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Mild, Metal-Free Oxidative Ring-Expansion Approach for the Synthesis of Benzo[*b*]azepines

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Supporting Information

ABSTRACT: Benzo[*b*]azepines are important structural motifs for the pharmaceutical industry. However, their syntheses are usually lengthy, involving several steps, transition-metal catalysts, and/or harsh conditions. A novel, general, mild, and metal-free oxidative ring expansion tandem reaction of hydroquinolines with $TMSCHN_2$ as a versatile soft nucleophile to gain access to these valuable compounds in a simple and straightforward manner is presented.

Benzannulated medium-size *N*-heterocycles are key structural motifs in numerous natural products, pharmaceuticals, and agrochemicals.[1] In particular, 7-membered heterocycles such as benzo[*b*]azepines represent an important class of compounds, because of their broad bioactivity (Figure 1).

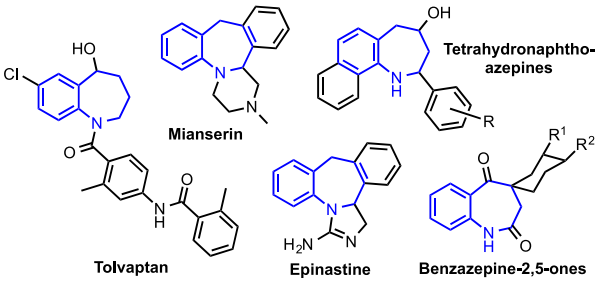
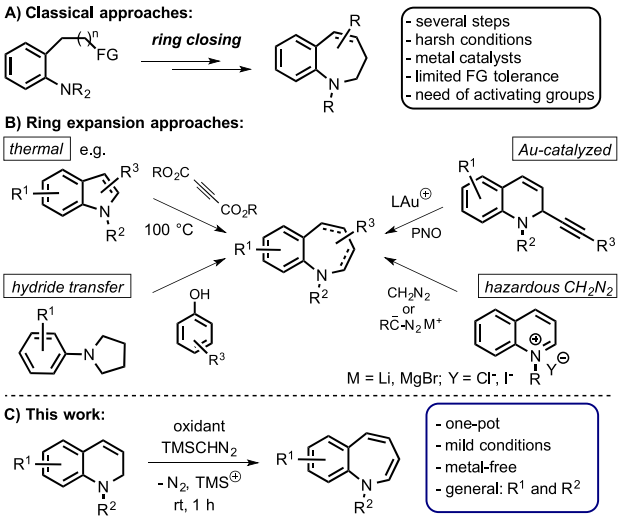


Figure 1. Selected examples of bioactive derivatives.

For example, the benzo[*b*]azepines mianserin[2] and tolvaptan[3] are used as an antidepressant and a diuretic drug, respectively. In addition, epinastine[2] and benzazepinediones[4] are employed as antiallergic and anticancer agents, whereas tetrahydronaphthoazepines show antiparasitic activity.[5]

To gain access to this class of 7-membered heterocyclic compounds, several synthetic strategies have been developed. However, their classical synthesis often requires a multistep ring-closing reaction,[6] including intramolecular aminations,[6a] rearrangements,[6b,c] transition-metal-based catalysts, and harsh conditions (Scheme 1A).[6d−g] Besides these methods, the ring expansion reaction represents a different appealing approach.[7] Consequently, although they are reliant on elaborated precursors, various methods have been reported to gain benzo[*b*]azepines (Scheme 1B), including the thermal ring expansion of dihydroquinolines with azides[7a,b] or indoles with activated acetylenes,[7d] as well as gold-catalyzed[7c] and hydride-transfer[7e]-initiated reactions. In this context, although diazomethane derivatives arose as ideal reagents, it is noteworthy to

Scheme 1. Synthetic Approaches to Benzo[*b*]azepines



mention that the reported to date ring expansion reactions to give rise to benzo[*b*]azepines that rely on the use of hazardous diazomethane (or its Li/Mg salts) and preisolated quinolinium ions, which dramatically limit their synthetic application.[8]

