ASYMMETRIC HALOFUNCTIONALIZATION OF OLEFINS

Reported by Shauna M. Paradine April 12, 2010

INTRODUCTION

The functionalization of olefins is a commonly employed strategy for the rapid construction of molecular complexity in organic synthesis. Since the hybridization change from sp^2 to sp^3 at the reactive carbon atoms creates new stereocenters, performing these reactions in a well-controlled and highly asymmetric manner is ideal. Development of highly enantioselective olefin functionalization reactions has been a major focus of organic methodology for the past thirty years, and a number of useful and general methods have emerged for the asymmetric epoxidation, dioxygenation, aminooxygenation, hydrogenation, and hydroboration of olefins.[1]

Although halogen functionality is not as ubiquitous as oxygen and nitrogen in natural products, halogenated natural products still represent a pharmacologically important subclass[2] and halogens themselves can be useful for further functionalization.[3] The asymmetric addition of halogen functionality onto a carbon framework, therefore, has been of recent interest in synthetic methodology development. Synthetically useful asymmetric methods for the α–halogenation of carbonyls have been developed in response to this challenge,[4] but general methods for the highly enantioselective halofunctionalization of olefins has thus far eluded organic chemists. Over the past few years, a number of research groups have developed methods seeking to fill this clear gap in asymmetric synthesis. This recent progress will be presented here.

MECHANISTIC AND STEREOCHEMICAL CONSIDERATIONS

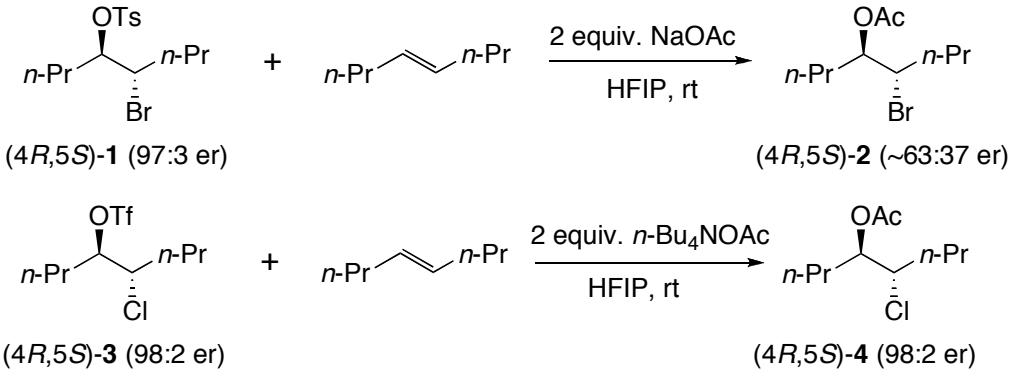
The electrophilic halogenation of olefins is one of the oldest and most basic transformations in organic synthesis. In fact, "olefin", which means "oil-forming", was a term used to describe compounds, typically low molecular weight gaseous alkenes, that became oily liquids upon chlorination. Electrophilic halogenation is also one of the first reactions that students typically learn in introductory organic chemistry.[5] Because of this, the basic mechanism of electrophilic halogenation is generally well understood. Approach of the halogen electrophile to the olefin results in formation of a three-membered cyclic halonium intermediate, which has been well-studied and characterized.[6] This intermediate is then intercepted via attack of a nucleophile from the opposite face, resulting in diastereospecific formation of an *anti*-disubstituted product.

Although halogenation reactions are diastereospecific, in the simple transformation there is generally no facial selectivity in the approach of the olefin to the halogen electrophile, resulting in a

racemic product. Since halonium ion formation is often the enantio-determining step, the ideal enantioselective transformation would selectively form the halonium ion at either the *si*- or *re*-face of the olefin. Nucleophilic attack at the opposite face would then afford the *anti*-halofunctionalized product in an asymmetric fashion. However, realizing high enantioselectivities for halofunctionalization reactions is complicated by a number of factors. Inherent site-selectivity issues can make both regio- and enantio-control difficult, often resulting in product mixtures. Further, olefin-to-olefin halonium transfer processes are known[6] and could lead to racemization even if the halonium intermediate is initially formed with perfect facial selectivity.

