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Authors: Troels Skrydstrup, Aske Donslund, Karoline Neumann, Nicklas Corneliussen, Ebbe Grove, Domenique Herbstritt, and Kim Daasbjerg

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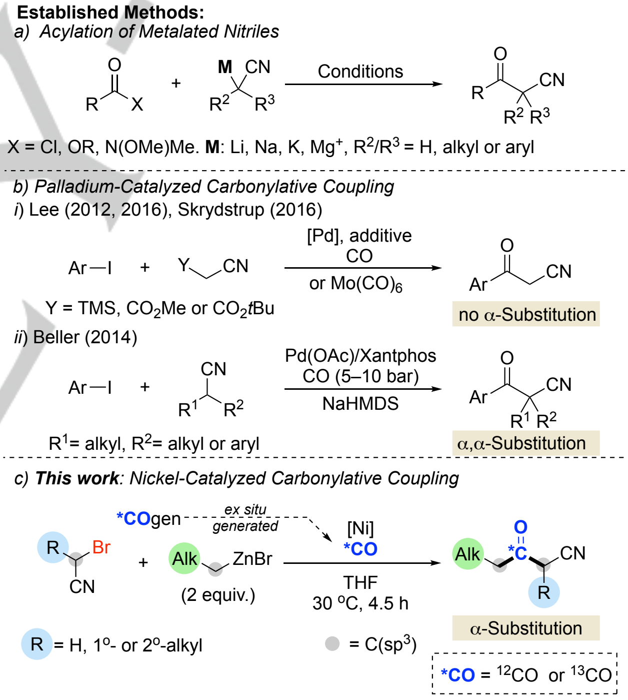
Access to β-Ketonitriles via Nickel-Catalyzed Carbonylative Coupling of α-Bromonitriles with Alkylzinc Reagents

Aske S. Donslund, Karoline T. Neumann, Nicklas P. Corneliussen, Ebbe K. Grove, Domenique Herbstritt, Kim Daasbjerg and Troels Skrydstrup*

Abstract: Herein, we report a nickel-catalyzed carbonylative coupling of α-bromonitriles and alkylzinc reagents with near stoichiometric carbon monoxide to obtain β-ketonitriles in good yields. The reaction is catalyzed by a readily available and stable nickel(II) pincer complex. The developed protocol tolerates substrates bearing a variety of functional groups, which would be problematic or incompatible with previous synthetic methods. Additionally, we demonstrate the suitability of the method for carbon isotope labeling by the synthesis of ^{13}C-labeled β-ketonitriles and their transformation into isotopically labeled heterocycles.

β-Ketonitriles serve as useful reactive precursors in organic synthesis.[1] Due to the relative position of the ketone and nitrile functionalities, this class of organic compounds has been exploited for the synthesis of numerous heterocycles, including isoxazoles,[2] pyrazoles,[3] pyrimidines,[4],[5] pyrans,[6] and thiazolidines,[7] representing important structural fragments of biologically active molecules. Furthermore, the enantioselective reduction of β-ketonitriles yields β-hydroxynitriles[8] that are common intermediates for the preparation of various pharmaceuticals, e.g. the antiparasitic agent, levamisole.[9]

Numerous protocols for the synthesis of β-ketonitriles have been developed, which still remains an active research area, including substitution of α-haloketones with cyanide or the electrophilic cyanation with nucleophilic carbon species.[10] The most direct approach relies on the acylation of metalated nitriles (Scheme 1a).[11] Nevertheless, a drawback of this well-established acylation method is the incompatibility of various electrophilic functionalities with the harsh anionic conditions, which is clearly reflected in the substrate scope. To achieve higher functional group tolerance, palladium-catalyzed carbonylative couplings have been developed as an alternative approach to β-ketonitriles. As reported by Lee and coworkers in 2012, the carbonylative coupling of aryl iodides and (trimethylsilyl)acetonitrile tolerates a number of sensitive functionalities including nitrile, carboxylate and ketone functionalities (Scheme 1b).[12] Additionally, the same group reported that methyl cyanoacetate and aryl iodides could be used for the synthesis of β-ketonitriles through a carbonylation-decarboxylation sequence.[13] In 2016, we reported a similar carbonylation-decarboxylation sequence using (hetero)aryl bromides and *tert*-butyl cyanoacetate as the coupling partners.[14] Common for these protocols is the limitation to aryl electrophiles generating 3-oxo-3-arylpropanenitriles, and all the obtained β-ketonitriles were unsubstituted on the α-position. With regard to the α-substitution, the group of Beller developed a carbonylative coupling of aryl iodides and alkyl nitriles yielding α,α-disubstituted products (Scheme 1b).[15] Conversely, due to the strong anionic conditions the functional group tolerance is diminished.



