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Synthesis of 2,3-disubstituted indenones by cobalt-catalyzed [3+2] annulation of *o*-methoxycarbonylphenylboronic acid with alkynes†

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Treatment of alkynes with *o*-methoxycarbonylphenylboronic acid in the presence of a cobalt catalyst resulted in the corresponding 2,3-disubstituted indenones in good yields. Excellent regioselectivities were observed, when silyl aryl alkynes were used. The intermediate 3-silyl-2-aryl-substituted indenones were converted to 2,3-diaryl indenones by a three-step protocol involving C–Si bromination and Suzuki–Miyaura coupling reaction.

Indenones constitute an important class of carbon frameworks found in natural products and biologically active compounds.^{1,2} Efficient synthesis of 2,3-diaryl-substituted indenones is particularly desirable in medicinal chemistry. For instance, pauciflorol F and quadranguarin A, which were isolated from the stem bark of *Vatica pauciflora* and the stem of *Cissus quadrangularis* respectively, are known as effective candidates for cancer growth inhibitors (Fig. 1).³

Transition-metal-catalyzed [3+2] annulation reactions of *ortho*-substituted arylboronic acids⁴ with alkynes have been studied as a useful tool for the synthesis of substituted indenones.^{5,6} In 2005, Murakami and coworkers reported that Rh-catalyzed annulation of *o*-cyanophenylboronic acid with internal alkynes gave 2,3-disubstituted indenones.⁵ Tsukamoto and coworkers reported that Pd-catalyzed reaction of *o*-alkoxycarbonylphenylboronic acids with internal alkynes also gave 2,3-disubstituted indenones.⁶ In these [3+2] annulation reactions, unsymmetrically disubstituted alkynes gave a mixture of the corresponding 2,3-disubstituted indenones with variable regioselectivities.

Co-catalyzed hydroarylation of alkynes with organoboronic acids was first reported by Cheng and coworkers in 2008, in which they used the Co(acac)₂(DPPE) complex as the catalyst.⁷ We investigated the potential of Co-catalyzed [3+2] annulation for the synthesis of substituted indenones and found that the Co-catalyzed [3+2] annulation of *o*-methoxycarbonylphenylboronic acid with alkynes proceeds efficiently, giving a high degree of regioselectivity for some of the alkynes. We also report the

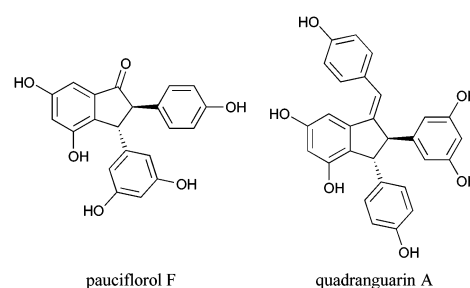


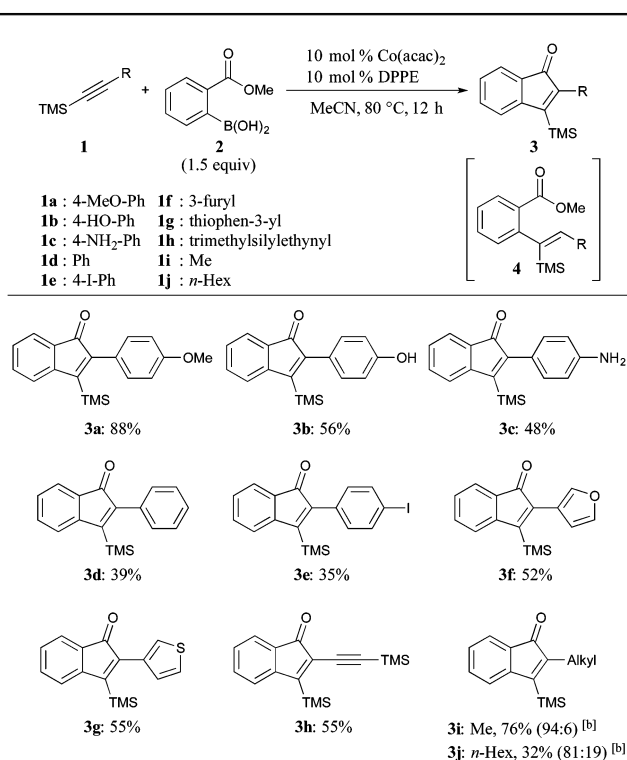
Fig. 1 Biologically active compounds related to an α,β -diaryl indenone structure.

