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Three-Component [1 + 1 + 1] Cyclopropanation with Ruthenium(II)

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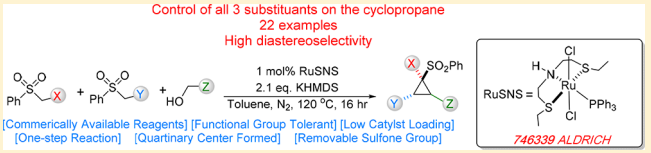
Supporting Information

ABSTRACT: We report a one-step, Ru(II)-catalyzed cyclopropanation reaction that is conceptually different from the previously reported protocols that include Corey−Chaykovsky, Simmons−Smith, and metal-catalyzed carbene attack on olefins. Under the current protocol, various alcohols and esters are transformed into sulfone substituted cyclopropanes with excellent isolated yields and diastereoselectivities. This new reaction forms highly congested cyclopropane products with three new C−C bonds, three or two new chiral centers and one new quaternary carbon center. Twenty-two examples of isolated substrates are given. Previously reported synthetic routes for similar substrates are all multistep, linear routes that proceed with overall low yields and poor control of stereochemistry. Commercially available Ru(II) dehydrogenation catalysts, that were recently developed for the dehydrogenative synthesis of esters and amides from alcohol and amine substrates, were used in the reaction, with the best catalyst showing excellent activity at 0.2−1 mol % catalyst loading. Mechanistic investigation showed that in the case of alcohol substrates, the catalyst is only responsible for the first dehydrogenation step, and that the identity of the base and the countercation is crucial in achieving high yields. The catalyst is also required for the cyclopropanation of esters, although no dehydrogenation can proceed in this case, suggesting that substrates sensitive to H_2 may be acylated prior to reaction.

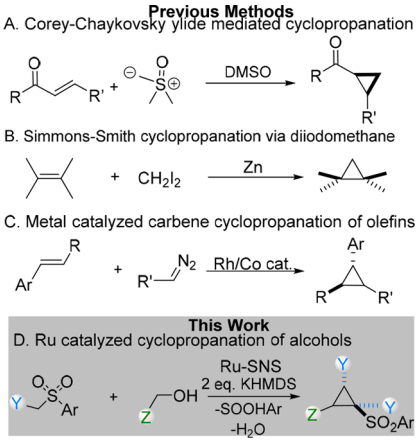


INTRODUCTION

Cyclopropanes are an important structural motif in many biosynthetic pathways and are present in a large number of natural products.[1] Compounds bearing it have found use in the pharmaceutical industry as drugs and antibiotics and as useful precursors in the synthesis of industrially relevant compounds.[2] However, the high ring strain presents many synthetic challenges. These challenges are further compounded when forming highly substituted or quaternary center bearing rings. The most common pathways to accessing cyclopropanes proceed through the generation of a reactive carbene or ylide species. These reagents often require multistep preparation of the olefin and carbene precursors. Historical examples include the Simmons−Smith cyclopropanation, which uses multiple equivalents of zinc (recently catalytic zinc reagents have been utilized),[3] and the Corey−Chaykovsky cyclopropanation, where a sulfur ylide adds to an electron-poor olefin (Scheme 1).[4,5] Other popular methods for synthesizing cyclopropanes include olefin additions of carbenes,[6] often metal-catalyzed and formed from the decomposition of diazo reagents.[7] More specialized reactions involving organocatalysis,[4g,i,8] ene-yne catalyzed ring closure,[9] and metal-catalyzed additions to cyclopropenes[10] have also been reported. In the vast majority of cases, these approaches are specific to polarized or electron-deficient olefins, where a β-carbon substituent often acts as a directing group.

In this work, we report a new one-step catalytic cyclopropanation of alcohols with sulfones. This new reaction has advantages over previous methods by offering control over substituents on all three ring carbons, excellent diastereoselectivity, and no need for prefunctionalization of complex olefins or sensitive diazo reagents beforehand. The three-component assembly of the ring also offers a new retrosynthetic analysis to cyclopropanes, maximizing the convergence of a synthetic route. Although quaternary center

Scheme 1. Summary of Cyclopropane Syntheses



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sulfone cyclopropanes have been reported in the literature,[11] their syntheses are multistep and often involve the preparation of an advanced thioether intermediate followed by oxidation. Our new synthetic method eliminates multiple steps and redox manipulations, while also using benign building blocks that are all commercially available and cheap. The reaction proceeds with low catalyst loadings (down to 0.2 mol %) of Ru dehydrogenation catalyst and gives products with two or three new stereocenters, one of which is quaternary carbon (Scheme 1).

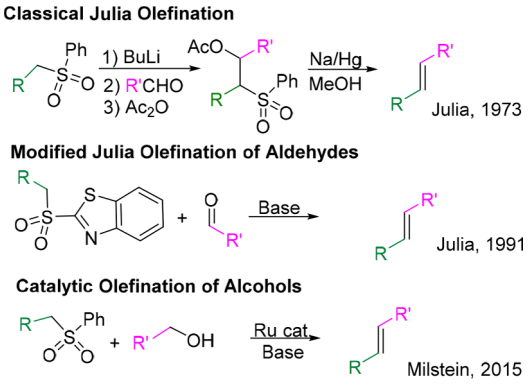
Currently, there is only one previous report by Antonchik, where all three ring carbons are joined in one step from different molecules.[12] The report mostly shows couplings between two readily available components to form structurally unique cyclopropanes. However, the three-component procedure is limited to methyl aryl ketones with the conditions requiring 10 mol % of catalyst, excess peroxide, and only forming symmetric products with the same R group on all ring carbons.