Alternatively, more convenient diazoacetates have been employed in an oxidative, two-step approach with tetrahydroiso-quinolines toward benzo[*d*]azepines. However, this method requires transition metals to induce the last ring-expansion step.[9]

Because of these limitations, our group lately focused on the development of more-convenient methods for the ring expansion of benzo-fused heterocycles. Subsequently, oxidative C−H functionalization[10] of xanthenes, acridanes, and tetrahy-

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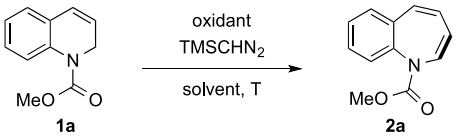
droisoquinolines with $TMSCHN_2$, followed by rearrangement, successfully gave access to the corresponding 7-membered heterocycles.[11] Even though these approaches overcame some of the previously mentioned limitations, they still require either a transition-metal catalyst or high temperatures. Therefore, a simple, mild, and efficient metal-free synthetic approach for the construction of 7-membered heterocycles is still in high demand. Based on this criterion, we herein describe a general methodology for the straightforward synthesis of benzo[*b*]-azepines by a novel, mild and metal-free oxidative C−H bond functionalization/ring expansion tandem reaction from readily available dihydroquinolines (see Scheme 1C).

We started our screening with *N*-methylcarboxylate dihydroquinoline (**1a**)[12,13] as a model substrate for the optimization of the reaction conditions of the metal-free ring expansion with $TMSCHN_2$ (Table 1; see the Supporting Information (SI) for a complete screening).

Table 1. Optimization of the Reaction Conditions with 1a[a]



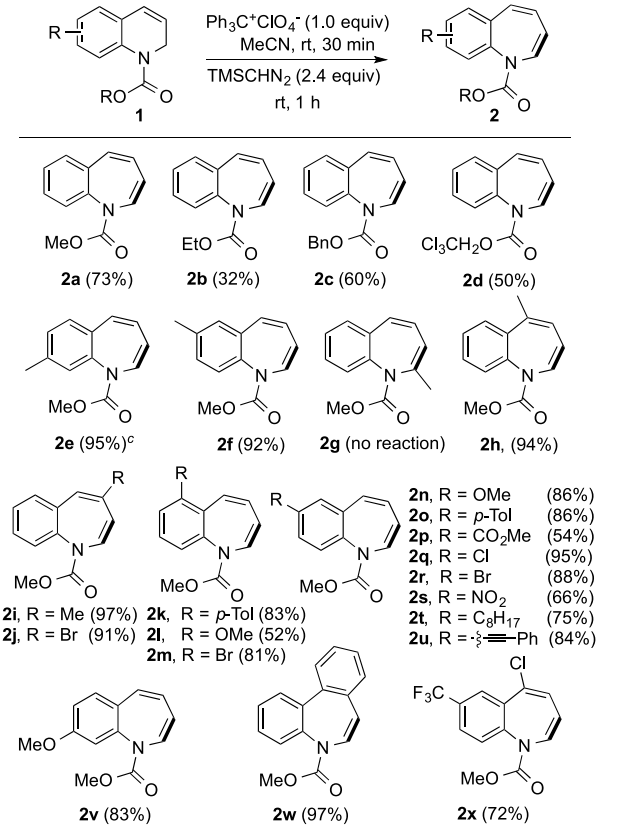
entry	oxidant[b] (equiv)	solvent	temperature (°C)	yield[c] (%)
1	$Ph_3C^+ClO_4^-$ (1.1)	DCM	rt	42 (45)[d]
2	$Ph_3C^+ClO_4^-$ (1.1)	DCM	0	41
3	$Ph_3C^+ClO_4^-$ (1.1)	DCM	50	33
4	$Ph_3C^+BF_4^-$ (1.1)	DCM	rt	22
5	$T^+ClO_4^-$ (1.1)	DCM	rt	45
6	$Ph_3C^+ClO_4^-$ (1.1)	MeCN	rt	51
7	$T^+ClO_4^-$ (1.1)	MeCN	rt	48
8	$Ph_3C^+ClO_4^-$ (1.0)	MeCN	rt	73
9	$Ph_3C^+ClO_4^-$ (1.5)	MeCN	rt	43
10	$Ph_3C^+ClO_4^-$ (1.1)	MeCN	rt	28[e]

