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# Enantioselective Dichlorination of Allylic Alcohols

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## Abstract

The development of an enantioselective allylic alcohol dichlorination catalyzed by dimeric cinchona alkaloid derivatives and employing aryl iododichlorides as chlorine sources is reported. Reaction optimization, exploration of the substrate scope, and a model for stereoinduction are presented.

Despite tremendous advances in the development of chiral methods, asymmetric olefin dichlorination[1] remains a challenging problem. Such a reaction would be useful for the synthesis of oligo- and polychlorinated compounds.[2] Originally discovered from the membranes of freshwater algae,[3] chlorosulfolipids have gained significant attention since 2001[4] due to their putative link to diarrheic shellfish poisoning. Their biosynthesis likely proceeds through a series of site- and stereoselective enzymatic chlorinations of unfunctionalized positions on sulfolipid precursors.[5] In contrast, synthetic chemists generally can control chlorination only at functionalized sites. Evaluation of existing synthetic approaches[1] and the structure of chlorosulfolipid cytotoxin **1** (the most complex member of the family; see Figure 1)[6] suggested a need for asymmetric olefin dichlorination methods, especially those applicable to allylic alcohols. Most recent approaches have relied on substrate control of stereochemistry, and required substrate derivatization (e.g. epoxidation of the olefin[1e–g] or esterification of an allylic alcohol[1h]). In the Snyder group's total synthesis of napyradiomycin A1,[1c] there is an isolated example of a practical enantioselective olefin dichlorination employing a stoichiometric chiral auxiliary. Although the above methods have been employed in total syntheses of several chlorosulfolipids,[7] there remains a need for additional asymmetric dichlorination methods. We present herein the development of an enantioselective dichlorination of allylic alcohols.

As shown in Scheme 1, olefin dichlorination is a challenging reaction to render enantioselective. The reaction proceeds through an initial electrophilic chlorination (see **2**) to form chloronium species **3**. Even if this process is rendered facialselective,[8] there remains a regioselectivity challenge in the subsequent nucleophilic chlorination; attack of the two chloronium positions of homochiral species **3** leads to opposite antipodes of **4**. Additionally, the configurational stability of chloronium species **3** may be degraded by reversibility and/or direct chlorenium transfer to another molecule of the olefinic substrate (**2**).[9]

In view of these potential challenges, we selected *trans*-cinnamyl alcohol (**5**, Table 1) as a model substrate. The benzylic nature of the intermediate chloronium species would enforce

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Supporting Information Available: Experimental procedures and characterization data for key compounds (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org/.

a regiocontrolled chloride attack. The hydroxyl moiety might hydrogen bond with a catalyst or reagent, rigidifying the system and potentially improving stereocontrol. Our first clue suggesting a direction for catalyst screening came from observations that electrophilic halogenation is dramatically accelerated by tertiary amines.[10] Screening of common amine catalysts (e.g. proline and imidazolidinone derivatives,[11] small peptides,[12] and cinchona alkaloids[1a,8,13]) and a range of chlorine sources (e.g. $Cl_2$ gas, $Et_4NCl_3$, and $PhICl_2$) revealed the dimeric cinchona alkaloid derivative $(DHQ)_2PHAL$ (commonly employed as a ligand for Sharpless asymmetric dihydroxylation) and $PhICl_2$ as a uniquely promising reagent combination for further studies.

Interestingly, the quality of $PhICl_2$ proved to be critical, with the use of $PhICl_2$ generated from PhI and NaOCl (Chlorox® or a solution from Sigma–Aldrich) resulting in poor reproducibility. However, employing $PhICl_2$ freshly prepared from PhI and $Cl_2$ gas yielded consistent results. Furthermore, catalyst aging in the presence of $PhICl_2$ degraded both reactivity and selectivity. Therefore, since the uncatalyzed reaction is very slow, the catalyst was added last to a reaction mixture already containing the substrate and $PhICl_2$. An initial addition of 10 mol % catalyst followed by slow addition of another 10 mol % catalyst gave the best results.

