JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

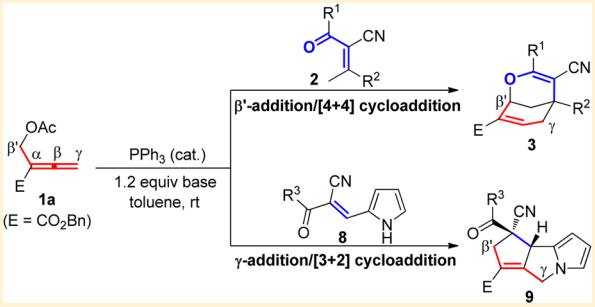
Phosphine-Catalyzed Addition/Cycloaddition Domino Reactions of β′-Acetoxy Allenoate: Highly Stereoselective Access to 2-Oxabicyclo[3.3.1]nonane and Cyclopenta[a]pyrrolizine

Yiting Gu,[⊥] Pengfei Hu,[⊥] Chunjie Ni, and Xiaofeng Tong*

Shanghai Key Laboratory of Functional Materials Chemistry, East China University of Science and Technology, Shanghai 200237, China

Supporting Information

ABSTRACT: Two classes of phosphine-catalyzed addition/cycloaddition domino reactions of β′-acetoxy allenoate **1** have been developed. The reaction of **1** with 2-acyl-3-methyl-acrylonitrile **2** readily occurs to give 2-oxabicyclo[3.3.1]nonane **3**, furnishing the β′-addition/[4 + 4] cycloaddition domino sequence. In this sequence, β′C of allenoate **1** is an electrophilic center, and its β′C and γC serve as a 1,4-dipole. When the other reaction partner is switched to 2-acyl-3-(2-pyrrole)-acrylonitrile **8**, a γ-addition/[3 + 2] cycloaddition domino reaction is instead observed, in which allenoate **1** exhibits dual electrophilic reactivity of γC and 1,3-dipole chemical behavior of βC and β′C. Furthermore, both of these two asymmetric variants have also been achieved with up to 93% ee. The domino reactions presented in this report are valuable for highly stereoselective construction of complex structures under mild reaction conditions.



INTRODUCTION

Since the pioneering report of Lu's [3 + 2] cycloaddition,[1] the research paradigm of the phosphine-catalyzed cycloadditions of activated allenes has been well established.[2] From a mechanistic point of view, this chemistry strongly depends on the zwitterionic intermediates, which are generated via 1,4-addition of phosphine catalyst to activated allenes and exhibit excellent dipolar-type cycloaddition reactivity toward various electrophiles. In addition to zwitterionic intermediate **A** for Lu's [3 + 2] cycloaddition (Scheme 1a), zwitterionic intermediate **B**, which is reported by Kwon's group on the basis of α-substituted activated allene, is prone to undergo [4 + 2] cycloadditions with activated alkenes and imines (Scheme 1b).[3] Interestingly, Lu's group has also demonstrated that intermediate **B** is capable of reacting with β,γ-unsaturated α-keto ester, providing an alternative [4 + 2] cycloaddition (Scheme 1c).[4] Moreover, Huang and Marinetti independently developed the phosphine-catalyzed [4 + 2] cycloadditions of γ-substituted allenoates and activated alkenes, in which zwitterionic intermediate **C** has been proposed to be involved (Scheme 1d).[5]

Despite these contributions, the major limitation of this chemistry is the requirement of an electrophile as the other cycloaddition partner. The main issue is considered to be the preferential nucleophilic carbanion reactivity of the involved zwitterionic intermediates **A**–**C**. In contrast, we have developed the phosphine-catalyzed [4 + 1] cycloaddition of β′-acetoxy allenoate **1**, which features the utilization of a bisnucleophile as the other reaction partner (Scheme 1e).[6]

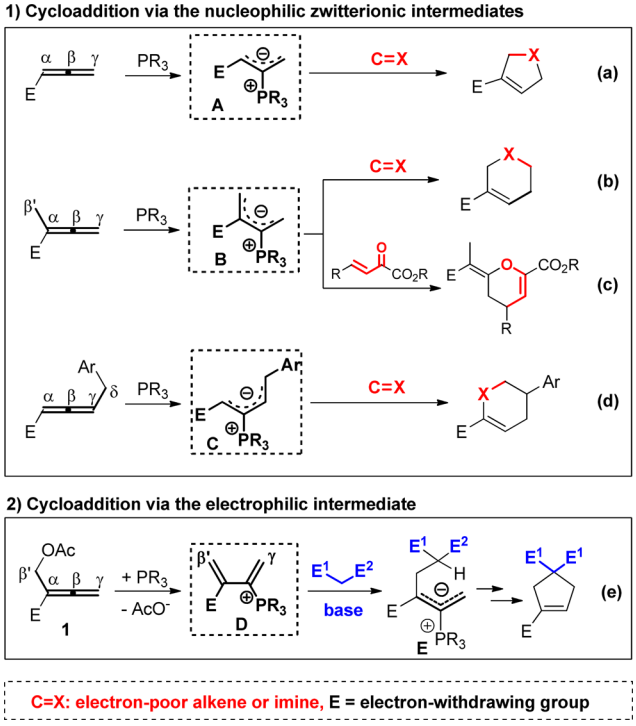
The installation of an acetoxy group at β′C of allenoate **1** is essential for the generation of the key double activated buta-1,3-diene intermediate **D** via the process of 1,4-addition of phosphine followed by 1,2-elimination of the acetate group.[7] The electrophilicity of intermediate **D** eventually allows the attack of the bisnucleophile, leading to the formation of intermediate **E**.[8] Then, the carbanion of intermediate **E** is implemented as a base to promote intramolecular addition of the second nucleophilic center, thus furnishing this [4 + 1] cycloaddition (Scheme 1e).[9]

