Nickel-Catalyzed Reductive Coupling of γ-Metallated Ketones with Unactivated Alkyl Bromides

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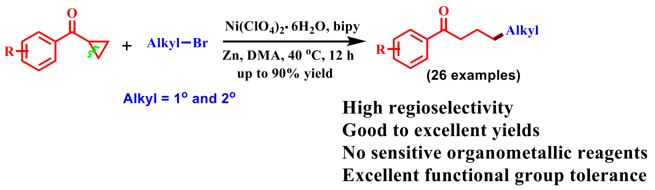
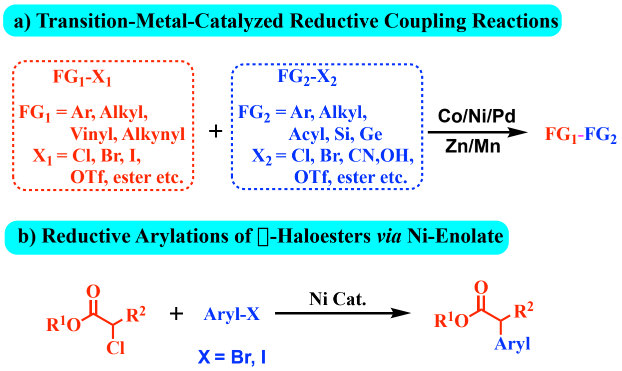
Supporting Information Placeholder



ABSTRACT: A nickel-catalyzed reductive cross-coupling reaction of aryl cyclopropyl ketones with easily accessible unactivated alkyl bromides to access aryl alkyl ketones has been developed. This strategy facilitates access to various of γ-alkyl substituted ketones *via* ring opening of cyclopropyl ketones (26 examples, 50−90% yield). Initial mechanistic studies revealed that the reaction proceeds via a radical cleavage of the alkyl bromide.

Nickel-catalyzed reductive coupling reactions are highly desirable, with the operational advantage of circumventing the use of preformed organometallic reagents of traditional cross-coupling reactions.[1] These synthetically useful reductive processes have been widely developed by Gosmini,[2] Weix,[3] Gong,[4] Reisman,[5] Diao,[6] Shu,[7] Wang[8] and others using diverse electrophiles (Scheme 1a). A subset of such transformations include nickel-catalyzed reductive coupling of enolizable intermediates, which have been demonstrated to be valuable in the synthesis of bioactive molecules.[9] Usually, such transformations involve nickel-enolate intermediates.[10] For example, Durandetti and Gosmini,[9b, 9e] our team,[9d] and the Reisman[9a] group have reported the reductive arylations of α-haloesters to generate anti-inflammatory drug derivatives, NSAIDs (Scheme 1b). More recently, a nickel-catalyzed asymmetric tandem alky arylation of acrylates was developed by us.[9c] Like the reductive coupling of enolizable carbonyl compounds, the reductive coupling of homoenolates and their higher homologues (γ-metallated carbonyls) are under developed.[11]

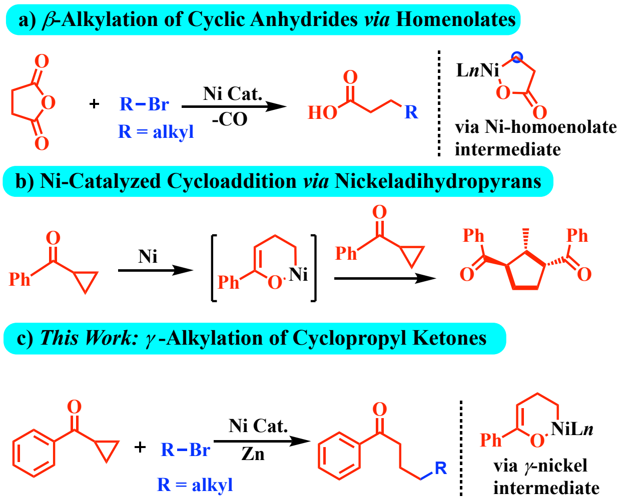
Scheme 1. Transition-Metal-Catalyzed Reductive Cross-Coupling Reactions



We have been interested in reductive coupling of carbonyl-containing electrophiles, including asymmetric variants.[9c, 9d, 11] One of our goals is the use of α-functionalized electrophiles that undergo transposition of functionality to positions further removed from the carbonyl group. Recently, our team developed a nickel-catalyzed reductive coupling of nickel-bound homoenolates in which the homoenolate was catalytically generated via decarbonylation of cyclic anhydrides (Scheme 2a).[11a] These recent findings led us to wonder if γ-nickel carbonyl intermediates could be utilized in reductive alkylations to elaborate carbonyl compounds.

