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Lewis-Acid Promoted Enantioselective Dearomative Spirocyclizations of Allenes

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Abstract

A chiral oxazaborolidine combined with SnCl₄ has been found that promotes the dearomative spirocyclization of electron rich benzyl allenyl ketones. The reaction outcome is sensitive to the nature of activating acid which was rationalized using HSAB theory. The spirocyclic product was obtained with up to 72% ee, the best result reported to date for these substrates. The formation of cross-conjugated or conjugated products is readily controlled by changing the oxygen protecting groups.

Graphical abstract

Dearomatization reactions are a powerful means to convert relatively simple aromatic substrates into more complex three-dimensional structures.¹ Lewis acid promoted reaction of electron rich arenes with allenes, in particular leads to spirocyclic dienones, a subclass of spiro[4,5]decane natural products (Figure 1). Cyclization of such substrates have been reported using boron trifluoride, mercury salts, zinc iodide, silver nitrate, molecular iodine, aluminum trichloride and tin dichloride.² To date, there is only one example of an enantioselective dearomative spirocyclization producing such a product in 23% ee.^{2a} Highly selective transformations of this kind would be valuable, opening routes for the enantioselective synthesis of multiple natural products. In this communication, we outline our strategy and results in devising such a method.³

For our initial studies we focused on the spirocyclization of highly electron-rich 2,4-dimethoxy allenyl ketone **1** (Figure 2).⁴ We envisioned developing a chiral Lewis acid

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ASSOCIATED CONTENT

Supporting Information

Copies of spectral data. Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>.

library that could be assessed via high-throughput experimentation (HTE).⁵ This technique allows rapid screening of a range of different catalysts and reaction conditions, and has proven to be a very efficient and reliable method for optimization of target transformations.⁶ A total of 23 different Lewis acids were selected encompassing the major classes of chiral Lewis acid catalysts with demonstrated utility for monodentate substrates including the CBS⁷, TADDOL, STEIN, PYBOX, and salen motifs (Figure 2).⁸ These catalysts were all screened simultaneously against substrate **1** on a microscale. Reactions were assessed (Figure 2) for chemical yield using an internal standard (HPLC) and for enantiomeric excess (SFC). With this approach, it was possible to narrow the field of leads within a few days after preparation of the catalyst library, which can also be stored and deployed to examine other transformations.

The activated CBS catalysts, as well as scandium and ytterbium PYBOX complexes provided the largest amounts of product (bold entries bold, Figure 2). Despite only moderate reactivity with the aluminum and titanium catalysts, STIEN-AlMe did provide the best selectivity. The best conditions from this screen were then validated on a bench-scale (parenthetical entries in Figure 2). Only the CBS catalyst combined good conversion with high selectivity, and the others did not perform nearly as well as in the micro-scale screening.

Considering the unique mode of action of CBS catalysts⁹, we analyzed the effect of the separate components (Figure 3). Lewis acids are arranged according to the degree of activation of the CBS moiety as outlined by Tonner, Hilt, and coworkers.⁶ Strong Brønsted acids caused decomposition (entries 1–2) while lower temperature (10 °C) attenuated decomposition but resulted in low yield (<20% for entry 1). Milder Lewis acids¹⁰ (entries 4–5) did not provide sufficient activation of the CBS to garner any reaction. The adducts of TMSOTf, TiCl₄, and Sc(OTf)₃ (entries 6–8) and SnCl₄ did give rise to the spirocyclic product. Stronger activators (entries 9–11) did not provide any product, despite being known to be very efficient CBS activators; rather, the halide adduct was observed with these reagents.

According to the proposed mechanism,^{2e} the Lewis acid coordinates to the carbonyl group, polarizing the allene (Figure 4). With stronger activators, greater charge builds up on the carbon generating harder electrophiles. However, the arene portion of the molecule is a relatively soft nucleophile. As a consequence of the hardness mismatch, the arene does not efficiently interact with electrophilic carbon when activation is provided by a strong Lewis acid. When hard nucleophiles are present in the reaction mixture, they can quickly intercept hard vinyl cation forming halide adducts, for example (Figure 4).¹¹

Moderate CBS activators give rise to the softer electrophile needed for the target reaction (e.g. entries 6–8, 12, Figure 3), but are complicated by an equilibrium between unbound and bound forms (Figure 5). In the present case, unbound SnCl₄ promotes the reaction alone; with 100 mol % SnCl₄ in the absence of CBS, the spiro product **2** is obtained in 95% yield over the same time frame (20 h). To address this issue, reactions were conducted with lesser amounts of SnCl₄ (20 mol%), but a dramatic drop in yield was observed (13%).