A recent study by Denmark and co-workers[7] explored the absolute configurational stability of bromonium and chloronium ions in the presence of olefin, mirroring catalytic conditions in which the olefin starting material would be present in greater amounts than the halonium intermediate for the majority of the reaction (Scheme 1). They observed that significant racemization occurred in the solvolysis product of bromotosylate **1**, while chlorotriflate **3** suffered no loss of chiral information. Conversely, **3** was much more susceptible to decomposition pathways than **1**. This indicates that configurational and chemical stability are inversely related and are based on the distribution of positive charge throughout the bridged halonium ion intermediate. As bromine is less electronegative than chlorine, it will have a greater relative positive charge, making it more susceptible to an olefin transfer process and thus less configurationally stable, consistent with the authors' observations. While this is not a major concern for a stoichiometric process where little olefin is present after halonium ion formation, it is potentially a serious obstacle to the development of a highly enantioselective catalytic bromofunctionalization.

Scheme 1. Study of Halonium Ion Stability in the Presence of an Olefin



ASYMMETRIC HALOCYCLIZATION METHODS

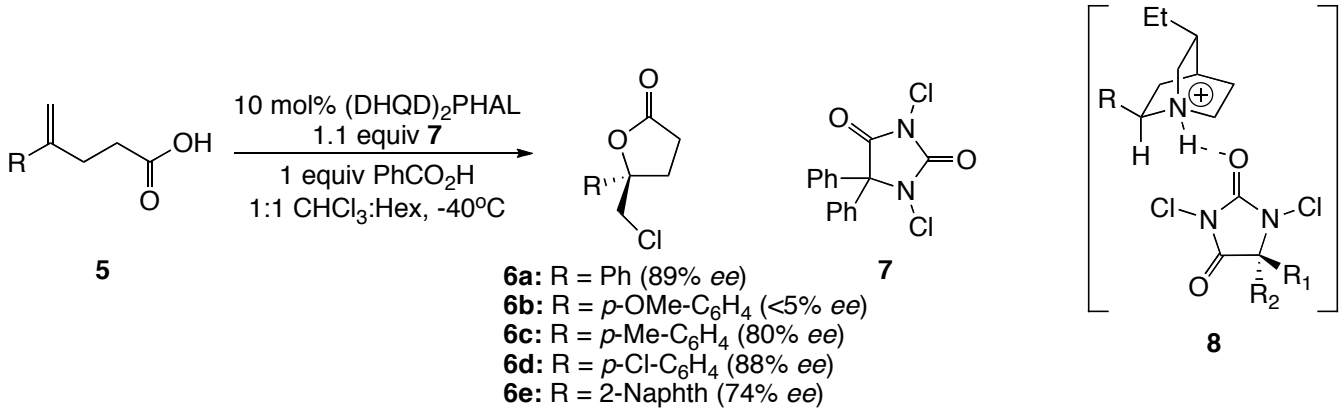
Because halocyclization reactions have the ability to rapidly construct molecular frameworks, development of asymmetric variants is of great interest. However, early efforts to develop asymmetric halocyclization reactions suffered from both low enantioselectivities (<45% *ee*) and the use of

stoichiometric chiral promoters.[8,9] One type of halocyclization reaction, asymmetric halolactonization, differentiates itself from standard lactonization strategies in that it allows for stereochemical flexibility, and incorporation of a halogen into the product provides a functional handle from which to further elaborate the molecular structure. As lactones are prevalent moieties in biologically active molecules, asymmetric halolactonization methodologies could have broad applications in organic synthesis. Recently, significant progress has been made toward the use of asymmetric halocyclization reactions as a viable synthetic strategy.

