Synthetic Methods

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Oxidative C–H Bond Functionalization and Ring Expansion with $TMSCHN_2$: A Copper(I)-Catalyzed Approach to Dibenzoxepines and Dibenzoazepines**

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Dedicated to Professor José Luis García Ruano on the occasion of his retirement

Abstract: *Tricyclic dibenzoxepines and dibenzazepines are important therapeutic agents for the pharmaceutical industry and academic research. However, their syntheses are generally rather tedious, requiring several steps that involve a Wagner–Meerwein-type rearrangement under harsh conditions. Herein, we present the first copper(I)-catalyzed oxidative C–H bond functionalization and ring expansion with $TMSCHN_2$ to yield these important derivatives in a facile and straightforward way.*

Dibenzo[*b,f*]xepine and dibenzo[*b,f*]azepine derivatives (**I**, Figure 1) are important therapeutic agents, which present a broad spectrum of pharmaceutical properties. For example, derivatives **II**–**V** are used for the treatment of depression in some countries.[1] Moreover, derivatives such as metapramine (**II**) also present analgesic properties,[2] whereas opipramol (**V**) shows an anxiolytic profile.[3] Besides other activities, some of these tricyclic structures are known as receptor antagonists (**VI**). Oxcarbazepine (OXC, Trileptal, **VII**) represents the first narrow-spectrum antiepileptic drug (AED) and more recently was used as a monotherapy for the treatment of partial seizures in adults.[4]

Despite the great importance of these types of heterocycles, there is a lack of simple, mild, and direct synthetic methods for their preparation.[5] The classical synthesis of dibenzoxepines and dibenzazepines are so far based on multistep processes (Scheme 1). In these approaches several steps are required for the introduction of a CH_2-LG (LG = leaving group) unit at the benzylic position of xanthenes or acridanes using stoichiometric reagents[6] as well as harsh conditions for the Wagner–Meerwein rearrangement with

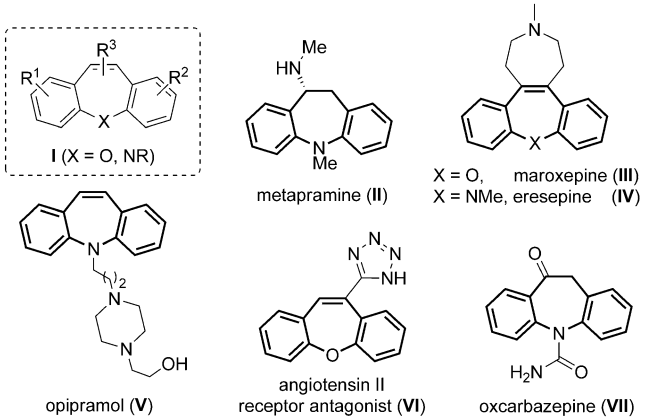
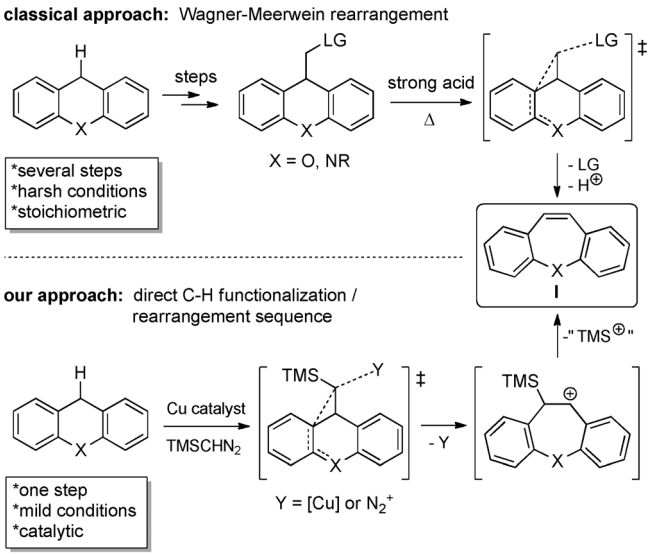


Figure 1. Biologically active dibenzoxepines and dibenzazepines.



Scheme 1. Classical and present approach for the synthesis of dibenzoxepines and dibenzazepines **I**.

