Iron-Catalyzed Ring-Closing C–O/C–O Metathesis of Aliphatic Ethers

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Dedicated to Professor Christoph A. Schalley on the occasion of his 50th birthday

Abstract: Among all metathesis reactions known to date in organic chemistry, the metathesis of multiple bonds such as alkenes and alkynes has evolved into one of the most powerful methods to construct molecular complexity. In contrast, metathesis reactions involving single bonds are scarce and far less developed, particularly in the context of synthetically valuable ring-closing reactions. Herein, we report an iron-catalyzed ring-closing metathesis of aliphatic ethers for the synthesis of substituted tetrahydropyrans and tetrahydrofurans, as well as morpholines and polycylic ethers. This transformation is enabled by a simple iron catalyst and likely proceeds through cyclic oxonium intermediates.

Metathesis reactions involving multiple bonds are arguably among the most interesting reactions in organic synthesis.[1] In particular, ring-closing alkene[2] and alkyne[3] metathesis have become powerful synthetic tools for the synthesis of small, medium and large rings. Researchers have recently been trying to translate the power of ring-closing metathesis reactions to other types of multiple bonds. Most notably, the Schindler and Li groups have reported catalytic ring-closing metathesis reactions between alkenes and carbonyls under iron catalysis.[4] This new reaction has already been applied in the synthesis of conjugated materials and unsaturated heterocycles.

By contrast, less effort has been dedicated to the development of catalytic single-bond metathesis reactions. This trend may originate from the lower reactivity of single bonds when compared to multiple bonds, a feature that complicates the design of suitable bond activation mechanisms in catalytic processes. Only a few examples of C–X bond metathesis reactions have been published, and include amide bond metathesis,[5] carbon-sulfur and carbon-phosphorus bond metathesis[6] and carbon-silicon bond metathesis.[7] Notably, a significant amount of these reactions involve the cleavage of C(sp^2)–X bonds through reversible oxidative addition, a mechanism which is not easily extendable to C(sp^3)–X bonds because of competing β-hydride elimination of the alkyl–M intermediates and higher barriers for oxidative addition.[8] Moreover, there is no example of a catalytic ring-closing metathesis reaction involving two single C(sp^3)–X bonds, despite the potential of such reactions to enable a rapid access to saturated carbo- and heterocyclic products that are key intermediates in organic synthesis.

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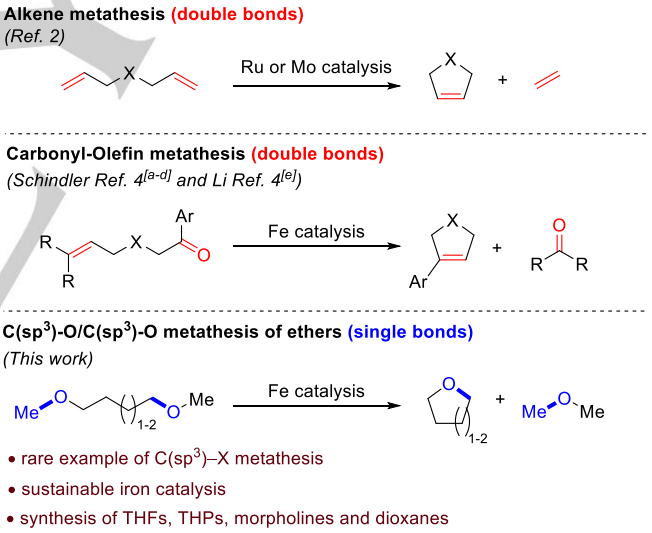
Following our continuous effort to develop new catalytic isodesmic reactions,[9] we were interested to investigate whether two C(sp^3)–O bonds could engage in a ring-closing metathesis manifold. Due to the ubiquity of aliphatic cyclic ethers, such as tetrahydrofurans and tetrahydropyrans, in all fields of chemistry,[10] we thought that the synthesis of these substrates through a metathesis strategy would efficiently complement traditional methods[11,12] for ether synthesis. In particular, the ability to engage two identical functionalities[13] (i.e. two ROR’ groups) in this reaction would reduce the overall number of synthetic steps when compared to traditional methods, such as the Williamson ether synthesis,[14] which require the separate preinstallation of two distinct functional groups (i.e. C–Br and C–O$^-$) prior to the etherification step.