Although aryl sulfones can be easily reduced in one step to afford all carbon-substituted cyclopropanes,[13] they also have a unique electron-withdrawing effect conducive to ring-opening reactions.[14] Sulfone-substituted cyclopropanes have been recently used in an elegant C−N bond coupling technique by the Baran group.[11a,15] Other ring-opening reactions of so-called "push−pull cyclopropanes" in organic synthesis, including ring expansion, have been summarized previously.[11a,16]

RESULTS AND DISCUSSION

Initial Studies and Optimization. In 2014, Milstein and Srimani reported on a reaction resembling the Julia olefination[17,18] but occurring between alcohols and sulfones (Scheme 2) in the presence of a Ru dehydrogenative coupling

Scheme 2. Julia Olefination and Related Reactions

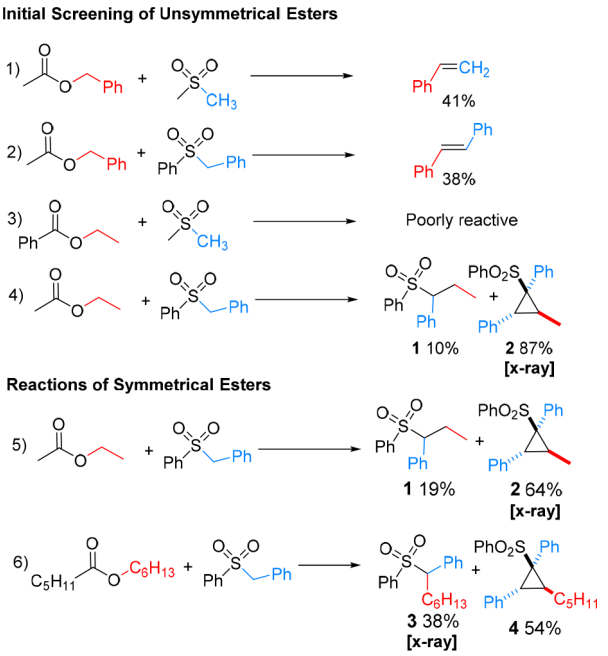


catalyst.[19] Similar to the above report, various other products can be obtained by introducing diverse substrates that can capture the intermediate aldehyde.[20,21] The Milstein procedure utilized simple sulfones, as in the classical Julia olefination (Scheme 2), to intercept the aldehyde intermediate, without the need for an external reductant to form the olefin. The mechanism of this interesting transformation was not fully established.

The Milstein procedure was limited to benzylic alcohols, which under our reaction conditions will also form the olefin and no cyclopropane. The aliphatic alcohols attempted by Milstein were reported to give a complex mixture of undetermined products. Pursuant to our recently published report on the ester metathesis of unsymmetrical esters,[22] we were interested to see if the commercially available Gusev Ru-SNS catalyst (structure given in Table 2 as catalyst **C**),[23] which is active in the ester scrambling reaction, could show novel reactivity in other systems, particularly if it was used together with esters in the earlier disclosed Milstein procedure.

Reacting unsymmetrical esters, we confirmed that olefins form as a result of coupling between the benzylic alcohol esters and alkyl or aryl sulfones (Scheme 3, eqs 1 and 2).

Scheme 3. Screening of Various Esters[a]



[a]Conditions: 0.1 mmol sulfone, 0.1 mmol ester, 0.5 mol % of Ru-SNS, 0.11 mmol KO^{t}Bu, N_2, 16 h, 80 °C closed system, quench with aq NH_4Cl. Qualitative yields were obtained via GC/MS against a mesitylene internal standard.

Surprisingly, when the alkyl alcohol ester ethyl benzoate and benzyl phenyl sulfone were coupled, we observed only trace styrene formation and two new products that at the time could not be identified based on NMR spectra alone (Scheme 3, eq 4). To avoid the minor product styrene that presumably arose as a byproduct of ester metathesis, we used the symmetrical ester, ethyl acetate, on a 1 mmol scale to cleanly form and isolate the same products. Product **2** conveniently crystallized after column chromatography. Another symmetrical ester, hexyl hexanoate, gave related products **3** and **4**, with **3** crystallizing. The structures of **2** and **3** were unambiguously identified by single-crystal X-ray diffraction analysis (Figure 1), showing agreement with NMR data and allowing us to make structural assignments and identify related compounds **1** and **4**. Both the linear and the cyclopropane product were unexpected based on previously known chemistry.

Cyclopropanation of Alcohols. We observed only the alcohol unit of the ester reacting in the mixed ester experiments, so we quickly established that it was possible to replace the ester by a primary, nonbenzylic alcohol, thus making the reaction more atom economical and offering a wider range of commercial starting materials. The yield of linear product **3** could be lowered significantly when 2 equiv

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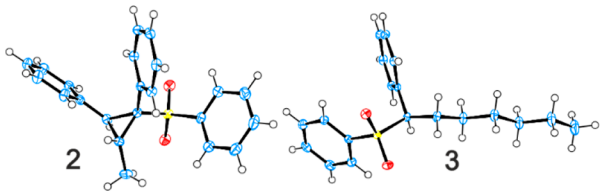


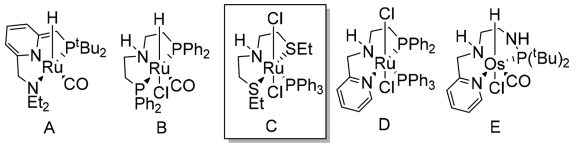
Figure 1. ORTEP projections of cyclopropane **2** and linear product **3**, showing anisotropic displacement ellipsoids at the 50% probability level.

