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Letter

Cobalt-Catalyzed Cyclization of Unsaturated *N*-Acyl Sulfonamides: a Diverted Mukaiyama Hydration Reaction

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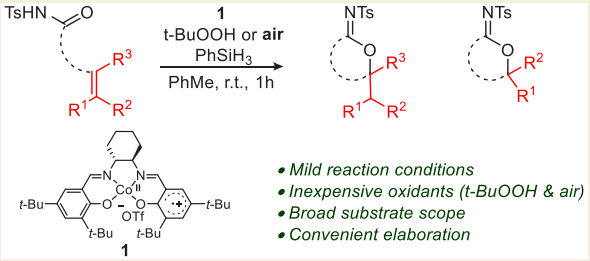
ABSTRACT: The cycloisomerization of *β*-, *γ*-, and *δ*-unsaturated *N*-acyl sulfonamides to *N*-sulfonyl lactams and imidates is reported. This transformation is effected in the presence of a Co^{III}(salen) catalyst using *t*-BuOOH or air as the oxidant. The method shows good functional group tolerance (alkyl, aryl, heteroaryl, ether, *N*-Boc) and furnishes an underexplored class of cyclic building blocks. The strong solvent dependence of the transformation is investigated, and the synthetic versatility of the *N*-sulfonyl imidate product class is highlighted.

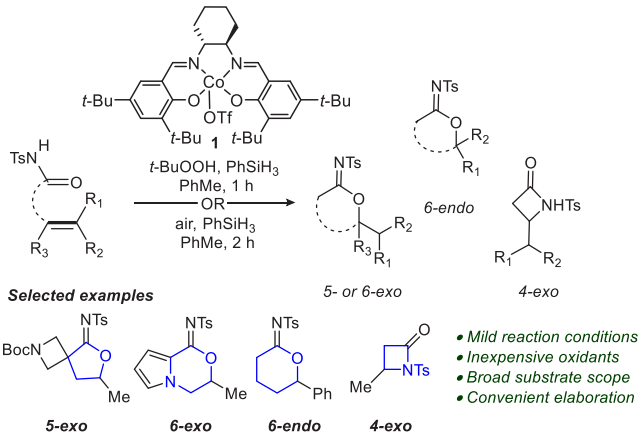


KEYWORDS: *cycloisomerization, N-acyl sulfonamides, N-sulfonyl imidates, cobalt catalysis, diverted Mukaiyama hydration*

Hydrofunctionalization of unactivated olefins using inexpensive first-row transition metals, such as Fe, Mn, Co, and Ni, has received considerable attention.[1,2] Early examples of their application include earth-abundant metal-mediated olefin hydration[3] and hydroperoxidation,[4] pioneered by Drago[5] and Mukaiyama,[6] respectively. Since then there has been considerable evolution of olefin hydrofunctionalization to include oximation,[7] cyanation,[8] hydrazination,[9] azidation,[8b,10] amination,[11] and halogenation.[8b,12] More recently, Shigehisa and others have demonstrated intermolecular olefin hydroalkoxylation,[13] hydrofluorination,[13b] intramolecular hydroarylation,[14] hydrothioetherification,[15] and hydroamination.[13e,16] Herein we report the Co-catalyzed cycloisomerization of unsaturated *N*-acyl sulfonamides, which provides ready access to a wide range of cyclic *N*-sulfonyl imidates, an underexplored functional group (Scheme 1). In addition to examination of conditions with *t*-BuOOH, a salient feature of the process is our discovery that the reaction can be performed with air as a convenient and safe oxidant. Additionally, over the course of this study we observed a notable solvent effect that governs the product distribution, which we attribute to solvent donor ability and the attendant electronic character of the cobalt metal complex.

Imidates are a synthetically versatile class of compounds that act as activated amide equivalents through their dual behavior as both electrophiles and nucleophiles. Thus, they provide access to a wide range of structural motifs, including oxazolines, indazoles, and isoquinolines.[17] Acyclic *N*-sulfonyl imidates have been investigated as surrogates for azahetarenes in steroidal antiproliferative agents.[18] They have also been examined in drug discovery as prodrugs for esters and sulfonamides, addressing challenges associated with bioavailability and metabolism.[19] While probenazole, a member of the class, has found applications as an antifungal agent against rice blast fungus and leaf blight, erythromycin derivatives modified through the incorporation of a cyclic imidate showed 4-fold increased activity against *Streptococcus pneumoniae*.[20] Cyclic *N*-sulfonyl imidates are less well studied, despite the fact that they could be useful in a prodrug approach as precursors toward lactones.

