Synthetic Methods

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Metal-Free Intramolecular Carbocyanation of Activated Alkenes: Functionalized Nitriles Bearing β-Quaternary Carbon Centers**

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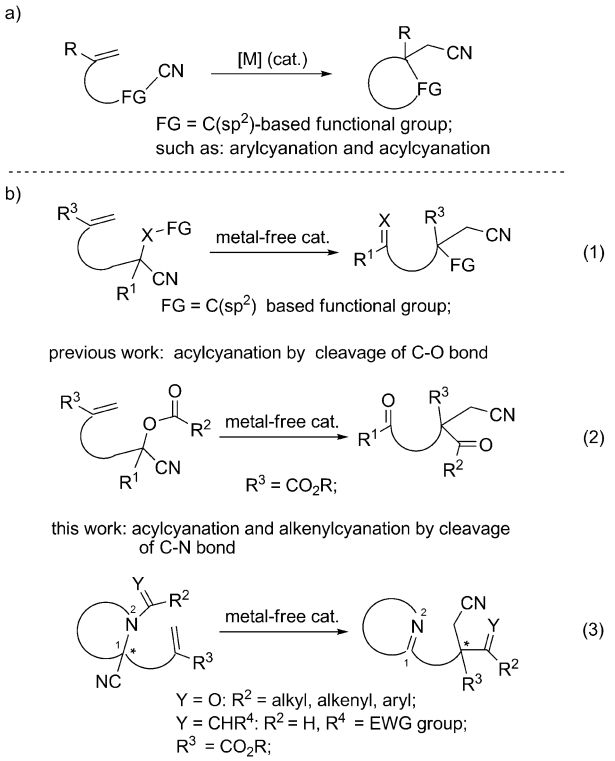
Dedicated to Professor Guo-Qiang Lin on the occasion of his 70th birthday

Nitriles[1] constitute one of the most important classes of organic compounds in both academic and industrial laboratories, and are found in a number of pharmaceuticals, agrochemicals, and materials. Furthermore, they can serve as synthetic scaffolds to a diverse array of building blocks such as aldehydes, ketones, amides, carboxylic acids, and amines. Because of their great importance in chemistry and biology, the development of novel and efficient synthetic methods for nitriles has been a major topic in synthetic organic chemistry.[2] As a straightforward and atom-economical strategy to access functionalized nitriles, the cyanofunctionalization reactions of alkenes and alkynes have thus gained much interest.[3] Among them, the metal-catalyzed intramolecular carbocyanation reactions of alkenes have received considerable attention,[4] because they address challenging issues such as generating all-carbon quaternary centers and the efficiency of C–C bond formation in synthetic organic chemistry.[5] Although significant achievements have been made over the years, this type of transformation has been confined to a fixed mode involving an initial metal-catalyzed cleavage of FG–CN bonds (FG = functional group having a $C(sp^2)$ center) under harsh reaction conditions and subsequent addition of both FG and CN groups to an electron-rich C=C bond, having limited functional-group compatibility, thus providing cyclic compounds (Scheme 1a). An alternative approach involving a different activation mode, and delivers complex and densely functionalized nitriles by adding cyano as well as other functional groups across a C=C bond simultaneously is rare, despite the fact that nonmetal-catalyzed cyanofunctionalization reactions of carbonyl compounds and imines have been studied extensively in recent years.[6] In addition, although a range of metal-catalyzed intramolecular carbocyanation reactions have been developed, intramolecular alkenylcyanation of alkenes has never been achieved. In this context, the exploration of a conceptually novel intramolecular carbocyanation, having an alternative synthetic pathway, to access a number of structurally diverse functionalized cyano-containing building blocks with improved functional group compatibility is needed.



Scheme 1. Strategies for intramolecular carbocyanation of alkenes. a) Metal-catalyzed processes. b) Catalytic metal-free transformations. EWG = electron-withdrawing group.

