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Phosphine-Catalyzed Annulations of 4,4-Dicyano-2-Methylenebut-3-enoates with Maleimides and Maleic Anhydride[**]

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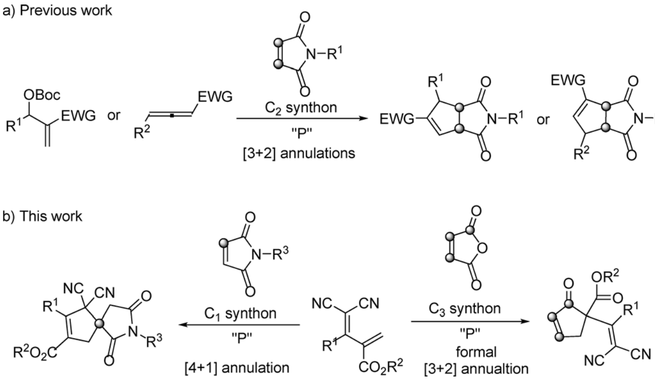
Abstract: *A novel phosphine-catalyzed [4+1] annulation of maleimides with 4,4-dicyano-2-methylenebut-3-enoates has been developed to afford spirocyclic products, and the maleimides serves as C_1 synthons. Moreover, a phosphine-catalyzed formal [3+2] annulation between 4,4-dicyano-2-methylenebut-3-enoates and maleic anhydride has been also achieved, and maleic anhydride behaved as a C_3 synthon in the reaction, thus efficiently affording the functionalized cyclopentenones. A stable phosphinium-containing zwitterionic compound is the key reactive intermediate in both annulations and was successfully isolated. Plausible mechanisms have been proposed on the basis of control experiments and deuterium-labeling experiments.*

Functionalized five-membered carbocycles as structural motifs have drawn tremendous interest in the area of synthetic organic chemistry and medicinal chemistry since they are the ubiquitous substructures in a variety of natural products and biologically active molecules.[1] Recently, remarkable progress has been made in the development of nucleophilic phosphine organocatalysis,[2] and now phosphine-mediated/catalyzed reactions have emerged as a powerful tool for the synthesis of a wide variety of novel compounds.[3] Among them, phosphine-catalyzed [3+2] annulations of activated allenes or Morita-Baylis–Hillman (MBH) carbonates have become powerful approaches to synthesize functionalized carbo- and heterocycles.[4] Apart from phosphine-catalyzed [3+2] annulations, phosphine-catalyzed [4+1] annulations[5] are also an efficient methodology to construct functionalized five-membered carbo- and heterocycles.

Maleimides as electron-deficient olefins have been widely used in annulations to give functionalized carbocyclic compounds.[6] More recently, several phosphine-catalyzed [3+2] annulations of maleimides have been developed by Lu, Shi, and co-workers to construct the corresponding functionalized cyclopentene derivatives (Scheme 1 a).[7] In all these reactions, maleimides were used as a C_2 synthon in annulations. However, to the best of our knowledge, there is no report that maleimides are used as a C_1 synthon to participate in phosphine-catalyzed annulations. Herein we report a novel phosphine-catalyzed [4+1] annulation of maleimides with 4,4-dicyano-2-methylenebut-3-enoates, a reaction wherein maleimides were used as a C_1 synthon, for the first time, in phosphine-catalyzed annulations (Scheme 1 b). Moreover, among the phosphine-catalyzed annulations, electron-deficient olefins are important reagents and often used as C_2 synthons.[4] Maleic anhydride as an electron-deficient olefin is also a useful reagent.[8] However, phosphine-mediated/catalyzed reactions of maleic anhydride are very scarce.[9] As far as we know, there is no report about phosphine-catalyzed annulations of maleic anhydride. Herein, we also disclose a novel phosphine-catalyzed formal [3+2] annulation of maleic anhydride with 4,4-dicyano-2-methylenebut-3-enoates to construct functionalized cyclopentenones. The maleic anhydride behaves as a C_3 synthon in the annulation reaction (Scheme 1 b).



Scheme 1. Previous work and this work. Boc = *tert*-butoxycarbonyl, EWG = electron-withdrawing group.

Based on our previous work on tertiary phosphine-catalyzed annulations of 4,4-dicyano-2-methylenebut-3-enoates with MBH carbonates and allenic esters,[5f,10] we initiated the study by investigating the reaction between 4,4-dicyano-2-methylene-3-(*p*-tolyl)but-3-enoate (**1a**) and *N*-phenylmaleimide (**2a**) using tertiary phosphines as the catalysts (for the optimization of the reaction conditions, see Table S1 in the Supporting Information). The reaction outcomes revealed that using 10 mol% PPh_3 as the catalyst and toluene as the solvent at 60 °C for 12 hours could produce

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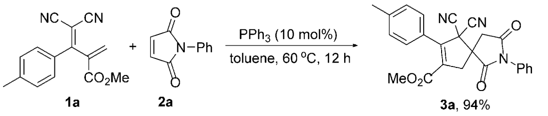
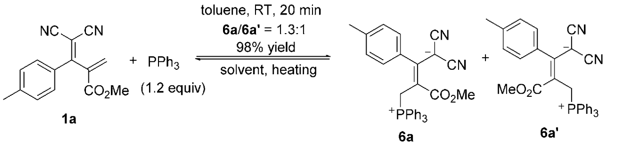
Supporting information for this article (spectroscopic data of the compounds shown in Tables 1 and 2 and Schemes 2 and 3 and detailed descriptions of experimental procedures) is available on the WWW under http://dx.doi.org/10.1002/anie.201406100.



Scheme 2. Optimization of the reaction conditions for [4+1] annulation.

3a in 94 % yield, and severed as the best conditions in this reaction (Scheme 2).

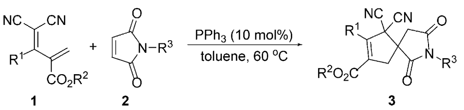
In 2007, Kwon and co-workers reported the first isolation and X-ray crystallographic structure of stable tetravalent phosphonium enolate zwitterions, and might explain the instability and high reactivity of phosphonium enolate zwitterions in MBH-type reactions.[11] Fortunately, in the process of optimizing the reaction conditions, we also found the formation of other stable tetravalent phosphinium-containing zwitterionic compounds (**6a** and **6a′**) through a Michael addition of PPh$_3$ to electron-deficient **1a** (Scheme 3). The presence of a carbomethoxy group within the zwitterions contributes to the delocalization of the negative charge to some degree, and it may therefore be a possible means of stabilization of the dipolar structure to prevent the isomerization of the phosphonium zwitterions into pentavalent phosphorane.[11–12] The relative configuration of **6a** has been assigned as *Z* by X-ray diffraction.[16] The ORTEP drawing and the CIF data are summarized in the Supporting Information. Simultaneously, the dissociation of the zwitterionic compounds **6a** and **6a′** proceeds upon heating to give **1a** and PPh$_3$ (see Figures S1–S4).



Scheme 3. Synthesis of the phosphinium-containing zwitterions **6a** and **6a′**.

