

Catalytic Cyanation of C–N Bonds with CO₂/NH₃

Fachao Yan, Jian-Fei Bai, Yanan Dong, Shaoli Liu, Chen Li, Chen-Xia Du, and Yuehui Li*

Cite This: *JACS Au* 2022, 2, 2522–2528

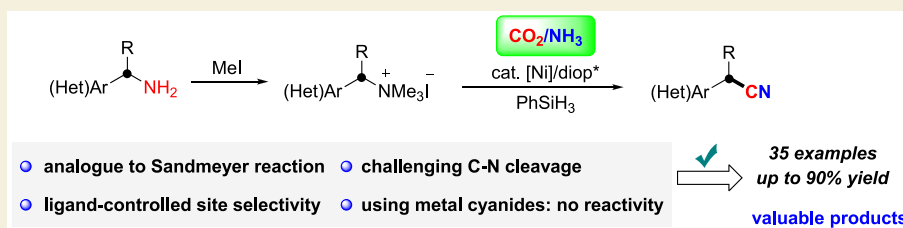
Read Online

ACCESS |

Metrics & More

Article Recommendations

Supporting Information



ABSTRACT: Cyanation of benzylic C–N bonds is useful in the preparation of important α -aryl nitriles. The first general catalytic cyanation of α -(hetero)aryl amines, analogous to the Sandmeyer reaction of anilines using reductive cyanation with CO₂/NH₃. A broad array of α -aryl nitriles was obtained in high yields and regioselectivity by C–N cleavage of intermediates as ammonium salts. Good tolerance of functional groups such as ethers, CF₃, F, Cl, esters, indoles, and benzothiophenes was achieved. Using ¹³CO₂, a ¹³C-labeled tryptamine homologue (five steps, 31% yield) and Cysmethynil (six steps, 37% yield) were synthesized. Both electronic and steric effects of ligands influence the reactivity of alkyl nickel species with electrophilic silyl isocyanates and thus determine the reactivity and selectivity of the cyanation reaction. This work contributes to the understanding of the controllable activation of CO₂/NH₃ and provides the promising potential of the amine cyanation reaction in the synthesis of bio-relevant molecules.

KEYWORDS: reductive cyanation, utilization of CO₂/NH₃, nitrile synthesis, α -(hetero)aryl amines, C–N activation, nickel, isotope labeling

INTRODUCTION

Selective transformation of C–N bonds is attractive but challenging.^{1–3} Although the transformation of amines to nitriles is a straightforward process, examples have been published only infrequently. The Sandmeyer reaction is the traditional method for the cyanation of anilines and involves *in situ* preparation of aryl diazonium salts (Figure 1a).^{4,5} In addition, the cyanation of C–N bonds is difficult to achieve *via* traditional S_N2- or S_N1-type reactions. Recently, Watson *et al.*

developed the nickel-catalyzed cyanation of Katritzky pyridinium salts with Zn(CN)₂ and one example of benzylic pyridinium salt was reported.⁶ C–N bond cleavage of enaminones promoted by I₂ for synthesis of β -cyano enones was also realized.⁷ Expanding the diversity of C–C coupling reactions is a main topic in modern chemistry,^{8–28} and utilization of CO₂ as the most abundant, nontoxic C1 synthon provides a promising approach to economically generate desirable products.^{29,30} Recently, Martin *et al.* and Yu *et al.* have reported carboxylation of C–N bonds in benzyl ammonium salts with CO₂.^{31,32} The utilization of CO₂ in catalytic synthesis of nitriles however is yet to be explored.

Inspired by the biological 2e-reduction process for the formation of cyanide ligands in [NiFe]-hydrogenase from CO₂ and NH₃,³³ we have prepared aryl nitriles by cyanation of aryl halides using CO₂.^{34,35} The wide application of the Sandmeyer reaction of anilines led us to envision a Sandmeyer reaction-like system for cyanation of α -aryl amines, and to the best of

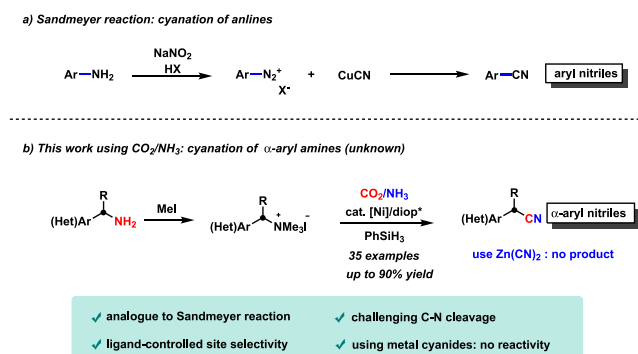
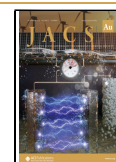


Figure 1. (a) Sandmeyer reaction and (b) cyanation of α -aryl amines using CO₂/NH₃.

Received: July 10, 2022
Revised: October 4, 2022
Accepted: October 4, 2022
Published: October 20, 2022

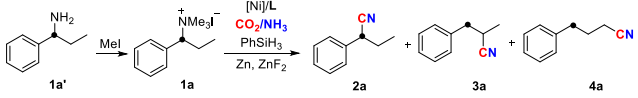


our knowledge, a general procedure of C–N bond cyanation to afford α -aryl nitriles has not yet been reported. Moreover, the selective incorporation of cyano group has attracted tremendous attention.^{36–43} Even by far, the most prominent production process for adiponitrile (>10⁶ tons per year) is suffering from toxic cyanide and costly purification.⁴⁴ Herein, we report the first example of general cyanation of α -aryl amines via the challenging C–N bond cleavage for the synthesis of α -aryl nitriles using CO₂/NH₃ (Figure 1b). This nickel-catalyzed reaction allows the synthesis of one carbon longer nitrile *via* a cyanation–reduction–cyanation sequence from a simple substrate, and it has been successfully applied to the convenient synthesis of isotopically labeled tryptamine precursors.^{45,46} Notably, no desired product was detected when metal cyanides were used. Thus, the reductive electrophilic cyanation process using cheap and abundant CO₂/NH₃ provides an alternative chemical platform for C–C coupling reactions and offers a hitherto unrecognized opportunity for cyanide-free synthesis of bio-relevant α -(hetero)aryl nitriles.

