Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201800781

Link to VoR: http://dx.doi.org/10.1002/adsc.201800781

10.1002/adsc.201800781

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DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Expedient Synthesis of 1,4-Benzodiazepines via a Tandem Condensation/[1,5]-Hydride Transfer/Cyclization Process

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract: An expedient approach to 1,4-benzodiazepines via a tandem condensation/[1,5]-hydride shift/cyclization process has been developed. This transformation started from readily available *o*-amino benzaldehyde and aminomalonate and was promoted by low-cost $FeCl_3$ with high step and atom economy.

Keywords: [1,5]-hydride shift/cyclization; benzodiazepine; tandem reaction; C(sp^3)-H functionalization; *N*-heterocycle

Benzodiazepines (BDZs), particularly 1,4-benzodiazepines, are present in many natural alkaloids[1] and have long been the center of attention because of their diverse array of pharmacological activities (Figure 1),[2] which make them potential candidates for use in anti-cancer,[2a] anti-infective,[2a,2b] antihypertensive, anxiolytic, hypnotic,[2c] and anti-HIV[2d] drugs. Furthermore, the application of benzodiazepines has been extended to the treatment of bipolar disorder[2e-2g] and chronic back pain.[2h] In addition, structurally many of these drugs and bioactive compounds contain a fused pyrrolidine or dihydropyrrole skeleton. Because of the significance of benzodiazepines, much effort has been devoted to accessing this class of compounds via, for example, the Ugi condensation[3a], Friedel-Crafts reaction[3b], click chemistry,[3c,3d] carboamination,[3e] ring expansion reactions,[3f,3g] and aza-Michael cyclization.[3h] While each of these methods affords a series of benzodiazepines and has great potential utility in the new drug discovery, preparative difficulties and complex operations have restricted their extensive application.[2b] Thus, the development of efficient methods for the construction of the benzodiazepine skeleton still remains a highly desirable yet challenging task.

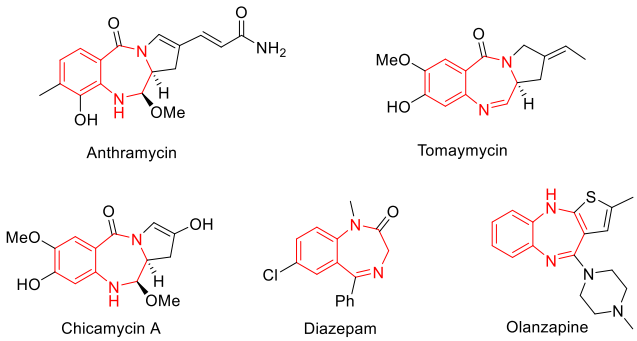

Figure 1. Representative alkaloids and drug molecules containing the benzodiazepine core.

On the other hand, the direct functionalization of a C(sp^3)-H bond by an intramolecular 1,5-hydride transfer/cyclization sequence, which is characterized by an "internal redox" process, has drawn much attention of the synthetic organic chemistry community, as this method can accomlish rapid increase of molecular complexity from simple precursors with high efficiency and excellent step/atom economy.[4] However, there are limited reports[5] on seven-membered ring formation by such C(sp^3)-H bond functionalization, although six-membered ring formation by this reaction sequence is very common. In particular, the synthesis of benzodiazepines with this strategy remains unexplored.

