

Nickel-Catalyzed Carbonylative Negishi Cross-Coupling of Unactivated Secondary Alkyl Electrophiles with 1 atm CO Gas

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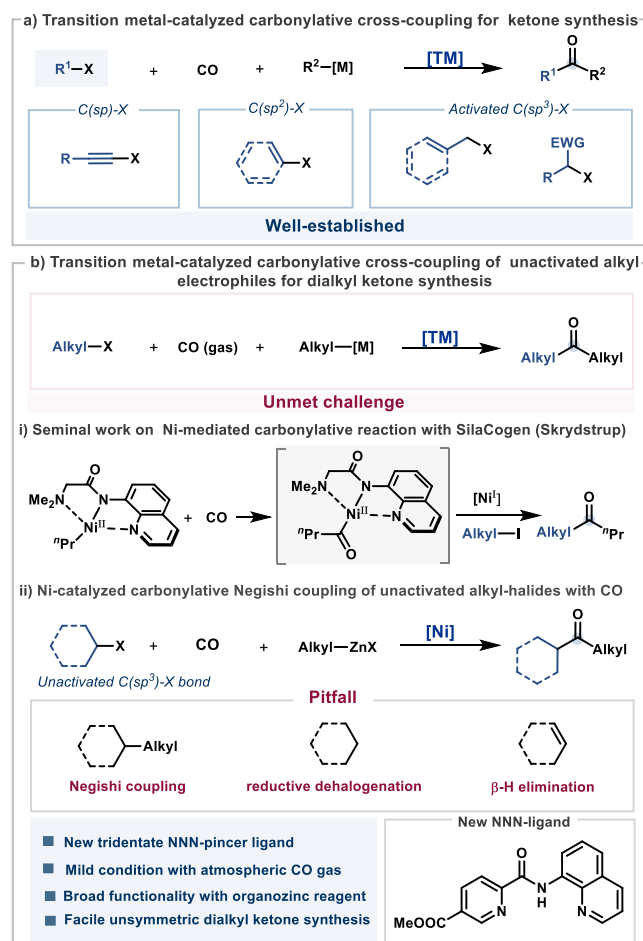


Supporting Information

ABSTRACT: We describe a nickel-catalyzed carbonylative cross-coupling of unactivated secondary alkyl electrophiles with the organozinc reagent at atmospheric CO gas, thus allowing the expedient construction of unsymmetric dialkyl ketones with broad functional group tolerance. The leverage of a newly developed NN_2 -pincer type ligand enables the chemoselective three-component carbonylation by overcoming the competing Negishi coupling, the undesired β -hydride elimination, and dehalogenation of alkyl iodides side pathways. Both alkyl iodides and alkyl tosylates are compatible in the single electron transfer involved mechanism.

Ketones are prevalent skeletons in various natural products, pharmaceuticals, and materials, which can also undergo a

Scheme 1. Transition Metal-Catalyzed Carbonylative Cross-Coupling of Unactivated Alkyl Halides



diverse array of transformations as a versatile synthetic intermediate in organic chemistry. Since the salient studies by Heck in the 1970s, the multicomponent palladium-catalyzed carbonylative cross-coupling reaction has stood out as one of the most practical strategies for constructing carbonyl functionality through judicious nucleophile selection (Scheme 1a).^{1,2} Despite the remarkable progress in transition metal-catalyzed cross-coupling reactions, recognized with the Nobel Prize in Chemistry in 2010, the development of carbonylative cross-coupling for ketone synthesis has notably lagged behind that of related carboxylic acid or derivative synthesis.^{3,4} An enduring and unmet challenge of carbonylation for ketone synthesis lies in the absence of a practical method to achieve the carbonylative coupling of unactivated alkyl halides, contrasting sharply with the well-established transformation in $C(sp)-X$, $C(sp^2)-X$, and reactive $C(sp^3)-X$ electrophiles, such as allylic, propargylic, and benzylic electrophiles.⁵ This is primarily attributed to the sluggish oxidative addition of sp^3 -hybridized $C-X$ to the low-valent palladium intermediate in the presence of the π -acidic CO. Despite the significant advancements in earth-abundant transition metal-catalyzed alkyl-alkyl cross-coupling over the past two decades, the analogous three-component carbonylative cross-coupling of unactivated alkyl halides, carbon-based organometallic nucleophile with CO gas under mild conditions to construct ketone remains an elusive goal (Scheme 1b).^{6–8}

