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A Dual Lewis Base Activation Strategy for Enantioselective Carbene-Catalyzed Annulations

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Supporting Information

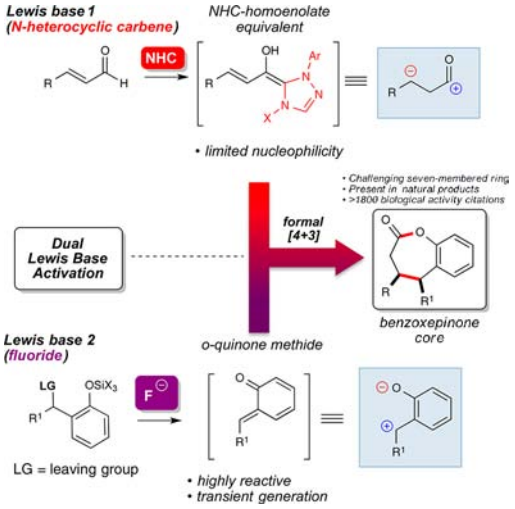
ABSTRACT: A dual activation strategy integrating N-heterocyclic carbene (NHC) catalysis and a second Lewis base has been developed. NHC-bound homoenolate equivalents derived from α,β-unsaturated aldehydes combine with transient reactive *o*-quinone methides in an enantioselective formal [4 + 3] fashion to access 2-benzoxopinones. The overall approach provides a general blueprint for the integration of carbene catalysis with additional Lewis base activation modes.

The advances made by employing chiral catalysts to forge new C−C and C−heteroatom bonds with high levels of stereoselectivity have provided efficient access to new chiral molecules with broad potential uses.[1] A majority of these strategies rely on a single activation mode, such as Lewis base[2] or acid[3] catalysis, enamine/iminium ion catalysis,[4] hydrogen-bond donor/Brønsted acid catalysis,[5] σ-bond activation,[6] or transition-metal chemistry.[7] With proper substrate and catalyst design, these diverse sets of reactions provide access to a myriad of distinct compound classes. However, there are inherent limitations of reactivity and selectivity within each activation "sphere", as some substrates are simply not reactive enough to engage with a catalyst or the combination of starting materials is ineffective because of poor pairing of electronic parameters (i.e., electrophilicity/nucleophilicity).

N-Heterocyclic carbenes (NHCs) are versatile Lewis bases that can promote a variety of powerful and unconventional bond-forming processes, including acyl anion reactions, homoenolate equivalents, enolate additions, and oxidations.[8] Inspired by early carbonyl anion catalysis,[9] one particularly versatile reaction mode is the NHC−homoenolate.[10] This process provides a metal-free approach for accessing β-anionic carbonyl systems, and we have been exploring this activation mode for the development of multiple new reactions. Carbene catalysis typically entails formal [*n* + *m*]-type cycloaddition transformations by virtue of the mechanistic pathway and catalyst turnover (see below). This distinct feature provides a powerful platform for convergent ring formation strategies *so long as the electrophilic partner is reactive enough to engage the NHC−homoenolate in an initial σ-bond-forming event.* While it is clear that these homoenolates can undergo additions to reactive electrophilic C═X π systems such as aldehydes and imines, many classes of less reactive potential partners typically result in no productive interactions. New opportunities in carbene catalysis over the next decade will undoubtedly focus on moving past these standard π systems, and the current challenge involves identifying what innovative concepts will expedite this evolution.

We hypothesized that it might be possible to drive NHC-generated homoenolate methodology in new directions by integrating a second mode of activation that could produce more reactive electrophiles beyond stable C═O or C═N π bonds. We successfully integrated Lewis acid activation modes with NHC catalysis[11] and utilized this knowledge base to consider additional activation modes such as in situ Lewis base-promoted electrophile creation (Scheme 1). There have been a few examples of combining carbene catalysis with Lewis acids[11,12] or Bronsted acids,[13] but to date, the idea of a utilizing a second Lewis base activation mode in conjunction with NHCs remains an underexplored strategy.

