Intramolecular Cyclization

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Phosphine-Catalyzed Intramolecular Formal [3+2] Cycloaddition for Highly Diastereoselective Synthesis of Bicyclo[*n*.3.0] Compounds**

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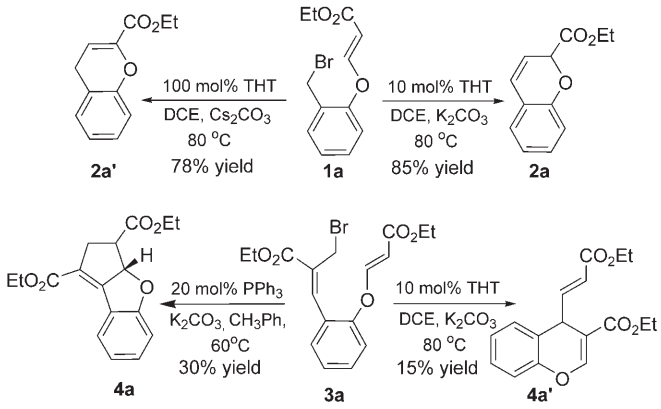
Ylides have been widely applied in constructing small-ring compounds such as epoxides,[1] cyclopropanes,[2] and aziridines.[3] Recently, several ylide cyclizations that go beyond the formation of three-membered rings have also been developed.[4–7] Lu and co-workers demonstrated in a number of elegant studies[4] that phosphines are good catalysts for the construction of cyclopentenes. Krische and co-workers developed the first intramolecular variant of the cycloaddition.[5] Catalytic asymmetric [3+2] cycloadditions have been reported by both Zhang and Fu, with their respective co-workers.[6] Recently, Aggarwal and co-workers documented an elegant protocol for the asymmetric synthesis of epoxide- and aziridine-fused heterocycles through a sulfur ylide route.[7]

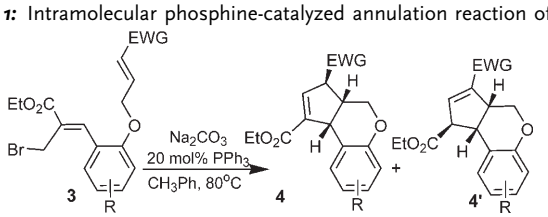
In a previous study on ylide chemistry,[8] we reported a tandem ylide Michael addition–elimination–substitution reaction for the controllable synthesis of 2*H*-chromenes **2a** and 4*H*-chromenes **2a′** (Scheme 1).[9] To further extend the reaction scope, **3a** was synthesized and subjected to the reaction. However, the desired compound **4a′** was obtained in only 15% yield under the same conditions. To improve the yield, other potential catalysts such as PPh_3 and 1,4-diazabicyclo[2.2.2]octane (DABCO) were tested instead of THT. When triphenylphosphine[10] was used, the bicyclic compound **4a** was, unexpectedly, isolated as the sole product in 30% yield with excellent diastereoselectivity (Scheme 1). Herein, we wish to report the preliminary results of this cyclization.



Scheme 1. Catalytic ylide annulation. THT: tetrahydrothiophene; DCE: 1,2-dichloroethane.

Further studies showed that the desired product was not observed in the absence of PPh_3. In the presence of PPh_3 (20 mol%) with Na_2CO_3 as a base, bromide **3b** afforded the corresponding benzobicyclo[4.3.0] compounds (**4b**/**4b′**) in 95% yield with excellent diastereoselectivity (entry 1, Table 1). To study the generality of the current reaction,

Table 1: Intramolecular phosphine-catalyzed annulation reaction of **3**.[a]



Entry	3	R	EWG	4/4′[b]	Yield [%][c]
1	**3b**	H	CO_2Et	91/9 (**4b**/**4b′**)	95 (89[d])
2	**3c**	4-Cl	CO_2Et	94/6 (**4c**/**4c′**)	99
3	**3d**	4-Br	CO_2Et	90/10 (**4d**/**4d′**)	96
4	**3e**	4-MeO	CO_2Et	91/9 (**4e**/**4e′**)	96
5	**3f**	4-MeO	CO_2Me	90/10 (**4f**/**4f′**)	99
6	**3g**	H	CO-*p*-ClC_6H_4	19/81 (**4g**/**4g′**)	81
7	**3h**	4-Cl	CO-*p*-BrC_6H_4	17/83 (**4h**/**4h′**)	77

