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N-Heterocyclic Carbene-Catalyzed Convenient Benzonitrile Assembly

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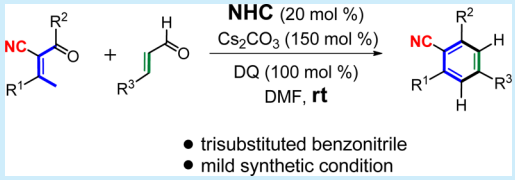
Supporting Information

ABSTRACT: The benzonitrile unit is widely found in natural products, pharmaceuticals, and agrochemicals. Synthesis of benzonitriles has received considerable interests from the chemical community over the last few decades. Present synthetic protocols mainly rely on the pre-existing benzene core to install a cyano moiety. A new NHC-catalyzed [4 + 2]-benzannulation protocol is reported to assemble the benzonitrile framework.



The wide distribution of a benzonitrile core in natural products, pharmaceuticals, and agrochemicals renders these kinds of molecules particularly interesting targets for the chemical community (Scheme 1, eq 1).[1] More specifically, the cyano group in benzonitriles represents one of the most prevalent functional groups and can feasibly transfer to other functional moieties, such as aldehydes, carboxylic acids, amidines, amides, and amines.[2] It has been long established that traditional S_NAr reactions can be utilized to incorporate a cyano group into the aromatic system through a C−C bond-forming process (Scheme 1, eq 2) but often suffers from harsh conditions and heavy metal wastes.[3] Since then, a number of transition-metal-catalyzed cross-coupling reactions with diversified cyanating reactants have been extensively investigated (Scheme 1, eq 3).[4] Although these methods are shown to possess promising substrate scope, their mechanisms generally require the attendance of toxic cyanide sources and often generate a stoichiometric amount of toxic wastes.[5] Very recently, several groups[6] found that the protocols of generating the cyano group in situ from other readily available "N" sources were also proven to be practicable (Scheme 1, eq 4). Notwithstanding these established promising achievements, designing a catalytic system to solve the consequences of environmental pollution has became a challenging task for synthetic chemistry. Moreover, the above methods can belong to a similar strategy of the cyano group incorporation relying on the pre-existing benzene core framework. We questioned whether it would be possible to identify a completely different strategy for benzonitrile assembly that proceeds via an alternative benzene framework construction using commercial or easily handled starting materials.

In the synthetic community, [4 + 2]-benzannulation reactions via the use of acyclic precursors have received much attention due to their efficient synthetic procedures and excellent regioselectivity control.[7] In this context, most of representative synthetic protocols focused on transition-metal-catalyzed [4 + 2]-benzannulation.[7] A conceptually new and environmentally friendly benzannulation strategy would be highly desirable and amenable.

Despite numerous achievements accomplished by transition metal catalysis, examples of organocatalytic [4 + 2]-benzannulation are still very scarce. In 2012, the Wang group reported a

