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Bis(amino)cyclopropenylidene-Catalyzed 1,6-Conjugate Addition of Aromatic Aldehydes to *para*-Quinone Methides: Expedient Access to α,α′-Diarylated Ketones

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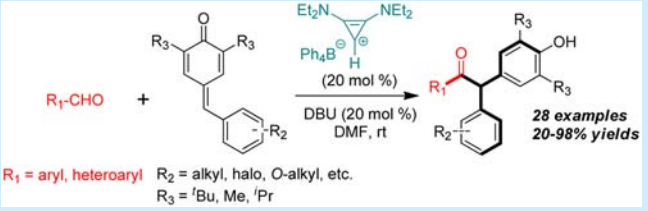
Supporting Information

ABSTRACT: A bis(amino)cyclopropenylidene-catalyzed direct method for the synthesis of α,α′-diarylated ketones from aromatic as well as heteroaromatic aldehydes has been developed. This unprecedented organocatalytic protocol offers access to a wide range of α,α′-diarylated ketones in moderate to excellent yields under mild conditions through umpolung of aldehydes followed by 1,6-conjugate addition with *para*-quinone methides.



In recent years, due to their ability to activate carbonyl compounds through diverse activation modes, N-heterocyclic carbenes (NHCs) are emerging as remarkable organocatalysts for carbon−carbon and carbon−heteroatom bond forming reactions.[1] The unique reactivity of NHCs led not only to the development of new organic transformations[1] but also to the advancement of new catalyst design.[2] It has been realized that the NHCs based on a heterocyclic core such as thiazole, triazole, imidazole, etc. dominate in organocatalysis due to their unmatched nucleophilicity[1] and high stability.[3] On the other hand, the scope of non-heterocyclic-based carbenes for the umpolung-type activation of carbonyl compounds is very limited, although their organometallic complexes are well studied.[4] However, cyclopropenylidene, the smallest aromatic compound with an inherent carbene center, was found to be a promising non-heterocyclic-based candidate in terms of reactivity toward metals and carbonyl compounds.[5] After the independent and seminal contributions by Weiss[6] and Yoshida[7] in the 1970s, the chemistry of cyclopropenylidenes has been explored particularly in organometallic chemistry.[8] Nevertheless, the immense development in this research area was realized when Bertrand and co-workers successfully isolated bis(diisopropylamino)-cyclopropenylidene derived from **1** (Figure 1) in 2006.[9,10]

The remarkable breakthrough by Bertrand's group[9] further led to the development of a few organocatalytic transformations using bis(amino)cyclopropenylidene as a catalyst.[11] Tamm and co-workers reported the synthesis of chiral bis(amino)-cyclopropenylidene precatalyst **3**.[12] Although their focus was to study the organometallic complexes of **3**, one example was included for an enantioselective benzoin reaction using **3** as a precatalyst.[12] Very recently, Gravel and co-workers successfully applied **2** as a precatalyst for highly chemoselective intermolecular Stetter[13] as well as aza-benzoin[14] reactions. Apart from these three reports, no other reports are available in the literature for the application of bis(amino)cyclopropenylidenes in organocatalysis.

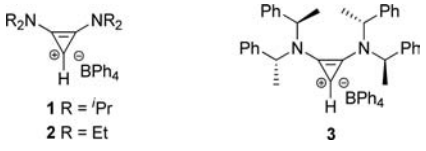


Figure 1. Bis(amino)cyclopropenylidene precursors.

While working on NHC-catalyzed chemoselective transformations,[15] we became interested in developing an efficient method for the synthesis of α,α′-diarylated ketones using **2** as a precatalyst through 1,6-conjugate addition of aldehydes to *p*-quinone methides (*p*-QMs). α-Arylated and α,α′-diarylated carbonyl compounds serve as versatile building blocks for many biologically important natural and unnatural compounds.[16] The most popular approach to access α-arylated and α,α′-diarylated carbonyl compounds involves transition-metal-catalyzed cross-coupling reaction between an enolizable carbonyl compound and a suitable aryl coupling partner.[17] A few metal-free coupling reactions were also reported for the synthesis of α-arylated carbonyl compounds.[18] Glorius and co-workers reported an efficient method for the synthesis of α,α′-diarylated carbonyl compounds through NHC-catalyzed cross-coupling between aromatic aldehydes and activated alkyl halides.[19] Recently, Mayr and co-workers reported kinetic studies involving the reaction of NHCs with *p*-quinone methides to characterize the relative nucleophilicities of NHCs.[20] The groups of Scheidt[21] and Ye[22] independently reported the synthesis of enantioenriched benzo-fused lactones through chiral NHC-catalyzed 1,4-addition of homoenolates to *o*-quinone methides. Recently, McErlean and co-workers reported NHC-catalyzed intramolecular vinylogous

