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Water-Accelerated Nickel-Catalyzed α-Crotylation of Simple Ketones with 1,3-Butadiene under pH and Redox-Neutral Conditions

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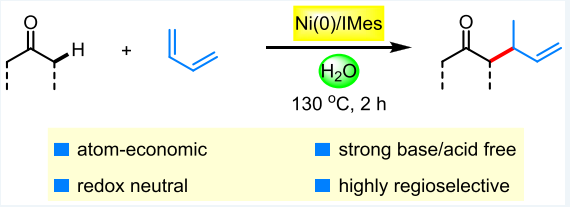
ABSTRACT: We report a nickel/NHC-catalyzed branched-selective α-crotylation of simple ketones using 1,3-butadiene as the alkylation agent. This reaction is regioselective and operated under pH and redox-neutral conditions. Water was used as the sole additive, which significantly accelerates the transformation.

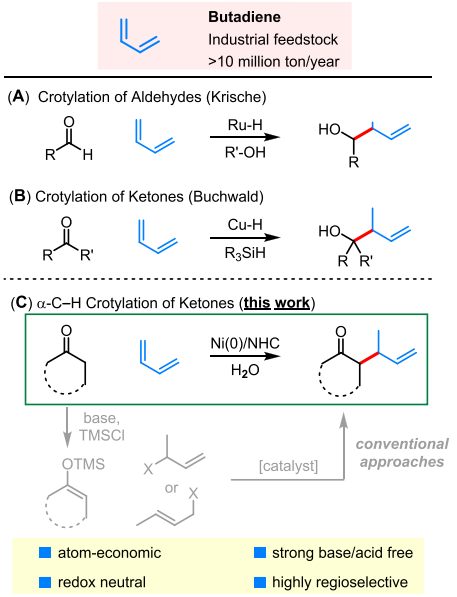


KEYWORDS: *nickel, 1,3-butadiene, crotylation, ketone, pH-neutral, atom-economy*

Carbon−carbon (C−C) bond formation is of central importance in organic synthesis.[1] From economical and environmental perspectives, it would be ideal to construct C−C bonds directly from simple chemical feedstocks in an atom-economic manner without producing stoichiometric by-products.[2] In this context, 1,3-butadiene, a "platform chemical" with an annual production of >10 million tons for the manufacture of rubbers, polymers, and fine chemicals,[3] has been an attractive candidate for the synthesis of value-added compounds through C−C bond forming reactions.[4] For example, Krische pioneered the use of 1,3-butadiene as a masked crotyl nucleophile for reductive carbonyl addition of aldehydes (Scheme 1A).[4b,d] Recently, a CuH-catalyzed reductive coupling strategy has been developed by Buchwald to realize crotylation of ketones (Scheme 1B).[4l] However, while 1,3-butadiene is known to be capable of generating electrophilic π-allyl intermediates with transition metals,[5] it remains challenging to couple such reactivity with less acidic nucleophiles, such as simple ketones. The challenges lie in the tendency of 1,3-butadiene for telomerization,[5d,6] as well as the relatively low nucleophilicity of simple ketones. Hence, the current scope has been mainly limited to 1,3-dicarbonyl compounds.[5] Considering the broad interest and significance on ketone alkylation, an atom-economical α-crotylation between readily available simple ketones and feedstock 1,3-butadiene could be a highly attractive method.

Recently, an elegant work by Zhou realized a Ni(0)-catalyzed α-allylation of ketones with substituted 1,3-dienes via *in situ* generation of enolates.[7a] While the reaction exhibited an impressive scope and selectivity, the non-aryl-substituted dienes gave much diminished yields and the use of simple 1,3-butadiene for α-crotylation remains unknown. Besides, a strong base additive, i.e., KO*t*-Bu, was required to generate enolate intermediates. As part of our continuous research interests in developing byproduct-free ketone α-alkylation through metal-hydride intermediates,[8] here we report a Ni-catalyzed α-crotylation of various regular ketones using simple 1,3-butadiene as the electrophile under *base-free* and *redox-*

Scheme 1. Crotylation of Ketones and Aldehydes with 1,3-Butadiene



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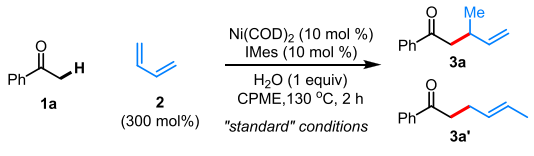
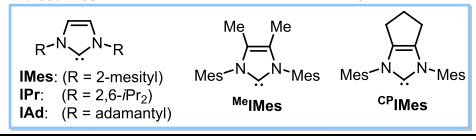
neutral conditions (Scheme 1C).[9,10] Notably, H_2O is used as the sole additive, which has been found to significantly accelerate the overall reaction rate. This approach could be valuable from the prospects of atom and step economies compared to the conventional alkylation approaches.[11]

