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Cyano-Borrowing Reaction: Nickel-Catalyzed Direct Conversion of Cyanohydrins and Aldehydes/Ketones to β-Cyano Ketone Zhao-Feng Li, Qian Li, Li-Qing Ren, Qing-Hua Li, Yun-Gui Peng*, Tang-Lin Liu*

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A direct nickel-catalyzed, high atom- and step-economical reaction of cyanohydrins with aldehydes or ketones *via* an unprecedented "cyano-borrowing reaction" has been developed. Cleavage of the C-CN bond of cyanohydrins, aldol condensation followed by conjugate addition of cyanide to α,β -unsaturated ketones proceeded to deliver a range of racemic β -cyano ketones with good to high yields. The practical procedure with the use of commercial and lower-toxic CN source bodes well for wide application of this protocol.

Introduction

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The nitriles are important synthesis intermediates in transformation¹ and are key components in various natural products, medicinal pharmacophores and drugs,² and in organic synthesis, cyano group is equivalent to amine or carbonyl group. The catalytic addition of cyano group to C=C bond has been established as one of the most direct pathways for the synthesis of nitriles.^{3,4} Among the important nitriles, β -cyanoketonesPare commonly utilized in organic synthesis.⁵ One of the classical approaches to deliver these compounds is the catalyzed conjugate addition of cyanide to α , β -unsaturated carbonyl compounds (Hydrocyanation procedure, Scheme 1a),6 which utilizes the highly toxicity and explosive HCN gas as the cyano source. An alternative strategy is the transfer hydrocyanation which involves the commercially available, lower-toxicity and lower-explosive cyanohydrin to deliver nitriles (Scheme 1b), but with low atom economy.⁷ Recently, Morandi developed a nickel-catalyzed transfer hydrocyanation reaction between alkyl nitriles and alkenes or aryl chlorides, which utilizes none toxicity alkyl nitriles as the cyanide source.8 Although the catalyzed hydrocyanation and transfer hydrocyanation reactions have been well developed,6-7 it remains an important challenge to bypass the usage of toxic HCN gas as the cyano source and overcome the issue of atomeconomy. To mitigate these concerns and inspired by the atomand step-economical procedure of β -alkylation of secondary alcohols with aldehydes via borrowing hydrogen reactions⁹⁻¹⁰, we postulated that the cyano group could be tolerated in the reaction with analogous mechanism as the borrowing hydrogen reactions. Guided by these considerations, we envisioned that, as shown in Scheme 1c, under the catalysis of transition metal,

a) Hydrocyanation





c) Our Hypothesis: Cyano-Borrowing Reaction



d) This work: Nickel-Catalyzed Cyano-Borrowing Reaction



High atom-economy: H₂O as the sole side product
C-CN bond cleavage and formation COmmercial, non-toxic CN source

Scheme 1 Development of Cyano-Borrowing.

cleavage of the C-CN bond^{11,12} of the cyanohydrin and deliver the corresponding ketones and metal-cyano intermediate ([M]ⁿ-CN), followed by Aldol condensation of ketones with aldehydes, subsequently conjugate addition of cyanide to

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chalcones and utilizes the [M]ⁿ⁺¹-CN as the cyano donor to deliver the desired products (Scheme 1c). This hypothesis is notable in that cyanohydrin plays a dual role both as the source of ketone and the cyanide donor with high atom- and stepeconomy. Herein, we report the first catalytic process of the direct transformation of cyanohydrins with aldehydes to deliver β -cyano ketones as the sole product *via* nickel catalyzed cyanoborrowing reactions.13

Results and discussion

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To test our hypothesis, we initiated the cyano-borrowing reaction using commercially available acetophenone cyanohydrin 1a which could be prepared from acetophenone and TMSCN and benzaldehyde 2a for the optimization of the reaction conditions. After screening an array of the transition metal catalyst, we found that nickel complex showed better performance. To our delight, a cocktail consisting of NiBr₂, PPh₃, and LiOH as base in dioxane at 100 °C could deliver the desired racemic β -cyano ketone **3aa** in 52% yield (table 1, entry 1). Notably, determined by the crude ¹H NMR of the reaction mixture, not even trace of 1,2-addition products were observed.¹⁴ As shown in Table 1, we then examined an

