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Cyclopropanations of Olefin-Containing Natural Products for Simultaneous Arming and Structure Activity Studies

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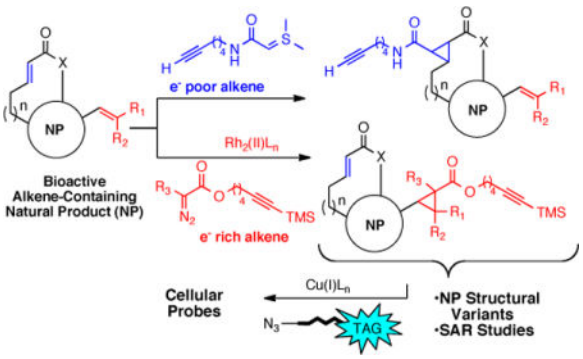
Abstract

Cyclopropanations of alkene-containing natural products that proceed under mild conditions are reported for simultaneous arming and structure-activity relationship studies. An alkynyl diazo ester under Rh(II) catalysis is employed for cyclopropanations of electron-rich olefins while an alkynyl sulfonium ylide is used for electron-poor olefins. This approach enables simultaneous natural product derivatization for SAR studies and arming (*i.e.* via alkyne attachment) for subsequent conjugation with reporter tags (*e.g.* biotin, fluorophores, photoaffinity labels) for mechanism of action studies including cellular target identification and proteome profiling experiments.

Graphical Abstract



Natural products are an enduring class of privileged structures that exhibit an incredible range of structural complexity and functional diversity. In addition, they display a plethora of biologically and medicinally important activities that include antibiotic, antifungal, antiparasitic, anticancer, and immunosuppressive properties. Historically, natural product extracts provided the first medicines to humankind and today account for roughly 50% of all

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Supporting Information Available: Detailed experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

drugs in clinical use, either directly or indirectly.[1] Natural products are also a highly productive source of leads for the development of new therapeutics,[2] and are often used as invaluable tools for the study of biological processes and the discovery of protein targets for therapeutic intervention.[3] A challenge to fully utilizing natural products in drug discovery programs is the lack of methods to enable direct modification of native natural products to tailor their properties. For this reason, we set out to develop chemo- and site selective methods to alter the structure of native natural products for structure-activity relationship (SAR) studies, generate new natural product-like structures, and to rapidly synthesize natural product-based cellular probes including biotin, fluorophore, and photoaffinity natural product conjugates.[4] To date, we have described methods for simultaneous arming and SAR studies of natural products employing mild Rh(II)-catalyzed O-H insertions with alkynyl diazo acetates of alcohol-containing natural products[5] and $In(OTf)_3$-catalyzed iodination of arene-containing natural products.[6] To expand these derivatizations to other commonly found functional groups, we now report the development of mild and selective cyclopropanation reactions of both electron-rich and electron-poor olefins. The utility of this strategy including the scope and functional group compatibility of these derivatizations is demonstrated by application to several commercially available natural products.

We initiated our studies with carvone (**1**) as a simple model system for the development of chemoselective cyclopropanations, since it contains both an electron-rich and electron-deficient alkene. For cyclopropanation of electron-rich alkenes we explored the reaction of carvone (**1**) and hexynyl diazo acetate **2a**[7] catalyzed by various transition metals (Table 1). The length of the tether between the diazo-bearing carbon and the alkyne were chosen to minimize undesired intramolecular cyclopropenation.[8] While it is well known that several metals are capable of catalyzing this process, several reaction conditions require elevated temperatures for cyclopropanations to proceed at reasonable rates.[9] With a goal of applying this strategy to the derivatization of complex and often sensitive natural products, we sought to develop the most mild and practical cyclopropanation conditions that proceeded at ambient temperature (22 °C). In our initial screening, we found that Rh(II) catalysts were the most efficient at promoting the site-selective cyclopropanation of the isopropylidene group of carvone (**1**) employing diazo acetate **2a** at 22 °C. Both copper and palladium catalysts proved ineffective under these reaction conditions (Table 1, entries 1–3), while $Rh_2(OCOCF_3)_4$, $Rh_2(OAc)_4$ and the Du Bois-Espino catalyst, $Rh_2(esp)_2$,[10] provided the desired cyclopropanes in 20, 28 and 45% yield, respectively (Table 1, entries 4–6). These reactions led to complete site selectivity but a mixture of only two diastereomeric cyclopropanes (dr 2:1, R^1 = H). Diazo esters **2b**–**2c**[7] led to cyclopropanation, however, the chemical yields remained modest (19 and 55%, Table 1, entries 7–8). Careful analysis of side-products revealed that the alkyne on the side-chain was in fact reacting competitively with the metallocarbenoid intra- and intermolecularly leading to the corresponding cyclopropenes. To circumvent this side reaction, a TMS-protected alkynyl diazo reagent **2d** was studied[8a,c] and found to completely supress cyclopropenations as evidenced by a dramatic increase in the desired diastereomeric cyclopropanes to 91% (dr 1:1:1:1, Table 1, entry 9). Under these optimized conditions, only 1.2 equivalents of the diazo reagent were needed for complete conversion of carvone.[11]

