

## 論文の内容の要旨

論文題目 Development of Late Transition Metal-Catalyzed Novel Aerobic Oxidative Cross-Dehydrogenative Coupling Reactions

(後期遷移金属触媒による酸素を酸化剤とした新規脱水素型クロスカップリング反応の開発)

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### 1. Introduction

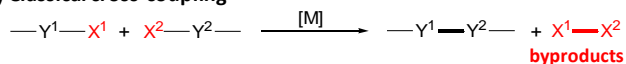
Cross-coupling reactions have become one of the most powerful procedures for synthesis of a wide range of valuable chemicals. Despite the great success of several cross-coupling reactions, e.g., Suzuki, Negishi, and Heck reactions, they have drawbacks of utilizing pre-activated substrates such as organo (pseudo) halides and organometallic compounds. Therefore, the traditional cross-coupling reactions require multi-step procedures, resulting in the low overall synthetic efficiencies and the generation of large amounts of byproducts (Figure 1, a).

The oxidative cross-dehydrogenative coupling reactions of C–H or X–H (X = hetero atoms) bonds employing molecular oxygen instead of transition metal- or organic-based oxidants have been of particular research interest.

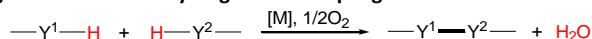
Because they do not require the pre-activated substrates and produce only water as the byproduct, consequently have higher synthetic efficiencies and more environmentally benign nature in comparison with the traditional cross-coupling reactions (Figure 1, b).

One of the key factors for the development of novel aerobic cross-dehydrogenative coupling reactions is the activation of molecular oxygen through one or multiple electron transfer between catalysts and molecular oxygen. This study is mainly focused on copper-based catalysts, gold nanoparticles, and manganese-based oxides because of their well known properties of activating molecular oxygen either in biological or chemical systems. Specifically, the following several reactions have successfully been developed; (1) copper-catalyzed cross-coupling of terminal alkynes or *H*-phosphonates with amides through the sequential coordination/reductive elimination/reoxidation pathways (Figure 1, c-i), (2) heterogeneously gold-catalyzed aerobic oxidative amination of  $\alpha,\beta$ -unsaturated aldehydes by the

#### (a) Classical cross-coupling

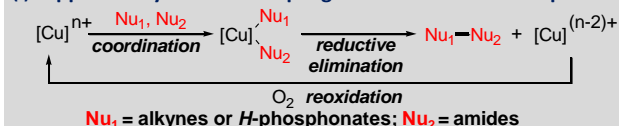


#### (b) Aerobic cross-dehydrogenative coupling

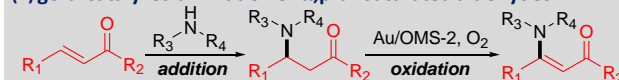


#### (c) This work

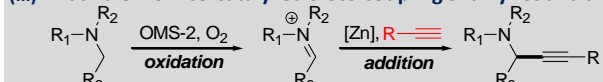
##### (i) copper-catalyzed cross-coupling of two different nucleophiles



##### (ii) gold-catalyzed amination of $\alpha,\beta$ -unsaturated aldehydes



##### (iii) zinc and OMS-2 co-catalyzed cross-coupling of alkynes and amines



**Figure 1.** Outline of this study.  $\text{X}^1, \text{X}^2$  = hetero atoms ;  $\text{Y}^1, \text{Y}^2$  = C or hetero atoms ;  $[\text{M}]$  = transition metals; Nu = nucleophiles. OMS-2 = manganese oxide-based octahedral molecular sieves.

sequential nucleophilic addition/aerobic oxidative dehydrogenation pathways (Figure 1, c-ii), and (3) zinc and OMS-2 co-catalyzed cross-coupling of terminal alkynes and tertiary amines by nucleophilic addition of in situ generated zinc acetylide species to in situ generated iminium species by two electron oxidation (Figure 1, c-iii).