(with respect to the alcohol) of sulfone was used, increasing the yield of **4**. Thus, no reagents are used in excess equivalents, making this reaction very efficient and preventing waste of potentially valuable intermediates. Table 1 showed that the catalyst is only responsible for dehydrogenation; however, the controlled rate of aldehyde formation is necessary for allowing the reaction to proceed with good yield. Using aldehyde as starting material resulted in side reactions, with ca. 20% of the desired product obtained (Table 1, entries 1 and 2).

Entries 4, 11, and 12 in Table 1 confirmed that the potassium cation had to be present in noncatalytic amounts, with 18-crown-6 acting to shut down the coupling. $RuCl_3 \times H_2O$, which is known to convert to Ru(II) species in situ when heated in alcohol,[24] was found to be a viable homogeneous precatalyst under the reaction conditions (entry 6) but also gave many unidentified, relatively low-boiling byproducts. Interestingly, even $NiBr_2$ was active to some extent, however, the number of byproducts and unreacted alcohol significantly exceeded that of even $RuCl_3$.

Catalyst Optimization. Although the above experiments suggest that perhaps first-row dehydrogenation catalysts may ultimately be superior on a cost basis, the catalyst identity is important to minimize formation of byproduct **3** and to enable an optimal rate of aldehyde formation. Catalyst screening (Table 2) showed that a number of commercially available Ru and Os catalysts active in alcohol dehydrogenative couplings were also competent in the cyclopropanation reaction. However, the best catalyst was the Ru-SNS (catalyst **C**) initially tested.[23] The commercially available Milstein catalyst **A**[25] was also very active, albeit at a higher loading. However, it also formed byproduct **3** in more significant amounts (20%). Ru-MACHO, catalyst **B**, normally is quite active in alcohol coupling and ester hydrogenation chemistry.[26] However, it reacted very poorly for this transformation and gave no selectivity for the cyclopropane over linear product. Catalysts **D**[27] and **E**[28] were not competitive on yield, although their selectivity was similar to that of **C**. KHMDS gave outcomes considerably better than those of KO^{t}Bu, whereas LiHMDS and NaHMDS lead to no product. THF with KHMDS was less active, and using both THF and KO^{t}Bu gave no product. Increasing the temperature to 120 °C in toluene led to significant improvements in the yield of **4**, while reducing or completely suppressing linear product formation. Control

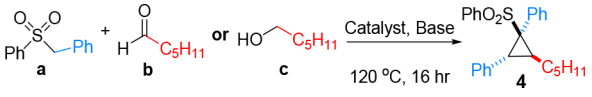
Table 2. Optimization of Cyclopropanation Reaction Conditions[a]



entry	cat. (mol %)	T (°C)	solvent	base	yield of **4** (GC/MS)
1	**A** (2)	80	toluene	KHMDS	80%[b]
2	**B** (3)	80	toluene	KHMDS	11%
3	**C** (0.5)	80	toluene	KHMDS	70%
4	**D** (0.5)	80	toluene	KHMDS	54%
5	**E** (2)	80	toluene	KHMDS	41%
6	**C** (0.5)	80	toluene	NaOH	0%
7	**C** (0.5)	80	toluene	LiHMDS	0%
8	**C** (0.5)	80	toluene	NaHMDS	0%
9	**C** (0.5)	80	toluene	KO^{t}Bu	70%[b]
10	**C** (0.5)	120	toluene	KHMDS	quantitative
11	**C** (0.2)	120	toluene	KHMDS	quantitative
12	**C** (0.5)	80	THF	KHMDS	35%
13	**C** (0.5)	80	THF	KO^{t}Bu	0%

[a]Conditions: 0.2 mmol hexanol scale, 200 mol % of sulfone, 210 mol % of base, N_2 closed vessel. [b]Significant amount of linear product **3** was obtained.

Table 1. Establishing Viability of Alcohols as Substrates[a]



entry	cat. (mol %)	**b** or **c**	additive	base	yield of **4** (GC/MS)
1	**C** (0.2)	**b**	none	KHMDS	21%
2	none	**b**	none	KHMDS	22%
3	**C** (0.2)	**c**	none	NaHMDS	no reaction
4	**C** (0.2)	**c**	10% KBr	NaHMDS	trace
5	**C** (0.2)	**c**	none	KHMDS	quantitative
6	$RuCl_3$ (5.0)	**c**	none	KHMDS	85%
7	**C** (0.2)	**c**	Hg drop	KHMDS	quantitative
8	$RuCl_3$ (5.0)	**c**	Hg drop	KHMDS	85%
9	$NiBr_2$ (2.0)	**c**	none	KHMDS	18%
10	**C** (0.2)	**c**	1 atm H_2	KHMDS	76%
11	**C** (0.2)	**c**	20% NaHMDS	KHMDS	trace
12	**C** (0.2)	**c**	20% 18-crown-6	KHMDS	9%

[a]Conditions: 0.2 mmol **b** or **c**, 200 mol % of sulfone, 210 mol % of base, N_2 closed vessel. Qualitative yields were obtained via GC/MS against a mesitylene internal standard.

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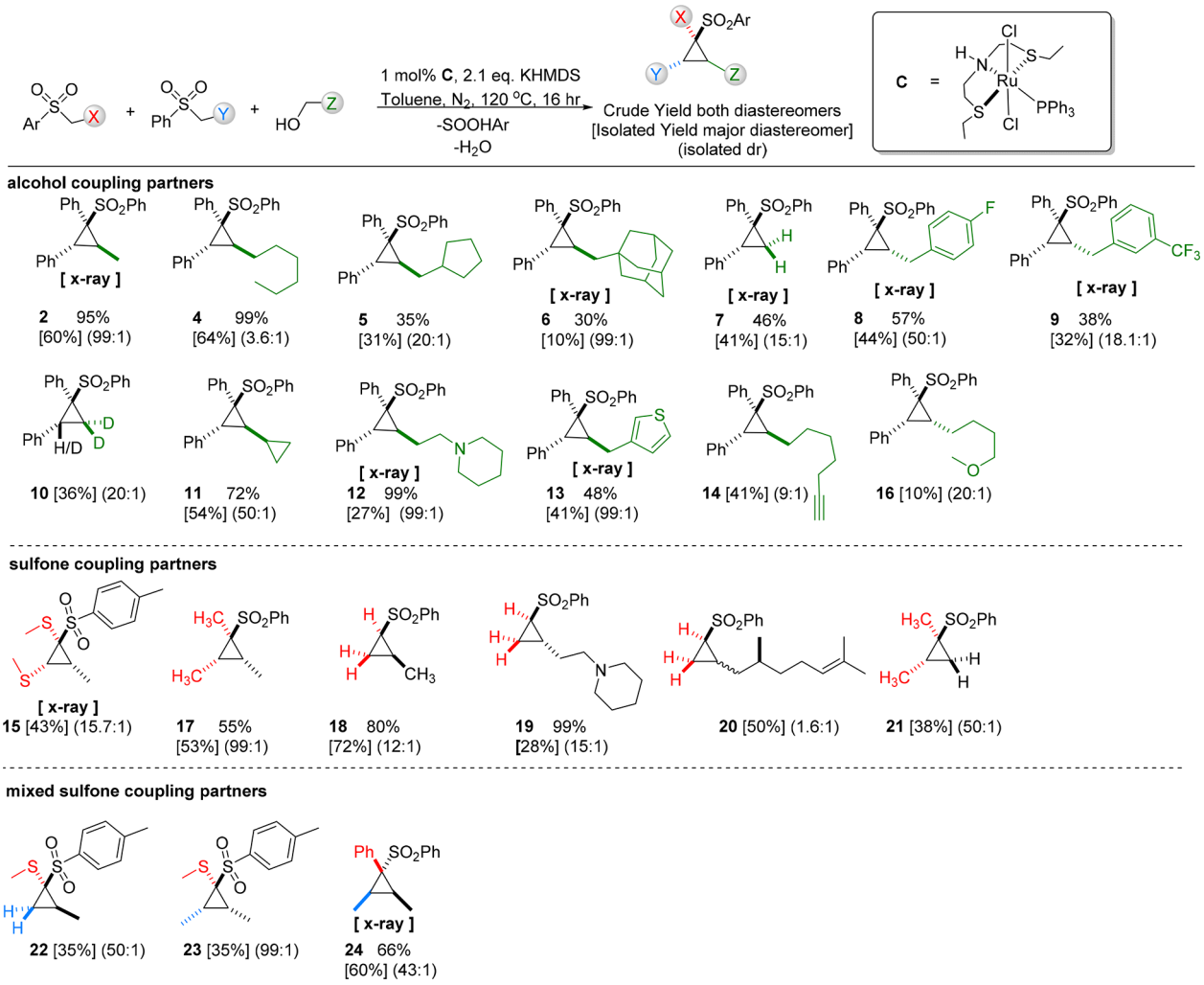

Figure 2. Compounds obtained in the course of coupling of alcohols with sulfones. Relative configuration of the major diastereomer is presented. All substrates with 1 mol % of **C** except **6**, **16**, **18**, and **20** (0.5 mol % of **C**). Substrate **7** can be synthesized from 2-butyne-1-ol or 3-butyne-1-ol under the same conditions but with a 72 h reaction time. **8** and **9** required 72 h of reaction time. Substrate **21** was synthesized from paraformaldehyde and no catalyst. **1** and **3** are byproducts isolated during synthesis of **2** and **4** from esters. Low isolated yields of products **12** and **19** due to unsuccessful column silica gel passivation.

experiments showed that the reaction did not proceed without the catalyst **C** and/or base for the alcohol and ester substrates.

Substrate Scope and Formation of Cross-Coupled Products. Under optimized conditions (Table 2, entries 10 and 11), we attempted cyclopropanation with a number of alcohols at the 1 mmol scale, with 0.5−1 mol % of catalyst loading, using benzyl phenyl sulfone as the model sulfone because of its low cost and its ability to form crystalline products, which were important in confirming the stereochemistry of the products. The structures of all isolated products whose stereochemistry could be determined are given in Figure 2.

