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Catalytic Enantioselective Dibromination of Allylic Alcohols

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Supporting Information

ABSTRACT: A new dibromination reaction involving the combination of dibromomalonate as the bromonium source and a titanium bromide species as the bromide source has been developed. Enantioselective catalysis has been achieved through apparent ligand acceleration by a tartaric acid-derived diol.

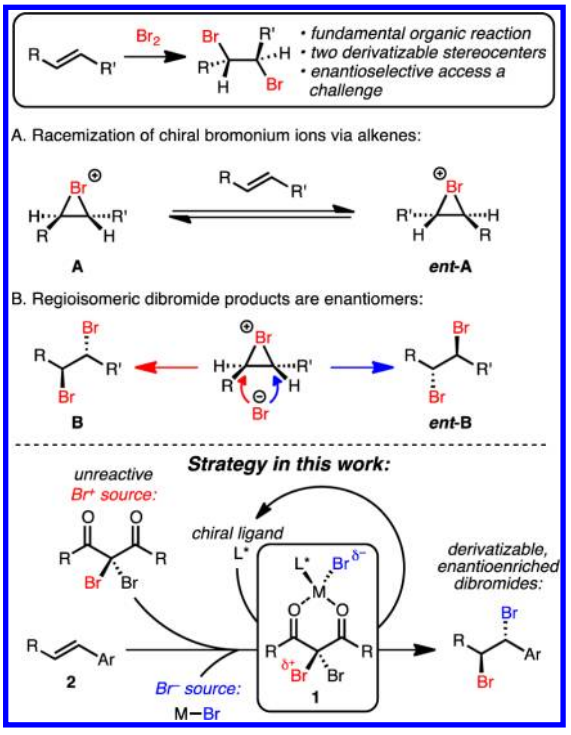
Alkene dibromination is a fundamental organic reaction that is not easily amenable to enantioselective catalysis.[1,2] The power of achieving asymmetric dibromination would stem from the versatility of alkyl bromides as building blocks in organic synthesis and the myriad of derivatizations to enriched chiral molecules that it could enable. Herein we report the development of a unique dibromination reaction that has been rendered enantioselective and catalytic in chiral diol through apparent ligand acceleration.

The difficulty in controlling the absolute stereochemical outcome of alkene dibromination may be attributed to a number of mechanistic factors in addition to the capriciousness of the reagents and intermediates involved (Scheme 1, top). First, bromine and other common dibrominating reagents react rapidly with alkenes, making the feat of achieving catalysis over nonselective background bromination a challenge. While one approach could involve enantioselective formation of the three-membered bromonium intermediate, Denmark[3] has shown that enriched bromonium ions can rapidly racemize (Scheme 1A) in the presence of alkene (i.e., the dibromination substrate).[4] Finally, control over the regioselectivity during bromide addition is crucial because regioisomeric chiral dibromides are enantiomeric (Scheme 1B). A successful asymmetric alkene dibromination must take into account the aforementioned issues.

Our approach was to formally separate Br_2 into electrophilic and nucleophilic components that are unreactive on their own but in combination would form an active dibrominating species, **1** (Scheme 1, bottom). In particular, we speculated that an α,α-dibromocarbonyl and a Lewis acidic metal bromide could serve this purpose and that this could allow for enantiocontrol with an appropriate chiral ligand regardless of the identity of the selectivity-determining step. We recognized that the regioselectivity of bromide delivery could be controlled by **1**, but as an initial simplification, we investigated aryl-substituted alkenes **2** wherein delivery should occur at the benzylic carbon.

Important precedents identifying reactivity and the potential for activation of α,α-dibromodicarbonyls include the following: (1) Trost's[5a] use of commercially available diethyl dibromomalonate (**3**) (Table 1) as a reagent for the transfer alkylation of dienolates;[5b] (2) Eames' report that **3** is capable of brominating phenol when the two are reacted neat at 100 °C;[5c] and (3) Yamamoto's use of chiral dichloromalonates as reagents for the $ZrCl_4$-mediated enantioselective chlorination of silyl enol ethers.[6] To the best of our knowledge, **3** or similar species have seen only a single use (in 1926) in the electrophilic halogenation of unactivated alkenes.[7]

Scheme 1. Challenges for Asymmetric Dibromination and a Strategy for Achieving Enantiocontrol



As desired, it was found that **3** alone is unreactive toward alkenes. The addition of bromotitanium triisopropoxide, however, resulted in alkene dibromination. This bromide source was an ideal choice as the promoter because of its trivial cost and ease of preparation[8] and titanium's privileged history and amenability to ligand acceleration in enantioselective catalysis.[9,10] *trans*-1-Phenylbut-1-ene (**4**) reacted with these two reagents in nitromethane solvent mixtures to give racemic dibromide **5** in low conversion along with equimolar diethyl bromomalonate as a byproduct (Table 1, entry 1).