Ligand-accelerated nickel-catalyzed carbonylative cross-coupling has emerged as a rapid development in the field of carbonylation chemistry, wherein the supportive ligand plays a crucial role in overriding the strong affinity of excess of CO with the nickel center, thus preventing the deactivation of the

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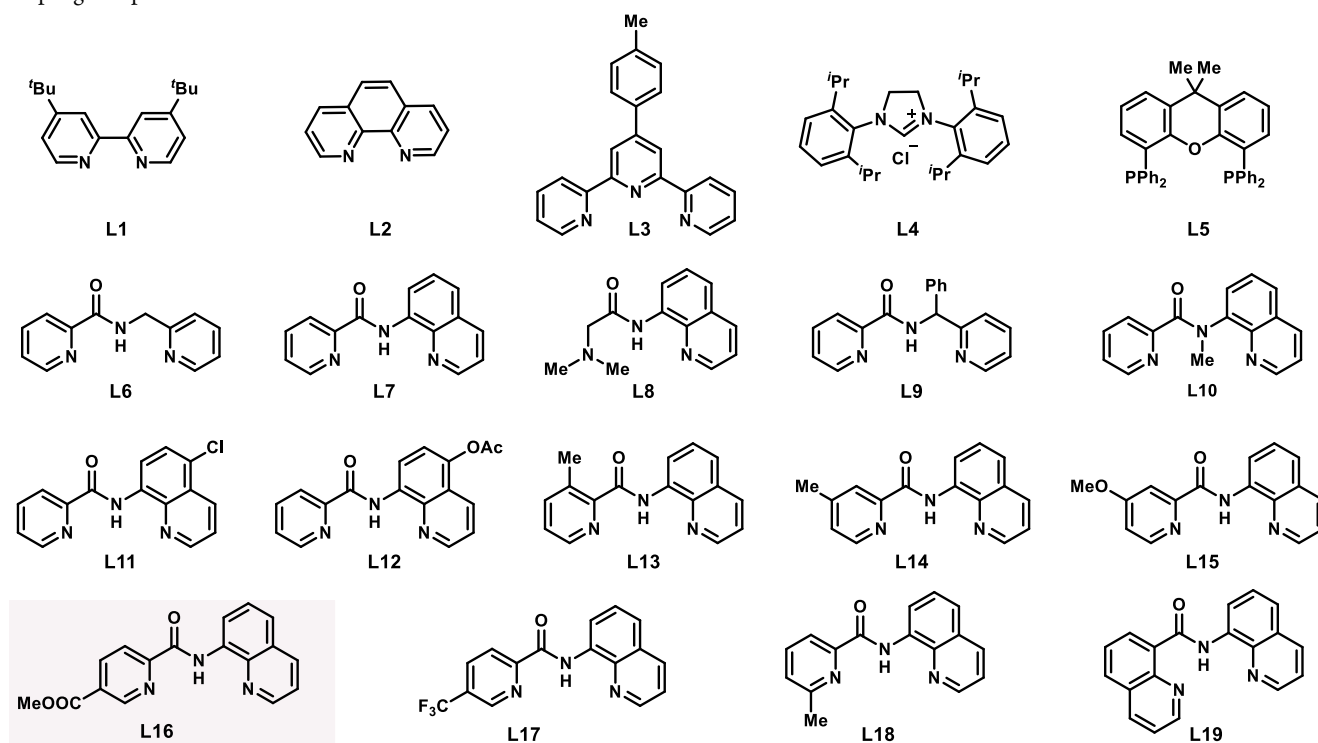
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Table 1. Optimization of the Reaction Conditions^a

