

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

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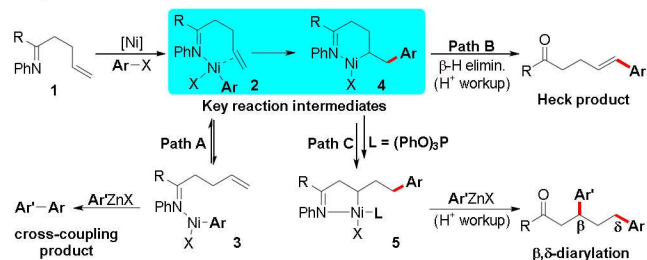
Supporting Information Placeholder

ABSTRACT: We disclose unprecedented synergistic bimetallic Ni/Ag and Ni/Cu catalysts for regioselective γ,δ -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 β -H elimination, the major side reaction that causes serious problems during alkene difunctionalization. This diarylation reaction proceeds at remote locations to imines to afford, after simple H⁺ workup, diversely substituted γ,δ -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.¹ Recent research has indicated that alkenes can be regioselectively difunctionalized² by reductive coupling with alkyl halides and aryl halides,³ and by cross-coupling with aryl/alkyl halides and ArZnX/ArBR₂ reagents.⁴ However, these reactions are generally successful with activated alkenes,⁵ vinylarenes⁶ and conjugated dienes.⁷ 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.⁸ In limited cases, these reactions have also produced 1,1-difunctionalized products by a β -H elimination/M-H reinsertion process.⁹

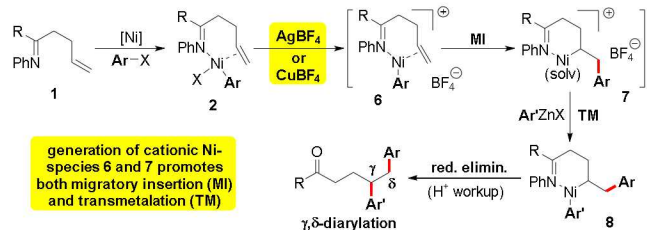
Recently, we¹⁰ and others¹¹ implemented a heteroatom coordination strategy to difunctionalize unactivated alkenes with organohalides and organometallic reagents. The idea was to promote migratory insertion by bidentate alkene/heteroatom coordination and stabilize alkylmetal species by metallacycle formation. However, this strategy generally remained successful with alkenes positioned to form rigid and planar five-membered metallacycles. When we attempted to regioselectively diarylate unactivated γ,δ -alkenes in aliphatic ketimines (**1**) poised to generate fluxional six-membered metallacycles, the reaction typically furnished biaryl products and Heck products (Scheme 1, via Paths A and B).^{10c} In the presence of (PhO)₃P, the reaction produced β,δ -diarylated

products,^{10c} rather than the anticipated γ,δ -diarylated products, via the contraction of fluxional six-membered metallacycles to five-membered metallacycles by a β -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 β -H elimination, and promote regioselective γ,δ -diarylation of unactivated alkenes in aliphatic ketimines with aryl halides and arylzinc reagents.



Scheme 1. Pathways for β,δ -diarylation and side reactions

We rationalized, based on the mechanistic pathways outlined in Scheme 1, that the reaction would furnish the Heck or β,δ -diarylation products if β -H elimination from the six-membered nickelacycle **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 β -H elimination.¹² Inefficient migratory insertion in species **2** would lead to the formation of direct cross-coupling products.

