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A One-Pot Reaction toward the Diastereoselective Synthesis of Substituted Morpholines

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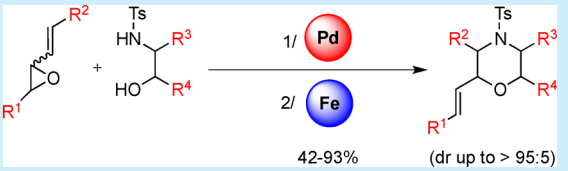
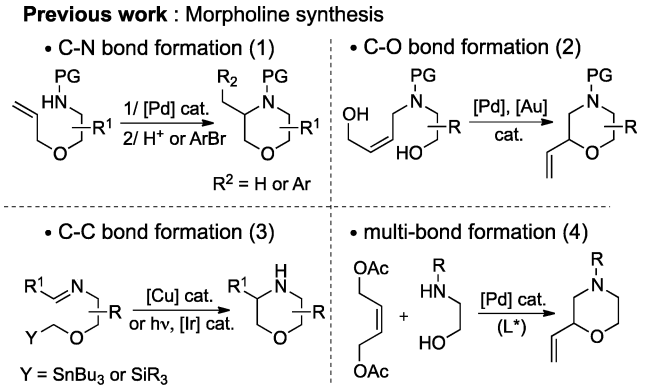
Supporting Information

ABSTRACT: The diastereoselective synthesis of various substituted morpholines has been achieved from vinyloxiranes and amino-alcohols under sequential Pd(0)-catalyzed Tsuji−Trost/Fe(III)-catalyzed heterocyclization. Using the same strategy, 2,6-, 2,5-, and 2,3-disubstituted as well as 2,5,6- and 2,3,5-trisubstituted morpholines were obtained in good to excellent yields and diastereoselectivities.



Developing new methods and processes toward polysubstituted "privileged"[1] scaffolds is a never-ending challenge for organic chemists. Among heterocycles of interest in the pharmaceutical and agrochemical areas, morpholines are widely encountered in biologically active compounds.[2] Therefore, the synthesis of morpholines has been extensively studied in recent decades and numerous strategies have emerged.[3] Particular efforts have been deployed in the field of metal-mediated reactions. Most of these methods consist of cyclization of *O*- or *N*-tethered substrates with the final formation of a C−N or a C−O bond respectively (Scheme 1).

Scheme 1. Metal-Catalyzed Syntheses of Morpholines



For example, Wolfe et al.[4a] reported the synthesis of *cis*-3,5-disubstituted morpholines with moderate yields and excellent diastereoselectivities by using a Pd-catalyzed intramolecular carboamination of a terminal olefin. Later, Michael and coworkers showed[4b] that a similar strategy, with a different palladium catalyst combined with $AgBF_4$, can lead to *trans*-2,5-disubstituted morpholines in good yields (Scheme 1, eq 1). Palladium was also used as a catalyst for the formation of *cis*-2,6-disubstituted morpholines by Saikia et al.[6a] to induce the cyclization of ω-hydroxy allylic alcohols, while Bandini and coworkers reported[6b] a gold-catalyzed cyclization of similar substrates toward *cis*-2,5-disubstituted morpholines (Scheme 1, eq 2).[7] In both cases, (*Z*)-olefins were necessary to have good yields and good diastereoselectivities. In addition, Bode et al. have explored the formation of morpholines through a radical construction of a C−C bond, from a stannylated imine under copper catalysis.[8a] The same group showed that the stannyl group could be replaced by a silyl group provided that the reaction was activated with an iridium catalyst under light irradiation (Scheme 1, eq 3).[8b−d] Another strategy reported by Saegusa et al. in 1990 consists of the sequential formation of several bonds in a one-pot reaction.[9a] Activation of 2-buten-1,4-diyl diacetate with Pd(0) in the presence of an amino-alcohol led to the formation of the 2-vinyl morpholine with an excellent yield through the sequential formation of a C−N and C−O bond (Scheme 1, eq 4). It is worth mentioning that the use of a chiral ligand can give access to enantioenriched morpholines.[9b,c,10]

A wide range of methods is thus available to synthesize substituted morpholines. However, some of the main drawbacks associated with these methods are the requirement of prolonged heating, the use of toxic metals/reagents, or the need for lengthy syntheses to access the starting materials generating important wastes. In addition, to the best of our knowledge, none of them has been applied to the synthesis of all the possible substitution patterns of the morpholine ring. Therefore, a flexible approach toward polysubstituted morpholines is still desirable while taking into account the atom economy principle.

