Accessing substituted pyrrolidines via formal [3+2] cycloaddition of 1,3,5-triazinanes and donor-acceptor cyclopropanes

Zhi-Yao Chu, Na Li, Dan Liang, Zheng-Hui Li, Yong-Sheng Zheng, Ji-Kai Liu

PII: S0040-4039(18)30028-5
DOI: https://doi.org/10.1016/j.tetlet.2018.01.016
Reference: TETL 49603

To appear in: *Tetrahedron Letters*

Received Date: 21 November 2017
Revised Date: 2 January 2018
Accepted Date: 5 January 2018

Please cite this article as: Chu, Z-Y., Li, N., Liang, D., Li, Z-H., Zheng, Y-S., Liu, J-K., Accessing substituted pyrrolidines via formal [3+2] cycloaddition of 1,3,5-triazinanes and donor-acceptor cyclopropanes, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.01.016

Tetrahedron Letters
journal homepage: www.elsevier.com

Accessing substituted pyrrolidines via formal [3+2] cycloaddition of 1,3,5-triazinanes and donor-acceptor cyclopropanes

Zhi-Yao Chu, Na Li, Dan Liang, Zheng-Hui Li, Yong-Sheng Zheng* and Ji-Kai Liu*

School of Pharmaceutical Sciences, South-Central University for Nationalities, Wuhan, 430074, China.

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Pyrrolidines
3+2 Cycloaddition
Donor-acceptor cyclopropanes
1,3,5-triazinanes

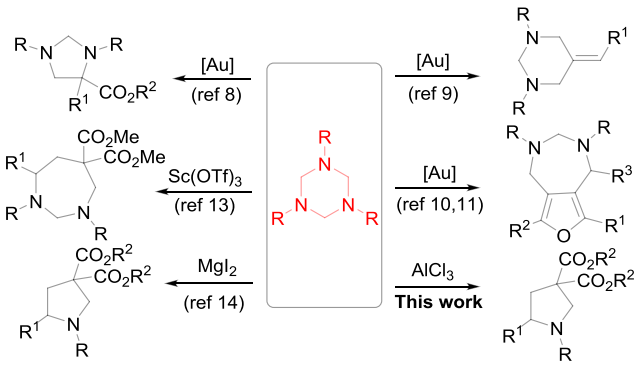
ABSTRACT

The formal [3+2] cycloaddition of 1,3,5-triaryl-1,3,5-triazinanes with donor-acceptor cyclopropanes has been found to provide pyrrolidines in good to excellent yields under mild reaction conditions. Preliminary mechanistic investigation indicates that this formal [3+2] cycloaddition reaction proceeds through competing S_N1 and S_N2 pathways.

Pyrrolidines are one of the most ubiquitous building blocks for a large number of natural products, pharmaceuticals and biologically active compounds.[1] They are also widely used as the core structure of synthetic catalysts.[2] Consequently, highly efficient strategies have been developed to construct pyrrolidine motifs.[3] Among the myriad of developed frameworks, the [3+2] cycloaddition of donor-acceptor cyclopropanes with various nitrogen-containing dipoles offers the most straightforward method and has received considerable attention with respect to atom economy and efficiency.[4] For example, Moshkin and co-workers employed spiroanthraceneoxazolidine as a synthetic equivalent of methanimine in the reaction with donor-acceptor cyclopropanes to afford pyrrolidines.[5]

1,3,5-Triaryl-1,3,5-triazinanes, which are readily available from the condensation of paraformaldehyde and various arylamines, are well-known as precursors of corresponding *N*-aryl formaldimines in the aminomethylation reactions with various nucleophiles in the presence of Lewis acids.[6] During the past few years, 1,3,5-triazinanes have attracted increasing attention in the synthesis of *N*-containing compounds due to their combination of nucleophilicity of the nitrogen atom and electrophilicity of the imine carbon. For example, Krische described the Ruthenium-catalyzed hydroaminomethylation of allenes/dienes by using 1,3,5-triazinanes as the surrogate of formaldimines.[7] Feng and co-workers reported the asymmetric Mannich-type reaction between *β*-keto-esters/amides and 1,3,5-triazinanes, in which 1,3,5-triazinanes were involved as bench stable Mannich reagents.[8]

