4] transition metal-catalyzed ring-closing metathesis (RCM),[5] and cycloisomerization reactions.[6] In contradistinction to the widespread use of these intramolecular processes, intermolecular counterparts for catalytic cyclohexene synthesis are less well developed.[7]

Nucleophilic phosphine catalysis has emerged recently as an efficient means of generating carbo- and heterocycles.[8] In particular, Lu's [3+2] cycloaddition[9] to form cyclopentenes from allenoates and alkenes under phosphine catalysis has been applied in the syntheses of several natural products.[10] Nevertheless, phosphine catalysis has not been utilized previously for the formation of cyclohexenes. Building upon our phosphine-catalyzed [4 + 2] annulation for the synthesis of tetrahydropyridines,[11] we reasoned that it might be possible to formulate an all-carbon variant of this strategy. Herein, we disclose the facile synthesis of cyclohexenes **3** and **4** via phosphine-catalyzed [4 + 2] annulations between allenoates **1** and activated olefins **2** (eq 1).

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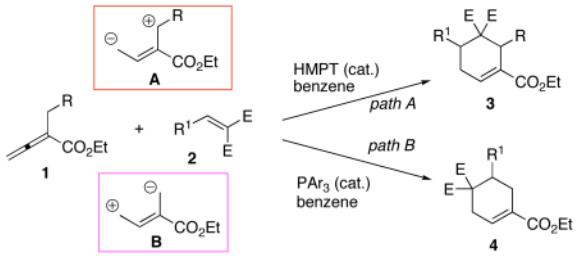

(1)

We initiated our investigation by seeking a viable phosphine catalyst for the [4 + 2] annulation of the allenoate **1a** and benzylidenemalononitrile **2a** to provide the cyclohexene **3a** (Table 1). The optimal conditions for tetrahydropyridine synthesis (20 mol% PBu_3, CH_2Cl_2, rt) were ineffective for the formation of the cyclohexene (entry 1).[12] Further examination revealed that hexamethylphosphorous triamide (HMPT) catalyzed the [4 + 2] reaction in benzene under reflux to provide **3a** in 98% yield (entry 2). Interestingly, use of the less-nucleophilic[13] PPh_3 induced preferable formation of the regioisomeric cyclohexene **4a** (entry 5). Among the triarylphosphines tested, we found that the more electron deficient the aryl groups, the greater the amount of **4a** obtained (entries 3–7). Using tris(*p*-chlorophenyl)phosphine, we obtained isomer **4a** exclusively (entry 7). Therefore, allenoate **1a** serves as dipole **A** under the influence of HMPT and as inverted dipole **B** under triarylphosphine catalysis (eq 1).

Success at identifying phosphine catalysts for the efficient syntheses of both isomers of the cyclohexenes prompted us to probe the generality of the reaction using other activated olefins (Table 2). In the presence of HMPT, the allenoate **1a** reacted with both electron-deficient and -rich arylidenes to provide the cyclohexenes **3a–3c** in high yields (Table 2, entries 1–3). With tris(*p*-fluorophenyl)phosphine, the regioisomeric cyclohexenes **4a–c** were obtained with high efficiency (entries 4–6). Notably, these conditions also worked well for activated heteroarylidenes, furnishing the cyclohexenes **4d–f** (entries 7–9).

The intriguing reversal of regioselectivity can be rationalized as indicated in Scheme 1. Under HMPT catalysis, the β-phosphonium dienolate intermediate **5**, formed through conjugate addition of the phosphine to the allenoate **1a**, adds to **2a** at the γ carbon atom to give adduct **6**. Zwitterion **6** converts into the allylic phosphonium intermediate **7** through proton transfer.[11a] Conjugate addition of the malononitrile anion in **7** and subsequent β-elimination of HMPT provide the cyclohexene **3a**. On the other hand, the phosphonium dienolate-to-phosphorous ylide equilibrium (**5** ⇆ **8**) favors the ylide when a more-electron-withdrawing triarylphosphine is used.[14] The vinylogous ylide **8** adds conjugatively to olefin **2a** to give the adduct **9**. Consecutive proton transfers provide the deconjugated enoate **10**, which allows 6-*endo* cyclization to generate the cyclic ylide **11**. Finally, 1,2-proton transfer and subsequent β-expulsion of the phosphine catalyst furnish the cyclohexene **4a**.