Recently we reported a metal-free intramolecular acylcyanation of electron-deficient alkenes and it relies on the Lewis-base-mediated nucleophilic cyanation of activated alkenes by cleavage of an ester C–O bond. The reaction furnishes densely functionalized acyclic nitriles bearing β-quaternary carbon centers [Scheme 1b, Eqs. (1) and (2)].[7a]

With the goal of developing efficient metal-free processes to prepare a variety of functionalized nitriles incorporating quaternary carbon centers,[7] we became interested in the possibility of utilizing this novel activation mode as a general protocol to develop diverse carbocyanation reactions through the cleavage of a relatively unreactive C–N bond in an economical fashion [Scheme 1b, Eq. (3)]. Herein, we disclose the first example of a catalytic metal-free intramolecular acyl- and alkenylcyanation from readily available materials. The

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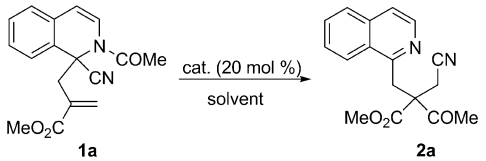
reaction undergoes the cleavage of a C–N bond and furnishes functionalized nitriles with a quaternary carbon center bearing a pendent N-heterocyclic motif under very mild reaction conditions. An asymmetric version of the reaction is also described.

Recently, our group reported a series of facile synthetic methods to prepare functionalized α-amino nitriles.[7c,d] We envisioned that these α-amino nitriles, which are readily manipulated at C1 and N2 [Scheme 1 b, Eq. (3)] and prepared from available materials, may serve as suitable scaffolds for exploring acyl- and alkenylcyanation. To assess the feasibility of this carbocyanation, the intramolecular acylcyanation of the N-acetyl-protected Reissert compound **1a** was investigated in acetonitrile with a catalytic amount of a phosphine catalyst, which was previously identified to be effective in intramolecular acylcyanation of cyanohydrins (Table 1).[7a,8] The reaction proceeded sluggishly and gave rise to the desired

Table 1: Optimization of reaction conditions.[a]



1a **2a**

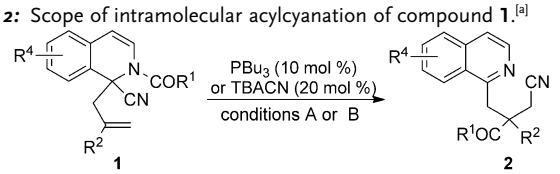
Entry	Cat.	Solvent	*T* [°C]	*t* [h]	Yield [%][b]
1	$PPhEt_2$	CH_3CN	30/60	24/48	24
2	PPh_2Et	CH_3CN	30/60	24/48	14
3	PPh_3	CH_3CN	60	48	0
4	PBu_3	CH_3CN	30	3	71
5	DABCO	CH_3CN	30/60	24/48	0
6	DMAP	CH_3CN	30/60	24/48	0
7	DBU	CH_3CN	30/60	24/48	37
8	TBACN	CH_3CN	30	0.5	81
9	PBu_3	DMSO	30	2.5	74
10[c]	PBu_3	DMSO	30	3.5	88
11	TBACN	DMF	30	0.5	85
12[c]	TBACN	DMF	30	0.5	73

[a] Reaction conditions: reaction was performed with **1** (0.1 mmol) and catalyst (20 mol%) in CH_3CN (1.0 mL). [b] Yield of isolated product. [c] The catalyst loading was 10 mol%. DABCO = 1, 4-diazobicyclo-[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide.

