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N,N-Dimethylaminobenzoates enable highly enantioselective Sharpless dihydroxylations of 1,1-disubstituted alkenes†

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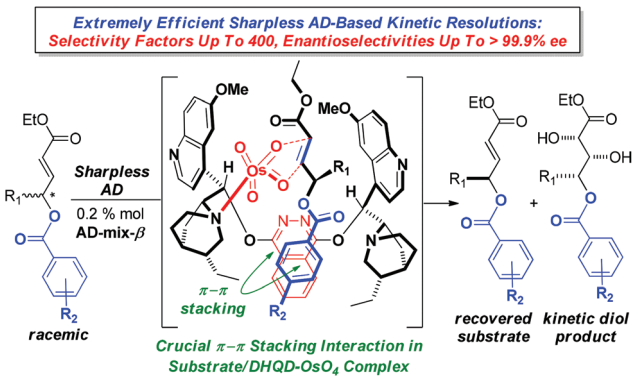
A design scenario aimed at exploring beneficial catalyst–substrate π–π stacking electronic interactions in the classical Sharpless asymmetric dihydroxylations (SAD) leads to the identification of highly polarizable allylic *N,N*-dimethylaminobenzoate as a remarkably efficient auxiliary for inducing high levels of enantioselectivities (up to 99% ee) in the traditionally challenging substrate class of 1,1-disubstituted aliphatic alkenes.

The Sharpless asymmetric dihydroxylation (SAD) reactions of alkenes serve as one of the cornerstone technologies of modern asymmetric catalysis and have found widespread applications in organic synthesis.[1] The unusually broad utility of SAD constitutes a continuous driving force for its further advancements in tackling some of the outstanding problems that remain to be solved. Such problems[2] include, but are not limited to, experimental realizations of efficient kinetic resolution[3] of chiral substances by means of SAD and of highly enantioselective dihydroxylations of traditionally challenging substrate classes of alkenes, notably purely aliphatic *gem*-1,1-disubstituted alkenes.[1] Asymmetric inductions on such compounds typically yield only low-to-mediocre enantiomeric excesses (ees). Recently, guided by new stereochemical insights gained through mechanistic analysis[3] of SAD by means of our electronic helix theory[4] for molecular chirality and chiral interactions, we were able to identify critical yet long-overlooked substrate–catalyst π–π stacking electronic interactions which in turn help explain why kinetic resolutions by means of SAD are usually difficult and how this might be solved. Specifically, as summarized in Scheme 1, we have previously demonstrated that, simply by employing an electronically polarizable allylic benzoate (highlighted in blue color, where the R_2 substituent denotes an electron-donating group) moiety capable of competing with the corresponding alkene double bond towards π–π stacking with the electron-deficient heterocyclic pyradazine π-cloud in the bis-cinchona alkaloid ligand of the so-called Sharpless AD-mix-β catalyst,[3] we were able to achieve extremely high selectivity factors (up to 400) and enantioselectivities (up to >99.9% ee) in the SAD-based kinetic resolution of a range of allylic unsaturated esters. In many cases, such racemic substrates were kinetically resolved with chiral recognition efficiencies close to the theoretical limits at their corresponding reaction conversions, yielding recovered substrate enantiomers and kinetic dihydroxylation products both in high enantiopurities. These achievements directly prompted us to further investigate the function of these π-stacking scaffolds in tackling the SAD reaction on aliphatic 1,1-disubstituted alkenes where high ees are typically difficult to attain with established protocols. We are delighted to report herein that the same design strategy enables continued successes in stereochemical control that transcends from the context of kinetic resolution to that of asymmetric induction.



Scheme 1 Explorations on substrate–catalyst π–π stacking interactions in the Sharpless asymmetric dihydroxylation leading to extremely efficient kinetic resolutions.