Scheme 1. Cyclization of Alkenyl *N*-Acyl Sulfonamides



Cycloisomerizations of alkenyl *N*-acyl sulfonamides to *N*-sulfonyl lactams have been described, mediated by Ph_3PAuCl,[21] Ir catalysts,[22] $NbCl_5$,[23] and $Zn(OTf)_2$/TfOH[24]

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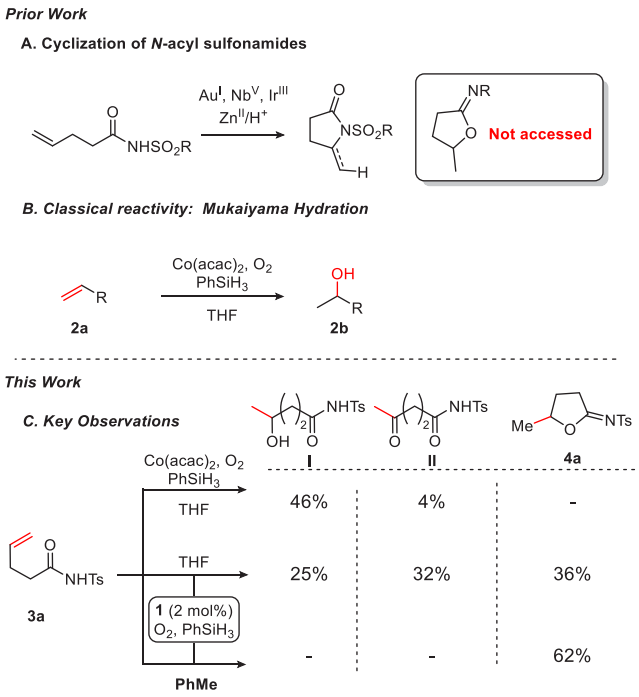


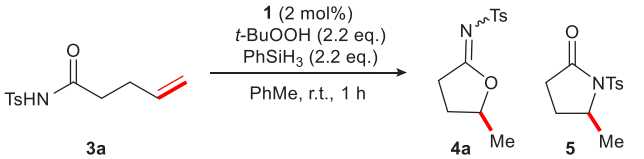
Figure 1. Background and initial observations.

(Figure 1A). Cyclic *N*-sulfonyl imidates have generally been accessed through electrophilic cyclization of *N*-acyl sulfonyl alkenes mediated by iodine,[25] *m*-CPBA,[26] Ph_2Se_2,[27] or TsN_3.[28,29,26] The direct cycloisomerization of alkenyl *N*-acyl sulfonamides to furnish cyclic *N*-sulfonyl imidates is unknown.[13e,16a]

We have been interested in identifying novel reactivity of olefins mediated by base metal−salen complexes.[9a,c,10,30] In the presence of a Co^{II} catalyst, silane, and oxidant, olefins classically proceed through Mukaiyama hydration pathways (Figure 1B). When we subjected *N*-acyl sulfonamide **3a** to Mukaiyama hydration conditions, a mixture of products **I** and **II** was formed in 46% and 4% yield, respectively, in line with early observations by Mukaiyama.[6a−c,f] Interestingly, when $Co(acac)_2$ was replaced by Co^{III}(salen)OTf complex **1** under otherwise identical conditions, the formation of *N*-sulfonyl imidate **4a** was observed (36%). Importantly, resubjecting **I** to Mukaiyama hydration conditions in the presence of catalyst **1** did not lead to **4a** (see the Supporting Information (SI)). When THF was replaced with toluene, **4a** was formed in 62% yield. Neither alcohol **I** nor ketone **II** was isolated from the reaction mixture. Collectively, these results compelled us to examine further the reaction in which Mukaiyama hydration of olefinic *N*-acyl sulfonamides is derailed to form cyclic imidates.

Although the cycloisomerization is isohypsic,[31] it has been noted that for Co-mediated olefin functionalization reactions, the addition of hydroperoxide can be beneficial.[6f,10a] Examination of the reaction conditions led to the identification of a procedure in toluene with 2 mol%**1**, *t*-BuOOH (2.2 equiv), and $PhSiH_3$ (2.2. equiv) that effects the cycloisomerization reaction **3a** → **4a** in 85% yield (Table 1, entry 1; see the SI). Control experiments revealed interesting details. No reactivity was observed in the absence of silane or catalyst **1** (entries 2 and 3). The use of a Co^{II}(salen-*t*Bu,*t*Bu) catalyst under otherwise identical conditions gave the product in merely 17% yield (entry 4; see the SI). Under an inert atmosphere, identical product yields were obtained (entry 5).