The scope of this reaction was assessed with several commercially available alkene-containing natural products (Scheme 1) using the established optimized conditions (Table 1, entry 9). Cyclopropanation of caryophyllene oxide provided the desired cyclopropanes **4** in 94% yield with high facial selectivity and with 3:1 diastereoselectivity at the newly generated quaternary carbon. The antineoplastic agent bexarotene methyl ester was also an excellent substrate delivering racemic cyclopropanes **5** in 93% yield and 8:1 dr. The insecticide rotenone gave all four possible diastereomeric cyclopropanes **6** in 88% yield and 3:3:1:1 ratio. Trisubstituted alkenes participate under these conditions as demonstrated with vitamin K1, providing four diastereomeric cyclopropanes **7** in 84% yield. The reaction of more sterically encumbered alkenes was more challenging as evidenced by attempted cyclopropanation of forskolin which required 3 equiv of diazo ester **2d** for complete conversion to deliver cyclopropanes **8** in 81% yield. To prevent OH insertion[5] with accessible free alcohols, mild global silylation was performed prior to cyclopropanation of forskolin and gibberellic acid methyl ester. However, in the case of forskolin, the hindered tertiary C6 and secondary C9 alcohols are not protected under these conditions and also did not undergo OH insertion. With the accessible alcohols protected, cyclopropanation proceeded smoothly to give cyclopropyl forskolin derivative **8** (81% yield, dr 1:1) and in the case of gibberellic acid methyl ester which contains two electron-rich olefins, only the less hindered 1,1-disubstituted olefin undergoes cyclopropanation to provide derivative **9** in 79% yield (dr 3:1). The TMS groups are readily removed simultaneouly during subsequent Sharpless-Huisgen cycloaddition (*vide infra*).

For cyclopropanation of electron-deficient alkenes,[12] we prepared the alkynyl amide-containing sulfonium salt **10**.[13] Addition of this salt to a solution of *t*-BuOK in DMSO generated the corresponding sulfur ylide which reacted selectively with electron-poor alkenes in several natural products (Scheme 2). Carvone (**1**) provided the desired cyclopropane **11** in good yield (94%) and diasteroselectivity (8:1 dr). Brefeldin A reacted under these conditions affording the cyclopropane **12** albeit in low yield (32%) and diastereoselectivity (2.5:1). Similarly, phorbol dibutyrate gave cyclopropane **14** in modest yield (24%) and low diastereoselectivity. In the case of parthenin and achillin, this reaction exhibited high chemosite (chemo- and site) selectivity providing monocyclopropane **13** in 32% yield (dr 6:1) and cyclopropane **15** in 72 % yield (dr >19:1), respectively. Parthenin reacted selectively at the more reactive *exo*-methylene and the structure of this adduct was verified by X-ray crystallography (Scheme 2, inset).

The need for global silylation prior to cyclopropanation to prevent OH insertion was readily accomodated since a procedure for *in situ* desilylation of TMS-alkynes and subsequent Sharpless-Huisgen cycloaddition was recently reported in the presence of tetrabutylammonium fluoride (TBAF).[14] The utility of this process was demonstrated by the synthesis of a biotin conjugate from the TMS-protected forskolin cyclopropane **8** (Scheme 3). This tandem desilylation/cycloaddition proceeded in good yield (76%) to give the deprotected, forskolin-biotin conjuate **17**.