Table 1 Screening studies of β -alkylation of cyanohydrin **1a** with benzaldehyde 2a^a

		,CHO	[Ni] (5 mol%) L (10 mol%)	~	O CN ↓ ↓ ☆
\bigcirc	+		Base (3.0 equiv.) Solvent, 4A MS		
1a	2	2a	100 °C		3aa
entry	[Ni]	L	base	Solvent	Yield (%) ^b
1	NiBr ₂	PPh₃	LiOH	Dioxane	52
2	NiCl ₂	PPh₃	LiOH	Dioxane	76
3	Ni(OAc) ₂	PPh₃	LiOH	Dioxane	66
4	Ni(OTf) ₂	PPh₃	LiOH	Dioxane	62
5	Ni(acac) ₂	PPh₃	LiOH	Dioxane	71
6	NiCl ₂	PCy ₃	LiOH	Dioxane	76
7	NiCl ₂	dppe	LiOH	Dioxane	72
8	NiCl ₂	dppp	LiOH	Dioxane	78
9	NiCl ₂	dppb	LiOH	Dioxane	37
10	NiCl ₂	BINAP	LiOH	Dioxane	44
11	NiCl ₂	ⁿ⁻ BuPAd ₂	LiOH	Dioxane	82
12	NiCl ₂	^{<i>n</i>-} BuPAd ₂	NaOH	Dioxane	28
13	NiCl ₂	^{<i>n</i>-} BuPAd ₂	KO ^{t-} Bu	Dioxane	trace
14	NiCl ₂	^{<i>n</i>-} BuPAd ₂	Cs ₂ CO ₃	Dioxane	0
15	NiCl ₂	^{<i>n</i>-} BuPAd ₂	DMAP	Dioxane	0
16	NiCl ₂	^{<i>n</i>-} BuPAd ₂	DBU	Dioxane	0
17	NiCl ₂	ⁿ⁻ BuPAd ₂	LiOH	Toluene	22
18	NiCl ₂	ⁿ⁻ BuPAd ₂	LiOH	TBME	23
19	NiCl ₂	ⁿ⁻ BuPAd ₂	LiOH	THF	72
20 ^c	NiCl ₂	ⁿ⁻ BuPAd ₂	LiOH	Dioxane	59
21			LiOH	Dioxane	<10
22	NiCl ₂	^{<i>n</i>-} BuPAd ₂		Dioxane	0

"The reaction was carried out with 0.4 mmol of **1a**. 0.4 mmol of **2a**. 5 mol% [Ni]. 10 mol% ligand (L) and 300 mol% base in 0.5 mL of solvent at 100 °C for 18 h. ^bIsolated vield. "The reaction was carried out at 80 °C, dopm Bis(diphenylphosphino)methane; dppe = Bis(diphenylphosphino)ethane; dppp = Bis(diphenylphosphino)-propane; dppb = Bis(diphenylphosphino)butane; BuPAd₂ = Di(1-adamantyl)-ⁿ⁻butylphosphine; TBME = Methyl tert-butyl ether.

extensive array of parameters. By varying the anion of the nickel salt (i.e., NiCl₂, Ni(OAc)₂, Ni(OTf)₂ and Ni(acac)₂) as precatalysts, NiCl₂ exhibited the best yield (Table 1, entries 3-5 vs 2). The screening of different phosphines revealed that this transformation requires a bulky, electron rich ligand, and t-BuPAd₂ showed the highest reactivity with 82% yield (table 1, entry 11 vs 2 and 6-10). Stronger base such as NaOH and KO^{t-}Bu shows low reactivity. Meanwhile, Cs₂CO₃ and organic base (i.e., DMAP and DBU), failed to provide the target products (table 1, entries 14-16). Optimization of the solvent led to no improvement (table 1, entries 17-19). Lowering the temperature to 80 °C gives a lower yield (table 1, entry 20). Control experiments verified that the presence of Ni-complex was necessary to achieve high yield in cyano-borrowing reaction (table 1, entry 21). No reaction occurred in the absence of LiOH (table 1, entry 22). After the screening of the reaction parameters, we found that NiCl₂ and ^{*n*}-BuPAd₂ as the precatalyst and LiOH as the base in dioxane at 100 °C for 20 h (82% yield) was the optimal conditions.

