Asymmetric Dihalogenation

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A Formidable Challenge: Catalytic Asymmetric Dichlorination**

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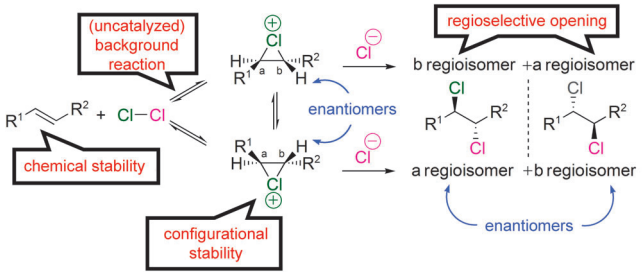
Dedicated to Professor Pavel Kočovský on the occasion of his 60th birthday

The publication of a new asymmetric transformation in one of the leading chemistry journals is usually granted when authors demonstrate significant substrate generality and achieve high enantioselectivity well above the 90% *ee* threshold. In some cases, meeting this target could be facilitated by extensive empirical testing exploiting new analytical technologies or methodologies such as organocatalysis, which are suitable for high-throughput screening. In other cases, authors will face more conceptual challenges. Yet is the simple search for a numeric value really the toughest challenge that researchers have to overcome? The achievement of high enantioselectivity certainly requires sound academic and practical ability. In some instances, however, the thorough analysis of theoretical issues linked to the asymmetric reaction could actually be the greatest hurdle.

Over the years, a consolidated asymmetric version has been developed for nearly every transformation found in organic chemistry textbooks. The olefin dihalogenation reaction,[1] one of the first diastereoselective transformations met by most chemists as undergraduate students, is a notable exception. For such a reaction, the development of a catalytic enantioselective variant seemed elusive until very recently (see Scheme 1).[2]



Scheme 1. Challenges to be tackled to develop an efficient asymmetric dichlorination reaction.

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The development of asymmetric dichlorination (or more generally an asymmetric dihalogenation) does not need to address the issue of diastereoselectivity. In these reactions, the formation of the product as a single diastereoisomer is often observed. However, a number of other daunting challenges must be faced. In particular:

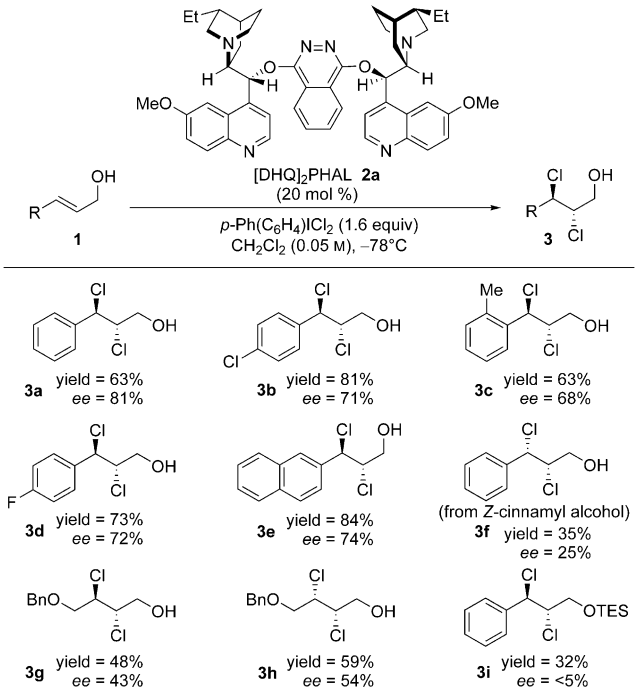
Background reactions: Halogenating reagents usually add to olefins in the absence of a catalyst; therefore, minimizing the background reaction is crucial to achieve high enantioselectivity.

Two-step transformation: Even if the three-membered ring halonium intermediate could be formed stereospecifically by the addition to one of the two enantiotopic olefin faces, non-regioselective nucleophilic opening by a second halogen ion leads to complete loss of enantioselectivity (in the case of a molecule constituted by two identical halogen atoms). Furthermore, the three-membered ring halonium intermediate might not be configurationally stable.[3]

Chemical stability: Dihalogen species can not only act as electrophiles but also as oxidants. In this case the substrates undergo subsequent structural modification, while the catalyst loses its activity.