Herein, we report an iron-catalyzed ring-closing C–O/C–O bond metathesis reaction for the synthesis of tetrahydrofurans, tetrahydropyrans and morpholines from simple aliphatic diethers.



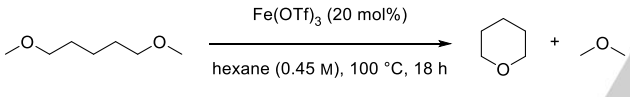
Scheme 1. Context of the work.

Inspired by our previous results in aromatic thioether metathesis,[6] we started our investigation with the evaluation of a wide range of Pd and Ni catalysts for the ring-closing metathesis of 1,5-dimethoxypentane (**1**). However, both the challenges involved with the oxidative addition of a very strong bond, C(sp^3)–O, and the known propensity of alkyl–M intermediates to undergo β-hydride elimination, forced us to reevaluate our design after unsuccessful preliminary results. We reasoned that Lewis acid catalysis, which had been successfully used by Schindler and Li in carbonyl-olefin metathesis,[4] might facilitate an ether bond metathesis reaction proceeding through the intramolecular attack of an ether group onto a Lewis acid activated ether group. The oxonium intermediate generated from this process may then

collapse with the M–OR species to regenerate the active catalyst and the two products. This rationale is indirectly supported by a report from Enthaler in which the authors realized the depolymerization of poly-THF under Fe-catalysis through the continuous removal of the monomeric product, THF, by distillation.[15]

Evaluation of suitable Lewis acids led us to the discovery of a practical $Fe(OTf)_3$ catalytic system for the cyclization of 1,5-dimethoxypentane (**1**) to generate the product (**2**) in 85% yield. Generally, MX_3 salts with relatively weak coordinating anions ($AlCl_3$, $Sc(OTf)_3$, $FeCl_3$, $FeBr_3$) performed well in this reaction, clearly indicating that the reaction indeed proceeds via Lewis acid catalysis. However, no other Lewis acid matched the activity of the $Fe(OTf)_3$ catalyst. A screening of various solvents revealed that more coordinating solvents (acetonitrile, chlorinated solvents) were detrimental to the reaction. A control reaction using triflic acid, which could possibly be formed under the reaction conditions in the presence of water traces, only led to low conversion to the product, confirming that Lewis acid catalysis is most likely responsible for the high reactivity observed. Further control reactions confirmed that a temperature of 100 °C and a concentration of 0.45 M are best for this transformation.

Table 1. Reaction Optimization.[a]