[a]**1a** (0.1 mmol, 1.0 equiv) and oxidant were stirred in appropriate solvent (0.1 M) for 30 min at room temperature (rt); $TMSCHN_2$ (2.0 M in Et_2O, 2.4 equiv) was added dropwise and the reaction mixture was stirred for 1 h at the appropriate temperature. [b]T^+ = 2,2,6,6-tetramethyl-1-oxopiperidinium. [c]Isolated yield. [d]The yield of the 16-h reaction is shown in brackets. [e]1.2 equiv of $TMSCHN_2$.

Initially, triphenylmethyl (trityl) perchlorate ($Ph_3C^+ClO_4^-$) was used as a mild, hydride abstractor-type oxidant, providing the desired benzazepine **2a** in a promising 42% yield in the reaction with an excess of $TMSCHN_2$ (2.4 equiv) at room temperature (rt) in dichloromethane (DCM) for 1 h (Table 1, entry 1). A prolonged reaction time of 16 h was tested, giving **2a** in a similar moderate yield of 45% (Table 1, entry 1). Therefore, a reaction time of 1 h was chosen for the following studies. Increasing or decreasing the temperature to 50 °C or 0 °C lead to a decrease of the yield (Table 1, entries 2 and 3). Various mild trityl and 2,2,6,6-tetramethylpiperidinyloxyl (TEMPO) oxoammonium salt-based oxidants were next screened (Table 1, entries 4 and 5), showing the superiority of the perchlorate versus the trifluoroborate salts, as well as a slightly enhanced yield when using $T^+ClO_4^-$, with respect to $Ph_3C^+ClO_4^-$ in DCM (45% vs 42%). To our delight, a solvent screening showed a significant increase of the yield of the ring-expansion reaction with both perchlorate salts when using acetonitrile (MeCN) as the solvent (Table 1, entries 6 and 7), in which $Ph_3C^+ClO_4^-$ provided the best results. Moreover, the equivalents of the oxidant showed great influence on the reaction outcome (Table 1, entries 8 and 9). Thus, **2a** was delightfully obtained in a high yield of 73% by employing just 1.0 equiv of $Ph_3C^+ClO_4^-$ (Table 1, entry 8), while the use of a 1.5 equiv of oxidant led to a notable decrease in yield (43%; see Table 1, entry 9). Also, an excess of the $TMSCHN_2$ reagent was crucial, since the use of 1.2 equiv instead of 2.4 equiv led to a low product yield (28%; see Table 1, entry 10).[14]

Under the optimized conditions (Table 1, entry 8), the scope of the reaction was investigated (see Table 2). A variety

Table 2. Substrate Scope with Dihydroquinolines 1[a,b]



[a]**1** (0.1 mmol, 1.0 equiv) and $Ph_3C^+ClO_4^-$ (1.0 equiv) were stirred in MeCN (0.1 M) for 30 min at rt; $TMSCHN_2$ (2.0 M in Et_2O, 2.4 equiv) was added dropwise and the reaction mixture was stirred for 1 h at rt. [b]Isolated yield. [c]Inseparable 3:1 mixture of 8-/6-Me benzo[*b*]azepines, from the reaction with commercially available **1e** as a 3:1 7-/5-Me isomeric mixture.

of carbamoyl *N*-protecting groups on the dihydroquinoline were first tested. While the ethylcarbamate provided **2b** in an inferior yield of 32%, Cbz- and Troc-protected dihydroquinolines **1c** and **1d** could be efficiently employed in the reaction, leading to the products in a synthetically acceptable yield of 50%−60%.