Cyclopropyl ketones are easily accessible materials and represent a class of important precursors for ring opening reactions.[12] Ogoshi, Nagata and Kurosawa demonstrated that in the presence of $Ni(COD)_2$, cyclopropyl ketones underwent ring opening to form nickeladihydropyran intermediates (Scheme 2b).[13] Notably, this nickel-bound intermediate is a γ-metallated enolate and is primed for further elaboration. Herein, we report a nickel-catalyzed reductive alkylation of cyclopropyl ketones via ring-opened γ-metallated intermediates. Such species enable generation of an array of γ-alkylated ketone products (Scheme 2c). During the final preparations of this manuscript, Wang and co-workers reported a related coupling of cyclopropyl ketones[14] with alkyl halides with a different catalyst. Interestingly, these two processes proceed by different reaction mechanisms (2-electron vs. radical).

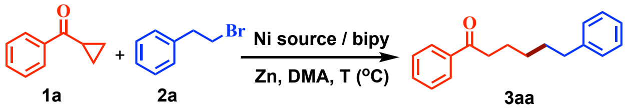
Scheme 2. Nickel-Catalyzed Cross-Coupling *via* Ring Opening of Carbonyl Compounds



We initiated our research with 1 equiv. cyclopropyl phenyl ketone **1a** and 1 equiv. (2-bromoethyl)benzene **2a** as model substrates. For the catalyst generation, 10 mol % $Ni(COD)_2$ and 15 mol % bipy were employed in the presence of 2 equiv. Zn powder and *N,N*-dimethylacetamide (DMA) at 80 °C for 12 h. Under these conditions the 1,6-diphenylhexan-1-one **3aa** was obtained in 32% yield (Table 1, entry 1). To improve the yield of the product, the Ni source was varied maintaining bipy as ligand. Compared to other nickel sources ($NiBr_2$, NiI_2, $NiBr_2$•DME, the commercially available $Ni(ClO_4)_2 \cdot 6H_2O$ provided 42% yield (Table 1, entry 5). $NiBr_2$, NiI_2, $NiBr_2$•DME led to decreased yields (Table 1, entries 2–4). The impact of temperature was next examined. Lowering the temperature from 80 to 60 °C resulted in an increase in the yield to 50% (Table 1, entry 6) and further decreasing the temperature to 40 °C afforded the desired product in 65% yield (Table 1, entry 7). No coupling product was detected at 20 °C (Table 1, entry 8).

We next examined how the ratio of **1a : 2a** impacted the reaction outcome. Increasing **1a : 2a** from 1 : 1 to 1 : 2.5 resulted in an improvement in the yield of **3aa** from 65% to 86% (Table 1, entry 7 vs. 9 – 11). The influence of other reaction parameters, including the use of different solvents, concentrations, ligands and reductants were tested (see the Supporting Information for full details). These studies did not lead to improvement on the conditions in Table 1 (Entry 11). Ultimately, the optimal conditions for this nickel-catalyzed reductive cross-coupling of cyclopropyl phenyl ketones entail **1a** (1.0 equiv), alkyl bromide **2a** (2.5 equiv), Zn powder (2 equiv), $Ni(ClO_4)_2 \cdot 6H_2O$ (10 mol %) and bipy (15 mol %) in DMA (0.5 M) at 40 °C for 12 h.

