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Expedient (3+3)-annulation of carbonyl ylides with azaoxyallyl cations: formal access to oxa-benzo[c]azepin-3-ones†

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The cascade carbon–carbon and carbon–nitrogen bond formation between *in situ* generated carbonyl ylides and azaoxyallyl cations, facilitated by Rh-catalysis and a base, has been achieved to furnish oxa-benzo[c]azepin-3-ones. Substrate scope, functional group diversity, scale-up and post-synthetic utilities are the important practical features.

Benzo[*c*]azepin-3-ones are privileged structural frameworks due to their interesting biological and medicinal properties.[1] For example, they are a key scaffold found in the galanthamine family and exhibit biological activities like vitronectin receptor antagonist,[1a] tyrosine kinase inhibitor[1c] and opioid receptor antagonist[1d] (Fig. 1). Considerable efforts have thus been made on the construction of these scaffolds utilizing intramolecular cyclization processes, radical cyclization,[2a] olefin-metathesis,[2b] Pictet–Spengler cyclization[2c] and Meyers lactamization[2d] *via* multi-step synthesis of intricate substrate precursors.[2e] Similarly, oxa-polycyclic motifs are the structural constituent of numerous compounds that are of pharmaceutical interest.[3] The development of effective synthetic strategies for the assembly of these structural frameworks would thus be valuable.

Diazocarbonyl compounds are versatile substrate precursors for constructing complex structural frameworks.[4–6] In particular, α-diazoesters are the prominent precursors for the generation of carbonyl ylides that are three-atom synthons for the (3+2) and (4+3)-cycloadditions to afford oxa-bridged scaffolds, which are otherwise difficult to achieve in a single-step.[7] However, the (3+3)-annulation of carbonyl ylides with suitable 1,3-dipolar coupling partners is scarce.[8] More recently, Werz,[8a] Schneider[8b] and Gao[8c] groups have reported the (3+3)-annulation using the acid-catalyzed dipolarophiles with carbonyl ylides (Scheme 1a). Meanwhile, α-halohydroxamates have gained significant attention for constructing amide containing scaffolds due to their stability, reactivity and easy accessibility. In the presence of a base, they undergo dehydrohalogenation to generate *in situ* azaoxyally cations, which are reactive 1,3-dipolar synthons useful for forming biologically relevant scaffolds.[9] Herein, we wish to report a cascade carbon–carbon and carbon–nitrogen bond formation of carbonyl ylides with azaoxyallyl cations that have been generated *in situ* using Rh-catalysis in the presence of a base to afford oxa-benzo[*c*]azepin-3-one frameworks at room temperature (Scheme 1b). The main challenge in the developed annulation is the simultaneous activation of both the synthons to facilitate the desired reaction while suppressing the side reactions. Additionally, constructing seven membered rings remains a challenging goal, possibly due to relative instability, and non-bonding interaction in the transition states.[10] This method offers an effective synthetic route for the (3+3)-annulation of carbonyl ylides with azaoxyallyl cations with a broad substrate scope, scalability, and useful post-synthetic applications.

First, we commenced the optimization studies using ethyl 2-(2-benzoylphenyl)-2-diazoacetate **1a** and *N*-(benzyloxy)-2-bromo-2-methylpropanamide **2a** as the model substrates (Table 1 and Table S1, ESI†). To our delight, a reaction occurred to furnish the tricyclic scaffold **3aa** in 43% yield when the substrates were stirred with $Rh_2(OAc)_4$ (5 mol%) and Cs_2CO_3 (1.5 equiv.) in $CHCl_3$ under a N_2 atmosphere for 16 h at room temperature (entry 1). In an array of bases screened *viz.* K_2CO_3, Cs_2CO_3, $NaHCO_3$ and DBU, the former gave the best result (entries 1–4). The yield increased to 86% employing a 1:1

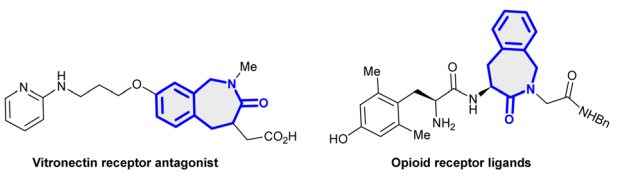

Fig. 1 Biologically active benzo[c]azepin-3-one scaffolds.

