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# A Trifunctional Catalyst for One-Pot Synthesis of Chiral Diols via Heck Coupling−N-Oxidation−Asymmetric Dihydroxylation: Application for the Synthesis of Diltiazem and Taxol Side Chain

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A heterogeneous bifunctional catalyst composed of $OsO_4^{2-}-WO_4^{2-}$ and a trifunctional catalyst comprising $PdCl_4^{2-}-OsO_4^{2-}-WO_4^{2-}$, designed and prepared by an ion-exchange technique using layered double hydroxides (LDH) as an ion-exchanger and their homogeneous bifunctional analogue, $K_2OsO_4-Na_2WO_4$ and trifunctional analogue, $Na_2PdCl_4-K_2OsO_4-Na_2WO_4$, devised for the first time are evaluated for the synthesis of chiral vicinal diols. These bifunctional and trifunctional catalysts perform asymmetric dihydroxylation−N-oxidation and Heck-asymmetric dihydroxylation−N-oxidation, respectively, in the presence of Sharpless chiral ligand, $(DHQD)_2PHAL$ in a single pot using $H_2O_2$ as a terminal oxidant to provide *N*-methylmorpholine oxide (NMO) in situ by the oxidation of *N*-methylmorpholine (NMM). The heterogeneous bifunctional catalyst supported on LDH (LDH−OsW) displays superior activity to afford diols with higher yields over the other heterogeneous catalysts developed by the ion exchange on quaternary ammonium salts covalently bound to resin (resin−OsW) and silica (silica−OsW) or homogeneous catalysts in the achiral dihydroxylation reactions. The LDH−OsW and its homogeneous analogue are found to be very efficient in performing a simultaneous asymmetric dihydroxylation (AD)−N-oxidation of a wide and varied range of aromatic, cyclic, and mono, di-, and trisubstituted olefins to obtain chiral vicinal diols with higher yields and ee's using $H_2O_2$. Further, the use of $OsO_4^{2-}-WO_4^{2-}$ catalysts as such or in the supported form offers a simplified procedure for catalyst recycling, which shows consistent activity for a number of cycles. In this process, $Os^{VI}$ is recycled to $Os^{VIII}$ by a coupled electron transfer-mediator (ETM) system based on NMO−$WO_4^{2-}$ using $H_2O_2$, leading to a mild and selective electron transfer. The one-pot biomimic synthesis of chiral diols is mediated by a recyclable trifunctional heterogeneous catalyst (LDH−PdOsW) consisting of active palladium, tungsten, and osmium species embedded in a single matrix. This protocol, which provides prochiral olefins and NMO in situ by Heck coupling and N-oxidation of NMM, respectively, required for the AD, unfolds a low cost process. We extended the present method to the one-pot synthesis of trisubstituted chiral vicinal diols with moderate to excellent ee's by AD of trisubstituted olefins that are obtained by in situ Heck arylation of disubstituted olefins. The heterogeneous trifunctional catalysts offers chiral diols with unprecedented ee's and excellent yields in the AD of prochiral cinnamates, which are obtained in situ from acrylates and halobenzenes for the first time. The new variants such as LDH support and $Et_3N{\cdot}HX$ inherently composed in the heterogeneous multicomponent system and slow addition of $H_2O_2$ facilitates the hydrolysis of osmium monogylcolate ester to subdue the formation of bisglycolate ester to achieve higher ee's. Without resorting to recrystallization, the chiral diols of cinnamates thus synthesized with 99% ee's and devoid of osmium contamination are directly put to use in the synthesis of diltiazem and Taxol side chain with an overall improved yield to demonstrate the synthetic utility of the trifunctional heterogeneous catalyst. The high binding ability of the heterogeneous osmium catalyst enables the use of equimolar ratio of ligand to osmium to give excellent ee's in AD in contrast to the homogeneous osmium system in which the excess molar quantities of the expensive chiral ligand to osmium are invariably used. Further, the XRD, FT-IR, UV−vis DRS, and XPS studies indicate the retention of the coordination geometries of the specific divalent anions anchored to LDH matrix in their monomeric form during the ion exchange and after the reaction.

## Introduction

Improving the efficiency of organic processes in terms of lowering the process time, inventory of equipment, utilization of manpower, consumption of energy and chemicals, and generation of waste is a major goal in synthetic chemistry. Performing the multistep synthesis in one pot is an attractive strategy to achieve this goal.[1] The cocktail approach has been realized in the in vitro

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synthesis of corrin from α-aminolevulinic acid using 12 enzymes with an overall yield of 20% in a single flask.[2] The elegant uncatalyzed multicomponent reaction (MCR), comprising the condensation of the five components, viz. primary amines, aldehydes, carbon dioxide, alcohols, and isocyanides, to α-acylaminocarbonamides based on a Zipper principle was developed by Ugi.[2a] The single molecule catalyst, which performs multifunctionality in C−C bond-forming reactions with high enantioface discrimination,[3] was developed by Shibasaki. Significant progress using homogeneous and heterogeneous bifunctional catalysts for one-pot reactions was achieved.[4] The recent design of the BINOL−BINAP copolymer catalyst for the tandem asymmetric diethylzinc addition and hydrogenation of acetyl benzaldehydes marks a new era in bifunctional catalysis.[4a]

Sharpless AD of olefins offers one of the most efficient methods for the preparation of chiral diols, the key intermediates for many biological compounds.[5,6] An effective reoxidation system that facilitates the Os(VI)/Os(VIII) cycle in the AD reactions naturally improves high throughput. Several reoxidation systems using *N*-methylmorpholine *N*-oxide (NMO),[7] potassium ferricyanide,[8] or molecular oxygen[9] have been developed. The use of the ferricyanide in AD reaction, which encounters the problem of effluent disposal due to handling of large amounts of salts (1.4 g per mmol of olefin), is not feasible practically or economically on a large scale. On the other hand, the use of NMO[7] has definite advantages such as facilitation of the reaction in higher concentrations, easy recyclability of the reduced *N*-methylmorpholine (NMM), and economical by a factor of 5 over the potassium ferricyanide. Besides, the ee's of the resultant chiral diols could be achieved as high as those obtained with $K_3Fe(CN)_6$ in case of aromatic olefins, by adopting the slow addition of olefin to the reaction mixture with the aid of an automated pump. Conversely, the lower ee's and over-oxidation in the case of aromatic olefins containing α-hydrogen are the major concerns in the use of $O_2$ as the reoxidant for osmium(VI) in AD reaction. $H_2O_2$ as direct reoxidant leads to the nonselective reaction with a low yield of diol due to over-oxidations.[10] Recently, Bäckvall developed the electron-transfer mediator (ETM) based on NMO/flavin for osmium-catalyzed AD of olefins using $H_2O_2$ as a terminal oxidant with high efficiency.[11]