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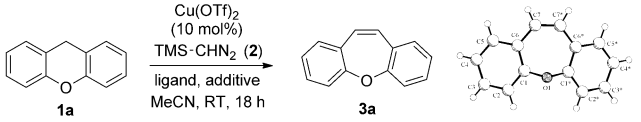
a large excess (or even as a solvent) of strong acids under heating (typically 140–200 °C). These features limited the preparation of new related tricyclic derivatives with broad substitution patterns, which have been shown to be extremely important to modulate their biological activity.[7]

Based on these precedents and driven by the need to develop more general and straightforward methods, we proposed a direct C–H functionalization approach (Scheme 1). From the recent advances in copper-catalyzed reactions of diazo compounds, we hypothesized that those would be the appropriate reagents for functionalization of the C–H bond.[8] Therefore, we chose trimethylsilyldiazomethane ($TMSCHN_2$), which already possess a silicon leaving group that might also facilitate or promote the in situ rearrangement to the tricyclic backbone of the desired products (**I**). Herein, we present a copper-catalyzed mild oxidative C–H bond functionalization and ring-expansion process for the straightforward preparation of dibenzoxepines and dibenzazepines from simple starting materials.

We started our screening with commercially available xanthene (**1a**) and $TMSCHN_2$ (**2**) in the presence of 10 mol% $Cu(OTf)_2$, which would be reduced in situ by **2** to the presumed active Cu^I species[9] (Table 1, entry 1). However,

Table 1: Optimization of the reaction of **1a** with $TMSCHN_2$.[a]



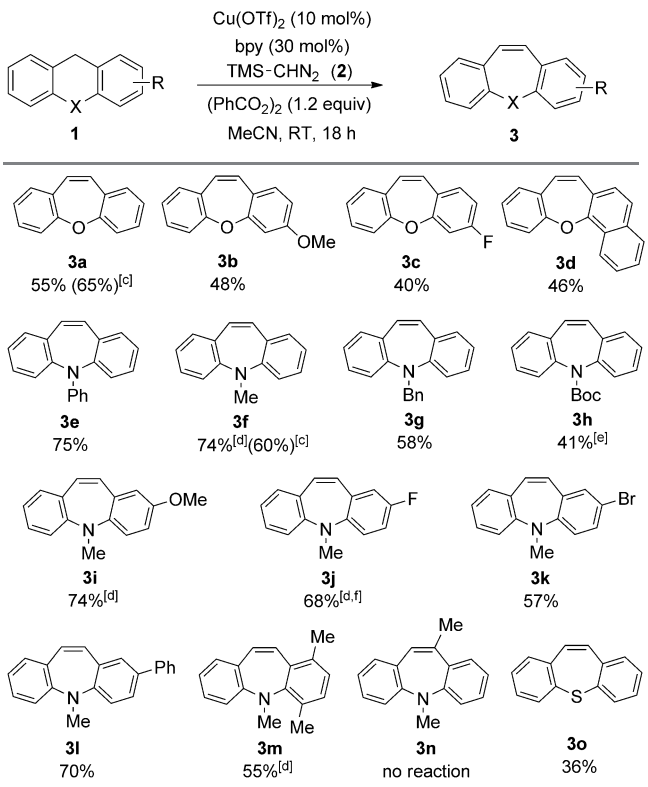
Entry[a]	Ligand (mol%)	Additive (1.2 equiv)	Yield [%][b]
1	–	–	–
2	–	$T^+BF_4^-$	traces
3	–	*t*BuOOH	traces
4	–	DDQ	7
5	–	$(PhCO_2)_2$	29
6	TMEDA (20)	$(PhCO_2)_2$	30
7	BINAP (20)	$(PhCO_2)_2$	39
8	1,10-phenanthroline (20)	$(PhCO_2)_2$	44
9	tpy (20)	$(PhCO_2)_2$	41
10	bpy (20)	$(PhCO_2)_2$	50
11	bpy (30)	$(PhCO_2)_2$	55

[a] Conditions: **1a** (0.2 mmol), **2** (0.48 mmol), $(PhCO_2)_2$ (0.24 mmol), $Cu(OTf)_2$ (10 mol%), and ligand in MeCN (2.0 mL) at RT for 18 h under argon. [b] Yield of isolated product. $T^+BF_4^-$ = 2,2,6,6-tetramethylpiperidine-1-oxoammonium tetrafluoroborate. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. tpy = 2,2′,2″-terpyridine. bpy = 2,2′-bipyridine.

