Communications to the Editor

A Mechanistic Insight Leads to a Greatly Improved Osmium-Catalyzed Asymmetric Dihydroxylation Process[†]
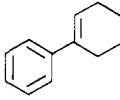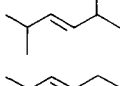
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We have discovered that the general procedure in our original communication[1] *on the osmium-catalyzed asymmetric dihydroxylation of olefins is probably among the least effective that could be devised for running that process.* We now report that with the trivial modification of adding the olefin slowly,[2] virtually all olefins give higher ee *and react faster* than in the earlier method[1] where all reactants, including the olefin, are present from the start.[3] Inspection of Table I reveals that the beneficial effect of slow addition, either alone or in concert with addition of acetate,[4] can be substantial (entries 3, 4, and 5). With this

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[†] Dedicated to Professor Satoru Masamune on the occasion of his 60th birthday.

(1) (a) Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (b) Jacobsen, E. N.; Markó, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.*, in press. This manuscript describes the kinetic role of the alkaloid ligands in the asymmetric catalytic dihydroxylation, as well as some of the unexpected benefits that accrue from the exceptionally strong ligand-acceleration phenomenon displayed by this system.

(2) **Procedure for asymmetric dihydroxylation of** *trans*-3-hexene under "slow addition" conditions. To a well-stirred mixture of 0.465 g (1 mmol, 0.25 equiv = 0.25 M in L) of dihydroquinidine 4-chlorobenzoate (Aldrich, 98%), 0.7 g (6 mmol, 1.5 equiv) of *N*-methylmorpholine *N*-oxide (NMO) (Aldrich, 97%), and 32 µL of a 0.5 M toluene solution of osmium tetroxide (16 µmol, 0.004 equiv) in 4 mL of an acetone–water mixture (10:1, v/v) at 0 °C, neat (0.5 mL, 0.34 g, 4 mmol) *trans*-3-hexene (Wiley, 99.9%) was added slowly, with a gas-tight syringe controlled by a syringe pump and with the tip of the syringe needle immersed in the reaction mixture, over a period of 10 h. The mixture gradually changed from heterogeneous to homogeneous. After the addition was complete the resulting clear orange solution was stirred at 0 °C for an additional hour. Solid sodium metabisulfite (Na$_2$S$_2$O$_5$, 1.2 g) was added, and the mixture was stirred for 5 min and then diluted with dichloromethane (8 mL) and dried (Na$_2$SO$_4$). The solids were removed by filtration and washed three times with dichloromethane. The combined filtrates were concentrated and the residual oil flash column chromatographed (silica gel, 25 g; elution with diethyl ether–dichloromethane, 2:3 v/v, R_f 0.33), affording 0.43 g (92% yield) of the hexanediol. The enantiomeric excess of the diol was determined by GLC analysis (5% phenylmethylsilicone, 0.25 µm film, 0.317 mm diameter, 29 m long) of the derived bis-Mosher ester to be 70%. [When the above reaction was repeated with 1.2 mL (6 mmol, 1.5 equiv) of 60% aqueous NMO (Aldrich) in 4 mL of acetone, an ee of 71% was obtained. Thus this aqueous NMO gives equivalent results and is almost 20 times less expensive than the 97% solid grade. With an alkaloid concentration of only 0.1 M (i.e. 0.186 g of L) and with an olefin addition period of 20 h at 0 °C, the ee was 65%. A small sacrifice in ee thus leads to a large saving in alkaloid. At 0 °C both *trans*-3-hexene and *trans*-β-methylstyrene reach their maximum ee value between 0.20 and 0.25 M alkaloid concentration.] A molar scale procedure will be reported, and in the meantime see ref 1a for a 1-mol scale workup not involving chromatography.

