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Communication

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Reagent control enables selective and regiodivergent opening of unsymmetrical phenonium ions

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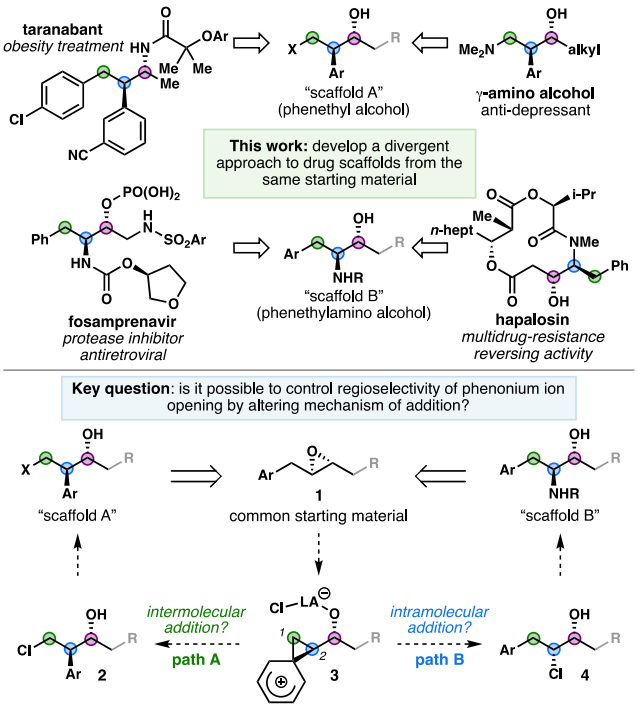
Supporting Information Placeholder

ABSTRACT: We report the first examples of selective and regiodivergent opening of unsymmetrical phenonium ions with chloride ions. These reactions are enabled by the dual role of $SnCl_4$ and $TiCl_4$ as Lewis acids and chloride nucleophiles. Reagent control dictates addition of chloride at either the substituted internal position ($SnCl_4$) or unsubstituted terminal position ($TiCl_4$) of the phenonium ion. These reactions are highly selective, stereospecific, operationally simple, and proceed in good to excellent yield. Diverse product utility is demonstrated.

Benzylic and homobenzylic stereocenters are present in numerous pharmaceuticals and agrochemicals, often embedded within common structural motifs (Figure 1, top). For example, phenethyl alcohol scaffold "A" contains a secondary aryl substituent (blue), a terminal homobenzylic substituent (green, X = aryl or heteroatom), and a secondary homobenzylic stereocenter bearing a heteroatom (purple).[1] Alternatively, phenethylamino alcohol scaffold "B" contains a terminal aryl substituent (green) and a 'phenethylamino alcohol' motif (blue and purple).[2] When assessing these two common substructures, we recognized that strategic functional group interconversion to chlorides **2** and **4** could enable a unified approach to both targets via a common phenonium ion intermediate **3** (Figure 1, bottom). Herein, we report the development of such an approach that is predicated on the selective and regiodivergent opening of a phenonium ion derived from a simple epoxide starting material (**1**).[3]