product **2a** in low conversion in the presence of $PPhEt_2$ (20 mol%), even at an elevated temperature (entry 1). PPh_2Et gave the much lower conversion, whereas the reaction did not occur in the presence of PPh_3 (entries 2 and 3). Gratifyingly, the increased yield was obtained by employing the more-electron-rich PBu_3 and the reaction proceeded smoothly under very mild reaction conditions (entry 4). Tertiary amines, such as DMAP, DABCO, and DBU, were also evaluated. No reaction occurred in the presence of DABCO or DMAP, even at an elevated temperature, however, DBU gave the desired product in low yield (entries 5–7). In addition, according to the previous work in which a catalytic amount TBACN (tetrabutylammonium cyanide) promoted the intramolecular acylcyanation of cyanohydrins,[7a,9] the reaction was investigated with TBACN (20 mol%). To our delight, this transformation worked very fast and furnished product in high yield, thus suggesting that TBACN also can serve as a suitable catalyst (entry 8). Further survey on solvents revealed that the acylcyanation reaction worked well in polar solvents.[10] In the presence of PBu_3, the reaction was completed in 2.5 hours in DMSO, and reducing the loading of catalyst to 10 mol% increased the yield of desired product markedly (entries 9 and 10). With regard to TBACN as the catalyst, an improved yield was obtained in DMF (entry 11). The attempt to reduce the amount of TBACN resulted in a slightly decreased yield (entry 12).

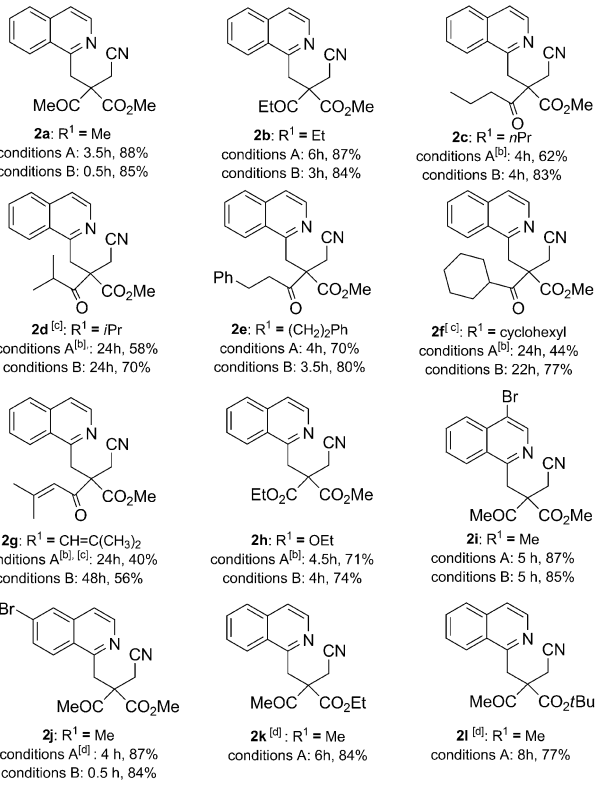
With the optimized reaction conditions established, a range of functionalized Reissert compounds (**1**), having various N-acyl substituents, were readily prepared from isoquinoline derivates and evaluated (Table 2). Other than **1a**, the acylcyanation of the substrates **1** having various N-alkylacyl groups performed well in the presence of either PBu_3 or TBACN (**2b–f**). Generally, a catalytic amount of

Table 2: Scope of intramolecular acylcyanation of compound **1**.[a]



1 **2**

1a–j: $R^2 = CO_2Me$; **1k**: $R^2 = CO_2Et$; **1l**: $R^2 = CO_2tBu$; **1a–h**, **1k,l**: R^4 = H; **1i,j**: R^4 = Br