Although the AD reactions catalyzed by $OsO_4$ could be applied to the synthesis of pharmaceuticals, fine chemicals, etc., the high cost, and possible contamination of toxic osmium in the product, restricts its use in industry. Heterogenization of $OsO_4$ via microencapsulation,[12] ion-exchange techniques,[13] and covalent anchoring[14] are employed to address the issue of complete recovery of osmium from the reaction media. We recently designed the unique single-pot biomimic synthesis of chiral diols mediated by a trifunctional heterogeneous catalyst, consisting of active palladium, tungsten, and osmium species embedded in a single matrix. This method provides prochiral olefins and NMO in situ by Heck coupling and N-oxidation of NMM, respectively, required for the AD.[13a] The ETM based on the NMO/$WO_4^{2-}$ system is indeed found to be excellent in AD reactions catalyzed in the heterogeneous phase.[15] We report herein (i) the one-pot synthesis of chiral diols using both bifunctional ($OsO_4^{2-}$−$WO_4^{2-}$) and trifunctional ($PdCl_4^{2-}$−$OsO_4^{2-}$−$WO_4^{2-}$) catalysts developed for the first time in homogeneous phase and compared with the heterogeneous analogues obtained via ion-exchange methods using LDH as an ion exchanger and $H_2O_2$ as a terminal oxidant in terms of activity and enantioselectivity, (ii) in situ synthesis and dihydroxylation of various functionalized and trisubstituted olefins using $H_2O_2$ as the terminal oxidant in which NMM is recycled to NMO in trifunctional heterogeneous catalysis, and (iii) without resorting to recrystallization, the chiral diols synthesized with unprecedented higher ee's can be directly put to use in the synthesis of diltiazem and taxol side chain to demonstrate the synthetic utility of the trifunctional heterogeneous catalyst.

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## Results and Discussion

**Preparation and Characterization of Catalysts.** Homogeneous bifunctional catalytic systems composed of admixtures of $K_2OsO_4-Na_2WO_4$ and trifunctional catalytic system comprising $Na_2PdCl_4-K_2OsO_4-Na_2WO_4$ and their heterogeneous analogues exchanged on a single matrix, LDH, and quaternary ammonium resin and silica[16−18] were prepared and examined in dihydroxylation reactions in a single pot using $H_2O_2$ as a terminal oxidant under identical conditions. LDH is a class of layered material, consisting of alternating cationic $M(II)_{1-x}M(III)_x(OH)_2^{x+}$ and anionic $A^{n-}\cdot zH_2O$ layers.[19] The cationic layers are separated from each other by the anions and water molecules. The positively charged layers in LDH contain edge-shared metal M(II) and M(III) hydroxide octahedra, with charges neutralized by the $A^{n-}$ anions located in the interlayer spacing or at the edges of the lamellae. A wide variety of LDHs containing various divalent and trivalent cations [M(II) = Mg, Zn, Ni, Cu; M(III) = Al, Ga, In, Cr, Fe] in combination with different anions can be prepared. LDHs have been investigated extensively in a wide range of applications such as catalysts,[13,16] materials,[19,20] and bioactive nanocomposites.[21] Small hexagonal LDH crystals with $Mg_{1-x}Al_x(OH)_2(A)_x\cdot zH_2O$ [A = Cl, $NO_3$, $CO_3$] composition were synthesized following the existing procedures.[19b] Resins are another class of polymeric supports originating from organic precursors, which are widely employed as catalyst carriers and in solid phase organic synthesis. Silica gel, an inorganic support, a commonly employed support in heterogeneous catalysis, is also considered for the immobilization of osmium. $OsO_4^{2-}$ and $WO_4^{2-}$ were co-exchanged concomitantly onto a chloride saturated LDH to obtain the bifunctional catalyst, LDH−[$OsO_4$,$WO_4$] (abbreviated as LDH−OsW). Further, three bivalent anions, $PdCl_4^{2-}$, $OsO_4^{2-}$ and $WO_4^{2-}$ were simultaneously coexchanged onto a single LDH matrix to yield LDH−[$PdCl_4$,$OsO_4$,$WO_4$] (abbreviated as LDH−PdOsW). Similarly, $OsO_4^{2-}-WO_4^{2-}$ were co-exchanged onto the quaternary ammonium form of resin and silica to obtain bifunctional resin−OsW and silica−OsW.

**TABLE 1. Measured Binding Energies for Palladium, Osmium, and Tungsten of Bifunctional and Trifunctional Catalysts**

| | Pd | | | Os | | W | |
|---|---|---|---|---|---|---|---|
| catalyst | $3d_{5/2}$ | $3d_{3/2}$ | 4p | $4f_{7/2}$ | $4f_{5/2}$ | $4f_{7/2}$ | $4f_{5/2}$ |
| LDH−OsW[a] | | | | 54.2 | 56.8 | 34.9 | 36.9 |
| LDH−OsW[b] | | | | 54.3 | 56.8 | 34.9 | 37.0 |
| LDH−PdOsW[a] | 337.2 | 342.8 | 50.5 | 54.5 | 57.0 | 35.0 | 37.0 |
| LDH−PdOsW[b] | 337.1 | 342.6 | 50.2 | 54.3 | 56.6 | 34.7 | 36.9 |

[a] Fresh catalyst. [b] Used catalyst.

X-ray powder diffraction patterns of the initial LDH and the exchanged catalysts LDH−OsW and LDH−PdOsW hardly differ in the range $2\theta$ = 3−65°. The observed basal spacings remain unchanged after the anion exchange, which indicates the location of divalent anions $OsO_4^{2-}$ and $WO_4^{2-}$ in the bifunctional catalyst and $PdCl_4^{2-}$, $OsO_4^{2-}$, and $WO_4^{2-}$ in trifunctional catalyst on the edge positions of LDH. In the FTIR spectra of these exchanged catalysts, broad absorption bands appear near 830−860 $cm^{-1}$, which are assigned to the vibrational asymmetric O═M═O (M = Os and/or W) stretching in contrast to the sharp bands observed at 819 $cm^{-1}$ for potassium osmate and 831, 857 $cm^{-1}$ for sodium tungstate. The observation of broad bands in the same region for the catalysts indicates that the $OsO_4^{2-}$ and $WO_4^{2-}$ are unaffected upon exchange onto the support both in bifunctional and trifunctional catalysts while experiencing very weak interactions with the support. The Pd−Cl stretching of $PdCl_4^{2-}$ is also observed at 335 $cm^{-1}$ for LDH−PdOsW. The UV−vis diffuse reflectance spectra of the catalysts show broad bands with the absorption maxima at 253 ($WO_4^{2-}$), 280 ($PdCl_4^{2-}$), and 293 nm ($OsO_4^{2-}$). No shift in the absorption maxima for these multifunctional heterogeneous catalysts was observed compared to the spectra of their pure precursors. These results indicate the presence of related divalent anions in trifunctional and bifunctional catalysts as assigned. All these studies indicate the retention of the coordination geometries of the specific divalent anions anchored to LDH matrix in their monomeric form. The BET surface areas of LDH−OsW and LDH−PdOsW are found to be 60 and 68 $m^2\ g^{-1}$, respectively.

