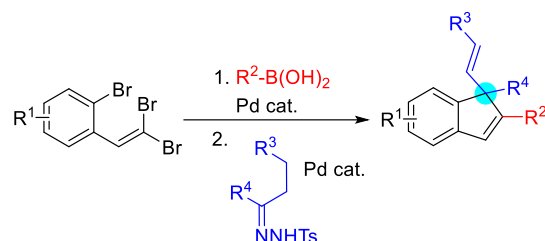


Synthesis of 1,1-disubstituted indenenes and dihydronaphthalenes through C-C/C-C bond forming Pd-catalyzed autotandem reactions

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Supporting Information Placeholder



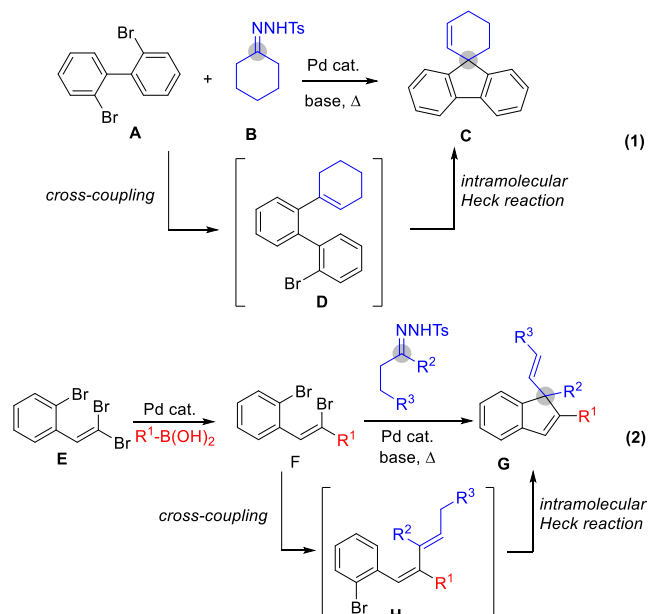
ABSTRACT: A novel synthesis of 1,1-disubstituted-1*H*-indenenes is described, involving the Pd-catalyzed cascade reaction between *o*-bromophenyl- β -bromostyrenes and *N*-tosylhydrazones in a process comprising the consecutive formation of two Csp³-C bonds on the same carbon atom: the cross-coupling of the *N*-tosylhydrazone with the alkenylbromide, and the intramolecular Heck reaction on the newly formed double bond. A similar approach has been applied to the preparation of 1,1-disubstituted naphthalenes.

Palladium-catalyzed cascade reactions stand nowadays as highly reliable methods for the construction of carbo- and heterocyclic complex molecules.¹ In these processes, various C-C or C-heteroatom bonds are formed in one single reaction, enabling the creation of molecular complexity from relatively simple starting materials. Within these methodologies, those processes in which the same catalyst promotes two or more individual bond forming reactions with distinct catalytic cycles, so called autotandem catalysis, represent a separate family that have experienced a notable development over the last two decades.² The construction of cyclic structures through autotandem catalysis relies on designs that combine sequential bond forming reactions on complementary ambidentate reaction partners. Following this general approach, over the last years a number of Pd-catalyzed methods for the synthesis of carbo- and heterocycles have been uncovered through the judicious programming of the C-C and C-heteroatom bond forming steps.³

In recent years, we have focused on the development of cascade reactions based on *N*-sulfonylhydrazones oriented to the synthesis of carbo and heterocycles.^{4,5} Thus, we have recently disclosed a new method for the synthesis of spirofluorenes through a Pd-catalyzed "autotandem" cascade. This process involves the formation of two consecutive C-C bonds on the same carbon atom by the reaction of 2,2'-dibromobiphenyl derivatives and *N*-tosylhydrazones (Scheme 1, eq 1).⁶ Noteworthy, two independent Pd-catalyzed reactions take place in a sequential manner: 1) cross-coupling of the *N*-tosylhydrazone with the aryl bromide,⁷ to generate the intermediate alkene D; 2) intramolecular Heck reaction of the intermediate D, that provides the final product C through a 5-*exo*-trig cyclization. This approach

proved to be fairly general, and allowed for the preparation of a wide variety of spirofluorenes and related structures with extended π -conjugation.

Scheme 1. (1) Synthesis of spirofluorenes by Pd-catalyzed autotandem reaction between 2,2'-dibromobiphenyls and *N*-tosylhydrazones. (2) Synthesis of 1,1-disubstituted-1*H*-indenenes discussed in this work.