Based on our experience in the environmentally benign $FeCl_3$-catalyzed diastereoselective formation of various heterocycles,[11] we envisioned the construction of the morpholine core from an ω-hydroxy allylic alcohol intermediate. This intermediate could result from a Pd-catalyzed Tsuji−Trost reaction[12] between readily available vinyl oxiranes and amino-alcohols (Scheme 2). We furthermore envisioned that it should

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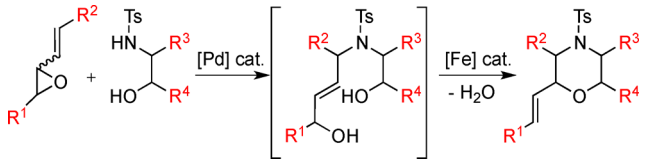
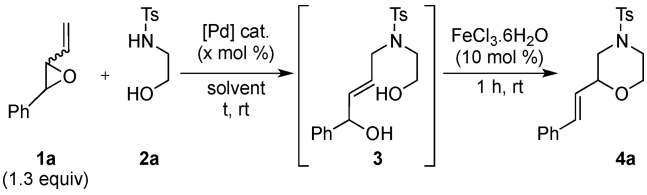
not be necessary to control the *cis*/*trans* configuration of the vinyl oxiranes. This method could lead to various substitution patterns, generating only water as a byproduct (Scheme 2).

Scheme 2. Sequential Pd(0)/Fe(III) Catalysis



To validate our hypothesis, phenylvinyl oxirane **1a**[13] (1.3 equiv) was reacted with *N*-Ts amino-ethanol **2a**. In the presence of 10 mol % of $Pd(PPh_3)_4$ in THF, full conversion of the amino-alcohol was observed after 1 h with concomitant formation of the Tsuji–Trost adduct **3** (Table 1, entry 1). Disappointingly, no conversion of **3** was observed after the addition of 10 mol % of $FeCl_3{\cdot}6H_2O$ to the reaction, while 1 equiv of Fe(III) led to the cyclized product **4a** in only 10% yield (Table 1, entry 2). This result was attributed to the possible deactivation of the iron catalyst by complexation with THF. Indeed, switching from THF to CH_2Cl_2 did not affect the Tsuji–Trost reaction but improved the cyclization: a promising 50% conversion of **3** to **4a** was observed with 10 mol % of $FeCl_3{\cdot}6H_2O$ (Table 1, entry 3). The low conversion during the iron-catalyzed step was presumably due to a partial deactivation of the catalyst by triphenylphosphine oxide,

Table 1. Optimization of the Conditions



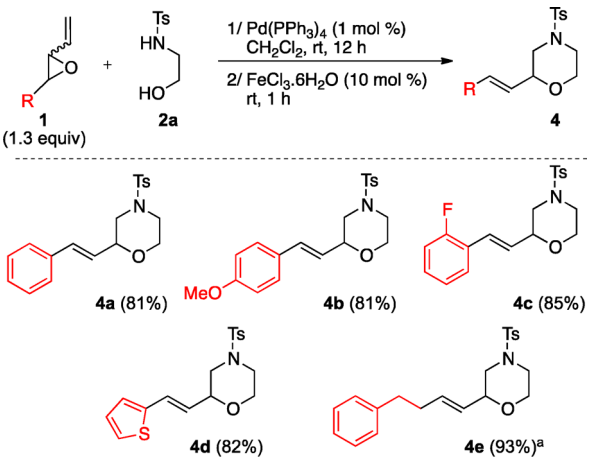
entry	solvent	[Pd] cat. (x mol %)	*t*	2a/3	3/4a
1	THF	$Pd(PPh_3)_4$ (10)	1 h	0:100	100:0
2[a]	THF	$Pd(PPh_3)_4$ (10)	1 h	0:100	90:10
3	CH_2Cl_2	$Pd(PPh_3)_4$ (10)	1 h	0:100	50:50
4	CH_2Cl_2	$Pd(PPh_3)_4$ (1)	12 h	0:100	0:100 (81)[b]
5	CH_2Cl_2	$Pd_2(dba)_3$ (1) + PPh_3 (2)	12 h	8:92	–
6	CH_2Cl_2	$PdCl_2$ (1) + PPh_3 (2)	12 h	100:0	–