Further improvements in selectivity were sought by altering the structure of the CBS portion. With large β -aryl groups, only a slight increase in selectivity was observed with yields declining substantially (Figure 6). Decreasing the reaction temperature had a similar effect. Change of the dichloroethane solvent to CH_2Cl_2 or mixed $\text{MeCN}/\text{CH}_2\text{Cl}_2$ systems did not substantially affect selectivity.¹²

In the proposed mechanism, the turnover step is likely a decomposition of the enolate with liberation of Lewis acid. This process can be achieved by a reaction with electrophile at the oxygen (a), the α -carbon (b) or the γ -carbon (c). With an oxophilic protecting group, it is also possible to imagine a Brook-type rearrangement (Figure 7).

Accordingly, we tested various additives to facilitate these reaction pathways and permit reduced catalyst loading. Unfortunately, no additive enhanced the catalyst turnover (Figure 8) with the yields never exceeding 50%.

With the TBS-protected phenol **4**, similar yields and selectivities were seen (Figure 9) relative to the 2,4-dimethoxy allenyl ketone **1** (Figure 6). Only the spirocycle products were observed in all cases rather than any O- or C-alkyl/acyl/silyl adducts. Interestingly, TBS protection causes a switch of the regioselectivity of the process, furnishing the novel unsaturated ketone **5** instead of the cross-conjugated isomer **2**. Such easy control of the reaction outcome may prove valuable for synthetic applications of this method.

In summary, we have identified a CBS/ SnCl_4 system as a chiral Lewis acid that promotes the spirocyclization of electron rich arene derived allenyl ketones. The reaction outcome is sensitive to the nature of activating acid which was rationalized using HSAB theory. The spirocyclic product was obtained with up to 72% ee, the best result reported to date for these substrates. We hope that our findings will facilitate further development of this intriguing transformation.

EXPERIMENTAL SECTION

All non-aqueous reactions were carried out under an atmosphere of dry argon unless otherwise noted. Commercial reagents were used as received without additional purification unless otherwise noted. Dichloromethane and 1,2-dichloroethane were distilled from CaH_2 , and toluene was distilled from metallic sodium prior to use. Reactions were monitored by thin layer chromatography (TLC) using Silicycle glassbacked TLC plates with 250 μm silica and F254 indicator. Visualization was accomplished by UV light and/or KMnO_4 . ^1H NMR and ^{13}C NMR spectra were recorded on a AM-500 Fourier transform NMR spectrometer at 500 MHz and 125 MHz, respectively. Chemical shifts are reported relative to the solvent resonance peak δ 7.26 (CDCl_3) for ^1H and δ 77.16 (CDCl_3) for ^{13}C . High resolution mass spectra were obtained using a VG autospec with an ionization mode of either ESI or CI. Infrared spectra are reported in cm^{-1} . Melting points are uncorrected. Unless otherwise noted, yields refer to isolated material on the basis of 95% product purity as judged by ^1H NMR following silica gel chromatography with Silica-P flash silica gel (50–63 μm mesh particle size). Enantiomeric excess was determined utilizing chiral stationary phase (CSP) HPLC or SFC on OD [cellulose tris(3,5-dimethylphenylcarbamate) coated on silica gel] 0.46

cm $\times$ 25 cm or IA [amylose tris(3,5-dimethylphenylcarbamate) immobilized on silica gel] 0.46 cm $\times$ 25 cm columns.

Starting material **1** (1-(2,4-dimethoxyphenyl)penta-3,4-dien-2-one) was prepared from the corresponding phenyl acetic acid via a Weinreb amide following known protocol.^{2e} The Grignard reagent and the corresponding Weinreb amide were prepared using reported procedures.^{13,14} Phenol **3** was synthesized according to procedure reported by Vanderwal.¹⁵

CBS catalysts (Me-CBS and Ph-CBS) were purchased from Strem Chemicals Inc. The following catalysts for the chiral Lewis acid plate (See Figure 2) were made following known procedures: Salen complexes AlCl₃¹⁶, Co(OAc)¹⁷, CrCl₃¹⁸, MnCl₂¹⁹, TiCl₂²⁰, Zn²¹, Cu²², Pd, Ni²³; PYBOX complexes AlCl₃, In(OTf)₃, Sc(OTf)₃, Yb(OTf)₃²⁴, CuCl₂, PdCl₂, NiCl₂, ZnCl₂²⁵; STEIN complexes AlMe, TiCl₂²⁶; TADDOL complexes AlMe, TiCl₂²⁷.

General procedure for cyclization.

