Zinc-Mediated Transformation of 1,3-Diols to Cyclopropanes for Late-Stage Modification of Natural Products and Medicinal Agents
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ABSTRACT: A method for incorporating cyclopropane motifs into complex molecules has been developed. Herein we report a zinc dust-mediated cross-electrophile coupling reaction of 1,3-dimesylates to synthesize cyclopropanes. 1,3-Dimesylates can be readily accessed from 1,3-diols, a functionality prevalent in many natural products and medicinal agents. The reaction conditions are mild, such that functional groups, including amides, esters, heterocycles, and alkenes, are tolerated. Notably, we have demonstrated late-stage cyclopropanation of statin medicinal agents.

Natural products provide the structural frameworks and starting points for the discovery of many medicinal agents; >35% of drugs approved from 1981 to 2019 are natural products and synthetic analogues.1 Late-stage modification provides a strategy for remodeling the structures of complex scaffolds and altering activity.2 This field has evolved significantly in the past two decades, with exciting developments in chemoselective and site-selective reactions, including alcohol functionalization and C–H activation.3−6 Late-stage introduction of cyclopropane moieties would also be desirable, because the cyclopropane motif is important in medicinal chemistry.7 Alkene cyclopropanation has been employed to introduce cyclopropanes as epoxide isosteres, for example, in epothilone derivatives,8 and as a derivatization and tagging strategy for chemical biology studies.9 These strategies require alkenes in the natural product scaffold (Figure 1a).

We envisioned conversion of 1,3-diols to cyclopropanes as an orthogonal approach. The appeal of this strategy is the prevalence of the alcohol functional group in natural products and medicinal agents (Figure 1b).10 The 1,3-diol motif is central to the backbone of polyketides, secondary metabolites with diverse biological activity ranging from anticancer to antibiotic to cholesterol-lowering activity.11 1,3-Diols are also found in medicinal agents such as rosuvastatin and lumigan. In addition to modifying the pharmacokinetic properties, transformation of a 1,3-diol moiety to a cyclopropane could be employed to alter the overall conformation and relative orientation of functional groups while retaining a C(sp3)-rich backbone.12 We set out to establish a method that would achieve late-stage synthesis of cyclopropanes from complex 1,3-diols employing mild reagents. On the basis of our prior work in the development of nickel-catalyzed intramolecular cross-electrophile coupling (XEC) reactions of 1,3-dimesylates,13 we hypothesized that 1,3-dimesylates would undergo a
reducing metal-mediated XEC reaction to form cyclopropanes.\textsuperscript{14–17} In this work, we report a zinc-mediated conversion of 1,3-dimesylates to cyclopropanes and demonstrate this reaction on several natural product and medicinal agent cores, including a series of statins.

To initiate our investigation, we chose 1,3-dimesylate 1 as a suitable test substrate to identify the reaction conditions for an intramolecular XEC reaction to generate cyclopropane 2 (Table 1). Due to the functional group compatibility of reducing metal reagents, zinc dust was chosen as the reductant.\textsuperscript{18} We also included halide salts, including MgX\textsubscript{2} and NaX, in the reaction based on a working hypothesis that these reactions would proceed through 1,3-dihalide intermediates.\textsuperscript{19,20} In the presence of zinc dust and magnesium bromide in DMA, 1,3-dimesylate 1 was converted to cyclopropane 2 in 69% yield (entry 1). We observed no product formation in the absence of MgBr\textsubscript{2} (entry 2). Increasing the number of equivalents of MgBr\textsubscript{2} did not significantly impact the yield (entry 3). Diminished yields were observed with the alternative halide salts MgI\textsubscript{2}, NaBr, and NaI (entries 4–6, respectively). Notably, NaI resulted in 49% recovered starting material. Increasing the amount of NaI from 2 to 8 equiv and changing the solvent from DMA to THF provided a moderate increase in conversion from entry 6 (entry 7). Finally, combining MgBr\textsubscript{2} and NaI did not afford a higher yield (entry 8).

