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Nickel-Catalyzed Highly Regio- and Stereoselective Three-Component Assembly of Allenes, Aryl Iodides, and Alkenylzirconium Reagents

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Transition metal-mediated multicomponent assembly of organic moieties has attracted considerable attention recently due to the fact that complex organic molecules can be conveniently synthesized in one pot.¹ In this regard, the addition of an electrophile and nucleophile to an unsaturated carbon-carbon bond proves to be a powerful method in organic synthesis.^{2,3} However, the control of both regio- and stereoselectivity of this addition reaction remains a great challenge. Moreover, it is necessary to suppress competitive reactions such as direct coupling of the electrophile and nucleophile, β -hydride elimination, and polymerization of the unsaturated carbon-carbon bond. Allenes have been shown to be very useful substrates for three-component assembling reactions using aryl or alkenyl halides as electrophiles and amines, malonates, and main-group dimetal reagents as nucleophiles.⁴⁻⁷ Palladium complexes are the main catalysts for these types of reactions. Another useful allene-based three-component assembly involves the use of carbon electrophiles and nucleophiles to give products having two new C-C bonds. However, in these palladium-catalyzed double C-C bond formation reactions of allenenes, the regio- and stereoselectivity of the resulting C-C double bond is generally low, giving various regio- and stereoisomers.^{4f,5,7} To date, there is no nickel-catalyzed three-component assembly of allenenes and also no report of using alkenylzirconium complexes⁸ as nucleophiles for three-component assembling reactions. Herein, we report a nickel-catalyzed highly regio- and stereoselective assembly of allenenes, aryl halides, and alkenylzirconium reagents. The methodology offers a mild and convenient route for the synthesis of 1,4-diene derivatives in moderate to good yields.

Treatment of cyclohexyl allene **1a** with 4-iodoanisole (**2a**) and alkenylzirconium reagent **3a** in the presence of $\text{NiCl}_2(\text{PPh}_3)_2$ (5 mol %) and zinc powder in THF at 50 °C for 24 h led to a three-component assembling product **4a** in 82% yield (Scheme 1). The catalytic reaction is highly regioselective with the phenyl group adding to the middle carbon and the alkenyl group from zirconium reagent **3a** adding to the unsubstituted terminal carbon of **1a**. Product **4a** was fully characterized by its spectral data. The stereoselectivity was established on the basis of the results of NOE experiments.

To gain a better understanding of this nickel-catalyzed three-component reaction, the catalytic conditions were investigated for the reaction of **1a** with **2a** and **3a**. In the absence of either nickel catalyst or zinc powder, no reaction occurs. The use of $\text{NiI}_2(\text{PPh}_3)_2$ and $\text{NiBr}_2(\text{PPh}_3)_2$ afforded **4a** in 30% and 61% yields, respectively. Addition of 4 equiv of PPh_3 to the $\text{NiBr}_2(\text{PPh}_3)_2$ system strongly retarded the reaction to give **4a** in 5% yield. $\text{Ni}(\text{COD})_2$ was found to be totally inactive for this three-component assembly. Nickel complex with a bidentate phosphine ligand $\text{NiBr}_2(\text{dppe})$ afforded **4a** in only 19% yield. The most active nickel complex for this three-component assembling reaction appears to be $\text{NiCl}_2(\text{PPh}_3)_2$, furnishing **4a** in 85% yield. The halide on the nickel complex shows a profound effect on the yield of **4a**, but the reason is not yet clear.

