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Iron-catalyzed synthesis of cyclopropanes by *in situ* generation and decomposition of electronically diversified diazo compounds†

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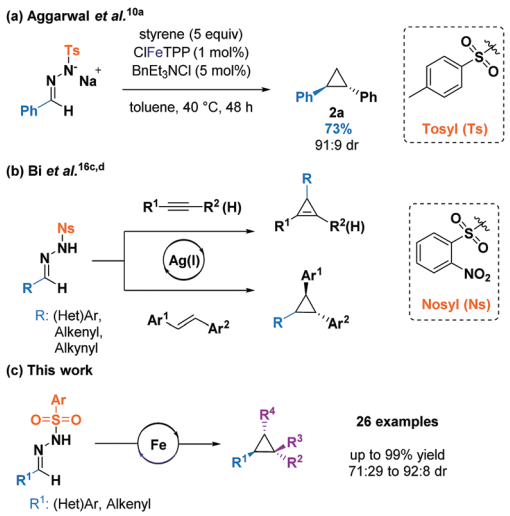
The modular synthesis of a variety of *trans* 1,2-disubstituted cyclopropanes in a safe and user-friendly one-pot iron-catalyzed cyclopropanation reaction is described. Easily synthesized *N*-nosylhydrazones are used as diazo precursors, allowing the *in situ* generation of electron-rich diazo compounds under mild reaction conditions and their direct participation in the cyclopropanation reaction.

The cyclopropane core has been ranked as the 10th most commonly used cyclic scaffold for the elaboration of new drugs[1] and is present in a large number of bioactive compounds.[2] Among all the possible substitution patterns, *trans* 1,2-diarylcyclopropanes moieties are of particular interest, being a motif often screened during the development of biologically relevant molecules.[3] These *trans* 1,2-disubstituted cyclopropanes are generally obtained by reactions between toxic and unstable aryldiazomethanes[4] (or their corresponding metal carbenes) and styrene derivatives. For obvious safety reasons, many efforts have been invested to develop safer generation and utilization protocols of those electron-rich entities. Recently, continuous flow strategies have been described by us and others in order to produce and use right away streams of various aryl diazo compounds without the need to handle them directly.[5] Alternatively, classical batch methodologies allowing the *in situ* generation and consumption of those reagents have also been described: the Aggarwal group was the first to report the use of *N*-tosylhydrazones to that effect, taking advantage of the Bamford–Stevens reaction[6] to generate the wanted diazo compounds and subsequently engaging them in various metal-catalyzed reactions such as epoxidations,[7a] aziridinations,[7b] olefinations,[7c] C–H[8] and X–H insertions[9] or cyclopropanations[7b,10] in the same pot.[11] For example, 1,2-diphenylcyclopropane **2a** has been synthesized in 73% yield with a 91 : 9 *trans*/*cis* ratio after 48 hours at 40 °C *via* iron catalysis using styrene and the sodium salt of the tosylhydrazone derived from benzaldehyde as precursors (Scheme 1a).[10a] This cyclopropanation methodology was then applied to substrates varying from styrene derivatives,[10a] to dehydroaminoacids,[10b] proving its compatibility with a wide array of alkenes. The limiting point was however the modulation of the hydrazone component: in all examples, very few electronically enriched or impoverished phenyldiazomethane precursors were described or successfully used. This lack of results may be explained by the high temperature that is often needed to trigger the decomposition of the tosylsulfonylhydrazones, which can be incompatible with the sensitive diazo compound that is generated and the subsequent cyclopropanation. We therefore decided to attempt the development of smoother conditions for a modular cyclopropanation reaction in which a wide variety of electronically and sterically modified aryl diazo compounds would be generated *in situ*.[12] Concerning the cyclopropanation step by itself, we decided to focus on iron chemistry using the well-known ClFe^{III}(TPP)



Scheme 1 (a) First *in situ* process developed by Aggarwal and co-workers.[10a] (b) Silver-catalyzed cyclopropenation[16c] and cyclopropanation[16d] of 1,2 disubstituted alkenes using *N*-nosylhydrazones as diazo surrogates. (c) This work: modular synthesis of cyclopropanes *via* iron catalysis.