The [4 + 1] cycloaddition via electrophilic intermediate **D** provides a complement to the aforementioned zwitterion-involved reaction mode. Accordingly, we are encouraged to further design novel phosphine-catalyzed reactions on the basis of **D**. Our design plan is illustrated in Scheme 2. In conjunction with compound **2** bearing both a pronucleophile (NuH) and an electrophilic C═X group (activated alkene or imine), we envisioned that intermediate **D** would also be reliable for the Michael-type addition of **2** to its β′C and/or γC. Such addition(s) might lead to the formation of zwitterionic intermediate(s) **F** and/or **G**. As a result, an intramolecular dipolar-type cycloaddition[10] between the newly formed zwitterion moiety and the prearranged C═X group was anticipated (Scheme 2). Herein, we report the phosphine-catalyzed addition/cycloaddition domino reaction of allenoate **1** and compound **2** with the hope to having access to complex structures, which not only exploits the potential of allenoate **1**,

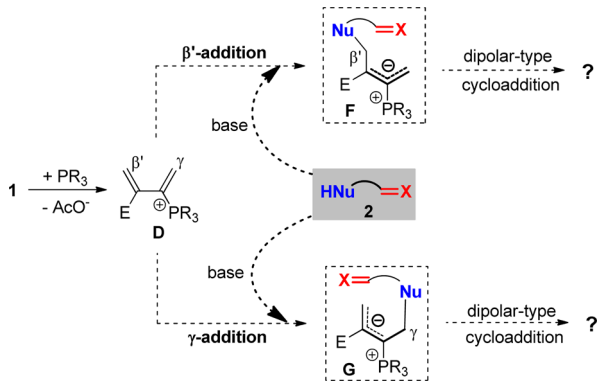
Received: March 29, 2015
Published: April 23, 2015

DOI: 10.1021/jacs.5b03273
J. Am. Chem. Soc. 2015, 137, 6400–6406

Scheme 1. Variants of the Phosphine-Catalyzed Cycloadditions of Activated Allenes



Scheme 2. Design Plan for the Addition/Cycloaddition Domino Reaction

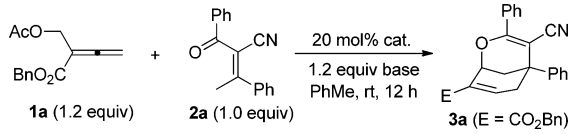


but also extends the existing phosphine-catalyzed cycloaddition scope.

RESULTS AND DISCUSSION

PPh_3-Catalyzed β'-Addition/[4 + 4] Cycloaddition Domino Reaction. To challenge our hypothesis shown in Scheme 2, we commenced our study with the screening of appropriate compounds **2**. After extensive screening,[11] we were delighted to find that, with the help of 20 mol % PPh_3 and 1.2 equiv Na_2CO_3, compound **2a**[12] indeed reacted with allenoate **1a** in toluene at room temperature to give the bridged cycle **3a** in 25% yield after 12 h (Table 1, entry 1). The structural assignment of **3a** was corroborated by the X-ray crystallography of compound **3o** (Figure 1).[13] Apparently, the methyl group and oxo-diene moiety of **2a** serve as our desired nucleophilic and electrophilic functions, respectively, providing a nice opportunity for the realization of β'-addition/[4 + 4] cycloaddition domino reaction with allenoate **1a**. Then, the

Table 1. Condition Optimization for the Phosphine-Catalyzed Reaction of 1a and 2a[a]



entry	cat.	base	yield (%)[b]
1	PPh_3	Na_2CO_3	25
2	PPh_3	K_2CO_3	34
3	PPh_3	KO^tBu	complex
4	PPh_3	Et_3N	18
5	PPh_3	$^iPr_2NEt$	34
6	PPh_3	Cs_2CO_3	78
7	P(2-furyl)$_3$	Cs_2CO_3	28
8	P(4-F—C_6H_4)$_3$	Cs_2CO_3	72
9	PBu_3	Cs_2CO_3	56
10	$MePPh_2$	Cs_2CO_3	75
11[c]	PPh_3	Cs_2CO_3	87
12[d]	PPh_3	Cs_2CO_3	56
13[c,e]	PPh_3	Cs_2CO_3	81

[a]Reaction conditions: to the solution of **2a** (0.2 mmol), phosphine (0.04 mmol) and base (0.24 mmol) in PhMe (2 mL) was slowly added a solution of **1a** (0.24 mmol) in PhMe (2 mL) over 30 min. [b]Isolated yield. [c]10 mol % PPh_3 was used. [d]50 mol % PPh_3 was used. [e]The reaction was run in the 5.0 mmol scale.

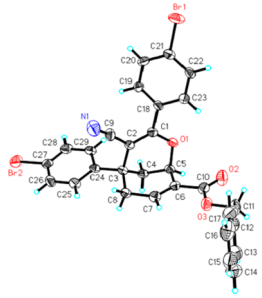


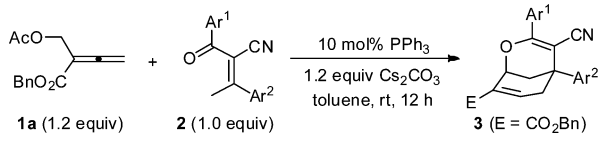
Figure 1. X-ray Structure of **3o**.

base additive was evaluated. The use of K_2CO_3 slightly improved the yield of **3a** to 34% while KO^tBu led to a complex mixture (Table 1, entries 2 and 3). Organic bases, such as Et_3N and $^iPr_2NEt$, gave similar results (Table 1, entries 4 and 5). Fortunately, the use of Cs_2CO_3 afforded a promising result with 78% isolated yield of **3a** (Table 1, entry 6). Furthermore, the examination of phosphine catalysts showed that neither electron-deficient nor electron-rich phosphines exhibited any superior performance over PPh_3 (Table 1, entries 7–10). Surprisingly, reducing the catalyst loading to 10 mol % provided a much cleaner reaction and the yield of **3a** was further improved to 87% (Table 1, entry 11). These results suggested that keeping relatively lower concentration of catalyst might be beneficial for the reaction performance. Indeed, the yield of **3a** dropped to 56% when 50 mol % PPh_3 was used (Table 1, entry 12). Notably, the optimal conditions were found to be reliable for the gram-scale reaction of **1a** (6.0 mmol) and **2a** (5.0 mmol) without affecting the reaction outcome (Table 1, entry 13).