Scheme 1

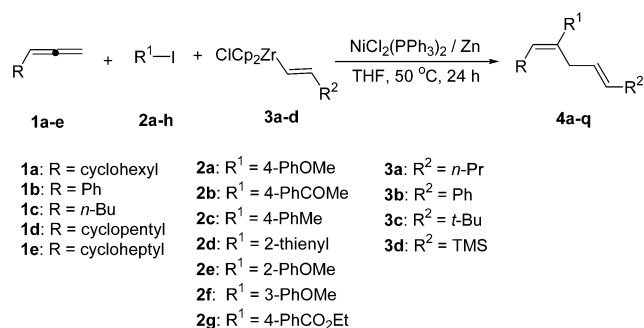


Table 1. Results of the Three-Component Assembling Reaction^a

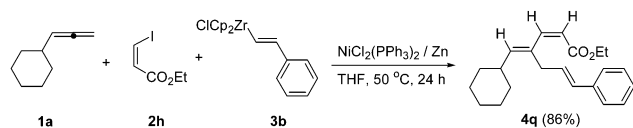
| entry | 1 (R) | 2 (R ¹) | 3 (R ²) | | E/Z | yield (%) ^b |
|-------|--------------|----------------------------|----------------------------|-----------|------|------------------------|
| 1 | cyclohexyl | 4-PhOMe | <i>n</i> -Pr | 4a | 99/1 | 82 (85) |
| 2 | cyclohexyl | 4-PhCOMe | <i>n</i> -Pr | 4b | 98/2 | 81 |
| 3 | cyclohexyl | 4-PhMe | <i>n</i> -Pr | 4c | 98/2 | 85 |
| 4 | cyclohexyl | 2-thienyl | <i>n</i> -Pr | 4d | 99/1 | 65 |
| 5 | cyclohexyl | 2-PhOMe | <i>n</i> -Pr | 4e | 99/1 | 37 |
| 6 | cyclohexyl | 3-PhOMe | <i>n</i> -Pr | 4f | 99/1 | 68 |
| 7 | cyclohexyl | 4-PhCO ₂ Et | <i>n</i> -Pr | 4g | 99/1 | 81 |
| 8 | Ph | 4-PhOMe | <i>n</i> -Pr | 4h | 94/6 | 83 |
| 9 | cyclohexyl | 4-PhCOMe | Ph | 4i | 98/2 | 69 |
| 10 | Ph | 4-PhOMe | Ph | 4j | 98/2 | 65 |
| 11 | cyclohexyl | 4-PhOMe | <i>t</i> -Bu | 4k | 99/1 | 73 |
| 12 | cyclohexyl | 4-PhCOMe | TMS | 4l | 99/1 | 61 |
| 13 | <i>n</i> -Bu | 4-PhCOMe | Ph | 4m | 99/1 | (80) ^c |
| 14 | <i>n</i> -Bu | 4-PhOMe | <i>n</i> -Pr | 4n | 99/1 | (63) ^c |
| 15 | cyclopentyl | 2-thienyl | <i>n</i> -Pr | 4o | 99/1 | (67) ^c |
| 16 | cycloheptyl | 4-PhCOMe | <i>n</i> -Pr | 4p | 99/1 | 78 |

^a All reactions were carried out using allene **1** (1.0 mmol), aryl iodide **2** (0.50 mmol), zirconium reagent **3** (1.25 mmol), $\text{NiCl}_2(\text{PPh}_3)_2$ (0.025 mmol), zinc powder (1.37 mmol), and THF (3 mL) at 50 °C for 24 h. ^b Isolated yields; yields in parentheses were determined by the ¹H NMR integration method using mesitylene as an internal standard. ^c These products are difficult to separate from the starting materials.

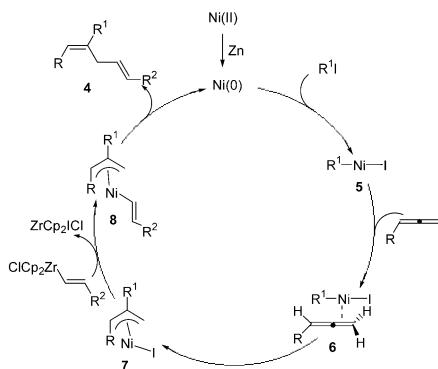
A brief survey of the solvent using $\text{NiCl}_2(\text{PPh}_3)_2/\text{Zn}$ as the catalyst revealed that the yield of **4a** is very sensitive to the solvent used. THF was the solvent of choice, giving **4a** in 85% yield. The other solvents such as CH_3CN and DMF were totally inactive, whereas toluene afforded **4a** in only a trace amount.