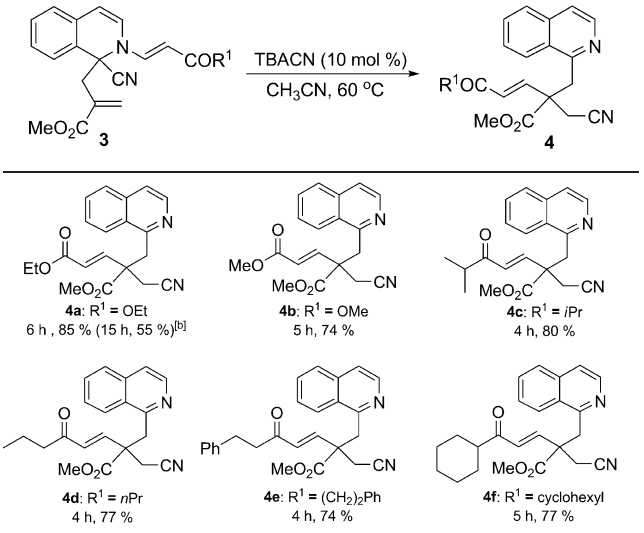


[a] Reaction conditions: conditions A: **1** (0.1 mmol) and PBu_3 (10 mol%) in DMSO (1.0 mL) at 30°C; conditions B: **1** (0.1 mmol) and TBACN (20 mol%) in DMF (1.0 mL) at 30°C. Yields shown are those of the isolated products. [b] Catalyst (20 mol%) was used. [c] The reactions were carried out at 60°C. [d] The reactions were carried out at 40°C.

PBu_3 can promote the reaction and provide the desired nitriles **2** in good to high yield, and TBACN can serve as an alternative catalyst to provide an improved outcome of the transformation in some cases. For example, the acylcyanation of N-cyclohexanecarbonyl-substituted compound proceeded slowly and gave the corresponding product **2f** in 44% yield by using PBu_3 (20 mol%), and a better yield was obtained with a catalytic amount of TBACN. An α,β-unsaturated acyl group was also be inserted intramolecularly into a C=C bond and gave the unsaturated ketone product **2g**, albeit with decreased yield. The acylcyanation of substrates with N-arylacyl groups failed to give the desired products.[10] Performing this reaction with an N-ethoxycarbonyl analogue under optimal reaction conditions afforded the desired product **2h** in good yield. Reissert compounds substituted in the 4- or 6-positions can also be employed and both 4-bromo- and 6-bromo-substituted Reissert compounds provided the desired products in good yields (**2i** and **2j**). Moreover, **1** having different ester moieties were used and both ethyl and *tert*-butyl ester analogues gave the desired products in good yields (**2k** and **2l**).

Encouraged by these results, we next investigated the challenging intramolecular alkenylcyanation which has not yet been achieved (Table 3). The N-vinyl-substituted Reissert compound **3a** (R^1 = OEt) was exposed to the optimized reaction conditions. To our delight, the intramolecular

Table 3: Intramolecular alkenylcyanation of compound **3**.[a]

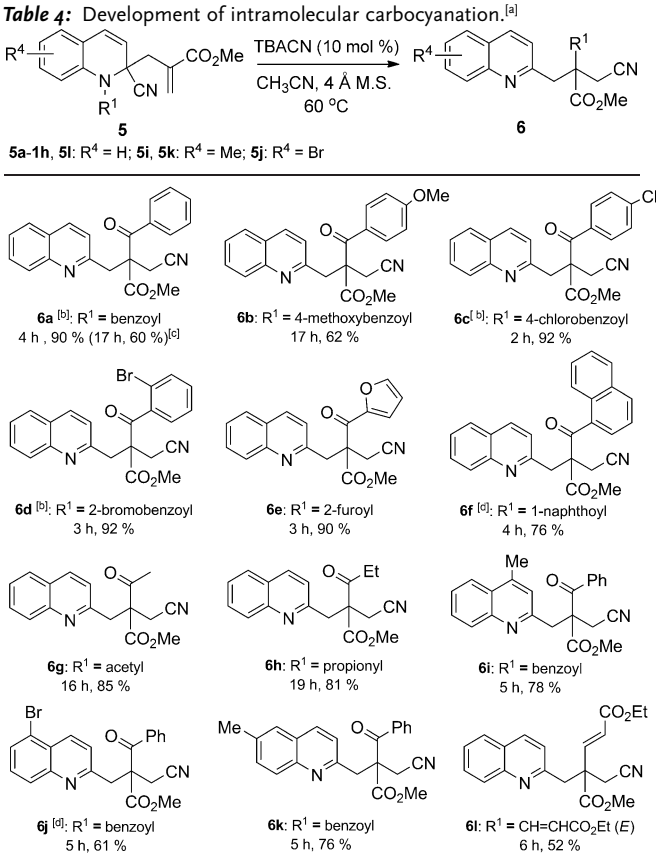


[a] Reaction conditions: **3** (0.1 mmol) and TBACN (10 mol%) in CH_3CN (1.0 mL) at 60°C. Yields shown are those of the isolated products. [b] The reaction was performed with PBu_3 (10 mol%) in DMSO (1.0 mL) at 30°C.