Scheme 1. Dual Lewis Base Activation Strategy



To pursue this new strategy, we proposed that the production of highly reactive *o*-quinone methides (*o*-QMs) generated under fluoride conditions through a desilylation/elimination cascade could be combined with an NHC−homoenolate catalytic cycle.[14] *o*-QMs are considerably more reactive than regular α,β-unsaturated ketones and esters since nucleophilic attack at the external carbon produces an aromatic alcohol (phenol/phenoxide) and this aromatization process of the ring is highly thermodynamically favorable. Although stable *o*-QMs are

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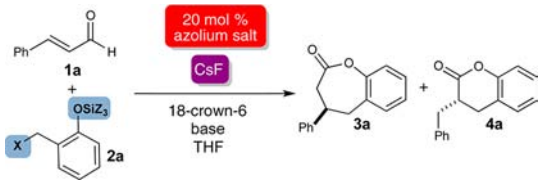
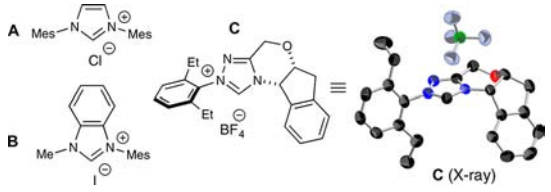
known, the more reactive variants are useful intermediates in synthesis and can be produced in situ using light, oxidants, or fluoride.[15] We desired to access as many different *o*-QM structures as possible through an in situ approach (e.g., fluoride). However, the fleeting nature of many of these species combined with their propensity to undergo dimerization via a [4 + 2] pathway or react with even weak nucleophiles were possible obstacles.[15c] The successful realization of this new dual Lewis base activation strategy would produce 2-benzoxopinones, seven-membered lactones that are found in natural products and are the core constituents for numerous small molecules with broad biological activity.[16]

We initially considered four challenges to this potential reaction: (1) the compatibility of the second Lewis base with the in situ-generated NHC, (2) the compatibility of the highly reactive *o*-QM with a nucleophilic NHC catalyst, (3) the potential for unproductive behavior of transient *o*-QMs (e.g., dimerization) under the reaction conditions, and (4) the requirement of equilibrium populations of *both* the NHC–homoenolate and the *o*-QM to achieve a productive bond-forming process. Guided by these complex, interconnected issues of compatibility and competing rates, we performed extensive tuning of the major reaction parameters (catalyst structure, base composition, and fluoride source). The proper rate of *o*-QM production was achieved by using a crown ether/fluoride combination with a *tert*-butyldimethylsilyl (TBS)-protected phenol substrate (Table 1). In the initial experiments, the bromide leaving group in the presence of Cs_2CO_3 or CsOAc provided encouraging levels of conversion (but low product yields) with achiral carbenes prepared in situ from imidazolium **A** and benzimidazolium **B** (entries 1–3).[17]

Table 1. NHC/Fluoride-Promoted Reaction of 1a and 2a[a]



entry	azolium	base	X/SiZ_3	ratio (**3a**:**4a**)	% yield (er[b])
1	**A**	Cs_2CO_3	Br/TBS	4:1	32
2	**A**	CsOAc	Br/TBS	4.5:1	37
3	**B**	CsOAc	Br/TBS	4:1	57
4	**C**	CsOAc	Br/TBS	4.5:1	47(91:9)
5	**C**	CsOAc	Cl/TBS	4.5:1	45 (87:13)
6	**C**	CsOAc	Br/TIPS	4.5:1	42 (89:11)
7	**C**	CsOAc	Br/TES	–	no product
8	**C**	*n*-Bu_4N·OAc	Br/TBS	4.5:1	62 (92:8)
9[c]	**C**	*n*-Bu_4N·OAc	Br/TBS	5.5:1	64 (96:4)



