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# Nickel-catalyzed $\gamma$ -alkylation of cyclopropyl ketones with unactivated primary alkyl chlorides: balancing reactivity and selectivity via halide exchange†

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A novel method was developed for synthesizing  $\gamma$ -alkyl ketones via nickel-catalyzed cross-electrophile coupling of cyclopropyl ketones and non-activated primary alkyl chlorides. High reactivity and selectivity can be achieved with sodium iodide as a crucial cocatalyst that generates a low concentration of alkyl iodide via halide exchange, thus avoiding the formation of alkyl dimers. This reaction possessed excellent regioselectivity and high step economy circumventing *in situ* or pregenerated organometallics.

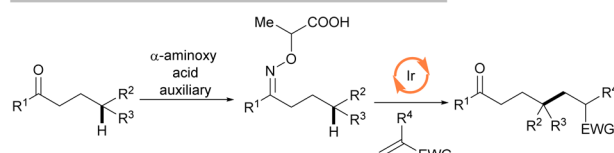
Ketones are among the most versatile and fundamental functional groups in organic synthesis, widely present in natural products, pharmaceuticals, and materials.<sup>1</sup> More efforts have been committed to developing novel and efficient synthetic ketone methods over the past decades.<sup>2</sup> The emergence of cross-electrophile coupling reactions provided a turning point for synthesizing ketones.<sup>3</sup> A large number of commercially available coupling reagents were exploited, significantly increasing the substrate range of the ketones and avoiding the use of low abundance starting materials. While progress in the synthesis of ketones has been obtained to a certain extent, modifying the remote sites of ketones, specifically those bearing  $\gamma$ -substitutions, remains challenging. Only limited examples of the highly stereoselective synthesis for  $\gamma$ -functionalized ketones have been reported. For example, Studer *et al.*<sup>4</sup> developed a photoredox-catalyzed  $\gamma$ -C(sp<sup>3</sup>)-H functionalization of ketones using the stoichiometric  $\alpha$ -aminoxy propionic acid as an auxiliary (Scheme 1A). Thus, developing new coupling partners without auxiliaries directly to prepare the  $\gamma$ -functionalized ketones is still highly desirable.

Cyclopropyl ketones serve as valuable building blocks, readily attainable from diverse initial substrates,<sup>5</sup> facilitating the synthesis of  $\gamma$ -functionalized ketone molecules via ring-opening reactions.<sup>6</sup>

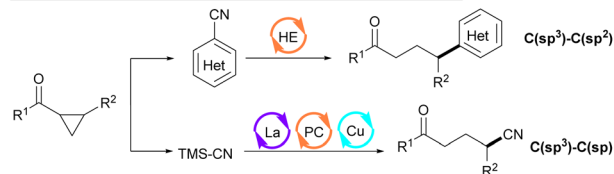
In this vein, Opatz and co-workers developed a Hantzsch ester-mediated synthesis of  $\gamma$ -hetarylketones starting from cyclopropyl ketones.<sup>7</sup> Furthermore, Xiao groups found a triple

catalytic system merging photoredox catalysis with Lewis acid and copper catalysis, which fulfilled the ring-opening cyanation reaction of cyclopropyl ketones with TMS-CN (Scheme 1B).<sup>8</sup> However, all these reactions are constrained to affording the C(sp<sup>3</sup>)-C(sp<sup>2</sup>) or C(sp<sup>3</sup>)-C(sp) bond formation. Therefore, a general and efficient procedure for C(sp<sup>3</sup>)-C(sp<sup>3</sup>) bond

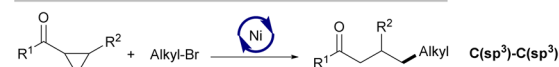
### A) Photoredox-catalyzed $\gamma$ -C(sp<sup>3</sup>)-H functionalization of ketones



### B) The synthesis of $\gamma$ -aryl/CN ketones using cyclopropyl ketones

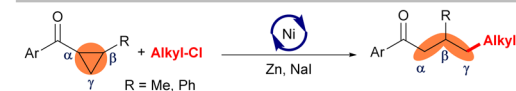


### C) The synthesis of $\gamma$ -alkyl ketones using cyclopropyl ketones



Challenge: unactivated alkyl chlorides can't work

### D) This work: $\gamma$ -Alkylation of cyclopropyl ketones with primary alkyl chlorides



- High regioselectivity  $\gamma$ -alkylation
- Overcoming dimerization of alkyl halides
- Readily available alkyl chlorides
- C(sp<sup>3</sup>)-Cl bond activation via halide exchange

 Scheme 1 Synthesis of the  $\gamma$ -substituted ketones.

