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Nickel-catalyzed intermolecular carboiodination of alkynes with aryl iodides†

Toshifumi Takahashi,‡ Daiki Kuroda,‡ Toru Kuwano,‡ Yuji Yoshida,‡
Takuya Kurahashi * and Seijiro Matsubara*

Nickel-catalyzed intermolecular carboiodination of alkynes with aryl iodides to form highly substituted and functionalized alkenyl iodides has been developed. The reaction involves radical-mediated formal alkyne insertion into the carbon–nickel bond and carbon–iodine reductive elimination facilitated by Ni(III) species.

Organohalogen compounds such as alkenyl iodides are versatile and essential building blocks in organic synthesis.[1,2] Many established reactions (*e.g.* transition-metal-catalyzed cross-coupling reactions) require organohalogen compounds as coupling partners, and halogen atoms are easily replaced with other organic structures or heteroatoms to construct new chemical bonds.[3] Although the carbometallation of an alkyne followed by reaction with a halogen source such as *N*-iodosuccinimide or I_2 is well known as a conventional synthetic method, the development of a direct, facile method to afford tetrasubstituted alkenyl halides remains a research topic of great interest. In the last decade, the transition-metal-catalyzed insertion of an alkyne into the carbon–halogen bond of an organohalogen compound, *i.e.* carbohalogenation, has been identified as a significant reaction which enables straightforward access to highly substituted alkenyl halides without by-product formation.[4] However, based on Hartwig's study of the chemistry of ArPd(II)X complexes, the reductive elimination of a carbon–halogen bond from a transition metal is disfavored and largely promoted by sterically bulky ligands (Fig. 1(a)).[5] Thus, Lautens' group succeeded in developing intramolecular carbohalogenation reactions of alkynes by using bulky Q-Phos, tri-*tert*-butylphosphine, or aryl phosphaadamantanes as ligands for the palladium catalysts, and sterically demanding mesityl or TIPS groups as substituents of the alkynes to facilitate the key reductive elimination step (Fig. 1(b)).[6] However, the steric bulkiness of both ligands and alkyne substituents retards alkyne insertion, and therefore, the reaction was designed as an intramolecular process to overcome the steric hindrance. Thus, under this circumstance, there is a trade-off between the promotion of reductive elimination and alkyne insertion. Herein, we report the intermolecular carboiodination of alkynes with aryl iodides to form highly substituted and functionalized alkenyl iodides enabled by nickel catalysis and radical-involving reaction mechanism (Fig. 1(c)).

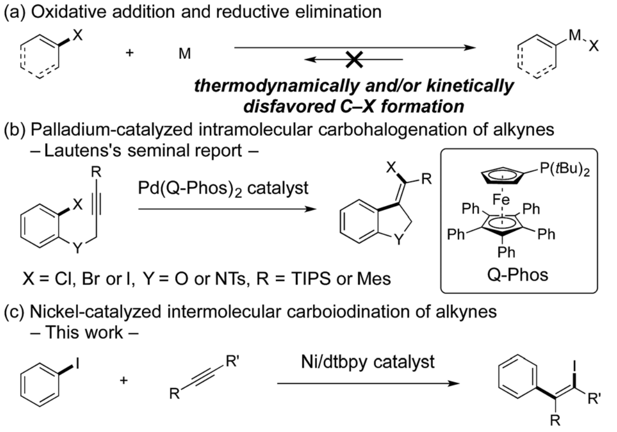

Fig. 1 Transition-metal-catalyzed carboiodination.

We initially hypothesized that the aryl radical species generated by homolysis of the carbon–nickel bond could react with alkynes, and recombination of the obtained alkenyl radical and Ni(II)I_2 forms an alkenylNi(III)I_2 complex, followed by facile reductive elimination to form the carbon–iodine bond from this high-valent complex would generate the desired alkenyl iodide. Accordingly, intermolecular formal alkyne insertion into carbon–halogen bonds would be achieved. To prove our hypothesis, we examined the nickel-catalyzed carboiodination of 4-octyne (**2a**) with iodobenzene (**1a**) in toluene at 50 °C (Table S1, ESI†), and we found that alkenyl iodide **3aa** was obtained in 92% yield when dtbpy was employed as the ligand (Scheme 1) (Fig. 2).