Having established the optimal reaction conditions, we explored various substitution partners on compounds **2** to examine the substrate scope. The results are summarized in Table 2. When Ar^2 was a phenyl group, the Ar^1 groups with

DOI: 10.1021/jacs.5b03273
J. Am. Chem. Soc. 2015, 137, 6400–6406

Table 2. Reaction Scope of Substrates 2 with Aromatic Substituents[a]



entry	2 (Ar^1, Ar^2)	3/yield (%)[b]
1	**2a** (Ar^1 = Ph, Ar^2 = Ph)	**3a**/87
2	**2b** (Ar^1 = 4-MeOC$_6$H$_4$, Ar^2 = Ph)	**3b**/76
3	**2c** (Ar^1 = 4-BrC$_6$H$_4$, Ar^2 = Ph)	**3c**/74
4	**2d** (Ar^1 = 2-BrC$_6$H$_4$, Ar^2 = Ph)	**3d**/80
5	**2e** (Ar^1 = 2-furyl, Ar^2 = Ph)	**3e**/81
6	**2f** (Ar^1 = Ph, Ar^2 = 4-MeOC$_6$H$_4$)	**3f**/65
7	**2g** (Ar^1 = Ph, Ar^2 = 4-MeC$_6$H$_4$)	**3g**/75
8	**2h** (Ar^1 = Ph, Ar^2 = 4-FC$_6$H$_4$)	**3h**/72
9	**2i** (Ar^1 = Ph, Ar^2 = 4-ClC$_6$H$_4$)	**3i**/75
10	**2j** (Ar^1 = Ph, Ar^2 = 4-BrC$_6$H$_4$)	**3j**/73
11	**2k** (Ar^1 = Ph, Ar^2 = 2-furan)	**3k**/80
12	**2l** (Ar^1 = Ph, Ar^2 = 2-thiophene)	**3l**/85
13	**2m** (Ar^1 = Ph, Ar^2 = naphthalen-2-yl)	**3m**/63
14	**2n** (Ar^1 = Ph, Ar^2 = 3-BrC$_6$H$_4$)	**3n**/54
15	**2o** (Ar^1 = 4-BrC$_6$H$_4$, Ar^2 = 4-BrC$_6$H$_4$)	**3o**/55

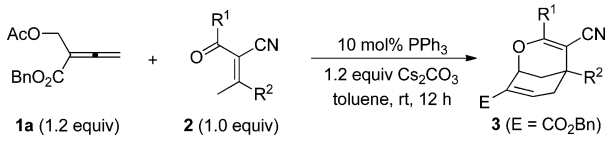
[a]Reaction conditions: to the solution of **2** (0.2 mmol), PPh_3 (0.02 mmol) and Cs_2CO_3 (0.24 mmol) in PhMe (2 mL) was slowly added a solution of **1a** (0.24 mmol) in PhMe (2 mL) over 30 min. [b]Isolated yield.

different electronic properties (e.g., electron-neutral, -rich, or -deficient) were well tolerated and the corresponding products **3a**−**3d** were obtained in high yields (Table 2, entries 1−4). Even 2-furyl group could be introduced, giving **3e** in 81% yield (Table 2, entry 5). However, when Ar^1 was a phenyl group, the electronic properties of the Ar^2 groups also had little influence on the yields of the corresponding products **3f**−**3l** (Table 2, entries 6−12). However, the steric properties of the Ar^2 groups strongly affected the reaction yield. For instance, substrate **2m** with a naphthalen-2-yl substituent gave the product **3m** in 63% yield (Table 2, entry 13). Moreover, the yield of **3n** with a *meta*-BrC$_6$H$_4$ substituent significantly dropped to 54% (Table 2, entry 14).

As shown in Table 3, the reaction scope was also successfully extended to substrates **2** with alkyl substituent(s). When R^1 was a phenyl group, various alkyl R^2 groups were tolerated, including methyl, isopropyl as well as cyclopropyl, and the products **3p**−**3r** were obtained in high yields (Table 3, entries 1−3). However, for the case of **2v** with an ethyl R^2 substituent, a regioselectivity issue appeared, leading to the isolation of two isomers **3v** and **3v**′ with the former as majority (eq 1). When R^2 was a methyl group, either primary or secondary alkyl R^1 group was tolerated, affording the corresponding products **3s**−**3u** in somewhat lower yields (Table 3, entries 4−6). More interestingly, the PPh_3-catalyzed domino reaction could be used to prepare more complex molecular architecture in addition to bridged rings **3a**−**3v**. Indeed, the reaction of substrate **2w** under the optimal conditions gave product **3w** in 63% yield (eq 2).

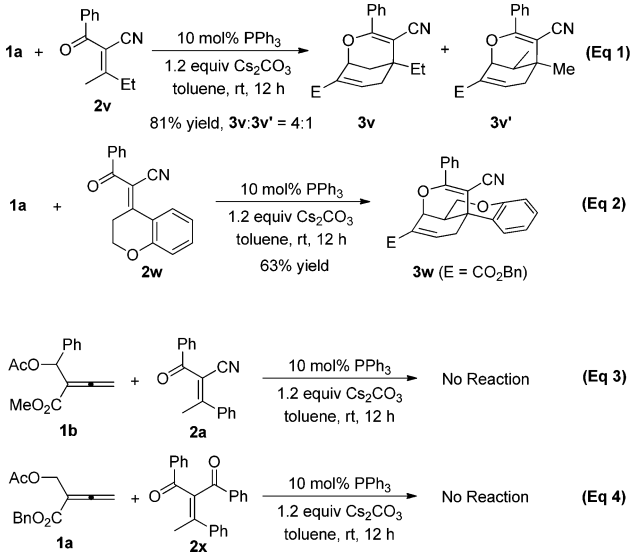
Unfortunately, *β*′-phenyl allenoate **1b** was found to be inert to **2a** under the catalytic systems (eq 3), notably because of the steric hindrance of *β*′-phenyl group preventing the *β*′-addition event on the related intermediate **D**. When 1,3-dicarbonyl derivative **2x** was subjected to the standard conditions, no

Table 3. Reaction Scope of Substrates 2 with Alkyl Substituent(s)[a]



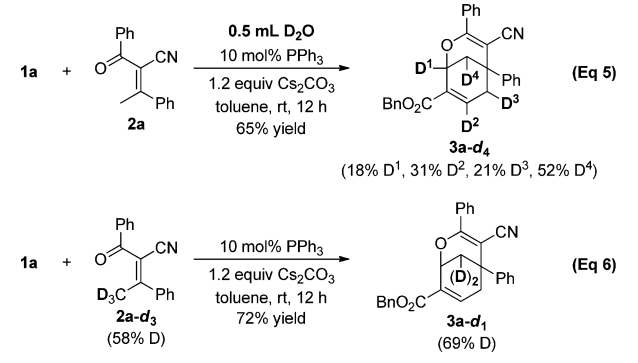
entry	2 (R^1, R^2)	3/yield (%)[b]
1	**2p** (R^1 = Ph, R^2 = Me)	**3p**/88
2	**2q** (R^1 = Ph, R^2 = ^{i}Pr)	**3q**/86
3	**2r** (R^1 = Ph, R^2 = cyclopropyl)	**3r**/83
4	**2s** (R^1 = C_5H_{11}, R^2 = Me)	**3s**/45
5	**2t** (R^1 = cyclohexyl, R^2 = Me)	**3t**/61
6	**2u** (R^1 = cyclopropyl, R^2 = Me)	**3u**/63

[a]Reaction conditions: to the solution of **2** (0.2 mmol), PPh_3 (0.02 mmol) and Cs_2CO_3 (0.24 mmol) in PhMe (2 mL) was slowly added a solution of **1a** (0.24 mmol) in PhMe (2 mL) over 30 min. [b]Isolated yield.



reaction was observed (eq 4). This result clearly demonstrated the important role of the nitrile group of **2a** on the activation of the pronucleophile methyl group.

After having investigated the reaction scope, we turned our attention to the reaction mechanism. Two deuterium-labeled control experiments were conducted. When D_2O (0.5 mL) was introduced into the standard catalytic systems, product **3a**-d_4, containing 18% D^1, 31% D^2, 21% D^3, and 52% D^4, was isolated in 65% yield (eq 5). The results implied that intermediates with

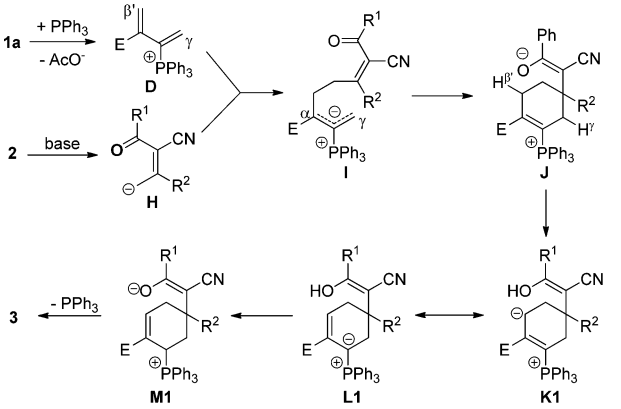


DOI: 10.1021/jacs.5b03273
J. Am. Chem. Soc. 2015, 137, 6400−6406

a carbanion at these four carbon centers should be involved.[14] The somewhat higher deuterium content of D[4] led us to speculate that the formation of intermediate **H** via the deprotonation of **2a** might be a slow step. Indeed, the reaction of **2a**-d_3 (58% D) under the standard conditions gave **3a**-d_1 (69% D) with enriched deuterium content, showing a slight isotopic effect (eq 6).

On the basis of the above observations, a proposed mechanism of the β'-addition/[4 + 4] cycloaddition domino reaction of **1a** and **2** is depicted in Scheme 3. Addition of PPh_3

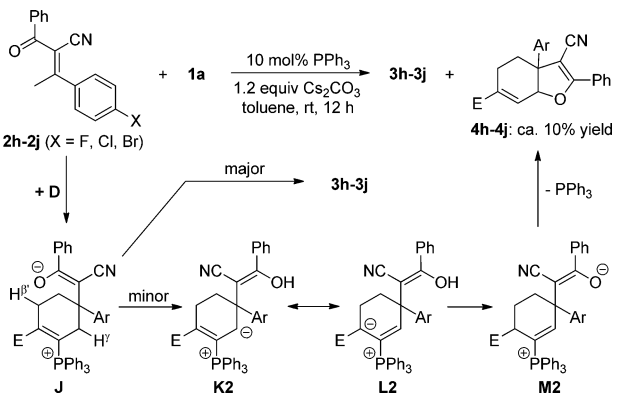
Scheme 3. Plausible Mechanism of the Reaction of 1a and 2



to **1a** followed by 1,2-elimination of acetate group generates the electrophilic intermediate **D**, which is attacked by the carbanion of **H** at the β'C position to form the zwitterionic intermediate **I**. Likely due to the slow step of carbanion **H** formation and high activity of intermediate **D**, a relatively lower concentration of **D** was supposed to be beneficial for the reaction performance. Then, the γ-carbanion of **I** undergoes an intramolecular addition to yield the enolate intermediate **J**. The resulting enolate serves as a base to abstract a β'H to produce intermediate **K1** which coexists with its resonance form **L1**. After an H-shift process, intermediate **L1** is converted to **M1**, which is followed by a S_N2'-type process to release product **3** and regenerate PPh_3 catalyst (Scheme 3).