Different from these aminomethylation protocols, triazinanes were also employed as dipolar adducts in cycloadditions to synthesize heterocycles (Scheme 1). For example, Sun and co-workers described gold-catalyzed [4+1]/[4+3] cycloaddition reactions of triazinanes with diazo esters to construct five- and seven-membered heterocycles.[9] Soon after, the same group reported [2+2+2] annulations of 1,3,5-triazinanes with functionalized allenes to provide the six-membered heterocycles.[10] In addition, Xu[11] and Sun[12] et al. developed the gold catalyzed [3+2+2] tadem dual heterocyclization reaction of



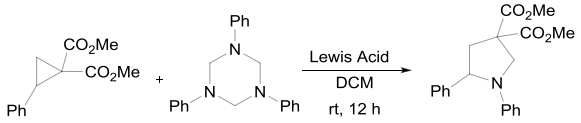
Scheme 1. Cycloadditions of 1,3,5-triazinanes

* Corresponding author.
E-mail adress: zhysh@mail.scuec.edu.cn (Y.-S. Zheng),
jkliu@mail.kib.ac.cn (J.-K. Liu)

enynones with 1,3,5-triazinanes to prepare 3,4-fused bicyclic furan compounds, respectively. Werz reported the aza-[3+4] cycloaddition reactions of 1,3,5-triazinanes with donor-acceptor cyclopropanes to obtain seven-membered heterocycles.[13] During our preparation of this paper, the [3+2]/[4+2] cycloadditions of 1,3,5-triazinanes were disclosed by Werz to synthesize pyrrolidines and piperidines in the presence of MgI_2.[14] We herein describe the formal [3+2] cycloaddition of 1,3,5-triazinanes with donor-acceptor cyclopropanes catalyzed by $AlCl_3$, expediently delivering pyrrolidines in good to excellent yields under mild reaction conditions through competing S_N1 and S_N2 pathways. (**Scheme 1**).

In our preliminary screening, the donor-acceptor cyclopropane **1a** and 1,3,5-triphenyl-1,3,5-triazinane **2a** were chosen as the model substrates to optimize the reaction conditions. Initially, the catalytic effects of Lewis acids on the cycloaddition reaction were evaluated in CH_2Cl_2 at room temperature. To our satisfaction, in the presence of 20 mol% $AlCl_3$, the desired product **3aa** was obtained in 70% isolated yield (**Table 1**, entry 1). However, other Lewis acids, such as $ZnCl_2$, $FeCl_3$ and $CuCl_2$, failed to catalyze the transformation even with prolonged time (**Table 1**, entries 2-4). $Cu(OTf)_2$ was also ineffective, and yielded only a trace amount of product by TLC analysis (**Table 1**, entry 5). $Sc(OTf)_3$ afforded full conversion of cyclopropane 1a, but delivered a complex mixture with 13% isolated yield (**Table 1**, entry 6). Thus $AlCl_3$ was determined to be the optimal catalyst and used in the subsequent investigation. Then various solvents were evaluated. Methanol and tetrahydrofuran delivered poor yields (**Table 1**, entries 7 and 8). When acetonitrile was used, moderate yield was obtained (**Table 1**, entry 9). Since the acceptable result was obtained in CH_2Cl_2, two other chlorinated solvents were screened to improve the yields. Unfortunately, reactions in dichloroethane and chloroform gave poor yields as well (Table 1, entries 11 and 12). Hence, dichloromethane was identified as the most favorable solvent in this reaction.