The reaction tolerated a wide range of allenylic β′ substituents on the allenoate **1**, including aryl, ester, alkyl, and vinyl moieties, to provide the cyclohexenes **3** in excellent isolated yields (Table 3). For these β′-substituted allenoates **1**, only **3** was formed, independent of the phosphine employed, presumably because of steric hindrance and the resulting diminished reactivity at the allenylic carbon atom. Good diastereoselectivities resulted when using α-benzylallenoates (entries 1–3), except when the benzyl group incorporated an ortho substituent (entry 4).[15] The reactions of α-alkylallenoates occurred with improved diastereoselectivities upon increasing the size of the allenylic substituent (entries 5–7), although α-isobutylallenoate **1k** manifested a unique preference for the trans isomer (entry 8). The diastereoselectivity was highest for the reactions of α-allylallenoates (entries 9 and 10).

Scheme 2 demonstrates the potential utility of this [4 + 2] annulation for the synthesis of biologically active natural products: rapid entry into the tetracyclic framework **12** of nodulisporic acids[16] via the Houben–Hoesch reaction of **4f**.

In summary, we have developed novel phosphine-catalyzed [4 + 2] annulation processes that enable regio-differentiating syntheses of cyclohexenes. In these all-carbon [4 + 2] annulations, simply switching the catalyst from HMPT to a triarylphosphine changes the reactivity of the α-alkylallenoate from that of a 1,4-dipole **A** to an inverted dipole **B**. These highly efficient and regioselective processes serve as rapid conduits toward the scaffolds of many natural products. Our future efforts will focus on developing asymmetric variants of these reactions and applying them to the construction of other biologically significant natural products.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This study was funded by the NIH (R01GM071779). We thank Dr. Saeed Khan for performing the crystallographic analyses. O.K. thanks Dr. Chulbom Lee for helpful discussions.

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12. Phosphines that resulted only in the oligomerization of the allenoate **1a** without incorporation of benzylidenemalononitrile **2a** (DCM, rt; or benzene, reflux) included Bu_3P, Bn_3P, Me_3P, Me_2PhP, $MePh_2P$, $P(OEt)_3$, $(4\text{-}CF_3C_6H_4)_3P$, $(3,5\text{-}FC_6H_3)_3P$, and BINAP. DABCO, Et_3N, and DBU were not effective catalysts for the desired transformation.
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14. The exclusive formation of isomer **3** when using HMPT hints at the diminished acidity of the β′ proton in **5**, presumably because of back bonding of the nitrogen atom's lone pair of electrons to the phosphonium center ($P{=}N^+Me_2$); see: Mark V. J Am Chem Soc 1963;85:1884.
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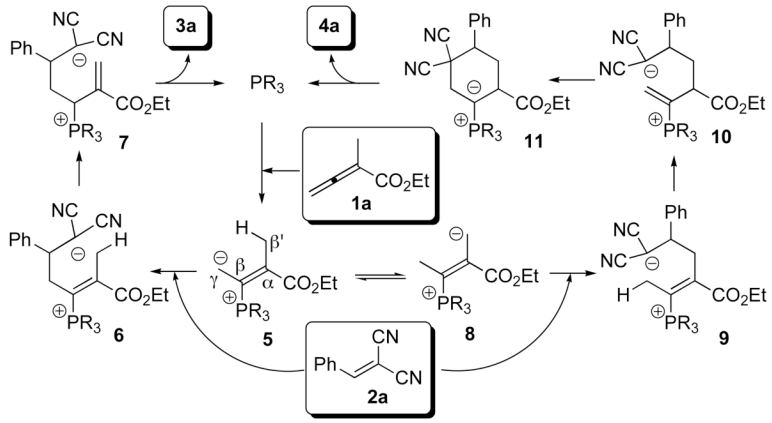
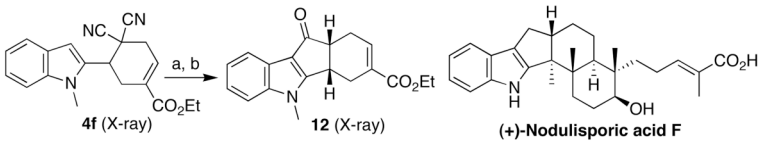


Scheme 1.
Mechanistic proposal for the formation of cyclohexenes **3a** and **4a** with polarity inversion of the 1,4-dipole synthon **1a**



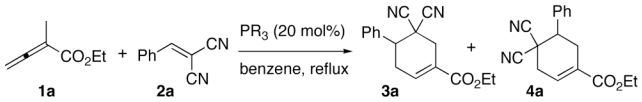
Scheme 2.