RESULTS AND DISCUSSION

Initially, our investigation began by carrying out reactions on benzyl ammonium salt (**1a**) formed *in situ* by the reaction of the amine (**1a'**) with MeI (Table 1). During optimization,

Table 1. Ligand Screening for Nickel-Catalyzed C–N Bond Cyanation^a



Reaction scheme showing the conversion of benzyl ammonium salt **1a'** to **1a** using MeI, followed by nickel-catalyzed cyanation with CO₂/NH₃, PhSiH₃, Zn, and ZnF₂ to yield products **2a**, **3a**, and **4a**.

Ligand structures shown:

- (*R,R*)-DIOP (L1)
- (*R,R*)-3,5-^tBu-DIOP (L2) Ar = 3,5-di^tBu-C₆H₃
- (*R,R*)-3,5-Me-DIOP (L3) Ar = 3,5-diMe-C₆H₃
- (*R,R*)-Cp-DIOP (L4)
- (*R,R*)-Cy-DIOP (L5)
- (*R,R*)-Ph-DIOP (L6)
- (*R,R*)-4-F-Ph-DIOP (L7)

entry	ligand (mol %)	yield (%)	rr (2a:3a:4a)
1	dppb	49	18:29:53
2	L1	87	68:10:22
3	L2	trace	trace
4	L3	80	84:5:11
5	L4	66	60:16:24
6	L5	22	76:16:8
7	L6	26	72:15:13
8	L7	35	86:6:8

^aReaction conditions: benzyl ammonium salts **1a** (0.15 mmol, 1.0 equiv), NiBr₂·(diglyme) (12 mol %), ligand (15 mol %), CO₂/NH₃ (15/15 mL), Zn (1.2 equiv), PhSiH₃ (5.0 equiv), and ZnF₂ (50 mol %) were stirred in NMP:diglyme (0.5:0.1 mL) at 120 °C for 28 h. Yields and regioselectivities were determined by GC. dppb = 1,4-bis(diphenylphosphino)butane.

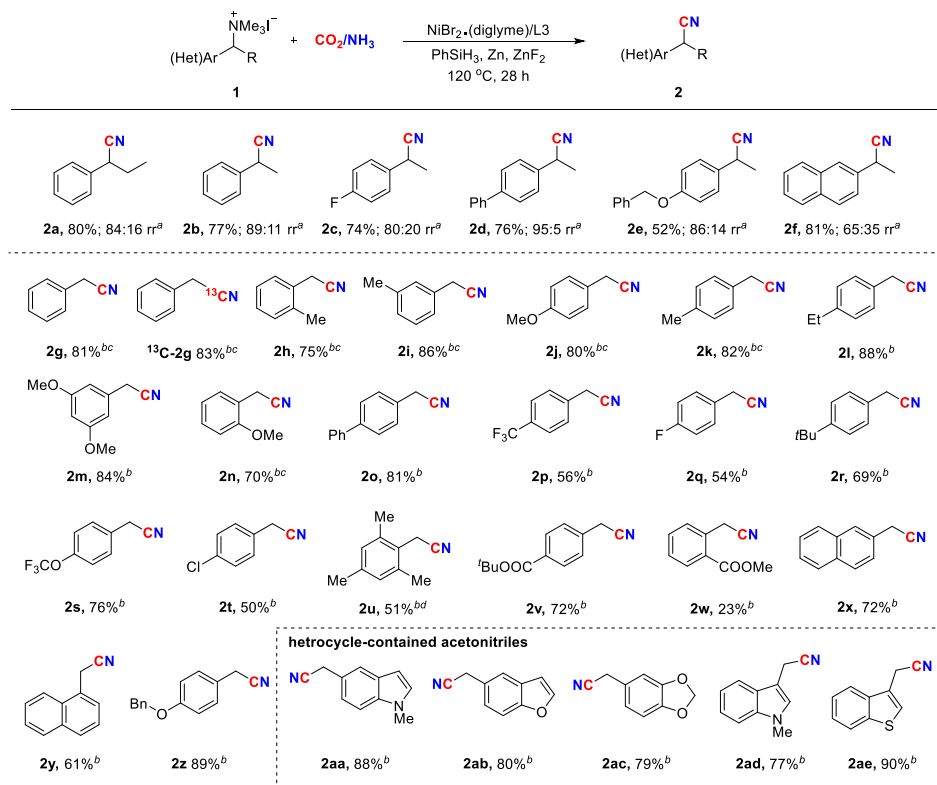
careful selection of reductants is crucial to evade the undesired reduction pathways, such as hydrolysis of ammonium salt, reduction of CO₂, and/or reduction of nitrile products. Under CO₂ and NH₃, both at atmospheric pressure, the use of phenyl silane efficiently provided the cyanated products, albeit in low to moderate regioselectivities (Table 1, entries 1 and 2, 49–87% yields; 18–68% selectivity for **2a**). DIOP turned to be the best ligand among the various ligands tested (Table S2).^{47–50} Since ligands containing a DIOP backbone proved to be suitable for the reaction, various DIOP derivatives (L1–L7) with different steric and electronic properties were synthesized and tested. It was found that the more sterically hindered

ligand L3 ((*R,R*)-3,5-Me-DIOP) provided a better reactivity (entries 3–8 and Table S2).^{51–53} Also, when using L3 as the ligand, the switchable regioselectivity between the α -aryl nitrile (**2a**) and linear nitrile (**4a**) could be well tuned, and the desired product (**2a**) was obtained in good yield with high regioselectivity (entry 4, 80% yield; 84:5:11 rr). These results highlight the adjustment of the ability of ligands for selective cyanation on the benzylic carbon over other positions.

With the optimal conditions in hand, we next examined the substrate scope in the synthesis of different α -(hetero)aryl nitriles (Table 2). Considering the electronic properties, we found that benzyl ammonium salts (**1**) bearing electron-rich or electron-deficient groups could deliver the α -aryl nitriles in moderate to good yields with high regioselectivity (**2a–2f**). However, the reaction gave racemic products. Substrates containing various functional groups such as fluorine (**1c**), phenyl (**1d**), and naphthalene (**1f**) were examined. All were smoothly converted to the corresponding α -aryl nitriles in yields of 74–81%. Notably, selective cyanation between C–N and C–O bonds to form the α -aryl nitrile product (**2e**) could be achieved, albeit in diminished yield under the established conditions.