under these conditions no formation of the desired product **3** occurred and only starting material could be detected in the NMR spectrum. Driven by our experience in the oxidative functionalization of benzylic C–H bonds,[10] we decided to add an oxidant to the reaction media to facilitate the nucleophilic attack at this position. Although the TEMPO oxoammonium salt $T^+BF_4^-$ and *t*BuOOH gave no results, the use of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) allowed the isolation of the desired product **3a** (confirmed by X-ray analysis,[11] see Table 1) in low yield (entries 2–4). The change to the nonprotic peroxide $(PhCO_2)_2$ gave a promising 29% yield (entry 5). To improve the properties and stability of the copper catalyst, different P and N ligands (for full screening see the Supporting Information) were assayed (entries 6–11). From the set of tested ligands (20 mol%), the bidentate bpy provided the best reactivity (entry 10), which was improved when 30 mol% was used (entry 11). Thus, the challenging C–H "activation", insertion, and rearrangement sequence led to the dibenzoxepine **3a** in a good 55% yield, with 41% of the starting material **1a** recovered.

Under these optimized conditions, the scope of the reaction with different substituted xanthene and acridane derivatives **1** was investigated (Table 2). Different electron-donating (MeO, **3b**) and electron-withdrawing groups (F, **3c**) as well as bulkier substituents such as a fused phenyl group (**3d**) were tolerated under these conditions. Nitrogen-containing compounds were next explored. The substitution of the oxygen by a nitrogen atom in **1e**, which possesses a phenylamino group, led to a significant improvement in the yield (75%, **3e**). Considering that most of the bioactive dibenzazepines contain an *N*-alkyl substitution, the methyl- and benzylacridanes **1f** and **1g**[12] were investigated. The reaction proceeded satisfactorily, with an enhanced yield of 74% for the *N*-Me derivative **3f**.[13] The reaction tolerated different substitution with varied electronic properties,

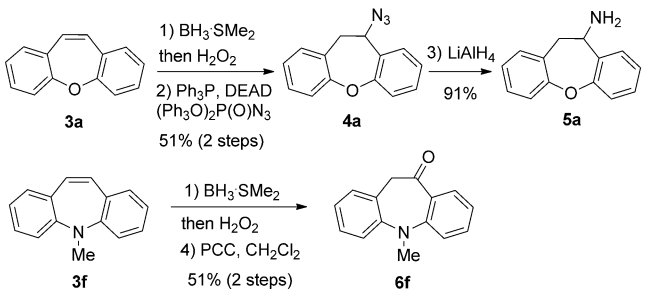
Table 2: Scope of the $Cu(OTf)_2$-catalyzed reaction.[a,b]



[a] Conditions: **1** (0.2 mmol), **2** (0.48 mmol), $(PhCO_2)_2$ (0.24 mmol), $Cu(OTf)_2$ (10 mol%), and bpy (30 mol%) in MeCN (2.0 mL) at RT for 18 h under argon. [b] Yields are of isolated products. [c] Reaction on a 5.0 mmol scale. [d] Reaction in the presence of KF (1.1 equiv). [e] 45% of **1h** recovered. [f] Along with an inseparable by-product.

thereby providing the tricyclic compounds **3i–m** in comparably good yields. Moreover, the less-reactive *N*-Boc-protected acridine **1h** could also be employed, thus providing an easy entry for late deprotection towards a broader scope of substituted derivatives **3**. On the other hand, 9-methyl-substituted acridine showed no reactivity under the standard conditions and **1n** was recovered almost quantitatively. In addition, the sulfur derivative **1o** also gave the tricyclic thio compound **3o**, but in a lower yield. Finally, the reaction was scaled-up to 5 mmol for xanthene **1a** and acridine **1f**, which led to **3a** and **3f** in good yields (65% and 60%, respectively).

The synthetic applicability of the developed method was demonstrated by the further derivatization of **3** (Scheme 2).



