EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Sc(OTf)3-Catalyzed Selective Reactions of Donor-Acceptor Cyclopropanes with 1,1-diphenylethanols: A New Approach to Polysubstituted Olefins

Authors: Xiaoyan Zhu, Gang Hong, Chen Hu, Shengying Wu, and Limin Wang

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201700221

Link to VoR: http://dx.doi.org/10.1002/ejoc.201700221

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201700221

$Sc(OTf)_3$-Catalyzed Selective Reactions of Donor-Acceptor Cyclopropanes with 1,1-diphenylethanols: A New Approach to Polysubstituted Olefins

Xiaoyan Zhu,[a] Gang Hong,[a] Chen Hu,[a] Shengying Wu,[a] and Limin Wang*[a]

Dedication ((optional))

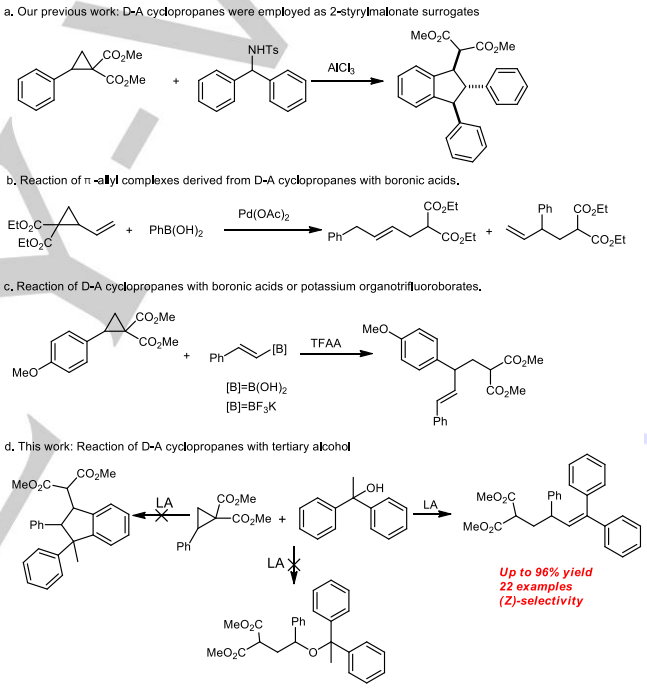
Abstract: An unexpected synthetic approach to a library of polysubstituted olefins *via* $Sc(OTf)_3$ catalyzed ring-opening reaction of D-A cyclopropanes with 1,1-diphenylethanols is herein described. The reactions, which are experimentally easy to handle, feature tolerance of various functional groups, mild reaction conditions. Based on experimental evidence, a plausible mechanism is also proposed.

Introduction

Donor-Acceptor cyclopropanes (D-A cyclopropanes) have recently become versatile building blocks in synthetic methodologies in the presence of activating agent.[1] Owing to their versatility and special reactivity, they have been widely used in the synthesis of various acyclic and cyclic compounds. In the presence of Lewis acid, D-A cyclopropanes are easily went though ring opening to form 1,3-dipolar, and widely deployed in [3+2] or [3+3] cycloaddition with dienes, dipolarophiles, or 1,3-dipoles to build functionalized five-, six-membered compounds.[2] Moreover, D-A cyclopropanes can also act as sources of 1,2- and 1,4-dipoles[3] under Lewis acid conditions. Recently, our group[4] has revealed that D-A cyclopropane can undergo reaction as the less developed 1,2-dipole in a formal [2+3] annulations reaction.

Compared with abundant reports about the cycloaddition of D-A cyclopropanes, nucleophilic attack to afford acyclic compounds is less developed in organic synthesis. Due to the ring strain, D-A cyclopropanes can undergo ring opening via C-C bond cleavage under Lewis acid, providing access to the nucleophiles, which is one of the rapid developing methods to 1,3-bifunctionalized products.

For example, the ring opening reactions[5] of D-A cyclopropanes with nucleophiles such as amines, alcohols, thiols and carboxylic acids were demonstrated by Feng and co-workers. Subsequently, $Yb(OTf)_3$ catalyzed ring opening reactions of cyclopropanes with indolines, and $Mn(OAc)_3$ catalyzed cycloaddition of the N-alkyl indulines, were recently uncovered by Michael.[6] Moreover, D-A cyclopropanes were undergone nucleophilic ring opening by N,N-dimethylaniline, and the group of Kim[7] further advanced the ring opening strategy by investigating the ring opening and intramolecular Micheal addition cascade reaction of D-A cyclopropanes with m-*N,N*-dimethylaminophenyl-α , β-unsaturated carbonyl compounds. Our group also has been interested in the use of D-A cyclopropanes to react with N-benzylic sulfonamides in the presence of Lewis acid (Scheme 1a).