Scheme 1. Established methods for the synthesis of β-ketonitriles *via* a) acylation of metalated nitriles, b) palladium-catalyzed carbonylative cross couplings and c) nickel-catalyzed carbonylative cross coupling.

During the last 20 years, a plethora of Ni-catalyzed cross coupling protocols applying alkyl electrophiles have been reported.[16] Nevertheless, the corresponding three-component carbonylative version is rare, which can be ascribed to the possibility for generating the toxic and volatile $Ni(CO)_4$, or catalytically inactive nickel carbonyl species. Such difficulties were earlier observed by the groups of Ogoshi, Troupel and Weix, requiring slow CO release

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[*] Aske S. Donslund, Dr. Karoline T. Neumann, Nicklas P. Corneliussen, Ebbe K. Grove, Domenique Herbstritt and Prof. Dr. Troels Skrydstrup
Carbon Dioxide Activation Center (CADIAC), Department of Chemistry and the Interdisciplinary Nanoscience Center (iNANO), Aarhus University
Gustav Wieds Vej 14, 8000 Aarhus C (Denmark)
E-mail: ts@chem.au.dk

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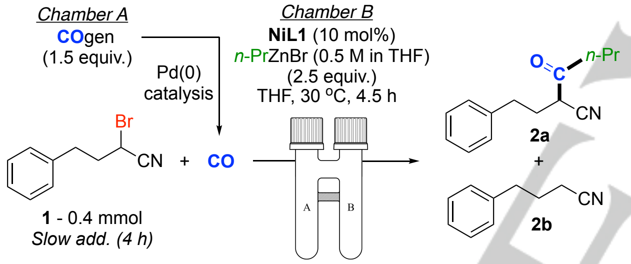
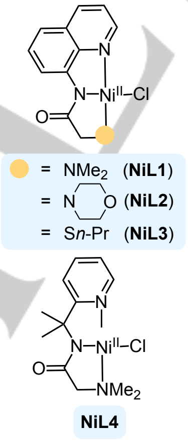
from carbon monoxide releasing molecules for successful carbonylative couplings.[17] Recently, the group of Hu published a nickel-catalyzed reductive carbonylation of alkyl halides using ethyl chloroformate as the CO source.[18]

In 2018, we reported the nickel(II)-catalyzed carbonylative coupling of benzyl bromides with alkylzinc reagents to produce benzyl alkyl ketones.[19] The method relies on the use of a nickel(II) pincer complex, which we proposed was essential for avoiding multiple CO binding to the metal center. Mechanistic investigations provided evidence for a radical based mechanism, and a Ni(II/III/I) catalytic cycle involving bimetallic oxidative addition.[20] Furthermore, for successful carbonylation, the system proved to be highly dependent on the pressure and release rate of CO, originating from COgen in the two chamber system COware,[21] which confirms the aforementioned sensitivity of nickel towards CO poisoning. In order to expand this chemistry, we envisioned that the nickel-catalyzed carbonylative protocol could be applied for the carbonylative coupling between α-bromonitriles and alkylzinc reagents to obtain 3-oxo-3-alkylpropanenitrile products (Scheme 1c). In this case, substitution on the α-position would be feasible and due to the mild conditions, it should be possible to tolerate a broader range of functionalities compared to the anionic acylation approach (Scheme 1a).