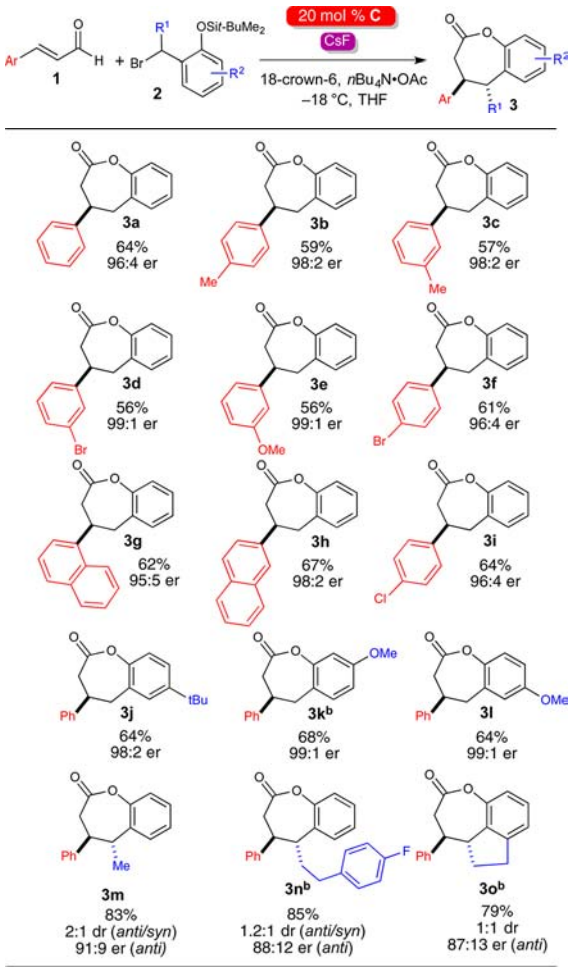
[a]Conditions: **1a** (1 equiv), **2a** (2 equiv), CsF (2 equiv), 18-crown-6 (2 equiv), base (30 mol %), THF (0.15 M in **1a**), 23 °C, 3 h, unless otherwise noted. Mes = 2,4,6-$Me_3C_6H_2$. [b]Determined by chiral-stationary-phase HPLC. [c]The reaction was run at −18 °C for 12 h.

A competing reaction pathway generated **4a** via protonation of the NHC–homoenolate followed by a formal [4 + 2] pathway (see discussion below). With CsOAc as the base and chiral triazolium-based NHC **C**, good enantioselectivity (91:9 er) but only a moderate yield (47%) were observed (entry 4). Further examination of the *o*-QM precursor indicated that triisopropyl (TIPS) could also facilitate the reaction in the presence of fluoride with similar results (entry 4 vs 6). In contrast, the more labile triethylsilyl (TES) group gave no product (entry 7).

The leaving group to expedite elimination and produce the *o*-QM in situ can be either bromide or chloride without noticeable differences in overall reactivity. The optimal combination of CsF/18-crown-6 for *o*-QM generation and *n*-Bu_4N·OAc as a mild base provided the formal [4 + 3] lactone product in moderate yield (62%) with excellent enantioselectivity 92:8 er) (entry 8). Decreasing the reaction temperature from 0 to −18 °C increased the time necessary for consumption of **1a** but also provided better stereoselectivity (5.5:1 dr, 96:4 er; entry 9).[18]

Having established conditions to generate each reactive intermediate independently at productive concentrations, we explored the scope of this transformation (Table 2). Cinnamaldehyde derivatives bearing electron-donating or -withdrawing groups were well-tolerated (**3a–i**). Aryl modifications

Table 2. Scope of Dual-Activation Formal [4 + 3] Annulation[a]



[a]Reactions were performed at 0.4 mmol with **1** (1 equiv), **2** (2 equiv), base (0.3 equiv), CsF (2 equiv), and 18-crown-6 (2 equiv) in THF (0.15 M in **1**). Isolated yields of **3** are shown; er's were determined by chiral-stationary-phase HPLC. [b]The benzylic chloride was used.

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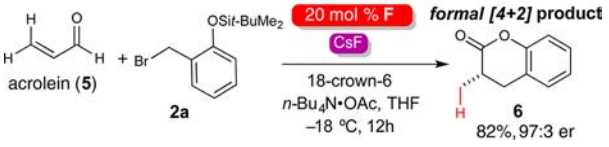
on the aldehyde substrate did not substantially impact the yield or chemoselectivity. The ability to use either bromide or chloride as the leaving group (Table 1) allowed benzylic chloride *o*-QM precursors to be used successfully when the corresponding benzylic bromides were too unstable (e.g., **3k**, **3n**, and **3o**).

