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Nickel-catalysed novel β , γ -unsaturated nitrile synthesis⁺

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Through a nickel-catalysed Heck-type reaction, a direct coupling of alkenes with α -cyano alkyl bromides was achieved. This procedure provides a novel way for the synthesis of β , γ -unsaturated nitriles.

 β , γ -Unsaturated nitrile moieties are important constituents in some potential drugs and natural products.1 However, quite limited methods have been reported for their synthesis up to now.² Generally, the synthesis of β_{γ} -unsaturated nitriles was achieved from the cyanation process of allylic substituted compounds (Scheme 1, path a).³ Nevertheless, most of these methods require either toxic reagents or materials that are not easily available. From the disconnection of the designed products, an alternative approach also has high potential, which is the direct alkenylation of α -cyano alkyl halides. However, it remained nearly unstudied until now. To our knowledge, only one example has been demonstrated by Fu and co-workers by using alkenylzinc reagents to couple with a-cyano alkyl bromides (Scheme 1, path b).⁴ Obviously, the direct utilization of alkenes as coupling partners with α-cyano alkyl halides to construct β_{γ} -unsaturated nitriles would be a much more appealing approach, as both alkenes and α -halide nitriles are readily available



Scheme 1 Synthesis of β , γ -unsaturated nitriles.

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and quite easy to obtain. Herein, we report the first novel β , γ -unsaturated nitrile synthesis *via* Ni-catalysed Heck-type alkenylation of α -cyano alkyl bromides with olefins (Scheme 1, path c).

To our knowledge, scarce reports exist on the alkenylation of α -carbonyl alkyl halides with olefins, which were however based on intramolecular reactions.⁵ Until recently, our group has achieved the first intermolecular coupling of secondary and tertiary α -carbonyl alkyl bromides with olefins to achieve α -alkenylation of carbonyls in the presence of a nickel catalyst.⁶ As an extension, employing α -cyano alkyl halides as the alkyl electrophiles may open a door for the general synthesis of β , γ -unsaturated nitriles.

However, the reaction between olefins and α -cyano alkyl bromides has limitations when conducted under the optimized conditions for non-electron-rich olefins.⁶ For example, only a trace amount of the desired product could be observed with p-fluorostyrene, while no alkenylation product formed for simple styrene (Scheme 2). This result clearly showed the distinction of reactivity among activated alkyl electrophiles. & Cyano alkyl bromides might achieve alkenylation with more difficulty compared to α -carbonyl alkyl bromides. During investigation into the efficient alkenylation of α -cyano alkyl bromides, a tendency should be noted. When the reaction was conducted under 60 °C without the addition of any additive, no alkenylation product was observed. In contrast, the alkenylation product was observed in a yield of 34% when the reaction was conducted at 120 °C (determined by NMR) (Scheme 3). From this point of view, it could be seen that the generation of the alkenylation product was solely promoted by the increase in reaction temperature. In other words, temperature may play a key role in promoting the formation of the alkenylation product.



 $\mbox{Scheme 2}$ Attempts for the alkenylation of $\alpha\mbox{-cyano}$ alkyl bromide with non-electron-rich olefins.

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As we know, temperature has always been regarded as an indispensable factor in organic reactions. However, attention has mainly been paid to its ability to accelerate reaction rates. While it has been revealed that temperature could affect the selectivity of multiple reactions, some examples of successfully controlling the selectivity to obtain certain products by just changing the reaction temperature have been reported.⁷ Based on the clues we found in the nickel-catalysed alkenylation of α -cyano alkyl bromides, we decided to further investigate the reaction by changing the reaction temperature.

Moreover, alkyl halides have been proposed to undergo a single electron transfer (SET) process to generate free radicals with a nickel catalyst.^{6,8} As it has been shown that the β -hydride elimination from the nickel species and the reductive elimination of nickel hydride are not as facile as for palladium,⁹ we first outlined the following radical pathway shown in Scheme 4 for the alkenylation of α -cyano alkyl bromides. The reaction of α -cyano alkyl bromides with Ni⁰ generates the active Ni^I species A (this step was proved by EPR detection, see ESI⁺), which then donates an additional electron to α -cyano alkyl bromides to generate the radical species 2I and a Ni^{II} species B through a SET reduction step (step 1). Afterwards, the radical addition of 2I to olefin 1 generates benzylic radical 3I (step 2), which is followed by the SET oxidation of radical 3I by B to generate 3II (step 3). Ultimately, benzylic cation 3II was deprotonated by base to release the final product 3 (step 4). During the whole process, step 3 was believed to be the key step for the generation of the final product. This viewpoint was supported by the fact that an electron-donating substituent, which is in favor of cation formation, is beneficial for the product formation. Accordingly, it is easy to understand that non-electron-rich olefins are not in favor of cation formation so that the alkenylation product is not easily obtained. We believe that increasing the temperature can raise the redox potential of



Scheme 4 Proposed mechanism.

nickel(II) intermediate **B**. Consequently, higher temperature may promote the oxidation of radical **3I** by **B** to generate **3II**.



