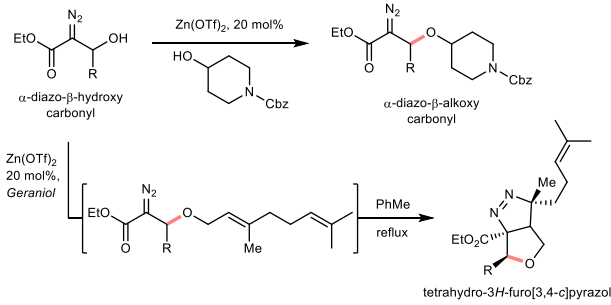
Lewis Acid-Catalyzed Oxa-Michael Addition to give α-Diazo-β-alkoxy Carbonyls and Tetrahydro-3H-furo[3,4-c]pyrazoles.

Avery M. Peck and Matthias Brewer*

Department of Chemistry, The Univeristy of Vermont, 82 University Place, Burlington, VT 05405, United States.

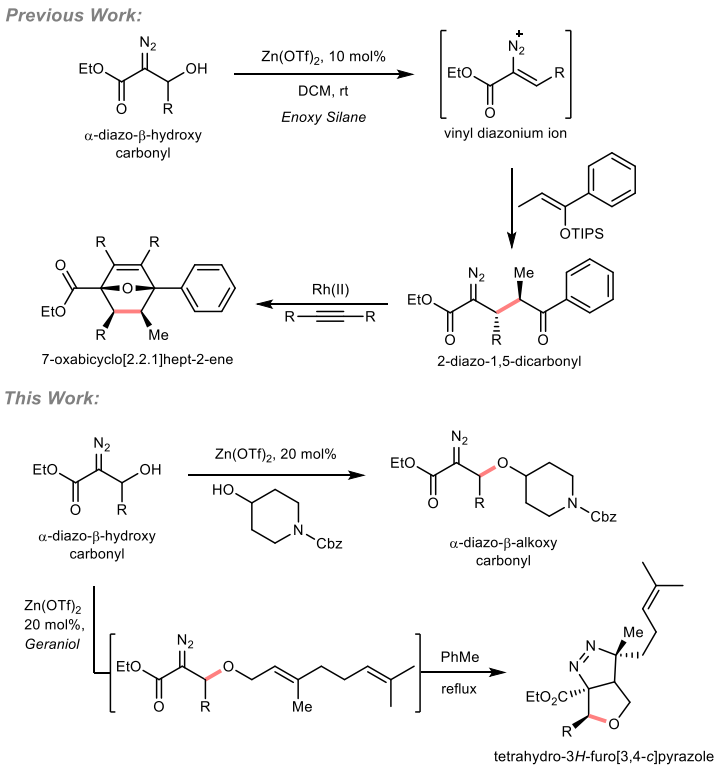
Supporting Information Placeholder



ABSTRACT: The conjugate addition of alcohols to vinyl diazonium ions formed via $Zn(OTf)_2$-catalysis gives α-diazo-β-alkoxy carbonyls. The diazo group is retained in this reaction, and this process is an efficient way to couple a reactive partner to the diazo fragment. As an example, we disclose that addition of allyl alcohols provides tetrahydro-3H-furo[3,4-c]pyrazoles via an addition/cycloaddition sequence. This two-step sequence provides good yields and good diastereoselectivity of these sterically hindered pyrazoline scaffolds with up to three quaternary centers and four stereogenic centers. These products can be elaborated to cyclopropane-fused tetrahydrofurans upon liberation of nitrogen. The reaction conditions are mild, operationally simple, and avoid the use of expensive transition metal catalysts.

The conjugate addition of nucleophiles to α,β-unsaturated carbonyls is one of the most fundamental and important reactions in organic chemistry. Our group has shown that vinyl diazoniums are strong Michael acceptors that react via conjugate addition with even weak carbon nucleophiles (Scheme 1, a).[1, 2] These reactions give complex scaffolds in high yields and diastereoselectivity and preserve the diazo functional group for further manipulation. For example, the 2-diazo-1,5-dicarbonyl compounds prepared by the Mukaiyama-Michael addition reaction of enoxysilanes to vinyl diazoniums can be used in subsequent carbonyl ylide 1,3-dipolar cycloaddition reactions to give 7-oxabicyclo[2.2.1]hept-2-enes (Figure 1) or in intramolecular O-H insertion reactions to give stereochemically rich monocyclic tetrahydrofurans.[3] The genesis of that work was computational results we obtained which indicated that the Lewis acid catalyzed formation of vinyl diazonium ions via dehydroxylation of α-diazo-β-hydroxy carbonyls was reversible, thus opening the possibility to capture the vinyl diazonium with an alternative carbon nucleophile. [4] We thought that it might also be possible to take advantage of this reactivity by trapping the vinyl diazonium with an alcohol to form an ether linkage giving α-diazo-β-alkoxy carbonyl products.

