Synthesis of 1-methyleneindenes *via* palladium-catalyzed tandem reactions†‡

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Palladium-catalyzed tandem reactions of 2-alkenylphenylacetylenes with $CuCl_2$ or $CuBr_2$ afforded 3-chloro- or 3-bromo-1-methyleneindenes in good yields; these compounds could be further elaborated *via* palladium-catalyzed coupling reactions.

As a privileged scaffold, the indene core has been found in many drug candidates with remarkable biological activities.[1] Moreover, indenes have been attractive in metallocene complexes, which are utilized as catalysts in olefin polymerization.[2] In addition, applications of these molecules have been discovered in materials science.[3] Thus, the importance of indenes has stimulated the development of a number of approaches for the synthesis of the indene ring system.[4–7] However, less attention has been paid to 1-methyleneindenes,[8] which are easily transformed into functionalized indenes. It is well-established that tandem C–C bond formations are powerful methods for the generation of molecular complexity from relatively simple starting materials in a convergent way.[9–11] Recently, we have developed efficient tandem reactions for the expeditious synthesis of biologically-relevant heterocyclic compounds.[12] Based on these results, we have also investigated the tandem reaction of 2-(2-(alkynyl)-benzylidene)malonate with indole.[13] In this process, the reaction was initiated *via* nucleophilic addition of a nucleophile to the α,β-unsaturated system (Fig. 1, **A**). Prompted by the advancement of halopalladation chemistry,[14,15] we conceived that during the process, the tandem cyclization reaction might be initiated *via* nucleophilic attack of the triple bond motif in the presence of a suitable transition metal catalyst (Fig. 1, **B**). Herein, we disclose that 2-alkenylphenylacetylenes **1** undergo Pd-catalyzed tandem reactions in the presence of a copper(II) halide, leading to 3-halo-1-methyleneindenes. These compounds could be further elaborated *via* Pd-catalyzed cross-coupling reactions to generate highly functionalized 1-methyleneindenes.

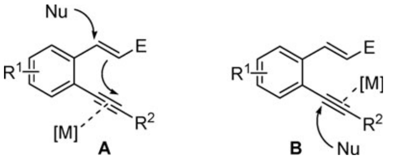
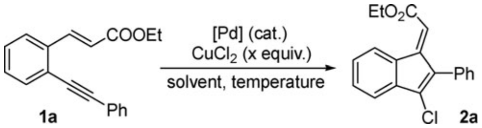


Fig. 1 Tandem cyclization of 2-alkenylphenylacetylene **1**.



Scheme 1 Initial studies of the Pd-catalyzed reaction of **1a**.

Initial studies were performed using (*E*)-ethyl-3-(2-(2-phenylethynyl)phenyl)acrylate (**1a**) as a model substrate (Scheme 1). This compound could be easily synthesized starting from 2-alkynylbenzaldehyde. At the outset, the reaction was catalyzed by $PdCl_2$ (10 mol%) in the presence of $CuCl_2$ (2.0 equiv.) in DMAc at 120 °C. Gratifyingly, the desired 3-chloroindene, **2a**, was generated in 40% yield. Decreasing the temperature to 80 °C did not affect the reaction efficiency. However, the reaction was retarded at lower temperatures. We then examined other solvents in this reaction, and DMAc was demonstrated to be the best choice. The yield increased to 57% when 4.0 equiv. of $CuCl_2$ was employed in the reaction. However, the result could not be improved when the amount of copper(II) chloride was increased to 6.0 equiv. A blank experiment indicated that no reaction occurred in the absence of the palladium catalyst. The reaction also failed without the addition of the copper salt. A similar result was observed when 5 mol% of $PdCl_2$ was utilized in the reaction. Further screening of palladium catalysts revealed that $Pd(OAc)_2$ was the best for this transformation (66% yield), and only 3 h was necessary for completion of the reaction. An inferior result was displayed when the amount of $Pd(OAc)_2$ was decreased to 2 mol% (for details, see the ESI‡).