With suitable reaction conditions in hand, a variety of monosubstituted cyclopropanes were synthesized to demonstrate the functional group compatibility of this transformation. Monosubstituted cyclopropanes 3–8 were synthesized in good to great yields (Figure 2a). The reaction was tolerant of trifluoromethyl groups (3), PMB-protected diols (4), \(\beta\)-branched substrates (3 and 5), and aryl ethers (6). Cyclopropane derivatives of a terpene, (−)-borneol, and a steroid, \(\beta\)-sitosterol, were synthesized (7 and 8, respectively). We next sought to evaluate the synthesis of aryl- and alkyl-1,2-disubstituted cyclopropanes (Figure 2b). Aryl ether and alkyl ether substituents were well tolerated (9, 11, and 12). Notably, cyclopropane 11 containing a pendant ether was synthesized in a 47% yield. Dibenzofuran-substituted cyclopropane 10 and furanyl cyclopropane 12 demonstrate this method’s compatibility with heterocyclic motifs. Additionally, a series of 1,2-disubstituted cyclopropanes from polyketide scaffolds were

| entry | deviation from standard conditions | dimesylate | cyclopropane (%) | dr (trans/cis) |
|-------|-----------------------------------|------------|-----------------|----------------|
| 1     | none                              | 12         | 69              | 3.6:1          |
| 2     | no MgBr\textsubscript{2}         | 63         | <5              | NA             |
| 3     | 3.0 equiv of MgBr\textsubscript{2} | 21         | 68              | 3.9:1          |
| 4     | MgI\textsubscript{2} instead of MgBr\textsubscript{2} | 40         | 19              | 3.8:1          |
| 5     | NaBr instead of MgBr\textsubscript{2} | 21         | 52              | 4.2:1          |
| 6     | NaI instead of MgBr\textsubscript{2} | 49         | 33              | 4.5:1          |
| 7\textsuperscript{b} | 8.0 equiv of NaI instead of MgBr\textsubscript{2} | 35         | 47              | 3.7:1          |
| 8     | add 2.0 equiv of NaI             | 11         | 50              | 4.1:1          |

“Yields determined by comparison to PhTMS as the internal standard. \textsuperscript{b}THF instead of DMA.

Figure 2. Scope of cyclopropane formation.
synthesized (Figure 2c). An aldol reaction followed by sodium borohydride reduction provides rapid access to the desired diol motifs from commercially available β-ketoesters and the corresponding aldehydes or primary alcohols. To facilitate the XEC reaction toward cyclopropanes 13−15, we found that Zn dust with 8 equiv of NaI in THF provided the best yield for this class of substrate. Cyclopropane 13 was formed in 46% yield. The natural product (S)-citronellal was derivatized into a 1,3-dimesylate to form cyclopropane 14 in 41% yield. Likewise, (R)-nopol was derivatized to form cyclopropane 15 in 43% yield. To determine whether the reaction would be amenable to larger scales, we performed the reaction of 1,3-dimesylate 16 on a 400 mg scale and were pleased to see that the yield improved to 87% (eq 1).

Statins contain or can be rapidly converted into 1,3-diol motifs, making them optimal substrates for our XEC reaction. Natural statins, such as mevastatin and lovastatin, are polyketides isolated from fungal sources. The potent ability of statins to regulate cholesterol metabolism led to the creation of many synthetic variants, such as atorvastatin and rosuvastatin. Many synthetic statins are available as 3,5-dihydroxy carboxylate salts. However, natural statins such as lovastatin and simvastatin are instead available as the β-hydroxy lactone. We aimed to perform a late-stage modification on these medicinal agents utilizing mild reaction conditions to form cyclopropane products (Scheme 1). To cyclize these complex diols, the carboxylic acids were protected as esters and 1,3-diols were converted to 1,3-dimesylates. In some cases, a styrene was reduced or arylated prior to the XEC reaction. Derivatives of atorvastatin (17), rosuvastatin (19), fluvastatin (21), pitavastatin (23), and simvastatin (25) provided cyclopropanes 18, 20, 22, 24, and 26, respectively. In addition to 1,3-dimesylates, 1-chloro-3-mesylates underwent the zinc-mediated reaction to afford cyclopropane 24.

