Angewandte Chemie
International Edition

**C–H Activation**

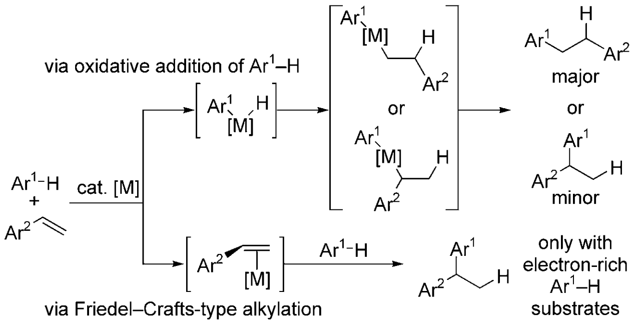
DOI: 10.1002/anie.201001470

# Nickel-Catalyzed Hydroheteroarylation of Vinylarenes**

*Yoshiaki Nakao,* Natsuko Kashihara, Kyalo Stephen Kanyiva, and Tamejiro Hiyama**

*In memory of Keith Fagnou*

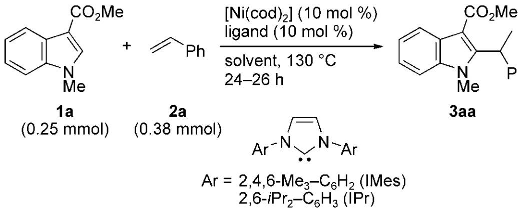
The metal-catalyzed hydroarylation of vinylarenes is a versatile and highly atom-economical way to obtain 1,1-diarylmethyl structural motifs that are found in many pharmaceuticals and biologically active molecules.[1] This catalytic reaction can be classified into two major types depending on the possible mechanism (Scheme 1). The reaction can be initiated by oxidative addition of aromatic C–H bonds to a metal catalyst, before hydrometalation and reductive elimination. However, to the best of our knowledge, there is only a single report of this mechanism affording 1,1-diarylethane compounds,[2] with 1,2-diarylethanes being generally obtained as the major products from this mechanistic pathway.[3] Another type of hydroarylation reaction of vinylarenes involves the Friedel–Crafts-type alkylation of arenes, wherein a metal catalyst acts as a Lewis acid to activate the double bond of vinylarenes.[4] Although 1,1-diarylethanes are generally obtained from this reaction with good to excellent regioselectivity, the scope of arenes that can participate in this mechanism is severely limited to highly electron-rich arenes, including indoles that contain an electron-donating substituent and a few furan and thiophene derivatives.[4] On the other hand, we recently reported that a nickel/tricyclopentylphosphine ($PCyp_3$) catalyst effects the hydroarylation of 2-vinylnaphthalene with a highly electron-poor arene, pentafluorobenzene.[5] Subsequent studies on the mechanism of the alkyne hydrofluoroarylation by the same nickel catalyst revealed that the catalysis was initiated by oxidative addition of the C–H bonds of fluoroarenes to nickel(0).[6] These studies prompted us to examine the hydroarylation of vinylarenes that contain relatively electron-poor heteroarenes. These compounds also undergo addition across alkynes, possibly through oxidative addition of C–H bonds to nickel(0).[7] Herein, we report the hydroheteroarylation of vinylarenes to give 1,1-diarylalkanes that contain a variety of heteroaryl groups.[8]



*Scheme 1.* Possible mechanisms for the metal-catalyzed hydroarylation of vinylarenes. M = (transition) metal.

First, we examined the reaction of methyl 1-methylindole-3-carboxylate (**1a**) with styrene (**2a**) in the presence of a nickel catalyst that was derived from $[Ni(cod)_2]$ (5–10 mol %) and a ligand (Table 1). We found that the use of 1,3-dimesitylimidazol-2-ylidene (IMes) in nonpolar solvents, such as hexane and toluene, was crucial to obtaining methyl 1-methyl-2-(1-phenylethyl)indole-3-carboxylate (**3aa**) in over 80 % yield (Table 1, entries 1 and 2 vs 3 and 4); the use of a different ligand, 1,3-(2,6-diisopropylphenyl)imidazol-2-ylidene (IPr), in toluene also gave inferior results (Table 1, entry 5). The carbene ligand, IMes, is known to be effective in the C6-selective alkylation of 2-pyridone derivatives with 2-

*Table 1:* Hydroheteroarylation of styrene (**2a**) with **1a**.