Table 1
Optimization of the reaction conditions.[a]



1a 2a 3aa

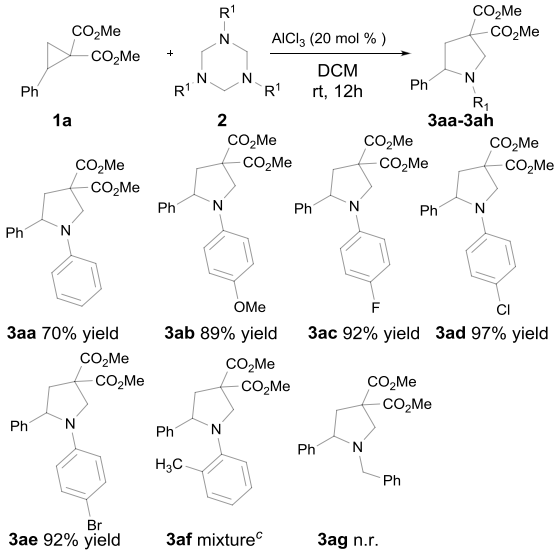
Entry	Lewis acid	Solvent	Time (h)	Yield %
1	$AlCl_3$	DCM	12	70
2	$ZnCl_2$	DCM	48	NR
3	$FeCl_3$	DCM	48	NR
4	$CuCl_2$	DCM	48	NR
5	$Cu(OTf)_2$	DCM	48	Trace
6	$Sc(OTf)_3$	DCM	12	13[c]
7	$AlCl_3$	MeOH	12	38
8	$AlCl_3$	THF	12	28
9	$AlCl_3$	CH_3CN	12	58
10	$AlCl_3$	Toluene	48	NR
11	$AlCl_3$	DCE	12	39
12	$AlCl_3$	$CHCl_3$	12	36

[a] Unless otherwise noted, the reactions were performed with **1a** (0.40 mmol), **2a** (0.40 mmol) and Lewis acid (0.08 mmol) in 4.0 ml solvent.

[b] Isolated yield of the product.

[c] Isolated by preparative thin layer chromatography.

Table 2
Substrate scope of 1,3,5-triazinanes[ab]



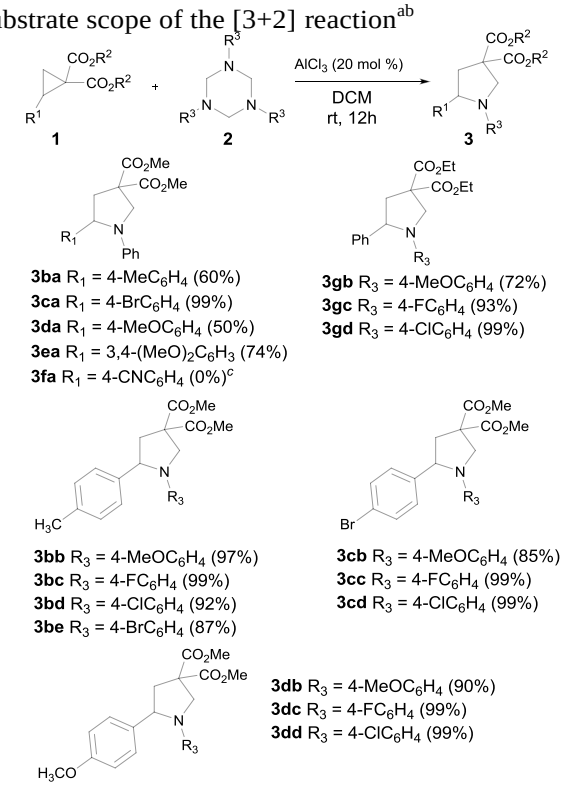
[a] See Supporting Information for experimental detail.

[b] Isolated yield.

[c] Inseparable mixture was obtained.

Having established the feasibility and optimal conditions, the generality of this formal [3+2] cycloaddition with a range of cyclopropanes and triazinanes was investigated. Firstly, the scope

Table 3
Substrate scope of the [3+2] reaction[ab]



[a] See Supporting Information for experimental detail.

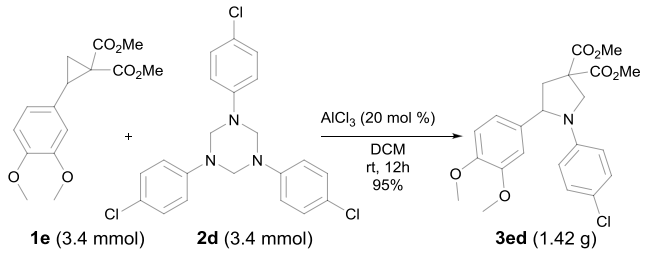
[b] Isolated yield.