In summary, we report a zinc-mediated cross-electrophile coupling reaction to afford allyl and aryl cyclopropanes for late-stage modification of natural products and medicinal agents. This transformation allows for the synthesis of cyclopropanes from monosubstituted 1,3-dimesylates, 1,2-disubstituted 1,3-dimesylates, and polyketide scaffolds. As an application of this method, statin medicinal agents were converted into 1,2-disubstituted cyclopropanes.
ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02362. Experimental details and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For natural products in drug discovery, see: (a) Newman, D. J.; Cragg, G. M. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. J. Nat. Prod. 2020, 83, 770–803. (b) Rodrigues, T.; Reker, D.; Schneider, P.; Schneider, G. Counting on Natural Products for Drug Design. Nat. Chem. 2013, 5, 531–541. (c) Truax, N. J.; Romo, D. Bridging the Gap Between Natural Product Synthesis and Drug Discovery. Nat. Prod. Rep. 2020, 37, 1436–1453. (d) Henkel, T.; Brunne, R. M.; Müller, H.; Reichel, F. Statistical Investigation into the Structural Complementarity of Natural Products and Synthetic Compounds. Angew. Chem., Int. Ed. 1999, 38, 643–647.

(2) For reviews of synthetic modification of natural products, see: (a) Shugrue, C. R.; Miller, S. J. Applications of Nonenzymatic Catalysts to the Alteration of Natural Products. Chem. Rev. 2017, 117, 11894–11951. (b) Robles, O.; Romo, D. Chemo- and Site-Selective Derivatizations of Natural Products Enabling Biological Studies. Nat. Prod. Rep. 2014, 31, 318–334. (c) Majhi, S.; Das, D. Chemical Derivatization of Natural Products: Semisynthesis and Pharmacological Aspects- A Decade Update. Tetrahedron 2021, 78, 131801–131823.

(3) (a) Lewis, C. A.; Miller, S. J. Site-Selective Derivatization and Remodeling of Erythromycin A by Using Simple Peptide-Based Chiral Catalysts. Angew. Chem., Int. Ed. 2006, 45, 5616–5619. (b) Peddibhotla, S.; Dang, Y.; Liu, J. O.; Romo, D. Simultaneous Arming and Structure/Activity Studies of Natural Products Employing O–H Insertions: An Expedient and Versatile Strategy for Natural Products-Based Chemical Genetics. J. Am. Chem. Soc. 2007, 129, 12222–12231.

(4) (a) Moir, M.; Danon, J. J.; Reekie, T. A.; Kassiou, M. An Overview of Late-Stage Functionalization in Today’s Drug Discovery. Expert Opinion on Drug Discovery 2019, 14, 1137–1149. (b) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Kraska, S. W. The Medicinal Chemist’s Toolbox for Late Stage Functionalization of Drug-Like Molecules. Chem. Soc. Rev. 2016, 45, 546–576. (c) Zhang, L.; Ritter, T. A Perspective on Late-Stage Aromatic C–H Bond Functionalization. J. Am. Chem. Soc. 2022, 144, 2399–2414. (d) Guillemand, L.; Kaplaneris, N.; Ackermann, L.; Johansson, M. Late-Stage C–H Functionalization Offers New Opportunities in Drug Discovery. Nature Reviews Chemistry 2021, 5, 522–545. (e) White, M. C.; Zhao, J. Aliphatic C–H Oxidations for Late-Stage Functionalization. J. Am. Chem. Soc. 2018, 140, 13988–14009. For an example of a late-stage C–H activation of atorvastatin, see: (f) Nagib, D. A.; MacMillan, D. W. C. Trifluoromethylation of Arenes and Heteroarenes by Means of Photoredox Catalysis. Nature 2011, 480, 224–228.

(5) For examples of deamination reactions for natural product editing, see: (a) Basch, C. H.; Liao, J.; Xu, J.; Plane, J. J.; Watson, M. P. Harnessing Alkyl Amines as Electrophiles for Nickel-Catalyzed Cross Couplings via C–N Bond Activation. J. Am. Chem. Soc. 2017, 139, 5313–5316. (b) Fier, P. S.; Maloney, K. M. NHC-Catalyzed Deamination of Primary Sulfonamides: A Platform for Late-Stage Functionalization. J. Am. Chem. Soc. 2019, 141, 1441–1445. (c) Kennedy, S. H.; Dherange, B. D.; Berger, K. J.; Levin, M. D. Skeletal Editing Through Direct Nitrogen Deletion of Secondary Amines. Nature 2021, 593, 223–227. (d) Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.; Yeung, C. S.; Sarpong, R. PhotoMediated Ring Contraction of Saturated Heterocycles. Science 2021, 373, 1004–1012.