Scheme 1. Vinyl diazonium ions in the preparation of oxabicycles.



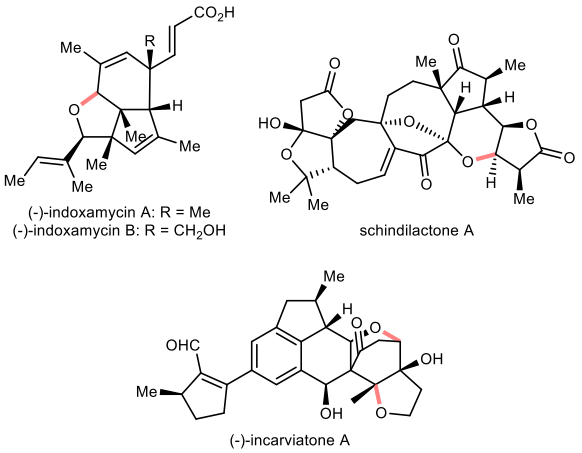


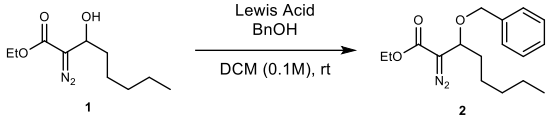
Figure 1. Natural products whose synthesis includes an oxa-Michael reaction.

Since initially reported by Loydl in 1878, the conjugate addition of oxygen nucleophiles (a.k.a. oxa-Michael addition) has become a convenient way to form carbon-oxygen bonds and has been used in the synthesis of natural products and biologically active compounds (Figure 1).[5-11] One advantage of the oxa-Michael disconnection in synthesis is that alcohol nucleophiles are readily available and naturally abundant, which makes methods that incorporate these fragments into complex molecular architectures particularly attractive. Herein, we disclose a Lewis-acid catalyzed oxa-Michael addition of alcohols to vinyl diazonium ions. This reaction is operationally simple, and because the diazo group is retained over the course of this reaction, this process is an efficient way to couple a reactive partner to the diazo fragment. For example, herein we report an operationally simple way to prepare tetrahydro-3H-furo[3,4-c]pyrazoles *en* route to 3-oxabicyclo[3.1.0]hexanes.

We began our studies by treating diazo **1** (Table 1) with 20 mol% of $Zn(OTf)_2$ in the presence of two equivalents of benzyl alcohol, which gave ether **2** in 75% yield. While the starting material was completely consumed in this reaction, no other compounds were isolated from the reaction mixture. It seemed possible that a portion of the starting material may decompose in the presence of TfOH that could be generated by the reaction of the benzyl alcohol with the $Zn(OTf)_2$. However, attempts to increase the product yield by adding a non-nucleophilic base failed (Table 1; Entry 2 and 3). Additional Lewis acid (Entry 4), lowering the temperature (Entry 5), or using alternative Lewis acids (Entries 6-8) also failed to increase the yield, and Schreiner's thiourea catalyst did not promote the reaction. We noted that the reaction occurred nearly instantly as monitored by TLC when $Al(OTf)_3$ and $BiCl_3$ were used as Lewis acid (Entries 6-8) whereas reactions facilitated by $Zn(OTf)_2$ were slightly slower, typically requiring about 15 minutes to achieve full conversion. We elected to use $Zn(OTf)_2$ as the catalyst of choice for further reaction development because we favored the use of a milder, earth-abundant Lewis-acid that would potentially tolerate a wider range of substrates.

