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Nickel-catalyzed Carboannulation Reaction of *o*-Bromobenzyl Zinc Bromide with Unsaturated Compounds

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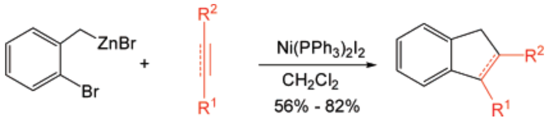
ABSTRACT



A number of indenes have been prepared in good yields by treating *o*-bromobenzyl zinc bromide 1 with various terminal and internal alkynes in the presence of a nickel catalyst. The nickel-catalyzed carboannulation reaction was successfully extended to the synthesis of indane derivatives by reaction of 1 with acrylates and styrene.

Indene ring frameworks are present in a large number of biologically active compounds,[1] and their metallocene complexes are able to catalyze olefin polymerization.[2] Recently, various Pd-,[3] Ni-,[4] and Co-catalyzed[5] carboannulation of alkynes with *o*-halophenyl aldehydes (or ketones) or *o*-iodophenyl malonates have been used to synthesize indenes, but the disadvantage of these methods is that only internal alkynes could participate in the carboannulation reaction. Here we report a mild preparative method for indenes by a nickel-catalyzed carboannulation reaction of *o*-$BrC_6H_4CH_2ZnBr$ with either internal or terminal alkynes. Acrylates and styrene also undergo the carboannulation reaction with *o*-$BrC_6H_4CH_2ZnBr$ to afford indane products.

Intramolecular Suzuki, Heck, and Stille reactions play important roles in the synthesis of cyclic natural products.[6] On the other hand, the intramolecular Negishi coupling (INC) reaction is scarcely reported in the literature.[7] Since *o*-$BrC_6H_4CH_2ZnBr$ could be easily prepared from commercially available *o*-$BrC_6H_4CH_2Br$,[8] we decided to use this zinc reagent to test the INC reaction. Our hypothesis of the INC reaction for the synthesis of indenes is shown in Scheme 1. The oxidative addition of Ni(0) to the Br−C(phenyl) of the *o*-$BrC_6H_4CH_2ZnBr$ would lead to an arylnickel species, and the following step may go through two different pathways:

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[6] For a review, see: Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.

[7] Jackson reported an INC reaction in 33% yield see: Pérez-González, M.; Jackson, R. F. W. *Chem. Commun.* **2000**, 2424.

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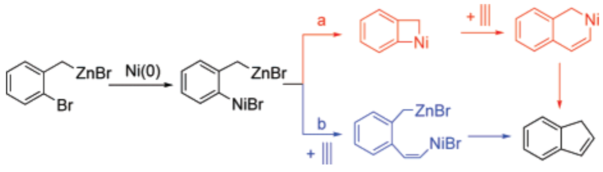
Scheme 1

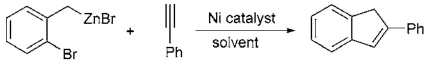


(a) arylnickel species undergoes intramolecular transmetalation[9a] to form a nickelacyclobutabenzene,[9b−d] which would undergo alkyne coordination[10] and subsequent alkyne insertion to afford indene; (b) arylnickel coordination to alkyne and subsequent insertion[4] of the alkyne would form a vinylic nickel intermediate, which would undergo intramolecular transmetalation and subsequent reductive elimination to give an indene product. Thus both pathways a and b could be regarded as interrupted INC reactions.

Since Ni(II) could be easily reduced to a Ni(0) species by benzylzinc reagent,[11] we initiated our efforts by employment of air stable $Ni(PPh_3)_2X_2$ (X = Cl, Br, I).[12] As shown in Table 1, phenylacetylene **2a** was used as the model substrate, and various Ni species and solvents were investigated to increase the yield (Table 1).