When considering the crude yield that can be determined from the NMR of the isolated crude, we established that some linear alcohols react quantitatively under these conditions if both cyclopropane diastereomers are counted as the product. The role of sterics for ring closure is illustrated by the low yield of products **5** and **6**. For the latter, the crude yield of ca. 30% was still reasonable; however, separation from the linear byproduct that formed in substantial amounts and had a very similar polarity proved problematic. Due to subtle differences in sterics, the slightly bulkier isobutyl alcohol was unreactive, but cyclopropyl alcohol gave product **11** in good yield. In all cases, we counted the yield as that of the major diastereomer only after column isolation; however, the similar polarity of the diastereomers and sometimes the linear byproduct meant that the isolated yields of one diastereomer could be quite lower than the crude yield, even if the initial crude selectivity was quite good. This is especially true of compound **6**, where there was ca. 60% linear byproduct obtained together with 30% of the cyclopropane (one diastereomer exclusively), and the polarity is dominated by the adamantyl moiety; after column chromatography, we only obtain 10% pure product.

Notably, this reaction tolerates many common functional groups found in natural products and pharmaceutical drugs. Alkene (**20**), terminal alkyne (**14**), and sterically demanding alkyl products (**6**, **11**) arising from common terpene building blocks were all amenable to the reaction conditions. Interestingly, aromatic heterocycles (**13**) that often are deleterious in other transition-metal-catalyzed reactions were obtained in moderate yields. Ether (**16**), thioethers (**15**, **22**, **23**), amines (**12**, **19**), and aryl fluorides/trifluoromethyl groups (**8**, **9**) were also well-tolerated. Some substrates allowed for their isolation in an impressive ca. 70% yield range; however,

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even reaction yields of 10−40% for obtained highly complex products greatly outperform all other viable approaches for their synthesis.

Methanol was also amenable to cyclopropanation under the reaction conditions to give the corresponding C3-unsubstituted cyclopropane sulfone **7**. The reaction was run with methanol-d_4 to give deuterated product **10**; to the best of our knowledge, this is the only example of a one-step method to produce a deuterated cyclopropane. Interestingly, product **7** was also observed after long reaction times with 2-butyn-1-ol and 3-butyn-1-ol, hinting at a complicated rearrangement mechanism accompanied by formal C−C bond cleavage for substrates where the triple bond is close to the alcohol functionality. In these cases, however, long reaction times of 72 h are required to achieve similar 40% yields.

We performed a number of "mixed sulfone" reactions in order to extend the utility of the current method by introducing substituents from two different sulfones on the ring carbons of the cyclopropane. Using 1 equiv of each sulfone often led to selective reactions for cross-coupled products, with relatively small amounts of the homocoupling cyclopropane. The selectivity could be predicted based on sulfone pK_a values (see Table S1 in the Supporting Information), with the more acidic sulfone remaining on the ring presumably because this sulfone is the first to capture the in situ produced aldehyde.

Many of the cyclopropanes synthesized by us managed to crystallize well after column chromatography via slow evaporation of solvent. Suitable single crystals were studied by means of X-ray diffraction (Figure 3). Section 7 of the Supporting Information contains full experimental details regarding data collection and structure refinement. Figures 1 and 3 illustrate molecular structure and configuration of compounds analyzed. Interestingly, racemic samples of cyclopropanes **2** and **6** crystallize in the Sohncke space group $P2_1$ of the monoclinic crystal system as *conglomerates* of enantiomer crystals, which makes direct resolution of their racemates possible. The other substances studied form *racemic compounds* in crystals, containing both enantiomers in the unit cell.

Based on NMR NOESY data and XRD data (Figure 3), some conclusions can be made on ring substitution trends. The alcohol unit provides the source of diastereoselectivity, with the sulfone substituents arranged in a *cis* configuration. Interestingly, fluorine-containing cyclopropanes **8** and **9** and oxygen-containing **16** have a *trans* configuration of the alcohol moiety to the remaining sulfone. Because these electronegative atoms are far away from the cyclopropane core, F/O coordinating to potassium in the transition state is more likely the cause of the observed stereochemistry rather than electronic effects. For products **17**, **23**, and **24**, *meso* compounds are formed preferentially, possibly reflecting the different coordination environment around the potassium when smaller sulfones are used.

A number of other structurally interesting alcohols and sulfones could be cyclopropanated, but resulted in mixtures that could not be separated. A table of these substrates, that includes a tetrazole sulfone from the recent report on complex sulfone synthesis[13] along with an explanation of why isolation was not further pursued, is given in the Supporting Information (Figure S85).

