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Novel and Facile Synthesis of 1-Benzazepines via Copper-Catalyzed Oxidative C(sp^3)-H/C(sp^2)-H Cross-Coupling†

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A novel and facile synthetic strategy for the construction of 1-benzazepines has been developed via copper-catalyzed oxidative C(sp^3)-H/C(sp^2)-H cross-coupling directly from two inert C-H bonds. This transformation represents an atom- and step-economic way to synthesize biologically important seven-membered benzo-heterocycles compared with the known methods.

Benzannulated heterocycles exist extensively as key structural motifs in multitudinous biologically active molecules, including different kinds of natural products, pharmaceuticals, and agrochemicals.[1] Among these pivotal heterocycles, benzo-fused, seven-membered, aza-heterocycles, commonly known as 1-benzazepines, have already been incorporated into many commercial pharmaceuticals, such as Fedovapagon (antidiuretic), Benazepril (ACE inhibitor), Imipramine (antidepressant) and Eslicarbazepine (anticonvulsant), as core skeletons due to their significant value in drug development and medicinal chemistry (Fig. 1).[2] Hence, the development of efficient methods to construct 1-benzazepine skeletons in a facile way is always of great academic and practical values. Various synthetic methods have been reported by a number of research groups, for instance, Beckmann or Schmidt rearrangements,[3] transition-metal catalyzed cross-coupling,[4] cooperative NHC/Pd-catalyzed annulation[5] *etc*.

From an ecological and economical point of view and in consideration of green and sustainable chemistry, seeking more efficient methods to construct C-C bonds remains a big challenge and has drawn great interest for synthetic chemists. Accordingly, several novel strategies based on direct C-H functionalization, including Friedel-Crafts reaction,[6] Mannich-type reactions[7] and [1,5]-hydride shift/7-endo cyclization,[8] have been reported for the efficient synthesis of 1-benzazepines (Scheme 1a). However, all these methods are limited to the functionalization of a single relatively active C-H bond, and the cross-coupling of inert aromatic and inert aliphatic C-H bonds,[9] obviously the most efficient and ideal method to make 1-benzazepines, still remains an unresolved problem. As one part of our continuous efforts to develop new methods for selective cross-coupling of C(sp^3)-H and C(sp^2)-H bonds,[10] herein, we report a novel copper-catalyzed oxidative C(sp^3)-H/C(sp^2)-H cross-coupling for facile construction of various 1-benzazepines (Scheme 1b). The key to success is that the selective cleavage of C(sp^3)-H bonds in alkyl chains can be realized via [1,5]-hydrogen atom transfer ([1,5]-HAT) with aniline used as the directing group. It should be noted that the starting material for this transformation can be easily obtained from inexpensive and easily available anilines and ketones (see the ESI†).

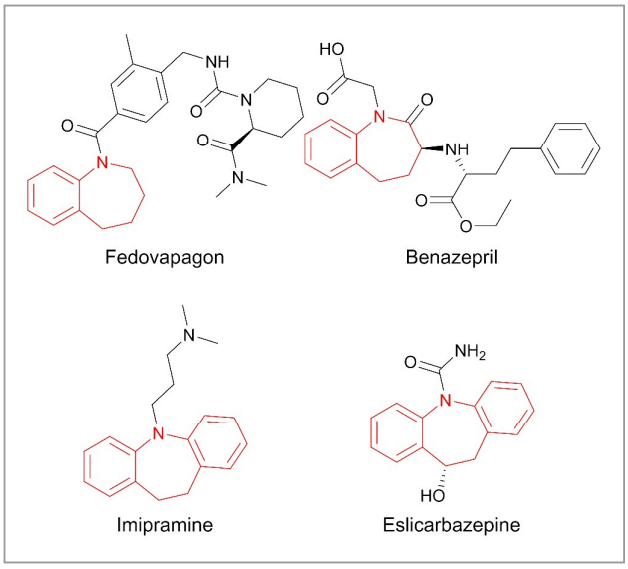

Fig. 1 Pharmaceuticals and bioactive compounds containing 1-benzazepine structures.