To explore this reaction further, we tested the addition of a variety of alcohols to 1 (Table 2). In general, the yields of the addition were good, and a wide variety of functional groups were tolerated. 1° and 2° alcohols bearing aryl and heteroaryl substituents were well tolerated (**2**, **4**, and **6**, Table 2), although the less nucleophilic phenol only added in 25% yield (**3**, Table 2). A thiol was also a competent nucleophile

Table 1. Optimization of conjugate addition reaction.



entry	conditions	yield
1	**$Zn(OTf)_2$ (20 mol%)**	**75%**
2	Zn(OTf) (10 mol%), DBU (10 mol%)	68%
3	Zn(OTf) (20 mol%), DBU (10 mol%)	57%
4	Zn(OTf) (1.0 equiv.)	58%
5	$Zn(OTf)_2$, 20 mol%, 0 °C	61%
6	$Dy(OTf)_3$ (10 mol%)	63%
7	$Al(OTf)_3$ (10 mol%)	54%
8	$BiCl_3$ (10 mol%)	51%

under the standard conditions with **5** being formed in 65% yield. Using this reaction, alkenes and alkynes were readily tethered to the diazo carbonyl (entries, **7-9**, 19, table 2). Unprotected amino alcohols were not tolerated, presumably they poison the catalysts, but protected amino alcohols featuring typically acid-sensitive protecting groups were well tolerated (entries **10**, **12-14**, Table 2). We recognized that with alcohols being naturally abundant, this reaction could be a useful way to install the diazo functional group onto a variety of chiral pool compounds and small biologically active molecules (entries **15-18**, Table 2). Predictably, steric hindrance associated with the nucleophile was a factor in determining the efficiency of the addition. We noticed the formation of a side product when 2.0 equivalents of 2° alcohols were used. Interestingly, the side product was the result of the diazo alcohol acting as a nucleophile to form dimer **20** (Scheme 2). Indeed, when 1 was treated with 20 mol% of $Zn(OTf)_2$ in the absence of an exogeneous nucleophile, **20** was formed in 76% yield (Scheme 2). In order to suppress this dimerization pathway, it became necessary to adjust the reaction conditions when 2° and 3° oxa-nucleophiles were used. Increasing the amount of 2° alcohols employed in the reaction to 3.0 equivalents gave comparable yields of conjugate adducts. In the case of 1-phenylethanol, the yield of **11** increased from 65% to 73% yield when 3.0 equivalents of the alcohol were used (Table 2). When 3° nucleophiles were employed, diazo dimer **20** was the only product of the reaction when the reaction was run in CH_2Cl_2. However, using the alcohol itself as the solvent gave good yields of the addition products with a variety of diazo carbonyls (**19**, Table 2; **31-35**, Table 3). A similar substrate tolerance was observed with these conditions as compared to the standard conditions.

Scheme 2. Dimerization of **1**.

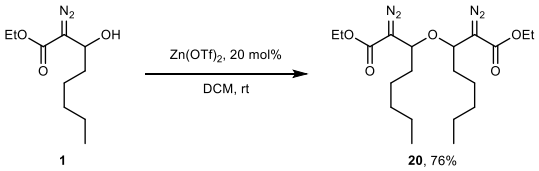
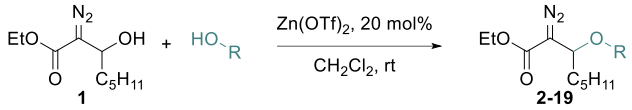
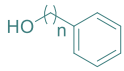
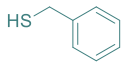
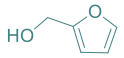
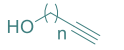
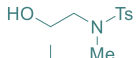
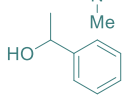
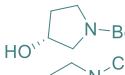
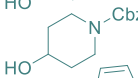
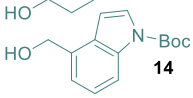
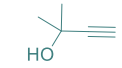


Table 2. Alcohol scope in conjugate addition reaction.



Alcohol	Product	yield
	**2**, n = 1	75%[a] (82%)[a,b]
	3, n = 0	25%[a]
	**4**, n = 3	57%[a]
	5	76%[a]
	**6**	58%[a]
	**7**	61%[a]
	**8**, n = 1	79%[a]
	9, n = 2	48%[a]
	**10**	47%[a]
	**11**	73%[c] (7.2:10 d.r.)