**X-ray Photoelectron Spectroscopy (XPS).** The X-ray Photoelectron spectroscopic (XPS) results of the fresh and used bifunctional LDH−OsW and trifunctional LDH−PdOsW catalysts show almost identical binding energies for Os,[22] W,[23] and Pd[24] (Table 1). It confirms that the oxidation states of the respective metals remain static

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**TABLE 2. Achiral Dihydroxylation of *trans*-Stilbene Using $H_2O_2$ as the Terminal Oxidant[a]**

| entry | NMM (equiv) | $Na_2WO_4$ (equiv) | yield (%) |
|---|---|---|---|
| 1 | | | 15 |
| 2 | 0.27 | | 52 |
| 3 | 0.27 | 0.01 | 95 |

[a] The *trans*-stilbene (1 mmol), $K_2OsO_4{\cdot}2H_2O$ (1 mol %), $H_2O_2$ (1.5 mmol), and $H_2O$−acetone (1:5) were stirred at room temperature for 20 h.

during ion-exchange process and at the end of the reaction. These results also ruled out the formation of bimetallic species.

**Multifunctional Catalysis.** Osmium-catalyzed AD of olefins using NMO oxidant provides NMM as a byproduct and requires additional unit operations for recycling of NMM in the process. Similarly, an additional unit operation necessitates for the production of substituted prochiral olefins used in the usual AD reactions. Hence, the need to develop a multifunctional catalyst for the synthesis of prochiral substrates, oxidant, and finally chiral diols in one pot is highly desirable.

**A. One-Pot Synthesis of Diols via Achiral Dihydroxylations.** We first investigated the dihydroxylation of *trans*-stilbene using $H_2O_2$ as the terminal oxidant. In a general experimental procedure, to a mixture comprising the olefin and 1 mol % of the $K_2OsO_4{\cdot}2H_2O$ in $H_2O$−acetone (1:5), $H_2O_2$ was charged slowly over a period of 12 h and stirred at room temperature for a further period of 8 h. Direct reoxidation of Os(VI) by $H_2O_2$ led to a nonselective reaction, wherein diol was obtained in 15% yield (Table 2). In another experiment, wherein NMM was introduced in the system, which was oxidized to generate NMO by a slow addition of $H_2O_2$, gave diol in 52% yield. Recently, we reported the oxidation of tertiary amines using tungstate catalyst.[16c] Indeed, the use of catalytic amount of the $Na_2WO_4$ in the osmium catalyzed dihydroxylation of olefins accelerated the generation of NMO in situ from NMM, as is evident from an enhanced yield (95%) of the corresponding diol under identical conditions (Table 2). The rate of reaction is comparable to the osmium catalyzed dihydroxylation using NMO cooxidant. More interestingly, both the catalysts ($K_2OsO_4{\cdot}2H_2O$ and $Na_2WO_4{\cdot}2H_2O$) could be recovered from the reaction by an aqueous workup.

Recently, we developed the heterogeneous osmium catalyst by an ion-exchange of $OsO_4^{2-}$ on various ion exchangers for AD of olefins.[13b] At the same time, we also developed the heterogeneous tungsten catalyst via an ion-exchange of $WO_4^{2-}$ on LDH for oxidation of various tertiary amines to the corresponding *N*-oxides in water with high atom economy.[16c] These two discoveries prompted us to design a new heterogeneous bifunctional catalyst consisting of osmium and tungsten oxides on a single matrix to perform AD and N-oxidation reactions simultaneously in a single pot.

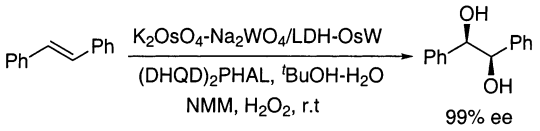
The heterogeneous bifunctional catalyst, consisting of osmium and tungsten oxides and their homogeneous counterparts were first screened for achiral dihydroxylation of *trans*-stilbene. An activity profile of the dihydroxylation of *trans*-stilbene with various catalysts conducted under similar conditions (12 h) described in Table 3 reveals that LDH−OsW displays the highest activity

**TABLE 3. Achiral Dihydroxylation of *trans*-Stilbene Using Various Bifunctional Catalytic Systems[a]**

| entry | catalyst | yield (%) |
|---|---|---|
| 1 | $K_2OsO_4{\cdot}2H_2O$−$Na_2WO_4{\cdot}2H_2O$ | 50 |
| 2 | LDH−OsW | 95 |
| 3 | resin−OsW | 87 |
| 4 | silica−OsW | 79 |

[a] The *trans*-stilbene (1 mmol), catalyst (0.01 mmol), and NMM (0.5 mmol) were taken in a round-bottomed flask containing $H_2O$−acetone (1:5, 5 mL), and $H_2O_2$ (1.5 mmol) was slowly added over 12 h under stirring.

**SCHEME 1. Asymmetric Dihydroxylation of *trans*-Stilbene Using Bifunctional Catalysts**




and the heterogenized catalysts in general have distinctly faster reactivity than $K_2OsO_4{\cdot}2H_2O$−$Na_2WO_4{\cdot}2H_2O$.

**B. One-Pot Synthesis of Chiral Diols. 1. Osmium−Tungsten Catalytic System.** Buoyed with the results obtained in the achiral dihydroxylation, we employed the heterogeneous bifunctional catalyst LDH−OsW for simultaneous AD of *trans*-stilbene and *N*-oxidation of NMM in the presence of $H_2O_2$ using the Sharpless chiral ligands. To a mixture of 1 mol % of LDH−OsW or $K_2OsO_4{\cdot}2H_2O$−$Na_2WO_4{\cdot}2H_2O$, 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine ($(DHQD)_2PHAL$), *trans*-stilbene and NMM in $^t$BuOH−$H_2O$ (5:1), $H_2O_2$ was slowly added over a period of 12 h (for heterogeneous system) and 20 h (for homogeneous system) to afford the desired diol in 93% yield with 99% ee (Scheme 1).