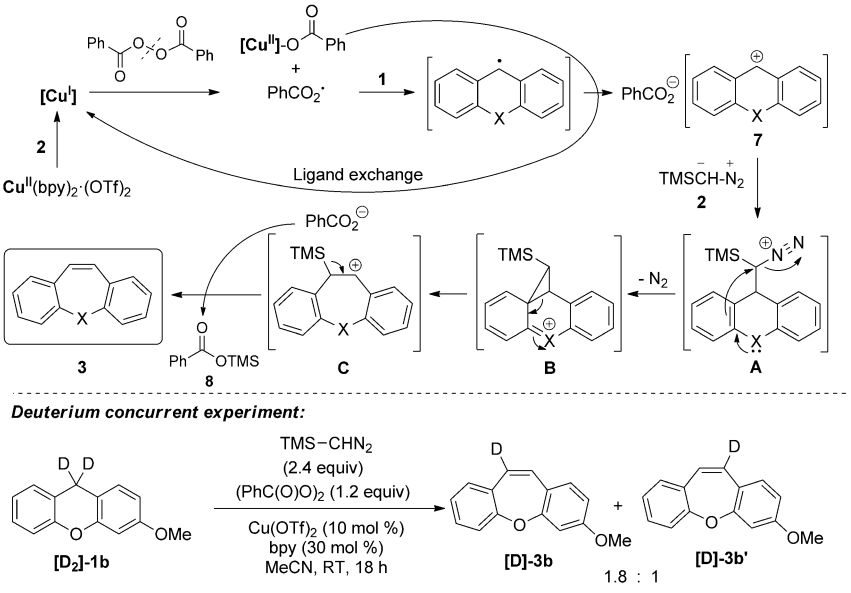
Scheme 2. Derivatization of **3** to important biological products. DEAD = diethyl azodicarboxylate, PCC = pyridinium chlorochromate.

Thus, the synthesis of the amino derivative **5a** with analgesic properties[2b] and an important precursor of cularine-type alkaloids was carried out.[14] Moreover, compound **6f**, an analogue of the potent central nervous system agent oxcarbazepine, was also synthesized from **3f** by a simple two-step hydroboration and oxidation sequence.[15]

The proposed mechanism is outlined in Scheme 3. The initially formed $Cu(bpy)_2$ complex[16] is reduced in situ by the diazoalkane reagent to an active Cu^I species[9] that catalyzed the reductive O–O bond cleavage of the peroxide at room temperature to form the $PhCO_2^{\bullet}$ radical and the corresponding Cu^{II}-carboxylate species.[17] In agreement with Klussman and co-workers as well as other authors,[18] the oxidation of the benzylic position of compounds of general structure **1** takes place next through a two-electron radical oxidation ($H^{\bullet}$ abstraction and further oxidation with the regenerated Cu^{II}) to afford carbocation **7**. The reaction was inhibited by the addition of typical radical scavengers such as BHT (butylated hydroxytoluene) and TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxyl), thus suggesting the participation of a radical intermediate in the formation of **7**. Next, this carbocation (**7**) reacts with the diazo compound **2** to generate an intermediate **A**, which can undergo a ring expansion driven by the exclusion of a nitrogen molecule via the cationic intermediates **B** and **C**. To confirm that the carbocation is an intermediate, compound **7a** was synthesized and isolated following known procedures[19] and treated with trimethylsilyldiazomethane (**2**). The ring-expansion product **3** was then obtained,[20] thereby excluding the participation of carbene species and indicating that **7** is the key intermediate in this transformation. Good evidence for the described mechanism was confirmed by labeling experiments (Scheme 3, bottom). Thus, a 1.8:1 mixture of products [D]-**3b** and [D]-**3b′** were obtained, which was in accordance with the higher electron donation of the methoxy-substituted aromatic ring of $[D_2]$-**1b**.

To achieve a better understanding of the unexpected ring-expansion process, high-level density functional theory calculations in the gas phase were performed. Using the gaussian09 program package,[21] the geometries of the involved compounds and intermediates were optimized with the B3LYP/6-311 + G(d,p) method.[22] The corresponding energies were subsequently refined by calculations at the B2PLYP-D3/def2-TZVP level of theory, including zero-point corrections (Figure 2). The high-energy carbocation **7** reacts with **2** to give the more stable intermediate **A**,[23] which evolves to the cyclopropane **B** through an exothermic intramolecular S_N2-type reaction involving the exclusion of N_2 as a leaving group. A ring expansion takes place to deliver a tricyclic carbocation, which adopts the strained conformation **C** when starting from the energetically most favorable conformer of **A**. Then, **C** relaxes quickly by ring inversion to give **C′**. Elimination of the silicon group delivers the final product **3** with concomitant formation of trimethylsilylbenzoate (**8**). This silyl ester by-product **8** was detected by GC-MS and NMR spectroscopy.