Alcohol	Product	yield
	**12**	55%[c] (1:1 d.r.)
	**13**	44%[c] (1:1 d.r.)
	**14**	32%[c]
Cholesterol	**15**	29%[c]
Menthol	**16**	49%[c] (2:1 d.r.)
Borneol	**17**	65%[c] (1:1 d.r.)
Carveol	**18**	69%[c]
	**19**	84%[d]

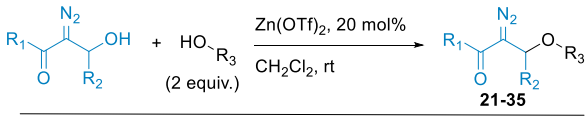
a) reaction run with 2.0 equivalents of alcohol.
b) 1 mmol scale
c) reaction run with 3.0 equivalents of alcohol.
d) reaction run neat in 1.0 mL of 2-methylbut-3-yn-2-ol.

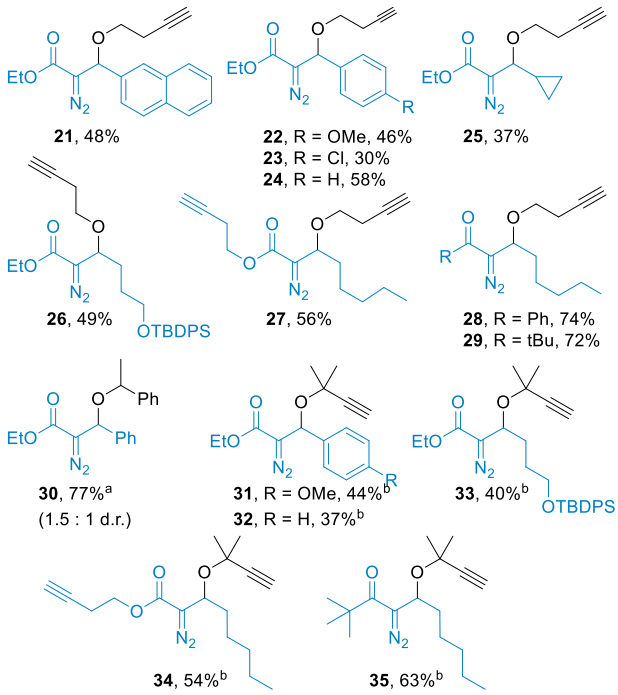
While the neat protocol represents an effective and Green Chemistry approach when cheap or liquid nucleophiles are used, we sought to develop a slow-addition protocol to accommodate higher-valued and solid nucleophiles. By slowly adding 1 to a mixture of $Zn(OTf)_2$ and 2-methylbut-3-yn-2-ol in CH_2Cl_2 over eight hours, a 5:3 ratio of product **19** and dimer **20** was observed in the crude reaction mixture with 46% yield of **19** isolated. In contrast, when the reaction was run under normal conditions in CH_2Cl_2 (0.1M), **20** is the only product of the reaction.

We further explored the scope of the diazo carbonyl in this reaction (Table 3). Electron rich, neutral, or poor aryl rings at the β-position of the diazo alcohol reacted well with 1° (**21-24**), 2° (**30**), and 3° (**31**, **32**) alcohols. Aliphatic substituents at the β-position were also well tolerated (**25-27**, **34**, **35**), and a silyl ether survived the reaction intact (**26, 33**). Changing the ester from ethyl to 3-butynyl had little effect on the reaction (**27**, **35**) whereas β-hydroxy-α-diazo ketones gave higher product yields (**28**, **29**, **35**). The reaction was readily scalable and increasing the reaction to 1.0 mmol scale gave **2** in 82% yield (Table 1). We reasoned that the detrimental effect of trace moisture on the reaction outcome is mitigated on larger scale.

This conjugate addition reaction provides a convenient method for linking reactive groups to the diazo group for intramolecular reactions. Indeed, when allyl alcohols were used as nucleophiles the conjugate adducts spontaneously underwent a subsequent cycloaddition reaction to give fused bicyclic tetrahydrofuran products. When geraniol was used, the alkoxy diazo ester could be isolated cleanly by chromatography, but on standing overnight, the neat mixture underwent a cycloaddition with the tethered alkene to give the tetrahydro-3H-furo[3,4-c]pyrazole **36** (Table 4) as a single diastereomer. Structural and stereochemical assignment of **36** were determined through 2D NMR

Table 3. Scope of α-diazo-β-hydroxy carbonyl in conjugate addition reaction.