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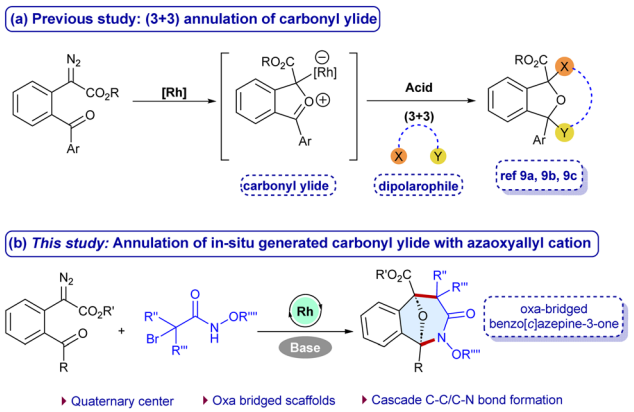
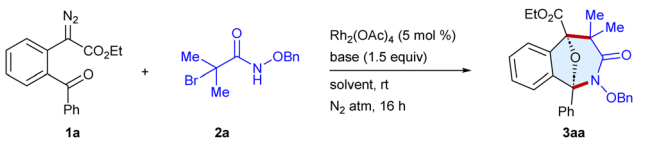


Scheme 1 Approaches for (3+3)-annulation of carbonyl ylides.

Table 1 Optimization of the reaction conditions[a]

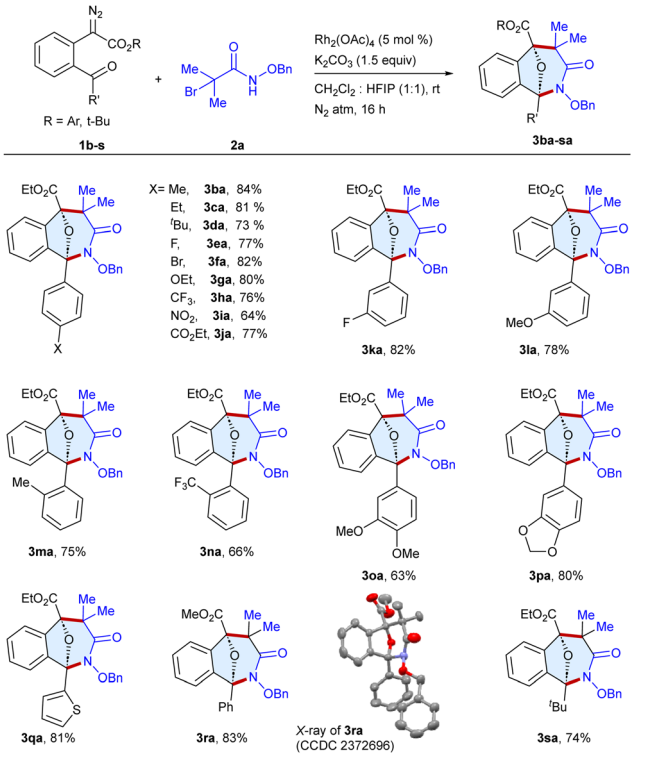


Entry	Base	Solvent	Yield[b] (%)
1	Cs_2CO_3	$CHCl_3$	43
2	K_2CO_3	$CHCl_3$	65
3	$NaHCO_3$	$CHCl_3$	Trace
4	DBU	$CHCl_3$	58
5	K_2CO_3	CH_2Cl_2	73
6	K_2CO_3	Toluene	n.d.
7	K_2CO_3	CH_3CN	n.d.
8	K_2CO_3	HFIP	68
9	**K_2CO_3**	**CH_2Cl_2:HFIP**	**86**

