

Facile insertion reaction of arynes into carbon–carbon σ -bonds†

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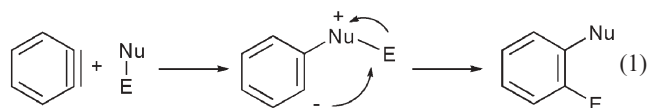
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The carbon–carbon σ -bond of various β -dicarbonyl compounds was found to add to the triple bond of arynes under extremely mild conditions, leading to direct introduction of different carbon functional groups into the aromatic skeletons.

Arynes have been recognized as useful reactive intermediates in organic synthesis, which undergo a wide variety of reactions such as pericyclic reactions, electrophilic coupling and transition metal-catalyzed reactions.¹ Irrespective of the reaction patterns, insertion reactions of arynes into an element–element σ -bond particularly have high synthetic significance, because both elements can be introduced into the carbon–carbon triple bond simultaneously, leading to the formation of polysubstituted arenes, which are otherwise difficult to prepare.² In this context, we have recently disclosed the insertion reactions of a carbon–tin,³ silicon–silicon⁴ or tin–tin σ -bond⁵ in the presence of a palladium complex. Moreover, we have also developed the thiostannylation (sulfur–tin σ -bond)⁶ and aminocarbonylation (nitrogen–carbonyl σ -bond)⁷ of arynes, where nucleophilic attack of the respective heteroatom (nucleophilic site) to the arynes and the successive intramolecular nucleophilic substitution at the electrophilic site are key steps (eqn. (1)).

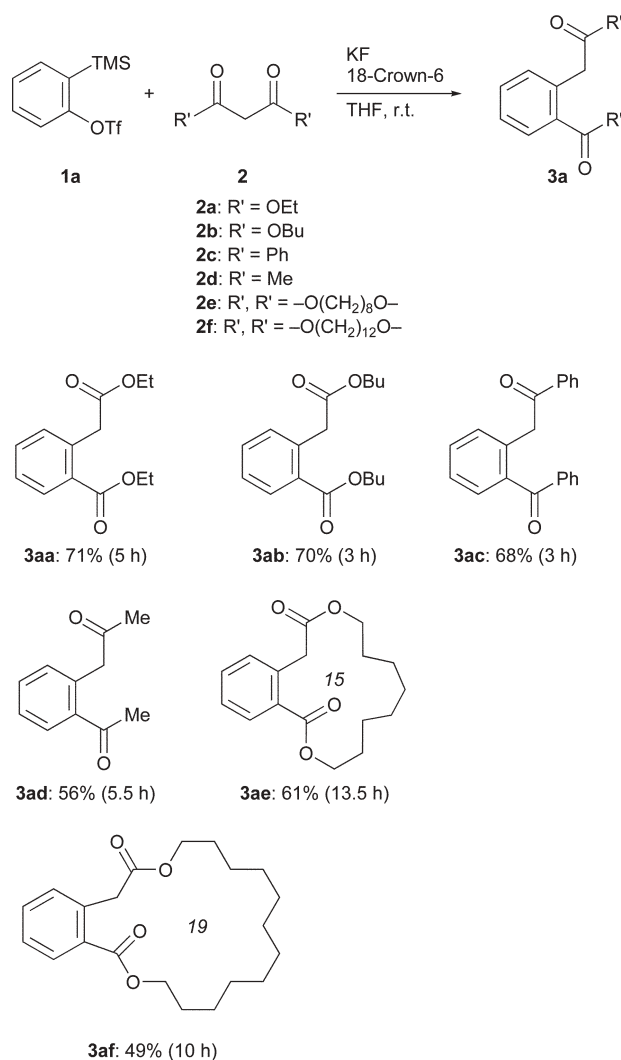


Based upon these results, we envisaged that β -dicarbonyl compounds should be appropriate reagents for the insertion reaction of arynes into their active methylene (potentially nucleophilic)–carbonyl (electrophilic) σ -bonds, leading to direct introduction of different carbon functional groups into the 1,2-positions of the aromatic skeletons. Herein we report on the insertion reaction of arynes into the carbon–carbon σ -bond of β -dicarbonyl compounds, which enables two carbon–carbon bond-forming processes to take place simultaneously. Quite recently, a similar insertion reaction of arynes into the carbon–carbon σ -bond of β -ketoesters has been disclosed by Stoltz.⁸

First we carried out the reaction of benzyne with diethyl malonate (**2a**) and observed that insertion into the methylene–carbonyl σ -bond proceeded smoothly under extremely mild conditions by simply mixing benzyne precursor **1a**,⁹ **2a** and a fluoride ion (KF–18-crown-6), affording the insertion product (**3aa**) in 71% yield (Scheme 1).¹⁰ Dibutyl malonate (**2b**) could also participate in the reaction to give a 70% yield of **3ab**, and

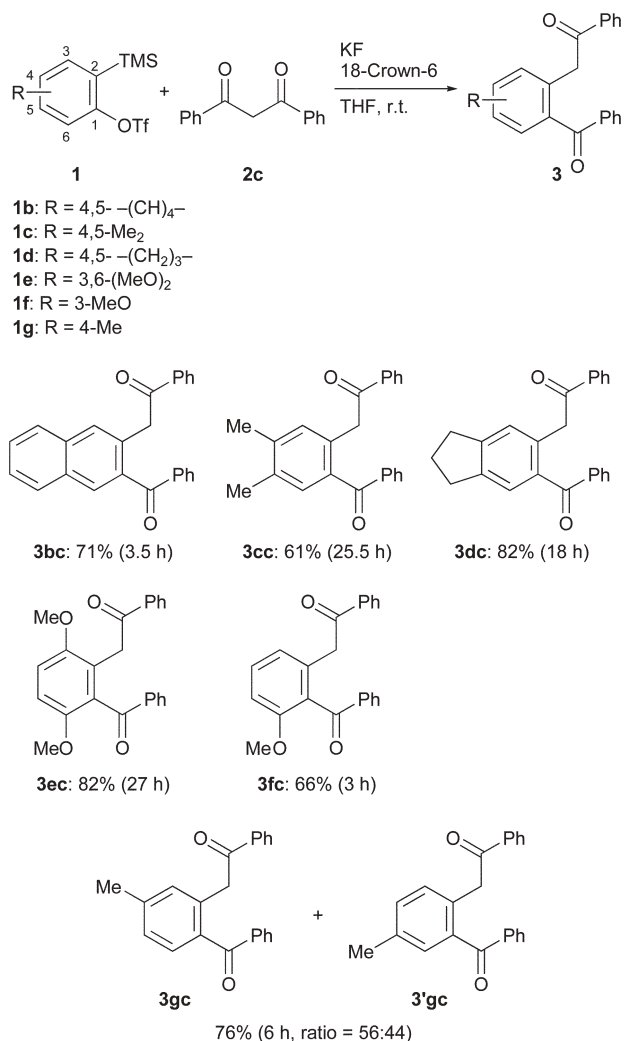
furthermore, reaction with such a β -diketone as dibenzoylmethane (**2c**) or acetylacetone (**2d**) provided the corresponding product (**3ac** or **3ad**) in 68% or 56% yield. Benzo-annulated macrocyclic compounds were readily available, and thus, treatment of a cyclic malonate (**2e** or **2f**) with benzyne afforded a 15-membered (**3ae**) or 19-membered ring (**3af**)¹¹ straightforwardly in 61% or 49% yield, respectively.‡

In addition to simple benzyne, variously substituted arynes could also be applied to the reaction. When 3-(trimethylsilyl)-2-naphthyl triflate (**1b**), a 2,3-naphthalene precursor, was allowed to react with **2c**, **3bc** was formed in 71% yield (Scheme 2). Facile



Scheme 1 Insertion reaction of benzyne into the carbon–carbon σ -bond of β -dicarbonyl compounds.

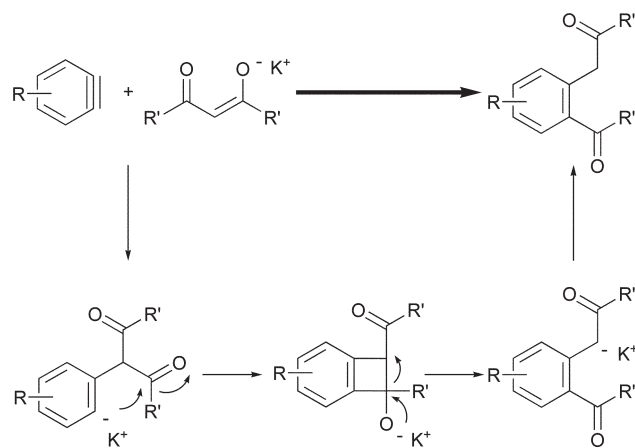
† Electronic supplementary information (ESI) available: Synthesis and characterisation details. See <http://www.rsc.org/suppdata/cc/b5/505392g/>
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Scheme 2 Insertion reaction of substituted arynes into the carbon-carbon σ -bond of **2c**.

insertion into **2c** was also observed in the reaction of other 4,5-disubstituted arynes (from **1c** or **1d**) or sterically congested 3,6-dimethoxybenzynes (from **1e**) to give good yields of the products (**3cc**, **3dc** or **3ec**). An unsymmetrical aryne, 3-methoxybenzynes (from **1f**), reacted efficiently with perfect regioselectivity to afford **3fc** bearing the benzoylmethyl moiety at the sterically less hindered position of the aryne, whereas the reaction of 4-methylbenzynes (from **1g**) furnished almost equal amounts of regioisomeric products **3gc** and **3'gc**.¹²

Scheme 3 depicts a plausible reaction pathway of the reaction. First, nucleophilic attack of an *in situ*-generated enolate to the aryne occurs to produce an aryl anion.¹³ Subsequent intramolecular nucleophilic attack to the carbonyl moiety, followed by ring expansion of the resulting benzocyclobutene gives the product. The perfect regioselectivity observed in the reaction of 3-methoxybenzynes can be rationally explained by the steric and/or electron-withdrawing effects of the methoxy group, both of which favor nucleophilic attack at the *m*-position of the substituent. In contrast, steric and electronic effects around the triple bond would be negligible in the reaction of 4-methylbenzynes, and equal addition of the enolate to both ends of the triple bond occurs.¹⁴



In conclusion, we have demonstrated that the carbon-carbon σ -bond of various β -dicarbonyl compounds can readily be cleaved and added to the carbon-carbon triple bond of arynes under extremely mild conditions. The present insertion reaction enables direct introduction of different carbon functional groups into adjacent positions of the aromatic skeleton, and provides diverse polysubstituted arenes straightforwardly, which are hardly accessible by conventional methods. Further studies on extension of the reaction scope are in progress.

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Notes and references

‡ Representative experimental procedure: to a THF solution (4.0 mL) of 18-crown-6 (0.127 g, 0.48 mmol), **1a** (0.072 g, 0.24 mmol) and **2c** (0.045 g, 0.20 mmol) was added KF (0.028 g, 0.48 mmol), and the resulting mixture was stirred at room temperature for 3 h. The mixture was diluted with ethyl acetate, filtered through a Celite plug, washed three times with brine and dried over MgSO_4 . Evaporation of the solvent followed by gel permeation chromatography (chloroform as an eluent) gave **3ac** in 68% yield.

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