Table 1. Optimization of the Reaction Conditions



entry	deviation from the standard conditions	yield of **4a** (%)
1	none	85
2	without $PhSiH_3$	0
3	without **1**	0
4	Co^{II}(salen-*t*Bu,*t*Bu) instead of **1**	17
5	under N_2	84
6	air instead of *t*-BuOOH, 48 h	56
7	air, 10 mol% **1**, and 4 equiv of $PhSiH_3$	82

Importantly, we found that the reaction could be conducted with air as the oxidant, leading to **4a** in 56% yield after 48 h (entry 6). Under conditions in which the catalyst loading was increased to 10 mol% with 4 equiv of silane and air, product **4a** was formed in 82% yield (entry 7). The fact that reaction conditions prescribe air and avoid the use of expensive or toxic oxidants makes this transformation attractive.[32] Moreover, the use of air instead of oxygen renders the process safer.

With the optimized reaction conditions in hand, the scope and functional group tolerance of this transformation was investigated (Figure 2). Substrates incorporating a wide range of alkyl or aryl substituents, including rings at C_α, were well-tolerated in the transformation, leading to products **4b−g** (62−83%). Ether-containing and *N*-Boc-amine-substituted alkenyl *N*-acyl sulfonamides readily underwent cycloisomerization and gave rise to products **4h−j** in 63−97% yield. *β*-Substituted olefins also underwent cyclization to give products **4k−m**. The reaction tolerated disubstituted olefins, allowing access to *N*-sulfonyl imidate **4n** in 55% yield.

For selected examples, namely, **4a−h**, **4j**, **4p**, and **4o**, the cycloisomerization reaction was repeated to showcase the broad applicability of air as the oxidant. The products were generally obtained in yields comparable to those under conditions employing *t*-BuOOH. The structures of the imidate products **4b**, **4h**, **4q**, and **4w** formed in this study were assigned by X-ray crystallography. For characterization of the remaining products, IR spectroscopy proved to be useful. *N*-Sulfonyl imidates display distinctive IR C═N absorbances at 1620 cm^{-1}, in stark contrast to $\nu_{C=O}$ = 1720 cm^{-1} for *N*-tosyl lactams.

We next evaluated the formation of six-membered *N*-sulfonyl imidates. Gratifyingly, **3o−q** provided access to **4o−q** in 71−87% yield. Imidocarbonate **4r** was prepared in 52% yield from homoallylic *N*-sulfonyl carbamate **3r**. When **3s** was subjected to the reaction conditions, *β*-lactam **4s** was formed in 30% yield. The transformation was also amenable to 1,2-disubstituted olefins, with alkenoyl *N*-acyl sulfonamide **3t** giving a mixture of five- and six-membered-ring products. In contrast, styrene derivative **4u** and diene **4v** were formed as single products. Finally, we established the feasibility of performing the reaction in a system with a trisubstituted olefin (**3w**), affording **4w** in 71% yield.

The effect of different sulfonamides on the transformation was investigated next (Figure 3). High yields were maintained for aryl sulfonamide substrates bearing arene groups

