ORGANIC LETTERS

2004
Vol. 6, No. 11
1857−1860

Phosphine-Mediated [4 + 2] Annulation of Bis(enones): A Lewis Base Catalyzed "Mock Diels–Alder" Reaction

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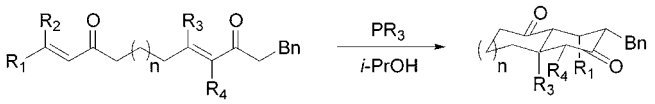
Received April 2, 2004

ABSTRACT



acyclic & achiral (8 examples)

bicyclic & up to 5 stereogenic centers

Lewis-base-catalyzed cycloisomerization of bis(enones) to decalins has been demonstrated as an alternative to the traditional Lewis acid catalyzed Diels–Alder cycloaddition. In this process, a trialkylphosphine mediates both bond formation steps in two distinct catalytic cycles. The single-pot operation generates two carbon–carbon bonds and up to five contiguous stereocenters in one step, starting from achiral, aliphatic substrates; eight examples are provided.

Efficient processes that lead to complex polycyclic frameworks from simpler acyclic substrates are playing an increasingly important role in synthesis. With the concerted formation of two carbon−carbon bonds and four contiguous stereogenic centers, the Diels−Alder cycloaddition stands as one of the most efficient tools in synthetic organic chemistry.[1] Although the thermal version may require elevated temperatures, Lewis acid catalysis lowers the activation barrier and provides the opportunity to develop enantioselective methods,[2] as evidenced by numerous recent examples.[3]

In contrast to formal Diels−Alder cycloadditions, nonconcerted processes such as the transition-metal-catalyzed [4 + 2] cycloisomerization,[4] anionic polycyclization,[5] and MIMIRC's (Michael−Michael ring closure)[6] can give rise to different stereochemical outcomes and offer alternative opportunities for stereoinduction with achiral substrates. With the current advent of phosphine-mediated activation of enones,[7] we reasoned that another pathway to [4 + 2]-type

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(2) For reviews on enantioselective Diels−Alder cycloadditions, see: (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650. (b) Evans, D. A.; Rovis, T.; Johnson, J. S. *Pure Appl. Chem.* **1999**, *71*, 1407.

(3) For recent selected examples, see: (a) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3059. (b) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992. (c) Huang, Y.; Iwama, T.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 5950. (d) Heckel, A.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 913. (e) Roush, W. R.; Limberakis, C.; Kunz, R. O.; Barda, D. A. *Org. Lett.* **2002**, *4*, 1543. (f) Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (g) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

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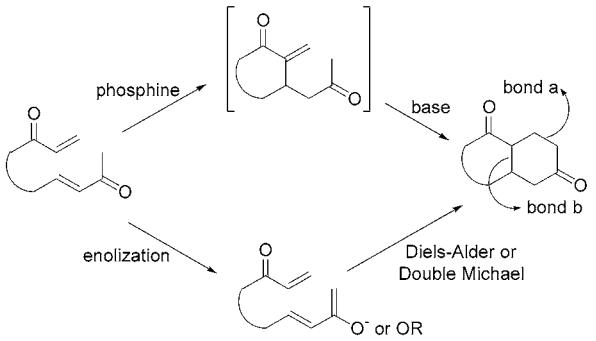
(6) (a) Posner, G. H.; Webb, K. S.; Asirvatham, E.; Jew, S.-S.; Degl'Innocenti, A. *J. Am. Chem. Soc.* **1988**, *110*, 4754. (b) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831.

(7) (a) Wang, J.-C.; Ng, S.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 3682. (b) Zhu, X.-F.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716. (c) Du, Y.; Lu, X.; Zhang, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 1035. (d) Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, *67*, 8901. (e) Lu, C.; Lu, X. *Org. Lett.* **2002**, *4*, 4677.

10.1021/ol049392v CCC: $27.50
Published on Web 05/05/2004

cycloadducts lies in a Rauhut−Currier/Michael domino reaction. The Rauhut−Currier reaction can be viewed as a vinylogous Morita−Baylis−Hillman reaction[8] and involves the nucleophillic activation of a Michael acceptor, followed by conjugate addition to a second acceptor.[9] Conceptually, a proper disposition of the enones would create an opportunity for a subsequent Michael addition to occur, leading to a product reminiscent of a Diels−Alder cycloadduct (Scheme 1).

