

### Communication

# Synergistic Bimetallic Ni/Ag and Ni/Cu Catalysis for Regioselective #,#-Diarylation of Alkenyl Ketimines: Addressing #-H Elimination by in situ Generation of Cationic Ni(II)-Catalysts

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# Synergistic Bimetallic Ni/Ag and Ni/Cu Catalysis for Regioselective γ,δ-Diarylation of Alkenyl Ketimines: Addressing β-H Elimination by in situ Generation of Cationic Ni(II)-Catalysts

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Supporting Information Placeholder

**ABSTRACT:** We disclose unprecedented synergistic bimetallic Ni/Ag and Ni/Cu catalysts for regioselective  $\gamma$ , $\delta$ -diarylation of unactivated alkenes in simple ketimines with aryl halides and arylzinc reagents. The bimetallic synergy, which generates cationic Ni(II) species during reaction, promotes migratory insertion and transmetalation steps, and suppresses  $\beta$ -H elimination and crosscoupling, the major side reactions that cause serious problems during alkene difunctionalization. This diarylation reaction proceeds at remote locations to imines to afford, after simple H<sup>+</sup> workup, diversely substituted  $\gamma$ , $\delta$ -diarylketones that are otherwise difficult to access readily with existing methods.

Regioselective dicarbofunctionalization of alkenes with two different carbon sources affords a new convergent strategy to construct complex carbon skeletons rapidly from readily available starting materials.<sup>1</sup> Recent research has indicated that alkenes can be regioselectively difunctionalized<sup>2</sup> by reductive coupling with alkyl halides and aryl halides,<sup>3</sup> and by cross-coupling with aryl/alkyl halides and ArZnX/ArBR2 reagents.<sup>4</sup> However, these reactions are generally successful with activated alkenes,5 vinylarenes<sup>6</sup> and conjugated dienes.<sup>7</sup> Examples of dicarbofunctionalization of unactivated alkenes are rare. Unactivated alkenes are generally reluctant to undergo migratory insertion, one of the key steps in alkene dicarbofunctionalization. Even after successful migratory insertion, in situ generated alkylmetal species readily undergo β-H elimination to form Heck products.<sup>8</sup> In limited cases, these reactions have also produced 1,1-difunctionalized products by a β-H elimination/M-H reinsertion process.<sup>9</sup>

48 Recently, we<sup>10</sup> and others<sup>11</sup> implemented a heteroatom coordina-49 tion strategy to difunctionalize unactivated alkenes with organohalides and organometallic reagents. The idea was to promote 50 migratory insertion by bidentate alkene/heteroatom coordination 51 and stabilize alkylmetal species by metallacycle formation. How-52 ever, this strategy generally remained successful with alkenes 53 positioned to form rigid and planar five-membered metallacycles. 54 When we attempted to regioselectively diarylate unactivated  $\gamma$ , $\delta$ -55 alkenes in aliphatic ketimines (1) poised to generate fluxional six-56 membered metallacycles, the reaction typically furnished biaryl 57 products and Heck products (Scheme 1, via Paths A and B).<sup>10c</sup> In the presence of  $(PhO)_{3}P$ , the reaction produced  $\beta,\delta$ -diarylated 58

products, <sup>10c</sup> rather than the anticipated  $\gamma$ , $\delta$ -diarylated products, via the contraction of fluxional six-membered metallacycles to fivemembered metallacycles by a  $\beta$ -H elimination/Ni-H reinsertion process (via Path C). Herein, we report an unprecedented strategy to solve these serious problems in alkene difunctionalization with the synergistic bimetallic Ni/Ag and Ni/Cu catalysts, which generate cationic Ni(II)-species during reaction to overcome  $\beta$ -H elimination, and promote regioselective  $\gamma$ , $\delta$ -diarylation of unactivated alkenes in aliphatic ketimines with aryl halides and arylzinc reagents.



Scheme 1. Pathways for  $\beta$ , $\delta$ -diarylation and side reactions

We rationalized, based on the mechanistic pathways outlined in Scheme 1, that the reaction would furnish the Heck or  $\beta$ , $\delta$ -diarylation products if  $\beta$ -H elimination from the six-membered nickellacycle **4** proceeded faster than its transmetalation with ArZnX because of the fluxional nature of the metallacycle **4**, which could readily attain a suitable geometry for  $\beta$ -H elimination.<sup>12</sup> Inefficient migratory insertion in species **2** would lead to the formation of direct cross-coupling products.