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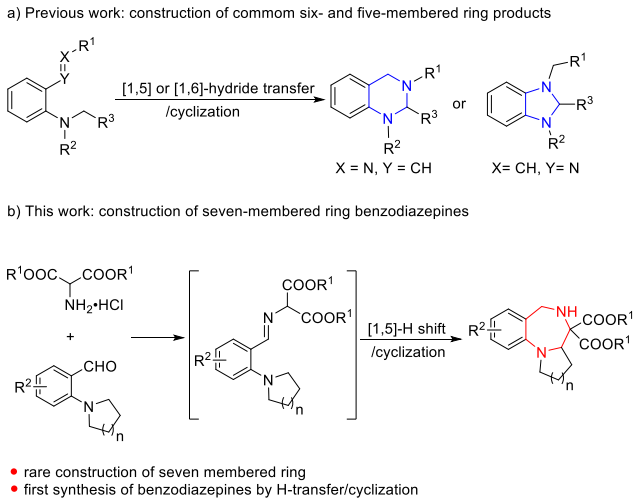
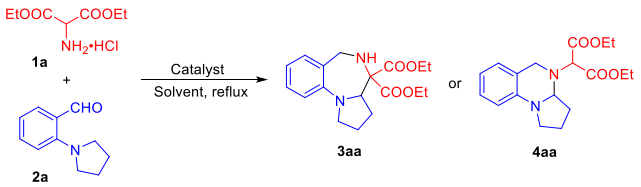


Scheme 1. Strategies for the synthesis of diazacycle via condensation/[1,5]-hydride transfer/cyclization sequences.

In continuation of our interest in the 1,5-hydride transfer/cyclization strategy[6] and as part of our research program on the development of potentially bioactive *N*-heterocyclic systems,[7] we envisioned a one-pot reaction involving acid-catalyzed condensation of aminomalonic acid ester hydrochloride with *o*-amino-substituted benzaldehyde, followed by an intramolecular 1,5-hydride transfer/7-cyclization sequence, to afford multi-substituted benzodiazepines (Scheme 1).

Our study began with the selection of the two-component coupling of diethyl aminomalonate hydrochloride **1a** and 2-(pyrrolidin-1-yl)-benzaldehyde **2a** as a model reaction to identify the optimal reaction conditions (Table 1). Albeit with a low yield of 29%, the initial experiment revealed that substrates **1a** and **2a** could be converted into the desired product **3aa** in ethanol without any extra catalyst (entry 1). In order to improve the product yield, we then screened various catalysts for the model reaction in refluxing ethanol. A brief survey of Brønsted acid catalysts (entries 2-5) showed that **3aa** could be obtained in an acceptable yield of 47%, in 4.5 h, when using 10 mol% diphenyl phosphate (DPP) (entry 5). Some Lewis acids were also tested as catalysts to promote this process (entries 6-14). It was encouraging to find that the reaction catalyzed by the low-cost $FeCl_3$ (10 mol%) proceeded to completion in 3 h and afforded **3aa** with an increased yield of 53% (entry 13). Further investigation was carried out by screening various reaction media and the amounts of solvent and catalyst (entries 15-24). However, owing to the generation of complex, highly polar compounds which are difficult to identify, higher conversion was not obtained. Moreover, we expected that neutralization of HCl in the reaction medium by adding an equivalent amount of $NaHCO_3$ would furnish higher yield (entry 25). Surprisingly, instead of the desired **3aa**, six-membered ring product **4aa** was obtained in a high yield of 84% in this case. The structures of **3aa** and **4aa** were confirmed by the comparative analysis of their ^1H NMR spectra. In the spectrum of **4aa**, a sharp singlet peak assigned to the α-C-H of the malonate moiety appeared at 4.41 ppm, while for **3aa** a diagnostic broad singlet signal assigned to the N-H moiety appeared at 3.43 ppm. In addition, the structure of **3aa** was further confirmed by the DEPT technique.