Under these conditions, $(DHQ)_2PHAL$-catalyzed dichlorination of *trans*-cinnamyl alcohol (**5**) by $PhICl_2$ at ambient temperature (Table 1, entry 1) afforded dichloride **6** in 22% *ee*. Lowering the temperature (entries 2–4) prolonged reaction times, but improved enantioselectivity. A solvent screen (entries 4–7) revealed $CH_2Cl_2$ to be uniquely suitable. Mixed solvents containing $CH_2Cl_2$ could also be used (entries 8 and 9), but the reactions became more sluggish (likely due to reduced solubility of the catalyst and $PhICl_2$), and selectivities were not improved. An exploration of alternative aryl iododichlorides (entries 10–12) revealed some effects on the level of enantioselectivity, with the use of *p*-$Ph(C_6H_4)ICl_2$ (entry 11) delivering dichloride **6** in 85% *ee*.

Scaling up the reaction conditions in entry 11 of Table 1 and reducing the amount of aryl iododichloride to 1.6 equivalents gave dichloride **6** in 63% yield and 81% *ee* (see entry 1a, Table 2). Under otherwise identical conditions, but employing the pseudo-enantiomeric catalyst $(DHQD)_2PHAL$, dichloride *ent*-**6** was obtained in 58% yield and 61% *ee*. As shown in Table 2, the reaction was tolerant of some changes in electronics (entries 1a–e). Very electron-deficient olefins failed to react. Electron-rich cinnamyl substrates underwent rapid dichlorination, but the products were prone to epimerization, chloride elimination, and other decomposition reactions, presumably due to facile benzylic $S_N1$-type reactions. This is not a limitation of the method, but of compound stability; racemic reference samples were similarly labile. Naphthyl substrates reacted in the same manner (entries 2 and 3). Steric congestion was tolerated both on the aryl ring (entry 4) and near the allylic alcohol (entry 5). Importantly, the reaction is stereospecific. Thus, as shown in entry 6, although the efficiency and enantioselectivity of the reaction of *cis*-cinnamyl alcohol (**8**) left much to be desired, it proceeded to give the opposite diastereoisomer (**9**) as compared with the dichlorination of the *trans* isomer (contrast with entry 1a). Furthermore, the allylic alcohol proved to be a critical substrate feature; masking of this moiety as a TES ether (entry 7) abolished enantioselectivity.

We also investigated the suitability of our reaction conditions on selected non-cinnamyl substrates in order to ensure that we were developing a generally useful catalytic system. We decided to investigate the reactions of monobenzylated *cis*- and *trans*-butendiol since differentially protected hydroxyl moieties might be useful for further elaborations of the products.[14] The use of *p*-$Ph(C_6H_4)ICl_2$ resulted in impractically long reaction times at −78 °C, so the more reactive oxidant $PhICl_2$ was employed instead. Pleasantly, as shown in

entries 8 and 9 of Table 2, the reactions proceeded with comparable efficiency and enantioselectivity as those of cinnamyl substrates.

Enantiopure dichlorination products **7** (entry 1d, Table 2) and *ent*-**10** (see entry 9, Table 2) (obtained by preparative HPLC) were converted into *p*-nitrobenzoate esters **7′** and *ent*-**10′** (Figure 2). X-Ray crystallographic analysis of the *p*-nitrobenzoates allowed assignment of their absolute configurations. The other di-chlorination products of *trans*-cinnamyl alcohols were presumed to have the same absolute configuration as **7**; however, we currently have no experimental proof of these assignments.

Since the dichlorination is stereospecific, it likely proceeds through the intermediacy of a chloronium species in the manner outlined in Scheme 1. Furthermore, the relative configuration of the products eliminates the possibility of anchimeric assistance in chloronium attack (see **3**→**4**, Scheme 1). The sense of absolute stereoinduction is consistent with preferential chloronium formation on the face of the olefin that would react in a Sharpless asymmetric dihydroxylation employing $(DHQ)_2PHAL$ as a ligand. We propose a chlorenium ion transfer from an electrophilic chlorinating reagent generated through attack of the aryl iododichloride by one of the quinuclidine nitrogens of the catalyst (see **11**, Figure 3).[10,15] Chlorenium delivery might then proceed in a manner analogous to that proposed by Corey and Noe[16] for the Sharpless asymmetric dihydroxylation. Since an unmasked allylic alcohol is required, we postulate the presence of a hydrogen bond to one of the pyridazine nitrogens of the catalyst (see **11**, Figure 3). Consistent with this hypothesis, $(DHQ)_2AQN$ (Figure 3), lacking the pyridazine nitrogens, provides minimal stereoinduction [(10% *ee* in favor of *ent*-**6**, compare with 85% *ee* in favor of **6** (entry 11, Table 1)]. We acknowledge that the outlined model is speculative; ongoing studies will test and refine this working model.

