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Phosphine-catalyzed [3 + 2] annulation of β-sulfonamido-substituted enones with *trans*-α-cyano-α,β-unsaturated ketones for the synthesis of highly substituted pyrrolidines†

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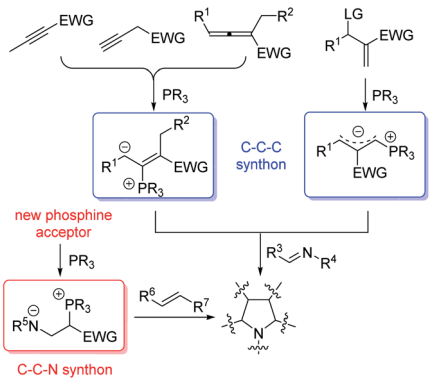
To synthesize highly substituted pyrrolidines, we developed a phosphine-catalyzed [3 + 2] annulation of β-sulfonamido-substituted enones with *trans*-α-cyano-α,β-unsaturated ketones. We prepared a series of pyrrolidines under mild conditions with high yields and moderate-to-good diastereoselectivities. A catalytic mechanism for this reaction is suggested.

Nucleophilic phosphine catalysis is a practical and powerful synthetic approach to obtain heterocyclic compounds using various annulation reactions, the advantages of which are it being mild and metal-free, ecologically friendly, and inexpensive.[1] Phosphine-catalyzed intermolecular [3 + 2],[2] [4 + 1],[3] [2 + 2 + 1][4] and intramolecular annulations are often used to obtain pyrrole derivatives. Intermolecular [3 + 2] annulations of imines and phosphorus ylides formed *in situ* from allenoates, alkynes, or Morita–Baylis–Hillman carbonates under the presence of phosphine catalysts are especially the most widely used approach to synthesize pyrrolidine derivates. In these reactions, phosphorus ylides act as C–C–C synthons for the [3 + 2] annulations with a C=N bond converting to a pyrrolidine ring (Scheme 1). However, literature reports on exploring new activation modes, namely, phosphorus ylides acting as C–C–N synthons for the [3 + 2] annulations, are rare.

β-Sulfonamido-substituted enones could be used as C–C–N synthons to form various N-based heterocycles. Catalytically activated (by amines) β-sulfonamido-substituted enones act as nucleophiles towards electron-deficient olefins or imines during [3 + 2] annulation reactions. Du's[5] and Pan's groups[6] have made outstanding contributions to this field.[7] In 2018, Guo's group developed a Bu_3P-catalyzed [5 + 1] annulation of γ-sulfonamido-substituted enones with *N*-sulfonyl-imines to obtain chiral 2,4-di-substituted imidazolidines. They also synthesized γ-sulfonamido-substituted enones attacked by phosphine catalyst and acting as C–C–C–C–N synthon (see Scheme 2).[8] Recently, Guo *et al.*[9] used β-sulfonamido-substituted enone as a phosphine acceptor as well as a C–C–N synthon for the [3 + 2] annulation with sulfamate-derived cyclic imines (see Scheme 2). Using of β-sulfonamido-substituted enone as a novel phosphine acceptor is very promising for phosphine-catalyzed reactions. Inspired by Guo's work, we further extended the substrate scope of this reaction from sulfamate-derived cyclic imines to unsaturated ketones for the construction of pyrrolidine rings. Therefore, in this work, we report phosphine-catalyzed [3 + 2] annulation of β-sulfonamido-substituted enones and *trans*-α-cyano-α,β-unsaturated ketones, to synthesize highly substituted pyrrolidines (see Scheme 2), which are among the primary building blocks and the core structures of natural and bioactive compounds.[10]



Scheme 1 Pyrrolidine ring formation through reaction of phosphorus ylides act as C–C–C and C–C–N synthons.