We also demonstrated that the described Rh(II)-catalyzed cyclopropanation/conjugation strategy is amenable to microscale,[15] as demonstrated by the derivatization of 1 mg of bexarotene methyl ester (**18**). The two step sequence provided the bexarotene-biotin

conjugate **19** cleanly and in sufficient quantities to be characterized by ^{1}H NMR (500 MHz) and HRMS (Scheme 4).

In summary, we have developed reagents for selective cyclopropanations that enable simultaneous derivatization and arming of both electron rich and electron poor olefin-containing natural products under mild conditions. We anticipate that use of chiral Rh(II)-catalysts and chiral sulfoximines could alter observed diastereoselectivity and most importantly could alter site selectivity in natural products with multiple electron rich and electron poor alkenes, respectively.[9] The described methods enable SAR studies of native or transiently protected natural products in addition to subsequent conjugation, via the appended alkyne, with reporter tags for cellular target identification, mechanism of action studies and the synthesis of activity-based molecular probes for global protein profiling.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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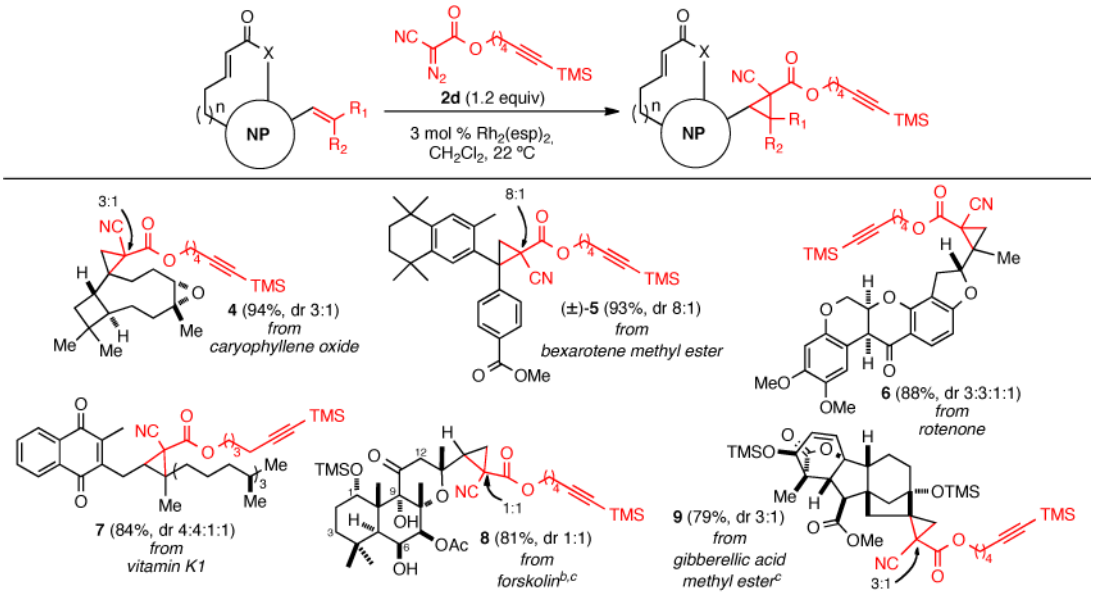
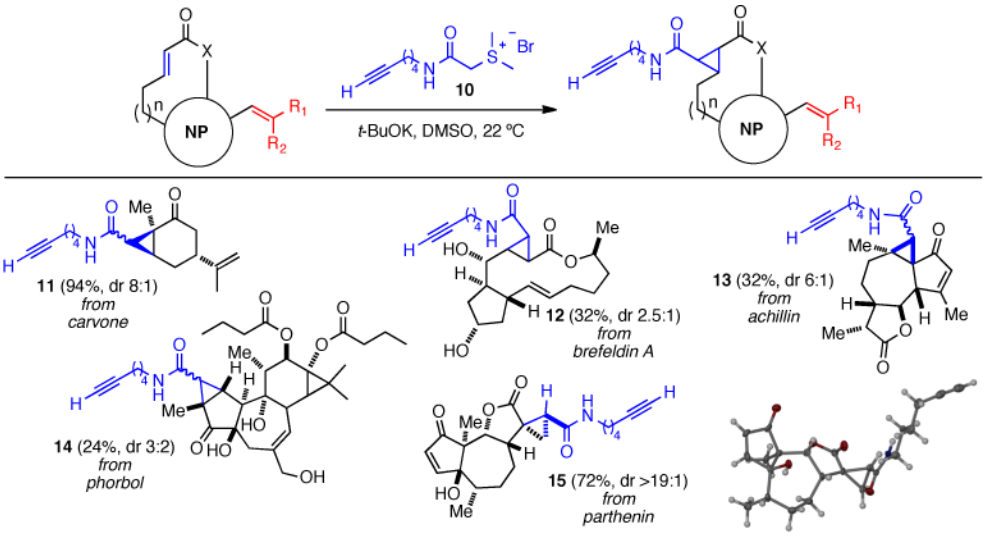


