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# Synergistic effect of additives on cyclopropanation of olefins†

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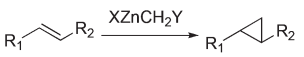
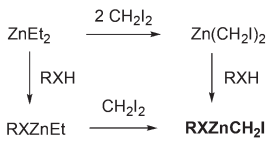
**An efficient cyclopropanation of olefins with $Zn(CH_2I)_2$, a catalytic amount of $CCl_3CO_2H$, and 1,2-dimethoxyethane at room temperature is described. A wide variety of olefins, including acid-sensitive substrates, can be cyclopropanated in 71–99% yield.**

Cyclopropanes are present in many biological and medicinal molecules,[1] and are synthetically useful intermediates.[2] The Simmons–Smith reaction is a very effective method to synthesize cyclopropanes from olefins (Scheme 1).[3] Since the initial report of the Simmons–Smith reaction,[4] lots of modifications have been reported.[5] A variety of strategies have also been developed to generate various zinc species, including $XZnCH_2X$,[6a,b] $RZnCH_2I$ or $Zn(CH_2I)_2$,[6c–g] $Zn(CH_2Cl)_2$,[6h] $RCO_2CH_2ZnR$,[6i,j] $ArOZnCH_2I$,[6k] and $(RO)_2P(O)OZnCH_2I$.[6l–n] In 1998, we reported a novel class of tunable cyclopropanation zinc species ($RXZnCH_2I$) generated by reacting appropriate zinc reagents with RXH ranging from alcohols to acids (Scheme 2).[7,8] The zinc species, derived from acids like $CF_3CO_2H$, display very high reactivities for the cyclopropanation of olefins and have found a variety of applications in synthesis.[8] However, one of the drawbacks of our earlier procedures is that stoichiometric amounts of $CF_3CO_2H$ are usually used. For some unreactive substrates such as stilbenes, excess $CF_3CO_2H$ is frequently needed to obtain high conversions.[8] Therefore, the development of a cyclopropanation procedure requiring only substoichiometric amounts of RXH is highly desirable.[9,10] Herein, we wish to report our preliminary studies on this subject.




Scheme 1




Scheme 2

Initial studies were carried out with relatively unreactive *trans*-stilbene (**1a**) as the substrate. As shown in Fig. 1, a poor conversion of *trans*-stilbene was observed with no additive (Fig. 1, curve A). The conversion only slightly increased with the addition of 0.2 equiv. of $CF_3CO_2H$ or $CCl_3CO_2H$[7b,11] (Fig. 1, curves B and C). However, in the case of $CCl_3CO_2H$, the conversion greatly increased when 1 equiv. of 1,2-dimethoxyethane

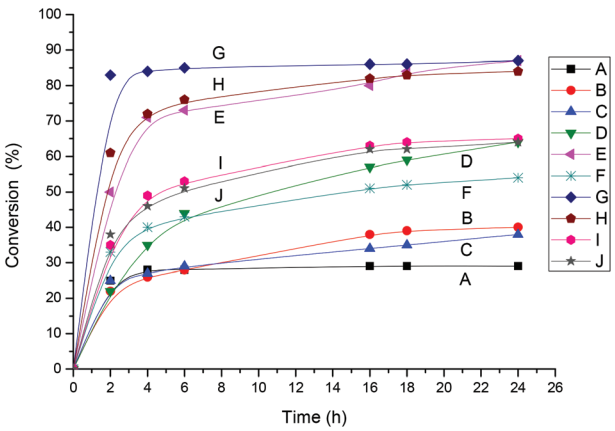



**Fig. 1** Plot of the conversion of *trans*-stilbene against time (h). All reactions were carried out with *trans*-stilbene (0.50 mmol), $Et_2Zn$ (1.0 mmol, 1.0 M in *n*-hexane), $CH_2I_2$ (2.0 mmol), and additives in $CH_2Cl_2$ (2.5 mL) at 30 °C for 24 h. The conversions were determined using GC analysis. The curves presented are: (A) no additive, (B) $CF_3CO_2H$ (0.10 mmol), (C) $CCl_3CO_2H$ (0.10 mmol), (D) $CF_3CO_2H$ (0.10 mmol), DME (0.50 mmol), (E) $CCl_3CO_2H$ (0.10 mmol), DME (0.50 mmol), (F) DME (0.50 mmol), (G) $CCl_3CO_2H$ (1.0 mmol), (H) $MeCOCO_2H$ (0.10 mmol), DME (0.50 mmol), (I) 2,4,6-trichlorophenol (0.10 mmol), DME (0.50 mmol), (J) $CF_3CH_2OH$ (0.10 mmol), and DME (0.50 mmol).