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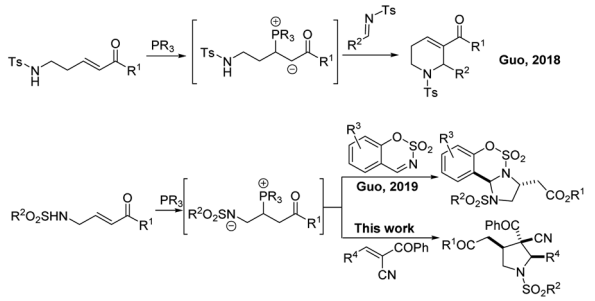
† Electronic supplementary information (ESI) available: Experimental conditions and spectroscopic data of all new compounds. CCDC 2081095. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra07881j

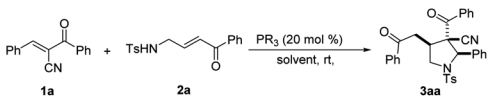


Scheme 2 Phosphine-catalyzed annulation of γ-sulfonamido-substituted enones and β-sulfonamido-substituted enones.

We first used *trans*-α-cyano-α,β-unsaturated ketone **1a** and β-sulfonamido-substituted enone **2a** as model substrates to obtain optimum reaction conditions. Tertiary phosphine catalysts were screened with 1,2-dichloroethane (DCE) as solvent at room temperature (see Table 1, entries 1–6). After 8 h, the desired pyrrolidine products (**3aa**) were obtained. Among them, $MePPh_2$, Me_2PPh, and PMe_3 promoted the [3 + 2] cycloaddition reactions with 85%, 82%, and 84% yields and 5 : 1, 3 : 1, and 6 : 1 dr diastereo-selectivities, respectively (entries 1, 4 and 6). Judging by the highest yield, PMe_3 showed the highest catalytic activity. It also produced the product **3aa** with the highest diastereoselectivity. Thus, for further tests, we used PMe_3 as catalyst. Then, to further enhance the diastereoselectivity, we screened different solvents. THF behaved similarly to toluene, providing **3aa** with 7 : 1 dr (entries 7 and 8). The EtOAc was not as efficient as other solvents, and its usage resulted in the formation of **3aa** with 5 : 1 dr (entry 9). The best solvent was $CHCl_3$ because the yield of **3aa** compound was 88%, and the diastereoselectivity was a little higher (8 : 1 dr, entry 10). When we used 3 Å and 4 Å molecular sieves as additives, the diastereoselectivities could not be further enhanced (entries 11 and 12). A significantly enhanced diastereoselectivity was obtained at lower concentrations (entries 13–15). Both the yield and diastereoselectivity were excellent (86% yield and 14 : 1 dr, respectively) with a concentration of 0.02 mol L^{-1}(see entry 16 in Table 1), albeit requiring a longer reaction time of 72 h. Further screening of temperatures and additives are listed in the ESI.† Thus, the optimum reaction conditions were determined as follows: using 20 mol% of PMe_3 as catalyst, $CHCl_3$ as solvent at room temperature.

Under the optimum conditions, the performance of various *trans*-α-cyano-α,β-unsaturated ketone **1** with β-sulfonamido-substituted enones **2a** in the cycloaddition reactions was analyzed (see Table 2). The reactions proceeded well in the presence of a wide range of substituted unsaturated ketones (**1a–1p**) acting as substrates and capable of producing pyrrolidines with good yieldsand diastereoselectivities. However, the presence of electron-deficient or -rich substituents on the benzene ring affected the reaction outcome strongly. When unsaturated ketones with electron-donating groups on the benzene ring were used, only moderate yields (up to 80%) were obtained, however the diastereo-selectivities were excellent (10.5 : 1–14 : 1 dr, entries 2–5). The unsaturated ketone **1f**

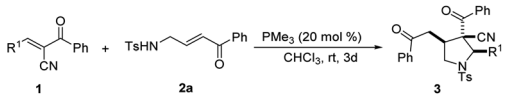
Table 1 Optimization of reaction conditions[a]



