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Synergistic Catalysis

Synergistic Catalysis: Enantioselective Addition of Alkylbenzoxazoles to Enals

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Abstract: A novel catalytic enantioselective methodology based on synergistic catalysis is reported. The strategy involves: 1) the metal-Lewis-acid activation of alkylazaarenes, and 2) the secondary-amine activation of enals. Consequently, highly functionalized chiral alkylazaarenes were obtained in good yields and with reasonable stereoselectivity.

In Nature, the concurrent activation of nucleophiles and electrophiles using different catalysts is prevalent. For example, in enzymatic processes, several amino acid residues activate nucleophiles and electrophiles simultaneously to facilitate chemical reactions. This dual activation is known as synergistic catalysis.[1]

The concept of activating the nucleophile and electrophile of a reaction simultaneously has been used for a long time in organic synthesis. The most common approach in organocatalysis[2] has been the use of bifunctional catalysts such as tertiary amine/thiourea catalysts that activate the nucleophiles and electrophiles via Brønsted base and hydrogen-bond donor interactions, respectively. Bifunctional catalysts[3] have several advantages such as a well-ordered transition state; however, there are several disadvantages such as the necessity to synthesize a new catalyst each time one of the subunits needs to be modified. In contrast, synergistic catalysis allows optimizing each catalyst almost independently from the other co-catalyst and, in principle, allows the use of several sources of chirality in each of the co-catalysts, thus improving the stereoselectivity.

Recently, in asymmetric synthesis, the use of two catalysts and two catalytic cycles, working in concert to create a single new bond, has emerged as a powerful strategy for developing new reactions. This concurrent activation of both the nucleophile and electrophile using different catalysts enhanced the chemical reactivity and allowed the synthesis of difficult scaffolds (Figure 1). One of the first examples in asymmetric synthesis based on synergistic catalysis was reported by Cordova and co-workers in 2006. They developed the direct α-allylic alkylation of unactivated aldehydes with allyl acetates using both enamine and Pd catalysis.[4] Later, Zhang reported an efficient asymmetric variant using Cordova's synergistic strategy and Pd catalysts bearing C_2-symmetrical chiral metallocene ligands.[5] MacMillan and Sibi reported examples of asymmetric synergistic catalysis based on enamine catalysis and metal-bonded electrophiles.[6] In this area, List also reported his research efforts joining phosphoric acid derivatives and transition-metal catalysts with excellent results in allylation, Overman rearrangement and epoxidation reactions.[7] On the other hand, synergistic catalysis using α,β-unsaturated carbonyl compounds has attracted much interest recently. The pioneering works of Cordova in β-silylation or β-borylation using iminium and transition-metal activation demonstrated the importance of this approach.[8]

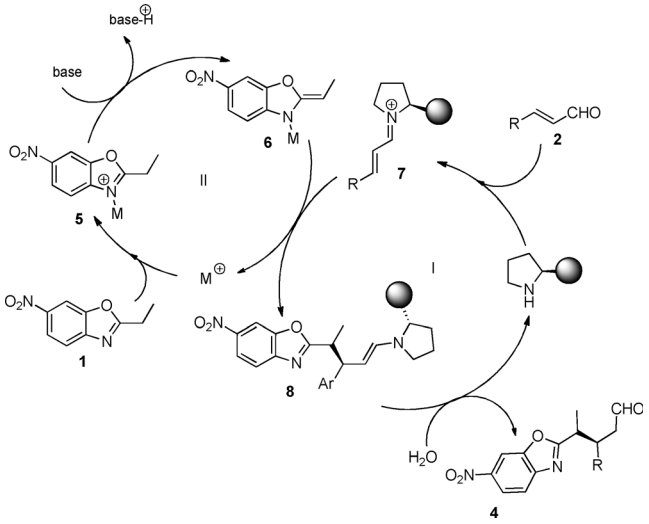

Figure 1. Proposed mechanism.