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), $Rh_2(OAc)_4$ (5 mol%), base (1.5 equiv.), solvent (2 mL), rt, N_2 atm, 16 h. [b] Isolated yield. n.d. = not detected. HFIP = 1,1,1,3,3,3-hexafluoroisopropanol.

mixture of CH_2Cl_2 and HFIP as a solvent due to enhanced stabilization of both the transient species *via* hydrogen bonding,[9a,9i] whereas using CH_2Cl_2 alone gave 73% yield (entry 5) and HFIP alone gave 68% yield (entry 8). In contrast, toluene and CH_3CN were not effective and the formation of **3aa** was not observed.

Having the optimized conditions in hand, the scope of the procedure was examined with a series of α-diazo esters **1b–s** utilizing *N*-(benzyloxy)-2-bromo-2-methylpropanamide **2a** as a standard substrate (Scheme 2). The reaction of alkyl substituted diazo esters at the *para*-position of the phenyl rings such as methyl **1b**, ethyl **1c** and *tert*-butyl **1d** gave the target products **3ba–da** in 73–84% yields. In addition, halogen and electron-donating group-bearing diazo esters, fluoro **1e**, bromo **1f** and ethoxy **1g** underwent reaction to afford the cyclic scaffolds **3ea–ga** in 77–82% yields. Likewise, the diazo esters with electron withdrawing trifluoromethyl **1h**, nitro **1i** and carboxylate **1j** groups at the *para*-position underwent annulation to produce **3ha–ja** in 64–77% yields, whereas the substrates with fluoro **1k** and methoxy **1l** groups at the *meta*-position furnished **3ka** and **3la** in 82% and 78% yields, respectively. Similar results were



Scheme 2 Scope of α-diazo esters.[a,b] [a] Reaction conditions: **1b–s** (0.1 mmol), **2a** (0.11 mmol), $Rh_2(OAc)_4$ (5 mol %), K_2CO_3 (0.15 mmol), CH_2Cl_2 : HFIP (1 : 1, 2 mL), rt, N_2 atm, 16 h. [b] Isolated yield.

observed with diazo esters bearing *ortho*-methyl **1m** and trifluoromethyl **1n** groups, furnishing **3ma** and **3na** in 75% and 66% yields, respectively. Intriguingly, disubstituted **1o–p** and thiophene **1q** tethered diazo esters were able to afford the cyclic scaffolds **3oa–qa** in 63–81% yields. Moreover, the methyl substituted ester moiety of diazo ester **1r** gave **3ra** in 83% yield, whose structure was determined by single crystal X-ray analysis (CCDC= 2372696, see ESI†). Gratifyingly, changing the phenyl ring to *tert*-butyl diazo ester **1s** successfully gave the target heterocycle **3sa** in 74% yield.

The scope of the procedure was further examined for the annulation of a series of α-halohydroxamates **2b–j** with ethyl 2-(2-benzoylphenyl)-2-diazoacetate **1a** as a standard substrate (Scheme 3). The reaction of the substrates bearing methoxy **2b** and ethoxy **2c** protecting groups on the nitrogen atom of haloamide afforded **3ab** and **3ac** in 82% and 75% yields, respectively, whereas *tert*-butyl bearing **2d** was an unsuccessful substrate, which might be due to steric hindrance. Furthermore, phenoxy **2e** and allyloxy **2f** bearing haloamides underwent reaction to furnish **3ae** and **3af** in 81% and 68% yields, respectively. Moreover, the reaction of the *para*-methyl benzyl **2g** substituted haloamide afforded **3ag** in 78% yield, whereas the reaction of α-bromoamide with a monomethyl group **2h** yielded **3ah** in a trace amount, which may be due to the formation of a less stable carbocation. Moreover, the substrate **2i** bearing a diethyl group gave **3ai** in 70% yield, whereas **2j** with cyclohexyl yielded **3aj** in a trace amount.