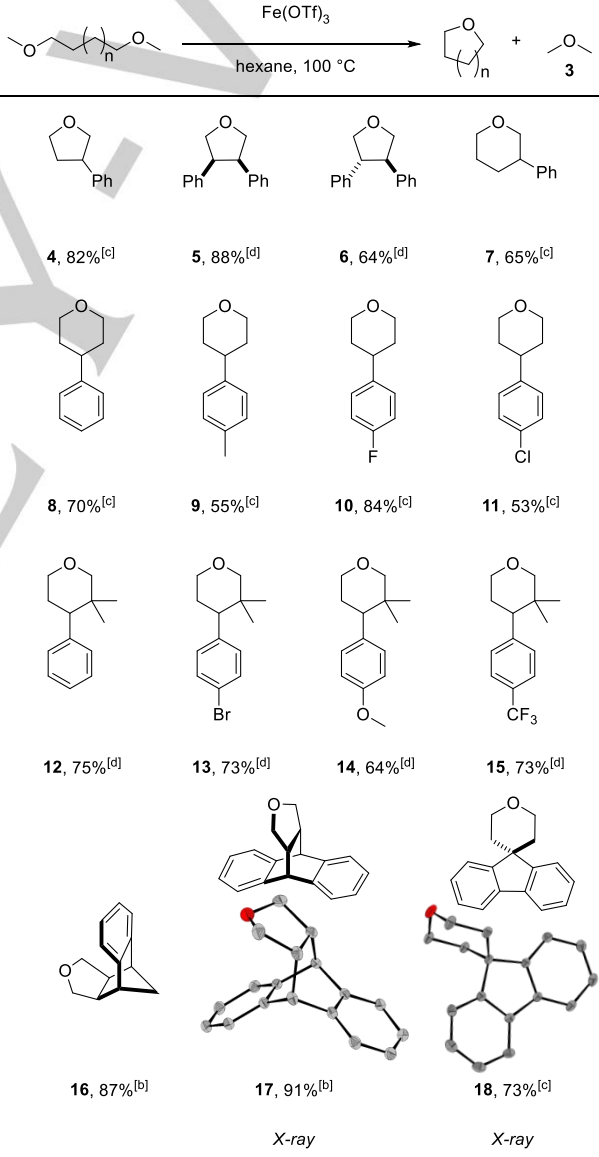


Entry	Deviation from Standard Conditions	Yield of
1	none	85
2	$AlCl_3$ instead of $Fe(OTf)_3$	78
3	$Sc(OTf)_3$ instead of $Fe(OTf)_3$	67
4	Other Lewis acids[c]	11-72
5	TfOH instead of $Fe(OTf)_3$	28
6	Acetonitrile, DCM, benzene instead of hexane	11-71
7	80 °C instead of 100 °C	72
8	0.22 M instead of 0.45 M	69
9	No Lewis acid	0

[a] see SI for detailed conditions. [b] GC-yields in % using dodecane as an internal standard. [c] $B(C_6F_5)_3$, $FeBr_3$, $AlMe_2Cl$, $FeCl_3$.

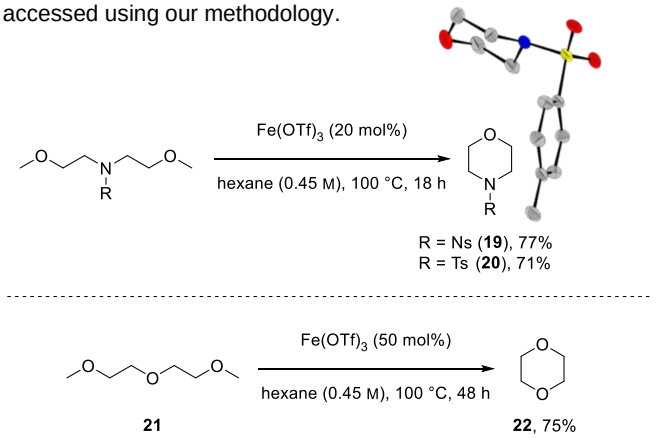
With optimal conditions for the C–O/C–O metathesis in hand, we explored the substrate scope of this transformation (Table 2). Generally, five- as well as six-membered rings can be accessed using our new single-bond metathesis reaction by simple variation of the chain-length of the aliphatic ethers. Notably, totally unbiased substrates can also cyclize efficiently under these reaction conditions. This result stands in contrast to many other cyclization reactions that require a Thorpe-Ingold effect to efficiently generate cyclized products, often limiting the substrate scope.[16] Aromatic rings bearing various functional groups (arylfluoride, -chloride, -bromide, -methoxy, -methyl, -trifluoromethyl) that offer a handle for further functionalization were well tolerated and provided the corresponding products (**9**-**15**) in good to excellent yields. More sterically demanding substrates with a *gem*-dimethyl group at the 3-position (**12**-**15**) were converted in good yields into the corresponding products, when the catalyst loading was increased to 50 mol%, suggesting that the catalyst is somewhat sensitive to steric bulk. When the two methoxyethers were appended to a carbocyclic ring system, we observed a particularly fast reaction with clean formation of the corresponding polycyclic tetrahydrofuran products (**16**-**17**). Moreover, the reaction could be extended to spirocycle synthesis (**18**), showcasing the potential of this method to rapidly generate unusual heterocyclic architecture that are of potential interest to drug discovery. Benzylic and secondary ethers, as well as substrates that contained alkenes or amides (for full details see SI) were not tolerated in this reaction.