Catalytic dehydrogenation of alcohols and their subsequent use in a reaction has been used in "hydrogen borrowing" chemistry developed by Williams,[29] as well as in C—C bond

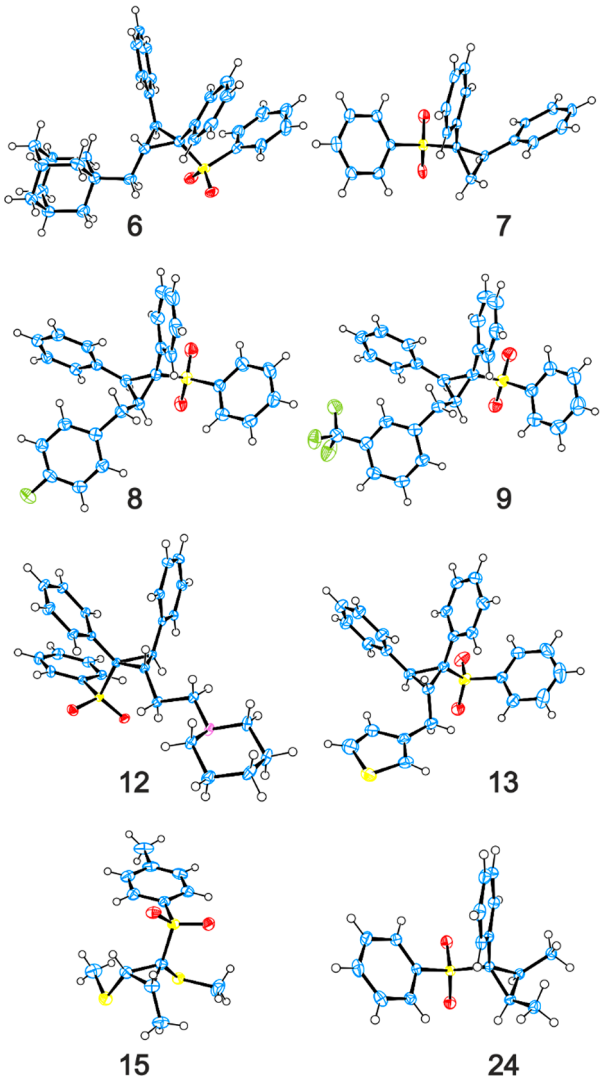

Figure 3. ORTEP projections of cyclopropanes **6**−**9**, **12**, **13**, **15**, and **24**, showing anisotropic displacement ellipsoids at the 50% probability level. The minor components of the disordered trifluoromethyl group (**9**) and thiophene moiety (**13**) are omitted for clarity.

formation reactions disclosed by Krische.[30] Alcohol dehydrogenation and subsequent coupling reactions where the H_2 is subsequently not used[20] are more rare. Interestingly, the reactions with esters showed that dehydrogenation of a free alcohol is not necessary, although a "Milstein-type" pincer dehydrogenation catalyst is still required for the reaction to proceed, and it is mostly the alkoxy part of the ester that reacts.

Mechanistic Discussion. Previous methods for the diastereoselective synthesis of cyclopropanes, which are summarized in Scheme 1, often required low temperatures to enable selectivity. We were thus interested in obtaining insight into the unusual mechanism of the current reaction. In 1991, Julia showed that addition of sulfone carbon anions could be catalyzed by nickel complexes to add across double bonds and give cyclopropanes in various degrees of diastereoselectivity.[31] Other examples in the literature showed that carbanions can add to vinyl sulfones to give cyclopropanes where the sulfone functionality is maintained[32] or eliminated. In the case of elimination, the SO_2Ph moiety leaves as a phenyl sulfinate.[31−33]

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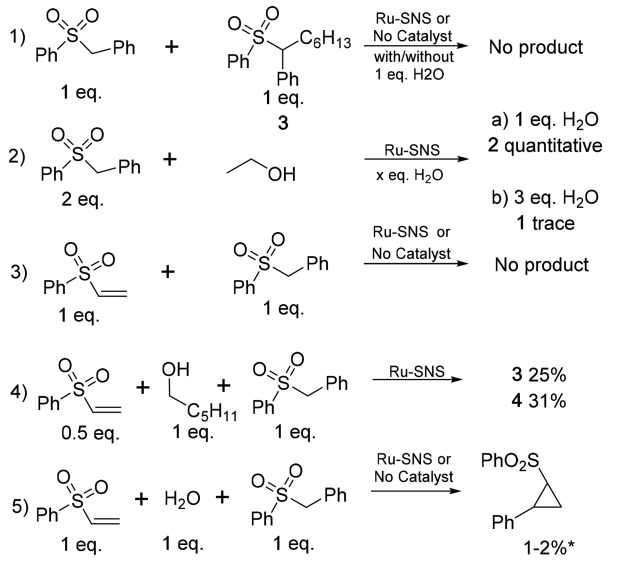
Cyclopropanation of methanol-d_4 (Figure 2, compound **10**) showed that the carbon atom from the alcohol was still fully deuterated, with the other sulfone-based CH being partially deuterated due to exchange with the D atom of methanol's OD. The retention of deuterium in the product shows that exchange does not occur after the formation of the initial aldehyde.

Based on Table 2, it is also clear that the noncoordinating HMDS anion improves the reactivity when compared to that of other potassium bases. THF, which can compete for binding with potassium, inhibits the reaction. It is presently not clear whether coordination of a ligand to potassium is strictly required.