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†Electronic Supplementary Information (ESI) available: Detailed experimental procedures, detailed reaction conditions screening, detailed mechanism studies, characterization data and spectroscopic data. CCDC 1562122. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

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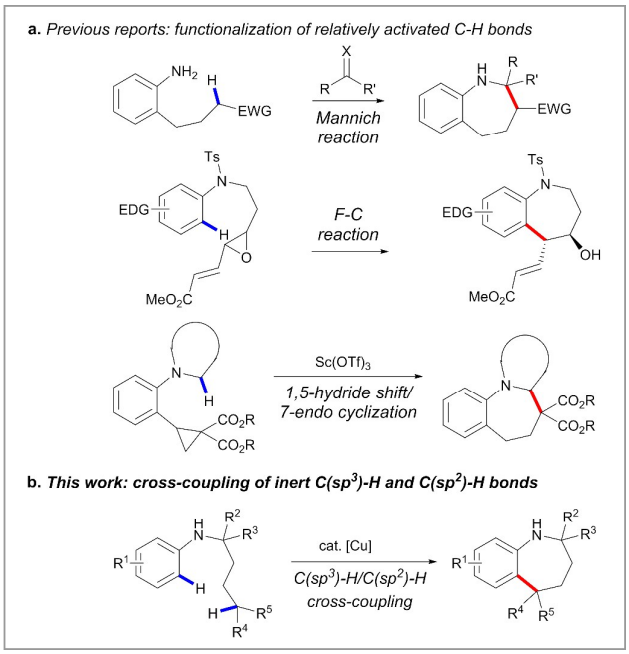

Scheme 1 Synthesis of 1-benzazepines via direct C-H functionalization.

Our initial study began with aniline **1a** (0.3 mmol) as the pilot substrate in the presence of a catalytic amount of $Cu(OAc)_2$ (20 mol%) in DCE (2.0 mL). As expected, the desired product **2a** was successfully obtained with addition of Ag_2CO_3 (2.0 equiv) at 135 ˚C for 24 h, albeit with a relatively low yield (20%, Table 1, entry 1). To increase the yield further, a careful screening of the oxidants (Table S2, ESI†) was then performed, which showed that Ag_2O gave the best result with 48% yield (entry 3). However, further optimization of the reaction conditions with Ag_2O as the oxidant failed to provide higher yields. While AgOAc had been demonstrated not as a good oxidant (entry 5), addition of extra Na_2CO_3 as base into the reaction system exhibited significant increment of yield. Copper catalysts were next examined with AgOAc and Na_2CO_3 used, which revealed that CuO was optimal (Table S5, ESI†; Table 1, entries 8, 9). After re-screening of the bases (Table S6, ESI†), $NaHCO_3$ was eventually selected as the best choice (85%, Table 1, entry 12). After further careful investigation of experimental details, it was interesting to find that introduction of Na_2SO_4 into this system and stirring the reaction system at room temperature for 5 min before heating could slightly improve the yield (entry 13). Moreover, lowering the reaction temperature to 125 °C afforded 1-benzazepine **2a**, with the best isolated yield (93%, entry 14). Finally, control experiments showed that almost none of **2a** was detected without addition of either copper catalyst or silver oxidant (entries 15, 16).

With the optimal conditions in hand, the scope of this strategy was then elucidated by synthesis of a variety of 1-benzazepines (Scheme 2). First, the investigation of substituent effects of the aryl ring indicated that both electron-donating groups, such as alkyl (**2b**-**d**, **2i**, **2n**), phenyl (**2e**) and methoxy (**2m**), and electron-withdrawing groups, such as halogen (**2g**-**g**, **2h**) and trifluoromethyl (**2k**), were well compatible with this transformation in good to excellent yields. 1-Naphthyl-derived benzazepine **2f** could be obtained as well, albeit in a low yield (21%). Meanwhile, a number of anilines **1** with *para*-, *meta*-, as well as *ortho*-substituted groups on the aryl rings were smoothly cyclized to furnish the corresponding 1-benzazepines **2** with good to excellent yields. Interestingly, methyl (**2i**), chloro (**2j**) and trifluoromethyl (**2k**) at the *meta*-position cyclized selectively at the less sterically hindered position in good yields, showing a significant steric effect in this transformation. Yet intriguingly, the *meta*-cyano-substituted aniline **1l** and the *meta*-methoxy-substituted aniline **1m** afforded both 8- and 6-substituted cyclic products with 2.22:1 (**2l**) and 1.04:1 (**2m**) selectivity, respectively, which indicated that the electronic effect might also play an important role in the regioselectivity. Notably, *ortho*-methyl substrate could be well tolerated with good yield (55%, **2n**). Not surprisingly, the corresponding yields decreased slightly along with the increase of steric hindrance of alkyl groups at α-position of nitrogen atom (**2o**-**r**). In particular, the C-H/C-H