Our study started with acetophenone (**1a**) as the model substrate. After thorough investigation of various reaction parameters, the desired α-crotylation product **3a** was ultimately obtained in 84% isolated yield (96% NMR yield) with excellent regioselectivity (Table 1, entry 1). Using

Table 1. Condition Optimizations[a]



Entry	Variations from the "standard" conditions	Yield of **3a** (%)[b]	rr (**3a**:**3a'**)[c]
1	none	96 (84)[d]	>20:1
2	IPr instead of IMes	67	>20:1
3	IAd instead of IMes	95	>20:1
4	^{Me}IMes instead of IMes	93	>20:1
5	^{CP}IMes instead of IMes	87	>20:1
6	without H_2O	43	>20:1
7	without H_2O; substrates treated with 4Å MS	< 5	--
8	MeOH instead of H_2O	52	>20:1
9[e]	HFIP or TFE instead of H_2O	< 5	--
10	toluene instead of CPME	77	>20:1
11	*m*-xylene instead of CPME	83	10:1
12	THF instead of CPME	80	>20:1
13	dioxane instead of CPME	86	>20:1
14	without Ni(COD)$_2$	0	--
15	without IMes	0	--

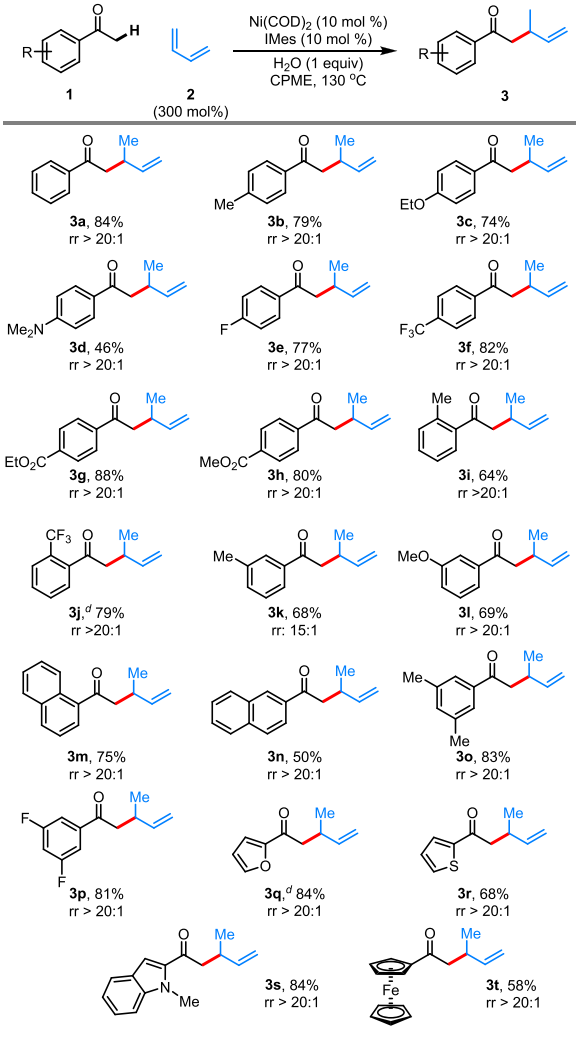


[a]Unless otherwise noted, the reaction was run on a 0.2 mmol scale of **1a** in 0.4 mL of solvent at 130 °C for 2 h; **2** was used as a 2 M solution in THF. **1a**:**2** = 1:3. [b]Yield determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [c]Regioselectivity ratio (rr) is the ratio of **3a** to **3a'**, determined by ^{1}H NMR of the reaction mixture. [d]Isolated yield shown in parentheses. [e]HFIP: 1,1,1,3,3,3-hexafluoroisopropanol. 2,2,2-Trifluoroethanol.