(*S*)-Phenyl-CBS catalyst (11.7 mg, 0.035 mmol) was added to a flame dried 8 mL microwave vial equipped with stir bar in an inert atmosphere glovebox. The vial was sealed with a Teflon cap, removed from the glovebox, put under an argon atmosphere, and dissolved in 1,2-dichloroethane (416 μ L). A solution of SnCl₄ (0.028 mmol, 100 μ L of a 0.28 M solution in CH₂Cl₂/1,2-dichloroethane) was added and the mixture was allowed to stir for 30 min. Allenyl ketone **1** (0.069 mmol, 200 μ L of a 0.35 M solution in 1,2-dichloroethane) was added to the reaction mixture and stirred for an additional 4 h. The resultant reaction mixture was diluted with CH₂Cl₂ (5 mL), quenched with 1 M HCl (5 mL), and extracted with CH₂Cl₂ (3 $\times$ 10 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated. Chromatography (20% to 80% EtOAc in hexanes) afforded the product.

6-Methoxy-4-methylspiro[4.5]deca-3,6,9-triene-2,8-dione (2).—The compound was prepared in 89% yield (12.4 mg) as amorphous solid. ¹H NMR (500 MHz, CDCl₃) δ 6.37 (d, *J* = 9.8 Hz, 1H), 6.33 (dd, *J* = 9.8, 1.0 Hz, 1H), 6.17 (d, *J* = 1.0 Hz, 1H), 5.75 (s, 1H), 3.73 (s, 3H), 2.84 (d, *J* = 18.4 Hz, 1H), 2.47 (d, *J* = 18.4 Hz, 1H), 1.84 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 205.4, 187.5, 176.0, 173.5, 145.6, 133.0, 129.7, 104.3, 56.3, 54.4, 45.2, 15.0; chiral HPLC (OD column, 70:30 hexanes:*i*-PrOH, 0.8 mL/min, 220 nm): *t*_R: 17.3 min and 20.8 min. Spectroscopic data match those reported in the literature.^{2e}

4-Chloro-1-(2,4-dimethoxyphenyl)pent-3-en-2-one (3).—The compound was isolated as colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.02 (d, *J* = 9.0 Hz, 1H), 6.46 (m, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.63 (s, 2H), 2.53 (d, *J* = 1.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 196.4, 160.5, 158.5, 151.9, 131.6, 123.2, 115.5, 104.7, 98.9, 55.6, 55.8, 45.4, 24.3; IR (film) 2935, 1691, 1609, 1508, 1209 cm⁻¹; HRMS (ESI, TOF) calculated for C₁₃H₁₅ClO₃. [M]⁺ *m/z* = 254.0710; found 254.0718

1-(2-((*tert*-Butyldimethylsilyl)oxy)-4-methoxyphenyl)-penta-3,4-dien-2-one (4).

The compound was prepared as colorless oil. ¹H NMR (500 MHz, CDCl₃) δ 7.00 (d, *J* = 8.4 Hz, 1H), 6.47 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 5.84 (t, *J* = 6.6 Hz, 1H),

5.21 (d, $J = 6.6$ Hz, 2H), 3.83 (s, 2H), 3.76 (s, 3H), 0.98 (s, 9H), 0.23 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 216.5, 197.9, 159.7, 154.6, 131.7, 118.1, 105.9, 105.4, 96.2, 79.6, 55.4, 41.0, 25.9, 18.3, -4.1; IR (film) 2955, 2931, 2858, 1692, 1611, 1584, 1507, 1163, 840 cm^{-1} ; HRMS (ESI, TOF) calculated for $\text{C}_{18}\text{H}_{26}\text{O}_3\text{Si}$. $[\text{M}]^+$ $m/z = 318.1651$; found 318.1648

8-Methoxy-4-methylspiro[4.5]deca-3,7,9-triene-2,6-dione (5).—General procedure was followed using (*S*)-naphthyl-CBS (0.016 mmol, 320 μL of a 0.05 M solution in toluene), SnCl_4 (0.013 mmol, 113 μL of a 0.12 M solution in CH_2Cl_2 /1,2-dichloroethane) and 0.033 mmol (150 μL of a 0.22 M solution in 1,2-dichloroethane) of the corresponding allenyl ketone **3**. Chromatography provided the product (6.4 mg) in 96% yield as amorphous solid. ^1H NMR (500 MHz, CDCl_3) δ 6.31 (dd $J = 9.9, 2.0$ Hz, 1H), 6.21 (d, $J = 9.8$ Hz, 1H), 6.12 (d, $J = 2.0$, 1H), 5.60 (s, 1H), 3.82 (s, 3H), 2.80 (d, $J = 18.1$ Hz, 1H), 2.36 (d, $J = 18.1$ Hz, 1H), 1.86 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 206.8, 198.5, 176.4, 172.3, 143.1, 132.5, 123.3, 100.7, 60.9, 56.3, 47.1, 15.5; IR (film) 2925, 2854, 1721, 1693, 1652, 1622, 1571 cm^{-1} ; HRMS (ESI, TOF) calculated for $\text{C}_{12}\text{H}_{13}\text{O}_3$. $[\text{M}+\text{H}]^+$ $m/z = 205.0865$; found 205.0873; chiral HPLC (IA, 90:10 hexanes:*i*-PrOH, 0.8 mL/min, 220 nm): t_R : 22.9 min and 24.7 min.