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†Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and NMR spectra. See DOI: 10.1039/c3ob40751a



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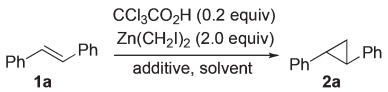
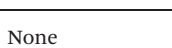
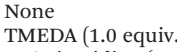
**Table 1** Studies on reaction conditions[a]




| Entry | Additive | Solvent | Conv.[b] (%) |
|---|---|---|---|
| 1 | None | $CH_2Cl_2$ | 29 |
| 2 | TMEDA (1.0 equiv.) | $CH_2Cl_2$ | 6 |
| 3 | 2,2′-Bipyridine (1.0 equiv.) | $CH_2Cl_2$ | 52 |
| 4 | $Et_2O$ (1.0 equiv.) | $CH_2Cl_2$ | 64 |
| 5 | $^t$BuOMe (1.0 equiv.) | $CH_2Cl_2$ | 55 |
| 6 | THF (1.0 equiv.) | $CH_2Cl_2$ | 82 |
| 7 | Dioxane (1.0 equiv.) | $CH_2Cl_2$ | 84 |
| 8 |  (1.0 equiv.) | $CH_2Cl_2$ | 77 |
| 9 |  (1.0 equiv.) | $CH_2Cl_2$ | 70 |
| **10** | **DME (1.0 equiv.)** | **$CH_2Cl_2$** | **85** |
| 11 | DME (0.2 equiv.) | $CH_2Cl_2$ | 64 |
| 12 | DME (0.5 equiv.) | $CH_2Cl_2$ | 73 |
| 13 | DME (2.0 equiv.) | $CH_2Cl_2$ | 56 |
| 14 | DME (5.0 equiv.) | $CH_2Cl_2$ | 8 |
| 15 | DME (1.0 equiv.) | DCE | 75 |
| 16 | DME (1.0 equiv.) | Toluene | 47 |
| 17 | DME (1.0 equiv.) | *n*-Hexane | 66 |

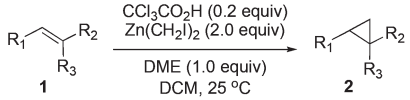
[a] All reactions were carried out with *trans*-stilbene (**1a**) (0.50 mmol), $Et_2Zn$ (1.0 mmol, 1.0 M in *n*-hexane), $CH_2I_2$ (2.0 mmol), $CCl_3CO_2H$ (0.10 mmol), and additive in solvent (2.5 mL) at 30 °C for 18 h. [b] The conversions were determined using GC analysis.

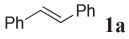
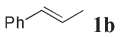
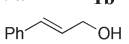
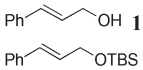
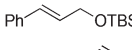
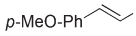
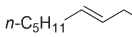
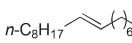
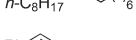
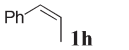
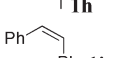
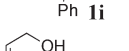
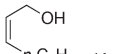
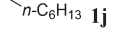
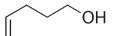
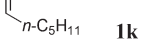
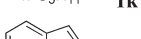
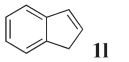
(DME)[6l,9,12] was added (Fig. 1, curve E). This result was comparable to the conversion obtained with 2 equiv. of $CCl_3CO_2H$ (Fig. 1, curve G). A similar synergistic effect of additives on the cyclopropanation of olefins was also observed with $MeCOCO_2H$ (Fig. 1, curve H).

The observed beneficial effect of DME on the cyclopropanation prompted us to systematically examine various other additives. As shown in Table 1, TMEDA was found to be detrimental to the reaction (Table 1, entry 2).[13] The ether-type additives were favorable for the reaction, with DME being the best (Table 1, entries 4–10). Further studies showed that the amount of DME was important for the reaction conversion, with 1 equiv. being optimal (Table 1, entries 10–14). While a precise understanding of the beneficial effect of additives like DME on the cyclopropanation awaits further study, the additives could coordinate with the zinc carbenoids to increase their stabilities and/or disrupt inactive aggregates.[12] At the same time, the additives could also reduce the reactivity of the zinc carbenoids. As a result, the reaction conversion is dependent on the amount of the additives added. Among the solvents examined (Table 1, entries 10 and 15–17), the highest conversion was obtained with $CH_2Cl_2$.

The cyclopropanation procedure with 0.2 equiv. of $CCl_3CO_2H$ and 1 equiv. of DME can be extended to a wide variety of olefins, giving the corresponding cyclopropanes in 71–99% yield (Table 2). The effective substrates include *trans*-, *cis*-, terminal, and trisubstituted olefins. Various functional groups, such as OH, OTBS, and $CO_2R$, can be tolerated (Table 2, entries 3, 4, 6, 7, 10, and 11). For acid-sensitive silyl