Table 1. Screening of optimal reaction conditions[a)]



Entry	Catalyst	Solvent	t (h)	Yield[b)]
1	--	EtOH	5	29
2	AcOH	EtOH	5	32
3	TsOH	EtOH	4	25
4	TFA	EtOH	3	40
5	DPP	EtOH	4.5	47
6	$Bi(OTf)_3$	EtOH	10	--
7	$Cu(OTf)_2$	EtOH	10	--
8	$La(OTf)_3$	EtOH	10	21
9	$Zn(OTf)_3$	EtOH	4	40
10	$Yb(OTf)_2$	EtOH	3	46
11	$SnCl_4$	EtOH	5	14
12	$ZnCl_2$	EtOH	4	42
13	$FeCl_3$	EtOH	3	53
14	$BF_3{\cdot}Et_2O$	EtOH	5	47
15	$FeCl_3$	DCE	20	23
16	$FeCl_3$	toluene	10	trace
17	$FeCl_3$	THF	10	trace
18	$FeCl_3$	dioxane	10	trace
19	$FeCl_3$	MeCN	6	23
20	$FeCl_3$	*i*-PrOH	4	48
21[c)]	$FeCl_3$	EtOH	5	38
22[d)]	$FeCl_3$	EtOH	3	48
23[e)]	$FeCl_3$	EtOH	6	36
24[f)]	$FeCl_3$	EtOH	3	50
25[g)]	--	EtOH	1.5	84[h)]

[a)] All reactions were carried out with **1** (0.48 mmol), **2** (0.40 mmol) in solvent (4.0 mL) at room temperature. After the catalyst (10 mol%) was added, the reaction was heated to reflux until completion of the reaction. [b)] Isolated yield of **3aa**. [c)] Temperature 60 °C. [d)] 20 mol% catalyst. [e)] 5 mol% catalyst. [f)] Solvent 2 mL. [g)] Addition of 0.48 mmol $NaHCO_3$. [h)] Isolated yield of **4aa**.

With the optimal reaction conditions in hand, we next focused on the generality of the 1,5-hydride transfer/7-*endo* cyclization process. First, we carried out the reaction of tertiary amino benzaldehydes **2** with diethyl aminomalonate hydrochloride **1a** to examine the substrate scope (Scheme 2). The reaction outcome suggested that substrates bearing halogen, alkyl, alkynyl, or aryl substituents at the 4-position of the benzene ring successfully underwent the reaction to form the desired products in 50%-61% yields (Scheme 2, **3ab**-**3af**). Moreover, substrates with

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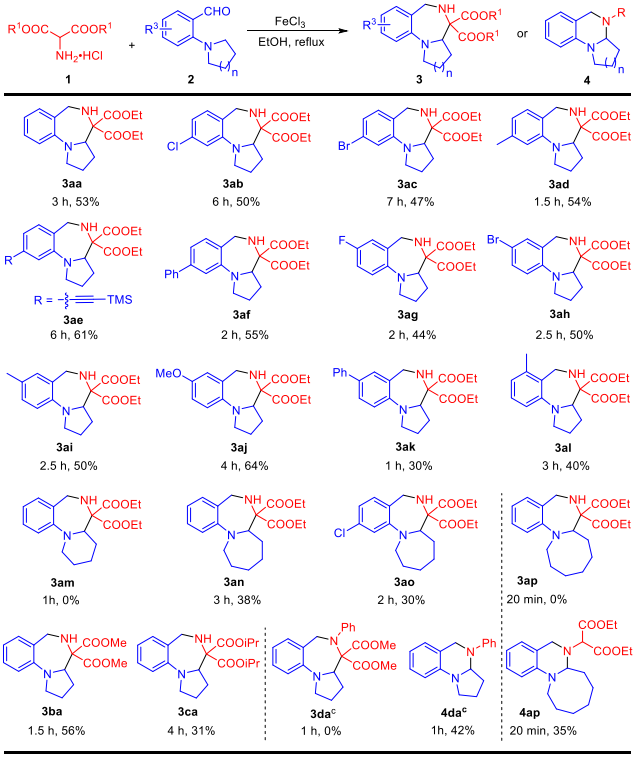
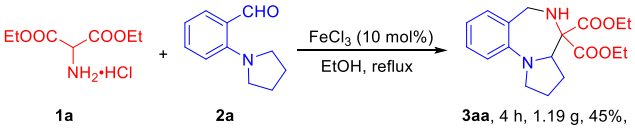
substituents of halogen, alkyl, alkoxyl, and aryl at the 5-position could also be smoothly transformed into the corresponding products in 30-64% yields (**3ag-3ak**). The substrates with a halogen groups showed high reaction efficiency probably because of the electron-withdrawing effect in the condensation step. Next, a methyl group was introduced to the 6-position of the *o*-amino benzaldehyde, and the desired product **3al** was successfully formed in 40% yield. To further broaden the scope of this reaction, related larger-membered azacyclic substrates were employed. However, owing to the generation of some complex by-products, the reaction of diethyl aminomalonate hydrochloride **1a** and 2-(piperidin-1-yl)benzaldehyde **2m** could not afford the desired product **3am.** But excitedly, when the tertiary amino benzaldehyde was changed to 2-(azepan-1-yl)benzaldehydes (**2n** and **2o**), the target products **3an** and **3ao** were obtained in 38% and 30% yield, respectively. In addition, eight-membered azacyclic substrate **2p** was also tried in this reaction. Interestingly, instead of the seven-membered ring product **3ap**, the six-membered ring product **4ap** was obtained in 35% yield.



