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Phosphine-catalyzed [4+1] annulation of 2-tosylaminochalcones with allenoates: synthesis of *trans*-2,3-disubstitued indolines†

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Phosphine-catalyzed [4+1] annulation of 2-tosylaminochalcones with allenoates has been achieved, giving *trans*-2,3-disubstitued indolines as major diastereoisomers in moderate to good yields.

Indolines are prevalent in a large number of natural products and extremely important in medicinal chemistry (Fig. 1),[1] exhibiting diverse bioactivities including anti-cancer, anti-bacteria, anti-viral, anti-inflammatory and anti-obesity.[2] Among various indolines, functionalized 2,3-disubstitued indolines are of great significance. This structural motif is present in many bioactive compounds and natural products. For example, the natural product **3** exhibits a wide range of bioactivities, using as acyl-CoA inhibitors, neuropeptide neurotransmitter antagonists, topoisomerase inhibitors and antibiotics.[3a] Indoline-fused tricyclic heterocycle **4** shows excellent inhibitory activity against LBT_4 production.[3b] 2,3-Disubstitued indoline **5** inhibits focal adhesion kinase activity by 45% at 10 μM.[3c] Moreover, functionalized 2,3-disubstitued indolines could serve as valuable tools to construct complex polycyclic natural products.[4]

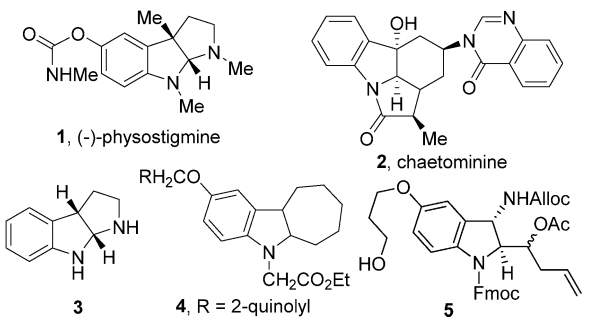

Fig. 1 Selected examples of bioactive natural products and compounds bearing 2,3-disubstitued indoline unit.

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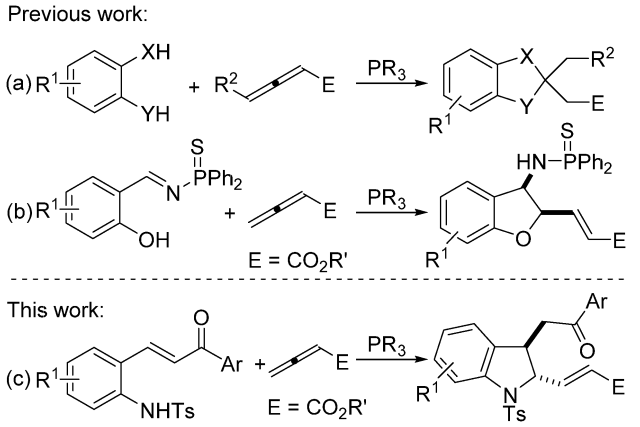
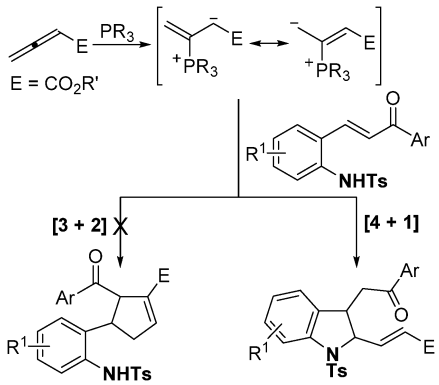
Owing to the above facts, the development of synthetic methods for 2,3-indolines continues to be highly desirable.

Nucleophilic phosphine-catalyzed annulations are well established as powerful tools for the synthesis of carbo- and heterocycles from simple starting materials and total synthesis of natural products.[5] In recent years, phosphine-catalyzed [4+1] annulation reactions have been developed as one of alternative methods to the [3+2] annulation reactions for accessing five-membered carbocyclic and heterocyclic compounds.[6–8] Under phosphine catalysis conditions, certain activated allenes, alkynes or Morita–Baylis–Hillman (MBH) carbonates could work as C_4 or C_1 synthons to react with electrophilic reaction partners, furnishing [4+1] annulations. Among these substrates, activated allenes are versatile substrates for [4+1] annulations. With allenoates as C_4 synthons, Tong,[6b] Lu[6d] and Fu[6e,f] reported several [4+1] annulations of 1,1-bisnucleophiles and their asymmetric variants. With activated allenoates as C_1 synthons, Kwon developed a phosphine-catalyzed [4+1] annulation reaction of 1,4-bisnucleophiles, providing six different C_2-functionalized benzannulated 1,3-diheteroatom five-membered rings (Scheme 1a).[6c] Huang also achieved a bifunctional phosphine-catalyzed [4+1] annulation reaction of salicyl *N*-thiophosphinyl imines to generate *cis*-2,3-dihydrobenzofurans with high stereoselectivity (Scheme 1b).[6a] Herein, we anticipate to use allenoates as C_1 synthons and develop phosphine-catalyzed [4+1] annulation of TsNH-tethered chalcones to give biologically important 2,3-indolines (Scheme 1c).

Phosphine-catalyzed [3+2] cycloadditions of allenoates with electron-deficient olefins provide an important tool for the synthesis of cyclopentenes.[9] The reaction mechanism for this reaction has been studied in depth.[10] It is commonly accepted that the catalytic cycle is triggered by the addition of the Lewis basic phosphine to the electrophilic allenoates, leading to the formation of zwitterionic intermediates, which act as 1,3-dipoles, reacting with an electron-deficient alkene to furnish [3+2] annulation. In this reaction, the proton shift has been proved to convert one zwitterionic intermediate to another reactive zwitterionic intermediate, thus promoting the reaction. Since the proton shift highly depends on the acidity of the proton source, when a



Scheme 1 Phosphine-catalyzed [4+1] annulation reactions with allenoates as C_1 synthons.

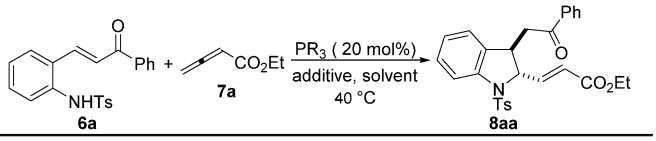


Scheme 2 Phosphine-catalyzed [4+1] annulation reaction of allenoates.

NHTs group is tethered to activated alkene, this TsNH group might be involved in the proton shift process, thus leading to a new [*m*+*n*] annulation reaction (Scheme 2). Following this idea, we designed and prepared 2-tosylaminochalcones, and evaluated their reaction with allenoates in the presence of phosphine.

We initiated our study by examining the reaction of 2-tosylaminochalcone (**6a**) with allenoate (**7a**). In the presence of 20 mol% PPh_3, the reaction did not occur in CH_2Cl_2 at rt (Table 1, entry 1). When the temperature was increased to 40 °C, trace of a new product was observed on the TLC (Table 1, entry 2). To our delight, when PBu_3 was used, the new product (**3a**) was isolated in 43% yield with >20 : 1 d.r. and its structure was established to be a [4+1] cycloaddition product 2,3-disubstituted indoline by NMR spectroscopy (entry 3). However, employing other phosphines as the catalysts, whether they have stronger or weaker nucleophilicity as compared with PBu_3, the yields could not be further improved (entries 4–6). The investigation of effects of the solvents showed that THF was the optimal choice (entries 7–9), leading to the product in 57% yield and DMSO, DMF, CH_3CN and 1,4-dioxane could only afford a trace amount of the product (data not shown). In some phosphine-catalyzed reactions, protic reagents such as water, alcohol or benzoic acid could promote the [1, 2], [1, 3] or [1, *n*] proton shift and accelerate the reaction rates.[10b,d–f,11] Therefore, we next screened several protic reagents.

Table 1 Screening of the reaction conditions[a]



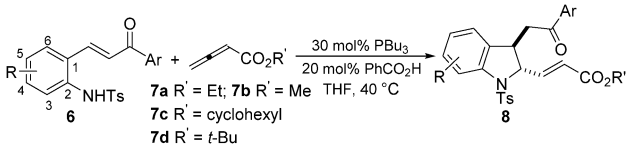
Entry	PR_3	Additive	Solvent	*t* (h)	Yield[b] (%)
1[c]	PPh_3	—[d]	CH_2Cl_2	48	NR
2	PPh_3	—	CH_2Cl_2	48	Trace
3	PBu_3	—	CH_2Cl_2	48	43
4	PMe_3	—	CH_2Cl_2	48	35
5	$MePPh_2$	—	CH_2Cl_2	48	41
6	Me_2PPh	—	CH_2Cl_2	48	32
7	PBu_3	—	Toluene	36	37
8	PBu_3	—	THF	36	57
9	PBu_3	—	CH_3OH	36	Trace
10	PBu_3	$PhCO_2H$	THF	36	70
11	PBu_3	H_2O	THF	48	60
12	PBu_3	2-$IC_6H_4CO_2H$	THF	36	24
13	PBu_3	3-$NO_2C_6H_4CO_2H$	THF	36	66
14	PBu_3	4-$FC_6H_4CO_2H$	THF	36	63
15	PBu_3	4-$MeC_6H_4CO_2H$	THF	36	64
16	PBu_3	PhOH	THF	36	58
17	PBu_3	CH_3CO_2H	THF	24	Trace
18[e]	PBu_3	$PhCO_2H$	THF	24	60
19[f]	PBu_3	$PhCO_2H$	THF	12	71
20[g]	PBu_3	$PhCO_2H$	THF	12	57

[a] Unless otherwise stated, reactions of **6a** (0.2 mmol) and **7a** (0.3 mmol) were carried out in the presence of PBu_3 (0.04 mmol) and additive (0.04 mmol) in 2 mL of the solvent. [b] Isolated yield. Unless otherwise stated, dr is >20 : 1, determined by ^1H NMR analysis. [c] The reaction was performed at rt. [d] No additive. [e] 50 mol% of $PhCO_2H$ was used. [f] 30 mol% of PBu_3 was used. [g] The reaction temperature was 60 °C.

It was found that the additive employed is critically important to the yield (entries 10–17). Using $PhCO_2H$ as the additive, the yield was dramatically increased to 70%. Subsequently, several substituted benzoic acids, H_2O and PhOH, were also examined, but disappointedly, no better results were obtained. Particularly, CH_3CO_2H could nearly completely inhibit the reaction (entry 17). An increase in the amount of $PhCO_2H$ caused a decrease in the yield of **8aa** to 60% (entry 18). When the catalyst loading of PBu_3 was increased to 30 mol%, the reaction proceeded with more efficiency and the reaction time could be reduced to 12 h (Table 1, entry 19). Increasing the reaction temperature to 60 °C led to a drop in the yield (entry 20). The structure and configuration of the product **8aa** were confirmed by single-crystal X-ray analysis.[12]

With the optimal conditions in hand, the substrate scope for the [4+1] annulation was studied. As summarized in Table 2, variation of the electronic nature and position of the substituent at the benzene ring of *N*-Ts protected chalcone (**6**) was possible. Incorporation of an electron-withdrawing group (*e.g.* fluoro, chloro, bromo) or an electron-donating group (*e.g.* methyl, methoxyl) was very well tolerated in this reaction, giving the desired indoline products in moderate to high yields with high diastereoselectivities (Table 2, entries 2–22). In addition, a variety of allenoates **7** were also tested to further extend the generality of the reaction. Changing the ester moieties in allenoates with Me, *t*-Bu and Cy groups has no significant influence on the reactivity. Using these allenoates, the reaction proceeded smoothly to

Table 2 Substrate scope of PBu_3-catalyzed [4+1] annulation of *N*-Ts chalcones (**6**) with allenoates (**7**)[a]

