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Access to α-Cyano Carbonyls Bearing a Quaternary Carbon Center by Reductive Cyanation

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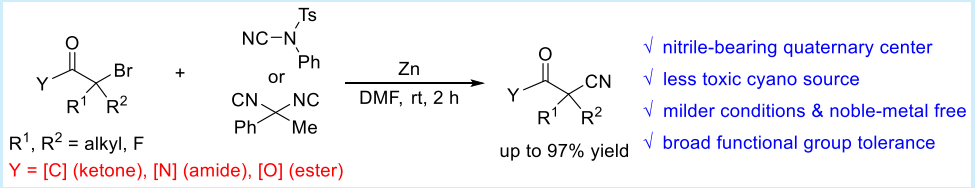
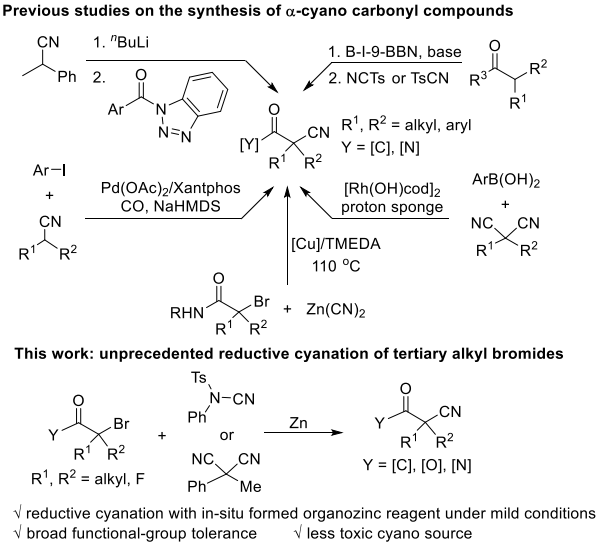


ABSTRACT: Reductive cyanation of tertiary alkyl bromides using electrophilic cyanating reagent and zinc reductant was developed, providing various α-cyano ketones, esters, and carboxamides containing a nitrile-bearing all-carbon quaternary center in good to excellent yields under mild reaction conditions. The corresponding reaction mechanism involving in situ generated organozinc reagent and reactivity distinction was elucidated by density functional theory computation.

Given by the indispensability of α-cyano carbonyl compounds to constructing bioactive molecules,[1,2] the challenge of constructing congested all-carbon quaternary centers in organic synthesis[3] and the unique role of all-carbon quaternary center in metabolic stability of pharmaceuticals,[4] developing practical methods of synthesizing α-cyano carbonyl compounds with nitrile-bearing all-carbon quaternary center is a long-lasting attractive issue. Despite the significant advancements in the synthesis of α-cyano carbonyl compounds,[5−8] most of them focus on the preparation of simple α-cyano ketones, whereas the accesses to the ketones with nitrile-bearing all-carbon quaternary center is still limited. The reported protocols include the substitution of deprotonated α,α-disubstituted nitriles with *N*-acylbenzotriazoles,[5] palladium-catalyzed carbonylation of aryl iodide with deprotonated α,α-disubstituted nitriles,[6] electrophilic cyanation of enol boronate with *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTs),[7] and rhodium-catalyzed addition of aryl boronic acids to α,α-disubstituted malononitriles (Scheme 1).[8] Nevertheless, these approaches demand high temperature and pressure conditions, use air/moisture-sensitive reagents or costly noble metal catalyst, or display confined functional-group tolerance. On the other side, the development on preparing methods of other α-cyano carbonyls manifests sharp contrast to the diverse strategies to obtain α-cyano ketones. As we know, only one elegant pathway to α-cyano carboxamides via copper-catalyzed cyanation of tertiary bromides with zinc cyanide was reported by Nishikata and Kuninobu recently.[9] Therefore, the reaction protocol, which can be simultaneously applicable for the synthesis of α-cyano ketones, esters, and carboxamides bearing a quaternary center, has yet to be established. Considering the thriving progress on oxidative cyanation with nucleophilic cyanating reagent,[10] we envisioned that reductive cyanation with two electrophilic partners and opposite reaction mode might offer an efficient and convenient solution to construct C−CN bond, which would not only

Scheme 1. Strategies for Synthesis of α-Cyano-Carbonyls Bearing a Quaternary Carbon Center



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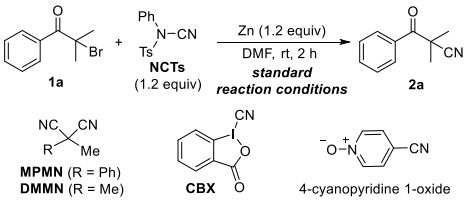
eliminate the usage of poisonous cyanide and vulnerable organometallic reagents but also exhibit both impressive robustness and remarkable flexibility.