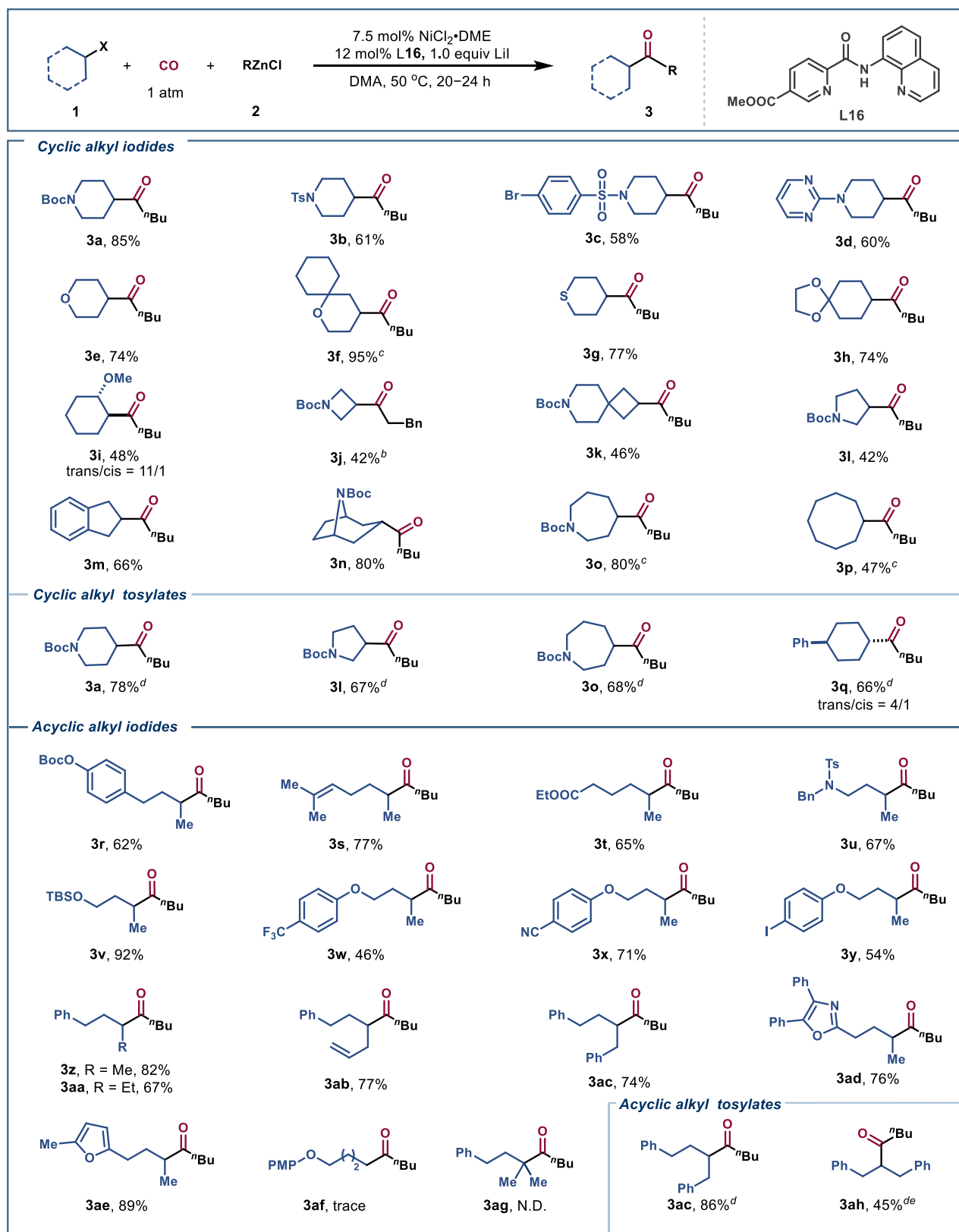
entry	ligand	conversion of 1a (%)	yield of 3a/4a/5a/6a (%) ^a	entry	ligand	conversion of 1a (%)	yield of 3a/4a/5a/6a (%) ^a
1	L1	100	33/46/10/0	13 ^{b,c}	L11	100	84/0/10/2
2	L2	100	24/37/28/0	14 ^{b,c}	L12	100	87/0/6/3
3	L3	83	21/22/16/0	15 ^{b,c}	L13	95	69/0/3/2
4	L4	90	5/63/6/0	16 ^{b,c}	L14	100	86/0/10/2
5	L5	88	0/0/14/53	17 ^{b,c}	L15	100	77/0/18/3
6	L6	61	10/0/8/12	18 ^{b,c}	L16	100	88/0/6/2
7	L7	67	32/0/32/0	19 ^{b,c}	L17	100	67/0/16/1
8 ^b	L7	100	53/0/24/4	20 ^{b,c}	L18	100	17/13/50/1
9 ^b	L8	88	39/0/30/5	21 ^{b,c}	L19	99	38/2/30/2
10 ^b	L9	96	49/0/8/9	22 ^{c,d}	L16	100	90 (85) ^e /0/4/1
11 ^{b,c}	L7	100	84/0/4/1	23 ^{c,d,f}	L16	60	36/0/8/3
12 ^{b,c}	L10	95	11/47/10/1	24 ^{c,d,g}	L16	6	0/0/0/2

