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Phosphine-catalyzed domino reaction: a novel sequential [2+3] and [3+2] annulation reaction of γ-substituent allenoates to construct bicyclic[3, 3, 0]octene derivatives†

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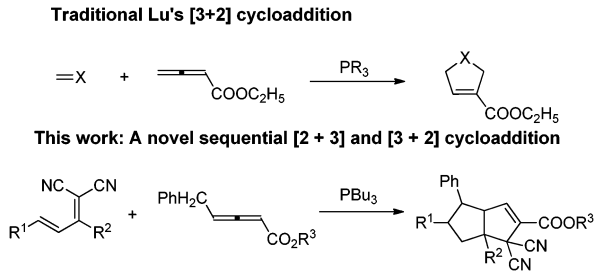
We have successfully developed a novel and efficient phosphine-catalyzed sequential [2+3] and [3+2] annulation reaction of γ-substituent allenoates to construct bicyclic[3, 3, 0]octene derivatives. The protocol uses readily available γ-substituent allenoates as the starting materials, inexpensive PBu_3 as the catalyst, and the corresponding products were obtained in good to excellent yields under mild conditions.

Bicyclic[3, 3, 0]octene skeletons are essential building blocks for the synthesis of natural products, pharmaceuticals and materials,[1] and developing efficient and general strategies to construct bicyclic skeletons is important for organic synthesis. Success in this area has mainly been achieved by using transition-metal-catalyzed intramolecular annulation reactions.[2] Recently, organocatalyst-catalyzed domino reactions have developed an effective strategy to construct cyclic compounds, while step economical construction of these interesting bicyclic compounds has continuously challenged the imagination of synthetic organic chemists.[3]

Owing to their comparatively strong and readily tunable nucleophilicity, nucleophilic phosphine catalysts have been shown to be a powerful tool to construct cyclic compounds in organic synthesis.[4] In particular, phosphine-catalyzed domino annulation reactions of allenoates have been extensively investigated. Lu *et al.* were the first to develop a phosphine-catalyzed [3+2] domino annulation reaction using 2,3-butadienoates.[5] Since then, enantioselective variants of these reactions have also been reported by the groups of Zhang, Lu and Fu.[6] Further studies showed that 2,3-butadienoates can also function as one- or two-carbon synthons, which undergo [1+4],[7] [2+3][8] and [2+2+2][9] annulation reactions. Based on these pioneering studies, Kwon *et al.* reported a novel [4+2] annulation reaction of α-enoates with imines to afford tetrahydropyridines.[10] Follow-up studies suggested that the α-alkyl allenoates with a variety of electrophilic coupling partners could act as two- or three-carbon synthons that undergo [2+1],[11] [3+2][12] and [3+3][13] cycloaddition reactions (Scheme 1).



Scheme 1 Phosphine-catalyzed cycloaddition reactions of allenoates.

Recently, with the explosive development of organophosphine-catalyzed domino reactions, γ-substituted allenoates have been used as substrates in many domino reactions. Typically, they have been used in phosphine-catalyzed [2+4] cycloaddition,[14] [3+2] cycloaddition,[15] [4+2] cycloaddition[16] and benzannulation reactions.[17] While, to the best of our knowledge, phosphine-catalyzed intermolecular annulation reactions to construct bi- or polycyclic compounds have been rarely reported.[18] We report herein novel phosphine-catalyzed, intermolecular, highly diastereoselective sequential [2+3] and [3+2] annulation reactions for the production of bicyclic[3, 3, 0]octene derivatives.