regioselective synthesis of 2,3-diaryl-substituted indenones by a three-step protocol involving (i) Co-catalyzed [3+2] annulation, (ii) bromination of a C–Si bond, and (iii) Suzuki–Miyaura coupling reaction with arylboronic acids. It should be noted that very recently, Co-catalyzed [3+2] annulation of alkyl benzoate with internal alkynes to give 2,3-disubstituted indenones in good yields has been reported by Zhang's group and Yu and Li's group, independently.⁸

In the presence of 10 mol% of Co(acac)₂ and DPPE,⁹ the reaction of [4-(methoxyphenyl)ethynyl]-trimethylsilane (**1a**) with *o*-methoxycarbonylphenylboronic acid (**2**) in acetonitrile at 80 °C for 12 h produced 2-(4-methoxyphenyl)-3-silyl indenone **3a** as a single regioisomer in 88% yield (Table 1). The reaction of [4-(trimethylsilyl)ethynyl]phenol (**1b**) and [4-(trimethylsilyl)ethynyl]aniline (**1c**) with **2** also proceeded regioselectively to form the corresponding 3-silyl-substituted indenones **3b** and **3c** in 56% and 48% yields, respectively. Although trimethylsilyl aryl acetylenes **1d** (R = phenyl) and **1e** (R = 4-iodophenyl) showed modest reactivity,¹⁰ the corresponding products **3d** and **3e** were obtained again as a single regioisomer. Furan-3-ylethynyl-trimethylsilane (**1f**) and 3-(trimethylsilylethynyl)thiophene (**1g**) tolerated the reaction conditions and formed the corresponding indenones **3f** and **3g** in 52% and 55% yields, respectively. In these cases, the modest yields are mainly due to the hydroarylation leading to **4**. The reaction of 1,4-bis(trimethylsilyl)butadiyne (**1h**) with **2** gave indenone **3h** having an enyne moiety in moderate yield.

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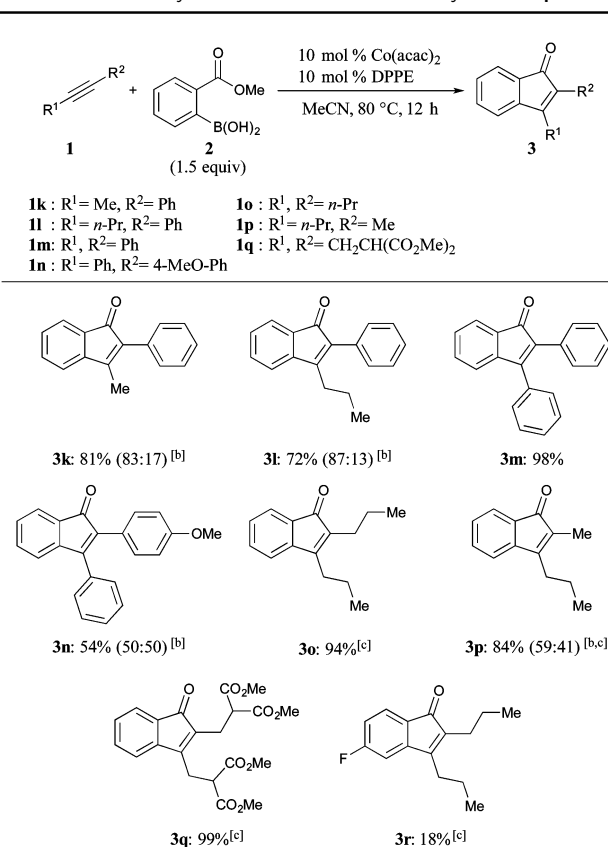
Table 1 Cobalt-catalyzed regioselective annulation of silyl alkynes **1a–1j** with **2**^a

^a Reaction conditions: **1** (0.5 mmol), **2** (1.5 equiv.), Co(acac)₂ (10 mol%), DPPE (10 mol%) in MeCN (2 mL) at 80 °C for 12 h. ^b Determined by NMR analysis.