With a new method for dibromination that appeared suitable for modification, the effect of chiral ligands was next examined. The TADDOL[11] ligand class was found to be most compatible

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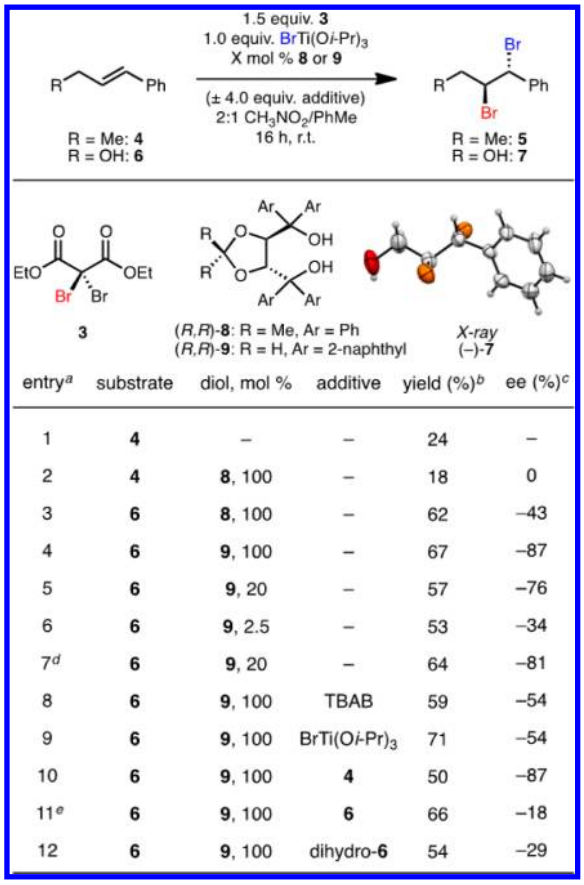
Table 1. Development of a Catalytic Enantioselective Dibromination Reaction



entry[a]	substrate	diol, mol %	additive	yield (%)[b]	ee (%)[c]
1	**4**	–	–	24	–
2	**4**	**8**, 100	–	18	0
3	**6**	**8**, 100	–	62	–43
4	**6**	**9**, 100	–	67	–87
5	**6**	**9**, 20	–	57	–76
6	**6**	**9**, 2.5	–	53	–34
7[d]	**6**	**9**, 20	–	64	–81
8	**6**	**9**, 100	TBAB	59	–54
9	**6**	**9**, 100	$BrTi(Oi\text{-}Pr)_3$	71	–54
10	**6**	**9**, 100	**4**	50	–87
11[e]	**6**	**9**, 100	**6**	66	–18
12	**6**	**9**, 100	dihydro-**6**	54	–29

[a]Reactions were conducted on a 0.1 mmol scale; absolute stereochemistry was determined by X-ray crystallography. [b]Determined by ^{1}H NMR analysis. [c]Determined by chiral HPLC. [d]Substrate and $BrTi(Oi\text{-}Pr)_3$ were added over 8 h. [e]Yield based on $BrTi(Oi\text{-}Pr)_3$.