^aReaction conditions: **1a** (0.10 mmol), **2a** (0.18 mmol, 1.8 equiv), NiCl₂·DME (0.010 mmol, 10 mol %), Ligand (0.015 mmol, 15 mol %), CO (1 atm), DMA (0.1 M) under 30 °C for 5 h. Yields determined by GC using dodecane as internal standard. ^b**2a** (0.23 mmol, 2.3 equiv), 20 h. ^cDMA (0.8 M), 50 °C. ^d**1a** (0.20 mmol), **2a** (0.40 mmol, 2.0 equiv), NiCl₂·DME (0.0075 mmol, 7.5 mol %), Ligand (0.012 mmol, 12 mol %), LiI (0.10 mmol, 1.0 equiv), 20 h. ^eIsolated yield in parentheses. ^fAlkyl bromide was used as the coupling component. ^gAlkyl chloride was used as the coupling component.

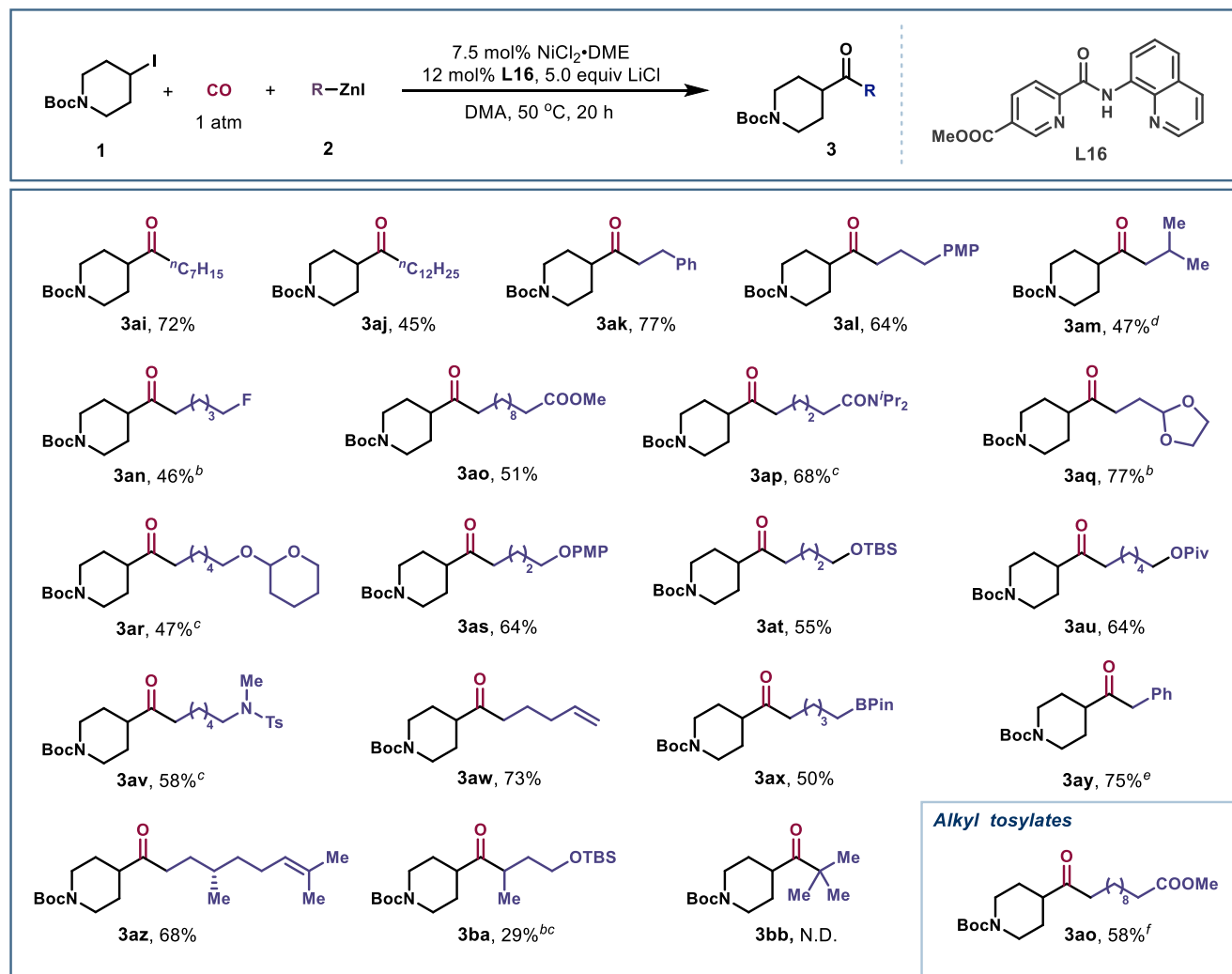


nickel catalyst center.⁹ In addition to the utilization of abundant and inexpensive CO gas,^{10–12} several CO surrogates including CO-gen, chloroformate, and metal carbonyl complex through the slow release of CO gas have proven successful in the nickel-catalyzed carbonylations.^{13–15} We recently realized the carbonylation of allylic alcohol with organoalanes under 1 atm of CO gas to regioselectively access the β,γ -unsaturated ketones, wherein the nickel serves as the sole catalyst, enabling the direct use of alcohol as organoelectrophiles.¹⁶ We aim to tackle the carbonylative cross-coupling by the inception of unactivated alkyl (pseudo)halides and organometallic reagent