[a] EWG: electron-withdrawing group. PPh_3 (20 mol%), **3** in CH_3Ph (0.10 M), room temperature, 15 min, then Na_2CO_3 (1.5 equiv), 80°C, 5–11 h. [b] Determined by 300 MHz ^1H NMR spectroscopy. [c] Yield of isolated product. [d] 10 mol% of PPh_3 was used.

various α,β-unsaturated carbonyl compounds were investigated. As shown in Table 1, both α,β-unsaturated esters and α,β-unsaturated ketones furnished the benzobicyclo[4.3.0] compounds with excellent diastereoselectivities in good to excellent yields. The substituents on the benzene ring had almost no effect on the yields and diastereoselectivities (entries 2–4, Table 1). In all of the cases investigated, isomerization of **4** into **4′** was observed. For esters, less than 10 mol% was transformed into **4′** (entries 1–5, Table 1), while more than 80 mol% was isomerized in the case of ketones **3g** and **3h** (entries 6 and 7, Table 1), probably due to the stronger acidity of the α-H atoms of the ketones relative to those of

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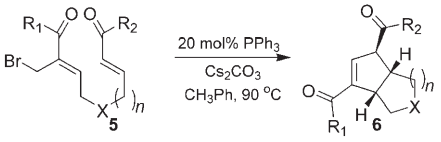
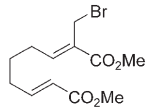
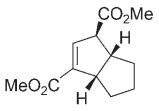
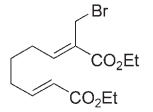
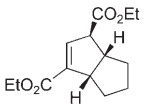
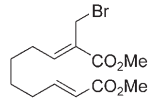
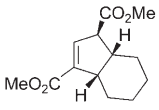
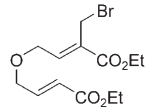
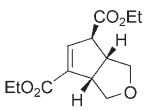
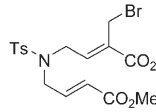
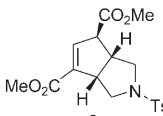
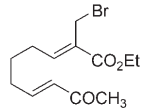
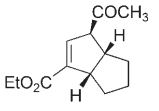
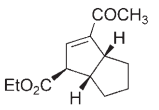
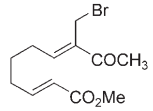
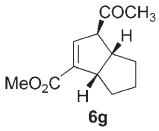
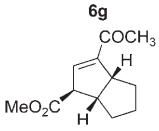
esters. In addition, the reaction could also be performed in the presence of 10 mol% of PPh_3 (entry 1, Table 1).

We next considered the possibility of extending the reaction to aliphatic substrates to make bicyclic compounds, a process which would complement the excellent methodology for the synthesis of bicyclo[3.3.0] ring compounds developed by Krische and co-workers.[5] As shown in Table 2, under the optimal conditions (20 mol% of PPh_3, 1.5 equiv of Cs_2CO_3, 90°C), substrates **5a**–**5g** afforded the corresponding bicyclo[3.3.0] compounds with high diastereoselectivities in moderate to good yields. Methyl and ethyl esters had almost no effect on this ylide annulation reaction (entries 1 and 2, Table 2). In addition, the reaction could also furnish the corresponding bicyclo[4.3.0] compound but with a reduction of diastereoselectivity (entry 3, Table 2). Tetrahydropyrrole and tetrahydrofuran derivatives could be synthesized in 56 and 88% yields, respectively (entries 5 and 4, Table 2). α,β-Unsaturated ketone **5f** was also a good substrate for this annulation reaction (entry 6, Table 2). It should be mentioned that isomerization of the products **6f** and **6g** was observed under the reaction conditions. The corresponding compounds **6f′** and **6g′**, respectively, were obtained as the major products in each case (entries 6 and 7, Table 2).