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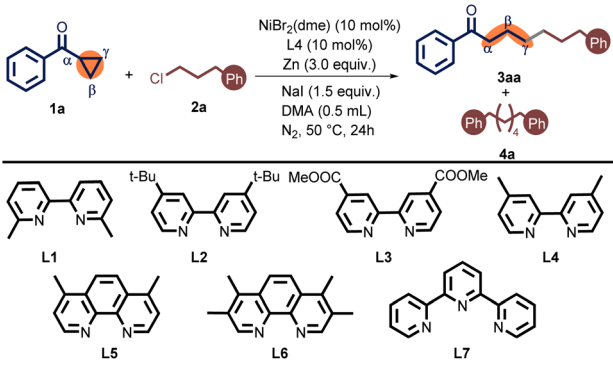


formation by the ring opening reactions of cyclopropyl ketones is still highly demanded.

Recently, nickel-catalyzed reductive ring opening reaction of cyclopropyl ketones with alkyl bromides was independently reported by Wang and Mao groups.<sup>9</sup> The above two works elucidate the activation mechanism of alkyl bromide through a two-electron process or a single electron transfer (SET) process, wherein the alkyl chloride moieties exhibit notable tolerance (Scheme 1C). Considering alkyl chlorides as versatile building blocks in organic synthesis due to their commercial availability and chemical stability,<sup>10</sup> we wish to develop the ring opening reactions of cyclopropyl ketones with non-activated alkyl chlorides to synthesize  $\gamma$ -alkyl ketones. The main challenge to realizing this transformation was balancing alkyl-Cl bond reactivity and cross-selectivity.<sup>11</sup> There is a pressing need to develop a highly efficient catalytic system with mild reaction conditions to overcome the dual reactivity-selectivity challenge of unactivated alkyl chlorides. Herein, we show that this can be accomplished by halide exchange to generate a low concentration of more reactive alkyl iodides from the alkyl-Cl starting material, thereby avoiding the formation of alkyl dimers (Scheme 1D).

We first conducted the optimized conditions for the  $\gamma$ -alkylation of cyclopropyl phenyl ketone **1a** with Phenylpropyl chloride **2a** (Table 1). As a result, 10 mol% NiBr<sub>2</sub>(dme), and 10 mol% 4,4'-dimethyl-2,2'-bipyridine (**L4**) were employed in the presence of 3 equiv. of Zn powder and 1.5 equiv. of sodium iodide (NaI) in *N,N*-dimethylacetamide (DMA) at 50 °C for 24 h. Under these conditions, 1,7-diphenylheptan-1-one (**3aa**) was obtained in 72% isolated yield. Meanwhile, we detected the byproduct of alkyl homo-coupling (**4a**) in 7% of GC yield (entry 1). Initially, the 6,6'-dimethyl-2,2'-bipyridine ligand **L1** was ineffective for this reaction (entry 2). When electron-rich bipyridine ligand **L2** was employed instead of **L4**, the yield of **3aa** was only slightly decreased (entry 3). Furthermore, the electron-poor bipyridine ligand **L3** also turned out to be inappropriate (entry 4). Compared to bipyridine ligands, phenanthroline ligands **L5** and **L6** exhibited a propensity for greater alkyl dimerization. The enhanced yield observed with the **L6** was attributed to its electronic effect (entries 5 and 6). When using terpyridine **L7** as a ligand, no cross-coupling product was observed, but it was accompanied by a significant dimer byproduct (entry 7). Overall, the choice of the ligand had an unneglectable impact on the outcome distribution (See Table S1 in the ESI† for full details). When switching the catalyst from NiBr<sub>2</sub>(dme) to NiCl<sub>2</sub>(dme) or NiCl<sub>2</sub>, the desired product was afforded a lower yield (entries 8–10). The reaction using NiBr<sub>2</sub> gained a terrible result (entry 9) (See Table S2 in the ESI†). Reducing the amount of NaI to 50 mol% resulted in a sharply decreased yield (entry 11). Notably, the target coupling product **3aa** was not generated when this reaction was conducted without NaI (entry 12). The catalyst loading can be reduced by 5 mol%, diminishing the reaction yield (entry 13). Employing Mn instead of Zn gave an inferior outcome (entry 14). Lessening the temperature from 50 °C to r.t. produced **3aa** only in 29% yield (entry 15). Raising the temperature to 80 °C resulted in a trace amount of the desired product (entry 16).

