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Nickel-Catalyzed Alkyl-Alkyl Cross-Coupling Reactions of Nonactivated Secondary Alkyl Bromides with Aldehydes as Alkyl Carbanion Equivalents

Chenghao Zhu, Junliang Zhang*

A novel nickel-catalyzed alkyl-alkyl cross coupling of unactivated secondary alkyl bromides with aldehydes via hydrazone intermediates has been developed. Aldehyde as an alkyl carbanion equivalent replaces traditional organometallic reagents. This coupling occurs on the carbon of the hydrazone rather than the nitrogen. In addition, non-activated primary and tertiary alkyl bromides also undergo the cross-coupling reaction to form new C(sp³)-C(sp³) bond in moderate yield.

Transition metal-catalyzed cross-coupling reactions to form carbon-carbon bonds have been extensively developed for many years.¹ The cross coupling reactions of alkyl halides had been difficult to achieve because of the reluctance of alkyl halides to undergo oxidative addition, reductive elimination and alkyl metal intermediates are more reactive and cause more side reactions such as β -H elimination and protonation.² For all that, this coupling reaction of alkyl halides is still getting faster development, especially primary alkyl halides.^{3, 4}

Compared to primary alkyl halides, alkyl-alkyl cross-coupling reactions of secondary alkyl halides to form C(sp³)-C(sp³) bond pose more considerable challenge, especially non-activated secondary alkyl halides.⁴ Fu, Kambe, Hu and other groups developed cross coupling reactions of non-activated secondary alkyl halides with organometallic reagents⁵ (Scheme 1a). Gong, Liu, Peng and others achieved reductive coupling reactions between alkyl halides to form C(sp³)-C(sp³) bond by using stoichiometric reducing metals (Scheme 1b).⁶ Yu and co-workers have successfully developed palladium-catalyzed radical alkylation of C-H bonds with unactivated alkyl bromides to form C(sp³)-C(sp³) bonds driven by visible-light.⁷ The main disadvantage of generating C(sp³)-C(sp³) bonds is the use of stoichiometric metals according to existing reports which would

undoubtedly cause metal waste and environmental pollution. So we need to find new alkyl nucleophiles and new transition metal catalysis mode to solve above challenges.





In 2017, Li and co-workers have developed an elegant strategy for C-C bond formation reaction via umpolung of carbonyl groups as alkyl carbanion equivalents to react various electrophiles.⁸ Very recently, they successfully extend this strategy to palladium-catalyzed cross-coupling with allylic actetae (Scheme 1c) and nickel-catalyzed cross-coupling with aryl halides (Scheme 1d).^{8e} This novel alkyl carbanion equivalent had not well employed in coupling with the more challenging unactivated secondary and tertiary alkyl bromides. Inspired by Li's work, we reported herein a nickel-catalyzed alkyl-alkyl cross-coupling between non-activated secondary bromides and aldehyde hydrazones to form C(sp³)-C(sp³) bonds (Scheme 1e), in which no *N*-coupling products or not *C*-coupling products were observed.¹⁰

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⁺ Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See

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To study this alkyl-alkyl cross coupling reaction, the hydrazone (1a) generated in situ from benzaldehyde and (3-bromobutyl)benzene (2a) were selected as the model substrates. Fortunately, the desired product 3a was obtained in nickel-catalyzed system (Table 1, entries 1-4). We screened different ligands but the yield was not improved (Table 1, entries 5-8). The yield can be slightly improved with increasing the catalyst loading (Table 1, entry 9). While the coupling product 3a was not detected when other bases such as DBU, K₃PO₄, Cs₂CO₃ were uesd (Table 1, entries 10-12). With the temperature increases, the yield of 3a was improved to 65% when the reaction was run at 80 °C (oil bath, Table 1, entry 15). When either nickel, dppf, or NaO^tBu was removed, the yield dropped (Table 1, entries 16-18). When Hydrazine hydrate was added, the product was not detected (Table 1, entry 19).

Table 1. Optimization reaction conditions

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		[Ni] (5 mol%)	[Ni] (5 mol%), Ligand (10 mol%)	
1a	¹ 2 ⁺ Ph ² 2a	Base (2 equiv	.), THF, 60 °C, 12 h	3a
Entry	[Ni]	Ligand	Base	Yield (%) ^d
1	Nil ₂	dppf	NaO ^t Bu	30
2	NiBr ₂	dppf	NaO ^t Bu	11
3	Ni(PPh ₃) ₄	dppf	NaO ^t Bu	13
4	Ni(COD) ₂	dppf	NaO ^t Bu	31
5	Ni(COD) ₂	PPh_3	NaO ^t Bu	7
6	Ni(COD) ₂	PCy ₃	NaO ^t Bu	16
7	Ni(COD) ₂	bpy	NaO ^t Bu	n.d.
8	Ni(COD) ₂	dmpe	NaO ^t Bu	25
9 ª	Ni(COD) ₂	dppf	NaO ^t Bu	42
10ª	Ni(COD) ₂	dppf	DBU	n. d.
11ª	Ni(COD) ₂	dppf	K ₃ PO ₄	n. d.
12ª	Ni(COD) ₂	dppf	Cs_2CO_3	n. d.
13ª	Ni(COD) ₂	dppf	KO ^t Bu	22
15 ^{a, b}	Ni(COD) ₂	dppf	NaO ^t Bu	65
16 ^{a, b}	-	dppf	NaO ^t Bu	n. d.
17 ^{a, b}	Ni(COD) ₂	-	NaO ^t Bu	39
18 ^{a, b}	Ni(COD) ₂	dppf	-	n. d.
19 ^{a, b, c}	Ni(COD) ₂	dppf	NaO ^t Bu	n. d.