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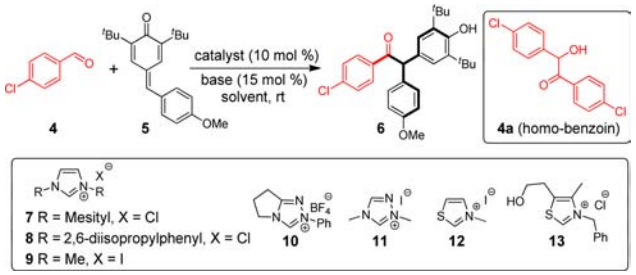
Stetter reaction of aldehydes with 1,6-acceptors.[23] However, the synthesis of α,α'-diarylated ketones via intermolecular 1,6-conjugate addition of aldehydes to *p*-quinone methides[24] using NHC or bis(amino)cyclopropenylidene as a catalyst remains unprecedented, which triggered us to investigate this transformation in detail.

Optimization studies were carried out using *p*-chlorobenzaldehyde **4** and *p*-quinone methide **5** under various conditions (Table 1). Our initial attempts using conventional imidazolium-based (**7**–**9**) and triazolium-based (**10** and **11**) NHC precatalysts did not give encouraging results as the expected product **6** was not obtained in any of the cases (entries 1–5). Interestingly, even homobenzoin product **4a** was not observed in all those cases. Since the reaction between NHC and *p*-QM to form an adduct has already been reported,[20] we presume that NHC prefers to react with **5** over **4**, so the NHC is probably not available to react with **4** to generate either the desired product **6** or the homobenzoin product **4a** during the reaction. However, surprisingly, when the reaction was carried out using thiazolium salts such as **12** or **13** as a precatalyst, the expected product **6** was obtained in 10 and 73% yield, respectively, after 36 h (entries 6 and 7). When **2** was used as a precatalyst in DMF, **6** was obtained in 90% yield in 3 h (entry 8). This result clearly indicates that the carbene derived from **2** prefers to react with **4** over **5**. Another possibility is that the reaction between **2** and **5** could be reversible under the reaction conditions. Further optimization experiments were performed using different bases (entries 9–11) and also in different solvents (entries 12–15). In all of these experiments, the yield of **6** was found to be lower compared to that in entry 8.

Table 1. Catalyst Screen and Optimization Studies[a]

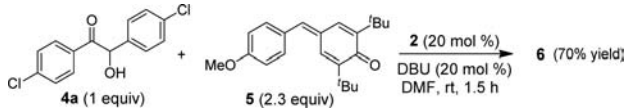


entry	catalyst	base	solvent	time [h]	yield **6**[%][b]
1	**7**	DBU	DMF	24	0
2	**8**	DBU	DMF	24	0
3	**9**	DBU	DMF	24	0
4	**10**	DBU	DMF	24	0
5	**11**	DBU	DMF	24	0
6	**12**	DBU	DMF	36	10
7	**13**	DBU	DMF	36	73
8	**2**	DBU	DMF	3	90
9	**2**	Cs_2CO_3	DMF	6	40
10	**2**	$^iPr_2NEt$	DMF	18	0
11	**2**	KO^{t}Bu	DMF	12	22
12	**2**	DBU	PhMe	48	42
13	**2**	DBU	THF	24	60
14	**2**	DBU	DMSO	3	60
15	**2**	DBU	1,4-dioxane	48	37
16[c]	**2**	**DBU**	**DMF**	**1.5**	**98**

[a]Reaction conditions: 0.16 M of **4** in solvent. Use of 1.05 equiv of **5** was found to be optimal. [b]Isolated yield. [c]20 mol % of **2** and 20 mol % of DBU were used; rt = 25–28 °C; DBU = 1,8-diazabicyclo[5.4.0]-undec-7-ene.

