Straightforward construction of diarylmethane skeletons *via* aryne insertion into carbon–carbon σ-bonds†

Hiroto Yoshida,* Masahiko Watanabe, Takami Morishita, Joji Ohshita and Atsutaka Kunai*

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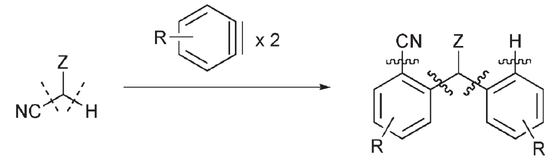
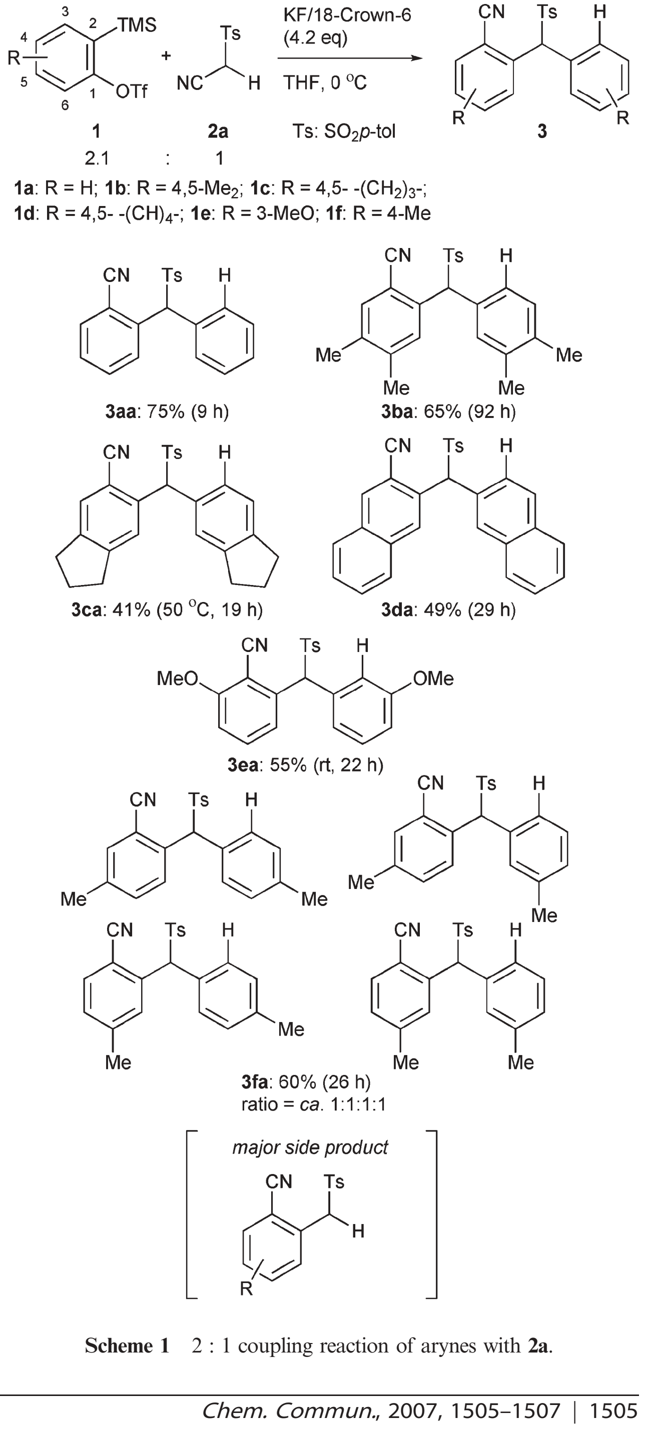
Two molar amounts of arynes were found to couple with nitriles *via* carbon–carbon σ-bond cleavage, assembling diverse diarylmethane skeletons in a straightforward manner.

Arynes are useful reactive intermediates in synthetic organic chemistry, which can be transformed into polysubstituted arenes and benzo-annulated structures, being otherwise unobtainable.[1] Despite their transient and kinetically unstable character arising from the strained carbon–carbon triple bond, the use of appropriate combinations of aryne precursors, reaction partners and/or catalysts enables arynes to undergo such controlled and unprecedented reactions as transition metal-catalyzed cyclizations,[2] multi-component couplings[3] and element–element σ-bond insertions.[4] In particular, insertion reactions of arynes into a carbon–carbon σ-bond, reported recently by Stoltz's[5] and our group,[6] have high synthetic significance, because the reactions can directly assemble complex carbon frameworks *via* two carbon–carbon bond forming processes. In this context, we have been studying the aryne insertion to expand the reaction scope, and have found that certain nitriles couple with two molar amounts of arynes at their carbon–carbon and carbon–hydrogen σ-bonds. Herein we report on the straightforward construction of diarylmethane skeletons depending upon the new 2 : 1 coupling reaction of arynes and nitriles, in which three carbon–carbon and one carbon–hydrogen bonds are formed all in one pot (eqn (1)).