(6) For representative late-stage cross-coupling and cross-electrophile coupling reactions, see: (a) Leroux, M.; Vorherr, T.; Lewis, I.; Schaefer, M.; Koch, G.; Karaghisos, K.; Knochel, P. Late-Stage Functionalization of Peptides and Cyclopeptides Using Organozinc Reagents. Angew. Chem., Int. Ed. 2019, 58, 8231–8234. (b) Mennie, K. M.; Vara, B. A.; Levi, S. M. Reductive sp²−sp³ Coupling Reactions Enable Late-Stage Modification of Pharmaceuticals. Org. Lett. 2020, 22, 556–559. (c) Dong, Z.; MacMillan, D. W. C. Metallaphotoredox-Enabled Deoxygenative Arylation of Alcohols. Nature 2021, 598, 451–456.

(7) For cyclopropane as a privileged motif in medicinal chemistry, see: (a) Talee, T. T. The "Cyclopropyl Fragment" is a Versatile Player that Frequently Appears in Preclinical/Clinical Drug Molecules. J. Med. Chem. 2016, 59, 8712–8756. (b) Salaj, J. Cyclopropane Derivatives and their Diverse Biological Profile. In Small Ring Compounds in Organic Synthesis VI; De Meijere, A., Ed.; Springer-Verlag: Berlin, 2000; pp 1–67.

(8) (a) Johnson, J.; Kim, S.–H.; Bifano, M.; Dimarco, J.; Fairchild, C.; Gougoutas, J.; Lee, F.; Long, B.; Tokarski, J.; Vite, G. Synthesis, Structure Proof, and Biological Activity of Epothilone Cyclopropanes. Org. Lett. 2020, 22, 1537–1540. (b) Robles, O.; Serna-Saldivar, S. O.; Gutierrez-Uribe, J. A.; Romo, D. Cyclopropanations of Olefin-Containing Natural Products for Simultaneous Arming and Structure Activity Studies. Org. Lett. 2012, 14, 1394–1397.

(9) For the prevalence of alcohols in natural products and medicinal agents, see: (a) Ref 1d. (b) Cramer, J.; Sager, C. P.; Ernst, B. Hydroxyl Groups in Synthetic and Natural-Product-Derived Therapeutics: A Perspective on a Common Functional Group. J. Med. Chem. 2019, 62, 8915–8930.

(10) For comprehensive Natural Products II Chemistry and Biology; Townsend, C. A., Ebizuka, Y., Eds.; Elsevier: Kidlington, U.K., 2010; Vol. 1.

(11) (a) Koskinen, A. M. P.; Karisalmi, K. Polyketide Stereotetrads in Natural Products. Chem. Soc. Rev. 2005, 34, 677–690. (b) Walsh, C. T.; Tang, Y. In Natural Product Biosynthesis: Chemical Logic and Enzymatic Machinery; The Royal Society of Chemistry: Croydon, U.K., 2017. (c) Mander, L.; Liu, H.-W. In Comprehensive Natural Products II Chemistry and Biology; Townsend, C. A., Ebizuka, Y., Eds.; Elsevier: Kidlington, U.K., 2010; Vol. 1.