Table 2. Scope of the iron-catalyzed ring-closing metathesis.[a]



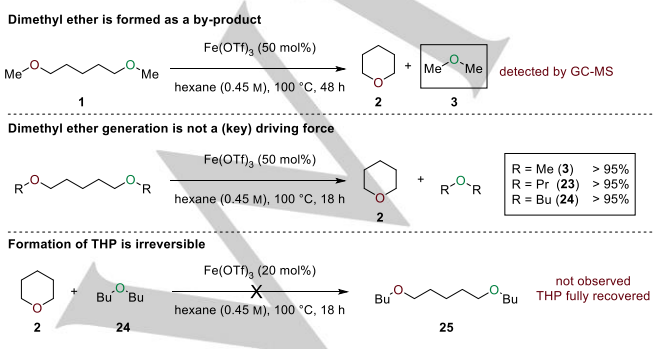
[a] Yields of isolated products. [b] 20 mol%, 18 h. [c] 20 mol%, 48 h. [d] 50 mol%, 48 h.

Dioxanes and morpholines are among the most commonly encountered heterocycles in drug design. We were thus interested to test whether these saturated heterocycles could be accessed with our methodology through the cyclization of the corresponding heteroatom-rich starting materials. Excitingly, while the strong coordinating ability of those substrates could have been deleterious to the reaction, we obtained the desired products in high yields (Scheme 2). 1,4-dioxane (**22**) as well as nosyl- and tosyl-protected morpholines (**19**, **20**) could thus be accessed using our methodology.



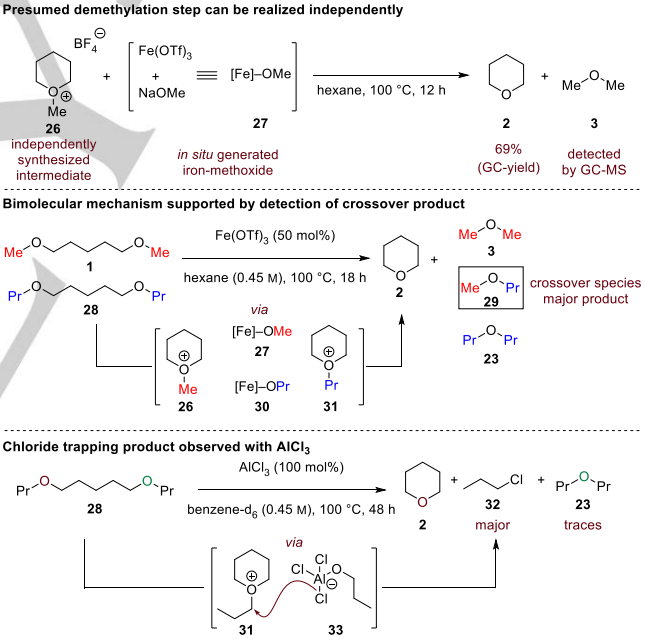
Scheme 2. Applying ring-closing metathesis to morpholine and dioxane synthesis.

We next aimed to detect and possibly understand the role of the dimethyl ether that should be formed as a by-product under the reaction conditions (Scheme 3). First, we ran the model reaction on a 1.7 mmol scale in a pressure-vial equipped with a septum cap. Using a gastight syringe, the gases present in the head space were subsequently analyzed by GC-MS and the presence of dimethyl ether (**3**) was unambiguously confirmed by comparison with two independent library spectra (for more details see SI). Next, we wondered if the formation of gaseous dimethyl ether (**3**) as a by-product was the determining factor in driving forward the equilibrium of this potentially reversible reaction. This was ruled out by a set of experiments which, despite involving the formation of heavier, non-volatile ether by-products (**23**, **24**) instead of dimethyl ether (**3**), led to identical conversions and yields of the product (**2**). This result, together with the absence of reactivity between THP (**2**) and dibutyl ether (**24**), suggests that the formation of THP (**2**) is irreversible under these reaction conditions.