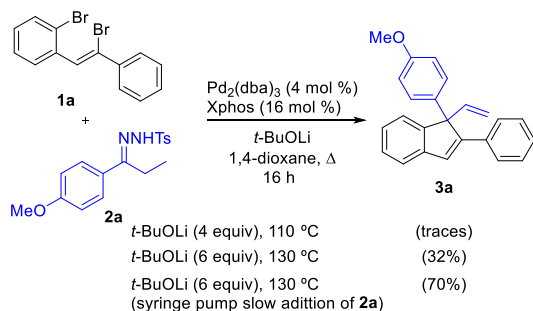
To continue with the exploration of the synthetic usefulness of this general approach, we decided to investigate the participation of an alkenyl halide instead of one of the aryl halides in the tandem reaction, and therefore, replace one of the aromatic rings by a C-C double bond. This new process might lead to new classes of substituted indenenes G featuring an all-carbon quaternary stereocenter (Scheme 1, eq 2).

Noteworthy, indenenes are an important family of carbocycles present in a wide variety of molecules with biological activity and therapeutic applications,⁸ as well as in materials chemistry.⁹ Indeed, the development of efficient methods for the synthesis of indenenes has attracted great attention in recent years.¹⁰ In particular, the main routes for the synthesis of 1,1-disubstituted-1*H*-indenenes are intramolecular processes: (i) electrophilic cyclizations,¹¹ (ii) rearrangements of naphthols.¹² Unlike the existing methods, in our design, the five membered ring of the indene is constructed through an intermolecular reaction, by formation of two bonds on the same carbon atom in the tandem process. Moreover, the required dihalides F could be easily prepared from the corresponding *o*-bromo-1,1-dibromostyrenes E, also through cross-coupling chemistry,^{13,14} rendering a highly modular synthesis of the 1,1,3-trisubstituted indenenes G.

At the outset of the project we anticipated that the proposed cascade reaction might be a quite challenging transformation. Taking into consideration the relative reactivity of vinyl and aryl bromides towards oxidative addition to Pd(0) species, it should be expected that the process would start by the vinyl bromide position to give the diene H. However, the cross-coupling reactions of vinyl halides with *N*-tosylhydrazones to give 1,3-dienes had been poorly studied,¹⁵ and in some cases very modest yields were reported. Indeed, a very recent study from our laboratory, revealed that a requisite for the successful cross-coupling of *N*-tosylhydrazones with alkenyl bromides was the employment of sterically hindered vinyl bromides.¹⁶ This observation set the basis for the development of the new tandem process.

Thus, we selected as prototype substrates for the tandem reaction the dibromide 1a, and the tosylhydrazone 2a derived from 4-methoxypropiophenone (Scheme 2). Noteworthy, *N*-tosylhydrazone 2a had been competent in the auto-tandem reactions with 2,2'-dibromobiphenyls.

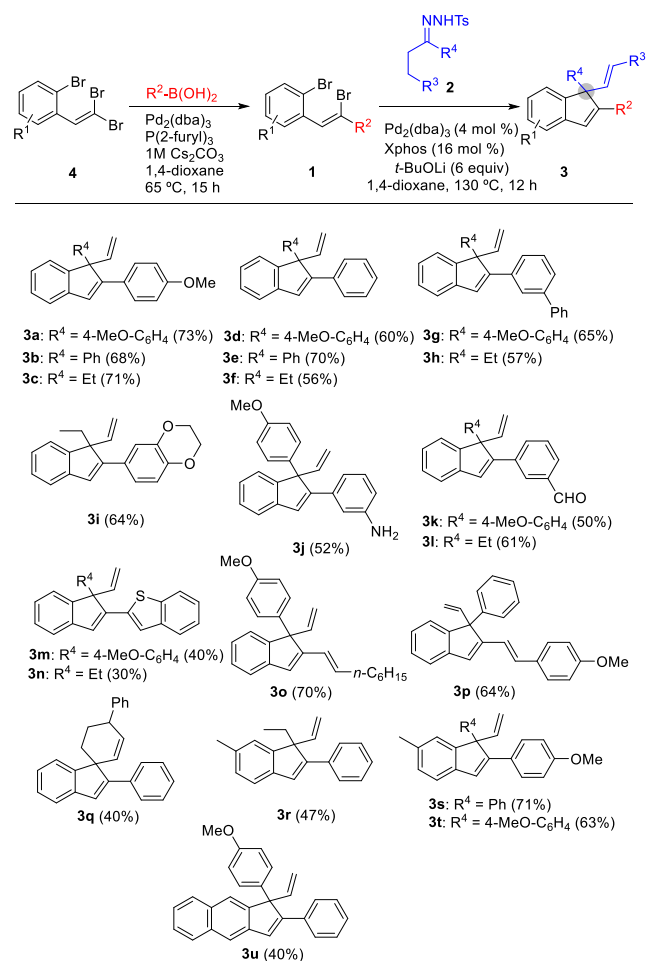
Scheme 2. Selected experiments of the optimization of the auto-tandem reaction of 1a with 2a for the synthesis of indene 3a