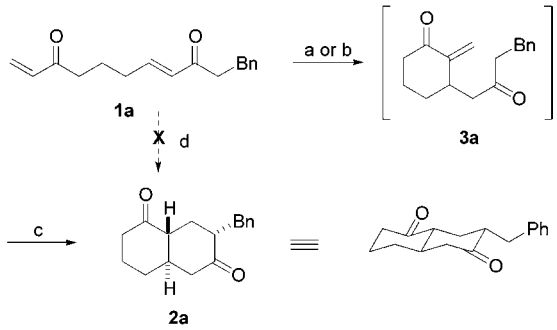
Scheme 1



An attractive feature of this strategy is the reversal of bond-forming events, such that bond **b** is formed prior to bond **a**.[10] This could be a more facile cyclization than the alternative double-Michael or Diels−Alder reactions due to stereoelectronic considerations: either bond **a** formation precedes bond **b** as a discrete bond-forming step in the double-Michael cyclization or bond **a** is shorter than bond **b** at the transition state of a concerted, asynchronous cyclization in the Diels−Alder reaction. This strategy also allows for direct cyclization of bis(enones) without recourse to enol ether formation. By way of a novel mechanism, a Lewis base could catalyze the process and complement the traditional Lewis acid-catalyzed version of the Diels−Alder cycloaddition. Through this process, two carbocyclic rings and up to five stereogenic centers can be generated in a single operation. We report herein the first example of a phosphine-mediated intramolecular cycloisomerization of bis(enones) leading to a "mock Diels−Alder" product.

Initial studies were performed with bis-enone **1a** to define conditions for the cycloisomerization to decalin **2a** (Scheme 2). Screening of the common amine nucleophiles used in Baylis−Hillman reactions (e.g., DABCO, DBU) showed no conversion. Switching to phosphines, trimethylphosphine

Scheme 2[a]



[a] Key: (a) Cy_3P, benzene, rt, 77%; (b) (*R*,*R*)-Et-BPE, benzene, rt, 79%, er 60:40; (c) CsF, MeCN, reflux, 50%, er 60:40; (d) CsF, MeCN, reflux, 0%.

proved to be too reactive and led to extensive decomposition of the substrate. Tricyclohexylphosphine provided optimal reactivity, providing the enone intermediate **3a** within 1 h at room temperature (entry 1).

As the basicity of the phosphine was insufficient to promote the third Michael addition, we next sought a phosphine-compatible base to effect the second cyclization. Evaluation of several amines showed that DBU and DBN were able to catalyze the final cycloisomerization, albeit sluggishly. Fortunately, cesium carbonate, and to a better extent, cesium fluoride in acetonitrile provided cleaner reaction profiles; this provided the decalin ring system as a 12:1:1 mixture of diatereoisomers in 64% yield. (Table 1, entry 4).[11] The major component, *trans*-decalin **2a**, was isolated and its structure was unambiguously established by single-crystal X-ray analysis. The observed mixture of diastereomers reflects the thermodynamic stability of the individual isomers, as evidenced by the following experiment. Resubjecting the major isomer to the reaction conditions led to epimerization and reformation of the same diastereomeric ratio initially observed.

These reaction conditions raised the possibility of a retro-Michael addition of **3a**[5a] and subsequent Diels−Alder cyclization (or double Michael addition) of an acyclic substrate to provide **2a**. To ascertain that such a mechanism is not operative, we prepared enantiomerically enriched intermediate **3a** using (*R*,*R*)-Me-BPE[12] and found that the initial enantiomeric ratio, albeit modest, remained identical in the *trans*-decalin **2a** after the fluoride-mediated cyclization (entries 2 and 3). This result is consistent with direct conversion of **3a** to **2a**, without the intermediacy of an acyclic (and necessarily achiral) structure. Another control experiment was designed to determine if fluoride simply depro-

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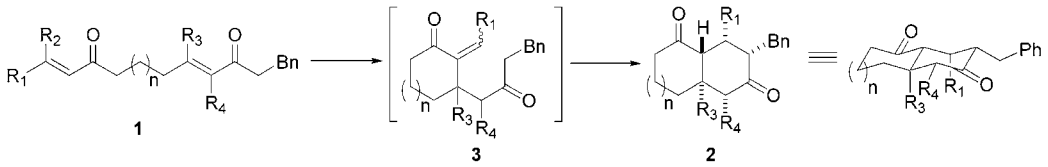
(10) Based on the kinetic preference for six-membered (bond b) vs 10-membered (bond a) ring closure.

(11) **General Procedure.** To a magnetically stirred solution of bis-enone (1 mmol) in N_2-sparged acetonitrile (200 mL) was added tricyclohexylphosphine (1 mmol) and cesium fluoride (4 mmol). The resulting suspension was heated to reflux, and upon reaction completion, the reaction mixture was cooled to room temperature and filtered over Celite. The filtrate was concentrated, and the residual material was purified by silica gel chromatography to yield the bicyclic compound.

