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Catalytic cascade synthesis of cyanohydrin esters *via* water/O_2-induced cyanide transfer from $K_3Fe(CN)_6$†

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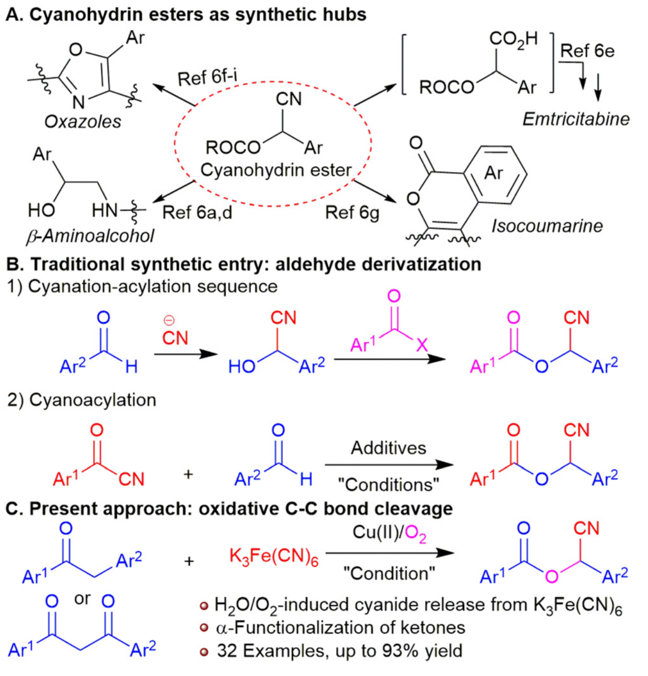
The copper-catalyzed α-oxygenation of aryl benzyl ketones is merged with a unique water/O_2-induced release of cyanide ions from $K_3Fe(CN)_6$ and a benzil-cyanide reaction. This strategy gives expedient access to cyanohydrin esters starting directly from broadly accessible aryl benzyl ketones. The cyanide release strategy was further integrated with a copper catalyzed oxygenation-decarbonylation sequence to produce cyanohydrin esters from 1,3-diketones.

The selective incorporation of a cyano group into an organic small molecule to access value-added compounds in a well-defined manner is a significant transformation of fundamental importance. However, the cyanide anion is exceedingly poisonous to living organisms due to binding to cytochrome *c* and obstructing the mitochondrial electron transport chain.[1] Therefore, the use of soluble cyanide salts should be restricted to prevent severe environmental destruction. The use of an essentially non-toxic, inexpensive, abundant and safe-to-handle cyanating agent, such as $K_3Fe(CN)_6$ and $K_4Fe(CN)_6$, is beneficial in view of the above.[2] $K_3Fe(CN)_6$ releases cyanide ions upon the action of *in situ* formed $K_4Fe(CN)_6$ under the condition that allows for the transition of Fe(III) to Fe(II) and *vice versa*.[3,4a] A literature survey reveals that $K_3Fe(CN)_6$ was employed in the synthesis of diarylfumaronitriles, or C–H cyanation of arenes and isoquinolines; likewise, $K_4Fe(CN)_6$ was used for the cyanation of aryl halides, the Strecker reaction or the preparation of dibromoacrylonitriles, among others.[4,5] Here, we present a hitherto unexplored use of $K_3Fe(CN)_6$ in accessing cyanohydrin esters from aryl benzyl ketones.

Cyanohydrin esters, *i.e.* *O*-acylated cyanohydrins, are versatile synthons for a range of valuable compound classes including oxazoles, isocoumarines, α-amino alcohols, *etc.* and approved drugs, *e.g.* emtricitabine (Scheme 1A).[6] Moreover, they set up the structural foundation of pyrethroid insecticides.[7] Classical synthesis of cyanohydrin esters consists of reacting an aldehyde with a toxic cyanide agent and a subsequent *O*-acylation process (Scheme 1B).[8] An alternative approach is cyanoacylation of aldehydes with (a) acyl halides and aqueous KCN,[9a] (b) acyl cyanides in the presence of an additive, *e.g.* K_2CO_3, DABCO, Bu_3SnCN, *etc.*[9b–d] or (c) TMSCN and acid anhydride catalyzed by $FeCl_3$.[9e] The benzil-cyanide reaction, giving a solvent-controlled product range, has also been studied, among others.[10,11] Despite the many



Scheme 1 Synthetic manipulations and approaches for cyanohydrin esters.

