Volume 1 | Number 1 | Jan 2013 | Pages 1–100

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Synergistic catalysis: Highly diastereoselective benzoxazole addition to Morita–Baylis-Hillman carbonates

Victor Ceban,[a] Piotr Putaj,[a,b] Marta Meazza,[a] Mateusz B. Pitak,[a] Simon J. Coles,[a] Jan Vesely,[b] and Ramon Rios[a]*

An expedited method has been developed for the diastereoselective synthesis of highly functionalized alkyl-
10 **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**
15 **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 concerted fashion to create a single new bond, has emerged as a powerful
20 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
25 otherwise (Figure 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
30 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
35 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 photoredox-mediated α-
40 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
45 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
50 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]

55 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 strong nucleophiles such as malonates, amines, or alcohols for suitable reactivity.
60 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
65 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
70 that the use of FeCl$_2$ or Ti(O^{i}Pr)$_4$ 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-
75 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
80 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]

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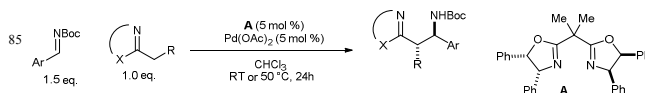
Scheme 1: Organometallic methodology for the synthesis of azaarenes developed by Lam (2012).

90 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 Figure 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.
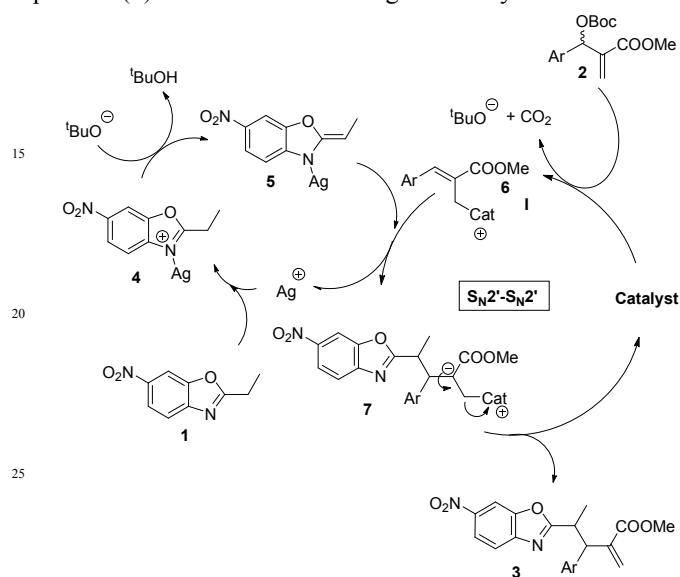

Figure 1: Suggested mechanism

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); PdCl₂ 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 different solvents. DMF gave good conversions, but without any diastereoinduction (entry 8), CHCl₃ 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. AgSbF₆ 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).

Table 1: Reaction Optimization
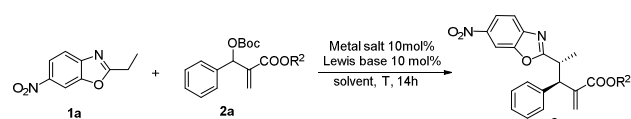
Entry	Solvent	Lewis acid	T	Lewis base	Conv.[b]	d.r.[c]
1	Toluene	Pd(OAc)₂	50ºC	DABCO	71%	2:1
2	Toluene	Cu(OAc)₂	50ºC	DABCO	Traces	n.d.[e]
3	Toluene	YbTf₃	50ºC	DABCO	9%	2.5:1
4	Toluene	CuTf₂	50ºC	DABCO	9%	4:1
5	Toluene	PdCl₂	50ºC	DABCO	50%	2:1
6	Toluene	AgOBz	50ºC	DABCO	43%	8:1
7	Toluene	AgOAc	50ºC	DABCO	50%	15:1
8	DMF	AgOAc	50ºC	DABCO	50%	1:1
9	CHCl₃	AgOAc	50ºC	DABCO	n.r.	-
10	THF	AgOAc	50ºC	DABCO	25%	5:1
11[d]	toluene	AgOAc	r.t.	DABCO	100%	>15:1
12[d]	toluene	AgOAc	0ºC	DABCO	100%	>15:1
13[d]	toluene	AgSbF₆	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 14h.[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

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 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.
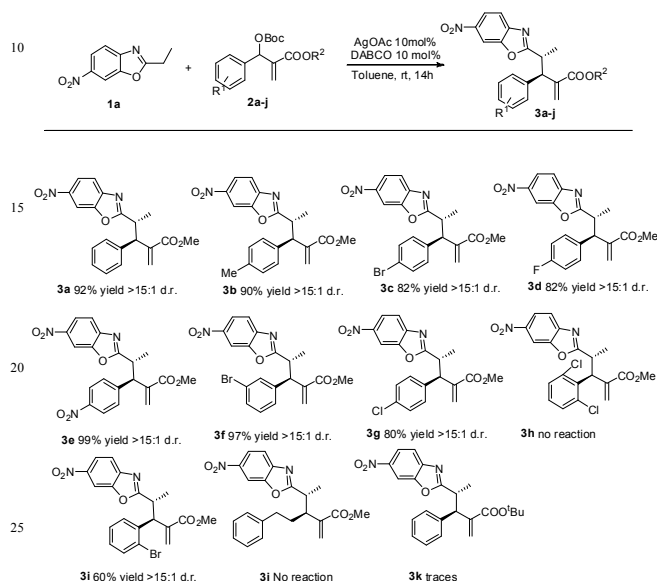
Scheme 2: Reaction scope using MBH carbonate[12]