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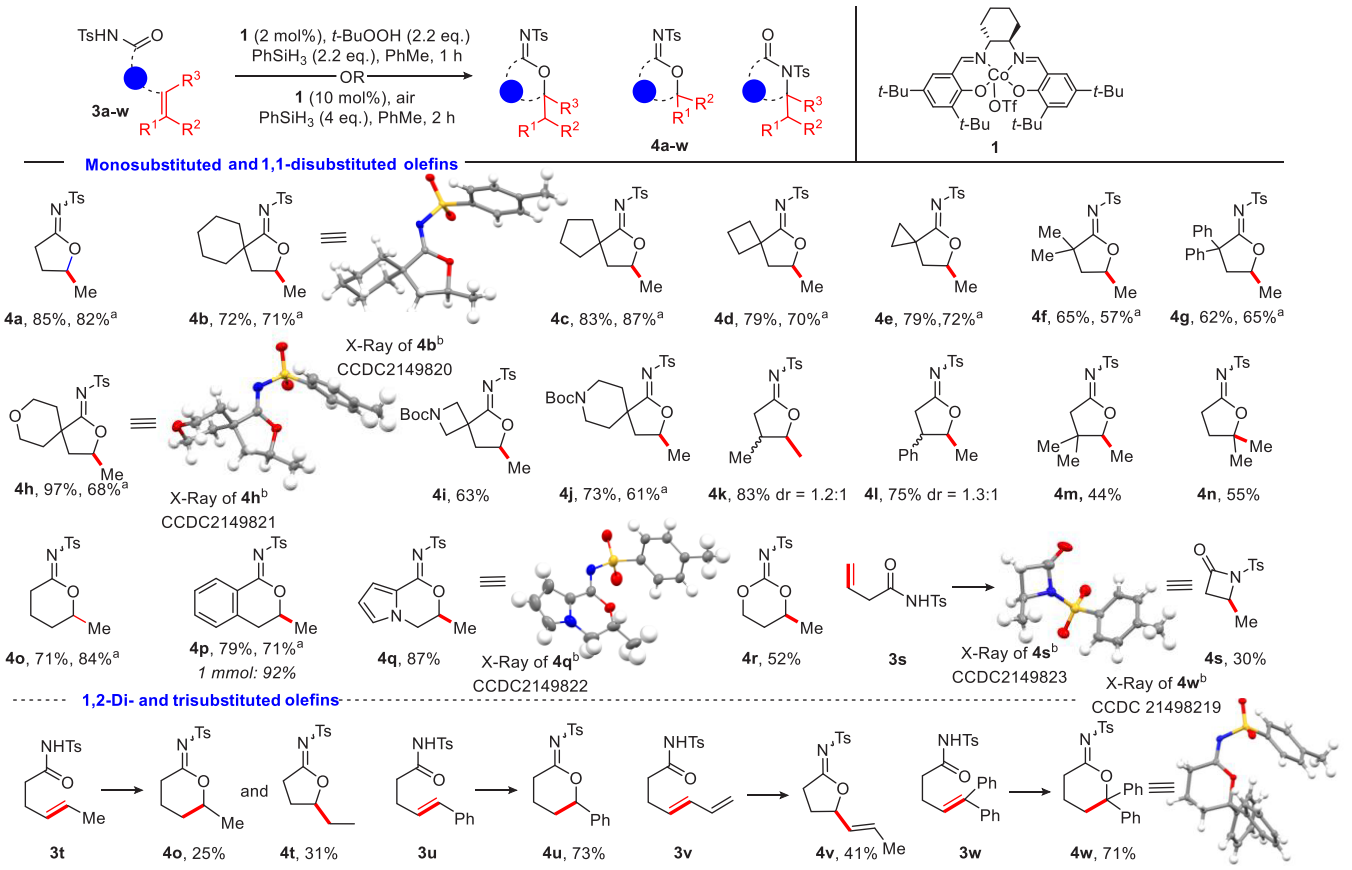

Figure 2. Substrate scope of the Co-catalyzed cycloisomerization of alkenyl *N*-acyl sulfonamides. [a]Reaction yield obtained employing 10 mol%**1**, 4 equiv of $PhSiH_3$, and air. [b]Thermal ellipsoids are shown at the 50% probability level.

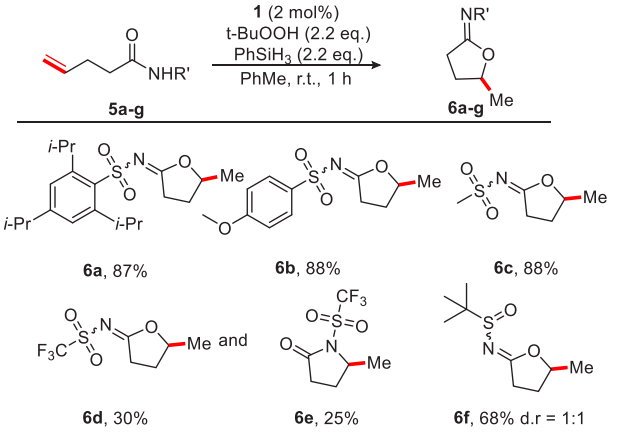

Figure 3. Co-catalyzed cycloisomerization of a variety of sulfonamide and sulfinamide derivatives.