Table 1. Optimization of the Reaction Conditions[a]



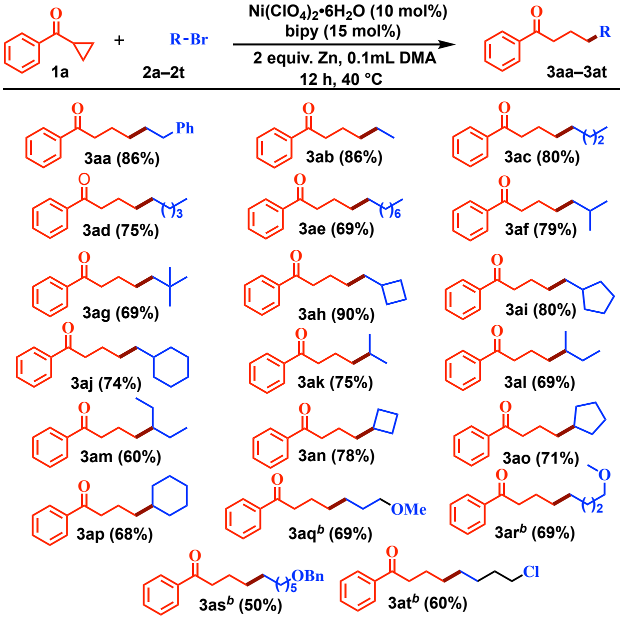
Entry	Ni source	Temp (°C)	**1a : 2a**	Yield[b] (%)
1	$Ni(COD)_2$	80	1 : 1	32
2	$NiBr_2$	80	1 : 1	17
3	NiI_2	80	1 : 1	24
4	$NiBr_2 \cdot DME$	80	1 : 1	30
5	$Ni(ClO_4)_2 \cdot 6H_2O$	80	1 : 1	42
6	$Ni(ClO_4)_2 \cdot 6H_2O$	60	1 : 1	50
7	$Ni(ClO_4)_2 \cdot 6H_2O$	40	1 : 1	65
8	$Ni(ClO_4)_2 \cdot 6H_2O$	20	1 : 1	trace
9	$Ni(ClO_4)_2 \cdot 6H_2O$	40	1 : 1.5	69
10	$Ni(ClO_4)_2 \cdot 6H_2O$	40	1 : 2	73
11	$Ni(ClO_4)_2 \cdot 6H_2O$	40	1 : 2.5	86

[a] Reactions were conducted on a 0.1 mmol scale using **1a**, **2a**, Ni source (10 mol %), bipy (15 mol %), and DMA (0.5 M). [b] Isolated yield. Trace means the yield <5%.

With the optimized reaction conditions above (Table 1, entry 11), we then determined the scope of the reaction with respect to alkyl bromide substrates (Scheme 3). The parent (2-bromoethyl)benzene **2a** reacted to give the cross-coupling product **3aa** in 86% isolated yield. Primary *n*-alkyl bromides containing 2, 4, 6, or 8 carbon chains furnished the linear coupled products in 69% to 86% yield (**3ab–3ae**). Primary alkyl bromides with branching, such as *iso*-butyl bromide (**2f**) and neopentyl bromide (**2g**), furnished products **3af** and **3ag** with 79% and 69% yield, respectively. Furthermore, primary cyclic alkyl bromides bearing 4, 5, or 6-membered rings (**2h–2j**), provided the cross-coupling products **3ah–3aj** in 74–90% yield.

Secondary alkyl bromides were next evaluated. Acyclic secondary alkyl bromides **2k – 2m** and cyclic secondary alkyl bromides **2n–2p** were all suitable under the standard conditions, providing the coupled products **3ak–3ap** with 56–78% yield. Unfortunately, when functionalized alkyl bromides bearing ether and chloride were employed, cross-coupling products were not observed (the starting materials remained). These results inspired a search for suitable conditions for these important substrates. By rescreening the ligands and temperatures, we identified modified conditions with 5,5'-dimethyl-2,2'-dipyridyl in place of bipy at a higher temperature (80 °C). Under the modified conditions, functionalized alkyl bromides bearing ether (**2q–2s**) and chloro (**2t**) provided the corresponding functionalized products **3aq–3at** in 50–69% yield.

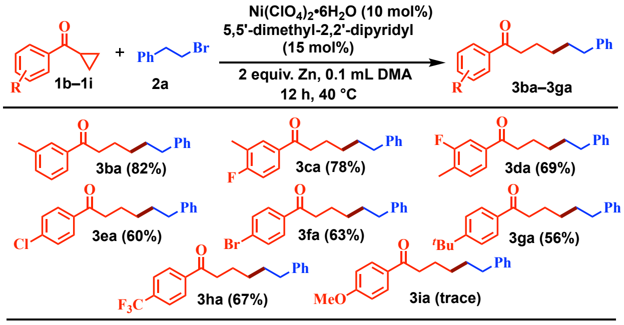
Scheme 3. Substrate Scope of Alkyl Bromides[a]



[a]Reactions performed on a 0.1 mmol scale with **1a** (1.0 equiv.), **2** (2.5 equiv.), $Ni(ClO_4)_2 \cdot 6H_2O$ (10 mol %), bipy (15 mol %), DMA (0.5 M) under 80 °C for 12h. [b] 5,5'-dimethyl-2,2'-dipyridyl instead of bipy.

