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SHORT COMMUNICATION

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Regioselective Construction of Indene Skeletons by Palladium-Catalyzed Annulation of Alkynylborates with *o*-Iodophenyl Ketones

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A palladium-catalyzed annulation reaction of alkynylborates with *o*-iodophenyl ketones to form indenes is described. Highly substituted indene skeletons are efficiently constructed with site-specific installation of the substituents.

Introduction

Indenes are important structural motifs found in a number of biologically active compounds.[1] For example, an indene framework with an *exo*-alkylidene moiety is imbedded in sulindac, which is a nonsteroidal antiinflammatory drug,[1a] and dimethindene, an oral antihistamine agent, has an indene core tethered to an amine moiety.[1b] In addition to these commercial medicines, indene derivatives have also been exploited as materials for optoelectronics[2] and as ligands for transition-metal complexes.[3] Consequently, the development of a new method for constructing indene skeletons is an attractive subject in organic synthesis.[4]

Alkynylboron compounds have been utilized as useful intermediates in organic synthesis.[5] We have previously developed the palladium-catalyzed reaction of alkynylborates with aryl halides;[6] (trisubstituted alkenyl)boranes, which are otherwise difficult to synthesize, can be readily obtained in a regio- and stereoselective fashion by this method. In this work, we extended the scope of this palladium-catalyzed reaction to the construction of indene skeletons. Alkynylborates react with *o*-iodophenyl ketones to afford 2,3-disubstituted indenols with specific installation of substituents at the 2- and 3-positions.

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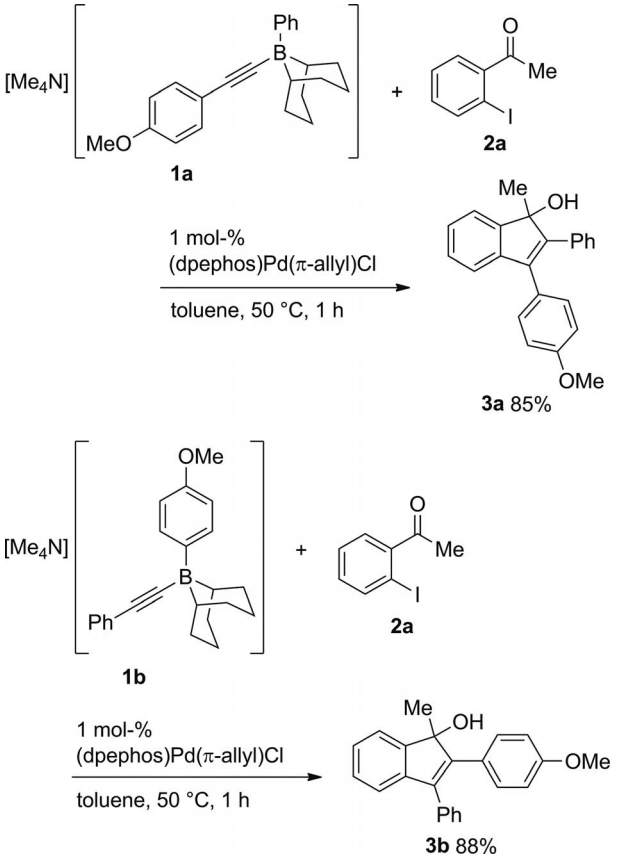
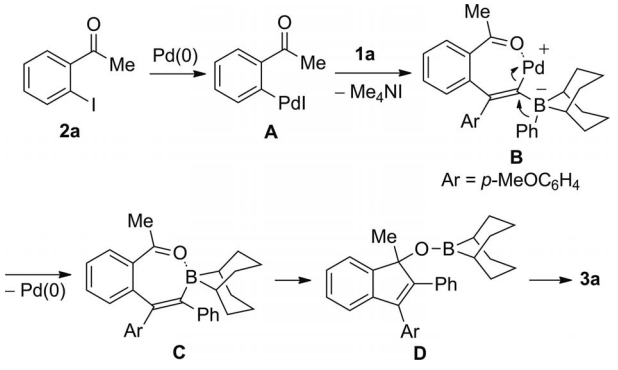
Results and Discussion

