Letter

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Catalytic Asymmetric Intra- and Intermolecular Haloetherification of Enones: An Efficient Approach to (−)-Centrolobine

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ABSTRACT: A catalytic asymmetric intra- and intermolecular haloetherification of electron-deficient alkenes (halogen = Cl, Br, I) has been realized by the use of chiral metal complexes of *N,N′*-dioxides. In the presence of a chiral Fe(III) complex, a series of tetrahydropyran derivatives were obtained in good yields (up to 99% yield) with high level of enantioselectivities (up to 97% *ee*). Promoted by a chiral Ce(III) complex, chiral oxepane derivatives could be given in good results. Moreover, the intermolecular haloetherification of chalcones catalyzed by Sc(III) complex using MeOH as nucleophile is demonstrated. This methodology also can been successfully applied to the synthesis of (−)-Centrolobine. Meanwhile, a reasonable reaction mechanism was proposed.

KEYWORDS asymmetric catalysis• enones• haloetherification• Lewis acid• oxa-heterocycles

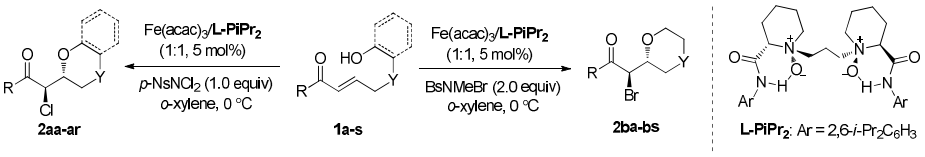
Catalytic asymmetric halofunctionalization of olefins is an attractive transformation to install two functional groups across C−C double bonds in one step.[1] In recent years, enantioselective haloesterification,[2,3] haloamination[4] and haloetherification[5,6] of electron-rich alkenes, such as styrene derivatives, have been studied extensively [2-7] with substantial efforts on mechanistic insight[8] and methodology development. However, compared with simple electron-rich alkenes which facilitate the formation of key halonium ion intermediates, the enantioselective halofunctionalization of electron-deficient alkenes (*e.g.* enones) is less explored and still limited to haloamination and carbochlorination reactions developed by our[9] and MacMillan's[10] group employing sulfonamides and aromatic π-nucleophiles as nitrogen and carbon sources, respectively. The asymmetric intramolecular haloetherification of olefins is one of the most straight-forward methods to construct enantioenriched oxa-heterocycles (*e.g.* tetrahydropyran and oxepane) which are common motifs in natural products.[11] Previous works in this field focused on the structural favored five- and six-membered ones[5] and the asymmetric synthesis of larger heterocycles through this protocol remains a challenge owing to both entropic and enthalpic barriers.[12] To the best of our knowledge, the synthesis of chiral oxepanes via halocyclization has not been reported to date.[13] For the intermolecular process, despite haloetherification of chalcone has long been known, the catalytic asymmetric version of this reaction remains elusive.[14]

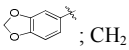
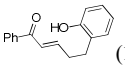
Herein, we document a method for the asymmetric haloetherification of electron-deficient enones mediated by chiral *N,N′*-dioxide/metal complexes.[15] Six- and seven-membered halocyclizations (Cl, Br, I) are achieved, delivering chiral THPs and oxepanes in good yields with high diastereo- and enantioselectivities. Tetrahydrobenzopyran is also available using phenol as the nucleophile. Employing secondary alcohol as nucleophile in six-membered halocyclization, an excellent kinetic resolution was observed and the product can be applied to the total synthesis of (−)-Centrolobine. Notably, the first catalytic asymmetric intermolecular haloetherification (Cl, Br) of chalcones by employing MeOH as nucleophile is also realized.

Our attention was initially paid to the intramolecular haloetherification. Using **1a** as model substrate in the bromocyclization reaction and after systematically screening the reaction parameters (see SI), we gratifyingly found that employing $Fe(acac)_3$ complex of chiral *N,N′*-dioxide ligand **L-PiPr$_2$** as the catalyst and BsNMeBr (Bs = benzosulfonyl) as the electrophilic bromine reagent, **1a** could be successfully transformed into the desired THP product **2ba** in good yield with high level of enantioselectivity and diastereoselectivity (Table 1, entry 1). This optimal reaction conditions could also be applied to the chloro- and iodocyclization using *p*-$NsNCl_2$ and NIS as chlorine and iodine source instead of BsNMeBr (Table 1, entry 1 and Scheme 1).