In conclusion, an intermolecular copper(I)-catalyzed oxidative C–H bond functionalization and ring expansion sequence with $TMSCHN_2$ has been developed. The reaction



Scheme 3. Mechanistic proposal and labeling experiment.

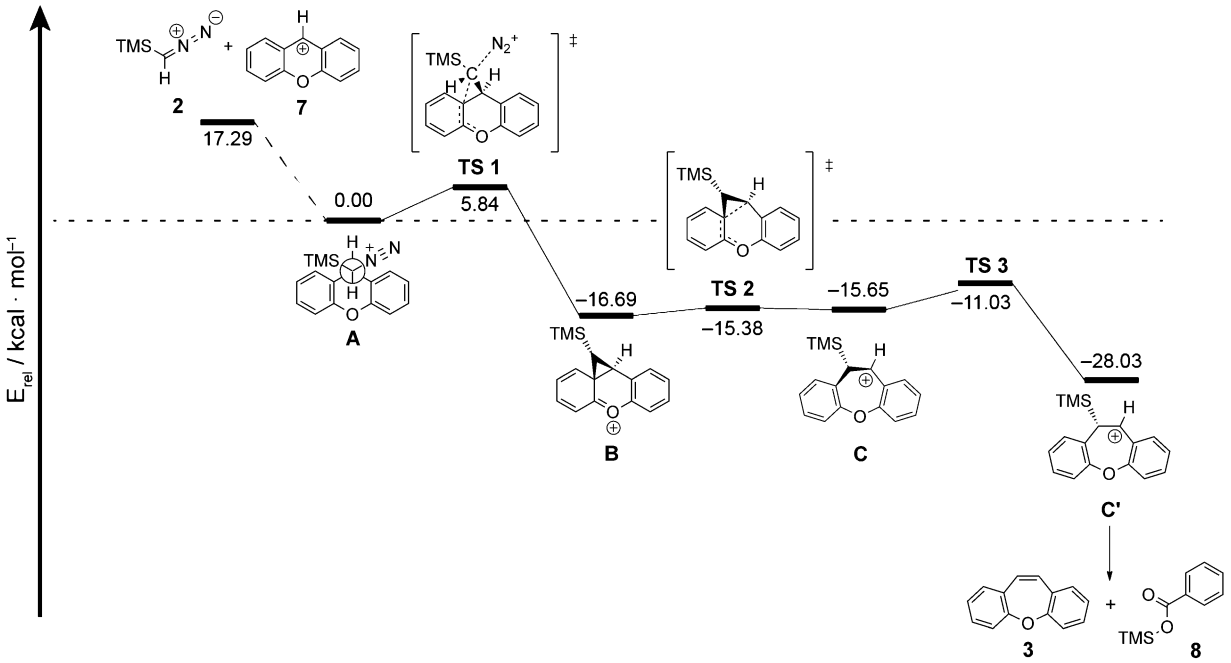


Figure 2. DFT (B2PLYP-D3/def2-TZVP//B3LYP/6-311 + G(d,p)) reaction energy profile in the gas phase. The relative energies [kcal mol^{-1}] are based on the sums of the respective total energies E_{tot} of all species, including nitrogen.

proceeds with high selectivity to form tricyclic dibenzoxepines and dibenzazepines, which are important therapeutic agents.