As an organometallic reagent easily available from zinc dust and α-halogen ester, Reformatsky reagent is equipped with better functional-group tolerance than organolithium or Grignard reagent.[11−13] The Zn−C addition of organozinc reagent onto electrophilic C−X (X = C, N, and O) π bonds represents a classic mode of building C−C bonds.[12,13] Blaise reaction, which goes through the Zn−C addition onto C≡N bond, can transform nitrile to either carbon-chain elongated ketone/imine or nitrogen-containing heterocycles in different terminating manner.[12−14] As we know, the β-carbon or β-heteroatom elimination following Zn−C addition to C≡N bond was unexploited. In addition, the ketone- and amide-type of organozinc reagent, which could be generated from zinc and α-halogenated ketones or *N*,*N*′-disubstituted amides, was an far less cultivated field in organic synthesis.[14a,15] These inspired us to explore the potential application of Reformatsky reagent in the reductive cyanation by combining the Zn−C addition of Blaise reaction and β-atom elimination (i.e., retro-Thorpe fragmentation).[16] Herein, we presented treating tertiary alkyl halides and electrophilic cyanation reagents with zinc dust provided a practical and safe route to α-cyano carbonyls (Scheme 1).

At the beginning of our studies, cyanation of sterically demanding α-bromoketone **1a** was selected as the model reaction to survey the reaction parameters (Table 1). The

Table 1. Optimization of Reaction Conditions[1]



entry	deviation from standard conditions	2a
1	none	90% (88%)
2	MPMN instead of NCTs	40%
3	DMMN instead of NCTs	0
4	CBX instead of NCTs	0
5	4-cyanopyridine 1-oxide instead of NCTs	0
6	butyronitrile instead of NCTs	0
7	adding 10% mol $NiBr_2$·glyme	64%
8	adding 10% mol $Ni(acac)_2$	75%
9	Mn instead of Zn	0
10	In instead of Zn	86%
11	THF or Et_2O instead of DMF	0

[1]Reaction conditions: **1a** (0.50 mmol, 1.0 equiv), NCTs (0.60 mmol, 1.20 equiv), zinc (0.60 mmol, 1.20 equiv), DMF (2.0 mL). Yield determined by GC using *n*-decane as internal standard. In the parentheses is the isolated yield of **2a**.

combination of electrophilic NCTs and reductive zinc dust delivered the desired nitrile **2a** in 90% yield after 2 h reaction at room temperature in DMF (entry 1, standard reaction conditions). 2-Methyl-2-phenylmalononitrile (MPMN),[17] 2,2-dimethylmalononitrile (DMMN),[18] cyanobenziodoxolone (CBX),[19] 4-cyanopyridine 1-oxide,[20] and butyronitrile[21] are five kinds of reported cyanating reagents. Replacing NCTs with them led to significant lower yield of **2a** (entry 2) or completely stopped the proceeding of desired cyanation (entries 3−6). In some of these cases (entries 4 and 5), reductive debromination of **1a** was determined as the major side reaction. Adding $Ni(acac)_2$ or $NiBr_2$·glyme (10 mol %), which mimicked the reported protocol of alkene hydrocyanation,[22] hindered the reaction, decreasing the yield (entries 7 and 8). Using other metal reductants like indium or manganese dust resulted in no bromide conversion (entry 9) or lower yield (entry 10). When DMF was switched to either THF or Et_2O, nearly quantitative amount of starting material was recovered (entry 11), which implied that without employing Rieke-type activated zinc[23] or reflux conditions,[24] the formation of Reformatsky reagent in ether-type solvent was rather sluggish at ambient temperature.

With the optimized reaction conditions in hand, the substrate scope and functional group tolerance were extensively inspected (Figure 1). For various substituted α,α-dimethyl α-bromo acetophenones, the reaction afforded the