Scheme 2. Synergistic Ni/Cu and Ni/Ag catalysis strategy to address cross-coupling and  $\beta$ -H elimination problems

We hypothesized that both the migratory insertion of alkenes and subsequent transmetalation with organometallic reagents could be promoted if cationic Ni-species were generated from the oxidative addition (Ar-Ni-X) intermediate **2**, by abstraction of the halide (X<sup>-</sup>) (Scheme 2).<sup>13</sup> Our rationale is based on the facts that cationic transition metals activate electron-rich alkenes better than neutral transition metals due to stronger  $\sigma$ -donation by alkenes and C=C bond polarization.<sup>14</sup> Migratory insertion of alkenes in species **6** to cationic [Ar-Ni]<sup>+</sup> would then generate a new cationic [alkyl-Ni]<sup>+</sup> species **7**, which could be expected to undergo transmetalation with nucleophilic organometallic reagents faster than the analogous neutral [alkyl-Ni] species **4**.<sup>15</sup>

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Therefore, we began to examine cationic metal salts such as AgBF<sub>4</sub> and Cu(MeCN)<sub>4</sub>BF<sub>4</sub> as additives with expectation to generate cationic Ni(II)-catalysts in situ. Indeed, we found that both AgBF<sub>4</sub> and Cu(MeCN)<sub>4</sub>BF<sub>4</sub>, in catalytic amounts, along with NiBr<sub>2</sub> promoted  $\gamma$ , $\delta$ -diarylation of the aliphatic alkenyl ketimine **9** at room temperature in 1 h, and furnished the expected product 11 in 39% and 16% yields, respectively (entries 1-2). Further optimization showed that the  $\gamma$ , $\delta$ -diarylated product **11** was formed in best yields when Ni(cod)<sub>2</sub> was used as a catalyst in the presence of AgBF4, Cu(MeCN)4BF4 or Cu(MeCN)4OTf (entries 3-5).16 Large scale reaction (2 mmol) furnished the product 11 in 72% isolated yield (entry 3). No β,δ-diarylated product was observed. AgBF4 could also be replaced with CuI without compromising the product yield (entry 6). However, the Heck products were generated in lesser amounts with AgBF4 than with CuI. In the absence of Ag or Cu-salts, the Heck and the diarylated products 10 and 11 were formed in 22% and 38% yields, respectively (entry 7).

#### Table 1. Optimization of reaction conditions<sup>a</sup>

PhN Me	$\begin{array}{c} 5 \text{ mol } \% \text{ Ni-cat.} \\ \hline \textbf{Ar}-\textbf{X}, \text{ PhZnX} \\ \textbf{9} \\ \textbf{G}_{H^+} \text{ workup)} \\ (H^+ \text{ workup)} \\ \textbf{H}_{F_3C_6H_4} \end{array} \qquad $	• + 0	Me Me Ph 11
entry	reaction condition	% yield of <b>10</b>	% yield of <b>11</b>
1	NiBr <sub>2</sub> , 15 mol % AgBF <sub>4</sub>	7	39
2	NiBr <sub>2</sub> , 15 mol % Cu(MeCN) <sub>4</sub> BF <sub>4</sub>	9	16
3	Ni(cod) <sub>2</sub> , 15 mol % AgBF <sub>4</sub>	11	80 (76, 72) <sup>b</sup>
4	Ni(cod) <sub>2</sub> , 15 mol % Cu(MeCN) <sub>4</sub> BF <sub>4</sub>	20	65
5	Ni(cod) <sub>2</sub> , 15 mol % Cu(MeCN) <sub>4</sub> OTf	19	72
6	Ni(cod) <sub>2</sub> , 15 mol % Cul	15	78 (73) <sup>c</sup>
7	Ni(cod) <sub>2</sub>	22	38

<sup>*a*</sup>Reactions run in 0.1 mmol scale. Yields determined by <sup>1</sup>H NMR with pyrene as a standard. Isolated yields in parenthesis. <sup>*b*</sup>Isolated from 0.5 mmol (76%) and 2.0 mmol (72%). <sup>*c*</sup>Isolated from 0.5 mmol (73%).