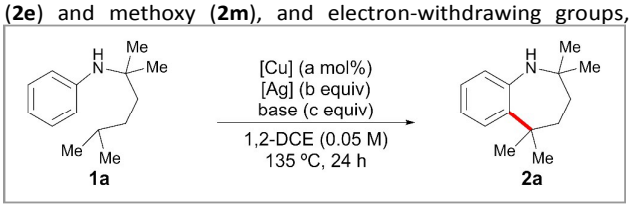

Table 1 Optimization of reaction conditions[a]

entry	[Cu] (mol%)	[Ag] (equiv)	base (equiv)	%yield[b]
1	$Cu(OAc)_2$	Ag_2CO_3	none	19 (20[c])
2	$Cu(OAc)_2$	AgOTf (4.0)	none	0
3	$Cu(OAc)_2$	Ag_2O (2.0)	none	48
4	$Cu(OAc)_2$	AgOAc (4.0)	none	7
5	$Cu(OAc)_2$	AgOAc (4.0)	Na_2CO_3 (2.0)	44
6	Cu_2O (10)	AgOAc (4.0)	Na_2CO_3 (2.0)	34
7	$Cu_2(OH)_2CO_3$ (10)	AgOAc (4.0)	Na_2CO_3 (2.0)	61
8	CuO (20)	AgOAc (4.0)	Na_2CO_3 (2.0)	70
9[d]	CuO (20)	AgOAc (4.0)	Na_2CO_3 (2.0)	77
10[d]	CuO (20)	AgOAc (4.0)	NaOAc (4.0)	61
11[d]	CuO (20)	AgOAc (4.0)	K_3PO_4 (1.3)	50
12[d]	CuO (20)	AgOAc (4.0)	$NaHCO_3$ (4.0)	85
13[d,e]	CuO (20)	AgOAc (4.0)	$NaHCO_3$ (4.0)	88
14[d,e,f]	CuO (20)	AgOAc (4.0)	$NaHCO_3$ (4.0)	91 (93[c])
15[d,e,f]	none	AgOAc (4.0)	$NaHCO_3$ (4.0)	n.d.
16[d,e,f]	CuO (400)	none	$NaHCO_3$ (4.0)	trace

[a]Unless otherwise noted, the reaction conditions were as follows: **1a** (0.1 mmol), [Cu] (a mol%), [Ag] (b equiv) and [base] (c equiv) in 1,2-DCE (0.05 M) at 135 °C for 24 h. [b]GC yields are reported; n.d., not detected. [c]Isolated yield, **1a** (0.3 mmol). [d]30 h. [e]Na_2SO_4 (2.0 equiv) was added and the reaction was stirred at rt for 5 min before heating. [f]125 °C.

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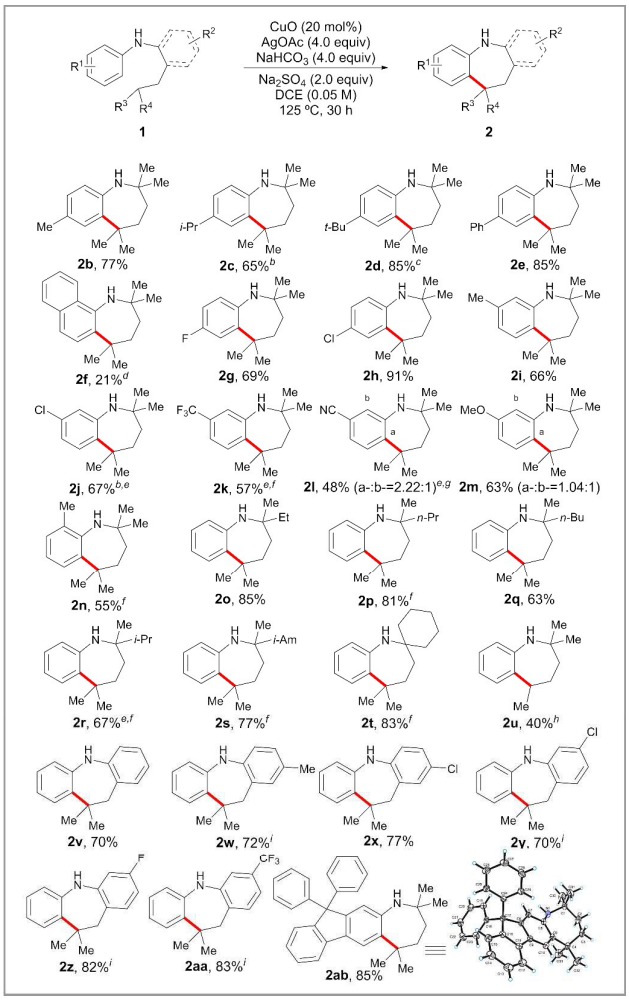