Scheme 2. Substrate scope of aminomalonic acid esters and *o*-amino-substituted benzaldehydes[a, b] [a] The reaction was carried out on a 0.4 mmol scale with $FeCl_3$ (10 mol %) in 4.0 mL EtOH, the ratio of **1**/**2** was 1.2/1. [b] Isolated yields. [c] The reaction was carried out with 2-(phenylamino)malonate (**1d**) and 2-(pyrrolidin-1-yl)-benzaldehyde (**2a**) as the substrates.

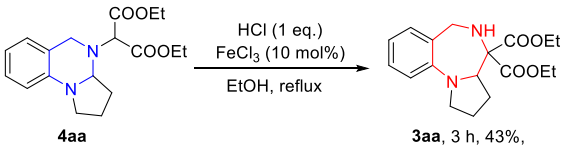
Further extension of the substrate scope was then attempted by focusing on amino malonic ester **1**. Both dimethyl and diisopropyl aminomalonic esters were tolerated in the H-shift/7-*endo* ring closure with **2a**, affording the corresponding **3ba** and **3ca** in 56% and 31% yield, respectively. The slightly lower yield of **3ca** as compared to that of **3aa** and **3ba** was probably due to steric hindrance from the isopropyl group. Next, a phenyl group was introduced to the amine moiety of the diethyl aminomalonate substrate. Surprisingly, instead of seven-membered-ring product **3da**, the demalonate product **4da** was obtained in 42% yield.[8] And the structure of **4da** was verified by comparing to the reported ^1H and ^{13}C NMR spectra.[8a]

To demonstrate the practical utility of the 1,5-hydride shift/7-cyclization process, a gram-scale reaction of **1a** (9.6 mmol) with **2a** (8.0 mmol) was conducted, and the desired product **3aa** (1.19 g, 3.6 mmol) was obtained with 45% yield in 4 h (Scheme 3).

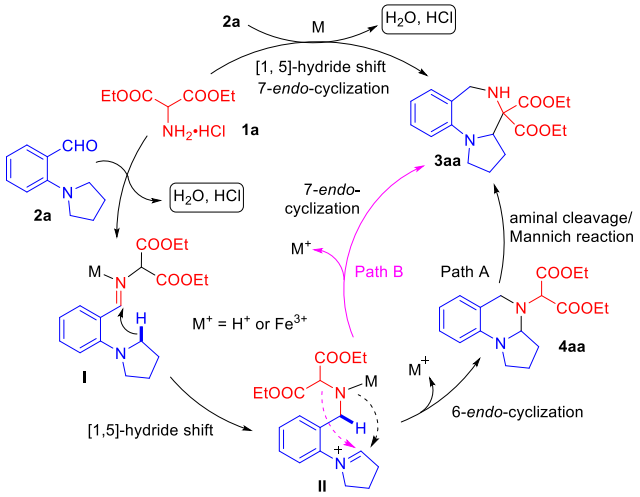


Scheme 3 Gram scale synthesis of **3aa**.