Recently, our research group became interested in developing new methodologies for the synthesis of chiral azaarenes. Despite the fact that alkylbenzoxazoles are an interesting class of heterocycles because of their importance in agro- and medicinal chemistry, only a few enantioselective methodologies have been developed for their synthesis. Recently, Lam and co-workers reported the addition of alkylazaarenes to nitrostyrenes catalyzed by Pd-bisoxazoline complexes to afford excellent results.[9] Recently, we reported the addition of alkylbenzoxazoles to Morita–Baylis–Hillman (MBH) carbonates,

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based on a synergistic approach, in a highly diastereoselective manner.[10]

Based on these previous studies and our own experience in organocatalysis,[11] we envisioned that the metal activation of benzoxazoles would work in concordance with enantioselective organocatalytic processes in order to build a new C–C bond in an enantioselective manner.

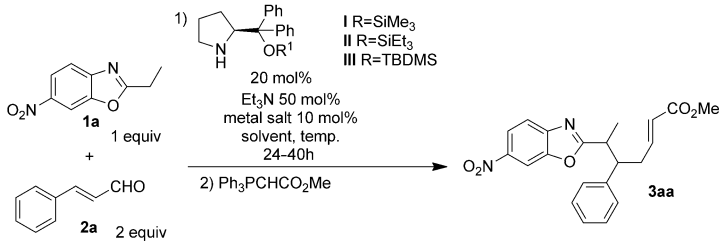
In this study, we report the first example of enantioselective alkylazaarene addition to enals using synergistic catalysis. This catalytic enantioselective methodology affords highly functionalized chiral alkylazaarenes and may potentially lead to the development of new scaffolds of interest in the agrochemical and pharmaceutical industries.

We focused our research efforts on the combination of the metal-Lewis-acid activation of alkylazaarenes and the secondary-amine activation of enals. The proposed mechanism is shown in Figure 1.

As shown in Figure 1, we envisioned that the metal Lewis acids would interact with the alkylbenzoxazole (compound **1**) by coordinating to the nitrogen of **1**, thus increasing the acidity of the α-carbon of **1**. After treating the metallated alkylbenzoxazole (compound **5**) with a base, a nucleophile (compound **6**), suitable to react with the electrophile (enal), was obtained. The enal reacts with the secondary amine (organocatalyst) to form the corresponding activated iminium form (compound **7**). The *S* catalyst efficiently shields one face of the enal. After the addition, the hydrolysis of compound **8** affords **4** and releases the catalyst, thus completing the second catalytic cycle.

First, we investigated the reaction of enal **2a** with 2-ethyl-6-nitrobenzoxazole (**1a**) in the presence of different metal Lewis acids, solvents, and organic Lewis bases. We selected compound **1a** because the presence of an electron-withdrawing group in the benzoxazole ring increases the acidity of the α-CH, thus making the compound more reactive. Moreover, the final aldehyde products decompose very fast; therefore, we subjected the aldehydes in situ to a Wittig reaction that affords bench-stable compounds. As shown in Table 1, the best solvent for the reaction was EtOAc, affording the final products in moderate conversions and with reasonable stereoselectivity. Instead, CH_3CN or DMSO gave higher conversions but almost racemic compounds (Table 1, entries 1–5). After screening several metals, it resulted that only $Pd(OAc)_2$ afforded the final products, while Ag, Yb, Ni, or Cu salts did not afford the desired product (Table 1, entries 6–9). Moreover, the addition of the base was crucial as the reaction did not proceed in the absence of a base; 50 mol% Et_3N was found to be the optimal base. The reaction had some disadvantages: the reaction time was crucial; higher reaction times resulted in lower stereoselectivity. Thus, we assumed that the reaction suffers from an epimerization process, affording racemic mixtures. Temperature also had a pivotal importance. To accelerate the reaction, heating was required; however, high temperatures resulted in low diastereoselectivity. After extensive study of the reaction conditions, the best result was obtained using acetonitrile as the solvent at 35 °C, 20 mol% amine catalyst, 5 mol% $Pd(OAc)_2$, and 50 mol% Et_3N. We tested several diphenylprolinol derivatives as the secondary amine; the *tert*-butyldimethylsilyl derivatives afforded better stereoselectivity when used with ACN as the solvent (Table 1, entry 15).