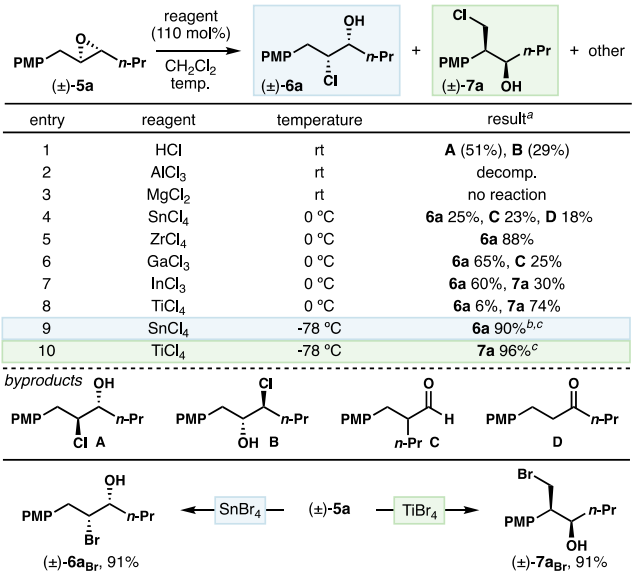
Phenonium ion formation results from neighboring group participation of an aryl ring. Its formation has been studied extensively as a fundamental phenomenon,[4-6] but its utility in synthesis is, perhaps, less appreciated.[7] Our reaction design centered on phenonium ion formation from epoxide **1** followed by selective ring opening at C1 or C2 (Figure 1, bottom). A chloride nucleophile was targeted because it would serve as a useful functional handle for product diversification. We hypothesized that with the appropriate Lewis acid, formation of chloride **2** may be favored through intermolecular chloride addition (path A).[8] Alternatively, chloride **4** may be favored by intramolecular addition at C2 (path B).[7c] The ability to dictate regioselectivity of nucleophilic addition to a phenonium ion in this way has not been reported. Additionally, phenonium ion formation would need to (i) outcompete direct epoxide opening, (ii) suppress Meinwald rearrangement,[9] and (iii) proceed with high levels of stereofidelity. Gaining such control would represent a significant expansion in the synthetic utility of phenonium ions.[10]

Figure 1. A regiodivergent approach to benzylic and homobenzylic motifs present in medicinally-relevant molecules



Racemic epoxide **5a** was selected as a model substrate for reaction development (Table 1). Early experiments using exogenous chloride sources (e.g., HCl) afforded a mixture of *anti* chlorohydrins **A** and **B** (Table 1, entry 1). This result suggested that free chloride ions in solution outcompete the pendant aryl ring in opening the epoxide. We hypothesized that Lewis acids of general formula MCl_n may promote phenonium ion formation over direct epoxide opening because chloride would be generated only *after* aryl participation. Epoxide decomposition was observed with $AlCl_3$ (entry 2) and no reaction occurred with $MgCl_2$ (entry 3). Exposure of epoxide **5a** to $SnCl_4$ at 0 °C afforded *syn*-chlorohydrin **6a** in 25% isolated yield alongside 41% of Meinwald rearrangement products **C** and **D** (entry 4). The regioselectivity of chloride addition to epoxide **5a** was determined after oxidation to the corresponding ketone and subsequent analysis of the splitting pattern of the benzylic hydrogens in the ^{1}H NMR. The stereochemistry of **6a** was determined after cyclization to the corresponding *cis* epoxide and comparison of the ^{1}H and ^{13}C NMR to an authentic sample.[11] The use of $ZrCl_4$ at this temperature afforded chlorohydrin **6a** exclusively in 88% yield (entry 5). $GaCl_3$ afforded chlorohydrin **6a** in 65% yield, alongside aldehyde **C** (*via* Meinwald rearrangement, entry 6). The use of $InCl_3$ resulted in a mixture of chlorohydrin **6a** (65% yield) and alcohol **7a** (30% yield, entry 7). Selectivity for alcohol **7a** was obtained when $TiCl_4$ was employed (80%, 10:1 **7a**:**6a**, entry 8).[12] The stereochemistry of alcohol **7a** was determined after cyclization to oxetane **16** and subsequent nOe analysis (see Figure 4B).[11] Ultimately, it was found that use of $SnCl_4$ at -78 °C in toluene afforded chlorohydrin **6a** in 90% yield (entry 9). The yield of alcohol **7a** increased to 96% with $TiCl_4$ after cooling the reaction to -78 °C (entry 10). Use of $SnBr_4$ and $TiBr_4$ in place of $SnCl_4$ and $TiCl_4$ enabled installation of bromide in high yield and selectivity in both cases (**6a$_{Br}$** and **7a$_{Br}$**).[11,13]