Keywords: C–H functionalization · copper · heterocycles · ring expansion · $TMSCHN_2$

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Angew. Chem. **2015**, *127*, 5137–5141

[1] For a general chapter on this topic, see a) J. M. Vela, H. Buschmann, J. Holenz, A. Párraga, A. Torrens, *Antidepressants, Antipsychotics, Anxiolytics: From Chemistry and Pharmacology to Clinical Application*, Weinheim, Wiley-VCH, **2007**, p. 248; for the biological properties of metapramine, see b) A. M. Bougerolle, G. Dordain, J. A. Berger, A. Eschalier, *Life Sci.* **1992**, *50*, 161–168; for opipramol, see c) H.-J. Möller, H. P. Volz, L. W. Reimann, K.-D. Stoll, *J. Clin. Psychopharmacol.* **2001**, *21*, 59–65; for maroxepine/eresepine, see d) S. Bischoff, A. Vassout, A. Delini-Stula, P. Waldmeier, *Pharmacopsychiatry* **1986**, *19*, 306–307.

[2] a) A. Michael-Titus, J. Costentine, *Pain* **1987**, *31*, 391–400; b) K. Kawai, *Nippon Yakurigaku Zasshi* **1960**, *56*, 971–983.

[3] W. E. Müller, B. Siebert, G. Holoubek, C. Gentsch, *Pharmacopsychiatry* **2004**, *37*, 189–197.

[4] a) M. M. Kalis, N. A. Huff, *Clin. Ther.* **2001**, *23*, 680–700; b) S. Shorvon, *Seizure* **2000**, *9*, 75–79.

[5] For selected examples based on the Wagner–Meerwein rearrangement, see a) R. J. Stolle, *Prakt. Chem. Naturforsch.* **1922**, *105*, 137–148; b) J. Martinet, A. Dansette, *Bull. Soc. Chim. Fr.* **1929**, *45*, 101–109; c) F. A. Anet, P. M. G. Bavin, *Canadian J. Chem.* **1957**, *35*, 1084–1087; d) M. S. Newman, W. H. Powell, *J. Org. Chem.* **1961**, *26*, 812–815; e) Z. Razavi, F. McCapra, *Luminescence* **2000**, *15*, 239–244; f) E.-C. Elliott, E. R. Bowkett, J. L. Maggs, J. Bacsa, B. K. Park, S. L. Regan, P. M. O'Neill, A. V. Stachulski, *Org. Lett.* **2011**, *13*, 5592–5595; for a ring-closing metathesis approach, see g) T. Matsuda, S. Sato, *J. Org. Chem.* **2013**, *78*, 3329–3335, and references therein.

[6] For selected examples, see a) K. Chiba, H. Tagaya, M. Karasu, T. Ono, M. Kugiya, *Chem. Lett.* **1990**, 39–42; b) T. Storz, E. Vangrevelinghe, P. Dittmar, *Synthesis* **2005**, 2562–2570; see also Ref. [4f].

[7] Y. Wu, J. P. Sanderson, J. Farrell, N. S. Drummond, A. Hanson, E. R. Bowkett, N. G. Berry, A. V. Stachulski, S. E. Clarke, W. J. Pichler, M. Piromohamed, B. K. Park, D. J. J. Naisbitt, *J. Allergy Clin. Immunol.* **2006**, *118*, 233–241.

[8] X. Zhao, Y. Zhang, J. Wang, *Chem. Commun.* **2012**, *48*, 10162–10173.

[9] For practical and stability issues, $Cu(OTf)_2$ was used as the stable Cu^I precursor. Moreover, CuOTf proved to be less efficient than $Cu(OTf)_2$ (see the Supporting Information). For the reduction of $Cu^{II}(OTf)_2$ to Cu^I with CH_2N_2, see R. G. Salomon, J. K. Kochi, *J. Am. Chem. Soc.* **1973**, *95*, 3300–3310.

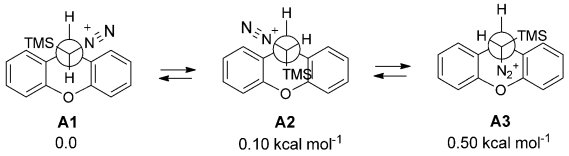
[10] See, for example: a) H. Richter, R. Fröhlich, C. G. Daniliuc, O. García Mancheño, *Angew. Chem. Int. Ed.* **2012**, *51*, 8656–8660; *Angew. Chem.* **2012**, *124*, 8784–8788; b) H. Richter, R. Rohlmann, O. García Mancheño, *Chem. Eur. J.* **2011**, *17*, 11622–11627; c) H. Richter, O. García Mancheño, *Eur. J. Org. Chem.* **2010**, 4460–4467.