Aryl acetonitrile compounds are valuable intermediates and are generally used for diverse modification at their α -carbon to synthesize chiral α -amino acid precursors.^{54–57} Remarkably, the devised protocol is applicable to synthesize aryl acetonitriles (**2**) from the corresponding primary benzyl ammonium salts (**1**), showcasing the versatile utility of this methodology. Initially, we evaluated the catalytic cyanation of the benzyl ammonium salt (**1g**) with CO₂ and NH₃ (Tables S3–S5). Examination of the reaction parameters showed that the cyanation of **1g** with CO₂/NH₃ and organophosphorus ligands catalyzed by NiBr₂ proceeds efficiently (Table S4). Evaluation of various ligands showed that phosphine-containing ligands outperformed ligands containing nitrogen in both reactivity and chemoselectivity. Systematic investigation of phosphine ligands by changing the chain length between two phosphorus atoms was found to improve the yield of **2g**. The ligand 1,2-bis(diphenylphosphino)ethane (dppe) showed a remarkable performance, producing **2g** in 81% yield.

Generally, studies of the substrate scope revealed that ammonium salts bearing various substituents are tolerated and afford the desired aryl acetonitriles in moderate to high yields (Table 2). Use of ¹³CO₂ led us to explore a catalytic protocol to prepare isotopically labeled nitriles. First, using ¹³CO₂, we obtained ¹³C-**2g** in 83% yield, showing that the carbon source of the CN group in the product was derived from CO₂. This reaction exhibited excellent chemoselectivity, and it was found that benzyl ammonium salts substituted with either electron-donating groups (Me, OMe, Et, *t*-Bu, and OCF₃) or electron-withdrawing groups (CF₃, F, COOMe, and COO*t*-Bu) are well tolerated, giving **2h–2n**, **2p–2s**, and **2v–2w**. The reaction is applicable to aromatic substrates with fused rings (**2o**, **2x**, and **2y**), indicating that molecules with expanded π -conjugated systems are tolerated. A substrate with chlorine on the aromatic ring provided the chlorophenyl nitrile (**2t**) in 50% yield, together with phenyl nitrile as a byproduct formed by dehalogenative hydrogenolysis. It is noteworthy that the benzylic C–N bond of the ammonium salt (**1z**) was selectively converted to the corresponding nitrile (**2z**) in 89% yield with the benzylic C–O bond remaining intact. In contrast, only a trace amount of product was formed in the presence of the

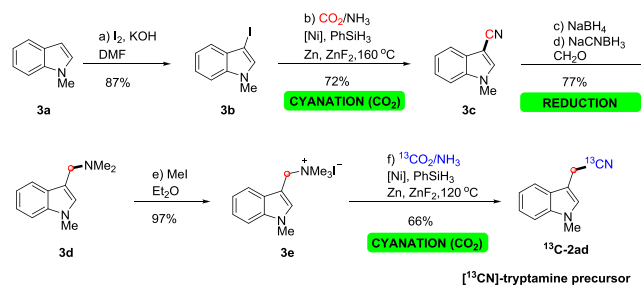
Table 2. Applicability Study of α -(Hetero)Aryl Amines

^aReaction conditions: ammonium salt (**1**) (0.15 mmol, 1.0 equiv), NiBr₂·(diglyme) (12 mol %), L3 (15 mol %), CO₂/NH₃ (15/15 mL), Zn (1.2 equiv), ZnF₂ (50 mol %), NMP:diglyme (0.5:0.1 mL), 120 °C, 28 h. Isolated yields. ^bNiBr₂ (12 mol %), dppe (12 mol %), NMP:toluene (0.5:0.1 mL), 120 °C, 24 h. Isolated yields. ^cGC yields reported using *n*-tetradecane as the internal standard. ^d30 h. rr represents the ratio of the major product to the sum of all other isomers as determined by GC analysis.

cyanating reagent, Zn(CN)₂.⁶ We studied the reaction of heterocyclic substrates such as indole and furan and found the method to be applicable, obtaining **2aa–2ae** in yields of 77–90%. Specifically, cyanation of the 3-substituted indole ammonium salt provided the tryptamine precursor (**2ad**) in a good yield. Subsequent reduction of **2ad** with LiAlH₄ provided the tryptamine derivative in two steps, a method that is far superior to the classical method that requires more steps and a tedious workup. At the same time, different aliphatic amines were tested and almost no desired nitrile products could be obtained.⁴⁵

Tryptamine precursors produced from indole are a privileged motif in biological and pharmaceutical research, but only limited methods are known for their preparation.^{45,46,58,59} We prepared the intermediate indole-3-carbonitrile (**3c**) in 72% yield with a nickel-catalyzed reaction with CO₂ and NH₃. Treatment of ¹³C-CO₂ with ammonium salt (**3e**) and NH₃ under standard conditions gave the ¹³C-labeled tryptamine precursor (¹³C-**2ad**) in 66% yield (Scheme 1). This protocol provides an alternative valuable route to construct homologous tryptamines or ¹³C-labeled indole derivatives efficiently. This methodology has also been applied to the production of ¹³C-labeled Cysmethynil (Scheme 2). The reaction of the indole ammonium salt (**4e**) with ¹³CO₂ and NH₃ provided the ¹³C-labeled intermediate indole derivative (**4f**) in 62% yield, and this was finally converted by treatment with potassium hydroxide to ¹³C-labeled Cysmethynil (**4g**) in 89% yield.^{60,61}

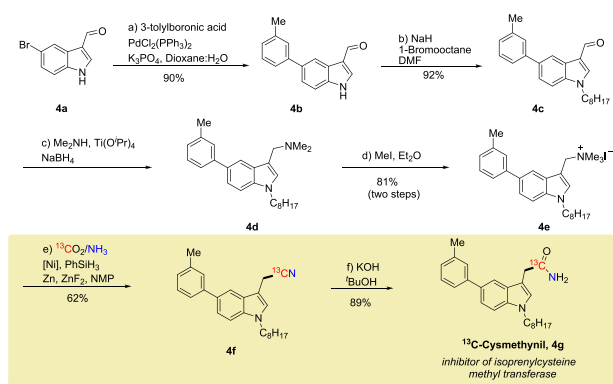
Scheme 1. Synthetic Application for Aryl Acetonitrile. I: Cyanation–Reduction Sequence for ¹³C-Labeled Tryptamine Precursors