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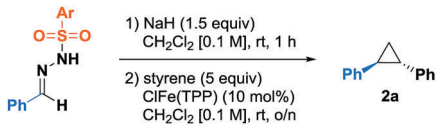
(TPP = tetraphenylporphyrin) catalyst, as this metal is one of the most abundant on earth.[13,14]

In order to achieve our goal, we needed to find a way to decompose our hydrazones at lower temperature. In the literature, two main strategies have been described in this optic. First, it is possible to increase the steric bulk of the aromatic ring sitting on the sulfonylhydrazone. By doing so, the steric decompression during the diazo formation renders this step more favourable, as illustrated by the use of 2,4,6-triisopropylphenyl (Trip)[15] or mesityl (Mes)[5e] sulfonylhydrazones. Alternatively, electronic effects can be used instead of steric ones.[16] For example 2-nosylhydrazones have been shown to decompose into the corresponding diazo compounds at room temperature once deprotonated by sodium hydride and are compatible with silver catalyzed cyclopropenation[16c] and cyclopropanation[16d] reactions. Another important aspect of those *N*-nosylhydrazones is that the diazo compound is slowly generated over time:[16c] therefore, there would be no diazo accumulation, risk of dimerization or degradation, as it would be consumed right away in the subsequent reaction.

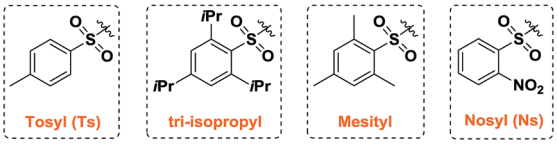
We began our studies by screening those different phenylsulfonylhydrazones in an iron-catalyzed cyclopropanation reaction of styrene: after a one-hour deprotonation step using sodium hydride in dichloromethane, an excess of the alkene was added along with 10 mol% of the commercially available ClFe^{III}(TPP) catalyst, and the reaction was stirred overnight at room temperature. When the tosylhydrazone derivative was used in these conditions (Table 1, entry 1), by ^{1}H NMR we were able to observe only 27% of the desired product along with the rest of the starting material untouched. This corroborates the hypothesis that stronger conditions are needed to degrade such hydrazones. Although delivering the desired cyclopropane in the same range of yields, the corresponding triisopropylphenylhydrazone and mesitylhydrazone experiments showed no more hydrazone left but stilbene generated (Table 1, entries 2 and 3). This suggested that the diazo compound was generated too quickly for the cyclopropanation reaction in those experiments, and that the metal carbene could react with an equivalent of diazo to deliver this product of formal dimerization. Finally, the *N*-nosylhydrazone gave the more promising result, the desired product being observed in 65% yield and displaying an excellent diastereoselectivity (Table 1, entry 4). Despite an extensive initial screening of solvents and bases, dichloromethane and sodium hydride proved to be the best for this reaction.[17] Lowering the temperature of the deprotonation step to 0 °C instead of room temperature allowed us to minimize the formation of stilbene and to obtain a slightly higher 75% yield (Table 2, entry 2). Additionally, a higher dilution of 0.05 M allowed us to observe the desired product in 85% yield after 19 hours (Table 2, entry 3) and in a quantitative yield after 24 hours (Table 2, entry 4).[17] This compound **2a** was isolated in a slightly lower 92% yield due to its volatility.

Table 1 Screening of *N*-arylsulfonyl hydrazones as diazo surrogates



Entry	Ar	Yield[a,b] (%)	dr[c]	Mass balance
1	Tolyl	27	—	Hydrazone recovered
2	Trip	24	92 : 8	Dimerization
3	Mes	17	—	Dimerization
4	*o*-Nitroaryl	65	92 : 8	Dimerization

[a] Determined by ^{1}H NMR (Ph_3CH used as internal standard). [b] Combined ^{1}H NMR yields of both diastereomers. [c] dr *trans*/*cis*, *trans* diastereomer as major.



