Anomalous Face-Selectivity in Sharpless Asymmetric Dihydroxylation of *o*-Allylbenzamides

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The osmium tetraoxide-catalyzed asymmetric dihydroxylation (AD) of olefins has proved to be one of the most useful and reliable procedures, in both the homogeneous[1] and the heterogeneous[2] phase, for the synthesis of chiral diols. An important feature of this reaction is the possibility of achieving both enantiomers using, as chiral ligands, derivatives of the pseudoenantiomeric alkaloids dihydroquinine (DHQ) and dihydroquinidine (DHQD). Moreover, an empirical face-selectivity rule (Figure 1) proposed by Sharpless *et al.*[3a] allows[3] predictions upon the absolute stereochemistry of diols obtained in the AD process with the two classes of alkaloid ligands. This rule, based on a very large amount of examples and supported by molecular mechanics studies,[1] is commonly used as a guideline for the choice of the right ligand. To date, only a few exceptions have been found to the Sharpless rule, mainly concerning the AD of vinylidenic substrates,[4] and of chiral olefins,[5] where double diastereoselection was involved. A sole case of reversal of π-facial selectivity in an achiral monosubstituted olefin has been recently reported.[6] Herein, we report several exceptions to the Sharpless face-selectivity rule in the AD of differently substituted *o*-allylbenzamides.

Looking for new synthetic methods toward optically active dihydroisocoumarins,[7,8] we designed a strategy involving at first the copper-mediated regioselective allylation of benzamides[9] for the construction of the carbon skeleton. Afterwards, the AD process was used for the introduction of the chiral centers (Scheme 1).

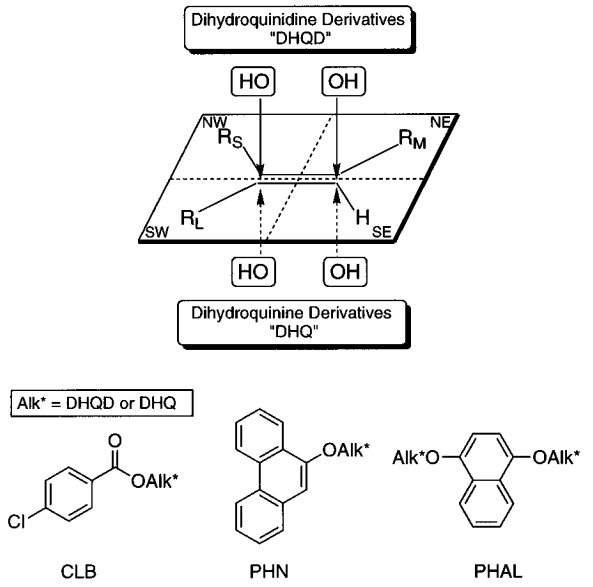
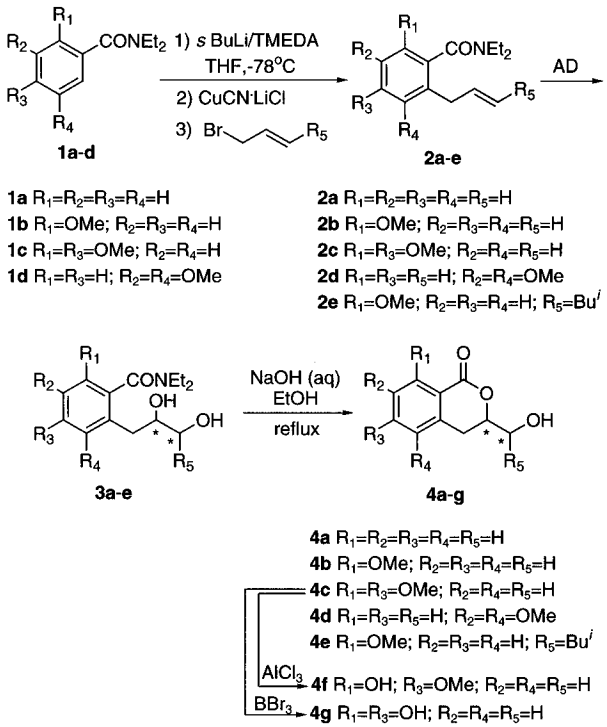


Figure 1.