Aliphatic alkynylsilanes, such as 1-(trimethylsilyl)propyne (**1i**) and 1-(trimethylsilyl)octyne (**1j**), were also examined. The reaction of **1i** with **2** led to 2-methyl-3-silyl indenone **3i** in 76% yield with high regioselectivity (94 : 6).¹¹ On the other hand, the reaction of **1j** with **2** was sluggish and formed the annulation product **3j** in 32% yield with a regioselectivity of 3-silyl/2-silyl = 81 : 19.

In contrast to regioselective products of silyl-substituted alkynes, other internal alkynes **1k–1q** showed variable regioselectivities depending on the substitution patterns of alkynes (Table 2). The reaction of methyl phenyl acetylene **1k** with **2** formed **3k** in good yield with 83:17 selectivity in favor of 2-phenyl orientation. 1-Phenylpentyne (**1l**) gave **3l** in 72% yield with a similar regioselectivity. Diphenylacetylene **1m** also reacted with **2** to give 2,3-diphenyl indenone **3m** in 98% yield. Similarly 4-octyne **1o** formed the corresponding **3o** in 94% yield. The reaction of unsymmetrical diaryl and dialkyl acetylenes **1n** and **1p** with **2** proceeded well; however, no significant regioselectivity was observed in these cases. The internal alkyne **1q** including methyl ester moieties tolerated the reaction conditions to furnish the corresponding 2,3-disubstituted indenone **3q** in 99% yield. We also examined the reaction of 5-fluoro-2-methoxycarbonylphenylboronic acid with **1o**. As a result, the corresponding indenone **3r** was afforded, albeit in low yield for the sluggish reaction.

Having encountered region-uncontrolled synthesis of 2,3-diaryl indenone in the case of **1n**, we focused on the regioselective

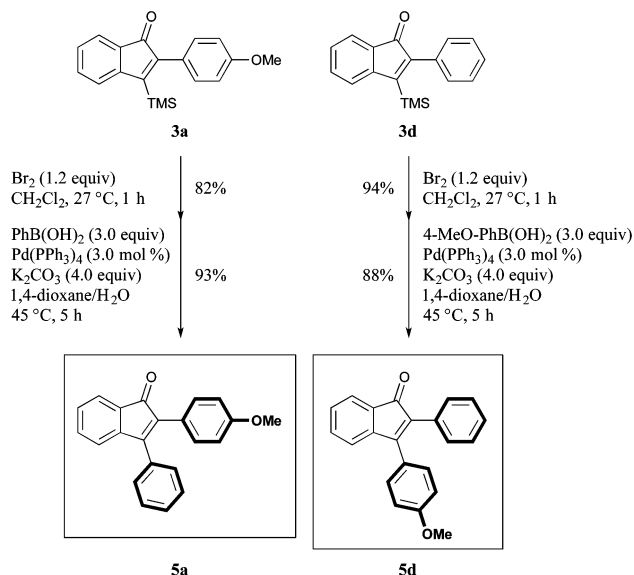
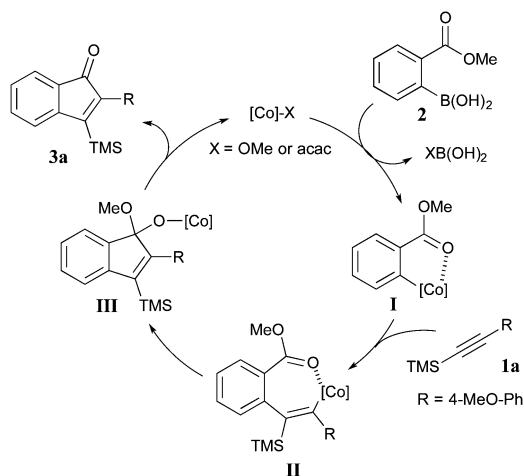
Table 2 Cobalt-catalyzed annulation of internal alkynes **1k–1p** with **2**^a