**Effect of Solvent.** We have also examined the effect of solvent on activity and enantioselectivity in the LDH−OsW-catalyzed AD of *trans*-stilbene using $H_2O_2$ as the terminal oxidant. The $H_2O$−acetone proved to be a good solvent for obtaining high yields. However, $H_2O$−$^t$BuOH was found to be the best solvent to obtain high ee's similar to that obtained in the case of homogeneous catalysis,[5] and the order was found to be: $H_2O$−$CH_3CN$ < $H_2O$−$CH_3CN$−acetone < $H_2O$−acetone < $H_2O$−$^t$BuOH.

**Variation of Tertiary Amine.** Although NMO is employed extensively in dihydroxylations, trimethylamine *N*-oxide is also used as an efficient oxidant in the dihydroxylation of sterically hindered olefins and allylic alcohols.[25] As LDH−$WO_4$ catalyzes the oxidation of various tertiary amines to their corresponding *N*-oxides,[16c] it is of interest to investigate the dihydroxylations using various tertiary amines. Under optimized conditions, as described above, dihydroxylation of *trans*-stilbene gave the diol in good to excellent yields, although the activity varies with the nature of amine (Table 4).

The bifunctional heterogeneous catalyst LDH−OsW and its homogeneous counterpart $K_2OsO_4{\cdot}2H_2O$−$Na_2WO_4{\cdot}2H_2O$ were further subjected to AD of various olefins ranging from mono- to trisubstituted and activated to simple to give vicinal chiral diols with excellent yields and ee's, and the results are summarized in Table 5. Slow

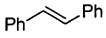
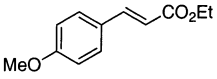
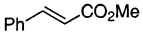
(25) Donohoe, T. J.; Waring, M. J.; Newcombe, N. J. *Synlett* **2000**, *1*, 149.

**TABLE 4. Asymmetric Dihydroxylation of *trans*-Stilbene Using Various Tertiary Amines Mediated by Heterogeneous Bifunctional Catalyst[a]**

| entry | amine | yield of diol (%) | ee (%) |
|---|---|---|---|
| 1 | NMM | 95 | 99 |
| 2 | $NEt_3$ | 91 | 97 |
| 3 | $NMe_3$ | 70 | 88 |

[a] The *trans*-stilbene (1 mmol), LDH−OsW (0.01 mmol), $(DHQD)_2$-PHAL (0.01 mmol), and amine (50 mol %) were taken in a round-bottomed flask containing $H_2O$−$^t$BuOH (1:5, 5 mL), and $H_2O_2$ (1.5 mmol) was slowly added over 12 h under stirring.

**TABLE 5. Asymmetric Dihydroxylation of Olefins Using $K_2OsO_4{\cdot}2H_2O$/NMM/$Na_2WO_4{\cdot}2H_2O$/$H_2O_2$ and LDH−OsW/NMM/$H_2O_2$ Systems**

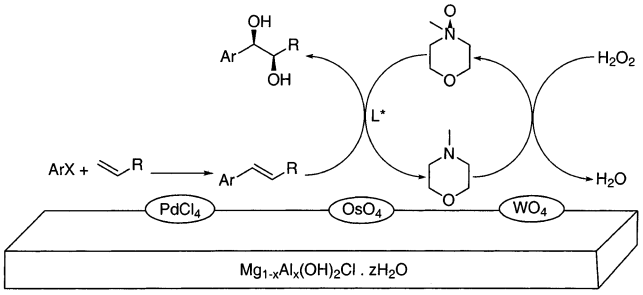
| Entry | Olefin | $K_2OsO_4.2H_2O$-$Na_2WO_4.2H_2O$[a] | | LDH-OsW[b] | |
|---|---|---|---|---|---|
| | | yield(%) | ee(%)[c] | yield(%) | ee(%)[c] |
| 1 |  | 90 | 95 | 92 | 96 |
| 2 |  | 93 | 92 | 95 | 93 |
| 3 |  | 92 | 94 | 93 | 96 |
| 4[d] |  | 87 | 92 | 90 | 93 |
| 5[d] |  | 91 | 90 | 89 | 91 |
| 6[e] |  | 85 | 99 | 93 | 99 |
| 7 |  | 82 | 99 | 89 | 99 |
| 8[f] |  | 91(85) | 99(99) | 92(90) | 99(99) |

[a] $K_2OsO_4{\cdot}2H_2O$ (3.68 mg, 0.01 mmol), $Na_2WO_4{\cdot}2H_2O$ (3.29 mg, 0.01 mmol), NMM (0.5 mmol), TEAA (2 mmol), and $(DHQD)_2PHAL$ (0.03 mmol, 23 mg) in $H_2O$−$^t$BuOH (1:3, 5 mL) were stirred at room temperature for 20 min. To this mixture were added an olefin (1 mmol) and $H_2O_2$ (1.5 mmol) over a period of 20 h using separate syringe pumps. [b] 1 mol % of LDH−OsW and $(DHQD)_2PHAL$, NMM (0.5 mmol) were used. Olefin and $H_2O_2$ were added slowly over a period of 12 h. [c] ee determined by HPLC analysis. [d] Two equivalents of TEAA was used. [e] In this case, the olefin was charged in one portion. [f] The yields and ee's described in parentheses are obtained at the end of the fifth cycle.

addition of olefin to the reaction mixture is warranted, except in the case of *trans*-stilbene to keep the availability of the olefin at a bare minimum level to achieve higher ee.[26] Trisubstituted olefins were also dihydroxylated to the corresponding diol with higher ee's in the presence of tetraethylammonium acetate (TEAA) additive (Table 5, entries 4 and 5). This phenomenon substantiates that the hydrolysis of osmate ester, a pronounced slow process in the case of trisubstituted olefins, is accelerated with the addition of the additive to afford higher yield and ee. All these catalysts were reused for five cycles with almost consistent activity and enantioselectivity (Table 5, entry 8). Although similar ee's and yields were obtained using both the homogeneous and heterogeneous systems, the former system took a longer reaction time (20 h). Nevertheless, the use of a less toxic and nonvolatile osmium source, $K_2OsO_4{\cdot}2H_2O$, in combination with $Na_2WO_4{\cdot}2H_2O$ makes the catalytic system the most promising and

(26) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421.