alkenylcyanation of **3a** took place at 60°C in the presence of PBu_3 (10 mol%) and furnished the desired nitrile **4a**, bearing an α,β-unsaturated ester moiety, albeit with moderate yield (55%). Further investigation revealed that TBACN (10 mol%) can also promote this transformation, and a better result was obtained.[10] Subsequently, a variety of N-electron-deficient vinyl-substituted Reissert compounds (**3**) was surveyed to explore the generality of this unique transformation. The results are summarized in Table 3. In addition to **3a**, the methoxy analogue can also provide the desired γ,δ-unsaturated-functionalized nitrile in good yield (**4b**). Substrates with various vinyl alkyl ketone moieties were employed and the corresponding alkenylcyanation reactions afforded the nitriles bearing diverse α,β-unsaturated alkyl ketone moieties in good yields, regardless of whether vinyl alkyl ketone moieties are linear or branched (**4c–f**).[11]

In the course of exploring the scope of this intramolecular transformation, the carbocyanation of quinoline-derived Reissert compounds (**5**) was investingated (Table 4). In

Table 4: Development of intramolecular carbocyanation.[a]

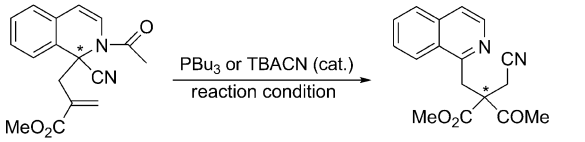


[a] Reaction conditions: **5** (0.1 mmol), TBACN (10 mol%) and 4 Å M.S. in CH_3CN (1.0 mL) at 60°C. Yields shown are those of isolated products. [b] TBACN (5 mol%) was used. [c] PBu_3 (10 mol%) was used. [d] The reaction was carried out with TBACN (20 mol%). M.S. = molecular sieves.

contrast to the acylcyanation of **1**, a reaction which was unable to give the desired product, **5a** smoothly underwent the intramolecular acylcyanation to give the β-benzoyl nitrile **6a** in 60% yield by using PBu_3 (10 mol%). An improved yield (90%) of **6a** can be obtained in the presence of TBACN (5 mol%) in CH_3CN with 4 Å molecular sieves. Substrates bearing an N-arylacyl group with neutral or electron-withdrawing substituents can be smoothly employed in the process to furnish products in high yields by using only 5 mol% TABCN (**6a, 6c**, and **6d**), whereas a substrate with an

electron-donating substituent on the N-arylacyl group gave **6b** in 62% yield after a prolonged reaction time with 10 mol% catalyst. These results indicate that the reactivity of the carbonyl group of the N-arylacyl component influences the chemical outcome of this transformation, and is in accordance with the proposed mechanism (see Scheme 3). N-naphthoyl- and heteroaromatic-subsititued Reissert compounds (**5**) can also serve as good substrates and provide the desired products in comparably good yields (**6e** and **6f**). Similar to the isoquinoline analogues, quinoline-derived substrates with N-alkylacyl components also can take part in the reaction and provide the desired products in high yields (**6g** and **6h**). Substituents at either the 4- or 6-positions of the 1, 2-dihydroquinoline ring can be tolerated and give products in good yields (**6i** and **6k**), whereas a 5-bromo-substituted substrate afforded the product **6j** in relatively low yield. In addition, quinoline-derived Reissert compounds with an N-electron-deficient vinyl substituent could also be utilized to participate in the intramolecular alkenylcyanation transformation, as exemplified by the synthesis of the desired γ,δ-unsaturated nitrile **6l** in moderate yield from the corresponding substrate.

