Organic LETTERS
Letter
pubs.acs.org/OrgLett

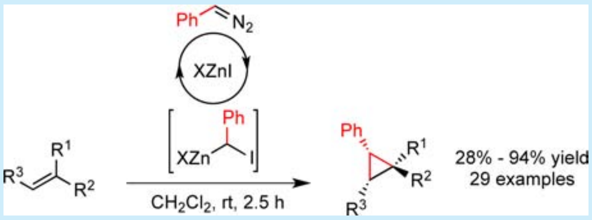
Improved Zinc-Catalyzed Simmons–Smith Reaction: Access to Various 1,2,3-Trisubstituted Cyclopropanes

Éric Lévesque, Sébastien R. Goudreau, and André B. Charette*

Centre in Green Chemistry and Catalysis, FAS-Department of Chemistry, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, Québec, Canada, H3C 3J7

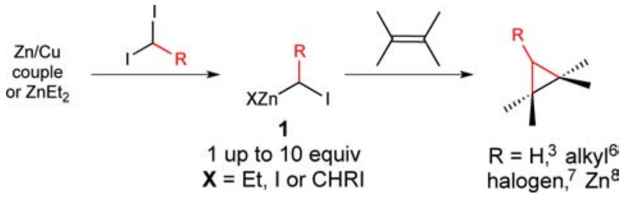
Supporting Information

ABSTRACT: The Simmons–Smith reaction of zinc carbenoids with alkenes is a powerful method to access cyclopropanes containing various substitution patterns. This work exploits the high reactivity of aryldiazomethanes toward zinc halides to generate aryl-substituted carbenoids catalytically. These carbenoids are able to cyclopropanate various alkenes diastereoselectively, including unfunctionalized substrates such as styrenes. The zinc catalyst can be modified to tolerate the use of free allylic alcohols.



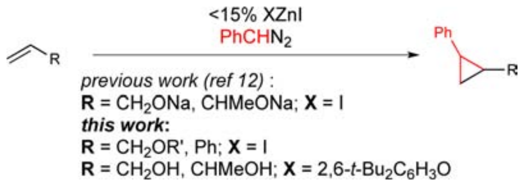
Cyclopropanes are important structural units in the field of synthetic chemistry. They are present in many natural and bioactive products[1] and can also participate in useful chemical reactions, taking advantage of their unique ring strain.[2] The zinc-mediated reaction of *gem*-diiodoalkanes with alkenes, first reported by Simmons and Smith,[3] is among the most widely used approaches to access complex cyclopropanes.[4] The typical procedure[5−8] involves generating an excess of the desired zinc carbenoid[9] (**1**) before introducing the substrate alkene (Scheme 1). Such a procedure can suffer from solubility issues, as coordinating additives are often required to solubilize the zinc reagent.[7,8,9b] On a larger scale, the handling of air-sensitive organozinc compounds[5] and the generation of metal-containing waste also become problematic. Using only a catalytic amount of zinc would be a straightforward way to circumvent these issues.

Scheme 1. Typical Simmons–Smith Procedure



The key for the establishment of a viable catalytic cycle would be to use a precursor able to regenerate the reactive carbenoid from the zinc halide produced after the cyclopropanation. Alkyl-[10] and aryl-[11] diazo reagents have been demonstrated to fit such a requirement. Recently, our group successfully used this approach to generate enantioenriched arylcyclopropanes using stoichiometric amounts of both zinc halide and chiral tartrate-derived dioxaborolane.[12] Furthermore, a few examples of this transformation using catalytic amounts of zinc halides have been reported, but they either require a large excess of alkene[11a] or are limited to sodium allyloxides.[12] Herein we report the scope and applications study of the first zinc-catalyzed system to cyclopropanate styrenes[13] and allylic ethers efficiently (Scheme 2). Also, a simple modification of the catalyst enables direct cyclopropanation of free allylic alcohols without deprotonation.

Scheme 2. Arylcyclopropanations Using a Catalytic Amount of Zinc



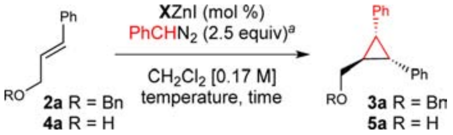
We started our investigation by treating the benzyl ether of cinnamyl alcohol (**2a**) with zinc iodide[14] and slowly adding phenyldiazomethane at −20 °C (Table 1, entry 1). During the addition, significant accumulation of the deep red diazo reagent was noticed, only fading away when the mixture was warmed to room temperature. As zinc carbenoids react faster with diazo compounds than with alkenes,[11b] this led to poor conversions and the undesired formation of stilbenes. Adding the diazo reagent at room temperature increased the turnover rate enough to keep its concentration low at all times (Table 1, entry 2), thus favoring the desired quantitative formation of cyclopropane. This also has the advantage of reducing reaction times such that complete conversion was reached shortly after the end of the diazo compound addition.