The scope of the aryl substituent of the aryl cyclopropyl ketone was subsequently examined under the modified conditions (Scheme 4). It is found that when the aryl was substituted with a 3-Me (**1b**), the target product **3ba** was obtained in 82% yield. Disubstituted aryl groups 4-fluoro-3-methylphenyl and 3-fluoro-4-methylphenyl afforded coupling products **3ca** and **3da** in 78% and 69% yield, respectively. Ketones supporting 4-Cl, and 4-Br successfully participated to generate, 60 and 63% yields of the halogenated products. The 4-*tert*-butyl-containing substrate provided **3ga** in 56% yield. In addition, when cyclopropyl(4-(trifluoromethyl)phenyl)methanone **3h** was used as coupling partner, the target product **3ha** was generated in 67% yield. However, cyclopropyl(4-methoxyphenyl)methanone **3i** exhibited poor reactivity, producing only trace product.

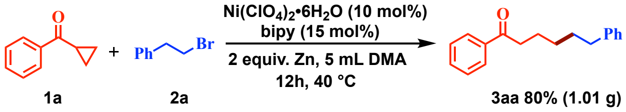
Scheme 4. Substrate Scope of Aryl Cyclopropyl Ketones [a]



[a]Reactions performed on a 0.1 mmol scale with **1** (1.0 equiv.), **2a** (2.5 equiv.), $Ni(ClO_4)_2 \cdot 6H_2O$ (10 mol %), 5,5'-dimethyl-2,2'-dipyridyl (15 mol %), DMA (0.5 M) under 80 °C for 12h.

To test the scalability of this transformation, 5.0 mmol of cyclopropyl phenyl ketone **1a** was coupled with (2-bromoethyl)benzene **2a** under the standard conditions (Scheme 5). The desired cross-coupling product **3aa** was isolated in 80% yield (1.01 g).

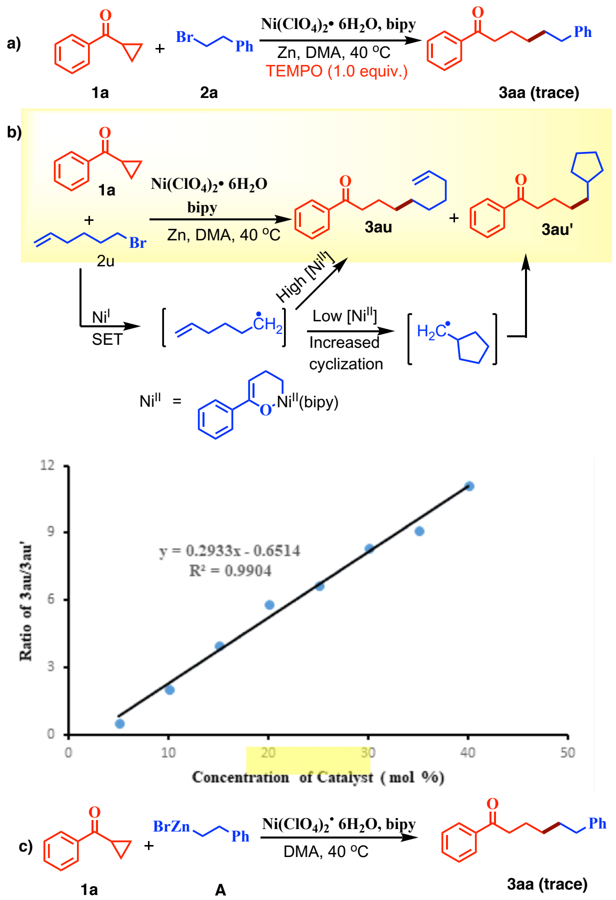
Scheme 5. Scale-up to 5.0 mmol.