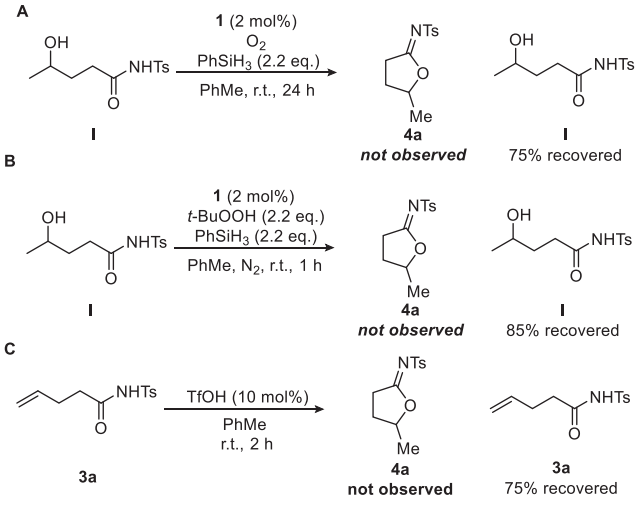

Figure 4. Control experiments for the Co-catalyzed cycloisomerization reaction.

substituted with sterically demanding and electron-donating substituents (**6a** and **6b**). Methanesulfonamide derivative **5c** also produced the corresponding cyclic *N*-sulfonyl imidate **6c** in 88% yield. The use of olefinic *N*-acyl trifluoromethane sulfonamide **5d** yielded cycloisomerization products, albeit as a mixture of imidate **6d** and lactam **6e** in 30% and 25% yield, respectively. *N*-Sulfinyl imidate **6f** was formed in 68% yield, expanding the reaction to *N*-acyl sulfinamides.

The observation that the reaction conditions resemble those typically employed for Mukaiyama hydration[6b] of olefins compelled us to conduct key control experiments (Figure 4A,B). In this respect, when **I** was subjected to either Mukaiyama hydration conditions or the reaction conditions, imidate **4a** was not formed, and the starting secondary alcohol was reisolated in 75 or 85% yield, respectively. This result precludes a mechanistic pathway for the overall transformation **3a** → **4a** involving Mukaiyama hydration of the olefin followed by ring closure. To rule out the possibility that the reaction is mediated by triflic acid formed from $Co^{III}OTf$ catalyst **1**, starting material **3a** was exposed to a catalytic amount of

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TfOH (10 mol%) (Figure 4C). No product formation was observed after 2 h, and **3a** was recovered in 75% yield.

Interestingly, there is paucity of data on the behavior of cyclic *N*-sulfonyl imidates. Accordingly, we conducted a brief study on **4a**. It displayed fast *E*/*Z* isomerization at room temperature as determined by HSQC and NOE NMR spectroscopy. The isomer (*E*)-**4a** prevails in toluene-d_8 (see the SI) on the basis of a cross-peak between the ring H_2C_α and *o*-CH_{aryl}. Cyclic imidates bearing C_α substituents crystallized solely as the *Z* isomer (see **4b**, **4h**, and **4q**). The barrier for *E*/*Z* isomerization of parent compound **4a** was determined to be $\Delta G^{\ddagger}$ = 16.0 kcal mol^{-1} (Figure 5).[33]

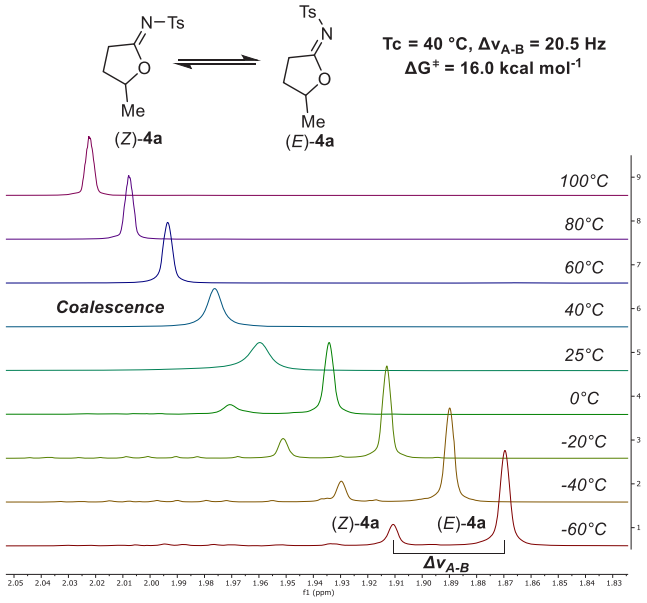

Figure 5. Determination of the barrier to *E*/*Z* isomerization in *N*-sulfonyl imidate **4a**. ^{1}H NMR spectra were recorded at 500 MHz in toluene-d_8 at −60 to 100 °C.

