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Organocatalytic synthesis of densely functionalized oxa-bridged 2,6-epoxybenzo[*b*][1,5]oxazocine heterocycles†

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Metal-free addition of salicylhydrazones to electron deficient internal alkynes catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO) to yield oxa-bridged 2,6-epoxybenzo[*b*][1,5]oxazocine heterocycles was achieved. The demonstrated protocol proceeds through an *o*-quinone methide formation, aza-Michael addition, stereoselective protonation, enamine promoted aromatization, *O*,*O*-acetalization and *O*,*N*-aminalization sequence to provide privileged heterocycles in good yields with high diastereoselectivities.

The privileged *O*,*O*-acetal and *N*,*O*-aminal scaffolds are common in the pharmaceutical industry and are found in myriad natural products and biologically active skeletons.[1] The demand for accessing these diverse architectures continues to inspire the development of novel strategies.[2] Additionally, developing protocols that are operationally simple and can provide complex skeletons containing fragile ketal-derived aminal ether (a OCOCN-bond) linkages with functional groups that can be further derivatized is of great importance. Recently, transition metal catalysed strategies have been developed to build this diacetal linkage using salicylaldehyde derivatives as precursors.[3,4] For instance, Shi and co-workers developed a Rh(II) catalysed intramolecular cycloisomerization technique to construct aza-bridged benzodioxepine derivatives (Fig. 1, eqn (a)).[3] In a similar fashion, an *O*,*O*,*N*-linked skeleton could be effectively constructed through the cyclization of α-imino carbenes generated *in situ* from tosyl triazoles (Fig. 1, eqn (b)).[4a,b] Alternatively, the oxa-bridged core skeleton can be accessed from the cycloaddition of azomethine ylides to ethyl diazoacetate in the presence of a copper(II) trifluoroacetoacetate ($Cu(tfacac)_2$) catalyst (Fig. 1, eqn (c)).[4c,d] The use of alkynes and their derivatives as useful substrates for accessing diverse complex architectures has received much attention in transition metal catalysis.[5,6] In this scenario, we wondered if a metal-free strategy could be used to access epoxy-bridged azaheterocyclic skeletons by utilizing 2-oxo-3-butynoates as bis-electrophiles.

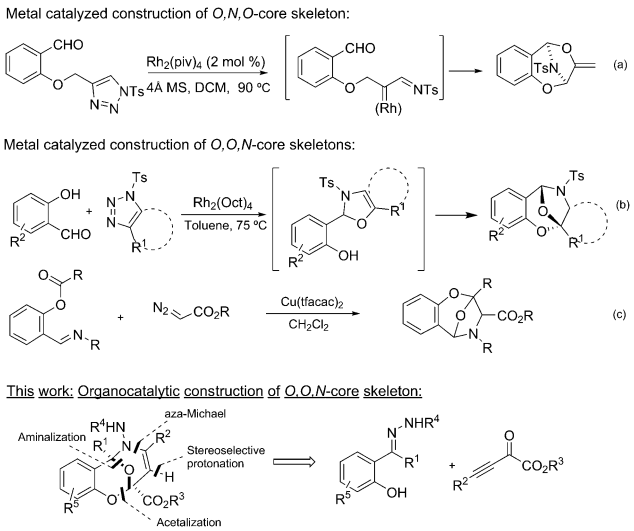

Fig. 1 Metal-mediated construction of aza-bridged (a) and oxa-bridged (b and c) skeletons and the organocatalytic strategy from 2-oxo-3-butynoates and salicylhydrazones.