(3) In addition to not calling for slow addition of olefin, the other important flaw in the original[1a] procedure was that reaction mixtures (which are heterogeneous with an NMO rich aqueous phase at the bottom) were shaken occasionally but otherwise left to stand in the refrigerator without stirring. We now recommend stirring throughout the reaction. With stirring, even the original[1a] procedure gives better ee's, presumably due to better incorporation of water into the organic phase and facilitation of hydrolysis of the key intermediate (vide infra).

(4) The most important early clue was an increased ee for 1-phenylcyclohexene from 8% to 52% when 2 equiv of Et$_4$NOAc·4H$_2$O was present as an additive. The use of nucleophiles such as acetate is known to facilitate hydrolysis of osmate esters (and hence turnover) in catalytic osmylations,[5] but it was difficult to see how such an effect could increase the ee.

(5) Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1986. Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2063.

Table I. Enantiomeric Excesses Obtained in the Asymmetric Dihydroxylation of Olefins under Different Conditions

			catalytic		
entry	olefin	stoichiometric[a]	original[b]	acetate[c]	slow addition[d]
1		61	56	61	60 (5 h)
2		87	65	73	86 (5 h)
3		79	8[e]	52	78 (26 h)[f]
4		80	12[g]	61	46 (24 h)[h] 76 (24 h + OAc)
5		69	20	64	70 (10 h)

[a] All stoichiometric reactions were carried out in acetone–water, 10:1 v/v, at 0 °C and at a concentration of 0.15 M in each reagent. [b] All reactions were carried out at 0 °C according to the original procedure reported in ref 1a. [c] All reactions were carried out exactly as described in ref 1a (i.e. *without* slow addition) except that 2 equiv of Et$_4$NOAc·4H$_2$O were present. [d] All reactions were carried out at 0 °C as described in note 2 for *trans*-3-hexene with an alkaloid concentration of 0.25 M. The period for slow addition of the olefin is indicated in parentheses. The ee's shown in the table were obtained with dihydroquinidine *p*-chlorobenzoate as the ligand. Under the same conditions, the pseudoenantiomer, dihydroquinine *p*-chlorobenzoate, provides products of opposite configuration with ee's 5–10% lower. In all cases the isolated yield was 85–95%. [e] This reaction took 7 days to complete. [f] With an addition period of 16 h, ee's of 63 and 65% were obtained at 0 and 20 °C, respectively; with the combination of slow addition over a period of 16 h and the presence of 1 equiv of Et$_4$NOAc·4H$_2$O at 0 °C, an ee of 81% was realized. [g] This reaction took 5 days to complete. [h] When the reaction was carried out at 20 °C and the olefin was added over a period of 24 h, an ee of 59% was obtained.

advance the scope of the asymmetric dihydroxylation process is greatly enlarged and now includes simple hydrocarbon olefins bearing no aromatic substituents or other functional groups (entries 4 and 5).

A breakthrough in our conception of the mechanism of this catalytic olefin dihydroxylation process made these improvements possible. Several of our seemingly inexplicable observations[4] could be understood if there were *more than one catalytic cycle operative for olefin to vicinal diol conversion.* Pursuit of this idea brought dramatic results—within a few weeks overwhelming evidence supported the existence of at least two diol-producing cycles. Our proposed mechanism is outlined[6] in Figure 1; the key, putative intermediate is the osmium(VIII) trioxoglycolate complex **3**.[7] Complex **3** occupies the pivotal position at the junction between the two cycles, hence its properties are believed to determine how diol production is partitioned between the cycles. This latter point is crucial since, as revealed by the experiment described below, only the first cycle appears to give high ee.

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(6) This proposed scheme (Figure 1) is simplified for clarity, and the most notable omissions are the various fast equilibria involving association and dissociation of the alkaloid ligand (L).