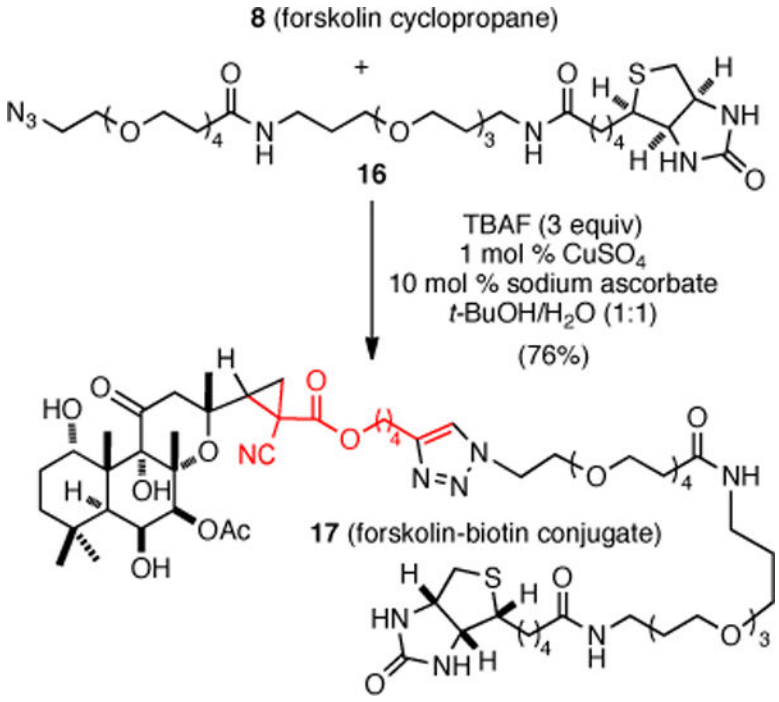
Scheme 1. $Rh_2(Esp)_2$-Catalyzed Cyclopropanations of Natural Products Bearing Electron-Rich Alkenes with Alkynyl Diazo Ester 2d.[a]

[a]Diastereomeric ratios were determined by ^1H NMR (500 MHz); the relative stereochemistry of the major diastereomers was not determined since in some cases they were inseparable (see Supporting Information). [b]3.0 equiv of diazo ester **2d** were employed. [c]Silylation was performed prior to cyclopropanation (TMSCl, DMAP, Et_3N, CH_2Cl_2, 22 °C).