Having determined the optimal reaction conditions, we subsequently turned our attention to the substrate scope and limitations of this [4+1] annulation of maleimides with 4,4-dicyano-2-methylenebut-3-enoates, and the results are summarized in Table 1. All reactions proceeded smoothly to give the corresponding products **3** in good to excellent yields under the optimized reaction conditions (Table 1). We initially utilized **2a** as a substrate to react with a variety of substrates **1** and found that regardless of whether R^1 is an electron-rich or electron-deficient aromatic ring, the reactions proceeded smoothly to give the corresponding annulation products **3b–j** in 81–95 % yield (entries 1–9). When R^1 is a heteroaromatic group (R^1 = furan-2-yl) or a more sterically bulky 2-naphthalene moiety (R^1 = naphth-2-yl) or multisubstituted aromatic group, the reactions also proceeded efficiently to afford the corresponding products **3k–n** in 87–95 yields (entries 10–13). Changing the ester groups in 4,4-dicyano-2-methylenebut-3-enoates resulted in reactions which also worked well, even if R^2 is a more sterically bulky *tert*-butyl or diphenylmethyl group, thus providing the corresponding cycloadducts **3o–q** in good to excellent yields (86–93 %; entries 14–16). Next, the investigation of maleimides was continued by using **1a** as the substrate (entries 17–22). For the maleimides **2b–e**, the reactions proceeded smoothly to give the corresponding products in good yields (82–87 %) by increasing the amount of PPh$_3$ to 20 mol %, the temperature to 80 °C, and the reaction time to 72 hours (entries 17–20). The change in reaction parameters was perhaps required because of the electronic effect. Furthermore, the reaction also tolerated aliphatic moieties in maleimides. Weather R^3 is a benzyl or methyl group, the reactions also proceeded efficiently, thus affording the corresponding products **3v** and **3w** in 73 and 85 % yield, respectively (entries 21 and 22). The structure of **3h** has been assigned by X-ray diffraction.[16] The ORTEP drawing and the CIF data are summarized in the Supporting Information.

Table 1: The substrate scope of [4+1] annulation.[a]

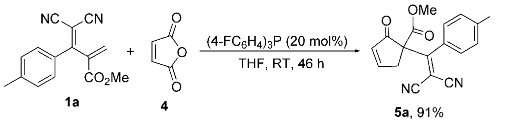


Entry	1 (R^1, R^2)	2 (R^3)	*T* [°C]	*t* [h]	Yield[b] [%]
1	**1b** (*p*-MeOC$_6$H$_4$, Me)	**2a** (Ph)	60	9	**3b**, 93
2	**1c** (*o*-MeOC$_6$H$_4$, Me)	**2a** (Ph)	60	10	**3c**, 91
3	**1d** (*m*-MeOC$_6$H$_4$, Me)	**2a** (Ph)	60	10	**3d**, 95
4	**1e** (*p*-FC$_6$H$_4$, Me)	**2a** (Ph)	60	11	**3e**, 88
5	**1f** (*p*-ClC$_6$H$_4$, Me)	**2a** (Ph)	60	12	**3f**, 90
6	**1g** (*m*-BrC$_6$H$_4$, Me)	**2a** (Ph)	60	12	**3g**, 86
7	**1h** (*p*-BrC$_6$H$_4$, Me)	**2a** (Ph)	60	12	**3h**, 86
8	**1i** (Ph, Me)	**2a** (Ph)	60	12	**3i**, 92
9	**1j** (*p*-CF$_3$C$_6$H$_4$, Me)	**2a** (Ph)	60	12	**3j**, 81
10	**1k** (furan-2-yl, Me)	**2a** (Ph)	60	12	**3k**, 95
11	**1l** (naphth-2-yl, Me)	**2a** (Ph)	60	12	**3l**, 93
12	**1m** (3,4,5-(MeO)$_3$C$_6$H$_2$, Me)	**2a** (Ph)	60	11	**3m**, 94
13	**1n** (3-Br,4-FC$_6$H$_3$, Me)	**2a** (Ph)	60	12	**3n**, 87
14	**1o** (*p*-MeC$_6$H$_4$, Et)	**2a** (Ph)	60	12	**3o**, 93
15	**1p** (*p*-MeC$_6$H$_4$, *t*Bu)	**2a** (Ph)	60	12	**3p**, 86
16	**1q** (*p*-MeC$_6$H$_4$, diphenylmethyl)	**2a** (Ph)	60	13	**3q**, 92
17[c]	**1a** (*p*-MeC$_6$H$_4$, Me)	**2b** (*p*-FC$_6$H$_4$)	80	72	**3r**, 87
18[c]	**1a** (*p*-MeC$_6$H$_4$, Me)	**2c** (*p*-ClC$_6$H$_4$)	80	72	**3s**, 86
19[c]	**1a** (*p*-MeC$_6$H$_4$, Me)	**2d** (*p*-MeC$_6$H$_4$)	80	72	**3t**, 82
20[c]	**1a** (*p*-MeC$_6$H$_4$, Me)	**2e** (*p*-*i*PrC$_6$H$_4$)	80	72	**3u**, 86
21[c]	**1a** (*p*-MeC$_6$H$_4$, Me)	**2f** (Bn)	80	120	**3v**, 73
22[c]	**1a** (*p*-MeC$_6$H$_4$, Me)	**2g** (Me)	80	120	**3w**, 85