Scheme 1[a]



[a] Key: synthetic route to **4a**−**e**.

The regioselective *ortho*-allylation of the *N*,*N*′-diethylbenzamides was carried out *via* a sequence of lithiation, copper transmetalation, and coupling with an allylic bromide (84−93% yield). The *o*-allyl benzamides **2a**−**e** were submitted to AD reaction and the resulting diols **3a**−**e** cyclized under basic conditions to 3-(hydroxymethylene)dihydroisocoumarins **4a**−**e** (60−71% yield).

The stereochemical outcome of the AD process, in terms of ee and absolute configuration (Table 1), was determined for the dihydroisocoumarins **4a**−**e**, as the cyclization step did not affect the chiral centers. Indeed,

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Table 1. Preparation of Dihydroisocoumarins 4a−e from *o*-allylbenzamides 2a−e

entry	olefin	ligand[a]	product	absolute config	ee[b]	Sharpless rule agreement
1	**2a**	DHQD-PHN	**4a**	*R*	44	Y
2	**2a**	$(DHQD)_2PHAL$	**4a**	*S*	16	N
3	**2a**	DHQD-CLB	**4a**	*R*	15	Y
4	**2b**	DHQD-PHN	**4b**	*R*	40	Y
5	**2b**	$(DHQD)_2PHAL$	**4b**	*S*	16	N
6	**2c**	DHQD-PHN	**4c**	*R*	40	Y
7	**2c**	DHQ-PHN	**4c**	*S*	32	Y
8	**2c**	$(DHQD)_2PHAL$	**4c**	*S*	10	N
9	**2c**	$(DHQ)_2PHAL$	**4c**	*R*	7	N
10	**2c**	DHQD-CLB	**4c**	*S*	11	N
11	**2d**	DHQD-PHN	**4d**	*S*	30	N
12	**2d**	$(DHQD)_2PHAL$	**4d**	*S*	64	N
13	**2e**	DHQD-PHN	**4e**	*R,R*	90	Y
14	**2e**	DHQ-PHN	**4e**	*S,S*	86	Y
15	**2e**	$(DHQ)_2PHAL$	**4e**	*S,S*	81	Y

[a] AD reactions were carried out according to ref 3b for PHN and CLB-based ligands and according to ref 3c for PHAL-based ligands. [b] Ee's were determined by HPLC on a Chiralpack AD column.

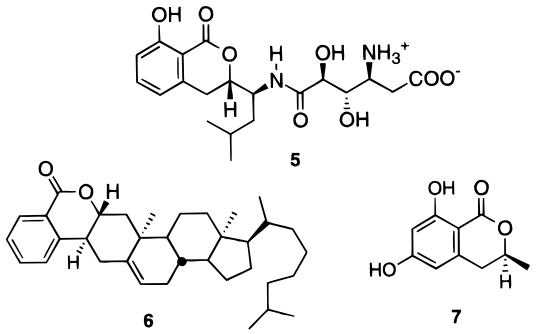

Figure 2.

the hindered rotation of the benzamido group[10] in diols **3a−e** generates an additional atropoisomeric chiral center, complicating both the HPLC and NMR analyses of such compounds. In many cases the final product **4a−e** was obtained with an unexpected absolute configuration (*vide infra*).

The absolute configuration of dihydroisocoumarins **4a−e** was determined either by chemical correlation to **5**[8,11] (Figure 2) or by comparison of CD spectra (Table 2) with compounds of known stereochemistry, such as **6**[12] and **7**[12] (Figure 2).