Scheme 1. Selected Important Benzonitriles and Synthetic Strategies

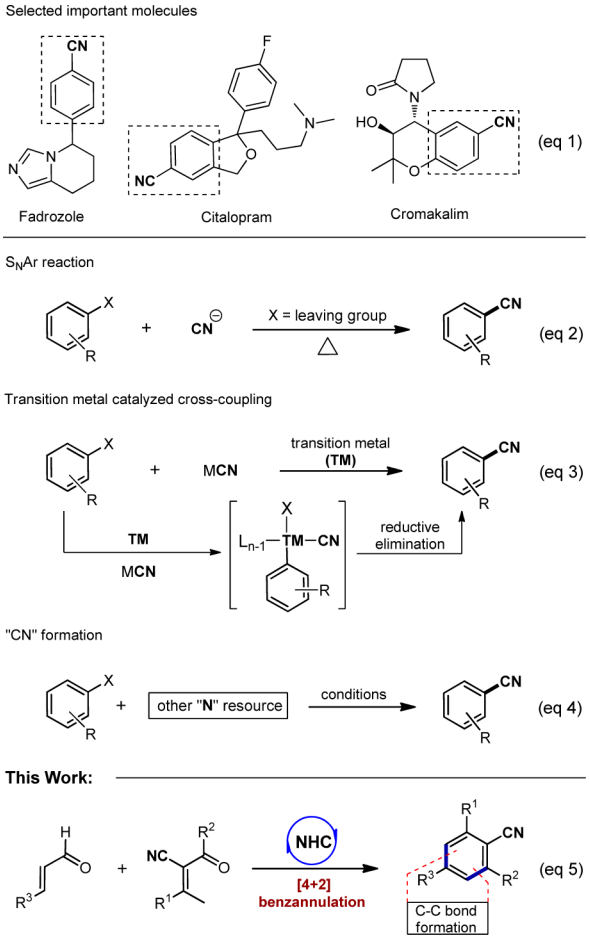


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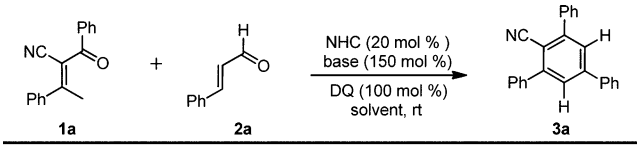
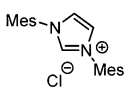
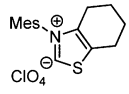
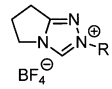
Table 1. Optimization of the Reaction Conditions[a]



NHC:


A

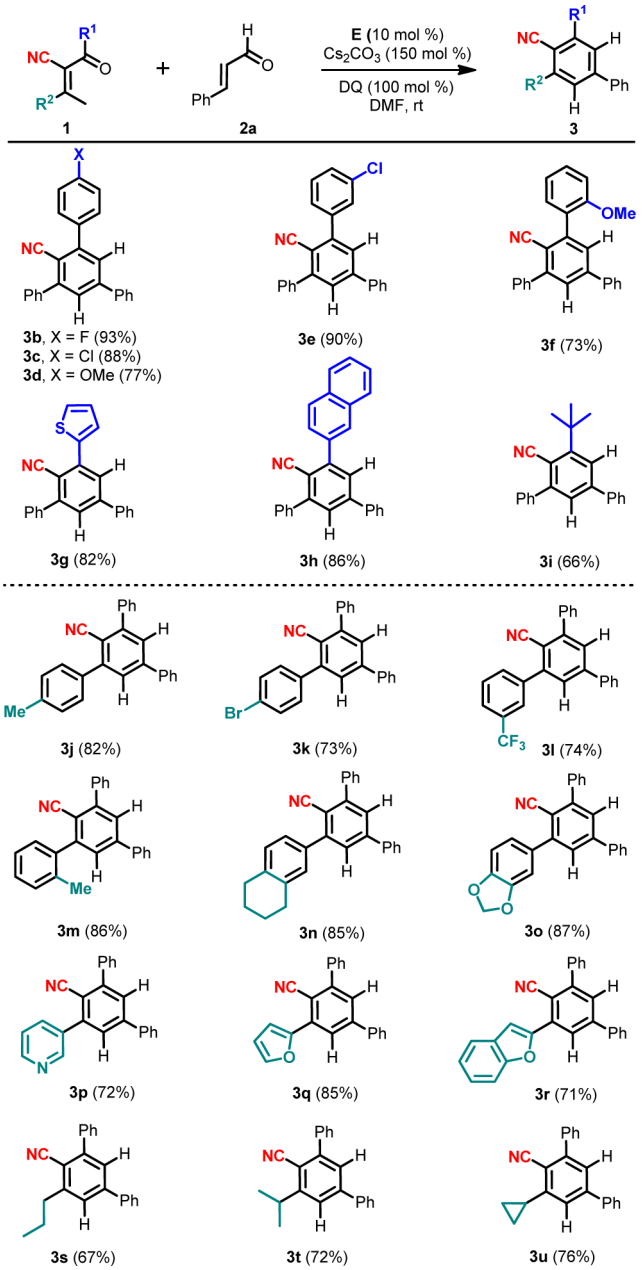

B


C, R = Ph
D, R = Mes
E, R = 2,6-(Et)$_2$C$_6$H$_3$
F, R = 2,6-(*i*Pr)$_2$C$_6$H$_3$