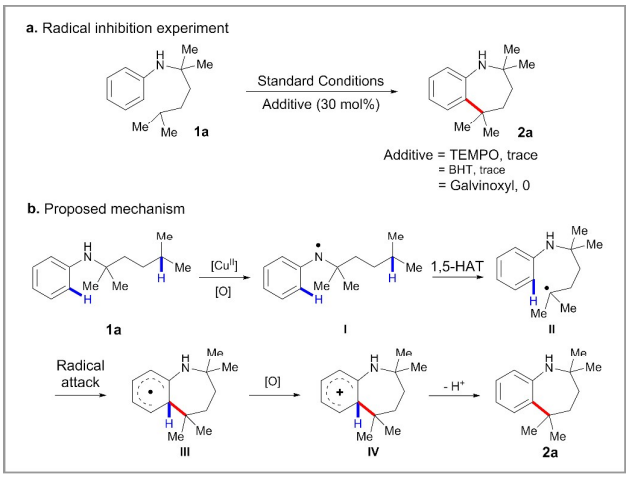
cyclization of anilines bearing both tertiary C(sp^3)-H and primary (**2p**) or secondary (**2q**) C(sp^3)-H bonds occurred at the

Scheme 2 Substrate scope[a]

[a]Unless otherwise noted, the reaction conditions were as follows: **1** (0.3 mmol), CuO (20 mol%), AgOAc (4.0 equiv), $NaHCO_3$ (4.0 equiv) and Na_2SO_4 (2.0 equiv) in 1,2-DCE (6.0 mL) at 125 °C for 30 h; for **2f, 2v**-**aa**, reactions were performed on **1** (0.3 mmol), $Cu(OAc)_2$ (20 mol%) and Ag_2CO_3 (1.5 equiv) in 1,2-DCE (6.0 mL) at 125 °C for 8 h; isolated yields were reported. [b]25 h. [c]AgOAc (3.0 equiv). [d]20 h. [e]140 °C. [f]35 h. [g]45 h, CuO (30 mol%). [h]2-DCE/cyclohexane (1:1) as the solvent. [i]6 h.

tertiary C-H position exclusively. The excellent chemoselectivity could be explained by the relatively higher stability of the tertiary carbon radical. A symmetric substrate with two C(sp^3)-H bonds suitable for [1,5]-hydrogen atom abstraction in both alkyl side chains also worked pretty well (**2s**). Importantly, a spiro skeleton, normally difficult to make, could also be obtained in good yield (**2t**). Moreover, the secondary C(sp^3)-H bond could be selectively cleaved and coupled as well, albeit in a lower but still acceptable yield (**2u**).

As one more representative structure of 1-benzazepine derivatives, iminodibenzyl has also been examined as a further



testament to the synthetic utility of our strategy. Gratifyingly, the corresponding coupling products bearing different

Scheme 3 Radical Inhibition Experiment and Proposed Mechanism.

substituent groups, including Me, Cl, F, and CF_3, could be obtained smoothly with good yields (**2v**-**aa**). It is worth noting that the iminodibenzyl derivatives serve as a class of important frameworks with various uses, including natural occurrence,[11] synthetic applications[12] and versatile biological activities.[13] For instance, it is the only precursor for present-day construction of tricyclic antidepressant (TCA) drugs,[14] such as Imipramine, Clomipramine and Trimipramine. Meanwhile, the cross-coupling occurred exclusively at the tertiary C(sp^3)-H site, and the relatively more active benzylic C(sp^3)-H bond has not been affected, which further revealed the excellent regioselectivity of our method was controlled only by 1,5-HAT. To confirm the seven-membered ring structure of the products, an interesting aniline **1ab**, which possesses a 9,9-diphenylfluorene motif that is useful in pharmaceuticals and photoelectric devices, was synthesized and tested in our reaction system. Fortunately, benzazepine **2ab** was obtained successfully with 85% yield, and the exact structure was further confirmed by X-ray analysis.[15]

To verify the mechanism of this novel transformation, several free radical inhibitors, including TEMPO, BHT and galvinoxyl, were added to the standard conditions, and all of them showed strong inhibition effects, even with only 30 mol% loading (Table S8; Scheme 3a). Based on these results and our previous report,[10] a conceivable mechanism is outlined in Scheme 3b. Initial interaction of Cu(II) with aniline **1a** generates the nitrogen radical **I**. The carbon-centered radical **II** is then formed via [1,5]-hydrogen atom transfer and subsequently captured by the phenyl ring of the aniline. After further oxidation and deprotonation, the final 7-membered product **2a** is obtained.

In conclusion, we have developed a novel method for the facile construction of 1-benzazepines via copper-catalyzed oxidative C(sp^3)-H/C(sp^2)-H cross-coupling. Compared with known methods, this transformation represents an atom- and

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step-economical way to synthesize biologically important seven-membered benzo-heterocycles, and has demonstrated excellent regioselectivity, broad scope, and high efficiency from easily available starting materials.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB20000000), the National Basic Research Program of China (973 Program 2015CB856600), and the National Science Foundation of China (21602213, 21522208, 21372209) for financial support.

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15 CCDC 1562122 contains the supplementary crystallographic data for **2z**. 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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