Table 1. Effect of reaction parameters and final optimization.[a]



Entry	Deviation from shown conditions	**2a**:**2b** ratio[b] (isolated yield%)
1	None	71(63):29
2	**NiL2**	0:100
3	**NiL4**	37:63
4	Slow add. 2 h	41:59
5	Slow add. 6 h	71:29
6	5 mol% **NiL1**	65:35
7	50 °C	60:40
8	PhZnBr in THF	0:100
9	2.0 equiv. *n*-PrZnBr	74(72):26
10[c]	**NiL3**	65:35
11	*n*-PrCN	68:32
12	Toluene	23:77
13	EtOAc	49:51
14	DMF	68:32

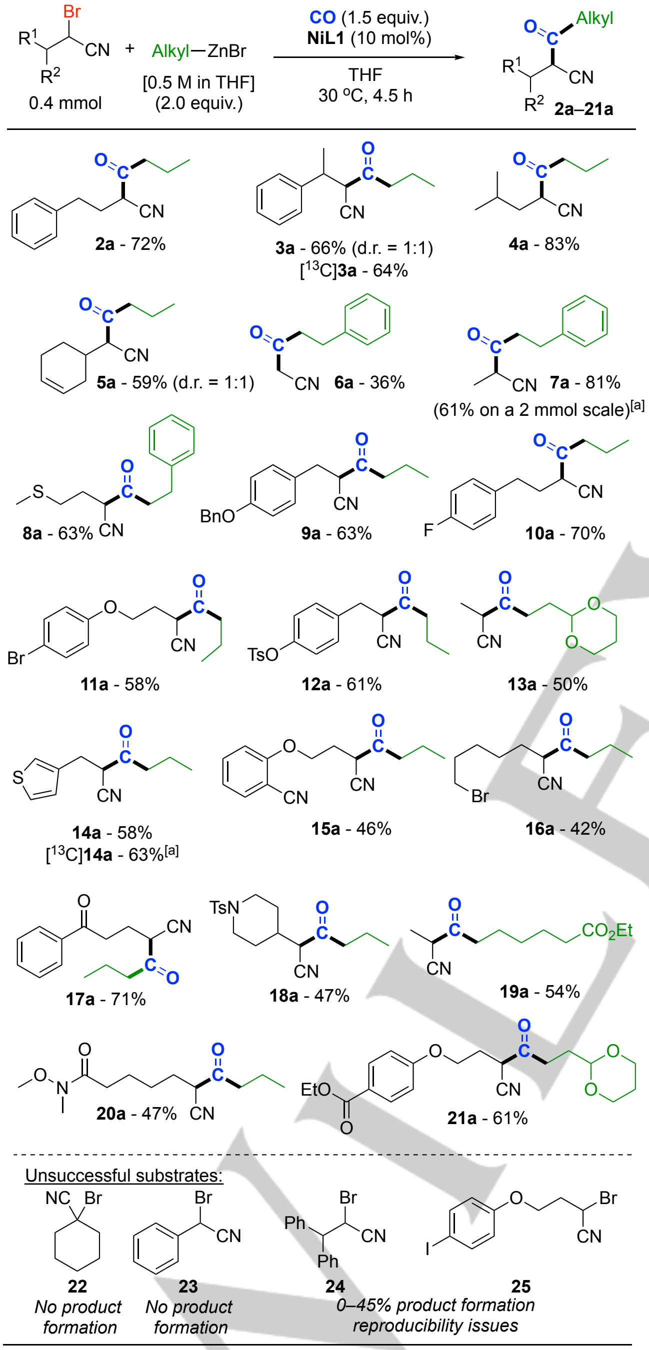


[a] All reactions were set up using a two-chamber reactor, COware® (See Supporting Information). [b] The ratio of **2a** and **2b** was determined by ^{1}H-NMR spectroscopy. Full conversion of **1** was observed for all entries. [c] 2.0 equiv. of *n*-PrZnBr were used. THF = Tetrahydrofuran. DMA = *N*,*N*-Dimethylacetamide.

Preliminary stoichiometric and catalytic reactions indicated that α-bromonitriles were suitable electrophiles for the nickel(II)-catalyzed carbonylative coupling. Optimization using α-bromonitrile **1** with *n*-propylzinc bromide and 1.5 equivalents of CO generated from COgen, led initially to ketone **2a** formation accompanied by the debromination adduct **2b** as the only two products. From a control experiment without the nickel catalyst and CO, **2b** was observed as the only product, possibly arising from a zinc-halide exchange between **1** and *n*-propylzinc bromide, followed by protonation during workup. A similar metal halide exchange with α-bromonitriles was reported by the group of Knochel with organomagnesium, -copper and -lithium species.[11e],[11f]