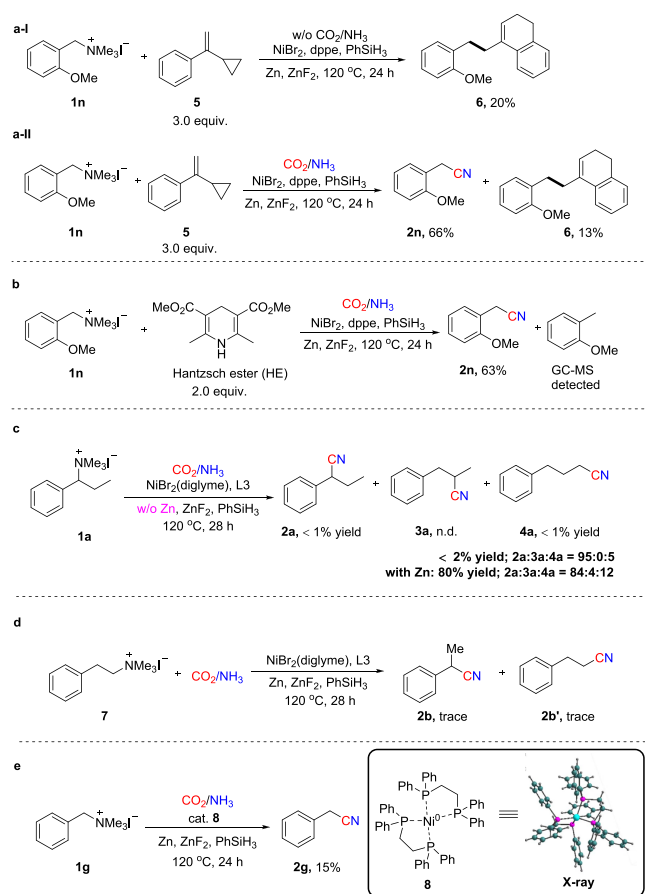
STUDIES OF THE MECHANISM

Additional experiments were conducted in an effort to understand the mechanism of this transformation. Radical clock experiments were conducted with benzyl ammonium salts (**1n**) and α -cyclopropylstyrene (**5**). The ring-expanded product (**6**) was obtained in 20% yield (Scheme 3a-I).^{62,63} The benzyl ammonium salt (**1n**) was converted to *o*-methoxyphenyl acetonitrile (**2n**) in 66% yield along with the ring-expanded product (**6**) (Scheme 3a-II) in 13% yield. These results indicate that although the well-known oxidative addition of ammonium salts to Ni(0) is regarded as a major pathway, the alternative radical pathway cannot be excluded.⁶⁴ In the presence of a Hantzsch ester, the benzyl ammonium salt (**1n**), a hydrogen donor capable of trapping carbon radicals (Scheme 3b), was transformed into the nitrile (**2n**), which was

Scheme 2. Synthetic Application for Aryl Acetonitrile. II: Synthesis of Isotopically Labeled Cysmethynil



Scheme 3. (a–e) Mechanistic Studies



formed as a major product in 63% yield, with the formation of a minor product, 2-methylanisole, under standard conditions.^{63,65} This result is in accord with the hypothesis that a benzylic radical was formed in the mixture and subsequently reacted with a hydrogen of the Hantzsch ester to give 2-methylanisole. Control experiments were conducted to gain more information on the active benzyl-nickel species. As shown in Scheme 3c, in the absence of zinc powder, only trace amounts of branched and linear nitriles were detected to be formed, with 95:0:5 regioselectivity. Since nickel(II) complexes can be reduced to nickel(I) complexes by zinc powder through a single-electron transfer process and nickel(I) species can participate in Ni-catalyzed coupling or chain walking

processes, a radical mechanism with nickel(I) active intermediates in which cyanation is taking place. As shown in Scheme 3d, when the ammonium salt of 2-phenyl ethylamine (7) was the substrate, only trace amounts of nitriles were obtained. This result implies that an efficient C–N bond activation and the formation of benzyl-nickel intermediate are crucial for the efficient cyanation of terminal sp^3 C–H bonds. We attempted to isolate the active intermediate in the reaction of the *ortho*-COOMe benzyl ammonium salt (1w) (see III-8 in the SI).^{66,67} Ni(dppe)₂ (8) was obtained, and its structure was confirmed by X-ray crystallography (Scheme 3e). Using compound 8 as the catalyst in the cyanation of the benzyl ammonium salt (1n), the desired product was obtained in 15% yield. This implies that the nickel(0) active species is involved and the use of more ligand (in a ratio to Ni of 2:1) decreases the reactivity. When DIPAMP* (L9: (1,2-Bis((R)-(2-methoxyphenyl)(phenyl)phosphino)ethane) was used as the ligand, only 13% selectivity for 2a was observed (Table S2). In order to understand the regioselectivity differences between the bisphosphine ligand, DIOP* (L3), and DIPAMP* (L9), density functional theory (DFT) calculations based on the hybrid of the Becke's three-parameter exchange functional and the Lee, Yang, and Parr correlation functional (B3LYP) were performed for the benzylic nickel species.^{68–70} The basis set used for C, H, O, P, and Br atoms was 6-31G, and the LANL2DZ pseudopotential basis set was employed for the Ni atom. The vibrational frequency was computed at the same level of theory to determine whether each optimized structure represented an energy minimum or a transition state. The natural population analysis charge was also calculated using the same method as in the optimization. As shown in Figure S3, different electronic densities on the Ni center (0.365 vs 0.345) and bite angles (P–Ni–P: 94.59 vs 78.22°) were obtained for these two ligands. This suggests that both the electronic and steric effects of ligands influence the reactivity with silyl isocyanates of alkyl nickel species and the tendency of chain walking *via* an iterative β -H elimination and reinsertion process.

