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Phosphine- and Nitrogen-Containing Lewis Base Catalyzed Highly Regioselective and Geometric Selective Cyclization of Isatin Derived Electron-Deficient Alkenes with Ethyl 2,3-Butadienoate

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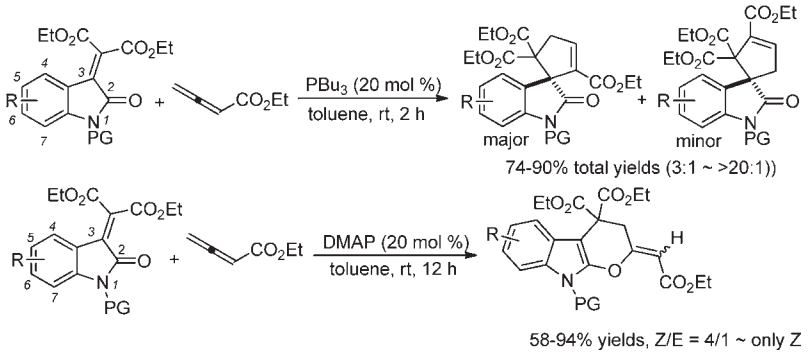
ABSTRACT



An interesting phosphine-containing Lewis base catalyzed highly regioselective [3 + 2] cycloaddition and a novel nitrogen-containing Lewis base catalyzed highly geometric selective [4 + 2] cycloaddition of isatin derived α,β-unsaturated diesters with α-allenic ester have been disclosed to give the corresponding cyclic products in good to excellent yields under mild conditions. A plausible reaction mechanism has also been proposed on the basis of previous literature and our own investigation.

Recently, phosphine- and nitrogen-containing Lewis base catalyzed cyclization reactions of allenoates have emerged as powerful synthetic tools in the rapid construction of cyclic molecular complexity via metal-free, mild conditions and an easy manipulation process with readily

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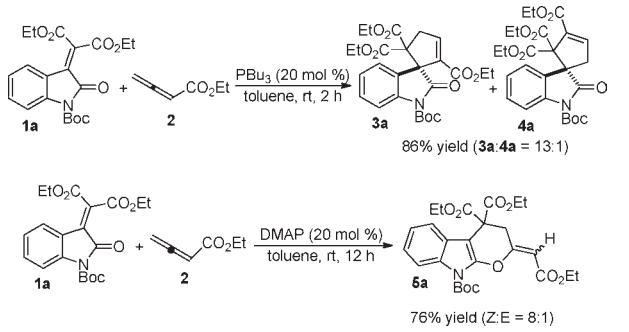
available organocatalysts.[1−3] The synthetic utility of these cycloaddition reactions has been largely demonstrated by the preparation of biologically active natural products and pharmaceutically interesting substances.[1k] During our ongoing investigation on phosphine- and nitrogen-containing Lewis base catalyzed cyclization reactions of allenoates, herein, we wish to report an interesting phosphine-containing Lewis base catalyzed highly regioselective [3 + 2] cycloaddition of isatin derived α,β-unsaturated diesters with α-allenic ester as well as a novel nitrogen-containing Lewis base catalyzed [4 + 2] cycloaddition of isatin derived α,β-unsaturated diesters with α-allenic ester in good to excellent yields with high stereoselectivities under mild conditions. Moreover, these heterocyclic products are the core structure motifs in a variety of natural alkaloid derivatives such as *Calabar* alkaloids *physostigmine* and *physovenine*.[4,5]

We initially utilized diethyl 2-(1-(*tert*-butoxycarbonyl)-2-oxoindolin-3-ylidene)malonate **1a** (1.0 equiv) and allenic ester **2** (1.5 equiv) as the substrates to investigate their cyclization behavior in toluene at room temperature in the presence of 20 mol % PBu_3. It was found that the [3 + 2] cycloaddition reaction took place smoothly to give the corresponding cyclic products **3a** and **4a** in 86% total yield within 2 h and this cyclization is highly regioselective because the ratio of **3a**:**4a** is 13:1 (Scheme 1 and Table SI-1 in the Supporting Information, entry 1). Subsequently, we screened various phosphine catalysts for this reaction, and

Scheme 1. PBu_3 and DMAP-Catalyzed Cyclization of **1a** with **2**



the results are summarized in Table SI-1 in the Supporting Information. Sterically bulky tri(*tert*-butyl)phosphine (P^tBu_3) and the least nucleophilic phosphine tris(4-fluorophenyl)phosphine ($P(p\text{-}FC_6H_4)_3$) did not catalyze this reaction (Table SI-1, entries 3 and 7). Other phosphines could smoothly promote the reaction under the standard conditions, affording the corresponding cyclization products **3a** and **4a** in good total yields along with moderate regioselectivities (Table SI-1, entries 2, 4−6, and 8−9). The examination of solvent effects using PBu_3 as the catalyst revealed that, in acetonitrile, no reaction occurred and toluene is the solvent of choice, giving the cyclic adducts **3a** and **4a** in higher total yield (Table SI-1, entries 10−14). Using 10 mol % PBu_3 as the catalyst produced the corresponding cyclization products **3a** and **4a** in 80% total yield (**3a:4a** = 9:1) (Table SI-1, entry 15).