Among various Ni(II) species and solvents investigated (Table 1, entries 1−7, 10−13), $Ni(PPh_3)_2I_2$ in CH_2Cl_2[13] was found to be the most reactive (Table 1, entry 7). $Ni(PPh_3)_2I_2$ is more effective than $Ni(PPh_3)_2Cl_2$ and $Ni(PPh_3)_2Cl_2$ probably because iodide coordination could stabilize either Ni(0) or Ni(II) species as Percec addressed.[12d] Although solvents such as THF, DMF, and CH_3CN are frequently used in the intermolecular Negishi reaction, each of them is ineffective toward this INC-type reaction. A bidentate ligand (dppe) is not favorable for increasing the reactivity of the Ni catalyst (Table 1, entry 11). The addition of 0.2 equiv of PPh_3 to the reaction disfavored the carboannulation reaction (Table 1, entry 8).

Table 1. Optimization of Reaction Conditions[a]



1 2a 3a

entry	catalyst	solvent[b]	**3a** yield [%]
1	$Ni(PPh_3)_2Cl_2$	THF	trace
2	$Ni(PPh_3)_2Br_2$	THF	5
3	$Ni(PPh_3)_2I_2$	THF	8
4	$Ni(PPh_3)_2I_2$	CH_3CN	trace
5	$Ni(PPh_3)_2I_2$	DMF	trace
6	$Ni(PPh_3)_2I_2$	toluene	trace
7	$\mathbf{Ni(PPh_3)_2I_2}$	$\mathbf{CH_2Cl_2}$	**82**
8	$Ni(PPh_3)_2I_2/2PPh_3$	CH_2Cl_2	17
9	$Pd(PPh_3)_2Cl_2$	CH_2Cl_2	3
10	$Ni(acac)_2$	CH_2Cl_2	4
11	$Ni(dppe)I_2$	CH_2Cl_2	2
12	$NiPy_2Cl_2$	CH_2Cl_2	6
13	$Ni\{P(p\text{-}MeOC_6H_4)_3\}_2Cl_2$	CH_2Cl_2	10
14	$Ni(PPh_3)_4$	CH_2Cl_2	31
15	$Ni(PPh_3)_2I_2/Zn$	CH_2Cl_2	17

[a] The reaction was carried out by the addition of 3.5 equiv of Zinc reagent to a solution of 1.0 equiv of alkyne and 0.1 equiv of Ni catalyst in different solvents, and yield was calculated based on GC with acetophenone as an internal standard. [b] All reactions were conducted at refluxing temperature of solvents except DMF (at 80 °C) and toluene (at 80 °C).

The employment of $Pd(PPh_3)_2Cl_2$ gave a low yield of **3a** (Table 1, entry 9). The Ni(0) species such as $Ni(PPh_3)_4$only gave **3a** in 31% yield (Table 1, entry 14). Other Ni(0) species from the reduction of $Ni(PPh_3)_2I_2$ by zinc dust also afforded **3a** in low yield (Table 1, entry 15).

Control experiments indicated that no desired product was observed in the absence of $Ni(PPh_3)_2I_2$.

With optimized reaction conditions in hand, we explored the scope and limitation of this method (Table 2). All 1-arylacetylenes underwent carboannulation reaction with **1** to give 2-arylindene products in high regioselectivities and good yield regardless of the nature and the position of the substituents (Table 2, entries 1−6). 1-Naphthyl acetylene could also react with **1** to afford indene **3g** in good regioselectivities (Table 2, entry 7). As entry 8 demonstrates, this transformation tolerates internal alkenes. 1-Alkyl acetylenes gave the desired 2-alkyl indene products under identical reaction conditions (Table 2, entries 9, 10). The reaction of **1** with symmetrical alkynes such as diphenylacetylene afforded the desired product in 76% yield (Table 2, entry 11). The annulation process is regioselective for internal alkynes containing TMS, yielding the regioisomers with the more sterically demanding TMS group in the 2 position of the indene ring (Table 2, entries 13, 14). In the reaction of **2l**, two regioisomers **3l** and **3l′** were obtained in the ratio of 3/1, and the major isomer **3l** again has the more bulky phenyl group in the 2-position of the indene ring (Table 2, entry 12). In the case of **2o**, product **3o** has the COOMe in the