Alkynylborate **1a** and its constitutional isomer **1b** were prepared from the corresponding *B*-aryl-9-borabicyclo[3.3.1]nonane (Ar-9-BBN) and terminal alkyne according to the reported method.[6c] The borate **1a** (1.0 equiv.) was treated with *o*-iodoacetophenone (**2a**; 1.05 equiv.) in the presence of [(dpephos)Pd(π-allyl)Cl] (1 mol-%) at 50 °C for 1 h (Scheme 1). The reaction mixture was then treated with hydrogen peroxide to oxidize the organoboron residue. Purification by column chromatography on silica gel afforded 2,3-diarylindenol **3a** in 85% yield. In contrast, the reaction of the borate **1b** with **2a** selectively provided the regioisomeric indenol **3b** in 88% yield. Thus, this palladium-catalyzed reaction makes possible the selective production of both regioisomers of 2,3-diarylindenols, which is difficult to achieve by using the conventional annulation reaction of *o*-halophenyl ketones with 1,2-diarylalkynes.[4h]

The selective formation of **3a** from **1a** and **2a** can be explained by the mechanism shown in Scheme 2, which is based on the mechanism proposed for the palladium-catalyzed reaction of alkynylborates with simple aryl halides.[6c] Oxidative addition of **2a** to palladium(0) leads to arylpalladium **A**. Regioselective *cis*-carbopalladation across the carbon–carbon triple bond of **1a** gives alkenylpalladium **B**. The phenyl group on the anionic boron migrates onto the α carbon atom and the carbon–palladium bond is substituted with inversion of the stereochemistry to afford alkenylborane **C**.[7] The ketone moiety remains intact during the course of the palladium-catalyzed reaction; the generated *B*-alkenyl-9-BBN moiety undergoes intramolecular addition at the carbonyl group[8] to form the boron indenolate **D**. Upon oxidative work-up with $NaOH/H_2O_2$, **D** is hydrolyzed to the indenol **3a**.



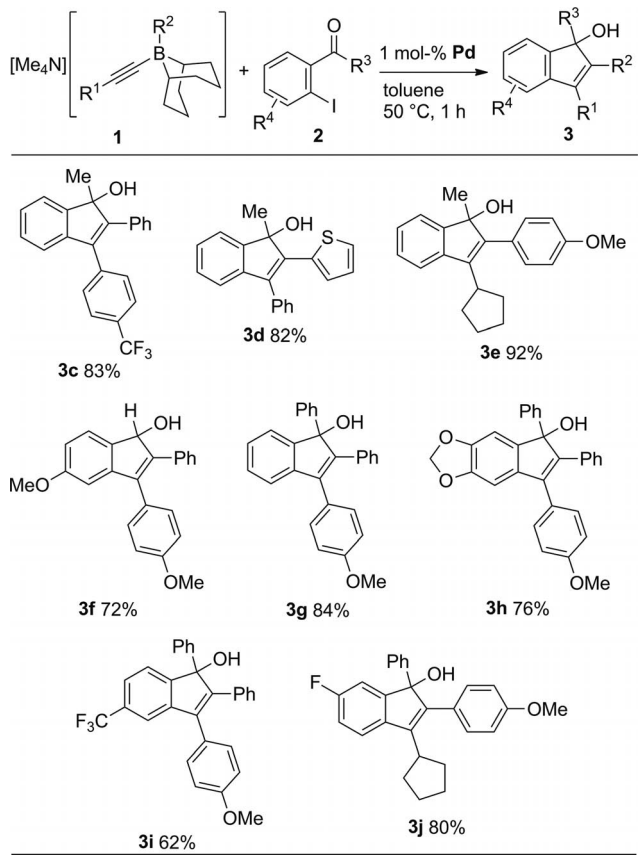
Scheme 1. Reactions of alkynylborates **1** and *o*-iodoacetophenone (**2a**).