under CO gas.^{16–18} Our inspiration stems from Skrydstup's seminal work, which demonstrated nickel-mediated carbonylative coupling with organozinc through the formation of stoichiometric acyl-nickel complexes, leading to the in situ generation of the reactive CO species, known as the SilaCogen reagent (Scheme 1b-i).¹⁹ Based on this excellent precedent and our success on carbonylative Negishi coupling, we have chosen the organozinc reagent as the nucleophile.^{17,20} However, several challenges must be addressed in realizing this carbonylative coupling (Scheme 1b-ii). First, in addition to the previously mentioned deactivation by CO gas, the strong

Scheme 2. Unactivated Alkyl Electrophile Scope of Nickel-Catalyzed Carbonylative Negishi Reaction^a

^aReaction conditions: **1** (0.20 mmol), **2** (0.40 mmol, 2.0 equiv), NiCl₂·DME (0.015 mmol, 7.5 mol %), **L16** (0.024 mmol, 12 mol %), LiI (0.20 mmol, 1.0 equiv), CO (1 atm), DMA (0.25 mL, 0.8 M) under 50 °C for 20–24 h. ^bBnCH₂ZnI (0.40 mmol, 2.0 equiv), LiCl (1.00 mmol, 5.0 equiv) instead of LiI (0.20 mmol, 1.0 equiv). ^cNiCl₂·DME (0.030 mmol, 15 mol %), **L16** (0.048 mmol, 24 mol %). ^d**1** (0.20 mmol), **2** (0.46 mmol, 2.3 equiv), NiCl₂·DME (0.020 mmol, 10 mol %), **L15** (0.024 mmol, 12 mol %), LiI (0.50 mmol, 2.5 equiv), CO (1 atm), DMA (0.25 mL, 0.8 M) under 50 °C for 20–24 h. ^e60 °C for 36 h.