After reaction optimization, we examined the scope of the  $\gamma$ , $\delta$ diarylation reaction with a variety of ArZnI using imine **9** and 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>I (Table 2). The reaction works with both electron-rich and electron-deficient arylzinc reagents, and tolerates a variety of functional groups such as Me, OMe, Cl, F and CO<sub>2</sub>Me on arylzinc reagents. The reaction also tolerates dihalogenated arenes on arylzinc reagents, which furnishes the diarylated products in good yields (**18-19**). Both AgBF<sub>4</sub> and CuI co-catalysts also furnished the diarylated products in comparable yields (**16** and **20**).<sup>17</sup>

We further examined the scope of the reaction with respect to aryl halides and alkenyl imines (Table 3). The reaction proceeds with a variety of electron-rich and electron-deficient aryl iodides containing a variety of functional groups such as Me, F, Cl and CF<sub>3</sub>.<sup>18</sup> The reaction also tolerates sensitive functional groups like nitriles, ketones and esters (**25**, **26** and **39**), and dihalides on aryl iodides, which generates the diarylated products in good yields (**23**, **24** and **31**). The aryl iodides and arylzinc reagents can be utilized in dif-

ferent combinations with ketimines derived from a variety of aliphatic γ,δ-alkenylketones.<sup>19</sup> Ketimines derived from 5-hexen-2one, 7-octen-4-one, 1-phenyl-6-hepten-3-one, 1-phenyl-4-penten-1-one, 1-(furan-3-yl)-4-penten-1-one and 1-(4-methoxy-phenyl)-5-hexen-2-one furnished variously substituted  $\gamma$ , $\delta$ -diarylketones in good yields (22-34, 42-46). The reaction also proceeds with ketimines derived from aliphatic alkenyl ketones with substitutions both at distal (35-39) and proximal (40-41)  $\alpha$ -carbons to the unactivated alkenes. Products 40 and 41 were formed as single diastereomers. The remarkable 1,3-diastereoselectivity can be explained based on the formation of a six-membered pseudochair confirmation during the stereodefining alkene insertion step (see SI for details). There is no convenient way to construct  $\gamma,\delta$ diarylketones without a multi-step synthesis.<sup>20</sup> Our method provides a modular and most straightforward method to generate  $\gamma$ , $\delta$ diarylketones, which occur as natural products (galcatine).<sup>20</sup>

#### Table 2. Scope with arylzinc reagents<sup>a</sup>



<sup>a</sup>Isolated from 0.5 mmol. ArZnI (1.5 equiv), ArI (1.5 equiv), NMP (2.5 mL). Yields with CuI in parenthesis.

We also monitored the progress of the  $\gamma$ , $\delta$ -alkene diarylation reaction by in situ <sup>19</sup>F NMR. Monitoring of the reaction of alkenyl imine 9 with 4-FC<sub>6</sub>H<sub>4</sub>ZnI and 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>I in the presence of 5 mol % Ni(cod)<sub>2</sub> and with and without 15 mol % AgBF<sub>4</sub> or CuI demonstrated that the Ag and Cu-salts dramatically increased the rates of the alkene diarylation reaction (Fig. 1a). Moreover, comparison of the reaction rates for the formation of alkene diarylation products and biaryl side products by cross-coupling in the presence and absence of AgBF4 indicated that the migratory insertion of the cationic [Ar-Ni]<sup>+</sup> into bound alkenes in species 6 (Scheme 2) proceeded faster to generate diarylation products than its transmetalation with ArZnI to form cross-coupling products (Fig. 1b). A similar result was also observed when CuI was used instead of AgBF<sub>4</sub> (see the SI). The rate enhancement with CuI also proceeded with an induction period, as indicated by a sigmoidal curve (Fig.1a, green line), along with the formation of greater amounts of cross-coupling (25% vs. 16% with AgBF<sub>4</sub>), which indicated that the iodide abstraction from Ar-Ni-I proceeded slower with CuI than with AgBF4. Comparison of the yields of the Heck product 48 without the co-catalyst (37%) and in the presence of AgBF<sub>4</sub> (16%) and CuI (21%) also indicated that the formation of cationic Ni(II)-catalysts promoted transmetalation of **52** (Scheme 3) with ArZnI faster than its  $\beta$ -H elimination, and, therefore, addressed the problem of  $\beta$ -H elimination.<sup>21</sup>

#### Table 3. Scope with ketone derivatives, ArI and ArZnI<sup>a</sup>



<sup>a</sup>Isolated from 0.5 mmol. ArZnI (1.5 equiv), ArI (1.5 equiv), NMP (2.5 mL). Yields with CuI in parenthesis. <sup>b</sup>Single diastereomer

observed by GC of crude reaction mixtures and by  ${}^{1}\text{H}$  and  ${}^{13}\text{C}$  NMR of isolated products.



