/ *Review*

Nickel-Catalyzed Hydrocyanation of Allenes and Its Application

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Received December 3, 2018

Cyano (CN) groups are equivalent to carbonyl as well as amino- and hydroxymethyl groups. Therefore, their catalytic introduction under metal catalysis is an important issue in synthetic organic chemistry. Ni-catalyzed hydrocyanation is one of the most well-investigated, powerful tools for installing a CN group. However, it is still difficult to control chemo- and regioselectivity. In this review, the author uses allenes to enable regio-, stereo-, and face-selective transformations to natural product synthesis and axial chirality transfer.

Key words alkaloid; allene; catalysis; cyanation; cyclization; nickel

1. Introduction

Cyano (CN) groups are the synthetic equivalent of carboxylic acids along with formyl and aminomethyl groups and, due to their biological activities, they play important roles in many pharmaceuticals.¹⁾ Therefore, their introduction to organic molecules, particularly by catalytic protocols, has been a major challenge in synthetic chemistry. In general, cyanation has been achieved by nucleophilic addition using cyanides [hydrogen cyanide (HCN), trimethylsilyl cyanide (TMSCN), and Me₂C(OH)CN] to electron-deficient C–C, C–O, and C–N multiple bonds. On the other hand, transition metal catalysis offers various cyanation protocols to use nonpolarized C–C multiple bonds with X–CN (X = H,^{2–5)} aryl,⁶⁾ fluoroarene,⁷⁾ acyl,^{8,9)} alkyl,¹⁰⁾ allyl,¹¹⁾ alkynyl,¹²⁾ N,¹³⁾ O,^{14,15)} Si,¹⁶⁾ Ge,¹⁷⁾ B,¹⁸⁾ S,¹⁹⁾ Br,²⁰⁾ I,²¹⁾ and Sn²²⁾) under metal catalysis (Chart 1). Other approaches for multicomponent connective cyanation to install CN,^{23–25)} CF₃,²⁶⁾ Cl,²⁷⁾ and S²⁸⁾ functionalities have been reported.

The oldest and most thoroughly investigated cyanation is Ni-catalyzed hydrocyanation (X = H), which enables the use of olefins,^{29,30)} alkynes,³¹⁾ and conjugated dienes,³²⁾ and thus is considered to be one of the most significant, fundamental cyanation reactions. On the other hand, perfect, predictable regioselectivity can be observed only with limited substrates such as styrene derivatives.³³⁾ This limitation reflects a lack of generality, and regiocontrolled hydrocyanation is still a key problem to be solved even 40 years after its discovery.

Most previous reports on hydrocyanation reactions summarized the substrate scope. No previous ones evaluated the relative reactivities of C–C multiple bonds in detail. Therefore, this study investigated the reactivity order of C–C multiple

bonds in Ni-catalyzed hydrocyanation. This approach should help to improve the synthetic strategy and contribute to rational reaction design for the facile, rapid synthesis of useful molecules.

2. Reaction between Allenes and Alkynes

2.1. Hydrocyanative Cyclization Using Enyne and Allene-Ynes To clarify the relative reactivities of olefins and alkynes, **1a** was initially examined for hydrocyanative cyclization (Chart 2). Although 4 unsaturated carbons in **1a** could be reactive for the initial hydrometallation, the single product **2a** was exclusively obtained through this cyclization.³⁴⁾ Initial C–H bond formation preferably occurs at a terminal methylene of **1a**, and subsequent 5-*exo*-cyclization gives **3a-1**. Sequential formation of a Ni-carbene intermediate (**3a-2**), followed by reductive elimination, gives **2a** as a single isomer. The origin of the olefinic stereochemistry would be steric repulsion between the triisopropylsilyl (TIPS) and *c*-Hex groups to promote C–C bond rotation³⁵⁾ in **3a-2** before reductive elimination from **3a-3** to form a C–CN bond (*anti*-carbocyanation).

Bulky substituents were essential for higher selectivity in the above hydrometallation, as were harsh reaction conditions (150°C). This result prompted the use of more reactive C–C multiple bonds, and **4a** and **4b** were next used in a competitive experiment (Chart 3). Interestingly, **4a** exclusively reacted at 100°C to give three products (**5–7a**), and **4b** was fully recovered. This result suggests that: 1) allenyl double bonds are more reactive than C–C triple bonds; and 2) an *sp* carbon of

X = H, C, N, O, X, S, Si, Sn, B, Ge

Chart 1. Metal-Catalyzed Cyanation of C–C Multiple Bonds

This review of the author's work was written by the author upon receiving the 2018 Pharmaceutical Society of Japan Award for Divisional Scientific Promotion.

Chart 2. Hydrocyanative Cyclization of **1a**
(Color figure can be accessed in the online version.)

Chart 3. Hydrocyanation of **4a** and **4b**

4a is more favored in C–H bond formation.