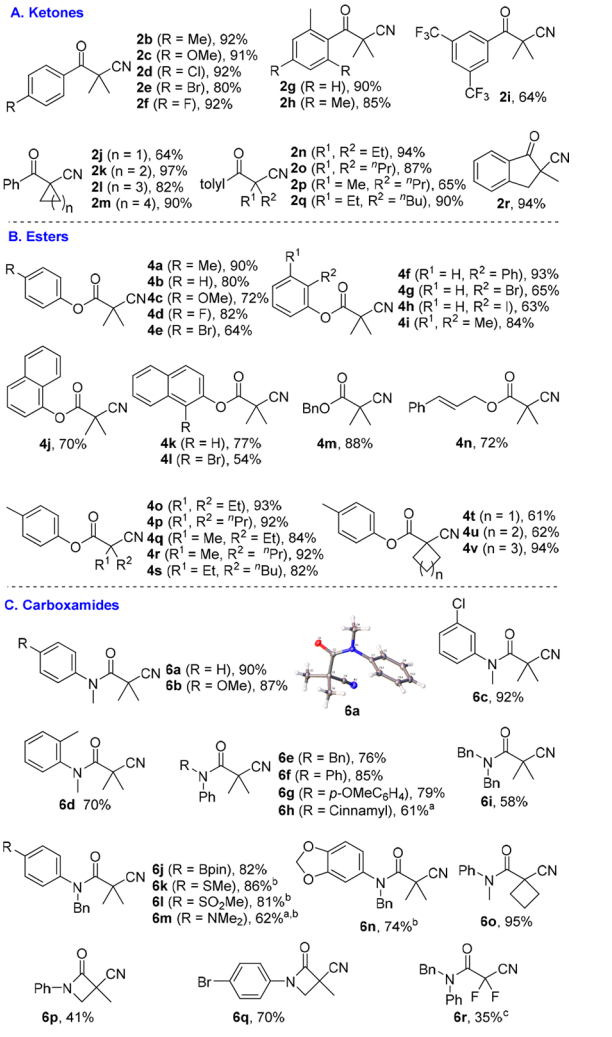


Figure 1. Reductive cyanation of α-bromo ketones, esters, and carboxamides. Unless otherwise noted, reaction conditions: substrate (0.50 mmol, 1.0 equiv), zinc dust (0.60 mmol, 1.20 equiv), DMF (2.0 mL), rt, 2 h. For **1** or **3**, adding NCTs (0.60 mmol, 1.20 equiv). For **5**, adding MPMN (0.60 mmol, 1.20 equiv). Isolated yields. (a) 80 °C. (b) 0.2 mmol scale. (c) 0.2 mmol scale, NCTs (0.24 mmol, 1.20 equiv), zinc dust (0.24 mmol, 1.20 equiv), THF (2.0 mL), 100 °C, 12 h.

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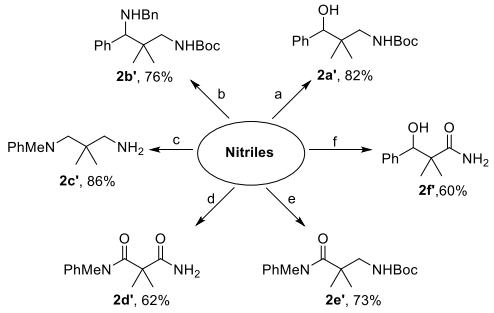
desired nitriles **2b**−**2i** in moderate to excellent yields (Section A). The electron-donating or -withdrawing nature of substituent has little impact on the reactivity. The bromo or chloro substituents on the phenyl ring remain inert. Both cyclic and acyclic alkyl units at the α-position of the halides were tolerated, resulting in 64−94% yields of **2j**−**2q**. Tertiary bromide **1r** derived from 2-methyl-1-indanone was smoothly transformed into the nitrile with 94% yield under standard conditions. The remarkable versatility of this approach was further demonstrated by reductive cyanation of α-bromo phenol esters **3** (Section B) and α-bromo carboxamides **5** (Section C). Isobutyrates of phenol, nathpanol, benzyl alcohol, and allylic alcohol **3a**−**3n** were converted to the corresponding nitriles **4a**−**4n** in reasonable to excellent yields. Among these cases, bromo or iodo substituents on the aryl ring (**4e**, **4g**, **4h**, **4l**) and C=C bond of cinnamyl group (**4n**) were preserved. For carboxylic ester of *p*-cresol with longer aliphatic chain (**3o**-**3s**) or cyclic substituent (**3t**−**3v**), the protocol also achieved good cyanation yields in most of the cases. In some cases, using *N*-cyano-*N*-phenylbenzenesulfonamide (NCPs) instead of NCTs facilitated the isolation of cyanation products (**4b**−**4h**, **4j**−**4n**). By using MPMN instead of NCTs, α-bromo *N*-aryl or *N*-alkyl isobutyramides as well as cyclobutanecarboxylic amide smoothly underwent reductive cyanation, resulting in the products **6a**−**6o** with high yields in most of the scenarios. The molecular structure of **6a** was identified by X-ray crystallography. Thanks to the noble-metal-free and neutral conditions, boronic acid pinacol ester group (Bpin), methyl sulfide group, dimethylamino group, and piperonyl group did not impose negative impact on this reductive cyanation (**6j**, **6k**, **6m**, and **6n**). The merit demonstrated by **6j** is beneficial to further transformation with the miscellaneous tools of transition-metal-catalyzed cross coupling. More impressively, this protocol can be applied to introducing nitrile group and quaternary carbon center into β-lactams at the same time by employing α-halo-β-lactams as the substrates (**6p** and **6q**). Notably, α,α-difluorinated α-bromo acetate amide can also be cyanated (**6r**) in acceptable yield, along with unwanted reductive debromination of **5r**. The above-mentioned results of products **4q**−**4v** and **6o** demonstrated an practical alternative of avoiding the selectivity obstacle in the preparation of α,α-disubstituted β-amino amides via the dialkylation or cycloalkylation of cyanoacetate with two different alkyl halides or terminal dihalogenated alkanes.[25]