Department of Material Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 615-8510, Japan. E-mail: kurahashi.takuya.2c@kyoto-u.ac.jp, matsubara.seijiro.2e@kyoto-u.ac.jp

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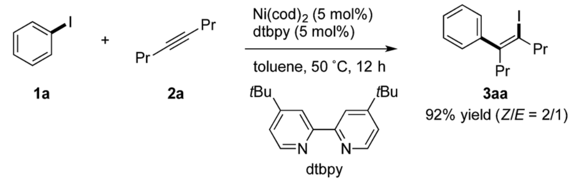
‡ These authors contributed equally.



Scheme 1 Nickel-catalyzed carboiodination of **2a** with **1a**.

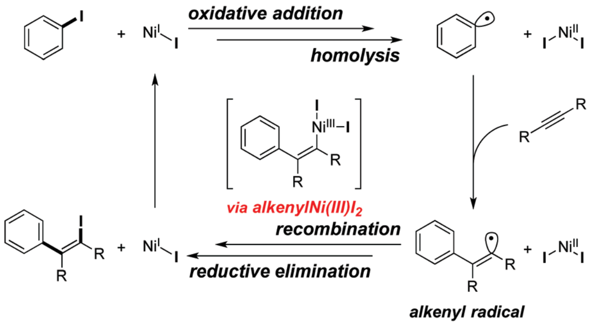
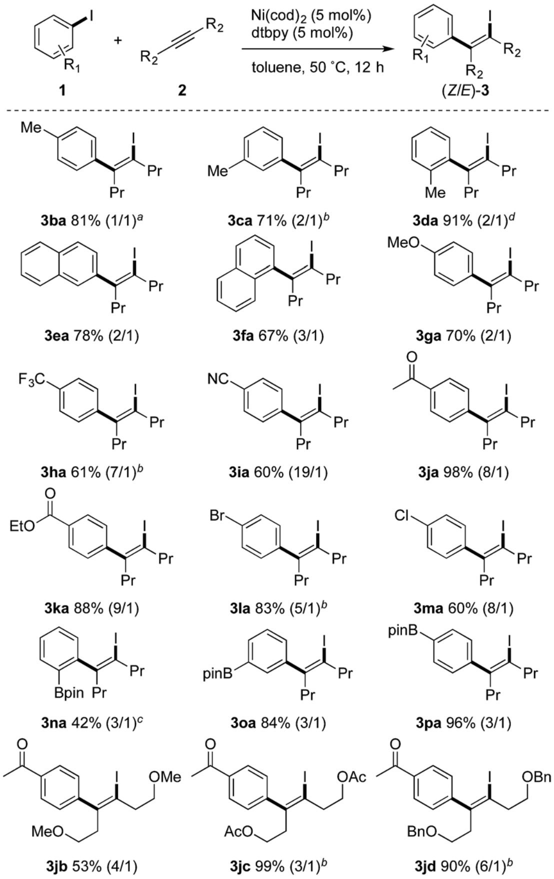


Fig. 2 Working hypothesis for intermolecular carboiodination.



Scheme 2 Substrate scope in the carboiodination of alkynes with aryl iodides. All reactions were carried out using Ni(cod)$_2$ (5 mol%), ligand (5 mol%), **1** (0.5 mmol), and **2** (0.75 mmol) in 1 mL of toluene at 50 °C for 12 h, unless otherwise noted. Isolated yields are given. *Z*/*E* ratio were determined by ^{1}H NMR analysis and given in parentheses. [a] 24 h. [b] 48 h. [c] 72 h. [d] 96 h.

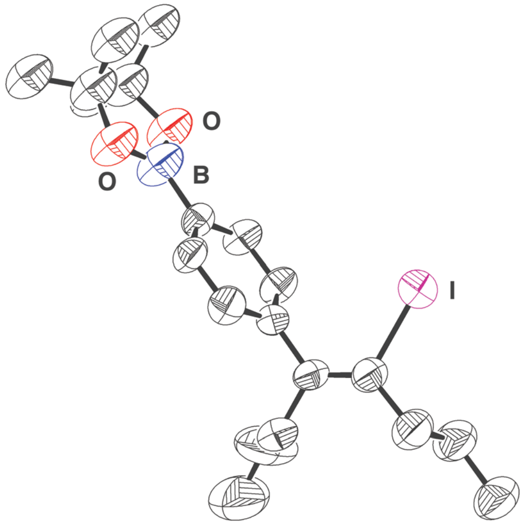


Fig. 3 ORTEP drawing of **3pa**.

To determine the scope of the reaction, we next performed the nickel-catalyzed carboiodination of alkynes with substituted iodobenzenes to obtain the corresponding tetrasubstituted alkenyl iodides (Scheme 2). The reaction of 4-tolyl iodide with 4-octyne **2a** gave **3ba** in 81% isolated yield. Even though a longer reaction time was required, *m*- or *o*-methyl-substituted phenyl iodides also afforded alkenyl iodides in high yields (**3ca**: 48 h, 71%; **3da**: 96 h, 91%). Naphthyl iodides also participated in the reaction to give the corresponding alkenyl iodides (**3ea**, **3fa**). Furthermore, various functional groups were tolerated under the reaction conditions; aryl iodides possessing alkoxy (**3ga**), trifluoromethyl (**3ha**), nitrile (**3ia**), ketone (**3ja**), or ester (**3ka**) substituents participated in the reaction to provide the corresponding alkenyl iodides in moderate to high yields. Of note, aryl iodides possessing bromine or chlorine substituents also participated in the reaction to give alkenyl iodides **3la** and **3ma** in 83% and 60% yields, respectively; clearly, bromine and chlorine atoms were tolerated under the reaction conditions, and the carboiodination proceeded in a chemoselective manner. Furthermore, boryl-substituted aryl iodides reacted with alkyne **2a** to afford the desired products in moderate-to-high yields (**3na**, **3oa**, and **3pa**) and the structure of **3pa** was confirmed with X-ray single crystal analysis (Fig. 3). Alkynes possessing alkoxy or ester groups successfully participated to provide alkenyl iodides **3jb**, **3jc**, and **3jd** in 53%, 99%, and 90% yield, respectively. The reaction of phenyl bromide with **2a** resulted in low yield ($<$5%). The use of alkyl iodides in place of aryl iodide did not afford the products. The reaction using non-symmetrical alkynes afforded mixture of isomers and the reaction with terminal alkynes resulted in low yield.

We next analyzed the catalytic reaction spectroscopically to gain insight into the reaction mechanism. The reaction mixture was subjected to electron paramagnetic resonance (EPR) measurements (Fig. 4). The mixture of catalytic amount of Ni(0)/dtbpy, iodobenzene (**1a**) and 4-octyne (**2a**) in toluene (25 mM) displays a signal at $g = 2.124$, which is significantly deviated from that of

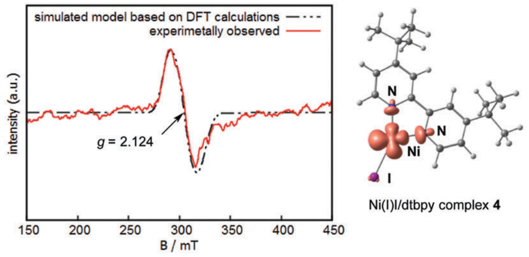


Fig. 4 X-Band EPR merged-spectrum of the reaction mixture (red solid line) and simulated spectrum based on DFT calculations of Ni(I)I/dtbpy complex **4** (black dashed line). Spin density plot of computed Ni(I)I/dtbpy complex **4**. Mulliken spin density: Ni, 0.93; N, 0.05; N, 0.03; I, 0.02.