## 2. Copper-Catalyzed Aerobic Oxidative Cross-Coupling of Two Different Nucleophiles

### ■ Cu(OH)<sub>2</sub>-Catalyzed Cross-Coupling of Terminal Alkynes and Amides

Copper catalysts show unique activity for several aerobic oxidative cross-coupling reactions of two different nucleophiles having acidic C–H or X–H bonds. Because (1) they are easily accessible to Cu<sup>0</sup>, Cu<sup>I</sup>, Cu<sup>II</sup>, and Cu<sup>III</sup> oxidation states via one or two-electron transfer processes, which allows both radical and palladium-like two-electron pathways, (2) various functional groups can readily coordinate to them via Lewis acidic interactions or  $\pi$ -coordination, and (3) their lower valence states can easily be reoxidized by molecular oxygen.

Ynamides are emerging as versatile synthons in organic synthesis, which are generally synthesized by cross-coupling of functionalized alkynes such as alkynyl halides and trifluoroborates with amides.

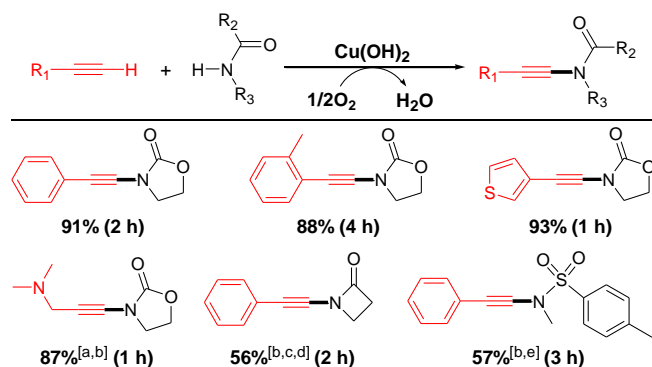
The direct cross-coupling of terminal alkynes and amides using molecular oxygen as the terminal oxidant represents one of the most effective synthetic procedures for ynamides. However, when using copper-based catalysts, the Glaser alkyne homo-coupling preferentially takes place, resulting in the low selectivity to the desired cross-coupling, unless a slow addition technique is employed. In this context, heterogeneous copper hydroxide catalysts are considered to be suitable for the achievement of the selective cross-coupling, because (1) hydroxyl groups on the surface could facilitate the abstraction of protons from acidic C<sub>sp</sub>–H and N–H bonds and (2) they are less active for the alkyne homo-coupling compared to homogeneous systems (especially in the presence of nitrogen donors).

In the present study, a simple commercially available Cu(OH)<sub>2</sub> was found to catalyze the selective aerobic oxidative cross-coupling of terminal alkynes and amides to ynamides in the presence of catalytic amounts of bases (Figure 1, c-i). Among various copper catalysts examined such as Cu(OH)<sub>2</sub>, CuO, Cu(acac)<sub>2</sub> (acac = acetylacetonate), Cu(OTf)<sub>2</sub> (OTf = triflate), Cu(OAc)<sub>2</sub>·H<sub>2</sub>O (OAc = acetate), CuI, CuCl<sub>2</sub>, and CuSO<sub>4</sub>·5H<sub>2</sub>O, Cu(OH)<sub>2</sub> was the most effective catalyst in terms of the selectivity and reactivity for the cross-coupling. In the present case, the desired ynamides could be obtained by simply mixing catalytic amounts of Cu(OH)<sub>2</sub> and an inorganic base as well as the two coupling partners in a single step (without slow addition). The substrate scope for the present cross-coupling was very broad with respect to both terminal alkynes (including both aromatic and aliphatic ones) and amides (including oxazolidinone, azetidinone, and sulfonamide derivatives) (Figure 2).

In addition, a novel atom economical (theoretically 100%) synthetic procedure for imides has also been developed by the oxidative cross-coupling and the sequential regioselective hydration of ynamides by the Sn–W mixed oxide catalyst, giving the corresponding imides in moderate to high yields.