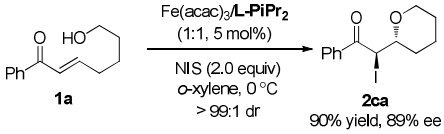
Then, the generality of six-membered halocyclization was evaluated. Considering the chloroetherification is less explored, compared with bromo- and iodoetherification, and the chlorine containing compounds play important roles in medicine science,[16] we surveyed the scope of chloro- and bromocyclization in parallel (Table 1). In general, chlorocyclization products are generated in lower enantioselectivities than bromocyclization products but with higher diastereoselectivities (**2aa**–**2ah** *vs.* **2ba**–**2bh**). The substituents on the benzoyl group of enones **1** with different electronic property and at varied position have no obvious effect on the reactivity and stereoselectivities. Furthermore, disubstituted enones **1i** and **1j** can also tolerate, even at a gram-scale, affording the corresponding chloroetherification products in 87% *ee* and 92% *ee* and bromoetherification products in 95% *ee* and 97% *ee*, respectively. 2-Naphthyl-substituted substrate **1k** also undergoes the catalytic asymmetric reaction well to give the chloroetherification product **2ak** in 94% yield and 87% *ee*, and the bromoetherification product **2bk** in 93% yield and 94% *ee*. However, 2-furyl substituent appears to have a negative effect on the stereoselectivities. To our delight, both 2-thienyl and 3-thienyl substituted substrates are capable of

Table 1. Substrate scope of chloroetherification and bromoetherification[a]



entry	yield (%)[b]	ee (%)[c]	dr[d]	R; Y	yield (%)[b]	ee (%)[c]	dr[d]
1	91 (**2aa**)	85	> 99:1	Ph; CH_2 (**1a**)	97 (**2ba**)	96	96:4
2	92 (**2ab**)	85	> 99:1	2-FC_6H_4; CH_2 (**1b**)	96 (**2bb**)	95	95:5
3	98 (**2ac**)	86	> 99:1	2-$MeOC_6H_4$; CH_2 (**1c**)	98 (**2bc**)	96	98:2
4	91 (**2ad**)	77	> 99:1	3-ClC_6H_4; CH_2 (**1d**)	89 (**2bd**)	95	95:5
5	95 (**2ae**)	76	> 99:1	3-MeC_6H_4; CH_2 (**1e**)	99 (**2be**)	95	96:4
6	80 (**2af**)	91	> 99:1	4-FC_6H_4; CH_2 (**1f**)	98 (**2bf**)	97	99:1
7	93 (**2ag**)	90	> 99:1	4-ClC_6H_4; CH_2 (**1g**)	90 (**2bg**)	96	93:7
8	97 (**2ah**)	89	> 99:1	4-$MeOC_6H_4$; CH_2 (**1h**)	99 (**2bh**)	97	96:4
9	82 (**2ai**)	87	> 99:1	3,4-$Cl_2C_6H_3$; CH_2 (**1i**)	83 (**2bi**)	95	96:4
10[e]	75 (**2aj**)	92	> 99:1	 ; CH_2 (**1j**)	98 (96) (**2bj**)	97 (93)	96:4
11	94 (**2ak**)	87	> 99:1	2-naphthyl; CH_2 (**1k**)	93 (**2bk**)	94	95:5
12	71 (**2al**)	44	> 99:1	2-furyl; CH_2 (**1l**)	93 (**2bl**)	78	94:6
13	85 (**2am**)	81	> 99:1	2-thienyl; CH_2 (**1m**)	94 (**2bm**)	95	95:5
14[f]	90 (**2an**)	82	> 99:1	3-thienyl; CH_2 (**1n**)	98 (**2bn**)	94 (*R, R*)	96:4
15	54 (**2ao**)	73	88:12	$PhCH_2CH_2$; CH_2 (**1o**)	90 (**2bo**)	93	95:5
16	88 (**2ap**)	87	> 99:1	Ph; O (**1p**)	97 (**2bp**)	95	96:4
17	85 (**2aq**)	40	93:7	Ph; NTs (**1q**)	93 (**2bq**)	77	88:12
18	86 (**2ar**)	90	80:20	 (**1r**)	--	--	--
19	--	--	--	Me; CH_2 (**1s**)	68 (**2bs**)	73	94:6