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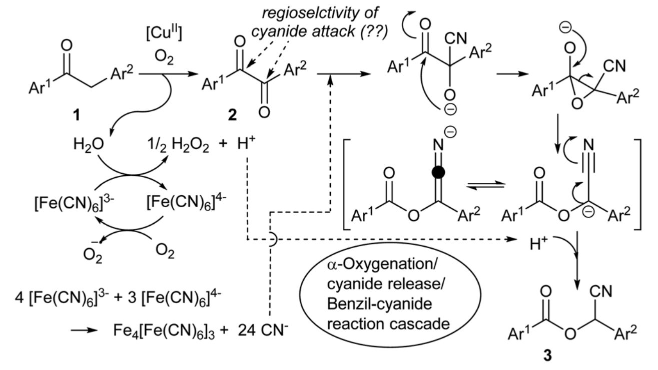
successes, all approaches rely on the derivatization of reactive aldehyde groups with toxic cyanides. Herein, we introduce a new catalytic route to cyanohydrin esters *via* oxidative C–C bond cleavage of benzyl ketones aided by water/O_2-mediated, highly selective, cyanide transfer from $K_3Fe(CN)_6$ (Scheme 1C).

A copper-catalyzed single electron transfer (SET) process has recently received tremendous attention from numerous research groups, including ours.[12,13] It is known that a copper catalyst can promote the α-oxygenation of benzyl ketones to form benzils *via* an SET process; however, to the best of our knowledge, no example of unifying this process with a carbonyl group transformation strategy has been reported.[14] We envisioned that cyanohydrin esters can be accessed directly from aryl benzyl ketones by integrating a copper catalyzed oxygenation process with the cyanide transfer from $K_3Fe(CN)_6$. However, challenges remain in releasing cyanide ions from $K_3Fe(CN)_6$ and controlling the regioselectivity of the cyanide attack to the intermediate benzil, which may be governed by the electronic as well as the steric effect executed by the aryl substituents.

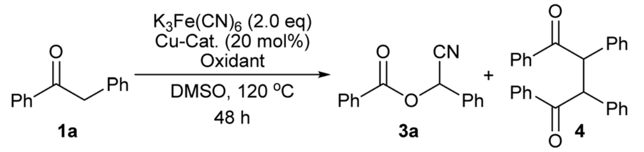
The mechanistic concept, as outlined in Scheme 2, consists of a copper(II)/O_2-based cycle for the α-oxygenation of aryl benzyl ketones to benzils, linked with a benzil-cyanide reaction strategy. Water formed in the copper catalyzed oxygenation step is likely to reduce $[Fe(CN)_6]^{3-}$ to $[Fe(CN)_6]^{4-}$ *via* an SET process with the formation of H^+ ions.[15] Fe(II), thus formed, can be reoxidized with molecular O_2 to give Fe(III).[8,10a] The concurrent existence of both Fe(III) and Fe(II) can lead to the formation of Prussian blue and release cyanide ions, that attack preferably to the more electrophilic carbonyl center of benzil **2** and subsequently undergoes benzil-cyanide reaction to give **3**.

To probe the viability of this concept, we studied the reaction of deoxybenzoin (**1a**) with $K_3Fe(CN)_6$ in 1 : 2 molar ratio in DMSO using CuI as the catalyst (Table 1 and Table S1, ESI†). However, **3a** was formed in a small quantity, accompanied by the diketone **4** as the predominat product due to a competitive copper catalyzed radical dimerization of **1a** (entry 1).[16] Replacing CuI with a copper salt bearing a coordinating anion could not improve the yield of **3a** (entry 2). Since Cu(II) salts with non-coordinating anions enhance the rate of aerobic C–H oxidation reactions, we employed $CuBr_2$, among others, as the catalyst.[12a]



Scheme 2 Mechanistic proposal.