entry	NHC	base	solvent	3a (%)[b]
1	A	Cs_2CO_3	THF	56
2	B	Cs_2CO_3	THF	<5
3	C	Cs_2CO_3	THF	46
4	D	Cs_2CO_3	THF	74
5	E	Cs_2CO_3	THF	80
6	F	Cs_2CO_3	THF	<5
7	E	DBU	THF	47
8	E	DIEA	THF	32
9	E	KO^{t}Bu	THF	45
10	E	$NaHCO_3$	THF	28
11	E	Cs_2CO_3	CH_2Cl_2	24
12	E	Cs_2CO_3	toluene	13
13	E	Cs_2CO_3	DMSO	68
14	E	Cs_2CO_3	DMF	86
15[c]	**E**	**Cs_2CO_3**	**DMF**	**84**
16[d]	E	Cs_2CO_3	DMF	68
17		Cs_2CO_3	DMF	NR

[a]Reaction conditions: mixture of **1a** (0.1 mmol), **2a** (0.1 mmol), base (0.15 mmol), DQ (0.1 mmol), and catalyst (20 mol %) in solvent (1.0 mL), stirred at rt for 8 h. [b]Isolated yield after flash chromatography. [c]10 mol % of catalyst **E**, 18 h. [d]5 mol % of catalyst **E**, 36 h.

Scheme 2. Scope of Enones[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.2 mmol), cat. **E** (0.02 mmol), oxidant DQ (0.2 mmol), Cs_2CO_3 (0.3 mmol), DMF (1.0 mL), rt, 8−24 h.

remarkable formal [4 + 2]-aromatization strategy to generate substituted aromatic aldehydes catalyzed by the Hayashi−Jørgenson organocatalyst.[8] Early in 2015, the Lupton group uncovered an elegant N-heterocyclic carbene (NHC)-catalyzed redox isomerization method to make tetrasubstituted benzaldehydes.[9] Impressively, Chi and co-workers disclosed a unique multisubstituted arene synthesis via a [4 + 2]-process of unsaturated aldehydes in the presence of an achiral NHC catalyst.[10] Inspired by this progress, we report here a concise and scalable NHC-catalyzed formal [4 + 2]-benzannulation approach (Scheme 1, eq 5).[11]

Key results of condition optimization are summarized in Table 1. Evaluation was initially examined with enone **1a** and enal **2a** as starting materials and a series of NHC catalysts using 3,3′,5,5′-tetra-*tert*-butyldiphenoquinone (DQ, oxidant), Cs_2CO_3 (base), and THF (solvent). We were delighted to find that the proposed benzonitrile product **3a** was indeed formed in the presence of *N*-Mes imidazolium **A**[12] or *N*-Ph triazolium **C**[13] (Table 1, entries 1 and 3). An enhanced efficiency was achieved in the presence of *N*-Mes triazolium **D**[14] or *N*-2,6-(Et)$_2$C$_6$H$_3$-substituted triazolium **E**[15] (Table 1, entries 4 and 5). However, bulky substituted triazolium **F** (*N*-2,6-(*i*Pr)$_2$C$_6$H$_3$) or thiazolium **B** resulted in dramatic decreases in yield (Table 1, entries 2 and 6). Control experiments have indicated that both solvent (DMF) and base (Cs_2CO_3) are essential for achieving a high level of transformation (Table 1, entry 14). A survey of catalyst loadings revealed that 5 mol % of **E** can still afford a moderate chemical yield in an endurable time (68%, 36 h) (Table 1, entry 16). Distinctly, **3a** will not be formed in the absence of catalyst **E** (Table 1, entry 17).