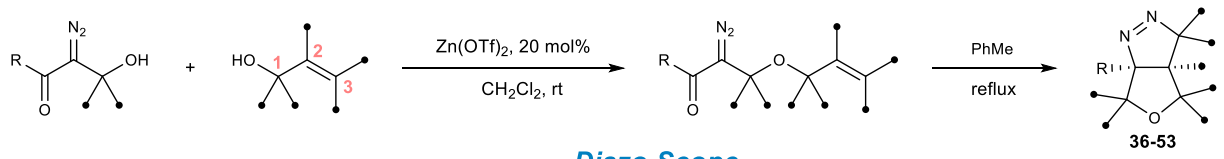




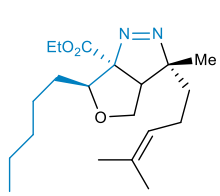
a) Reaction run with 3.0 equivalents of alcohol.
b) Reaction run neat in 1.0 mL of 2-methylbut-3-yn-2-ol.

experiments. Given the generality of the conjugate addition step, we thought this two-step reaction sequence might represent a general strategy to form pyrazoline-fused tetrahydrofurans from which N2 could be extruded to give cyclopropane-fused products. [12-15] Notably, this intramolecular reaction forms two congested ring systems in a single step. Thus, with optimized conditions for the initial conjugate addition step in hand, we explored a two-step addition/cycloaddition protocol. In most cases we were unable to isolate the allyl ether intermediates cleanly due to partial cyclization, but simply heating the crude reaction mixture from the conjugate addition in refluxing toluene gave the tetrahydro-3H-furo[3,4-c]pyrazoles in good yields over two steps. We assessed the scope of this reaction using geraniol as the allyl alcohol as we favored a non-volatile alcohol that would demonstrate the robust nature of the cycloaddition (Table 4). The majority of the α-diazo-β-hydroxy diazo starting materials used to generate the compounds shown in Tables 2 and 3 were subjected to the two-step protocol giving the compounds shown in Table 4. In general, the yields of the two-step cycloaddition were good, and the reaction often afforded a single diastereomer of the product. Both alkyl and aryl substituents at the beta position of the diazo carbonyl were tolerated. While all of these examples feature two quaternary centers on the pyrazole, a quaternary center on the furan portion of the bicycle could also be incorporated as shown in **40** (39% yield) and in the spirocycle **41**, albeit in low yield for this latter case (8% yield). These products were derived from α-diazo-β-hydroxy diazo esters with tertiary β-alcohols, which proved to be capricious under the conjugate

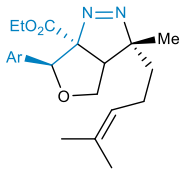
Table 4. Scope of addition/cycloaddition sequence.



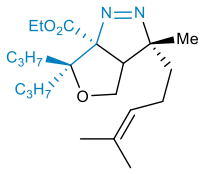
Diazo Scope



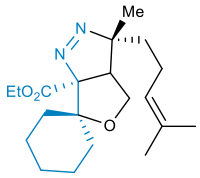
36, 49%
(1.0 mmol, 67%)



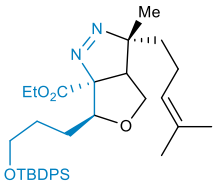
37, Ar = 2-napthyl, 52%
38, Ar = Ph, 28%
39, Ar = 4-ClPh, 24%



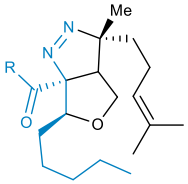
40, 39%



41, 8%

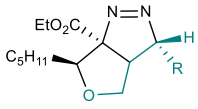


42, 41%

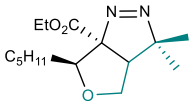


43, R = tBu, 43%
44, R = O-but-3-yne, 49%

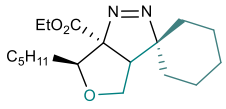
Alcohol Scope



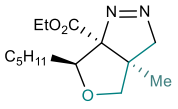
45, Ar = Ph, 57%
46, Ar = 4-OMePh, 34%
47, Ar = 4-NO_2Ph, 37%
48, R = C_3H_7, 77% (10:1 d.r.)