^a Reaction conditions: **1** (0.5 mmol), **2** (1.5 equiv.), Co(acac)₂ (10 mol%), DPPE (10 mol%) in MeCN (2 mL) at 80 °C for 12 h. ^b Determined by NMR analysis. ^c 2 mol% of Co(acac)₂ and DPPE were used.

synthesis, which is based on the treatment of 2-aryl-3-silyl indenones with molecular bromine and a subsequent Suzuki–Miyaura coupling reaction. This strategy worked quite well and the 3-silyl moieties of **3a** and **3d** were converted to phenyl and 4-MeO-phenyl forming **5a** and **5d**, respectively (Scheme 1). Thus using the suitable combination of aryl silyl acetylenes and arylboronic acids, we can obtain both regioisomers of 2,3-diaryl substituted indenones quite easily.

A proposed mechanism for the Co-catalyzed annulation process is shown in Scheme 2. Arylcobalt complex **I** would be generated *via* the transmetalation of [Co]–X (X = OMe or acac) with *o*-methoxycarbonylphenylboronic acid (**2**).¹² The regioselective insertion of a silyl alkyne **1a** gives vinylcobalt complex **II**. The [Co]–carbon bond of complex **II** undergoes migratory insertion into the ester to form alkoxy cobalt complex **III**, which undergoes elimination to give the corresponding product **3a** and regenerates the [Co]–X catalyst.

For unsymmetrical silyl alkynes, the reaction generally proceeded in a regioselective fashion, and the trimethylsilyl group favored the 3-position of indenones. Although similar [3+2] annulation of silyl alkynes by Rh-catalysis is known,⁵ higher regioselectivities and a wider scope of silyl alkynes are exhibited in our Co-catalysis compared to previous work. The replacement of the methyl group with a bulkier hexyl group led to a

Scheme 1 Regioselective synthesis of 2,3-diaryl indenones **5a** and **5d**.

Scheme 2 Proposed reaction mechanism.

decrease in regioselectivity (**3i** and **3j** in Table 1). In the case where 1-trimethylsilyl-3,3-dimethyl-1-butyne and bis(trimethylsilyl)-acetylene were used as bulky silyl alkynes, the reaction did not proceed. These results reveal that the [Co]-carbon bond of complex **II** does not likely prefer a sterically bulky group.

In conclusion, we have demonstrated that the Co-catalyzed system is useful for achieving [3+2] annulation of *o*-methoxy-carbonylphenylboronic acid and alkynes leading to the formation of 2,3-disubstituted indenones. Interestingly, when silyl alkynes were used, regioselective annulation took place to give 3-silyl-substituted indenones. The resulting vinylsilane moiety of 3-silyl indenones was readily converted to a vinylarene moiety by a bromination/cross-coupling protocol, enabling regio-controlled synthesis of 2,3-diaryl substituted indenones.

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- 9 A survey of other cobalt catalysts, ligands, and solvents revealed that the optimal reaction conditions were as follows: 10 mol% Co(acac)₂, 10 mol% DPPE, MeCN, 80 °C, 12 h. See the ESI† for details.
- 10 We also examined the reaction of silyl aryl alkynes including an electron withdrawing group, such as 3-(trimethylsilylethynyl)benzotrile and trimethyl[(4-trifluoromethylphenyl)ethynyl]silane. As the results, the corresponding hydroarylation products were mainly obtained, and only a trace amount of the corresponding indenones were given.
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