Using nitrogen-containing Lewis bases as the catalysts, we found that no reaction occurred in the presence of 1,8-diazabicyclo[5,4,0]-7-undecene (DBU) or triethylamine in toluene (Table SI-2 in the Supporting Information, entries 1 and 2). However, it was surprising to find that, by using 4-*N*,*N*-dimethylpyridine (DMAP) (10 mol %) as the catalyst, the reaction of **1a** (1.0 equiv) with **2** (2.0 equiv) produced the corresponding [4 + 2] cycloaddition product **5a** in 70% yield as *Z*- and *E*-isomeric mixtures (*Z*/*E* = 6:1) in toluene overnight (12 h) (Table SI-2, entry 3). Increasing the employed amount of DMAP to 20 mol % afforded **5a** in 76% yield (*Z*/*E* = 8:1) (Scheme 1). The screening of solvent indicated that toluene is still the best solvent, affording **5a** in higher yields (Table SI-2, entries 5−9). Using 1,4-diazabicyclo[2,2,2]octane (DABCO) (20 mol %) as the catalyst provided cyclic adduct **5a** in 68% yield (*Z*/*E* = 1:2) along with a double bond migrated product **6a** in 31% yield (Scheme 2).

Having identified the optimal reaction conditions, we next set out to examine the scope and limitations of the [3 + 2] cycloaddition reaction catalyzed by PBu_3 using various isatin derivatives **1** with different substituents on the benzene rings, and the results are summarized in Table 1. As can be seen from Table 1, whether electron-withdrawing or electron-donating groups at the 5-, 6- or 7-position of the benzene ring of *N*-Boc protected isatins **1** were employed, the reactions proceeded smoothly to give the corresponding products **3** and **4** in good total yields along

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Scheme 2. DABCO-Catalyzed [4 + 2] Cyclization of **1a** with **2**

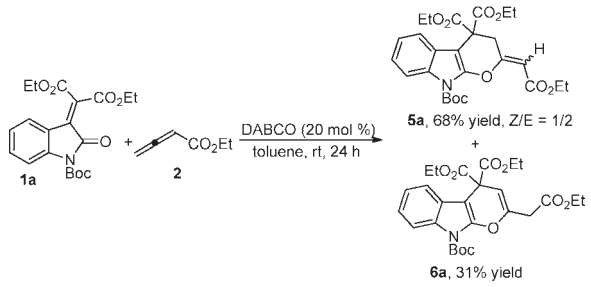
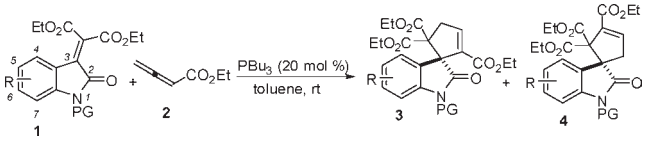


Table 1. Substrate Scope of the Reactions Catalyzed by PBu_3[a]



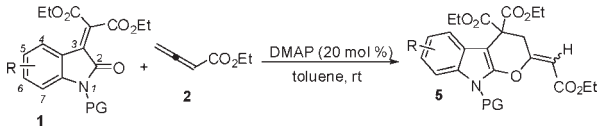
entry	no.	PG	R	yield (%)[b]	no.	3:4[c]
1	**1b**	Boc	5-F	75	**3b:4b**	11:1
2	**1c**	Boc	5-Cl	82	**3c:4c**	>20:1
3	**1d**	Boc	5-Br	77	**3d:4d**	>20:1
4	**1e**	Boc	5-Me	79	**3e:4e**	13:1
5	**1f**	Boc	5-MeO	79	**3f:4f**	12:1
6	**1g**	Boc	6-Br	74	**3g:4g**	17:1
7	**1h**	Boc	5,7-$(Me)_2$	75	**3h:4h**	10:1
8	**1i**	Bn	H	90	**3i:4i**	10:1
9	**1j**	Me	H	90	**3j:4j**	7:1
10	**1k**	Cbz	H	76	**3k:4k**	11:1
11	**1l**	allyl	H	80	**3l:4l**	3:1
12	**1m**	PMB	H	77	**3m:4m**	13:1

[a] The reaction was carried out on a 0.1 mmol scale with 20 mol % catalyst under Ar in toluene (1.0 mL) at room temperature for 2 h, and the ratio of **1:2** was 1.0:1.5. [b] Isolated total yield. [c] The regioisomeric ratio of **3:4** was determined by ^1H NMR spectroscopic data, and these regioisomerscan not be easily separated by column chromatography.

with high regioselectivities (up to **3:4** > 20:1) (Table 1, entries 1−7). It should also be noted that, as in the case of other isatin derivatives **1i**−**1m** bearing different N-protecting groups, the reactions proceeded smoothly to produce the corresponding cyclic products **3i**−**3m** and **4i**−**4m** in good to high total yields (up to 90%) and moderate to high regioselectivities (up to 13:1) (Table 1, entries 8−12). Only in the case of a N-allylic group protected isatin derivative **1l**, the corresponding cyclization product **3l** was formed in moderate regioselectivity (**3l:4l** = 3:1), presumably due to the steric effect (Table 1, entry 11). In all cases, the cycloadducts **3** were obtained as the major products. The structure of the major cycloaddition product **3i** was unambiguously assigned by X-ray diffraction, and its CIF data are summarized in the Supporting Information.[6]

We next examined the scope and limitations of the [4 + 2] cycloaddition reaction catalyzed by DMAP using

Table 2. Substrate Scope of the Reactions Catalyzed by DMAP[a]



entry	no.	PG	R	yield (%) (*Z*/*E*)[b]
1	**1b**	Boc	5-F	**5b**, 85 (8:1)
2	**1c**	Boc	5-Cl	**5c**, 90 (4:1)
3	**1d**	Boc	5-Br	**5d**, 88 (5:1)
4	**1e**	Boc	5-Me	**5e**, 80 (5:1)
5	**1f**	Boc	5-MeO	**5f**, 91 (*Z*)
6	**1g**	Boc	6-Br	**5g**, 80 (5:1)
7	**1h**	Boc	5,7-$(Me)_2$	**5h**, 87 (*Z*)
8	**1i**	Bn	H	**5i**, 73 (*Z*)
9	**1j**	Me	H	**5j**, 78 (*Z*)
10	**1k**	Cbz	H	**5k**, 94 (7:1)
11	**1l**	allyl	H	**5l**, 91 (*Z*)
12	**1m**	PMB	H	**5m**, 58 (*Z*)

[a] The reaction was carried out on a 0.1 mmol scale with 20 mol % catalyst under Ar in solvent (1.0 mL) at room temperature overnight, and the ratio of **1:2** was 1.0:2.0. [b] Isolated total yield and these stereoisomers cannot be easily separated by column chromatography.

various isatin derivatives **1** with different substituents on the benzene rings, and the results are summarized in Table 2. All of the reactions proceeded smoothly under the optimal conditions, producing the desired cyclic products **5b**−**5h** in good to excellent yields (80−91%) along with good to excellent geometric selectivities (*Z*/*E* = 4:1 to only *Z*-isomer), no matter whether they had electron-withdrawing or electron-donating substituents on their aromatic rings at the 5-, 6- or 7-position (Table 2, entries 1−7). Varying the N-protecting groups also gave the cyclic adducts **5i**−**5m** in good to high yields along with good geometric selectivities (Table 2, entries 8−12). The structure and the configuration of product *Z*-**5j** was unequivocally determined by X-ray diffraction, and its CIF data are shown in the Supporting Information.[7]

We also investigated the DABCO-catalyzed cyclization of **1i** with **2** in toluene, and the result is outlined in Scheme 3. The corresponding [4 + 2] cycloadducts **5i** (*Z*-isomer) and **5i′** (*E*-isomer) were formed in 10% and 16% yields, respectively along with a double bond migrated product **6i** in 72% yield (Scheme 3). The structures of **5i′** and **6i** have been established by X-ray diffraction, and their CIF data are presented in the Supporting Information.[8,9]

Interestingly, we found that, in the PBu_3 (10 mol %) catalyzed cyclization of **1i** with ethyl but-2-ynoate **7**, the

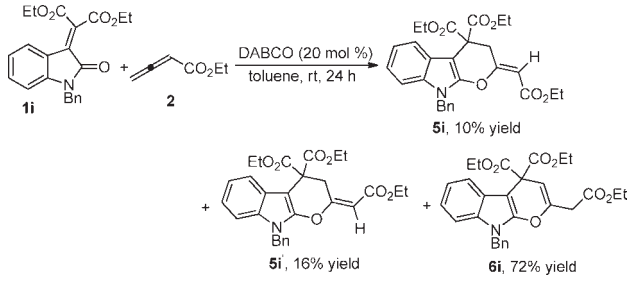
(6) The crystal data of **3i** have been deposited in the CCDC with number 798143.

(7) The crystal data of Z-**5j** have been deposited in the CCDC with number 802125.

