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Direct Synthesis of Mono-α-arylated Ketones from Alcohols and Olefins via Ni-Catalyzed Oxidative Cross-Coupling

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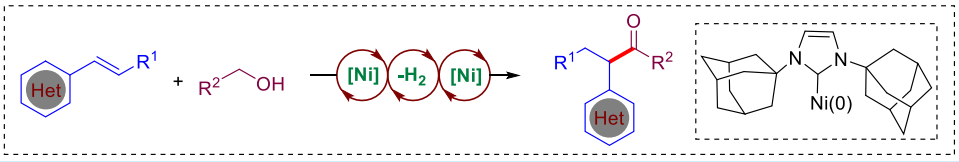
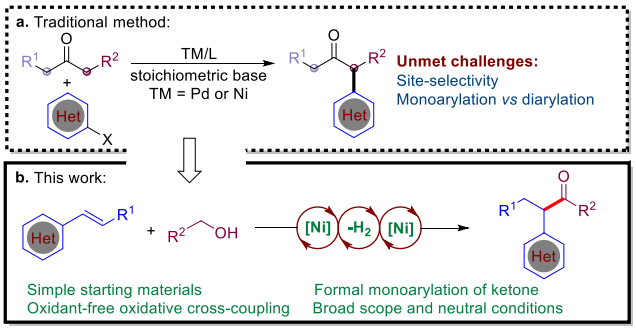


ABSTRACT: Controlled synthesis of α-monoarylated ketones is significant yet challenging due to the site-selectivity issues and nonproductive overarylation reactions. Herein, we reported the direct synthesis of α-arylated ketones enabled by Ni-catalyzed dehydrogenative cross-coupling reaction cascade between alcohols and olefins. The use of readily available and cost-effective alcohols and olefins provides a straightforward access to monoarylated ketones in good yields with exclusive selectivity without using any advanced synthetic intermediates.

Ketones are ubiquitous in natural products, drugs, and functional materials and serve as key intermediates in the synthesis of C−C bonds and other functional groups.[1] Ketones are most often synthesized by the addition of an organometallic reagent to an aldehydes or acid derivatives, followed by oxidation.[1a,2,3] Furthermore, site-selective and controlled synthesis of mono-α-arylated ketones is attractive yet challenging due to the competitive site-selectivity issues and unproductive diarylation processes.[4] Over the past decades, selective synthesis of mono-α-aryl ketones has received much attention. Buchwald,[5] Hartwig,[6] and Miura[7] intensively developed the catalytic conditions for selective direct monoarylation from ketones. These methods suffer from the limited scope of ketones with specific substitution patterns or preformed ketone enolates (Scheme 1a).[8] On the other hand, transition-metal-catalyzed hydroacylation of olefins is a potential and straightforward alternative for ketone synthesis with high atom and step economy.[9] This ideal process involves a metal-catalyzed insertion of a C−H bond to form an acyl-metal-hydride intermediate and a following addition across olefins and reductive elimination to form the desired ketones. In 1972, the Sakai group reported the first example of metal-mediated intramolecular hydroacylation of olefins by using a stoichiometric amount of a rhodium complex to afford cyclopentanones.[10] Over the past decades, significant advances on metal-catalyzed intra- and intermolecular hydroacylation of olefins have been made.[11] However, an intermolecular version of hydroacylations requires additional coordinating/directing groups on aldehydes or olefins to facilitate the addition process due to the competitive decarbonylation reaction of the acyl-metal-hydride intermediate.[12]

Additionally, most current hydroacylation protocols heavily rely on precious metals such as rhodium, which significantly limits the opportunity for broad application of this strategy.[13] Moreover, existing protocols for hydroacylation basically could be applied to strained olefins, electronically biased olefins, or terminal aliphatic olefins.[14] Regioselective intermolecular hydroacylation of styrenes remains a formidable challenge, thus not being able to afford formal α-arylation of ketones. In 2016, the Zhou group reported the first nickel-catalyzed intermolecular hydroacylation reaction of styrenes with simple aldehydes to afford α-arylated ketones via ligand-to-ligand