Keeping this assumption in mind, we tried to conduct the reaction at a much higher temperature. By changing the solvent to mesitylene which has a higher boiling point, the reaction was conducted at a temperature of 160 $^{\circ}$ C. To our delight, the desired product was selectively obtained with an isolated yield of 82% (eqn (1)), which supported our viewpoint on efficient oxidation of radical **3I**.

After we obtained this exciting result, we tried to apply the conditions to other substrates in the Ni-catalysed direct synthesis of β , γ -unsaturated nitriles. First of all, various non-electron-rich olefins were employed to couple with 2-bromopentanenitrile (Table 1). In the optimized catalysis system for the alkenylation reaction, 2-bromopentanenitrile was applied to couple with a range of non-electron rich olefins in good to excellent yields (entries 1–6). Simple styrene afforded the desired product in 67% yield (entry 3). *tert*-Butyl, *para-* and *ortho*-methyl substituted styrenes afforded the coupling products in good yields (entries 4, 5 and 7). The C–Cl bond was well tolerated in this transformation



^{*a*} Isolated yields. ^{*b*} Method A: the reactions were carried out with 1 (0.50 mmol), 2 (0.75 mmol), Ni(PPh₃)₄ (5 mol%), dppp (6 mol%), K_3PO_4 (1.0 mmol), mesitylene (2 mL), 160 °C, 3 h. ^{*c*} Method B: the reactions were carried out with 1 (0.50 mmol), 2 (0.75 mmol), Ni(PPh₃)₄ (5 mol%), dppp (6 mol%), K_3PO_4 (1.0 mmol), toluene (2 mL), 100 °C, 10 h.

and the reaction proceeded chemoselectively to afford the desired alkenylation product (entry 2). An electron-donating substituent like *p*-methoxystyrene afforded good results at a lower temperature (100 °C, entry 6). Styrene bearing a methyl group at the α -position also gave the desired product (entry 8). To our delight, 1,1-diaryl substituted ethylenes were also suitable substrates for this alkenylation (entries 9–11). Both an electron-donating group (entry 11) and a strong electron-withdrawing trifluoromethyl group (entry 10) were introduced into the 1,1-diaryl substituted ethylene, providing the alkenylation products in good yields.

Since an excess of PPh₃ ligand may cause the formation of phosphonium salts,¹⁰ alkenylation did occur but with low conversion for primary α -cyano alkyl bromides under the present conditions.¹¹ Thus we turned to further optimization of the reaction systems. To our knowledge, Ni(PPh₃)₄ is usually prepared by the reduction of the mixture of Ni(acac)₂ and PPh₃ with Diisobutylaluminium Hydride (DIBAL-H).¹² Therefore, Ni(PPh₃)₄ was replaced by the combination of Ni(acac)₂ and DIBAL-H for further optimization. Subsequent ligand scanning showed that dppf was the most efficient ligand for the alkenylation of primary α -cyano alkyl bromides (see ESI[†] for detailed condition optimization).

With our optimized method, primary α -cyano alkyl bromides could give the alkenylation product in good yields (Table 2, entries 1–3). Upon expanding the substrate scope, the temperature was still important for the reaction with non-electron-rich styrenes, the reaction of *p*-methylstyrene should be conducted at a higher temperature of 120 °C (Table 2, entry 2). To our pleasure, 2-bromo-2-phenylacetonitrile presented high efficiency to couple with 1,1-diphenylethylene (Table 2, entry 6). At the same time,



^{*a*} Method C: the reactions were carried out with **1** (0.50 mmol), **2** (0.75 mmol), 5 mol% Ni(acac)₂, dppf (6 mol%), DIBAL-H (12 mol%), K₃PO₄ (1 mmol), toluene (2 mL), 100 $^{\circ}$ C, 10 h. ^{*b*} Isolated yields. ^{*c*} The reaction was conducted at 120 $^{\circ}$ C. ^{*d*} 48 h.

secondary α -cyano alkyl bromides are still suitable substrates under the present conditions (Table 2, entries 4, 5, 8 and 9). Tertiary α -cyano alkyl bromides were too reactive and they could not be tolerated at the moment. While under the conditions that developed with primary α -cyano alkyl bromides, we did get the cross-coupling product 2-bromo-2-methylpropanenitrile with 1,1-diphenylethylene in 14% yield (Table 2, entry 7). This result showed the generality for the construction of β , γ -unsaturated nitriles using this nickel catalysed alkenylation system.

In conclusion, we have demonstrated the first nickel catalysed Heck-type alkenylation of α -cyano alkyl bromides for the general synthesis of β , γ -unsaturated nitriles. Importantly, high temperature contributed to the selective alkenylation with non-electron-rich olefins, which provides an example of successfully controlling the oxidation of radicals. Further optimization to expand the substrate scope as well as more mechanistic investigation is underway in our laboratory.

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