In an initial experiment, 1a was reacted with two equiv of 2a under the conditions previously described for the reactions with 2,2'-dibromobiphenyl: Pd₂(dba)₃ (4 mol %), Xphos, (16 mol %), *t*-BuOLi, 1,4-dioxane, 110 °C. The reaction was quite sluggish, although the indene derived from the autotandem process could be detected by

GC-MS, albeit in very poor yield. Increasing the amount of base to 6 equiv and rising the temperature to 130 °C the indene 3a could be isolated in a promising 32% yield. In an attempt to improve the yield of the cascade reaction, an array of different conditions was examined, with variations in the base, ligand and Pd source. Nevertheless, the employment of the Pd₂(dba)₃/Xphos catalytic system in the presence of 6 equiv of *t*-BuOLi turned out to provide the best results. The main subproduct formed in the course of the reactions was 1-(4-methoxyphenyl)propene, which derives from the thermal uncatalyzed decomposition of the *N*-tosylhydrazone. Formation of this subproduct takes place when the catalyzed reaction is too slow, and therefore the uncatalyzed reaction outcompetes the catalyzed process. To minimize the undesired background reaction and synchronize the decomposition of the *N*-sulfonylhydrazone with the catalytic turnover, different experiments with slow addition of the hydrazone 2a were attempted. Indeed, by slow syringe pump addition of the solution of 2a to the reaction mixture a substantial improvement in the reaction yield could be achieved, to obtain the indene 3a derived from the cascade reaction in a 70% yield.

Scheme 3. Synthesis of 1,1-disubstituted-1*H*-indenenes through the Suzuki coupling – Pd-catalyzed autotandem sequence.^{a,b}



^aReaction conditions for the second step: Dibromide 1 (0.1 mmol), Pd₂(dba)₃ (4 mol %), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) (16 mol %), lithium *tert*-butoxide (0.6 mmol, 6 equiv) and 1,4-dioxane (1.2 mL); *N*-tosylhydrazone 2 (2 equiv) in 1,4-dioxane (1.2 mL) is added via syringe pump over 2 h at 130 °C and kept at 130 °C for 16h.

The optimized reaction conditions were applied for the preparation of a collection of unprecedented 1,1-disubstituted-1*H*-indenes 3 (Scheme 3). Taking advantage of the modularity of the synthetic approach, it was possible to prepare a structural variety of indenes 3 by combining the stereoselective Suzuki-Miyaura cross-coupling that leads to dibromides 1 with the Pd-catalyzed autotandem reaction. With regard to the structure of the *N*-tosylhydrazone, reaction proceeded successfully for *N*-tosylhydrazones obtained from ethyl ketones, featuring either an aliphatic or an aromatic substituent, leading to 1*H*-indenes substituted with a vinyl and an aryl or alkyl substituent at the quaternary C1. Moreover, the employment of a cyclic *N*-tosylhydrazone led to the obtention of a spiroindene derivative 3r, although with only moderate yield.¹⁷

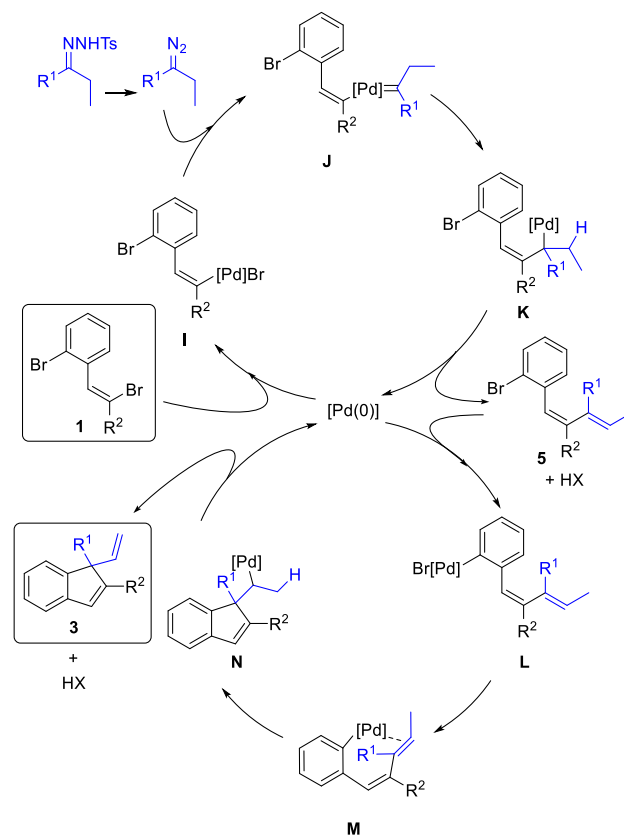
The reaction is highly general regarding the substitution at position 2 of the indene, which is incorporated in the first step of the synthesis through the Suzuki reaction from the tribrominated precursor 4 (Scheme 3). Thus, different aryl substitutions can be incorporated at C2. Importantly, the reaction tolerates the presence of potentially reactive functional groups such as unprotected formyl (3k, 3l) and amine NH₂ groups (3j) which could be employed to insert the indenyl fragment into more complex structures. Additionally, heteroaryl (3m, 3n) and alkenyl (3o, 3p) substituents can be introduced at C2. Finally, diversity in the benzene ring of the indene nucleus can be introduced by selecting a proper tribrominated precursor as illustrated by examples 3r-3u.