Based on the experimental results and previous reports, we propose a plausible reaction mechanism for the benzyl nitriles (Figure 2).^{34,35,63,64} First, the nickel(II)-precursor formed *in situ* is reduced and the nickel(0)-species (I) is generated in the presence of silanes and Zn. Subsequently, the benzyl ammonium salt (1a) can be reduced by nickel(0) to give a benzyl radical and a nickel(I) species (II) followed by a radical addition reaction, which delivers the nickel(II) intermediate (III). This intermediate is then reduced by Zn and silanes to generate the thermodynamically favored benzyl-nickel(I) intermediate (IV), which is inserted by silyl isocyanate intermediates to give a transient imidate species (V) in the presence of DIOP* (L3) as the ligand. As a minor process, the β -hydrogen elimination of the intermediate benzyl-nickel(I) (IV) would form the nickel(I) hydride species, subsequently delivering the chain walking nitrile products.^{71–74} The key to success is the careful choice of the ligand, which favors the reactivity of the benzyl-nickel(I) intermediate and/or the silyl isocyanate insertion step. The transient imidate species (V) are then transformed into benzyl nitriles *via* a plausible 1,3-silyl N-to-O migration,^{27,75,76} accompanied by the formation of a nickel silicate intermediate (VI), which upon reduction by hydrosilane and zinc, regenerates the species (I), closing the catalytic cycle.

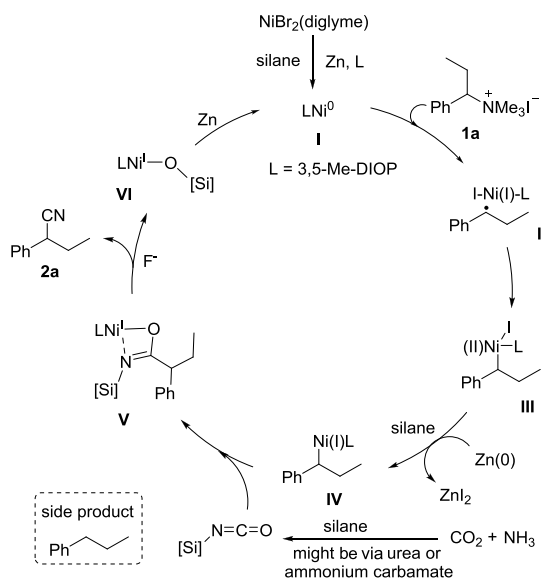


Figure 2. Plausible reaction pathway for nitriles using CO_2 and NH_3 .

CONCLUSIONS

In summary, we have developed the catalytic cyanation of α -aryl amines *via* ammonium salt intermediates with CO_2/NH_3 as a source of the cyano group. This versatile protocol provides a straightforward and cyanide-free route to an array of valuable benzylic nitriles in moderate to good yields. The success of this cyanation reaction is attributed to the careful selection of a bisphosphine ligand that can control the formation and/or reactivity of the benzyl-nickel(I) intermediate. This reaction exhibits broad functional group tolerance and operational simplicity. ^{13}C -containing nitriles can be obtained conveniently using $^{13}\text{CO}_2$. The cyanation of C–N bonds with CO_2/NH_3 allows electrophilic cyanation of the C–N bond to form cyano products and supports downstream applications in synthesis and their prospective use in the synthesis of bio-relevant molecules.

METHODS

General Procedure for the Reductive Cyanation of Ammonium Salts Forming Nitriles

Under a nitrogen atmosphere, the nickel-catalyst (12 mol %, 0.018 mmol), ligand (15 mol %, 0.0225 mmol), ZnF_2 (50 mol %, 0.075 mmol), Zn (1.2 equiv, 0.18 mmol), ammonium salts (1.0 equiv, 0.15 mmol), and a stirring bar were placed in a 10 mL oven-dried sealed tube (Figure S4). Then, the respective solvents and PhSiH_3 (5.0 equiv, 0.75 mmol) were injected by a syringe. The tube was sealed, and CO_2 (15 mL) and NH_3 (15 mL) were injected by a syringe after N_2 was removed under vacuum. Then, the mixture was stirred for the indicated time in a preheated alloy block. After the reaction was finished, the tube was cooled to room temperature and the pressure was released. The yield was measured by GC analysis or isolated by preparative thin-layer chromatography on silica gel plates to give nitriles (for the detailed procedure, see Figures S5 and S6).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacsau.2c00392>.

General notes, reaction details, characterization data, and ^1H , ^{13}C , and heteroatom NMR spectral data (PDF)

AUTHOR INFORMATION

Corresponding Author

Yuehui Li – State Key Laboratory for Oxo Synthesis and Selective Oxidation, Suzhou Research Institute of LICP, Center for Excellence in Molecular Synthesis, Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences, Lanzhou 730000, P. R. China; orcid.org/0000-0002-4520-1418; Email: yhli@licp.cas.cn

Authors

Fachao Yan – State Key Laboratory for Oxo Synthesis and Selective Oxidation, Suzhou Research Institute of LICP, Center for Excellence in Molecular Synthesis, Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences, Lanzhou 730000, P. R. China; University of Chinese Academy of Sciences, Beijing 100049, P. R. China

Jian-Fei Bai – State Key Laboratory for Oxo Synthesis and Selective Oxidation, Suzhou Research Institute of LICP, Center for Excellence in Molecular Synthesis, Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences, Lanzhou 730000, P. R. China

Yanan Dong – State Key Laboratory for Oxo Synthesis and Selective Oxidation, Suzhou Research Institute of LICP, Center for Excellence in Molecular Synthesis, Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences, Lanzhou 730000, P. R. China

Shaoli Liu – College of Chemistry and Chemical Engineering, Yantai University, Yantai 264005, P. R. China; orcid.org/0000-0001-7197-8805

Chen Li – State Key Laboratory for Oxo Synthesis and Selective Oxidation, Suzhou Research Institute of LICP, Center for Excellence in Molecular Synthesis, Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences, Lanzhou 730000, P. R. China

Chen-Xia Du – College of Chemistry and Molecular Engineering, Zhengzhou University, Zhengzhou 450001, P. R. China

Complete contact information is available at: <https://pubs.acs.org/10.1021/jacsau.2c00392>

Author Contributions

Y.L. supervised this study. F.Y. performed the catalytic experiments and mechanistic studies. J.-F.B., Y.D., C.L., and C.-X.D. discussed the result. S.L. performed the theoretical calculations. Y.D. performed part of synthetic experiments. Y.L. and F.Y. wrote the paper. All authors have given approval to the final version of the manuscript. CRediT: Fachao Yan data curation, investigation, methodology, writing-original draft; Jian-Fei Bai conceptualization, investigation; Yanan Dong data curation, formal analysis, investigation, methodology, validation; Shaoli Liu data curation, investigation, software; Chen Li formal analysis, methodology, validation; Chen-xia Du methodology, resources; Yuehui Li conceptualization, funding acquisition, methodology, project administration, supervision, writing-original draft, writing-review & editing.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors would like to dedicate this work to Professor Matthias Beller (LIKAT) on the occasion of his 60th birthday

and acknowledge financial support by the NSFC (22022204, 22072167, and 22001257). F.Y. thanks Dr. Qiming Sun (Soochow University) for valuable discussions and help.