[c] Inseparable mixture was obtained.

of 1,3,5-triazinanes was examined. As shown in **Table 2**, the electronic nature of the substituents on the 1,3,5-triazinanes had little influence on the yields (**3aa**-**3ae**). Substrates bearing either electron-donating or electron-withdrawing groups on the benzene part of triazinanes gave the corresponding cycloaddition products **3aa**-**3ae** in good to excellent yields (70-97%). However, substrates with sterically bulky group, such as 2-substituted 1,3,5-triazinanes, exerted more effect on the reaction efficiency, and gave inseparable mixtures (**3af**). When 1,3,5-tribenzyl-1,3,5-triazinane was employed, no desired product was observed (**3ag**).

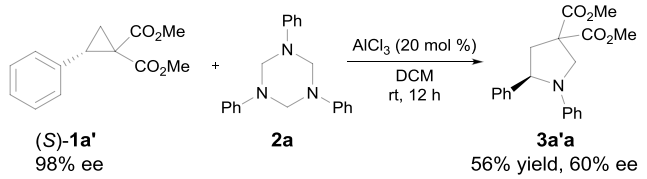
Subsequently, further substrate scope was investigated (**Table 3**). To our delight, the reaction of 1,3,5-triphenyl-1,3,5-triazinanes with different substituted donor-acceptor cyclopropanes proceeded smoothly to afford the cycloaddition product in good to excellent yields (**3aa**, **3ba**-**3ea**). However, donor-acceptor cyclopropane with a cyano group (-CN) on the benzene part gave an inseparable mixture (**3fa**). Ethyl-substituted donor-acceptor cyclopropane was also tolerated and led to the corresponding products in good to excellent yields (**3gb**-**3gd**). Finally, various para-substituted 1,3,5-triazinanes and different cyclopropanes were subjected to the reaction and gave structurally diverse pyrrolidines in excellent yields (**3bb**-**3be**, **3cb**-**3cd**, **3db**-**3dd**).

To evaluate the synthetic value of this formal [3+2] cycloaddition reaction, a gram-scale reaction was performed under the optimized conditions. As shown in **Scheme 2**, in the presence of 20 mol% $AlCl_3$, the reaction between **1e** and **2d** proceeded smoothly and gave the corresponding product in 95% yield, This results reflected the present protocol was amenable to large scale production.



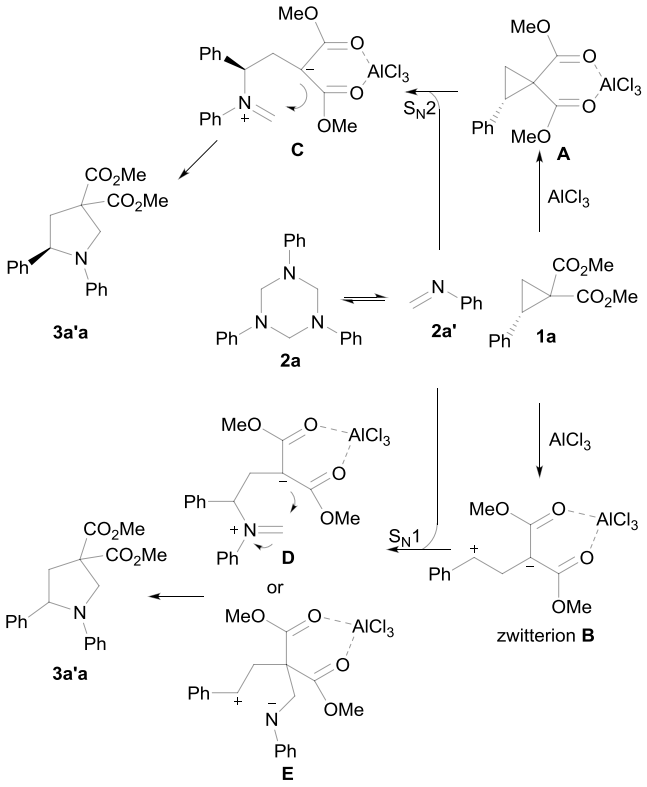
Scheme 2. Gram-scale version of the reaction.