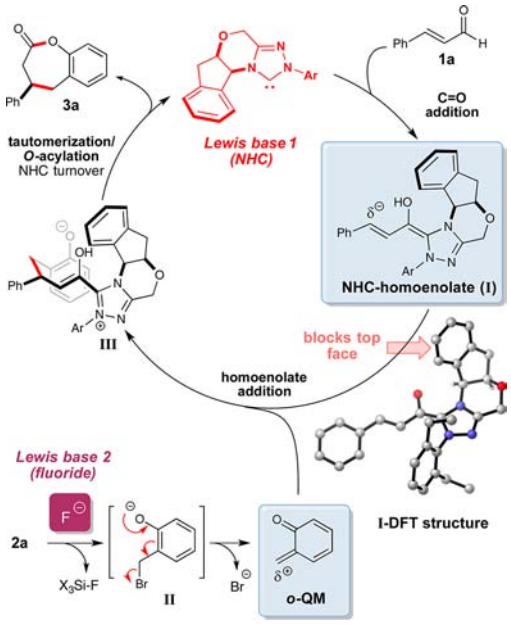
We also explored the scope of the *o*-QM precursor. A brief survey of substituents on the aromatic ring showed that electron-donating groups gave higher yields (**3j–l**). An unsurprising current limitation is that electron-withdrawing groups on the *o*-QM did not furnish any product (data not shown). These groups presumably stabilize the resulting anionic phenoxide intermediate to the point where ejection of the bromide or chloride leaving group is not favored. The incorporation of additional substitution at the benzylic position of the *o*-(bromomethyl)-phenyl TBS ether is possible (**3m–o**) and extends the scope of the formal [4 + 3] process to include the generation of vicinally substituted products. The diastereoselectivity for these reactions is moderate, but this particular process is more challenging since β-substitution of the α,β-unsaturated electrophile (in this case, the *o*-QM) greatly slows down typical Michael/conjugate additions. The highly reactive aldehyde acrolein (**5**) unexpectedly afforded dihydrocoumarin **6** exclusively in excellent yield and enantioselectivity (Scheme 2). The high yield is surprising giving the penchant for acrolein to oligomerize under typical nucleophilic conditions.[19]

Scheme 2. Formal [4 + 2] Reaction with Acrolein



Scheme 3 shows our current understanding of the pathway. The initial addition of the NHC (**Lewis base 1**) to the α,β-unsaturated aldehyde furnishes extended Breslow intermediate **I** after formal 1,2-hydrogen migration. The second Lewis base, F^-,

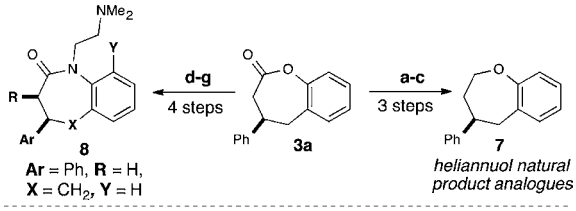
Scheme 3. Reaction Pathway



promotes generation of the *o*-QM electrophile from silylated phenol **2** via a desilylation/elimination cascade (**2** → **II** → *o*-QM). On the basis of density functional theory (DFT) calculations (B3LYP/6-31G*, gas phase), NHC–homoenolate **I** exhibits a strong preference for reaction away from the more hindered face generated by the aminoindanol phenyl framework (**I-DFT**, as drawn). This nucleophile captures the transient *o*-QM through a C–C bond-forming conjugate addition with what seems to be an open transition state. For *o*-QMs with β-substitution (leading to products **3m**, **3n**, and **3o**), this leads to low levels of diastereocontrol. At this point in the cycle, intermediate **III** undergoes taumerization and intramolecular O-acylation of the phenoxide anion,[20] thereby releasing the carbene catalyst (**C**) and the benzoxopinone product (**3**). The absolute strereochemistry of the product was confirmed by X-ray analysis and then further assigned by analogy [see the Supporting Information (SI)]. We attribute the difference in reactivity of acrolein (formal [4 + 2]) versus the β-aryl substrates (formal [4 + 3]) to fast protonation of this specific NHC–homoenolate intermediate to give an NHC–enolate equivalent that undergoes a subsequent Michael addition/O-acylation process similar to the catalytic cycle above, this time forming the observed six-membered ring.[21] The addition of a proton (H^+) to the β-position is competitive if there is no aryl substitution at this location (e.g., acrolein, crotonaldehyde). However, this pathway is slower than C–C bond formation with the *o*-QM when a β-aryl substituent is present (e.g., cinnamaldehyde). Essentially, the fluoride ion promotes the generation of the *o*-QM electrophile and the stability of the extended Breslow intermediate determines the fate of the nucleophilic NHC intermediate.