Scheme 1. Examples of reaction of D-A cyclopropanes and proposed reaction

Inspired by above researches, we demonstrated the Lewis acid catalyzed reactions of D-A cyclopropanes with 1,1-diphenylethanols to generate dimethyl2-(2,4,4-triphenylbut-3-en-1-yl)malonates. Though there are some reports about the preparation of the analogue of dimethyl2-(2,4,4-triphenylbut-3-en-1-yl)malonates using D-A cyclopropanes[8] (Scheme 1b, 1c). The preparation of trisubstituted olefins employing D-A cyclopropanes, to the best of our knowledge, has never been reported. In addition, active boronic organic compounds[9], though efficiently taking part in the nucleophilic reaction, are not easily accessible. Herein, the reaction of D-A cyclopropanes with 1,1-diphenylethanols was studied as a model reaction. Formal [2+3] cycloadditions where D-A cyclopropanes act as 1,2-dipoles to offer the five-membered rings was not found in this work. And the reaction of D-A cyclopropanes reacted with the carbon nucleophiles instead of the oxygen nuclephiles. Dramatically, accessible 1,1-diphenylethanol was directly

[a] Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, P. R. China
E-mail: wanglimin@ecust.edu.cn.

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

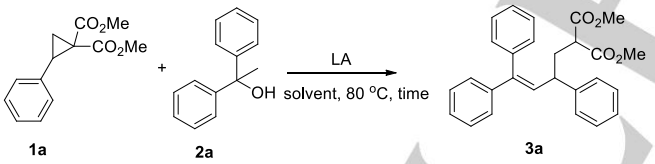
10.1002/ejoc.201700221

developed to react with D-A cyclopropane, and the sp^3 C-C bond was connected to the electrophilic site of the D-A cyclopropane rather than the site of tertiary alcohol, which was less investigated.

Results and Discussion

Herein, we reported the reaction of D-A cyclopropanes with 1,1-diphenylethanols catalyzed by $Sc(OTf)_3$ to give the corresponding dimethyl2-(2,4,4-triphenylbut-3-en-1-yl)malonates. Based on above considerations, we studied a model reaction between D-A cyclopropane **1a** and 1,1-diphenylethanol **2a** to optimize the reaction conditions (Table 1). To our delight, the desired product **3a** could be isolated in 32% yield by using 200 mol% $AlCl_3$ as the catalyst in 1,2-DCE at 80 °C for 12 h (Table 1, entry 1). Inspired by this result, various catalysts including $Cu(OTf)_2$, $FeCl_3$, and BF_3•OEt_2 were employed with no improvement in yield (Table 1, entries 8-10). When rare-earth triflates were investigated, only $Sc(OTf)_3$ can give 60% yield of the product (Table 1, entries 2-5). We also applied the rare earth perfluorooctanoates [$Sc(OPF)_3$] and pentafluorobenzoates [$Sc(Pfb)_3$] developed by our group to catalyze the reaction. Disappointingly, these catalysts had a negative effect on the reaction (Table 1, entries 6 and 7). Efforts to enhance yield by replacing 1,2-DCE with other solvents such as CH_3NO_2, Toluene and EtOH (Table 1, entries 11-14) proved that the yield gradually decreased, while DCM had positive effect on the reaction affording the product in 77% yield (Table 1, entry 11). There was a slight decrease in yield when the reaction was conducted under argon (Table 1, entry 15). Further screening of temperature revealed that the reaction was the most efficient when it was proceeded in DCM at 80 °C for 12 h under air in presence of $Sc(OTf)_3$ (5 mol %) (Table 1, entries 16 and 17).

Table 1. Optimization of Reaction Conditions.