We then investigated derivatization of this underexplored product class (Figure 6). Compound **4p** was hydrolyzed to lactone **7a** in 88% yield (DMF−H_2O, 0.2 equiv of DBU, r.t., 12 h).[29b,34] We wondered whether *N*-sulfonyl imidates could be employed as directing groups for arene C−H functionalization.

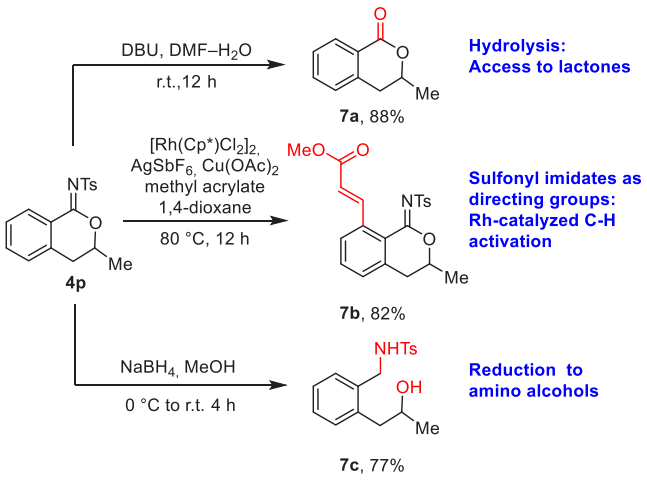

Figure 6. Selected functionalization of sulfonyl imidates.

The closest analogy we could find was in the work with Rh-catalyzed functionalization of cyclic *N*-sulfonyl ketimines.[35] Subjecting **4p** to $[(Cp^*)RhCl_2]_2$, $AgSbF_6$, $Cu(OAc)_2$, and methyl acrylate in 1,4-dioxane led to formation of *o*-C−H-alkenylated imidate **7b** (82% yield). Finally, reduction of **4p** with $NaBH_4$ gave amino alcohol **7c** in 77% yield.

The reactivity reported herein is intriguing and unexpected given previous studies involving cobalt complexes and simple olefins under similar conditions.[9a,c,10,30b] A number of spectroscopic and computational investigations have suggested that canonical Co^{III}(salen) complexes such as **1** may be in equilibrium with species described as Co^{II}(salen$^{\bullet+}$).[36] Various independent studies have separately indicated that equilibria involving Co species are sensitive to factors such as temperature, counterions, donor ligands, and solvent (CD_2Cl_2 vs DMSO-d_6 vs pyridine). Combined NMR and quantum-chemical studies revealed that Co(salen)Cl in THF-d_8 is present in diamagnetic and paramagnetic forms.[36]

Our leading results outlined in Figure 1C hinted at a solvent effect (THF vs toluene), with the latter proving optimal for cyclization vis-à-vis the formation of Mukaiyama hydration/oxidation products **I** and **II**. Accordingly, we conducted a study of the cyclization reaction of **3a** with air as the oxidant over a range of solvents (Figure 7A). In proceeding from toluene to DMF, the relative amount of cyclization product decreases while the Mukaiyama products increase. A plot of the yield of cyclization product **4a** against solvent donor number[37] reveals a linear relationship (Figure 7; see the SI for details), with the yield of **4a** decreasing as a function of solvent coordination ability.[38] A recent report on olefin hydroamination reactions suggests a dependence of the product distribution *S* (cyclization vs Mukaiyama products) on solvent viscosity.[16c] However, in the cyclization reactions of **3a** we did not observe such a dependence on the viscosity (R^2 = 0.02; see the SI); instead, once again a strong correlation (R^2 = 0.94) involving *S* and solvent donor ability was observed (Figure 7C).