Analogously, environmentally benign metal-free strategies were developed for electron deficient alkynes.[7–10] Alkynal and ynone precursors are a challenging class of electron deficient internal alkynes, where the incoming nucleophiles could add either across the triple bond to provide unsaturated carbonyls or at the carbonyl site to generate propargylic alcohols in which the alkyne component would be intact unless an additional electrophilic reagent was used.[9,11] To the best of our knowledge, harnessing the chemoselectivity of the reaction of internal alkynes with a labile carbonyl site, such as in 2-oxo-3-butynoates, under metal-free conditions, is relatively rare.[12] On the other hand, salicylhydrazones have been explored by utilizing either their free hydroxyl group or their amine functionality as a nucleophilic partner; however,

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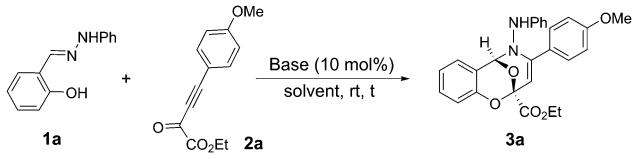
Table 1 Optimization of the cascade process



Entry[a]	Catalyst	Solvent	t (h)	dr[b]	Yield[c] (%)
1	DABCO	DCM	36	>19 : 1	81
2	DBU	DCM	36	>19 : 1	35
3	DMAP	DCM	24	>19 : 1	76
4	PPh_3	DCM	36	>19 : 1	44
5	TMG	DCM	36	>19 : 1	24
6	Et_3N	DCM	36	>19 : 1	12
7	K_2CO_3	DCM	36	>19 : 1	11
8	DABCO	THF	36	>19 : 1	79
9	DABCO	EtOH	36	>19 : 1	34
10	DABCO	$CHCl_3$	36	>19 : 1	46
11[d]	DABCO	DCM	36	>19 : 1	96

[a] All reactions were carried out with 0.2 mmol of **1a**, 0.24 mmol of **2a** (1.2 equiv.) and 10 mol% of the base in the given solvent at ambient temperature. [b] dr was determined from crude ^{1}H-NMR analysis. [c] Isolated yield. [d] Reaction was carried out with 1.5 equiv. of **2a**.

literature precedent, which also reports the use of the electrophilic imine, is scarce.[13,14] From this perspective, we were inspired by the anomalous reactivity of salicylhydrazone towards 2-oxo-3-butynoates, in which the electrophilic imine acts as a nucleophile in the facile *o*-quinone methide formation.[15,16] As a result, as part of our development of organocatalytic reactions of activated alkynes,[17] we established a triple cascade reaction sequence between 2-oxo-3-butynoates and salicylhydrazones using DABCO as a catalyst.

The initial optimization was carried out with salicylhydrazone **1a** and 2-oxo-3-butynoate **2a** under DABCO catalysis in DCM as the solvent at ambient temperature. To our delight, the desired cascade product **3a** was obtained in good yield with excellent diastereoselectivity (81% yield, >19 : 1 dr) (Table 1, entry 1). We observed that DMAP provided a better yield of the desired product than other organic bases (DBU, DMAP, PPh_3, TMG and Et_3N) that were screened for this reaction (up to 76% yield, entries 2–6). We also examined the applicability of an inorganic base (K_2CO_3) in the cascade process; however, it resulted in a poor yield (11%, entry 7). Furthermore, we attempted to improve the yield by varying the solvent under DABCO catalysis at ambient temperature. Fortunately, among the solvents that were screened, we obtained the desired product **3a** in a comparable yield (up to 79%) with good diastereoselectivity in THF (Table 1, entries 8–10). To our surprise, a poor yield was observed with a similar chlorinated solvent, $CHCl_3$ (46% yield, entry 10). Finally, we increased the loading of electrophile **2a** (1.5 equiv.) to improve the yield of the desired heterocycle **3a**. Gratifyingly, an excellent yield with satisfactory diastereoselectivity (up to 96% yield, >19 : 1 dr) was achieved (Table 1, entry 11).

