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Synthesis of Substituted Indene Derivatives via Silver-Catalyzed Annulative 1:1 Coupling of Secondary Benzyl Alcohols with Alkynes

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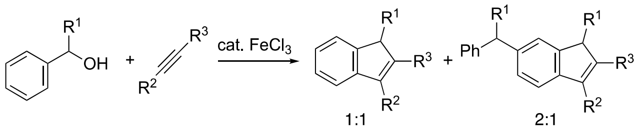
The annulative coupling of secondary benzyl alcohols with internal alkynes efficiently proceeds in the presence of a silver catalyst. The reaction gives 1,2,3-substituted indene derivatives selectively as 1:1 coupling products. The procedure provides a straightforward synthetic route to indenes from readily available starting materials upon treatment with a simple reaction system under mild conditions.

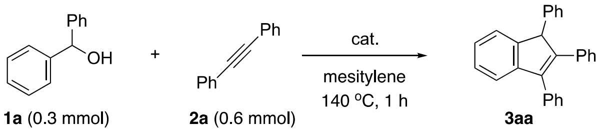
Keywords: silver catalyst; annulative coupling; indenes

Indene frameworks can be widely seen in naturally occurring and synthetic molecules possessing biological activities.[1] Substituted indenes have also been utilized as functional ligand precursors in organometallic field.[2] Therefore, the development of effective synthetic methods for constructing the important structures from readily available starting materials has been a significant subject in organic synthesis.[3] Recently, indene synthesis by the annulative coupling of benzyl alcohols with alkynes has been achieved.[4] Thus, Zhou's group reported the iron-catalyzed annulation of secondary benzyl alcohols with alkynes (Scheme 1).[4a] A number of 1,2,3-substituted indenes could be prepared by the method. However, especially in cases using electron-rich alcohols or electron-deficient alkynes, it was difficult to suppress further benzylation after annulation to predominantly form their 2:1 coupling products. Because of the applicability of 1,2,3-substituted indenes as ligands,[2b-e] their synthetic methods with high selectivity has been still desired.



Scheme 1.

Meanwhile, benzyl alcohols have been recognized as promising substrates for transition-metal-catalyzed direct coupling. Their hydroxy function is known to act as a directing group, which leads to regioselective C–H bond cleavage and functionalization at the *ortho*-position.[5] During our study on the direct transformation of benzyl alcohols,[6] we found that treatment of diphenylmethanol (**1a**) with diphenylacetylene (**2a**) in the presence of catalytic amounts of $[Cp^*IrCl_2]_2$ and $AgSbF_6$ gives an annulative coupling product, 1,2,3-triphenyl-1*H*-indene (**3aa**) in 25% yield (Scheme 2).[7] Unexpectedly, a similar amount of **3aa** was obtained even in the absence of the iridium catalyst. In contrast to the previous iron-catalyzed reaction,[4a] no 2:1 coupling product was formed under conditions using $AgSbF_6$ as a sole catalyst. Therefore, we examined the reaction system further and found that various 1,2,3-substituted indene derivatives can be prepared selectively under mild conditions (see below). The new findings are described herein.

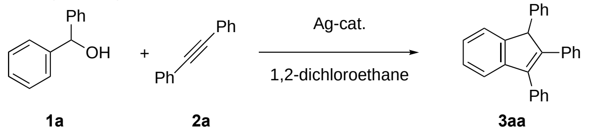


cat.	yield of **3aa** (%)
$[Cp^*IrCl_2]_2$ (0.01 mmol)/$AgSbF_6$ (0.04 mmol)	25
$AgSbF_6$ (0.04 mmol)	32

Scheme 2.

As described above, **1a** (0.3 mmol) reacted with **2a** (0.6 mmol) in the presence of $AgSbF_6$ (0.04 mmol) under argon in mesitylene (2.5 mL) at 140 °C for 1 h to afford **3aa** in 32% yield (entry 1 in Table 1). The product yield was dramatically improved to 94% by decreasing the reaction temperature to 80 °C in 1,2-dichloroethane (entry 2). The reaction system composed of just substrates and a catalyst is simple, no other additives being required. Further decreasing the temperature to 60 °C slightly reduced the **3aa** yield (entry 3). Decreasing amounts of **2a** (entry 4) or $AgSbF_6$ (entry 5) also reduced the yield. Other silver catalysts such as $AgBF_4$, $AgNTf_2$, and AgOAc showed poor activities (entries 6-8).

Table 1. Reaction of diphenylmethanol (**1a**) with diphenylacetylene (**2a**)[a]



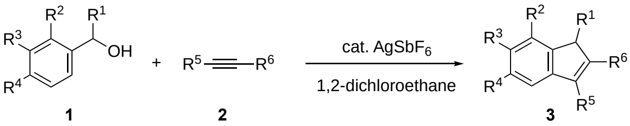
entry	Ag-cat.	temp. (°C)	yield of **3aa** (%)[b]
1[c]	$AgSbF_6$	140	32
2	$AgSbF_6$	80	94 (87)
3	$AgSbF_6$	60	83
4[d]	$AgSbF_6$	80	86
5[e]	$AgSbF_6$	80	83
6	$AgBF_4$	80	23
7	$AgNTf_2$	80	4
8	AgOAc	80	0