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 lengh 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**).
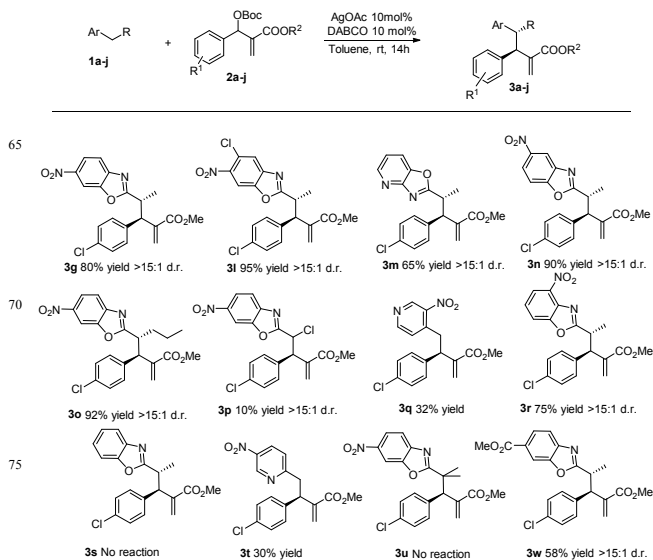
Scheme 3: Reaction scope using alkyl azaarenes[12]

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.

Table 2: Catalyst loading[a]
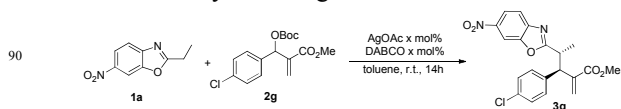
Entry	% Ag(OAc)	% DABCO	Conv.[b]	d.r.[c]
1	20	10	100%	>15:1
2	10	10	100%	>15:1
3	5	10	62%	>15:1
4	1	10	35%	>15:1
5	5	5	50%	>15:1
6	1	1	20%	>15:1
7	10	5	traces	-

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

The relative configuration of the products was ascertained by X-ray diffraction analysis of a single crystal of **3i**. The major diastereomer of the addition possessed an (*R,R*) relative configuration (Figure 2).
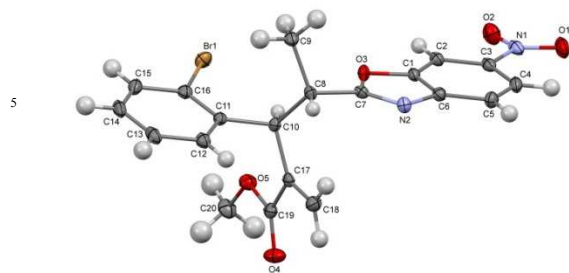
excellent yields and total diastereoselectivity. Mechanistic studies, synthetic applications, development of a suitable chiral version of this new methodology, and the discovery of new reactions based on this concept are currently ongoing in our laboratory.

Figure 2: X-ray ORTEP of compound **3i**. The displacement ellipsoids are drawn at the 50% probability level, selected hydrogens omitted for clarity[13]

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 (Figure 3).
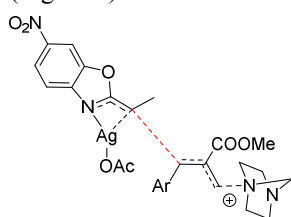

Figure 3: Proposed Transition State

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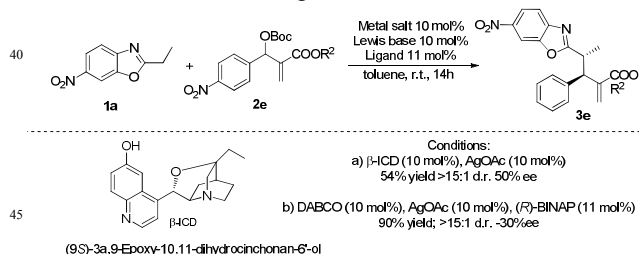
Scheme 4: Asymmetric addition of benzoxazole **1a** to MBH carbonate **2e**

Conclusions

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

Notes and references

a Chemistry, Faculty of Natural & Environmental Sciences, University of Southampton, Highfield Campus, Southampton, SO17 1BJ, UK E-mail: R.Rios-Torres@southampton.ac.uk
b Department of Organic Chemistry, Faculty of Science, Charles University in Prague, Hlavova 2030, 128 43 Praha 2, Czech Republic
† Electronic Supplementary Information (ESI) available: [Experimental Procedures and spectroscopic data]. See DOI: 10.1039/b000000x/
‡ Footnotes should appear here.

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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 (10mol%) were added in 1 mL of Toluene, The reaction was stirred at room temperature for 14h. Next the crude reaction was purfied by column chromatography to afford compound **3a** (See supp inf.).
13   Crystallographic data (excluding structure factors) for the structure **3i** have been deposited with the Cambridge Crystallographic Data Centre with CCDC number 978247. Copies of the data can be obtained, free of charge, on application to Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).