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Palladium(0)-Catalyzed Regioselective and Multicomponent Synthesis of 1,2,3-Trisubstituted 1*H*-Indenes

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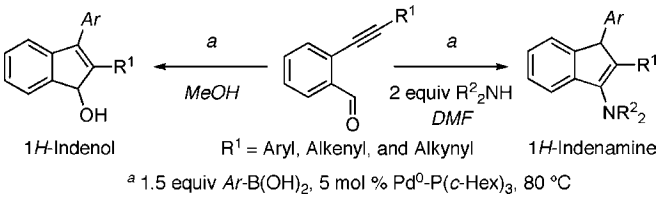
ABSTRACT



A multicomponent synthesis of biologically important indenes bearing three substituent groups at the 1-, 2-, and 3-positions from available *o*-ethynylbenzaldehyde derivatives and organoboron reagents under palladium(0) catalysis is described. A two-component coupling reaction in methanol provides 1*H*-indenols, whereas a three-component reaction involving secondary aliphatic amines as the third component in DMF affords 1*H*-indenamines. This method allows combinatorial preparation of unsymmetrically substituted 1*H*-indenes that cannot be prepared via previous synthetic routes.

The increasing significance of combinatorial chemistry in pharmaceutical and material sciences demands the development of new strategies to synthesize a collection of analogues of interesting compounds.[1] Indenes are an important class of carbocyclic compounds that are biologically active, functional materials and structural constituents of metallocene-based catalysts for olefin polymerization.[2−4] Despite their utility, their preparative methods are fewer[5−11] than those for structurally related heterocycles such as indoles and benzofurans. For 1*H*-indenols **1**,[2a−e] most of their synthetic routes belong to carboannulation of internal alkynes **4** with *o*-(metalated)benzaldehydes generated in situ (Scheme 1, route A).[5−9] However, they cannot generate the opposite

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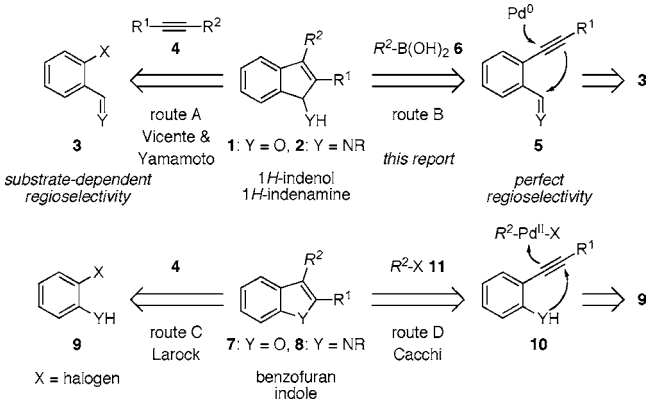
Scheme 1. Pd^0-Catalyzed Synthesis of **1**, **2**, **7**, and **8**

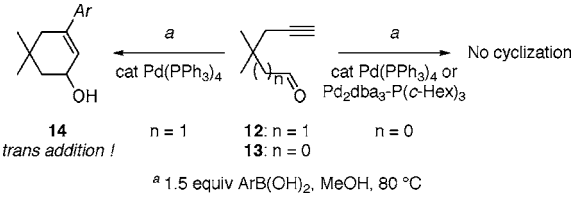


regioisomer (regiochemical diversity) because the regioselectivity of the carbocyclization using unsymmetrical alkynes **4** is under a powerful substrate control.