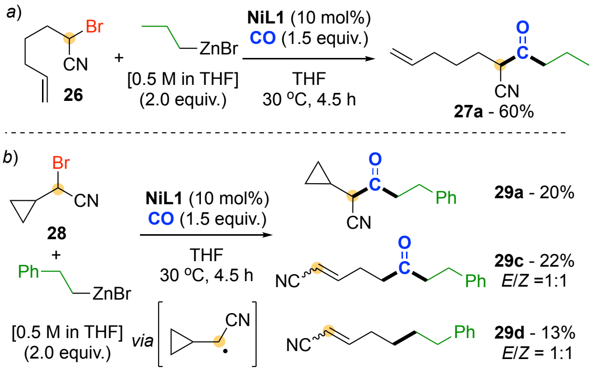
The impact of various reaction parameters and the final optimization is depicted in Table 1. The conditions displayed (entry 1) result in full conversion into the products **2a** and **2b** in a 71:29 ratio and **2a** was isolated in a 63% yield. Using **NiL2** instead of **NiL1** led to a complete shutdown of the catalytic reaction (entry 2), which might be the result of the increased bulk on the datively coordinating amine. **NiL4** with a pyridine instead of the quinoline motif proved to be an active catalyst, but produced a lower product selectivity compared to **NiL1**. If the addition rate of the bromide was doubled, the yield diminished (entry 4), whereas decreasing the addition rate resulted in an unaltered ratio of products (entry 5). Lowering the catalyst loading (entry 6) or increasing the reaction temperature (entry 7) only led to reduced yields. Unfortunately, access to 3-oxo-3-arylpropanenitrile products using PhZnBr proved ineffective (entry 8). It was discovered that the amount of *n*-propylzinc bromide added could be reduced to 2.0 equiv., which marginally improved the product ratio, and as such **2a** could be isolated in a 72% yield (entry 9). Switching to **NiL3** under similar conditions gave a slightly poorer ratio of **2a**:**2b** (entry 10). Other solvents were examined including, butyronitrile, toluene, ethyl acetate and DMF (entries 11–14), but no improvements in the selectivity of the reaction was observed. Lastly, it was shown that secondary alkylzinc reagents are not compatible with the optimized conditions. Employing cyclohexylzinc bromide only afforded the corresponding β-ketonitrile in a 5% isolated yield (see Supporting Information).

With acceptable reaction conditions in hand, we examined the scope and limitations of this Ni-catalyzed carbonylative cross coupling. Various unfunctionalized aliphatic α-bromonitriles were tolerated, leading to the formation of the corresponding β-ketonitriles **2a**–**4a**, **6a** and **7a** in modest to high yields. The difference in yields between entries **6a** and **7a**, 36% and 81% respectively, could be attributed to different putative radicals formed from 2-bromoacetonitrile and 2-bromopropionitrile. The α-bromonitrile containing an internal alkene underwent smooth transformation to the desired product **5a**. Additionally, the thio- and benzylether containing substrates were tolerated leading to the β-ketonitriles **8a** and **9a** in good isolated yields. A few aryl (pseudo)halides endured the reaction conditions, providing β-ketonitriles displaying an aryl fluoride (**10a**), aryl bromide (**11a**) and aryl tosylate (**12a**), allowing for further synthetic manipulation. Utilizing an acetal containing alkylzinc reagent and 2-bromopropionitrile as coupling reagents produced the intended β-ketonitrile **13a** in an acceptable 50% yield. A substrate containing a terminal alkyl bromide also proved to be compatible with the described method yielding the β-ketonitrile **16a** in a 42% yield. a product, which under conventional anionic conditions, might have cyclized. Furthermore, substrates possessing electrophilic functional groups including a nitrile, ketone, sulfonamide, carboxylate and carboxamide worked well under the standard conditions leading to compounds **15a** and **17a-21a**. The substrate displaying a thiophene ring transformed smoothly into the desired product **14a**, and by employing [^{13}C]-COgen as the CO source, ^{13}C-labeled **14a** could be isolated in a good yield. This, along with the formation of ^{13}C-**3a**, demonstrates the utility of the two-chamber system and the catalytic system for the convenient ^{13}C-labeling of β-ketonitriles. Some substrates, also proved to be unsuccessful. This included an aryl iodide containing α-bromonitrile **25**, as well as the more substituted and sterically hindered α-bromonitriles **22–24**.[22] In the case of compound **25**, we believe unproductive iodine abstraction may be taking place as earlier observed in our work on the Ni(II)-catalyzed carbonylative coupling of benzyl bromides (see also mechanistic discussion).[19] To conclude, we examined the possibility for scaling up this Ni-catalyzed transformation. As such in the synthesis of 7a, the reaction was run on a 2 mmol scale resulting in a 61% isolated yield of **7a** (see Supporting Information).