To explore substrate generality, a series of protected allylic alcohols were submitted to the ZnI_2-catalyzed reaction

Received: January 28, 2014
Published: February 20, 2014

dx.doi.org/10.1021/ol500267w | *Org. Lett.* 2014, 16, 1490−1493

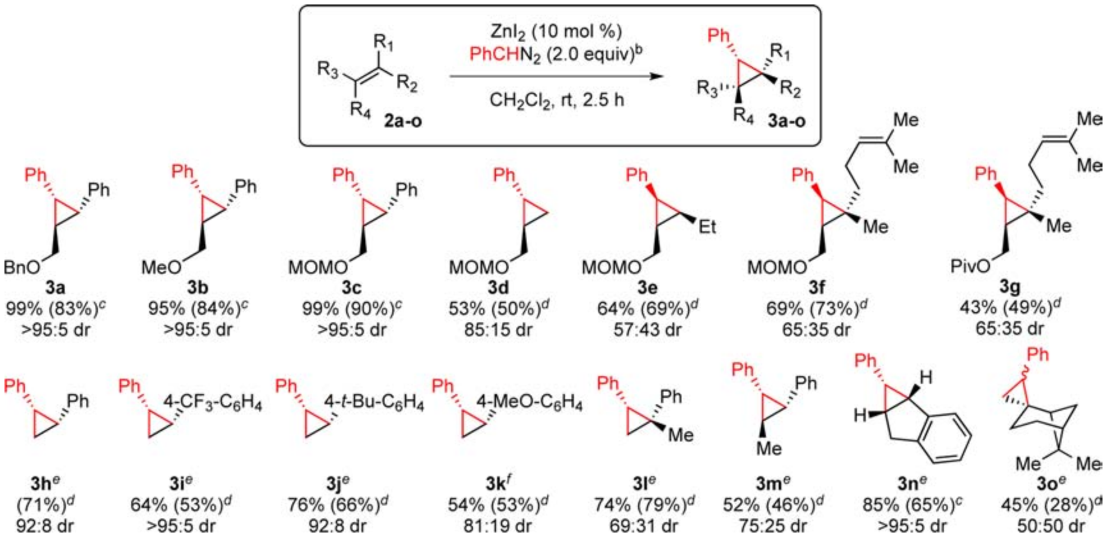
Table 1. Screening of the Cyclopropanation Conditions



entry	initial R	temp (°C)	Zn (mol %)	X anion	time (h)	yield **5a** (%)[b]	yield **3a** (%)[b]
1	Bn	−20 to rt	10	I^-	16	–	48
2	Bn	rt	10	I^-	2.5	–	99
3	H	rt	10	I^-	2.5	60	23
4	H	rt	10	$(BuO)_2PO_2^-$	2.5	65	8
5	H	rt	10	PhO^-	2.5	65	5
6	H	rt	10	2,6-*t*-$Bu_2C_6H_3O^-$	2.5	70	5
7	H	rt	13	2,6-*t*-$Bu_2C_6H_3O^-$	2.5	81	8

[a] 0.75 M solution in CH_2Cl_2, added dropwise over 1.5 h. [b] Yields determined on the crude reaction mixture by ^1H NMR analysis using Ph_3CH as an internal standard.

Scheme 3. Synthesis of Phenylcyclopropanes from Protected Allylic Alcohols and Styrenes[a]



