

# Bis(amino)cyclopropenylidene (BAC) Catalyzed Aza-Benzoin Reaction

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**(5)** Supporting Information

**ABSTRACT:** A bis(amino)cyclopropenylidene (BAC) catalyzed aza-benzoin reaction between aldehydes and phosphinoyl imines has been developed. The reaction is general with a wide range of aromatic aldehydes and aromatic imines. The reaction displays excellent chemoselectivity favoring aza-benzoin products over homobenzoin products.



rganocatalysis can be an efficient metal-free way to construct complex organic molecules.<sup>1</sup> In recent years, organocatalysis based on the umpolung of functional groups with N-heterocyclic carbenes (NHCs) has enabled numerous attractive modes of reactivity and has led to the development of several reactions accomplishing otherwise challenging bond connections.<sup>2</sup> We recently disclosed the ability of bis(amino)cyclopropenylidenes (BACs) to competently catalyze the intermolecular Stetter reaction between an aldehyde and a Michel acceptor.<sup>3</sup> The BAC catalysts are advantageous, as they can easily be prepared in a one-pot reaction. These BAC species are also intriguing because they possess similar characteristics to NHCs, such as the ability to catalytically induce acyl anion reactivity in aldehydes.<sup>3–5</sup> However, they exhibit markedly different organocatalytic behavior. In our prior work, several umpolung reactions were observed using BACs without the generation of benzoin side products, and no benzoin products were observed when reaction progress was followed by <sup>1</sup>H NMR or thin layer chromatography.<sup>3</sup> Indeed, the benzoin reaction using BACs is extremely limited, even under ideal conditions. This is in stark contrast to most popular NHCs for which benzoin reactivity is often concomitant with the reaction of interest.

The aza-benzoin reaction is a carbene catalyzed coupling between an aldehyde and an imine to generate an  $\alpha$ -amino ketone (Scheme 1).<sup>6,7</sup> It is an attractive transformation due to





its convergent nature, the convenient accessibility of the starting materials, and the potential to direct stereoselectivity at the new stereogenic center. The resulting  $\alpha$ -amino ketone motif is present in a number of medicinal agents,<sup>8</sup> and these moieties can be reduced to useful  $\alpha$ -amino alcohols<sup>9</sup> or they can be converted to a number of substituted heterocycles<sup>10</sup> such as oxazoles or imidazoles which can also be bioactive.<sup>11</sup>

Among early work, Miller and Mennen used benzoyl aldimines for enantioselective aza-benzoin-reactions catalyzed by a thiazolium-containing tripeptide.<sup>6b</sup> You's group developed a robust reaction using achiral thiazolium salts and *N*-Ph aldimines.<sup>6f</sup> However, the resulting products feature a difficult to cleave *N*-phenyl substituent making deprotection and derivatization difficult. The Rovis group has reported a highly enantioselective method using well developed chiral triazolium catalysts with aliphatic aldehydes and *N*-Boc protected imines.<sup>6k</sup> This methodology, though efficient, is reportedly not tolerant to aromatic aldehydes.

A potential problem encountered when performing azabenzoin reactions is the formation of benzoin side products (Scheme 1). When these products are formed reversibly, the thermodynamic drive toward aza-benzoin products simplifies the matter considerably. Ensuring this reversibility however introduces an unnecessary limitation upon aldehyde substrates, potential aza-benzoin acceptors, and suitable reaction conditions. Under the conditions reported by Murry, Frantz and co-workers for instance,<sup>6b</sup> the benzoin products were formed irreversibly, underscoring the importance of developing other methods of governing chemoselectivity in the aza-benzoin reaction. The presence of benzoin products can also complicate the purification of the desired aza-benzoin products. The Scheidt group has reported a methodology using acylsilanes as aldehyde surrogates, along with the easily removable Ndiphenylphosphinoyl protecting group.<sup>12</sup> They posit the acylsilane is required specifically to avoid the formation of the benzoin product, thus facilitating purification. Based on our previous observation that BACs are poor catalysts for the benzoin reaction, we hypothesized that an appropriate choice of reactants and conditions would allow the formation of azabenzoin products without any of the problems associated with competing benzoin reactivity.

