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N-Heterocyclic Carbene-Catalyzed Construction of 1,3,5-Trisubstituted Benzenes from Bromoenals and α-Cyano-β-methylenones

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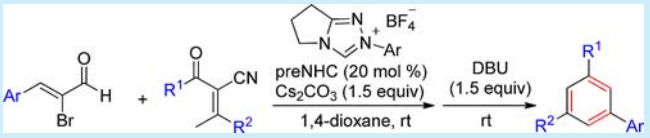
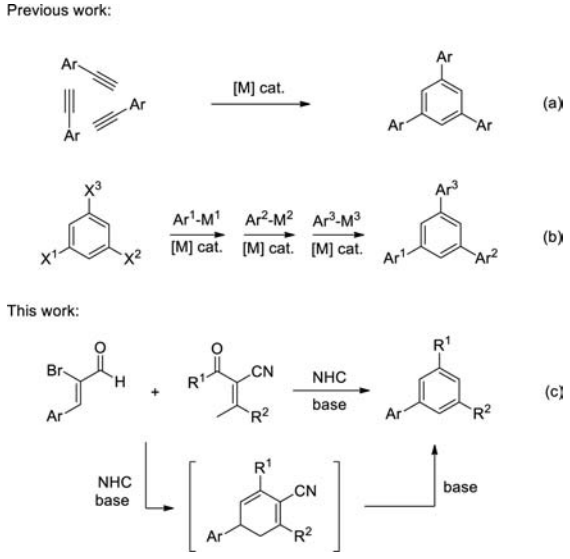
Supporting Information

ABSTRACT: A direct and efficient approach to 1,3,5-trisubstituted benzenes has been developed via N-heterocyclic carbene-catalyzed [2 + 4] annulation of α-bromoenals and α-cyano-β-methylenones. The reaction worked well for both aryl- and alkylenones.



1,3,5-Trisubstituted benzenes are of great importance for their diverse applications in material science. They have been widely employed as building blocks in the design and synthesis of organic electroluminescent devices,[1] porous materials,[2] potential chemosensors,[3] and bulky ligands[4] due to their π-conjugation, high-rate electron transfer, and nonplanner characteristics. Hence, much attention has been focused toward the synthesis of 1,3,5-trisubstituted benzenes. In particular, transition-metal-catalyzed [2 + 2 + 2] cycloaddition of alkynes, pioneered by Reppe et al. in 1948,[5] emerged as the most convenient and straightforward methodology (Scheme 1, reaction a).[6] However, this approach is limited to homotrimerization of alkynes.[7] Otherwise, a complex mixture of 1,3,5-triarylbenzenes would be produced for the heterotrimerization of two or more alkynes.[6e,8] Alternatively, the transition-metal-catalyzed cross-coupling reaction has been proven to be a versatile tool to the access of homo- and hetero-1,3,5-triaryl benzenes (Scheme 1, reaction b).[9] However, this strategy requires a multistep synthesis from a pre-existing benzene ring equipped with heteroatoms or other functional groups and the difficulty of removing the toxic metal species from the desired products has led to growing concern.[10] The rapid construction of 1,3,5-trisubstituted, particularly hetero-1,3,5-trisubstituted, benzenes with excellent regio- and chemoselectivities under mild conditions is still highly desired.[11] In this paper, we report the N-heterocyclic carbene-catalyzed rapid construction of homo- and hetero-1,3,5-trisubstituted benzenes from readily available bromoenals and α-cyano-β-methylenones (Scheme 1, reaction c).

Scheme 1. Synthesis of 1,3,5-Trisubstituted Benzenes



In the past decades, N-heterocyclic carbenes (NHCs) have emerged as one of the most powerful organocatalysts to construct various organic molecules.[12] However, the NHC-catalyzed synthesis of multisubstituted benzenes was extremely limited. In 2014, Chi and co-workers first reported the direct construction of benzene ring via oxidative NHC-catalyzed γ-addition of enals to activated enones,[13] followed by the related [4 + 2] annulation via oxidative NHC-catalyzed δ-addition of α,β−γ,δ-diunsaturated aldehydes to 1,3-dicarbonyl compounds.[14] In 2015, Lupton and co-workers reported the synthesis of multisubstituted benzenes via NHC-catalyzed cleavage of the ester and recombination.[15] Very recently, Wang et al. and our group independently developed a mild and convenient multisubstituted benzenes synthesis through oxidative NHC-catalyzed β-addition of enals to α-cyano-β-methylenones.[16] Based on our previous work, we envisioned that the NHC-catalyzed annulation of bromoenals[17] and α-cyano-β-methylenones may give the corresponding cyanocyclo-