Having identified the optimized reaction conditions, we further explored the substrate scope of this reaction. Various commercially available ketones cyanohydrins were examined with benzaldehyde (2a) and the results are summarized in Scheme 2. The electron-deficient substrate with varying substituent patterns at p-position did not dramatically influence yields (**3ba-3da**). Substituting the cyanohydrin with *p*-methyl also shows high reactivity and 72% of desire product was obtained (Scheme 2, 3ea). However, substituting the para position with a more electron-rich functionality (i.e., p-MeO) led to diminished yields, but the desired product could be delivered with 86% yield while increasing the reaction temperature to 120 °C (Scheme 2, 3fa). Reactions of cyanohydrin with ortho- and meta-substituted on aryl groups gave excellent yields (Scheme 2, 3ga-3ja). The reaction proceeds smoothly in the case of the

CHO.

3ba (X = Cl), 70% yield **3ca** (X = Br), 90% yield **3da** (X = F), 85% yield

3ha, 72% yield

R¹ `Me

3aa, 82% yield

3ga, 65% yield

3ka, 53% yield

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cyanohydrin bearing a thienyl group, affording the corresponding product 3la in 82% isolated yield. In terms of thealkyl substituents, cyanohydrin derived from butanone proceeded smoothly to afford the desired product with 40% yield (Scheme 2, 3ma). Substrate bearing a cyclopropyl group was well tolerated, leading to the cyclopropyl substituted product with 57% yield (Scheme 2, 3na). Importantly, the cyclopropyl group remains untouched, which indicates that this nickel-catalyzed protocol does not go thought radical pathway. Next, various aldehydes were investigated with acetophenone cyanohydrin (1a) using the optimized reaction conditions, and representative results are summarized in Scheme 3. Benzaldehydes bearing various electron-deficient (3ab-3ad and 3ag-3ah), electron-neutral (3al and 3am) and electron-rich (3ae-3af and 3ai-3ak) substituent reacted with 1a to deliver the desired products in moderate to excellent yields (58-90%). Furthermore, the reaction is also compatible with heteroaryl rings, such as 2-furanyl (3an), 2-thiophenyl (3ao) and unprotected 3-indolyl (3ap), providing diverse 2-cyano ketones in 51-77% yield. Remarkably, compared with the aryl aldehydes, the alkyl substituted aldehydes (e.g., 2-phenylacetaldehyde and cyclohexanecarbaldehyde) reacted with 1a to afford the corresponding products 3aq and 3ar in 64% and 80% yields, respectively. The aldehyde containing a sulfur atom is also tolerated under the nickel-catalyzed protocol and deliver the desired product 3as with a slightly lower yield. To demonstrate the practicality and scalability of our protocol, we proceeded to carry out a gram-scale reaction with 5.0 mmol 2i reacted with 10.0 mmol 1a catalyzed by 5 mmol% of NiCl₂, affording 1.12 g 3ai in 85% yield, suggesting that this procedure is quite reliable and have practically applicable.



°The reaction was carried out with 0.4 mmol of **1a**, 0.4 mmol of **2**, 5 mol% NiCl₂, 10 mol% "BuPAd₂ and 300 mol% LiOH in 0.5 mL of dioxane at 100 °C for 18 h. The yields are isolated yield. ^{*b*}The reaction was carried out at 120 °C.

Scheme 3. Reaction Scope of Aldehydes.

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Inspired by the success with nickel-catalyzed cyano-borrowing aldehydes, we further demonstrate the cyano-borrowing protocol to the more challenging substrates such as aldehyde cyanohydrin 5. To our delight, benzaldehyde cyanohydrin 5a reacted with acetophenone 4a smoothly under standard condition, yielded the corresponding product 3aa with full conversion and 83% isolated yield. To indicate the generality of this protocol, we then examined the scope of benzaldehyde cyanohydrins and ketones. In addition to the phenyl group, it was found that substrates bearing electron-rich or electrondeficient on the benzene ring were well tolerated to give the β cyano ketones in moderate to good yields (3ba, 3ea, 3ad and **3af** in Scheme 4). Moreover, heteroaryl and alkyl substitutes also participated in this protocol very well (Scheme 4, 3la, 3ma, 3ao and 3ar).