[a]1 equiv of $FeCl_3.6H_2O$ was used. [b]Yield of isolated product **4a** in parentheses.

producing the iron complex $FeCl_3(OPPh_3)_2$ which has a lower Lewis acidity than $FeCl_3$.[14] The Pd catalyst loading was then decreased to 1 mol %. Under these conditions, 12 h were necessary to ensure full conversion of the amino-alcohol **2a** to the *N*-tethered intermediate **3**. Subsequent addition of 10 mol % of $FeCl_3{\cdot}6H_2O$ to the medium pleasingly led to a full conversion of **3**, and morpholine **4a** was isolated in a good 81% yield (Table 1, entry 4). Other sources of palladium(0) led to lower or no conversion of **2a** (Table 1, entries 5–6).

With this first set of conditions in hand, we explored the influence of the vinyl oxirane R^1 group (Scheme 3). Different substituted aromatic rings were tolerated, as the corresponding morpholines **4b** and **4c** were isolated with yields of 81% and 85% respectively. A thiophene ring is also compatible with the conditions, as morpholine **4d** was isolated in 82% yield. An alkyl substituent was not detrimental to the Tsuji–Trost reaction; however, the cyclization did not occur at rt, but if the reaction was heated at 50 °C for 1 h, the morpholine **4e** was isolated with an excellent yield of 93%.

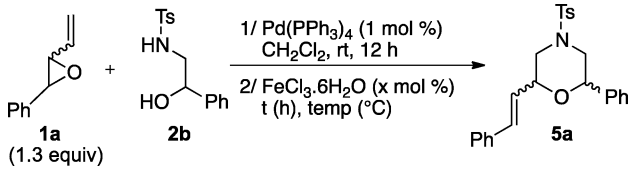
Scheme 3. Synthesis of Morpholines from Diverse Vinyl Oxiranes[a]



[a]Cyclization occurred at 50 °C in a sealed tube.

We next turned our attention to the synthesis of disubstituted morpholines. Phenyl substituted amino-alcohol **2b** was reacted with phenyl vinyl oxirane **1a** under the previous optimized conditions. While the Tsuji–Trost adduct was formed with full conversion of the amino-alcohol, its cyclization with 10 mol % of $FeCl_3{\cdot}6H_2O$ (1 h, rt) led to morpholine **5a** with a disappointing *cis*/*trans* ratio of 55:45, as proven by NOESY analysis of the crude mixture (Table 2,

Table 2. Optimization for the Diastereoselective Synthesis of 2,6-Morpholines



entry	$FeCl_3{\cdot}6H_2O$ (x mol %)	temp (°C)	*t* (h)	*cis*/*trans*[a]	yield[b] (%)
1	10	rt	1	55:45	–
2	10	50[c]	2	66:34	–
3	15	50[c]	2	79:21	–
4	20	50[c]	2	95:5	–
5	20	50[c]	4	95:5	89

[a]Diastereomeric ratio was measured by ^1H NMR of the crude mixture. The major diastereoisomer was identified by NOESY. [b]Isolated yield. [c]Reactions were run in a sealed tube.

entry 1). Heating the reaction at 50 °C for 2 h slightly improved the ratio to 66:34 (Table 2, entry 2). Resubmitting the isolated morpholine to 10 mol % of $FeCl_3{\cdot}6H_2O$ in CH_2Cl_2 at 50 °C for 2 h led to an increase of the diastereoisomeric ratio up to 95:5 in favor of the *cis* compound. These results highlight, as previously observed,[11] that an iron-induced