As shown in Table 1, the stereochemical sense of the AD process was, in many cases, opposite to that expected from the Sharpless rule, which predicts, for these substrates, the *R* configuration from DHQD-based ligands and the *S* configuration from DHQ-based ligands. Moreover, in most cases, changing the ligand from phenanthrene (PHN) to phthalazine (PHAL), while keeping the chiral cinchona alkaloid constant, reversed the sense of the π-facial selectivity of the AD reaction (Table 1, entries 1−10). A similar behavior has recently been observed in the AD of a vinylidenic olefin.[4b] The chlorobenzoate-based catalyst DHQD−CLB gave in one case the expected major enantiomer (olefin **2a**, entry 3, Table 1) and in another the opposite enantiomer (olefin **2c**, entry 10, Table 1), but always with poor ee's.

Table 2. CD Data of Dihydroisocoumarins 4a−g and Compounds 6[a] and 7[a]

product	λ_{max} (nm) ($\Delta\epsilon$)[b,c]
(*R*)-**4a**	278 sh (+2.4), 251 (+7.3), 230 (−8.4), 206 (+19)
(*S*)-**4b**	302 (−2.8), 257 (−5.7), 237 (+1.4), 207 (−9.8)
(*R*)-**4c**	296 (+3.0), 268 (+9.6), 248 (−2.4), 231 (+6.7), 215 (+0.6), 203 (+11)
(*S*)-**4d**	316 (−1.9), 261 (−5.9), 240 (+0.1), 224 sh (−2.9), 209 (−12)
(*S,S*)-**4e**	305 (−2.2), 258 (−4.7), 238 (+3.2), 209 (−7.7)
(*R*)-**4f**	295 (−1.2), 268 (+6.8), 248 (−1.8), 233 (+6.6), 221 (−1.4), 200 (+15)
(*R*)-**4g**	295 (−2.7), 268 (+7.4), 247 (−2.4), 234 (+8.1), 221 (−2.1), 200 (+15)
6[a]	290 sh (−1.6), 282 sh (−2.4), 254 (−6.7), 232 (+9.2), 207(−16)
(*S*)-**7**[a]	302 (−0.4), 268 (+3.0), 246 (−0.8), 232 (+2.6), 195 (+2.4)

[a] See ref 12. [b] $\Delta\epsilon$ values were corrected considering the ee's of the samples. [c] All spectra were recorded on methanolic solutions of products, except for **6** (EtOH) and **7** (CH_3CN).

To be more precise, the major enantiomer in the phenanthrene catalyzed (DHQD−PHN and DHQ−PHN) reactions of **2c** (entries 6 and 7, Table 1) was the minor enantiomer in the phthalazine-catalyzed ($(DHQD)_2$−PHAL and $(DHQ)_2$−PHAL) reactions of the same olefin (entries 8 and 9, Table 1). The same was found for olefins **2a** (entries 1 and 2, Table 1) and **2b** (entries 4 and 5, Table 1). The unexpected enantiomers were always obtained with phthalazine catalysts. Olefin **2d** always gave the product **4d** with the unexpected configuration, both with DHQD−PHN and $(DHQD)_2$−PHAL, although a higher ee was reached with the phthalazine catalyst (entries 11 and 12, Table 1). Finally, the internal *trans* olefin **2e** provided the expected enantiomer in high ee's with all the ligands employed (DHQD−PHN, DHQ−PHN, and $(DHQ)_2$−PHAL), showing a definitely different behavior from its analogous terminal olefin **2b**.

These results confirm that the Sharpless mnemonic model fails with several monosubstituted olefins containing a benzamido group,[6] although it preserves its effectiveness with an extremely large variety of olefins. Any attempt to rationalize these results are beyond the scope of this paper. Still, it provides an insight into this special class of terminal olefins, which constitute important exceptions to the π-facial selectivity model. We hope that these findings can help and stimulate further work aimed at refining such models and establishing a reliable mechanism for AD reaction.

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Supporting Information Available: General procedures, ^1H and ^{13}C NMR data, elemental analyses of all new products (**2a−d** and **4a−g**), CD spectra of dihydroisocoumarins **4a−g** from Table 2, and a detailed discussion on absolute configuration assignments (15 pages).

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