It was worth mentioning that, for the cases of **2h**−**2j** with an electron-deficient phenyl group, side products **4h**−**4j** were isolated in ca. 10% yield along with the major products **3h**−**3j** (Scheme 4). These observations fit well with the proposed reaction mechanism shown in Scheme 3. Indeed, the formation of side products **4** might arise from an alternative pathway

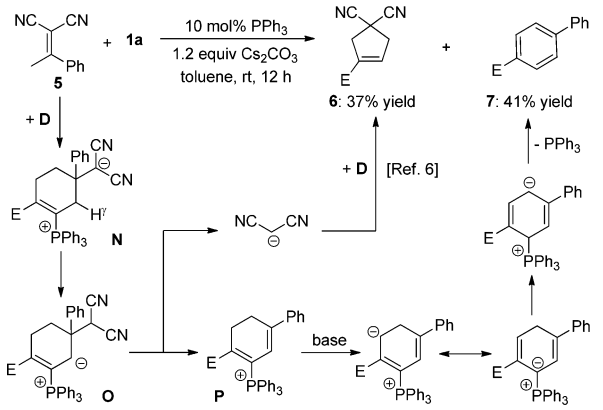
Scheme 4. Reactions of 1a with Substrates 2h−2j



starting from intermediate **J** which has two different activated H atoms, β'H and γH (Scheme 4). For most cases of substrates **2**, the impediment to γH abstraction might be due to the steric congestion imposed by the neighboring quaternary carbon center and phosphonium. However, in the cases of **2h**−**2j**, a small percentage of the corresponding γH atom was abstracted along with the major β'H abstraction, enabling the formation of intermediates **K2** and **L2**. Then, following a similar reaction pathway to that of phosphine-catalyzed umpolung γ-addition,[15] the side product **4** is formed instead (Scheme 4).

In line with the observation of side products **4**, the reaction of **1a** and **5** afforded products **6** and **7** in 37% and 41% yields, respectively (Scheme 5). We surmised that, for the related

Scheme 5. Reaction of 1a and 5



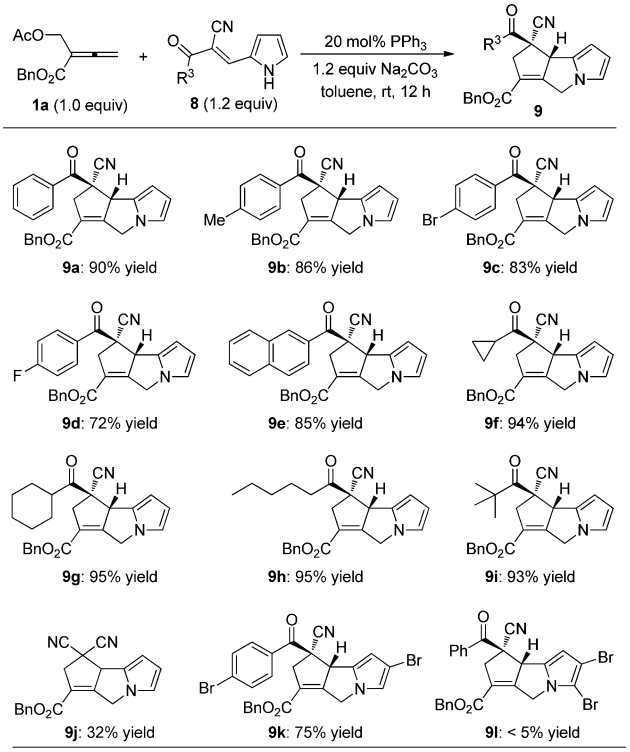
intermediate **N**, a γH would be selectively abstracted to afford intermediate **O**. Then, a 1,2-elimination process seemed to occur,[16] giving dicyanomethanide and intermediate **P**. The former underwent [4 + 1] cycloaddition with **D** to afford product **6**.[6] Although the exact mechanism cannot be entirely concluded at this stage, a reasonable route to the benzannulation product **7** via intermediate **P** was illustrated in Scheme 5.

PPh_3-Catalyzed γ-Addition/[3 + 2] Cycloaddition Domino Reaction. The success of the β'-addition/[4 + 4] cycloaddition domino reaction between **1a** and **2** clearly pointed out that the β'C position of intermediate **D** was liable to be attacked by a *C*-nucleophile. On the other hand, the γC is a potential reactive β-position of the vinylphosphonium moiety. Vinylphosphonium salts are important organophosphorus compounds and one of the most attractive transformations is aza-Michael addition.[17] Thus, to access the anticipated γ-addition/cycloaddition domino reaction of **1a**, several amphiphilic compounds bearing both *N*-nucleophiles and activated alkenes were examined.[11] Finally, we found that 2-benzoyl-3-(2-pyrrole)-acrylonitrile **8a** was a suitable reaction partner for **1a** with the help of 10 mol % PPh_3 and 1.2 equiv Cs_2CO_3, giving tetrahydrocyclopenta[a]pyrrolizine product **9a** in 47% yield. Further optimization of reaction conditions disclosed that the combination of 20 mol % PPh_3 and 1.2 equiv Na_2CO_3 ensured product **9a** being obtained in 90% yield and as one single isomer, thus furnishing γ-addition/[3 + 2] cycloaddition domino reaction with excellent diastereoselectivity.

Under the optimal reaction conditions, the substrate scope of the γ-addition/[3 + 2] cycloaddition domino reaction was further explored, and the results are summarized in Scheme 6.

DOI: 10.1021/jacs.5b03273
J. Am. Chem. Soc. 2015, 137, 6400−6406

Scheme 6. Substrate Scope of the γ-Addition/[3 + 2] Cycloaddition Domino Reaction[a]



[a]Reaction conditions: to the solution of **8** (0.24 mmol), PPh_3 (0.04 mmol), and Na_2CO_3 (0.24 mmol) in PhMe (2 mL), was slowly added a solution of **1a** (0.2 mmol) in PhMe (2 mL) over 30 min. Isolated yields were presented.