(1)

First we conducted the reaction of *in situ*-generated benzyne (from **1a**[7] and KF/18-crown-6) with *p*-toluenesulfonylacetonitrile (**2a**) in THF at 0 °C, and observed that two molar amounts of benzyne were inserted into the methylene carbon–cyano carbon and methylene carbon–hydrogen bonds of **2a** to afford (2-cyanophenyl)phenyl(*p*-toluenesulfonyl)methane (**3aa**) in 75% yield (Scheme 1).[8,9] Arynes possessing alkyl substituents at their 4,5-positions (from **1b** or **1c**) or 2,3-naphthalyne (from **1d**) also reacted efficiently with **2a**, giving the respective diarylmethanes (**3ba–3da**) in moderate yield. It should be noted that the reaction of 3-methoxybenzyne (from **1e**) occurred with perfect regioselectivity, where the methine carbon of **3ea** was connected to the *meta* positions of each methoxy moiety. The intermediacy of an aryne in the present insertion reaction has been verified by the use of



Scheme 1 2 : 1 coupling reaction of arynes with **2a**.

Department of Applied Chemistry, Graduate School of Engineering, Hiroshima University, Higashi-Hiroshima, 739-8527, Japan.
E-mail: yhiroto@hiroshima-u.ac.jp; Fax: +81-82-424-5494;
Tel: +81-82-424-7724

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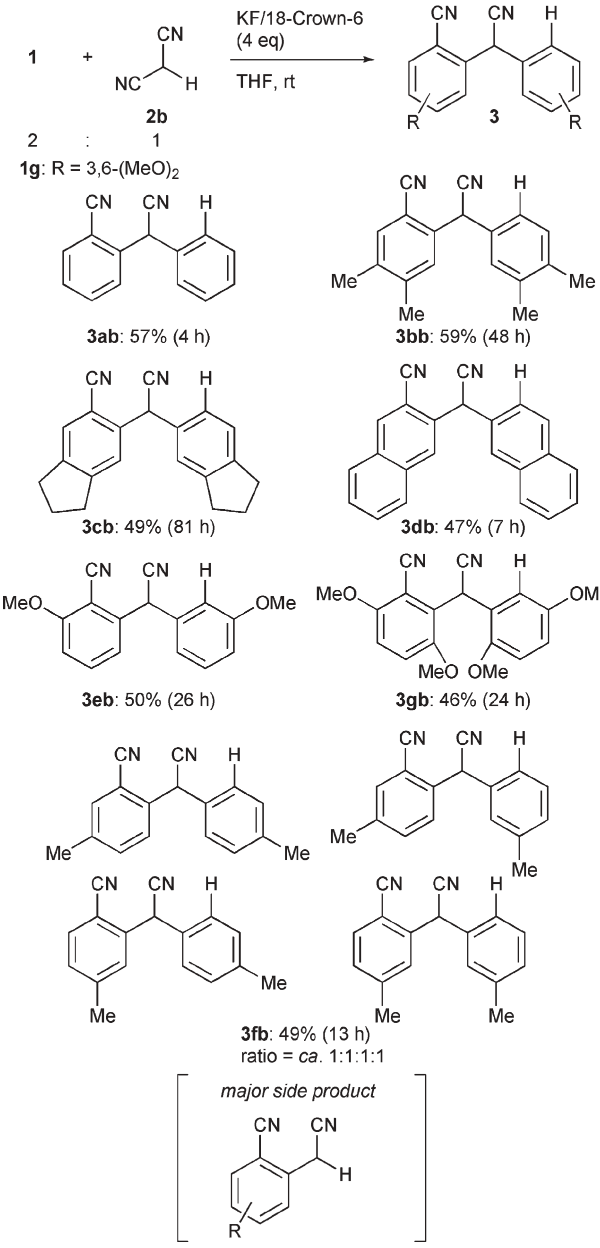
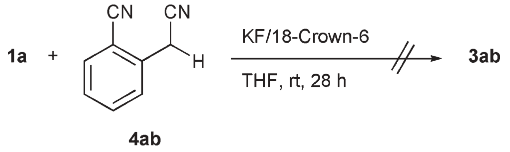


Scheme 2 2 : 1 coupling reaction of arynes with **2b**.