Table 1. Optimization.[a]

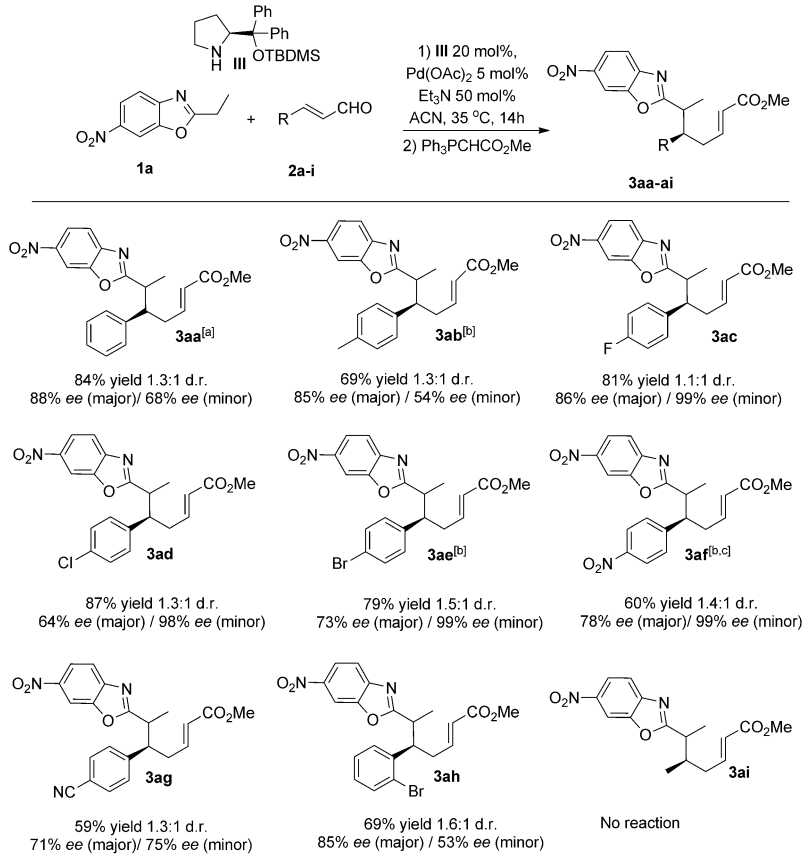


Entry	Solvent	Metal	*T* [°C]	Yield[a] [%]	d.r.[b]	*ee*[c] [%]	*ee*[c] [%]
1[d]	$CHCl_3$	$Pd(OAc)_2$	40	n.r.	–	–	–
2[d]	EtOAc	$Pd(OAc)_2$	40	32	2:1	53	47
3[d]	toluene	$Pd(OAc)_2$	40	n.r.	–	–	–
4[d]	DMSO	$Pd(OAc)_2$	40	72	1.2:1	rac.	rac.
5[d]	ACN	$Pd(OAc)_2$	40	85	1.3:1	rac.	rac.
6[d]	EtOAc	CuOTf	40	n.r.	–	–	–
7[d]	EtOAc	$Yb(Otf)_3$	40	n.r.	–	-	–
8[d]	EtOAc	$Cu(OAc)_2$	40	n.r.	–	–	–
9[d]	EtOAc	$Ni(OAc)_3$	40	n.r.	–	–	–
10[d]	EtOAc	AgOAc	40	n.r.	–	–	–
12[d]	EtOAc	–	40	n.r.	–	–	–
13[e]	EtOAc	$Pd(OAc)_2$	35	80	1.2:1	61	19
14[f]	EtOAc	$Pd(OAc)_2$	35	trace		–	–
15[f,g]	ACN	$Pd(OAc)_2$	35	84	1.3:1	88	68

[a] Yields are the sum of pure isolated diastereomers; [b] d.r. calculated from the crude NMR comparing the aldehyde signals; [c] *ee* were determined by chiral HPLC analysis on the isolated products; [d] **I** as catalyst; [e] **II** as catalyst; [f] **III** as catalyst; [g] reaction time 14 h.