Asymmetric Chlorolactonization

In 2010, Borhan and co-workers reported the first example of a catalytic asymmetric chlorolactonization reaction.[10] Using $(DHQD)_2PHAL$ as an organocatalyst and chlorohydantoin **7** as the chlorine source, the authors were able to form chlorolactones **6** in a highly asymmetric manner (Scheme 2). This represents a significant improvement over previous methods both in terms of chiral promoter loading and in chiral induction.[8,9] A variety of aryl-substituted γ,δ-alkenoic acids **5** were cyclized to afford chlorolactones **6** in generally high yields (55-99%) and good enantioselectivities. Notable exceptions occur when a strongly electron-donating substituent is present on the aryl ring (**6b**); this is likely due to preferential formation of a stabilized chlorocarbocation as opposed to the typical cyclic chloronium ion.[11] Bulky substituents such as naphthyl (**6e**) also gave lower selectivities.

Scheme 2. Catalytic Asymmetric Chlorolactonization of Alkenoic Acids.



6a: R = Ph (89% *ee*)
6b: R = *p*-OMe-C_6H_4 (<5% *ee*)
6c: R = *p*-Me-C_6H_4 (80% *ee*)
6d: R = *p*-Cl-C_6H_4 (88% *ee*)
6e: R = 2-Naphth (74% *ee*)

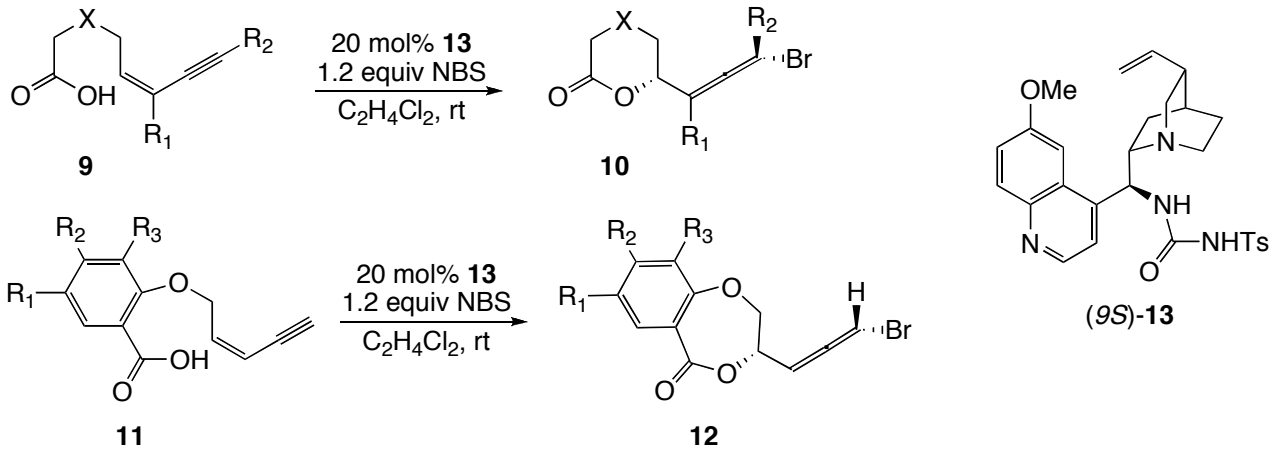
Increasing the steric demand of the substituents on chlorohydantoin **7** resulted in a slight increase in enantioselectivity (81% *ee* for $R_1 = R_2 = H$, 89% *ee* for $R_1 = R_2 = Ph$). Although the change is not very significant in a thermodynamic sense (<0.4 kcal/mol), it suggests that **7** is involved in the enantio-determining step. The authors propose the formation of intermediate **8** (Scheme 2), resulting from interaction of **7** with $(DHQD)_2PHAL$. Low temperature ^1H-NMR experiments showed a change in the chlorohydantoin proton peak ($R_1=R_2=H$) from a singlet at δ 4.35 ppm to an AB quartet at δ 4.30 ppm when $(DHQD)_2PHAL$ was added to a solution of the chlorohydantoin in $CDCl_3$, providing evidence for

the existence of complex **8**. No stereochemical model was reported, but the proposed intermediate **8** implies selective delivery of chlorine to a single face of the olefin in **5** via catalyst-halogen source interactions.

Asymmetric Bromolactonization

Shortly following Borhan's report,[10] Tang and co-workers published a catalytic enantioselective 1,4-bromolactonization reaction starting from conjugated (*Z*)-enynes.[12] Similar to Borhan's chlorolactonization method, this method employs a cinchona alkaloid as the chiral promoter (Scheme 3). Catalyst optimization led to the development of novel urea-functionalized quinuclidine **13**, which is believed to serve as a bifunctional catalyst by deprotonating the carboxylic acid and activating the halogen source (NBS) via hydrogen-bonding interactions. Treatment of conjugated enynes **9** with catalyst **13** and NBS afforded allene-substituted bromolactones **10** in good to excellent yields (70-88% yield) and high enantioselectivities (80-93% *ee*). Good compatibility was exhibited with a variety of alkyne and olefin substitution patterns, and the 1,4-*syn* addition product was favored >20:1 over the corresponding *anti* product in all cases. Fused benzocycles **11** were also prepared in generally high yields (44-88% yield) and excellent enantioselectivities (94-99% *ee*).

Scheme 3. Asymmetric Bromolactonization of Enynes.

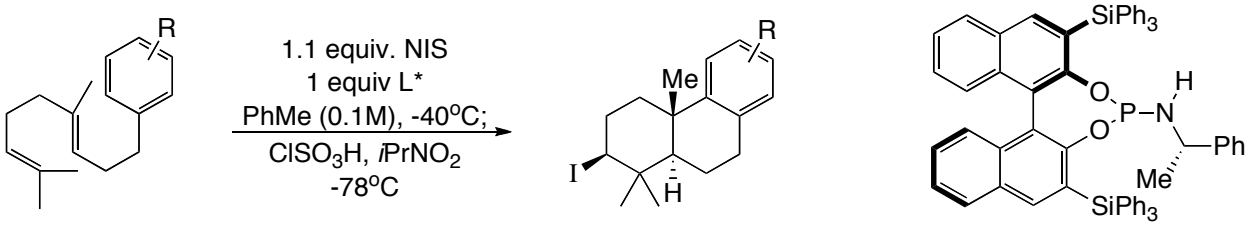


Asymmetric Halocyclization of Polyprenoids

In 2007 Ishihara and co-workers[13] reported a biomimetic enantioselective halocyclization reaction using phosphoramidite **16** as a chiral promoter (Scheme 4). Treatment of (homogeranyl)toluene **14** with *N*-iodosuccinimide (NIS) and phosphoramidite **16** gave fused tricycle **15** in good yield (57%) and high enantioselectivity (95% *ee*). Variation of chiral catalyst **16** loading was not reported, but the use of 30 mol% of achiral phosphines as nucleophilic activators afforded racemic products in high yields, suggesting that use of substoichiometric quantities of chiral promoter may be feasible. A selection of substrates with electron-rich substituents on the aryl ring and varying chain length gave

similarly high enantioselectivities, and produced only *trans*-fused cyclic products. Formation of incompletely cyclized product under the reaction conditions was ameliorated by treating the product mixture with chlorosulfonic acid, resulting in complete conversion to **15**. Unfortunately, this methodology is only useful for enantioselective iodocyclization, as replacing NIS with NBS gave drastically lower selectivities (re-optimized to a maximal 36% *ee*), and NCS did not give any cyclized product.