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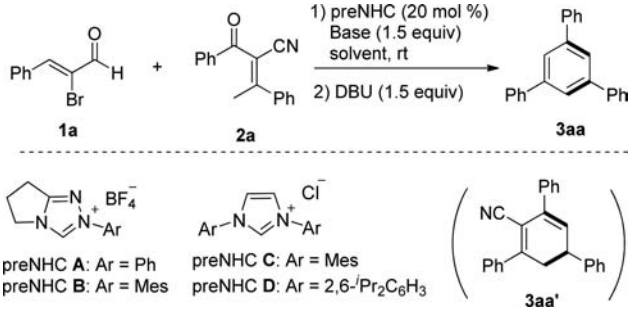
hexadiene, which can be transformed to the desired multi-substituted benzenes (Scheme 1, reaction c).

Initially, the model reaction of bromoenal **1a** and enone **2a** was investigated under NHC catalysis (Table 1). It was found

Table 1. Reaction Optimization[a]



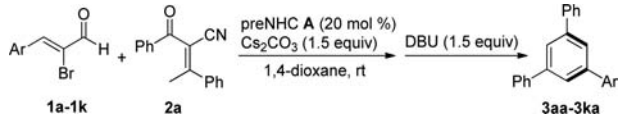
entry	preNHC	base	solvent	yield (%)[b]
1[c]	**A**	Cs_2CO_3	DCM	0 (86)[d]
2	**A**	Cs_2CO_3	DCM	78
3	**B**	Cs_2CO_3	DCM	64
4	**C**	Cs_2CO_3	DCM	trace
5	**D**	Cs_2CO_3	DCM	trace
6	**A**	K_2CO_3	DCM	70
7	**A**	DIPEA	DCM	39
8	**A**	Cs_2CO_3	toluene	74
9	**A**	Cs_2CO_3	THF	85
10	**A**	Cs_2CO_3	Et_2O	59
11	**A**	Cs_2CO_3	CH_3CN	44
12	**A**	Cs_2CO_3	1,4-dioxane	87
13[e]	**A**	Cs_2CO_3	1,4-dioxane	78
14[f]	**A**	Cs_2CO_3	1,4-dioxane	46
15	**A**	DBU[g]	1,4-dioxane	36

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.2 mmol) in the presence of preNHC (0.04 mmol) and Cs_2CO_3 (0.3 mmol) at room temperature until complete consumption of the starting material as monitored by TLC, and then DBU (0.3 mmol) was added. [b]Isolated yield. [c]3.0 equiv of Cs_2CO_3 and no DBU was used. [d]Isolated yield of **3aa′** in parentheses. [e]preNHC **A** (10 mol %) was used. [f]preNHC **A** (5 mol %) was used. [g]DBU (3.0 equiv) was used in a one-step instead of a two-step addition of Cs_2CO_3 and DBU. DBU = 1,8-Diazabicyclo-[5.4.0]undec-7-ene.

that the reaction catalyzed by bicyclic *N*-phenyltriazolium NHC precursor **A** in the presence of 3.0 equiv of Cs_2CO_3 gave no desired 1,3,5-triphenylbenzene **3aa** but cyanocyclohexadiene **3aa′** in 86% yield (entry 1). We were pleased to find that 1,3,5-triphenylbenzene **3aa** was isolated in 78% yield when DBU was used as the second base for the elimination of cyanide (entry 2). *N*-Mesityl NHC precursor **B** led to similar results as NHC precursor **A** (entry 3), but monocyclic imidazolium NHC precursors **C** and **D** did not work for the reaction (entries 4 and 5). The screening of bases revealed that K_2CO_3 performed well but diisopropylethyl amine (DIPEA) did not (entries 6 and 7). The reaction worked in several solvents, and 1,4-dioxane is the best choice (entries 8−12). Reducing the loading of NHC to 10 or 5 mol % resulted in some loss of the yields (entries 13−14). It should be noted that use of DBU as the sole base instead of Cs_2CO_3/DBU resulted in a much lower yield (entry 15), which suggests different bases are required for the generation of NHC from its precursor and the elimination of cyanide from cyanocyclohexadiene.

