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**Catalytic Cyanation**

# Hydrocyanative Cyclization and Three-Component Cross-Coupling Reaction between Allenes and Alkynes under Nickel Catalysis**

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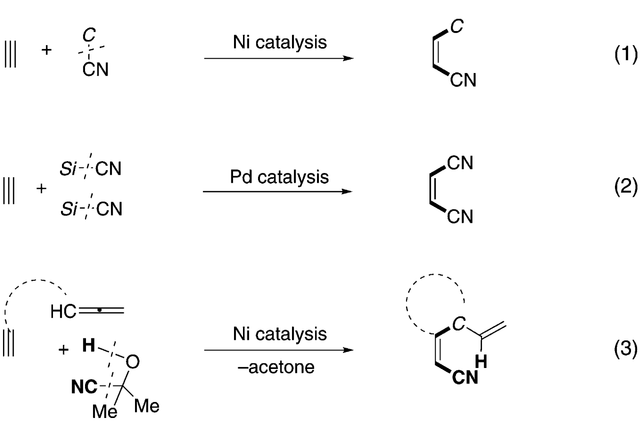
Since a cyano group is equivalent to a carbonyl group and related functionalities, its introduction into organic molecules, particularly by a catalytic protocol, is an important topic in synthetic chemistry. Recent research in this area has focused on the carbocyanation of simple, non-activated C–C multiple bonds under nickel catalysis (Scheme 1),[1] including direct C–CN bond cleavage and transfer of the resulting two moieties to each alkynyl carbon atom by cooperative catalysis with $Ni^0$ and Lewis acid catalysis [Eq. (1)]. We also succeeded in an alternative cyanation reaction that does not involve C–CN bond cleavage [Eq. (2)]. This method involves nucleophilic cyanation (cyanopalladation)[2] and enables the connection of three components by the action of a single catalyst. These transformations have been applied to novel cyclization[2a,c] and cycloaddition[2d,e] reactions.

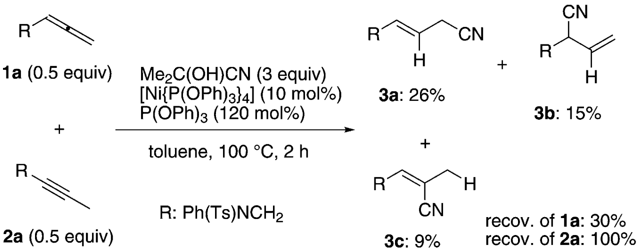


**Scheme 1.** Nickel- and palladium-catalyzed carbocyanation.

To establish a more general and facile protocol for carbocyanation and carbocyanative cyclization through the addition of a cyano group to C–C multiple bonds, we focused on the reactivity of allenes, which readily generate a carbanion equivalent under transition-metal catalysis. Herein, we report an alternative carbocyanation strategy that involves the hydrometalation of allenes followed by the carbocyanation of alkynes in a regio- and stereoselective manner [Eq. (3)].

The nickel-catalyzed hydrocyanation of various C–C multiple bonds, both alkenes[3] and alkynes,[4] is one of the most fundamental cyanation procedures. However, further synthetic applications, such as ring formation and/or multi-component coupling reactions, have not been well investigated. To the best of our knowledge, only one example of the nickel-catalyzed hydrocyanation of allenes has been reported.[5] Therefore, we initially evaluated the reactivities of allenes and alkynes.

When both **1a** and **2a** were treated with acetone cyanohydrin[6] (AC) under nickel catalysis,[4] three products **3a–c** were obtained, all of which were derived from **1a**, and **2a** was recovered quantitatively (Scheme 2). This result suggests that the allene functionality is easily discriminated from an alkyne under hydronickelation conditions. Therefore, we next investigated sequential C–C bond-forming reactions of allenyne substrates (Scheme 3).



**Scheme 2.** Competitive study with **1a** and **2a**. Ts = *p*-toluenesulfonyl.

When **4a** was treated with AC under nickel catalysis, the reaction proceeded smoothly at 70 °C to give **5a** in 70 % yield, with complete stereoselectivity in the formation of the tetrasubstituted olefin. The structural assignment of the product was confirmed by X-ray crystallography of **5c**,[7] which was obtained when **4c** was used as the substrate. We found that various functionalities on the alkyne, di- and trisubstituted allenes, free OH and ether groups, and substituents on the pyrrolidine ring were compatible with this cyclization reaction. A quaternary carbon center was also constructed at the allylic position of **5j** and **5k** in the cyclization.