Table 1. Reaction discovery and optimization



entry	reagent	temperature	result[a]
1	HCl	rt	**A** (51%), **B** (29%)
2	$AlCl_3$	rt	decomp.
3	$MgCl_2$	rt	no reaction
4	$SnCl_4$	0 °C	**6a** 25%, **C** 23%, **D** 18%
5	$ZrCl_4$	0 °C	**6a** 88%
6	$GaCl_3$	0 °C	**6a** 65%, **C** 25%
7	$InCl_3$	0 °C	**6a** 60%, **7a** 30%
8	$TiCl_4$	0 °C	**6a** 6%, **7a** 74%
9	$SnCl_4$	-78 °C	**6a** 90%[b,c]
10	$TiCl_4$	-78 °C	**7a** 96%[c]

[a]Yields determined by ^{1}H NMR of the crude reaction mixture using an internal standard. [b]Toluene as solvent. [c]Isolated yield.

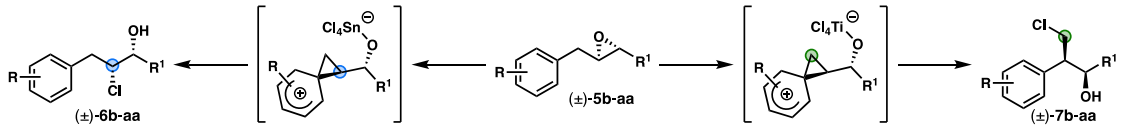
With the optimized conditions in hand, the scope of both reaction conditions was evaluated. A large selection of substituted arenes work efficiently under both sets of reaction conditions (Table 2, top). Electron-rich arenes such as 3,4-dimethoxyphenyl (**5b**), benzodioxole (**5c**), and 2-naphthyl (**5d**) all work well. Electron-neutral arenes such as phenyl (**5e**) and 4-tolyl (**5f**) derivatives were tolerated. Indole derivative **5g** was also efficient in both cases.

A common requirement for phenonium ion formation is an electron-rich arene.[7d,7e] It was important, therefore, to determine the limit of aryl participation in these reactions.[14] Introduction of halogen atoms in the *para* position of the aryl ring afforded the desired products in good to excellent yield (**5h**-**k**). Inductively-withdrawing substituents at the *meta* position were also tolerated (**5l**-**o**) in good to excellent yields. 3,4-Difluoro derivative **5p** performed well in both cases however, a 3,4,5-trifluorosubstituted arene failed to engage in phenonium ion formation (*vide infra*). The formation of phenonium ions with the deactivated arenes discussed above *greatly surpasses* a common limitation for using such intermediates in synthesis.

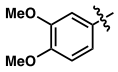
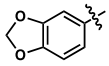
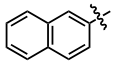
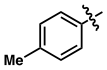
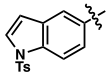
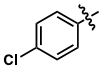
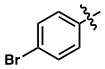
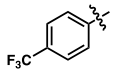
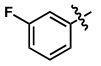
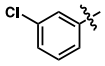
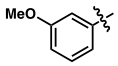
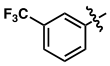
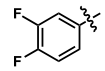
A number of functional groups were examined under the two reaction conditions (Table 2, bottom). A primary chloride (**5q**) and Lewis basic nitrile (**5r**) performed well. A series of oxygen-containing derivatives were surveyed: primary tosylate **5s** was stable to the $SnCl_4$ conditions (**6s**, 96%) but underwent substantial decomposition with $TiCl_4$;[15] benzyl ether **5t** was not compatible under the $SnCl_4$ conditions but performed well with the $TiCl_4$ (**7t**, 82% yield); silyl ether **5u** was stable to $SnCl_4$ (**6u**, 89%

yield) but underwent deprotection with $TiCl_4$, although the desired rearrangement still occurred to afford diol **7u** (78% yield); aryl ether **5v** proceeded in high yield under both reaction conditions. The reactions of phthalimide **5w** and sulfone **5x** gave excellent yields of the desired products. Epoxide **5y**, derived from an α,β-unsaturated ketone, underwent rearrangement in 93% yield with $TiCl_4$. Epoxides bearing saturated heterocyclic scaffolds such as tetrahydropyran **5z**, piperidine **5aa**, and azetidine **5ab** afforded the corresponding products **6** and **7**, in good to excellent yields. Use of a tosyl protecting group is required in the case of $SnCl_4$ whereas a Boc group is compatible with $TiCl_4$. Overall, both sets of reaction conditions display excellent functional group tolerance and the respective products are formed in excellent yield and selectivity.