### ■ Cu(OAc)<sub>2</sub>-Catalyzed Cross-Coupling of *H*-Phosphonates and Amides

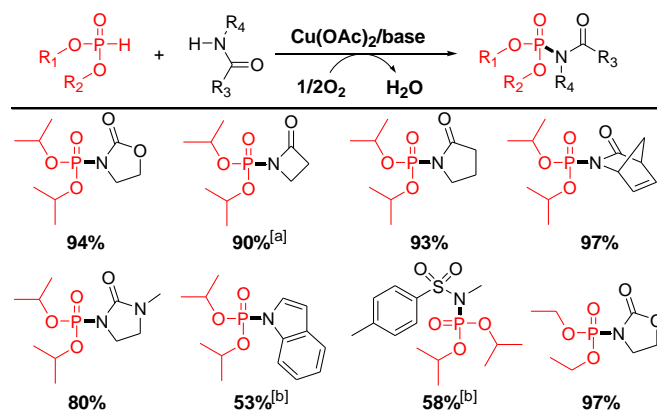
Next, a novel synthetic procedure for *N*-acylphosphoramidates by the cross-coupling of terminal alkynes and *H*-phosphonates having acidic P–H bonds has been developed (Figure 1, c-i). *N*-Acylphosphoramidates are important structural key motifs in various bioactive natural products and pharmaceuticals. They are typically synthesized by multi-step non-green procedures, for example,



**Figure 2.** Oxidative cross-coupling of terminal alkynes and amides. The isolated yields (based on alkyne) are reported (unless otherwise noted). Reaction conditions: alkyne (0.1 mmol), amide (0.3 mmol), Cu(OH)<sub>2</sub> (5 mol%), K<sub>2</sub>CO<sub>3</sub> (5 mol%), mesitylene (1 mL), 100 °C, under air (1 atm). [a] alkyne (0.2 mmol), amide (0.4 mmol), Cu(OH)<sub>2</sub> (10 mol%), Cs<sub>2</sub>CO<sub>3</sub> (5 mol%). [b] Yields were determined by GC using biphenyl as an internal standard. [c] 110 °C. [d] Cu(OH)<sub>2</sub> (10 mol%), CsOH (5 mol%). [e] Cu<sub>2</sub>O (20 mol%), Cs<sub>2</sub>CO<sub>3</sub> (20 mol%), 120 °C.

nucleophilic substitution of chlorophosphonates with amides in the presence of strong bases, e.g., *n*-BuLi. These procedures have utilized chlorophosphonates as starting materials, which are generally prepared by chlorination of *H*-phosphonates or phosphates using hazardous reagents, e.g., Cl<sub>2</sub>, COCl<sub>2</sub>, or SO<sub>2</sub>Cl<sub>2</sub>. Therefore, the development of novel synthetic procedures for *N*-acylphosphoramidates directly using *H*-phosphonates as starting materials is highly desirable.

In this study, Cu(OAc)<sub>2</sub> in combination with an appropriate base was revealed to efficiently promote the oxidative cross-coupling of *H*-phosphonates and amides using air as the terminal oxidant. This is the first metal-catalyzed aerobic oxidative cross-coupling of phosphorus and nitrogen nucleophiles to form P–N bonds. Various dialkyl *H*-phosphonates could efficiently react with nitrogen nucleophiles to give the corresponding *N*-acylphosphoramidates in moderate to high yields (Figure 3).

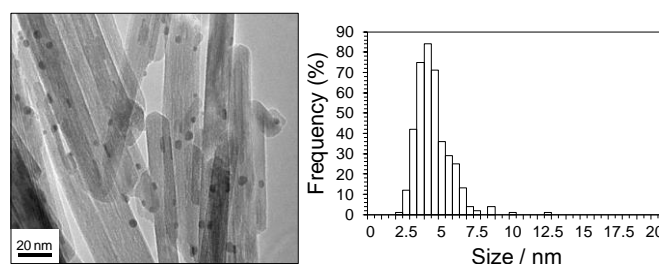


**Figure 3.** Oxidative cross-coupling of *H*-phosphonates and nitrogen nucleophiles. Reaction conditions: *H*-phosphonate (0.2 mmol), nitrogen nucleophile (0.6 mmol), Cu(OAc)<sub>2</sub> (10 mol %), K<sub>2</sub>CO<sub>3</sub> (0.2 mmol), MS 4 A (100 mg), toluene (2 mL), 80 °C, under air (1 atm). A toluene solution of **5** (1 mL, 0.2 M) was added to the reaction mixture over 30 min by a syringe pump, and the reaction mixture was stirred for further 10 min (unless otherwise noted). The isolated yields (based on **5**) are reported. [a] 1.5 h. [b] 4-methylpyridine (0.8 mmol) instead of K<sub>2</sub>CO<sub>3</sub> (0.2 mmol).