Scheme 3. Organozinc Scope of Nickel-Catalyzed Carbonylative Negishi Reaction^a

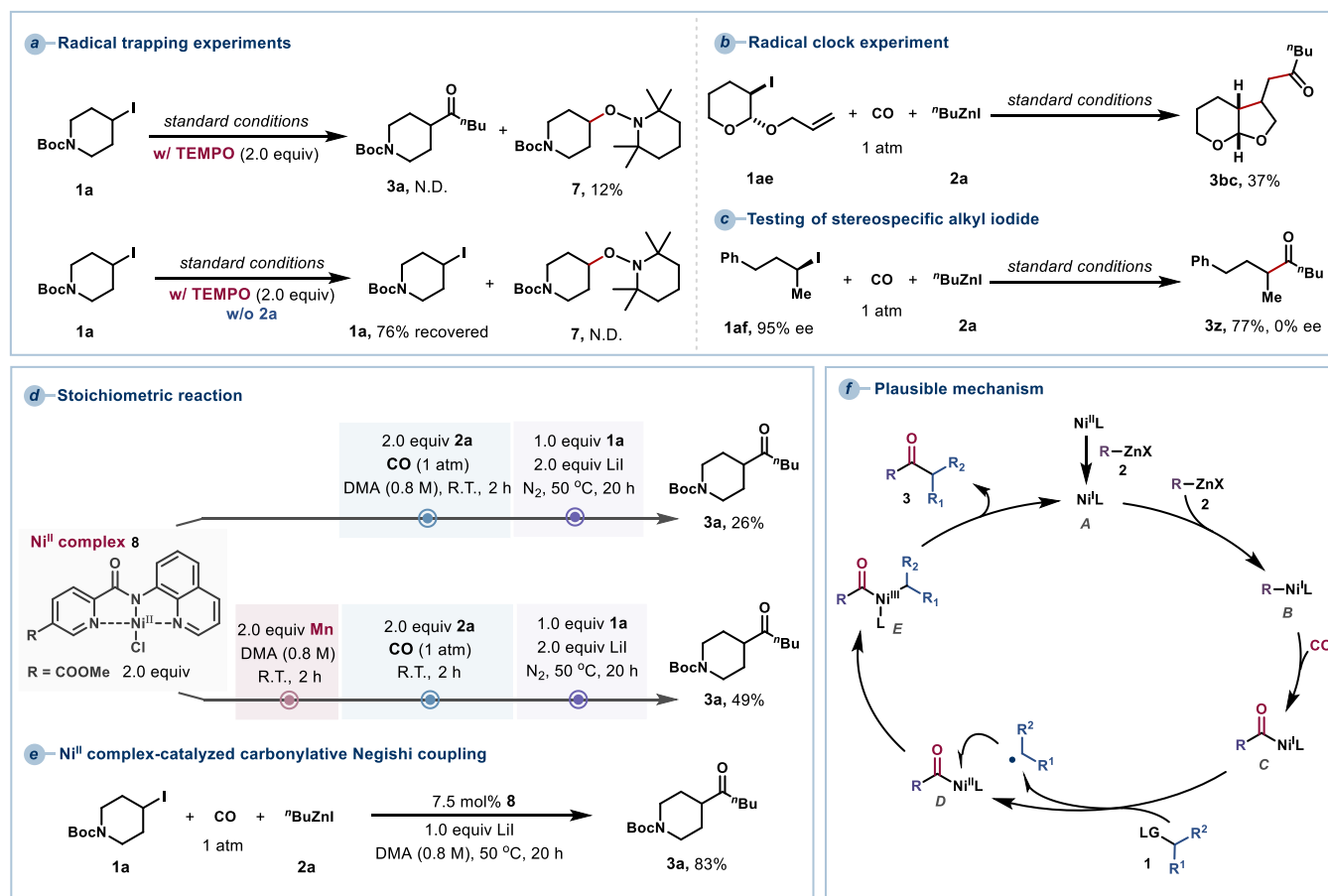
^aReaction conditions: **1** (0.2 mmol), **2** (0.40 mmol, 2.0 equiv), NiCl₂·DME (0.015 mmol, 7.5 mol %), **L16** (0.024 mmol, 12 mol %), LiCl (1.00 mmol, 5.0 equiv), CO (1 atm), DMA (0.25 mL, 0.8 M) under 50 °C for 20 h. ^bLiI (0.20 mmol, 1.0 equiv) instead of LiCl (1.00 mmol, 5.0 equiv). ^cNiCl₂·DME (0.030 mmol, 15 mol %), **L16** (0.048 mmol, 24 mol %). ^dLiCl (1.40 mmol, 7.0 equiv), 60 °C. ^e**2** (0.30 mmol, 1.5 equiv), 60 °C. ^fNiCl₂·DME (0.030 mmol, 15 mol %), **L15** (0.048 mmol, 24 mol %), LiCl (1.00 mmol, 5.0 equiv), LiI (0.50 mmol, 2.5 equiv).

nucleophilicity of the organozinc reagent could lead to a two-component Negishi coupling, a well-established protocol in nickel catalysis.^{21,22} Furthermore, direct reductive dehalogenation and β -hydride elimination represent potential side reaction pathways prior to the desired carbonylation process.²³ Herein, we present the unprecedented nickel-catalyzed carbonylative Negishi cross-coupling with secondary alkyl iodides under 1 atm of CO gas. Leveraging the newly developed NNN-type pincer ligand enables a variety of unsymmetrical dialkyl ketones with a broad substrate scope and functional group tolerance.