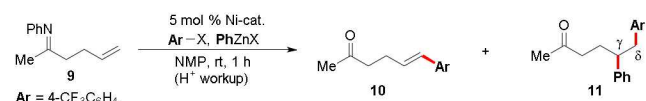


Scheme 2. Synergistic Ni/Cu and Ni/Ag catalysis strategy to address cross-coupling and β -H elimination problems

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⁻) (Scheme 2).¹³ Our rationale is based on the facts that cationic transition metals activate electron-rich alkenes better than neutral transition metals due to stronger σ -donation by alkenes and C=C bond polarization.¹⁴ Migratory insertion of alkenes in species **6** to cationic [Ar-Ni]⁺ would then generate a new cationic [alkyl-Ni]⁺ species **7**, which could be expected to undergo transmetalation with nucleophilic organometallic reagents faster than the analogous neutral [alkyl-Ni] species **4**.¹⁵

Therefore, we began to examine cationic metal salts such as AgBF₄ and Cu(MeCN)₄BF₄ as additives with expectation to generate cationic Ni(II)-catalysts in situ. Indeed, we found that both AgBF₄ and Cu(MeCN)₄BF₄, in catalytic amounts, along with NiBr₂ promoted γ,δ -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 γ,δ -diarylated product **11** was formed in best yields when Ni(cod)₂ was used as a catalyst in the presence of AgBF₄, Cu(MeCN)₄BF₄ or Cu(MeCN)₄OTf (entries 3-5). 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).

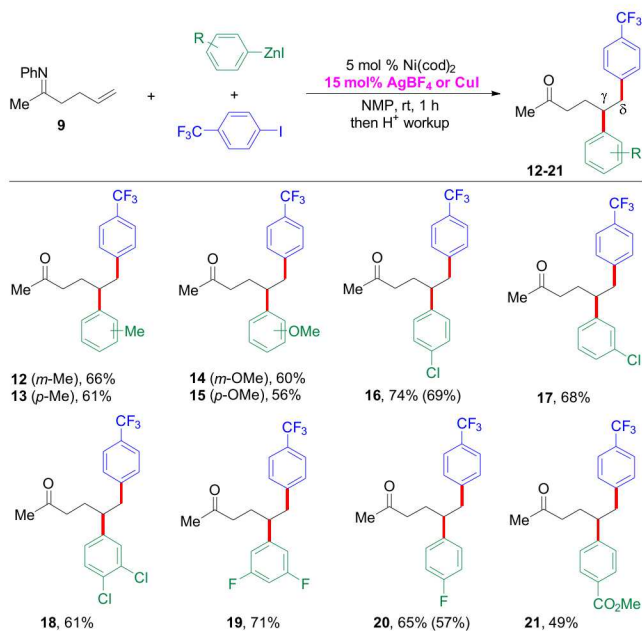
Table 1. Optimization of reaction conditions^a



entry	reaction condition	% yield of 10	% yield of 11
1	NiBr ₂ , 15 mol % AgBF ₄	7	39
2	NiBr ₂ , 15 mol % Cu(MeCN) ₄ BF ₄	9	16
3	Ni(cod) ₂ , 15 mol % AgBF ₄	11	80 (76)
4	Ni(cod) ₂ , 15 mol % Cu(MeCN) ₄ BF ₄	20	65
5	Ni(cod) ₂ , 15 mol % Cu(MeCN) ₄ OTf	19	72
6	Ni(cod) ₂ , 15 mol % CuI	15	78 (73)
7	Ni(cod) ₂	22	38

^aReactions run in 0.1 mmol scale. Yields determined by ¹H NMR with pyrene as a standard. Isolated yields (0.5 mmol) in parenthesis.