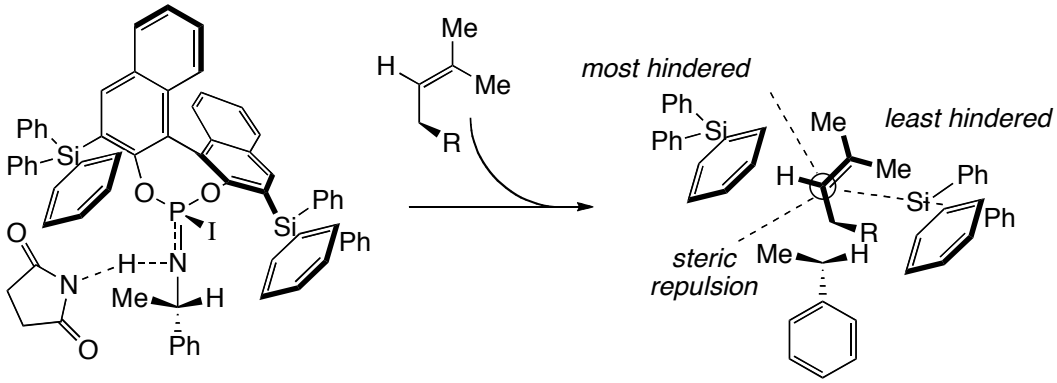
Scheme 4. Asymmetric Iodocyclization of Polyprenoids.



14 **15** (*R*)-binaphthyl-(*S*)-phenethyl-**16**

The high selectivities in this reaction are rationalized by the proposed formation of tight ion pair **17** between the chiral phosphoramidite **16** and NIS via hydrogen-bonding interactions (Scheme 5). This stereochemical model favors *si*-face approach of the olefin due to steric repulsion with the *N*-(1-phenethyl) moiety that would result from *re*-face approach. The proposed model is supported by the observation that the highest enantioselectivities are observed in non-polar solvents such as toluene. No chiral induction was observed with CH_2Cl_2 and when 1 equiv. DMF was added to the standard reaction in toluene, the enantioselectivity was greatly eroded (7% *ee*).

Scheme 5. Proposed Tight Ion-Pair Intermediate and Stereochemical Model.



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ASYMMETRIC DIHALOGENATION METHODS

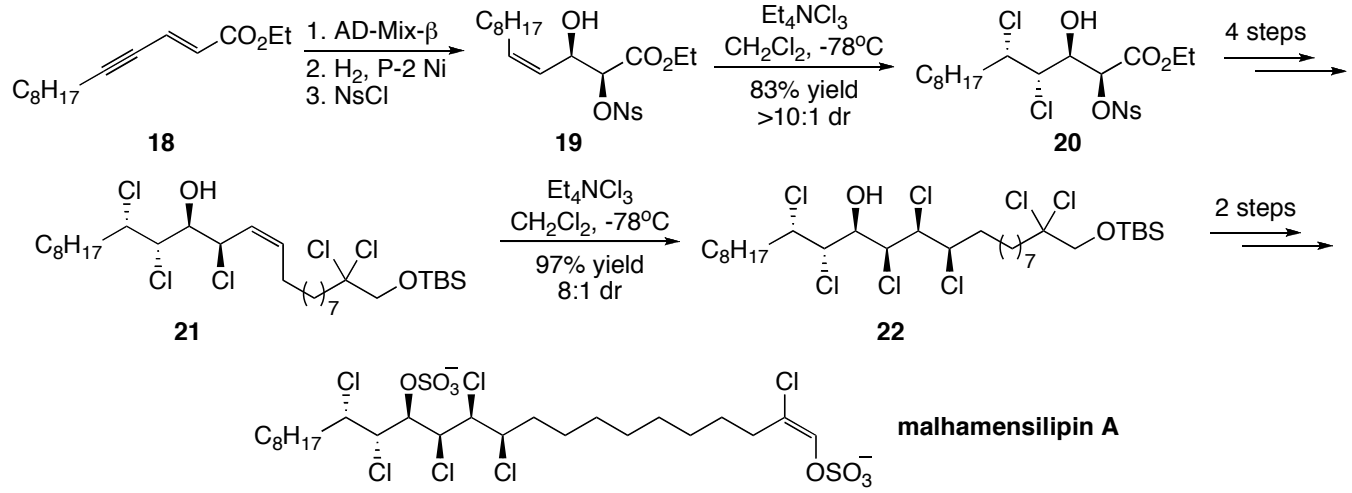
Asymmetric dihalogenation reactions of isolated olefins are arguably a more challenging class of halofunctionalization reactions than intramolecular halocyclizations (*vide supra*), as external delivery of the nucleophile could increase the potential for isomerization and detrimental background reactivity. Site-selectivity issues are of greater concern in intermolecular transformations, adding another layer of