Next, different substituted *N*-methoxycarbamoyl dihydroquinoline derivatives **1** were explored. Substitution in almost all positions of the dihydroquinoline core were well-tolerated, except for the C2-position, which hampered both the oxidation and the nucleophilic attack of the $TMSCHN_2$ reagent.[15] Thus, the 3- to 7-methyl-substituted benzazepines **2e** and **2f**/**2h** and **2i** were obtained in excellent yields (92%−97%), whereas the reaction of 2-substituted methyl dihydroquinoline **1g** only led to recovery of the starting material, along with decomposition

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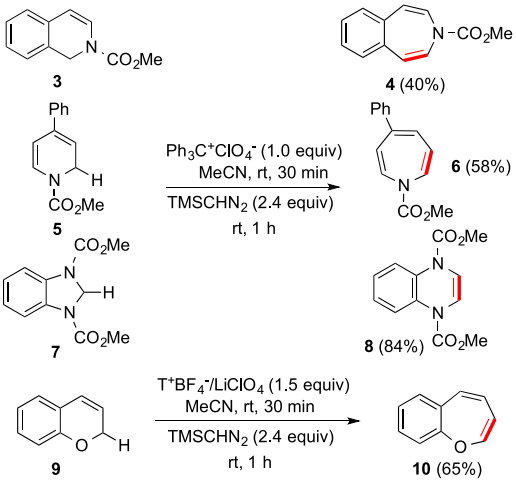
products. Further derivatives carrying other electron-donating groups, such as the methoxy group (**1l**, **1n**, and **1v**; 52%, 86%, and 83%), electron-rich arene substituents (**1k** and **1o**; 83% and 86%), alkynylic (**1u**; 84%), and alkylic (**1t**; 75%) provided the corresponding benzo[*b*]azepines **2** in good yields. When bromo- and chloro-containing derivatives were employed, the benzazepines **2j**, **2m**, **2q**, and **2r** were formed in excellent yields of 81%−95%. Deactivating electron-withdrawing groups such as a carboxylic ester, nitro or trifluoromethyl groups were also tolerated in the ring-expansion reaction, providing **2p**, **2s**, and **2x** in moderate to good yields (54%, 66% and 72% yield, respectively). In addition, the benzo-fused phenantridine derivative **1w** was converted almost completely, giving **2w** in an excellent 97% yield.

The extension of this ring-expansion method to other N- and O-heterocycles was performed next (see Scheme 2). The

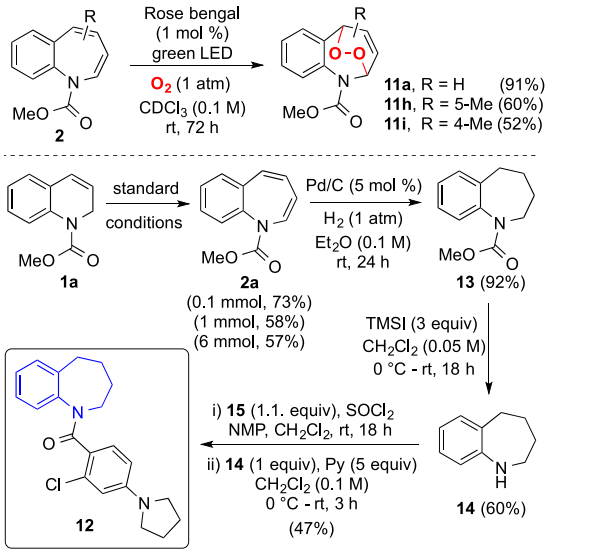
Scheme 2. Ring Expansion of Further N- and O-Heterocycles



expansion of dihydroisoquinoline **3** and the more challenging expansion of dihydropyridines such as 4-phenyl dihydropyridine **5** was also possible under our standard conditions, leading to the corresponding azepines **4** and **6** in yields of 40% and 58%, respectively. To our delight, we were also able to apply the optimized conditions in the ring-expansion reaction of 5- to 6-membered heterocycles. Accordingly, the double N-protected benzimidazole **7** reacted smoothly, giving quinoxaline **8** in 84% yield. Finally, the analogous oxygen-containing heterocycle 2*H*-chromene (**9**) was able to ring-expand to the corresponding benzoxepine **10**;[16] however, a stronger oxidant such as a TEMPO oxoammonium salt was required. In this case, the use of $LiClO_4$ as an additive provided the best results, leading to the product in a good yield of 65% (see the SI for the reoptimization study).