With optimal conditions in hand, we investigated the scope of enones (Scheme 2). Interestingly, variation of the electronic nature of the aromatic ring (R^1) has little influence on the reaction efficiency (**3b−h**). With respect to aromatic rings, an alkyl group (R^1 = *tert*-butyl group) is also compatible with the reaction conditions (**3i**). Moreover, the protocol appears to be tolerant of a broad range of substituents at the R^2 position and provides the corresponding products with useful reaction efficiency (**3j−u**, 67−87%).

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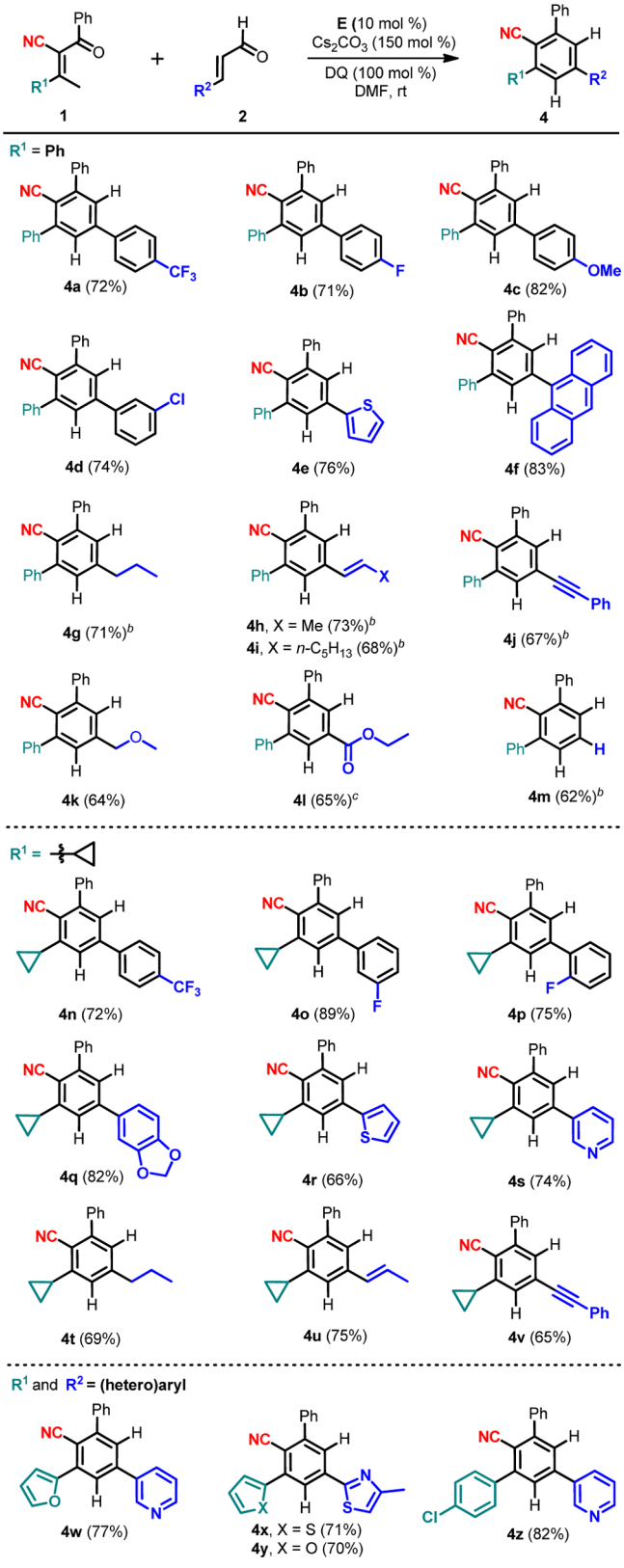
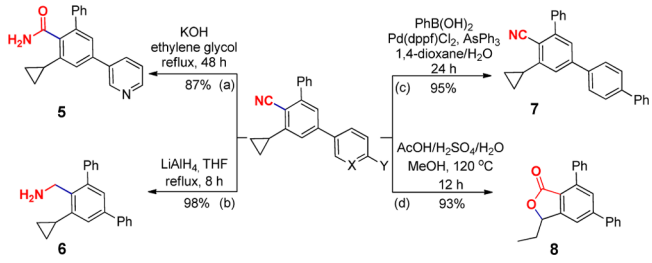
Scheme 3. Scope of Enals[a]