Experimentally, our initial studies were focused on the reaction of (*E*)-2-(1,3-diphenylallylidene)malononitrile **1a** and γ-substituent allenoates **2a** (Table 1). Preliminary screening of the catalysts was conducted in $CHCl_3$ at 60 °C using 50 mol% of PPh_3 (Table 1, entry 1), the desired product **3a** was only obtained in 56% yield because of the low conversion. Firstly, screening of the catalysts revealed that PBu_3 was the best choice (Table 1, entries 1–4). When PBu_3 (50 mol%) was used, the reaction proceeded smoothly to afford the desired product **3a** in 91% yield (Table 1, entry 4). It should be noted that the sequential [2+3] and [3+2] cycloaddition reaction is completely regioselective and highly diastereoselective (only one isomer

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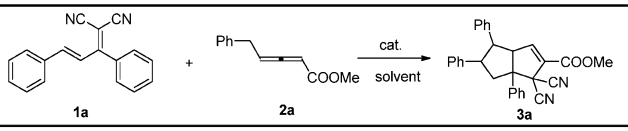
Table 1 Screening of the reaction conditions[a]



Entry	Cat. (%)	Solvent	Temp (°C)	T (h)	Yield[b] (%)
1	PPh_3 (50)	$CHCl_3$	60	24	56
2	$PEtPh_2$ (50)	$CHCl_3$	60	24	67
3[c]	Ar_3P (50)	$CHCl_3$	60	24	80
4	PBu_3 (50)	$CHCl_3$	60	2	91
5	PBu_3 (30)	$CHCl_3$	60	2	89
6	PBu_3 (20)	$CHCl_3$	60	2	92
7[d]	PBu_3 (20)	$CHCl_3$	60	2	88
8	PBu_3 (20)	$(ClCH_2)_2$	60	2	89
9	PBu_3 (20)	CH_3CN	60	2	91
10	PBu_3 (20)	Toluene	60	2	97
11	PBu_3 (20)	CH_2Cl_2	40	2	81
12	PBu_3 (20)	THF	60	2	90
13	PBu_3 (10)	$CHCl_3$	60	2	95
14	**PBu_3 (10)**	**$CHCl_3$**	**40**	**2**	**98**
15	PBu_3 (10)	$CHCl_3$	rt	6	74
16	DMAP (20)	$CHCl_3$	60	12	—
17	DABCO (20)	$CHCl_3$	60	12	—

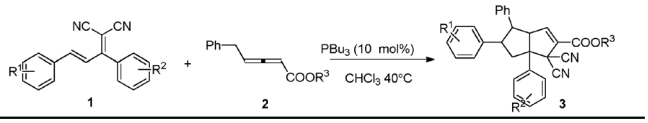
[a] Unless otherwise noted, all reactions were carried out with **1a** (0.3 mmol) and **2a** (0.6 mmol) in $CHCl_3$ (3.0 mL). [b] Yield of the isolated product. [c] Ar = $(4\text{-}CH_3OC_6H_4)_3P$. [d] The ratio of 1a : 2a = 1 : 3.

was detected in all reactions). The loading of catalysts has no influence on the yield (Table 1, entries 4 –6). And the ratio of **1a** and **2a** led to a slightly decreased yield (Table 1, entries 6 and 7). Subsequent solvent screening demonstrated that $CHCl_3$ was the best choice (Table 1, entries 8–12). Lowering the loading of catalyst to 10 mol% and the reaction temperature to 40 °C, a nearly equivalent yield was obtained (Table 2, entry 14). Unfortunately, no reaction occurred at room temperature. Furthermore, the amine catalysts were ineffective in the reaction (Table 1, entries 16 and 17). The structure and stereochemistry of **3** were determined using a combination of NMR and HRMS spectroscopies and single-crystal X-ray analysis (**3a**) (see ESI†).[19]

With the optimized conditions in hand, the substrate scope was investigated further and the results are listed in Table 2. The efficiencies and selectivities of this reaction were relatively insensitive to changes in the aryl substituents when various (*E*)-2-(1,3-diarylallylidene)malononitrile **1** were used, the reaction could proceed smoothly to produce the desired adducts in good to excellent yields (Table 2, entries 1–18). When the substituents were phenyl groups with strong electron-donating groups or heterocycles (such as furyl, thienyl), a slightly higher catalyst loading (20 mol% PBu_3) was needed (Table 2, entries 6, 8, 14, 20 and 21). To our delight, malononitrile **2** containing 2-naphthyl or heteroaryl groups could also be used in the reaction (Table 2, entries 19–21). In some cases, a slightly increased loading of catalysts was needed, it might be because of the oxidation of the catalysts. In addition, the steric properties of the esters had only a slight influence on the yield (Table 2, entries 1, 22 and 23).