During the course of the reaction process, it was observed that the six-membered aminal prodcut **4aa** was initially formed in large amount, which gradually disappeared with the accumulation of diazepine **3aa**. In order to prove the possibility of the rearrangement of **4aa** to **3aa**, the aminal **4aa** was exposed to equiequivalent hydrochloric acid and 10 mol% $FeCl_3$ in refluxing EtOH. As a result, interestingly, benzodiazepine **3aa** was obtained in 43% yield (Scheme 4). Based on this result, a plausible mechanism for the formation of benzodiazepine **3aa** was proposed and depicted in Scheme 5. First, with the activation by the acid promoter, diethyl aminomalonate hydrochloride (**1a**) reacts with 2-(pyrrolidin-1-yl)benzaldehyde (**2a**) to form the Schiff base **I** by condensation. Then, with the activation of the imine by ferric chloride, the key hydride transfer occurs, followed by [1,6]-*endo*-cyclization to give the six-membered ring product **4aa**, which then rearranged to the azepine product **3aa** through cleavage of the aminal moiety and the ensuing Mannich procedure (Path A). On the other hand, the direct 7-*endo*-cyclization from intermediate **II** might also occur to give straightforwardly the diazepine product **3aa** (Path B).



Scheme 4. Transformation of **4aa** to **3aa**.



Scheme 5. Proposed mechanism for the construction of **3aa**.

In conclusion, we have developed a new strategy for the direct synthesis of benzodiazepines via a sequential condensation/[1,5]-hydride shift/cyclization process by using an inexpensive catalyst $FeCl_3$, featuring high step and atom economy. With this concise strategy, benzodiazepines of potential pharmaceutical relevance with a novel structure can be readily obtained in synthetically useful yields (30%-64%). The reaction has an extensive substrate scope and can afford the desired product on a gram scale. Additional efforts to realize similar versions of H-shift/7-*endo*-cyclization with a diverse range of hydride acceptors are ongoing in our laboratory, and the results will be reported in due course.

Experimental Section

General procedure for the synthesis of products 3

To a solution of **1** (0.48 mmol) and **2** (0.40 mmol) in EtOH (4.0 mL), $FeCl_3$ (10 mol%) was added, then the reaction mixture was refluxed until completion (monitored by TLC). After purification by column chromatography on silica gel (ethyl acetate/petroleum ether = 1:5 as eluent), benzodiazepine product **3** was obtained.

Acknowledgements

We thank the Fundamental Research Funds for the Central Universities (DUT18LAB16) for support of this work.

References

[1] a) A. Witt, J. Bergman, *J. Org. Chem.* **2001**, *66*, 2784-2788; b) R. Ookura, K. Kito, T. Ooi, M. Namikoshi, T. Kusumi, *J. Org. Chem.* **2008**, *73*, 4245-4247; c) C.-M. Cui, X.-M. Li, C.-S. Li, H.-F. Sun, S.-S. Gao, B.-G. Wang *Helv. Chim. Acta* **2009**, *92*, 1366-1370; d) G. Yang, X. Siwe, A. Lertou, *Nat. Prod. Sci.* **2009**, *15*, 130-133.