In conclusion, we have developed an enantioselective dichlorination of allylic alcohols employing the dimeric cinchona alkaloid derivative $(DHQ)_2PHAL$ [or its pseudoenantiomer $(DHQD)_2PHAL$] and aryl iododichlorides. Further screening of catalyst and iododichloride modifications is under way, and promises to lead to improved enantioselectivity and generality.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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12. Colby Davie EA, Mennen SM, Xu Y, Miller SJ. Chem Rev. 2007; 107:5759. [PubMed: 18072809]
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14. β,γ-Dichloroalcohols are amenable to Dess–Martin oxidation and elaboration of the resulting aldehyde without loss of configurational stability.[7d]
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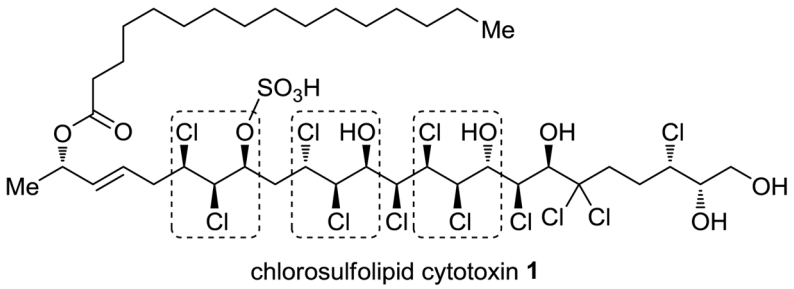



**Figure 1.**
Molecular structure of chlorosulfolipid cytotoxin **1**, and opportunities for asymmetric allylic alcohol dichlorination.

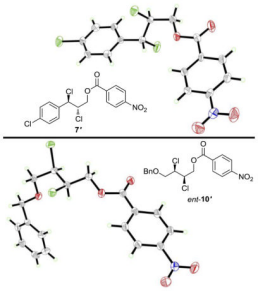


**Figure 2.**
Molecular structures and ORTEPs of *p*-nitrobenzoate esters **7′** and *ent*-**10′**.

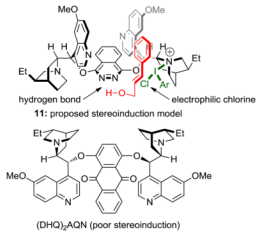
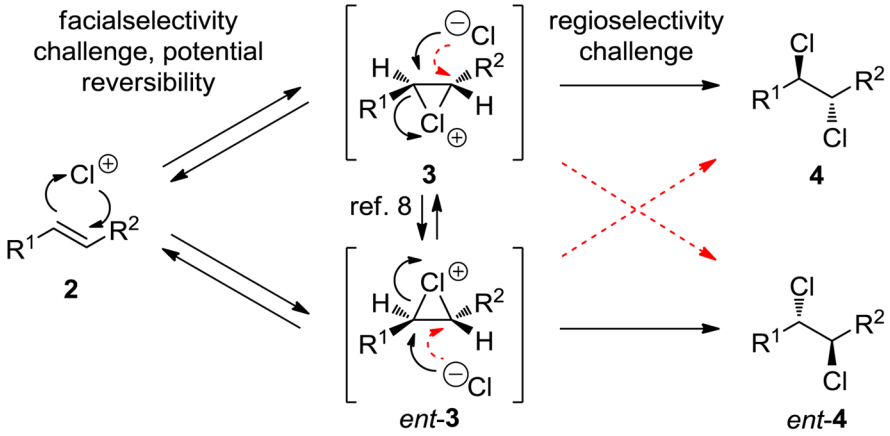


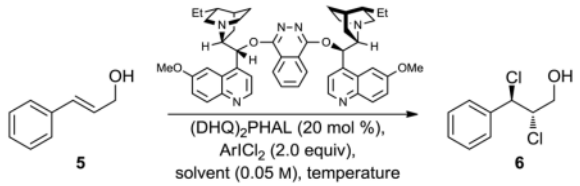

**Figure 3.**
Proposed stereoinduction model (**11**), and the molecular structure of $(DHQ)_2AQN$.




**Scheme 1.**
Mechanism of Olefin Dichlorination and Challenges for Enantioselectivity

## Table 1

Screening of Reaction Conditions for Enantioselective Di-chlorination[a]



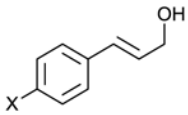
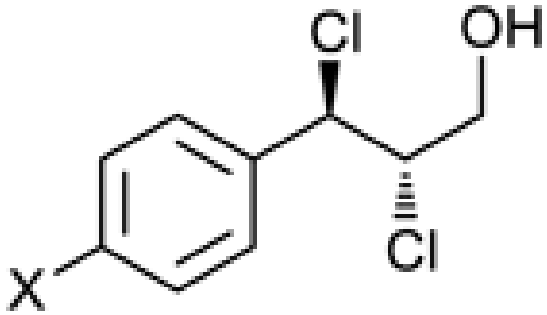
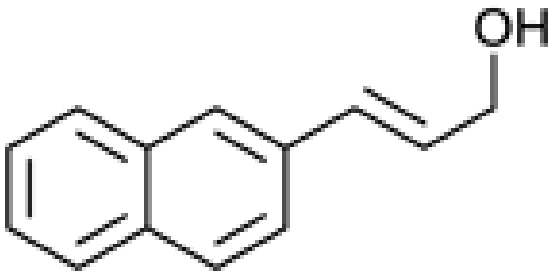
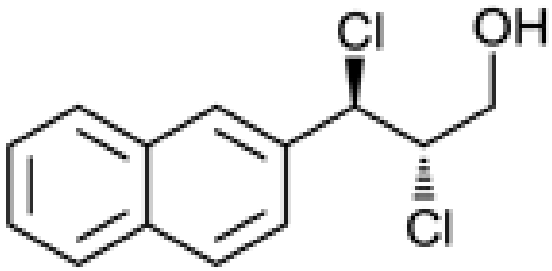
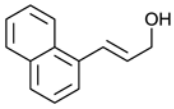
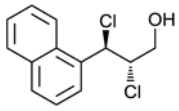
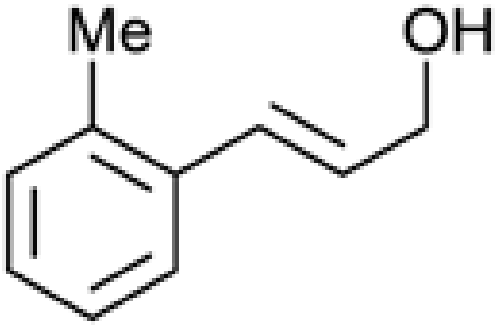
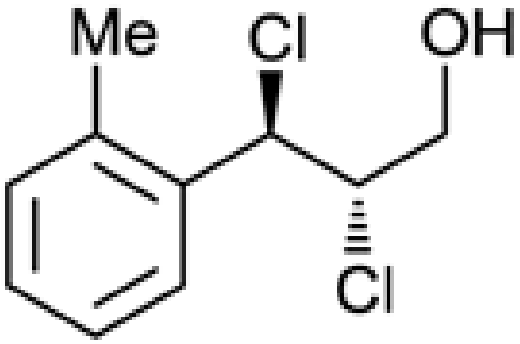

| Entry | $ArICl_2$ | Solvent | Temp. (°C) | *ee* (%)[b] |
|---|---|---|---|---|
| 1 | $PhICl_2$ | $CH_2Cl_2$ | 25 | 22 |
| 2 | $PhICl_2$ | $CH_2Cl_2$ | 0 | 23 |
| 3 | $PhICl_2$ | $CH_2Cl_2$ | −40 | 41 |
| 4 | $PhICl_2$ | $CH_2Cl_2$ | −78 | 82 |
| 5 | $PhICl_2$ | THF | −78 | <5 |
| 6 | $PhICl_2$ | EtOAc | −78 | 10 |
| 7 | $PhICl_2$ | $Et_2O$ | −78 | <5 |
| 8 | $PhICl_2$ | $CH_2Cl_2$: hexanes (1:1) | −78 | 75 |
| 9 | $PhICl_2$ | $CH_2Cl_2$: PhMe (1:1) | −78 | 75 |
| 10 | *o*-Me($C_6H_4$)$ICl_2$ | $CH_2Cl_2$ | −78 | 56 |
| 11 | *p*-Ph($C_6H_4$)$ICl_2$ | $CH_2Cl_2$ | −78 | 85 |
| 12 | *p*-*t*-Bu($C_6H_4$)$ICl_2$ | $CH_2Cl_2$ | −78 | 73 |