To further understand the cycloaddition process, we conducted this reaction using enantioenriched (98% ee) cyclopropane (*S*)-**1a'** to explore the stereochemistry of this transformation (**Scheme 3**). The corresponding **3a'a** was obtained with significant loss in the stereochemical information from the enantioriched cyclopropane.



Scheme 3. Stereochemistry and mechanistic investigation.

Based on the key piece of mechanistic evidence obtained and related studies on formal [3+2] cycloaddition of donor-acceptor cyclopropanes,[15] a plausible mechanism was proposed. As shown in **Scheme 4**, in the presence of $AlCl_3$, in situ generated *N*-phenyl formaldimine **2a'** attacked the activated cyclopropane A through an S_N2-like pathway, leading to inversion at the benzyl position of the donor-acceptor cyclopropane. Subsequently, the cationic imine **C** was trapped by the intramolecular carbanion to deliver the stereospecific product pyrrolidine **3a'a.** Meanwhile, the racemic product was generated through the ring opened zwitterion **B,** which served as both a nucleophile and an electrophile to react with *N*-penyl formaldimine. The ee value of **3a'a** suggested that the S_N2-like product dominated over the ring opened zwitterionic pathway product.



Scheme 4. Proposed working model.

Conclusions

In summary, we have developed a formal [3+2] cycloaddition reaction of donor-acceptor cyclopropanes with 1,3,5-triazinanes, leading to the synthesis of highly functionalized pyrrolidines under very mild reaction conditions in moderate to excellent yields (up to 99%). Preliminary mechanistic studies and stereochemical information implied that donor-acceptor cyclopropanes react with *N*-aryl formaldimine through competing S_N1 and S_N2 pathways. Extending studies on the cycloadditions of 1,3,5-triazinanes in our lab are in progress and will be reported in due course.

Acknowledgments

We are grateful to the National Natural Science Foundation of China (No. 81561148013, 31560010), the Key Projects of Technological Innovation of Hubei Province (No. 2016ACA138) and "the Fundamental Research Funds for the Central Universities", South-Central University for Nationalities (NO. CZQ17010) for support of this research. We thank Dr. Yu Yuan from UCF for great suggestions.

References and notes

1. (a) O'Hagan D. *Nat Prod Rep*. 2000; 17: 435-446;

(b) Cossy J, Dumas C, Pardo DG. *Eur J Org Chem.* 1999; 7: 1693-1699;
(c) Sebahar PR, Williams RM. *J Am Chem Soc*. 2000; 122: 5666-5667;
(d) Honda T. Kimura M. *Org Lett*. 2000; 2: 3925-3927;
(e) Cossy J, Mirguet O, Pardo DG, Desmurs JR. *Eur J Org Chem.* 2002; 21: 3543-3551;
(f) Ori M, Toda N, Takami K, Tago K, Kogen H. *Angew Chem Int Ed.* 2003; 42: 2540-2543;
(g) Fiaux H, Popowycz F, Favre S, Schutz C, Vogel P, Lemaire SG, Jeanneret LJ. *J Med Chem.* 2005; 48: 4237-4246;
(h) Vartak AP, Nickell JR, Chagkutip J, Dwoskin LP, Crooks PA. *J Med Chem*. 2009; 52: 7878-7882;
(i) Larsen NK, Delgar CG, Koch KP, Brown MGE, Møller C, Han LW, Huynh THV, Hansen SW, Nielsen B, Bowie D, Pickering DS, Kastrup JS, Frydenvang K, Bunch L. *J Med Chem.* 2017; 60: 441-457.

