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From Alkyl Halides to Ketones: Nickel-Catalyzed Reductive Carbonylation Utilizing Ethyl Chloroformate as a Carbonyl Source

Renyi Shi[a] and Xile Hu*[a]

Abstract: Ketones are an important class of molecules in synthetic and medicinal chemistry. Rapid and modular synthesis of ketones remains in high demand. Here we describe a nickel-catalyzed three-component reductive carbonylation method for the synthesis of dialkyl ketones. A wide range of both symmetric and asymmetric dialkyl ketones can be accessed from alkyl halides and a safe CO source, ethyl chloroformate. Our approach offers complementary substrate scope to existing carbonylation methods while avoiding the use of toxic CO or metal carbonyl reagents.

Ketone is an recurring moiety in numerous natural products, pharmaceutical molecules (Figure 1a) and materials.[1] Ketones are also ubiquitous synthetic intermediates in chemical synthesis. The synthesis of ketone is a cornerstone of modern organic chemistry. Classic methods are based on transformations of pre-existing functional groups, for example, oxidation of alcohols and conversion of carboxylic acid derivatives.[1-2] Transition-metal-catalyzed carbonylative cross-coupling is an attractive alternative because a diverse set of ketones can be rapidly assembled from smaller building blocks (Figure 1b).[3] Nevertheless, carbonylative cross-coupling suffers from several limitations: (i) the methodology works well for the synthesis of aryl ketones, but not alkyl ketones. Like in conventional cross-coupling,[4] the reactions of alkyl electrophiles in carbonylative cross-coupling is problematic due to β-H elimination. (ii) the carbonyl sources are mostly CO gas or metal carbonyl complexes, which are toxic and can be inconvenient to handle, although a few practical CO surrogates have been developed to mitigate this issue.[5] To address the first limitation, Ni-catalyzed reductive cross-coupling of alkyl halides with carboxylic acid derivatives has recently been developed to give dialkyl ketones (Figure 1b).[6] However, these reactions require carboxylic acid derivatives as reagents and are not well suited for the synthesis of symmetric dialkyl ketones. Here we describe a three-component, reductive coupling approach that complements the above-mentioned methods and overcome their limitations. Using Ni catalysis, we are able to prepare a wide range of both symmetric and asymmetric dialkyl ketones from two molecules of alkyl halides and ethyl chloroformate (ClCOOEt),[7] a safe and easy to handle CO source (Figure 1c).

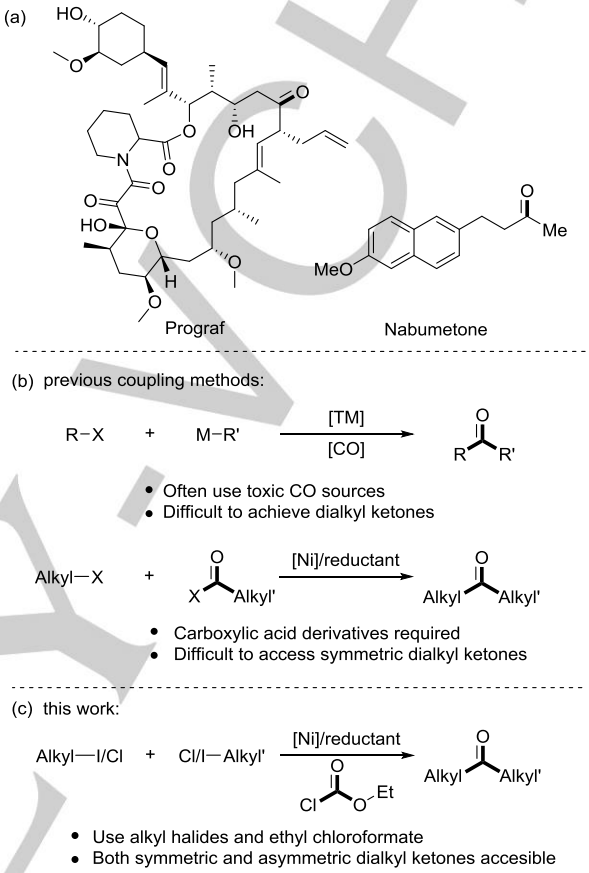

Figure 1. (a) Examples of bio-active ketones. (b) Previous cross-coupling type carbonylation methods. (c) Ni-catalyzed reductive carbonylation described in this work.

