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Tetrahedron Letters 49 (2008) 3713–3715
Tetrahedron Letters

Synthesis of 1-arylidene-2,3-dihydro-1*H*-inden-2-ols through a tandem carbopalladation/Suzuki–Miyaura sequence

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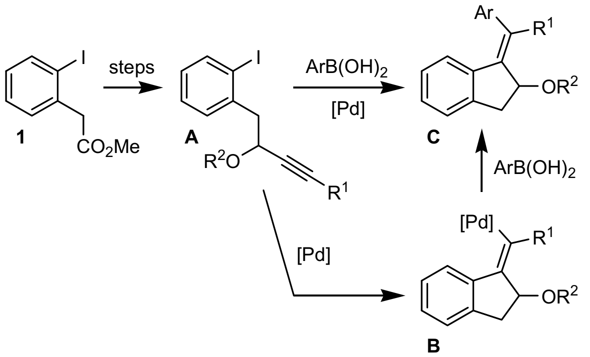
Received 14 March 2008; revised 2 April 2008; accepted 7 April 2008
Available online 10 April 2008

Abstract

A regio- and stereoselective synthesis of arylidene indenols has been developed. The key step involves a palladium-catalyzed tandem carbocyclization/Suzuki–Miyaura sequence.

Metal-catalyzed carbocyclization/cross-coupling reaction has emerged as one of the most versatile and powerful methods for the construction of polycyclic molecules from acyclic precursors.[1] Recently 3-alkylidene oxindoles, an important class of natural alkaloids, were prepared by intramolecular Heck reaction of arylbromides or iodides to alkynes involving terminations of insertion cascades as Sonogashira, Suzuki–Miyaura, or Heck cross-coupling reactions.[2] Zhu and co-workers achieved the synthesis of 3-arylidene oxindoles via a novel approach based on the multicomponent reaction concept using a palladium-catalyzed domino Songashira/carbopalladation/C–H activation/C–C bond forming sequence.[3] Cyclocarbopalladation of alkynes following a Suzuki–Miyaura cross-coupling termination was also employed for the synthesis of dibenzoxapines.[4] One example reported in the literature described the preparation of alkylidene indenols by an intramolecular domino Heck double cyclization.[5]

As a continuation of our ongoing work on the preparation of potent photoprotective compounds,[6] we report herein our preliminary studies on the preparation of arylidene indenols. The general approach we have employed is outlined in Scheme 1. The key step was the projected tandem cyclocarbopalladation/Suzuki–Miyaura coupling sequence. In this Letter, we describe a cascade bond formation proceeding smoothly by the use of palladium diacetate–triphenylphosphine as catalyst's system in the presence of CsF as base.



Scheme 1. General approach.

Substrates **3–6** for the tandem reaction were synthesized in correct yields in few steps from the methyl 2-(2-iodophenyl)acetate **1** (Scheme 2).

In an initial investigation, **3** was employed as the model substrate in combination with $PhB(OH)_2$ to examine the best reaction conditions. Various palladium sources, bases, and solvents were tested but no satisfactory and reproducible result was observed. Probably the presence of the free

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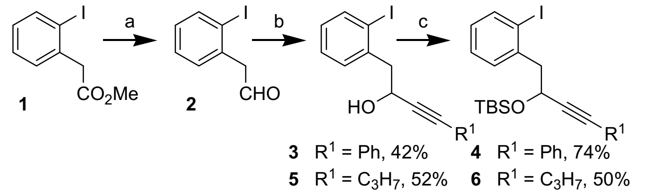
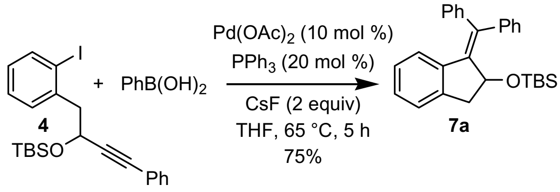
doi:10.1016/j.tetlet.2008.04.042



Scheme 2. Synthesis of substrates **3–6** for the tandem reaction. Reagents and conditions: (a) DIBAH, Tol, −78 °C, 4 h (82%); (b) R^1–C≡CH, BuLi, THF, 0 °C then **2**, THF, rt, 12 h; (c) TBSCl, Im, CH_2Cl_2, rt, 12 h.

hydroxyl group raises problem. Compound **4**, prepared after protection of the hydroxyl group of **3** as silylether, was then submitted to various condition reactions. Best conversions and yields were obtained by the use of 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, CsF as the base upon THF at 65 °C (Eq. 1). We subsequently discovered that the reaction is dependent on the base and solvent employed. For example, in toluene instead THF or with K_3PO_4 as the base, the starting material **4** was partially recovered after 12 h (50–85% conversion following the reaction conditions).