[11] See the Supporting Information for the X-ray crystal structure data of **3a** (CCDC 1001790 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.).

[12] **1f** can also be prepared in large amounts from *N*-methylacridone by reduction with BH_3 or $LiAlH_4$: a) J. Shi, X. Zhang, D. C. Neckers, *J. Org. Chem.* **1992**, *57*, 4418–4421; b) A. Mustafa, W. Asker, M. E. El-Din Sobhy, *J. Am. Chem. Soc.* **1955**, *77*, 5121–5124. See also the Supporting Information.

[13] Dibenzazepine **3f** was obtained under the standard conditions in 67% yield, which was improved to 74% by using of 1.1 equiv of KF as an additive. This effect was not observed for **3e** (NPh) and **3g** (NBn).

[14] A. Garcia, L. Castedo, D. Domínguez, *Tetrahedron* **1995**, *51*, 8585 – 8598.
[15] A Scifinder survey revealed more than 2471 biological studies on this structure: a) N. Kaniwa, Y. Saito, *Ther. Adv. Drug. Saf.* **2013**, *4*, 246; b) E. Kaiser, C. Prasse, M. Wagner, K. Broeder, T. A. Ternes, *Environ. Sci. Technol.* **2014**, *48*, 10208 – 10216; c) D. Kim, J.-H. Seo, E. Joo, L. Yeon, W. Hyang, W. C. Shin, S. B. Hong, *Clin. Neuropharmacol.* **2014**, *37*, 100 – 107; synthetic approaches to oxcarbazepines: d) K. Hirpara, K. Jesunadh, M. K. Sharma, C. H. Khanduri, PCT Int. Appl. WO 2014049550A1 20140403, **2014**, and references therein.
[16] The expected in situ formed precatalyst $Cu(bpy)_2\cdot(OTf)_2$ was preformed by reaction of a 1:2 mixture of $Cu(OTf)_2$ and bpy. This complex was used under standard conditions, and the same result (**3a**, 55%) was obtained as with the preformed and in situ catalyst (see the Supporting Information).
[17] J. K. Kochi, *Organometallic Mechanisms and Catalysis: The Role of Reactive Intermediates in Organic Processes*, Academic Press, New York, **1978**, chap. 4, pp. 50 – 83.
[18] See, for example: a) A. Pintér, A. Sud, D. Sureshkumar, M. Klussmann, *Angew. Chem. Int. Ed.* **2010**, *49*, 5004 – 5007; *Angew. Chem.* **2010**, *122*, 5124 – 5128; b) F. Benfatti, M. Guiteras Cappdevila, L. Zoli, E. Benedetto, P. G. Cozzi, *Chem. Commun.* **2009**, 5919 – 5921; c) B. Zhang, S.-K. Xiang, L.-H. Zhang, Y. Cui, N. Jiao, *Org. Lett.* **2011**, *13*, 5212 – 5215; d) B. Zhang, Y. Cui, N. Jiao, *Chem. Commun.* **2012**, *48*, 4498 – 4500.
[19] See, for example: S. Sugawara, S. Kojima, Y. Yamamoto, *Chem. Commun.* **2012**, *48*, 9735 – 9737.
[20] **7a** was synthesized from **1a** by hydride abstraction with Ph_3CSbCl_6. The isolated rather unstable carbocation **7a** was immediately treated with **2** to give **3a** in good yield. However, the one-pot reaction with the trityl cation and **2** led to **3a** only in trace amounts (< 5%) (see the Supporting Information).
[21] Gaussian 09 (Revision B.01), M. J. Frisch et al., Gaussian, Inc., Wallingford CT, **2010**.
[22] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648 – 5652.
[23] Intermediate **A** is conformationally highly flexible in terms of rotation about the initially formed C–C bond. The three possible conformers present almost degenerate energy levels in the gas phase (B2PLYP-D3/def2-TZVP + ZPE//B3LYP/6-311 + G(d,p) (see below). Both the relative most stable one **A1** and the slightly less favorable **A2** can serve as entry points to similar reaction paths which are equally feasible, but comprise diastereomeric intermediates. For brevity's sake, only the path starting from **A1** is presented. See the Supporting Information for a complete overview of the examined pathways.



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