Ni(COD)$_2$/IMes as the catalyst and 1 equiv of H_2O as the sole additive, the reaction went full conversion with complete branched selectivity in 2 h at 130 °C. To gain insights into the role of each reactant, a set of control experiments were conducted. Among different NHC ligands tested, IMes gave the highest yield and selectivity while IAd as well as ^{Me}IMes and ^{CP}IMes bearing substituents on the unsaturated backbone also showed good reactivity and regioselectivity (entries 3−5). IPr gave a lower yield while maintaining excellent regioselectivity (entry 2). Without H_2O, **3a** was obtained in only 43% yield (entry 6). We concluded that the moderate reactivity came from the trace amount of water in the butadiene/THF solution. This is because, when the substrates were predried with 4 Å molecular sieves before being subjected to the reaction without adding H_2O, **3a** was observed in less than 5% yield (entry 7). These results suggest the critical role of water for this transformation. When MeOH instead of H_2O was added, this reaction still proceeded but with decreased efficiency (entry 8). When H_2O was replaced with HFIP or TFE, the desired product was not observed, indicating that a more acidic proton source may not be compatible with the current catalytic system (entry 9). Cyclopentyl methyl ether (CPME) as the solvent was proved to be superior in terms of both the reactivity and regioselectivity (entries 10−13). Unsurprisingly, this transformation did not proceed without Ni(COD)$_2$ or IMes (entries 14 and 15).[12]

With the optimized reaction conditions in hand, different substituted acetophenones were tested first (Scheme 2). Both

Scheme 2. Substrate Scope of Substituted Aryl Methyl Ketones[a,b,c]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol, 2 M solution in THF), Ni(COD)$_2$ (0.02 mmol), IMes (0.02 mmol), and H_2O (0.2 mmol) in CPME (0.4 mL) at 130 °C for 2 h. [b]Isolated yields. [c]Regioselectivity ratio (rr) was determined by ^{1}H NMR of the reaction mixture. [d]The crotylation products derived from dimerized butadiene were observed in a 1:10 ratio to the desired product.

electron-rich (**3b−3d**, **3i**, **3k**, **3l**) and -deficient aryl ketones (**3e−3h**, **3j**) bearing various substituents at *para*, *ortho*, or *meta* positions all worked well, affording the corresponding α-crotylation products in moderate to good yields with high to excellent regioselectivities. Substituents such as fluoro (**3e**), trifluoromethyl (**3f**, **3j**), ethyl or methyl ester (**3g**, **3h**) could all be tolerated. 1-Naphthyl and 2-naphthyl ketones, as well as

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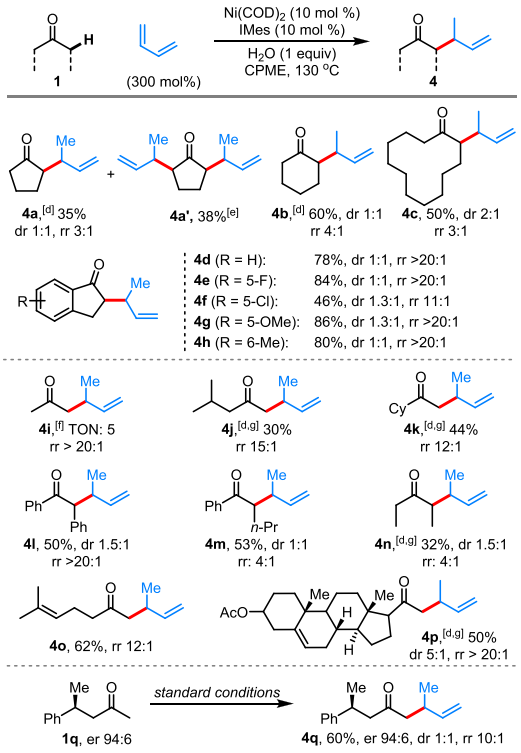
disubstituted aryl ketones were good substrates, affording the desired α-crotylation products (**3m**−**3p**) in good efficiency. Heteroaryl ketones bearing a 2-furyl or 2-thienyl group, as well as *N*-methyl-2-acetylindole or 2-ferrocenyl methyl ketone, also reacted smoothly in moderate to good yields with excellent branched selectivity (**3q**−**3t**).