For reactions involving Co complexes, silane, and an oxidant, it has been suggested in the literature that hydrometalation of the starting olefin affords an organocobalt species.[9a,c,10,13a−d,14,16a,30b] Our results are consistent with this putative intermediate partitioning itself between two possible pathways as a function of the solvent, namely, reaction with oxygen to form Mukaiyama hydration products **I** and **II** or, alternatively, a diverted course to give **4a**. It remains unclear whether the cyclization process we describe subsequently proceeds via cationic or radical intermediates.[39] In mechanistic inorganic studies of Co(salen) complexes,[36a] Fuji has discussed the importance of the redox-active salen ligand in understanding the electronic structure of these complexes. This raises the question of whether the ability of canonical **1** to access its Co^{II}(salen$^{\bullet+}$) form may be crucial to diverting the reaction from classical Mukaiyama reactivity to cycloisomerization. The design of complexes incorporating redox-non-innocent ligands for olefin functionalization reactions may provide new avenues for the identification of preparatively useful transformations.

In conclusion, we have reported the Co-catalyzed cycloisomerization of olefinic *N*-acyl sulfonamides employing *t*-BuOOH or air as the oxidant. The transformation was successful for a broad spectrum of olefin substrates and tolerated a variety of functional groups.[40] The barrier to *E*/*Z* isomerization of the imidates was determined by NMR coalescence experiments. We elaborated the imidate products

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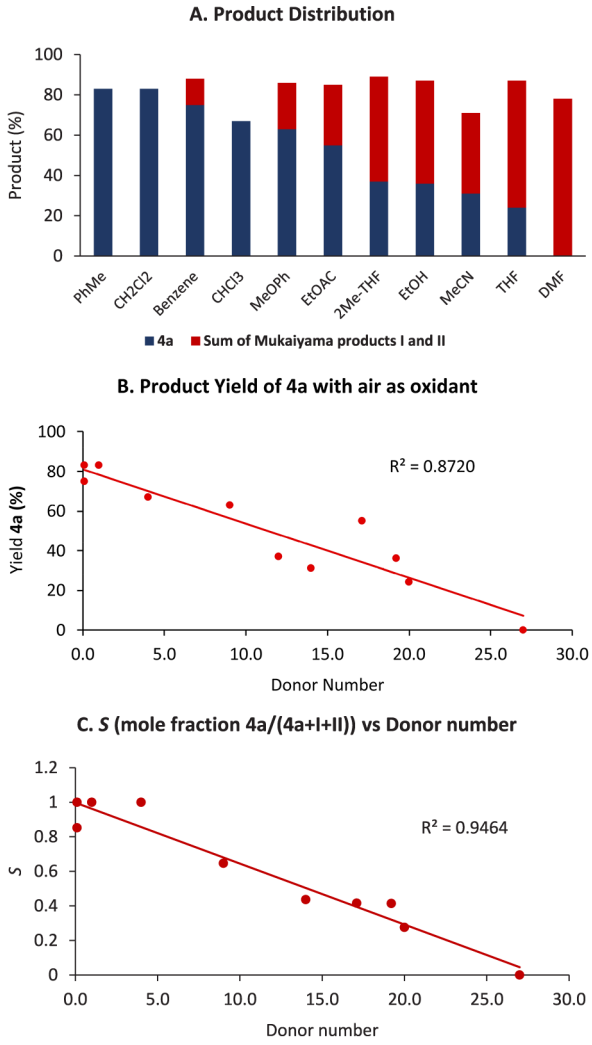

Figure 7. Solvent trends in the cycloisomerization of *N*-acyl sulfonamides. (A) Product distribution in various solvents. (B) Relationship between solvent donor number (Gutmann[37]) and yield of **4a**. (C) Correlation between *S* (=**4a**/(**4a** + **I** + **II**)) and solvent donor number.

in further transformations, including cleavage of the sulfonamide, *N*-tosyl imidate reduction, and CH functionalization. Finally, we investigated the product distribution as a function of solvent, confirming that cycloisomerization is preferred over the traditional Mukaiyama hydration pathways in noncoordinating solvents. The access to cyclic *N*-sulfonyl imidate products provided by this method opens new possibilities for these structures as potentially useful building blocks in small-molecule discovery endeavors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.2c00186.

Experimental and computational details and NMR data (PDF)
X-ray crystallographic data for **4w** (CIF)
X-ray crystallographic data for **4b** (CIF)
X-ray crystallographic data for **4h** (CIF)
X-ray crystallographic data for **4q** (CIF)
X-ray crystallographic data for **4s** (CIF)

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Notes

The authors declare no competing financial interest.

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(40) When the reaction was attempted in an intermolecular fashion employing phenylbut-4-ene and an excess of *N*-acetyl sulfonamide, no product was isolated.

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