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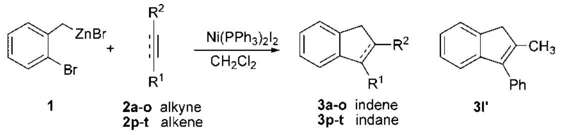
(13) (a) After **1** was prepared in THF as in ref 8, the THF was removed by concentration in vacuo. The remaining gray solid was dissolved in dry CH_2CI_2. See: Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 366. (b) On the basis of GC and NMR analysis, 62% of **1** in entry 7 (Table 1) was converted to 9,10-dihydroanthracene via intermolecular Negishi coupling reaction and 4% of **1** was converted to 9,10-dihydrophenanthrene.

Table 2.



entry	alkyne or alkene	product	**3** yield [%][a, b]
1	**2a** R^1 = H, R^2 = Ph	**3a**	77
2	**2b** R^1 = H, R^2 = p-MeOC$_6$H$_4$	**3b**	76
3	**2c** R^1 = H, R^2 = 3,5-diMeOC$_6$H$_3$	**3c**	73
4	**2d** R^1 = H, R^2 = p-FC$_6$H$_4$	**3d**	70
5	**2e** R^1 = H, R^2 = 3,4,5-triMeOC$_6$H$_2$	**3e**	60
6	**2f** R^1 = H, R^2 = 3,4-MethylenedioxyC$_6$H$_3$	**3f**	75
7	**2g** R^1 = H, R^2 = 1-naphthyl	**3g**	72
8	**2h** R^1 = H, R^2 = (E)-styryl	**3h**	68
9	**2i** R^1 = H, R^2 = cyclopropyl	**3i**	56
10	**2j** R^1 = H, R^2 = n-Bu	**3j**	66
11	**2k** R^1 = Ph, R^2 = Ph	**3k**	76
12	**2l** R^1 = Me, R^2 = Ph	**3l/3l′**	73
13	**2m** R^1 = Ph, R^2 = TMS	**3m**	75
14	**2n** R^1 = n-Bu, R^2 = TMS	**3n**	65
15	**2o** R^1 = n-Bu, R^2 = COOMe	**3o**	65
16	**2p** R^1 = COOMe, R^2 = H	**3p**	82
17	**2q** R^1 = COOEt, R^2 = H	**3q**	80
18	**2r** R^1 = COOnBu, R^2 = H	**3r**	78
19	**2s** R^1 = Ph, R^2 = H	**3s**	80
20	**2t** R^1 = 3,4-Methylenedioxy C$_6$H$_3$, R^2 = H	**3t**	78

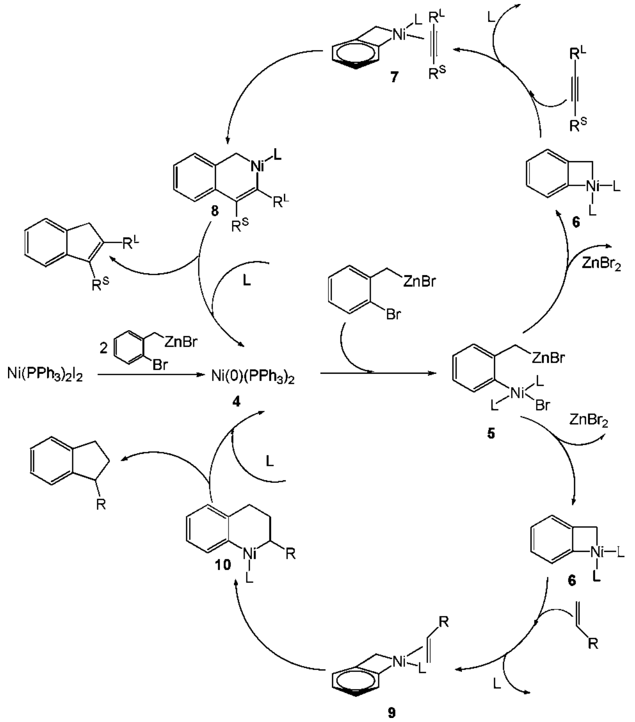
[a] Isolated yield. [b] Zinc reagent (3.5 mmol, 3.5 equiv) in 3.5 mL CH_2Cl_2 was added to a refluxing CH_2Cl_2 solution (8 mL) of the unsaturated substrate (1.0 mmol, 1.0 equiv) and $Ni(PPh_3)_2I_2$ (0.1 mmol, 0.1 equiv). The resultant mixture was refluxed until complete by TLC.