NMR yields (after hydrolysis): no additive, **20**, 29%; **47**, 32%; **48**, 37% with AgBF<sub>4</sub>, **20**, 68%; **47**, 16%; **48**, 14%; with Cul, **20**, 61%; **47**, 25%; **48**, 21%



**Figure 1.** In situ <sup>19</sup>F NMR monitoring of reaction progress by generating cationic Ni-species for the reaction of alkenyl imine **9** with 4-FC<sub>6</sub>H<sub>4</sub>ZnI and 4-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>I. (a) Reaction profiles with and without AgBF<sub>4</sub> and CuI. Blue: with AgBF<sub>4</sub>; green: with CuI; red: without AgBF<sub>4</sub> or CuI. (b) Comparison of reaction rates for the formation of diarylation product **20** and biaryl side product **47** by cross-coupling in the presence and absence of AgBF<sub>4</sub>. Blue: with AgBF<sub>4</sub>; red: without AgBF<sub>4</sub>; hollow square and circle: cross-coupling (**47**); solid square and circle: alkene diarylation (**20**).

Based on our results, we propose a catalytic cycle for the  $\gamma$ , $\delta$ -alkene diarylation reaction (Scheme 3, cycle A/B). We believe that ArX undergoes oxidative addition to the alkene-bound species **49** followed by the abstraction of the halide (X<sup>-</sup>) from the intermediate **50** by AgBF<sub>4</sub> or CuI to generate a cationic Ar-Ni(II) species **51**. The bound alkene then undergoes migratory insertion into the Ar-Ni bond of the cationic Ni-species **51**, which generates a new cationic Ni(II) species **52** that subsequently proceeds by transmetalation with ArZnX followed by reductive elimination to generate the diarylation product **54**.



Scheme 3. Proposed catalytic cycle

An alternative explanation for the dramatic rate enhancements by AgBF<sub>4</sub> and CuI is that the reaction could also be promoted by the initial transmetalation of ArZnI with AgBF<sub>4</sub> and CuX, which would generate more reactive [Ar-Ag] and [Ar-Cu] complexes as new transmetalating species that could potentially transmetalate with the alkyl-Ni-X species **55** faster than ArZnI (Scheme 3, catalytic cycle C/D). Cu-salts are generally used as additives in the Pd-catalyzed Stille coupling to generate [R-Cu] species from RSnX<sub>3</sub> and promote the transmetalation step.<sup>22</sup> Ar<sub>2</sub>Zn is also known to undergo transmetalation with Ag and Cu-salts to generate [ArAg] and [ArCu] complexes.<sup>23</sup> However, in situ monitoring

by <sup>19</sup>F NMR of the stoichiometric reactions between 4-FC<sub>6</sub>H<sub>4</sub>ZnI and AgBF<sub>4</sub>, and between 4-FC<sub>6</sub>H<sub>4</sub>ZnI and CuI showed that there were no reactions, and that [Ar-Ag] and [Ar-Cu] species were not generated. These experiments indicated that, unlike diarylzinc reagents (Ar<sub>2</sub>Zn), monoarylzinc reagents (ArZnX) do not react with Ag and Cu-salts under our reaction conditions and that the current  $\gamma$ , $\delta$ -alkene diarylation reaction was not promoted by a sequential Zn to Ag/Cu to Ni transmetalation. Therefore, the catalytic cycles C and D are unlikely to be operative for this process.



**Scheme 4.** <sup>19</sup>F NMR monitoring of the reactions between ArZnI and AgBF<sub>4</sub>, and ArZnI and CuI.

In summary, we have developed new synergistic bimetallic Ni/Ag and Ni/Cu catalysts for regioselective diarylation of unactivated alkenes located at the  $\gamma$ , $\delta$ -position of ketimines. The reaction, after simple H<sup>+</sup> workup, furnishes  $\gamma$ , $\delta$ -diarylketones in good yields. The synergistic Ni/Ag and Ni/Cu catalytic systems generate cationic Ni(II)-species in situ by abstracting halides (X<sup>-</sup>) from Ar-Ni-X species. In situ monitoring of reaction progress by <sup>19</sup>F NMR indicates that the cationic Ni-catalyst promotes the migratory insertion and transmetalation steps, and suppresses  $\beta$ -H elimination, the fundamental process that causes significant problems during alkene difunctionalization. We believe that this new approach of synergistic bimetallic cationic catalytic systems will stimulate further research in solving problems in alkene difunctionalization reactions.

#### ASSOCIATED CONTENT

#### Supporting Information

Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at <u>http://pubs.acs.org</u>.

Crystallographic data for  $\pm$ **41**-DNP can be found at CCDC deposition number 1871839.

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Notes

The authors declare no competing financial interests.

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