| Entry | Ligand | Solvent | Yield of **3aa** [%][a] |
|---|---|---|---|
| 1[b] | IMes | hexane | 83 |
| 2 | IMes | toluene | 82 |
| 3 | IMes | THF | 35 |
| 4 | IMes | NMP | 35 |
| 5 | IPr | toluene | 2 |
| 6 | $PCyp_3$ | toluene | $<5$ |
| 7 | $P(nBu)_3$ | toluene | $<5$ |

[a] Estimated by GC based on **1a**. [b] Run with 5 mol% of nickel and IMes. IMes = 1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene, IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, $Cyp_3$ = tricyclopentylphosphine, NMP = 1-methyl-2-pyrrolidinone.

---

[*] Dr. Y. Nakao, N. Kashihara, K. S. Kanyiva, Prof. Dr. T. Hiyama
Department of Material Chemistry, Graduate School of Engineering
Kyoto University, Katsura, Nishikyo-ku, Kyoto 615-8510 (Japan)
Fax: (+81) 75-383-2445
E-mail: yoshiakinakao@npc05.mbox.media.kyoto-u.ac.jp
thiyama@z06.mbox.media.kyoto-u.ac.jp

[**] This work has been supported financially by a Grant-in-Aid for Scientific Research (S) from MEXT. K.S.K. acknowledges Honjo International Scholarship Foundation for financial support.

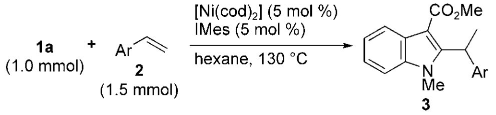
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201001470.

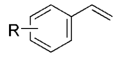
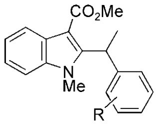
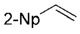
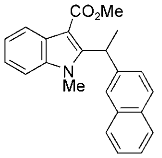
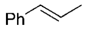
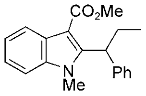
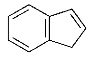
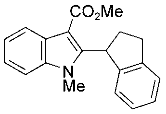
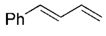
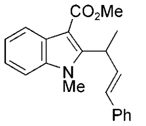
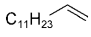
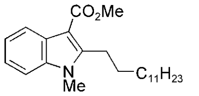
© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

WILEY InterScience DISCOVER SOMETHING GREAT

vinylnaphthalene.[9] No trace amount of the regioisomeric 1,2-diarylethane product was detected. PCyp$_3$, the ligand of choice for hydrofluoroarylation of vinylarenes,[5] and P($n$Bu)$_3$ were completely ineffective (Table 1, entries 6 and 7). In the presence of the nickel/IMes catalyst, a variety of vinylarenes that contain phenyl groups bearing both electron-rich and electron-poor substituents reacted successfully with **1a** (Table 2). In particular, an Ar−F bond was tolerated under the reaction conditions, even though a related nickel/N-heterocyclic carbene catalyst was reported to effect Ar−F bond activation.[10] In addition to vinylarenes, 1-phenylpropene (**2i**) and indene (**2j**) also participated in the hydroheteroarylation reaction to give 1,1-diarylethane **3ai** and 1-heteroarylindane **3aj**, respectively (Table 2, entries 9 and 10). The vinylogous styrene, 1-phenyl-1,3-butadiene (**2k**), reacted exclusively at its terminal double bond to give C2-functionalized indole **3ak** (Table 2, entry 11). The same regioselectivity was also observed in the reaction of pentafluorobenzene with **2k**, and is presumably derived from a π-allylnickel intermediate.[5] On the other hand, 1-tridecene (**2l**) gave linear adduct **3al** exclusively (Table 2, entry 12). Lack of functionalities that contain a π system could retard the formation of a secondary alkylnickel intermediate in the absence of any stabilization available with π-benzyl- or π-allylnickel species to favor the migration of a hydride to the C2-position of the aliphatic 1-alkene.

*Table 2:* Hydroheteroarylation of vinylarenes with **1a**.

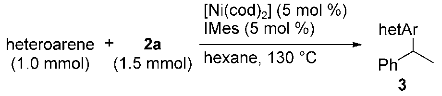


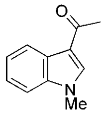
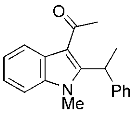
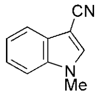
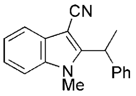
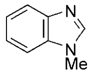
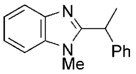
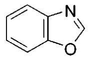
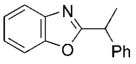
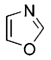
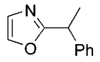
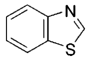
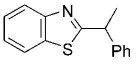
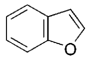
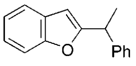
| Entry | **2** (R) | | $t$ [h] | Product | | Yield of **3** [%][a] |
|---|---|---|---|---|---|---|
| |  | | | | | |
| 1 | **2a** | H | 31 |  | **3aa** | 90 |
| 2 | **2b** | 2-MeO | 32 | | **3ab** | 85 |
| 3[b] | **2c** | 3-MeO | 10 | | **3ac** | 100 |
| 4 | **2d** | 4-MeO | 10 | | **3ad** | 86 |
| 5 | **2e** | 4-Me | 22 | | **3ae** | 94 |
| 6[b,c] | **2f** | 4-F | 22 | | **3af** | 98 |
| 7[b] | **2g** | 4-MeO$_2$C | 12 | | **3ag** | 80 |
| 8[b] | **2h** |  | 8 |  | **3ah** | 80 |
| 9[b] | **2i** |  | 2 |  | **3ai** | 89 |
| 10[b,d] | **2j** |  | 22 |  | **3aj** | 17 |
| 11[e] | **2k** |  | 9 |  | **3ak** | 62 |
| 12[f] | **2l** |  | 4 |  | **3al** | 80 |

[a] Yield of isolated product based on **1**. [b] Run with 10 mol% of nickel and IMes. [c] Run in toluene. [d] Conversion of **1a** was estimated to be 36%. [e] Run with [Ni(cod)$_2$] (10 mol%) and P($n$Bu)$_3$ (10 mol%) as a ligand. [f] Run with 1-tridecene (5.0 mmol), [Ni(cod)$_2$] (10 mol%), and IPr (10 mol%). Np = naphthyl.

The nickel/IMes catalysis also showed a wide scope of tolerance for heteroarenes (Table 3). Indoles that have an acetyl or a cyano group at the C3-position were alkylated to give their corresponding 1,1-diarylethanes in good yields (Table 3, entries 1 and 2). Azoles, including benzimidazole (**1d**), benzoxazole (**1e**), oxazole (**1f**), and benzothiazole (**1g**) underwent hydroheteroarylation to give modest to good yields (Table 3, entries 3–6). The addition of benzofuran (**1h**) across styrene (**2a**) proceeded exclusively at the C2-position (Table 3, entry 7).

*Table 3:* Hydroheteroarylation of **2a**.

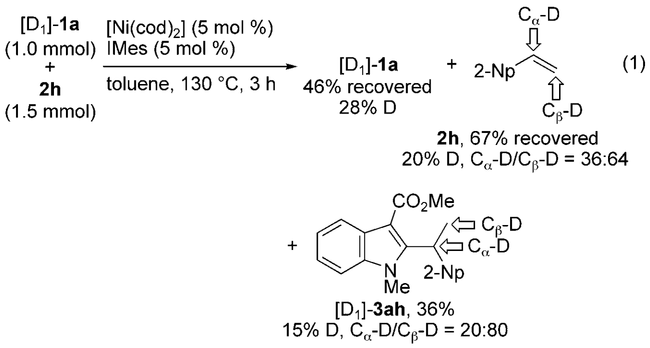


| Entry | Heteroarene | | $t$ [h] | Product | | Yield of **3** [%][a] |
|---|---|---|---|---|---|---|
| 1 |  | **1b** | 23 |  | **3ba** | 89 |
| 2[b,c] |  | **1c** | 7 |  | **3ca** | 85 |
| 3 |  | **1d** | 9 |  | **3da** | 86 |
| 4 |  | **1e** | 2 |  | **3ea** | 97 |
| 5 |  | **1f** | 7 |  | **3fa** | 41 |
| 6 |  | **1g** | 4 |  | **3ga** | 81 |
| 7 |  | **1h** | 6 |  | **3ha** | 77 |

[a] Yield of isolated product based on **1**. [b] Run with 10 mol% of nickel and IMes. [c] Run with 3.0 mmol of **2a**. hetAr = heteroaryl.

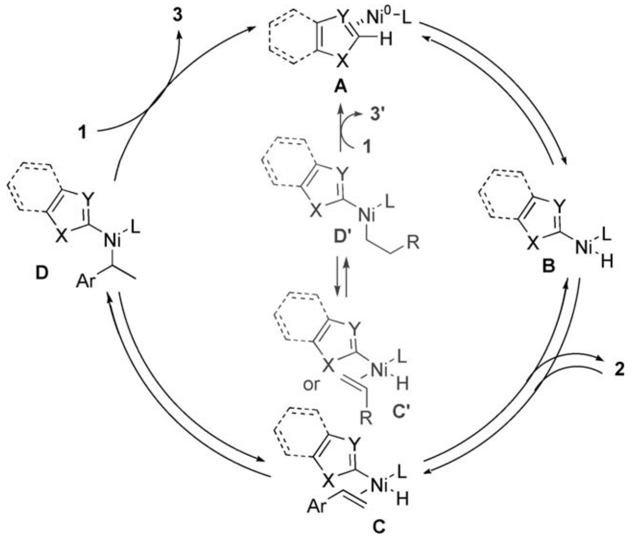
To gain insight into the reaction mechanism we prepared methyl 2-deutero-1-methylindole-3-carboxylate ([D$_1$]-**1a**) and examined its reaction with **2h** under the optimized conditions [Eq. (1)]. The reaction was stopped after 3 hours to obtain [D$_1$]-**3ah** in 36% yield with 15% total deuteration [Eq. (1)]. Interestingly, deuteration occurred not only at the terminal methyl group (C$_\beta$-D) but also at the benzylic position (C$_\alpha$-D). In addition, recovered [D$_1$]-**1a** and **2h** showed partial deuteration: both the α and β positions of the vinyl group in **2h** were deuterated. These data suggest a plausible catalytic

© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



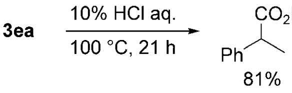
(1)

cycle that is initiated by reversible oxidative addition of an Ar–H bond to the nickel(0)/IMes catalyst to give nickel hydride **B** through $\eta^2$-arenenickel **A** (Scheme 2). The coordination of vinylarenes **C** and subsequent hydronickelation are both reversible and give 1-arylethylnickel **D**, that reductively eliminates 1,1-diarylethanes irreversibly to regenerate **A**. The final step could be the rate-determining step, as has been discussed previously for the nickel-catalyzed hydrocyanation[11] and hydroalkynylation[12] of vinylarenes. The primary reaction pathway could compete with the coordination and migratory insertion of alkenes to give 1,2-diarylethanes via **C′** and **D′**. Whilst this minor pathway is not product-forming for vinylarenes, it becomes an exclusive reaction pathway with aliphatic 1-alkenes, presumably because of the lack of stabilization of the alkylnickel species and steric repulsion (Table 2, entry 12). Deuteration at both the α and β positions of **3ah**, the recovery of **2h**, as well as the loss of deuteration and scrambling in [D$_1$]-**1a** can be understood in terms of these major and minor reversible reaction pathways.



*Scheme 2.* A plausible mechanism for the hydroheteroarylation of vinylarenes. L = IMes; X = NMe, O, S; Y = C(H)–EWG, N; EWG = electron-withdrawing group.

The synthetic application of this hydroheteroarylation reaction is demonstrated by the hydrolysis of **3ea** with 10% HCl (aq) at 100 °C for 21 hours to give 2-phenylpropanoic acid in 81% yield [Eq. (2)]. This two-step reaction could be an alternative way to access 2-arylpropanonic acid derivatives, which are also found in many biologically active compounds.



(2)

In summary, we have demonstrated the nickel-catalyzed hydroheteroarylation of vinylarenes to exclusively give a variety of 1,1-diarylethanes that contain a heteroaryl motif. A catalytic cycle, initiated by the oxidative addition of the heteroarene C2–H bonds, is suggested on the basis of some mechanistic studies. The use of relatively electron-poor heteroarenes in this study is complementary to the well-documented Friedel–Crafts-type hydroarylation of vinylarenes with electron-rich arenes to give a wide variety of 1,1-diarylethanes. Current efforts are directed toward further expansion of the scope of the reaction, especially with the aid of a Lewis acid co-catalyst to activate the otherwise unreactive C–H bonds of heteroarene[13] and amide[14] substrates as well as development of an enantioselective protocol using a chiral N-heterocyclic carbene ligand.