A range of substrates **8** with an aryl ketone moiety, including electron-neutral, electron-donating, as well as electron-withdrawing arenes, reacted well with allenoate **1a** to give products **9a**–**9e** in high yields. We were also delighted to find that substrates **8f**–**8i** with an aliphatic ketone moiety exhibited better reaction performance, affording the corresponding products **9f**–**9i** in almost quantitative yields. Moreover, the reaction could be applicable to substrate **8j**, which was derived from the condensation of 2-pyrrolaldehyde and malononitrile, although product **9j** was obtained in a lower yield (32%) due to some decomposition of **8j** under the conditions. 3-Bromopyrrole substrate **8k** gave product **9k** in 75% yield. However, no reaction was observed for 2,3-dibromo-pyrrole substrate **8l**, likely due to the steric hindrance. It should be mentioned that all of these products **9a**–**9k** were isolated as a single isomer. The relative stereochemistry of **9h** was determined by X-ray crystallography (Figure 2).[13] The stereochemistry of other products **9** was assigned by analogy with **9h**.

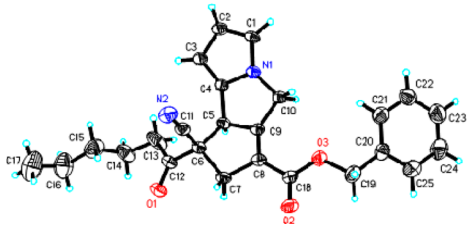
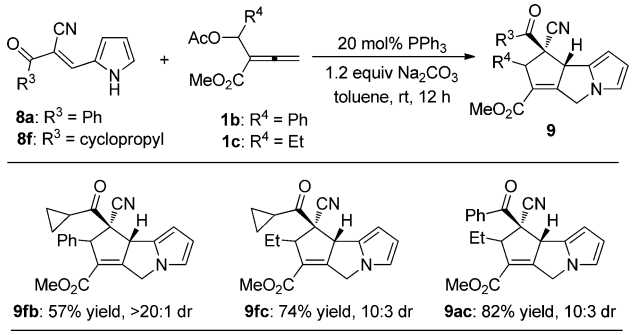


Figure 2. X-ray Structure of **9h**.

In sharp contrast to its inert reaction with substrate **2a**, β′-phenyl allenoate **1b** reacted smoothly with **8f** to afford product **9fb** in 57% yield (Scheme 7). Again, only one isomer of **9fb** was

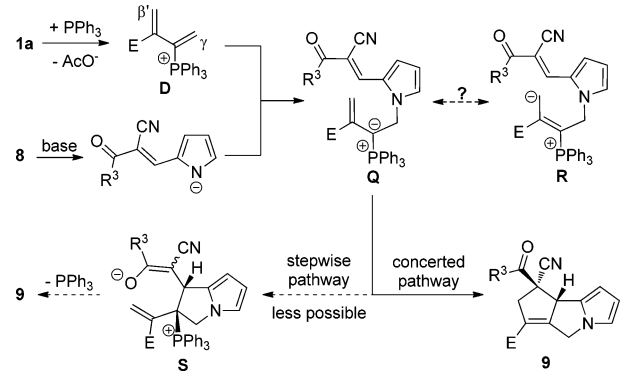
Scheme 7. Reactions of Allenoates 1b and 1c



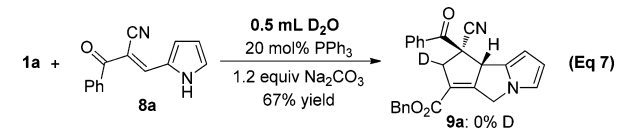
isolated, demonstrating the excellent diastereoselectivity of this reaction. However, relatively lower diastereoselectivity (10:3) was observed for the reaction of β′-ethyl allenoate **1c** with **8f**. These results clearly implied that the stereochemistry might be mainly determined by the β′C substituent of allenoate and be fairly insensitive to the steric factor of the ketone moiety of **8**. Indeed, the reaction of **1c** and **8a** gave **9ac** with the same diastereoselectivity as that of **9fc** (Scheme 7).

A plausible mechanism of the γ-addition/[3 + 2] cycloaddition domino reaction was illustrated in Scheme 8. With the

Scheme 8. Plausible Mechanism of the Reaction of 1a and 8



assistance of Na_2CO_3, substrate **8** undergoes aza-Michael addition to γC of intermediate **D**, resulting in the formation of **Q**. Surprisingly, no deuterium incorporation into product **9a** was observed when additional D_2O (0.5 mL) was introduced into the reaction of **1a** and **8a** under the otherwise identical conditions (eq 7). This result implied that intermediate **Q**



might not coexist with its resonance structure **R**.[6] This might be attributed to the stable ylide characteristic of intermediate **Q**. Another reason might stem from the concerted intramolecular [3 + 2] cycloaddition between dipole moiety and highly activated alkene in intermediate **Q**, affording product **9** directly. The stepwise pathway via intermediate **S** was proposed to be an

DOI: 10.1021/jacs.5b03273
J. Am. Chem. Soc. 2015, 137, 6400–6406

alternative route to product **9**. However, the observed excellent diastereoselectivity of the reaction indicated that the concerted pathway would be more possible (Scheme 8).[18]

As shown in Figure 3, the cases of allenoates **1b** and **1c** would bring about an additional stereochemical issue related to