We initiated our study by evaluating the nickel-catalyzed carbonylative cross-coupling of *tert*-butyl 4-iodopiperidine-1-carboxylate **1a** and 1.8 equiv of ⁿBuZnCl as coupling component with 10 mol % NiCl₂·DME in DMA at 30 °C to generate *tert*-butyl 4-pentanoylpiperidine-1-carboxylate **3a** under 1 atm of CO. The utilization of the commercially available nitrogen containing ligand **L1**–**L3**, NHC ligand **L4** indeed afforded the desired ketone **3a**, as well as the direct Negishi coupling product **4a** and the reduced side product **5a**,

while the employment of Xantphos **L5** completely inhibited the carbonylation process with the formation of dehalogenative alkene **6a** (Table 1, entries 1–5). Notably, the amide-type tridentate nitrogen-based ligand **L6** completely suppressed Negishi coupling, albeit with a low yield (Table 1, entry 6). Encouragingly the valuation of other more rigid tridentate pincer ligand **L7**–**L9** led to the formation of the ketone **3a** in 53% yield with 2.3 equiv of ⁿBuZnCl in extended 20 h (Table 1, entries 7–10).^{24,25} Particularly, the higher concentration at the elevated 50 °C could further promote the carbonylative cross-coupling process with 84% desired product (Table 1, entry 11). When the methyl-protected **L10** was present, it largely inhibited the desired pathway, revealing that the Pincer-type ligand was essential for the carbonylation process (Table 1, entry 12). Next, exploration of substitution effects at either the pyridine or quinoline fragment based on the backbone of **L7** was symmetrically evaluated with the leveraging of **L11**–**L19** (Table 1, entries 13–21). It was found that the incorporation of an electron-withdrawing methyl ester group at the C-5 position of pyridine ring **L16** could further increase

Scheme 4. Preliminary Mechanistic Studies



the yield to 88% (Table 1, entry 18). Eventually, decreasing the loading of nickel catalyst and Pincer ligand with 1.0 equiv Lil as additive afforded the 3a in 85% isolated yield (Table 1, entry 22).²⁶ The investigation of the less reactive alkyl bromide has led to the significant decrease on the reaction efficiency, while no product was observed with the use of corresponding unactivated alkyl chloride as the coupling component (Table 1, entries 23–24).

With the optimized conditions, we first endeavored to investigate the generality of unactivated alkyl electrophiles (Scheme 2). A variety of six-membered heterocyclic alkyl iodides, including piperidine, tetrahydropyran, and tetrahydrothiopyrane rings, readily engaged in the carbonylative Negishi coupling, yielding unsymmetrical dialkyl ketone products 3a–3g in 58–95% isolated yields. This carbonylative protocol also exhibited notable versatility, accommodating functionalities such as acetal (3h) and aryl bromide (3c). The carbonylation of 2-methoxyiodocyclohexane resulted in the formation of ketone 3i in 48% yield with good stereoselectivity. Furthermore, medically relevant azetidine (3j), spiro- (3k), bridged-heterocyclic alkyl iodide (3n) were explored, providing the corresponding ketones with moderate to good yields. Medium-sized unactivated cyclic alkyl iodide including seven-membered azepine and eight-membered rings was successfully utilized, affording alkyl ketones (3o, 3p). Notably, cyclic unactivated alkyl tosylates, which was generally formed via one-step synthesis from corresponding alcohol, could also participate this carbonylative Negishi coupling, thus allowing to forge the unsymmetric ketone in synthetically useful yields.

The use of alkyl tosylate provided high yields for the five-membered pyrrolidine-substituted ketone 3l, indicating that alkyl tosylate could offer an alternative route for the Ni-catalyzed carbonylative cross-coupling process. In addition to cyclic alkyl electrophiles, the acyclic secondary alkyl halides were also suitable, delivering the corresponding ketone (3r–3ae) in a moderate to excellent isolated yield. The utilization of organic zincs as nucleophiles also enables good functional compatibility with alkyl electrophiles, such as alkene (3s, 3ab), protected ether (3r, 3v, 3w–3y), ester (3t), nitrile (3x), heteroarene oxazole (3ad), and furan (3ae). It is worth noting that the electrophile containing both aryl iodide and alkyl iodide functionalities selectively underwent the reaction at the site of the sp³-hybridized fragment (3y), further highlighting the uniqueness of this nickel-catalyzed carbonylation protocol. It should be noted that the current protocol is not suitable for the primary and tertiary unactivated alkyl iodides. Furthermore, the reaction of unactivated acyclic alkyl tosylate smoothly yielded the unsymmetrical ketones 3ac and 3ah.