With the optimized reaction conditions in hand, we investigated the substrate scope of the reaction with respect to enal derivatives. As shown in Scheme 1, the reactions afforded the corresponding products in good yields and with good enantioselectivity when different aromatic enals were used (**3aa**–**3ah**). In contrast, the reactions of aliphatic enals afforded complex mixtures due to their decomposition (**3ai**). However, in almost all the examples, the diastereoselectivity of the reaction was very low. Better results were obtained with 4-halogen-substituted cinnamaldehydes. For example, the fluoro derivative, **3ac**, was obtained in 81% yield and with 1.1:1 d.r. and 86 and

99% *ee*. Compounds **3 ad** and **3 ae** (Cl and Br derivatives, respectively) were obtained in similar yields and stereoselectivities. Electron-withdrawing groups in the aromatic ring resulted in similar yields and stereoselectivities in the 4-nitro substituted compound (**3 af**) but lower enantioselectivity when 4-cyano cinnamaldehyde was used (**3 ag**). It should be noted that in some examples the use of catalyst **III** gave longer reaction times (more than 48 h) which render worse yields due the decomposition of the formed aldehyde. In order to shorten the reaction times catalyst **II** was used in these examples (**3 af**) with good overall results in terms of yield and stereoselectivity.



Scheme 1. Scope of the reaction with several enals. a) DIPEA as a base, b) reaction conducted at 30 °C; c) **II** as catalyst.

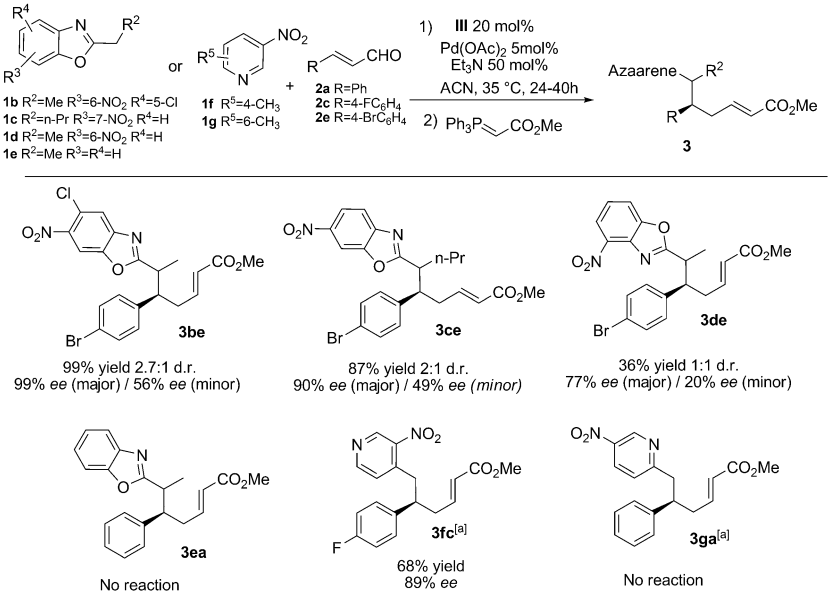
Next, we investigated the substrate scope of the reaction with respect to benzoxazole derivatives. As shown in Scheme 2, the presence of electron-withdrawing groups in the azaarene ring was crucial for the reactivity. In order to generate more complex scaffolds that can be further modified we chose azaarene **1 b** bearing a Cl atom close to the nitro. We were very pleased to confirm that the reaction produces the final compound **3 be** with excellent yields, good d.r. and excellent *ee* in the major diastereomer. Compound **3 de**, bearing a nitro group at 3-position of the benzoxazole ring, was obtained in moderate yields and with moderate-to-low stereoselectivity. The low yield can be attributed to the steric effects, causing difficulty in the coordination of the Lewis acid to the benzoxazole ring. We also investigated the reaction with other functional groups in the benzoxazole ring. The simple benzoxazole was unreactive under the reaction conditions (**3 ga**), probably because of the low acidity of the alkyl azaarenes. Next, we investigated the effect of the substituent in the alkyl position. Our results confirm that larger substituents could be used such as *n*-butyl. The reaction afforded the final product, **3 ce**, in a good yield and enantioselectivity with moderate diastereoselectivity. Remarkably, The reaction with 4-methyl pyridines (**3 fe**), gave longer reaction times (more than 72 h) when catalyst **III** was used. For this reason catalyst **II** was used instead giving good yields and very good stereoselectivities, while 3-nitro-6-methylpyridine was unreactive (**3 ga**). During the preparation of this paper, Wang and co-workers reported the reaction of 3-nitro-4-methylpyridines with enals catalyzed by only a secondary amine in DMSO as the solvent. However, when the reaction was conducted under our conditions but without $Pd(OAc)_2$, it failed to afford the addition product. This clearly indicates that synergistic catalysis was needed in our case.