This observation indicates that these two functionalities are easily discriminable. Therefore allene-ynes (**9**) were next examined as cyclization precursors. The reaction would be triggered by regioselective hydrometallation to allene, and a single reaction pathway could be proposed. It was found that various allene-ynes were smoothly converted to single cycli-

Chart 4. Hydrocyanative Cyclization Using **9**
(Color figure can be accessed in the online version.)

zation products (**10a–m**), including 5-membered carbo- and heterocycles with silyl, hydroxy, and amide functionalities as well as quaternary carbons. The proposed catalytic cycle initiates regioselective C–H bond formation at an *sp* carbon of **9**, and the resulting formation of a π -allyl Ni intermediate (**11a-1**), followed by *syn*-carbometallation to alkyne, gives **10** after reductive elimination from **11a-2**. Their structure reasonably explains the regio- and stereoselectivity of C–H and C–CN bonds in **10a–m** based on the proposed reaction

Biography

Dr. Shigeru Arai was born in Sapporo, Japan, in 1968. He received a B.S. from Hokkaido University (1992), where he worked with Prof. Masakatsu Shibasaki. He moved to the University of Tokyo Graduate School to study asymmetric catalysis using rare earth metal complexes under the direction of Prof. Shibasaki and received a Ph.D. in 1998. In 1996, Dr. Arai started his academic career under Prof. Takayuki Shioiri at Nagoya City University. He contributed to studies on asymmetric phase-transfer catalysis using chiral ammonium salts and its application. He became an associate professor at Chiba University (Prof. Atsushi Nishida) in December 2001. He was also a member of the Chemistry Department at MIT (Prof. G.C. Fu) as a postdoctoral fellow (JSPS) during 1999–2000. His research focuses on natural product synthesis and reaction development under transition-metal catalysis.

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Chart 5. Formal Synthesis of (±)-Kainic Acid

pathway^{36,37}) (Chart 4).

The use of **9n** as a cyclization precursor in the formal synthesis of (±)-kainic acid^{38,39}) was investigated next. A BnOCH_2 group is a synthetic equivalent of carboxylic acid, and the hydrocyanative cyclization of **9n** using PMePh_2 proceeded smoothly to give a mixture of stereoisomers of **10n** in 65% yield (*syn-anti* = 4:1). A major diastereomer was assigned to be *syn* by nuclear Overhauser effect spectroscopy (NOESY) after conversion to **11n** and **12n** by hydrogenation. Treatment of **10n** with CsF promoted desilylation and olefin isomerization to give **13** in 93% yield, and subsequent Mukaiyama hydration⁴⁰) and pyridinium chlorochromate (PCC) oxidation gave **14** in 40% yield in 2 steps. Next, acetalization and sequential reduction of a cyano group to Trost's intermediate **16**⁴¹) furnished the formal synthesis of (±)-kainic acid (Chart 5).

2.2. Multicomponent Coupling Reaction Using Allenes and Alkynes Allenes and alkynes are also discriminable when they are located in different molecules. The reaction could be triggered by chemoselective hydrometallation to allene, and the resulting organonickel species could act as a nucleophile to the electrophilic C–C triple bonds through an intermolecular reaction. Some advantages of this protocol are operational simplicity and less metal waste because organometallic species are catalytically generated. To demonstrate such a cross-coupling reaction, the regiocontrol of π -allyl Ni(II)

Chart 6. Hydrocyanative 3-Component Coupling Reaction

species in nucleophilic attack and the choice of electrophilic C–C triple bonds were key issues. The former was addressed by the use of a monosubstituted allene such as **4a**, and the latter was resolved by the use of alkynoates, as shown in Chart 6.

The reactive allylic sp^2 carbons in **8a** were discriminable in *syn*-carbocyanation. A less-substituted sp^2 carbon is more suitable for the formation of a C–C bond *via* conjugated addition, and **18a** was obtained in a regio- and stereoselective fashion. A side product was characterized to be **5a**, which was given by reductive elimination from **8a**. This result supports the reaction pathway described in Chart 6. The substrate scope revealed that alkynoates as well as alkynylketones bearing aryl and oxygen functionalities were suitable in regio- and stereoselective cross-coupling reactions to give **18a–f**.^{36,42})

2.3. Cyclization Using Bis-allenes Bis-allenes are also suitable for this 5-*exo* cyclization. Symmetric bis-allenes [**20a**: R = H, X = NTs, **20b**: R = H, X = C(CO₂Et)₂] are smoothly converted to the corresponding adducts (**21a, b**) through regioselective cyclization, and their stereochemistry was assigned to be *syn*.⁴³) Nonsymmetric substrates such as **20c–e** were also applicable. Hydrometallation prefers less-hindered or less-substituted allenes to form a C–H bond at sp carbons while avoiding steric repulsion³⁷) (Chart 7).