REFERENCES

- (1) Ouyang, K.; Hao, W.; Zhang, W.-X.; Xi, Z. Transition-metal-catalyzed cleavage of C-N single bonds. *Chem. Rev.* **2015**, *115*, 12045–12090.
- (2) Wang, Q.; Su, Y.; Li, L.; Huang, H. Transition-metal catalyzed C-N bond activation. *Chem. Soc. Rev.* **2016**, *45*, 1257–1272.
- (3) García-Cárceles, J.; Bahou, K. A.; Bower, J. F. Recent methodologies that exploit oxidative addition of C-N bonds to transition metals. *ACS Catal.* **2020**, *10*, 12738–12759.
- (4) Sandmeyer, T. Ueber die ersetzung der amid-gruppe durch Chlor, brom und cyan in den aromatis substanzen. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 1633–1635.
- (5) Xu, W.; Xu, Q.; Li, J. Sandmeyer cyanation of arenediazonium tetrafluoroborate using acetonitrile as a cyanide source. *Org. Chem. Front.* **2015**, *2*, 231–235.
- (6) Xu, J.; Twitty, J. C.; Watson, M. P. Nickel catalyzed deaminative cyanation: nitriles and one-carbon homologation from alkyl amines. *Org. Lett.* **2021**, *23*, 6242–6245.
- (7) Liu, T.; Wan, J.; Liu, Y. Metal-free enaminone C-N bond cyanation for stereoselective synthesis of (E)- and (Z)- β -cyano enones. *Chem. Commun.* **2021**, *57*, 9112–9115.
- (8) Sundermeier, M.; Zapf, A.; Beller, M. Palladium-catalyzed cyanation of aryl halides: recent developments and perspectives. *Eur. J. Inorg. Chem.* **2003**, *2003*, 3513–3526.
- (9) Anbarasan, P.; Schareina, T.; Beller, M. Recent developments and perspectives in Palladium-catalyzed cyanation of aryl halides: synthesis of benzonitriles. *Chem. Soc. Rev.* **2011**, *40*, 5049–5067.
- (10) Wang, C.-S.; Dixneuf, P. H.; Soulé, J.-F. Photoredox catalysis for building C–C bonds from C(sp²)–H bonds. *Chem. Rev.* **2018**, *118*, 7532–7585.
- (11) Kurono, N.; Ohkuma, T. Catalytic asymmetric cyanation reactions. *ACS Catal.* **2016**, *6*, 989–1023.
- (12) Pimparkar, S.; Koodan, A.; Maiti, S.; Ahmed, N. S.; Mostafa, M. M.; Maiti, D. C-CN bond formation: an overview of diverse strategies. *Chem. Commun.* **2021**, *57*, 2210–2232.
- (13) Ding, S.; Jiao, N. *N,N*-Dimethylformamide: a multipurpose building block. *Angew. Chem., Int. Ed.* **2012**, *51*, 9226–9237.
- (14) Wang, T.; Jiao, N. Direct approaches to nitriles via highly efficient nitrogenation strategy through C–H or C–C bond cleavage. *Acc. Chem. Res.* **2014**, *47*, 1137–1145.
- (15) Ahmad, M. S.; Pulidindi, I. N.; Li, C. Recent advances in C–CN and C–H bond activation of green nitrile (MeCN) for organo-complexation, cyanation and cyanomethylation. *New J. Chem.* **2020**, *44*, 17177–17197.
- (16) Wang, F.; Chen, P.; Liu, G. Copper catalyzed radical relay for asymmetric radical transformations. *Acc. Chem. Res.* **2018**, *51*, 2036–2046.
- (17) Schareina, T.; Zapf, A.; Cotté, A.; Gotta, M.; Beller, M. A versatile protocol for copper-catalyzed cyanation of aryl and heteroaryl bromides with acetone cyanohydrin. *Adv. Synth. Catal.* **2011**, *353*, 777–780.
- (18) Mills, L. R.; Graham, J. M.; Patel, P.; Rousseaux, S. A. L. Ni-catalyzed reductive cyanation of aryl halides and phenol derivatives via transnitration. *J. Am. Chem. Soc.* **2019**, *141*, 19257–19262.
- (19) Jagadeesh, R. V.; Junge, H.; Beller, M. Green synthesis of nitriles using non-noble metal oxides-based nanocatalysts. *Nat. Commun.* **2014**, *5*, 4123.
- (20) Malapit, C. A.; Reeves, J. T.; Busacca, C. A.; Howell, A. R.; Senanayake, C. H. Rhodium-catalyzed transnitration of aryl boronic acids with dimethylmalonitrile. *Angew. Chem., Int. Ed.* **2016**, *55*, 326–330.
- (21) Sundermeier, M.; Zapf, A.; Beller, M. A convenient procedure for the palladium-catalyzed cyanation of aryl halides. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661–1664.
- (22) Sundermeier, M.; Mutyala, S.; Zapf, A.; Spannenberg, A.; Beller, M. A convenient and efficient procedure for the palladium-catalyzed cyanation of aryl halides using trimethylsilylcyanide. *J. Organomet. Chem.* **2003**, *684*, 50–55.