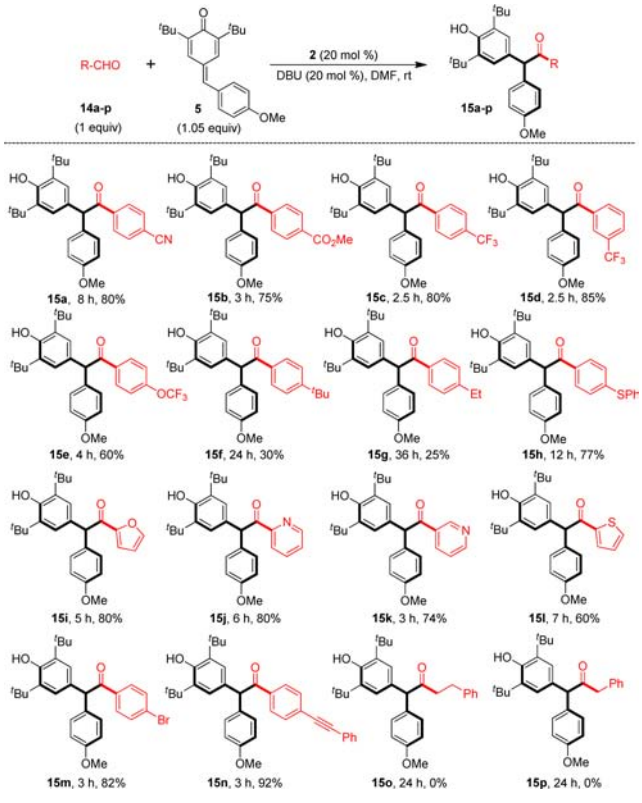
Gratifyingly, when the reaction was carried out with 20 mol % of **2** and 20 mol % of DBU in DMF, **6** was isolated in 98% yield in 1.5 h (entry 16). Careful monitoring of the standard reaction in DMSO-d_6 by ^{1}H NMR spectroscopy revealed that **4a** was observed in small quantities along with **6** (ratio **4**/**4a**/**6** = 1:0.3:1.5) within 5 min after addition of all the reagents and catalyst precursor (**2**). The concentration of **4a** decreased as the reaction progressed, and we could not detect even trace amounts of **4a** after completion of the reaction. This observation clearly suggests that the formation of **4a** is reversible under the standard reaction conditions.[25] The observation of benzoin and retrobenzoin reactivity with this catalyst is in contrast to observations by Gravel and co-workers;[13,14] however, the reaction conditions were different in their case. The reversible formation of **4a** was further confirmed by a crossover experiment, in which the homobenzoin **4a** (as an aldehyde equivalent) was treated with 2.3 equiv of **5** under standard conditions. In this case, as expected, **4a** was converted into **6** in 70% yield in 1.5 h (Scheme 1).

Scheme 1. Crossover Experiment



Then, the substrate scope of this transformation was examined using *p*-quinone methide **5** and a wide range of aromatic and heteroaromatic aldehydes (Scheme 2) under optimal conditions (entry 16, Table 1). As represented in Scheme 2, this

Scheme 2. Substrate Scope Using Different Aldehydes[a]



[a]Reaction conditions: 0.16 M of **14** in solvent; rt = 25–28 °C.

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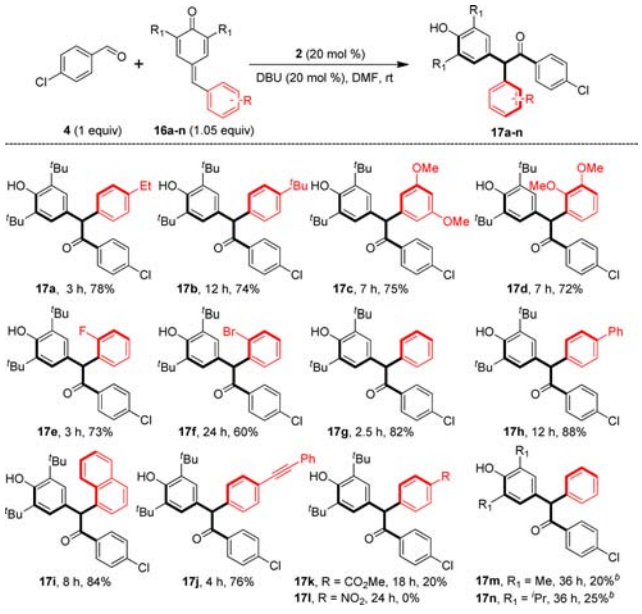
methodology worked well for electron-poor aromatic aldehydes, and the desired α,α′-diarylated ketones (**15a**−**15e**) were obtained in moderate to good yields (60−85%) in short reaction times. However, in the cases of electron-rich aldehydes, such as 4-*tert*-butyl benzaldehyde and 4-ethyl benzaldehyde, the reaction was sluggish and products (**15f** and **15g**) were obtained in lower yields. Surprisingly, 4-phenylmercaptobenzaldehyde gave the corresponding α,α′-diarylated ketone **15h** in 77% yield. This methodology was further elaborated to heteroaromatic aldehydes (**14i**−**14l**), and in those cases, the expected products (**15i**−**15l**) were isolated in good yields. Under the standard conditions, 4-bromobenzaldehyde (**14m**) and 4-alkynyl benzaldehyde (**14n**) underwent smooth transformation to their corresponding α,α′-diarylated ketones **15m** and **15n** in 82 and 92% yields, respectively. Unfortunately, in the cases of aliphatic aldehydes, such as hydrocinnamaldehyde (**14o**) and 2-phenylacetaldehyde (**14p**), only decomposition of the reaction mixture was observed.