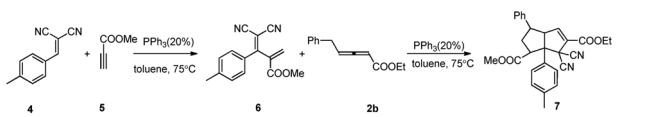
Encouraged by these results, we envisioned that the domino reaction could proceed in one pot. Pleasingly, when 2-(4-methylbenzylidene)malononitrile **4**, methyl propiolate **5** and γ-substituent

Table 2 Substrate scope for the sequential [2+3] and [3+2] annulation reactions of (*E*)-2-(1,3-diarylallylidene)malononitrile 1 with allenoates 2[a]



Entry	R^1	R^2	R^3	Yield[b] (%)
1	H	H	Me	98
2	H	*p*-Me	Me	87
3	H	*p*-Br	Me	87
4	H	*p*-Cl	Me	89
5	H	*p*-F	Me	73
6[c]	H	*p*-OMe	Me	97
7	H	*m*-Cl	Me	98
8[c]	H	*m*-OMe	Me	95
9	H	*m*-Br	Me	95
10	*p*-Cl	H	Me	87
11	*p*-Br	H	Me	83
12	*p*-Me	H	Me	90
13	*p*-F	H	Me	98
14[c]	*p*-OMe	H	Me	98
15	*m*-Me	H	Me	98
16	*m*-Cl	H	Me	79
17	*o*-Me	H	Me	98
18	*o*-Br	H	Me	96
19	1-Naphthyl	H	Me	98
20[c]	2-Furyl	H	Me	57
21[c]	2-Thienyl	H	Me	93
22	H	H	Et	97
23	H	H	Bn	88

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.3 mmol) and **2a** (0.6 mmol) in $CHCl_3$ (3.0 mL) at 40 °C for 2 h. [b] Yield of the isolated product. [c] The reactions were carried out in the presence of 20 mol% catalyst.

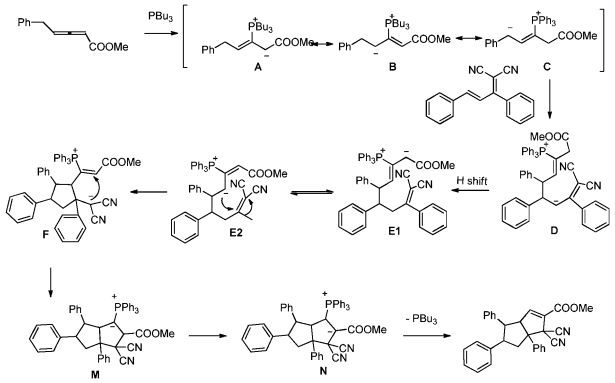


Scheme 2 One pot phosphine-catalyzed domino annulation reaction.

allenoates **2b** were used, the corresponding cycloaddition adduct **7** was obtained in one pot in 56% yield (Scheme 2).

According to our experimental results and related studies,[7,20] we propose a possible mechanism for this domino reaction (Scheme 3). The crucial event is the formation of the zwitterionic intermediate C, which undergoes a sterically favored δ-carbanion addition to the (E)-2-(1,3-diarylallylidene)malononitrile producing the intermediate D. A H-shift occurs to give intermediates E1 and E2 by a reverse equilibrium. Subsequently, a nucleophilic addition reaction yields the intermediate F, which undergoes another nucleophilic addition to give intermediate M. Proton transfer and subsequent β-elimination of the phosphine lead to the formation of the corresponding adducts.

We have developed a novel method for the synthesis of bicyclic-[3, 3, 0]octene derivatives through a phosphine-catalyzed sequential [2+3] and [3+2] annulation reaction, with excellent yields and high diastereoselectivities. More importantly, we developed a novel domino reaction in which γ-substituent allenoates were used at three reaction sites. Further investigations will focus on designing new phosphine-catalyzed sequential [2+3] and [3+2]



Scheme 3 Proposed mechanism.

annulation reactions and on performing asymmetric versions of the annulation.

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