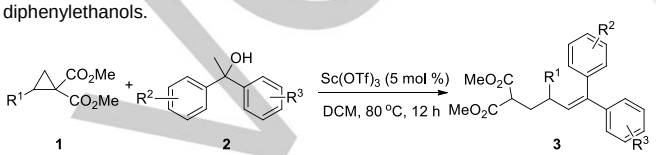


Entry[a]	Catalyst (mol %)	Solvent	Time (h)	Yield (%)[b]
1	$AlCl_3$(200)	1,2-DCE	12	32
2	$Sc(OTf)_3$(5)	1,2-DCE	12	60
3[c]	$Sc(OTf)_3$(20)	1,2-DCE	12	57
4	$Y(OTf)_3$ (5)	1,2-DCE	12	28
5	$Yb(OTf)_3$(5)	1,2-DCE	12	39
6	$Sc(OPF)_3$ (5)	1,2-DCE	12	25
7	$Sc(Pfb)_3$ (5)	1,2-DCE	12	24
8	$Cu(OTf)_2$(20)	1,2-DCE	12	41
9	$FeCl_3$ (20)	1,2-DCE	12	23
10	BF_3•OEt_2(20)	1,2-DCE	12	48
11	$Sc(OTf)_3$ (5)	DCM	12	77
12	$Sc(OTf)_3$ (5)	CH_3NO_2	12	32
13	$Sc(OTf)_3$ (5)	Toluene	12	30
14	$Sc(OTf)_3$ (5)	EtOH	12	none
15[d]	$Sc(OTf)_3$ (5)	DCM	12	73
16	$Sc(OTf)_3$ (5)	DCM	6	53
17	$Sc(OTf)_3$ (5)	DCM	24	67

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), Lewis acid (x mol %), and solvent (1 mL), at 80 °C. [b] Isolated yield. [c] 20 mol % of $Sc(OTf)_3$. [d] Under argon.

With the optimized reaction conditions in hand, we then explored the substrate scope of D-A cyclopropanes **1** and 1,1-diphenylethanols **2** (Table 2). First, a series of D-A cyclopropanes containing electron-donating or electron-withdrawing substituents were investigated (Table 2, entries 1-10). Substituents such as Me, OMe, F, Cl and Br on 3-position or 4-position of the phenyl ring worked well to afford the corresponding products in 70-89% yields (Table 2, entries 2-8). Delightedly, the D-A cyclopropane with 2-naphthyl group could also afford corresponding product in 64% yield (Table 2, entry 9) However, pyridine-substituted D-A cyclopropanes could not afford the desired product (Table 2, entry 10).

Table 2. $Sc(OTf)_3$ catalyzed reactions of D-A cyclopropanes with 1,1-diphenylethanols.

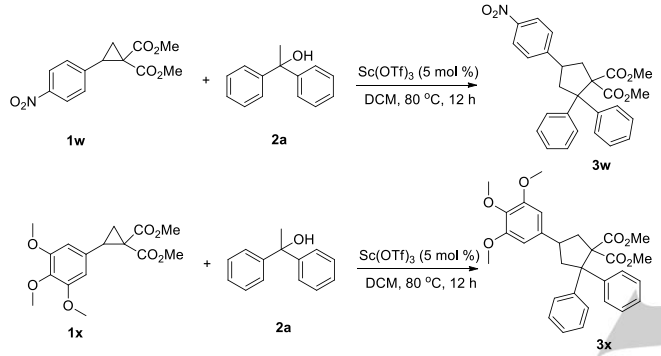


Entry[a]	R^1	R^2	R^3	3	Yield (%)[b]
1	Ph	H	H	**3a**	77
2	4-MeC_6H_4	H	H	**3b**	78
3	3-MeC_6H_4	H	H	**3c**	86
4	4-$OMeC_6H_4$	H	H	**3d**	70
5	4-FC_6H_4	H	H	**3e**	79
6	3-FC_6H_4	H	H	**3f**	89
7	4-ClC_6H_4	H	H	**3g**	76
8	4-BrC_6H_4	H	H	**3h**	79
9	2-naphthyl	H	H	**3i**	64
10	2-pyridine	H	H	**3j**	ND[c]
11	Ph	4-Me	4-Me	**3k**	91
12	Ph	4-OMe	4-OMe	**3l**	86
13	Ph	2-OMe	2-OMe	**3m**	70
14	Ph	4-^{t}Bu	4-^{t}Bu	**3n**	96
15	Ph	4-F	4-F	**3o**	49
16	Ph	4-Cl	4-Cl	**3p**	32
17	Ph	4-Me	H	**3q**	85
18	Ph	4-F	H	**3r**	64
19	Ph	4-Cl	H	**3s**	42
20	Ph	4-Br	H	**3t**	54
21	Ph	2,6-F,F	H	**3u**[d]	30
22	4-$NO_2C_6H_4$	4-Me	4-Me	**3v**	86

[a] The reaction was conducted with **1** (0.25 mmol), **2** (0.25 mmol), Lewis acid (5 mol %), CH_2Cl_2 (1 mL), 80 °C and 24 h. [b] Isolated yield. [c] ND = no product. [c] The configuration of **3u** was determined by its NOESY H-H interactions.