Table 1 Optimization of the reaction conditions[a]

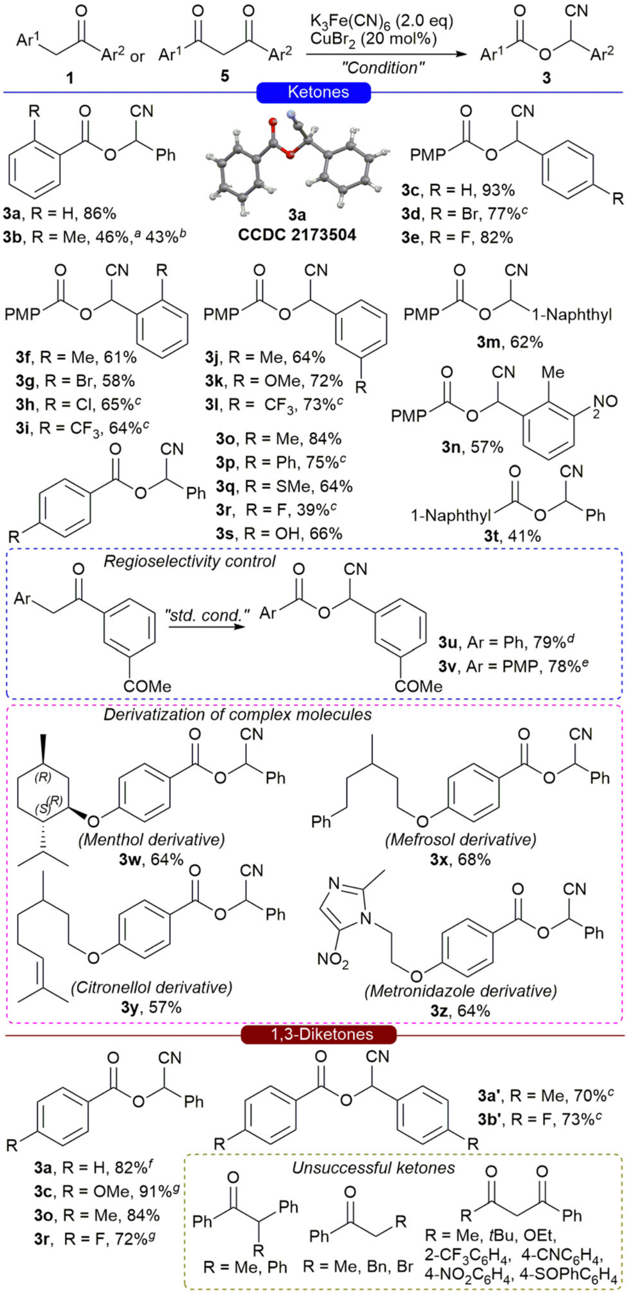


Entry	Cu-Cat.	Oxidant	**3a** (%)	**4** (%)
1	CuI	Air	30	50
2	$Cu(OAc)_2$	Air	15	60
3	$CuBr_2$	Air	65	15
4[b]	$CuBr_2$	O_2	86	Trace
5[b]	—	O_2	0	10
6[c]	$CuBr_2$	—	0	8
7[d]	$CuBr_2$	O_2	85	Trace

[a] Reaction conditions: **1a** (0.5 mmol), $K_3Fe(CN)_6$ (1.0 mmol), Cu Cat. (20 mol%), DMSO (0.5 mL), 120 °C, 48 h; Isolated yield of pure product. [b] Using oxygenated DMSO. [c] Using degassed DMSO and N_2 atmosphere. [d] Water (10 μL) was added.

Gratifyingly, **3a** was formed in an enhanced yield (entry 3). Additional improvement was achieved by employing oxygenated DMSO as the solvent (entry 4). Without $CuBr_2$, the reaction resulted in only a small quantity of **4**, possibly *via* $K_3Fe(CN)_6$ mediated formation of an α-carboradical from **1a** and a subsequent radical homodimerization process (entry 5). Further experiments revealed that while the reaction did not proceed using degassed DMSO under inert conditions, **3a** was formed in a comparable yield with water as an additive (entries 6 and 7). Our efforts to reduce further the molar proportion of $K_3Fe(CN)_6$ led to **3a** in a diminished yield, possibly due to a slow cyanide transfer under the catalytic conditions.[17] Variation of other factors, *e.g.* solvent, temperature, time, effect of ligands and additives *etc.* showed a deleterious effect (see Table S1, ESI†).

Next, we investigated the scope of the reaction. Pleasingly, a wide-range of aryl benzyl ketones with varied substitution patterns were transformed into the corresponding cyanohydrin ester in practically useful yields (Scheme 3). A variety of functional groups, including fluoro, chloro, bromo, methyl, methoxy, hydroxy, nitro, keto, thiomethyl, trifluoromethyl, *etc.*, diversely located in the *ortho*-, *meta*- and/or *para*-positions of both the aromatic rings were tolerant to the reaction conditions (**3a–3z**, **3a′–3b′**). Of note, no copper-catalyzed aromatic cyanation took place at the C(aryl)–Br and C(aryl)–Cl bonds. Remarkably, this new approach provides access to cyanohydrin esters bearing an additional keto substituent that are challenging to achieve by means of traditional strategies (**3u–3v**). Furthermore, a few unsymmetrically substituted aryl acetophenone-bearing natural products, perfumery compounds, pharmacophores, *etc.* were successfully converted (**3w–3z**). In general, all reactions were very clean and did not produce a mixture of isomeric cyanohydrin esters. In all cases, the cyanide ion had attacked regioselectively to the carbonyl group that is attached with the relatively electron-deficient aryl ring of the intermediate benzil, formed by the α-oxygenation of the corresponding aryl benzyl ketone (except **3r**). For intermediate benzils bearing electronically alike aryl rings, the cyanide attack took place



Scheme 3 Scope of the cyanohydrin ester synthesis. Reaction conditions: **1** or **5** (0.5 mmol), $K_3Fe(CN)_6$ (1.0 mmol), $CuBr_2$ (20 mol%), oxygenated DMSO (0.5 mL), 120 °C, 48 h; isolated yield of pure product. [a] From 1-phenyl-2-(*o*-tolyl)ethan-1-one **1b**, [b] from 2-phenyl-1-(*o*-tolyl)ethan-1-one **1b′**. [c] 72 h. [d] 24 h. [e] 36 h. [f] 12 h. [g] 15 mol% $CuBr_2$, PMP = *para*-methoxyphenyl.

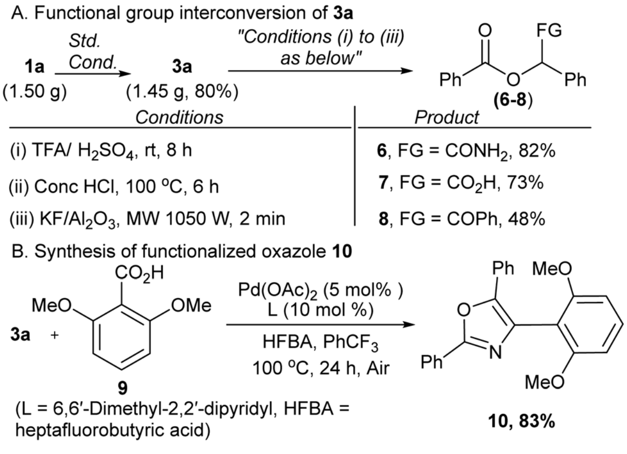
selectively at the carbonyl group attached with the less crowded aryl ring (**3b**, **3t**). However, some reactions, where the cyanide attack is a rather slower event, led to a mixture of cyanohydrin ester with unreacted intermediate benzil (*e.g.* **3b**, **3g**, **3n**, **3r**, **3t**, *etc.*). Notably, the formation of Prussian blue was observed in all cases. However, alkyl aryl ketones and α,α-disubstituted benzyl ketones remained unreactive.

Furthermore, we anticipated that cyanohydrin esters can be prepared directly from 1,3-diketones by merging a known copper-catalyzed oxygenation-decarbonylation sequence with the present cyanide transfer process.[18] Indeed, dibenzoylmethane **5a** reacted with $K_3Fe(CN)_6$, under the optimized conditions of **1a**, to give the desired cyanohydrin ester **3a** in satisfactory yield (Scheme 3). Subsequently, numerous symmetrical and unsymmetrical 1,3-diketones were successfully converted. Notably, the formation of cyanohydrin esters from 1,3-diketones followed an analogous trend to that of aryl benzyl ketones. However, dibenzoylmethanes, bearing a strong electron-withdrawing group, and acylbenzoylmethanes failed to give the desired product.