With the optimized conditions in hand, we turned our attention to the scope of substrates with different substituents on salicylhydrazones **1** and 2-oxo-3-butynoates **2** in the presence of DABCO (Fig. 2). In most of the cases, the desired heterocycles **3** were obtained in good to excellent yields with satisfactory diastereoselectivities. As expected, we noticed that substrates with

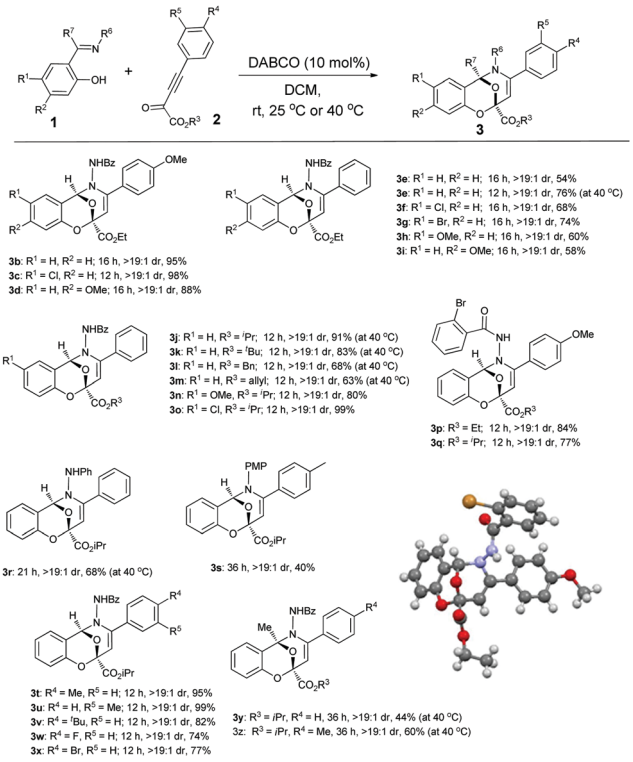
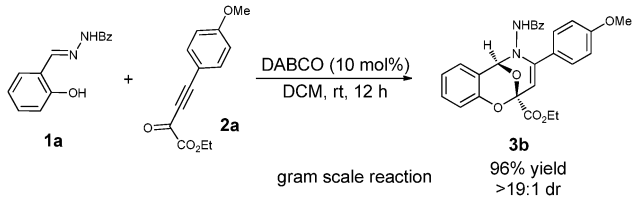


Fig. 2 Substrate scope.

electron-withdrawing groups on the aryl group of either the salicylaldehyde component or the hydrazine component of the salicylhydrazones afforded good to excellent yields and required relatively shorter reaction times at ambient temperature. This could be attributed to the facile formation of *o*-quinone methide with electron-deficient salicylhydrazides. The *O*-isopropyl substituent in ynoate performed better than the other *O*-alkyl substitutions (*tert*-butyl, Bn and allyl; **3j–3m**) and the methoxy phenyl group enhanced the reactivity of the reaction (**3b** *vs.* **3e**). The reactions required a slightly higher temperature (40 °C) to obtain good yields for **3j–3m** and **3r**, where the substrates do not contain electron-withdrawing groups on the aryl moiety of the salicylhydrazones or electron-donating groups on the aryl moiety of the 2-oxo-3-butynoates **2** (Fig. 2). The relative configuration of the cascade products was tentatively assigned from the X-ray crystal structure of the heterocycle **3p**.[18]

Interestingly, when sterically hindered (*E*)-*N*′-(1-(2-hydroxyphenyl)ethylidene)benzohydrazide was used as the starting material, the desired products **3y** and **3z** were obtained in moderate to good yields (44 and 60%, respectively) and with excellent diastereoselectivities (>19 : 1 dr).

We attempted to extend this protocol to a salicylimine that was derived from salicylaldehyde and *p*-anisidine, and we obtained the desired heterocycle with excellent diastereoselectivity, albeit, in a moderate yield (**3s**, 40% yield, >19 : 1 dr). The current protocol suffers from a few limitations as 1,3-diphenylprop-2-yn-1-one did not yield any of the desired products with *N*-benzoyl salicylhydrazide under the optimized reaction conditions.



Scheme 1 A gram-scale reaction of the cascade process.