In addition, the derivatization of the obtained benzo[*b*]-azepines was explored (see Scheme 3). To our delight, the ring-expansion reaction could be easily scaled up from 0.1 to 1.0 and 6.0 mmol with only slight detriment of the yield (**2a**, 58 and 57% vs 73%; see Scheme 3). Several endoperoxides **11**, which are valuable precursors for the synthesis of *d*-fused benzo[*b*]azepines with antitumor activity,[17] were then prepared (Scheme 3, top). The Schenck-ene reaction of **2a** using rose bengal as a photosensitizer in order to generate singlet oxygen provided **11a** in an excellent yield of 91%.

Scheme 3. Scale-Up Reaction and Derivatization of 2



Similarly, the reaction of methyl-substituted benzazepines **2h** and **2i** led to the corresponding endoperoxides **11h** and **11i** in moderate yields (52% and 60%, respectively). A further synthetic application of the developed methodology was demonstrated by the synthesis of the tolvaptan-like arginine vasopressin (AVP) receptor agonist **12** (see Scheme 3, bottom).[18] The hydrogenation of **2a** using Pd/C and deprotection with trimethylsilyl iodide (TMSI) provided the intermediate **14**. The final condensation of **14** and the acyl chloride, derived from the appropriate benzoic acid **15**, afforded the desired AVP receptor agonist **12** in 47%.

Considering the mechanism of the one-pot C−H functionalization/ring expansion reaction, two possible pathways for the ring expansion step could be envisioned (see Scheme 4, top). Thus, after hydride abstraction and nucleophilic attack of the diazomethane on the iminium ion intermediate **I**, the formed diazo compound **II** undergoes nitrogen release upon nucleophilic attack of the olefinic carbon in 3-position or the N atom, leading to the cyclopropane cationic intermediate **III** or the aziridinium **IV**, respectively. Subsequent rearrangement and ring expansion results in the formation of the 7-membered cationic intermediate **V** or **VI**, respectively. Finally, release of TMS^+ as the leaving group leads to the formation of benzazepine **2a**. In order to gain some insight into the mechanism of the ring-expansion reaction, both experimental and computational studies were performed. In order to rule out one of the possible pathways for the ring expansion step, the reaction of **1a** with $TMSCDN_2$ (~50% D; see the SI) was performed (Scheme 4, middle). In the case of a high selective reaction, either the 2- or 3-substituted benzazepine should be formed. The ring expansion resulted in the sole formation of the 3-deuterated product **2a-3D** in 32% yield, which is produced from the C-pathway. Moreover, the quantum chemistry calculations[19] at the density functional theory (DFT) level of theory[20] with $TMSCHN_2$ as model nucleophile revealed that both pathways might be possible (Scheme 4, bottom), although it shows that the C-pathway is thermodynamically and kinetically more favored (lower barrier (**TS2**) and more stable than the key intermediate (**III**)) (see the SI for details). Nonetheless, the product obtained via the N-pathway may be also potentially formed because (i) the

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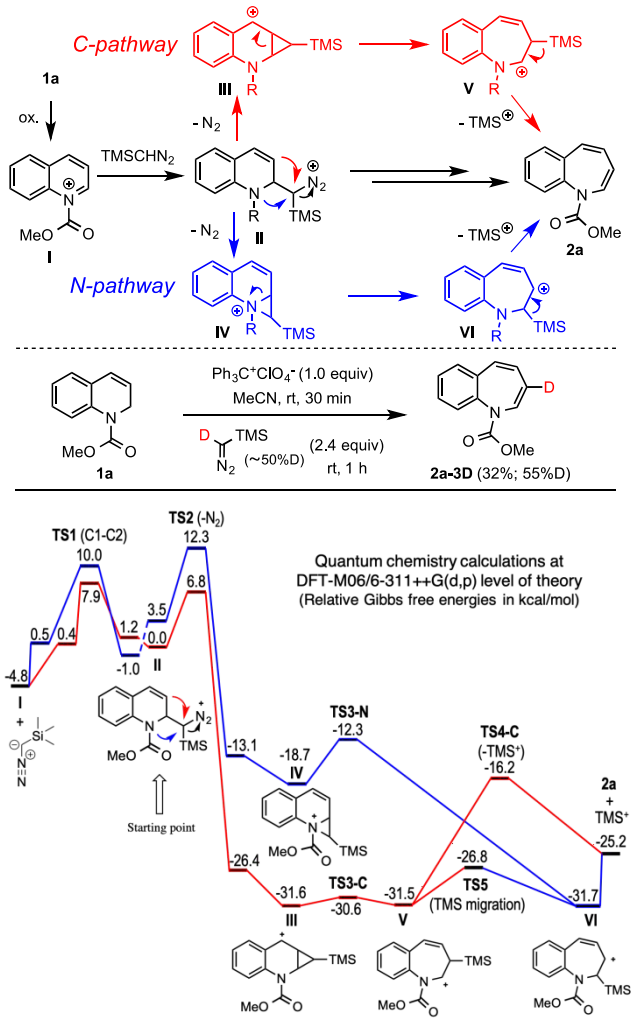
Scheme 4. Mechanistic Considerations



