Silicon as a directing group in the phosphine-catalyzed [2 + 3]-cycloaddition of aryl allenones with electron-deficient olefins†

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This Communication describes a highly efficient phosphine-catalyzed [2 + 3]-cycloaddition reaction using α-trimethylsilyl-substituted aryl allenones and electron deficient olefins; both good yields and good asymmetric induction were obtained.

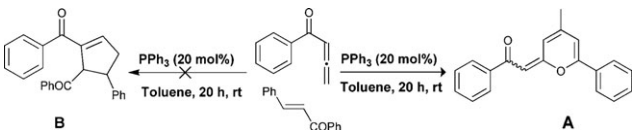
Functionalized five-membered rings are featured widely in many drugs and natural products.[1] Accordingly, much effort has been directed towards the development of new synthetic methods for their construction.[2,3] Among the methods available, the synthesis of functionalized cyclopentenes *via* [2 + 3]-cycloaddition reactions using allenoates, electron deficient olefins and catalytic amounts of phosphine, first reported by Lu and Zhang in 1995, has been shown to be one of the most powerful methods,[4] and the products can be easily derivatized into highly functionalized cyclopentanes. In recent years, highly asymmetric versions of this reaction have also emerged.[5] Furthermore, this method has also been applied to the total synthesis of several natural products.[6] A variation of this method *via* a [4 + 2] process to construct six-membered rings has also been elegantly demonstrated by Kwon[7a,b] and Fu.[7c]

While allenoates have been widely used,[8] the corresponding allenones have only just recently been revealed by Wallace and Sidda.[9] Although it has been shown to work with many different aliphatic allenones, one of the major limitations of this method is that higher Michael acceptors, such as aromatic allenones, afford self-dimerized [4 + 2] Diels–Alder products (*e.g.* **A**) instead of the desired [2 + 3]-cycloaddition adducts (*e.g.* **B**) (Scheme 1).[9] We envisaged that the use of α-trimethylsilyl substituted allenones[10] may solve this problem by suppressing formation of the self-[4 + 2] adduct due to the steric bulk of the silicon, thus affording the desired cross-[2 + 3]-cycloaddition adduct. For a similar reason, substitution at the α-position will lead to preferential attack at the γ-position, leading to the γ-adduct. Herein, we report a highly regioselective synthesis of functionalized cyclopentenes *via* [2 + 3]-cycloaddition reactions using α-silyl-substituted aromatic allenones and electron deficient olefins.

Initial studies were carried out with *trans*-chalcones using α-trimethylsilyl-substituted aromatic allenone **1**, in the presence of a catalytic amount of triphenylphosphine (20 mol%) in toluene. To our delight, the reaction proceeded smoothly at room temperature to afford the desired [2 + 3]-cyclized product (**2a**) in 84% yield (Table 1, entry 1). Only a trace amount (5% yield) of the [4 + 2] Diels–Alder product was isolated. The reaction also worked with a wide variety of other electron deficient olefins (Table 1, entries 2–8). Investigating this reaction with DABCO (1,4-diazabicyclo[2.2.2]octane) or triethylamine instead of triphenylphosphine led to no reaction.

To further explore the synthetic value of this method, we extended it to furan-2-yl allenones **3**. These are more versatile compounds as the furan ring can be easily manipulated,[11] and results are summarized in Table 2. In all cases (Table 2, entries 1–8), the results were similar to the reactions involving allenone **1**. This method works well with a range of electron deficient olefins, including ethyl-4,4,4-trifluorocrotonoate (Table 1 and Table 2, entries 7), which provided easy access to biologically important trifluoromethyl-substituted cyclopentenoids. It is important to note that the silicon group was not retained in the final product. The stereochemistry of the diethylmaleate (*Z*) (Table 1 and Table 2, entries 4) was retained in the product, implying that the mechanism of this cycloaddition reaction could be concerted.