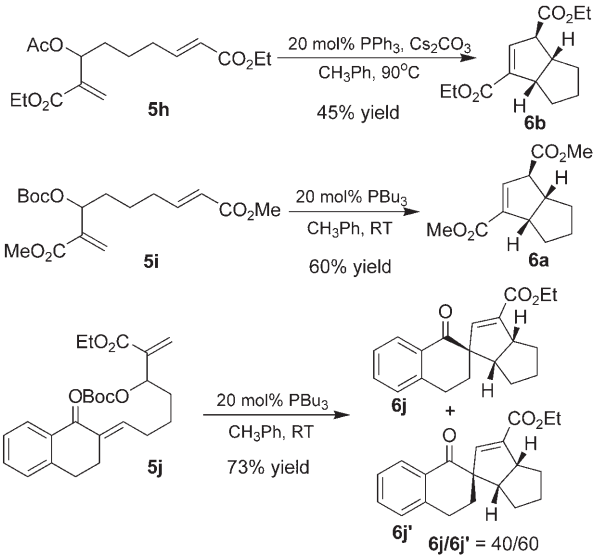
Table 2: Intramolecular phosphine-catalyzed ylide annulation reaction.[a][11]



Entry	Substrate	d.r.[b]	Product	Yield [%][c]
1	 **5a**	>20:1	 **6a**	73
2	 **5b**	>20:1	 **6b**	65
3	 **5c**	6:1	 **6c**	55
4	 **5d**	>19:1	 **6d**	88
5[d]	 **5e**	>20:1	 **6e**	56
6[d][e]	 **5f**	>20:1	 **6f**  **6f′**	48[f]
7[d][e]	 **5g**	>20:1	 **6g**  **6g′**	51[g]

[a] PPh_3 (20 mol%), **5** in CH_3Ph (0.10 M), room temperature, 15 min, then Cs_2CO_3 (1.5 equiv), 90°C, 10–16 h. [b] Determined by 300 MHz ^1H NMR spectroscopy. [c] Yield of isolated product. [d] 4-Å molecular sieves were added. [e] At 60°C. [f] **6f′**/**6f** = 82/18. [g] **6g′**/**6g** = 86/14.

The catalytic annulation reaction could occur smoothly not only from the bromides **5** but also from the corresponding acetates. For example, **5h** gave the desired product in 45% yield under the same reaction conditions (Scheme 2). When



Scheme 2. Annulation of carbonate and acetate derivatives. Boc: *tert*-butoxycarbonyl.

20 mol% of tributylphosphine was employed and *tert*-butyl carbonate **5i** was used instead of acetate **5h** or bromide **5a**, it was found that the annulation reaction also proceeded well to give the desired product, even under neutral conditions at room temperature (Scheme 2). In this case, *tert*-butoxide, generated in situ, played a role as the base to form the ylide. By the same strategy, substrate **5j** worked well to give spirocyclic compounds **6j** and **6j′** (Scheme 2), which could be readily separated by flash chromatography, in 73% yield.

Products **4a**–**f**, **4g′**, **4h′**, and **6a**–**g** were well characterized by NMR spectroscopy and either high-resolution mass spectrometry or elemental analysis. The relative configuration of the products was established by ^1H NMR spectroscopic analysis.[11] The structures of compounds **4g′** and **6j**

were further confirmed by single-crystal X-ray diffraction analysis (Figure 1).

The produced bicyclo[*n*.3.0] compounds are potentially useful in organic synthesis. For example, the electron-deficient carbon–carbon double bond might be subjected to hydrogenation[12] and conjugate addition of dimethyl copper lithium,[13] while the ester group could be reduced by $LiAlH_4$.[14] Interestingly, upon exposure to 5.0 equivalents of $LiEt_3BH$, both of the two ester groups of **6a** were readily reduced to afford **7a** in 81% yield at room temperature, while 3.0 equivalents of $LiEt_3BH$ selectively reduced the nonconjugated ester group to afford **7b** in 74% yield at 0°C, but the carbon–carbon double bond had isomerized in the latter case (Scheme 3). Unexpectedly, upon treatment with K_2CO_3 in EtOH under an air atmosphere, bicyclic compound **6b** was transformed into tertiary alcohol **8** in excellent yield with excellent diastereoselectivity, as shown in Scheme 3. To further demonstrate the scope of this finding and confirm the relative stereochemistry of the product, the annulation product **4g′** was subjected to the same reaction and the corresponding tertiary alcohol **9** was isolated. The structure of **9** was further corroborated by single-crystal X-ray diffraction analysis (Figure 2).