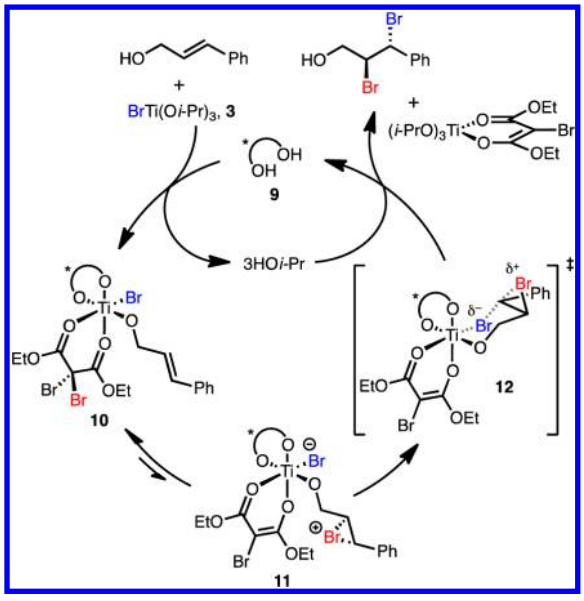
with the reaction conditions, with BINOL and dialkyl tartrates both inhibiting reactivity. While no selectivity was seen with isolated olefin substrates (Table 1, entry 2), we suspected that the introduction of polar functionality capable of binding to the metal might lead to improvements in the reactivity, selectivity, and product utility. Indeed, cinnamyl alcohol (**6**) was converted to dibromide (−)-7 with 43% ee using (*R*,*R*)-TADDOL **8** (entry 3). Allylic ethers, amides, and sulfonamides were all less reactive, and the products were racemic. Optimization[12] of the backbone and aryl groups on the diol led to the identification of (*R*,*R*)-**9** as the optimal diol, with 100 mol % loading leading to the dibromination of cinnamyl alcohol with 87% ee (entry 4). Clear indications that the diol acts as a catalyst for this reaction were the observations that lowering its loading to 20 mol % led to only an 11% decrease in ee (entry 5) and that the addition of 2.5 mol % diol still resulted in significant enantioinduction (entry 6). Slow addition of substrate and titanium to a solution of **3** and **9** was found to restore some selectivity under substoichiometric conditions, delivering (−)-7 with 81% ee (entry 7). It is of practical and mechanistic significance that the diol was recoverable in nearly quantitative yield under all conditions, further demonstrating its role as a catalyst even when stoichiometric quantities are used.

A number of findings have informed our current mechanistic thinking. Excess bromide in the form of anhydrous tetrabutylammonium bromide (TBAB) or additional bromotitanium triisopropoxide caused a reduction in selectivity to 54% ee in both cases (Table 1, entries 8 and 9), consistent with bromide being involved in the selectivity-determining step. *trans*-Phenylbutene **4** has no effect on the selectivity of the bromination of cinnamyl alcohol **6**, and no crossover dibromophenylbutane **5** was observed (entry 10). These observations indicate that bromonium transfer between alkenes is either inoperative or irrelevant in this system[4b] and that these conditions offer a chemoselective method for dibromination of allylic alcohols. Excess cinnamyl alcohol greatly reduced the selectivity of the reaction (entry 11), but the addition of an equal amount of hydrocinnamyl alcohol had a similar effect (entry 12), suggesting that excess free alcohol, not alkene, negatively affects the selectivity, likely because of disruption of the coordination chemistry that is crucial for selectivity. Similar evidence was provided by the result that the use of more coordinating acetonitrile [ε = 38.0, donor number (DN) = 14.1 kcal/mol] in place of nitromethane (ε = 35.9, DN = 2.7 kcal/mol)[13] provided racemic dibromide.

Additionally, while diethyl dichloromalonate was found to be unreactive, the use of chlorotitanium triisopropoxide as the halide source gave a lower yield of a single bromochloride product with 88% ee in which chloride was delivered at the benzylic position.[12] This confirmed the role of diethyl dibromomalonate as the bromonium source and titanium halide as the halide anion source.

The above results are consistent with the proposed catalytic cycle shown in Scheme 2. Ligand exchange on titanium might

Scheme 2. Proposed Catalytic Cycle



lead to the combination of substrate, titanium bromide, **3**, and **9** into a coordinatively saturated titanium complex (**10**) in which **3**, bromide, and substrate are arranged to allow for both intramolecular bromonium delivery and intramolecular bromide capture. In such a monomeric structure,[14] the metal should activate the malonate, promoting potentially reversible intramolecular bromine atom transfer to form bromonium **11**. Charge separation within zwitterion **11** should increase the nucleophilicity of the bromide, which could then add to the bromonium through hypothetical transition state **12** wherein the two bidentate ligands enforce an octahedral geometry.

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Correspondingly, the replacement of **3** with other brominating agents led to reduced enantioselectivity in the reaction employing 100 mol % **9** (*N*-bromosuccinimide, 33% ee; tetrabromocyclohexadienone, 69% ee; tetrabutylammonium tribromide, 55% ee). Seebach[11] and others[15] have invoked monomeric species akin to **10** in other Ti–TADDOL-mediated transformations.

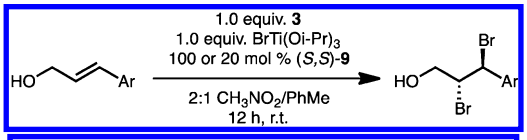
Experimental evidence thus far is most consistent with bromide delivery being selectivity-determining (**12**). Such a scenario may manifest itself through an effective dynamic kinetic resolution of the reversibly formed transient bromonium intermediate **11**. Selectivity-determining bromonium formation or a concerted dibromination step, however, cannot be unequivocally ruled out at this time.