In the case of benzoxazoles, our study shows the necessity of a strong electron-withdrawing group on the heteroarene.

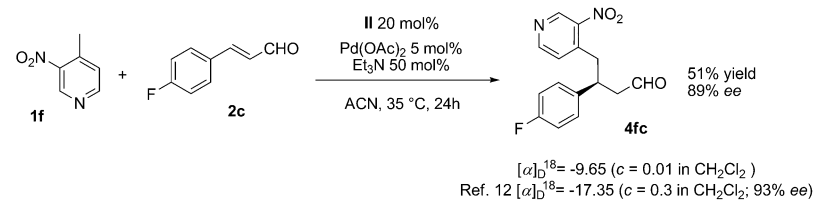
The absolute configuration of the compounds was determined by comparing the optical rotation of compound **4 fc** (remarkably the aldehydes products derived from pyridines are stable in the reaction conditions and after isolation, in contrast with the compounds derived from benzoxazoles) with that of a compound previously reported by Wang (Scheme 3).[12] The absolute configuration was consistent with the mechanism proposed for the iminium activation with the diphenylprolinol catalysts.[13]

The relative configuration of compounds **3** and **4** was ascertained by the X-ray diffraction analysis of a single crystal of the minor diastereomer of **3 af**. The minor diastereomer of the addition product possessed an *S,R* relative configuration (Figure 2).

In summary, we have developed a new methodology for the synthesis of chiral azaarene derivatives based on the concept of synergistic catalysis. Two different catalytic cycles: 1) the metal-Lewis-acid activation of azaarenes, and 2) secondary-amine activation of enals worked in concordance to afford the final products in good yields and with moderate-to-excellent



Scheme 2. Scope of the reaction with several azaarenes: a) **II** as a catalyst.



Scheme 3. Synthesis of **4 fc**.

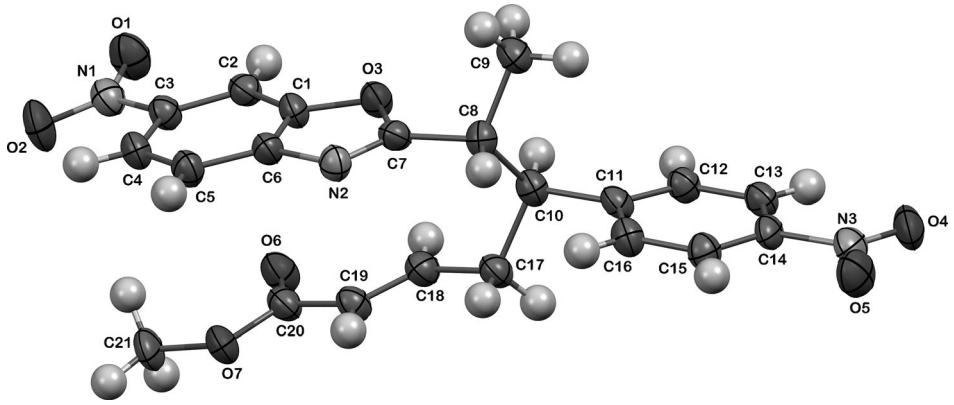


Figure 2. X-ray structure of compound **3 af**. The displacement ellipsoids are drawn at the 50% probability level.[14]