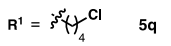
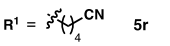
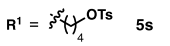
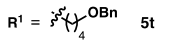
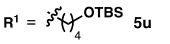
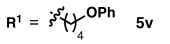
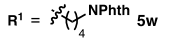
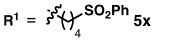
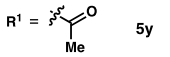
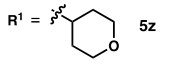
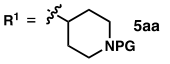
Table 2. Reaction scope[a,b]



Aryl scope (R^1 = *n*-Pr)

Starting material	Yield of **6**	Yield of **7**	Starting material	Yield of **6**	Yield of **7**	Starting material	Yield of **6**	Yield of **7**
 **5b**	80% (**6b**)	91% (**7b**)	 **5c**	91% (**6c**)	97% (**7c**) (x-ray)	 **5d**	86% (**6d**)	96% (**7d**)
 **5e**	82% (**6e**)	96% (**7e**)	 **5f**	87% (**6f**)	94% (**7f**)	 **5g**	91% (**6g**)	81% (**7g**)
 **5h**	65% (**6h**)	97% (**7h**)	 **5i**	61% (**6i**)	89% (**7i**)	 **5j**	69% (**6j**)	74% (**7j**)
 **5k**	50% (**6k**)	43% (**7k**)	 **5l**	74% (**6l**)	71% (**7l**)	 **5m**	73% (**6m**)	78% (**7m**)
 **5n**	83% (**6n**)	88% (**7n**)	 **5o**	64% (**6o**)	43% (**7o**)	 **5p**	72% (**6p**)	64% (**7p**)

Functional group tolerance (R = 4-MeO)

Starting material	Yield of **6**	Yield of **7**	Starting material	Yield of **6**	Yield of **7**	Starting material	Yield of **6**	Yield of **7**
 **5q**	93% (**6q**)	96% (**7q**)	 **5r**	87% (**6r**)	96% (**7r**)	 **5s**	96% (**6s**)	–
 **5t**	–	82% (**7t**)	 **5u**	93% (**6u**)	78% (**7u**)[c]	 **5v**	89% (**6v**)	72% (**7v**)
 **5w**	92% (**6w**)	93% (**7w**)	 **5x**	93% (**6x**)	91% (**7x**)	 **5y**	–	94% (**7y**)
 **5z**	95% (**6z**) (x-ray)	77% (**7z**)	 **5aa**	92% (**6aa**) [PG = Ts]	66% (**7aa**) [PG = Boc]	 **5ab**	90% (**6ab**) [PG = Ts]	60% (**7ab**) [PG = Boc]

