

Double Diastereoselection in Asymmetric Dihydroxylation

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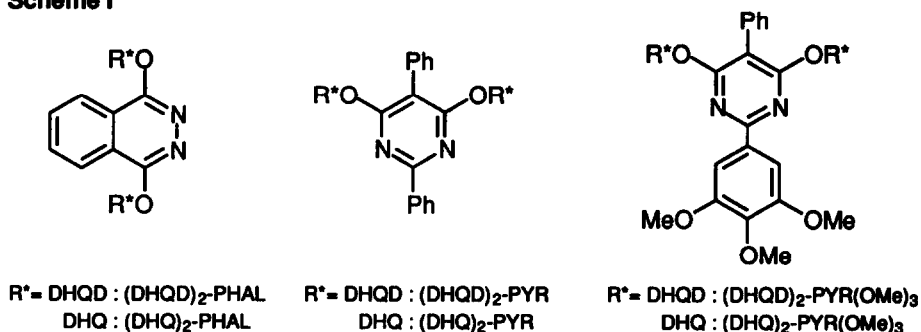
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Abstract: New ligands give improved double diastereoselection in asymmetric dihydroxylation (AD) of chiral olefins.

Since the discovery of asymmetric dihydroxylation (AD),² there have been a number of reports of "matching and mismatching"³ experiments with substrates bearing a stereogenic center in the vicinity of reacting olefinic group.⁴ The diastereoselection achieved in some of these cases was in the useful range, but in general the results were disappointing, especially when compared to the more reliable diastereoselectivities one has come to expect from the titanium-catalyzed asymmetric epoxidation (AE).⁵

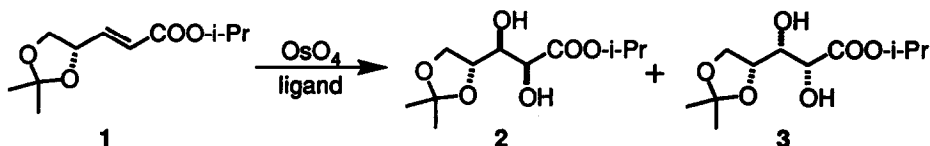
We recently introduced two new and highly effective ligand classes, the phthalazine (PHAL)⁶ and the pyrimidine (PYR)⁷ (Scheme I).

Scheme I



These new ligands are evaluated here for their ability to achieve matching and mismatching in the context of the carbohydrate precursor, unsaturated ester 1 (Scheme II).

Scheme II



All reactions in the Table were run in the presence of 3 equiv $\text{K}_3\text{Fe}(\text{CN})_6$, 3 equiv K_2CO_3 , 1 mole % (or 0.2 mole % for entries 4, 5, 7) of OsO_4 , 5 mole % (or 10 mole % for entries 1-3 or 1 mole % for entries 4, 5, 7) of ligand and 1 equiv $\text{CH}_3\text{SO}_2\text{NH}_2$ at 0°C for 24 h.^{8,9}

Table

entry	ligand	mole % of ligand	ratio of 2:3 ^a	yield ^b
1	quinuclidine	10	2.6 : 1	85 %
2	DHQD-CLB ^c	10	10 : 1	87 %
3	DHQ-CLB ^d	10	1 : 1.0	85 %
4	(DHQD) ₂ -PHAL	1	39 : 1	84 %
5	(DHQ) ₂ -PHAL	1	1 : 1.3	52 % ^e
6		5	1 : 2.3	95 %
7	(DHQD) ₂ -PYR	1	6.2 : 1	84 %
8		5	6.9 : 1	90 %
9	(DHQ) ₂ -PYR	5	1 : 4.1	86 %
10	(DHQD) ₂ -PYR(OMe) ₃	5	12 : 1	89 %
11	(DHQ) ₂ -PYR(OMe) ₃	5	1 : 7.0	90 %

a) Determined by GLC of diols.¹⁰ b) Isolated yield. c) Dihydroquinidine 4-chlorobenzoate. d) Dihydroquinine 4-chlorobenzoate. e) 36 % of starting material was recovered.

In the matched case,¹¹ the phthalazine ligand (DHQD)₂-PHAL gave the best result (entry 4) and showed progress compared to the earlier AD ligand DHQ-CLB (entry 2). In the mismatched case however, the phthalazine ligand gave only 1:2.3 ratio (entry 6) and the old DHQ-CLB ligand gave an extremely poor result (entry 3). On the other hand, the pyrimidine analogs, (DHQ)₂-PYR and (DHQ)₂-PYR(OMe)₃, were able to substantially override the resident asymmetric induction in the mismatched case (entries 9 and 11), despite their

modest performance in the matched case (entries 8 and 10) when compared to the phthalazine analog (entry 4).

The combination of these new ligands [for example, (DHQD)₂-PHAL for the matched case and (DHQ)₂-PYR(OMe)₃ for the mismatched case] is expected to give improved results in future applications of the AD for achieving useful levels of double diastereoselectivity.

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8. In all the reactions, the molar ratio of dihydroquinidine (or dihydroquinine) moiety and OsO₄ were held constant at 10 : 1.
9. A typical procedure: To a well stirred mixture of (DHQD)₂-PYR(OMe)₃ (49 mg, 0.05 mmol, 5 mole %), K₃Fe(CN)₆ (0.99 g, 3 mmol, 3 equiv), K₂CO₃ (0.42 g, 3 mmol, 3 equiv), and CH₃SO₂NH₂ (0.095 g, 1 mmol, 1equiv) in a *t*-BuOH-H₂O mixture (5 mL/5 mL) was added an OsO₄ toluene solution (0.026 mL of a 0.393 M solution, 0.01 mmol, 1 mole %). The solution was cooled to 0°C, and α,β -unsaturated ester 1 (0.214 g, 1 mmol) was then added. The reaction mixture was stirred for 24 h at 0°C. Solid sodium sulfite (1 g) was added and the mixture was stirred for 30 min at 0°C and then warmed to room

temperature. Ethyl acetate (10 mL) was added to the reaction mixture and after separation of the layers, the aqueous phase (lower layer) was further extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were dried over anhydrous MgSO_4 and concentrated [GLC analysis¹⁰ to determine the ratio of 2 : 3 (1:7.0 in this case) was performed prior to concentration] to give an oil, which was purified by flash chromatography (silica gel) using hexane-ethyl acetate (1 : 1) to afford a mixture of the pure diols as a colorless oil (0.223 g, 90 %). ¹HNMR (δ , CDCl_3) diol 2 (minor product) : 1.31 (dd, $J=1.7$ and 6.3Hz , 6H), 1.37 (d, $J=0.4\text{Hz}$, 3H), 1.45 (d, $J=0.4\text{Hz}$, 3H), 2.32 (d, $J=9.6\text{Hz}$, 1H), 3.21 (d, $J=4.8\text{Hz}$, 1H), 3.83~3.88 (m, 1H), 4.03~4.14 (m, 3H), 4.37~4.39 (m, 1H), 5.10~5.30 (m, 1H); diol 3 (major product) : 1.31 (d, $J=6.3\text{Hz}$, 6H), 1.39 (d, $J=0.4\text{Hz}$, 3H), 1.46 (d, $J=0.4\text{Hz}$, 3H), 2.71 (d, $J=7.5\text{Hz}$, 1H), 3.26 (d, $J=5.7\text{Hz}$, 1H), 3.83~3.88 (m, 2H), 4.09~4.12 (m, 2H), 4.30~4.35 (m, 1H), 5.10~5.30 (m, 1H).

10. J & W, DB-1 (100 % methyl silicon, 30 m capillary column).
Conditions: initial temperature 100°C , program rate $3^\circ\text{C}/\text{min}$.
Retention time: diol (2) 15.3 min, diol (3) 15.9 min.
11. The dihydroquinidine (DHQD) ligands direct dihydroxylation to the β -face of **1,6** which is defined as the matched case if one accepts that entry 1 in the Table with the achiral ligand, quinuclidine, is a fair point of reference for the substrates inherent diastereofacial preference in these reactions.

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