2-position of the indene ring (Table 2, entry 15). The regiochemistry of this product suggests that the catalytic carboannulation reaction is governed by the electronic effect of substrate.

The present nickel-catalyzed reaction was successfully implemented for the synthesis of indane derivatives via carboannulation reaction of **1** with acrylates or styrene derivatives. Treatment of **1** with methyl acrylate under identical reaction conditions proceeded smoothly to afford methyl 2-indane carboxylate **3p** in 82% yield (Table 2, entry 16). Surprisingly, the observed regiochemistry for **3p** is opposite to those observed for **3a**−**j** and **3o** (n-BuC≡CCO$_2$Me **2o**). In the present case, **3p** has the COOMe in the 1 position of the indane ring. Similar regiochemistry was observed in entries 17 and 18 (Table 2). The carboannulation reaction of **1** with styrene **2s** and its derivative **2t** also worked well, affording 1-aryl indanes **3s** and **3t** in 80% and 78% yields, respectively.

The exact mechanism for the present catalytic reaction is not yet clear, but the reaction of acrylates **2p**-**2t** through pathway b (Scheme 1) should give 2-substituted indane products[14,15] instead of **3p**-**3t**. Thus, a plausible mechanism based on pathway a[16] is proposed for this annulation process in Scheme 2, but the pathway b could not be excluded from the reaction of alkynes because the regioselective insertion[17] of alkynes into arynickel species via pathway b would also settle the observed regiochemistry in **3a**−**o**.

Scheme 2 [a]



[a] L = PPh_3, R^L = large (or −COOMe) substituent, R^S = small substituent.

As Scheme 2 indicated, reduction[11] of Ni(II) to Ni(0) by **1** initiates the catalysis. After the formation of **6** from **1** and Ni(0) via pathway a, the coordination of alkyne to **6** via ligand exchange forms a nickel−alkyne complex **7**, in which the coordination position of the alkyne is presumed to be cis[18] to the Ni−C$_{sp2}$ bond. The subsequent regioselective

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(14) (a) Control experiments indicated that methyl acrylate was inert to BnZnBr under nickel catalysis. This result excludes the direct Michael-type addition of the benzylzinc of **1** to acrylate. (b) Allylic zinc reagents are relatively unreactive toward alkenic bonds as ref 13 addressed.

(15) (a) It is known that the insertion of electron-deficient olefins into Ni−aryl (or alkyl) bonds generally gives only terminal products with aryl (or alkyl) at the β position to electron withdrawing group. See: Montgomery, J. Organometallic Complexes of Nickel. In *Science of Synthesis*; Trost, B. M., Lautens, M., Eds.; Thieme: Stuttgart, Germany, 2001; Vol. 1, pp 11−62. (b) The insertion of styrene into the Ni−aryl bond of $NiBr(Ph)(PPh_3)_2$ gave similar terminal products with nickel attached to the most hindered terminus of styrene. See: Otsuka, S.; Nakamura, A.; Yoshida, T.; Naruto, M.; Ataka K.; *J. Am. Chem. Soc.* **1973**, *95*, 3180.