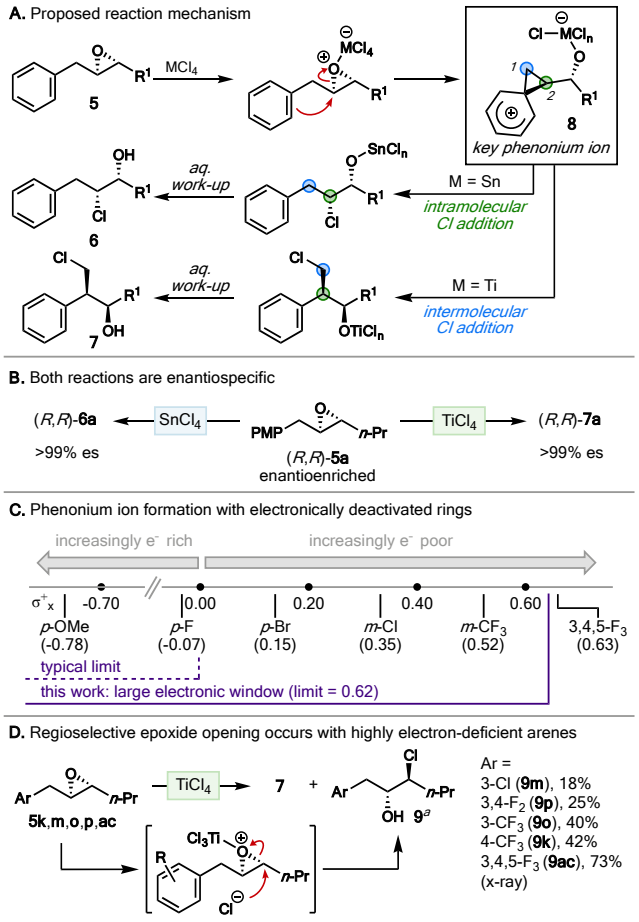
[a]Isolated yield reported. In all cases the ratio of major:minor regioisomer (**6** or **7** depending on the conditions employed) was determined to be >25:1 in favor of the reported product, based on ^{1}H NMR analysis of the crude reaction mixture. [b]The connectivity and relative stereochemistry of all products were assigned by analogy to **6a** or **7a**, with the exception of **6z** and **7c** for which crystallographic analysis was carried out. [c]TBS deprotection occurred under the reaction conditions.

To explain the high levels of stereo- and regiocontrol in this divergent reaction, the mechanism in Figure 2A is proposed. Coordination of epoxide **5** to the Lewis acid promotes formation of phenonium ion-'ate' complex **8**. In the case of $SnCl_4$, intramolecular '5-*exo*' chloride delivery to C2 is proposed to afford chlorohydrin **6**.[16-18] With $TiCl_4$, phenonium ion formation may occur with concomitant loss of a chloride from titanium.[19] Subsequent intermolecular addition of chloride could

then occur at C1 of phenonium ion **8** to afford alcohol **7**.[20,21] The use of a metal chloride as a Lewis acid *and* chloride source is important because nucleophilic chloride is generated *in situ* only as a consequence of phenonium ion formation. The stereospecific nature of the reactions was confirmed through transformation of enantioenriched epoxide (*R*,*R*)-**5a** into chlorohydrin (*R*,*R*)-**6a** and alcohol (*R*,*R*)-**7a** with >99% enantiospecificity in both cases (Figure 2B).[11,22]

It should be noted that the ability to use electron-deficient arenes in this chemistry represents a significant expansion of the 'electronic window' for reactions involving phenonium ions. Only one prior example of phenonium formation from a benzyl-substituted acyclic epoxide is reported and an electron-rich arene is required.[23] In the present work, phenonium ion formation occurs with electron deficient arenes (**5k**,**m**,**o**,**p**), albeit with decreased efficiency (Figure 2C).[14] In these cases, Meinwald rearrangement becomes competitive with formation of **6** ($SnCl_4$) and generation of chlorohydrin **9** becomes competitive with formation of **7** ($TiCl_4$, Figure 2D). Chlorohydrin **9ac** was isolated in 73% yield as the sole product from reaction of epoxide **5ac** with $TiCl_4$. Thus, the limit of aryl participation exists when the arene substituents' σ^+ values are >+0.61. The exclusive regioselectivity observed for formation of **9** from **5** is noteworthy for an unsymmetrical, unactivated epoxide and may be dictated by inductive effects of the arene.[24]