Table 1 Screening of optimal reaction conditions<sup>a</sup>



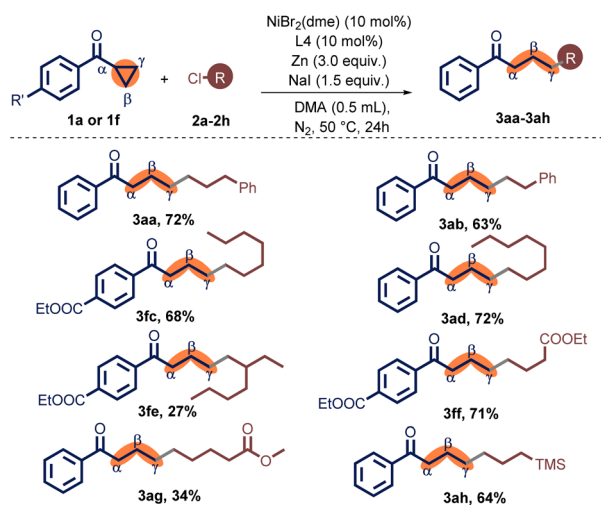
Entry	Variations from standard conditions	<b>3aa</b> <sup>b</sup> (%)	<b>4a</b> <sup>b</sup> (%)
1	None	78 (72) <sup>c</sup>	7
2	<b>L1</b> instead of <b>L4</b>	N.D.	N.D.
3	<b>L2</b> instead of <b>L4</b>	74	5
4	<b>L3</b> instead of <b>L4</b>	21	18
5	<b>L5</b> instead of <b>L4</b>	23	19
6	<b>L6</b> instead of <b>L4</b>	61	15
7	<b>L7</b> instead of <b>L4</b>	N.D.	36
8	NiCl <sub>2</sub> (dme) instead of NiBr <sub>2</sub> (dme)	67	8
9	NiBr <sub>2</sub> instead of NiBr <sub>2</sub> (dme)	20	13
10	NiCl <sub>2</sub> instead of NiBr <sub>2</sub> (dme)	61	11
11	NaI (50 mol%) was used	33	2
12	W/O NaI	0	0
13	5 mol% catalyst loading	30	26
14	Mn instead of Zn	31	22
15	At r.t.	29	3
16	At 80 °C	Trace	29

<sup>a</sup> Unless otherwise specified, the reactions were carried out in a Schlenk tube under nitrogen in the presence of **1a** (0.2 mmol), **2a** (0.4 mmol), NiBr<sub>2</sub>(dme) (10 mol%), **L4** (10 mol%), NaI (1.5 equiv.), and Zn (3.0 equiv.) in DMA (0.5 mL) at 50 °C for 24 h. <sup>b</sup> Yields are corrected GC yields vs. hexadecane internal standard. <sup>c</sup> Yields of the isolated product through column chromatography. N.D. = not detected.

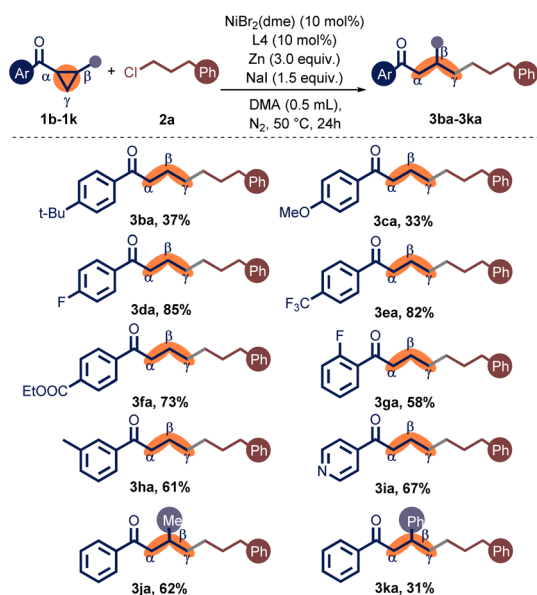
We also tested the influence of other reaction parameters, including the use of different additives, solvents and concentrations, but these studies did not lead to an improvement on the conditions in Table 1, entry 1 (see the ESI† for full details).