The above issues are currently being tackled by K. C. Nicolaou and co-workers. One of their recent papers featured the development of an asymmetric dichlorination reaction, which is the subject of this Highlight.[4] Aryl-substituted allylic alcohols or analogous molecules, in which the resulting three-membered ring halonium species can be regioselectively attacked only at a defined position, have been selected as the substrates. Both the choice of the halonium source and of the catalyst was crucial. After a vast screening of chiral amines often employed as the catalysts in asymmetric transformation, $[DHQ]_2PHAL$ was selected as the most promising one. However, not surprisingly, a further addition of the catalyst (initially 10 mol% and then a further 10 mol%) was required to prevent its "ageing" due to possible degradation in the presence of an oxidant. The usage of hypervalent iodine(III) dichlorides as the source of halonium reagent was fundamental to achieve consistent reproducible results, while the conventional reagents such as chlorine gas or *N*-chlorosuccinimide (NCS) afforded only racemic products. The reaction temperature was lowered from room temperature to −78°C, accompanied by an increase in enantioselectivity, which is possibly due to the slowing down of the background reaction. Implementing these observations, the authors were finally

able to obtain a significant (although not elevated) level of stereocontrol with a variety of substrates, employing $[DHQ]_2PHAL$ **2a** as the organocatalyst; selected results are reported in Scheme 2. A consistently good degree of stereo-

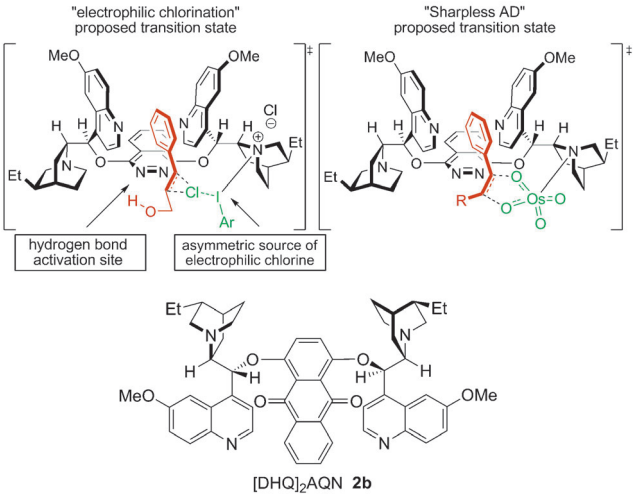


Scheme 2. Selected dichlorinated chiral nonracemic compounds prepared by K. C. Nicolaou and co-workers. TES = triethylsilyl.

selection was obtained in the dichlorination of substituted *E*-cinnamyl alcohols **1a–e** to produce compounds **3a–e** (68–81% *ee*), whilst the dihalogenation of *Z*-cinnamyl alcohol **1f** proceeded in low enantioselectivity (product **3f**, 25% *ee*). Non-arylsubstituted allylic alcohols such as **1g–h** afforded the resulting adducts **3g–h** in moderate enantioselectivity (**3g**, 43% *ee*; **3h**, 54% *ee*).

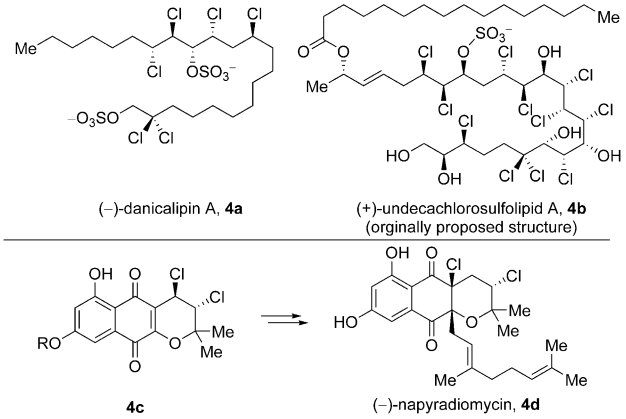
The activation mode suggested by the authors involves the transfer of a chloronium moiety by an electrophilic chlorinating reagent generated from $[DHQ]_2PHAL$ **2a** and $PhICl_2$; however, the authors acknowledge that their model is still speculative. Hydrogen bonding could be crucial to achieve a high level of stereoselectivity, since the organocatalyst $[DHQ]_2AQN$ **2b**, closely related to $[DHQ]_2PHAL$ **2a**, but lacking the nitrogen moiety, afforded only disappointingly low enantiomeric excesses (10% *ee* vs 81% *ee* for the preparation of **3a**). Employing triethylsilyl(TES)-protected alcohol **1i** led to a racemic product (**3i**, *ee* < 5%). The transition state (Scheme 3, left) is proposed in analogy with the one reported by Corey and Noe for Sharpless asymmetric dihydroxylation (Scheme 3, right).[5]

Asymmetric dichlorinated compounds do not only serve as useful synthetic intermediates, but the chemistry depicted above could also be exploited to tackle the total synthesis of polychlorinated natural compounds.[6a,b] The dichloro moiety is not only present in several natural products (such as



Scheme 3. Transition state proposed by K. C. Nicolaou and co-workers and structure of $[DHQ]_2AQN$.