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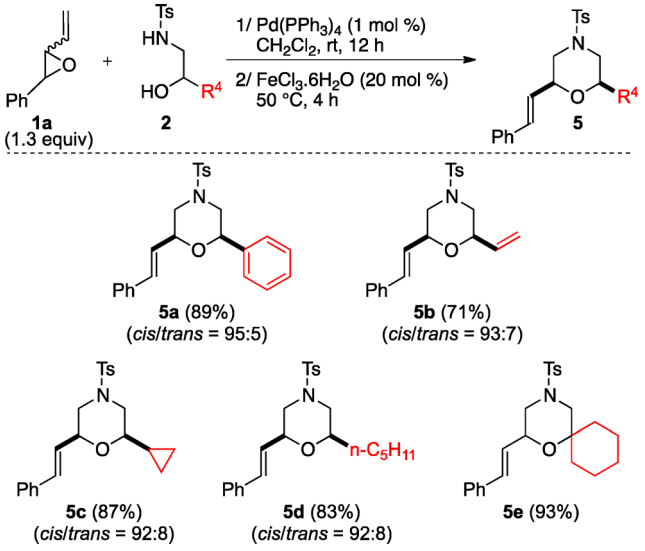
equilibration between the *cis*- and the *trans*-stereoisomers occurs, leading to the most stable diastereoisomer as the major product. With 15 mol % of $FeCl_3 \cdot 6H_2O$, an encouraging 79:21 ratio was obtained, in favor of the *cis*-morpholine (Table 2, entry 3). The best result was obtained with 20 mol % of iron catalyst by heating the reaction for 4 h at 50 °C (Table 2, entry 5). Under these conditions, morpholine **5a** was isolated in a good yield of 89% and an excellent *cis*/*trans* ratio of 95:5.

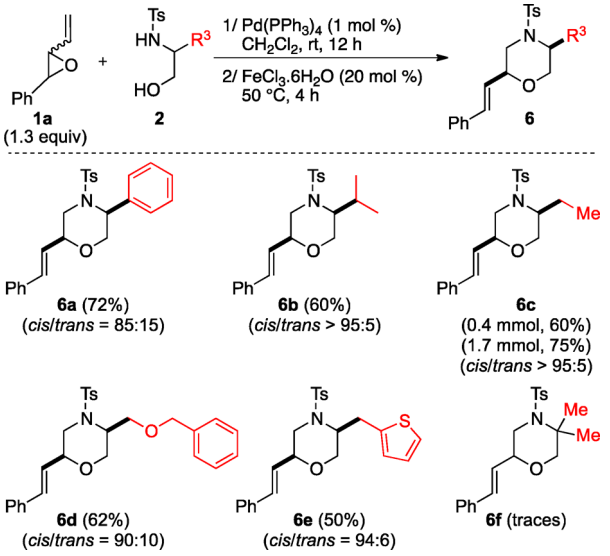
These optimized conditions were next applied to amino alcohols differing from their R^4 substituent (Scheme 4). A vinyl substituent was tolerated, as morpholine **5b** was isolated in 71% yield with a good dr (*cis*/*trans* = 93:7). The 6-cyclopropylmorpholine **5c** was obtained in 87% yield with a dr of 92:8 in favor of the *cis*-isomer. An alkyl chain has no influence on the reaction as the corresponding morpholine **5d** was isolated in 83% yield and with similar diastereoselectivity as previously. It is worth mentioning that the spirocyclic morpholine **5e** was also isolated with an excellent 93% yield.

Scheme 4. Diastereoselective Synthesis of *cis*-2,6-Disubstituted Morpholines



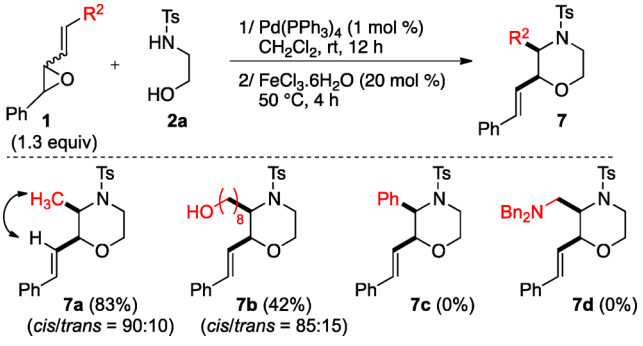
The synthesis of 2,5-disubstituted morpholines was then examined, and we were pleased to see that the corresponding products were formed with good to excellent diastereoselectivities albeit with slightly lower yields than for 2,6-disubstituted morpholines (Scheme 5). Thus, the phenyl substituted morpholine **6a** was isolated with a yield of 72% and a dr of 85:15 in favor of the *cis* compound.[15] Isopropyl and ethyl substituted morpholines **6b** and **6c** were obtained in moderate yields (60%) but as single *cis*-diastereoisomers. The methylbenzyloxy substituted morpholine **6d** was isolated with a similar yield (*cis*/*trans* = 90:10). It is worth noting that a thiophene moiety was tolerated under these conditions, as the corresponding thienyl morpholine **6e** was isolated in 50% yield with a good dr of 94:6 still in favor of the *cis* compound. The 5,5-dimethyl morpholine **6f** was, for its part, only observed as traces. In all these cases, the unreacted starting amino-alcohol may be partially recovered. Steric hindrance of the nucleophilic nitrogen caused by the R^3 substituent during the Tsuji–Trost reaction may account for the lower yields obtained in this series compared with the 2,6-disubstituted morpholines.