(12) (a) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (b) Burk, M. J.; Feaster, J. E.; Harlow, J. L. *Tetrahedron: Asymmetry*. **1991**, *2*, 569.

Table 1. Organocatalytic [4 + 2] Cycloisomerization of Bis(enones)[d]



entry	substrate	R_1	R_2	R_3	R_4	n	catalyst	solvent	time (h)	major product[b]	yield[c] (%)	isomeric ratio[a]
1	**1a**	H	H	H	H	1	Cy_3P	benzene	1	**3a**	77	
2	**1a**	H	H	H	H	1	(*R*,*R*)-Me-BPE	benzene	2	**3a**	79	er 60:40[f]
3	**3a**[g]	H	H	H	H	1	CsF	MeCN	1.5	**2a**	50	er 60:40[f]
4	**1a**	H	H	H	H	1	Cy_3P/CsF	MeCN	10	**2a**	64	12:1:1
5	**1a**	H	H	H	H	1	Cy_3P/H_2O	MeCN	24	**2a**	50	12:1:1
6	**1a**	H	H	H	H	1	*n*-Bu_3P	*i*-PrOH	2	**2a**	46[e]	12:1:1
7	**1b**	H	H	H	H	0	Cy_3P	MeCN			0	
8	**1c**	H	H	H	H	2	Cy_3P/CsF	MeCN	30	**2c**	58	9:1:1
9	**1d**	Me	H	H	H	1	Me_3P/CsF	MeCN	11	**2d**	71	8:3:2:1
10	**1e**	H	Me	H	H	1	Me_3P/CsF	MeCN	8	**2d**	74	8:3:2:1
11	**1f**	H	H	H	Me	1	Cy_3P/CsF	MeCN	15	**2f**	76	12:2:2:1
12	**1g**	H	H	Me	H	1	Cy_3P/Cs_2CO_3	MeCN	2.5	**2g**	33	6:3:1
13	**1h**	Me	H	Me	Me	1	Me_3P/Cs_2CO_3	MeCN	16	**2h**	75	4:3:2:1

[a] Determined by ^{1}H NMR. [b] Relative stereochemistry determined by single-crystal X-ray analysis. [c] Isolated yield after purification. [d] Reaction conditions: see ref 11. [e] Reaction performed using 20 mol % of catalyst at 20 °C. [f] Determined by chiral HPLC analysis. [g] er 60:40.

tonates the enone to provide an electron-rich dienolate which then undergoes a Diels−Alder cycloaddition. To that end, bis(enone) **1a** was heated in the presence of CsF in acetonitrile in absence of phosphine, which led to decomposition with no trace of decalin products.

We next examined the effect of ring size. As evidenced by decomposition of **1b** under the reaction conditions, the lower cyclopentane homologue is conformationally restricted from undergoing the initial cyclization. On the other hand, the seven-membered series did provide the bicyclo[5.4.0]-undecane ring system as a 9:1:1 mixture of diatereoisomers in 58% yield. The major component **2c** was isolated and its structure was unambiguously established by single-crystal X-ray analysis.

To further explore the stereochemical outcome of this reaction, we examined substrates with alkyl substituents appropriately positioned on the prochiral sites of the two olefins. As expected, a methyl group at the β-position on the terminal enone (**1d** and **1e**) slowed the initial Michael addition of phosphine, such that PCy_3 was no longer an effective promoter. However, use of the less hindered PMe_3 in conjunction with CsF led to an 8:3:2:1 mixture of stereoisomers from both **1d** and **1e**, from which the major isomer was isolated and identified as the trans-anti-cis isomer **2d**. Olefin geometry of the terminal enone is of no consequence as, in the absence of CsF, both (*E*)-**1d** and (*Z*)-**1e** enones led predominantly (>15:1) to the same intermediate *E*-enone **3d** in good yield (83−87%). Interestingly, for the corresponding Diels−Alder to directly provide the same relative stereochemistry would require an exo approach of a cis dienophile with the trans-cis diene geometry.[13]

We also examined the cycloisomerization of bis(enone) **1f** and found that the general procedure effected the desired cycloaddition to decalin **2f** in 76% yield (entry 11). The initial cycloisomerization of **1g** proceeded readily to furnish a nonconverting mixture of cyclohexenone conformers **3g**, but the final cycloisomerization to the decalin **2g** was sluggish with cesium fluoride. The use of cesium carbonate, however, increased the rate of conversion and provided the desired decalin **2g** bearing a quaternary center at the ring junction in 33% yield (entry 12). The last example (entry 13), albeit displaying modest stereoselectivity, merits mention as five contiguous stereocenters are formed in one operation.