[2] a) J. K. Annor-Gyamfi, J. M. Jarrett, J. O. Osazee, D. Bialonska, C. Whitted, V. E. Palau, A. G. Shilabin, *Heliyon* **2018**, *4*, e00539; b) O. A. Attanasi, L. D. Crescentini, G. Favi, F. Mantellini, S. Nicolini, *J. Org. Chem.* **2011**, *76*, 8320-8328; c) G. Colussi, C. Catena, D. Darsiè, L. A. Sechi, *Am. J. Hypertens.* **2018**, *31*, 402-404; d) W. Ho, M. J. Kukla, H. J. Breslin, D. W. Ludovici, P. P. Grous, C. J. Diamond, M. Miranda, J. D. Rodgers, C. Y. Ho, E. D. Clercq, R. Pauwels, K. Andries, M. A. C. Janssen, P. A. J. Janssen, *J. Med. Chem.* **1995**, *38*, 794-802; e) C.-M. Chang, C.-S. Wu, Y.-W. Huang, Y.-L. Chau, H.-J. Tsai, *J. Clin. Psychopharm.* **2016**, *36*, 32-44; f) L. Bjørklund, H. T. Horsdal, O. Mors, S. D. Østergaard, C. Gasse, *Acta Neuropsychiatr.* **2016**, *28*, 75-84; g) L. Wingård, H. Taipale, J. Reutfors, A. Westerlund, R. Bodén, J. Tiihonen, A. Tanskanen, M. Andersen, *Bipolar Disord.* DOI: org/10.1111/bdi.12626; h) M. A. F. García, A. O. L. Lima, I. Ferrer Lopez, C. Bermúdez-Tamayo, *J. Clin. Psychopharm.* **2018**, *11*: 1.

[3] a) U. K. Sharma, N. Sharma, D. D. Vachhani, E. V. Van Eycken, *Chem. Soc. Rev.* **2015**, *44*, 1836-1860; b) J. Yang, X. Che, Q. Dang, Z. Wei, S. Gao, X. Bai, *Org. Lett.* **2005**, *7*, 1541-1543; c) D. K. Mohapatra, P. K. Maity, M. Shabab, M. I. Khan, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5241-5245; d) J. R. Donald, S. F. Martin, *Org. Lett.* **2011**, *13*, 852-855; e) J. D. Neukom, A. S. Aquino, J. P. Wolfe, *Org. Lett.* **2011**, *13*, 2196-2199; f) L. Loudni, J. Roche, V. Potiron, J. Clarhaut, C. Bachmann, J.-P. Gesson, I. Tranoy-Opalinski, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4819-4823; g) A. C. Araújo, F. Nicotra, C. Airoldi, B. Costa, G. Giagnoni, P. Fumagalli, L. Cipolla, *Eur. J. Org. Chem.* **2008**, *2008*, 635-639; h) R. A. D. Silva, S. Santra, P. R. Andreana, *Org. Lett.* **2008**, *10*, 4541-4544; i) M. Yar, E. M. McGarrigle, V. K. Aggarwal, *Org. Lett.* **2009,** *11*, 257-260.

[4] a) S. J. Pastine, K. M. McQuaid, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 12180-12181; b) S. Murarka, I. Deb, C. Zhang, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 13226-13227; c) Y. K. Kang, S. M. Kim, D. Y. Kim, *J. Am. Chem. Soc.* **2010**, *132*, 11847-11849; d) Z.-W. Jiao, S.-Y. Zhang, C. He, Y.-Q. Tu, S.-H. Wang, F.-M. Zhang, Y.-Q. Zhang, H. Li, *Angew. Chem., Int. Ed.* **2012**, *51*, 8811-8815; e) M. C. Haibach and D. Seidel, *Angew. Chem., Int. Ed.* **2014**, *53*, 5010-5036; f) L. Wang and J. Xiao, *Adv. Synth. Catal.* **2014**, *356*, 1137-1171; g) L. Wang and J. Xiao, *Top. Curr. Chem.* **2016**, *374*, 17; h) L. Wang and J. Xiao, *Org. Chem. Front.* **2016**, *3*, 635-638; i) Y.-W. Huang, A. J. Frontier, *Org. Lett.* **2016,** *18*, 4896-4899; j) S. Zhu, C. Chen, M. Xiao, L. Yu, L. Wang and J. Xiao, *Green Chem.* **2017**, 19, 5653-5658; k) M. Xiao, S. Zhu, Y. Shen, L. Wang and J. Xiao, *Chin. J. Org. Chem.* **2018**, *38*, 328-340.