## Experimental Section

A general procedure for nickel-catalyzed hydroheteroarylation of vinylarenes: A solution of [Ni(cod)$_2$] (14 mg, 50 μmol) and IMes (15 mg, 50 μmol) in hexane (1.0 mL) was added to a heteroarene (1.0 mmol) in a 3 mL-vial in a dry box before addition of the vinylarene (1.5 mmol). After undecane (internal standard, 78 mg, 0.50 mmol) was added, the vial was screw-capped, taken outside the dry box, and heated at the required temperature for the time specified in Tables 1–3. The resultant mixture was filtered through a pad of silica gel and then concentrated in vacuo. The residue was purified by flash chromatography on silica gel to give the corresponding products in the yields listed in Tables 1–3.

Received: March 11, 2010
Published online: April 30, 2010

**Keywords:** carbene ligands · C–H activation · heterocycles · nickel · vinylarenes

---

[1] a) D. Lednicer, L. A. Mitscher, *The Organic Chemistry of Drug Synthesis, Vol. 1*, Wiley, New York, **1977**, Chapter 4; b) D. Lednicer, L. A. Mitscher, *The Organic Chemistry of Drug Synthesis Vol. 1*, Wiley, New York, **1980**, Chapter 2.
[2] Y. Uchimaru, *Chem. Commun.* **1999**, 1133.
[3] a) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, *Nature* **1993**, *366*, 529; b) F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda, N. Chatani, S. Murai, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 62; c) T. Matsumoto, R. A. Periana, D. J. Taube, H. Yoshida, *J. Mol. Catal. A* **2002**, *180*, 1; d) C.-H. Jun, C. W. Moon, J.-B. Hong, S.-G. Lim, K.-Y. Chung, Y.-H. Kim, *Chem. Eur. J.* **2002**, *8*, 485; e) R. Martinez, J.-P. Genet, S. Darses, *Chem. Commun.* **2008**, 3855.

© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[4] a) J. Kischel, I. Jovel, K. Mertins, A. Zapf, M. Beller, *Org. Lett.* **2006**, *8*, 19; b) H.-B. Sun, B. Li, R. M. Hua, Y. W. Yin, *Eur. J. Org. Chem.* **2006**, 4231; c) M. Rueping, B. J. Nachtsheim, T. Scheidt, *Org. Lett.* **2006**, *8*, 3717; d) Z. B. Zhang, X. Wang, R. A. Widenhoefer, *Chem. Commun.* **2006**, 3717; e) M.-Z. Wang, M.-K. Wong, C.-M. Che, *Chem. Eur. J.* **2008**, *14*, 8353.

[5] Y. Nakao, N. Kashihara, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2008**, *130*, 16170.

[6] K. S. Kanyiva, N. Kashihara, Y. Nakao, T. Hiyama, M. Ohashi, S. Ogoshi, unpublished results.

[7] a) Y. Nakao, K. S. Kanyiva, S. Oda, T. Hiyama, *J. Am. Chem. Soc.* **2006**, *128*, 8146; b) K. S. Kanyiva, Y. Nakao, T. Hiyama, *Heterocycles* **2007**, *72*, 677.

[8] During the course of this study, Miura and co-workers reported addition of 1,3,4-oxadiazoles across vinylarenes by a nickel catalyst, see: T. Mukai, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 6410.

[9] Y. Nakao, H. Idei, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2009**, *131*, 15996.

[10] V. P. W. Böhm, C. W. K. Gstottmayr, T. Weskamp, W. A. Herrmann, *Angew. Chem.* **2001**, *113*, 3500; *Angew. Chem. Int. Ed.* **2001**, *40*, 3387.

[11] A. L. Casalnuovo, T. V. Rajanbabu, T. A. Ayers, T. H. Warren, *J. Am. Chem. Soc.* **1994**, *116*, 9869.

[12] M. Shirakura, M. Suginome, *Org. Lett.* **2009**, *11*, 523.

[13] a) Y. Nakao, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2008**, *130*, 2448; b) K. S. Kanyiva, F. Löbermann, Y. Nakao, T. Hiyama, *Tetrahedron Lett.* **2009**, *50*, 3463.

[14] Y. Nakao, H. Idei, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2009**, *131*, 5070.

© 2010 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim