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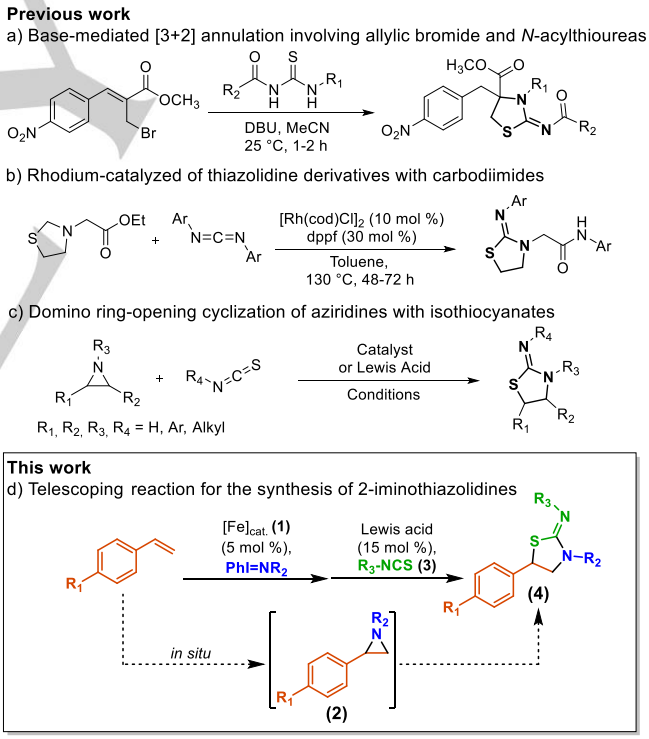
Expedient synthesis of 2-iminothiazolidines via telescoping reactions including iron-catalyzed nitrene transfer and Domino Ring-Opening Cyclization (DROC)

Guillaume Coin*[a],[b]‡, Oriane de Ferrier de Montal,[a] Patrick Dubourdeaux[a] and Jean-Marc Latour*[a]

Abstract: 2-iminothiazolidines are important scaffold for pharmaceutical drugs. Herein, we describe a fast and easy procedure for their synthesis by a telescoping reaction integrating an iron-catalyzed nitrene transfer under mild conditions. The aziridination reaction of olefins is followed by the domino ring-opening cyclization (DROC) of the aziridine intermediates with organic isothiocyanates catalyzed by a Lewis acid leading to the desired product. This new synthetic route allows time, step and purification economies, which is in agreement with the development of more efficient processes for the synthesis of small molecules.

Over the last decades *N*-heterocycles appeared as prevalent structural scaffolds of pharmaceuticals.[1,2] Among them, 2-iminothiazolidines are structural architectures found in several drugs and biologically active compounds.[3] They possess a wide range of biological and pharmaceutical activities as anti-inflammatory, anti-hypertensive, anti-Alzheimer, progesterone receptor binding agents and antidepressant. This class of compounds also exhibits radioprotective properties. The synthesis of such compounds is therefore an important issue for chemists. Consequently, large efforts have been devoted to the development of efficient 2-iminothiazolidines syntheses and a few representative ones are given in Scheme 1. Among them, Sá *et al.* have described a base-mediated [3+2] annulation involving allyl bromide and N-acylthioureas (Scheme 1a).[4] Alper *et al.* have reported a rhodium-catalyzed synthesis of thiazolidine using carbodiimides (Scheme 1b).[5] But one of the most promising routes is the domino ring-opening cyclization (DROC) of aziridines with isothiocyanates (Scheme 1c).[6] This reaction requires the use of catalysts such as phosphines,[7] pyrrolidines,[8] palladium complex[9] or Lewis acid[10–13] to open aziridine ring. A few drawbacks are noticeable for some of these methods: (i) the use of harsh opening conditions (high temperature, work under pressure); (ii) the use of Lewis acids in stoichiometric quantities. Recently, a significant improvement was achieved by the groups of Ghorai[9] and Punniyamurthy[10] and their coworkers who described the synthesis of 2-iminothiazolidines from aziridines with respectively, $BF_3.OEt_2$ (15 mol %) and an Al(salen) complex (5 mol %) as catalysts. Very recently, Patel and co-workers disclosed a catalyst-free version using aroyl isothiocyanates (ArCO-NCS).[14]

To further improve this synthetic route to 2-iminothiazolidines, we investigated the possibility of developing telescoping reactions. These are at least a two-step synthesis where reactants are added successively in the same flask without isolation and purification of synthetic intermediates.[15] Their operation simplicity and solvent- and time-saving make them more economically attractive.[16] As a matter of fact, they were described as the best way to "clean up" organic synthesis[17] and have sharply emerged as a synthetic route for the construction of a large range of compounds,[18–27] including numerous heterocycles of pharmaceutical and agrochemical interest.[28–30]



Scheme 1. Previous routes for the synthesis of 2-iminothiazolidines and design of the telescoping reaction including iron-catalysed nitrene transfer.

Therefore, we intended to use telescoping reactions integrating the *in situ* generation of the aziridine followed by its ring-opening and insertion of an organic isothiocyanate. The aziridine will be formed by a nitrene transfer reaction using an iron catalyst. In 2015, the first such telescoping reaction including nitrene transfer was described by Dauban and co-workers with a bis-rhodium catalyst.[31] To our knowledge no other such reactions including nitrene transfer have been published.

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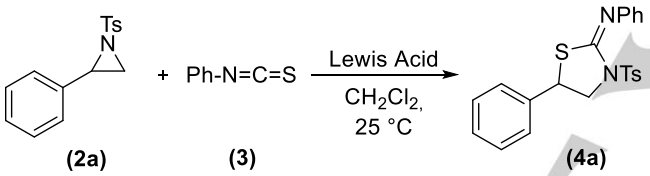
Nitrene transfer is a powerful synthetic route because of its ability to form a wide range of amines without pre-functionalisation nor post-deprotection steps.[32] Over the years, iron has emerged as a ubiquitous metal in the field of catalysis, due to its high abundance, low price and non-toxicity.[33–35] We reported that the diiron(III,II) catalyst **(1)** (Scheme S1) is capable to mediate the intermolecular nitrene insertion from an imino-iodinane (PhI=NTs) to a large range of substrate.[36–40] This complex is able to form aziridine from styrene with a very good yield (87 %) using PhI=NTs at room temperature in dichloromethane for four hours.[36,40]

In this paper, we first illustrate the effectiveness of $Al(OTf)_3$ and $In(OTf)_3$ as Lewis acids for the ring opening of aziridine followed by the insertion of an organic isothiocyanate. Then, we describe the first telescoping reaction including nitrene transfer mediated by an iron catalyst with good yields in mild conditions. Mechanistic insights allow us to propose a plausible mechanism for the entire process.

First, we conducted a screening of various Lewis acids for the aziridine ring-opening with phenyl isothiocyanate. 2-phenyl-*N*-tosylaziridine was chosen as representative substrate, independently prepared and fully characterized, notably by X-ray crystallography. The reaction was realized in the presence of a catalytic amount of various Lewis acids in dichloromethane under mild conditions (Scheme 2).

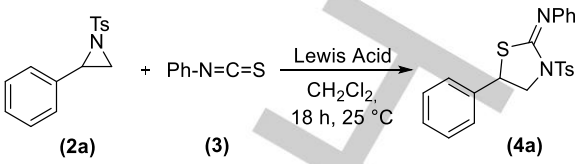


Scheme 2. Lewis acid-catalysed domino ring-opening cyclization of 2-phenyl-*N*-tosylaziridine with phenyl isothiocyanate.