Encouraged by these results, we further demonstrated the benefits of this synthetic tool from the following aspects: (i) varied transformation of cyanation products (Scheme 2); (ii) the late-stage functionalization of pharmaceuticals and bioactive molecules (Scheme 3); (iii) gram-scale synthesis (Scheme 4). The synthetic utility of this reductive cyanation was projected on the diverse transformation of products. A variety of transformations from nitriles to molecules, including 3-amino alcohol, 1,3-diamines with two primary amine moieties with different *N*-protecting groups, α,α-disubstituted malonamide with different *N*-terminus, and β-hydroxy[26] or -amino amide, were accomplished in moderate to high yields (Scheme 2). Late-stage functionalization represents an opportunity to expand the toolbox in hands of medicinal chemists and in turn increase the chemical space explored in drug discovery efforts.[27] Because of the facile accessibility of α-ketone substituted tertiary alkyl bromides by brominating the corresponding ketone with hydrogen bromide, we achieved the cyanative modification of acetylcholinesterase inhibitor Donepezil (**8a**) by transforming Donepezil to its tertiary alkyl bromide derivative and then implanting nitrile group with this method (Scheme 3). Anesthetic Propofol, antihistamine drug Desloratadine, antidepressant Fluoxetine, steroid Estrone, and quetiapine's active metabolite norquetiapine were converted to the corresponding α-bromo esters or amides, and after applying this cyanation method, products **8b**−**8f** were delivered in reasonable to high yields. The 2,2-dimethyl cyanoacetyl group can be installed as a degradation-resistant "tether" into these pharmaceuticals through this process. By further transformation of implanted nitrile group to amino group, these pharmaceuticals could be affixed to bioactive peptides or proteins, providing potent option to explore the vast potential of well-established drugs. Larger-scale reaction of tertiary alkyl bromides with NCTs or MPMN and zinc dust was performed. The corresponding α-cyano molecules were produced gram-scale in 89−91% yields without any modification of the optimized conditions (Scheme 4).

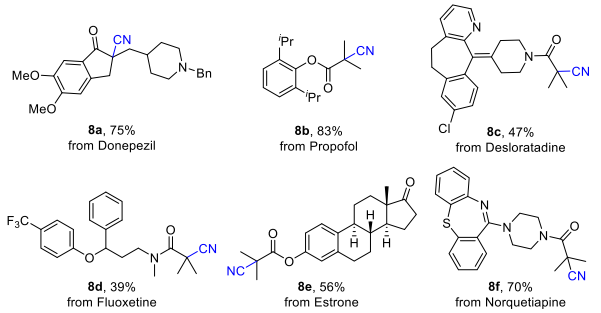
To validate the reaction pathway, a couple of control experiments were designed and conducted (Scheme 5). No

Scheme 2. Transformation of α-Cyanocarbonyls Reaction Conditions[1]

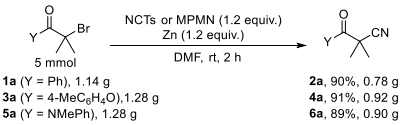


[1](a) **2a** (0.5 mmol, 1.0 equiv), $CoCl_2$ (1.5 mmol, 3.0 equiv), $(Boc)_2O$ (3.0 mmol, 6.0 equiv), $NaBH_4$ (5.0 mmol, 10.0 equiv), MeOH (5 mL), 0 °C, overnight. (b) **2a** (0.5 mmol, 1.0 equiv), $BnNH_2$ (0.6 mmol, 1.2 equiv), $Ti(OEt)_4$ (2 mL), 85 °C, 6 h; then with the conditions of panel (a). (c) **6a** (0.5 mmol, 1.0 equiv), $LiAlH_4$ (2.5 mmol, 5.0 equiv), 80 °C, overnight. (d) **6a** (0.5 mmol, 1.0 equiv), K_2CO_3 (1.0 mmol, 2.0 equiv), 30 wt % H_2O_2 solution (2.5 mmol, 5.0 equiv), DMSO (2 mL), rt, 20 h. (e) **6a** (0.5 mmol, 1.0 equiv) with the conditions of (a). (f) **2a**, with the method reported in ref 26.