One application of the allene–alkene [4 + 2] annulation[a]

[a] (a) Conc. HCl/EtOAc (10:1), cat. H_2SO_4. (b) EtOH, cat. H_2SO_4, 85% isolated yield over two steps.

Table 1

Survey of phosphine catalysts for [4 + 2] annulation of allenoate **1a** and alkene **2a**[a]



entry	phosphine	3a:4a[b]	% yield[c]
1[d]	PBu_3	NA	NR
2	$P(NMe_2)_3$	100:0	98
3	$P(4\text{-}MeOC_6H_4)_3$	33:67	96
4	$P(4\text{-}Me_2NC_6H_4)Ph_2$	32:68	95
5	PPh_3	26:74	93
6	$P(4\text{-}FC_6H_4)_3$	8:92	98
7[e]	$P(4\text{-}ClC_6H_4)_3$	0:100	93

[a] Reaction conditions: **1a** (1.2–1.4 mmol), **2a** (1 mmol), and the phosphine (20 mol%) were heated under reflux in benzene (10 mL) for 14 h.

[b] Determined through NMR spectroscopic analyses.

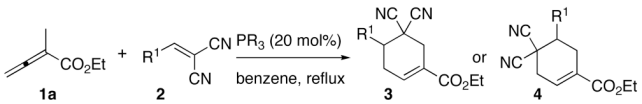
[c] Isolated yields.

[d] Reference 12.

[e] This transformation required a reaction time of 120 h.

Table 2

Survey of alkenes for [4 + 2] annulation with allenoate **1a**[a]



entry	R^1	phosphine	product	% yield[b]
1	Ph (**2a**)	$P(NMe_2)_3$	**3a**	98
2	4-$MeOC_6H_4$ (**2b**)	$P(NMe_2)_3$	**3b**	94
3	4-BrC_6H_4 (**2c**)	$P(NMe_2)_3$	**3c**	86
4	Ph (**2a**)	$P(4\text{-}FC_6H_4)_3$	**4a**	93
5	4-$MeOC_6H_4$ (**2b**)	$P(4\text{-}FC_6H_4)_3$	**4b**	90
6	4-BrC_6H_4 (**2c**)	$P(4\text{-}FC_6H_4)_3$	**4c**	85
7	2-furyl (**2d**)	$P(4\text{-}FC_6H_4)_3$	**4d**	88
8	3-pyridyl (**2e**)	$P(4\text{-}FC_6H_4)_3$	**4e**	80
9	*N*-Me-2-indolyl (**2f**)	$P(4\text{-}FC_6H_4)_3$	**4f**[c]	91

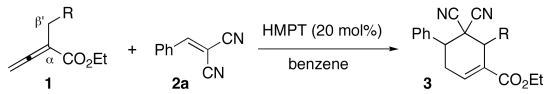
[a] Reaction conditions: **1a** (1.2 mmol), **2** (1 mmol), and the phosphine (20 mol%) were heated under reflux in benzene (10 mL) for 14 h.

[b] Isolated yields.

[c] Confirmed through single-crystal X-ray analysis.

Table 3

Survey of allenoates **1** for [4 + 2] annulations with the alkene **2a**[a]



entry	R	product	T (°C)	cis:trans[b]	% yield[c]
1	Ph (**1d**)	**3d**[d]	45	82:18	93
2	*p*-BrC_6H_4 (**1e**)	**3e**	45	84:16	96
3	*m*-$MeOC_6H_4$ (**1f**)	**3f**	45	78:22	92
4	*o*-MeC_6H_4 (**1g**)	**3g**	45	64:36	90
5	CO_2Et (**1h**)	**3h**	rt	66:33	96
6	Me (**1i**)	**3i**	88	80:20	95
7	Et (**1j**)	**3j**	88	92:8	98
8	*i*-Pr (**1k**)	**3k**	88	34:66	77
9	$CH=CH_2$ (**1l**)	**3l**	45	91:9	94
10	CH=CHPh (**1m**)	**3m**	45	91:9	93

[a] Reaction conditions: **1** (1.2–1.4 mmol), **2a** (1 mmol), and HMPT (20 mol%) were stirred in benzene (10 mL) for 14 h at the designated temperature.

[b] Determined through NMR spectroscopic analysis and comparison with the spectra of *cis*-**3d**, for which a single-crystal X-ray structure was obtained.

[c] Isolated yield.

[d] Confirmed through single-crystal X-ray crystallographic analysis.