COMMUNICATION

Synergistic catalysis: highly diastereoselective benzoxazole addition to Morita–Baylis–Hillman carbonates†

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An expedited method has been developed for the diastereoselective synthesis of highly functionalized alkyl-azaarene systems with good yields and high diastereoselectivities (>15 : 1 dr). The methodology includes a synergistic catalysis event involving organometallic (10 mol% AgOAc) activation of an alkyl azaarene and Lewis base (10 mol% DABCO) activation of a Morita–Baylis–Hillman carbonate. The structure and relative configuration of a representative product were confirmed by X-ray analysis.

Synergistic catalysis,[1] in which two catalytic cycles involving two separate catalysts work in a concerted fashion to create a single new bond, has emerged as a powerful approach for the development of new reactions. The concurrent activation of both nucleophile and electrophile using distinct catalytic species facilitates the enhancement of inherent chemical reactivity and allows for the synthesis of complex scaffolds that might be difficult to obtain otherwise (Fig. 1). While synergistic catalysis is more prevalent in nature, the principle has now begun to emerge as a recognized and valued approach to bond-forming processes in organic chemistry.

Based on our previous experience in organocatalysis and organometallic chemistry,[2] we envisioned that a system in which an organometallic catalyst and organocatalyst operate in synergy could provide further opportunities for the development of new reaction.

Several examples of synergistic catalyst systems mixing organocatalytic and organometallic processes can be found in the literature; for example, Cordova demonstrated the β-arylation[3] or β-silylation[4] of enals by combining iminium and Pd catalytic processes with excellent results; further representative procedures include
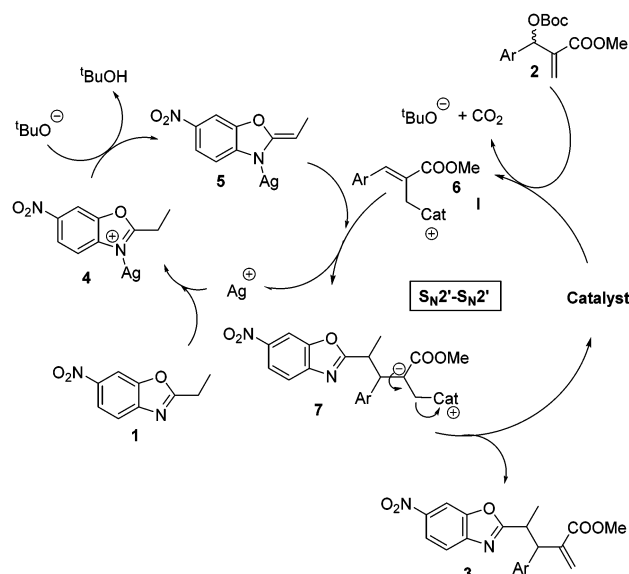

Fig. 1 Suggested mechanism.

photoredox-mediated α-alkylations, as developed by MacMillan.[5] However, the use of a simple metallic Lewis acid and organic Lewis base as a synergistic catalytic system has been less extensively explored, probably due to the presumption that self-quenching would occur, which renders both catalysts inactive. The first example was reported by Corey and Wang in 1993, who applied this method to the cyanation of aldehydes;[6] they developed a dual catalytic system wherein a chiral Lewis base creates a chiral cyanide nucleophile, while a chiral Lewis acid activates the aldehyde. More recently, several research groups developed Lewis base-catalyzed cycloadditions and cyclizations using *Cinchona* alkaloids or N-heterocyclic carbenes and a metallic Lewis acid.[7] Concurrently, Lectka and coworkers developed a synthesis of β-lactams based on this concept.[8]

Recently, we became interested in studying the reactivity of Morita–Baylis–Hillman (MBH) carbonates;[9] however, one of the drawbacks of their use in nucleophilic additions is the need for

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strong nucleophiles such as malonates, amines, or alcohols for suitable reactivity. Some less active nucleophiles, such as alkyl azaarenes, are unreactive.

Based on the idea of synergistic catalysis, we devised the addition of alkyl azaarenes (specifically, benzoxazoles and pyridines) to MBH carbonates by the use of two different catalysts (metal Lewis acid and organic Lewis base).