3. Reaction of Allenes

3.1. Hydrocyanation of Simple Allenes The above results show that C–C triple bonds are essential for regio- and stereoselective hydrometallation to discriminate allenyl C–C double bonds in hydrocyanative cyclization and cross-coupling reactions. Is it possible to control the regiochemistry using simple allenes without the assistance of any C–C triple bonds? Only one example of this approach was reported, which described lower selectivity using mono- and disubstituted allenes.⁴⁴) Similar results were achieved to give a mixture of **5–7** and **22** with the use of **4a, c**, although this selectivity was dramatically improved when **4d** was used instead. This latter

Chart 9. Hydrocyanation Using **4e-r**Chart 7. Hydrocyanative Cyclization Using **20**

(Color figure can be accessed in the online version.)

Chart 8. Hydrocyanation Using **4a-d**

reaction was sufficiently rapid to be completed within 2 h, and the major product (**7d**) with trans olefin was selectively obtained in 83% yield (Chart 8).

This protocol showed broad generality in regioselectivity with the use of various substrates (**4e-r**) including indole, thiophene, and substituted benzene rings as well as a cyclopropane ring^{45,46} (Chart 9).

Further application to the formal synthesis of (±)-quebrachamine⁴⁷⁻⁵⁰ was achieved.⁵¹ The cyclization precursor **4s** was synthesized from **23** via **24**, and then regioselective hydrocyanation using 2-PyPPH₂ as an external ligand gave **25** as an exclusive product in 53% yield. Subsequent hydrogenation and alkylation gave **27**, which was converted to **28** by a reduction-nosylation sequence. A Mitsunobu reaction after removal of a *tert*-butyldimethylsilyl (TBS) group gave piperidine (**29**), which was transformed to a known intermedi-

Chart 10. Formal Synthesis of (±)-Quebrachamine

Chart 11. Hydrocyanation of **31a** Chart 12. Hydrocyanation of **34**

Chart 13. Hydrocyanation Using DCN

ate (**30**) after desulfonylation, followed by chloroacetylation.⁴⁹⁾ The key hydrocyanation of allene was notably sensitive to the steric environment because 2,3-disubstituted indoles such as **4t** and the tri-substituted allene (**4u**) were both inert for hydrocyanation⁵¹⁾ (Chart 10).

3.2. Cyclopropane Cleavage through Hydrocyanation Since a cyclopropane ring can be cleaved by transition metal complexes, a combination of regioselective C–H bond formation and C–C bond cleavage would enable remote cyanation.^{45,46)} Arylcyclopropylallene (**31a**) was a suitable substrate for regioselective hydrometallation to give **33a-1**, and translocation of a C–Ni bond would be expected through the ring-opening process to **33a-2**. However, the isolated product was not **35a**, but rather a secondary carbonitrile (**32a**) together with *trans*-**34** in respective yields of 72 and 10% (Chart 11). The conjugated trienes (**34**) were both reactive in regioselective

Chart 14. Scope of Hydrocyanative Cyclopropane Cleavage

Chart 15. Chirality Transfer Using (*R*)-**36**

Fig. 1. Face Selectivity in Hydronickelation

tive hydrocyanation to give **32a** as a sole product, suggesting that *trans*-**34** acts as a reaction intermediate (Chart 12).

The results of a D-labeling experiment supported this mechanistic insight. *In situ* generation of deuterium cyanide (DCN) from TMSCN and MeOD gave the corresponding D-labeled products. As expected, C–D bonds observed in specific carbons in **32a-D** and *trans*-**34-D** suggest that two regioselective hydrometallation processes are involved in the catalytic cycle^{45,46)} (Chart 13).

Perfect D-incorporation in **32a** and *trans*-**34** was not observed, which indicates that $\beta\text{-H}$ elimination from **33a-2** re-

heterocycle (**10n**) via an optically active Ni(II) intermediate. The reaction using (*R*)-**9n** (92% ee) proceeded smoothly to give (*S*)-**10n**⁵⁴ with 64% ee, which suggests that optically active allyl Ni(II) intermediates (**11n**) could be generated from the axial chirality of (*R*)-**9n**.

4. Conclusion

The new reactions described here all originate from the unique reactivity of allene, and these transformations should be useful for the synthesis of various cyclic and acyclic molecules. This review shows that a simple C=C=C functionality is a key structure in nickel catalysis and natural product synthesis. Studies with D-labeling and chirality transfer were important for revealing the reaction mechanism and regioselectivity. These results demonstrate the utility of both Ni catalysis and allenyl functionalities in chemical transformations.

Acknowledgments The author thanks Prof. Atsushi Nishida and Prof. Shinji Harada (Chiba University) for their helpful support and fruitful discussions. He also appreciates the following collaborators for their efforts: Dr. Yuka Amako; Dr. Hiroto Hori; Mr. Tomohiro Igarashi; Dr. Xiaofei Yang; and Mr. Koki Matsumoto. This project was financially supported by the Japan Society for the Promotion of Science (JSPS), Uehara Memorial Foundation, and Naito Foundation.

Conflict of Interest The author declares no conflict of interest.

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