**Table 2** Cyclopropanation of olefins[a]




| Entry | Substrate | Time (h) | Conv.[b] (%) | Yield[c] (%) |
|---|---|---|---|---|
| 1 |  **1a** | 48 | 86 | 77 |
| 2 |  **1b** | 18 | 100 | 77 |
| 3 |  **1c** | 2 | 100 | 97 |
| 4 |  **1d** | 18 | 100 | 95 |
| 5 |  **1e** | 18 | 99 | 94 |
| 6 |  **1f** | 18 | 100 | 88 |
| 7 |  **1g** | 18 | 97 | 96 |
| 8 |  **1h** | 18 | 100 | 84 |
| 9 |  **1i** | 24 | 87 | 71 |
| 10 |  **1j** | 4 | 100 | 99 |
| 11 |  **1k** | 18 | 100 | 77 |
| 12 |  **1l** | 18 | 100 | 94 |
| 13 |  **1m** | 18 | 100 | 72 |
| 14 |  **1n** | 18 | 99 | 71 |
| 15 |  **1o** | 18 | 100 | 82 |
| 16 |  **1p** | 18 | 100 | 76 |
| 17 |  **1q** | 18 | 100 | 93 |
| 18 |  **1r** | 20 | 100 | 90 |
| 19 |  **1s** | 18 | 100 | 91 |
| 20 |  **1t** | 3 | 100 | 90 |
| 21 |  **1u** | 3 | 100 | 84 |

[a] All reactions were carried out with olefins (0.50 mmol), $Et_2Zn$ (1.0 mmol, 1.0 M in *n*-hexane), $CH_2I_2$ (2.0 mmol), $CCl_3CO_2H$ (0.10 mmol), and DME (0.50 mmol) in $CH_2Cl_2$ (2.5 mL) at 25 °C unless otherwise noted. For entries 1 and 2, reactions were carried out with olefins (1.0 mmol), $Et_2Zn$ (2.0 mmol), $CH_2I_2$ (4.0 mmol), $CCl_3CO_2H$ (0.20 mmol), and DME (1.0 mmol) in $CH_2Cl_2$ (5.0 mL). [b] The conversions were determined from the crude reaction mixture either using GC or $^1$H NMR analysis. [c] Isolated yield.

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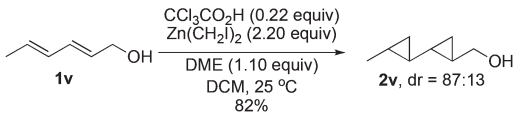
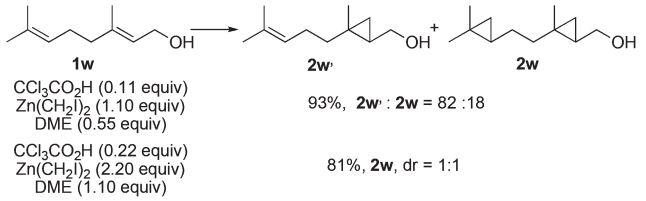
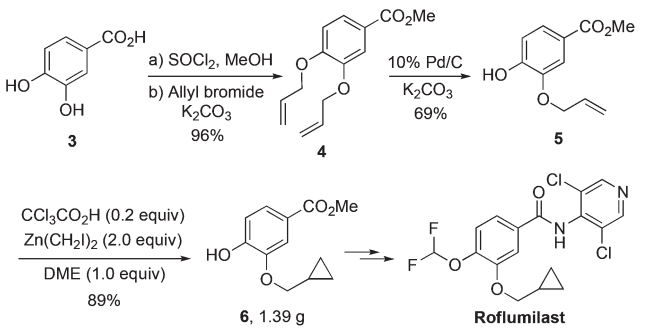



**Scheme 3**




**Scheme 4**




**Scheme 5** Synthesis of a key intermediate for Roflumilast.

enol ethers **1t** and **1u**, the cyclopropane products were obtained in high yields without desilylation (Table 2, entries 20 and 21).[7b] The cyclopropanation of dienol **1v** afforded the corresponding bicyclopropane **2v** in 82% yield with good diastereoselectivity (dr = 87 : 13) (Scheme 3).[14] For geraniol **1w**, the allylic alcohol can be selectively cyclopropanated in 93% yield along with bicyclopropane **2w** (Scheme 4).[15]

As illustrated in the case of compound **5**, the cyclopropanation is amenable to the gram scale, giving cyclopropane **6** in 89% yield (Scheme 5). Compound **6** is a key intermediate towards Roflumilast, a selective long-acting PDE-4 inhibitor for the treatment of inflammatory conditions of lungs.[16]

## Conclusion

In summary, we have developed an efficient cyclopropanation procedure for olefins with a catalytic amount of $CCl_3CO_2H$ and one equiv. of DME. A wide variety of olefins including acid-sensitive substrates have been cyclopropanated in 71–99% yield. The synergistic effect of $CCl_3CO_2H$ and DME dramatically reduces the amount of acid used, which makes this cyclopropanation procedure milder and more practical. Further understanding the mechanism and developing more effective catalytic systems with high reactivity and selectivity are currently under way.

## Acknowledgements

The authors gratefully acknowledge the National Basic Research Program of China (973 program, 2011CB808600) and the Chinese Academy of Sciences for financial support.

## Notes and references

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