**SCHEME 2. Catalytic Cycle in the LDH−PdOsW-Catalyzed Synthesis of Chiral Diols Using $H_2O_2$ as the Terminal Oxidant**



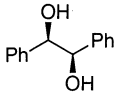
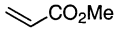
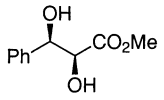
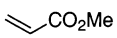
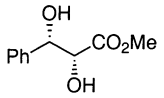
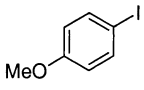
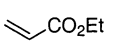
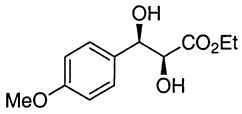
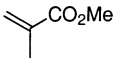
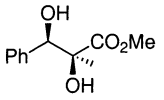
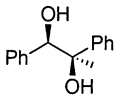

attractive candidate as such. Further, being water-soluble, the homogeneous composite catalyst could be easily separated from the organic product upon usual workup, but a higher molar ratio of ligand to osmium (L/Os = 3) is employed to obtain optimum ee's. In contrast, the use of equimolar ratio of ligand to osmium is sufficient to give the diols with excellent ee's in the heterogeneous catalytic system. This is attributed to the high binding ability of the heterogeneous osmium with the chiral ligand. The use of heterogeneous bifunctional catalyst makes the process more efficient in terms of higher activity and easier catalyst recovery by simple filtration over the homogeneous analogue.

This novel protocol described here realized chiral diols using the heterogeneous catalyst, NMM in substoichiometric amounts and a cheaper oxidant, $H_2O_2$ instead of NMO in stoichiometric amounts in currently practiced dihydroxylations. This methodology offers the diols with higher yields and ee's than the Kobayashi MC $OsO_4$/NMO system.[12] This process rivals the one employed by Bäckvall et al. using flavine, a biomolecule-induced homogeneous catalytic oxidation of NMM to NMO in dihydroxylation.[11] The flavine-based process encounters the problem of catalyst recovery and the use of $OsO_4$, flavine, and chiral ligand, as high as 2−6 mol %, whereas the basic advantage of our heterogeneous process is the easy recyclability of the bifunctional catalytic system, comprising 1 mol % of each component: osmium, tungsten, and chiral ligand. Even so, the homogeneous bifunctional system composed of 1 mol % of each component, osmium, tungsten, and 3 mol % chiral ligand, did give chiral diols with excellent yields and ee's. Further, these bifunctional catalysts offer 99% ee, as opposed to the 91% ee observed using flavine in the AD of *trans*-stilbene (Table 5, entry 6). It is very significant to note that our bifunctional systems, both homogeneous and heterogeneous, offer higher yields and excellent ee's in AD of cinnamate esters over the Sharpless methodology (Table 5, entries 7 and 8), which could be ascribed to the slow addition of both olefins and oxidant.

**2. Palladium−Osmium−Tungsten Catalytic System.** To generate the prochiral olefins in situ for AD reaction, the trifunctional catalyst LDH−PdOsW was examined in a tandem Heck−N-oxidation-AD, composed of a multicomponent system in a single-pot, while the continuous supply of NMO was ensured through the oxidative cycle of NMM in situ by $H_2O_2$ as described in Scheme 2.

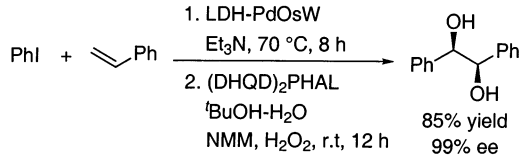
A mixture of iodobenzene, styrene, and $Et_3N$ in the presence of 1 mol % of LDH−PdOsW was stirred without

**TABLE 6. Synthesis of Chiral Diols Using Heterogeneous Multifunctional Catalyst (LDH−PdOsW)[a]**

| entry | aryl halide | olefin | product | yield (%) | ee (%)[b] | abs. config.[c] |
|---|---|---|---|---|---|---|
| 1 | PhI |  |  | 85 | 99 | R,R |
| 2[d] | | | | 82 | 99 | R,R |
| 3[e] | | | | 89 | 99 | R,R |
| 4 | PhI |  |  | 93 | 99 | 2S,3R |
| 5[f] | PhBr |  |  | 90 | 99 | 2R,3S |
| 6 |  |  |  | 93 | 99 | 2S,3R |
| 7 | PhI |  |  | 92 | 98 | 2S,3R |
| 8 | PhI |  |  | 90 | 47 | R,R |

[a] LDH−PdOsW (0.01 mmol), aryl halide (1 mmol), olefin (1 mmol), and $Et_3N$ (1.1 mmol) were stirred at 70 °C for 8−16 h. After completion of the Heck coupling, as monitored by TLC, the heating was stopped, and a mixture of $(DHQD)_2PHAL$ (0.01 mmol) and NMM (0.5 mmol) in $^tBuOH-H_2O$ (5:1, 5 mL) was added in one portion to the reaction flask. $H_2O_2$ (1.5 mmol) was then slowly added over a period of 15 h. [b] ee determined by chiral HPLC analysis. [c] The absolute configuration was determined by comparison of specific rotations with literature values. [d] After fifth cycle. [e] $Na_2PdCl_4-K_2OsO_4{\cdot}2H_2O-Na_2WO_4{\cdot}2H_2O$. [f] $(DHQ)_2PHAL$ is used as a ligand.

**SCHEME 3. Synthesis of Chiral Diols Using Heterogeneous Multifunctional Catalyst**




solvent at 70 °C for 8 h. The use of acetonitrile solvent is recommended for the solid substrates. At this stage, the heating was stopped, and to this was added a mixture of $(DHQD)_2PHAL$ (1 mol %) and NMM in $^tBuOH-H_2O$ (5:1). Subsequently, $H_2O_2$ was slowly added over a period of 12 h to afford the desired diol in 85% yield with 99% ee (Scheme 3).

As shown in Table 6, various chiral diols were obtained in good yields with higher ee's using the trifunctional heterogeneous catalyst. The methodology described here uses bulk chemicals such as styrene and acrylates as starting materials to prepare prochiral substrates, stilbenes, and cinnamates in situ and those upon dihydroxylation gives chiral diols in a single-pot. The reaction mediated by $Na_2PdCl_4-K_2OsO_4-Na_2WO_4$ system in homogeneous medium is slow and time-consuming (Table 6, entry 3) similar to the one observed in the bifunctional catalysis.

Next, we applied the present method for the synthesis of chiral diols via trisubstituted olefins and subsequent AD in a single pot. Using methyl methacrylate for Heck coupling with iodobenzene, a complete conversion was observed within 5 h, generating trisubstituted olefin, which was in turn subjected to AD under identical conditions described above with an addition of additive to give chiral diol with excellent ee (Table 6, entry 7).[9c,27] Similarly, trisubstituted stilbene and corresponding chiral diol were prepared by Heck coupling and AD in a single pot (Table 6, entry 8) in excellent yield, but ee is moderate. The ee's of these products are determined as their ketal derivatives.[27a] This forms one of the few examples making trisubstituted olefins directly by Heck coupling.[28]

The LDH−PdOsW was recovered quantitatively by simple filtration, while the chiral ligand was recovered by simple acid/base extraction (>95% recovery). The recovered catalyst was reused with the addition of the replenished chiral ligand (to makeup 1 mol %) at the appropriate stage and consistent activity was noticed even after the fifth cycle (Table 6, entry 2). In AD of methyl cinnamate, we obtained 99% ee with our heterogeneous multifunctional catalyst (entry 4, slow addition of $H_2O_2$) as against 87−88% ee's reported by Sharpless and others. It is significant to note a higher ee for the AD of methyl cinnamate was obtained, despite availability of all the olefin from the beginning of the reaction.