The three-component coupling of (3-iodopropyl)benzene (**1a**), iodocyclohexane (**2a**), and ClCOOEt was used as the test reaction (Table 1). After optimization (Figure S1-S8, SI), the optimized conditions were: $NiBr_2$·Diglyme (10 mol%) as pre-catalyst, bipyridine (15 mol%) as ligand, Zn (4 equiv) as reductant, 1:2:2 ratio of (3-iodopropyl)benzene to iodocyclohexane to ClCOOEt, TMSCl (50 mol%) as activator of Zn, and THF/DMA (3/1; 2.0 mL) as solvent, and 40 °C as the reaction temperature. The desired product, 1-cyclohexyl-4-phenylbutan-1-one (**3a**), was obtained in 75% yield after 1h (entry 1, Table 1). Compound **4a and 4c**, the symmetric dialkyl ketones, were formed in 10% and 59% (relative to **1a**), respectively. Here **2a** was used in excess (2 equiv) to favor a high yield of asymmetric dialkyl ketone. If 1 equiv of **2a** was used, then the yields of **3a**, **4a**, and **4c** were 49%, 23%, 18%, respectively (entry 2, Table 1). If **1a** was used in excess (2 equiv), the yields of **3a**, **4a**, and **4c** (relative to **2a**) were 62%, 62%, 12%, respectively (entry 3, Table 1). There was no reaction without the nickel pre-catalyst (entry 4, Table 1). The yield was 69% with 10 mol% $NiCl_2$· dme as the pre-catalyst (entry 5, Table

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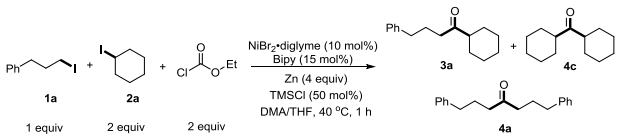
1). The reaction did not occur without Zn or Bipy (entries 6-7, Table 1). Without ClCOOEt, no carbonylative coupling but only alkyl-alkyl coupling products were detected (entry 8, Table 1). Without TMSCl the yield was only 10% (entry 9, Table 1). With THF or DMA as the sole solvent, the yield decreased greatly (entries 10-11, Table 1). Replacing Zn with Mn led to 14% yield (entry 12, Table 1). When the reaction was conducted at room temperature the yield was 70% (entry 13, Table 1).

Table 1. Summary of the effects of reaction parameters and conditions on the reaction efficiency[a]

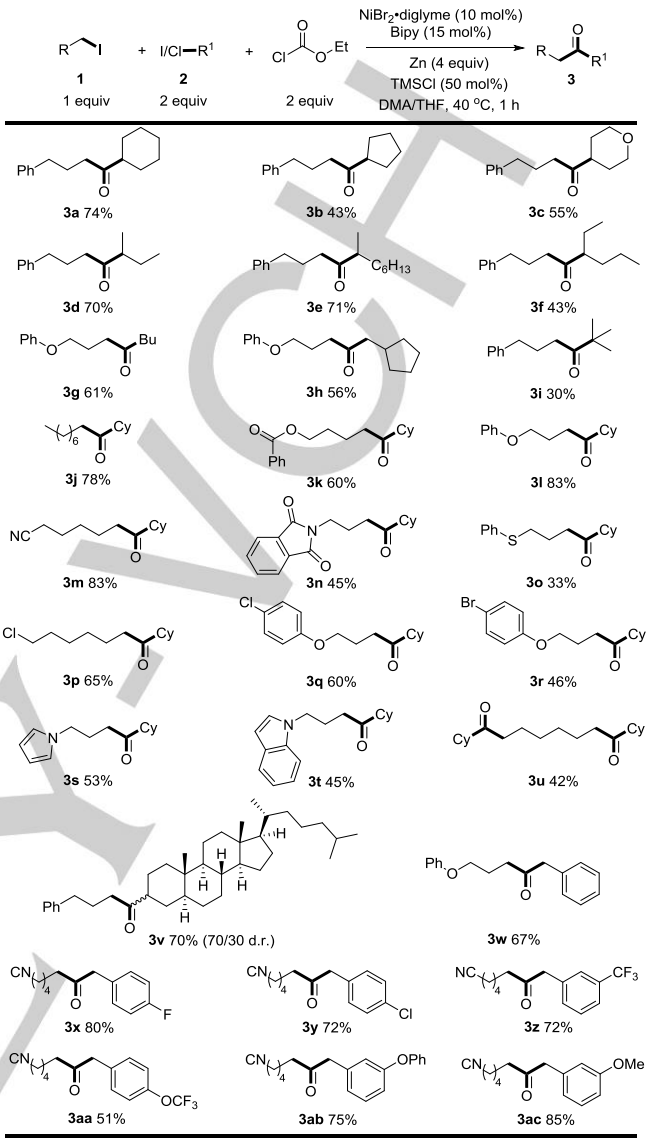


Entry	Variation from standard conditions[b]	Yield of **3a** (%)	Yield of **4a** (%)	Yield of **4c** (%)
1	None	75	10	59
2	**1a**/**2a** = 1/1	49	23	18
3	**1a**/**2a** = 2/1	62	62	12
4	No $NiBr_2$· diglyme	0	0	0
5	10 mol% $NiCl_2$ · dme instead of $NiBr_2$ · diglyme	69	6	61
6	No Zn	0	0	0
7	No Bipy	0	0	0
8	No ClCOOEt	0	0	0
9	No TMSCl	10	2	8
10	2.0 mL THF instead of THF/DMA	4	1	5
11	2.0 mL DMA instead of THF/DMA	31	2	37
12	Mn instead of Zn	14	3	8
13	Room temperature instead of 40 °C	70	6	65

[a] Yields determined by GC using *n*-dodecane as an internal standard.[b] The optimized reaction conditions were **1a** (0.2 mmol), **2a** (2 equiv), $NiBr_2$· diglyme (10 mol%), Bipy (15 mol%), ClCOOEt (2 eq.), TMSCl (50 mol%), Zn (4 eq.) THF 1.5 mL and DMA (0.5 mL), 1 hour, 40 °C.

The optimized conditions in table 1 were employed to synthesize a wide range of asymmetric dialkyl ketones (Table 2). Various secondary (cyclic and acyclic) and primary alkyl iodides could be coupled (**3a-3h**). Even a tertiary alkyl iodide was a viable coupling partner (**3i**), albeit in a low yield of 30%. The scope of primary alkyl iodides was explored using iodocyclohexane as a second partner (**3j**-**3u**). Alkyl groups containing ester, ether, cyano and amide groups were well tolerated (**3k**, **3l**, **3m** and **3n**). The carbonylative reductive coupling yield was only 33% for a thioether-containing substrate (**3o**), and some non-carbonylative C-C reductive coupling products were also formed (Figure S9, SI). The coordination of S to the Ni catalyst might be responsible for significant byproduct formation. Chloro and bromo groups were

Table 2 Nickel-catalyzed reductive carbonylative cross-coupling



[a] The reaction was carried out with **1** (0.2 mmol), **2** (2 equiv), $NiBr_2$· diglyme (10 mol%), Bipy (15 mol%), ClCOOEt (2 eq.), TMSCl (50 mol%), Zn (4 eq.), THF (1.5 mL) and DMA (0.5 mL), 1 hour, at 40 °C. Yield is that of the isolated product.

tolerated (**3p**, **3q** and **3r**), offering opportunities for subsequent functionalization. Substrates containing a heterocycle group such as pyrrole and indole were coupled in moderate yields (**3s** and **3t**). When a substrate containing two iodo groups, 1, 6-diiodohexane, was used, the double carbonylation product, 1, 8-dicyclohexyloctane-1, 8-dione (**3u**), was obtained in 42% yield. This protocol was suitable for the derivatization of a natural product, dihydrocholesterol, offering **3v** in 70% yield. Functional groups such as –COOH, -OH and N-Boc were unfortunately not tolerated. Benzyl chlorides were also suitable substrates (**3v-3ab**). Both electron-withdrawing groups such as F, Cl, CF_3 (**3w**, **3x** and **3y**) and electron donating groups such as OCF_3, OPh, and OMe (**3z**, **3aa** and **3ab**) were tolerated as a substituent in the aryl ring of the benzyl chlorides. When two different secondary alkyl iodides, i.e., cyclopentyl and cyclohexyl iodide, were used, the asymmetric dialkyl ketone was formed in 40% yield while a