The demonstration of an asymmetric carbocyanation transformation was carried out with the enantioenriched isoquinoline-derived Reissert compound **1a**. As illustrated in Scheme 2, the enantioenriched substrate **1a** was subjected to the optimized reaction conditions and pleasingly provided the



1a, 91%ee — **2a**

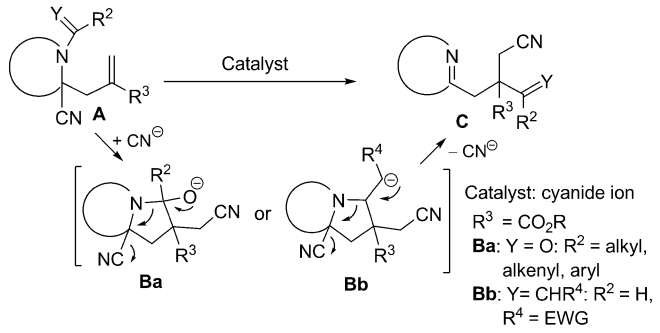
conditions A: PBu_3 (20 mol%), CH_3CN, 30 °C, 71% yield, 88% *es*;
conditions B: TBACN (20 mol%), DMF, 0 °C, 87% yield, 99% *es*;

Scheme 2. Asymmetric carbocyanation transformation of compound **1a**. *es* = (product *ee*/starting material *ee*) 100%.

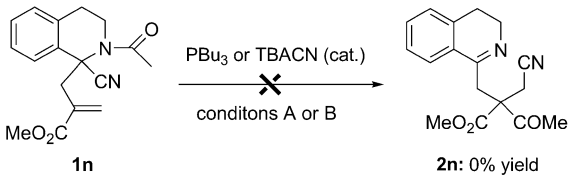
desired product **2a** in 87% yield with excellent chirality transfer (99% es) in the presence of the catalytic amount of TBACN. Moderate chirality transfer was obtained by using PBu_3 as a catalyst.[10]

On the basis of the above experiments and the previous results,[7a] a possible reaction pathway is proposed (Scheme 3). We hypothesized that a conjugate addition of the catalyst, such as a cyanide ion, to the activated terminal alkene moiety of the Reissert compound **A** (**1, 3**, or **5**) proceeds with subsequent tandem intramolecular addition to C=O or C=C and cleavage of the C–N bond to afford the product **C** (**2**, **4**, or **6**).[12] Moreover, the dihydro-Reissert compound **1n** did not undergo acylcyanation reaction in the control experiment, thus indicating that the cleavage of the C–N bond as the driving force may stem from the rearomatization of dihydro-Reissert compound.[13]

Mechanistic proposal:



Control Experiment:



1n — **2n:** 0% yield

Scheme 3. Mechanistic proposal and control experiment.

In summary, we have developed a novel metal-free catalytic intramolecular carbocyanation (acyl- and alkenylcyanation) reaction of activated alkenes by cleavage of a C–N bond. The starting materials are readily available and this protocol provides facile access to functionalized nitriles incorporating quaternary carbon centers with a pendent N-heterocyclic motif under neutral and mild reaction conditions. The broad scope and versatility of the process were demonstrated. Moreover, the asymmetric version of this transformation has been accomplished and excellent chirality transfer was obtained. Further studies on the asymmetic synthesis as well as the synthetic applications of the reaction are ongoing and will be reported in due course.

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[10] For details, see the Supporting Information.

[11] The alkenylcyanation reaction of the Reissert compounds **3**, including an α,β-unsaturated aryl ketone moiety, was complex under the optimized reaction conditions, and failed to give the desired product.

[12] When PBu_3 is used, the possible mechanism is that the initial attack of phosphine at the C=C double bond, which follows the similar reaction pathway to that of TBACN, would result in the release of cyanide ion, which may serves as authentic catalyst to promote the reaction.

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