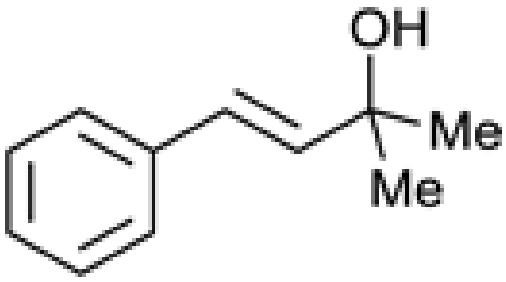
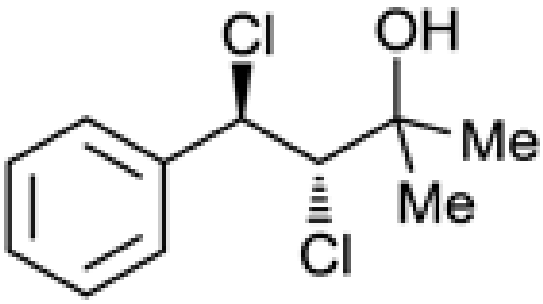
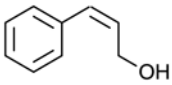
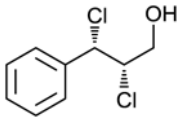
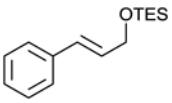
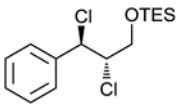
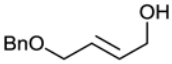
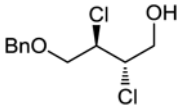
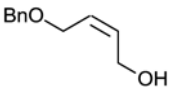
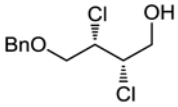
[a] Reactions were performed on 7 mg (50 μmol) scale, and run to completion (TLC analysis).

[b] Determined by chiral HPLC analysis.

## Table 2

Generality and Scope of Enantioselective Dichlorination[a]

| Entry | Substrate | Product | Yield (%)[b] | *ee* |
|---|---|---|---|---|
| 1a |  |  | 63 | 81 |
| 1b | | | 65 | 44 |
| 1c[d] | | | 75 | 48 |
| 1d | 1a: X = H (**5**) | | 81 | 71 |
| 1e | 1b: X = Me<br>1c: X = $CF_3$<br>1d: X = Cl<br>1e: X = F | 1a: X = H (**6**)<br>1b: X = Me<br>1c: X = $CF_3$<br>1d: X = Cl (**7**)<br>1e: X = F | 73 | 72 |
| 2 |  |  | 84 | 74 |
| 3 |  |  | 66 | 47 |
| 4 |  |  | 63 | 68 |

| Entry | Substrate | Product | Yield (%)[b] | *ee* |
|---|---|---|---|---|
| 5[e] |  |  | 90 | 43 |
| 6 |  |  | 35 | 25 |
| 7 |  |  | 32[g] | <5 |
| 8[e] |  |  | 48 | 43 |
| 9[e] |  |  | 59 | 54 |

[a] Reactions were performed on 40–50 mg scale using 20 mol % of $(DHQ)_2PHAL$ and 1.6 equiv of *p*-$Ph(C_6H_4)ICl_2$ in $CH_2Cl_2$ (0.05 M) at −78 °C, and run to completion (TLC analysis).

[b] Isolated yield after flash column chromatography.

[c] Determined by chiral HPLC analysis.

[d] Reaction performed at −40 °C.

[e] $PhICl_2$ used in place of *p*-$Ph(C_6H_4)ICl_2$.

[f] Absolute configuration not determined.

[g] Incomplete reaction. Yield and *ee* determined after desilylation.

[h] Determined by NMR analysis of the corresponding Mosher ester.