The dehydrogenation catalyst is active at lower temperatures, as shown in earlier reports,[22,23] and does not necessarily require high temperature to form the aldehyde intermediate. Consequently, we believe it is the (likely potassium-promoted) cyclization that requires high temperatures. Linear product was not observed in Table 1, entry 2, where hexanal and no catalyst was used, suggesting that formation of linear species **1** and **3** is catalyst-mediated. Large amounts of byproducts **1** and **3** were isolated in the initial prescreening experiments that could be used in interrogating the mechanism. We treated isolated **3** with 1 equiv of base and sulfone under the catalytic reaction conditions with and without catalyst and in the presence or absence of 1 equiv of water because water is a likely product of the cyclopropanation reaction (Scheme 1). In all cases, the intermediate was completely unreactive. As **3** fails to give the final product **4**, its formation was minimized by using high reaction temperatures and catalysts that do not lead to its formation as easily (i.e., **C** but not **A**). Addition of 1 equiv of water to the reaction did not lead to an effect, but 3 equiv was deleterious, likely due to immediate quenching of the base or by altering the coordination environment around potassium (Scheme 4). This could also be due to the catalyst being shut down in the presence of excess water or hydroxide, which is a known degradation pathway of similar catalysts.[20a] However, addition of molecular sieves to the reactions did not affect the yields.

Scheme 4. Mechanistic Investigation Reactions[a]

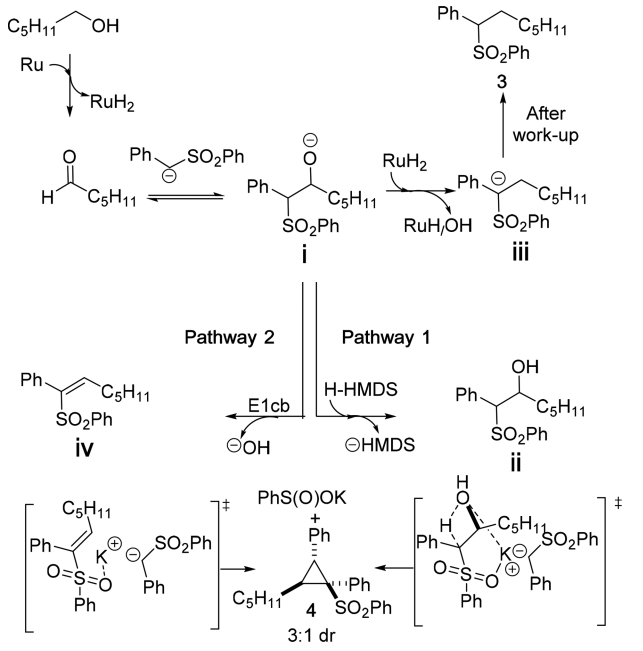


[a]120 °C/N_2/0.5 mol % catalyst C/toluene. 1.05 eq. of KHMDS for every 1 eq. of benzyl phenyl sulfone. Qualitative yields via GC/MS against mesitylene internal standard. *Yield determined by GC/MS.

The lack of reactivity with stoichiometric vinyl sulfone, which is modeling the intermediate that would be produced in the synthesis of product **17** (Scheme 4, reaction 3), suggests that olefin species are not intermediates formed in large amounts, in contrast with the earlier results obtained by Julia.[31] A catalytic reaction with hexanol set up with an open system under a flow of argon gas that would allow generated H_2 to escape did not alter the yields or selectivity of the reaction. However, it is possible that vinyl sulfone polymerizes under our reaction conditions, which offers an explanation for why no cyclopropane was detected when vinyl sulfone was used stoichiometrically. On the other hand, adding 1 equiv of vinyl sulfone with 2 equiv of benzyl phenyl sulfone and 1 equiv of alcohol under the normal reaction conditions lowered the yield of **4** and increased the amount of **3**, while also forming more byproducts, thus suggesting a retarding effect for the olefinic vinyl sulfone species. A reaction set up with vinyl sulfone and 1 equiv of water and benzyl phenyl sulfone (Scheme 4, reaction 5) did give a trace peak of a cyclopropane that would be expected if addtion of water to the double bond did occur and formed an intermediate similar to **ii**, suggesting that the reaction proceeds from an alkoxy-type species and not an olefin. This product was completely absent when no water was present (Scheme 4, reaction 3).

Based on the above mechanistic studies and previous literature examples, we considered two main pathways leading to **4** that are outlined in Scheme 5. Initial formation of an intermediate aldehyde[34] is followed by attack of a sulfone anion to create intermediate **i**. The initial dehydrogenation step is likely irreversible judging by the deuterated methanol experiment (Figure 2, entry 10). Formation of **iii** is catalyst-mediated, but using a higher temperature either allows the cyclopropanation to proceed more readily or decomposes the catalyst before too much **iii** is made; thus relatively less **3** is formed at 120 °C. No olefins (species like **iv**) were ever

Scheme 5. Proposed Mechanism



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isolated, detected by GC/MS, or observed by in situ NMR, so it is proposed that this intermediate is highly reactive and formation of either **3** or **4** will happen instantaneously upon formation of **iv**. Unfortunately, the reaction produces a heterogeneous slurry which prevented effective detection of trace intermediates by in situ NMR techniques.

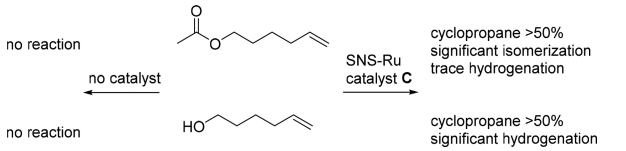
It is important to note that the catalyst must maintain the right kinetic balance of aldehyde (and thus intermediate **i**), without over-reacting to lead to Tishchenko or aldol pathways. The catalyst must also not enable the formation of **3**, which can be considered an interesting product in its own right. Catalyst **C** contains the ideal properties to control the right balance of reagents and not react to give side product **3**. Whereas **A** and **B** also form **i** at an appropriate rate, they also readily form **iii**, which leads to greater amounts of side product **3**.