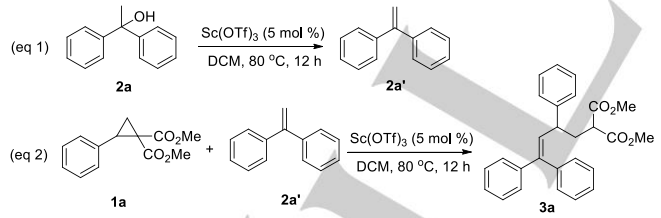
Then, we studied the scope of 1,1-diphenylethanols. Various substituted 1,1-diphenylethanol derivatives smoothly reacted with D-A cyclopropane under $Sc(OTf)_3$ to afford the dimethyl 2-(2,4,4- triphenylbut-3-en-1-yl)malonates in good yields (Table 2, entries 11-22). In general, 70-96% results were obtained when electron-donating groups such as 4-Me, 4-OMe, 2-OMe and 4-^{t}Bu were present on the phenyl of the 1,1-diphenylethanols (Table 2, entries 11-14). Interestingly, the 1,1-bis(4-(tert-butyl)phenyl)ethanol afforded **3n** in 96% yield. While 1,1-diphenylethanols with substituents (F, Cl) at the 4-position on

the phenyl R^2 and R^3, produced the corresponding products **3o** and **3p** in 49% and 32%, respectively (Table 2, entries 15, 16). Subsequently, unsymmetrically substituted 1,1-diphenylethanols were investigated (Table 2, entries 17-21). It should be noted that the products with exact (*Z*)-selectivity were observed when employing unsymmetrically substituted 1,1-diphenylethanols. 1,1-diphenylethanols with electron-donating (Me) at the 4-position on the phenyl R^2 gave the corresponding products in higher yields than 1,1-diphenylethanol possessing electron-withdrawing (F, Cl, Br) at the 4-position on the phenyl R^2. 1-(2,6-difluorophenyl)-1-phenylethanol afforded the corresponding product in 30% yield (Table 2, entry 21). The olefin geometry was established unambiguously by differential NOE ^{1}H NMR experiments (See ESI for details). In addition, 86% yield was obtained when NO_2 substituted D-A cyclopropane reacted with methyl substituted 1,1-diphenyldiethanol (Table 2, entry 22). The structure of **3n** was unambiguously confirmed by X-ray analysis (See ESI for details).



Scheme 2. The [3+2] cycloaddition reaction of substitutional D-A cyclopropanes.

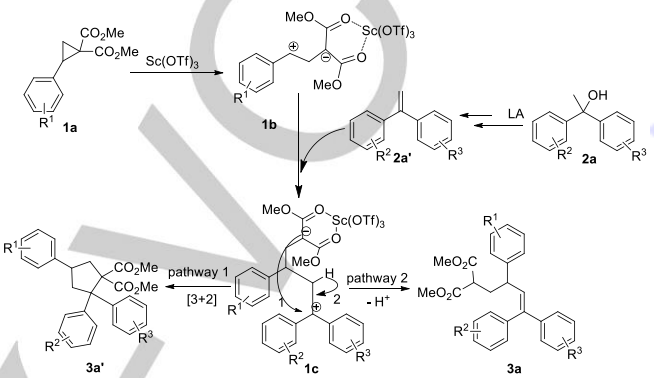
To our surprise, the D-A cyclopropanes with substituents 4-NO_2 and 3,4,5-trimethoxy[10] failed to give the desired products, instead [3+2] cycloaddition products were obtained in 36%, 76% yields, respectively (Scheme 2). The structure of **3w** was also unambiguously assigned by X-ray analysis (See ESI for details).



Scheme 3. Control experiments for investigating mechanism.

Next, control experiments were performed to gain insights into the reaction mechanism (Scheme 3). When **2a** was under standard condition, 1,1-diphenylethene[11] was isolated in 68 % yield (Scheme 3, eq 1). Subsequently, 1,1-diphenyiethene was employed to smoothly react with D-A cyclopropane under standard conditions, and the final product **3a** was observed in 69% yields. The results indicate that 1,1-diphenylethene might be an intermediate in the present reaction system.