For benzofuran **7** and indole **8**, there are two types of Pd^0-catalyzed synthetic methods. The first method involves heteroannulation of internal alkyne **4** with *o*-halophenol or aniline **9**, which cannot increase regiochemical diversity (route C).[12] The second method is based on an intramolecular nucleophilic addition of the heteroatom in *o*-ethynylphenol or aniline **10** to the alkyne coordinated by electron-deficient R^2-Pd^{II}-X, which is generated in situ from organic halide **11** and Pd^0 (route D).[13] The second method has an advantage of regioselectivity over the first one and inspired us to develop its counterpart process for indenols **1**, namely, an intramolecular electrophilic addition of the carbonyl group in *o*-ethynylbenzaldehyde **5** to the alkyne coordinated by electron-rich Pd^0 and concomitant transmetalation with an organometallic reagent **6** (route B). Herein, we describe the indenol synthesis based on the alkylative cyclization of 4-alkynal **5**, easily prepared by Sonogashira reaction of *o*-bromobenzaldehydes **3** and terminal alkynes, with organoboron reagents. Furthermore, we have also developed a three-component coupling reaction employing secondary aliphatic amines as the third component to provide indenamines **2** selectively.

Recently, we discovered that the novel alkylative cyclization of 5-alkynal **12** with organoboron reagents is effective in the formation of 2-cyclohexen-1-ol **14** (Scheme 2).[14]

Scheme 2. Pd^0-Catalyzed Arylative Cyclization of **12** and **13**



However, the cyclization reaction proved to be dramatically affected by tether length of the alkynals, and 4-alkynal **13** did not cyclize with less σ-donating PPh_3 and more σ-donating P(*c*-Hex)$_3$ ligated palladium catalysts.

The cyclization of *o*-ethynylbenzaldehyde (**5a**) with *p*-tolylboronic acid (**6A**) upon heating at 80 °C in MeOH in the presence of a catalytic amount of tris(dibenzylideneacetone)dipalladium (Pd_2dba_3) and tricyclohexylphosphine was unsuccessful (Table 1, entry 1). Next, the effect of substituents at the terminal alkyne carbon on the cyclization reaction was investigated.

In contrast to the alkyl group, the aryl group at the terminal alkyne carbon leads to formation of 2,3-diaryl-1*H*-indenols **1cA**−**1gA** in high yields (Table 1, entry 2 vs entries 3−7).[14] Substituent groups attached to the *para* position on the terminal phenyl ring also affect the cyclization, which is slowed by an electron-donating dimethylamino group and accelerated by an electron-withdrawing nitro group (entries 4 vs 7). Other sp^2-hybridized heteroaryl, alkenyl, and sp-hybridized alkynyl groups at the terminal alkyne carbon also prove to be effective for the cyclization (entries 8−11). During the course of our investigation, (η^3-allyl)PdCp[15] turned out to be a more effective Pd source than Pd_2dba_3[16] (entries 9 vs 10). It is worth noting that chemoselective hydrogenation of the disubstituted olefin at the 2-position in the cyclized product **1iA** in the existence of tetrasubstituted alkene affords the 2-alkyl-3-aryl-1*H*-indenol **15** (Scheme 3), which could not be prepared by our or any previous methods[5−9] (cf. Table 1, entry 2).

These cyclization reactions also occur with arylboronic acids **6A**−**D** with electron-donating or -withdrawing groups

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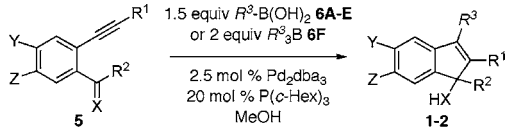
Table 1. Pd^0-Catalyzed Synthesis of 1*H*-Indenols **1**



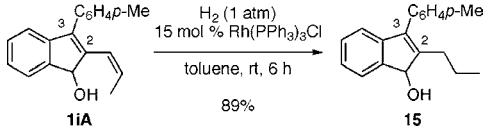
5a-j: R^2 = Y = Z = H, X = O
5k: R^2 = Me, Y, Z = OCH_2O, X = O
5l: R^2 = Ph, Y = Z = H, X = O
5m: R^2 = Y = Z = H, X = NBn
5n: R^2 = Y = Z = H, X = NPh
5o: R^2 = Y = Z = H, X = NTs

entry	5	R^1	R^3	product	time (h)	yield (%)
1[a]	**5a**	H	*p*-Me-C_6H_4 **6A**	**1aA**	24	0
2[a]	**5b**	Bu	**6A**	**1bA**	24	0
3[a]	**5c**	Ph	**6A**	**1cA**	9	85
4[a]	**5d**	*p*-Me_2N-C_6H_4	**6A**	**1dA**	24	80
5[a]	**5e**	*p*-MeO-C_6H_4	**6A**	**1eA**	9	87
6[a]	**5f**	*p*-Ac-C_6H_4	**6A**	**1fA**	9	74
7[a]	**5g**	*p*-NO_2-C_6H_4	**6A**	**1gA**	1	68
8[b]	**5h**	2-thiophene	**6A**	**1hA**	5	100
9[b]	**5i**	*cis*-propenyl	**6A**	**1iA**	18	68
10[b,c]	**5i**	*cis*-propenyl	**6A**	**1iA**	3	88
11[a,c]	**5j**	CCPh	**6A**	**1jA**	1	80
12[a]	**5c**	Ph	*p*-MeO-C_6H_4 **6B**	**1cB**	9	87
13[a]	**5c**	Ph	Ph **6C**	**1cC**	9	76
14[a]	**5c**	Ph	*p*-Ac-C_6H_4 **6D**	**1cD**	9	74
15[a]	**5c**	Ph	*cis*-propenyl **6E**	**1cE**	24	71
16[b,c]	**5c**	Ph	Et **6F**	**1cF**	1.5	81
17[b,c]	**5k**	*p*-Ac-C_6H_4	**6B**	**1kB**	1	97
18[b]	**5l**	Ph	**6A**	**1lA**	18	77
19[b,d]	**5m**	Ph	**6A**	**2mA**	24	0
20[b,d]	**5n**	Ph	**6A**	**2nA**	24	0
21[b,d]	**5o**	Ph	**6A**	**2oA**	24	73

[a] Reaction at 80 °C. [b] Reaction at 100 °C. [c] (η^3-Allyl)PdCp is used for Pd_2dba_3. [d] Reaction in *t*-BuOH.

(entries 3, 12−14). Generally, electron-rich boronic acids give higher yields than their electron-deficient counterparts. Alkenylboronic acid **6E** and triethylborane (**6F**) also participate in this process (entries 15 and 16).

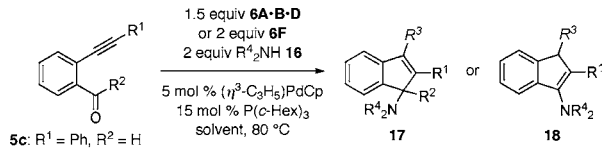
Scheme 3. Chemoselective Hydrogenation of **1iA**



Arylative cyclization reactions of phenylketones **5k,l** require higher temperatures but provide tertiary allylic alcohols in high yields (entries 17 and 18). Preparation of 1*H*-indenamines **2** from the corresponding aldimines **5m−o** was also explored to generate further diversity. However, only electron-withdrawing *p*-toluenesulfonyl substituted aldimine **5o** gives cyclized product **2oA** in good yield with reaction in *t*-BuOH to prevent decomposition of the imine moiety (entries 19 and 20 vs 21).

For introduction of amine functionality, a three-component reaction involving secondary amines as the third component was also examined, because more electrophilic iminium ion would be formed in situ (Table 2). Addition of an excess

Table 2. Pd^0-Catalyzed Synthesis of 1*H*-Indenamines **17** and **18**



5c: R^1 = Ph, R^2 = H
5f: R^1 = *p*-Ac-C_6H_4, R^2 = H
5l: R^1 = R^2 = Ph

entry[a]	5	6	16	product	time (h)	yield (%)
1[b]	**5c**	**6A**	Bn_2NH **16A**	**18cAA**	0.5	32[c]
2[b]	**5c**	**6A**	16A	**18cAA**	0.5	60
3[b]	**5c**	**6A**	16A	**18cAA**	1	56
4[b]	**5c**	**6A**	16A	**18cAA**	0.5	86
5	**5c**	**6A**	Et_2NH **16B**	**18cAB**	1	89
6	**5c**	**6A**	pyrrolidine **16C**	**18cAC**	1	56
7	**5c**	**6A**	morpholine **16D**	**18cAD**	1	100
8	**5c**	**6A**	*i*-Pr_2NH **16E**	**18cAE**	6	0
9	**5c**	**6A**	PhNHMe **16F**	**18cAF**	6	0
10	**5f**	**6B**	**16B**	**18fBB**	1	94
11	**5c**	**6D**	**16B**	**18cDB**	1	88
12	**5c**	**6F**	**16B**	**17cFB**	1	73
13	**5l**	**6A**	**16B**	**18lAB**	24	0

[a] Reactions in MeOH (entry 1), toluene (entry 2), THF (entry 3), and DMF (entries 4−13). [b] Reaction with 2 equiv of **6A** and 6 equiv of **16A**. [c] **1cA** is also obtained in 53% yield.

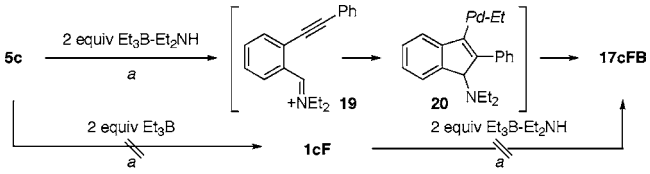
amount of dibenzylamine (**16A**) over **5c** and **6A** to the above reaction conditions resulted in formation of a mixture of 2,3-diaryl-1*H*-indenol **1cA** and 1,2-diaryl-1*H*-3-indenamine **18cAA**, which should be formed by isomerization of a thermodynamically unfavored 2,3-diaryl-1*H*-indenamine **17cAA** under basic conditions (entry 1).[10,17] Aprotic solvents prevent the formation of **1cA**, and most polar DMF leads to formation of **18cAA** in maximum yield (entries 2−4).

Both acyclic and cyclic secondary aliphatic amines **16B−D** participate in this process to afford 3-indenamines **18cA-(B−D)** in moderate to excellent yields (entries 5−7). Unfortunately, sterically hindered aliphatic amine **16E** and *N*-methylaniline (**16F**) gave no cyclized products (entries 8 and 9). In contrast to arylboronic acids **6A·B·D**, triethylborane (**6F**) provided 1*H*-1-indenamine **17cFB**, in which electron-donating ethyl group at 3-position decreased acidity of the proton at 1-position (entries 5, 10, and 11 vs 12). Nonenolizable ketone **5l** did not cyclize under the reaction conditions (entry 13). The reaction should not proceed through indenol formation but through iminium formation, since neither formation of indenol **1cF** under amine-free conditions nor conversion of **1cF** to indenamine **17cF** was observed (Scheme 4).

In summary, we have developed a new synthetic route for 1*H*-indenols and indenamines based on the Pd^0-catalyzed

(17) In some cases, mixtures of **17** and **18** were obtained but became single isomers **18** in $CDCl_3$ within 1 day.

Scheme 4. Plausible Mechanism without Indenol Formation



[a] 5 mol % (η^3-C_3H_5)PdCp, 15 mol % P(*c*-Hex)$_3$, DMF, 80 °C

trans-addition specific alkylative cyclization of *o*-ethynylbenzaldehydes with organoboron reagents. In addition to the functional group compatibility and additive-free conditions, completely regioselective introduction of aryl, alkenyl, and alkyl groups into the indene scaffold and availability of all building blocks make the process highly practical and suitable for combinatorial synthesis.

This study also gives us important information about the cyclization reaction as follows. (1) Aryl, alkenyl, and alkynyl groups at the terminal alkyne carbon would guide nucleophilic attack of the Pd^0 complex to the opposite alkyne position and are required for the cyclization of 4-alkynals. (2) Lewis acidity of the boron reagents would not be essential for the cyclization because it also goes well in the presence of secondary amines. (3) Methanol solvent, essential for the indenol synthesis and not for the indenamine synthesis, would work as hydrogen donor to activate less electrophilic carbonyl groups. Further studies probing the detailed mechanism and expanding the scope of the cyclization process are underway.

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Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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