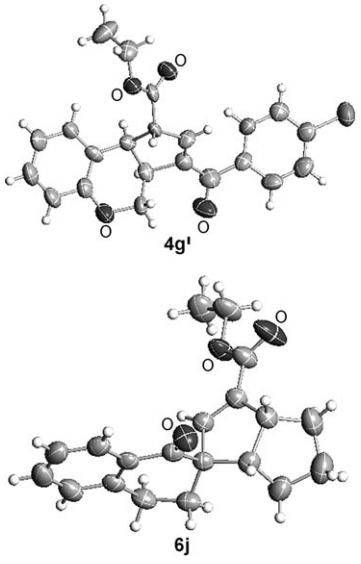
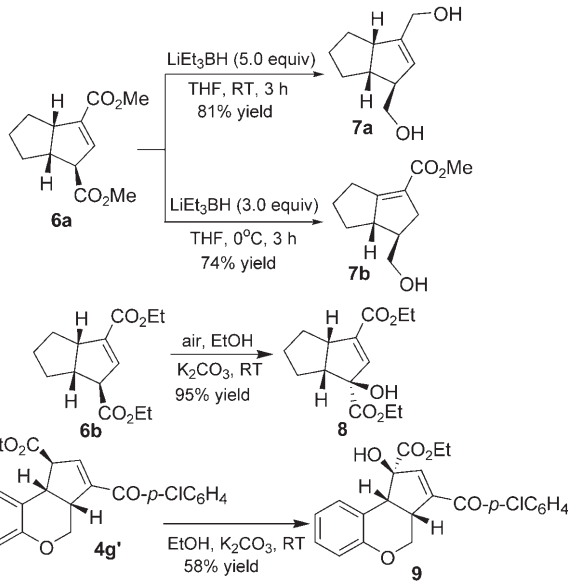
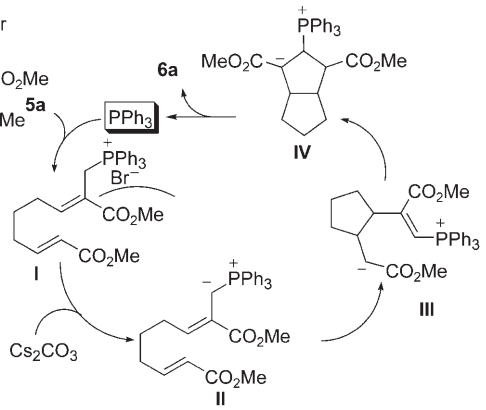


Figure 1. Structures of compounds **4g′** and **6j** in their crystals.[15]



Scheme 3. Chemical transformation of bicyclo[*n*.3.0] compounds. THF: tetrahydrofuran.



Scheme 4. A plausible mechanism for the annulation reaction.

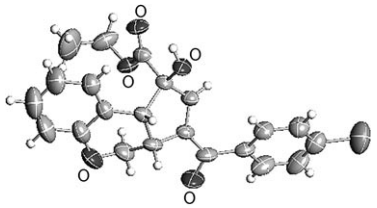


Figure 2. Structure of compound **9** in its crystal.[15]

A mechanism that could explain the aforementioned reactions is proposed in Scheme 4. Triphenylphosphine reacts with bromide **5a** to form phosphonium salt **I**, which is deprotonated by Cs_2CO_3 to generate the corresponding phosphonium ylide **II** in situ. An intramolecular Michael addition of the ylide, followed by a Michael addition of phosphonium salt **III** and then β-elimination of triphenylphosphine, completes the catalytic cycle.

In summary, a catalytic intramolecular ylide annulation has been developed for the construction of bicyclo[*n*.3.0] ring systems with three continuous stereogenic centers in a single manipulation. The high diastereoselectivity, cheap and readily available catalyst, simple procedure, mild conditions, and in particular, facile chemical transformations make this method potentially useful in organic synthesis. Further investigations into the scope, mechanism, and synthetic application of the current reaction are in progress in our laboratory.

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Keywords: annulation · bicyclic compounds · diastereoselectivity · homogeneous catalysis · intramolecular reactions

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[11] Experimental procedures and characterization data of new compounds, NOESY spectra of compounds **4b**, **6a**, **6j**, and **6j′**, and ^{1}H–^{1}H COSY spectra of compounds **4b** and **6a** are available in the Supporting Information.

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[15] CCDC-644663 (**4g′**), -644662 (**6j**), and -644664 (**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