On the basis of experimental results and previous related reports[12, 13], we proposed a possible mechanism for the formation of the ring-opening products and cycloaddition products (Scheme 4). First, the activation of **1a** using $Sc(OTf)_3$ possibly generate the ring-opening 1,3-dipole intermediate **1b**. In the meantime, 1,1-diphenylethene **2a'** is generated from **2a** catalyzed by Lewis acid[14]. After the formation of the 1,3-dipole and addition of the unsaturated compound **2a'**, intermediate **1c** is formed. Then, for the D-A cyclopropanes with substituents 4-NO_2 and 3,4,5-trimethoxy， the electrophilic center of **1c** is trapped by a malonate anion to undergo 1,5-cyclization forming cyclopentane **3a'** (pathway 1). For other substituted D-A cyclopropanes, final product **3a** is formed through $Sc(OTf)_3$ catalyzed proton abstraction (pathway 2).



Scheme 4. Possible mechanism

Conclusions

In summary, we have explored the novel reactivity resided in D-A cyclopropanes. A series of polysubstituted olefins are obtained in good to excellent yields through this simple synthetic approach. A plausible mechanism is proposed. Considering the chameleon features of D-A cyclopropanes, further investigation toward this substrate is underway.

Experimental Section

General Procedure for $Sc(OTf)_3$-Catalyzed Selective Reactions of Donor-Acceptor Cyclopropanes with 1,1-diphenylethanols: The mixture of donor-acceptor cyclopropanes **1a** (0.25 mmol), 1,1-diphenylethanols **2a** (0.25 mmol), $Sc(OTf)_3$ (5 mol %) and DCM (1 mL) were added into a sealed tube. After being stirred vigorously at 80 °C for 12 h, the mixture was evaporated under vacuum. The corresponding product was isolated by silica gel column chromatography with a petroleum ether/ethyl acetate mixture (100:4) as eluent.

Acknowledgements

This research was financially supported by the National Nature Science Foundation of China (21272069, 20672035) and the Fundamental Research Funds for the Central Universities and Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

Keywords: Lewis acid; Ring-opening reaction; D-A cyclopropanes; Olefins

[1] a) V. S. Korotkov, O. L. Larionov, A. Hofmeister, J. Magull, A. Meijere, J. Org. Chem. 2007, 72, 7504-7510; b) H. Xiong, H. Xu, S. H. Liao, Z. W.

Xie, Y. Tang, J. Am. Chem. Soc. 2013, 135, 7851-7854; c) S. Chakrabarty, I. Chatterjee, B. Wibbeling, C. G. Daniliuc, A. Studer, Angew. Chem. Int. Ed. 2014, 53, 5964-5968; d) H. L. Liu, C. H. Yuan, Y. Wu, Y. M. Xiao, H. C. Guo, Org. Lett. 2015, 17, 4220-4223.

[2] a) I. S. Young, M. A. Kerr, Angew. Chem. Int. Ed. 2003, 42, 3023-3026; b) E. O. Gorbacheva, A. A. Tabolin, R. A. Novikov, Y. V. Nelyubina, S. L. Ioffe, Org. Lett. 2013, 15, 350-353; c) R. Talukdar, D. P. Tiwari, A. Saha, M. K. Ghorai, Org. Lett. 2014, 16, 3954-3957; d) R. Talukdar, D. P. Tiwari, A. Saha, M. K. Ghorai, Org. Lett. 2014, 16, 3954-3957; e) Z. J. Wang, S. Chen, J. Ren, Z. W. Wang, Org. Lett. 2015, 17, 4184-4187; f) W. W. Ma, J. Fang, J. Ren, Z.W. Wang, Org. Lett. 2015, 17, 4180-4183; g) K. S. Halskov, L. Næsborg, F. Tur, K. A. Jørgensen, Org. Lett. 2016, 18, 2220-2223. h) S. Das, S. Chakrabarty, C. G. Daniliuc, Studer, Org. Lett. 2016, 18, 2784-2787; i) T. Chidley, N. Vemula, C. A. Carson, M. A. Kerr, B. L Pagenkopf, Org. Lett. 2016, 18, 2922-2925.