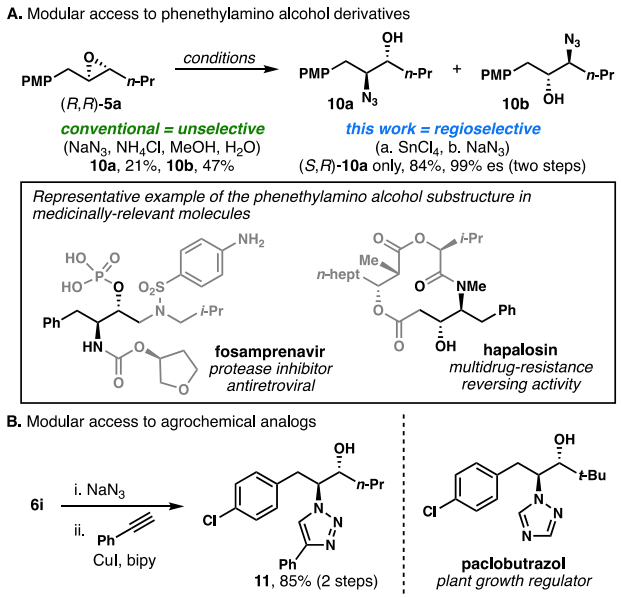
Figure 2. Mechanistic discussion



[a]The relative stereochemistry of **9m**, **9p**, **9o**, and **9k** was assigned by analogy to **9ac**.

Ring opening of unbiased epoxides typically proceeds with poor regioselectivity. For example, treatment of epoxide **5a** with azide under conventional conditions[25] affords a mixture of *anti*-azido alcohols **10a** (21%) and **10b** (47%) (Figure 3A). Our process can address this limitation. Regioselective opening of epoxide (*R*,*R*)-**5a** and subsequent azide displacement of the chloride provides azido alcohol (*S*,*R*)-**10a** (99% es) as the *sole product* in 84% yield over two steps.[26] Azido alcohol **10a** is a precursor to the phenethylamino alcohol substructure, an important motif in pharmaceutical and agrochemical agents.[27] For example, a cycloaddition between the azide and phenyl acetylene affords **11**, a 1,2,3-triazole analog of plant growth regulator paclobutrazol (Figure 3B).[28] In general, the two-step sequence from **5** to **10a** potentially enables direct, modular access to a broad range of unnatural phenethylamino alcohol derivatives with complete control of absolute and relative stereochemistry, while avoiding the need for expensive unnatural phenylalanine starting materials.

Figure 3. Phenethylamino alcohol derivatives from alcohol 6

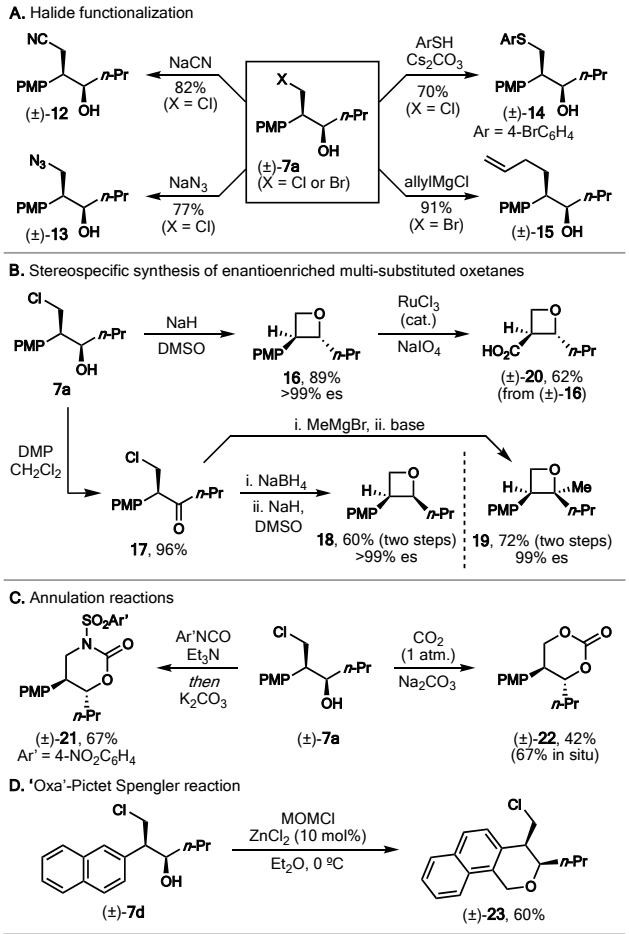


Alcohol **7** is a versatile chiral building block. Displacement of the primary chloride enables installation of a variety of nucleophiles, such as cyanide (**12**, 82%), azide (**13**, 77%), and thiolate (**14**, 70%) (Figure 4A). Introduction of alkyl substituents is also possible. For example, treatment of bromide $\mathbf{7a_{Br}}$ with allylmagnesium bromide affords alcohol **15** in 91% yield. The ability to install a (representative) variety of nucleophiles from **7** obviates the need to develop individual reaction conditions for opening epoxide **5** with each nucleophile of interest.