Scheme 5. Diastereoselective Synthesis of *cis*-2,5-Disubstituted Morpholines



Subsequently, the synthesis of 2,3-disubstitued morpholines was examined under the optimized conditions (Scheme 6). Substituted vinyl oxiranes were therefore evaluated, and pleasingly, the 2-styrenyl-3-methyl morpholine **7a** (R^2 = Me) was isolated with a good yield and diastereoselectivity (83%, *cis*/*trans* = 90:10). Unambiguous nuclear Overhauser effect between the protons of the methyl group and those of the styrenyl moiety confirmed the relative *cis* stereochemistry of the product. Switching to an octanol substituent on the vinyl oxirane led to the morpholine **7b** with a moderate yield of 42% but with a good diastereoselectivity of 85:15. It is interesting to note that both the allylation and the cyclization steps tolerate the presence of a free alcohol. Unfortunately, attempts to use substituted oxiranes where R^2 is Ph– or Bn_2NCH_2– only led to the decomposition of the starting material.

Scheme 6. Diastereoselective Synthesis of *cis*-2,3-Disubstituted Morpholines



The formation of polysubstituted morpholines was next investigated (Scheme 7). Under the conditions developed previously, (1*R*,2*S*)-*N*-Ts-1-amino-2-indanol led to the corresponding morpholine **8a** (89%) with excellent diastereoselectivity (dr = 94:6). *N*-Ts-(2*R**,3*R**)-Dimethylamino-ethanol gave morpholine **8b** with a lower dr (75:25), presumably because of the low steric hindrance of the methyl groups. Interestingly the trisubstituted morpholine **8c** can be obtained in a very good yield of 85% as a mixture of four

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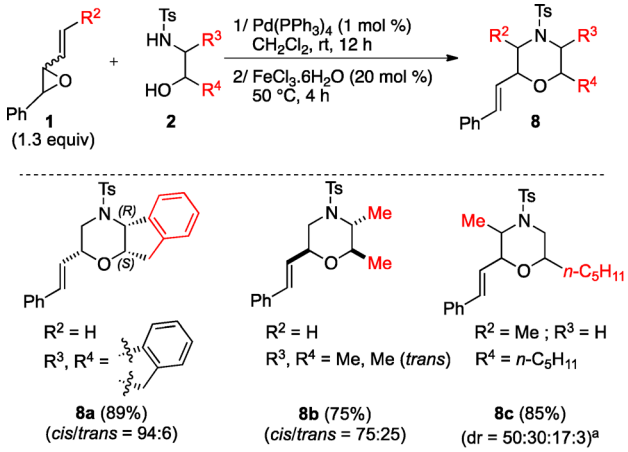
Scheme 7. Diastereoselective Synthesis of Polysubstituted Morpholines[a]