enantioselectivity and low diastereoselectivity. The mechanistic studies, synthetic applications, and development of new organocascade reactions based on this concept are currently ongoing in our laboratory.

Experimental Section

In a vial were added, in this sequence: the organic catalyst (20 mol% equiv), α,β-unsaturated aldehyde (2 equiv), azaarene (1 equiv), $Pd(OAc)_2$ (5 mol% equiv) and CH_3CN (1 mL). To the crude solution was finally added TEA (50 mol% equiv). The reaction mixture was stirred at the temperature and time reported in Table 1 and then concentrated in vacuo. In a vial were then added the crude obtained after the first reaction, an excess of methyl triphenylphosphoranylidene acetate (>3 equiv) and DCM as solvent. The reaction mixture was stirred at RT for 48 h and then concentrated in vacuo. The crude product was purified by flash column chromatography (hexane/EtOAc) to obtain the desired product.

Single-crystal X-ray diffraction data of **3 af** were collected at 100 K on Rigaku AFC12 goniometer equipped with an enhanced sensitivity (HG) Saturn 724+ detector mounted at the window of an FR-E+ Superbright $Mo_{K\alpha}$ rotating anode generator with HF Varimax optics.[15] Unit-cell parameters were refined against all data. An empirical absorption correction was carried out using CrystalClear software.[16] The crystal structure of **3 af** was solved by charge flipping methods[17] and refined on Fo^2 by full-matrix least-squares refinements using programs of the SHELX-2013 software.[18] All nonhydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were added at calculated positions and refined using a riding model with isotropic displacement parameters based on the equivalent isotropic displacement parameter (U_{eq}) of the parent atom.

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Keywords: alkyl azaarenes · iminium catalysis · Michael addition · palladium · synergistic catalysis

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[14] Crystal data for **3af**: $C_{21}H_{19}N_3O_7$, $M_r = 425.39$, light brown lath, $0.20 \times 0.03 \times 0.01$ mm^3, monoclinic, $C2$, $a = 17.969(2)$, $b = 11.0559(15)$, $c = 19.839(3)$ Å, $\beta = 90.528(6)^\circ$, $V = 3941.0(9)$ Å^3, $Z = 8$, $Z' = 2$, $\rho_{calcd} = 1.434$ g cm^{-3}, $\mu = 0.110$ mm^{-1}, $T = 100$ K, 25946 collected reflections, 8604 unique reflections ($R_{int} = 0.0895$), 4448 reflections with $F^2 > 2\sigma$, $R(F^2 > 2\sigma) = 0.0596$, $wR2 = 0.1285$, GoF = 0.893. CCDC-1001853 (**3af**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Synergistic Catalysis

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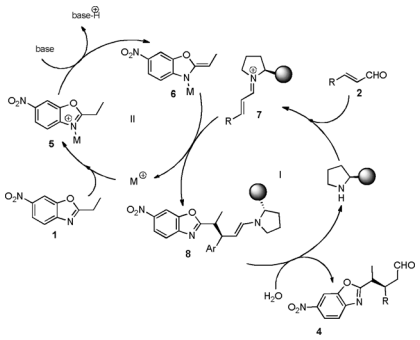

In good company: A novel catalytic enantioselective methodology based on synergistic catalysis is reported. The strategy involves: 1) the metal-Lewis-acid activation of alkylazaarenes, and 2) the secondary-amine activation of enals (see scheme). Consequently, highly functionalized chiral alkylazaarenes were obtained in good yields and with reasonable stereoselectivity.