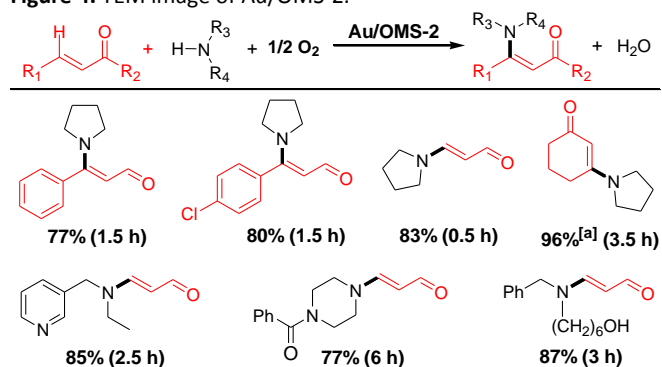
### 3. Gold-Catalyzed Heterogeneous Aerobic Oxidative Amination of $\alpha,\beta$ -Unsaturated Aldehydes

Enaminals ( $\beta$ -enaminals) are very important compounds that have been widely utilized for the synthesis of various heterocyclic and bioactive compounds. The most widely utilized synthetic procedures are (1) dehydrative condensation of malondialdehyde with amines and (2) hydroamination of propargylic aldehydes. However, these procedures have limitations in terms of the substrate scope, selectivity, and the availability of the starting materials. Direct dehydrogenative amination of readily available  $\alpha,\beta$ -unsaturated aldehydes would be a candidate for an efficient synthetic route to enaminals.

The design of catalysts to promote the dehydrogenation of saturated C–C single bonds would be the key for the achievement of the amination (Figure 1, c-ii). The last several decades have evidenced the great success of supported gold nanoparticles for the aerobic oxidative dehydrogenation reactions through activation of molecular oxygen. In addition, they can easily be separated and reused, and are highly durable against strong coordination of nitrogen nucleophiles. These properties of gold nanoparticles are envisioned to



**Figure 4.** TEM image of Au/OMS-2.



**Figure 5.** Selected examples of aerobic dehydrogenative amination of  $\alpha,\beta$ -unsaturated aldehydes. Reaction conditions:  $\alpha,\beta$ -unsaturated aldehyde (0.5 mmol), amine (1.0 mmol), Au/OMS-2 (3.6 mol%), THF (1.9 mL), H<sub>2</sub>O (0.1 mL), 50 °C, air (1 atm). Yields (based on **1**) of isolated products are shown. [a] amine (2.0 mmol), THF (1.8 mL), H<sub>2</sub>O (0.2 mL).

promote the dehydrogenation of various saturated C–C single bonds.

Among various supported metal catalysts examined such as Pd/Al<sub>2</sub>O<sub>3</sub>, Cu/Al<sub>2</sub>O<sub>3</sub>, Ru/Al<sub>2</sub>O<sub>3</sub>, Rh/Al<sub>2</sub>O<sub>3</sub>, and Au/Al<sub>2</sub>O<sub>3</sub>, only Au/Al<sub>2</sub>O<sub>3</sub> showed the catalytic activity for the amination. A cryptomelane-type manganese oxide-based molecular sieve (OMS-2) was the best support among Al<sub>2</sub>O<sub>3</sub>, TiO<sub>2</sub>, Co<sub>3</sub>O<sub>4</sub>, and OMS-2. Thus, in the presence of Au/OMS-2 (average particle size of gold: 4.1 nm; Figure 4), the amination efficiently proceeded to give the corresponding enaminals in high yields. The amination with a physical mixture of Au/TiO<sub>2</sub> and OMS-2 gave almost the same yield as that with Au/TiO<sub>2</sub>. OMS-2 alone could not promote the amination. Therefore, highly dispersed gold nanoparticles on the surface of OMS-2 would play an important role on the present amination. The nature of the observed catalysis was truly heterogeneous. In addition, the retrieved catalyst could be reused at least five times without a significant loss of its high catalytic performance.