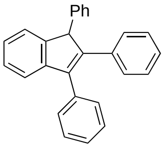
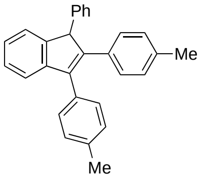
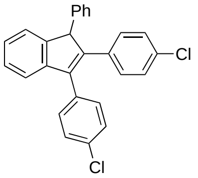
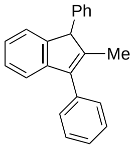
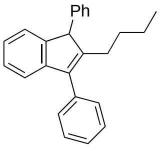
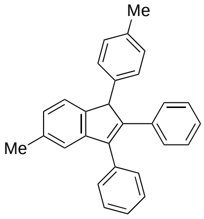
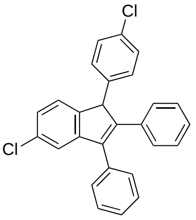
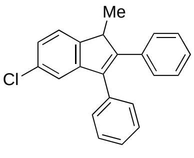
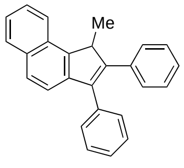
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), Ag-cat. (0.04 mmol) in 1,2-dichloroethane (2.5 mL) under Ar for 1 h, unless otherwise noted. [b] GC yield based on the amount of **1a** used. Value in parentheses indicates yield after purification. [c] In mesitylene (2.5 mL). [d] With **2a** (0.45 mmol). [e] With $AgSbF_6$ (0.02 mmol).

Under the optimized conditions (entry 2 in Table 1), we examined the reactions using various alkynes **2** with **1a** (Table 2). The reaction of electron-rich bis(4-methylphenyl)acetylene (**2b**) with **1a** proceeded efficiently to produce **3ab** in an almost quantitative yield, while that of electron-deficient bis(4-chlorophenyl)acetylene (**2c**) gave **3ac** in a moderate yield. Note that even the latter case, no 2:1 coupling product was detected at all. It was previously reported that the reaction of **1a** with electron-deficient alkynes such as **2c** under $FeCl_3$ catalysis tends to give 2:1 coupling products for relatively easier second benzylation.[4a] Unsymmetrical alkynes such as 1-phenyl-1-propyne (**2d**) and 1-phenyl-1-hexyne (**2e**) underwent the reaction with **1a** regioselectively to give **3ad** and **3ae** in 71 and 69% yields, respectively.[8,9]

Next, the scope of benzyl alcohols was examined. The reactions of 4-methyl (**1b**) and -chloro (**1c**) substituted diphenylmethanols with **2a** took place smoothly to produce the corresponding indenes **3ba** and **3ca** in 78 and 65% yields, respectively. Besides diphenylmethanols, 1-(4-chlorophenyl)ethan-1-ol (**1d**) also underwent the annulation with **2a** to produce **3da** in a moderate yield. 1-(Naphthalen-2-yl)ethan-1-ol (**1e**) also coupled with **2a** to form tricyclic **3ea** selectively.

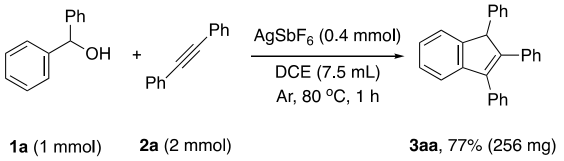
Table 2. Reaction of benzyl alcohols **1** with alkynes **2**[a]



product	yield (%)[b]
 **3aa**	87%
 **3ab**	97%
 **3ac**	41%
 **3ad**	71%
 **3ae**	69%
 **3ba**	78%
 **3ca**	65%
 **3da**	45%
 **3ea**	46%

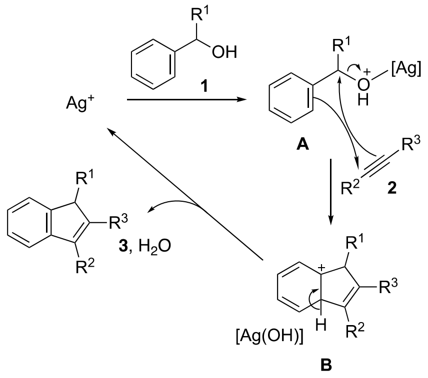
[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), $AgSbF_6$ (0.04 mmol) in 1,2-dichloroethane (2.5 mL) under Ar at 80 °C for 1 h. [b] Isolated yield.

The present annulative coupling could be readily scaled up to a 1 mmol scale. Thus, the reaction of **1a** (1 mmol) with **2a** (2 mmol) gave **3aa** in a reasonable yield (256 mg, 77%) (Scheme 3).



Scheme 3.

A plausible mechanism for the reaction of benzyl alcohols **1** with alkynes **2** is illustrated in Scheme 4. As proposed for the previous iron-catalyzed reaction,[4] $AgSbF_6$ catalyst seems to activate the C–O bond of **1** to form intermediate **A**. Then, annulation with **2** may take place to give intermediate **B**. In the final deprotonation step, product **3** and H_2O are formed to regenerate an active Ag^+ species.



Scheme 4.

In summary, we have demonstrated that 1,2,3-substituted indene derivatives can be prepared selectively from readily available benzyl alcohols and alkynes. The annulative coupling reaction of these substrates proceeds smoothly under silver catalysis. Further work is underway for developing the procedure.

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Supporting Information is available electronically on J-STAGE.

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8 Similar regioselectivity has been observed in Fe-catalyzed annulation (ref. 4a). As suggested in the precedent, a steric factor seems to be important.

9 Even under silver catalysis, the reaction of **1a** with aliphatic 4-octyne gave a complex mixture including 1:1 and 2:1 coupling products.

Graphical Abstract

Textual Information

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