[a] All reactions were performed with **1** (0.1 mmol), halogen reagent (for BsNMeBr 0.2 mmol, for *p*-$NsNCl_2$ 0.1 mmol), and $Fe(acac)_3$/**L-PiPr$_2$** (1:1, 5 mol%) in *o*-xylene (0.05 M) at 0 °C for 4 h, unless otherwise stated. [b] Yield of the isolated product. [c] Determined by HPLC. [d] Determined by HPLC and ^{1}H NMR. [e] The value in parentheses was conducted on a gram scale (4.0 mmol of **1j**). [f] The absolute configuration of **2bn** was verified by X-ray crystallography as (2*R*,3*R*).

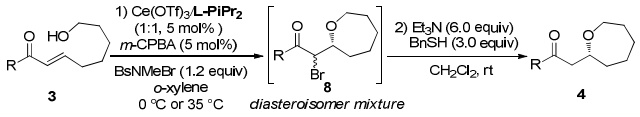


Scheme 1. Catalytic asymmetric iodocycloetherification of 1a.

tolerating the reaction, giving the haloetherification products in similar results in comparison with the standard substrate **1a**. A conceivable interpretation is that the oxygen atom on the furyl group coordinates competitively to Fe(III) center, leading to the erosion of the enantioselectivity. The absolute configuration of **2bn** is unambiguously verified by X-ray crystallography to be (2*R*,3*R*). In these cases, the *trans*-products are given in no less than 93:7 dr Notably, enone **1o** derived from benzyl acetone also furnishes the haloetherification products **2ao** and **2bo** with good stereocontrol. Enones embed a heteroatom (O, NTs) into the carbon chain are also compatible with this methodology, although afford the products **2aq** and **2bq** in lower stereoselectivities. It is worth pointing out that the chloroetherification of substrate **1r** bearing a phenolic nucleophile is equally successful under the chiral Fe(III)/**L-PiPr$_2$** catalytic system. Tetrahydrobenzopyran **2ar** was obtained in 86% yield and 80:20 dr with 90% *ee* for the major isomer. However, the related bromoetherification using bromine reagent BsNMeBr undergoes oxa-Michael reaction accompanied by direct bromination of phenol unit (see SI). Furthermore, simple acetone derived substrate **1s** could aslo tolerate this reaction and generate the bromoetherification **2bs** in 68% yield with 73% *ee*.

Next, we tried to apply this protocol for the asymmetric synthesis of chiral oxepanes. Under the standard reaction conditions of six-membered halocyclization, the seven-membered bromocyclization of **3a** delivering 2-substituted oxepane in 92% yield but with only 40% *ee* for the major isomer (see SI). Then we reoptimized several catalysts variables for catalysis of seven-membered bromocyclization and found the enantioselectivities could be highly enhanced to 98% and >99% *ee* by changing central metal from $Fe(acac)_3$ to $Ce(OTf)_3$ and using 5 mol% *m*-chloroperbenzoic acid (*m*-CPBA) as proton additive. Under the optimized reaction conditions, the scope of the seven-membered chloro- and bromocyclization was investigated and the outcomes indicated that many representative cases could give excellent enantioselectivities. The diastereoselectivity is moderate, but both isomers can be isolated by flash chromatography in most cases (see SI). Particularly, the α-bromine can be removed easily in the presence of BnSH and Et_3N at room temperature. As shown in Table 2, various substituted enones **3** including aryl, heteroaryl and alkyl-groups could be efficiently converted into the optically active γ-ketone oxepanes **4**

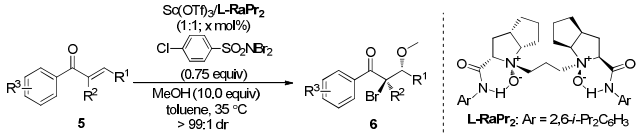
Table 2. Synthesis of chiral oxepane 4.[a]

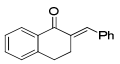
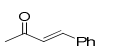