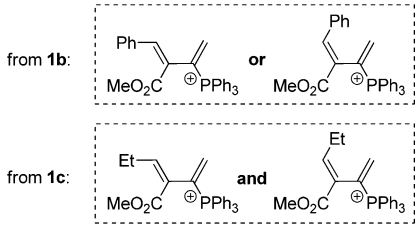


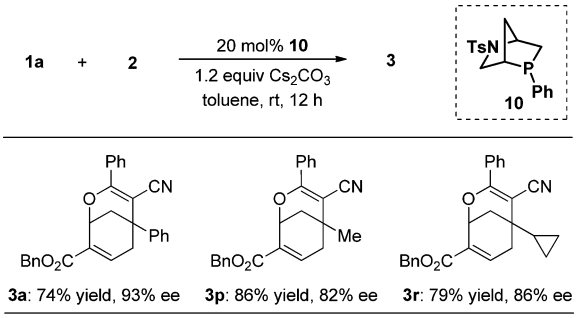
Figure 3. Corresponding intermediates **D** derived from **1b** and **1c**.

the alkene configuration in the corresponding intermediates **D**.[9,19] This issue might be an important element to account for the observed stereochemical outcome in products **9fb**, **9fc** and **9ac**.

The Development of Asymmetric Variants. The 2-oxabicyclo[3.3.1]nonane and cyclopenta[a]pyrrolizine are two classes of ubiquitous frameworks in natural products and biologically active compounds.[20] Thus, the development of an efficient asymmetric catalysis for their enantioselective synthesis would be very attractive.

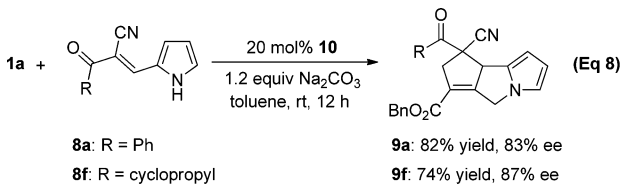
In a preliminary attempt, the asymmetric reaction of **1a** and **2a** was evaluated with several chiral phosphine catalysts. Fortunately, commercially available Kwon's phosphine[21] **10** was found to work well, enabling the isolation of product **3a** in 74% yield and with 93% ee (Scheme 9). Moreover, the reaction

Scheme 9. Kwon's Phosphine-Catalyzed Asymmetric Reaction of 1a and 2



of **1a** and **2p** afforded **3p** in 86% yield and with 82% ee. The smaller methyl substituent might impose negative effect on the asymmetric induction. Indeed, substrate **2r** with a larger cyclopropyl substituent afforded product **3r** with slightly higher enantioselectivity (86% ee).

We also examined the feasibility of phosphine **10** as catalyst for the asymmetric γ-addition/[3 + 2] cycloaddition domino reaction. It was found that, using 20 mol % **10** as the catalyst under the otherwise identical conditions, products **9a** and **9f** were obtained with 83% ee and 87% ee, respectively (eq 8).



CONCLUSIONS

In summary, we have developed two new classes of the phosphine-catalyzed addition/cycloaddition domino reactions of allenoates **1**, which strongly relied on the electrophilic intermediate **D**. With the help of a base, 2-acyl-3-methyl-acrylonitriles **2** well matched the reactivity of **D** to achieve the β'-addition/[4 + 4] cycloaddition domino sequence, which provided a facile access to 2-oxabicyclo[3.3.1]nonane derivatives **3** under mild reaction conditions. In this sequence, allenoate **1** exhibits both electrophilic reactivity at the β'C position and 1,4-dipole chemical behavior of the β'C and γC. However, when 2-acyl-3-(2-pyrrole)-acrylonitriles **8** were instead employed as the reaction partner for allenoate **1**, the γ-addition/[3 + 2] cycloaddition domino reaction smoothly occurred, giving cyclopenta[a]pyrrolizine products **9** with excellent diastereoselectivity, wherein allenoate **1** exhibits high electrophilic reactivity at the γC and 1,3-dipole chemical behavior of the β'C and βC. These results are believed to represent a new reaction mode of the phosphine catalysis. Furthermore, the asymmetric variants of these two reactions have also been realized with up to 93% ee using Kwon's phosphine **10** as catalyst. Further investigations on the asymmetric catalysis and synthetic applications are ongoing in our laboratories and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization of new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03273.

AUTHOR INFORMATION

Corresponding Author

*tongxf@ecust.edu.cn

Author Contributions

⊥Y.G. and P.H. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work is supported by NSFC (Nos. 21272066 and 21472042), the Fundamental Research Funds for the Central Universities, and the Program for New Century Excellent Talents in University (NCET-12-0851).

REFERENCES

(1) (a) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461. (b) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031.

(2) For selected reviews, see: (a) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (b) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035. (c) Lu, X.; Du, Y.; Lu, C. *Pure Appl. Chem.* **2005**, *77*, 1985. (d) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102. (e) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140. (f) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (g) Fan, Y. C.; Kwon, O. *Chem. Commun.* **2013**, *49*, 11588. (h) Xiao, Y.; Sun, Z.; Guo, H.; Kwon, O. *Beilstein J. Org. Chem.* **2014**, *10*, 2089. (i) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005. (j) Wang, S.-X.; Han, X. Y.; Zhong, F. R.; Wang, Y. Q.; Lu, Y. *Synlett* **2011**, 2766. (k) Zhao, Q.-Y.; Lian, Z.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, *48*, 1724. (l) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927.

DOI: 10.1021/jacs.5b03273
J. Am. Chem. Soc. 2015, 137, 6400−6406

(3) (a) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716. (b) Tran, Y. S.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12632. (c) Guo, H.; Xu, Q.; Kwon, O. *J. Am. Chem. Soc.* **2009**, *131*, 6318. (d) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234. (e) Xiao, H.; Chai, Z.; Wang, H.-F.; Wang, X.-W.; Cao, D.-D.; Liu, W.; Lu, Y.-P.; Yang, Y.-Q.; Zhao, G. *Chem.—Eur. J.* **2011**, *17*, 10562. (f) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Chem. Sci.* **2012**, *3*, 1231. (g) Xiao, H.; Chai, Z.; Cao, D.; Wang, H.; Chen, J.; Zhao, G. *Org. Biomol. Chem.* **2012**, *10*, 3195.