[5] a) G. Zhou, J. Zhang, *Chem. Commun.* **2010**, *46*, 6593-6595; b) G. Zhou, F. Liu, J. Zhang, *Chem. Eur. J.* **2011**, *17*, 3101-3104; c) M. C. Haibach, I. Deb, C. K. De, D. Seidel, *J. Am. Chem. Soc.* **2011**, *133*, 2100-2103; d) K. Mori, K. Kurihara, S. Yabe, M. Yamanaka, T. Akiyama,

10.1002/adsc.201800781

J. Am. Chem. Soc. **2014**, *136*, 3744-3747; e) Y.-Z. Chang, M.-L. Li, W.-F. Zhao, X. Wen, H. Sun, Q.-L. Xu, *J. Org. Chem.* **2015**, *80*, 9620-9627; f) C. W. Suh, S. J. Kwon, D. Y. Kim, *Org. Lett.* **2017**, *19*, 1334-1337; g) S.-S. Li, L. Zhou, L. Wang, H. Zhao, L. Yu, J. Xiao, *Org. Lett.* **2018**, *20*, 138-141.

[6] a) T. Zhao, H. Zhang, L. Cui, J. Qu, B. Wang, *RSC Adv.* **2015**, *5*, 86056-86060; b) T. Zhao, H. Zhang, L. Cui, C. Wang, J. Qu, B. Wang, *ChemistrySelect* **2016**, *1*, 3713-3717.

[7] a) G. Zhu, B. Wang, X. Bao, H. Zhang, Q. Wei, J. Qu, *Chem. Commun.* **2015**, *51*, 15510-15513; b) Q. Wei, G. Zhu, H. Zhang, J. Qu, B. Wang, *Eur. J. Org. Chem.* **2016**, 5335-5339; c) G. Zhu, S. Wu, X. Bao, L. Cui, Y. Zhang, J. Qu, H. Chen, B. Wang, *Chem. Commun.* **2017**, *53*, 4714-4717; d) G. Zhu, S. Liu, S. Wu, L. Peng, J. Qu, B. Wang, *J. Org. Chem.* **2017**, *82*, 4317-4327; e) G. Zhu, Q. Wei, H. Chen, Y. Zhang, W. Shen, J. Qu, B. Wang, *Org. Lett.* **2017**, *19*, 1862-1865; f) S. Wu, G. Zhu, S. Wei, H. Chen, J. Qu, B. Wang, *Org. Biomol. Chem.* **2018**, *16*, 807-815; g) L. Cui, G. Zhu, S. Liu, X. Bao, X. Zhao, J. Qu and B. Wang, *Tetrahedron* **2018**, *74*, 2369-2375; (h) L. Cui, G. Zhu, S. Liu, X. Zhao, J. Qu and B. Wang, *J. Org. Chem.* **2018**, *83*, 5044-5051. i) X. Bao, S. Wei, X. Qian, J. Qu, B. Wang, L. Zou, G. Ge, *Org. Lett.* **2018**, *20*, 3394-3398.

[8] a) C. Zhang, S. Murarka and D. Seidel, *J. Org. Chem.* **2009**, *74*, 419-422. b) See Scheme S1 in the Supporting Information for a proposed mechanism of this case.

10.1002/adsc.201800781

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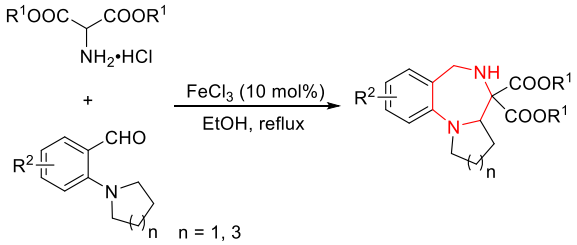

- rare construction of seven-membered ring
- first synthesis of benzodiazepines by hydride transfer/cyclization