It is well documented in the literature that the bases or less often acids are used in the dihydroxylation reactions for hydrolysis of osmate esters.[27] Introduction of additives and/or slow addition of olefin or oxidant to the reaction mixture indeed accelerates the hydrolysis

(27) AD of trisubstituted olefins: (a) Rosini, C.; Scamuzzi, S.; Focati, M. P.; Salvadori, P. *J. Org. Chem.* **1995**, *60*, 8289. (b) Mehltretter, G. M.; Dobler, C.; Sundermeier, U.; Beller, M. *Tetrahedron Lett.* **2000**, *41*, 8083. (c) Battaglia, A.; Barbaro, G.; Giorgianni, P.; Guerrinni, A.; Bertucci, C.; Geremia, S. *Chem. Eur. J.* **2000**, *6*, 3551.

(28) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.

**TABLE 7. Factors Affecting ee in the AD Reaction of Methyl Cinnamate**

| entry | catalyst | additive | slow addition (h) | ee (%) |
|---|---|---|---|---|
| 1 | $K_2OsO_4 \cdot 2H_2O$ | | | 88 |
| 2 | LDH−Os | | | 94 |
| 3 | LDH−Os | $Et_3N \cdot HI$ | | 95 |
| 4 | LDH−PdOs | $Et_3N \cdot HI$ | | 95 |
| 5 | LDH−PdOsW | $Et_3N \cdot HI$ | 12 | 98 |
| 6 | LDH−PdOsW | $Et_3N \cdot HI$ | 15 | 99 |

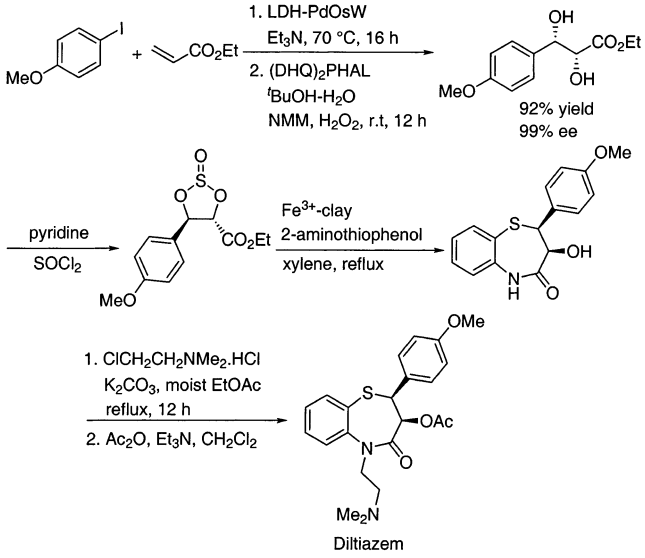
of the formed osmium monoglycolate to obtain higher ee in AD reactions.[26] We conducted separate experiments to study the effect of the support, $Et_3N.HI$ (a byproduct in the Heck reaction) and slow addition of oxidant on the ee in the AD of methyl cinnamate. As can be seen in the Table 7, the ee is enhanced from 88 to 94%, when an experiment was conducted with LDH−$OsO_4$ in place of $K_2OsO_4 \cdot 2H_2O$ using NMO as the oxidant in $H_2O$−$^t$BuOH (entries 1 and 2). It is ascribed to the basicity of the surface OH groups of LDH support, which accelerates the hydrolysis of the osmium monoglycolate ester. Next, we obtained 95% ee, when an experiment was conducted with LDH−$OsO_4$−$Et_3N \cdot HI$ or LDH−PdOs−$Et_3N \cdot HI$ and methyl cinnamate using NMO as the oxidant in $H_2O$−$^t$-BuOH (entries 3 and 4). The $Et_3N \cdot HI$ salt could accelerate the hydrolysis of the osmium monoglycolate complex to subdue the second cycle as was done by tetraethylammonium acetate (TEAA) additive, which is known for faster rates and higher ee. When, $H_2O_2$ was slowly added over a period of 12−15 h to a reaction mixture composed of LDH−OsW, methyl cinnamate, $Et_3N \cdot HI$, and NMM in $H_2O$−$^t$BuOH, a chiral diol was obtained with 98−99% ee.

Thus, these results unambiguously demonstrate that the present system composed of new variants such as LDH support, $Et_3N \cdot HX$ and slow addition of $H_2O_2$ facilitates the hydrolysis of osmium monogylcolate ester to subdue the formation of bisglycolate ester[5d] to achieve higher ee's as described in Tables 6 and 7.

**Synthetic Applications of Trifunctional Catalyst.** The chiral diols of cinnamates thus obtained with higher ee's (99%) and free from osmium (even in the crude product) as indicated by AAS and SEM−EDX in the AD reactions mediated by the trifunctional heterogeneous catalyst are directly used to make diltiazem and taxol side chain without recrystallization.

**Diltiazem.** Diltiazem, a typical calcium antagonist that has been used throughout the world as a remedy for angina and hypertension,[29,30] was synthesized as described in Scheme 4. Among the four possible stereoisomers of diltiazem, only the (+)-(2*S*,3*S*)-isomer exhibits potent coronary vasodilating activity. Synthesis of a (−)-*trans*-methyl glycidate, a key intermediate for the diltiazem, is mainly manufactured by the enzymatic kinetic resolution of the *trans*-methyl glycidate.[30g] However, there is an inherent drawback in the kinetic resolution, since the maximum yield of one enantiomer could not exceed 50%.

**SCHEME 4**




The crude chiral diol [ethyl (2*R*,3*S*)-2,3-dihydroxy-3-(4-methoxyphenyl)propionate] with 99% ee was obtained by a similar protocol using $(DHQ)_2PHAL$ ligand. The crude product, which does not show even traces of osmium by SEM−EDX and AAS was purified by column chromatography to remove other organic impurities. The chiral diol was converted to the corresponding sulfite and subsequently upon reaction with 2-aminothiophenol in the presence of $Fe^{3+}$-exchanged clay in xylene at 138 °C yields a cyclic lactam. *N*-alkylation, followed by acylation of lactam gave diltiazem [(+)-(2*S*,3*S*)-isomer] in 37% overall yield (Scheme 4). It is significant to note that $Fe^{3+}$-exchanged clay was used for this purpose as a new variant to the conventional acid catalysts to obtain quantitative yields.