In a subsequent experiment where glassware had not been thoroughly dried, we serendipitously found that the second cyclization would take place in the absence of exogenous base. Reproducible results were obtained when a drop of water was added to the reaction mixture. The wet acetonitrile solvent system was then replaced with a protic solvent and, when performed in 2-propanol with a catalytic amount of phosphine, the overall cycloisomerization to the decalin occurred at room temperature, again without added base. Hence, exogenous bases such as fluoride and carbonate are not required when the reaction is performed in a protic solvent. These results can be rationalized based on the recent work of Bergman and Toste.[14] Conjugate addition of the phosphine generates a phosponium enolate that is protonated by water (or alcohol), thereby releasing a hydroxide (or

(13) With substrates 1d and 1e, we have removed the strong bias for initial phosphine addition at the terminal enone. If phosphine addition were to occur at the internal enone, an enolate would be generated which could then form either a cyclooctane (Rahut−Currier mode), or cyclohexane (Baylis−Hillman mode) product. Neither product was observed, but the moderate yields (71−74%) preclude ruling out these competing pathways completely.

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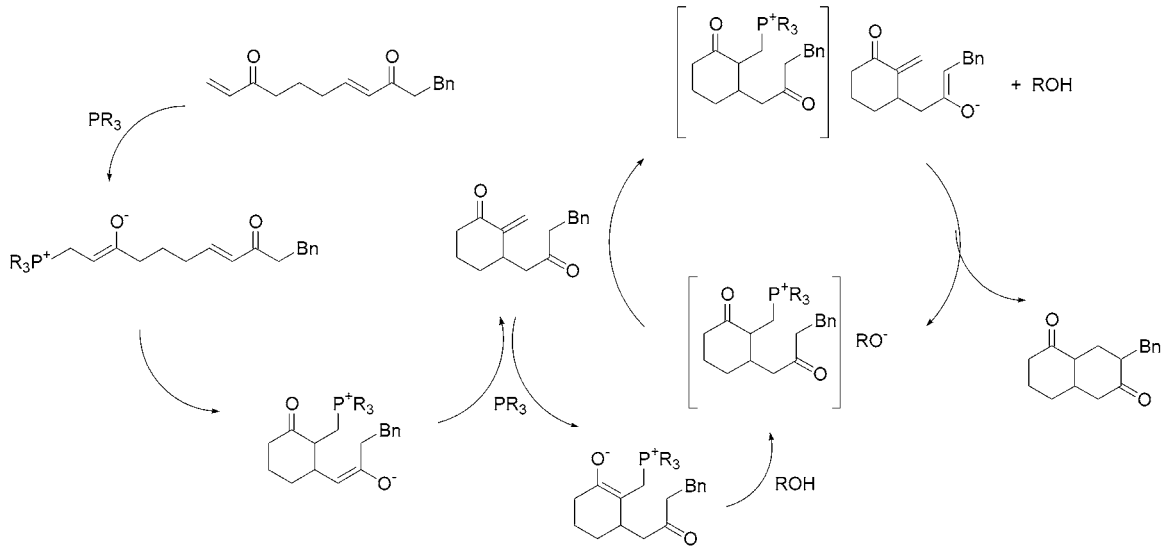
Scheme 3. Proposed Catalytic Cycle in Protic Solvents



alkoxide) ion pair that serves as the base for the second cycloisomerization (Scheme 3). Under these circumstances, the concentration of hydroxide (or alkoxide) ion pair decreases as the enone intermediate is consumed, which is consistent with the observation that the reaction stalls over time.

In this preliminary communication, we have disclosed a new [4 + 2] annulation of bis(enones) mediated by Lewis bases, which can generate up to five contiguous stereocenters and two carbocyclic rings from an acyclic and achiral precursor. Without prior recourse to enol ether formation, [4 + 2] cycloadducts can now be accessed through a novel mechanism. Further development of this methodology, including in depth analysis of the factors governing the stereoselectivity and identification of more effective chiral phosphine catalysts, is currently underway and will be reported in due course.

Acknowledgment. We are greatly indebted to Ernest Pollard for developing the chiral HPLC methods and Dr. Jon Bordner for X-ray crystallographic analyses. Andrew Jensen is also acknowledged for assigning several structures through NMR experiments.

Supporting Information Available: Compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049392V