Thus, as shown in Table 1 with **1a–f** as the substrate probes, by slightly optimizing and identifying a conducive π-stacking moiety R_π positioned allylic to the substrate double

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†Electronic supplementary information (ESI) available: Detailed experimental procedures, X-ray crystallographic structural analysis, NMR spectra, and chiral HPLC data are provided. See DOI: 10.1039/c4ob00621f

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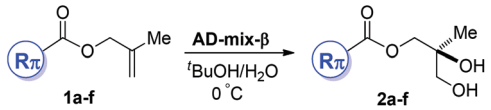
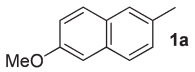
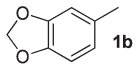
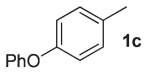
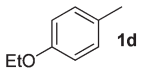
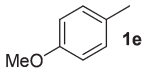
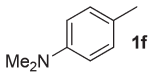
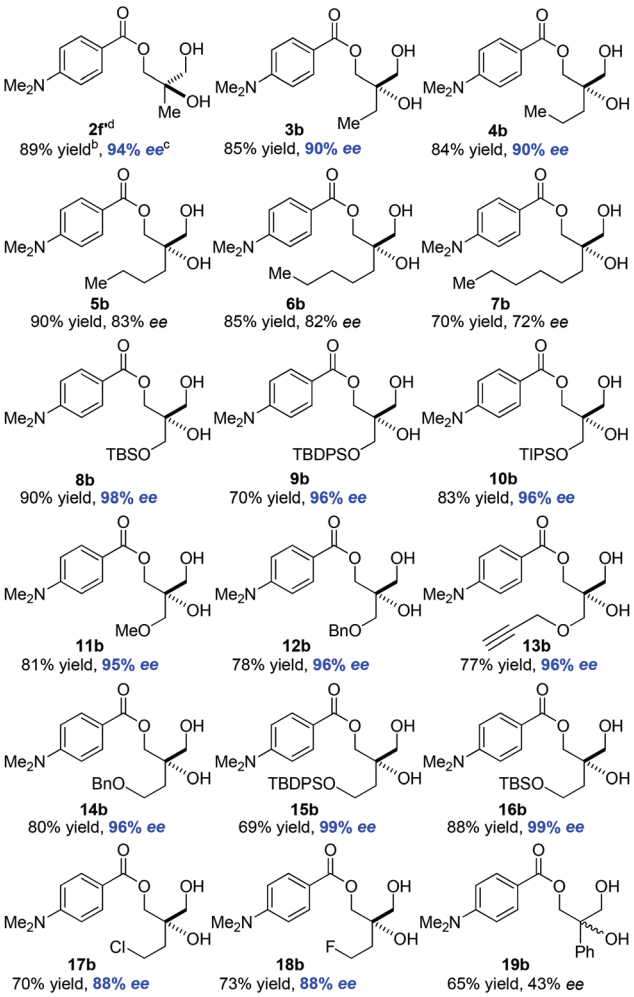
Table 1 Investigations of R_π substituents on the Sharpless asymmetric dihydroxylation of 1,1-disubstituted alkenes[a]



Entry	R_π	Yield[b]	ee[c]
1	 1a	68%	42%
2	 1b	67%	76%
3	 1c	83%	64%
4	 1d	76%	68%
5	 1e	88%	85%
6	 1f	92%	96%

[a] Reaction conditions: **1** (0.1 mmol), Sharpless AD-mix-β reagent (2.0 g $mmol^{-1}$), *t*BuOH–H_2O (1 mL, v/v = 1 : 1), 0 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Table 2 Survey on reaction scope: highly enantioselective Sharpless asymmetric dihydroxylations of a series of 1,1-disubstituted aliphatic alkenes[a]



[a] Reaction conditions: **1f** (0.1 mmol), Sharpless AD-mix-β (1.4 g $mmol^{-1}$), *t*BuOH–H_2O (1 mL, *v*/*v* = 1 : 1), 0 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] AD-mix-α was used as the reagent.