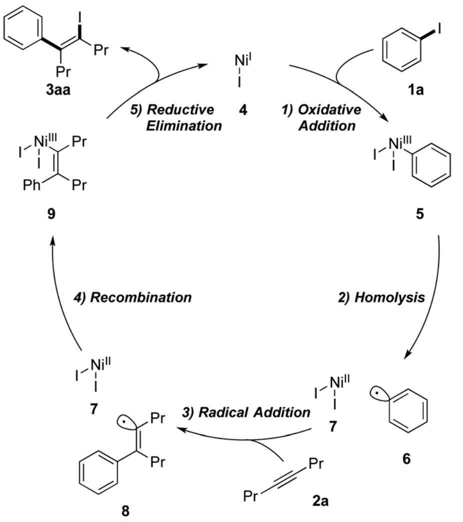
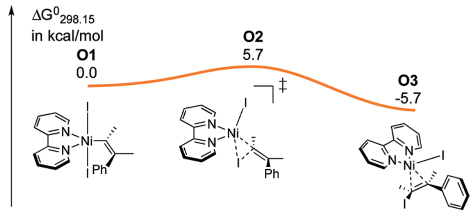


Fig. 5 Plausible catalytic cycle.

a free electron (g = 2.002). This result indicates the presence of paramagnetic nickel complex in the reaction mixture and unpaired electron is mostly nickel based.[7–10] Further computational studies revealed that Ni(I)I/dtbpy **4** simulates the experimentally observed EPR spectrum in good agreement.

– Favored path –

(a) Odd-valent mechanism of reductive elimination



– Disfavored path –

(b) Even-valent mechanism of reductive elimination

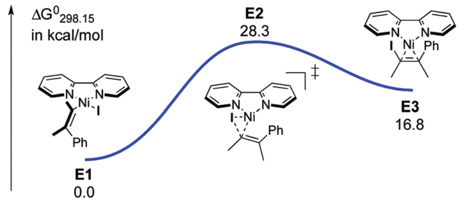


Fig. 6 Plausible reductive elimination mechanisms. These calculations were performed with M06/SDD(2f)(Ni),SDD(I),6-311+G(2d,p)(C,H,N)//M06/Lanl2dz(f)(Ni),Lanl2dz(I),6-31G(d)(C,H,N) with CPCM(toluene) solvation. Further details are given in the ESI.†

Based on these experiments, we propose a catalytic cycle involving odd-valent nickel complexes and radical species, *e.g.* Ni(I)I/dtbpy **4** which is generated *via* comproportionation *in situ* (Fig. 5).[12,13] The proposed mechanism is as follows: (1) oxidative addition of iodobenzene **1a** to Ni(I)I **4** gives unstable PhNi(III)I_2 **5**, which (2) forms phenyl radical **6** *via* carbon–nickel bond homolysis. (3) The alkenyl radical **8** formed from phenyl radical **6** and alkyne **2a**, so that (4) recombination with the Ni(II) **7** complex gives alkenylNi(III)I_2 **9**. Finally, (5) alkenyl iodides **3aa** are obtained as final products *via* facile reductive elimination from the unstable high-valent Ni(III) complexes **9**. This is consistent with preliminary computational studies (Fig. 6, see also ESI†); carbon–iodine reductive elimination from Ni(III) is exergonic with a sufficiently low activation barrier, in contrast to the endergonic reductive elimination from a Ni(II) complex with a high energy barrier. The observed reactivities of Ni(III) and Ni(II) in the reductive elimination are in good agreement with studies of the carbon–oxygen reductive elimination of nickel complexes reported by Hillhouse, MacMillan, Doyle, and their co-workers.[8a,11,14]

In summary, we have developed the nickel-catalyzed intermolecular carboiodination of alkynes with simple aryl iodides to afford tetrasubstituted alkenyl iodides. The nickel-catalyzed radical-involving reaction mechanism affords a new way to access direct carbohalogenation in an intermolecular fashion with atom- and redox-economy. The mechanism is based on the unique properties of nickel catalysts with redox-active ligands such as bipyridine that allow Ni(I) and Ni(III) oxidation states.[15] Further investigations on the reaction mechanism are underway, both experimentally and theoretically, and will be reported in due course.

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Conflicts of interest

There are no conflicts to declare.

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