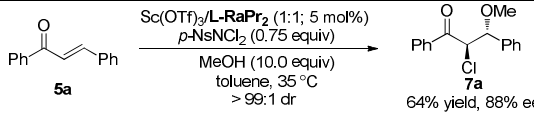
entry	R	dr[b]	yield (%)[c]	ee (%)[d]
1	Ph	57:43	86 (**4a**)	98
2	4-FC_6H_4	57:43	74 (**4b**)	98
3	4-$MeOC_6H_4$	57:43	57 (**4c**)	95
4	4-PhC_6H_4	57:43	84 (**4d**)	99
5		57:43	73 (**4e**)	97
6	3-thienyl	50:50	74 (**4f**)	98
7	$PhCH_2CH_2$	66:34	38 (**4g**)	95

[a] For details, see SI. [b] Determine by ^1H NMR. [c] Yield of the isolated **4** after two step transformations. [d] Determined by HPLC.

Table 3. Substrate scope of intermolecular haloetherification.[a]



entry	R^1	R^2; R^3	x	yield (%)[b]	ee (%)[c]
1[d]	Ph	H; H	0.5	92 (91)(**6a**)	96 (94) (*R*, *R*)
2	4-MeC_6H_4	H; H	5	81 (**6b**)	94
3	4-FC_6H_4	H; H	1	99 (**6c**)	95
4	4-$F_3CC_6H_4$	H; H	5	90 (**6d**)	95
5	3-ClC_6H_4	H; H	1	97 (**6e**)	94
6	2-naphthyl	H; H	5	80 (**6f**)	92
7	Ph	H; 4-MeO	5	98 (**6g**)	94
8	*i*-Pr	H; H	5	70 (**6h**)	75
9	*i*-Bu	H; H	5	66 (**6i**)	80
10[e]	Ph	CN; H	5	67 (**6j**)	60/60
11			5	64 (**6k**)	96
12			5	messy	--

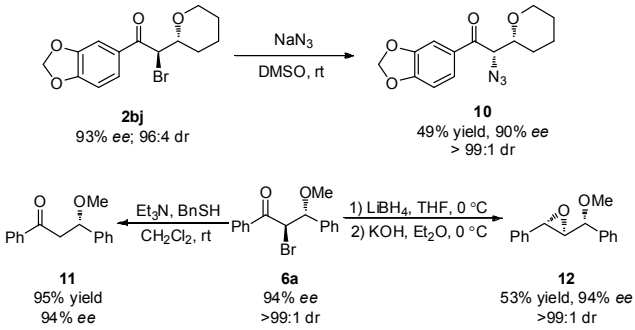


[a] Reaction conditions: **5** (0.1 mmol), MeOH (1.0 mmol), bromine reagent (0.075 mmol), $Sc(OTf)_3$/**L-RaPr$_2$** (1:1, x mol%), toluene (0.05 M), 35 °C. [b] Yield of the isolated product.. [c] Determined by HPLC. [d] The value in parentheses is conducted on 2.0 mmol scale of **5a** using 0.5 mol% catalyst, the absolute configuration of **6a** was verified as (2*R*, 3*R*) by X-ray crystallographic analysis. [e] dr = 75: 25.

with good yields and excellent enantioselectivities (95–99% *ee*) after two sequential bromocyclization and debromination transformations.

On the basis of intramolecular haloetherification, we started tackling a more ambitious proposal, wherein intermolecular haloetherification would be facilitated directly from chalcone and external alcohol nucleophile. Further survey of reaction conditions lead to the following optimal reaction conditions: 0.5 mol% chiral $Sc(OTf)_3$/**L-RaPr$_2$** complex as catalyst, 10.0 equiv MeOH as nucleophile, toluene as solvent and 35 °C as the reaction temperature (see SI). Under these reaction conditions, various enones were surveyed (Table 3). The electronic nature of substituents on the phenyl group of R^1 and benzoyl group affect the reactivity slightly. By improving the catalyst loading, aryl substituted substrates underwent bromoetherification smoothly with high levels of stereocontrol (entries 1-7). Nonetheless, the method was less tolerant with alkyl substituted enones **5h** and **5i**. Substrate with a electron-withdrawing cyano group at α-position also gave the corresponding addition product **6j** although with lower stereoselectivity. It was proven that rigid enone **5k** did not apparently affect the reaction course and excellent results were maintained. However, (*E*)-4-phenylbut-3-en-2-one failed to give the bromomethoxylation prodcut (entry 12). Notably, using *p*-$NsNCl_2$ as chlorine reagent could furnish the chloromethoxylation product **6a** in 64% yield with 88% *ee* as a single diastereoisomer. Regretfully, this system was not suitable for other alcohol nucleophiles.[17]

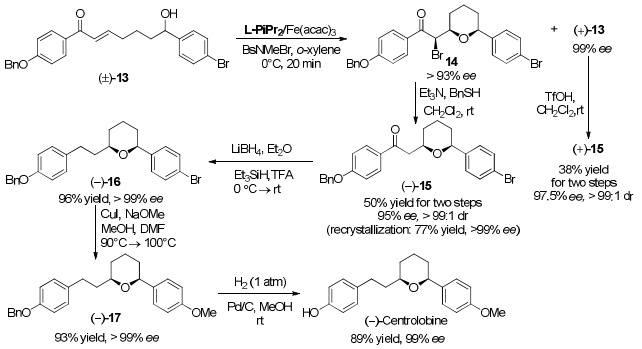
The synthetic utility of this reaction was demonstrated by the manipulation of generated bromine atom in the products. C–Br bond of **2bj** routinely transformed into C–N bond by a S_N2 reaction, affording α-azideketone **10**. In the presence of Et_3N and BnSH, bromine atom of **6a** was easily removed to furnish β-methoxy carbonyl compound **11** in 95% yield with maintenance of the enantioselectivity. Direct reduction of the 2-bromo-3-methoxy ketone product **6a** with $LiBH_4$ affords the corresponding alcohol product which can be transformed into optically active epoxide **12** without losing of any enantioselectivity.



Scheme 2. Further transformation of the products

Finally, the developed six-membered bromocyclization methodology was applied to the enantioselective synthesis of (−)-Centrolobine (Scheme 2), which is isolated from heartwood of *Centrolobium robustum* and exhibits anti-inflammatory, antibacterial, and antileishmanial activities.[18] Exposing racemic substrate (±)-**13** with a secondary alcohol nucleophile to 10 mol% $Fe(acac)_3$/**L-PiPr$_2$** catalyst and BsNMeBr bromine reagent at 0 °C for 20 min, an excellent kinetic resolution was observed and the bromocyclization

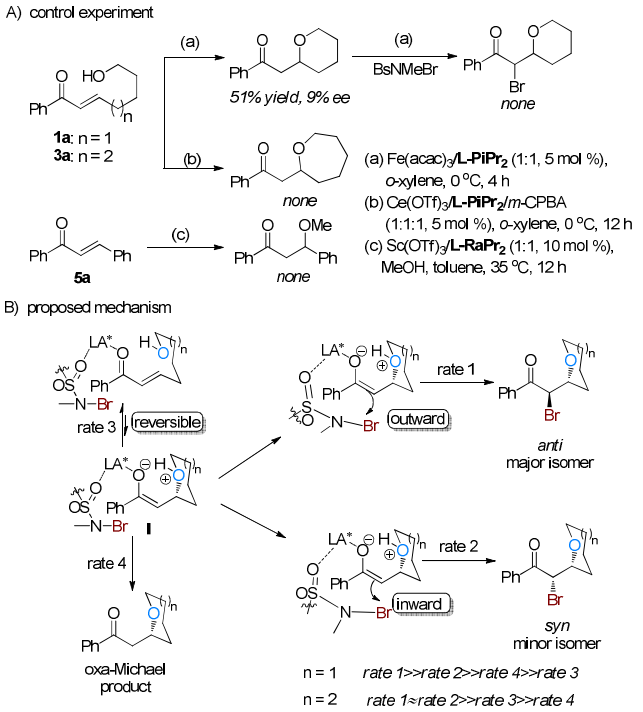
product **14** and recovered (+)-**13** were obtained in >93% ee and 99% ee, respectively. Debromination of **14** and cyclization of (+)-**13** gave (−)-**15** and (+)-**15** in 50% and 38% yield for two steps, respectively. To the best of our knowledge, no report regarding the kinetic resolution of secondary alcohol by halocyclization or intramolecular oxa-Michael addition. Then by treating the recrystallized (−)-**15** (>99% ee) with $LiBH_4$ prior to the addition of Et_3SiH and TFA, the deoxygenated product (−)-**16** was isolated in 96% yield. Finally, an Ullmann cross coupling reaction of (−)-**16** with NaOMe in the presence of CuI followed by the deprotection of benzyl group produced (−)-Centrolobine in 99% *ee*.



Scheme 3. Enantioselective total synthesis of (−)-Centrolobine.

The formation of both diastereoisomers in most cases (especially in bromocyclization) casts doubt on the reaction process and the stereocontrol elements of the asymmetric halocycloetherification. Firstly, the reaction is unlikely to proceed through a classical haliranium ion intermediate mechanism. There are three phenomenons observed can support this suppose during the course of this study. a) The low diastereoselectivity of most products conflict with the classical stereospecific ring-opening of halonium ion mechanism.[1e] b) The electron-richer substrate **3c** showed lower reactivity in this reaction (Table 2, entry 3, reaction temperature increased to 35 ºC). c) The configuration of the oxygen-jointed carbon center is uniform for the two diastereoisomers of **8** and no epimerization[19] process was observed in the reaction (see SI for details). Secondly, in the presence of the optimized chiral catalysts without halo-reagent, the Michael reactions performed sluggishly. Intramolecular six-, seven-membered Michael adducts[20] and intermolecular Michael adducts were given in 51%, 0% and 0% yield, respectively. Neither Michael adducts could undergo α-bromination to afford the final bromoetherification products (Scheme 4A). The aforementioned results helped ruling out the absolute stepwise Michael/α-halogenation reaction like MacMillan's report. [10]

The detailed reaction process is not fully understood until now. We proposed a possible reaction mechanism to explain the reason why the addition of electrophilic halogen reagent is crucial for the C–O bond formation and the stereocontrol element (Scheme 4B). Originally, the carbonyl group and sulfonyl group coordinated with the central metal of catalyst. Then the hydroxyl nucleophile proceed a reversible[21] addition (favoring starting material for substrate **3**) on the activated carbon carbon double bond, thus forming an enolate intermediate **I**, which is the enantioselectivity-determine step. In the presence of electrophilic bromine reagent, diastereoselective capture of enolate intermediate **I** by Br^+ generating the bromoetherification product is much faster than the rate of enolate **I** returning back to the starting material (rate 1, 2 »rate 3). Without the coordinated sulfonyl group of bromine reagent, the hydroxyl group addition step displays terrible stereocontrol (Scheme 3A, 9% *ee*). Moreover, the C–O bond formation product (oxa-Michael product) using **3a** as substrate was not observed in the absence of bromine reagent might be attributed to proton quenching enolate intermediate rate is much slower than retro rate of enolate **I** to the substate **3a**(n = 2; rate 3 »rate 4).



Scheme 4. Control experiment and proposed mechanism.

In summary, we have developed a general method for the catalytic asymmetric haloetherification of enones by using metal complexes of chiral *N,N′*-dioxides as the catalysts. The mild reaction conditions and broad substrate scope of halocyclization permit a rapid and efficient access to chiral THPs and oxepanes incorporating a pendant halogen even on a gram scale. The synthetic utility was demonstrated by the enantioselective synthesis of (−)-Centrolobine. In addition, a similar Sc(III)/*N,N′*-dioxide catalytic system can also be applied to realize the first catalytic asymmetric intermolecular haloetherificaiton of chalcones. Meanwhile, a reasonable mechanism was proposed to evalute the reaction process. Further studies on the detailed reaction mechanism and development of other enantioselective halofunctionalization reactions are ongoing.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, full spectroscopic data for all new compounds, and copies of ^1H, ^{13}C NMR, and HPLC spectra (PDF)

X-ray crystallographic data for **2bn** (CIF)
X-ray crystallographic data for **6a**(CIF)

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Notes

The authors declare no competing financial interest.

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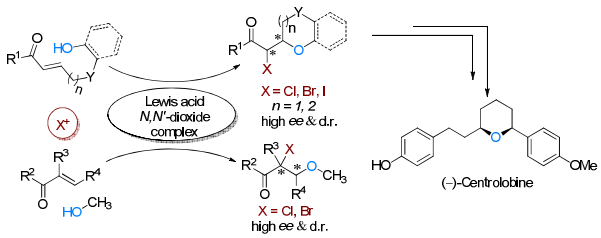
TOC


Lewis acid
N,N'-dioxide
complex
X = Cl, Br, I
n = 1, 2
high ee & d.r.
X = Cl, Br
high ee & d.r.
(–)-Centrolobine