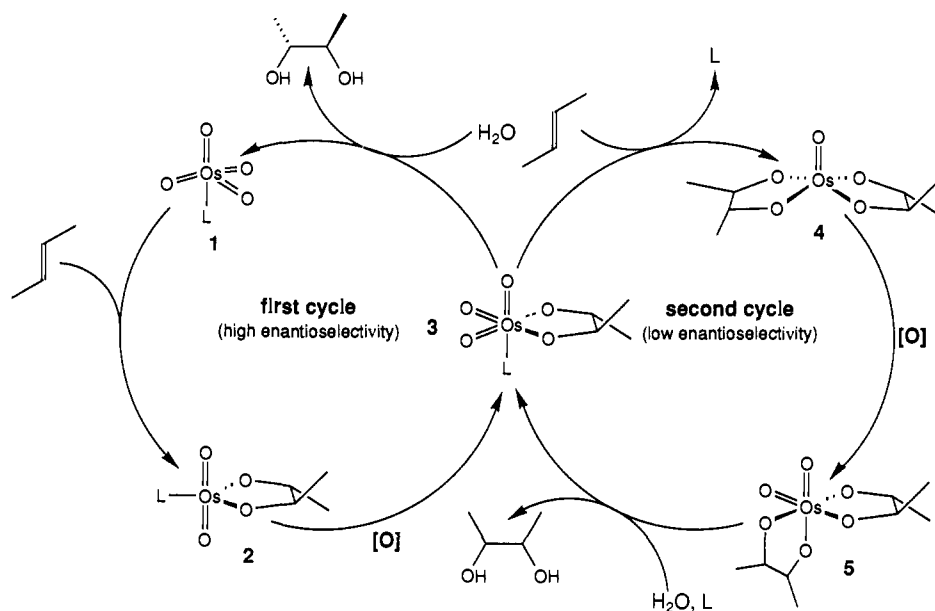(7) Criegee, R. *Liebigs Ann. Chem.* **1936**, *522*, 75.

Figure 1.

Evidence in favor of the intermediacy of **3** is provided by our finding that one can replicate the events proposed in Figure 1 by performing the process in a stepwise manner under stoichiometric conditions. These experiments were performed under *anhydrous* conditions in toluene. One equivalent of alkaloid osmium complex **1** was allowed to react with an olefin to give emerald green monoglycolate ester **2**.[8]   Then a different olefin was added, followed by an equivalent of an *anhydrous* amine *N*-oxide, and rapid formation of bisglycolate ester **4**[9] was observed. Upon reductive hydrolysis of **4**, precisely 1 equiv of each diol was liberated.[10]   These experiments indicate that the second cycle, presumably via **3**, is as efficient as the first in producing diols from olefins.[11]   Using the same olefin in both steps is an even more interesting way to run this tandem addition sequence. When this is done with 1-phenylcyclohexene, the ee for the first step is 81% and the ee for the second step is 7% in the opposite direction (i.e. in favor of the minor enantiomer in the first step)![10]   For this substrate, any intrusion of the second cycle is particularly damaging, and under the original catalytic conditions 1-phenyl-cyclohexene only gave 8% ee (entry 3, Table I).

Reduced ee is just part of the counterproductivity of turning on the second cycle; reduced turnover-frequency is the other liability. The rate of turnover in the second cycle is generally slower and therefore tends to tie up the catalyst. For example, the dihydroxylation of 1-phenylcyclohexene under the original conditions took 7 days to reach completion (the 8% ee cited above). With slow addition of the olefin, the oxidation was complete in

1 day and gave the diol in 95% yield and 78% ee (entry 3, Table I).

Among the proposed intermediates shown in Figure 1, complexes **1**, **2**, and **4** have been isolated and characterized,[10] while complexes **3** and **5** have not yet been isolated from the reaction mixtures nor independently prepared. Additional support for the involvement of **3** and for other features of the proposed mechanism (Figure 1) will be reported later. For this synthetically oriented report, it suffices to say that, so far, the hypothesis has led to uncannily accurate predictions of changes in reaction parameters that have enhanced both ee and turnover. The most important prediction, a spectacular success from its first testing, is the minimization of the second cycle if the olefin is added slowly. The idea was simply to give **3** sufficient time to hydrolyze so that the osmium catalyst does not get trapped into the second cycle by reacting with olefin.