(−)-danicalipin A **4a**[6c–e] and (+)-undecachlorosulfolipid A **4b**[6f]), but also in key intermediates, such as **4c**, which is pivotal in the total synthesis of (−)-napyradiomycin **4d** (Scheme 4).[2c]



Scheme 4. Dichlorinated natural substances or intermediates.

In conclusion, an original approach for the catalytic asymmetric dichlorination reaction has been proposed. Although a moderate level of enantioselectivity is obtained only by employing specific substrates, these results represent a significant advancement in this field. The development of a general asymmetric dihalogenation reaction or a dichlorination reaction with broad substrate scope is still an ongoing challenge.

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[1] a) P. B. D. De La Mare, R. Bolton in *Electrophilic Additions to Unsaturated Systems*, 2nd ed., Elsevier, New York, **1982**, pp. 136–197; b) G. H. Schmid, D. G. Garratt in *The Chemistry of Double Bonded Functional Groups* (Ed.: S. Patai), Wiley, New York, **1977**, Part 2, pp. 725–912; c) P. Kočovský, in *The Chemistry of Double-Bonded Functional Groups* (Ed.: S. Patai), John Wiley & Sons, Chichester, **1997**, Supp. A3, pp. 1135–1222.

[2] For examples of enantioselective dihalogenation reactions, see: dichlorination: a) Y. Tanaka, H. Sakuraba, H. Nakanishi, *J. Chem. Soc. Chem. Commun.* **1983**, 947–948; b) W. Adam, C. Mock-Knoblauch, C. R. Saha-Möller, M. Herderich, *J. Am. Chem. Soc.* **2000**, *122*, 9685–9691; c) S. A. Snyder, Z.-Y. Tang, R. Gupta, *J. Am. Chem. Soc.* **2009**, *131*, 5744–5745; d) S. A. Snyder, D. S. Treitler, A. P. Brucks, *J. Am. Chem. Soc.* **2010**, *132*, 14303–14314; dibromination: e) A. K. El-Qisairi, H. A. Qaseer, G. Katsigras, P. Lorenzi, U. Trivedi, S. Tracz, A. Hartman, J. A. Miller, P. M. Henry, *Org. Lett.* **2003**, *5*, 439–441; for a recent review on asymmetric halogenations, see: f) A. Castellanos, S. P. Fletcher, *Chem. Eur. J.* **2011**, *17*, 5766–5776.

[3] For a discussion on the configurational instability of three-membered ring halonium species, see: S. E. Denmark, M. T. Burk, A. J. Hoover, *J. Am. Chem. Soc.* **2010**, *132*, 1232–1233.

[4] K. C. Nicolaou, N. L. Simmons, Y. Ying, P. M. Heretsch, J. S. Chen, *J. Am. Chem. Soc.* **2011**, *133*, 8134–8137.

[5] a) E. J. Corey, M. C. Noe, *J. Am. Chem. Soc.* **1993**, *115*, 12579–12580; b) E. J. Corey, M. C. Noe, *J. Am. Chem. Soc.* **1996**, *118*, 319–329; c) E. J. Corey, M. C. Noe, *J. Am. Chem. Soc.* **1996**, *118*, 11038–11053.

[6] a) G. W. Gribble, *Acc. Chem. Res.* **1998**, *31*, 141–152; b) M. Kladi, C. Vagias, V. Roussis, *Phytochem. Rev.* **2004**, *3*, 337–366; for recent examples of polychlorinated natural substances asymmetric syntheses, see c) T. Umezawa, M. Shibata, K. Kaneko, T. Okino, F. Matsuda, *Org. Lett.* **2011**, *13*, 904; d) T. Yoshimitsu, R. Nakatani, A. Kobayashi, T. Tanaka, *Org. Lett.* **2011**, *13*, 908; e) D. K. Bedke, G. M. Shibuya, A. Pereira, W. H. Gerwick, T. H. Haines, C. D. Vanderwal, *J. Am. Chem. Soc.* **2009**, *131*, 7570–7572; f) C. Nilewski, N. R. Deprez, T. C. Fessard, D. B. Li, R. W. Geisser, E. M. Carreira, *Angew. Chem.* **2011**, *123*, 8087–8091; *Angew. Chem. Int. Ed.* **2011**, *50*, 7940–7943.