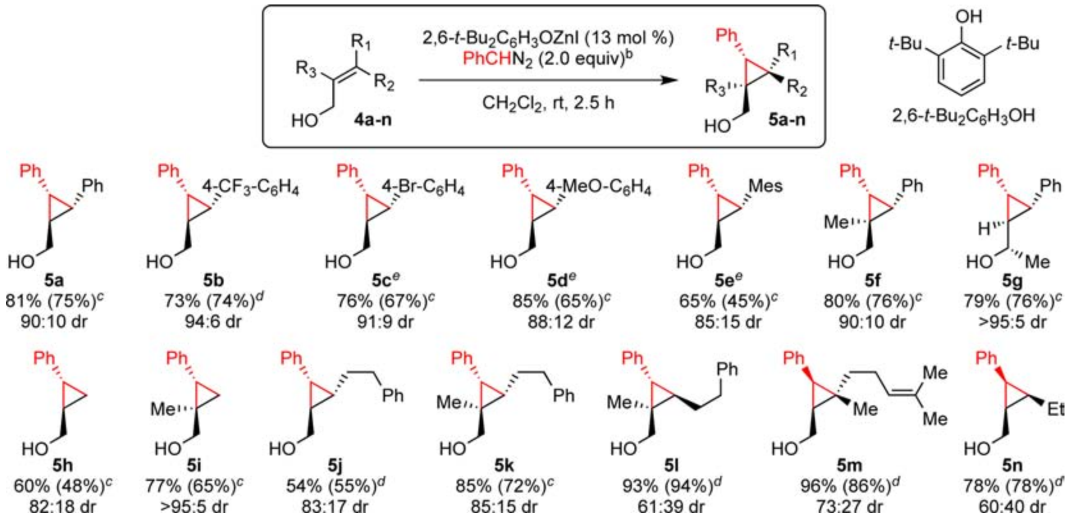
[a] Yields measured by ^1H NMR of crude mixture using Ph_3CH or DMAP as an internal standard. [b] 0.75 M solution in CH_2Cl_2, added dropwise over 1.5 h. [c] Isolated yield, major diastereomer. [d] Isolated yield, both diastereomers combined. [e] 15 mol % of ZnI_2 and 2.5 equiv of phenyldiazomethane were used. [f] 13 mol % of 2,6-*t*-$Bu_2C_6H_3OZnI$ were used instead of ZnI_2.

(Scheme 3).[15] It is noteworthy that aryl-substituted allylic ethers (**3a**−**c**) reacted with higher yields and higher diastereoselectivity than alkyl-substituted allylic ethers (**3d**−**g**). This led us to believe that styrenes may be sufficiently reactive to undergo this reaction without a Lewis basic directing group. Indeed, various styrene derivatives reacted smoothly (**3h**−**n**), only needing a slight increase in catalyst loading to improve the conversion (Scheme 3). To our knowledge, this is the first report of a zinc-catalyzed cyclopropanation of styrene derivatives. While similar transformations can be performed with other metals such as Rh,[16] Fe,[17] Ru,[18] or Os,[19] the diazo is always the limiting reagent, and large excesses (5−10 equiv) of the substrate are often required. Here the alkene is the limiting reagent and the required excess of diazo (2.5 equiv) is relatively small. This is probably due to the reactivity difference between zinc carbenoids and the carbenes usually formed with other metals.

When free allylic alcohol **4a** was treated with similar conditions, the undesired *O*-benzylated cyclopropane **3a** was observed (Table 1, entry 3). This product putatively arises from protonolysis of the carbenoid's C−Zn bond by the alcohol (*vide infra*), a reaction usually considered fast and quantitative.[20,21] The S_N2 reaction between the resulting benzyl iodide and zinc alkoxide yields the benzyl ether **3a**. As only one Zn−I bond is necessary to generate the carbenoid, we envisioned modulating its reactivity by replacing the catalyst's second iodide with another anion.[22] A screening of common anionic ligands[23] showed that zinc iodophosphates (entry 4) and iodophenoxides (entries 5−7) were suitable catalysts for this reaction. The hindered zinc phenoxide obtained from the deprotonation of 2,6-di-*tert*-butylphenol (2,6-*t*-$Bu_2C_6H_3OZnI$) gave the best results (entries 6−7).[24]

This catalyst enabled us to cyclopropanate allylic alcohols of various substitution patterns (Scheme 4) with a reduced amount of benzylated byproducts. Furthermore, some substrates (**4c**−**e**) only required 1.6 equiv of diazo reagent to achieve complete conversion, and no significant amount of benzyl iodide or alcohol was observed in the crude mixtures. These results suggest that the decreased Lewis acidity of the zinc phenoxide catalyst leads to less acidification of the substrate's OH when it is complexed to the carbenoid, making cyclopropanation more prevalent than protonolysis. A similar

Scheme 4. Synthesis of Phenylcyclopropanes from Allylic Alcohols[a]