2. (a) Dalko PI, Moisan L. *Angew Chem Int Ed.* 2001; 40: 3726-3748;
(b) Dalko PI, Moisan L. *Angew Chem Int Ed*. 2004; 43: 5138-5175;
(c) List B. *Synlett.* 2001; 11: 1675-1686;
(d) List B. *Tetrahedron*. 2002; 58: 5573-5590;
(e) List, B. *Acc Chem Res.* 2004; 37: 548-557;
(f) Notz W, Tanaka F, Barbas III CF. *Acc Chem Res.* 2004; 37: 580-591;
(g) Guillena G, Nájera C, Ramón DJ. *Tetrahedron Asymmetry*. 2007; 18: 2249-2293;
(h) Gruttadauria M, Giacalone F, Noto R. *Chem Soc Rev*. 2008; 37: 1666-1688;
(i) Retamosa MG, Cózar A, Sánchez M, Miranda JI, Sansano JM, Castelló LM, Nájera C, Jiménez A, Sayago IFJ, Cativiela C, Cossío FP. *Eur J Org Chem.* 2015; 11: 2503-2516.

3. (a) Pandey G, Banerjee P, Gadre SR. *Chem Rev*. 2006; 106: 4484-4517.
(b) Cabrera S, Arrayas RG, Carretero JC. *J Am Chem Soc*. 2005; 127: 16394-16395;
(c) Bellina F, Rossi R. Tetrahedron. 2006; 62: 7213-7256;
(d) Wolfe JP. *Eur J Org Chem.* 2007; 4: 571-582;
(e) Wang CJ, Liang G, Xue ZY, Gao F. *J Am Chem Soc.* 2008; 130: 17250-17251;
(f) Ivanov KL, Villemson EV, Budynina EM, Ivanova OA, Trushkov IV, Melnikov MY. *Chem Eur J.* 2015; 21: 4975-4987;
(g) Pilsl LKA, Ertl T, Reiser O. *Org Lett.* 2017; 19: 2754-2757.

4. (a) Reissig HU, Zimmer R. *Chem Rev.* 2003; 103: 1151-1196;
(b) Carson CA, Kerr MA. *J Org Chem.* 2005; 70: 8242-8244;
(c) Carson CA, Kerr MA. *Chem Soc Rev*. 2009; 38: 3051-3060;
(d) Schneider TF, Kaschel J, Werz DB. *Angew Chem Int Ed*. 2014; 53: 5504-5523.
(e) Kang YB, Tang Y, Sun XL. *Org Biomol Chem.* 2006; 4: 299-301;
(f) Parsons AT, Smith AG, Neel AJ, Johnson JS. *J Am Chem Soc.* 2010; 132: 9688-9692;
(g) Wang HN, Yang W, Liu H, Wan W, Li H. *Org Biomol Chem.* 2012; 10: 5032-5035;
(h) Goldberg AFG, O'Connor NR, Craig RA, Stoltz BM. *Org Lett.* 2012; 14: 5314-5317;
(i) Xiao JA, Li J, Xia PJ, Zhou ZF, Deng ZX, Xiang HY, Chen XQ, Yang H. *J Org Chem.* 2016; 81: 11185-11194;
(j) Pavlova AS, Ivanova OA, Chagarovskiy AO, Stebunov NS, Orlov NV, Shumsky AN, Budynina EM, Rybakov VB, Trushkov IV. *Chem Eur J*. 2016; 22: 17967-17971.

5. Buev EM, Moshkin VS, Sosnovskikh VY. *Tetrahedron Lett.* 2016; 57: 3731-3734.

6. (a) Bischoff CA, Reinfeld F. *Ber Dtsch Chem Ges*. 1903; 36: 41-53;
(b) Giumanini AG, Verardo G, Zangrando E, Lassiani L. *J Prakt Chem.* 1987; 329: 1087-1103;
(c) Ha HJ, Nam GS, Park KP. *Tetrahedron Lett.* 1990; 31: 1567-1568;
(d) Ha HJ, Lee YS, Ahn YG, *Heterocycles*. 1997; 45: 2357-2364;
(e) Ha HJ, Suh JM, Kang KH, Ahn O, Han YG. *Tetrahedron.* 1998; 54: 851-858;
(f) Ha HJ, Suh JM, Ahn YG, Dong Y, Yun H. *Heterocycles*. 1999; 50: 203-214;
(g) Ha HJ, Choi CJ, Ahn YG, Yun H, Dong Y, Lee WK. *J Org Chem.* 2000; 65: 8384-8386.