With the optimized reaction conditions in hand, a wide variety of α-bromoenals were then briefly explored (Table 2). It

Table 2. Scope of α-Bromoenals[a]



entry	1	Ar	2a	3	yield[b]
1	**1a**	Ph	**2a**	**3aa**	87
2	**1b**	4-$MeOC_6H_4$	**2a**	**3ba**	94
3	**1c**	4-MeC_6H_4	**2a**	**3ca**	89
4	**1d**	4-FC_6H_4	**2a**	**3da**	88
5	**1e**	4-ClC_6H_4	**2a**	**3ea**	87
6	**1f**	4-BrC_6H_4	**2a**	**3fa**	92
7	**1g**	4-CNC_6H_4	**2a**	**3ga**	89
8	**1h**	3-$MeOC_6H_4$	**2a**	**3ha**	98
9	**1i**	2-MeC_6H_4	**2a**	**3ia**	78
10	**1j**	2-BrC_6H_4	**2a**	**3ja**	79
11	**1k**	2-Br-5-$MeOC_6H_3$	**2a**	**3ka**	96
12[c]	**1a**	Ph	**2a**	**3aa**	86

[a]Reaction conditions: **1** (0.3 mmol), **2** (0.2 mmol) in the presence of preNHC **A** (0.04 mmol) and Cs_2CO_3 (0.3 mmol) at room temperature until complete consumption of the starting material as monitored by TLC, and then DBU (0.3 mmol) was added. [b]Isolated yield. [c]Gram scale reaction with 1.58 g (7.5 mmol) of bromoenal **1a**.

was found that both electron-rich (4-$MeOC_6H_4$, 4-MeC_6H_4) and electron-deficient (4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, and 4-CNC_6H_4) *para*-substituted β-aryl-α-bromoenals (**1b−1g**) could participate in the reaction to give the desired 1,3,5-triarylbenzenes **3aa−3ga** in high yields (entries 2−7). β-Aryl-α-bromoenals (**1h−1j**) with different substituents with varying electronic properties at the *meta*- (3-$MeOC_6H_4$) or *ortho*-position (2-MeC_6H_4 and 2-BrC_6H_4) were tolerated to give the corresponding products **3ha−3ja** in good yields (entries 8−10). In addition, the β-aryl-α-bromoenal **1k** with a *meta*, *ortho*-disubstituted aryl group (2-Br-3-$MeOC_6H_4$) worked well to give the 1,3,5-triarylbenzene **3ka** in excellent yield (entry 11). It is worth noting that the reaction could be carried out at gram scale without loss in yield (entry 12). However, no desired benzene product was observed when alkyl instead of aryl bromoenal was used for the reaction under the current conditions.

The scope of enones was then investigated (Table 3). To our delight, β-arylenones **2b−2f** with electron-rich (R^2 = 4-$MeOC_6H_4$, 4-MeC_6H_4) and electron-deficient substituents (R^2 = 4-ClC_6H_4, 4-BrC_6H_4, 4-$NO_2C_6H_4$) worked well to give the 1,3,5-triarylbenzenes **3fb−3ff** in high yields (entries 1−5). The reaction of β-arylenones **2g−2h** with *meta*-substituents (R^2 = 3-MeC_6H_4, 3-ClC_6H_4) also went smoothly to give products **3fg−3fh** in high yields (entries 6−7). β-Arylenones **2i−2h** with *ortho*-substituents (R^2 = 2-MeC_6H_4, 2-ClC_6H_4) were also tolerated despite the small decrease but still good yields (entries 8−9). The reaction of β-naphthylenone **2k** afforded the triarylbenzene **3fk** in 79% yield (entry 10). In addition, β-heteroarylenones **2l−2m** (R^2 = 2-furyl, 2-thienyl) gave the corresponding products **3fl−3fm** in good yields (entries 11−12). Interestingly, the reaction of β-methylenone **2n** was also feasible to give alkyldiarylbenzene **3en** in 65% yield (entry 13). Furthermore, arylenones with electron-rich (R^1 = 4-$MeOC_6H_4$) as well as electron-deficient groups (R^1 = 4-FC_6H_4) or

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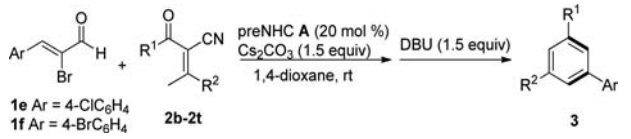
Table 3. Scope of Enones[a]