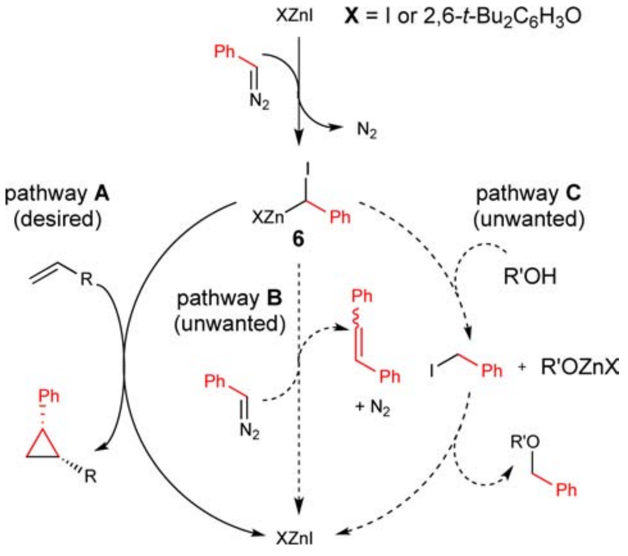
[a]Yields measured by ^{1}H NMR of crude mixture using Ph_3CH as an internal standard. [b] 0.75 M solution in CH_2Cl_2, added dropwise over 1.5 h. [c] Isolated yield, major diastereomer. [d] Isolated yield, both diastereomers combined. [e] Only 1.6 equiv of diazo used.

effect has already been reported for zinc phosphate derived carbenoids.[23b]

Throughout the reported products, the relative configuration of the introduced phenyl group was found to be dependent on the alkene's substitution pattern. For monosubstituted alkenes, the results show a *trans*-directing effect from an allylic oxygen (**3d**, **5h**), while aryl substituents are *cis*-directing (**3h**−**k**). These effects are reversed or diminished when an alkyl group is *trans* to an aryl (**3l**−**m**) or *cis* to an allylic oxygen (**3e**−**g**, **5l**−**n**), suggesting alkyls also exhibit a *cis*-directing effect. The inversion of diastereoselectivity between **5l** and **5n** and the sharp decrease in dr between **5k** and **5l** also highlight the *cis*-directing effect of the primary or secondary alkyl groups. These observations are correlated to earlier results using alkyl-substituted zinc carbenoids.[6a,25]

As previously reported,[12] the proposed mechanism for this reaction involves the formation of an iodo(phenyl)methylzinc carbenoid (**6**, Scheme 5) *via* double nucleophilic displacement[5] between phenyldiazomethane and the iodozinc catalyst **XZnI**. This carbenoid can react with the substrate alkene to yield the desired cyclopropane (pathway A), with another equivalent of diazo reagent to yield a stilbene molecule (pathway B), or with a free hydroxyl group (if present) to yield a benzyl ether (pathway C). All of these reactions regenerate the starting **XZnI** catalyst. The two undesired pathways were minimized respectively by slowly adding the diazo at room temperature and by reducing the carbenoid's Lewis acidity. The cyclopropanation is believed to proceed through a transition state similar to the classic Simmons−Smith reaction of halomethylzinc species with alkenes.[21] In the cases where the alkene possesses a vicinal Lewis basic group, precomplexation of the zinc salt to the substrate is probably involved.

Scheme 5. Proposed Mechanism for the Zinc-Catalyzed Cyclopropanation and Side Reactions



In summary, we have developed a catalytic Simmons−Smith reaction able to convert allylic ethers and styrenes into the corresponding phenylcyclopropanes. A modified catalyst even tolerates free allylic alcohols. Furthermore, this system theoretically allows the introduction of a chiral anionic ligand on the catalyst, enabling the potential development of the first enantioselective Simmons−Smith reaction using catalytic amounts of both zinc and a chiral mediator. The search for efficient chiral ligands is being pursued and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectra, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: andre.charette@umontreal.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Science and Engineering Research Council of Canada (NSERC), the Canada Research Chair Program, the FRQNT Centre in Green Chemistry, and Catalysis and Université de Montréal. E. L. is grateful to NSERC and Université de Montréal for postgraduate scholarships. The authors would like to thank former group members Dr. L.-P. B. Beaulieu, Dr. J. F. Schneider, and Dr. V. N. G. Lindsay of Université de Montréal for the synthesis of some allylic alcohols and styrenes.

■ REFERENCES

(1) Wessjohann, L.; Brandt, W.; Thiemann, T. *Chem. Rev.* **2003**, *103*, 1625.