With optimized reaction conditions, a range of non-activated primary alkyl chlorides were examined for the coupling reaction with **1a** or **1f**, furnishing a series of  $\gamma$ -alkylated ketones **3aa–3ah** (Table 2). In the synthesis of the relatively longer-chain product **3aa**, it was found that the coupling product was obtained with a satisfactory yield. In contrast, a shorter-chain alkyl substrate was converted to **3ab** in a moderate yield. Simple unsubstituted alkyl chlorides turned out to be an appropriate substrate. *n*-Alkyl chlorides containing alkyl chains with seven or eight carbon atoms, 1-chloroheptane (**2c**) and 1-chlorooctane (**2d**), the relevant products **3ac** and **3ad** were delivered in 68% and 72% yield, respectively. Alkyl chloride with branching, chloroiso-octane (**2e**), also provided the target yield, albeit in a 27% output. Other functional groups, such as ester (**3af**, **3ag**) and trimethylsilyl (**3ah**), were well tolerated.



Table 2 Substrate scope with regard to alkyl chlorides<sup>a</sup>

<sup>a</sup> Unless otherwise specified, the reactions were carried out in a Schlenk tube under nitrogen in the presence of **1a** (0.2 mmol), **2a** (0.4 mmol), NiBr<sub>2</sub>(dme) (10 mol%), L4 (10 mol%), NaI (1.5 equiv.), and Zn (3.0 equiv.) in DMA (0.5 mL) at 50 °C for 24 h.

Table 3 Substrate scope with respect to cyclopropyl ketone<sup>a</sup>

<sup>a</sup> Unless otherwise specified, the reactions were carried out in a Schlenk tube under nitrogen in the presence of **1a** (0.2 mmol), **2a** (0.4 mmol), NiBr<sub>2</sub>(dme) (10 mol%), L4 (10 mol%), NaI (1.5 equiv.), and Zn (3.0 equiv.) in DMA (0.5 mL) at 50 °C for 24 h.

Next, we explored the substituents on the phenyl ring of the aryl cyclopropyl ketones (Table 3). Initially, we discovered that electron-donating tertiary butyl and methoxy groups on the *para* position of the benzene ring provided the products **3ba**–**3ca** in low yields. Gratifyingly, electron-withdrawing CF<sub>3</sub>, F, and ester substituents on the *para* position of the benzene ring were well

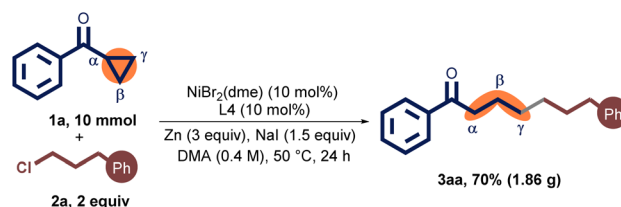
accommodated, and the products **3da**–**3fa** were delivered in 73–85% yields. In contrast, when the aryl group was substituted with 3-methyl, the target product **3ha** was obtained in a moderate yield. Remarkably, the 2-substituted phenyl cyclopropyl ketone (**1g**) provided a medium yield compared to the 4-substituted one (**1d**). To our delight, the pyridinyl cyclopropyl ketone was also well accommodated, producing the coupling products **3ia** in 67% yield. In addition, *trans*-disubstituted cyclopropanes (**1j**, **1k**) were pertinent precursors, albeit the more significant steric hindrance can cut the yield. Unfortunately, alkyl-substituted cyclopropyl ketones were unreactive in this reaction.

Moreover, the reaction was performed on a 10 mmol scale of **1a** under standard conditions (Scheme 2). The product **3aa** was also successfully isolated in 70% yield (1.86 g) that did not necessitate an extended reaction time, demonstrating the scalability of this transformation.

To further understand the reaction mechanism, several control experiments were performed (Scheme 3). First, when an alkyl bromide **2i** or alkyl iodide **2j** was employed instead of **2a**, **3aa** was obtained in only 9% or 3% yield, along with dimer product **4a** in 89% or 75% yield during the standard reaction conditions (Scheme 3A).<sup>12</sup>