Similarly, the hydrazone derived from *N*-(2-formylphenyl)acetamide did not furnish any desired product with **2a**. Presumably, this could be attributed to the delocalization of a nitrogen lone pair over the acyl group, resulting in it being unavailable for the *in situ* formation of *o*-quinone methide imine.[19] Finally, we examined the efficacy of the optimized conditions for a gram-scale synthesis of **3b**, and to our delight, we obtained the desired product in a desirable yield (up to 96%) and diastereoselectivity (>19:1 dr) (Scheme 1).

The putative mechanism is depicted in Fig. 3. We presume that salicylhydrazide **1** forms the *o*-quinone methide derivative **4** under Brønsted base catalysis, which would undergo an aza-Michael addition with 2-oxo-3-butynoates **2** to generate intermediate allenic enolate species **5**. The facial differentiation of these allenic species for protonation is crucial for delivering either the (*Z*)- or (*E*)-adduct as the major product.[20] Gratifyingly, the sterically bulky enaminone arm successfully shields its face from protonation, making the intermolecular protonation of the opposite face preferred, and this selective protonation leads to the formation of bis-enaminone **6**. Consequently, bis-enaminone **6** underwent enamine-promoted aromatization to provide transient phenoxide species **7**, which would undergo a reversible acetalization process with the proximal carbonyl group to generate alkoxide species **8**. Furthermore, the resulting iminium-alkoxide species is susceptible to facile *O*,*N*-aminalization to generate desired cascade products **3** with good diastereoselectivities.[2] Although the proposed mechanism is tentative, the plausibility of a concerted path for all off-cycle transformations (aromatization, *O*,*O*-acetalization and *O*,*N*-aminalization) cannot be ruled out as it is a possible outcome of the simple reorganization of the molecular structure that does not involve an atom transfer (Fig. 3).

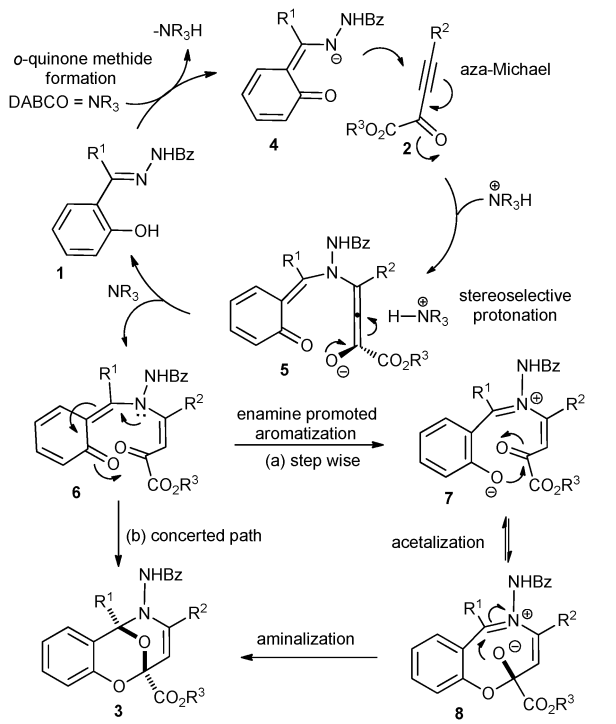


Fig. 3 Tentative mechanism for the triple cascade reaction sequence.

In conclusion, an organocatalytic method was developed for electron deficient internal alkynes by exploiting a unique activation mode in which a nucleophilic Brønsted base is not directly bound to the internal alkyne, unlike traditional nucleophilic phosphine/tertiary amine catalysis. Additionally, an unexpected intriguing reactivity pattern in the reaction of salicylhydrazones with 2-oxo-3-butynoates was observed and has the potential to inspire further developments. The current protocol has provided a wide range of functionalized heterocycles containing privileged ketal derived aminal ether linkages as a core skeleton in good yields (up to 99%) with excellent diastereoselectivities (>19:1 dr).

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Conflicts of interest

There are no conflicts to declare.

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