complexity to regio- and enantiocontrol in these transformations. There are few reports on intermolecular halofunctionalization methods; the earliest method afforded dichlorinated products in low enantioselectivities under phase transfer catalysis conditions.[14] A more recent report employed an optically active Mn^{III}(salen)Cl catalyst under oxidative conditions to afford dichlorinated products with minimal enantioselectivity (5% *ee*).[15] To date, there are no general highly asymmetric electrophilic dihalogenation methods, but there have nevertheless been some notable developments (*vide infra*).

Application of Dichlorination in the Total Synthesis of Malhamensilipin A

Chlorosulfolipids have recently attracted attention as interesting synthetic targets.[16,17,18] First isolated from freshwater algae in the 1960s, these compounds are thought to be a cause of shellfish poisoning in humans.[17] Some chlorosulfolipids have also been shown to inhibit protein tyrosine kinase and display antiviral and antimicrobial activity.[19] The racemic syntheses of two chlorosulfolipids were reported in 2009,[17,18] but Vanderwal's total synthesis of malhamensilipin A in 2010 was the first enantioselective synthesis.[16] After asymmetric dihydroxylation and (*Z*)-selective reduction of enyne ester **18**, the homoallylic alcohol was selectively protected as a nosyl ester to give the starting material **19** for the key dichlorination step (Scheme 6). Treatment of **19** with Et_4NCl_3 gave dichlorinated intermediate **20** in >10:1 dr (*anti*:*syn*, relative to the diol). The homoallylic nosyl ester was reported to be uniquely effective in selecting for the desired *anti* diastereomer; a selection of other diol derivatives gave either *syn*- or no selectivity. Further, a previous report demonstrated that a variety of allylic alcohol derivatives underwent dichlorination with good *syn*-selectivity.[19] The authors provide no explanation for the high selectivities observed in either case.[16] Completion of the synthesis, including a second stereoselective dichlorination of intermediate **21** with high *syn*-selectivity (relative to the homoallylic alcohol) to afford **22**,[17] gave enantioenriched malhamensilipin A in ~1.5% overall yield in 11 steps.