- (23) Ding, S.; Jiao, N. Direct transformation of *N,N*-dimethylformamide to -CN: Pd-catalyzed cyanation of heteroarenes via C-H functionalization. *J. Am. Chem. Soc.* **2011**, *133*, 12374–12377.
- (24) Li, J.; Zhang, Z.; Wu, L.; Zhang, W.; Chen, P.; Lin, Z.; Liu, G. Site-specific allylic C-H bond functionalization with a copper-bound *N*-centred radical. *Nature* **2019**, *574*, 516–521.
- (25) Yu, X.; Tang, J.; Jin, X.; Yamamoto, Y.; Bao, M. Manganese-catalyzed C–H cyanation of arenes with *N*-cyano-*N*-(4-methoxy)-phenyl-*p*-toluenesulfonamide. *Asian J. Org. Chem.* **2018**, *7*, 550–553.
- (26) Kim, J.; Choi, J.; Shin, K.; Chang, S. Copper-mediated sequential cyanation of aryl C-B and arene C-H bonds using ammonium iodide and DMF. *J. Am. Chem. Soc.* **2012**, *134*, 2528–2531.
- (27) Liu, R. Y. M.; Bae, M.; Buchwald, S. L. Mechanistic Insight Facilitates discovery of a mild and efficient copper-catalyzed dehydration of primary amides to nitriles Using hydrosilanes. *J. Am. Chem. Soc.* **2018**, *140*, 1627–1631.
- (28) Fang, X.; Yu, P.; Morandi, B. Catalytic reversible alkene-nitrile interconversion through controllable transfer hydrocyanation. *Science* **2016**, *351*, 832–836.
- (29) Aresta, M. *Carbon dioxide as chemical feedstock*. Wiley-VCH, Weinheim, 2010.
- (30) Liu, Q.; Wu, L.; Jackstell, R.; Beller, M. Using carbon dioxide as a building block in organic synthesis. *Nat. Commun.* **2015**, *6*, 5933.
- (31) Moragas, T.; Gaydou, M.; Martin, R. Nickel-catalyzed carboxylation of benzylic C-N bonds with CO₂. *Angew. Chem., Int. Ed.* **2016**, *55*, 5053–5057.
- (32) Liao, L.-L.; Cao, G.-M.; Ye, J.-H.; Sun, G.-Q.; Zhou, W.-J.; Gui, Y.-Y.; Yan, S.-S.; Shen, G.; Yu, D.-G. Visible-light-driven external-reductant-free cross-electrophile couplings of tetraalkyl ammonium salts. *J. Am. Chem. Soc.* **2018**, *140*, 17338–17342.
- (33) Reissmann, S.; Hochleitner, E.; Wang, H.; Paschos, A.; Lottspeich, F.; Glass, R. S.; Böck, A. Taming of a poison: biosynthesis of the NiFe-hydrogenase cyanide ligands. *Science* **2003**, *229*, 1067–1070.
- (34) Wang, H.; Dong, Y.; Zheng, C.; Sandoval, C. A.; Wang, X.; Makha, M.; Li, Y. Catalytic cyanation using CO₂ and NH₃. *Chem* **2018**, *4*, 2883–2893.
- (35) Dong, Y.; Yang, P.; Zhao, S.; Li, Y. Reductive cyanation of organic chlorides using CO₂ and NH₃ via triphos-Ni(I) species. *Nat. Commun.* **2020**, *11*, 4096.
- (36) Kim, J.; Kim, H. J.; Chang, S. Synthesis of aromatic nitriles using nonmetallic cyano-group sources. *Angew. Chem., Int. Ed.* **2012**, *51*, 11948–11959.
- (37) Rodrigues, R. M.; Thadathil, D. A.; Ponmudi, K.; George, A.; Varghese, A. Recent advances in electrochemical synthesis of nitriles: a sustainable approach. *ChemistrySelect* **2022**, *7*, No. e202200081.
- (38) Hu, H.; Wu, S.; Yan, F.; Makha, M.; Sun, Y.; Du, C.-X.; Li, Y. Recent developments in electrochemical synthesis of nitriles and electrocatalytic cyanations. *J. Energy Chem.* **2022**, *70*, 542–575.
- (39) Cheng, H.-C.; Guo, P.-H.; Ma, J.-L.; Hu, X.-Q. Directing group strategies in catalytic sp² C-H cyanations: scope, mechanism and limitations. *Catal. Sci. Technol.* **2021**, *11*, 3308–3325.
- (40) Wu, W.-B.; Yu, J.-S.; Zhou, J. Catalytic enantioselective cyanation: recent advances and perspectives. *ACS Catal.* **2020**, *10*, 7668–7690.
- (41) Nakao, Y. Metal-mediated C-CN bond activation in organic synthesis. *Chem. Rev.* **2021**, *121*, 327–344.
- (42) Patil, R. D.; Gupta, M. K. Methods of nitriles synthesis from amines through oxidative dehydrogenation. *Adv. Synth. Catal.* **2020**, *362*, 3987–4009.
- (43) Zeng, X.-P.; Sun, J.-C.; Liu, C.; Ji, C.-B.; Peng, Y.-Y. Catalytic asymmetric cyanation reactions of aldehydes and ketones in total synthesis. *Adv. Synth. Catal.* **2019**, *361*, 3281–3305.