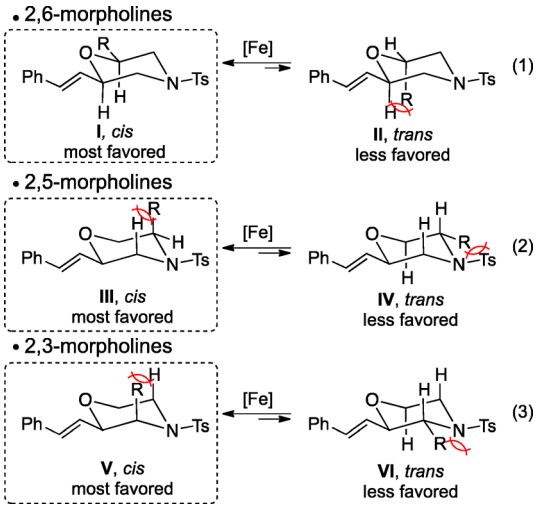


[a]Measured by GC-MS analysis.

diastereoisomers (dr = 50:30:17:3). Attempts to reach better diastereoselectivity by increasing the temperature or the catalyst loading led to decomposition of the product.

From a mechanistic point of view, the diastereoselective outcome of the reaction may be explained by the formation of a transient delocalized carbocation upon treatment of the Tsuji–Trost adduct by iron trichloride. After a *6-exo-trig* cyclization, the morpholine ring is formed as a *cis*/*trans* mixture (see scheme in Supporting Information). Then, an $FeCl_3$-catalyzed thermodynamic equilibrium may take place (Table 2, *vide supra*).[11] A ring-opening/ring-closure sequence then leads to the most stable diastereoisomer as the major compound (Scheme 8).

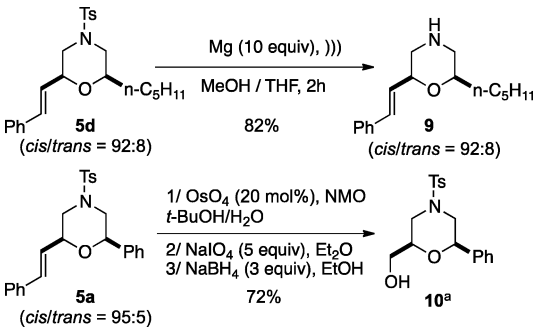
Scheme 8. Rational for the Observed Diastereomeric Outcome



It has been reported that *N*-Ts morpholines adopt a chair conformation with the sulfonyl group predominantly in an equatorial position.[16] In the case of 2,6-disubstituted morpholines, diastereoisomers **I** and **II** differ from the position of the R substituent, which stands in an equatorial or an axial position (Scheme 8, eq 1). 1,3-Diaxial interactions make the *trans*-diastereoisomer **II** less stable, thus favoring the formation of the *cis* compound. In the case of 2,5- and 2,3-disubstituted morpholines additional interactions between the R group and the *N*-Ts group have to be taken into consideration. It is known that ring substituents adjacent to a *N*-Ts tend to adopt an axial position to avoid $A^{1,3}$ strain.[17] Therefore, **III** represents the most stable 2,5-disubstituted diastereoisomer, where the R group stands in an axial position to avoid the allylic strain with the *N*-Ts group, at the expense of a 1,3-diaxial interaction with the C3-hydrogen (Scheme 8, eq 2). Similar reasoning can be applied to 2,3-disubstituted morpholines, with **V** being the most stable diastereoisomer (Scheme 8, eq 3).

To demonstrate the utility of the synthesized morpholines, the deprotection of the amine and the transformation of the styrenyl group were achieved (Scheme 9). In the presence of magnesium powder and with ultrasound activation,[18] morpholine **5d** was efficiently detosylated to give morpholine **9** in 82% yield with retention of the dr. The cinnamyl moiety in **5a** was cleaved by an oxidative cleavage/reduction sequence, to form morpholinol **10** (72% over three steps).

Scheme 9. Transformation of Synthesized Morpholines[a]



[a]The dr cannot be measured due to overlapping ^{1}H NMR signals.

In conclusion, we have developed a versatile method to access morpholines with different substitution patterns. This atom-economic method relies on the power of Pd(0)- and Fe(III)-catalysis and constitutes a unified strategy toward the synthesis of diversely substituted morpholines from readily available oxiranes and amino-alcohols, with water as the sole byproduct. As good to excellent diastereoselectivities were obtained, this method paves the way to access complex bioactive molecules or libraries of morpholines that can be useful to medicinal chemists.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03141.

Experimental procedures, product characterizations, and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(13) Vinyloxiranes were synthesized and used as a mixture of diastereoisomers, with the dr varying from 60:40 to 95:5. See SI.

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