(1)

Only regioisomer **7a** was isolated resulting from the formation of organopalladium **B** (Fig. 1). Based on the previous observations of Overman et al. with alkenes, the preferential formation of *exo*-arylidene organopalladium intermediate **B** could be explained by the preference for eclipsed alignment of the Pd–C σ and alkyne π bonds (as opposed to twisted leading the *endo* intermediate **D**) in the carbopalladation step.[7]

Under these optimized conditions, various arylboronic acids can be used to afford the products uniformly in high yields (Table 1).[8] The nature of the arylboronic acid does not seem to have influence on the result of the reaction. As expected, this tandem reaction is regio- and stereoselective, only the *E* isomer was obtained.

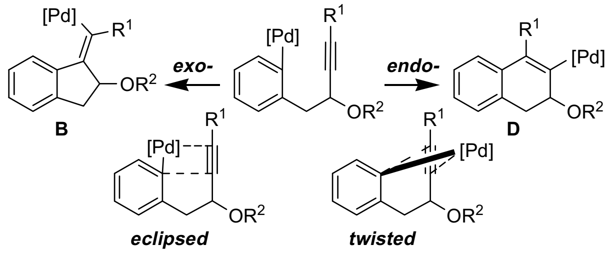
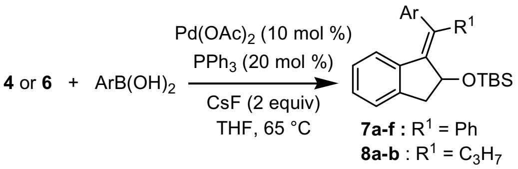


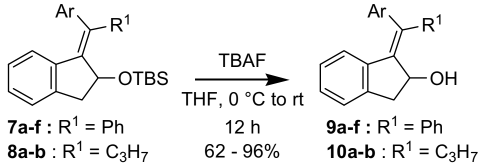
Fig. 1. Eclipsed versus twisted alignment.

Table 1
Palladium-catalyzed tandem reactions



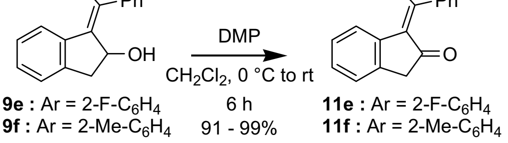
Entry	Substrate	Ar	Time (h)	Product	Yield[a] (%)
1	**4**	C_6H_5	5	**7a**	75
2	**4**	3,4-$(MeO)_2C_6H_3$	20	**7b**	71
3	**4**	3-Thienyl	20	**7c**	58
4	**4**	4-NHBoc–C_6H_4	3	**7d**	70
5	**4**	2-F–C_6H_4	20	**7e**	72
6	**4**	2-Me–C_6H_4	24	**7f**	77[b]
7	**6**	C_6H_5	20	**8a**	86
8	**6**	3,4-$(MeO)_2C_6H_3$	20	**8b**	75

[a] Isolated yield (average of two or three runs).
[b] 2 equiv arylboronic acid and 2.5 equiv CsF.



(2)

Desilylation of indenols **7** and **8** with TBAF in THF led to indenols **9** and **10** in good yields (Eq. 2). A careful analysis of the ^{1}H and ^{13}C NMR spectra of the silylated indenols **7e** and **7f** and deprotected indenols **9e** and **9f** showed that these derivatives were isolated as inseparable mixtures of two isomers in a 1/1 ratio. At first we thought that products were obtained as a mixture of *E* and *Z* isomers resulting from an isomerization in the course of the reaction. However, this hypothesis was quickly abandoned. Indeed oxidation of **9e** and **9f** with the Dess–Martin periodinane gave indenones **11e** and **11f** isolated as single compounds in quantitative yields (Eq. 3). We suppose that there is an absence of free rotation of the carbon–carbon bond bearing the *ortho*-substituted aromatic ring. Consequently, derivatives **7e**, **7f**, **9e**, and **9f** possess two sources of chirality; a stereogenic center disappearing during the oxidation step and a conformational chirality because of the hindrance of the free rotation of the C–C bond (Fig. 2).[9] The silylated indenols **7e** and **7f** and indenols **9e** and **9f** are thus obtained as mixtures of atropoisomers.



(3)

With the optimized palladium-catalyzed process in hand, we turned our attention to the preparation of 2*H*-indeno [2,1-*b*] furan-2-one **15** (Scheme 3). The transformation of aldehyde **2** into the precursor of cyclization **13** was readily

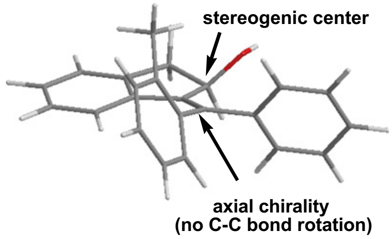
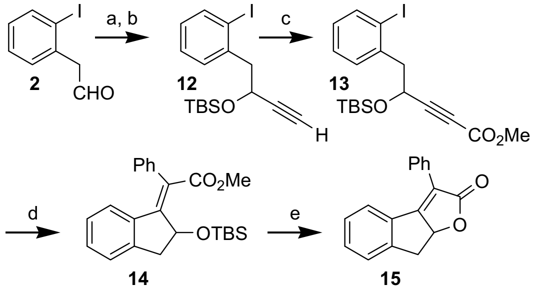


Fig. 2. Chem3D view of **9f**.



Scheme 3. Synthesis of indenofuranone **15**. Reagents and conditions: (a) HC≡C–TMS, *i*-PrMgCl, THF, 0 °C then 2, 0 °C to rt, 3 h (80%); (b) (i) TBSCl, Im, CH_2Cl_2, rt, 6 h; (ii) K_2CO_3 cat, MeOH, 10 h (85%); (c) 12, *i*-PrMgCl, THF, 0 °C then $ClCO_2Me$, 0 °C to rt, 3.5 h (64%); (d) $PhB(OH)_2$, 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, CsF, THF, 65 °C, 6 h (84%); (e) CF_3CO_2H (excess), THF/H_2O (1:1), 12 h (86%).

achieved in three steps. Reaction of **13** with $PhB(OH)_2$ in the presence of $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %) and CsF (2 equiv) in THF promoted the carbocyclization/cross-coupling sequence to give **14** in a high yield (84%). The desilylation–lactonization step was effected in good yield by the use of an excess of trifluoroacetic acid in THF-water at room temperature. The formation of this lactone confirms also the stereospecificity of the palladium-catalyzed cyclization/cross coupling reaction.

In summary, we have developed an efficient palladium-catalyzed tandem carbopalladation/Suzuki–Miyaura sequence for the synthesis of a series of arylidene indenols. By varying arylboronic acids we have in hand a procedure which allows to reach indenols with a wide diversity. This approach provides a straightforward tool for further synthetic applications. A study of photoprotective properties of these arylidene indenols is undertaken and the results will be reported in due course.

Acknowledgments

We gratefully acknowledge the CRMPO for mass measurements. We thank the Région Bretagne for the fellowship to E.M. Financial support of this project by the Université de Rennes 1 and Rennes Métropole is gratefully acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.042.

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8. *General procedure for tandem cyclization/cross-coupling reaction*: Under Ar to a solution of **4** or **6** (0.11 mmol) in 1 mL of anhydrous THF were added PPh_3 (0.022 mmol), arylboronic acid (0.17 mmol), CsF (0.22 mmol) and $Pd(OAc)_2$ (0.011 mmol). The reaction mixture was stirred at 60 °C. After the disappearance of the starting material, the reaction mixture was partitioned between water and ethyl acetate, the organic layers were extracted twice with ethyl acetate, washed with brine, and dried (Na_2SO_4). The solvents were removed under reduced pressure and the crude product was chromatographed on silica gel (eluent: cyclohexane/CH_2Cl_2 = 9/1).
9. This representation is freely inspired from X-ray structures published: see 3a and Kapoor, M.; Dhawan, S. N.; Mor, S.; Bhatia, S. C.; Gupta, S. C.; Hundal, M. S. *Tetrahedron* **2003**, *59*, 5027–5031.