The potential applicability of the current approach was illustrated by the representative example of a gram-scale synthesis of **3a** (1.45 g, 80% yield). Subsequent functional group interconversion of the cyano-group of **3a** gave numerous key intermediates, for example, hydrolysis/oxidation of the cyano group afforded an amide **6** and acid **7**; a rearrangement involving C–C cleavage gave a ketone **8**, *etc.* (Scheme 4A).[13c,19] Furthermore, **3a** was converted into an important class of functionalized oxazole *via* decarboxylation (Scheme 4B).[6i]

A series of experiments were carried out to shed some light on the proposed mechanism (see ESI†). The addition of a radical quencher, *e.g.*, 2,2,6,6-tetramethylpiperidine-*N*-oxyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) (2.0 equiv. each), totally inhibited the product formation, indicating the involvement of a radical species. The formation of a TEMPO(O_2)-adduct was observed by GC-MS in the reaction of **1a** with $K_3Fe(CN)_6$ with TEMPO under otherwise optimized conditions, suggesting the intermediacy of a superoxide anion (see ESI†).

Based on the literature report, we believed that the conversion of **1a** to **3a** might involve the formation of benzil **2a** as an intermediate.[14] Thus, when **1a** was heated in oxygenated DMSO in the presence or absence of $K_3Fe(CN)_6$ under otherwise optimized conditions, **2a** was isolated as the major product in 10 h. In addition, **3a** was obtained from **2a** upon treatment with $K_3Fe(CN)_6$ under otherwise optimized catalytic conditions. This further suggests the intermediacy of benzil in the cyanohydrin ester formation pathway. However, the possibility of a subsequent copper-mediated cyanide attack to benzil was



Scheme 4 Synthetic applicability of the present approach.

precluded as the reaction of **2a** with CuCN or TMSCN in the presence of $CuBr_2$ failed to produce **3a**. Fascinatingly, we observed rate enhancement in the reaction of **2a** with $K_3Fe(CN)_6$ without $CuBr_2$ in oxygenated DMSO upon the addition of water, indicating the crucial role of both molecular oxygen and water in the cyanide transfer process (see Fig. S2, ESI†). Moreover, the formation of a TEMPO(O_2)-adduct was detected by GC-MS analysis, when the reaction of **2a** with $K_3Fe(CN)_6$ in oxygenated DMSO containing traces of water was quenched with TEMPO. This indicates the participation of a superoxide anion and was further supported by an EPR study (see Fig. S3, ESI†).

Alternatively, **1a** is able to reduce $K_3Fe(CN)_6$ *via* an SET process to form the corresponding α-carbo radical. However, the reaction of **1a** with $K_3Fe(CN)_6$ without $CuBr_2$ led to the formation of **4** in a small quantity *via* dimerization of the α-carbo radical formed from **1a** (Table 1, entry 7). This result suggests that the reduction of $K_3Fe(CN)_6$ by benzyl ketone is not predominant in the copper-catalyzed cyanohydrin ester formation pathway.

Furthermore, when D_2O (~10 μL) was added in the reaction of **2a** (0.5 mmol) with $K_3Fe(CN)_6$ in oxygenated DMSO, **3a**-d_1 was formed as the major product. Next, **1a**-d_2 was treated with $K_3Fe(CN)_6$ in oxygenated DMSO at 120 °C to give **3a**-d_1 as the major product (see Fig. S5, ESI†). These results unambiguously confirm that the resource of protons in the cyanohydrin ester is water generated in the copper-catalyzed oxygenation step of aryl benzyl ketones and is in accordance with our proposed mechanism. The addition of water may also assist in solubilization of the highly charged cyanoferrate complexes.

In conclusion, a unified approach has been developed that combines the copper-catalyzed α-oxygenation of aryl benzyl ketones with water/O_2-induced release of cyanide ions from $K_3Fe(CN)_6$ and subsequent benzil-cyanide reaction. This constitutes a rare synthetic route to cyanohydrin esters starting from broadly accessible aryl benzyl ketones. The unique chemistry of cyanides was further integrated with a copper catalyzed oxygenation-decarbonylation sequence that gave access to cyanohydrin esters from 1,3-diketones. Nevertheless, more dedicated optimization is necessary in the future to accomplish an atom-economic cyanide transfer from $K_3Fe(CN)_6$, and water/O_2-induced release of cyanide ions, as disclosed in this paper, sets the stage for the development of numerous cyanation reactions without employing toxic metal cyanides.

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Conflicts of interest

There are no conflicts to declare.

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