Exploration of (*S*)-aryl-CBS catalyst with SnCl_4 .

Ligands (*S*)-*o*-tolyl-CBS (0.023 mmol, 451 μL of a 0.05 M solution in toluene) and (*S*)-naphthyl-CBS (0.023 mmol, 230 μL of a 0.1 M solution in toluene) were both synthesized by known procedures.^{28,29} The general procedure was followed using SnCl_4 (0.018 mmol, 18 μL of a 1 M solution in CH_2Cl_2). After addition of the allenyl ketone (0.046 mmol, 110 μL of 0.48 M solution in 1,2-dichloroethane) at 0 $^\circ\text{C}$, the mixture was allowed to warm to ambient temperature and stirred for 16 h.

Screen of CBS activators.

General procedure was followed using (*S*)-phenyl-CBS (7.8 mg, 0.023 mmol) and designated Lewis/Brønsted acid (0.018 mmol) in 1,2-dichloroethane (230 μL). After addition of allenyl ketone (0.046 mmol, 20 μL of a 0.2 M solution in 1,2-dichloroethane) at 0 $^\circ\text{C}$, the mixture was allowed to warm to ambient temperature and stirred for 20h.

Screen of additives for catalyst turnover.

General procedure was followed using (*S*)-phenyl-CBS (11.5 mg, 0.034 mmol) dissolved in 1,2-dichloroethane (200 μL) and SnCl_4 (0.028 mmol, 125 μL of a 0.2 M solution in CH_2Cl_2 /1,2-dichloroethane). After the reaction mixture stirred for 30 minutes, allenyl ketone (0.069 mmol, 165 μL 0.4 M solution in 1,2-dichloroethane) was added, followed by the indicated additive (0.069 mmol). The reaction mixture was stirred for 4 h with H_2O and MeOH. In the experiments using *i*Pr-OH, TMSOTf, TMSCl and MeI the reaction mixture was allowed to stir for 15 h, 4 h, 1 h and 15 h, respectively.

HTE Screening.

Solutions of Lewis acids (0.04 M solution in 1,2-dichloroethane) were prepared in a glovebox and allowed to stir at ambient temperature for 30 min. The solutions were

transferred to the corresponding vial on a 24-well reactor block (0.004 mmol, 100 μ L). PYBOX catalysts were prepared in situ: AlCl_3 (5.3 mg, 0.040 mmol), $\text{In}(\text{OTf})_3$ (22.5 mg, 0.040 mmol), $\text{Sc}(\text{OTf})_3$ (19.7 mg, 0.040 mmol) or $\text{Yb}(\text{OTf})_3$ (24.8 mg, 0.040 mmol) was added to a 20-dram vial equipped with stir bar in the glovebox. PYBOX ligand (15.7 mg, 0.040 mmol) and 1,2-dichloroethane (960 μ L) were added to each vial and stirred for 2 h. Each catalyst (100 μ L, 0.004 mmol) was then dosed to the 24-well reactor block. 1,2-Dichloroethane was removed with a Genevac.

A solution of AgSbF_6 (0.008 mmol, 25 μ L of a 0.32 M solution in CH_2Cl_2) and SnCl_4 (0.002 mmol, 25 μ L of a 0.08 M solution in CH_2Cl_2) were added to corresponding wells. A parylene stir-bar was added to each vial. The reactor block was sealed, removed from the glovebox and stirred for 45 minutes on an Alligator tumble stirrer (1000 rpm). The reactor block was brought into the glovebox after cooling to ambient temperature and 1,2-dichloroethane (50 μ L) was added to all the wells. A solution of 2,4-dimethoxy allenyl ketone (0.010 mmol, 50 μ L of a 0.2 M solution in 1,2-dichloroethane) was added. The reactor block was sealed, removed from the glove box and stirred for 43 h on an Alligator tumble stirrer (1200 rpm). The reactions were quenched via dilution with a solution of internal standard in 25% DMSO/MeCN (1.0 μ mol, 0.002 M, 500 μ L), and the contents were stirred for 15 min. Into a separate 96-well plate LC block was added 700 μ L of MeCN and 25 μ L of the diluted reaction mixtures. The 96-well plate LC block was sealed with a polypropylene 1 mL cap mat. The reaction mixtures were analyzed (SM/IS and P/IS) using an Agilent Technologies 1200 series HPLC with a 96 well-plate auto-sampler. Assay conditions: C_{18} column with reverse phase eluents (MeCN and 0.1% H_3PO_4 in H_2O); 1.8 mL/min; 10% in MeCN to 95% MeCN in 6 min, hold for 2 min (post time 2 min, column at 40 $^\circ\text{C}$; 210 nm). Select reaction mixtures were analyzed for enantiopurity via supercritical fluid chromatography (SFC) (AD column, 1.8 mL/min, 5% MeOH/ CO_2 , 120 bar, 220 nm): t_R of the cyclization product: 13.0 and 15.5 min.

Scale-up experiments of HTE leads.

(*R,R*)-STIEN- AlMe (9.5 mg, 0.0184 mmol) or (*R,R*)-STIEN- TiCl_2 (10.9 mg, 0.018 mmol) were added to a flame dried 8 mL microwave vial equipped with a stir bar, dissolved in 1,2-dichloroethane (230 μ L), sealed with a Teflon cap, removed from the glovebox and put under an argon atmosphere. A solution of allenyl ketone (0.046 mmol, 230 μ L of a 0.2 M solution in 1,2-dichloroethane) was added to the reaction mixture and stirred for 20 h. The products were isolated following the general procedure.

PYBOX- $\text{Sc}(\text{OTf})_3$ and PYBOX- $\text{Yb}(\text{OTf})_3$ were made *in situ*. PYBOX (7.6 mg, 0.019 mmol) and $\text{Sc}(\text{OTf})_3$ (9.1 mg, 0.018 mmol) or $\text{Yb}(\text{OTf})_3$ (11.4 mg, 0.018 mmol) were added to a flame dried 8 mL microwave vial equipped with stir bar, dissolved in 1,2-dichloroethane (230 μ L), sealed with a Teflon cap, removed from the glovebox and placed in a 50 $^\circ\text{C}$ oil bath for 10 min, allowed to cool to ambient temperature, and stirred for an additional 2 h. After addition of a solution of allenyl ketone (0.046 mmol, 230 μ L of a 0.2 M solution in 1,2-dichloroethane), each reaction mixture was stirred for 20 h. The products were isolated following the general procedure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Some spirocyclic natural products

Figure 2.

Performance of various Lewis acids in spirocyclization. Product-to-internal standard ratios (P/IS) and ee values are provided for the HTE screening results. Isolated yields and ee values obtained in bench scale experiments are listed in parenthesis. HTE screen used 0.010 mmol substrate (20 h), bench scale reactions used 0.046 mmol of substrate (43 h).

entry	acid	2 , %	3 , %	ee 2 , %	entry	acid	2 , %	3 , %	ee 2 , %
1	Tf ₂ NH		SM decomp		7	TiCl ₄	80	20	62
2	TsOH		SM decomp		8	Sc(OTf) ₃	>90	8	0
3	none	0	-	-	9	FeCl ₃	0	>20	-
4	MeI	0	-	-	10	AlCl ₃	0	>50	-
5	TMSCl	0	-	-	11	BBr ₃	0	quant	-
6	TMSOTf	47	-	45	12	SnCl ₄	89	6	66

Figure 3.
Effect of the CBS activators on the reaction.

Figure 4.
Modes of reactivity of activated aryl allenyl ketone.

Figure 5.
CBS activation equilibrium.

Figure 6.
Activity of various CBS catalysts.

Modes of reactivity with
external electrophile

Reactivity with
internal electrophile

Figure 7.
Reactions of spirocyclic enolate.

entry	additive	yield, %	ee, %	entry	additive	yield, %	ee, %
1	H_2O	29	34	7	AcCl	43	36
2	MeOH	37	50	8	Ac_2O	20	30
3	iPrOH	27	5	9	acrylonitrile	10	26
4	TMSOTf	53	57	10	$(\text{CCl}_3)_2\text{CO}$	49	46
5	TMSCl	33	57	11	none	89	66
6	MeI	32	58	12	3A MS	86	70

Figure 8.
Additives screening.

Figure 9.
TBS-protected phenol reactions.