With the goal of finding complementary or otherwise beneficial reactivity as well as potentially addressing some of the shortcomings of current methodologies, we set about

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exploring suitable approaches for a BAC catalyzed aza-benzoin reaction. Our first task was to evaluate the competency of BAC catalysts for the aza-benzoin reaction. Initial efforts with Boc protected imines or tosyl imines gave no product or ill defined mixtures. Boc imines were also found to inhibit otherwise productive Stetter reactions.<sup>3</sup> Fortunately, reactions between aldehydes and *N*-diphenylphosphinoylimines or their sulfinic acid adducts gave productive reactions using our reported bis(diethylamino)cyclopropenium salt **8** as a precatalyst. *N*-Diphenylphosphinoylimines<sup>13</sup> can be easily formed in one step by condensation of the corresponding aldehyde and diphenylphosphinamide.<sup>13d</sup> The corresponding sulfinic acid surrogates are trivial to prepare and are more practical to use, as they are less sensitive to moisture.<sup>13b</sup>

Once optimal conditions were established (see Supporting Information), a scope exploration was undertaken starting with the *p*-tolyl bearing acceptor 7b (Scheme 2). The reactivity of

# Scheme 2. Scope of the BAC Catalyzed Aza-Benzoin Reaction $^{a}$



<sup>*a*</sup>N-Dpp = NPOPh<sub>2</sub>. Reactions performed on a 0.15 mmol scale. <sup>*b*</sup> Yields of isolated pure products. <sup>*c*</sup> Reaction done with the imine of 7**b**. <sup>*d*</sup> 3 equiv of aldehyde were used. <sup>*e*</sup> The corresponding imine was used as substrate on a 0.3 mmol scale. <sup>*f*</sup> 5 equiv of aldehyde were used. <sup>*g*</sup> <sup>1</sup>H NMR conversion in parentheses.

this acceptor was found to be similar to that of substrate 7a (9 and 10). It was found that a good yield could be obtained with P,P-diphenyl-N-(4-methylphenyl(tosyl)methyl) phosphinic amide 7b and a number of *para* and *meta* substituted electron-deficient aromatic aldehydes (10, 12, 13, and 14) as well as heteroaromatic aldehydes (11). Benzaldehyde was also shown to be a competent reaction partner (15). As is typically the case in NHC organocatalysis, the use of electron-rich

aromatic or ortho substituted aromatic aldehydes led to sluggish and low yielding reactions (not shown). To better understand the influence of substituents on the imine acceptor, reactions were performed with *P*,*P*-diphenyl-*N*-(4-methoxyphenyl(tosyl)methyl) phosphinic amide 7c as well as p-P,P-diphenyl-N-(4bromophenyl(tosyl)methyl) phosphinic amide 7d. Excellent reactivity was observed with electron-rich acceptor 7c (16–18). Using electron-poor acceptor 7d also led to an efficient reaction, although difficulties were encountered in the isolation of the aza-benzoin product 20. Meta substitution on the imine acceptor (7e) led to product 21 in modest yield, though the use of more electrophilic imines was not explored. The imine derived from o-chlorobenzaldehyde was also probed, but its use only led to low conversion (<10%). At this point, modifications to the current methodology seem required to obtain the products of ortho-substituted imines in good yield.

In the course of our studies, we explored the effect of using additional equivalents of aldehyde to the reaction. It was found to be beneficial to use an excess of aldehyde in some instances (11, 14, 15, 17, and 18), and this could drive modestly yielding reactions further to completion. There were no instances where excess aldehyde was detrimental to the reaction. The excess aldehyde was still present in the crude reaction mixture, and it did not form any detectable amounts of benzoin product in the presence of catalyst 8. The excess aldehyde could even be recovered, though recovery was not practical on this scale.

There has been discussion in the literature regarding the reversible formation of adducts between NHC and imines,  $^{6e,k}$  so the direct use of imines instead of their sulfinic acid adducts was probed in this reaction. Good yields were obtained in the two cases investigated (10: 75%, 11: 96%), demonstrating the ability of phospinoylimines to undergo the aza-benzoin reaction efficiently. Nevertheless, the increased bench stability of the sulfinic acid adducts makes the latter the preferred reaction partners in most cases.

To compare the effectiveness of various catalysts in this transformation, a number of parallel experiments were undertaken (Table 1). Our previous experience with triazolium

#### Table 1. Catalyst Comparison



"Determined from <sup>1</sup>H NMR integration relative to a known amount of internal standard.

salts indicated their reactions with imines give much superior results to their reactions with sulfinic acid adducts. To establish a valid comparison between catalysts, we therefore opted to use phosphinoylimine **22** as a reaction partner. It was found that precatalyst **8** gave a suitable reaction with excess furfural (**6a**), with a large amount of aldehyde remaining after workup despite its volatility (entry 1). Thiazolium **24** gave a very high

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conversion as well, with a large amount of accompanying benzoin side-product 23 (entry 2). Triazolium 25 also afforded good conversion, again with substantial benzoin contamination, along with other unidentified side products (entry 3).