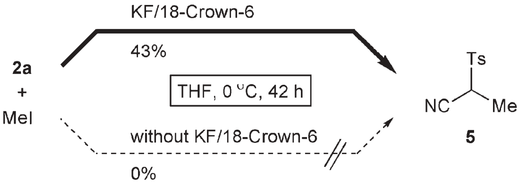
4-methylbenzyne (from **1f**), resulting in the formation of a mixture of four regioisomers (ratio = *ca.* 1 : 1 : 1 : 1). In all cases, the major side product was 2-cyanoaryl(*p*-toluenesulfonyl)methane (8% yield with **1a**, for example) derived from insertion of an aryne into the carbon–carbon bond.[10]

Besides **2a**, successive aryne insertion also took place with malononitrile **2b** (Scheme 2). Thus, treatment of **2b** with benzyne furnished a 57% yield of (2-cyanophenyl)phenylacetonitrile (**3ab**) straightforwardly.[11] The use of symmetrical arynes further enhanced the versatility of the reaction, and thus, (2-cyanoaryl) arylacetonitriles of structural diversity (**3bb–3db**) could be synthesized by simply mixing an aryne precursor (**1b–1d**), **2b** and a fluoride ion. As was the case with **2a**, exclusive formation of **3eb** was observed with 3-methoxybenzyne, whereas the reaction of 4-methylbenzyne produced almost equal amounts of four regioisomeric products (**3fb**). Moreover, 3,6-dimethoxybenzyne (from **1g**) could also participate in the reaction to give **3gb**, despite the steric congestion around the triple bond.



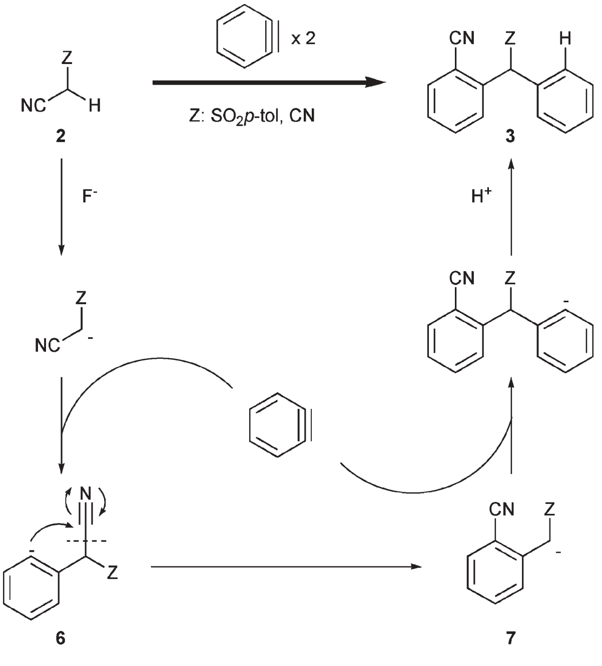
(2)

Because 2-cyanoarylacetonitrile, generated through the carbon–carbon bond cleavage, was obtained as the major side product also in the reaction of **2b** (7% yield with **1a**, for example),[10] we examined the reaction of 2-cyanophenylacetonitrile **4ab** with benzyne, assuming that the side product might be an intermediate species in producing **3** (eqn (2)). However, no trace of **3ab** was formed in this reaction, which implies that the successive aryne insertion should proceed *via* an anionic counterpart (**7**) and not the side product (*vide infra*).



(3)

Inferring that the reaction should be initiated by deprotonation of **2** by a fluoride ion, we examined the alkylation of **2a** as shown in eqn (3). Thus, treatment of **2a** with methyl iodide in the presence of KF/18-crown-6 resulted in the formation of methylated product **5**, whereas no trace of **5** was produced without an added fluoride ion, confirming that a fluoride ion acts not only as an aryne generator but also as a base. These results prompt to us to propose a reaction pathway described in Scheme 3. A nucleophilic attack of an *in situ*-generated anionic nitrile to an aryne would trigger the formation of **6**. Subsequent intramolecular nucleophilic substitution at a cyano moiety of **6** produces benzylic anion **7**,[12] which further reacts with a second aryne to afford **3**. The perfect



Scheme 3 Plausible pathway of the reaction.

regioselectivity observed in the reaction of 3-methoxybenzyne would be attributable to a steric and/or electron-withdrawing effect of the methoxy group, both of which favor the nucleophilic attack at *m*-position of the substituent.

In conclusion, we have demonstrated that arynes can successively couple with carbon–carbon and carbon–hydrogen σ-bonds of nitriles under extremely mild conditions. Overall, the present reaction enables three carbon–carbon and one carbon–hydrogen bond forming processes to occur all at once, resulting in the direct assembly of diverse diarylmethane skeletons, which constitute integral parts of biologically active compounds and pharmaceuticals. Further studies on extension of the reaction scope as well as on the reaction mechanism are in progress.

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9 The reaction of an α-cyanocarbonyl compound often gave such a 2 : 1 coupling product as a minor component in low yield, see ref. 6.

10 See ESI† for details.

11 The reaction of **1a** (1.2 equiv.) with **2b** also afforded **3ab** as a major product (28% yield) along with **4ab** (5% yield), which demonstrates the strong tendency to undergo the successive aryne insertion in contrast to the results reported in ref. 6.

12 A referee suggested that benzylic anion **7** would be also formed through a [2 + 2] cycloaddition of an aryne and a ketenimine anion, followed by a fragmentation of the resulting benzocyclobutene.