Entry	PR_3	Solvent	*t*/h	Con./mol L^{-1}	Yield[b] (%)	dr[c]
1	$MePPh_2$	DCE	8	0.1	85	5 : 1
2	$EtPPh_2$	DCE	8	0.1	74	4 : 1
3	*n*-$PrPPh_2$	DCE	8	0.1	76	4 : 1
4	Me_2PPh	DCE	8	0.1	82	3 : 1
5	PBu_3	DCE	8	0.1	78	3 : 1
6	PMe_3	DCE	8	0.1	84	6 : 1
7	PMe_3	THF	8	0.1	85	7 : 1
8	PMe_3	Toluene	8	0.1	75	7 : 1
9	PMe_3	EtOAc	8	0.1	78	5 : 1
10	PMe_3	$CHCl_3$	8	0.1	88	8 : 1
11[d]	PMe_3	$CHCl_3$	8	0.1	84	8 : 1
12[e]	PMe_3	$CHCl_3$	8	0.1	86	8 : 1
13	PMe_3	$CHCl_3$	24	0.05	85	9.5 : 1
14	PMe_3	$CHCl_3$	48	0.033	85	11 : 1
15	PMe_3	$CHCl_3$	24	0.02	65	14 : 1
16	PMe_3	$CHCl_3$	72	0.02	86	14 : 1

[a] Unless otherwise indicated, all reactions were carried out at room temperature using 0.12 mmol of **1aa** and 0.1 mmol of **2aa** in a solvent containing 20 mol% of the catalyst. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] 100 mg 3 Å molecular sieves were used. [e] 100 mg 4 Å molecular sieves were used.

Table 2 Screening of various *trans*-α-cyano-α,β-unsaturated ketones as substrates[a]



Entry	R^1	3	Yield[b] (%)	dr[c]
1	Ph (**1a**)	**3aa**	86	14 : 1
2	2-MeC_6H_4 (**1b**)	**3ba**	75	10.5 : 1
3	3-MeC_6H_4(**1c**)	**3ca**	77	12.5 : 1
4	4-MeC_6H_4 (**1d**)	**3da**	78	10.5 : 1
5	4-$OMeC_6H_4$ (**1e**)	**3ea**	80	14 : 1
6	4-CF_3-C_6H_4 (**1f**)	**3fa**	66	10.5 : 1
7	2-FC_6H_4 (**1g**)	**3ga**	72	9.5 : 1
8	3-FC_6H_4 (**1h**)	**3ha**	74	6 : 1
9	4-FC_6H_4 (**1i**)	**3ia**	76	5 : 1
10	2-ClC_6H_4 (**1j**)	**3ja**	74	8 : 1
11	3-ClC_6H_4(**1k**)	**3k**	76	10 : 1
12	4-ClC_6H_4 (**1l**)	**3la**	82	5 : 1
13	4-BrC_6H_4 (**1m**)	**3ma**	85	6 : 1
14	1-Naphthyl (**1n**)	**3na**	81	14 : 1
15	2-Naphthyl (**1o**)	**3oa**	80	8 : 1
16	2-thienyl (**1p**)	**3pa**	78	7 : 1
17	2-furyl (**1q**)	**3qa**	80	14 : 1

[a] Unless otherwise indicated, all reactions were conducted at room temperature for 3 days using 0.12 mmol of compound **1** and 0.1 mmol of compound **2** in 5 ml $CHCl_3$ in the presence of 20 mol% of PMe_3. [b] Isolated yield. [c] Determined by ^{1}H NMR.

bearing a CF_3 group at 4- position of benzene ring was also compatible with the reaction, and product **3fa** was obtained with 66% yield and 10.5 : 1 dr (entry 6). However, using of unsaturated ketones with halogen-substitutions on the corresponding phenyl groups produced relatively lower diastereoselectivities (5 : 1–9.5 : 1 dr) and only moderate yields (entries 7–13). All 1-naphthyl, 2-naphthyl- and 2-thienyl-substituted unsaturated ketones (**1n**, **1o** and **1p**, respectively) performed well, and the corresponding products **3na**, **3oa** and **3pa** were obtained with 81%, 80% and 78% yields and 14 : 1, 8 : 1, and 7 : 1 diastereoselectivities, respectively (entries 14–16). In addition, the 2-furyl derived unsaturated ketones **1q** also underwent the reaction, providing the product **3qa** in 80% yield and 14 : 1 dr (entry 17). The absolute configuration of the product **3aa** was verified by single-crystal X-ray diffraction.[11]