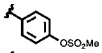
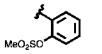
Under the optimized conditions, we next examined the reaction scalability and various substituted cinnamyl alcohols using both 100 and 20 mol % diol (*S,S*)-**9** (Table 2). With parent substrate **6**, a 100-fold increase in scale resulted in little change in overall reaction performance (Table 2, entry 1 vs Table 1, entries 4 and 7). The dibromination remained highly selective with electron-poor substitution at the ortho and para positions of the aromatic ring (entries 2–6 and 8) but was slightly less selective with meta substitution (entry 9). Nitro substitution resulted in poor conversion. Electron-donating substituents at the ortho and para positions resulted in low dibromide yields, but other dibromination methods on such substrates are similarly low yielding, suggesting that the poor performance is intrinsic to such substrates or the instability of the corresponding products. Electron-donating substitution at the meta position, however, was tolerated (entry 10). While the yields in most cases were moderate, diastereomeric dibromide products were not observed; starting material and malonate–alcohol transesterification products composed the majority of the remaining material. In the case of a *p*-vinyl substrate (entry 11), dibromination at the terminal olefin was not observed, although decomposition resulted in low mass balance. Multiply substituted substrates, including a differentially protected diphenol, were also viable (entries 7 and 12). Preliminary results with alkyl allylic alcohols (55% ee) indicated that some degree of regiocontrol and enantioselectivity is possible in the absence of aromatic substitution. Under the current conditions, homoallylic alcohols (75% ee) and *cis*-aryl-substituted allylic alcohols (51% ee) were also modest but encouraging substrates.[12]

The synthetic utility of enantioenriched dibromides relies strongly on whether they can be stereospecifically transformed. With newfound access to such species, an initial survey of subsequent reactions of **7** was undertaken, and it revealed that nearly perfect stereospecificity is possible in derivatizations (Scheme 3). Silver salts allow for stereoretentive substitution at the benzylic position, presumably via a configurationally stable bromonium. The nonbenzylic alkyl bromide can be selectively functionalized as well by intramolecular displacement of the pendant alcohol. Alcohol oxidation is also possible and proceeds with only a slight erosion of enantioselectivity. The present methodology thus enables the synthesis of chiral building blocks that are now accessible in highly enantioenriched form.

In conclusion, we have described a catalytic enantioselective dibromination of allylic alcohols. This reaction is enabled by a unique combination of reagents constituting a new strategy for alkene dihalogenation. Current efforts are underway to better understand this reactivity and the origins of the selectivity, to realize applications of the enabled products, and to find new uses for this reagent combination in other enantioselective halofunctionalization and olefin addition reactions.

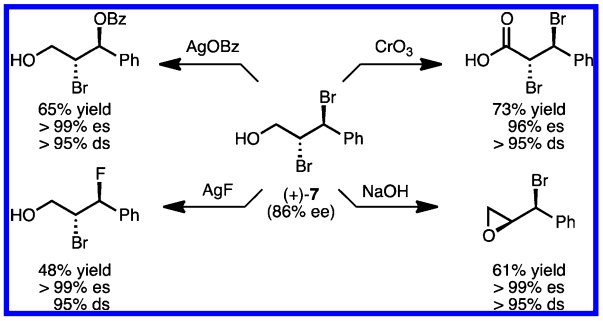
Table 2. Reaction Scalability and Cinnamyl Alcohol Aryl Substituent Effects



entry[a]	substrate (Ar =)	100 mol % yield (%)[b]	100 mol % ee (%)[c]	20 mol % yield (%)[b]	20 mol % ee (%)[c]
1[d]		63	86	60	76
2		65	88	47	79
3		64	90	60	85
4		64	90	51	84
5		61	91	50	82
6		57	89	55	83
7		70	83	60	73
8[e]		60	87	46	79
9[f]		55	84	62	76
10		71	82	72	76
11[f,g]		37	80	31	71
12[f,g]		70	86	65	76

[a]Reactions were conducted on a 1.0 mmol scale; absolute configurations were assigned by analogy to 7. [b]Isolated yields. [c]Determined by chiral HPLC. [d]Scale = 10.0 mmol (1.34 g of **6**). [e]Reaction time = 60 h. [f]Reaction time = 44 h. [g]2.0 equiv of **3**.

Scheme 3. Enriched Chiral Building Blocks Enabled by Enantiospecific Derivatizations[a]



[a]See the Supporting Information for assignment of product relative stereochemistries.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterizations, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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