(16) As one of the reviewers suggested, $C_6H_5CF_3$ is a solvent that oftentimes is used as a CH_2Cl_2 equivalent (polarity-wise) but with a higher boiling point. The reaction of **1** and **2a** in $C_6H_5CF_3$ at 40°C using $Ni(PPh_3)_2I_2$ as a catalyst gave **3a** in 62% yield, but the same reaction in $C_6H_5CF_3$ at 80°C only afforded **3a** in 31% yield. Nickelacyclobutabenzene complexes in ref 9b−d were usually kept at rt or lower temperature, so the dramatic effect of CH_2Cl_2 on the reaction in Table 1 probably could be explained by its medium polarity and relatively low boiling point (40°C), which may stabilize the proposed intermediate **6** in Scheme 2. Thus pathway a seems to be more reasonable than pathway b for the reaction of alkynes and **1**.

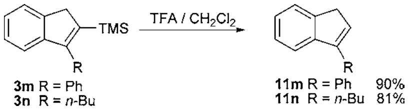
(17) (a) It is known that carbonickelation of unsymmetrical alkynes proceeds in a syn fashion, with insertion producing a vinylnickel species in which nickel attached to the most hindered terminus of the alkyne (see ref 4). (b) Carmona also found that the regiochemistry of unsymmetrical alkyne insertion into the Ni-C$_{sp2}$ bond was determined by the bulkiness of the alkyne substituent and also by electronic effects (see ref 10).

insertion[17] of the alkyne into the Ni−C_{sp2} bond forms **8** with nickel and R_L on the same carbon. Reductive elimination of Ni(0) from **8** gives indene product with the observed regiochemistry.

In the reaction of **1** with acrylates or styrene, the coordination position of the alkene in **9** is presumed to be cis to the Ni−C_{sp3} bond, and subsequent regioselective insertion[15a,19] of the alkene into the Ni−C_{sp3} bond forms **10** with nickel and R group on the same carbon. Reductive elimination of Ni(0) from **10** gives the indane product with the R substituent in the 1 position of the indane ring. While the reason for the exclusive insertion[20] of alkene into the Ni−C_{sp3} bond in **9** remains unknown, Montgomery did demonstrate the regioselective insertion of electron-deficient olefins into the Ni−C_{sp3} bond (not Ni−C_{sp2}) of a nickelcyclopentene intermediate in his work.[21]

The removal of TMS groups in **3m** and **3n** could be accomplished by TFA in CH_2Cl_2 in 90% and 81% yields, respectively. Combined with the TFA removal of TMS, this carboannulation reaction provides a general method for the synthesis of both 1-substituted (such as **11m** and **11n**) (Scheme 3) and 2-substituted indenes (Table 2, entries 1−10).

Scheme 3



In conclusion, we have demonstrated the $Ni(PPh_3)_2I_2$ catalyzed carboannulation reaction of *o*-bromobenzylzinc bromide with alkynes affords indenes in good regioselectivity under mild conditions. The substrates of the reaction can be extended to include acrylates and styrene for synthesis of 1-substituted indanes in good yields. Further mechanistic studies and synthetic applications of the procedure are in progress.

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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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(18) (a) According to Carmona's finding, alkyne inserts exclusively into the Ni−aryl bond of nickelacyclopentabezene as the result of cis coordination to Ni−aryl (see ref 10). (b) Montgomery also demonstrated the cis coordination of the alkyne to the Ni−C_{sp2} bond of the nickelacyclopentene and subsequent insertion of the alkyne into the Ni−C_{sp2} bond. See: Montgomery, J.; Seo, J. *Tetrahedron* **1998**, *54*, 1131.

(19) The insertion of styrene into the Ni−alkyl bond of NiBr(alkyl)-$(PPh_3)_2$ gave terminal products with nickel attached to the most hindered terminus of styrene (see ref 15b).

(20) Carmona investigated a number of insertion reactions of unsaturated substrates (CO, CO_2, CH_2O, CS_2, alkyne) into the Ni−C bonds of nickelacyclopentabenzene and found that a certain reagent inserts exclusively into either the Ni−alkyl or the Ni−aryl bond, but never into both (see ref 10).

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