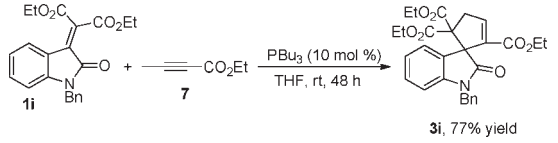
(8) The crystal data of **5i'** have been deposited in the CCDC with number 800399, and the crystal data of **6i** have been deposited in the CCDC with number 800400.

(9) (a) Evans, C. A.; Miller, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 12394. (b) Meng, L.-G.; Cai, P.; Guo, Q.-X.; Xue, S. *J. Org. Chem.* **2008**, *73*, 8491.

Scheme 3. DABCO-Catalyzed Cyclization of **1i** with **2**



Scheme 4. PBu_3-Catalyzed Cyclization of **1i** with Ethyl But-2-ynoate **7**



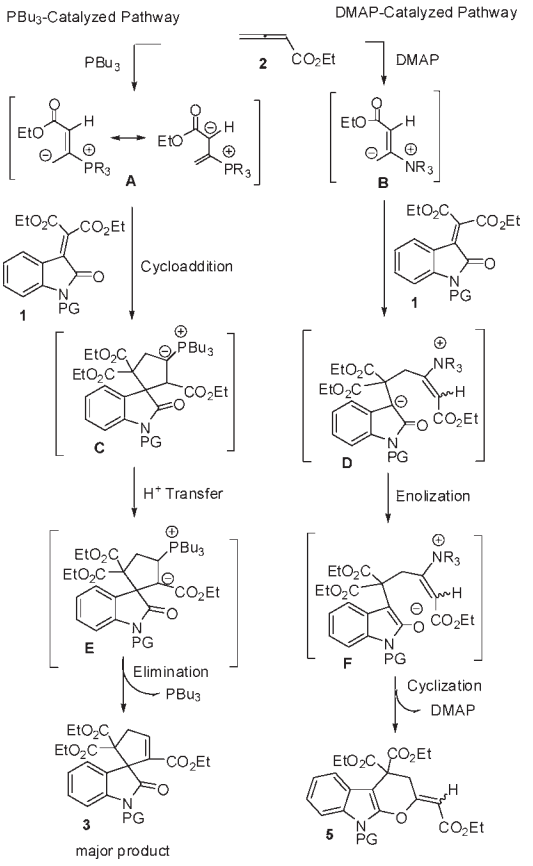
corresponding cyclization adduct **3i** was formed in 77% yield as the sole product in THF under the standard conditions although no reaction occurred in the presence of DMAP, presumably due to that the stronger nucleophilicity of a phosphine catalyst can produce the corresponding alleneoate from alkynoate **7** which can subsequently give **3i** (Scheme 4; also see Scheme 5).

The mechanism for the different reaction outcome caused by phosphine and nitrogen catalysts has not been unequivocally established. One reasonable explanation is shown in Scheme 5 based on the earlier reports and our own investigations.

In the case of the PBu_3-catalyzed reaction, the catalyst reacts with the allenic ester **2** to generate a zwitterionic intermediate **A**, which serves as a dipole for the subsequent [3 + 2] cycloaddition with **1** to give intermediate **C**.[1a] Subsequently, the facile 1,2-proton transfer affords intermediate **E**, and then, the elimination takes place to give the product **3** as the major product along with the regeneration of the catalyst. This mechanism, as proposed by others,[9] benefits from the ability of phosphorus to stabilize the ylide structure **C**. In contrast, the DMAP-catalyzed pathway does not benefit from a similar stabilization. The zwitterionic intermediate **B** reacts with **1** to give intermediate **D**, which undergoes enolization to give intermediate **F**. Subsequent cyclization produces cyclic adduct **5** and regenerates the DMAP catalyst. The cyclization step is assumed to be the rate-determining step, accounting for the longer reaction time required compared with the phosphine-containing Lewis base catalyzed one.

In summary, we have found and developed an interesting phosphine-containing Lewis base catalyzed highly regioselective [3 + 2] cycloaddition of isatin derived α,β-unsaturated diesters with α-allenic ester, affording the

Scheme 5. A Plausible Reaction Mechanism



functionalized spirocyclic products in good to excellent yields along with high regioselectivities. Moreover, a novel nitrogen-containing Lewis base catalyzed highly geometric selective [4 + 2] cycloaddition of isatin derived α,β-unsaturated diesters with α-allenic ester has been disclosed, giving the corresponding cyclic adducts in good to excellent yields under mild conditions. A plausible reaction mechanism has also been proposed on the basis of previous literature and our own investigation. Efforts are in progress to elucidate further mechanistic details of these reactions and to understand their scope and limitations.

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Supporting Information Available. Spectroscopic data and NMR charts of the compounds shown in Tables 1−4, X-ray crystal data of **3i**, *Z*-**5j**, **5i′**, and **6i** as well as the detailed descriptions of experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.