Shibata and coworkers reported one of the rare examples of the simultaneous use of a metal Lewis acid and organic Lewis base using this kind of substrate.[10] They reported that the use of $FeCl_2$ or $Ti(O^iPr)_4$ increase the enantioselectivity of their reaction but it was not crucial for reactivity.

Alkyl benzoxazoles are an interesting class of heterocycle that have found wide use in the fields of agro- and medicinal chemistry. Several methods have been developed for their synthesis and functionalization. Despite growing attention from the chemical community directed at these compounds, the synthesis of alkyl benzoxazoles remains unexplored. To the best of our knowledge, just a single example exists in the literature regarding the addition of alkyl benzoxazoles to imines catalyzed by Pd–bisoxazolidinone complexes with excellent results, as reported by Lam and coworkers in 2012 (Scheme 1).[11]
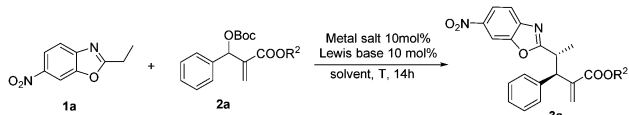
In this work we report the first example of alkyl-azaarene addition to MBH carbonates using synergistic catalysis. This methodology provides highly functionalized alkyl azaarenes and may potentially lead to the development of new scaffolds of interest to the agrochemical and pharmaceutical industries.

As shown in Fig. 1, we envisioned that a metal Lewis acid could interact with the alkyl azaarene *via* nitrogen coordination, thus increasing the acidity of the α-carbon. Simultaneous reaction of an organic Lewis base with the MBH carbonate *via* S_N2' addition with release of carbonic acid yields highly reactive intermediate **6**, which reacts with the previously activated nucleophile **5** to form the product (**3**) after release of the organic catalyst.

In our preliminary experiments, we investigated the reaction of MBH carbonate **2a** with 2-ethyl-6-nitrobenzoxazole (**1a**) in the presence of different metal Lewis acids, solvents, organic Lewis bases, *etc.* As shown in Table 1, the reaction is quite flexible in the nature of the metal Lewis acid. Satisfactorily, $Pd(OAc)_2$ and DABCO were able to catalyze the reaction, affording (after 14 h at 50 °C) a 2:1 diastereomeric mixture of adduct **3a** in 71% conversion.

We next tested several metal Lewis acids; copper and ytterbium salts gave low conversions after 14 h, with only moderate diastereoselectivities (Table 1; entries 2–4); $PdCl_2$ exhibited similar reactivity to that of $Pd(OAc)_2$ (entry 5). Fortunately, upon switching to silver salts, the reaction provided moderate to good conversions with excellent diastereoselectivities (entries 6–7). Once the optimal Lewis acid (AgOAc) was determined, the reaction was next examined with

Table 1 Reaction optimization[a]