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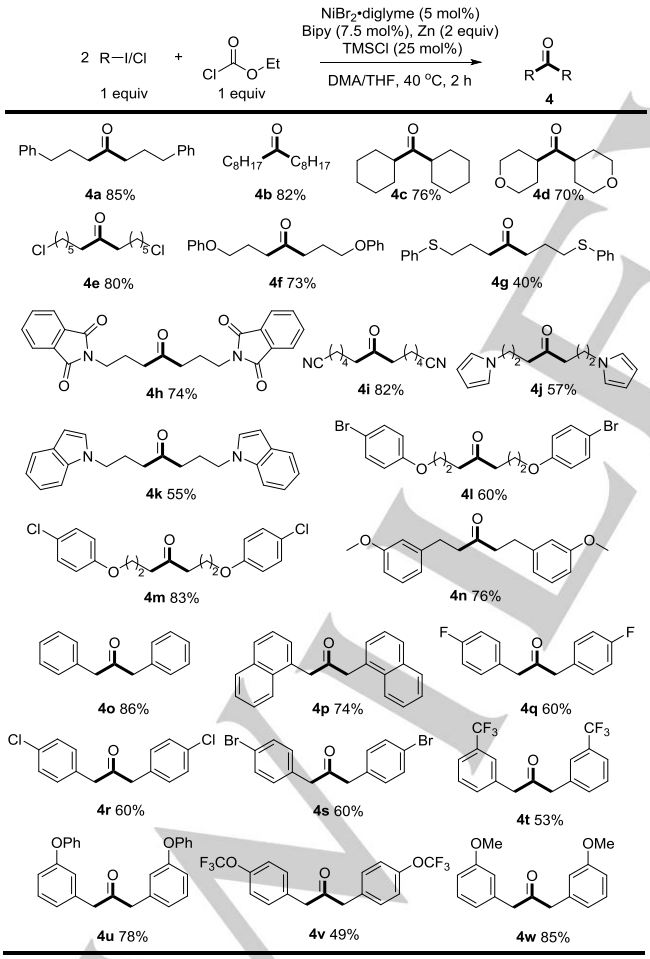
significant amount of symmetric dialkyl ketone byproducts were also formed (Figure S10, SI). When an aryl iodide or bromide was used as substrate, the desired asymmetric ketone was obtained in a low yield while many side products originated from C-C cross-coupling and homo-coupling were also formed (Figure S11, SI).

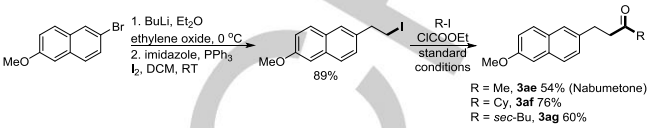
By using only one alkyl halide as coupling partner, the above method can be adapted for the synthesize of symmetric di-alkyl ketones (Table 3), which is less accessible using previous reported Ni-catalyzed reductive coupling of alkyl halides with carboxylic acid derivatives.[6a-f] Both primary and secondary alkyl halides could be used (**4a**-**4d**). Various functional groups such as chloro (**4e**), ether (**4f**), thioether (**4g**), amide (**4h**) and cyano (**4i**) were well tolerated. Heterocyclic functional groups such as pyrole (**4j**) and indole (**4k**) were also tolerated. Aryl-Cl and aryl-Br groups survived the reaction (**4l** and **4m**), which opened a possibility for subsequent coupling. 1, 5-bis(3-methoxyphenyl)pentan-3-one (**4n**), an important intermediate for the synthesis of chiral spiro-scaffolds,[8] was produced from 1-(2-iodoethyl)-3-methoxybenzene in 76% yield. Various benzyl chlorides, with either electron-withdrawing or electron-donating substituents, were also suitable substrates (**4o** to **4w**). Again benzyl chlorides with aryl-Cl and aryl-Br groups were selectively coupled (**4r** and **4s**).

Table 3. Nickel-catalyzed reductive carbonylative homo-coupling



[a] The reaction was carried out with alkyl iodides or benzyl chlorides (0.4 mmol), $NiBr_2$·diglyme (5 mol%), Bipy (7.5 mol%), ClCOOEt (1 eq.), TMSCl (25 mol%), Zn (2 eq.), THF (1.5 mL) and DMA (0.5 mL), 2 hours at 40 °C. Yield is that of the isolated product.

To illustrate its utility, the present carbonylation method was applied for the synthesis of Nabumetone, a non-steroidal anti-inflammatory drug.[9] The corresponding alkyl iodide reaction partner, 2-(2-iodoethyl)-6-methoxynaphthalene, was prepared from 2-bromo-6-methoxynaphthalene in one-pot and 89% yield. Carbonylation following the protocol in Table 2 gave Nabumetone in 54% yield (Scheme 1). Moreover, the same protocol furnished two other alkyl derivatives in high yields (Scheme 1)



Scheme 1. Application of the carbonylation method in the synthesis of Nabumtone and its analogues

The mechanism of this coupling is subject to a dedicated future study. Consistent with carbonylative coupling, a Ni carbonyl species should be a key intermediate. This intermediate is likely generated by first oxidative addition of ClCOOEt to a low-valent Ni center followed by decarbonylation, as proposed in an earlier report.[7] When hexadecyl chloroformate was used as a CO source, the carbonylative coupling also worked, and dihexadecyl carbonate was obtained as a byproduct (eq. 1, Figure 2). This result was consistent with Ni-mediated decarbonylation from hexadecyl chloroformate, which generated an alkyl alkoxide that was trapped by hexadecyl chloroformate. When the reaction was conducted using CO instead of ClCOOEt, the yield of **3a** was only 17% (Figure S12, SI). When of $Ni(bipy)(CO)_2$ (bipy = bipyridine) was used as the catalyst, the yield of **3a** was only 34% under standard conditions (Figure S13, SI). These results indicate that in-situ release of CO from ClCOOEt is advantageous probably by avoiding the formation of less active Ni-CO species. The activation of alkyl halide typically leads to radical intermediates. To confirm this, we conducted coupling reactions using radical-clock substrates (Figure 2). The coupling of 6-iodohex-1-ene led to both 1-cyclopentylhex-5-en-2-one and 1, 3-dicyclopentylpropan-2-one, with a ratio of 1:2 (eq. 2). The coupling of 6-iodohex-1-ene and (3-iodopropoxy)benzene gave a product that contains a cyclopentyl ring in 36% yield (eq. 3). The coupling of (iodomethyl)cyclopropane and (3-iodopropoxy)benzene gave 40% of 1-phenoxyoct-7-en-4-one in which the cyclopropyl ring was opened (eq. 4). These results confirmed the involvement of alkyl radicals in the coupling reactions.

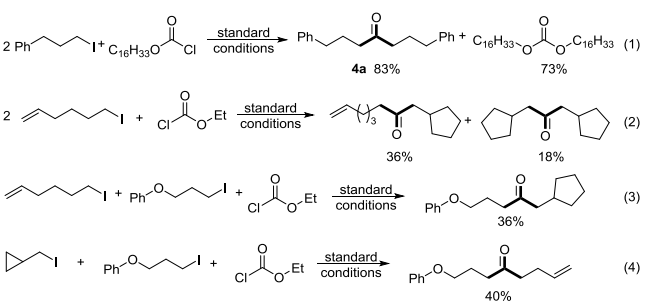


Figure 2. Mechanistic probes.

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The three-component coupling is selective for carbonylative cross-coupling of two different alkyl halides over carbonylative homo-coupling of the same alkyl halides (entries 1-3, Table 1). This selectivity is surprising because selective reductive cross-coupling was typically achieved using two different types of electrophiles, e.g., one alkyl halide and one aryl halide.[6d-f] Gong and co-workers reported examples of selective reductive cross-coupling of two alkyl halides, where the selectivity was partially achieved by using 3 equiv. of one alkyl halide.[10] In the present case, selectivity towards asymmetric dialkyl ketone was observed even when the two alkyl halides were in equal amount (entry 2, Table 1). To compare the reactivity of different alkyl halides, the reaction profiles of three reactions were monitored: the carbonylative cross-coupling reaction of **1a** and **2a** as in entry 2, Table 1 and the carbonylative homo-coupling reactions of **1a** or **2a** alone (Figure S14-16, SI). Under identical conditions, the primary alkyl iodide **1a** reacted slightly faster than the secondary alkyl iodide **2a**. The rate of formation followed the following order: **3a** > **4a** > **4c**. These observations might be explained by two different activation processes of alkyl halides, one favoring primary alkyl halide and one favoring secondary alkyl halides.