Scheme 2. Mechanism proposed for the formation of **3a**.

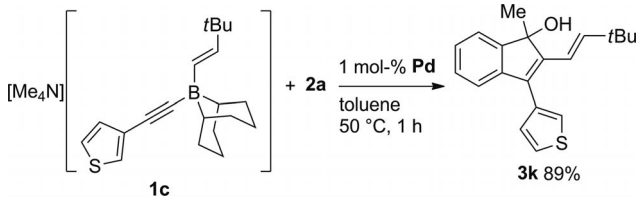
A wide variety of highly-substituted indenols have been generated by this reaction (Table 1). For example, thiophene-substituted **3d** and alkyl-substituted **3e** were obtained in yields of 82 and 92%, respectively. The use of *o*-iodobenzaldehyde and *o*-iodobenzophenone gave the corresponding indenols **3f** and **3g**. Indenols equipped with alkoxy, trifluoromethyl, and fluoro groups on the aromatic ring (**3h**–**j**) were also synthesized.

Table 1. Synthesis of indenols **3**.[a]



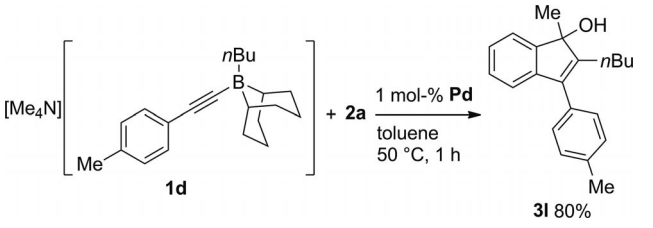
[a] Reagents and conditions: 1.0 equiv. of alkynylborate **1**, 1.05 equiv. of *o*-iodophenyl ketone **2**, 1 mol-% of [(dpephos)PdCl(π-allyl)], toluene, 50 °C, 1 h; then aq. H_2O_2, aq. NaOH, MeOH, room temp., 2 h. Isolated yields are shown.

Alkenyl-substituted **3k** and alkyl-substituted **3l** were also synthesized from *B*-alkenyl-9-BBN **1c** and *B*-alkyl-9-BBN **1d**, respectively; see Equations (1) and (2). The formation of **3l** is noteworthy from a mechanistic point of view; the *n*-butyl group on the anionic boron migrates onto the α-carbon atom in preference to the bridgehead sp^3 carbon of the 9-BBN framework.[9] This selectivity stands in sharp contrast to that observed in the reaction with iodine.[10]



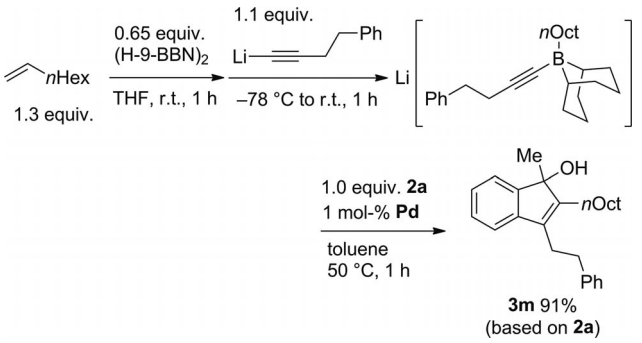
(1)

It was possible to directly synthesize 2,3-dialkylindenol **3m** in one-pot starting from 1-octene, 4-phenylbut-1-yne, and *o*-iodoacetophenone (**2a**) without isolation of the intermediates (Scheme 3). Hydroboration of 1-octene with H-9-BBN in THF afforded *B*-*n*-octyl-9-BBN, which was then