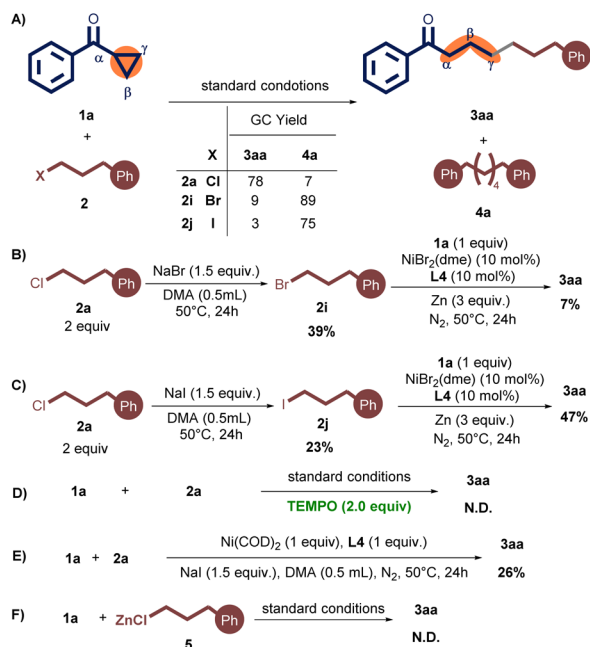
Next, the reaction between **2a** with NaBr (1.5 equiv.) produced **2i** in 39% yield, which upon reaction with **1a** under standard conditions produced **3aa** in a yield of only 7% (Scheme 3B). Analogously, employing NaI (1.5 equiv.) in the reaction of **2a** afforded **2j** in 23% yield. The ensuing reaction of **2j** with **1a** under standard conditions resulted in a 47% yield of **3aa** (Scheme 3C).<sup>13</sup> More importantly, the cross-coupled product **3aa** was not observed without NaI (Table 1, entry 12). These experiments showed that NaI as a crucial cocatalyst in this reaction likely serves a dual role: (1) generating a low concentration of more reactive alkyl iodides through halide exchange, thereby effectively suppressing the formation of alkyl dimers,<sup>11,14</sup> and (2) enhancing the reductive coupling process may be attributed to its potential facilitation of either the reduction of the nickel catalyst or the formation of a more reactive nickelate species.<sup>14,15</sup>

Furthermore, the radical scavenger 2,2,6,6-Tetramethylpiperidine 1-oxyl (TEMPO) was added under the standard reaction conditions, and the desired product **3aa** was not detected (Scheme 3D). This result suggests that the radical pathway may be involved in this protocol. In addition, in the presence of 1.0 equiv. of Ni(COD)<sub>2</sub>, the corresponding product **3aa** could be yielded in 26%, indicating the coupling started with Ni(0)



Scheme 2 Gram-scale experiment.

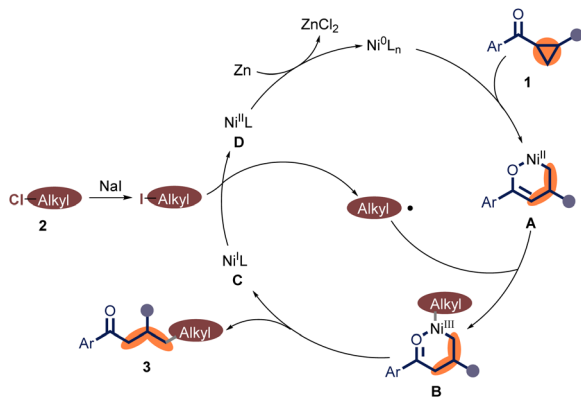




Scheme 3 Control experiments.

species (Scheme 3E).<sup>16</sup> Finally, phenethylzinc chloride **5** (0.25 M)<sup>17</sup> was synthesized and subjected to the reaction with **1a** in the absence of zinc powder (Scheme 3F). These experimental results support that excludes the possibility of an organozinc reagent in the reaction system.

Based on previous reports<sup>9,13,18</sup> and these control experiments, a proposed mechanism was shown in Scheme 4. Initially, the oxidative addition of aryl cyclopropyl ketone **1** to Ni(0) produces Ni(II) species **A**, which reacts with an alkyl radical to form Ni(III) species **B**. In the next step, intermediate **B** undergoes reductive elimination to generate the target product  $\gamma$ -alkyl ketones and the Ni(I) species **C**. Subsequently, the reaction of Ni(I) species **C** with alkyl iodide (formed *via* the halide exchange between the alkyl chloride **2** with NaI) affords the alkyl radical and the Ni(II) intermediate **D**. Finally, Ni(0) species is regenerated for the next catalytic cycle through reduction.



Scheme 4 Proposed possible mechanism.

## Conclusions

In conclusion, we have developed a nickel-catalyzed  $\gamma$ -alkylation reaction of aryl cyclopropyl ketones with non-activated preliminary alkyl chlorides, providing efficient chemo- and regioselectivity for cross-coupling products using halide exchange. Further efforts are currently under investigation in our labs regarding to the role of sodium iodide in the reaction process.

## Author contributions

Zheng-Ying Wang: experimental design and optimization, data curation, writing-original draft; Zheng-Ying Wang, Shi-Zheng Liu and Qiang Li: subject selection and writing-review & editing; Cong Guo and Yi-Zheng Cheng: validation; Qiang Li: supervision; Qiang Li, Jianmin Dou, and Dacheng Li: funding acquisition, project administration. All authors read and approved the final manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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