Scheme 1. Challenges and Strategies for Mono-α-arylated Ketone Synthesis



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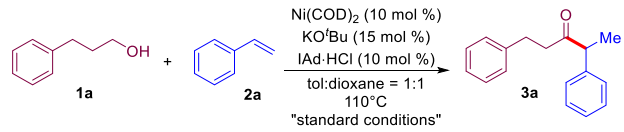
hydrogen transfer (LLHT) in the presence of a phosphine ligand.[15] Unfortunately, this protocol is not applicable to the reaction of alcohols with olefins. Due to the instability and high cost of aldehydes, the discovery of more cost-effective and user-benign equivalents as the aldehyde surrogate would be of synthetic interest in organic synthesis. Aliphatic alcohols are bulk chemicals in industrial production and serve as important precursors for the construction of value-added target molecules in organic synthesis.[16] Moreover, the use of alcohols instead of aldehydes to access mono-α-arylated ketones would be mechanistically interesting and challenging. First, nickel needs to play a twofold role with one ligand in dehydrogenation of alcohols to produce aldehydes[17] as well as formal regioselective hydroacylation of olefins with aldehydes. Second, a unified reaction condition has to be identified which is applicable to Ni-catalyzed transfer hydrogenation of alcohols with olefins, and regioselective hydroacylation of olefins in a sequential and controlled manner. Third, it would be of interest to understand whether the aldehyde intermediate is stoichiometrically or catalytically formed during the reaction course. Thus, we envisioned accessing formal mono-α-arylated ketones using alcohols as a more readily available, cost-effective, and challenging surrogate for aldehydes. Herein, we report the formal synthesis of mono-α-arylated ketones via a Ni-catalyzed oxidative cross-coupling of alcohols with olefins. The use of alcohols as latent carbonyl precursor allows for the α-arylation of ketones from inexpensive starting materials in a site-selective and controlled manner, circumventing the use of unstable and expensive aldehydes as a carbonyl source.

We set out to explore the reaction conditions using 3-phenylpropan-1-ol **1a** and styrene **2a** as substrates. After extensive condition evaluation, we defined the optimal conditions as the use of $Ni(COD)_2$ (10 mol %), IAd·HCl (10 mol %), and potassium *tert*-butoxide (15 mol %) in the mixture of toluene and dioxane (1:1) at 110 °C, coupling the alcohol with styrene to give α-phenyl ketone **3a** in 85% isolated yield (Table 1, entry 1). Due to the stoichiometric consumption of styrene by serving as a hydrogen acceptor, 3 equiv of **2a** were used. The ligand is crucial for this regioselective oxidative hydroacylation reaction, replacing the IAd·HCl with other NHC ligands, such as IMes·HCl, IPr·HCl, and ICy·HCl, giving inferior results, with partial starting material **1a** recovered (Table 1, entries 2−5). A catalytic amount of strong base is required for this transformation. The use of sodium *tert*-butoxide or lithium *tert*-butoxide in lieu of potassium *tert*-butoxide could catalyze the reaction, giving **3a** in 74% and 40% yields, respectively (Table 1, entries 6 and 7). The use of a weaker base, such as cesium carbonate, led to formation of a trace amount of the desired product **3a** (Table 1, entry 8). Investigation of the solvent effect revealed that the reaction proceeded in toluene, dixoane, or diglyme, albeit in lower efficiency (Table 1, entries 9−12). Both a transition metal and anchoring ligand are essential to the reaction, as no reaction occurred in the absence of nickel or ligand (Table 1, entry 13).[18]

With the optimized conditions in hand, we turned to examine the scope of this formal mono-α-arylation of ketones via Ni-catalyzed oxidative cross-coupling of alcohols with olefins. The results are summarized in Scheme 2. First, the scope of primary alcohols is investigated. Phenyl tethered alcohols with different alkyl chains are compatible under the reaction conditions, giving corresponding α-arylation of ketones **3a**−**3c** in good yields. 1-Pentanol, ethanol, and

Table 1. Conditions Evaluation for α-Monoarylated Ketones[a]



Entry	Variation from "standard conditions"	Yield (%)[b]
1	none	89 (85)[c]
2	IMes·HCl instead of IAd·HCl	5 (85)[d]
3	SIMes·HCl instead of IAd·HCl	3 (60)[d]
4	IPr·HCl instead of IAd·HCl	0 (95)[d]
5	ICy·HCl instead of IAd·HCl	0 (92)[d]
6	NaO^tBu instead of KO^tBu	74
7	LiO^tBu instead of KO^tBu	40 (35)[d]
8	Cs_2CO_3 instead of KO^tBu	trace (88)[d]
9	toluene	55
10	dioxane	84
11	diglyme	61
12	DMA	6 (51)[d]
13	no nickel or ligand	NR

[a]The reaction was conducted using 0.2 mmol of **1a** and 0.6 mmol of **2a** under indicated conditions for 10 h, NR = No reaction. [b]Yields were determined by GC using dodecane as internal standard. [c]Isolated yield after flash chromatography. [d]Recovery of **1a**.