Scheme 2. Scope of the Ni(II)-catalyzed carbonylative coupling . The reactions were set up in an argon-filled glovebox using a two-chamber system (See Supporting Information for full details). The yields are isolated and are an average of two separate reactions unless otherwise stated. [a] The reaction was performed once.

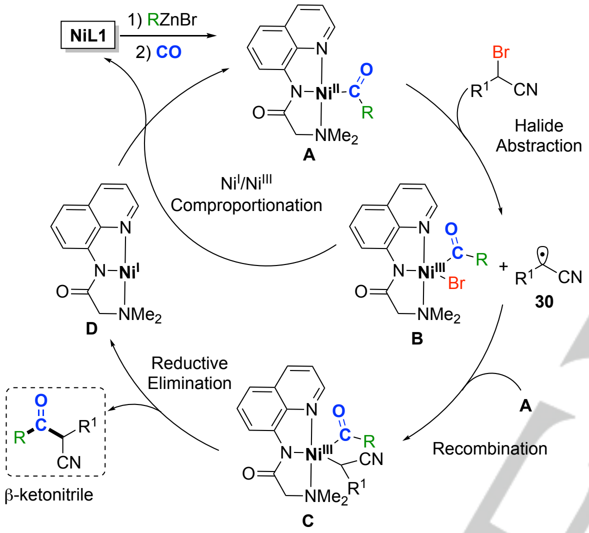
Having illustrated the applicability of the developed method, we proceeded to determine whether a similar mechanism involving radical intermediates was operating as that observed for the preparation of benzyl alkyl ketones.[19] Two radical probe experiments were carried out with α-bromonitriles **26** and **28**. Under standard conditions **26** was converted into β-ketonitrile **27a** in a 60% yield (Scheme 3a). No product from 5-*exo*-trig cyclization was detected, which is peculiar if a carbon centered radical is formed. However, the result is in accordance with our previous mechanistic findings for the nickel-catalyzed carbonylation of benzyl bromides with alkylzinc reagents and can be ascribed to the stability of the radicals formed. Using the cyclopropyl derivative **28** under standard conditions, led to formation of three different products (Scheme 3b). β-ketonitrile **29a** could be isolated in a 20% yield along with the ring-opened carbonylative adduct **29c** in a 22% yield. In addition, some ring-opened direct coupling product **29d** was also observed (13% yield**)**. The two latter products (**29c** and **29d**) suggest a carbon centered radical intermediate is formed, followed by cyclopropane ring-opening (Scheme 3b). The two observations that no 5-*exo*-trig cyclization takes place and that cyclopropane ring opening is incomplete suggests that the recombination of the supposed radicals (See proposed mechanism) is faster/or of similar rate to the intramolecular radical probe reactions, presumably due to the low concentration of alkyl radicals relative to the nickel acyl complex resulting from slow addition of the electrophile. The addition of 20 mol% of 1,4-dinitrobenzene, acting as a single electron transfer (SET) inhibitor, to the reaction



Scheme 3. Radical probe experiments.

lowered the yield by 16% (from 72% to 56%) of **2a** using **1** and *n*-propylzinc bromide under optimized conditions.[23]