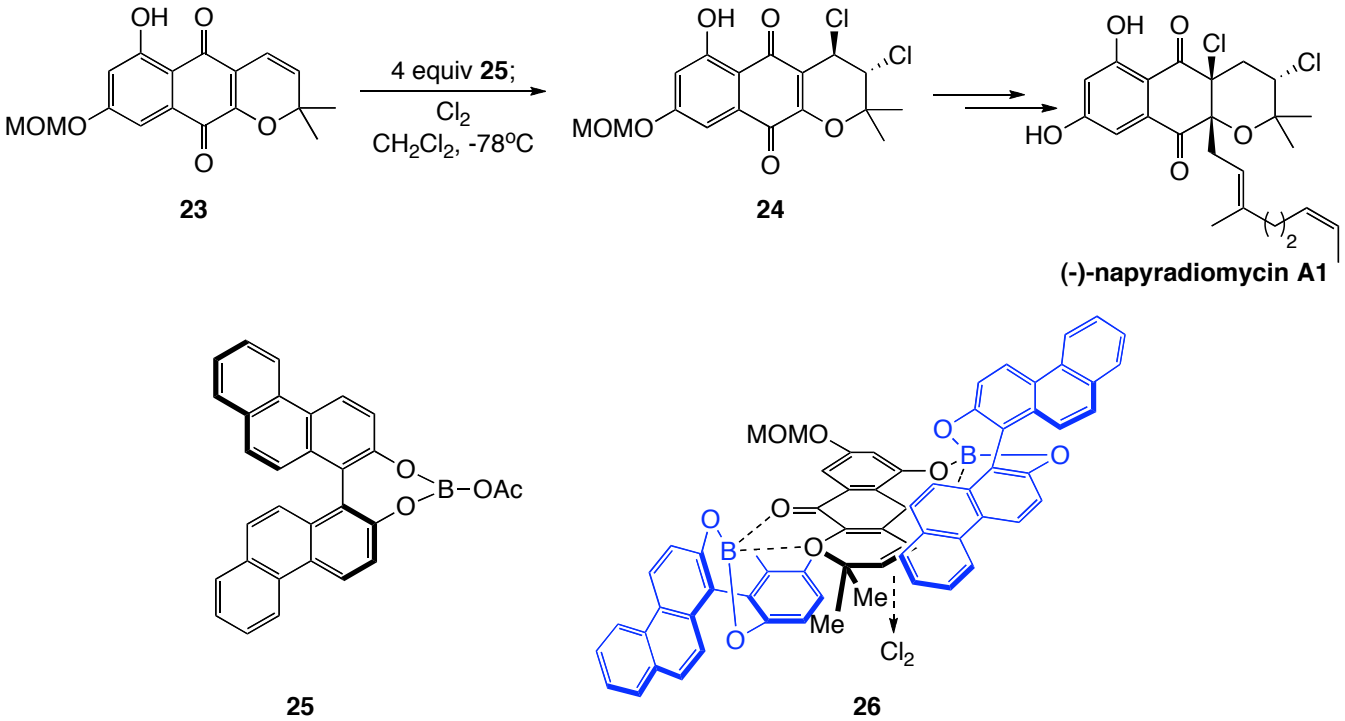
Scheme 6. Asymmetric Dichlorinations *en route* to Malhamensilipin A



Application of Dichlorination in the Total Synthesis of (-)-Napyradiomycin

In 2009, Snyder and co-workers[20] developed a highly asymmetric dichlorination reaction in the context of their total synthesis of (-)-napyradiomycin A1 (Scheme 7), the epimer of nonsteroidal estrogen antagonist napryadiomycin A1. Using 4 equiv of chiral promoter **25**, dichlorinated intermediate **24** was obtained in 93% yield with 87% *ee*. Coordination of substrate **23** with chiral promoter **25** gave proposed intermediate **26** (Scheme 7). The stereoselectivity of the transformation was rationalized via highly organized π-stacking of the aryl groups in the substrate and ligand in **26**, along with steric interaction of the olefin with the ligand, blocking the top face of the substrate. This forces selective approach of molecular chlorine to the bottom face of the olefin, resulting in the observed stereochemistry. The large excess of chiral promoter required for this transformation and the unique interactions with the substrate likely preclude application of this method to a wide range of substrate classes, but it is nonetheless an elegant example of the use of a reagent-controlled asymmetric dihalogenation reaction in the synthesis of a biologically active molecule.

Scheme 7. Asymmetric Dichlorination *en route* to (-)-Napyradiomycin



CONCLUSIONS

Despite the fact that olefin halofunctionalization reactions have been known for well over a century, the development of highly asymmetric variants of this class of reactions has lagged far behind that of other classes of olefin functionalization reactions.[1] The last few years have seen notable developments in both asymmetric halocyclization and dihalogenation methodology. There have also

been some highly asymmetric methods and elegant applications of enantioselective halofunctionalization in total synthesis. Despite this, it is clear that highly general and asymmetric halofunctionalization methods do not yet exist, and much work remains to be done in this field. Halogenated natural products are growing in interest from a pharmacological standpoint, and derivatization of biologically active molecules with halogens can also have broad utility in pharmaceutical drug development.[21] The necessity of forming stereochemically defined sp^3 C-X bonds in these molecules highlights the importance of developing asymmetric halofunctionalization reactions. Given the utility of enantioenriched halofunctionalization products, it seems that this is a field with a great deal of as yet unrealized potential.

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