- (44) Tolman, C. A. Steric and electronic effects in olefin hydrocyanation at Du Pont: A scientific and industrial success story. *J. Chem. Educ.* **1986**, *63*, 199–201.
- (45) Hock, K. J.; Knorrscheidt, A.; Hommelsheim, R.; Ho, J.; Weissenborn, M. J.; Koenigs, R. M. Tryptamine synthesis by iron porphyrin catalyzed C-H functionalization of indoles with diazoacetonitrile. *Angew. Chem., Int. Ed.* **2019**, *58*, 3630–3634.
- (46) Takano, S.; Nishimura, T.; Ogasawara, K. Efficient synthesis of tryptamine. *Heterocycles* **1977**, *6*, 1167–1171.
- (47) Gao, J.; Jiao, M.; Ni, J.; Yu, R.; Cheng, G.-J.; Fang, X. Nickel-catalyzed migratory hydrocyanation of internal alkenes: unexpected diastereomeric-ligand-controlled regio-divergence. *Angew. Chem., Int. Ed.* **2021**, *60*, 1883–1890.
- (48) Yu, R.; Rajasekar, S.; Fang, X. Enantioselective nickel-catalyzed migratory hydrocyanation of nonconjugated dienes. *Angew. Chem., Int. Ed.* **2020**, *59*, 21436–21441.
- (49) Gao, J.; Ni, J.; Yu, R.; Cheng, G.-J.; Fang, X. Ni-catalyzed isomerization-hydrocyanation tandem reactions: access to linear nitriles from aliphatic internal olefins. *Org. Lett.* **2021**, *23*, 486–490.
- (50) Zhang, S.; Neumann, H.; Beller, M. Pd-catalyzed cyanation of (hetero)aryl halides by using biphosphine ligands. *Chem. – Eur. J.* **2018**, *24*, 67–70.
- (51) Koschker, P.; Kähny, M.; Breit, B. Enantioselective redox-neutral Rh-catalyzed coupling of terminal alkynes with carboxylic acids toward branched allylic esters. *J. Am. Chem. Soc.* **2015**, *137*, 3131–3137.
- (52) Steib, P.; Breit, B. Enantioselective rhodium-catalyzed dimerization of omega-allenyl carboxylic acids: straightforward synthesis of C₂-symmetric macrodiolides. *Angew. Chem., Int. Ed.* **2018**, *57*, 6572–6576.
- (53) Ganss, S.; Breit, B. Enantioselective rhodium-catalyzed atom-economical macrolactonization. *Angew. Chem., Int. Ed.* **2016**, *55*, 9738–9742.
- (54) Wu, L.; Hartwig, J. F. Mild palladium-catalyzed selective monoarylation of nitriles. *J. Am. Chem. Soc.* **2005**, *127*, 15824–15832.
- (55) Shang, R.; Ji, D.-S.; Chu, L.; Fu, Y.; Liu, L. Synthesis of α -aryl nitriles through palladium-catalyzed decarboxylative coupling of cyanoacetate salts with aryl halides and triflates. *Angew. Chem., Int. Ed.* **2011**, *50*, 4470–4474.
- (56) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. Enantioselective cyanation of benzylic C-H bonds via copper-catalyzed radical relay. *Science* **2016**, *353*, 1014–1018.
- (57) Chen, Y.; Xu, L.; Jiang, Y.; Ma, D. Assembly of α -(hetero)aryl nitriles via copper-catalyzed coupling reactions with (hetero)aryl chlorides and bromides. *Angew. Chem., Int. Ed.* **2021**, *60*, 7082–7086.
- (58) Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L.; Pellicciari, R.; Cogolli, P. Reactions of ethyl diazoacetate with thianaphthene, indoles, and benzofuran. *J. Org. Chem.* **1977**, *42*, 3945–3949.
- (59) Tsotinis, A.; Vlachou, M.; Papahatjis, D. P.; Calogeropoulou, T.; Nikas, S. P.; Garratt, P. J.; Piccio, V.; Vonhoff, S.; Davidson, K.; Teh, M.-T.; Sugden, D. Mapping the melatonin receptor. 7. Subtype selective ligands based on β -substituted N-acyl-5-methoxytryptamines and β -substituted N-acyl-5-methoxy-1-methyltryptamines. *J. Med. Chem.* **2006**, *49*, 3509–3519.
- (60) Leow, J. L.; Casey, M.-W.; Casey, P. J.; Go, M. L.; Suresh, K. G. Small molecule inhibitors of isoprenylcysteine carboxyl methyltransferase with potential anticancer activity. 2014, U.S. Patent 8,742,100.
- (61) Winter-Vann, A. M.; Baron, R. A.; Wong, W.; dela Cruz, J.; York, J. D.; Gooden, D. M.; Bergo, M. O.; Young, S. G.; Toone, E. J.; Casey, P. J. A small-molecule inhibitor of isoprenylcysteine carboxyl methyltransferase with antitumor activity in cancer cells. *Proc. Natl. Acad. Sci.* **2005**, *102*, 4336–4341.
- (62) Chatalova-Sazepin, C.; Wang, Q.; Sammis, G. M.; Zhu, J. Copper-catalyzed intermolecular carboetherification of unactivated alkenes by alkyl nitriles and alcohols. *Angew. Chem., Int. Ed.* **2015**, *54*, 5443–5446.
- (63) He, R.-D.; Li, C.-L.; Pan, Q.-Q.; Guo, P.; Liu, X.-Y.; Shu, X.-Z. Reductive coupling between C-N and C-O electrophiles. *J. Am. Chem. Soc.* **2019**, *141*, 12481–12486.
- (64) Wang, Z.-X.; Yang, B. Chemical transformations of quaternary ammonium salts via C-N bond cleavage. *Org. Biomol. Chem.* **2020**, *18*, 1057–1072.
- (65) Huang, W.; Cheng, X. Hantzsch esters as multifunctional reagents in visible-light photoredox catalysis. *Synlett* **2017**, *28*, 148–158.
- (66) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. Nickel-catalyzed cross couplings of benzylic ammonium salts and boronic acids: stereospecific formation of diarylethanes via C-N bond activation. *J. Am. Chem. Soc.* **2013**, *135*, 280–285.
- (67) Matsubara, K.; Fukahori, Y.; Inatomi, T.; Tazaki, S.; Yamada, Y.; Koga, Y.; Kanegawa, S.; Nakamura, T. Monomeric three-coordinate N-heterocyclic carbene nickel(I) complexes: synthesis, structures, and catalytic applications in cross-coupling reactions. *Organometallics* **2016**, *35*, 3281–3287.
- (68) Lee, C.; Yang, W.; Parr, R. G. Development of the colle-salveti correlation-energy formula into a functional of the electron density. *Phys. Rev. B* **1988**, *37*, 785–789.
- (69) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
- (70) Becke, A. D. Density-functional exchange-energy approximation with correct asymptotic behavior. *Phys. Rev. A* **1988**, *38*, 3098–3100.
- (71) Zhang, Y.; He, J.; Song, P.; Wang, Y.; Zhu, S. Ligand-enabled NiH-catalyzed migratory hydroamination: chain walking as a strategy for regio-divergent/regioconvergent remote sp³C-H amination. *CCS Chem.* **2020**, *2*, 2259–2268.
- (72) Chen, J.; Zhu, S. Nickel-catalyzed multicomponent coupling: synthesis of α -chiral ketones by reductive hydrocarbonylation of alkenes. *J. Am. Chem. Soc.* **2021**, *143*, 14089–14096.
- (73) Kochi, T.; Kanno, S.; Kakiuchi, F. Nondissociative chain walking as a strategy in catalytic organic synthesis. *Tetrahedron Lett.* **2019**, *60*, 150938.
- (74) Zhou, F.; Zhu, J.; Zhang, Y.; Zhu, S. NiH-Catalyzed reductive relay hydroalkylation: a strategy for the remote C(sp³)-H alkylation of alkenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 4058–4062.
- (75) Zhou, S.; Addis, D.; Das, S.; Junge, K.; Beller, M. New catalytic properties of iron complexes: dehydration of amides to nitriles. *Chem. Commun.* **2009**, 4883–4885.
- (76) Enthaler, S. Straightforward Uranium-Catalyzed Dehydration of Primary Amides to Nitriles. *Chem. – Eur. J.* **2011**, *17*, 9316–9319.