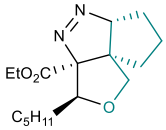
49, 44%



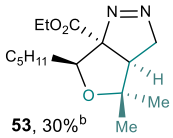
50, 44%



51, 51% (92%)[a]



52, 41%



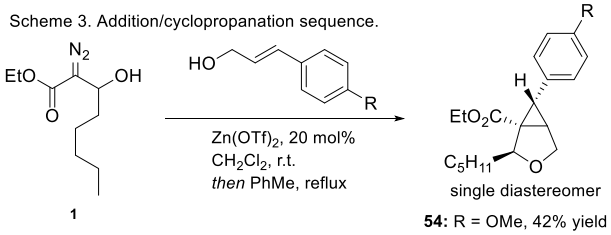
53, 30%[b]
8.2:10.0 d.r.

a) yield of cycloaddition step.
b) addition reaction run neat in 1.0 mL of 2-methylbut-3-en-2-ol

addition conditions as they tend to give an elimination product that was generally inseparable from the desired product. The scalability of the two-step conjugate addition/cycloaddition was very good, and **36** was prepared in 67% yield on 1.0 mmol scale (Table 4). We also examined the scope of different allyl alcohols in this cyclopropane reaction. Varying degrees of substitution at the 3-position of the allyl alcohol gave differentially substituted pyrazoline products (**48**, **49**, **51**). The unhindered E-hexene-1-ol gave **48** in 77% yield as a 10:1 mixture of diastereomers. We were pleased to discover that this method could deliver highly substituted pyrazolines bearing multiple all-carbon quaternary centers. For example, using 3,3-dimethyl allyl alcohol as the nucleophile gave **49** as a single diastereomer in 44% yield. This alkene substitution pattern was also well tolerated to make spirocycle **50** in 44% yield. Substitution at the 2-position of the alkene was also tolerated and the sterically encumbered **51** was formed in 51% yield. With this example we were also able to isolate the β-alkoxy-α-diazo precursor of **51** in 53% yield (0.11 mmol). After refluxing in toluene, 92% yield (0.10 mmol) of **51** was isolated, which indicates that the cycloaddition step is high yielding with the conjugate addition being the more moderate yielding of the two-step sequence. A tricyclic doubly-fused pyrazoline (**52**) was formed in 41% yield as a single diastereomer. Finally, when 2-methylbut-3-en-2-ol was used as the nucleophile, the product contained an all-carbon quaternary center on the tetrahydrofuran ring (**53**). In this case the Thorpe-Ingold effect seems to increase the rate of the cycloaddition step as the crude reaction mixture after the conjugate addition step contained the pyrazoline product with no detectable amounts of the conjugate adduct.

We extended this sequence to a Kishner-type cyclopropanation[16] to give cyclopropane-fused tetrahydrofuran products derived from cinnamyl alcohol derivatives. When the crude addition mixture containing **46** was subjected to prolonged heating, liberation of nitrogen occurred to give the 3-oxabicyclo[3.1.0]hexane **54** (Scheme 3) in 42% yield as a single diastereomer. NOESY NMR analysis indicates that the relative stereochemistry in the pyrazoline is retained through the cyclopropanation step (see supporting information). This addition/cyclopropanantion sequence also tolerated other aryl rings at the 3-position of the alkene to give **55** and **56** in similar yields (52% and 48% respectively, Scheme 3) also as single diastereomers. Pyrazolines with secondary and tertiary centers at the 3-position of the alkene were less amenable to N_2 liberation and cyclopropane formation, and we are currently investigating methods that provide a general addition/cyclopropanation sequence. In summary, we have developed an operationally simple and highly atom-economical method for the conjugate addition of oxygen nucleophiles to vinyl diazonium ions to give β-alkoxy-α-diazo carbonyls. This is a simple and convenient way to tether useful functionality to the diazo group, [17-24] one of the most versatile functional groups in organic chemistry. This is showcased by the sequential addition/cycloaddition sequence of allyl alcohols described here to give tetrahydro-3H-furo[3,4-c]pyrazoles *en* route to 3-oxabicyclo[3.1.0]hexanes with excellent diastereoselectivty. Importantly, this protocol does not require the use of expensive transition-metal catalysts.

Scheme 3. Addition/cyclopropanation sequence.



54: R = OMe, 42% yield
55: R = NO_2, 52% yield
56: R = H, 48% yield

ASSOCIATED CONTENT

Supporting Information

The data underlying this study are available in the published article and its Supporting Information.

Experimental procedures and compound characterization data (PDF).

AUTHOR INFORMATION

Corresponding Author

* Matthias Brewer – Department of Chemistry, University of Vermont, Burlington VT, 05495
orcid.org/0000-0003-4250-7195
Email: Matthias.brewer@uvm.edu

Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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