Next, we focused on a catalytic asymmetric version of this method by screening a number of commercially available chiral phosphines such as (+)-BINAP (0% yield, 0% ee), (2*S*,3*R*)-CHIRAPHOS (82% yield, 22% ee), (*S*,*S*)-Et-DUPHOS (30% yield, 60% ee), (*R*,*R*)-Et-DUPHOS (40% yield, −70% ee), (+)-DIOP (62% yield, 10% ee) and (*S*)-(−)-2-[2-(diphenylphosphino)phenyl]-4-isopropyl-2-oxazoline (75% yield, 37% ee). Although (*S*,*S*)-Et-DUPHOS showed moderate enantioselectivity, the yield was low. In order to increase the yield with (*S*,*S*)-Et-DUPHOS, different solvents were screened. Among them, CH_2Cl_2 was the best, providing the desired product in 52% yield with an improved ee of 71% (Table 3, entry 1). Increasing the catalyst loading and adding it slowly did not make any difference to the yield or ee of the product. Upon cooling the reaction to −10 °C in CH_2Cl_2, a decline in rate and yield were observed with (*S*,*S*)-Et-DUPHOS. With these optimized conditions (20 mol% (*S*,*S*)-Et-DUPHOS, rt, in CH_2Cl_2), asymmetric cycloaddition reactions using phenyl allenone **1** and furan allenone **3** with electron deficient olefins were carried out, and the results are



Scheme 1 The phosphine-catalyzed [4 + 2]-cyclization of aryl allenones.‡

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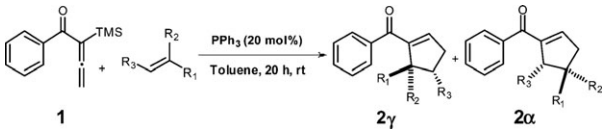
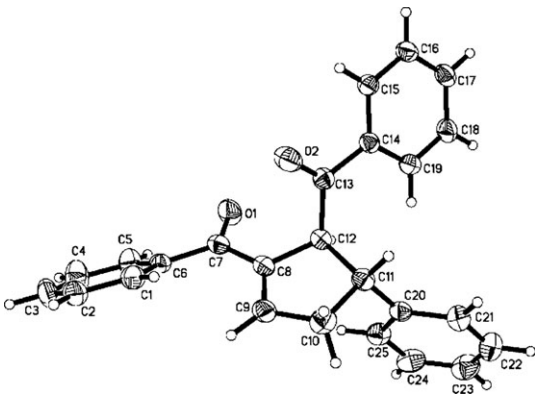
† Electronic supplementary information (ESI) available: Detailed experimental procedures and analytical data. CCDC 708751. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b819959k

Table 1 Trimethylsilyl-directed [2 + 3]-cycloaddition using a phenyl allenone[a]



Entry	R^1	R^2	R^3	Product (**2γ**)[b]	Yield (%)[c]
1	COC_6H_5	H	C_6H_5	**2a**	84
2	4-$MeCOC_6H_4$	H	4-$EtOC_6H_4$	**2b**	75
3	4-$MeCOC_6H_4$	H	4-MeC_6H_4	**2c**	78
4[d]	H	COOEt	COOEt	**2d**	72
5	COOEt	H	COOEt	**2e**	82
6[e,f]	COOMe	H	H	**2f**	80
7	CF_3	H	COOEt	**2g**	63
8[f]	CH_3	COOMe	H	**2h**	52

[a] See the ESI for the detailed experimental procedure. The relative stereochemistry of the product (**2a**) was identified by X-ray analysis (Scheme 2). [b] >99% of a single isomer (γ) was observed by ^{1}H NMR analysis. [c] Isolated yield. About 5% of the self-dimerized products were obtained. [d] Diethyl maleate (*Z*) was used as the enone. [e] Two regioisomeric products (**2γ** and **2α**) were observed in the ratio 5 : 1, respectively, by ^{1}H NMR analysis. [f] 10 mol% of enone was used.

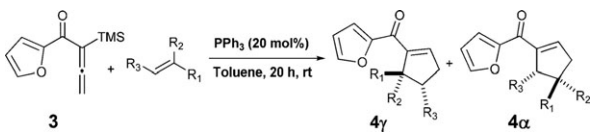


Scheme 2 X-Ray crystal structure of **2a**; 50% probability was chosen for the ellipsoids.†

shown in Table 3. In all cases, this asymmetric cycloaddition reaction delivered high enantioselectivities and moderate yields. Interestingly, the reaction of furan allenone **3** with *trans*-chalcone (Table 3, entry 2) afforded the product in a high enantioselectivity (92% ee), which further increases the synthetic utility of this method. Although CH_2Cl_2 showed good results, isomerization[12] of maleate to fumarate occurred under these reaction conditions. In these cases, toluene was the solvent of choice. (Table 3, entries 4 and 5)

In conclusion, we have demonstrated that the introduction of a silicon group at the α-position of allenones is the key to obtaining cross-cyclized [2 + 3] products. This is probably due to steric effects that suppress the [4 + 2] self-condensation reaction. In contrast to normal allenones, α-silyl substituted allenones lead to the preferential formation of γ adducts with β-unsubstituted olefins such as methyl acrylate and methyl methacrylate. In addition, entirely γ adduct product was observed with β-substituted olefins. Preliminary studies on the asymmetric version of the reaction using (*S*,*S*)-Et-DUPHOS, a commercially available chiral phosphine, lead to [2 + 3]

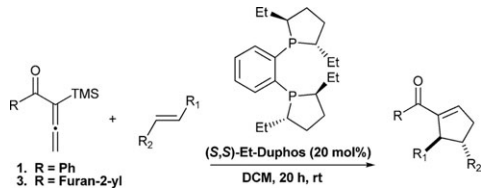
Table 2 Trimethylsilyl-directed [2 + 3]-cycloaddition using a furan-2-yl allenone[a]



Entry	R^1	R^2	R^3	Product (**4γ**)[b]	Yield (%)[c]
1	COC_6H_5	H	C_6H_5	**4a**	75
2	4-$MeCOC_6H_4$	H	4-$EtOC_6H_4$	**4b**	80
3	4-$MeCOC_6H_4$	H	4-MeC_6H_4	**4c**	78
4[d]	H	COOEt	COOEt	**4d**	83
5	COOEt	H	COOEt	**4e**	80
6[e,f]	COOMe	H	H	**4f**	83
7	CF_3	H	COOEt	**4g**	72
8[f]	CH_3	COOMe	H	**4h**	55

[a] See the ESI for the detailed experimental procedure. [b] >99% of a single isomer (γ) was observed by ^{1}H NMR analysis. [c] Isolated yield. [d] Diethyl maleate (*Z*) was used as the enone. [e] Two regioisomeric products (**2γ** and **2α**) were observed in the ratio 5 : 1, respectively, by ^{1}H NMR analysis. [f] 10 mol% of enone was used.

Table 3 Asymmetric [2 + 3]-cycloaddition reactions[a,b]



Entry	Allene	R^1	R^2	Yield (%)[c]	ee (%)[d]
1	**1**	COC_6H_5	C_6H_5	52	71
2	**3**	COC_6H_5	C_6H_5	54	92
3	**3**	4-$MeCOC_6H_4$	4-$EtOC_6H_4$	56	70
4[e,f]	**3**	$COOC_2H_5$	$COOC_2H_5$	62	74
5[e,f]	**1**	$COOC_2H_5$	$COOC_2H_5$	48	80

[a] See the ESI for the detailed experimental procedure. [b] The absolute stereochemistry was not determined. [c] >99% of a single isomer (γ) was observed. Isolated yield. [d] The ee was determined using chiral HPLC. [e] Diethyl maleate (*Z*) was used as the enone. [f] Toluene was used as solvent, when the reaction using CH_2Cl_2 two regio isomeric products were observed.

products in moderate-to-high enantioselectivities. Further investigations on the scope, mechanism and synthetic applications of this new approach to complex molecule synthesis are now in progress.

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Notes and references

‡ **General procedure for the phosphine-catalyzed [2 + 3]-cycloaddition of α-trimethylsilyl-substituted aryl allenones with electron deficient olefins:** To a stirred solution of the aryl allenone (50 mg, 0.23 mmol) and the enone or enolate (0.25 mmol) in toluene (1.5 mL) was added, drop-wise, the phosphine (5.3 mg, 20 mol%) (pre-dissolved in toluene) at 0 °C under N_2. After 20 h of stirring at room temperature under an N_2 atmosphere, the reaction mixture was concentrated and purified using flash column chromatography (15–20% ethyl acetate in hexane).

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12 When CH_2Cl_2 or $CHCl_3$ were used as the solvent, 30% of the other diastereomer was observed. A control experiment showed that 50% of the diethyl maleate isomerized when stirred with triphenylphosphine in CH_2Cl_2 or $CHCl_3$.