Reaction condition: **1a** (0.6 mmol), **2a** (0.3 mmol), [Ni] (10 mol%), ligand (20 mol%), NaO'Bu (0.6 mmol), THF (3 mL), 60 °C, 12 h. a Ni(COD)₂ (10 mol%), dppf (20 mol%). b 80 °C. c N₂H₄·H₂O (0.6 mmol). ^dYields were determined by crude 1 H NMR using CH₂Br₂ as an internal standard. e dppf = 1,1'-Bis(diphenylphosphino)ferrocene, bpy = 2,2'-bipyridine, dmpe = 1,2-Bis(dimethylphosphino)ethane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, n.d. = not detected.

With the optimized conditions in hand, the substrate scope of aldehyde hydrazones for this alkyl-alkyl cross coupling was investigated (Scheme 2). The reactions of aromatic aldehydes with electron-withdrawing and electron-donating groups delivered the corresponding products **3b-3k** in moderate yields. Specifically, *meta-, ortho*-substituted aromatic hydrazones have no significant impact on yield. Moreover, hydrazones derived from aldehydes such as 1-naphthaldehyde, 2-furaldehyde, ferrocenecarbaldehyde could deliver the desired products **3l-3n** in 42-61% yields. Aliphatic aldehyde hydrazones also gave the cross coupling products **3o-3q** in





Having studied the scope of aldehyde hydrazones, we turned our attention to non-activated secondary alkyl bromides (Scheme 3). Considering the fluorescence of the product, we chose **1k** as the model substrate. Compared with **2a**, longer linear secondary alkyl bromides include branched alkyl and alkenyl gave relatively lower yield **(4b, 4c)**. Secondary alkyl bromide containing trifluoromethyl also obtained the corresponding product in 43% yield (Scheme 3, **4d**). 54% yield was obtainded for ether-substituted alkyl bromide (Scheme 3, **4e**). Converts shorter linear alkyl bromide to the desired product in 42% yield (Scheme 3, **4f**). 3-bromopentane also provided

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moderate yield of 53% (Scheme 3, 4g). In addition, cyclic alkyl bromides including 1-bromocyclopentane, 1-bromocyclohexane, bromocycloheptane accomplished this conversion (Scheme 3, 4h-4i).

Finally, the cross coupling reactions with primary and tertiary alkyl bromides were investigated. 1-Bromoheptane **2k** and 1-bromoadamantane **2l** smoothly converted into the corresponding products in 43% and 45% yield, respectively (Eq 1 and 2). These results indicate our strategy for catalyzing alkyl-alkyl coupling was not limited to secondary alkyl bromide.



Although the exact mechanism is still unclear at this stage, we still tried hard to explore. We found that a mixture of olefin by-product was produced in the presence of base without the nickel catalyst (eq. 3). Cyclopropanecarbaldehyde derived hydrazone **1u** could not deliver the desired products under the reaction conditions (eq. 4). Secondary alkyl bromide **2m** with cyclopropyl group gave a mixture of ring opening products **9** rather than the corresponding product **4m** (eq. 5). This suggests that the reaction might involve a free radical process.



Scheme 4. Proposed mechanism

According to our previous works and literature reports^{4b, 50, 8d, 11}, a plausible reaction pathway was depicted in Scheme 4. Ni(0)

allowed single electron oxidation addition to give intermediate **B** and alkyl radical **C**, where an oxidative radical addition occurs to give 7a nickel(II)–dialkyl complex **D**, which underwent transmetalation with carbon-nucleophile **H** derived from deprotonation of hydrazone **1** to form the intermediate **E**. Reductive elimination gave the diimide **F** and regenerated Ni (0) catalyst. Finally, the desired product **3** was formed by denitrogenation assisted with the base.

In summary, a novel nickel-catalyzed alkyl-alkyl cross coupling reactions of non-activated secondary alkyl bromides with aldehydes as alkyl carbanion equivalents has been successfully developed. The method provides a simple strategy for alkyl-alkyl cross-couplings using naturally abundant aldehydes instead of organometallic reagents to synthesize some useful synthetic precursors having tertiary carbon centers,^{5e} filling the gaps in the classical cross-coupling reactions. Further studies on enantioselective version of this novel cross-coupling chemistry are underway in our laboratory. We gratefully acknowledge the funding support of NSFC (21425205,

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Page 4 of 5

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A novel nickel-catalyzed alkyl-alkyl cross coupling of unactivated secondary alkyl bromides with aldehydes via hydrazone intermediates has been developed.