To elucidate whether the absence of benzoin side products when using catalyst **8** is due to a facile retro-benzoin/azabenzoin reaction, benzoin compound **26** was subjected to reaction conditions as an aldehyde equivalent (Scheme 3). As no aza-benzoin product was observed, we conclude the benzoin reaction does not occur with catalyst **8** under these conditions.



As BACs were shown previously to be effective catalysts for the Stetter reaction, competition experiments were designed to explore the relative reactivity of phosphinoyl imines and Michael acceptors toward the putative Breslow intermediate formed between the aldehyde and catalyst (Table 2). In these



<sup>&</sup>lt;sup>*a*</sup>Determined from <sup>1</sup>H NMR integration on the crude reaction mixture. Homobenzoin product **26** was not detected, but could be present in small amounts. <sup>*b*</sup>Yields of isolated pure products.

reactions, we had a limiting amount of aldehyde 6b compete for p-tolyl phosphinoyl imine 22 and chalcone 27 to find out which reaction was favored with BAC catalysts. Under these conditions, the Stetter reaction was favored. To determine whether this reaction was under catalyst or substrate control, we then performed reactions with thiazolium 24 and triazolium 25. Both catalysts were less efficient and favored the azabenzoin reaction. The reversibility of the aza-benzoin reaction and the thermodynamic preference for the Stetter product was subsequently established (Scheme 4). Specifically, we found that subjecting aza-benzoin product 10 to the reaction conditions with chalcone in the absence of any aldehyde led to the Stetter product (28) and imine 22 when using 8 as the catalyst, in addition to recovered starting material 10. This result shows the reversible nature of the aza-benzoin reaction when using catalyst 8. Whether the selectivities observed in Table 2 are the result of kinetic or thermodynamic control (or both) is unclear and is the object of further investigations.





At this stage in the reaction development, efforts were undertaken to induce enantioselectivity in the reaction using chiral BAC catalyst **29** (Scheme 5). However, the product





obtained was found to be racemic under our optimal conditions. Miller and Mennen<sup>6d</sup> reported a high incidence of postreaction epimerization over time, and Rovis' group<sup>6k</sup> reported cooling the reaction to be necessary to minimize epimerization. As the same chiral BAC catalyst was found to induce modest enantioselectivities in the Stetter reaction,<sup>3</sup> it was hypothesized that the aza-benzoin product was undergoing racemization. This racemization could occur via a retro-azabenzoin process or base-induced epimerization. In an attempt to minimize the risk of epimerization, the reaction was performed using the imine substrate and substoichiometric amounts of base. Unfortunately, the product obtained under these conditions proved to be racemic as well. NMR experiments showed no deuterium incorporation at the stereogenic center in the presence of cesium carbonate and  $D_2O_1$ , suggesting a facile retro-aza-benzoin is the more likely scenario. Efforts to obtain enantiomerically enriched azabenzoin products using different chiral BAC catalysts are continuing.

There has been a range of conditions reported for the deprotection of phosphinic amides,  $^{12,14}$  so to further demonstrate the usefulness of this methodology a representative aza-benzoin product **11** was deprotected (Scheme 6). It

Scheme 6. Removal of Protecting Group



was found that stirring the product at rt in a mixture of THF and 2 N hydrochloric acid (1:1) was sufficient to effect complete deprotection. However, the product was not stable as the free base and it proved necessary to reprotect the amine with a Boc group to obtain a good yield.

To conclude, we report the first examples of the BAC catalyzed aza-benzoin reaction. As was the case for BAC catalyzed Stetter reactions, no competing benzoin dimerization

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was observed. The reaction is effective for various aromatic and heteroaromatic aldehydes and a wide range of aromatic phosphinoyl imines (as their sulfinic acid adducts). The phosphinoyl activating group was found to be compatible with this methodology and cleavable under mild conditions.

#### ASSOCIATED CONTENT

#### Supporting Information

Experimental details and full spectroscopic data are available for all substrates and aza-benzoin products, as well as their derivatives. <sup>1</sup>H NMR spectra of the crude reaction mixture are included for all competition experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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