The substrate scope for the present dehydrogenative amination was very broad with respect to both  $\alpha,\beta$ -unsaturated carbonyl compounds (including various cinnamaldehyde derivatives, aliphatic  $\alpha,\beta$ -unsaturated aldehydes, and cyclic  $\alpha,\beta$ -unsaturated ketones) as well as amines (including aliphatic, aromatic, and heterocyclic ones) with a wide range of functional groups (Figure 5).

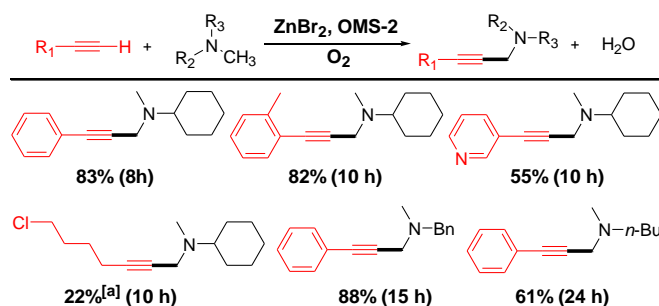
#### 4. Zn<sup>2+</sup> and OMS-2 Co-catalyzed Aerobic Oxidative Cross-Coupling of Terminal Alkynes and Tertiary Amines

Propargylamines are key structural motifs in various bioactive compounds and have been utilized as synthetic intermediates for various nitrogen-containing compounds. The oxidative cross-dehydrogenative coupling of terminal alkynes and tertiary amines has become a promising alternative for the synthesis of propargylamines due to its high efficiency and environmentally benign nature. The cross-coupling developed to date employs copper, iron, or silver catalysts together with organic-based oxidants, e.g., *t*-BuOOH, (*t*-BuO)<sub>2</sub>, and *N*-bromosuccinimide. Therefore, the development of new cross-coupling procedures with wide substrate scope and molecular oxygen as the terminal oxidant would be of great significance.

The key to achieve the target reaction is (1) to find catalysts which can form a metal acetylide species from terminal alkynes, and (2) to discover oxidants and/or catalysts that can promote the formation of electrophilic iminium species from tertiary amines. In addition, the reduced oxidants should readily be reoxidized by molecular oxygen. Recently, OMS-2 was reported to efficiently promote the formation of the iminium species by the aerobic oxidation of the corresponding tertiary amines. Therefore, a combination of transition metal catalysts, which can form the metal acetylide species, and OMS-2 is envisaged to promote the reaction (Figure 1, c-iii).

In this study, the aerobic oxidative cross-coupling of terminal alkynes and tertiary amines co-catalyzed by ZnBr<sub>2</sub> and OMS-2 has been developed for the first time. The reaction proceeds through the nucleophilic addition of zinc-acetylide species formed by the assistance of tertiary amines (base) to the iminium species (Figure 1, c-iii).

Among various transition metal catalysts examined such as NiCl<sub>2</sub>·6H<sub>2</sub>O, FeCl<sub>3</sub>, CuCl<sub>2</sub>·2H<sub>2</sub>O, CoCl<sub>2</sub>, Zn(OTf)<sub>2</sub> (OTf = triflate), ZnF<sub>2</sub>, ZnI<sub>2</sub>, and ZnBr<sub>2</sub>, ZnBr<sub>2</sub> showed the best performance. OMS-2 showed higher activity than the commercially available activated MnO<sub>2</sub> and  $\beta$ -MnO<sub>2</sub>. *t*-BuOOH was not the effective oxidant. In addition, OMS-2 could be reused several times. The cross-coupling was significantly suppressed in the presence of a radical scavenger of dibutylhydroxytoluene (BHT), which suggests the involvement of radical intermediates in the present reaction. Various combination of terminal alkynes (aromatic and aliphatic) and tertiary methyl amines selectively gave the corresponding propargylamines in moderate to high yields (Figure 6).



**Figure 6.** Scope of the present aerobic oxidative cross-coupling of terminal alkynes and tertiary amines. Reaction conditions: alkyne (1.0 mmol), amine (2.0 mmol), ZnBr<sub>2</sub> (5 mol%), OMS-2 (100 mg), CPME (2 mL), 100 °C, under O<sub>2</sub> (1 atm). Yields (based on alkyne) of isolated products are shown. [a] ZnBr<sub>2</sub> (20 mol%).