Next, the scope of the Pd-catalyzed tandem cyclization reaction of 2-alkenylphenylacetylenes **1** were investigated under the optimized conditions ($Pd(OAc)_2$ (5 mol%), $CuCl_2$ (4.0 equiv.), DMAc, 80 °C) and the results are shown in Table 1. From Table 1, it is found that for all cases, the Pd-catalyzed tandem cyclization reactions of 2-alkenylphenylacetylenes **1** furnish the corresponding 3-chloro-1-methyleneindenes **2** in moderate to good yields. For instance, when (*E*)-1-phenyl-3-(2-(2-phenylethynyl)-phenyl)prop-2-en-1-ones **1c** or **1d** were utilized in the reaction under the standard conditions, the desired products **2c** or **2d** were obtained in 90 and 71% yield, respectively (Table 1, entries 3 and 4).

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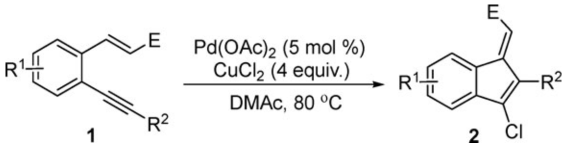
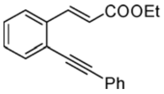
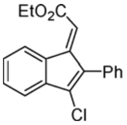
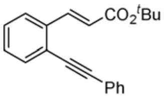
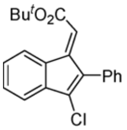
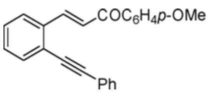
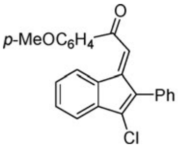
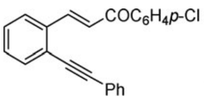
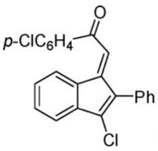
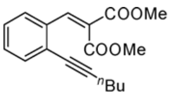
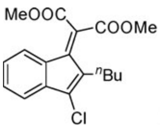
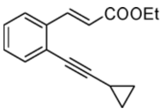
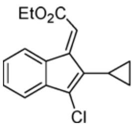
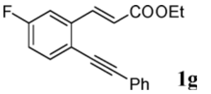
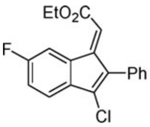
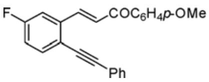
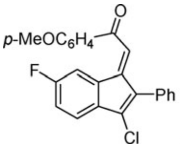
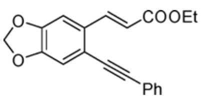
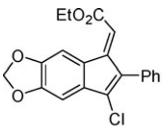
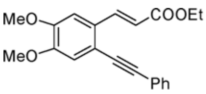
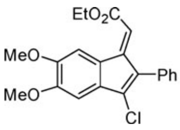
† This paper is dedicated to Professor Li-Xin Dai on the occasion of his 85th birthday.

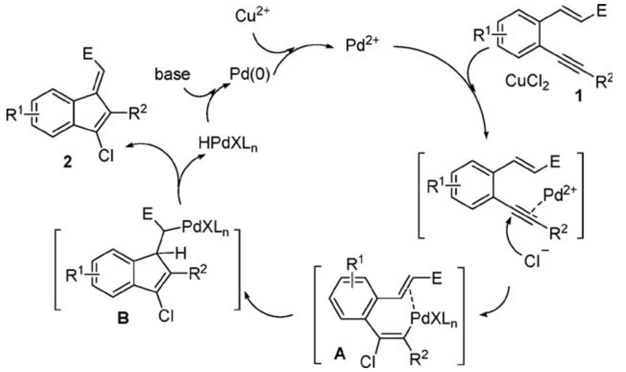
‡ Electronic supplementary information (ESI) available: Further experimental and characterisation data. CCDC 731568. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b909178e

Table 1 The Pd-catalyzed reaction of 2-alkenylphenylacetylenes **1** in the presence of $CuCl_2$



Entry	Substrate **1**	Product **2**	Yield (%)[a]
1	 **1a**	 **2a**	66
2	 **1b**	 **2b**	60
3	 **1c**	 **2c**	90
4	 **1d**	 **2d**	71
5	 **1e**	 **2e**	95
6	 **1f**	 **2f**	54
7	 **1g**	 **2g**	55
8	 **1h**	 **2h**	64
9	 **1i**	 **2i**	72
10	 **1j**	 **2j**	78

[a] Isolated yield based on 2-alkenylphenylacetylene **1**.