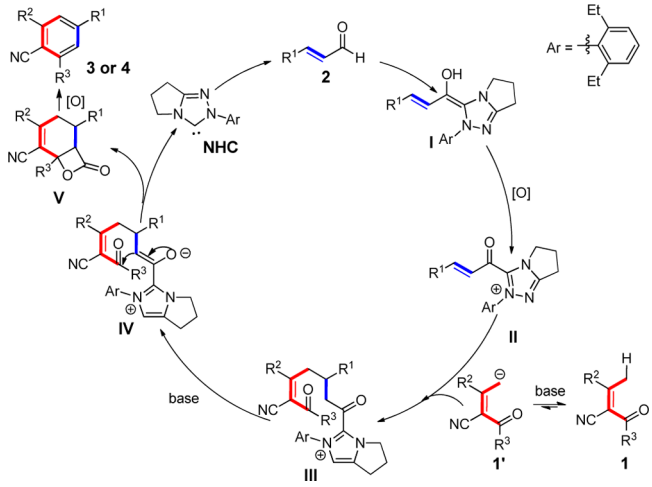
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), cat. **E** (0.02 mmol), oxidant DQ (0.2 mmol), Cs_2CO_3 (0.3 mmol), DMF (1.0 mL), rt, 8 h. [b]24 h. [c]**1** (0.2 mmol), **2** (0.3 mmol).

We next turned our attention to examine the scope of enals (Scheme 3). Enals containing electron-poor substituents (X = F, Cl, CF_3) and electron-rich substituents (X = OMe) on the phenyl ring are both well-tolerated and afforded good yields (**4a**–**e**). Replacement of the β-phenyl substituent with an anthracene **4f**, heteroaryl **4e**, and alkyl unit **4g** had limited effect on reaction conversion. In the case of enals that bear functional groups (e.g., alkenyl group, alkynyl group, ether, and ester) at the β-carbon position, the corresponding products were obtained in good yields (**4h**–**l**). While enal has hydrogen on the β-carbon position, the desired product **4m** was achieved in a moderate yield. Building upon the significance of a cyclopropane substituent in drug design, we chose enone **1t** as the model substrate to test the synthetic feasibility (Scheme 3). All corresponding desired products were obtained in good yields (**4n**–**v**). In addition, the mild nature of this protocol allows the presence of two or three (hetero)aryl substituents on one benzonitrile product (**4w**–**z**).

Scheme 4. Synthetic Transformations



Scheme 5. Proposed Mechanism



To highlight the utility of this transformation, we made a series of benzene derivatives (Scheme 4). Treatment of **4s** with KOH afforded benzamide **5** in 87%. When **3u** was subjected to $LiAlH_4$, functionalized benzylamine **6** was obtained in 98%. Suzuki coupling of **3u** with phenylboronic acid furnished derivative **7**. Hydrolysis of **3u** eventually led to the formation of isobenzofuranone **8** in 93%.

As outlined in Scheme 5, a reaction mechanism is proposed. Briefly, the addition of NHC catalyst to enal followed by deprotonation forms Breslow intermediate **I**,[16] which is oxidized by DQ to yield unsaturated acyl azolium intermediate **II**.[17] Then, 1,4-addition of deprotonated enone **1′**[18] to intermediate **II** generates adduct **III**.[19−21] Subsequent α-deprotonation of adduct **III** leads to intermediate **IV**. A subsequent intramolecular aldol reaction and β-lactonization yields the bicyclic adduct **V** accompanied by the liberation of NHC catalyst. Lastly,

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decarboxylation[22] of **V** followed by spontaneous oxidative aromatization[23] affords the substituted benzonitrile **3** or **4**.

In conclusion, an expedient formal [4 + 2]-NHC-catalyzed benzannulation has been developed. This strategy delivers products containing medicinally relevant, cyano-bearing benzene cores. Studies directed toward the development of other cyano-binding medicinally important scaffolds are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00844.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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