We also tested various substituted enones containing different R groups under the optimal reaction conditions (see Table 3). Benzene-sulfonyl-protected enone **2b** produced the desired product **3ab** with 84% yield and 10 : 1 dr (entry 2). However, the using of *p*-nitro-benzene-sulfonyl-protected enone **2c** resulted in lower yield and diastereoselectivity (equal to 81% yield and 4.5 : 1 dr, entry 3). Substituted enones **2** bearing a halogen (**2d–2h**), or two halogen groups (**2i**) on the phenyl ring were also used in this cycloaddition reaction. Yet, only moderate yields of product **3** were obtained (77–85%) but the diastereoselectivities were good (8 : 1–10 : 1 dr, entries 4–9). The using of substituted enones **2j** bearing a 4-CNC_6H_4 group also produced good results with 86% yield of product **3aj**, possessing good diastereoselectivity (11 : 1 dr, entry 10). Substituted enones bearing electron-rich methoxy group at the 3- and 4-positions of benzene ring supported the formation of products **3ak** and **3al** with 79% and 80 yields, 10 : 1 and 8.5 : 1 dr, respectively (entries 11, 12). In addition, the 4-Ph- and 2-naphthyl-modified enones underwent the [3 + 2] annulation reaction and produced the desired compounds in high yields (86 and 81%) with excellent diastereoselectivities (12.5 : 1 and 8 : 1 dr, entries 13 and 14, respectively).

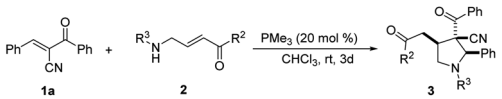
To demonstrate the synthetic potential of the cycloaddition reaction, a scale-up preparation of **3aa** and the derivatization of **3am** were performed (Scheme 3). The unsaturated ketone **1a** (699 mg, 3.0 mmol) reacted with substituted enone **2a** (788 mg, 2.5 mmol) under the standard condition to give **3aa** in 81% yield with 13 : 1 dr. In comparison with the reaction at 0.1 mmol of scale, no significant loss of yield and diastereoselectivity was observed. Reduction of the carbonyl group of **3ma** with $NaBH_4$ in $MeOH/CH_2Cl_2$ led to the formation of compound **4** in 85% yield and 5.5 : 1 dr.

The asymmetric variant of the present reaction had also been investigated (Table 4). Unfortunately, most commercial chiral phosphines did not work. To our delight, with the use of chiral phosphine P3 as the catalyst, the [3 + 2] annulation of unsaturated ketone **1a** with substituted enone **2a** worked at rt for 72 h to give chiral product **3aa** in 50% yield with up to 31% ee and >20 : 1 dr.

All these results allowed us to propose a catalytic cycle (see Scheme 4). Nucleophilic addition of the phosphine-based catalysts to β-sulfonamido-substituted enones yields phosphonium intermediate **A**, which converts into an intermediate **B** by proton transferation. The intermediate **B** undergoes intramolecular aza-Michael addition to an alkene yielding an intermediate compound **C**, followed by intramolecular nucleophilic substitution and the producing of product **3**, during which the phosphine regenerates.

In conclusion, we developed a synthesis method (under mild conditions) for highly substituted pyrrolidines through phosphine-catalyzed [3 + 2] annulation of β-sulfonamido-substituted enones with *trans*-α-cyano-α,β-unsaturated ketones. A series of pyrrolidine derivates were obtained in good yields with moderate-to-good diastereoselectivities. In this reactions, using of β-sulfonamido-substituted enone as a novel phosphine acceptor, the formed phosphorus ylides act as C–C–N synthons for annulations. Further investigations on the application of β-sulfonamido-substituted enones in the

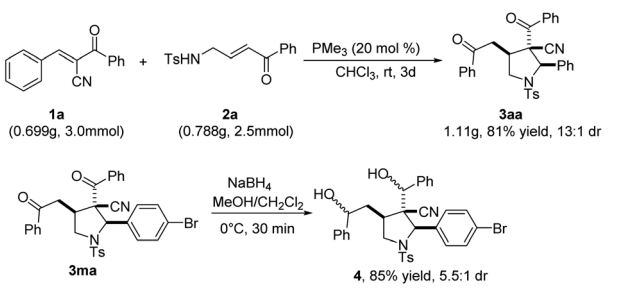
Table 3 Results of screening various β-sulfonamido-substituted enones **2** as substrates[a]