4,4,4-trifluorobutan-1-ol are good substrates, delivering corresponding arylated ketones **3d**−**3f** in 43%−81% yields, while methanol is not efficient enough to produce a corresponding α-arylated aldehyde. β-Branched alcohol could be also tolerated in the reaction, furnishing β'-branched-α-aryl ketone product **3g** in 74% yield. Tetrahydrogeraniol could be converted to corresponding α-monoarylated ketone **3h** in 81% yield. Heterocycles, such as pyridine and piperidine, derived alcohols could be transformed into α-monoarylated ketones **3i** and **3j** in 55% and 82% yields, respectively. Notably, α-branched alcohols could be converted into desired product, giving α,α'-arylated or α-arylated-α'-alkylation ketones in good to excellent yields (**3k**−**3o**). Moreover, benzyl alcohols are good substrates in this reaction, delivering α-arylated aromatic ketones (**3p** and **3q**) in synthetic useful yields. Unfortunately, benzylic alcohols with *para*-NO_2, NH_2, CO_2Me, CO_2H, CHO, CN, or vinyl are not good substrates under the reaction conditions. Next, we tested different aromatic alkenes to determine the variation of aromatic substitutions. *para*-, *meta*-, and *ortho*-Substituted styrenes with electron-donating or -withdrawing substitution patterns could couple with different alcohols to afford different aryl substituted α-monoarylated ketones in good yields (**4a**−**4i**). Notably, vinylpyridine is also compatible under the reaction conditions, affording mono-α-pyridinyl ketone **4j** in moderate yield. Internal styrene could be applied to the reaction, affording mono-α-arylation of ketones with other alkyl substitutions, albeit with moderate efficiency (**4k**). Norbornene could be coupled with styrene to give corresponding ketone **4l** in 74% yield with 4:1 dr. Ethylene could not be successfully incorporated in the reaction, probably due to poor mixing efficiency of two phases. To further demonstrate the scope of this methodology, natural product derived alcohols are tested. Primary alcohols based on β-pinene and lithocholic acid could be successfully coupled with styrene, furnishing mono-α-arylated ketones with complex structural scaffold **4m** and **4n** in 80% and 91% yields, respectively. Interestingly, β-citronellol and geraniol could