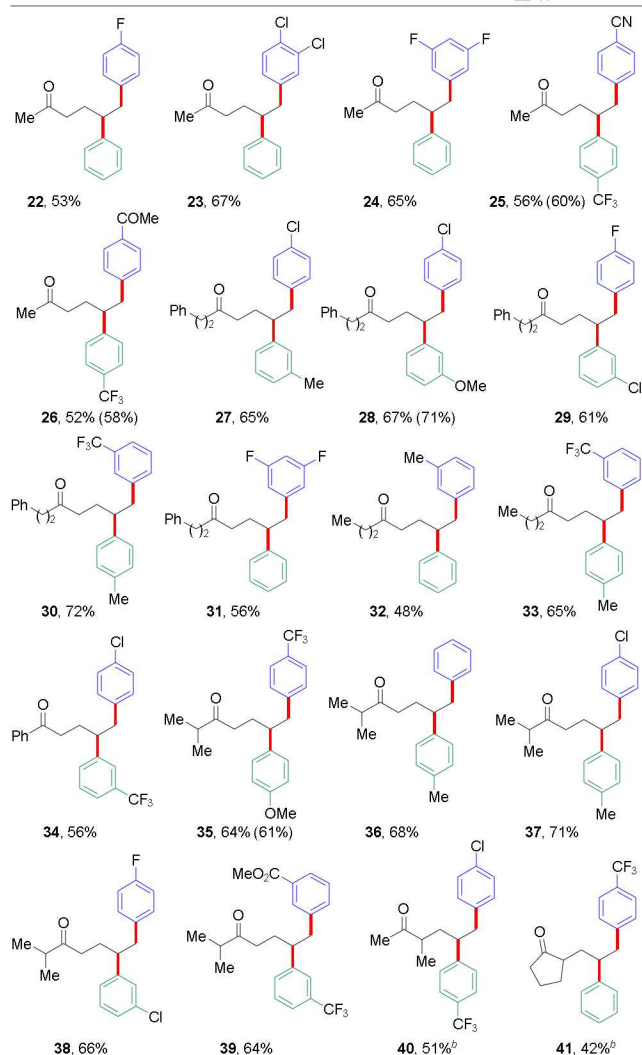
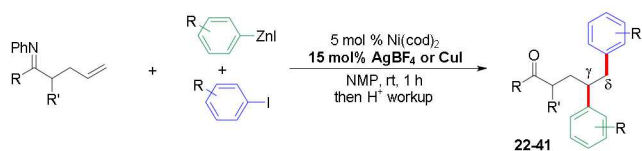
Table 2. Scope with arylzinc reagents^a



^aIsolated from 0.5 mmol. ArZnI (1.5 equiv), ArI (1.5 equiv), NMP (2.5 mL). Yields with CuI in parenthesis.

After reaction optimization, we examined the scope of the γ,δ -diarylation reaction with a variety of ArZnI using imine **9** and 4-CF₃C₆H₄I (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 CO₂Me on arylzinc reagents. The reaction also tolerates dihalogenated arenes on arylzinc reagents, which furnishes the diarylated products in good yields (**18-19**). Both AgBF₄ and CuI co-catalysts also furnished the diarylated products in comparable yields (**16** and **20**).

Table 3. Scope with ketone derivatives, ArI and ArZnI^a



^aIsolated from 0.5 mmol. ArZnI (1.5 equiv), ArI (1.5 equiv), NMP (2.5 mL). Yields with CuI in parenthesis. ^bSingle isomer observed by GC of crude reaction mixtures and by ^1H and ^{13}C NMR of isolated products.

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_3 . 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 different combinations with ketimines derived from a variety of aliphatic γ,δ -alkenylketones. Ketimines derived from 5-hexen-2-one, 7-octen-4-one, 1-phenyl-6-hepten-3-one and 1-phenyl-4-penten-1-one furnished variously substituted γ,δ -diarylketones in good yields (**22-34**). The reaction also proceeds with ketimines derived from aliphatic alkenyl ketones with substitutions both at distal (**35-39**) and proximal (**40-41**) α -carbons to the unactivated alkenes.