(12) (a) Lovering, F.; Bikkjer, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. J.
1,3-Dihalopropanes with SmI
Ohkita, T.; Tsuchiya, Y.; Togo, H. Radical 3-exo-tet Cyclization of
Chemistry: Where Have All the New Reactions Gone?
alpha.,omega.-dihaloalkanes. Evidence for Single-Electron-Transfer-
cyclopropanes, see: (a) With Na
Alkylcyclopropanes.
J. Am. Chem. Soc.
phile Coupling Reaction of 1,3-Dimesylates for the Synthesis of
Hong, X.; Jarvo, E. R. Nickel-Catalyzed Alkyl
Org. Lett.
Gagnier, R. P.; Patricia, J. J. Reactions of tert-butyllithium with.
Am. Chem. Soc.
Eine Neue Darstellungsmethode Des Trimethylens.
Reactions Using Alkyl-organometallics as Reaction Partners.
Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling
93
Polyfunctional Organozinc Reagents in Organic Synthesis.
Cyclization of Alkyl Dihalides.
1887
36
300–303. (c) With Zn3+ Shortridge, R. W.; Craig, R. A.;
Greenlee, K. W.; Derfer, J. M.; Boord, C. E. The Synthesis of Some
Cyclopropane and Spirane Hydrocarbons. J. Am. Chem. Soc. 1948,
70, 946. (d) With C2H5Kochi, J.; Singleton, D. Reductive Cyclization of.
alpha.,omega.-Dihalides with Chromium-(II) Complexes. J. Org.
1968, 33, 1027. (e) With Co3+ Chock, P. B.; Halpern, J.
Reactions of Pentacyanocobaltate(II) with Some Organic Halides. J.
Am. Chem. Soc. 1969, 91, 582–588. (f) With t-BuLi Bailey, W. F.;
Gagnier, R. P.; Patricia, J. J. Reactions of tert-butylithium with.
alpha.,omega.-dihaloalkanes. Evidence for Single-Electron-Transfer-
Mediated Metal-Halogen Interchange Involving Alkyl Radical-Halide
Ion Adducts. J. Org. Chem. 1984, 49, 2098–2107. (g) With SmI2:
Ohkita, T.; Tsuchiya, Y.; Togo, H. Radical 3-exo-tet Cyclization of
1,3-Dihalopropanes with SmI2 to Form Cyclopropanes. Tetrahedron
2008, 64, 7247–7251. (h) With In: Tsuchiya, Y.; Izumisawa, Y.;
Togo, H. 3-exo-tet Cyclization of 2,2-Disubstituted 1,3-Dihalopro-
panes with Indium in Aqueous and Ionic Liquid Solvent System. Tetrahedron
2009, 65, 7533–7537.
(15) Jana, S. K.; Maiti, M.; Dey, P.; Maji, B. Photoredox/Nickel
Dual Catalysis Enables the Synthesis of Alkyl Cyclopropanes via
C(sp3)−C(sp3) Cross Electrophile Coupling of Unactivated Alkyl
Electrophiles. Org. Lett. 2022, 24, 1298–1302.
(16) For general reviews of XEC reactions, see: (a) Knappke, C. E.
I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; Jacoby von
Wangelin, A. Reductive Cross-Coupling Reactions between Two
Electrophiles. Chem. - Eur. J. 2014, 20, 6828–6842. (b) Hewitt, K. A.;
Lin, P. C.; Raffman, E. T. A.; Jarvo, E. R. Comprehensive
Organometallic Chemistry IV; 2021.
(17) For intramolecular XEC of 1,5-dihalides and 1,6-dihalides, see:
(a) With alkali naphthalenes: Garst, J. F.; Barbas, J. T. Reactions of
(b) Jana, R.; Pathak, T. P.; Sigman, M. S. Advances in Transition Metal (Pd,Ni,Fe)-Catalyzed Cross-Coupling
Reactions Using Alkyl-organometallics as Reaction Partners. Chem.
Rev. 2011, 111, 1417–1492.
(19) See refs 12 and 13.
(20) For related coupling reactions of alkyl sulfonates that likely
proceed through alkyl halide intermediates, see: (a) Do, H. Q.;
Chandrashekar, E. R.; Fu, G. C. Nickel/Bis(oxyazoline)-Catalyzed
Asymmetric Negishi Arylations of Racemic Secondary Benzyl
Electrophiles to Generate Enantioenriched 1,1-Diarylcycloalkanes. J. Am.
Chem. Soc. 2013, 135, 16288–16291. (b) Liang, Z.; Xue, W.; Lin, K.;
Gong, H. Nickel-Catalyzed Reductive Methylation of Alkyl Halides
and Acid Chlorides with Methyl p-Tosylate. Org. Lett. 2014, 16,
5620–5623. (c) Xue, H.; Zhao, C.; Qian, Q.; Deng, W.; Gong, H.
Nickel-Catalyzed Cross-Coupling of Unactivated Alkyl Halides Using
Bis(pinacolato)diboron as Reductant. Chem. Sci. 2013, 4, 4022–4029.
(d) Komeyama, K.; Ohata, R.; Kiguchi, S.; Osaka, I. Highly
Nucleophilic Vitamin B12-Assisted Nickel-Catalyzed Reductive
Cyclization of Aryl Halides and Non-Activated Alkyl Tosylates. Chem.
Commun. 2017, 53, 6401–6404.