bond, we arrived at *para*-*N*,*N*-dimethylamino-benzoate **1f** as the auxiliary of choice in terms of both isolated yield and high enantio-control (96% ee of diol **2f**) over 5 h.[5] The preparation of diol **2f** by this new protocol could be readily scaled up to one-gram without compromising either the reaction yield or enantioselectivity (92% and 97% ee as compared to data in entry 6 of Table 1), thus demonstrating a high level of practicality and usefulness. It merits attention that at least in this case acyl transfer to the primary alcohol in **2f**, which apparently would be deleterious to its enantiopurity, was absent. The ability to achieve high enantiopurity on such multi-hydroxylated substances is of significant synthetic merit as it allows similar functionalities to be readily differentiated towards further needed structural elaborations.[6–12] Within this context it should be noted that the use of allylic 4-methoxy-benzoates as efficient substrates for SAD had been pioneered by Corey and co-workers.[5] Important distinctions between the present work and that of Corey *et al*. are three-fold: one, the present work derived the finding of *para*-*N*,*N*-dimethylamino-benzoate conceptually from stereochemical insights enabled by electronic polarizability analysis and electronic helix theory previously developed and published by us,[3,4] rather than from the known "U-shaped" binding theory where steric effects are dominant;[5] two, the present work emphasizes the critical significance of π–π stacking[2,3] between an alkene substrate's double bond moiety with the electron-deficient heterocyclic pyradazine π-cloud in the bis-cinchona alkaloid ligand of the Sharpless AD-mix-β catalyst, but not π–π stacking between an alkene substrate's aryl substituent with the ligand quinoline ring; and three, the present work employs the commercially available AD-mix-β or α catalyst, but not any purposefully designed Os complexes of other bis-cinchona-type alkaloids.

As shown in Table 2, a range of substrates with the *N*,*N*-dimethylamino benzoates **3a–19a** were conveniently prepared from their corresponding 1,1-disubstituted aliphatic allylic alcohols, and subsequently subjected to the Sharpless AD-mix-

β catalyst, except in the case of **1f** where its pseudo-enantiomeric AD-mix-α catalyst was employed. The ee of **2f′** thus obtained (94%) was virtually identical to that of entry 6 of Table 1 (96%). The absolute configuration of **2f** was determined by comparing its optical rotation sign with the literature value,[1p] and those of other diols **3b–18b** were assigned by analogy. The size of the aliphatic side chain R in **3b–7b** seems to have a negative influence on the reaction stereochemical control, as the product ee gradually decreases from 90% (R = ethyl or propyl) to 83% (R = butyl), 82% (R = pentyl), and further to 72% (R = hexyl), but these values remain substantial when compared to relevant literature reports.[1] Remarkably, some of the bulkiest allylic silyl ether protecting groups, such as TBS, TBDPS, TIPS, were surprisingly well tolerated, and the diols **8b–10b** were furnished in 98%, 96% and 96% ee, respectively. Allylic alkoxy groups were also compatible, and 95–96% ees were obtained in the cases of **11b–13b**. Moreover, homo-allylic substituents, being structurally either alkoxy or silyl ethers, demonstrated again excellent ees (96–99% in **14b–16b**). It is synthetically remarkable to access such highly oxygenated structural motifs as **8b–16b** in practically enantiopure forms and with chemically well-differentiated functionalities.

Homo-allylic chloro or fluoro-substituents present somewhat lower ees, but respectable 88% ees were nevertheless recorded. The above results collectively help showcase the dominant role of π–π stacking *N*,*N*-dimethyl-aminobenzoate in overriding stereoelectronic fluctuations incurred by other substituents, thereby yielding a new protocol with broad applicabilities. Finally, the reactions do not appear to be able to accommodate aromatic substituents, as a low ee (43%) was recorded when R = phenyl (diol **19b**). It should be added that, when an amide linkage was employed in placement of the ester in **1f**, asymmetric dihydroxylation only proceeded in 68% ee at 80% yield under otherwise identical reaction conditions.

In conclusion, by following the design concept of identifying appropriate π-stacking scaffolds capable of soliciting efficient catalyst–substrate electronic interactions, we report herein that *para*-*N*,*N*-dimethyl aminobenzoate, when tethered to various 1,1-disubstituted aliphatic alkenes, serves as an unusually efficient auxiliary for inducing high levels of enantiocontrol, yielding high-value multi-hydroxylated substances with stereochemical differentiation that are otherwise difficult or impossible to access. The protocol established in this work helped solve chiral induction problems in a challenging class of alkene substrates and should find uses in organic synthesis.

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