Treatment of alcohol **7a** with base promotes Williamson ether formation of oxetane **16** (89%, >99% es). Oxidation of the secondary alcohol to ketone **17** and subsequent reduction, under Felkin-Ahn control, followed by cyclization of the crude material provides *cis*-oxetane **18** (58% yield over three steps, >99% es). Alternatively, addition of MeMgBr to ketone **18** proceeds with excellent diastereocontrol and cyclization of the resultant alcohol affords trisubstituted oxetane **19** (69% yield over three steps, 99% es). Oxetanes are an important scaffold in medicinal chemistry,[29] however, enantioselective construction of multi-substituted oxetanes is challenging.[30] The chemistry described above enables the synthesis of multi-substituted oxetanes from simple starting materials with control over absolute and relative stereochemistry. Incorporation of these oxetane cores into molecules of interest should be possible *via* cross coupling onto an appropriately substituted aryl ring. Alternatively, oxidation of the arene to the corresponding carboxylic acid (**20**) provides an alternative functional handle for coupling.

Alcohol **7a** is amenable to alternate annulation reactions (Figure 4C). For example, treatment with 4-nitrophenyl isocyanate and catalytic Et_3N followed by K_2CO_3 affords oxazinan-2-one **21** in 67% yield (two steps). Cyclic carbonate **22** is accessible in 42% yield (67% *in situ*) *via* reaction with Na_2CO_3 under a CO_2 atmosphere.[31] Cyclic carbonate **22** and related compounds may find use as monomers for the synthesis of biocompatible polymers.[32] Finally, treatment of **7d** with MOMCl[33] and catalytic $ZnCl_2$ results in an 'oxa'-Pictet Spengler reaction to generate isochromane **23** (Figure 4D). Isochromanes are present in several natural products and bioactive compounds.[34]

Figure 4. Diversification of alcohol 7



In conclusion, we have developed a reagent-controlled, divergent chlorination of unsymmetrical benzyl-substituted epoxides. Our collective observations are consistent with the intermediacy of a phenonium ion. The regioselectivity of nucleophilic addition to this intermediate is dependent on the Lewis acid. In both cases, the reactions are operationally-simple, exhibit a broad scope (especially in terms of the arene), and proceed with excellent regioselectivity, stereospecificity, and yield. These features combined with the ease of (enantioenriched) substrate synthesis renders this a

potentially useful method for the synthesis of drug-like building blocks. We, therefore, anticipate this chemistry to find utility in drug discovery programs. Future work is focused on uncovering the selectivity differences between $SnCl_4$ and $TiCl_4$ in the reaction of epoxide **5** as well as broadening the utility of the phenonium ion as a control element in synthesis. These studies will be reported in due course.

ASSOCIATED CONTENT

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

Experimental procedures, characterization data, and crystallographic analysis.

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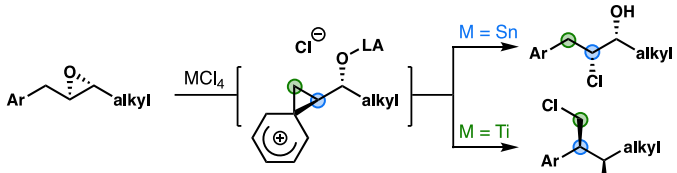

- *regiodivergent opening of an unsymmetrical phenonium ion*
- *27 examples, 43-96% yield, >20:1 selectivity in all cases*
- *diverse product utility highlighted*