To provide insight into the reductive cross-coupling reaction mechanism, several control experiments were performed (Scheme 6). When the radical scavenger TEMPO was added to the standard reaction conditions,[15] the product **3aa** was formed in only trace amounts (Scheme 6a). This result caused us to speculate that the reaction might proceed through radical intermediates. We explored the coupling with a substrate bearing a pendent olefin as a radical trap.[16] Cyclopropyl phenyl ketone (**1a**) and 5-hexenyl bromide (**2u**) were examined at various catalyst loadings. The idea is that if the reaction involves radical intermediates, lower loadings of the catalyst will decrease the rate of capture of the originally formed primary radical, resulting in increased cyclized product. As the loading of catalyst is increased, the rate of capture of the original primary radical before cyclization will also rise. When the Ni loading was increased from 5 mol % to 40 mol % (with concomitant increase of bipy), we observed the ratio of directly cross-coupled product **3au** to the cyclized product **3au'** increased linearly with catalyst loading (Scheme 6b). This relationship is consistent with a radical intermediate. (see the Supporting Information for full details, Supplementary Table S5)

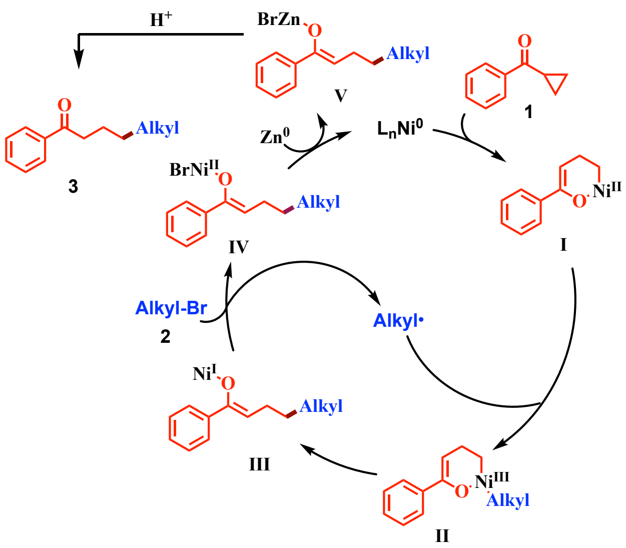
Finally, in order to exclude the possibility of an organozinc intermediate in the reaction system, phenethylzinc bromide **A** (1.0 M) was synthesized[17] and subjected to the cyclopropyl phenyl ketone (**1a**) in the absence of zinc powder (Scheme 6c). Only trace cross-coupled product **3aa** was observed. Taken together, these observations lead us to propose that the activation of the alkyl bromide likely involves a single electron transfer (SET) process. These results stand in contrast to the observations by Wang and co-workers, which suggest that in MeOH solvent and a different Ni catalyst, the alkyl bromide is activated by a 2-electron process.[14]

Scheme 6. Mechanistic Studies



On the basis of these studies, a proposed mechanism is described in Scheme 7. Ni^0 oxidatively adds cyclopropyl phenyl ketone **1** giving a six-membered cyclic Ni(II) species (**I**).[13-14] Next, oxidative capture of the alkyl radical affords the Ni^{III} species (**II**), which undergoes reductive elimination to forge the C–C bond and form a Ni^{I}-enolate species (**III**). The Ni(I) intermediate (**III**) initiates single-electron transfer (SET) with alkyl bromide **2** to generate alkyl radical and a Ni^{II} species (**IV**). Finally, the Ni^{II} intermediate **IV** is reduced by Zn^0 powder to regenerate Ni^0 and the zinc–enolate product **V**. Acidic workup liberates the cross-coupled ketone product **3**.

Scheme 7. Proposed Mechanism



In summary, we have developed a nickel-catalyzed reductive cross-coupling of γ-metallated ketones with unactivated alkyl bromides. This method can provide various γ-alkylated ketones in good to excellent yields. In addition, this transformation avoids use of preformed organometallic reagents. Initial mechanistic studies indicate that the reaction proceeds via an alkyl radical. Further efforts to expand the nickel-catalyzed reductive cross-coupling strategy are currently under investigation in our laboratories.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Supporting Information. (Experimental details, characterization data and NMR spectra)

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Notes

The authors declare no competing financial interest.

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