**Taxol Side Chain.** The Taxol side chain was also synthesized using the LDH−PdOsW-catalyzed multicomponent coupling reaction as the key step as described in the Scheme 5. Taxol,[31] isolated from the bark of yew species, is considered to be the most promising cancer chemotherapeutic agent and has been approved for the treatment of metastatic carcinoma of the ovary. Attachment of the C-13 side chain to the baccatin III[32] nucleus is the key synthetic strategy for Taxol. Since the presence of this side chain has proved to be essential for the biological activity of Taxol, the development of short and practical synthetic routes for phenylisoserine derivatives, which are adaptable for industrial-scale production, has become very important.[33]

Sharpless et al. developed a process for the Taxol side chain through AD of methyl cinnamate that led to 23% overall yield, but the diol needs to be recrystallized to

(29) Nagao, T.; Sato, M.; Nakajima, H.; Kiyomoto, A. *Chem. Pharm. Bull.* **1973**, *21*, 92.

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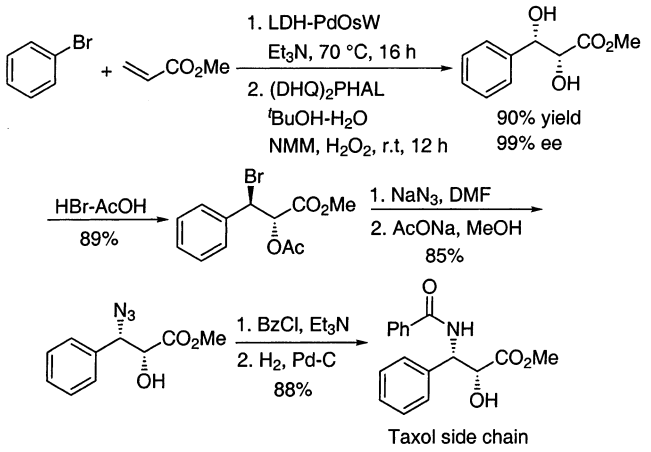
**SCHEME 5**




enrich the ee.[8c] As the trifunctional heterogeneous catalyst in the present case afforded the diol with 99% ee and without traces of osmium (Table 6, entry 5), it was directly used after column chromatography in the synthesis of Taxol side chain starting from bromobenzene and methyl acrylate as shown in Scheme 5. The treatment of methyl 2,3-dihydroxy-3-phenylpropionate with HBr−AcOH yields bromo acetate, which in turn reacts with $NaN_3$ in DMF followed by deacetylation with NaOAc in MeOH to afford azido alcohol.[34] Benzoylation followed by hydrogenation of azido alcohol gave the (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine methyl ester in 67% overall yield.

Both the homogeneous and heterogeneous bifunctional and trifunctional catalysts comprising of Pd/Os and W, performed Heck coupling, N-oxidation, and AD reactions exhibiting their own characteristic features in the diversified multifunctional activities without loosing their identity. These results substantiate the retention of coordination geometries of metal complexes in their monomeric form as supported by IR, UV−DRS, and XPS data of the heterogeneous catalysts and rule out the formation of bi- or tri-heterometallic species during the exchange process and dihydroxylation reaction. Further, the higher ee's obtained using a chiral ligand, $(DHQD)_2$-PHAL of the large dimension substantiate the location of $OsO_4^{2-}$ on the surface of LDH only, as the diffusion of the chiral ligand to interact with the $OsO_4^{2-}$ located in a very small interlamellar space, 3 Å of LDH, is very remote. The XRD data indeed confirms the location of $OsO_4^{2-}$ on the edge position of layered double hydroxides.

The large positive electric potential of the exchanged catalyst surface induces an enrichment of cooxidant close to the surface. Similarly, the olefin and aryl halide also build up their concentrations close to the surface as they have a high adsorption coefficient on the support surface. Apart from this, spatial organization and electrical shielding[16b] are responsible for the superior performance of the exchanged catalysts over the homogeneous osmium catalysts. This result is in consonance with LDH−$WO_4$ catalyzed oxidative bromination[16d] and ionic polymer supported osmium tetraoxide in achiral dihydroxylation.[35]

**C. Heterogeneity.** Several experiments were conducted to understand the stability and heterogeneity of the trifunctional catalysts. It was found that the Heck olefination occurs predominantly on the surface, although, there is a leaching of palladium in minor quantities from the heterogeneous catalyst.[36] However, the osmium and W oxides on the LDH matrix remain bound throughout the reaction. These results are in good agreement with the earlier results.[13b,14]

The plausible mechanistic path for the Heck coupling, AD, and N-oxidation mediated by trifunctional catalyst composed of Pd, Os, and W is depicted in Scheme 2. The Heck coupling and AD reaction likely follows an identical path.[5d,13a,36] The peroxo species generated from tungstate and $H_2O_2$ rapidly recycle the NMM to NMO, which in turn reoxidizes $Os^{VI}$ to $Os^{VIII}$.

## Conclusion

A single-pot biomimic synthesis of chiral diols mediated by the recyclable bifunctional catalysts composed of $OsO_4^{2-}$−$WO_4^{2-}$ and trifunctional catalysts comprising $PdCl_4^{2-}$−$OsO_4^{2-}$ −$WO_4^{2-}$ species both in the homogeneous phase and embedded on a matrix of the layered double hydroxides to unfold a low cost process is described. This protocol provides the desired prochiral olefins and NMO in situ from cheaper precursors for the synthesis of chiral vicinal diols to minimize the unit operations as exemplified with the synthesis of diltiazem and Taxol side chain. Dispensing the usual protocol of isolation and purification of the intermediates, the multifunctional catalyst triggers the reaction to obtain the chiral diols in one pot. The oxidant, $H_2O_2$, employed here in place of NMO is environmentally acceptable as the only byproduct is water. More interestingly, even the water produced from $H_2O_2$ during the N-oxidation is consumed in the dihydroxylation reaction to mark the highest atom economy in the production of chiral diols. The possible large-scale synthesis of diols employing this catalytic system using $H_2O_2$ as an oxidant directed to minimize the solid waste effluent is addressed. The simple procedure, easy recovery, and reusable catalytic systems are expected to contribute to the development of benign chemical processes and products.