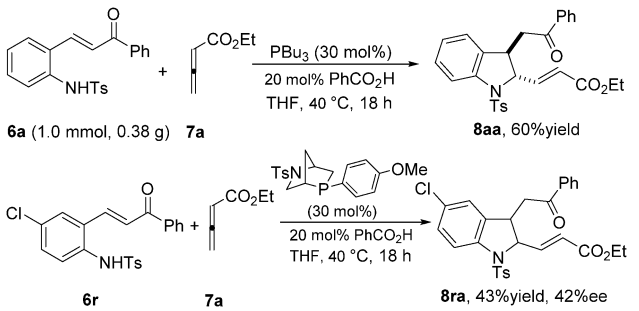


Entry	R in **6**	Ar in **6**	**7**	*t* (h)	**8**	Yield[b] (%)
1	H (**6a**)	Ph	**7a**	12	**8aa**	71
2	H (**6b**)	2-MeC_6H_4	**7a**	24	**8ba**	83
3	H (**6c**)	3-MeC_6H_4	**7a**	24	**8ca**	87
4	H (**6d**)	4-MeC_6H_4	**7a**	12	**8da**	81
5	H (**6e**)	4-$OMeC_6H_4$	**7a**	12	**8ea**	73
6	H (**6f**)	4-ClC_6H_4	**7a**	24	**8fa**	78
7	H (**6g**)	3-BrC_6H_4	**7a**	24	**8ga**	56
8	H (**6h**)	4-BrC_6H_4	**7a**	24	**8ha**	64
9	H (**6i**)	2-ClC_6H_4	**7a**	36	**8ia**	61
10	H (**6j**)	2-Naphthyl	**7a**	48	**8ja**	58
11	5-Me (**6k**)	Ph	**7a**	24	**8ka**	69
12	5-Me (**6l**)	2-$OMeC_6H_4$	**7a**	24	**8la**	78
13	5-Me (**6m**)	4-$OMeC_6H_4$	**7a**	36	**8ma**	83
14	5-Me (**6n**)	3-BrC_6H_4	**7a**	36	**8na**	61
15	5-Me (**6o**)	4-BrC_6H_4	**7a**	24	**8oa**	83
16	5-F (**6p**)	Ph	**7a**	48	**8pa**	67
17	5-F (**6q**)	4-BrC_6H_4	**7a**	24	**8qa**	85
18	5-Cl (**6r**)	Ph	**7a**	24	**8ra**	70
19	5-Cl (**6s**)	3-BrC_6H_4	**7a**	36	**8sa**	60
20	5-Cl (**6t**)	4-BrC_6H_4	**7a**	24	**8ta**	67
21	5-Br (**6u**)	4-BrC_6H_4	**7a**	24	**8ua**	69
22	6-Br (**6v**)	Ph	**7a**	36	**8va**	55
23	H (**6a**)	Ph	**7b**	24	**8ab**	59
24	H (**6a**)	Ph	**7c**	24	**8ac**	65
25	H (**6a**)	Ph	**7d**	24	**8ad**	68

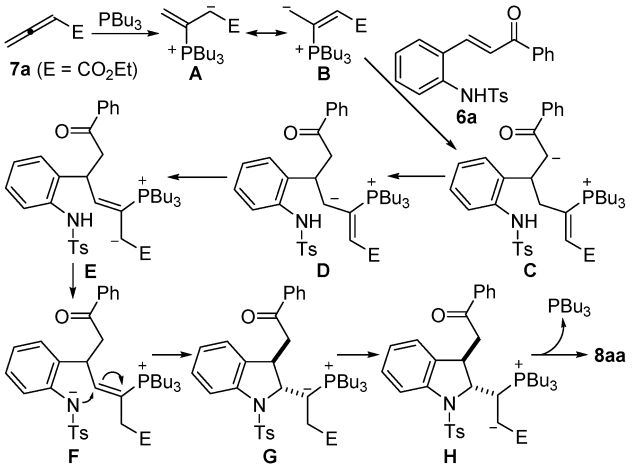
[a] Unless otherwise stated, reactions of **6** (0.2 mmol) and 7 (0.3 mmol) were carried out in the presence of PBu_3 (0.06 mmol) and $PhCO_2H$ (0.04 mmol) in 2 mL of THF. [b] Isolated yield. Unless otherwise stated, dr is >20 : 1, determined by ^1H NMR analysis.

form the desired 2,3-disubstituted indolines in 59–68% yield (entries 23–25).

To further demonstrate the preparative utility, a gram scale of reaction using substrates **6a** and **7a** was carried out. As shown in Scheme 3, on the 1 mmol (0.38 g) scale, the reaction proceeded smoothly to give 2,3-disubstituted indoline in 60% yield. The asymmetric variant of the present reaction had also been investigated. Unfortunately, most commercial chiral phosphines did not work. To our delight, Kwon phosphine catalyzed the reaction of *N*-Ts protected chalcone (**6r**) with **7a** to afford the product **8ra** in 43% yield and 42% ee (the absolute configuration had not been assigned).



Scheme 3 Scaled-up synthesis and asymmetric catalysis.



Scheme 4 A plausible mechanism for the [4+1] annulation of 2-tosylaminochalcone and allenoate.

On the basis of the reported mechanisms of nucleophilic phosphine-catalyzed reactions, a reasonable mechanism was proposed (Scheme 4). The phosphonium intermediate **B** resulting from addition of PBu_3 to allenoate **7a** undergoes Michael addition to **6a** to give the intermediate **C**. Consecutive proton shifts provide the enoate **F**, which undergoes intramolecular γ-addition to generate the ylide **G**. Subsequent 1,2-proton transfer and β-elimination of the phosphine catalyst lead to the 2,3-disubstitued indolines **8**.

In summary, a highly diastereoselective phosphine-catalyzed [4+1] annulation of 2-tosylaminochalcones and allenoate has been designed and developed. The reaction works very well under mild conditions to provide biologically important *trans*-2,3-disubstitued indoline derivatives as major diastereoisomers in moderate to good yields.

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