Scheme 3. Late-Stage Modification of Pharmaceuticals



Scheme 4. Gram-Scale Synthesis



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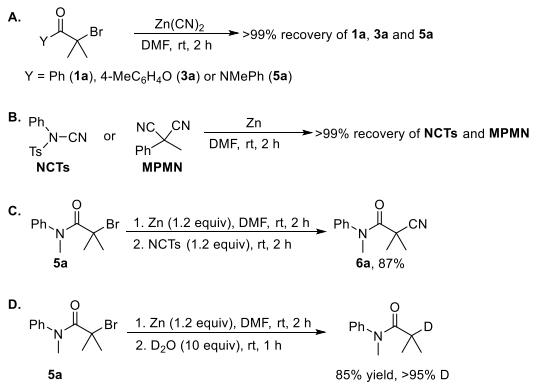
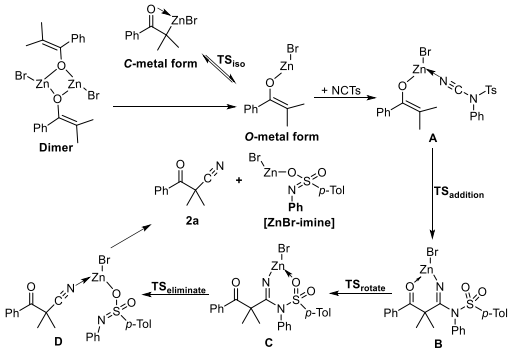
Scheme 5. Control Experiments of Probing the Mechanism



Scheme 6. Reaction Model for Reductive Cyanation of α-Bromo Ketone 1a Using NCTs as the Cyanating Reagent



reaction occurred between tertiary halides and nucleophilic cyanide (Scheme 5A), precluding the involvement of nucleophilic substitution. NCTs was inert to zinc dust reductant in the absence of alkyl halides (Scheme 5B), ruling out the reductive cleavage of N−CN or C−CN bonds by zinc dust. When the α-bromo carboxamide was poured into the zinc dust suspension of DMF for 2 h stirring and then adding NCTs, similar yield of cyanation product was attained (Scheme 5C). When using D_2O instead of NCTs, deuterated carboxamide was afforded in high yield and 95% deuterium incorporation, suggesting the in situ formation of Reformatsky reagent (Scheme 5D).

In the course of optimizing reaction conditions, the distinct reactivity of electrophilic cyanation reagents NCTs, MPMN, and DMMN (entries 1−3 in Table 1) has been observed. When the α-bromo ketone and esters were utilized as the substrates, NCTs as the cyanating reagent is more reactive than MPMN. For the reductive cyanation of the α-bromo amides, NCTs and MPMN showed the similar reactivity. These patterns and the intrinsic transient properties of organozinc intermediates led us to analyze the detailed reaction mechanism, to investigate the reactivity difference of cyanating reagent and elucidate the influence of substituent on cyanation reagent by the tool of density functional theory (DFT) based theoretical computation.[28] Given by the reported good performance for the description of elimination and treating the imine system,[16b] hybrid generalized-gradient-approximation (GGA) exchange−correlation functional PBE0[29] with the D3 version of Grimme's dispersion correction[30a] and Becke−Johnson damping (D3BJ)[30b] was adopted in our DFT computation. The distinct reactivity of different cyanating reagents in the reductive cyanation of α-bromo ketone and the good reactivity of Reformatsky reagent derived from ketone **1a** with NCTs at room temperature were revealed (Scheme 6, for detailed description see Supporting Information).

In conclusion, an efficient and convenient route to a variety of sterically demanding α-cyano ketones, esters, and amides was established. Various functional groups, including halogen atom, lactam, amine, ether, alkene, sulfide, sulfone, and borate, can be well tolerated. Late-stage modification of pharmaceutical and bioactive molecules demonstrated the potential application of this cyanating method in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00465.

Experimental details, DFT computation, characterization data, NMR spectra (PDF)

Accession Codes

CCDC 2054231 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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