The reaction starts with a regioselective hydronickelation of the allene. Once a Ni–H species is generated, hydride attack at the central carbon atom of the allene would give a π-allylnickel intermediate **7a**. A subsequent 5-*exo* cyclization to give **7c**, followed by elimination, would give the tetrasubstituted alkene **5** stereoselectively together with $Ni^0$. When

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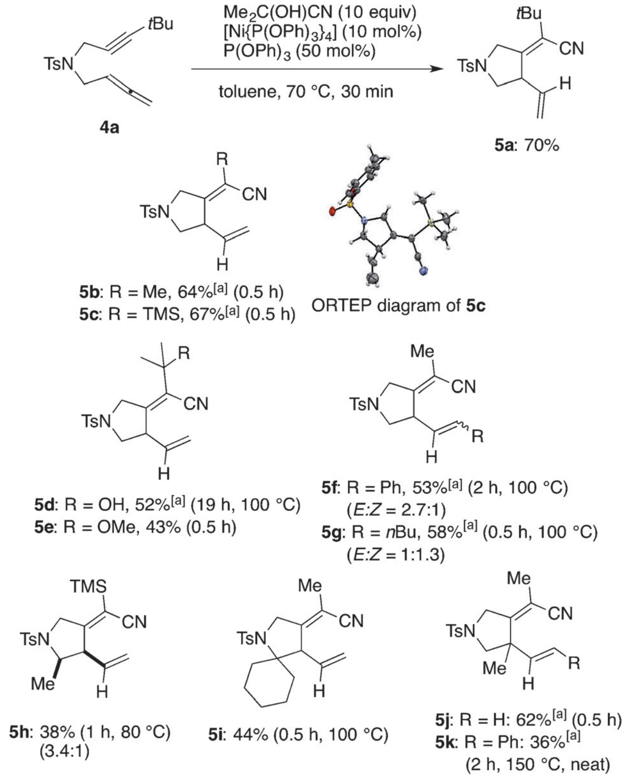
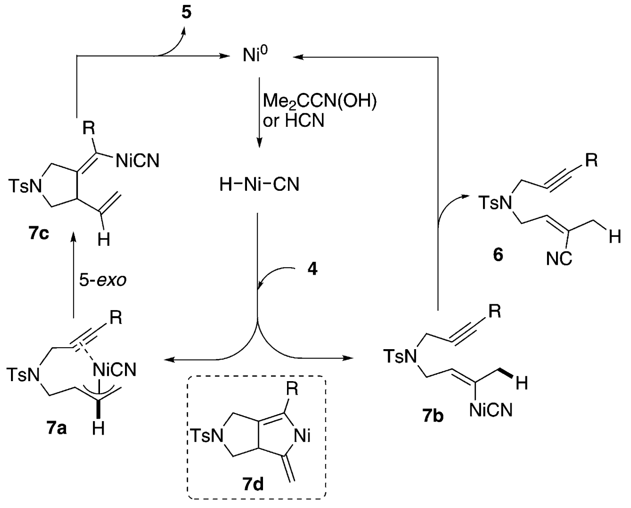
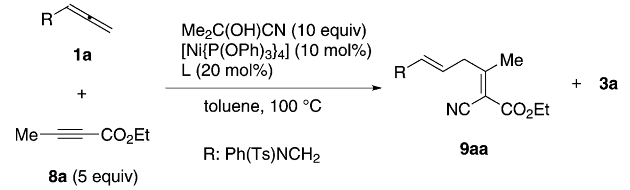


***Scheme 3.*** Nickel-catalyzed hydrocyanative allenyne cyclization. [a] The reaction was carried out with AC (20 equiv).



***Scheme 4.*** Plausible catalytic pathway.

***Table 1:*** Three-component coupling reaction of **1a**, **8a**, and AC.



| Entry | L | t | **9aa** [%] | Other compounds [%] |
|---|---|---|---|---|
| 1 | none | 22 h | 25 | **1a**: 43 |
| 2 | $P(OPh)_3$ | 20 min | 52 | **3a**: 6 |
| 3 | $P(OMe)_3$ | 15 min | 61 | **3a**: 30 |
| 4 | $P(OEt)_3$ | 24 h | 7 | **1a**: 70 |

the initial C–H bond formation occurs at the terminal allenyl carbon atom, the resulting organonickel species **7b** is not suitable for cyclization and gives **6** through reductive elimination. In fact, **6a** (R = *t*Bu) was obtained in 20% yield as the sole side product. The stereoisomers observed in **5f** and **5g** suggest the possibility of a $\pi$-allylnickel intermediate in this catalytic transformation. Since a cyano functionality is added exclusively to a C–C triple bond in a regio- and stereoselective fashion, it is unlikely that the two vinyl–nickel bonds in **7d**, which could be generated by the oxidative cyclization of **4**, react specifically with AC through protonation to give **7c** (Scheme 4).[8]