°The reaction was carried out with 0.4 mmol of **1a**, 0.4 mmol of **2**, 5 mol% NiCl₂, 10 mol% "BuPAd₂ and 300 mol% LiOH in 0.5 mL of dioxane at 100 °C for 18 h. The yields are isolated yield. ^{*b*}The reaction was carried out at 120 °C.

Scheme 4 Examples of aldehyde cyanohydrin with ketone.^a

To illustrate the scope and limitations of the new transformation, challenging substrates beyond methyl ketones were further examined, shown in Scheme 5. The propiophenone cyanohydrin 6 was selected to react with benzaldehyde 2a under the standard reaction conditions, the desired product 8 was obtained in 31% isolated yield and high diasteroselectivity (d.r > 10:1) (Scheme 5a, left). Furthermore, we also examined benzaldehyde cyanohydrin 5a and propiophenone 7, with nickel catalyst, the corresponding product 8 was obtained in 25% yield. (Scheme 5a, right). Notably, the bioactive ketone, epiandrosterone was tested in this reaction with the partner of benzaldehyde cyanohydrin 5a, and the corresponding product **10** was deliver in 57% yields with 5:1 dr (Scheme 5b), which shown the potential of this nickelcatalyzed cyano borrowing process for the selective modification of bioactive ketones.

To shed light on the mechanism for the nickel-catalyzed cyano-

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Scheme 5. Cyano-borrowing beyond methyl ketones.

borrowing protocol, a series of control experiments were conducted. As shown in Scheme 6, acetophenone cyanohydrin 1a reacted smoothly with chalcone 11 and give the corresponding product 3aa in excellent yields, which indicated that cyanohydrin are the source of cyano group in the transfer hydrocyanation under standard reaction condition. Benzaldehyde cyanohydrin 5a could also reacting with chalcone 11 efficiently, deliver 3aa with 89% yield, and the hydrogenborrowing product 12 was not observed, showing that cleavage the C-CN bond is more easy than the C-H bond in cyanohydrins. Meanwhile, in the crossover reaction of 1a, 2e and 11 under standard condition, we got the corresponding products 3aa and 3ae with the ratio of 1.05:1, which shows that the cyano group from the cleavage of C-CN bond of cyanohydrin was a free anion in this nickel-catalyzed protocol and has the same opportunity to conjugate to each chalcone. Together, these experimental results support our hypothesis on nickel-catalyzed step- and atom-economical cyano-borrowing reaction of cyanohydrin with aldehydes or ketones (Scheme 1c) (for more details of the mechanism studies, please see supporting information).



Scheme 6 Mechanism studies.

Experimental

General Procedure: Method A: To a vial equipped with a dried stir bar was added aldehydes (0.2 mmol) ketone cyanohydrins (0.4 mmol) NiCl₂ (5 mol%), ⁿ⁻BuPAd₂ (5 mol%), LiOH (0.6 mmol), 100 mg 4Å MS and anhydrous dioxane (1 mL) in the glovebox? The reaction mixture was taken outside the glovebox and allowed to stir at room temperature for 30 min. After then, the reaction mixture was allowed to stir at 100 °C for 18 hours. The crude reaction mixture was concentrated under reduced pressure and directly purified by silica gel chromatography to give pure products.

Method B: To a vial equipped with a dried stir bar was added ketones (0.2 mmol) aldehyde cyanohydrins (0.4 mmol) NiCl₂ (5 mol%), n-BuPAd₂ (5 mol%), LiOH (0.6 mmol), 100 mg 4Å MS and anhydrous dioxane (1 mL) in the glovebox. The same procedure as Method A.

Conclusions

In conclusion, we have developed an unprecedented nickelcatalyzed protocol for the direct conversion of cyanohydrins and aldehydes or ketones into racemic β -cyano ketones via nickel-catalyzed cyano-borrowing reaction. A range of cyanohydrins derived from aldehyde or ketone could be tolerated and delivered products with high regioselectivity and good to excellent yields. To the best of our knowledge, catalytic conversion of cyanohydrins into β -cyano ketones by reaction with aldehydes/ketones has not been reported. Further studies of catalytic cyano-borrowing reaction of cyanohydrins is in progress in our reasearch lab and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

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