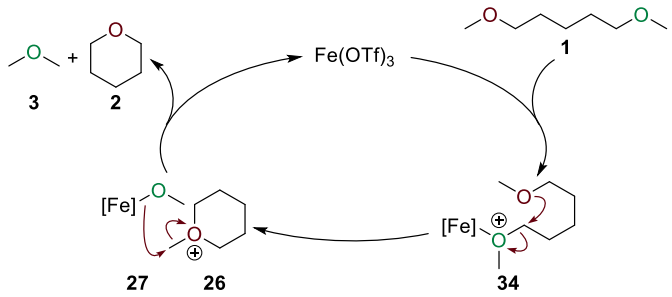
Scheme 3. Mechanistic experiments.

Our working model for the initial design of this reaction involved the intramolecular attack of a second ether onto a Lewis acid coordinated ether group through an intramolecular nucleophilic attack to generate a key oxonium intermediate along with a metal alkoxide. Several experiments support this mechanistic picture (Scheme 4). First, an independently generated cyclic oxonium intermediate (**26**) did react with an "Fe–OMe" (**27**) species, which was generated *in situ* by mixing $Fe(OTf)_3$ with equimolar NaOMe, to form the THP (**2**) product along with dimethyl ether (**3**). Second, a crossover experiment using two substrates (**1**, **28**) having different oxygen substituents, Me and Pr, resulted in the formation of MeOPr (**29**) as the major by-product, a result that supports a bimolecular reaction mechanism. The intermediacy of a cyclic oxonium species is also indirectly supported by a surprising result obtained when the reaction was performed with stoichiometric $AlCl_3$ instead of catalytic $Fe(OTf)_3$. In this experiment, 1-chloropropane (**32**) was obtained almost exclusively as a by-product instead of dipropyl ether (**23**), a result probably best explained by selective chloride delivery from a tetracoordinated $[AlCl_3(OPr)]^-$ (**33**) species onto the cyclic oxonium intermediate (**31**).



Scheme 4. Additional mechanistic experiments.

Collectively, these results are best explained by the mechanism depicted in Scheme 5. Iron(III) triflate first forms a Lewis acid/base adduct (**34**) with one of the ether oxygen atoms. Subsequent intramolecular nucleophilic attack of the non-coordinated oxygen atom furnishes the cyclic oxonium intermediate (**26**) and an iron methoxide complex (**27**). This methoxide complex (**27**) demethylates the oxonium species (**26**), thereby yielding tetrahydropyran (**2**) and dimethyl ether (**3**) while regenerating the active catalytic species.



Scheme 5. Proposed mechanism.

In conclusion, we have presented the first synthetically relevant aliphatic ether metathesis reaction, a reaction which is enabled by iron catalysis. The method described provides access to substituted tetrahydrofuran and tetrahydropyran derivatives in an efficient manner. Mechanistic experiments support a Lewis acid catalyzed pathway that likely proceeds via cyclic oxonium intermediates. Overall, our reaction design provides a blueprint for the development of new metathesis reactions involving inert C(sp^3)–X bonds.

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Keywords: metathesis, iron catalysis, ethers, tetrahydropyrans, tetrahydrofurans, morpholines

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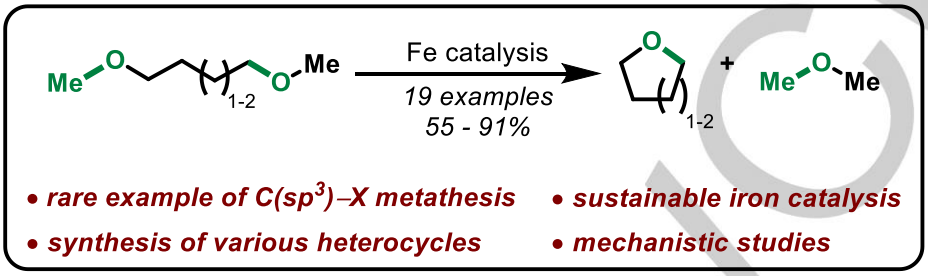
C(sp^3)–O/C(sp^3)–O metathesis of ethers (single bonds)



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