Having developed a new hydrocyanative cyclization of **4**, we next turned our attention to a three-component coupling reaction[9,10] between allenes and alkynes. After careful investigation, the reaction of **1a**, alkynoate **8a**, and AC gave a sole three-component-coupling product **9aa**. The nickel-catalyzed reaction required a higher temperature (100 °C), and its rate depended strongly on the presence of an external phosphite. For example, $P(OPh)_3$ (20 mol%) promoted the reaction to give **9aa** as the sole coupling product in 52% yield within 20 min, and the reaction rate decreased dramatically in its absence (Table 1, entries 1 and 2). In the presence of trimethylphosphite, the best ligand tested, the reaction was complete within 15 min (Table 1, entry 3). The bulkier ligand $P(OEt)_3$ was inert: **9aa** was obtained in only 7% yield even after 24 h, and **1a** was recovered in 70% yield (Table 1, entry 4). This result suggests that a deactivated nickel species is probably formed, such as $Ni(CN)_2$, which is known to be a poisoned catalyst in hydrocyanation reactions.[3] The side product **3a** was produced by the simple hydrocyanation of the allene.

Under the optimized conditions, various combinations of **1** and **8** were investigated (Scheme 5). The reactions of **8b–d** with **1a** gave **9ab**, **9ac**, and **9ad** in 53, 51, and 49% yield, respectively, whereas a lower yield was observed with **8e** (27%). In the case of ketone **8f**, the desired coupling product **9af** was obtained exclusively in 40% yield in a stereoselective manner. Interestingly, we found that the reaction was quite sensitive to the effect of the arylsulfonyl group in **1**. For example, the 4-methoxy group in **1b** hindered the reaction (**9ba**: 60% yield, 24 h), but this effect depended on the amount of $P(OMe)_3$ in the reaction mixture. The presence of 50 mol% of $P(OMe)_3$ accelerated the cross-coupling reaction to give **9ba** in 73% yield within only 2 h. In the case of **1c**, there was no critical substituent effect on the reaction rate, and **9ca** was obtained in 41% yield within 8 h. The substituents on the aniline moiety had no effect, and the reaction gave **9da** and **9ea** in 67 and 69%, respectively, within 1 h. A mesyl group was also compatible with the reaction (**9fa** was formed in 41% yield), and the allene **1g**, which does not possess a sulfonaminde functionality, did not require the use of $P(OMe)_3$ at all for a smooth reaction.

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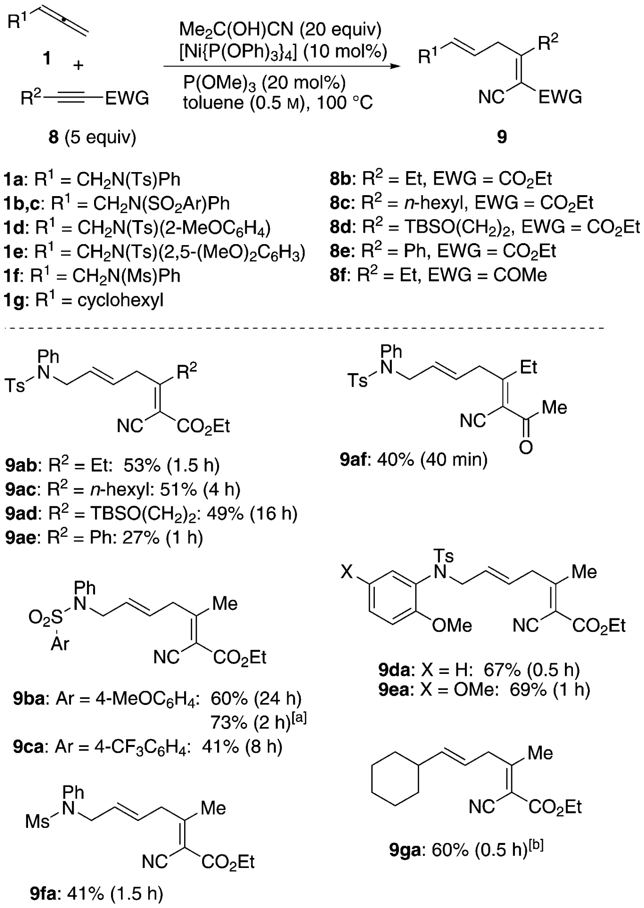
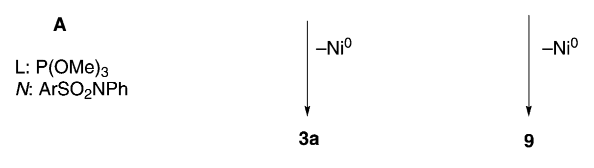