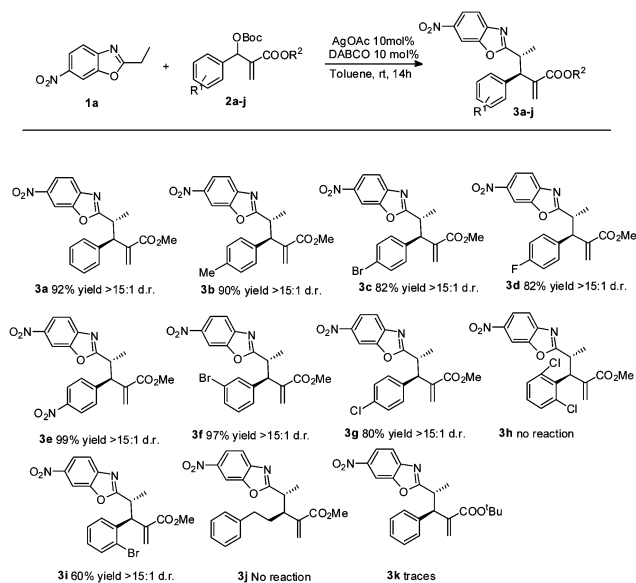| Entry	Solvent	Lewis acid	T (°C)	Lewis base	Conv.[b] (%)	d.r.[c]
1	Toluene	$Pd(OAc)_2$	50	DABCO	71	2:1
2	Toluene	$Cu(OAc)_2$	50	DABCO	Traces	n.d.[e]
3	Toluene	$YbTf_3$	50	DABCO	9	2.5:1
4	Toluene	$CuTf_2$	50	DABCO	9	4:1
5	Toluene	$PdCl_2$	50	DABCO	50	2:1
6	Toluene	AgOBz	50	DABCO	43	8:1
7	Toluene	AgOAc	50	DABCO	50	15:1
8	DMF	AgOAc	50	DABCO	50	1:1
9	$CHCl_3$	AgOAc	50	DABCO	n.r.	—
10	THF	AgOAc	50	DABCO	25	5:1
11[d]	Toluene	AgOAc	r.t.	DABCO	100	>15:1
12[d]	Toluene	AgOAc	0	DABCO	100	>15:1
13[d]	Toluene	$AgSbF_6$	r.t.	DABCO	100	>15:1
14[d]	Toluene	AgOAc	r.t.	—	n.r.[f]	—
15[d]	Toluene	—	r.t.	DABCO	n.r.[f]	—
16[d]	Toluene	AgOAc	r.t.	DMAP	Traces	n.d.[e]

[a] In a small vial, 1.0 equiv. of benzoxazole **1a**, 2 equiv. of MBH carbonate **2a** were added in 1 mL of the corresponding solvent in the presence of 10% Lewis acid and 10% Organic base. The reaction was stirred at the temperature shown in the table for 14 h. [b] Determined by ^1H NMR of the crude mixture. [c] Determined by ^1H NMR of the crude mixture. [d] Reaction carried out with 4 equiv. of MBH carbonate **2a**. [e] n.d. = not determined. [f] n.r. = no reaction.

different solvents. DMF gave good conversions, but without any diastereoinduction (entry 8), $CHCl_3$ yielded only traces of the final adduct after 14 h (entry 9), and THF gave lower conversions and diastereoselectivities than that observed for toluene (entry 10). Next, the reaction was performed at different temperatures while simultaneously increasing the equivalents used of MBH carbonate (**2a**; from 2 to 3). The reactions gave full conversions after 14 h and with total diastereoselectivity when conducted at room temperature (r.t.) or 0 °C (entries 11 and 12); this increase in the final conversion is likely due the decreased MBH carbonate decomposition at the low temperatures used. $AgSbF_6$ was used as a catalyst to determine whether acetate plays a role in the reaction (entry 13); a similar result was observed as that with AgOAc. Finally, the reactions were performed without Lewis acid or Lewis base to prove that synergistic catalysis indeed promotes this reaction; no reaction was observed in both cases, showing that activation of both compounds is necessary (entries 14 and 15). Using DMAP as Lewis base instead of DABCO did not provide any product (entry 16).

Once the optimal conditions were identified, we next examined the scope of the reaction in terms of the MBH carbonate. As shown in Scheme 2, the reaction provides the final adducts in excellent yields and diastereoselectivities in almost all examples; the reaction did not work only when aliphatic MBH carbonates or bulky di-*ortho*-substituted MBH carbonates (**3h** and **3i**) were employed. We also studied the effect of the ester substituent; *tert*-butyl derivatives only gave traces of **3j**, likely due to the higher steric hindrance. The reaction tolerates *para*- (**3c**, **3d**, and **3g**), *meta*- (**3f**), and *ortho*- (**3i**) halogen substitution on the aromatic ring, giving the final compounds in very good yields and
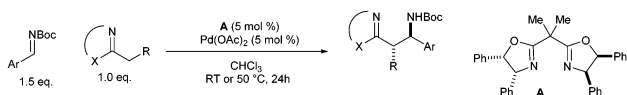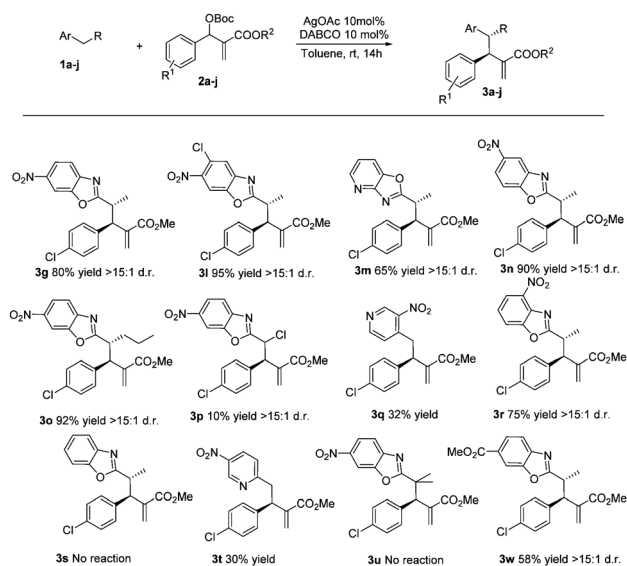