We also monitored the progress of the γ,δ -alkene diarylation reaction by in situ ^{19}F NMR. Monitoring of the reaction of alkenyl

imine **9** with $4\text{-FC}_6\text{H}_4\text{ZnI}$ and $4\text{-CF}_3\text{C}_6\text{H}_4\text{I}$ in the presence of 5 mol % Ni(cod)_2 and with and without 15 mol % AgBF_4 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 AgBF_4 indicated that the migratory insertion of the cationic $[\text{Ar-Ni}]^+$ 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_4 (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_4), which indicated that the iodide abstraction from Ar-Ni-I proceeded slower with CuI than with AgBF_4 . Comparison of the yields of the Heck product **43** without the co-catalyst (37%) and in the presence of AgBF_4 (16%) and CuI (21%) also indicated that the formation of cationic Ni(II) -catalysts suppressed β -H elimination.¹⁶

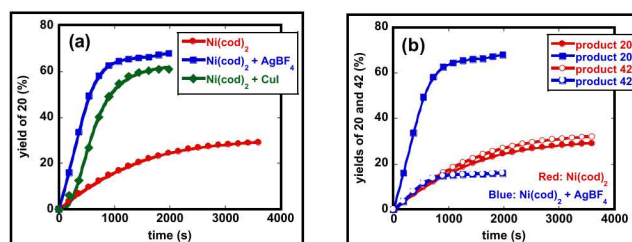
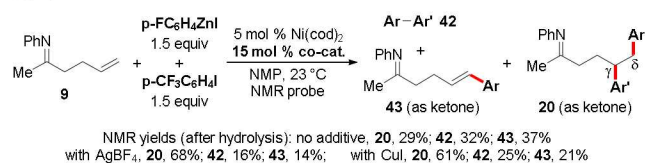
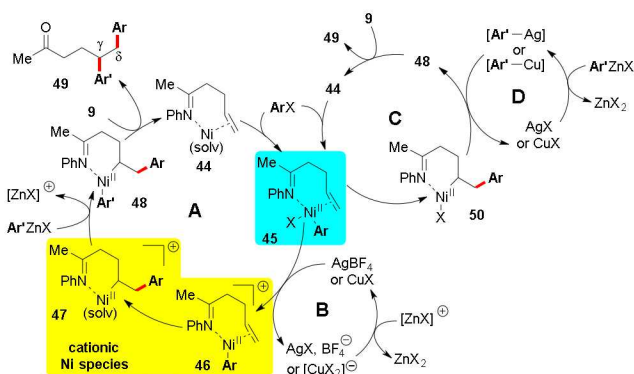


Figure 1. In situ ^{19}F NMR monitoring of reaction progress by generating cationic Ni-species for the reaction of alkenyl imine **9** with $4\text{-FC}_6\text{H}_4\text{ZnI}$ and $4\text{-CF}_3\text{C}_6\text{H}_4\text{I}$. (a) Reaction profiles with and without AgBF_4 and CuI . Blue: with AgBF_4 ; green: with CuI ; red: without AgBF_4 or CuI . (b) Comparison of reaction rates for the formation of diarylation product **20** and biaryl side product **42** by cross-coupling in the presence and absence of AgBF_4 . Blue: with AgBF_4 ; red: without AgBF_4 ; hollow square and circle: cross-coupling (**42**); solid square and circle: alkene diarylation (**20**).

Based on our results, we propose a catalytic cycle for the γ,δ -alkene diarylation reaction (Scheme 3, cycle A/B). We believe that ArX undergoes oxidative addition to the alkene-bound species **44** followed by the abstraction of the halide (X^-) from the intermediate **45** by AgBF_4 or CuI to generate a cationic Ar-Ni(II) species **46**. The bound alkene then undergoes migratory insertion into the Ar-Ni bond of the cationic Ni-species **46**, which generates a new cationic Ni(II) species **47** that subsequently proceeds by transmetalation with ArZnX followed by reductive elimination to generate the diarylation product **49**.



Scheme 3. Proposed catalytic cycle

An alternative explanation for the dramatic rate enhancements by AgBF_4 and CuI is that the reaction could also be promoted by the initial transmetalation of ArZnI with AgBF_4 and CuX , which would generate more reactive $[\text{Ar-Ag}]$ and $[\text{Ar-Cu}]$ complexes as new transmetalating species that could potentially transmetalate with the alkyl-Ni-X species **50** faster than ArZnI (Scheme 3, catalytic cycle C/D). Cu-salts are generally used as additives in the Pd-catalyzed Stille coupling to generate $[\text{R-Cu}]$ species from RSnX_3 and promote the transmetalation step.¹⁷ Ar_2Zn is also known to undergo transmetalation with Ag and Cu-salts to generate $[\text{ArAg}]$ and $[\text{ArCu}]$ complexes.¹⁸ However, in situ monitoring by ^{19}F NMR of the stoichiometric reactions between $4\text{-FC}_6\text{H}_4\text{ZnI}$ and AgBF_4 (Fig. 2a), and between $4\text{-FC}_6\text{H}_4\text{ZnI}$ and CuI (Fig. 2b) showed that there were no reactions, and that $[\text{Ar-Ag}]$ and $[\text{Ar-Cu}]$ species were not generated. These experiments indicated that, unlike diarylzinc reagents (Ar_2Zn), monoarylzinc reagents (ArZnX) do not react with Ag and Cu-salts under our reaction conditions and that the current γ,δ -alkene diarylation reaction was not promoted by a sequential Zn to Ag/Cu to Ni transmetalation.

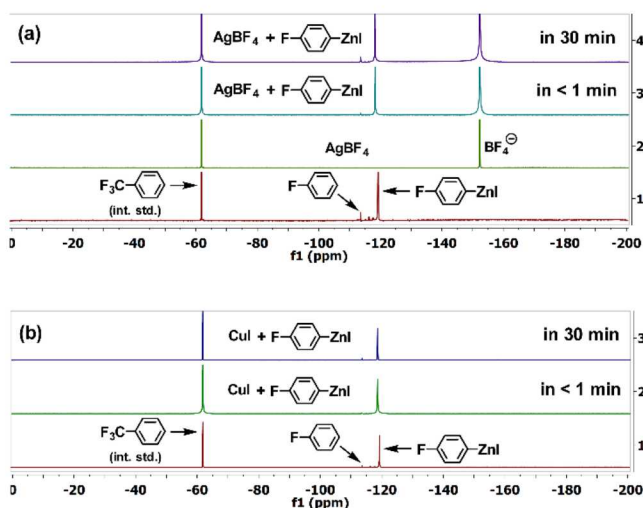
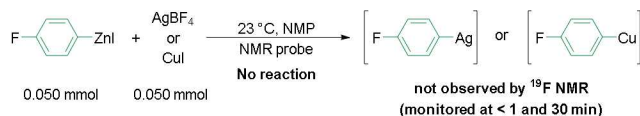


Figure 2. ^{19}F NMR monitoring of the reactions between (a) ArZnI and AgBF_4 and (b) ArZnI and CuI .

In summary, we have developed new synergistic bimetallic Ni/Ag and Ni/Cu catalysts for regioselective diarylation of unactivated alkenes located at the γ,δ -position of ketimines. The reaction, after simple H^+ workup, furnishes γ,δ -diarylketones in good yields. The

synergistic Ni/Ag and Ni/Cu catalytic systems generate cationic Ni(II)-species in situ by abstracting halides (X^-) from Ar-Ni-X species. In situ monitoring of reaction progress by ^{19}F NMR indicates that the cationic Ni-catalyst promotes the migratory insertion and transmetalation steps, and suppresses $\beta\text{-H}$ 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 <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interests.

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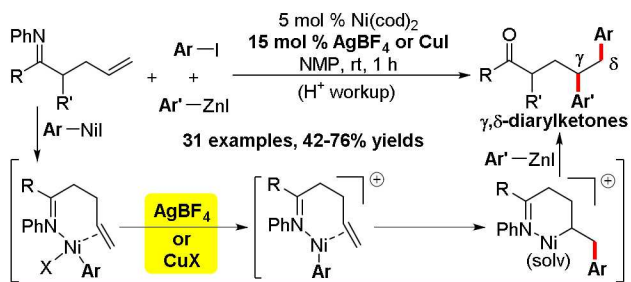
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