*Scheme 5.* Scope of the three-component coupling reaction. [a] The reaction was carried out with $P(OMe)_3$ (50 mol%). [b] The reaction was carried out in the absence of $P(OMe)_3$. EWG = electron-withdrawing group, Ms = methanesulfonyl, TBS = *tert*-butyldimethylsilyl.

On the basis of the above observations, plausible intermediates for a sequential cross-coupling reaction to give **9** are shown in Scheme 6. Initial hydrometalation of the allene gives the π-allyl $Ni^{II}$ species **A**, which could be stabilized by the Lewis basicity of a neighboring $SO_2$ functionality. The 4-methoxy group increases the electron density of the $SO_2$ functionality and thus contributes to the stabilization of **A** to prevent the subsequent insertion of **8**. When a methoxy group is installed on the other aromatic ring in **1** (see **1d,e**), this effect is not significant, and the subsequent insertion into the C−C triple bond proceeds smoothly.



*Scheme 6.* Plausible key intermediates in the three-component coupling reaction.

Although the role of trimethylphosphite is still unclear, this ligand has the following key features: 1) its suitable Lewis basicity[11] promotes the replacement of the sulfone to give **B**, and 2) its ready dissociation from $Ni^{II}$ promotes the coordination of the alkyne (**B**→**C**). In the absence of $P(OMe)_3$, the reaction was quite slow, and the presence of a stoichiometric amount (100 mol%) mainly led to **3a**, which indicates that excess phosphite prevents the coordination of the alkyne to the $Ni^{II}$ center and its insertion via **C**. The presence of a 4-methoxy group on $ArSO_2$ led to a decrease in the reaction rate, but when the amount of $P(OMe)_3$ used was increased to 50 mol%, the yield of the coupling product improved. This result suggests that an appropriate amount of $P(OMe)_3$ is effective in cleaving the $SO_2$−Ni bond to promote the formation of **B** from **A**. $P(OMe)_3$ was not essential in the reaction of **1g** because there were no Lewis basic functionalities to prevent the insertion of **8** to give **9**.

In summary, we have developed a new hydrocyanative cyclization and three-component cross-coupling reaction under nickel catalysis. These protocols offer 1) a new method for the addition of a CN functionality to C−C triple bonds, 2) a highly regio- and stereoselective synthesis of tetrasubstituted alkenes with a single catalyst, and 3) a metal-waste-free three-component cross-coupling process. These transformations may provide a new perspective for the synthesis of highly functionalized organic molecules through cyanation, and further studies are currently under way.

## Experimental Section

Synthesis of **5a**: A mixture of **4a** (48.2 mg, 0.15 mmol), $P(OPh)_3$ (20 mL, 0.096 mmol), $[Ni\{P(OPh)_3\}_4]$ (19.7 mg, 0.035 mmol, 10 mol%), and acetone cyanohydrin (139 μL, 1.5 mmol) in toluene (1.5 mL) was heated for 30 min at 70°C under an argon atmosphere and then poured onto silica gel. Purified by column chromatography (hexane/AcOEt 5:1) provided **5a** (36.4 mg, 0.11 mmol, 70%; m.p.: 90–91°C) as a colorless solid and **6a** (10.2 mg, 0.03 mmol, 20%) as a colorless oil.

Synthesis of **9aa**: A mixture of **1a** (91.2 mg, 0.3 mmol), **8a** (166.0 mg, 1.5 mmol), $P(OMe)_3$ (7.1 μL, 0.06 mmol), $[Ni\{P(OPh)_3\}_4]$ (39.0 mg, 0.03 mmol, 10 mol%), and acetone cyanohydrin (507 μL, 6.0 mmol) in toluene (0.6 mL) was heated for 15 min at 100°C under an argon atmosphere and then poured onto silica gel. Purification by column chromatography (hexane/AcOEt 10:1) gave **9aa** (95.1 mg, 61%) as a colorless oil and **3a** (28.9 mg, 30%) as a colorless oil.

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