reaction is exothermic and (ii) both mechanisms intercross, i.e., the migration of TMS (**TS5**) leading to the intermediate **VI**.[21]

In conclusion, we have developed a mild, metal-free method for the synthesis of benzo[*b*]azepines via a simple and practical one-pot oxidative C−H functionalization/ring expansion approach using $TMSCHN_2$ as versatile nucleophile bearing two potential leaving groups (N_2 and TMS^+). This method could also be extended to other type of N- and O-heterocycles, as well as applied for the synthesis of interesting synthetic intermediates and bioactive molecules, such as a tolvaptan-like AVP receptor agonist. Moreover, quantum chemistry calculations revealed that two competitive mechanisms for the ring-expansion step are possible, which access energetically similar intermediates (**V** and **VI**) from which the same main product is formed.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01433.

Experimental procedures, characterization data, and NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th Edition; Wiley−Blackwell, 2010. (b) Alvarez-Builla, J.; Vaquero, J. J.; Barluenga, J. *Modern Heterocyclic Chemistry*; Wiley−VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2011.

(2) Roszkowski, P.; Maurin, J. K.; Czarnocki, Z. *Beilstein J. Org. Chem.* **2015**, *11*, 1509−1513.

(3) Kondo, K.; Ogawa, H.; Shinohara, T.; Kurimura, M.; Tanada, Y.; Kan, K.; Yamashita, H.; Nakamura, S.; Hirano, T.; Yamamura, Y.; Mori, T.; Tominaga, M.; Itai, A. *J. Med. Chem.* **2000**, *43*, 4388−4397.

(4) Link, A.; Kunick, C. *J. Med. Chem.* **1998**, *41*, 1299−1305.

(5) Gómez-Ayala, S.; Castrillón, J. A.; Palma, A.; Leal, S. M.; Escobar, P.; Bahsas, A. *Bioorg. Med. Chem.* **2010**, *18*, 4721−4739.

(6) See, for example: (a) Qadir, M.; Priestley, R. E.; Rising, T. W.D.F.; Gelbrich, T.; Coles, S. J.; Hursthouse, M. B.; Sheldrake, P. W.; Whittall, N.; Hii, K. K. *Tetrahedron Lett.* **2003**, *44*, 3675−3678. (b) Gómez Ayala, S.; Stashenko, E.; Palma, A.; Bahsas, A.; Amaro-Luis, J. *Synlett* **2006**, *2006*, 2275−2277. (c) Ikemoto, T.; Ito, T.; Nishiguchi, A.; Miura, S.; Tomimatsu, K. *Org. Process Res. Dev.* **2005**, *9*, 168−173. (d) Fujita, K.-i.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 2785−2788. (e) Qadir, M.; Cobb, J.; Sheldrake, P. W.; Whittall, N.; White, A. J. P.; Hii, K. K. M.; Horton, P. N.; Hursthouse, M. B. *J. Org. Chem.* **2005**, *70*, 1545−1551. (f) Suh, C. W.; Kwon, S. J.; Kim, D. Y. *Org. Lett.* **2017**, *19*, 1334−1337. (g) Wang, R.; Jin, R.-X.; Qin, Z.-Y.; Bian, K.-J.; Wang, X.-S. *Chem. Commun.* **2017**, *53*, 12229−12232.