(4) Yao, W.; Dou, X.; Lu, Y. *J. Am. Chem. Soc.* **2015**, *137*, 54.

(5) (a) Meng, X.; Huang, Y.; Zhao, H.; Xie, P.; Ma, J.; Chen, R. *Org. Lett.* **2009**, *11*, 991. (b) Zheng, J.; Huang, Y.; Li, Z. *Org. Lett.* **2013**, *15*, 5064. (c) Li, E.; Huang, Y.; Liang, L.; Xie, P. *Org. Lett.* **2013**, *15*, 3138. (d) Li, E.; Jia, P.; Liang, L.; Huang, Y. *ACS Catal.* **2014**, *4*, 600. (e) Gicquel, M.; Gomez, C.; Retailleau, P.; Voituriez, A.; Marinetti, A. *Org. Lett.* **2013**, *15*, 4002.

(6) Zhang, Q.; Yang, L.; Tong, X. *J. Am. Chem. Soc.* **2010**, *132*, 2550.

(7) A related buta-1,3-diene intermediate has been detected by the ESI−MS analysis: Kramer, S.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 3803.

(8) Intermediate **E** arises from the attack of the nucleophile at β'C of **D**. Actually, the attack of the nucleophile at γC of **D** is also a workable pathway to this [4 + 1] cycloaddition (not shown in Scheme 1). For the detailed discussion, see ref 6.

(9) (a) Han, X.; Yao, W.; Wang, T.; Tan, Y. R.; Yan, Z.; Kwiatkowski, J.; Lu, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 5643. (b) Ziegler, D. T.; Riesgo, L.; Ikeda, T.; Fujiwara, Y.; Fu, G. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 13183.

(10) (a) Wang, J.-C.; Ng, S.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 3682. (b) Henry, C. E.; Kwon, O. *Org. Lett.* **2007**, *9*, 3069. (c) Ye, L.-W.; Sun, X.-L.; Wang, Q.-G.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5951. (d) Wang, Q.-G.; Zhu, S.-F.; Ye, L.-W.; Zhou, C.-Y.; Sun, X.-L.; Tang, Y.; Zhou, Q.-L. *Adv. Synth. Catal.* **2010**, *352*, 1914.

(11) For the details, see the SI.

(12) In this work, substrates **2** were used with (*E*)- and (*Z*)-form mixtures while only (*E*)-**8** were used.

(13) The crystallographic coordinates of **3o** and **9h** have been deposited with the deposition numbers CCDC 1008712 and CCDC 1054938, respectively. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, at deposit@ccdc.cam.ac.uk.

(14) (a) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470. (b) Mercier, E.; Fonovic, B.; Henry, C.; Kwon, O.; Dudding, T. *Tetrahedron Lett.* **2007**, *48*, 3617.

(15) (a) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 10819. (b) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 3167. (c) Trost, B. M.; Dake, G. R. *J. Org. Chem.* **1997**, *62*, 5670. (d) Smith, S. W.; Fu, G. C. *J. Am. Chem. Soc.* **2009**, *131*, 14231. (e) Sun, J.; Fu, G. C. *J. Am. Chem. Soc.* **2010**, *132*, 4568. (f) Lundgren, R. J.; Wilsily, A.; Marion, N.; Ma, C.; Chung, Y. K.; Fu, G. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 2525.

(16) For representative examples, see: (a) Bernasconi, C. F.; Kanavarioti, A.; Killion, R. B., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 3612. (b) Yang, G.; Luo, C.; Mu, X.; Wang, T.; Liu, X.-Y. *Chem. Commun.* **2012**, *48*, 5880.

(17) For representative examples, see: (a) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (b) Schweizer, E. E.; Light, K. K. *J. Am. Chem. Soc.* **1964**, *86*, 2963. (c) Schweizer, E. E.; Smucker, L. D. *J. Org. Chem.* **1966**, *31*, 3146. (d) Kumarn, S.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2006**, 3211. (d) Kumarn, S.; Shaw, D. M.; Longbottom, D. A.; Ley, S. V. *Org. Lett.* **2005**, *7*, 4189.

(18) (a) Wang, J.-C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855. (b) Lee, S. Y.; Fujiwara, Y.; Nishiguchi, A.; Kalek, M.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 4587.

(19) Li, C.; Zhang, Q.; Tong, X. *Chem. Commun.* **2010**, *46*, 7828.

(20) For 2-oxabicyclo[3.3.1]nonane frameworks, see: (a) Yokoyama, R.; Huang, J.-M.; Hosoda, A.; Kino, K.; Yang, C.-S.; Fukuyama, Y. *J. Nat. Prod.* **2003**, *66*, 799. (b) Zhu, Q.; Tang, C.-P.; Ke, C.-Q.; Wang, W.; Zhang, H.-Y.; Ye, Y. *J. Nat. Prod.* **2009**, *72*, 238. For cyclopenta[a]pyrrolizine frameworks, see: (c) Hartmann, T.; Witte, L. In *Alkaloids: Chemical and Biological Perspectives*, Vol. *9*; Pelletier, S. W., Ed.; Elsevier Science, Ltd.: Oxford, 1995; Chapter 4. (d) Liddel, J. R. *Nat. Prod. Rep.* **2002**, *19*, 773. (e) Schröder, F.; Sinnwell, V.; Baumann, H.; Kaib, K.; Francke, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 77.

(21) (a) Henry, C. E.; Xu, Q.; Fan, Y. C.; Martin, T. J.; Belding, L.; Dudding, T.; Kwon, O. *J. Am. Chem. Soc.* **2014**, *136*, 11890. (b) Andrews, I. P.; Kwon, O. *Chem. Sci.* **2012**, *3*, 2510.

DOI: 10.1021/jacs.5b03273
J. Am. Chem. Soc. 2015, 137, 6400−6406