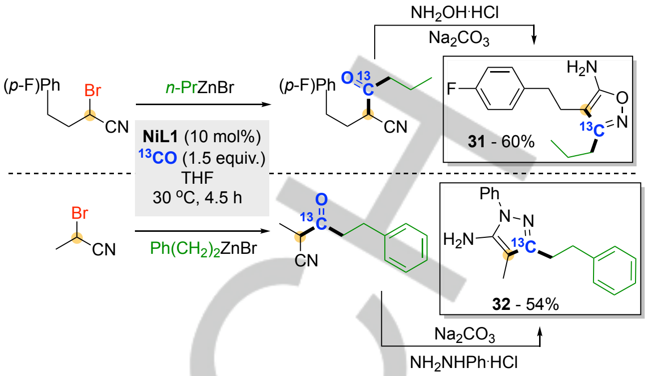
The proposed mechanism, depicted in Scheme 4, follows closely the bimetallic oxidative addition mechanism proposed by Hu and coworkers for the cross coupling of alkyl substrates catalyzed by Ni(II) pincer complexes.[20] Initially a transmetallation step is involved with **NiL1** followed by CO insertion to form the nickel(II) acyl complex **A**. Bromide abstraction from the α-bromonitrile substrate, generates the nickel(III) complex **B** and the nitrile stabilized radical **30**. Recombination of this carbon-centered radical with another equivalent of complex **A** leads to the nickel(III) complex **C**, which reductively eliminates to the desired β-ketonitrile product and the Ni(I) complex **D**. Lastly, comproportionation of **B** and **D** reforms **NiL1** and **A**, thereby completing the catalytic cycle.



Scheme 4. Proposed Mechanism

Finally, the utility of the synthesized β-ketonitriles was illustrated by their employment in the preparation of two ^{13}C-labeled heterocycles (Scheme 5). Carbonylative couplings applying ^{13}C-labeled COgen provided the two β-ketonitriles ^{13}C-**10a** and ^{13}C-**7a**. Subsequent transformation of the former into the ^{13}C-labeled isoxazole **31** proceeded smoothly providing an isolated yield of 60% over two steps. Further conversion of ^{13}C-**7a** generated the ^{13}C-labeled pyrazole **32** in a 54% yield (two steps).

In conclusion, we have developed a nickel-catalyzed carbonylation of β-ketonitriles from α-bromonitriles and alkylzinc reagents. The method tolerates functional groups, which are incompatible with conventional acylation of metalated nitrile. Additionally, the method gives access to β-ketonitrile products, which cannot be obtained *via* the known palladium-catalyzed carbonylative methods. Furthermore, the method is useful for the synthesis of ^{13}C-labeled β-ketonitriles, which subsequently can be converted into ^{13}C-labeled heterocycles, as exemplified by **31** and **32**. Currently, we are investigating the use of unactivated alkyl halides as coupling partner for similar carbonylative transformations.



Scheme 5. Post modification of two β-ketonitriles for heterocycle synthesis with selective carbon isotope labeling. See Supporting information for all details.

Acknowledgments

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Keywords: nickel catalysis • carbonylation • alkylzinc reagents • β-ketonitriles • isotope-labeling

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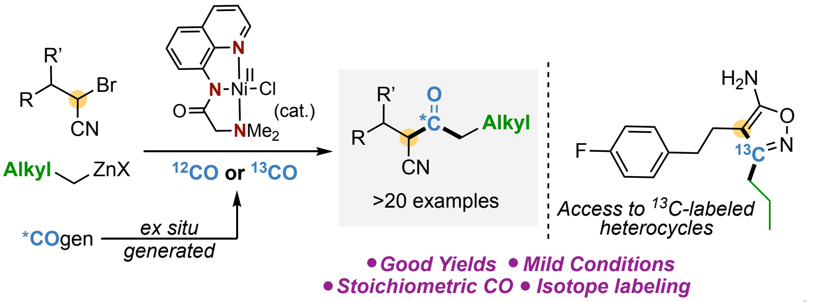
[22] We suspect the recombination of the sterically encumbered radicals formed from the substrates **22** and **24** makes them unviable substrates for the catalytic transformation. Substrate **23** could form a highly stabilized benzylic radical adjacent to the nitrile, which might be unreactive.

[23] This result contradicts that reported for our nickel-catalyzed carbonylation to benzyl alkyl ketones, where the addition of 20 mol% 1,4-dinitrobenzene resulted in a significantly reduced yield (>90% to 20%).



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Squeezing in CO! Herein, we describe the development of a nickel(II)-catalyzed carbonylative coupling of alkylzinc reagents and α-bromonitriles to afford β-ketonitriles in good yields under mild conditions. Key to the success of this carbonylative chemistry is the readily available nickel(II) chloride pincer complex, which forms stable nickel(II) alkyl and nickel(II) acyl complexes.