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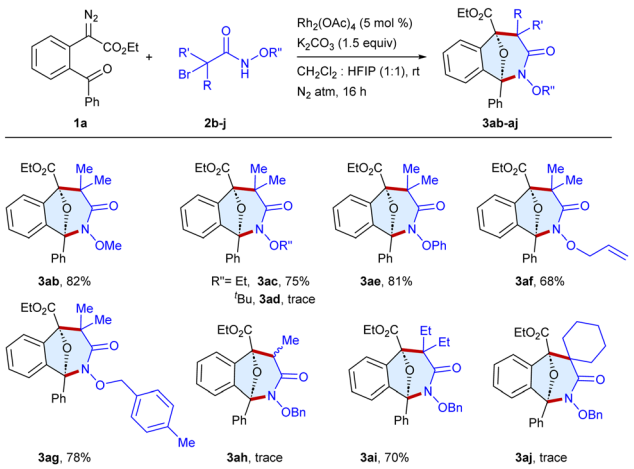
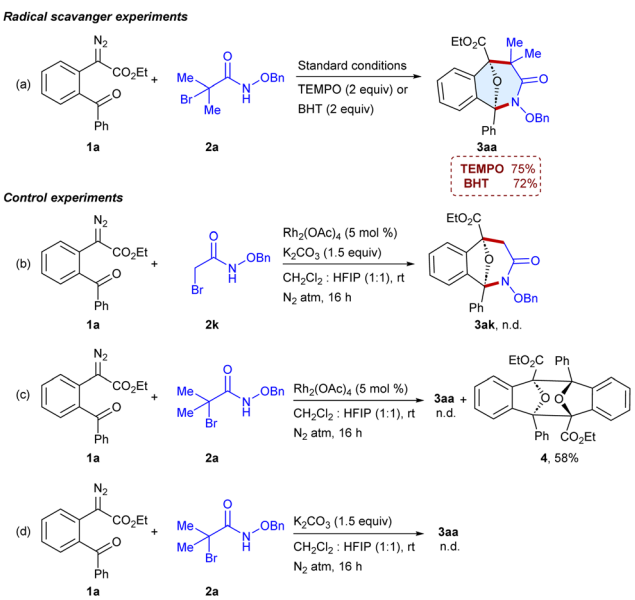


Scheme 3 Scope of α-halohydroxamate.[a,b] [a] Reaction conditions: **1a** (0.1 mmol), **2b–j** (0.11 mmol), $Rh_2(OAc)_4$ (5 mol %), K_2CO_3 (0.15 mmol) CH_2Cl_2:HFIP (1 : 1, 2 mL), rt, N_2 atm, 16 h. [b] Isolated yield.

To get insights into the reaction pathway, the radical scavenger experiments were carried out using 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and 2,6-di-*tert*-butyl-4-methylphenol (BHT) and the formation of **3aa** was observed in 75% and 72% yields, respectively (Scheme 4a), which indicates that the reaction may not involve a radical pathway. Furthermore, the reaction of ester **1a** with *N*-(benzyloxy)-2-bromoacetamide **2k** was unable to give **3ak**, which indicates that the generation of a *tertiary* carbocation is essential for the reaction (Scheme 4b). In addition, the reaction of **1a** with α-halohydroxamate **2a** in the absence of K_2CO_3 was unable to yield **3aa**; instead the dimer[11] **4** of the carbonyl ylide has been isolated in 58% yield (Scheme 4c), which suggests that the reaction involves the carbonyl ylide pathway. Moreover, the reaction of α-diazo ester **1a** with α-halohydroxamate **2a** in the absence of $Rh_2(OAc)_4$ failed to yield **3aa** (Scheme 4d). Thus, the Rh-catalyst and base are crucial for generating the transient intermediates, carbonyl ylides and azaoxyallyl cations. In addition, the reaction of **1a** and **2a** was examined using (*R*)-BINAP and chiral phosphoric acid; however, **3aa** was obtained in racemic form (ESI,† Table S3).