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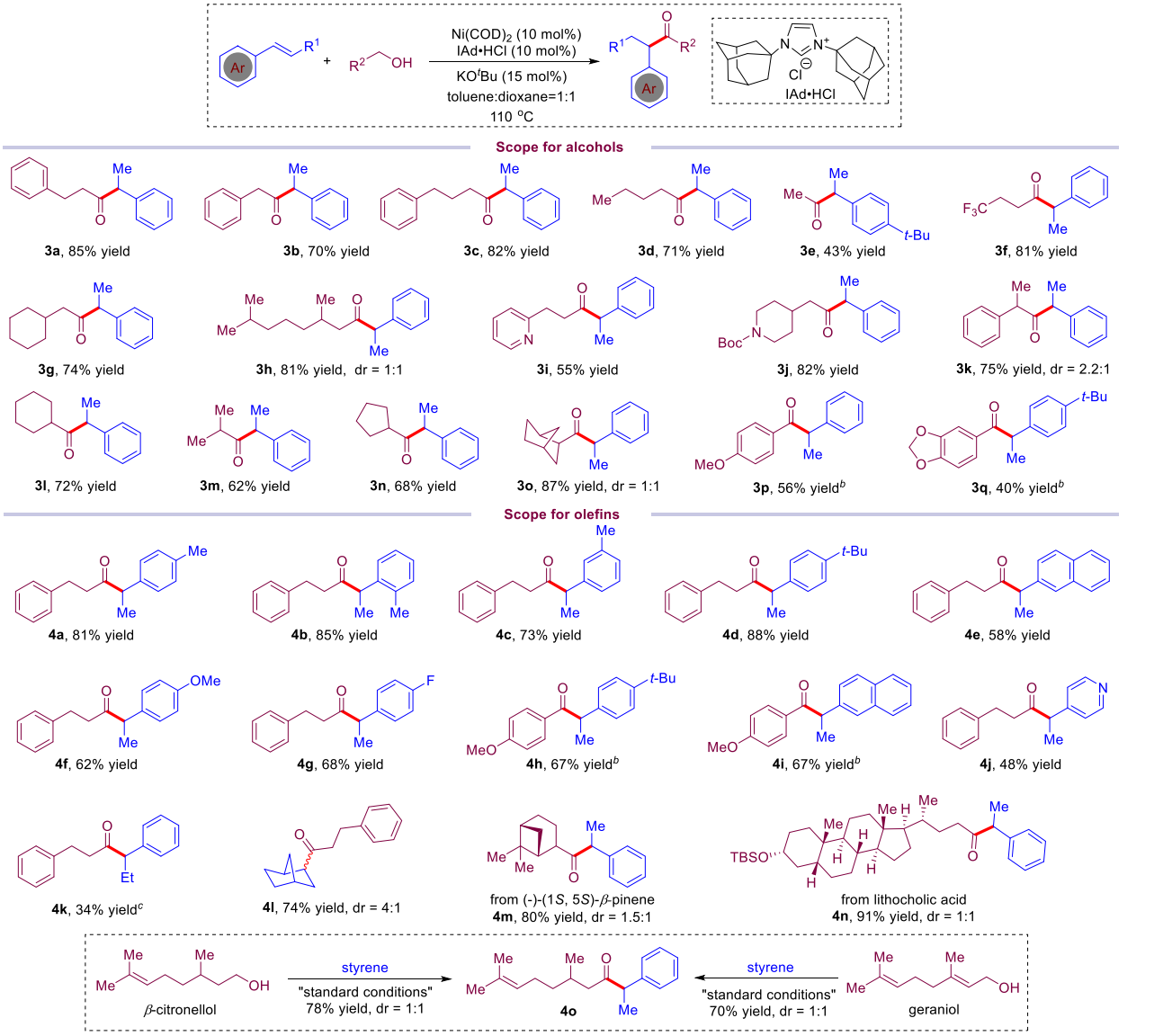
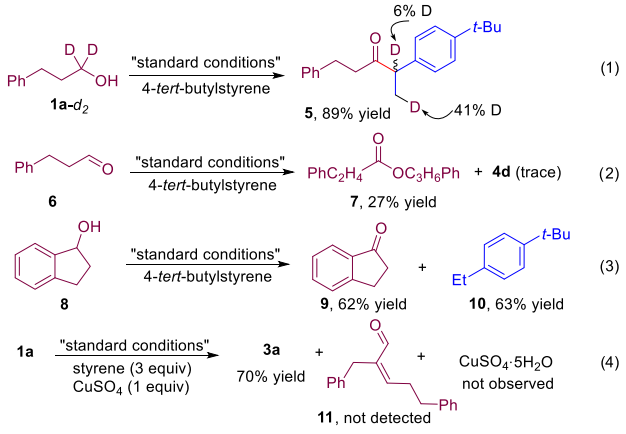
Scheme 2. Scope for Synthesis of α-Monoarylated Ketones in Terms of Alcohols and Olefins[a]



[a]The reaction was set up on 0.2 mmol scale. For detail reaction conditions, see Table 1, entry 1. [b]The reaction was carried out using IMes·HCl (10 mol %) as ligand. [c]The reaction was carried out at 130 °C using IMes·HCl (10 mol %) as ligand.

react with styrene to deliver the identical product **4o** under the reaction conditions in 78% and 70% yields, respectively.

To probe the mechanism of this reaction, we carried out the reaction using 3-phenylpropan-1,1-d_2-1-ol (**1a**-d_2) and 4-*tert*-butylstyrene under standard conditions. The desired α-monoarylated ketone **5** was obtained in 89% yield with deuterium scrambling observed (eq 1). When aldehyde **6** was submitted to the standard conditions instead of parent alcohol **1a**, 27% of ester **7** was observed with trace amount of **4d** (eq 2). This indicates that a stoichiometric amount of aldehyde is not compatible in the reaction, which may lead to fast dimerization to give ester byproduct under the reaction conditions. If secondary alcohol **8** was used in the reaction with 4-*tert*-butylstyrene, olefin hydrogenation product **10** was formed in 63% yield based on conversion along with forming an equal amount of ketone **9** (eq 3), suggesting the transfer hydrogenation process of alcohol to olefin. Moreover, the reaction of **1a** with styrene was conducted with anhydrous copper sulfate (1 equiv) under otherwise identical to standard



conditions. Desired ketone **3a** was formed in 70% yield without formation of bimolecular condensation product **11** via dehydration or copper sulfate hydrate (eq 4).