Mechanistic considerations: The key for the modular synthesis of indenes presented above takes advantage of the different reactivity of the three bromides present in the initial precursor 4. In the first step, the Suzuki cross-coupling takes place in a stereoselective manner at the less hindered *trans*-bromine position leading to 1.^{14b,18} Then, the coupling reaction with the *N*-tosylhydrazone might occur to either the alkenyl or the aryl bromide, as both intermediates would give rise to the same final product upon intramolecular Heck reaction. Nevertheless, it is well known that the oxidative addition to Pd(0) complexes is usually faster for alkenyl than for aryl bromides.¹⁹ Thus, we propose a first catalytic cycle that involves oxidative addition, formation of Pd-carbene complex J, migratory insertion to give K, and β-hydride elimination that releases diene 5 and the Pd(0) catalyst. Then, diene 5 enters a second catalytic cycle through an oxidative addition of the aryl bromide to generate L. Finally, 5-*exo*-trig carbopalladation and a second β-hydride elimination gives rise to the indene 3 (Scheme 4).

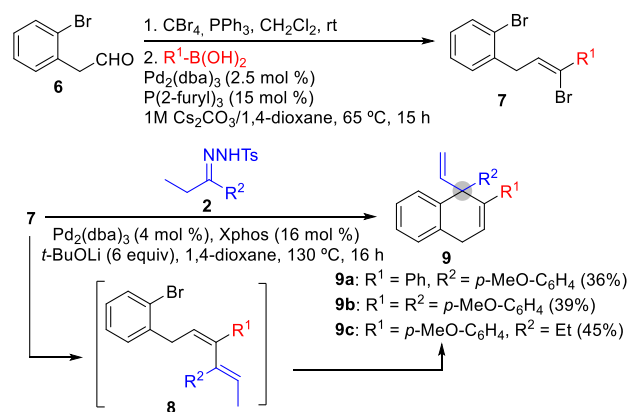
To expand the same method to other scaffolds, the same cascade reaction was considered with dibromide 7, that incorporates an additional methylene group. We expected that a similar sequence would provide dihydronaphthalenes 9 through a Pd-catalyzed cascade involving 6-*exo*-trig cyclization in the second step. The required dibromides 7 were easily prepared following the same Corey-Fuchs olefination/Suzuki cross-coupling sequence from *o*-bromophenylacetaldehyde 6. Then, the reaction with *N*-tosylhydrazones 2 under the similar conditions developed for the synthesis of indenes 3 led to the expected dihydronaphthalenes 9, although in substantially lower yields than the analogous reactions discussed above. In all cases, the reaction crude showed the presence of dihydronaphthalene 9 together with minor amounts of intermediate 8, revealing that the 6-

exo-trig cyclization is clearly less favourable than the 5-*exo*-trig. Nevertheless, the cascade reaction is still interesting, as it gives access to an unknown class of substituted dihydronaphthalenes.

Scheme 4. Mechanism proposed for the Pd-catalyzed autotandem sequence.



Scheme 5. Synthesis of 1,1-disubstituted-1,4-dihydronaphthalenes 9.^a



^aReaction conditions for the Pd-catalyzed autotandem reaction as is Scheme 3.

In summary, we have presented a new Pd-catalyzed C-C/C-C bond forming cascade that leads to unprecedented classes of indene derivatives featuring a quaternary stereocenter. The process involves the reaction of a *N*-tosylhydrazone with *o*-bromophenyl-β-bromostyrene derivatives through a cross-coupling/intramolecular Heck reaction sequence. Moreover, the same strategy could be applied for the preparation of dihydronaphthalenes. Interestingly, the cyclic

moieties are built through original [4+1] and [5+1] approaches, respectively, by formation of two C-C bonds on the same carbon atom. Additionally, the modularity of the synthesis allows for the preparation of a wide structural variety of these condensed cyclic structures.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, compound characterization data, and NMR spectra for compounds 1, 3, 4, 7, and 9 (PDF)

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