The results for the three-component assembly of various allenenes, aryl iodides, and zirconium reagents catalyzed by $\text{NiCl}_2(\text{PPh}_3)_2$ and zinc powder in THF are summarized in Table 1. Aryl iodides **2b-g** undergo three-component assembly effectively with **1a** and **3a** to afford the corresponding 1,4-diene products **4b-g** in moderate to good yields with very high *E* selectivity (entries 2-7). The reaction tolerates a variety of functional groups such as acetyl, methoxy, and ester on the aromatic ring of aryl iodide. It appears that the yield of this catalytic reaction is insensitive to the type of substituent on the aromatic ring of **2**, but does depend on the position of the

Scheme 2



Scheme 3

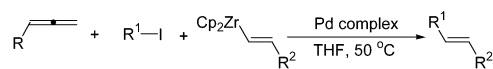


substituent on the ring. By using iodoanisoles as examples, *o*-iodoanisole gave the lowest product yield, while the corresponding para substrate afforded the highest result. Heterocyclic 2-iodothiophene (**2d**) was also tested for the three-component reaction with **1a** and **3a**. The expected product **4d** was isolated in 65% yield. In addition to **1a**, several allenes, phenylallene **1b**, *n*-butylallene **1c**, cyclopentylallene **1d**, and cycloheptyllallene **1e**, react with **2** and **3** to furnish the corresponding three-component products **4h–p** in 61–83% yields, with extremely high *E* selectivity. Other alkenylzirconium complexes ($\text{ZrCp}_2\text{CICHCHR}^2$: $\text{R}^2 = \text{Ph}$, CMe_3 , and SiMe_3) also underwent three-component assembly with various allenes and aryl iodides to afford the 1,4-diene derivatives in good yields. In all cases, the *E* isomer is formed predominantly with the ratios of *E/Z* lying in the range between 98/2 and 99/1, except entry 8.

The present assembling reaction is successfully extended to vinyl iodides (Scheme 2). Thus, treatment of cyclohexylallene **1a** with ethyl (*Z*)-3-iodoacrylate (**2h**) and styrylzirconium **3b** in the presence of the $\text{NiCl}_2(\text{PPh}_3)_2/\text{Zn}$ system afforded highly stereoselective triene **4q** in 86% yield (Scheme 2). In this product, the two carbon–carbon double bonds that come from **2h** and **3b**, respectively, maintain the same stereochemistry as that of the original substrates. On the other hand, the carbon–carbon double bond formed from the addition of the acrylate group to the allene moiety exhibits remarkable high *E* stereochemistry with an *E/Z* ratio of 99:1.

On the basis of the known nickel chemistry and three-component coupling reactions, a mechanism involving face-selective coordination of allene to the nickel center is proposed to account for the observed regio- and stereochemistry of products (Scheme 3). The reduction of Ni(II) to Ni(0) by zinc powder likely initiates the catalytic cycle.⁹ Oxidative addition of organic iodide to Ni(0) leads to the formation of nickel(II) intermediate **5**. The terminal double bond of allene is then coordinated favorably to the nickel center of intermediate **6** at the face opposite to the substituent R of allene to avoid steric congestion. Insertion of the coordinated double bond of allene to the Ni–R¹ bond affords π -allyl nickel complex **7** with the R anti to the R¹ group of the allyl moiety. Transmetalation of **7** with zirconium reagent **3** furnishes intermediate **8**. Subsequent reductive elimination gives the final desired product. The anti stereochemistry of π -allyl complexes **7** and **8** accounts for the high *E* stereoselectivity of products.

Scheme 4



It is noteworthy that, under similar reaction conditions for the nickel-catalyzed reaction (Scheme 1), palladium complexes including $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{dba})_2$, and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2/\text{Zn}$ afforded only the two-component coupling product of aryl iodide ($\text{R}^1 = 4\text{-PhOMe}$, 4-PhCOMe) and alkenylzirconium reagent ($\text{R}^2 = (\text{CH}_2)_2\text{CH}_3$) as shown in Scheme 4. Presumably, the insertion of allene into the Ar–Pd bond is slow as compared to the transmetalation of alkenylzirconium reagent with the $\text{Ar}(\text{Pd})\text{I}$ intermediate resulting in the formation of the two-component cross-coupling product. In contrast, in the nickel-catalyzed reaction, the insertion of allene into the Ar–Ni bond is faster than the transmetalation step, leading to the formation of the π -allyl complex and subsequently the formation of the three-component assembling product. There is no direct coupling product of aryl iodide and alkenylzirconium reagent under the nickel-catalyzed reaction conditions.

In conclusion, we have developed for the first time a nickel-catalyzed three-component assembling reaction of allenes, aryl halides, and zirconium reagents. This method allows an efficient synthesis of various 1,4-diene derivatives in moderate to good yields with excellent regio- and stereoselectivity. Further applications of the methodology in organic synthesis are in progress.

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Supporting Information Available: Preparation details, characterization data, NOE experimental data of **4a–q** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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