At first, we examined the efficiency of different Lewis Acids (Table 1). In the absence of catalyst, no reaction was observed (Table 1, entry 1). $BF_3.OEt_2$ appears as the best catalyst but surpasses marginally most triflate salts (Table 1, entries 2 and 4-11). As expected $AlCl_3$ is far less active than $Al(OTf)_3$. By contrast, AlCl(salen) is totally unreactive (Table 1, entry 3) in the same conditions used by Puniyamurthy and co-workers.[10] As a matter of fact salen and chloride coordination strongly reduce the acidity of Al which is still able to alkyl and benzyl aziridines but fails to bind the less basic tosylaziridines in the present work. Excellent yields were obtained with $Al(OTf)_3$, $In(OTf)_3$ and $Fe(OTf)_3$ (Table 1, entries 4-6) and rank these Lewis acids among the most performing reported catalysts for the Lewis acid-catalysed DROC of aziridines with isothiocyanates already reported.[10][12]

Due to the toxicity and the dangerousness of $BF_3.OEt_2$ for the experimentalist and the environment,[41] we decided to work with $In(OTf)_3$ and $Al(OTf)_3$. Then, an optimization of the experimental conditions was conducted with indium and aluminium triflates. At first, we varied the number of equivalents of cumulene. With one equivalent of phenyl isothiocyanate, the use of indium triflate allowed the formation of 22 % of 2-iminothiazolidine (Table 2, entry 1). Increasing the number of cumulene equivalents led to a steady rise in yield with a plateau (Table, entries 2 – 8) after 15 equivalents with excellent yields of 87% (Table, entry 7).

Table 1. Efficiency of various Lewis acid for the domino ring-opening cyclization of **(2)**[a]

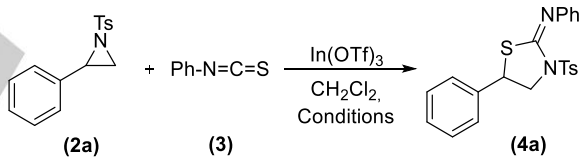


Entry	Lewis acid	**(4a)**[b] (%)	Entry	Lewis acid	**(4a)**[b] (%)
1	-	0	7	$Yb(OTf)_3$	34
2	$BF_3.OEt_2$	90	8	$AlCl_3$	8
3	(salen)AlCl	0	9	$Zn(OTf)_2$	69
4	$In(OTf)_3$	87	10	$Sc(OTf)_3$	80
5	$Al(OTf)_3$	86	11	$Sn(OTf)_2$	84
6	$Fe(OTf)_3$	85			

[a] Reaction conditions : Lewis Acid/ Ph-NCS/ Aziridine molar ratio = 0.15/15/1, CH_2Cl_2, 18 h, 25 °C. [b] Yields determined by ^1H NMR, using mesitylene as an internal standard.

Similar results were obtained using Al(OTf)3 (Table S1). Variation of the reaction time was considered, then and it was observed that the reaction was almost completed after 8 hours (Table 2, entry 11). A variation of the reagents concentration had no incidence on the yield. No improvement was observed by increasing the Lewis acid molar ratio (15, 20 and 30 mol %).

Table 2. Influence of time and number of cumulene equivalents for the DROC of **(2a)** with **(3)** catalysed by $In(OTf)_3$[a]

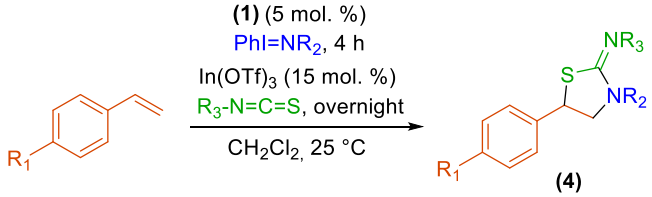


Entry	eq. of **(3)**	time (h)	**(4a)**[b] (%)	Entry	eq. of **(3)**	time (h)	**(4a)**[b] (%)
1	1	18	22	7	15	18	87
2	2.5	18	45	8	30	18	86
3	5	18	66	9	10	2	68
4	7.5	18	71	10	10	4	69
5	10	18	80	11	10	8	77
6	12.5	18	80				

[a] Reaction conditions : $In(OTf)_3$/ Ph-NCS/ Aziridine molar ratio = 0.15/x/1, CH_2Cl_2, 25 °C. [b] Yields determined by ^1H NMR, using mesitylene as an internal standard.

Next, telescoping reactions have been studied. Firstly, the aziridination reaction was accomplished with styrene, a nitrene precursor (PhI=NTs) and the iron catalyst. After the complete consumption of PhI=NTs, indium triflate and phenyl isothiocyanate were added into the same vessel and the reaction mixture was stirred overnight at room temperature to form 2-iminothiazolidine (Scheme 3). Using 15 equivalents of cumulene

led to a lower yield of 2-iminothiazolidine with respect to our initial conditions (48 % vs 87 %). We thus carried out the telescoping reaction with increasing numbers of equivalents of phenyl isothiocyanate. It appeared that 20 equivalents of the cumulene restored a good yield (ca. 70 %) and is thus a good compromise (Table 3). The conversion is not complete because of the formation of several by-products in little amount, which are probably coming from rearrangements when aziridine is opened.[42]



Scheme 3. Catalytic telescoping reaction for the synthesis of different 2-iminothiazolidines.

Table 3. Influence of the number of equivalents of cumulene on the telescoping reaction[a]

Entry	R_1	R_2	Eq. of Ph-NCS	**(4a)**[b] (%)
1	H	Ph	15	48
2	H	Ph	20	69
3	H	Ph	25	71

[a] Reaction conditions : **(1)**/ $In(OTf)_3$/ PhI=NTs/ Styrene/ Ph-NCS molar ratio = 0.05/0.15/1/10/20, CH_2Cl_2, 25 °C. [b] Yields determined by ^1H NMR, using mesitylene as an internal standard.

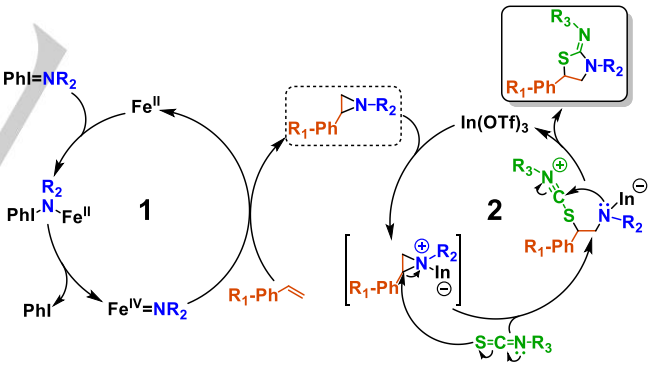
In order to investigate the substrate scope of the reaction and get insights into its mechanism, we have varied the para-substituent of styrene (R) and the substituent of the isothiocyanate (R').

In an initial set of experiments, a series of substrates bearing an electron-withdrawing or an electron-donating group on the para position of styrene have been tested with PhI=NTs as nitrene precursor (Table 4, entries 1-10). It can be seen that halogen substitution of styrene has little effect if any (Table 4, entries 5-7) ; by contrast electron donating substituents led to a significant lowering of the yield (Table 4, entries 8-10) and the formation of unidentified products. A drastic lowering of the yield is noted also for styrenes bearing electron-withdrawing substituents (Table 4, entries 2-4) and a quite significant amount of unreacted aziridine could be isolated. These observations suggest that the lowering of the yields observed either for electron-donating or electron-withdrawing substituents do not have the same origin. For the latter they are due to the failure to open the aziridine, which may be due to a poor interaction with the Lewis acid catalyst. To verify this hypothesis we used as nitrene precursor the nosyl analogue PhI=NNs, where the *p*-nitro substituent was anticipated to deactivate the aziridine with respect to its tosyl parent. This was indeed the case (Entries 11-13) and very low amounts of 2-iminothiazolidine were formed (< 30 %) whereas high amounts of unreacted aziridine were recovered (up to 83 %). By contrast, no aziridine was recovered in the case of electron-donating substituents, which suggests that the lower yield of 2-iminothiazolidine may be due to a higher reactivity of the opened intermediate, which orients it otherwise at the expense of 2-iminothiazolidine formation.

In a second set of experiments, we changed the nature of the isothiocyanate substituent in order to extend the scope of the reaction and synthesize new 2-iminothiazolidines (Table 4, entries 14-22). When *p*-OMe phenyl isothiocyanate is used, good yields were obtained with styrene and *p*-halogenated styrenes (Table 4, entries 14-17). As observed with phenyl isothiocyanate, the reaction with styrenes bearing electron-withdrawing substituents led to lower yields (Table 4, entries 18-20).