[3] a) R. A. Novikov, D. O. Balakirev, V. P. Timofeev, Y. V. Tomilov, Organometallics, 2012, 31, 8627-8638; b) R. A. Novikov, A. V. Tarasova, V. A. Korolev, V. P. Timofeev, Y. V. Tomilov, Angew. Chem. Int. Ed. 2014, 53, 1-6; c) R. A. Novikov, A. V. Tarasova, V. A. Korolev, E. V. Shulishov, V. P. Timofeev, Y. V. Tomilov, J. Org. Chem. 2015, 80, 8225-8235.

[4] M. Y. Zhu, J. Q. Liu, J. J. Yu, L. S. Chen, C. M. Zhang, L. M. Wang, Org. Lett. 2014, 16, 1856-1859.

[5] a) Y. Xia, L. Lin, F. Chang, X. Fu, X. Liu, X. Feng, Angew. Chem.Int. Ed. 2015, 54, 13748; b) Y. Xia, X. Liu, H. Zheng, L. Lin, X. Feng, Angew. Chem. Int. Ed. 2015, 54, 227; c) R. Karmakar, A. Suneja, V. K. Singh, Org. Lett. 2016, 18, 2636-2639.

[6] J. E. C. Tejeda, B. K. Landschoot, M. A. Kerr, Org. Lett. 2016, 18, 2142-2145.

[7] a) A. Kim, S. G. Kim, Eur. J. Org. Chem. 2015, 6419-6422; b) A. Kim, S. G. Kim, Adv. Synth. Catal. 2016, 358, 2701-2706.

[8] a) J. X. Yin, C. J. T. Hyland, J. Org. Chem. 2015, 80, 6529-6536; b) V. Ortega, A. G. Csákÿ, J. Org. Chem. 2016, 81, 3917-3923.

[9] A. J. J. Lennox, G. C. Lloyd-Jones, J. Am. Chem. Soc. 2012, 134, 7431-7441.

[10] Y. A. Volkova, E. M. Budynina, A. E. Kaplun, O. A. Ivanova, A. O. Chagarovskiy, D. A. Skvortsov, V. B. Rybakov, I. V. Trushkov, M. Y. Melnikov, Chem. Eur. J. 2013, 19, 6586-6590.

[11] Z. B. Wang, Y. F. Wong, J. W. Sun, Angew. Chem. Int. Ed. 2015, 54, 13711-13714.

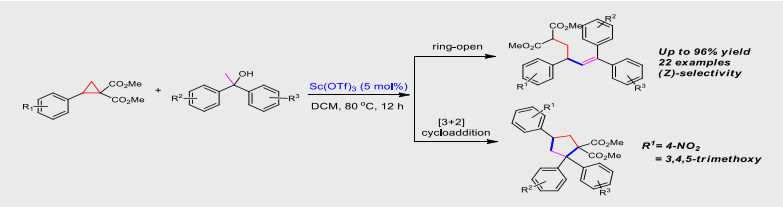
[12] Y. P. Han, X. R. Song, Y. F. Qiu, X. H. Hao, J. Wang, X. X. Wu, X. Y. Liu, Y. M. Liang, J. Org. Chem. 2015, 80, 9200-9207.

[13] T. Kaicharla, T. Roy, M. Thangaraj, R. G. Gonnade, A. T. Biju, Angew. Chem. Int. Ed. 2016, 55, 1-5.

[14] a) Y. S. Shao, K. Zhu, Z. C. Qin, E. Li, Y. Z. Li, J. Org. Chem. 2013, 78, 5731−5736; b) S. Jana, A. Dey, M. Singsardar, A. K. Bagdi, A. Hajra, J. Org. Chem. 2016, 81, 9489−9493.

10.1002/ejoc.201700221

COMMUNICATION



Accessible 1,1-diphenylethanol was directly developed to react with D-A cyclopropane, and the sp^3 C-C bond was connected to the electrophilic site of the D-A cyclopropane to form the trisubstituted olefins products. Dramatically, the D-A cyclopropanes with substituents 4-NO_2 and 3,4,5-trimethoxy offered the cycloaddition products.

* The sp^3 C-C bond of 1,1-diphenylethanol was directly connected to the electrophilic site of the D-A cyclopropane to form the products

D-A cyclopropane *

*Xiaoyan Zhu, Gang Hong, Chen Hu, Shengying Wu, Limin Wang**

Page No. – Page No.

Sc(OTf)3-Catalyzed Selective Reactions of Donor-Acceptor Cyclopropanes with 1,1-diphenylethanols: A New Approach to Polysubstituted Olefins