The maximum ee possible for the catalytic process is determined during the addition of **1** to the olefin (i.e. the first column in Table I), so stoichiometric additions allow one to establish the ee ceiling that can be reached or approached in the catalytic process if the hydrolysis of **3** can be made to dominate the alternative reaction with a second molecule of olefin to give **4**. In the case of terminal olefins, styrene (entry 1) for instance, the trioxoglycolate esters evidently hydrolyze rapidly,[1a] since slow addition or the acetate effect give only a slight increase in the ee. However, most olefins benefit greatly from any modification that speeds hydrolysis (entries 2–5), and in extreme cases neither acetate nor slow addition is sufficient alone. Diisopropylethylene (entry 4) only approaches its ceiling ee when both effects are used in tandem, with slow addition carried out in the presence of acetate. The other entries in the table reach their optimum ee's through slow addition alone, but even in these cases the addition times can be substantially shortened if acetate is present.[10]

At present we offer this preliminary sequence for optimizing the osmium-catalyzed asymmetric dihydroxylation. (1) If from the known examples there is doubt about what the ceiling ee is likely to be, determine it by performing the osmylation under stoichiometric conditions in acetone/water at 0 °C. (2) Try slow addition at 0 °C. Use the last column in Table I as a guide for choosing the addition time, bearing in mind that at a given temperature each olefin has its own "fastest" addition rate, beyond which the ee suffers as the second cycle turns on. When the olefin addition rate is slow enough, the reaction mixture remains yellow-orange (color of **1**); when the rate is too fast, the solution takes on a blackish tint, indicating that the dark-brown-to-black bis-glycolate complex **4** is being generated. (3) If you have not yet reached the ceiling ee, try slow addition plus acetate at 0 °C.[12]

(8) Cartwright, B. A.; Griffith, W. P.; Schröder, M.; Skapski, A. C. *J. Chem. Soc., Chem. Commun.* **1978**, 853.

(9) Collin, R.; Griffith, W. P.; Phillips, F. L.; Skapski, A. C. *Biochim. Biophys. Acta* **1974**, *354*, 152. Phillips, F. L.; Skapski, A. C. *Acta Crystallogr.* **1975**, *B31*, 1814.

(10) Wai, J. S. M.; Sharpless, K. B. Unpublished results.

(11) Another key factor which led us to suspect the involvement of tri-oxoglycolate species **3** was the remarkable discovery, shown below, by MIT colleagues Alan Davison and Ronald Pearlstein. The trioxotechnetium complex *i* is isoelectronic and isostructural with our putative osmium complex **3**. The reaction of *i* with olefins to give glycolate *ii* provides the first example of a cis-dihydroxylation of olefins by an oxometal species having less than four oxo groups. Pearlstein, R. M.; Davison, A. *Polyhedron* **1988**, *7*, 1981.
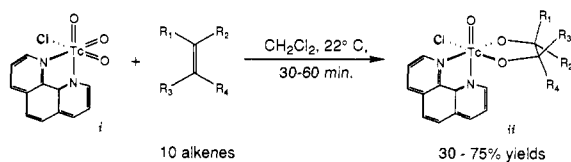
(4) The final option is slow addition plus acetate at room temperature.[12] For all these variations, stir the mixtures for the entire reaction period.[3] We now always recommend investigating slow addition—it may not help much in some cases, but it will never hurt.

Enzymes and the asymmetric dihydroxylation catalyst are at the opposite ends of the spectrum with respect to dependence on binding to achieve selectivity, and even the titanium-catalyzed asymmetric epoxidation and the various asymmetric hydrogenation catalysts all rely on a tethering group to achieve high ee's and rates. With the above improvements, the asymmetric dihydroxylation becomes the first catalytic process to achieve good enantioselectivity across an enormous range of substrates and without requiring prior binding of the substrate to the catalyst.

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(12) A caveat: in the case of α,β-unsaturated esters and allylic alcohols, the presence of acetate results in lower ee's.

Nickel-Catalyzed Cross-Couplings of Alkenyl and α-Metalated Alkenyl Sulfoximines with Organometallics: Stereoselective Synthesis of Carbacyclins

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Asymmetric synthesis of alkyl- and/or aryl-substituted exocyclic alkenes from ketones[1] (e.g., **11c** from 4-*tert*-butylcyclohexanone) still constitutes a challenge despite some success achieved recently through Wittig-type olefinations.[2,3] The synthesis of carbacyclins **1** from the key intermediate **2**[2b] represents a most sought after

a: R = *m*-C₆H₄COOH
**b:** R = (CH₂)₃COOH
c: R = CH₂OCH₂COOH
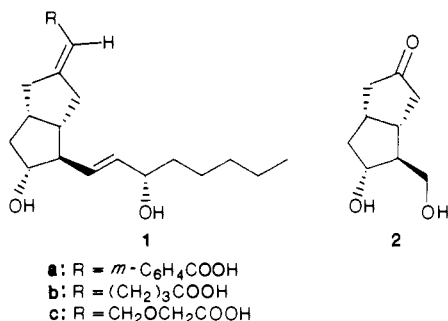
case where such a method would be of considerable practical

(1) Bestmann, H. J.; Lienert, J. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 796. Bestmann, H. J.; Heid, E.; Ryschka, W.; Lienert, J. *Liebigs Ann. Chem.* **1974**, 1684.
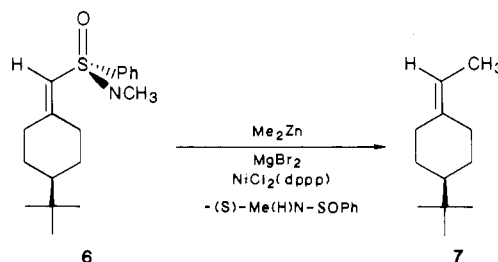
(2) (a) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754. (b) Gais, H.-J.; Schmiedl, G.; Ball, W. A.; Bund, J.; Hellmann, G.; Erdelmeier, I. *Tetrahedron Lett.* **1988**, *29*, 1773 and references cited therein. (c) Rehwinkel, H.; Skupsch, J.; Vorbrüggen, H. *Tetrahedron Lett.* **1988**, *29*, 1775.

(3) Also, see: Duhamel, L.; Ravard, A.; Plaquevent, J.-C.; Davoust, D. *Tetrahedron Lett.* **1987**, *28*, 5517. Fiaud, J. C.; Legros, J. Y. *Tetrahedron Lett.* **1988**, *29*, 2959.

Scheme I

R¹ = Si-*t*-BuMe₂
R³ = Si-*t*-BuPh₂

a: R² = Ph
b: R² = *m*-C₆H₄CH₂OR¹
c: R² = (CH₂)₄OR³
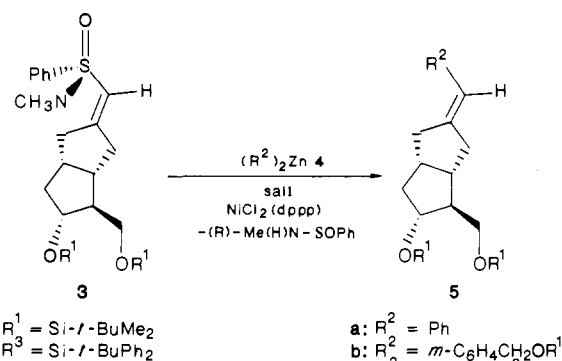
Scheme II

importance.[4] Previous syntheses of **1** from **2**[2b,c,4a,b] have failed to stereoselectively effect the geometry of the exocyclic double bond.[5] Transition-metal-catalyzed cross-coupling of alkenyl halides,[6] sulfones,[7a] sulfides,[6] selenides,[6] phosphates,[7b] ethers,[6,7c] or triflates[6] with suitable organometallics ought to be a most promising method therefore, given such derivatives can be prepared from ketones, e.g., **2**, in a stereocontrolled manner which is, unfortunately, not the case.[8] However, alkenyl sulfoximines **3** and **6**, e.g., are obtained with high diastereoselectivity (ds) from **2** (protected OH groups) and 4-*tert*-butylcyclohexanone, respectively, and enantiomerically pure LiCH₂SO(NMe)Ph[9] via asymmetric elimination.[10]

Here we report an *E*-selective synthesis of exocyclic alkenes **5**, ultimate precursors for **1**,[11,12] from **3** by Ni-catalyzed cross-

(4) **1a**,[4a] **1b**,[4b] **1c**[2c] and analogues are showing great promise as therapeutic agent for circulatory diseases: (a) Flohé, L.; Böhlke, H.; Frankus, E.; Kim, S.-M., A.; Lintz, W.; Loschen, G.; Michel, G.; Müller, B.; Schneider, J.; Seipp, U.; Vollenberg, W.; Wilsmann, K. *Arzneim.-Forsch./Drug Res.* **1983**, *33*, 1240. (b) Nickolson, R. C.; Town, M. H.; Vorbrüggen, H. *Med. Res. Rev.* **1985**, *5*, 1 and literature cited therein.

(5) For alternative *E*-selective syntheses of carbacyclins not starting from **2** or derivatives thereof, see: Sodeoka, M.; Satoh, S.; Shibasaki, M. *J. Am. Chem. Soc.* **1988**, *110*, 4823. Shibasaki, M.; Sodeoka, M.; Ogawa, Y. *J. Org. Chem.* **1984**, *49*, 4098. Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4755.

(6) For pertinent reviews, see: Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669. Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. V., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, p 799. Jolly, P. W. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. V., Eds.; Pergamon Press: Oxford; 1982; Vol. 8, p 713. Poetsch, E. *Kontakte (Darmstadt)* **1988**, *2*, 15.

(7) (a) Alvarez, E.; Cuvigny, T.; Hervé du Penhoat, C.; Julia, M. *Tetrahedron* **1988**, *44*, 111 and earlier work cited therein. (b) Hayashi, T.; Fujiawa, T.; Okamoto, Y.; Katsuro, Y.; Kumada, M. *Synthesis* **1981**, 1001. (c) Hayashi, T.; Katsuro, Y.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 3915.

(8) For asymmetric synthesis of cyclohexylidene bromomethanes from cyclohexyl methylmagnesium bromides[8a] and stereoselective cross-coupling[8a,b] of the former, see: (a) Solladié, G.; Zimmerman, G. *Tetrahedron Lett.* **1984**, *25*, 5769. (b) Walborsky, H. M.; Banks, R. B. *J. Org. Chem.* **1981**, *46*, 5074.

(9) Gais, H.-J.; Erdelmeier, I.; Lindner, H. J.; Vollhardt, J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 938. Johnson, C. R.; Schroeck, C. W.; Shanklin, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 7424.

(10) Erdelmeier, I.; Gais, H.-J.; Lindner, H. J. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 935 and further examples described therein.

(11) Konishi, Y.; Kawamura, M.; Iguchi, Y.; Arai, Y.; Hayashi, M. *Tetrahedron* **1981**, *37*, 4391.

(12) For selective deprotection of silyl ethers[12a] as well as oxidation of hydroxymethyl groups,[12b] see: (a) Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797. (b) Adler, E.; Becker, H. D. *Acta Chem. Scand.* **1961**, *15*, 849.