The scope of other ketones was then investigated (Scheme 3). As expected, cyclopentanone showed high reactivity, but

Scheme 3. Substrate Scope of Other Ketones[a,b,c]



[a]Unless otherwise noted, the reaction was run with **1** (0.2 mmol), **2** (0.6 mmol, 2 M solution in THF), $Ni(COD)_2$ (0.02 mmol), IMes (0.02 mmol), and H_2O (0.2 mmol) in CPME (0.4 mL) at 130 °C for 2 h. [b]Isolated yields. [c]Regioselectivity ratio (rr) was determined by ^1H NMR of the reaction mixture. [d]20 mol % of the catalyst. [e]NMR yield for **4a′** as a mixture of undistinguishable diastereomers. [f]With 0.25 mL of acetone; TON was based on Ni. [g]500 mol % of **2** was used.

giving a mixture of mono- and dicrotylation products (**4a** and **4a′**) with a modest regioselectivity. In comparison, less reactive cyclohexanone and cyclododecanone gave only the mono-crotylation products in higher yields (**4b** and **4c**). 1-Indanones with different substituents proved to be excellent substrates, generally affording the desired products in good yields with excellent regioselectivity (**4d**−**4h**). Gratifyingly, linear aliphatic ketones were also competent substrates. The coupling between acetone and 1,3-butadiene yielded the crotylation product **4i** with a TON of 5 and excellent branched selectivity. When 4-methyl-2-pentanone or cyclohexyl methyl ketone were used, the α-crotylation occurred exclusively at the less hindered methyl side albeit in a lower efficiency (**4j** and **4k**). In addition, non-methyl linear ketones could also be employed as substrates (**4l**−**4n**). Finally, alkene-substituted ketone **4o**, the progesterone-derived substrate with an α-stereocenter (**4p**), and the ketone with a β-stereocenter (**4q**) were also found to be suitable substrates.

To understand the role of H_2O in this transformation, kinetic monitoring of the parallel experiments with or without the addition of H_2O was conducted (Figure 1). With H_2O, a

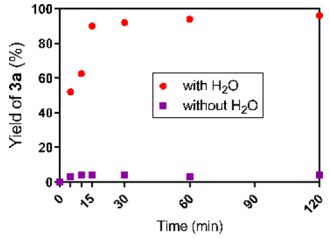
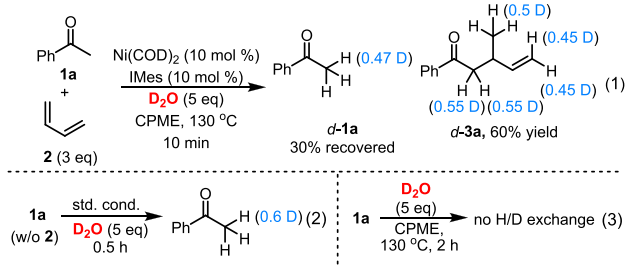


Figure 1. Parallel experiments with and without H_2O.

high reaction rate was observed without any induction period: product **3a** formed in nearly 60% yield within 5 min and the reaction was almost completed within 15 min. By contrast, in the absence of H_2O, the reaction was very slow and less than 5% of **3a** was obtained after 2 h.[13] This result implied the critical role of H_2O in accelerating the reaction rate of this transformation.

To gain some mechanistic understanding on this transformation, a deuterium-labeling experiment was conducted by adding D_2O instead of H_2O to the reaction system (Scheme 4,

Scheme 4. Deuterium-Labeling Studies



eq 1). After 10 min, the desired product *d*-**3a** was obtained in 60% yield, with H/D exchange at the terminal methyl, the terminal alkenyl, as well as the ketone α-positions.[14] Meanwhile, H/D scrambling was also observed at the methyl position for the recovered acetophenone **1a**. Furthermore, H/D scrambling at the ketone α position was observed when running the standard reaction with D_2O but in the absence of 1,3-butadiene (Scheme 4, eq 2). As a control experiment, no H/D scrambling was observed without $Ni(COD)_2$ and IMes (Scheme 4, eq 3).

While some mechanistic details of the reaction remain unclear and are the topic of the ongoing investigation, the current data and literature precedents allow us to propose a hypothesis of the catalytic cycle (Figure 2). First, the nickel(0)/IMes catalyst coordinates with 1,3-butadiene to form complex **A**.[15−17] Protonation of complex **A** at the terminal position of the bounded 1,3-butadiene leads to a nickel-π-allyl intermediate **B** that bears a hydroxide ligand. The hydroxide species should then deprotonate the ketone substrate to form the corresponding enolate intermediate **C**. Alternatively, direct oxidative addition of H_2O to Ni(0) would generate the HO−Ni−H species **D**.[18,19] The hydride on the Ni could insert into the π bond in 1,3-butadiene, while the hydroxide ligand could deprotonate the ketone substrate to give the same intermediate **C**. Given that proton-transfer steps