Scheme 4 Preliminary mechanistic investigations.

Based on the experimental results and literature precedents,[7–9] a plausible reaction pathway is proposed (Scheme 5). Firstly, the Rh-catalyzed decomposition of α-diazoester **1a**, followed by intramolecular capture of the rhodium carbene by the aryl keto group, leads to the formation of the carbonyl ylide **A**. At the same time, α-halohydroxamate **2a** can undergo base-mediated dehydrohalogenation to produce azaoxyallyl cation **B**. Both the *in situ* generated **A** and **B** can undergo the (3+3)-annulation in a concerted fashion to give the target heterocycle **3aa** (Path A). Alternatively, **B** can undergo a nucleophilic attack by **A** to form **C** that can lead to annulation in a step-wise fashion to produce **3aa** (Path B).

To demonstrate the practical applicability, we conducted a scale-up synthesis, the reaction of α-diazo ester **1a** with α-halohydroxamate **2a** as the representative examples, which afforded **3aa** in 68% (312 mg) yield (Scheme 6). Moreover, the products were modified to produce diverse scaffolds (Scheme 7). The oxa-bridged benzo[*c*]azepin-3-one **3fa** was coupled with phenylacetylene to give **5** in 85% yield, whereas Suzuki coupling with phenylboronic acid provided **6** in 82% yield. In addition, the reduction of the ester group of **3aa** in the presence of $LiBH_4$ furnished **7** in 79% yield. Likewise, the N–O bond cleavage of **3aa** has been achieved to afford **8** in 75% yield.

In summary, we describe the reaction of the carbonyl ylides and azaoxyallyl cations using Rh-catalysis in the presence of K_2CO_3 to assemble diverse oxa-benzo[*c*]azepin-3-ones in a 1 : 1 mixture of CH_2Cl_2 and HFIP at room temperature. The substrate scope, functional group diversity, scale-up, selectivity and post-synthetic utilities are the essential practical features.

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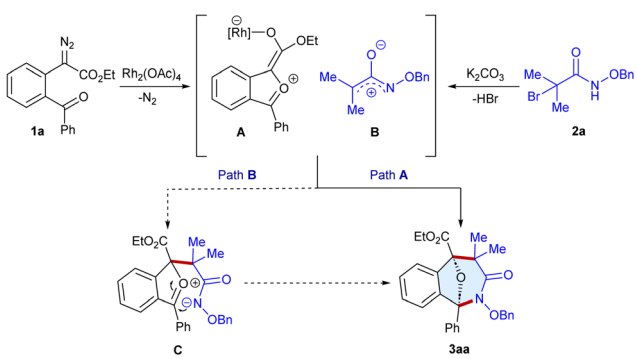

Scheme 5 Plausible reaction pathway.

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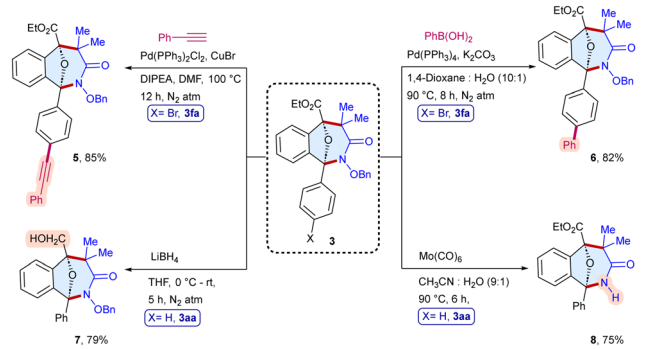
Scheme 6 Scale-up synthesis.



Scheme 7 Post synthetic transformations.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

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