7. (a) Oda S, Sam B, Krische MJ. *Angew Chem Int Ed*. 2015; 54: 8525-8528;
(b) Oda S, Frank J, Krishce MJ. *Chem Sci.* 2016; 7: 136-141.

8. Lian XJ, Lin LL, Fu K, Ma BW, Liu XH, Feng XM. *Chem Sci.* 2017; 8: 1238-1242.

9. Zhu CH, Xu GY, Sun JT. *Angew Chem Int Ed*. 2016; 55: 11867-11871.

10. Peng SY, Cao SY, Sun JT. *Org Lett*. 2017; 19: 524-527.

11. Zheng Y, Chi YJ, Bao M, Qiu LH, Xu XF. *J Org Chem.* 2017; 82: 2129-2135.

12. Liu S, Yang P, Peng SY, Zhu CH, Cao SY, Li J, Sun JT. *Chem Commun.* 2017; 53: 1152-1155.

13. Garve LKB, Jones PG, Werz DB. *Angew Chem Int Ed.* 2017; 56: 9226-9230.

14. Garve LKB, Kreft A, Jones PG. Werz DB. *J Org Chem.* 2017; 82: 9235-9242.

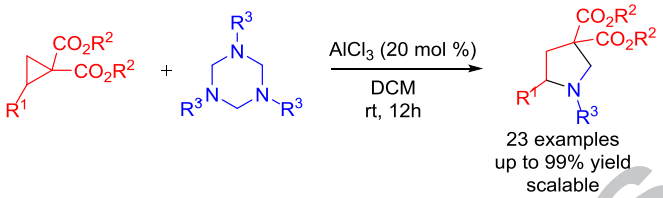
15. (a) Sapeta K, Kerr MA. *J Org Chem.* 2007; 72: 8597-8599;
(b) Pohlhaus PD, Sanders SD, Parsons AT, Li W, Johnson JS. *J Am Chem Soc.* 2008; 130: 8642-8650;
(c) Wales SM, Walker MM, Johnson JS. *Org Lett*. 2013; 15: 2558-2561;
(d) Garve LKB, Werz DB. *Org Lett*. 2015; 17: 596-599;
(e) Xia Y, Liu X H, Zheng HF, Lin LL, Feng XM. *Angew Chem Int Ed.* 2015; 54: 227-230;
(f) Xia Y, Lin LL, Chang FZ, Fu XA, Liu XH, Feng XM. *Angew Chem Int Ed*. 2015; 54: 13748-13752;
(g) Budynina EM, Ivanov KL, Chargarovskiy AO, Rybakov VB, Trushkov IV, Melnikov MY. *Chem Eur J*. 2016; 22: 3692-3696;
(h) Kaicharla T, Roy, T, Thangaraj M, Gonnade RG, Biju AT, *Angew Chem Int Ed*. 2016; 55: 10061-10064;
(i) Das S, Daniliuc CG, Studer A. *Org Lett*. 2016; 18: 5576-5579;
(j) Xia Y, Lin LL, Chang FZ, Liao YT, Liu XH, Feng XM. *Angew Chem Int Ed.* 2016; 55: 12228-12232;
(k) Wallbaum J, Garve LKB, Jones PG, Werz DB. *Org Lett.* 2017; 19: 98-101.

Graphical Abstract

Accessing substituted pyrrolidines via formal [3+2] cycloaddition of 1,3,5-triazinanes and donor-acceptor cyclopropanes

Leave this area blank for abstract info.

Zhi-Yao Chu, Na Li, Dan Liang, Zheng-Hui Li, Yong-Sheng Zheng* and Ji-Kai Liu*



Highlights

• Formal [3+2] cycloadddition of 1,3,5-triazinanes and donor-acceptor cyclopropanes.

• Highly efficient, mild approach for the synthesis of substituted pyrrolidines.

• Broad substrates scope of 1,3,5-triazinanes and donor-acceptor cyclopropanes.

• Illumination of the reaction mechanism.

• Successful demonstration of gram scale synthesis.