Scheme 1 Organometallic methodology for the synthesis of azaarenes developed by Lam (2012).

Scheme 2 Reaction scope using MBH carbonate.[12]

Table 2 Catalyst loading[a]

Entry	Ag(OAc) (%)	DABCO (%)	Conv.[b] (%)	d.r.[c]
1	20	10	100	>15:1
2	10	10	100	>15:1
3	5	10	62	>15:1
4	1	10	35	>15:1
5	5	5	50	>15:1
6	1	1	20	>15:1
7	10	5	Traces	—

[a] In a small vial, 1.0 equiv. of benzoxazole **1a**, 4 equiv. of MBH carbonate **2g** were added in 1 mL of toluene in the presence of Lewis acid and organic base. The reaction was stirred at room temperature for 14 h. [b] Determined by ^{1}H NMR of the crude mixture. [c] Determined by ^{1}H NMR of the crude mixture.

overall diastereoselectivities. Only in the case of 2-bromo substitution (**3i**) were the yields observed to drop slightly. A *para*-electron-withdrawing nitro group gave the final adduct **3e** in almost quantitative yield and in diastereopure form; *para*-methyl-substituted MBH carbonate gave **3b** in excellent yield and diastereoselectivity.

The scope of the reaction in terms of the alkyl azaarene employed was next examined, as shown in Scheme 3. Different substituents on the benzoxazole ring were first investigated; an electron-withdrawing substituent was found to be a requirement for reactivity. Nitro derivatives **3e**, **3l**, **3n**, **3o**, and **3r** provided adducts in good yields and overall diastereoselectivity. The benzoxazole with ester substitution gave final compound **3w** in low yield, but with the same diastereoselectivity. Unfortunately, the reaction did not take place when no electron-withdrawing

substituents were present on the aromatic ring (**3s**). These results suggest that an electron-withdrawing group is needed to lower the pK_a of the benzoxazole. Next, we decided to study the scope of the reaction with benzoxazoles bearing different alkyl chains. Increasing the length of the alkyl chain did not affect the outcome of the reaction (**3m**). However, the use of tertiary carbons in the α-position (**3u**) rendered the benzoxazole unreactive under the reaction conditions. Finally, we employed a highly reactive benzoxazole bearing a labile group in the alkyl chain; adduct **3p** was produced in excellent diastereoselectivities, albeit in low yields, probably due the decomposition of the starting benzoxazole in the reaction. Encouraged by the excellent results obtained with benzoxazoles, we tested the reaction with different heterocycles. Oxazolopyridine reacted with MBH carbonates to give adduct **3m** in excellent yield and in diastereopure form. Pyridine derivatives (4-methyl-3-nitropyridine) were also applicable in the reaction. However the reaction gave the alkyl azaarene derivatives in low yields (**3q** and **3t**).

Catalyst loading was next examined. As shown in Table 2, decreasing the AgOAc loading gave successively poorer conversions after 14 h; however, the diastereoselectivity remained the same (entries 1–6). In terms of DABCO, the reaction with 5 mol% DABCO and 10 mol% AgOAc only renders traces of the expected product.