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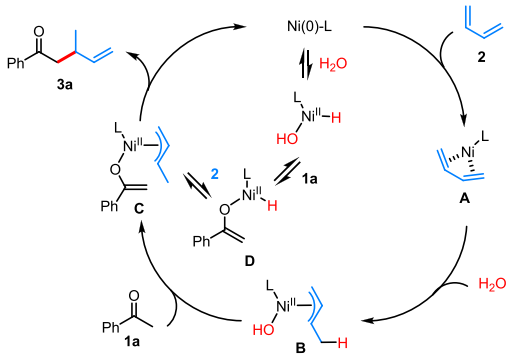


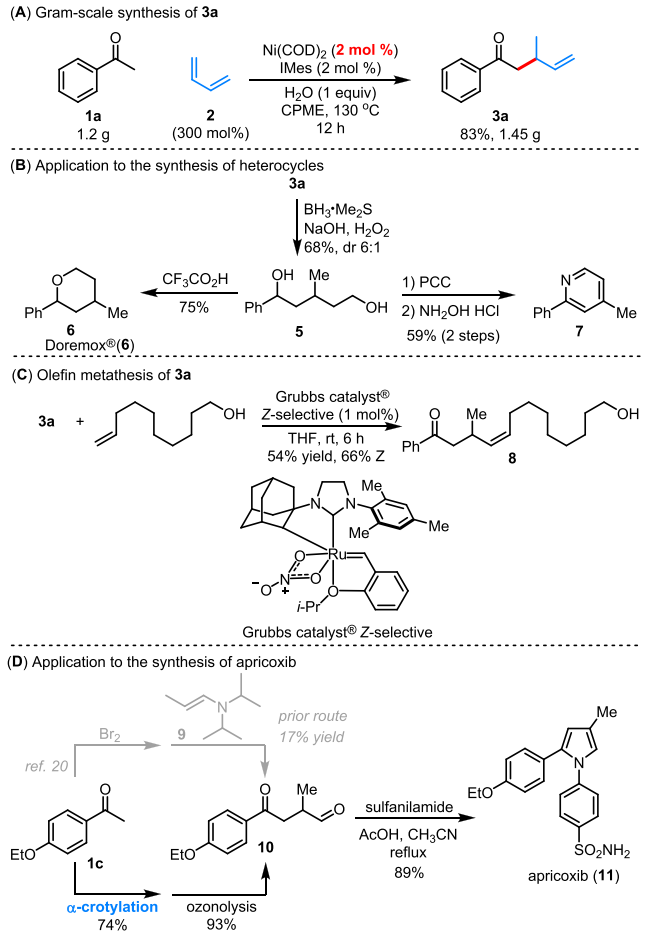
Figure 2. Proposed reaction pathways.

are typically reversible, both paths to intermediate **C** could be explained by the observed deuterium-labeling experiments. Subsequent C−C reductive elimination between the enolate and the allylic fragment delivers the α-crotylation product and regenerates the Ni(0) catalyst.

To show the synthetic utility of this transformation, a gram-scale reaction was conducted. This reaction was easily scaled up with only 2 mol % of the catalyst with no loss of yield (Scheme 5A). The γ,δ-unsaturated ketone product could be transformed into different structural motifs.[20] For example, **3a** could be readily converted into diol **5** in good yield. Diol **5** can be transferred to Doremox (**6**), a perfume additive,[21] in a single step, or 3-phenyl-3-methylpyridine **7** in two steps (Scheme 5B).[22] The terminal olefin can also undergo metathesis to give a *cis* enone product (**8**) (Scheme 5C). Finally, this method was applied to the synthesis of apricoxib (**11**), an orally active Cox-2 inhibitor and an anticancer agent (Scheme 5D).[23] Starting from commercially available *p*-ethoxyacetophenone **1c** and 1,3-butadiene, apricoxib can now be obtained in 61% yield over three steps with notable improvements from the conventional route.[24]

In summary, we have developed a nickel-catalyzed regioselective α-crotylation of simple ketones with 1,3-butadiene for preparing synthetically useful γ,δ-unsaturated ketones. The reaction is operated under pH and redox-neutral conditions without forming stoichiometric byproducts. Water plays a critical role as a mediator and significantly accelerates the reaction. The high scalability and broad functional group tolerance could make this method attractive for complex molecule synthesis. Efforts on more detailed mechanistic studies are ongoing.

Scheme 5. Synthetic Elaborations



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c00019.

General experimental information, experimental procedure with chemical structures and characterization data, deuterium experiments, experimental procedure for the synthetic applications with chemical structures and characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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