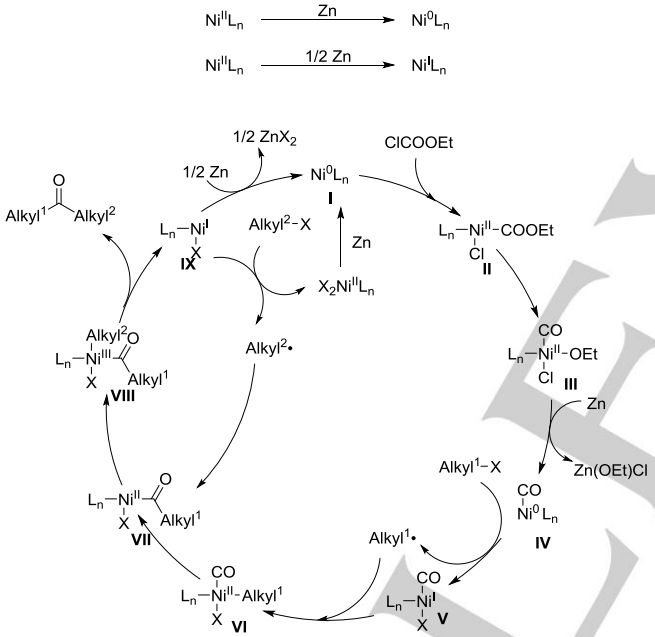

Figure 3. Proposed mechanism.

According to the above results and considerations, we propose a tentative mechanism (Figure 3). The Ni catalyst precursor is reduced to Ni^{I} and Ni^{o} species by Zn. Oxidative addition of ClCOOEt to Ni^{0} affords a Ni^{II} species **II**, which undergoes decarbonylation to give a Ni^{II} carbonyl species **III**. Reduction of **III** by Zn gives a Ni^{0} carbonyl species **IV**. Activation of an alkyl halide by **IV** through a radical process[11] gives eventually a Ni^{II} alkyl carbonyl intermediate **VI**, which upon CO insertion forms a Ni^{II} acyl complex **VII**. Meanwhile in a separate process a Ni^{I} species activates another alkyl halide to give an alky radical, which can be trapped by **VII** to give a Ni^{III} alkyl acyl species **VIII**. Reductive elimination from the latter furnishes the ketone product and regenerates a Ni^{I} species **IX**. Because we observe little if any non-carbonylative alkyl-alkyl coupling, the activation of an alkyl halide by the Ni^{0} CO species (**IV**) and the subsequent CO insertion to give **XII** should be faster than the activation of the second alkyl halide by an Ni^{I} species (e.g., **IX**). In the former process, a primary alkyl halide might be more active than a secondary alkyl halide due to sterics. In the later process, a secondary alkyl halide might be more active than a primary alkyl halide due to thermodynamics. The net result is the selectivity towards an asymmetric dialkyl ketone product. Alternatively, the insertion of CO into a secondary alkyl group is faster than the analogous insertion into a primary alkyl group. The resulting acyl species (**VII**) reacts faster with a primary alkyl radical than with a secondary alkyl radical, which leads to the selectivity towards an asymmetric dialkyl ketone product.

In conclusion, we have developed a nickel-catalyzed reductive carbonylation method to synthesize a wide range of both symmetric and asymmetric dialkyl ketones from readily available alkyl halides and a safe CO source, ethyl chloroformate. These carbonylation reactions occur under mild reaction conditions and have broad scope and high functional group tolerance. The method provides a valuable complement to existing approaches in the synthesis of ketones, which are ubiquitous synthetic intermediates and bio-active compounds.

Acknowledgements

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Keywords: ketone synthesis • reductive coupling • nickel catalysis • carbonylation •alkyl halides

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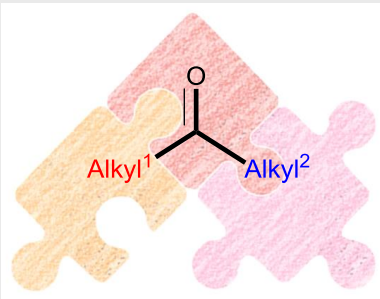
Nickel-catalyzed three-component coupling of alkyl halides and ethyl chloroformate can be used to prepare a wide range of unsymmetrical and symmetrical dialkyl ketones under mild conditions



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