Through all these experiments, a mechanistic scheme can be proposed which associates two catalytic cycles (Scheme 4). In cycle 1 the Fe^{II} catalyst first associates with the nitrene precursor PhI=NTs to give an adduct which rearranges in a two-electron process akin to an oxidative addition leading to PhI release and formation of the active species Fe^{IV}(=NTs).[38] Reaction with the olefin produces the desired aziridine and regenerates the catalyst in its initial Fe^{II} form.

The *in situ* formed aziridine enters in cycle 2 and interacts with the Lewis acid to induce the DROC. Coordination of the aziridine nitrogen by the Lewis acid facilitates an S_N2-type nucleophilic attack by the isothiocyanate sulphur to create the C_α-S bond. This attack is followed by the ring closure via the intramolecular nucleophilic attack of the nitrogen to the carbon of the nitrilium ion, leading to the formation of the final 2-iminothiazolidine. The intervention of a S_N2-type nucleophilic attack is supported by the non-formation of 2-iminothiazolidine when electron-withdrawing isothiocyanates are used (Table 4, entries 23-25). Indeed, their reduced nucleophilicity makes the attack at the benzylic position of the LA-coordinated aziridinium ion impossible.



Scheme 4. Proposed mechanism for the catalytic telescoping reaction.

In this work, we have designed and developed an original path for the direct synthesis of 2-iminothiazolidines from *p*-substituted styrenes by telescoping reaction methodology merging nitrene transfer reaction and domino ring-opening cyclization. To our knowledge, this is the first time that nitrene transfer is used for the synthesis of a wide range of 2-iminothiazolidines with moderate to good yields. This procedure represents a promising and attractive route, which allows time, step and purification economies for the synthesis of bio-targeted molecules. We can easily imagine that this new synthetic way can be applied with other catalysts and nitrene precursors. The use of this procedure with different cumulenes (isocyanates, isonitriles…) may offer a large range of diversely substituted *N*-heterocycles.

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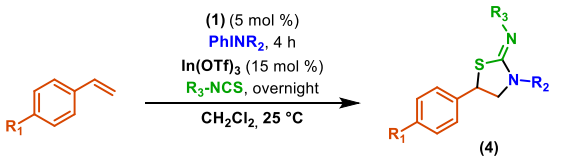
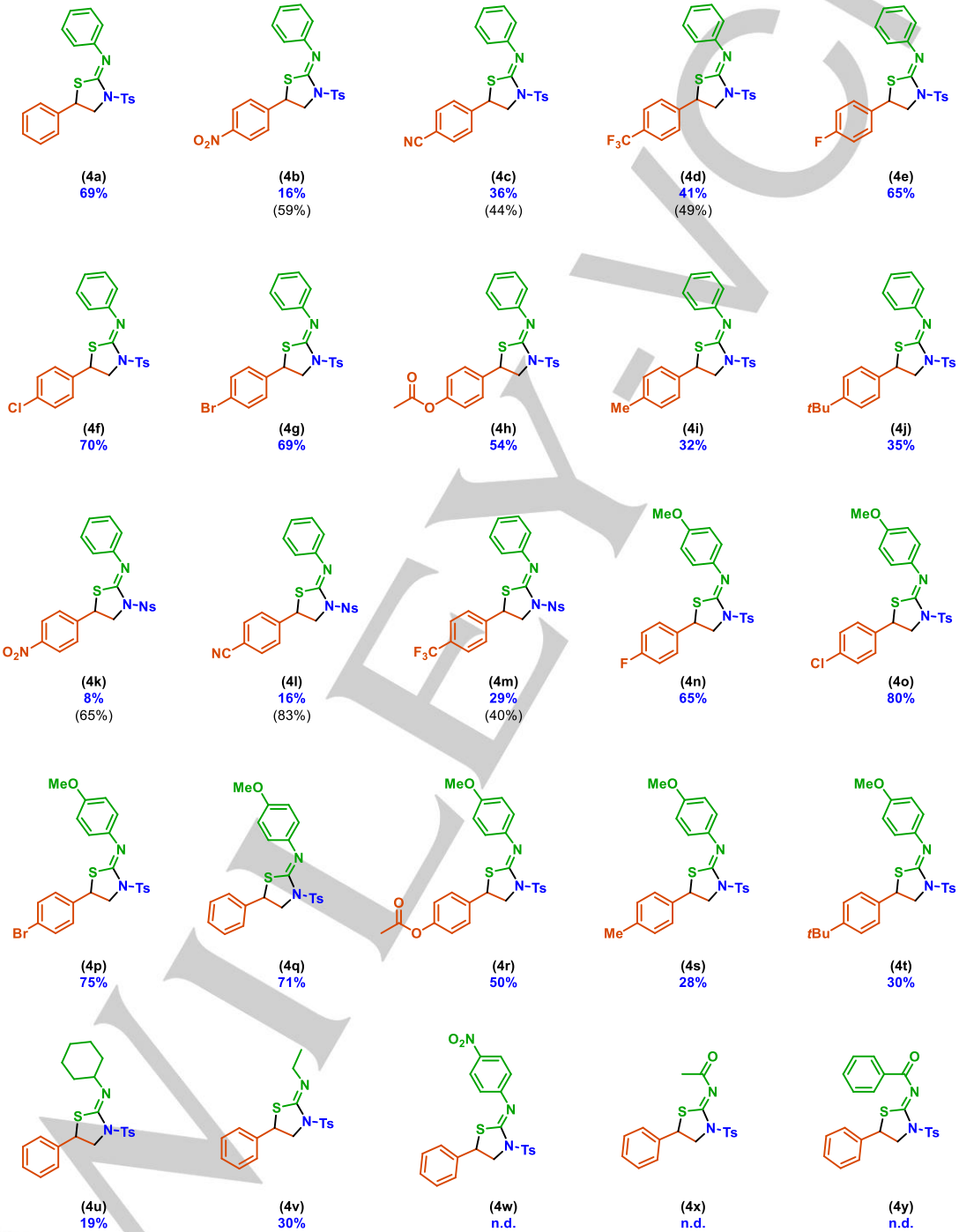
Table 4. Scope of the catalytic telescoping reaction[a]





[a] Reaction conditions: **(1)**/ In(OTf)$_3$/ PhI=NR$_2$ / *p*R$_1$-styrene/ R$_3$-NCS molar ratio = 0.05/0.15/1/10/20, CH_2Cl_2, 25 °C. [b] Yields determined by ^{1}H NMR, using mesitylene as an internal standard. [c] n.d. = not detected

Experimental Section

In a typical experiment, (1) (2.00 mg, 1.7 µmol) was dissolved in 1.7 mL of dichloromethane and 41 µL of styrene (354 µmol) were added. The blue solution was transferred on PhI=NTs (13.22 mg, 35.4 µmol). The mixture was stirred under argon in a thermostated bath regulated at 25°C for 5 h. Then, phenyl isothiocyanate (85 µL, 708 µmol) and indium triflate (2.98 mg, 5,31 µmol) were added to the solution. The mixture was stirred overnight and the solution was then deposited on a silica column and eluted with acetonitrile. The resulting solution was evaporated to dryness leaving an oil. The product was purified upon flash chromatography using silica gel using a gradient of hexane / EtOAc.

Identical procedures were used to prepare every differently substituted 2-iminothiazolidines.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Telescoping catalysis • 2-iminothiazolidines • Nitrene transfer • DROC • Iron catalyst

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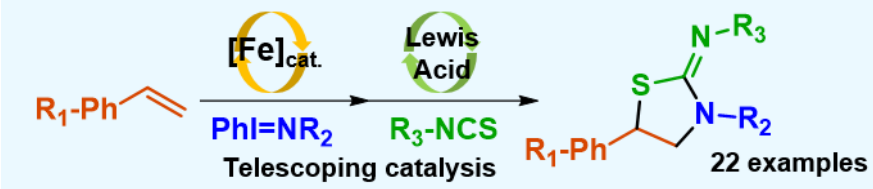

In this work, iron-catalyzed aziridination (nitrene transfer) is combined in a single process to aziridine ring opening (DROC) to produce 2-iminothiazolidines which constitute interesting cores of pharmaceuticals.

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