(7) See, for example: (a) Sato, Y.; Kojima, H.; Shirai, H. *J. Org. Chem.* **1976**, *41*, 3325−3326. (b) Quast, H.; Ivanova, S.; Peters, E.-M.; Peters, K. *Eur. J. Org. Chem.* **2000**, *2000*, 507−520. (c) Chen, M.; Chen, Y.; Sun, N.; Zhao, J.; Liu, Y.; Li, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 1200−1204. (d) Bakthadoss, M.; Kumar, P. V.; Reddy, T. T.; Sharada, D. S. *Org. Biomol. Chem.* **2018**, *16*, 8160−8168. (e) Wang, S.; An, X.-D.; Li, S.-S.; Liu, X.; Liu, Q.; Xiao, J. *Chem. Commun.* **2018**, *54*, 13833−13836.

(8) (a) Morita, M.; Hari, Y.; Aoyama, T. *Synthesis* **2010**, *2010*, 4221−4227. (b) Yadav, J. S.; Reddy, B. V. S.; Gupta, M. K.; Prabhakar, A.; Jagadeesh, B. *Chem. Commun.* **2004**, *40*, 2124−2125.

(9) Xiao, T.; Li, L.; Lin, G.; Mao, Z.-w.; Zhou, L. *Org. Lett.* **2014**, *16*, 4232−4235.

(10) For selected reviews, see: (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215−1292. (b) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362−3374. (c) Girard, S. A.; Knauber, T.; Li, C. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74−100. (d) Narayan, R.; Matcha, K.; Antonchick, A. P. *Chem. - Eur. J.* **2015**, *21*, 14678−14693. (e) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. *Chem. Rev.* **2015**, *115*, 12138−12204. (f) Gini, A.; Brandhofer, T.; García Mancheño, O. *Org. Biomol. Chem.* **2017**, *15*, 1294−1312.

(11) (a) Stopka, T.; Marzo, L.; Zurro, M.; Janich, S.; Würthwein, E.-U.; Daniliuc, C. G.; Alemán, J.; García Mancheño, O. *Angew. Chem., Int. Ed.* **2015**, *54*, 5049−5053. (b) Gini, A.; Bamberger, J.; Luis-Barrera, J.; Zurro, M.; Mas-Ballesté, R.; Alemán, J.; García Mancheño, O. *Adv. Synth. Catal.* **2016**, *358*, 4049−4056.

(12) Kong, D.; Han, S.; Zi, G.; Hou, G.; Zhang, J. *J. Org. Chem.* **2018**, *83*, 1924−1932.

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(13) The reaction of the preformed N-Troc, N-Boc, or N-CO_2Me salts with $TMSCHN_2$ did not lead to the desired benzazepine products.
(14) An excess of $TMSCHN_2$ only provided a small amount of secondary cyclopropanation byproducts that could only be detected via MS (<5%; see the SI).
(15) No example of 8-substituted substrates **1** is presented since they could not be obtained using the standard method (see the SI).
(16) For an alternative method, see: Courant, T.; Pasco, M.; Lecourt, T. *Org. Lett.* **2018**, *20*, 2757−2761.
(17) Link, A.; Kunick, C. *J. Med. Chem.* **1998**, *41*, 1299−1305.
(18) Kondo, K.; Ogawa, H.; Shinohara, T.; Kurimura, M.; Tanada, Y.; Kan, K.; Yamashita, H.; Nakamura, S.; Hirano, T.; Yamamura, Y.; Mori, T.; Tominaga, M.; Itai, A. *J. Med. Chem.* **2000**, *43*, 4388−4397.
(19) Frisch, M. J. et al. *Gaussian 16, Revision B.01*; Gaussian, Inc.: Wallingford, CT, 2016.
(20) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215−241.
(21) The electronically dissimilar *tert*-butyl diazoacetate seems to favor the N-pathway (see the SI), but it might imply a divergent mechanism.

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