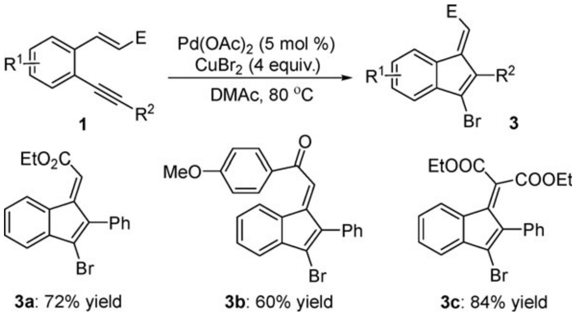


Scheme 2 The possible reaction mechanism.

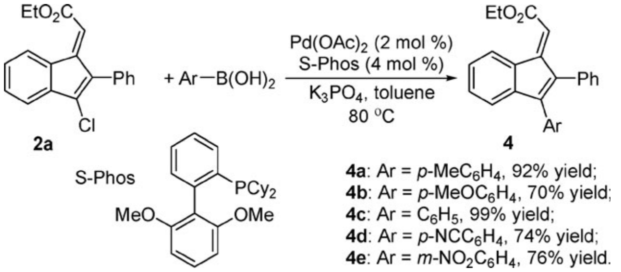
Dimethyl 2-benzylidenemalonate **1e** also worked well, leading to 3-chloro-1-methyleneindene **2e** in 95% yield (Table 1, entry 5). Substrates **1f–1j** were also examined, and the reactions proceeded smoothly to generate the desire products (Table 1, entries 6–10). Additionally, we have proposed a possible mechanism (Scheme 2) that is generally explained by a nucleophilic addition of chloride onto the Pd(II)-activated C≡C triple bond. This Pd(II) complex renders the C≡C triple bond moiety electrophilic, so triggering the intermolecular attack of chloride, giving rise to corresponding intermediate **A**. Insertion into the double bond and subsequent β-hydrogen elimination leads to the generation of desired product **2** and concomitant formation of Pd(0) in the presence of base, which then oxidizes it to Pd(II)[15a,16] so as to re-enter the catalytic cycle.

We also tested the Pd-catalyzed reactions of 2-alkenylphenylacetylene **1** in the presence of copper(II) bromide (Scheme 3). These reactions also proceeded well to afford bromo-containing indenes **3** in good yields.

After the successful generation of 3-chloro- and 3-bromo-1-methyleneindenes, we considered the introduction of more diversity into the indene scaffold *via* Pd-catalyzed cross-coupling reactions. Thus, the Suzuki reaction was investigated. After optimization, we identified that the combination of $Pd(OAc)_2$ and *S*-Phos showed high efficiency as a catalyst for the reaction of 3-chloro-1-methyleneindene (**2a**) with arylboronic acids (Scheme 4). For example, a 92% yield of product **4a** was obtained when 4-methylphenyl-boronic acid was employed in a reaction with 3-chloro-1-methyleneindene (**2a**). The structure of compound **4a** was also verified by X-ray crystallography.§



Scheme 3 The Pd-catalyzed reaction of 2-alkenylphenylacetylenes **1** in the presence of $CuBr_2$.



Scheme 4 Pd-catalyzed cross-couplings of **2a** with arylboronic acids.

In conclusion, we have described a novel and efficient method for the synthesis of highly functionalized 1-methyleneindenes *via* sequential Pd-catalyzed tandem cyclization and cross-coupling reactions of 2-alkenylphenylacetylenes **1**. The use of the substrates in other transformations is under investigation, and the results will be reported in due course.

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Notes and references

§ Crystal data and structure refinement for compound **4a**: empirical formula $C_{26}H_{22}O_2$ (molecular weight = 366.44), crystal system = monoclinic, unit cell dimensions a = 10.1464(3), b = 10.1719(3), c = 10.4892(3) Å, α = 72.9430(10), β = 79.8270(10), γ = 81.8610(10)°, volume = 1014.04(5) A^3, refine_1s_shift/su_max = 0.058, mean = 0.001, T = 296(2) K, space group = P-1, Z = 2, calculated density = 1.200 Mg m^{-3}Reflections collected/unique = 12010/3946 (R_{int} = 0.0246); final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0567, w$R2$ = 0.1464; R indices (all data): $R1$ = 0.0670, w$R2$ = 0.1593.‡

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