This process is a convergent, catalytic, enantioselective route to these seven-membered ring lactones and enables rapid access to biologically relevant structures, including related benzoxepanes and benzazepinones (Scheme 4). Prior routes to these

Scheme 4. Synthesis of Benzoxepanes and Benzazepinones[a]



[a]Reaction conditions: (a) Me_2S–BH_3, THF; 85%. (b) TsCl, Et_3N, CH_2Cl_2. (c) NaH, THF; 53% over two steps. (d) H_2SO_4, MeOH; 74%. (e) Tf_2O, DCM; 99%. (f) $Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, $H_2N(CH_2)_2N(CH_3)_2$, THF; 91%. (g) aq. LiOH, THF, then HBTU, *i*-Pr_2EtN, DMF; 65% (as the HCl salt).

compounds are scarce, and the dearth of convergent strategies to access them has presumably hampered investigation of their full potential. For example, benzoxopinone **3a** was smoothly transformed into benzoxepane **7**, which contains the core found in many compounds in the heliannuol family of natural products and could be utilized to access structural analogues.[22] In addition, the related benzoxepanes are known central nervous system depressants.[23] The overall replacement of the O atom in **3a** with a nitrogen substituent to give **8** was easily accomplished in four steps, providing access to benzazepinones that are structurally related to benzodiazepine drugs (e.g., Xanax,

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Valium).[24,25] Benzazepinones with the same *N*,*N*-dimethylaminoethyl side chain are related to the FDA-approved drug diltiazem,[26] a potent calcium channel blocker (Cardizem), and SQ 31,486, a candidate to reduce myocardial ischemia for cardioprotective treatments.[27]

This report highlights the new integration of two distinct Lewis base activation modes to achieve an enantioselective organocatalytic formal [4 + 3] heterocycloaddition. This challenging "dual activation" concept was successfully realized through concomitant in situ generation of two reactive, transient species: a nucleophilic NHC–homonenolate and a highly electrophilic *o*-quinone methide. In a broader strategic sense, the use of a second Lewis base compatible with NHCs to access reactive electrophiles greatly expands the potential for new reaction discovery with these powerful organocatalysts.

■ ASSOCIATED CONTENT

Supporting Information

Procedures, spectral data, and complete ref 25a. 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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(16) During review of this work, a related reaction involving the NHC-catalyzed addition of homoenolate equivalents to stable *o*-QMs was reported. See: Lv, H.; Jia, W.-Q.; Sun, L.-H.; Ye, S. *Angew. Chem., Int. Ed.* **2013**, DOI: 10.1002/anie.201303903.

(17) Other sources of F^- ($Me_4N{\cdot}F$, TBAF) gave only trace amounts of product (see the SI).

(18) Avoiding standard nucleophilic amine bases used to obtain NHCs from azolium salts (e.g., TBD, DBU, Et_3N) was essential. Omitting CsF from the reaction in Table 1, entry 9 gave no product.

(19) Cronotonaldehyde gave predominantly the formal [4 + 2] product in a 57:43 ratio of formal [4 + 2] to [4 + 3] products (overall yield of 48%). The er's for the [4 + 3] and [4 + 2] products were 95:5 and 99:1, respectively. Attempts to change this ratio by modulating the reaction conditions (e.g., base, solvent) have been unsuccessful.

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