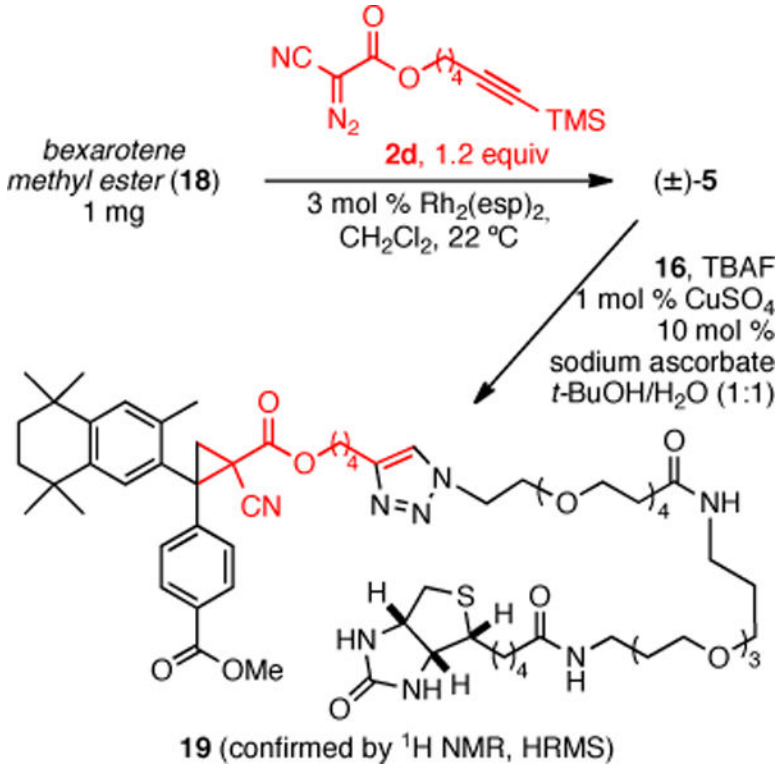
Scheme 2. Scope of the Cyclopropanation of Natural Products Bearing Electron-Poor Alkenes with Alkynyl Sulfonium 10.[a]

[a]Diastereomeric ratios were determined by ^{1}H NMR (500 MHz); the relative stereochemistry was not confirmed (with exception of **15**) but where indicated is based on conformational considerations of the natural product substrate.



Scheme 3.

Desilylation/Conjugation of Cyclopropyl-Forskolin **8** with a Biotin Tag via a Sharpless-Huisgen Cycloaddition.

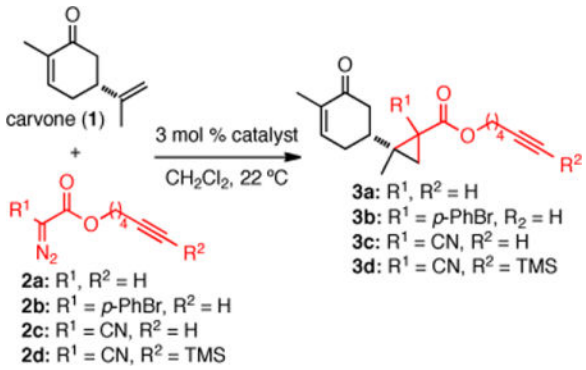


Scheme 4.

Microscale Cyclopropanation/Conjugation of Bexarotene Methyl Ester (**18**).

Table 1

Screening of Catalysts and Diazo Reagents for the Cyclopropanation of Carvone (**1**).[a]



entry	diazo	catalyst	% yield[b]	dr[c]
1	**2a**	$Cu(acac)_2$	0	–
2	**2a**	IprCuCl	trace	–
3	**2a**	$PdCl_2(CH_3CN)_2$	0	–
4	**2a**	$Rh_2(OCOCF_3)_4$	20%	2:1
5	**2a**	$Rh_2(OAc)_4$	28%	2:1
6	**2a**	$Rh_2(esp)_2$	45%	2:1
7	**2b**	$Rh_2(esp)_2$	19%	2:2:1:1
8	**2c**	$Rh_2(esp)_2$	55%	1:1:1:1
9[d]	**2d**	$Rh_2(esp)_2$	91%	1:1:1:1

[a] Reaction of carvone (**1**) and diazo esters **2a–c**, (4 equiv) at 22 °C.

[b] Values refer to isolated yields.

[c] Ratios were determined by ^{1}H NMR (500 MHz); the relative stereochemistry was not determined.

[d] Only 1.2 equiv of **2d** were used. acac = acetylacetonate; IPr = [1,3-bis(diisopropylphenyl)imidazole-2-ylidene]; esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate.