

Ni-Catalyzed Alkenylation of Ketone Enolates under Mild Conditions: Catalyst Identification and Optimization

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Supporting Information

ABSTRACT: A procedure for Ni-catalyzed cross-coupling of ketone enolates with alkenyl halides has been developed. Intermolecular coupling of aromatic and aliphatic ketone lithium enolates with a variety of alkenyl halides is achieved in the presence of Ni(cod)₂ catalyst (5 mol %), an N-heterocyclic carbene (NHC) ligand, and LiI (10 mol %) at 6–22 °C for 0.5–12 h with yields of up to 90%. During the initial development of this reaction, a misleading result with respect to the actual active catalyst was obtained using commercially available Q-Phos ligand, which was found to contain a trace of Pd metal contaminant sufficient to catalyze the reaction. However, under the final conditions optimized for Ni(cod)₂ in the presence of an NHC ligand, Pd was incompetent as a catalyst.

During recent decades, transition-metal-catalyzed cross-couplings have proven to be essential to modern synthetic chemistry.¹ Palladium has dominated as the catalyst of choice, whereas nickel, the “impoverished younger sibling of palladium”,² has been developed to a lesser extent. Ni is a more economical substitute for Pd, as it is about 3000 times less expensive on a molar basis, although the cost of ligands can offset this factor. Significant differences in reactivity of the two metals can also be important in catalyst selection. Consequently, investigations of Ni-catalyzed cross-couplings have increased considerably over the past decade.²

The transition-metal-catalyzed alkenylation of enolates is a strategy to mediate C–C bond formation between enolates and alkenyl halides to produce β,γ-unsaturated compounds (Figure 1).³ This functionality occurs in some biologically important

compounds,⁴ and the many possible manipulations of the carbonyl and alkene moieties present an attractive platform for synthetic diversity that has been utilized in a number of total syntheses.^{3,5} The α-alkenylation reaction remains at an early stage of development compared with the related α-arylation reaction with aryl halides.⁶ For instance, while procedures for both reactions are dominated by Pd catalysts, alternative catalysts have been developed for the α-arylation reaction, including ones based on Cu⁷ and Ni.⁸ The use of Ni in the α-alkenylation reaction has been limited to a procedure reported by Rathke in 1977 in which a ligandless Ni species was employed in stoichiometric or near-stoichiometric quantities for optimum results.⁹ This procedure was applied in the total synthesis of quadrone by Wender in 1985.¹⁰ While the arylation and alkenylation of enolates are considered to be similar reactions, the alkenylation presents additional challenges. Under basic conditions, issues arise with stereofidelity of secondary and tertiary α-alkenylated products, in which cis/trans isomerization or isomerization to an α,β-unsaturated compound can occur.¹¹ These complications are nonexistent for the arylation reaction. Here we describe the development of a new, efficient Ni-catalyzed α-alkenylation procedure that is able to accomplish cross-coupling of ketone enolates with alkenyl bromides under mild conditions, allowing high regiocontrol of the resulting alkene and providing a major cost advantage over the corresponding use of Pd. Our protocol is unique for the alkenylation reaction in that when aryl bromides are employed under the same conditions, no significant amounts of arylation products are obtained.

During our initial attempts to use Ni, we uncovered an unanticipated metal contamination of a commercial ligand that led to a misleading result, which emphasizes the need for careful control experiments in catalysis development.¹² In our previous synthesis of trichostatin A, a Pd/phosphine catalyst was employed to couple a zinc enolate with an alkenyl bromide in high yield.¹³ When catalytic quantities of Ni(cod)₂ were employed with Q-Phos as a phosphine ligand, a moderate yield of product was obtained. In the presence of Q-Phos, the coupling of the zinc enolate of propiophenone (**1a**) with 1-bromo-2-methylpropene (**2a**) was very efficient with Pd(dba)₂,

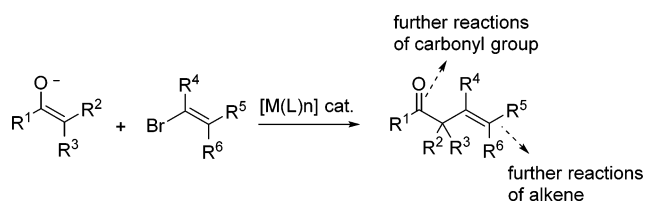


Figure 1. Transition-metal-catalyzed alkenylation of enolates.

Received: March 20, 2015

Published: May 29, 2015

but surprisingly, it also gave a high yield with $\text{Ni}(\text{cod})_2$ as well as with $\text{Cu}(\text{acac})_2$, $\text{Fe}(\text{acac})_2$, or $\text{Fe}(\text{acac})_3$ or even no metal additive (Figure 2). However, upon pretreatment of the

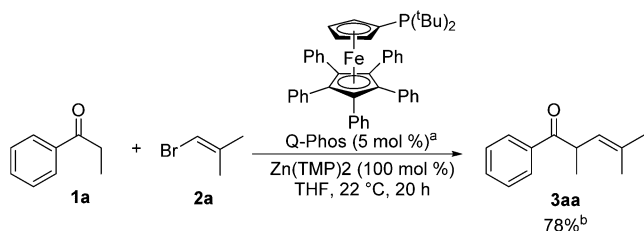


Figure 2. Trace-Pd-catalyzed alkenylation of enolates. ^aThe commercial Q-Phos used in this example was determined to contain 0.6 wt % Pd. ^bIsolated yield.

commercial Q-Phos ligand with a metal scavenger, QuadraPure TU,¹⁴ the alkenylation failed in the absence of added metal or in the presence of added Ni, Cu, or Fe, but it proceeded upon addition of as little as 0.1 mol % $\text{Pd}(\text{dba})_2$. Analysis of the commercial Q-Phos ligand by inductively coupled plasma optical emission spectroscopy and X-ray photoelectron spectroscopy indeed showed the presence of 0.6 and 0.7 wt % Pd, respectively, presumably remaining from the synthesis of Q-Phos.¹⁵ The development of optimum conditions for Pd catalysis provided a satisfactory protocol,¹⁶ but our results suggest that investigators using Q-Phos with catalysts other than Pd must proceed with careful scrutiny.

To reach our goal of developing a Ni-catalyzed alkenylation of enolates, we continued our attempts to use metal-scavenged Q-Phos. We found that the coupling of lithium enolates could be effected by $\text{Ni}(\text{cod})_2$, but only stoichiometrically because of precipitation of elemental Ni. We therefore recognized the need for an appropriate ligand to retain the Ni in solution, which prompted us to examine N-heterocyclic carbenes (NHCs) as supporting ligands.¹⁷

Preliminary screening employing imidazolium salts as precursors of NHCs demonstrated the need for moderate steric hindrance close to the reaction center (Table 1, entries 1 and 2). Only minor differences were found when the counterion was changed from Cl^- to BF_4^- (entries 2 and 3), when a saturated carbene (entries 4 and 5) or more extensive branching (entries 6 and 7) was used, or when a preformed free carbene (purchased or prepared separately) was employed (entries 7 and 8). We selected IPrHCl (**5a**) and SIPrHBF_4 (**6b**) for further studies because of their ready availability, high conversions of **1**, and high product yields. In all cases employing NHCs, the Ni was retained in solution in catalytic quantities throughout the reaction. Different bases and solvents were also examined, with LiHMDS and THF found to be the best combination (see the Supporting Information).

We next turned our attention to the choice of the alkenyl halide. Exchanging the bromide **2a** for the corresponding iodide resulted in higher conversion in a shorter time (Table 2, entries 1 and 2). Gratifyingly, even better results were obtained when bromide **2a** was combined with 40 mol % LiI at 22 °C (entry 3). Further improvements were obtained using a minimal amount of base (120 mol %), which was just sufficient to deprotonate both the ketone and NHC precursor **5a** (entry 4). Decreasing the catalyst, ligand, and additive loadings resulted in the highest conversion of 95% (entry 5). The same result could be obtained at 6 °C with a slight increase in reaction time (entry 7). We note that the corresponding Pd-catalyzed

Table 1. N-Heterocyclic Carbene Screen

entry	NHC	conversion (%) ^a
1	4	15
2	5a	75 (60) ^b
3	5b	76
4	6a	77
5	6b	85 (60) ^b
6	5c	64
7 ^c	7a	83
8 ^c	7b	77

Reactions were conducted on a 0.5 mmol scale relative to **1a**. ^aConversions of ketone based on NMR analysis using an internal standard. ^bIsolated yield in parentheses. ^c120 mol % LiHMDS.

Table 2. Screen of Reaction Conditions

entry	X ^a	Y ^b	5a ^b	Z ^b	LiI ^b	T (°C)	t (h)	conv. (%) ^c
1	Br	10	20	140	0	22	5	75
2	I	10	20	140	0	22	0.5	78
3	Br	10	20	140	40	22	0.5	84
4	Br	10	20	120	40	22	0.5	90
5	Br	5	5	105	20	22	0.5	95
6	Br	5	5	105	10	0	7	84
7	Br	5	5	105	10	6 ^d	2	95

Reactions were conducted on a 0.5 mmol scale relative to **1a**. ^a130 mol % alkenyl halide was used in entries 1–6 and 110 mol % in entry 7. ^bReported in mol %. ^cConversion of ketone based on NMR analysis using an internal standard. Only **3aa** was observed as the product. ^dDry ice/cyclohexane bath.

reaction employs 250 mol % base because of the increased acidity of the product α -hydrogens,¹⁸ but this problem does not appear to arise with Ni, thus allowing milder, less basic conditions. One possible explanation is that Ni functions as a more active catalyst, resulting in the starting ketone enolate

being converted to product faster than proton exchange between the starting ketone enolate and product.

The reaction conducted at ambient temperature (Table 2, entry 5) allowed us to isolate the product in 89% yield. To verify the role of Ni, we performed control experiments without metal and with Ni replaced by 5 mol % Pd(OAc)₂ or 2.5 mol % Pd₂(dba)₃, which gave yields of 0%, 5%, and 6%, respectively (see the Supporting Information). Thus, Pd is inferior as a catalyst under the conditions optimized for Ni.

Under the optimized low-temperature conditions (Table 2, entry 7), the ketone scope was explored using alkenyl bromide **2a** (Figure 3). Electron-neutral and -rich aryl ketones underwent coupling in high yields (**3aa** and **3ba**), while an electron-deficient aryl ketone resulted in a lower yield (**3ca**).

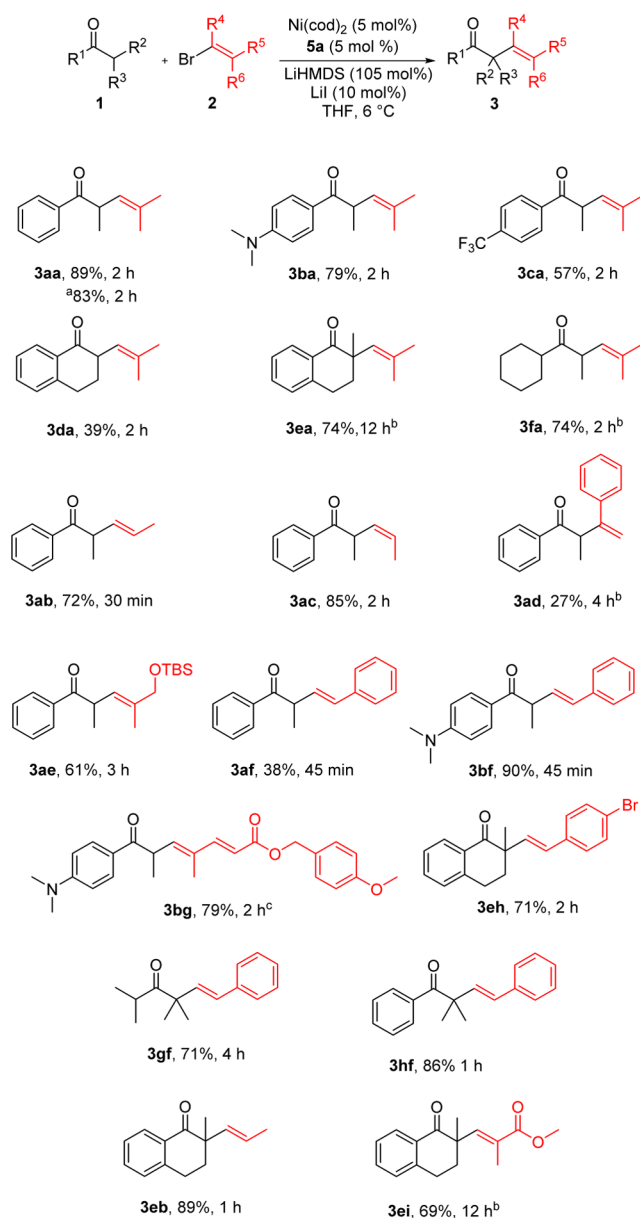


Figure 3. Substrate scope. Isolated yields (averages of two runs) are shown. Reactions were conducted on a 0.5 mmol scale relative to **1**. The first letter in the alphanumeric product designators refers to the starting ketone, and the second letter identifies the alkenyl halide. ^aConducted on an 8 mmol scale relative to **1a**. ^bReaction was run at 22 °C. ^cConducted on a 0.25 mmol scale relative to **1b**.

Reaction with a cyclic ketone was achieved but in much lower yield (**3da**). Generation of a quaternary α -center proceeded well, but required a temperature of 22 °C (**3ea**). An unsymmetrical aliphatic ketone could also be coupled readily at 22 °C to form **3fa** regioselectively. Our protocol was applicable to scale-up, producing 1.5 g (83% isolated yield) of **3aa**. Attempts to employ a methyl ketone resulted in low yields because of further reaction of the initially formed product. Amides and esters were investigated as potential nucleophiles but led to no reaction under our conditions.

Next, a range of alkenyl bromides was coupled with ketone **1a**. A *trans*-alkenyl bromide reacted faster than its *cis* analogue, but the *cis* product was obtained in higher yields (**3ab** and **3ac**). For these and subsequent examples, the β,γ -unsaturated products were formed stereospecifically and were stable under the reaction conditions; no formation of α,β -unsaturated products was observed. The hindered α -styryl bromide gave a low yield of **3ad**, which may be attributed to added steric hindrance of the electrophile at the α -styryl position. A silyl protecting group was partially removed, resulting in only a moderate yield of **3ae** along with desilylated material. *trans*- β -Bromostyrene gave only low yields with **1a** (**3af**) but reacted well with a more electron-rich ketone (**3bf**). To demonstrate the utility of our Ni-catalyzed protocol compared with the previously utilized Pd catalyst,¹⁵ we constructed the carbon backbone of trichostatin A in comparably high yield (**3bg**). No reaction was observed between **1a** and alkenyl chlorides, alkenyl triflates, or bromobenzene under the present mild conditions. For bromobenzene, increasing the reaction temperature to 40 °C for 24 h gave only a 32% yield of the arylation product. Consistent with the lower reactivity of bromobenzene, we found that **2h** containing both alkenyl bromide and aryl bromide moieties could be chemoselectively coupled with **1e** at 6 °C to afford the α -alkenylated product **3eh** in 71% isolated yield; no α -arylation product was detected in the crude mixture by ¹H NMR analysis.

In related Pd-catalyzed alkenylations, large excesses of base and reactant, high temperatures, and/or long reaction times have been employed to form quaternary α -centers,^{18,19} with the exception of our recent Pd protocol.¹⁶ With our Ni-catalyzed procedure, high yields were achieved under relatively mild conditions (6 °C) with short reaction times (1–4 h) to generate quaternary ketones when the alkenyl halide has exclusively *trans* substitution (**3eh**, **3gf**, **3hf**, **3eb**). Alkenyl halides having a *cis* substituent could be coupled in moderate to good yields (**3ea**, **3ei**) but required a higher temperature (22 °C) and a longer reaction time (12 h).

We further investigated the beneficial effects of LiI. There have been several reports of Ni- and Pd-catalyzed sp^2 halide exchanges of both alkenyl halides²⁰ and aryl halides,²¹ which would also be possible in our protocol. To test whether a similar exchange occurs in our system, alkenyl halide **2i** was subjected to LiI (120 mol %) in the presence of a Ni/IPrHCl catalyst. After 2 h, a 4:5 ratio of **2i** and the corresponding alkenyl iodide was observed. Similarly, *trans*- β -bromostyrene underwent this halide exchange. In the absence of Ni(cod)₂, no alkenyl iodides were formed. Therefore, it appears that a Ni-catalyzed halide exchange occurs in the presence of LiI under the conditions of our alkenylation reaction, although other potential effects of LiI cannot be ruled out at this point.

In summary, we have described the development of a Ni-catalyzed alkenylation of ketone enolates. Secondary and tertiary ketones were readily coupled by a Ni/NHC catalyst

with alkenyl bromides under relatively mild conditions in which the addition of LiI was shown to significantly enhance the reaction rate and yield. Our mild conditions allowed for retention of β,γ -unsaturated products without migration or cis/trans isomerization. Advantages of the new protocol include short reaction times at low temperatures, efficient use of reactants and reagents, broad scope, and lower costs of both the metal and the ligand relative to other alkenylations. A Ni-catalyzed sp^2 halogen exchange between alkenyl bromides and LiI was observed. Investigations to gain an understanding of the mechanism of this alkenylation reaction are currently underway in our laboratories. Finally, catalysis of the reaction by Pd-contaminated commercial Q-Phos emphasizes the need for detailed control experiments in catalysis development.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures, ^1H , ^{13}C , and ^{19}F NMR spectra, and characterization of all compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02945.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the National Science Foundation (CHE-1058075 and CHE-1261033), the Research Council of Sweden, the Shenzhen Peacock Program (KQTD201103), and AstraZeneca. We thank Prof. Dr. K. Henderson (Notre Dame) for sharing equipment and Prof. Dr. P. Andersson (Stockholm University) for providing laboratory facilities during a research visit by M.G.

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