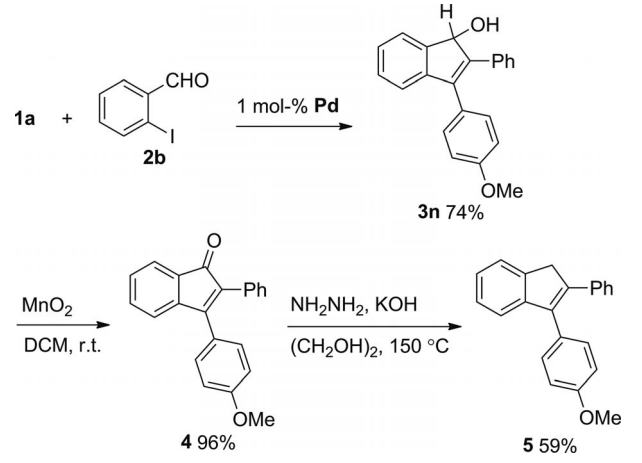
(2)

treated with 4-phenylbut-1-ynyllithium to form the corresponding lithium alkynylborate. A toluene solution containing *o*-iodoacetophenone (**2a**) and [(dpephos)Pd(π-allyl)Cl] was then added to the reaction mixture, which was heated at 50 °C for 1 h. Oxidative work-up and purification by column chromatography furnished **3m** in a 91% isolated yield based on **2a**.



Scheme 3. Synthesis of indenol **3m** from 1-octene.

The palladium-catalyzed annulation of **1a** with **2b** gave indenol **3n** in 74% yield, which was subjected to further derivatization (Scheme 4). Oxidation of **3n** with manganese(IV) oxide furnished the indenone **4**. The following Wolff–Kishner reaction reduced the carbonyl group without isomerization of the double bond to give indene **5** in 59% yield.[11]



Scheme 4. Synthesis of indenone **4** and indene **5**.

Conclusions

We have described the palladium-catalyzed annulation reaction of alkynylborates with *o*-iodophenyl ketones. A wide variety of highly substituted indenols can be regiospecifically synthesized by this method.

Experimental Section

Procedure for the Palladium-Catalyzed Reaction of Alkynylborate 1a with *o*-Iodoacetophenone (2a): Under argon, a toluene solution (1.0 mL) of alkynylborate **1a** (80.68 mg, 0.20 mmol), [(dpephos)PdCl(π-allyl)] (1.44 mg, 0.002 mmol), and *o*-iodoacetophenone was stirred for 1 h at 50 °C. Aqueous H_2O_2 (0.5 mL, 30 wt.-%), aqueous NaOH (0.5 mL, 20 wt.-%), and MeOH (0.5 mL) were added to the reaction mixture at 0 °C. After stirring for 2 h at room temperature, the resulting mixture was diluted with water and extracted with ethyl acetate (3× 15 mL). The combined organic layers were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography on silica gel (hexane/ethyl acetate = 5:1) to afford the indenol **3a** (55.9 mg, 0.17 mmol, 85% yield).

3a: ^{1}H NMR: δ = 1.59 (s, 3 H), 2.04 (br. s, 1 H), 3.82 (s, 3 H), 6.84–6.90 (m, 2 H), 7.21–7.30 (m, 8 H), 7.42–7.48 (m, 2 H), 7.51–7.55 (m, 1 H) ppm. ^{13}C NMR: δ = 23.9, 55.2, 83.2, 113.9, 120.8, 121.8, 126.5, 126.8, 127.2, 128.0, 128.4, 129.4, 130.5, 135.0, 138.2, 142.3, 146.2, 149.6, 158.9 ppm. IR (ATR): $\tilde{\nu}$ = 3315, 1508, 1248, 752, 694 cm^{-1}. HRMS (ESI$^+$): calcd for $C_{23}H_{21}O_2$ [M + H]$^+$ 329.1536; found 329.1556.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data of new compounds, ^{1}H and ^{13}C NMR spectra of compounds **3**–**5**.

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