The substrate scope of this methodology was also extended using various *p*-quinone methides (**16a**−**16n**), derived from electron-rich and electron-poor aromatic aldehydes, and the results are summarized in Scheme 3.

Scheme 3. Substrate Scope with Different *p*-QMs[a]

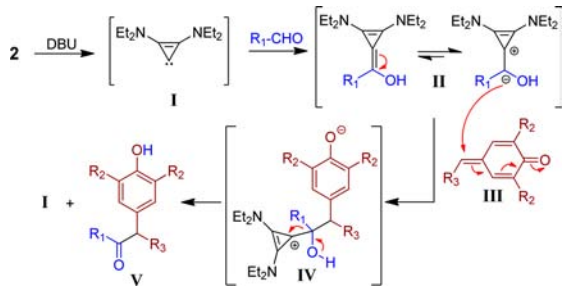


[a]Reaction conditions: 0.16 M of **4** in solvent. [b]1,2-Dichloroethane was used as a solvent; rt = 25−28 °C.

The reaction worked pretty well in the cases of *p*-QMs derived from electron-rich aromatic aldehydes (**16a**−**16d**), and the desired products (**17a**−**17d**) were obtained in reasonably good yields. In the case of *p*-QM derived from a moderately electron-poor aromatic aldehyde, such as 2-fluorobenzaldehyde (**16e**), the α,α′-diarylated ketone **17e** was obtained in 73% isolated yield. Similarly, *o*-bromo-substituted *p*-QM **16f** also underwent smooth conversion to the corresponding product **17f** in 60% yield. In the cases of *p*-QMs derived from benzaldehyde (**16g**) and other aryl-substituted benzaldehydes (**16h** and **16i**), the corresponding α,α′-diarylated ketones (**17g**−**17i**) were obtained in good yields (82−88%). Product **17j** was isolated in 76% yield under the standard condition when **16j** was used as a substrate. In the case of *p*-QM derived from an electron-deficient aldehyde such as **16k**, the reaction was sluggish and **17k** was obtained in only 20% yield. Unfortunately, no product (**17l**) was observed in the case of *p*-QM derived from 4-nitrobenzaldehyde (**16l**). The substrate scope for this transformation was also elaborated with *p*-QMs derived from other phenols such as 2,6-dimethylphenol (**16m**) and 2,6-diisopropylphenol (**16n**). In both cases, the expected products **17m** and **17n** were obtained in 20 and 25% yields, respectively, after 36 h.

Based on the outcome of this transformation, a plausible mechanism has been proposed (Scheme 4). In the initial step,

Scheme 4. Plausible Mechanism



DBU abstracts the acidic proton from **2** and generates carbene **I**, which reacts with aldehyde to produce intermediate **II**, which is similar to the Breslow intermediate.[26] Intermediate **II** then reacts with *p*-QM (**III**) to form another intermediate **IV**, which decomposes to **V** with the expulsion of carbene **I**.

In conclusion, we have demonstrated the scope of bis(amino)-cyclopropenylidene as an organocatalyst for the synthesis of α,α′-diarylated ketones through the extended conjugate addition of umpolung of aromatic aldehydes to *p*-quinone methides. The versatility of this protocol has been portrayed using a wide range of aromatic and heteroaromatic aldehydes as well as *p*-QMs. Efforts to elaborate this methodology to an enantioselective version is currently under investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01724.

General experimental procedures and characterization data of the products (PDF)

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Notes

The authors declare no competing financial interest.

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