In the non-olefin pathway, pathway 1, intermediate **i** is first protonated, then **ii** is attacked in an "interrupted E1cb" fashion. The other equivalent of sulfone carbanion attacks the hydroxonium carbon as it is forming, followed by immediate intramolecular ring closure by the back-attack of the newly formed carbanion sulfone on the α-carbon of the other sulfone. We propose the interaction of K^+ to set the stereochemistry by chelation to the sulfone oxygen and alcohol oxygen. In the olefin pathway, pathway 2, the olefin is first formed in a traditional E1cb fashion. The sulfone is then templated by potassium to give the cyclized product **4**. We currently do not possess enough data to rule out either pathway. Pathway 2 is only possible when the concentration of olefin is low, preventing its polymerization or other side reactions. There is also previous literature precedent for addition of anions to olefins to give cyclopropanes, but this process is metal-catalyzed, whereas we established that metal is not necessary in the aldehyde experiments.[31−33] The non-olefin pathway 1 is preferred by us because the proposed olefin intermediate was never isolated or detected in any of the reactions by GC/MS or NMR. The reaction using stoichiometric vinyl sulfone also failed to give any product, and when vinyl sulfone was added to a catalytic reaction, it partially inhibited the transformation. Furthermore, the yield remains largely unchanged when the reaction is run in an open system, or under 1 atm of H_2, although if the rate of ring closure were much faster than hydrogenation of the double bond, this would not rule out pathway 2. The olefin intermediate for cyclopropanation was shown to be necessary for Julia olefination, and it is the substrate in metal-catalyzed carbene synthesis. However, these examples appear to be fundamentally different mechanistically and also based on substrate and product nature.

Lastly, it should be mentioned that the first part of the mechanism would be different without a source of hydrogen from the alcohol and may have implications as to whether pathway 1 or 2 is active. We presented compound **20** as an example of a successful olefinic alcohol that can be cyclopropanated, but it has a protected, trisubstituted double bond that is not prone to hydrogenation or isomerization by the Ru catalyst. Although olefin substrates are amenable to the reaction, we find that partial hydrogenation or isomerization and subsequent isolation of only one product is a significant problem. Because catalysis is also possible with non-H_2-producing esters, we investigated a terminal olefin substrate on a small scale both as an ester and as an alcohol (Scheme 6).

It is possible to avoid hydrogenation of the olefin moiety by using the ester as the starting material; however, at this point, we could not solve the issue of isomerization, so the synthesis and isolation of this substrate was not attempted on a larger scale. However, it may be possible to use prior esterification as a general strategy for substrates that are sensitive to H_2 or that tend to produce too much linear product. In general, we only see a trace contribution to cyclopropane formation from the acyl moiety, and that is probably due to partial ester metathesis.[22] Because the ester is probably rapidly converted back to aldehydes in an outer sphere process, as shown by Gusev recently,[35] and in currently unpublished work on the Shvo catalyst, the selectivity and the high yield for the alkoxy part of the ester (>50%) are puzzling. This strategy will be explored as a pathway for poorly performing substrates in the future.

Scheme 6. Flow Chart for Nonhindered Olefin Substrates



CONCLUSIONS

In conclusion, we have outlined a new cyclopropanation reaction that utilizes homogeneous Ru dehydrogenation catalysts. This reaction uses alcohols and sulfones as diverse and cheap substrates that lead to complex products with three new carbon−carbon bonds, two or three new chiral centers, and one new quaternary carbon center formed in a single reaction. Esters, which cannot be dehydrogenated, are also catalytically transformed to cyclopropanes but require the catalyst for reactivity. This reaction is a rare example of all three ring substituents coming from separate synthetic units, opening up new possibilities for a more convergent, retrosynthetic analysis of cyclopropanes. Importantly, the catalyst is also commercially available and reasonably priced, which should help expedite the use of this new method in current research.

We are currently trying to enable reactivity of other substrates that were not active at high temperatures by screening suitable ligands for potassium or other cations that can produce a similar templating effect. We are also attempting to establish the correct mechanism of the reaction by experimental and DFT studies.

EXPERIMENTAL SECTION

General Procedure for Closed System: To an oven-dried 100 mL Schlenk flask in an N_2 glovebox were added benzyl phenyl sulfone (464 mg, 2 mmol), KHMDS (410 mg, 2.05 mmol), and Ru-SNS (6.3 mg, 0.01 mmol) before the addition of ∼10 mL of toluene. The alcohol or ester (1 mmol) was added to the reaction mixture; the vessel was sealed and stirred at 120 °C for 12 h. The reaction was allowed to cool to room temperature and then quenched with 5 mL of saturated NH_4Cl solution. The mixture was extracted with 20 mL of ethyl acetate (×3), and the organic layers were collected and dried over $MgSO_4$. The solution was concentrated under vacuum and purified by flash silica chromatography with a typical gradient of 100:0−88:12 (hexane/ethyl acetate). A picture of the experimental apparatus is presented in the Supporting Information.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00361.

Experimental details, NMR spectra of all products, discussion about assigning the structure, a listing of substrates that were attempted but did not work or were not pursued for isolation including the relevant discussion, and crystal structure details (PDF)

Accession Codes

CCDC 1562834−1562836, 1562838−1562844, 1562864, and 1562865 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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