[a] Reactions were performed with **1** (0.10 mmol) and **2** (0.15 mmol) in the presence of PPh$_3$ (10 mol %) and toluene (1 mL). [b] Yield of isolated product. [c] 20 mol % of PPh$_3$ was used.

Based on our previous work on chiral phosphines as nucleophilic catalysts in asymmetric phosphine catalysis,[13–14] we next attempted to realize the asymmetric variant of this novel [4+1] cycloaddition between **1a** and **2a**. However, the desirable chiral product **3a** was obtained in 82 % yield along with 11 % *ee* (see Table S2).

Considering the previous work on maleic anhydride and the fact that the application of maleic anhydride in phosphine-mediated/catalyzed reactions is very scarce,[8] we subsequently investigated the reaction between **1a** and maleic anhydride (**4**) catalyzed by tertiary phosphines (see Table S3). The reaction outcomes revealed that using $(4\text{-}FC_6H_4)_3P$ (20 mol %) as the catalyst and carrying out the reaction in THF at room temperature for 2 days gave **5a** in 91 % yield, and are the best reaction conditions for this reaction (Scheme 4).

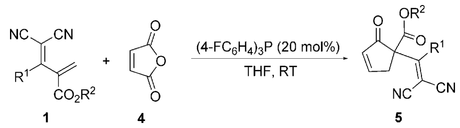


Scheme 4. Optimization of the reaction conditions for the formal [3+2] annulation. THF = tetrahydrofuran.

With the optimal reaction conditions established, the substrate scope and limitations of this phosphine-catalyzed formal [3+2] annulation of maleic anhydride with 4,4-dicyano-2-methylenebut-3-enoates was then explored, and the results are summarized in Table 2. Using **4** as a substrate, we found that regardless of whether R^1 is an electron-rich or electron-deficient aromatic ring, the reactions proceeded smoothly to give the corresponding annulation products **5b–j** in 39–90 % yields (entries 1–9). Only in the case of methyl 4,4-dicyano-2-methylene-3-(4-(trifluoromethyl)phenyl)but-3-enoate (**1j**), was the corresponding adduct **5j** obtained in relatively lower yield (39 %), perhaps because of the influence of the electronic effect (entry 9). When R^1 is a heteroaromatic group (R^1 = furan-2-yl) of lower reactivity was used, the use of PPh_3 with higher nucleophilicity was required, thus giving the corresponding product **5k** in 28 % yield (entry 10). When R^1 is a more sterically bulky 2-naphthalene moiety or multisubstituted aromatic group, the reactions also proceeded efficiently to afford the corresponding products **5l–n** and **5s–u** in 53–91 % yields (entries 11–13 and 18–20). Next, the investigation of the ester groups in 4,4-dicyano-2-methylene-but-3-enoates was continued (entries 14–17). When R^2 is an ethyl group, the reaction proceeded smoothly under the optimal reaction conditions to give the corresponding product **5o** in good yield (entry 14). When R^2 is a more sterically bulky such as *tert*-butyl, diphenylmethyl, or 9-anthrylmethyl groups, the reactions also worked very well using PPh_3 as the catalyst, thus giving the corresponding products **5p–r** in moderate to good yields (entries 15–17). The structure of **5p** has been determined by X-ray diffraction.[16] The ORTEP drawing and the CIF data are summarized in the Supporting Information.

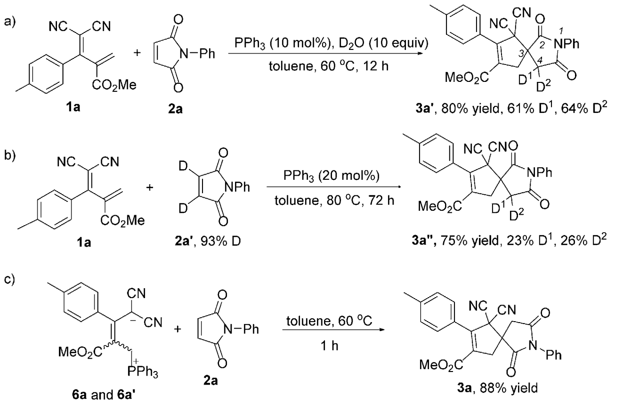
To understand the [4+1] cycloaddition reaction mechanism of maleimides with 4,4-dicyano-2-methylenebut-3-enoates, the following experiments were executed. First, two deuterium-labeling experiments were conducted. The reaction of **1a** with **2a** was carried out in the presence of D_2O (10 equiv) under the standard reaction conditions, and the reaction proceeded smoothly to give the corresponding partially deuterated annulation product **3a′** in 80 % yield, and deuterium incorporation occurred at C4 almost identically (Scheme 5a). Under the standard reaction conditions, using the 93 % deuterated *N*-phenylmaleimide **2a′** as substrate, produced the deuterated product **3a″** in 75 % yield, in which the extent of deuteration at C4 decreased, maybe because of the H_2O in the toluene (Scheme 5b). Both results indicated that the carbanion at the 4-position might be generated in the reaction. The relatively stable zwitterions **6a** and **6a′** were then treated with **2a** in toluene at 60 °C for 1 hour, thus affording the cycloaddition product **3a** in 88 % yield (Scheme 5c). This result revealed that the zwitterions **6a** and **6a′** were the effective reaction intermediates for this [4+1] reaction.

Table 2: The substrate scope of the formal [3+2] annulation.[a]



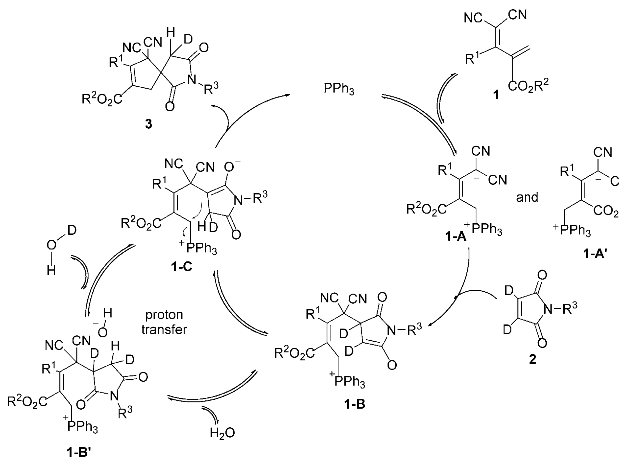
Entry	**1** (R^1, R^2)	*t* [h]	Yield[b] [%]
1	**1b** (*p*-$MeOC_6H_4$, Me)	36	**5b**, 74
2	**1c** (*o*-$MeOC_6H_4$, Me)	28	**5c**, 90
3	**1d** (*m*-$MeOC_6H_4$, Me)	28	**5d**, 87
4	**1e** (*p*-FC_6H_4, Me)	25	**5e**, 74
5	**1f** (*p*-ClC_6H_4, Me)	26	**5f**, 64
6	**1g** (*m*-BrC_6H_4, Me)	36	**5g**, 65
7	**1h** (*p*-BrC_6H_4, Me)	36	**5h**, 73
8[c]	**1i** (Ph, Me)	28	**5i**, 58
9	**1j** (*p*-$CF_3C_6H_4$, Me)	36	**5j**, 39
10	**1k** (furan-2-yl, Me)	36	**5k**, 28
11	**1l** (naphth-2-yl, Me)	36	**5l**, 79
12	**1m** (3,4,5-$(MeO)_3C_6H_2$, Me)	36	**5m**, 84
13	**1n** (3-Br,4-FC_6H_3, Me)	36	**5n**, 64
14	**1o** (*p*-MeC_6H_4, Et)	42	**5o**, 81
15[d]	**1p** (*p*-MeC_6H_4, *t*Bu)	48	**5p**, 72
16[d]	**1q** (*p*-MeC_6H_4, diphenylmethyl)	48	**5q**, 46
17[d]	**1r** (*p*-MeC_6H_4, 9-anthrylmethyl)	48	**5r**, 58
18	**1s** (3,4-$(MeO)_2C_6H_3$, Me)	28	**5s**, 91
19	**1t** (3,4-$Cl_2C_6H_3$, Me)	36	**5t**, 53
20	**1u** (3,5-$Cl_2C_6H_3$, Me)	28	**5u**, 61

[a] Reactions were performed with **1** (0.10 mmol) and **4** (0.20 mmol) in the presence of $(4\text{-}FC_6H_4)_3P$ (20 mol %) and THF (1 mL) at room temperature. [b] Yield of isolated product. [c] CH_2Cl_2 was used as the solvent. [d] PPh_3 was used as the catalyst.



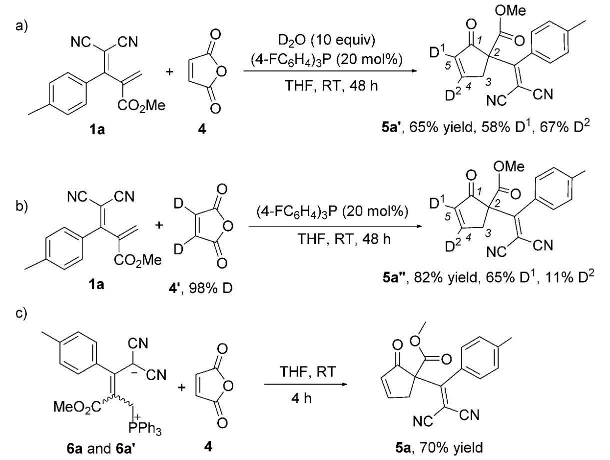
Scheme 5. Preliminary mechanistic investigation for [4+1] cycloaddition reaction of maleimide **2a**.

According to the above experimental results, a plausible reaction mechanism for phosphine-catalyzed [4+1] cycloaddition of maleimides with 4,4-dicyano-2-methylenebut-3-enoates has been outlined in Scheme 6. The reaction might be initiated with the in situ formation of the zwitterionic intermediates **1-A** and **1-A′** by the addition of tertiary phosphine to the terminal allylic carbon atom of **1**. Moreover, under the standard reaction conditions, **1-A** and **1-A′** can also decompose into **1** and PPh_3, as an equilibrium exists between them. Then nucleophilic attack of the key intermediate **1-A** on the maleimide **2** results in **1-B**, which is in equilibrium through a proton transfer with the intermediate **1-C**. Recently, Yu and co-workers reported that a trace amount of water could play a catalytic role in assisting the [1,*n*] proton transfer,[15] thus facilitating our understanding of the role of water in this annulation. Here, H_2O in the solvent could also act as a catalyst to assist the proton transfer between **1-B** and **1-C**. Then **1-C** produces the desired spirocyclic product **3** by an intramolecular S_N2 substitution and regenerates the tertiary phosphine catalyst.



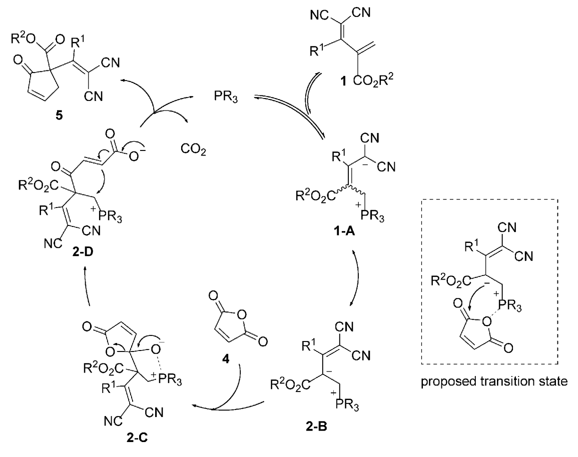
Scheme 6. Possible reaction mechanism for the formation of **3**.

Next, several experiments were deliberately conducted to probe some mechanistic insights into the formal [3+2] annulations of maleic anhydride with 4,4-dicyano-2-methylenebut-3-enoates. First, two deuterium-labeling experiments were conducted. Under the standard reaction conditions as listed in Table 2, adding D_2O (10 equiv) to the reaction of **1a** and **4** resulted in the partially deuterated product **5a′** in 65% yield and a 58% deuterium incorporation occurred at C5 along with 67% deuterium incorporation at the C4 (Scheme 7a). The deuterium incorporation resulted from the background reaction between phosphine and maleic anhydride (see Figures S5–S8). Under the standard reaction conditions, using the 98% deuterated maleic anhydride **4′** as a substrate produced the deuterated product **5a″** in 82% yield; the deuteration ratio of C4 and C5 decreased because of the H_2O in the THF (Scheme 7b). We also identified that no H–D exchange could take place upon treating **5** with D_2O under the standard reaction conditions. Then the relatively stable zwitterions **6a** and **6a′** were treated with **4** in THF at room temperature for 4 hours, thus giving the cycloaddition product **3a** in 70% yield (Scheme 7c).



Scheme 7. Preliminary mechanistic investigation for the formal [3+2] annulation of maleic anhydride **4**.

On the basis of above experimental results, we also proposed a plausible reaction mechanism for the phosphine-catalyzed formal [3+2] annulation of maleic anhydride with 4,4-dicyano-2-methylenebut-3-enoates (Scheme 8). The reaction might be initiated with the in situ formation of the key zwitterionic intermediate **1-A** by the addition of tertiary phosphine to the terminal allyl carbon atom of **1**, and results in another resonance structure (**2-B**) through electron delocalization. Under the standard reaction conditions, we speculate that there is an interaction between maleic anhydride and the tetravalent phosphonium ion in **2-B**, thus assisting the nucleophilic attack of **2-B** on the carbonyl carbon of maleic anhydride to afford **2-C**. The interaction between oxygen anion and phosphorus atom via a five-membered transition state in **2-C** might enhance the stabilization of **2-C**, and also facilitate this nucleophilic attack. Then **2-C** undergoes ring opening to give **2-D**. This intermediate produces **5** along with regeneration of tertiary phosphine through the dissociation of one molecule CO_2 (for evidence of the formation of CO_2, see Figure S9) and subsequent intramolecular S_N2 substitution.



Scheme 8. Possible reaction mechanism for the formation of **5**.

In conclusion, two novel phosphine-catalyzed [4+1] and formal [3+2] annulations of 4,4-dicyano-2-methylenebut-3-enoates with maleimides and maleic anhydride have been developed for the first time. Among them, maleimides and maleic anhydride acted as C_1 and C_3 synthons, respectively, to take part in the phosphine-catalyzed annulations, thus providing the corresponding five-membered spirocyclic compounds in good to excellent yields and functionalized cyclopentenones in moderate to excellent yields. The stable tetravalent-phosphinium-containing zwitterionic compounds are a key reactive intermediate in both annulations and were successfully isolated and characterized by X-ray diffraction. Plausible mechanisms have been also proposed on the basis of preliminary mechanistic investigations such as control experiments and deuterium-labeling experiments. Further efforts are in progress to develop the use of these reactions in the synthesis of biologically active molecular compounds.

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Keywords: anhydrides · cyclization · organocatalysis · phosphorus · zwitterions

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