Those conditions in hand, the scope of the reaction was investigated using styrene and various nosylhydrazones at first (Scheme 2). *p*-Chloro-, *p*-bromo- and *o*-fluoro-phenylhydrazones were successfully used under our reaction conditions, the corresponding products **2b**, **2c** and **2d** being isolated in 87, 85 and 81% respective yields with good diastereoselectivities. The product **2e** bearing a trifluoromethyl group in the *para* position was also isolated in an excellent 97% yield with a 91 : 9 *trans*/*cis* ratio, showing that hydrazones bearing electron-withdrawing substituents are well tolerated in this reaction. The presence of a cyano group at the *para* position proved to be more problematic: neither the desired cyclopropane **2f** nor the dimerization product were observed, although a complete consumption of the starting hydrazone. We hypothesized that the diazo compound was successfully generated but did not proceed to the carbene formation. Running the reaction at 40 °C instead of room temperature after the introduction of the alkene and the catalyst, we were pleased to isolate the desired product **2f** in 95% yield, displaying a satisfactory 85 : 15 *trans*/*cis* ratio. Concerning hydrazones bearing electron-donating effects, we also observed only little amounts of products when the reactions were run at room temperature (Scheme 2, entries **2g**, **2h**, **2i**, **2j**). For these examples, the starting hydrazones were recovered in the end, meaning that the diazo formation was the issue with electron rich hydrazones. Once again, heating the reaction at 40 °C was beneficial as the desired products were obtained in yields above 80% and displaying good diastereoselectivities. However, steric hindrance was detrimental to the reaction, as shown by compound **2k**, isolated with a moderate yield and a low diastereoselectivity even at 40 °C. We were pleased to see that heteroaryldiazoalkanes can also be successfully generated and cyclopropanated in our conditions (compounds **2l**, **2m** and **2n**). A low 44% NMR yield was however observed for product **2n** as those types of alkoxy-substituted cyclopropanes are generally prone to ring opening. We hence failed to obtain any isolated yield after flash column chromatography, even using deactivated silica gel.[18] Hydrazones derived from α,β-unsaturated aldehydes were also effectively fragmented into the corresponding diazo compounds, the cyclopropanation products **2o** and **2p** being isolated in moderate to good yields with good diastereoselectivities. We then investigated the alkene

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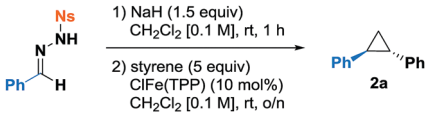
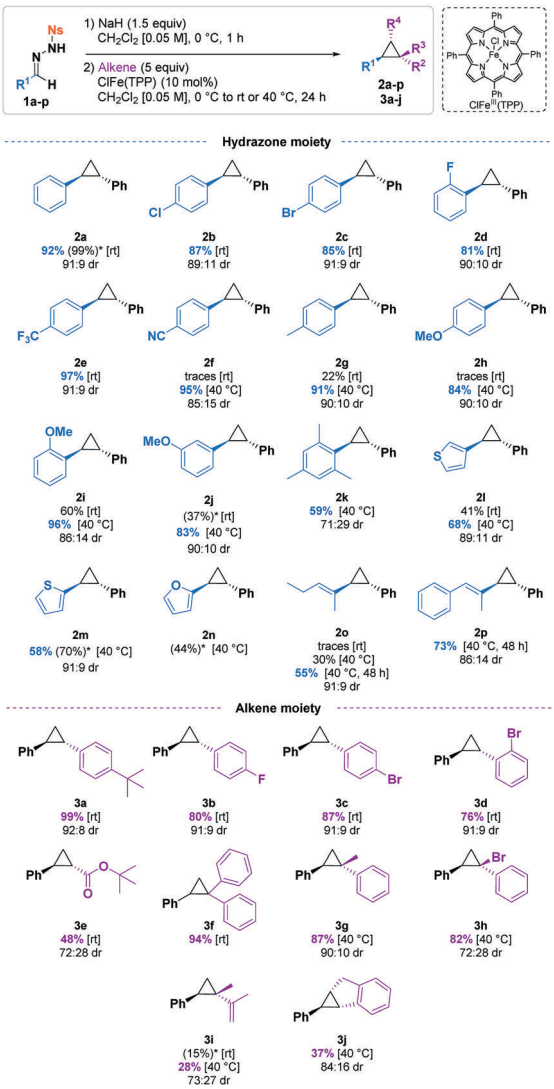
Table 2 Overview of the reaction optimization



Entry	Variation from the above conditions	Yield[a,b] (%)	dr[c]
1	None	65	92 : 8
2	Deprotonation at 0 °C	75	91 : 9
3	Deprotonation at 0 °C + concentration of [0.05 M] (19 h)	85	92 : 8
4	Deprotonation at 0 °C + concentration of [0.05 M] (24 h)	99 (92)[d]	91 : 9

[a] Determined by ^{1}H NMR (trimethoxybenzene used as internal standard). [b] Combined ^{1}H NMR yields of both diastereomers. [c] dr *trans*/*cis*, *trans* diastereomer as major. [d] Isolated yield (volatile compound).



Scheme 2 Scope of the reaction on 0.5 mmol scale. Yields on the isolated mixture of both combined diastereomers. Diastereomeric ratio determined by ^{1}H NMR on the isolated mixture. For each compound, the temperature of the reaction is specified in brackets. * ^{1}H NMR yield on the crude mixture.

component of our reaction using the phenyl *N*-nosylhydrazone. *p*-*t*-Butylstyrene worked well, the compound **3a** being isolated in an almost quantitative yield with a good diastereoselectivity. *p*-Fluoro- and *p*-bromostyrenes are also viable substrates, as the corresponding products **3b** and **3c** were isolated in good yields, albeit a bit lower than the model substrate. Positioning the bromine atom on the *ortho* position caused a drop of the isolated yield, although still at an acceptable 76% and good diastereoselectivity (compound **3d**). Interestingly, *t*-butyl acrylate successfully undergoes the cyclopropanation reaction, although the desired product **3e** was isolated in a modest 48% yield and a mediocre diastereoselectivity. 1,1-Diphenyl ethylene proved to be also compatible with our conditions: the desired cyclopropane **3f** being isolated in 94% yield. Replacing one phenyl ring on this substrate by a methyl group required to heat the reaction at 40 °C to provide compound **3g** that was isolated in 87% yield. Similarly, α-bromostyrene was successfully cyclopropanated at 40 °C, the product **3h** being isolated in an 82% yield although with poor diastereoselectivity. Product **3i** and **3j** were only isolated in low 28% and 37% yields respectively using 2,3-dimethyl-1,3-butadiene and indene, showing limitations concerning the substitution and the geometry of the starting alkene. It is worthy to note that the compounds **2c** and **3c** are identical and similar yields and diastereoselectivities were obtained starting from either the *p*-bromophenyl *N*-nosylhydrazone or the *p*-bromostyrene. As the styrene derivatives are often very unstable and expensive, this methodology offers the possibility to use relatively cheap and stable aldehydes instead to access to the same moieties.

We then attempted an intramolecular example using compound **1q** (Scheme 3a). We were glad to isolate compound **2q** in 89% yield, with a diastereoselectivity of 96 : 4. As the minor diastereoisomer observed here could only result from the inversion of the alkene's geometry, we think that this reaction goes through a stepwise radical mechanism described before as metalloradical catalysis (MRC) by the Zhang group.[10f] Finally, we decided to use our methodology for the synthesis of intermediate **3h** (Scheme 3b), that was used during the development of hepatitis C virus inhibitors.[3a] In the original patent, this compound was synthetized using Shi's carbenoid in a Simmons–Smith reaction of *trans*-stilbene followed by a bromination using NBS, giving an overall yield lower than 40% (Scheme 3b).[3a] Using our methodology, we synthesized efficiently **3h** in a 80% overall yield starting from the cheap and commercially available 4-bromobenzaldehyde and nosylhydrazide, and this, without the use of pyrophoric reagents.

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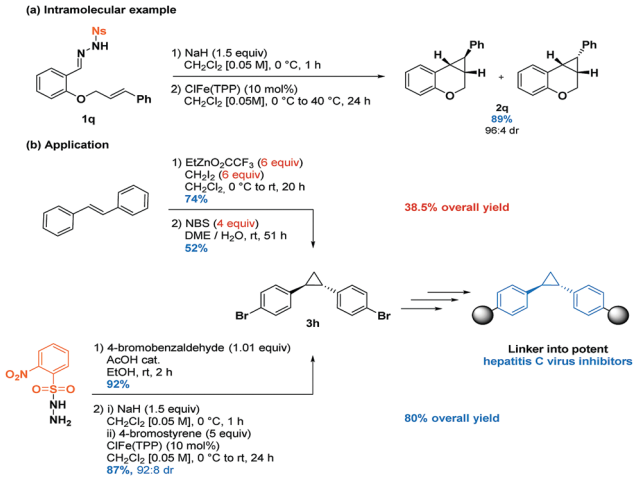

Scheme 3 (a) Intramolecular example. 0.5 mmol scale. Diastereomeric ratio determined by ^{1}H NMR on the crude mixture. (b) Application of the methodology developed. 0.5 mmol scale. Diastereomeric ratio determined by ^{1}H NMR on the isolated mixture.

In summary, we developed a safe and easy-to-handle protocol for the *in situ* generation of electronically diversified compounds and their implication in an iron-catalyzed cyclopropanation reaction in the same pot. The use of nosylhydrazones allowed us to broaden the scope accessible of diazo compounds by avoiding side reactions, therefore permitting an efficient, safe and modular synthesis of cyclopropanes bearing a multitude of substituents with various electronics properties for the first time in a one-pot methodology.

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Conflicts of interest

There are no conflicts to declare.

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