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To further understand the reaction mechanism, we conducted the reaction of **1a** with 4-*tert*-butylstyrene to monitor the kinetic behavior of this reaction (Figure 1).

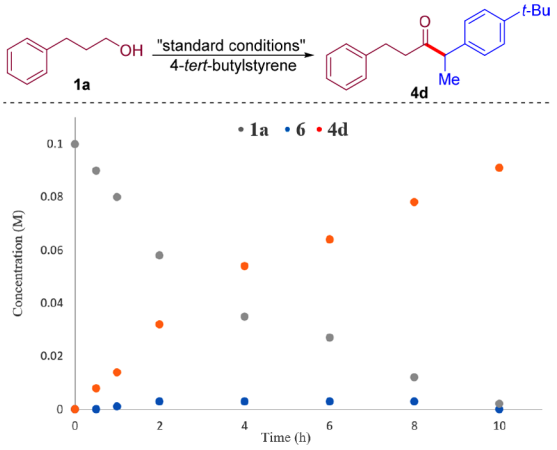

Figure 1. Reaction profile of **1a** with 4-*tert*-butylstyrene.

Desired ketone **4d** was formed from the beginning of the reaction and increased along the reaction time. Aldehyde could be observed throughout the reaction course, albeit in low concentration (<5%). These results further prove aldehyde is the intermediate formed catalytically during the reaction course.

Based on the results and literature precedence, a work proposal for the transformation is depicted in Figure 2. Nickel

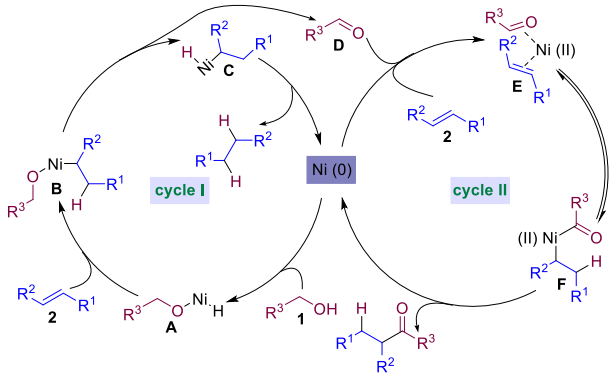

Figure 2. Proposed mechanism for the reaction.

plays a twofold role in two catalytic cycles. One cycle is for the oxidative dehydrogenation of alcohols to aldehydes, the other cycle is for regioselective hydroacylation of aldehydes with olefins. First, nickel(0) inserts into O−H bond to give Ni(II) intermediate **A**, which could undergo hydrometalation onto **2** to give intermediate **B**. This alkyoxylnickel intermediate undergoes site-selective β-H elimination to give aldehydes **D**[17] and nickel(II) intermediate **C**. **C** could undergo reductive elimination to regenerate Ni(0) species by excursion of alkane. Then, Ni(0) could initiate the second catalytic cycle. In the presence of alkene and aldehydes, nickel(0) coordinates with an aldehyde and an alkene to form intermediate **E**, which could undergo site-selective ligand-to-ligand hydrogen transfer (LLHT) to furnish ketone intermediate **F**.[15] **F** could form the final α-arylated ketones and regenerate nickel(0) via reductive elimination.

In summary, the Ni-catalyzed direct oxidative cross-coupling of alcohols with olefins is described for the first time, affording a variety of mono-α-arylated ketones in good yields. The judicious selection of NHC ligand along with reaction conditions enables the selective and sequential dehydrogenation and assembly of alcohols onto olefins. Nickel plays an essential twofold catalytic role in this reaction with one ligand. This operationally simple protocol features the use of readily available and cost-effective starting materials, allowing for the straightforward access of monoarylated ketones with broad functional group tolerance.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02340.

General procedures for the synthesis of α-monoarylated ketones from alcohols and olefins, conditions optimization, characterization of new compounds, mechanistic experiments, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(18) For more details on conditions optimization, see Supporting Information.

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