1a 2 3

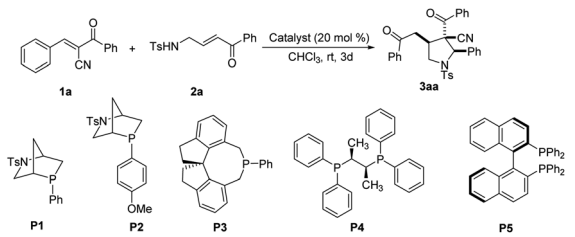
Entry	R^2/R^3	3	Yield[b] (%)	dr[c]
1	Ph/Ts (**2a**)	**3aa**	86	14 : 1
2	Ph/Bs (**2b**)	**3ab**	84	10 : 1
3	Ph/Ns (**2c**)	**3ac**	81	4.5 : 1
4	2-FC_6H_4/Ts (**2d**)	**3ad**	77	8 : 1
5	3-FC_6H_4/Ts (**2e**)	**3ae**	79	9 : 1
6	2-ClC_6H_4/Ts (**2f**)	**3af**	82	8 : 1
7	3-BrC_6H_4/Ts(**2g**)	**3ag**	74	9 : 1
8	4-BrC_6H_4/Ts (**2h**)	**3ah**	85	8 : 1
9	3,4-$Cl_2C_6H_3$/Ts (**2i**)	**3ai**	74	10 : 1
10	4-CNC_6H_4/Ts (**2j**)	**3aj**	86	11 : 1
11	3-$OMeC_6H_4$/Ts (**2k**)	**3ak**	79	10 : 1
12	4-$OMeC_6H_4$/Ts (**2l**)	**3al**	80	8.5 : 1
13	4-PhC_6H_4/Ts (**2m**)	**3am**	86	12.5 : 1
14	2-naphthyl/Ts (**2n**)	**3an**	81	8 : 1

[a] Unless otherwise noted, all reactions were performed at room temperature for 3 days using 0.12 mmol of compound **1** and 0.10 mmol of compound **2** in 5 ml $CHCl_3$ under the presence of 20 mol% PMe_3. [b] Isolated yield. [c] Determined by ^1H NMR.



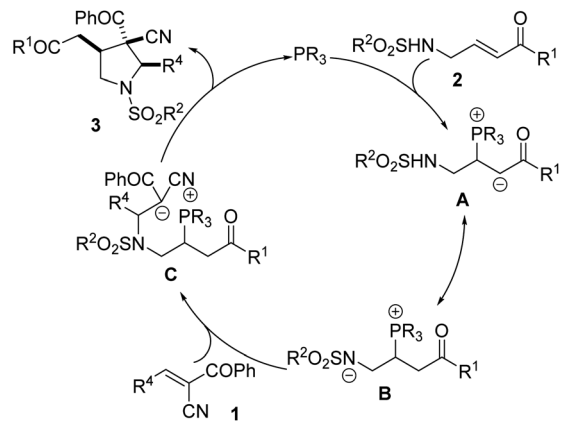
Scheme 3 The reaction on the gram-scale and further transformations.

Table 4 Investigation of the asymmetric [3 + 2] annulation[a]



Entry	Catalyst	t/h	Yield[b] (%)	dr[c]	ee[c]
1	P1	72	Trace	—	—
2	P2	72	20	>20 : 1	5
3	P3	72	50	>20 : 1	31
4	P4	72	NR[d]	—	—
5	P5	72	NR[d]	—	—

[a] Unless otherwise indicated, all reactions were carried out at room temperature using 0.06 mmol of **1aa** and 0.05 mmol of **2aa** in a solvent containing 20 mol% of the catalyst in 2.5 ml of $CHCl_3$. [b] Isolated yield. [c] Determined by HPLC on chiral column. [d] No reaction.



Scheme 4 Proposed mechanism.

asymmetric phosphine-catalyzed reactions are in progress in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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11 Crystallographic data for **3aa** has been deposited with the Cambridge Crystallograohic Data Centre as deposition number CCDC 2081095.†