The relative configuration of the products was ascertained by X-ray diffraction analysis of a single crystal of **3i**. The major

Scheme 3 Reaction scope using alkyl azaarenes.[12]
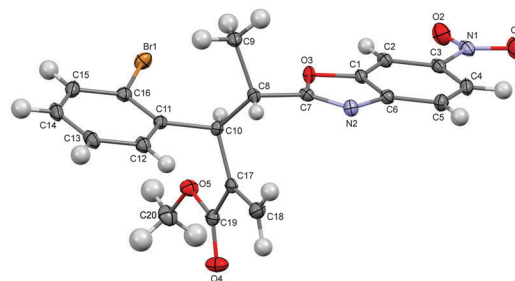
Fig. 2 Molecular structure of compound **3i**. Displacement ellipsoids are drawn at the 50% probability level.[13]
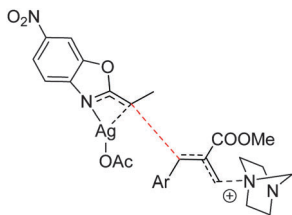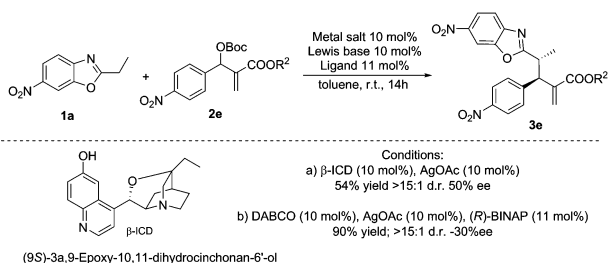
Fig. 3 Proposed transition state.

Scheme 4 Asymmetric addition of benzoxazole **1a** to MBH carbonate **2e**.

diastereomer of the addition possessed an (R,R) relative configuration (Fig. 2).

Based on the configuration of **3i**, we propose the following transition state in which the aromatic ring of the benzoxazole, organic Lewis base, and aryl substituent of the MBH carbonate are on opposite sides to avoid steric interactions (Fig. 3).

Initial experiments have been done in order to develop an enantioselective version of the present reaction. As shown in Scheme 4, the use of β-ICD instead DABCO, we get the final compound in moderate yields and enantioselectivities. We also explored the use of chiral ligands such as (R)-BINAP obtaining the final compound, in good yields but low enantioselectivities. Remarkably in both cases the diastereoselectivity of the reaction remains excellent. This initial data open a gate for the development of a chiral version of the present reaction.

In summary we have developed a new reaction based on synergistic catalysis between alkyl azaarenes and MBH carbonates. The reaction provides the final adducts in excellent yields and total diastereoselectivity. Mechanistic studies, synthetic applications, development of a suitable chiral version of this new methodology, and the discovery of new reactions based on this concept are currently ongoing in our laboratory.

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12 Experimental procedure: in small vial, benzoxazole **1a** (0.1 mmols), MBH carbonate **2a** (0.4 mmols), AgOAc 2 mg (10 mol%) and DABCO 1 mg (10 mol%) were added in 1 mL of toluene, the reaction was stirred at room temperature for 14 h. Next the crude reaction was purified by column chromatography to afford compound **3a** (see ESI†).
13 Crystal data for **3i**: $C_{20}H_{17}BrN_2O_5$, Mr = 445.26, colourless plate, $0.24 \times 0.20 \times 0.04$ mm^3, Triclinic, $P\bar{1}$, $a = 8.9971(4)$ Å, $b = 10.0949(4)$ Å, $c = 11.5631(8)$ Å, $\alpha = 70.132(5)°$, $\beta = 68.095(5)°$, $\gamma = 80.935(6)°$, $V = 915.83(9)$ Å^3, $Z = 2$, $D_c = 1.615$ g/cm^3, $\mu = 2.280$ mm^{-1}, $T = 100$ K, 12120 collected reflections, 4167 unique reflections ($R_{int} = 0.0244$), 3969 reflections with $F^2 > 2$, $R(F^2 > 2) = 0.0257$, $wR^2 = 0.0684$, GoF = 1.082. Crystallographic data (excluding structure factors) for the structure **3i** have been deposited with the Cambridge Crystallographic Data Centre with CCDC number 978247.