(2) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.

(3) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1958**, 5323.

(4) (a) Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1−395. Caution! Diazo compounds are presumed to be highly toxic and potentially explosive. All manipulations should be carried out in a hood. Although in numerous preparations we have never observed an explosion, all pyrolyses and distillations should routinely be carried out behind a safety shield. Acetic acid should be used to neutralize any spilled or unwanted material. (b) Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* **1974**, *12*, 83. (c) Charette, A. B.; Juteau, H. *J. Am. Chem. Soc.* **1994**, *116*, 2651.

(5) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.

(6) (a) Charette, A. B.; Lemay, J. *Angew. Chem., Int. Ed.* **1997**, *36*, 1090. (b) Bull, J.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 1895. (c) Wilb, N.; Charette, A. B. *Synlett* **2002**, *1*, 176−178.

(7) (a) Beaulieu, L.-P. B.; Zimmer, L. E.; Gagnon, A.; Charette, A. B. *Chem.—Eur. J.* **2012**, *18*, 14784. (b) Beaulieu, L.-P. B.; Schneider, J. F.; Charette, A. B. *J. Am. Chem. Soc.* **2013**, *135*, 7819.

(8) (a) Charette, A. B.; Gagnon, A.; Fournier, J.-F. *J. Am. Chem. Soc.* **2002**, *124*, 386. (b) Zimmer, L. E.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 15624.

(9) (a) Emschwiller, G. *Compt. Rend.* **1929**, *188*, 1555. (b) Charette, A. B.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1996**, *118*, 4539.

(10) Wittig, G.; Schwarzenbach, K. *Angew. Chem.* **1959**, 652.

(11) (a) Goh, S. H.; Closs, L. E.; Closs, G. L. *J. Org. Chem.* **1969**, *34*, 25. (b) Crumrine, D. S.; Haberkamp, T. J.; Sutherl, D. J. *J. Org. Chem.* **1975**, *40*, 2274. (c) Marvell, E. N.; Lin, C. *J. Am. Chem. Soc.* **1978**, *100*, 877. (d) Altman, L. J.; Kowerski, R. C.; Laungani, D. R. *J. Am. Chem. Soc.* **1978**, *100*, 6174.

(12) Goudreau, S. R.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 15633.

(13) A similar, metal-free transformation has already been reported, but it requires high temperatures and long reaction times: Barluenga, J.; Quiñones, N.; Tomás-Gamasa, M.; Cabal, M.-P. *Eur. J. Org. Chem.* **2012**, 2312.

(14) ZnI_2 was generated in situ from Et_2Zn and I_2 to ensure reproducibility. Commercial ZnI_2, which is hygroscopic, can also be used, but results are dependent on batch quality and storage conditions.

(15) After the cyclopropanation, the MOM group could be cleaved using aqueous HCl in refluxing MeOH for 2 h. The yield of isolated alcohol was 90%. This reaction was carried out on a 0.10 mmol scale.

(16) Verdecchia, M.; Tubaro, C.; Biffis, A. *Tetrahedron Lett.* **2011**, *52*, 1136.

(17) Hamaker, C. G.; Mirafzal, G. A.; Woo, L. K. *Organometallics* **2001**, *20*, 5171.

(18) Maas, G.; Seitz, J. *Tetrahedron. Lett.* **2001**, *42*, 6137.

(19) Hamaker, C. G.; Djukic, J.; Smith, D. A.; Woo, L. K. *Organometallics* **2001**, *20*, 5189.

(20) (a) Charette, A. B.; Brochu, C. *J. Am. Chem. Soc.* **1995**, *117*, 11367−11368. (b) Charette, A. B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* **2001**, *123*, 12160.

(21) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 2341.

(22) The previously reported preforming of the substrate's sodium alkoxide with NaH should also be a suitable way to avoid benzylation.[12] However, this procedure suffers from solubility and reproducibility problems when a calatytic amount of zinc is used.

(23) (a) Charette, A. B.; Francoeur, S.; Martel, J.; Wilb, N. *Angew. Chem., Int. Ed.* **2000**, *39*, 4539. (b) Lacasse, M.; Poulard, C.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 12440.

(24) The anion of butylated hydroxytoluene (BHT) is also a suitable ligand, giving 80% yield in the conditions depicted in Table 1, entry 7.

(25) Nishimura, J.; Kawabata, N.; Furukawa, J. *Tetrahedron* **1969**, *25*, 2647.