We next explored the scope of the alkylzinc in this catalytic carbonylative transformation (Scheme 3). A broad range of organozinc reagents proved to be effective in this cross-coupling to deliver the unsymmetric ketones 3ai–3ba with use of 1a as the model substrate. Intriguingly, various functional groups including fluoride (3an), methyl ester (3ao), amide (3ap), acetal (3aq), and protected ethers (3ar–3au, 3ba), and tertiary amine (3av) readily participated in the process, affording the functionalized ketone products in moderate to good isolated yields. Both terminal and internal alkene-

containing organozincs were converted to olefin-tether ketones **3aw** and **3az**. When the organometallic reagent contained both nucleophilic borane and a zinc skeleton, the carbonylation predominantly proceeded via Negishi type coupling to generate **3ax**, with the boronic ester functionality remaining. When the sterically *tert*-butyl organozinc reagent was utilized as the coupling component, no ketone was observed. Additionally, we found that a cyclic unactivated alkyl tosylate could also react with the functionalized organozinc reagent.

To elucidate the reaction mechanism, a series of preliminary experiments were conducted in Scheme 4. Initially, radical trapping experiments were executed (Scheme 4a). The addition of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) completely shut down the carbonylation process, while the TEMPO-trapped product **7** was obtained. A control experiment with the omission of ⁿBuZnCl revealed that 76% of **1a** was recovered, and **7** was not observed. These above results collectively revealed that the organozinc reagent is essential to initiate radical-type carbonylative coupling. The radical clock experiment was then carried out (Scheme 4b). It was found the reaction of alkyl iodide **1ae** proceeded in the cascade *5-exo-trig* type cyclization and carbonylative cross-coupling sequence, yielding the cyclized ketone **3bc**. Furthermore, when the stereospecific substrate **1af** was subjected to standard conditions, the corresponding ketone **3z** was generated in a racemic form, indicating that the formation of the secondary alkyl radical species led to racemization (Scheme 4c). The 2.0 equiv of Ni^{II} complex **8** that was formed by mixing the NiCl₂·DME with ligand **L16**, reacted with 2.0 equiv of ⁿBuZnCl under 1 atm of CO with 2 h, followed by addition of 1.0 equiv of alkyl iodide **1a** and 2.0 equiv of LiI, leading to the desired product **3a** in 26% yield. In contrast, the addition of 2.0 equiv of Mn could reduce **8** first, and then the stoichiometric reaction was performed similarly. It was found that the yield of ketone **8** was increased to 49%. These data collectively revealed that low-valent nickel is responsible for this carbonylative coupling process (Scheme 4d). The catalytic **8** was proven to be effect to promote this carbonylative Negishi coupling to forge **3a** in 83% yield (Scheme 4e). Therefore, a plausible reaction mechanism is temporarily proposed in Scheme 4f: the Ni^I intermediate **A** initially undergoes transmetalation with organozinc **2** to generate the alkyl nickel(I) intermediate **B**. CO gas may undergo the subsequent 1,1-insertion into intermediate **B**, resulting in the formation of an acyl nickel(I) species **C**, which further reacts with unactivated alkyl electrophiles **1** to produce acyl nickel(III) intermediate **E** through a single electron transfer process. Finally, **E** undergoes reductive elimination to yield the unsymmetric dialkyl ketone **3** and regenerate the intermediate **A**. It should be noted that the possibility for the formation of acyl radical intermediate could not be fully excluded.²⁷

In conclusion, we have successfully developed an unprecedented earth-abundant nickel-catalyzed three-component carbonylative Negishi cross-coupling reaction of unactivated secondary alkyl electrophiles and alkyl zinc reagents with atmospheric CO gas. By leveraging the newly developed amide-type NN₂-pincer ligand, the undesired side pathways of two-component Negishi reaction, reductive dehalogenation, and β-H elimination process were effectively suppressed. This strategy provides an efficient and straightforward approach to obtain a broad range of unsymmetrical dialkyl ketones with good functional group tolerance. Further efforts are underway to elucidate the detailed mechanism and achieve the

enantioselective carbonylative reactions of unactivated alkyl electrophiles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.4c02023>.

Experimental procedures, spectroscopic data for all new compounds including ¹H and ¹³C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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