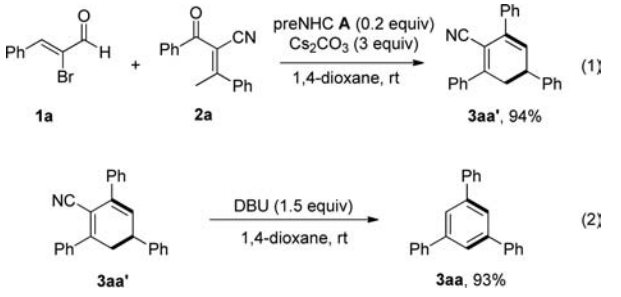
entry	1	2	R^1	R^2	3	yield[b]
1	1f	2b	Ph	4-$MeOC_6H_4$	3fb	89
2	1f	2c	Ph	4-MeC_6H_4	3fc	90
3	1f	2d	Ph	4-ClC_6H_4	3fd	95
4	1f	2e	Ph	4-BrC_6H_4	3fe	91
5	1f	2f	Ph	4-$NO_2C_6H_4$	3ff	72
6	1f	2g	Ph	3-MeC_6H_4	3fg	88
7	1f	2h	Ph	3-ClC_6H_4	3fh	89
8	1f	2i	Ph	2-MeC_6H_4	3fi	61
9	1f	2j	Ph	2-ClC_6H_4	3fj	66
10	1f	2k	Ph	β-naphthyl	3fk	79
11	1f	2l	Ph	2-fuyl	3fl	77
12	1f	2m	Ph	2-thienyl	3fm	90
13	1e	2n	Ph	Me	3en	65
14	1e	2o	4-$MeOC_6H_4$	Ph	3eo	85
15	1f	2p	4-FC_6H_4	Ph	3fp	91
16	1e	2q	2-thienyl	Ph	3eq	91
17	1f	2r	Me	Ph	3fr	60
18	1f	2s	Et	Ph	3fs	55
19	1f	2t	*i*-Pr	Ph	3ft	53

[a]Reaction conditions same as those in Table 2. [b]Isolated yield.

heteroaryl (R^1 = 2-thienyl) all worked to give the desired products in good yields (entries 14−16). Remarkably, alkylenones **2r**−**2t** were also tolerated to provide the 1,3,5-alkyldiarylbenzenes **3fr**−**3ft** in good yields (entries 17−19).

Several control experiments were carried out to further clarify the formation of cyanocyclohexadiene as the intermediate (Scheme 2). As expected, the reaction of bromoenal and

Scheme 2. Mechanistic Studies



cyanoenone gave cyanocyclohexadiene **3aa′** in 94% yield, which could be transformed to the corresponding 1,3,5-triphenylbenzene **3aa** in 93% yield in the presence of DBU as the base with elimination of the cyanide.

On the basis of the results, a plausible catalytic cycle for the reaction is depicted in Figure 1. As previously reported,[17] the addition of the NHC catalyst to bromoenal **1** and the following elimination of bromide under basic conditions gave the α,β-unsaturated acylazolium intermediate **I**. The Diels−Alder reaction of dienolate **2′**, generated in situ from enone **2** in the presence of base, and α,β-unsaturated acylazolium intermedate **I** as the dienophile, affords the adduct **II**. The intramolecular acylation of adduct **II** gives β-lactone-fused cyclohexene **III** and regenerates the NHC catalyst. The release

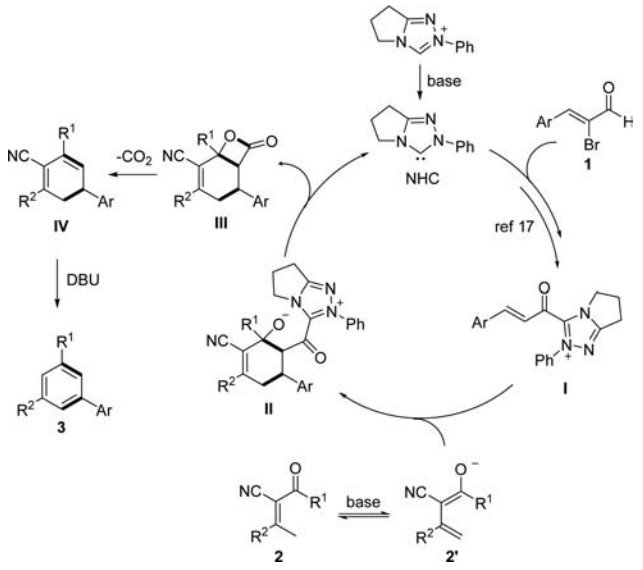


Figure 1. Plausible catalytic cycle.

of CO_2 from adduct **III** leads to the formation of cyclohexadiene **IV**.[18] The DBU-promoted elimination of cyanide from cyclohexadiene **IV** furnishes the final 1,3,5-trisubstituted benzene **3**.

In summary, we have developed an NHC-catalyzed [2 + 4] annulation of α-bromoenals and α-cyano-β-methylenones for the synthesis of homo- and hetero-1,3,5-trisubstituted benzenes. To the best of our knowledge, this transition-metal-free method represents the first example of direct construction of asymmetric 1,3,5-trisubstituted benzenes via NHC catalysis. The utility of the cyano moiety as a traceless activating group of α-cyano-β-methylenones is the key to this simple yet highly effective strategy. This approach features high yields, a broad substrate scope, and mild reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03306.

Experimental details and NMR and HPLC spectra for obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

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