## Experimental Section

**General Methods.** IR spectra for samples as KBr pellets were recorded on an FTIR spectrometer. Diffuse reflectance UV spectra for samples as KBr pellets were recorded on a UV−Vis spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded on a 200 MHz spectrometer. Chemical shifts ($\delta$) are reported in ppm, using TMS and $CDCl_3$ as internal standards for $^1H$ NMR and $^{13}C$ NMR, respectively. X-ray powder diffraction (XRD) data were collected on a diffractometer using Cu Kα radiation

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($\lambda$ = 1.5405 Å). X-ray photoemission spectra were recorded with a dual anode (Mg and Al) apparatus using the Mg K$\alpha$ anode. The pressure in the spectrometer was about $10^{-9}$ Torr. For energy calibration we have used the carbon 1s photoelectron line. The carbon 1s binding energy was taken to be 285.0 eV. Spectra were deconvoluted using Sun Solaris based Vision 2 curve resolver. The location and the full width at half-maximum (fwhm) for a species was first determined using the spectrum of a pure sample. The location and fwhm of products, which were not obtained as pure species, were adjusted until the best fit was obtained. Symmetric Gaussian shapes were used in all cases. Binding energies for identical samples were, in general, reproducible to within ±0.1 eV. Specific surface areas are calculated from BET nitrogen isotherms determined at −196 °C on samples degassed at 250 °C for 12 h before the experiment. SEM−EDX (scanning electron microscopy−energy-dispersive X-ray analysis) was performed. High performance liquid chromatography (HPLC) was performed using the following apparatus: SHIMADZU LC-10AT (liquid Chromatograph), SHIMADZU SPD-10A (UV detector), and SHIMADZU C-R6A Chromatopac. ACME silica gel (100−200 mesh) was used for column chromatography and thin-layer chromatography was performed on Merck precoated silica gel 60-$F_{254}$ plates. Optical rotations were obtained on a JASCO P-1020 polarimeter and reported as follows: $[\alpha]^{\text{temperature}}_{\text{wavelength}}$ (concentration ($c$ = g/100 mL), and solvent). Slow addition of olefins was carried out using a syringe pump.

$K_2OsO_4 \cdot 2H_2O$, $MgCl_2 \cdot 6H_2O$, $AlCl_3 \cdot 6H_2O$, TEAA, $(DHQD)_2$-PHAL, $(DHQ)_2$PHAL, and NMO were purchased from a commercial supplier. Allyl 1-naphthyl ether and ethyl (4-methoxyphenyl) cinnamate were prepared while the other olefins were purchased from a commercial supplier. All the other solvents and chemicals were obtained from commercial sources and used with further purification.

**Preparation of Catalysts.** The preparation of LDH (Mg−Al−Cl) was based on literature procedure.[19b]

**LDH−OsW.** LDH (1 g) was suspended in 100 mL of aqueous solution containing $K_2OsO_4 \cdot 2H_2O$ and $Na_2WO_4 \cdot 2H_2O$ (0.4 mmol each) and stirred at 25 °C for 12 h under nitrogen atmosphere. The solid catalyst was filtered, washed thoroughly with 500 mL of water, and vacuum-dried to obtain 1.172 g of LDH−OsW (0.34 mmol $g^{-1}$ each of Os and W).

**Resin−OsW.** Resin was obtained by quaternization of triethylamine (2.1 mL, 21 mmol) with 1 g of chloromethylated styrene−divinylbenzene copolymer (Merrifield resin, capacity ~2.1 mequiv/g) in chloroform (20 mL) under reflux for 24 h. Quaternary ammonium resin (1 g) was suspended in 100 mL of aqueous solution containing $K_2OsO_4 \cdot 2H_2O$ and $Na_2WO_4 \cdot 2H_2O$ (0.4 mmol each) and stirred at 25 °C for 12 h under nitrogen atmosphere. The solid catalyst was filtered, washed thoroughly with 500 mL of water, and vacuum-dried to obtain resin-OsW.

**Silica−OsW.** Modified silica was obtained by quaternization of triethylamine (0.7 mL, 7 mmol) with bromopropylsilica (capacity 0.7 mequiv/g) in chloroform (20 mL) under reflux for 24 h. Quaternary ammonium silica (1 g) was suspended in 100 mL of aqueous solution containing $K_2OsO_4 \cdot 2H_2O$ and $Na_2WO_4 \cdot 2H_2O$ (0.4 mmol each) and stirred at 25 °C for 12 h under nitrogen atmosphere. The solid catalyst was filtered, washed thoroughly with 500 mL of water, and vacuum-dried to obtain Silica-OsW.

**LDH−PdOsW.** LDH (1 g) was suspended in 100 mL of aqueous solution containing $Na_2PdCl_4$, $K_2OsO_4 \cdot 2H_2O$, and $Na_2WO_4 \cdot 2H_2O$ (0.3 mmol each) and stirred at 25 °C for 12 h under nitrogen atmosphere. The solid catalyst was filtered, washed thoroughly with 500 mL of water, and vacuum-dried to obtain 1.181 g of LDH−PdOsW (0.25 mmol $g^{-1}$ each of Pd, Os, and W).

**Asymmetric Dihydroxylation of Olefins Using LDH−OsW with Slow Addition of Olefin and $H_2O_2$.** Heterogeneous bifunctional LDH−OsW (0.01 mmol) or a homogeneous composite mixture of $K_2OsO_4 \cdot 2H_2O$ (3.68 mg, 0.01 mmol), $Na_2WO_4 \cdot 2H_2O$ (3.29 mg, 0.01 mmol), $(DHQD)_2$PHAL (0.03 mmol, 23 mg), and NMM (0.5 mmol) were taken in a round-bottomed flask containing $^t$BuOH−water (5:1, 5 mL) and stirred at room temperature for 20 min. To this mixture were added an olefin (1 mmol) and $H_2O_2$ (1.5 mmol) over a period of 12 h for LDH−OsW and 20 h for $K_2OsO_4 \cdot 2H_2O$−$Na_2WO_4 \cdot 2H_2O$ using separate syringe pumps. After the addition was complete, the reaction mixture was stirred for another 2 h. Toluene was added to the reaction mixture to get the phase separation, and the aqueous phase was extracted with toluene (2 × 5 mL). The organic phase was washed with 1 N HCl to recover the chiral ligand. The organic solvent was removed, and the crude material was chromatographed on silica gel to afford the corresponding *cis*-diol.

**General Procedure for the Synthesis of Chiral Diols Using LDH−PdOsW.** LDH−PdOsW (40 mg, 0.01 mmol), aryl halide (1 mmol), olefin (1 mmol), and $Et_3N$ (111 mg, 1.1 mmol) were introduced into a round-bottomed flask and stirred at 70 °C for 8−16 h under nitrogen atmosphere. After completion of the Heck coupling, as monitored by TLC, the heating was stopped and the reaction was allowed to reach room temperature. A mixture of $(DHQD)_2$PHAL (7.8 mg, 0.01 mmol) and NMM (50 mg, 0.5 mmol) in $^t$BuOH−$H_2O$ (5:1, 5 mL) was added in one portion to the reaction flask under stirring. $H_2O_2$ (169 $\mu$L, 30% aqueous, 1.5 mmol) was then slowly added over 15 h using a syringe pump. After the addition was complete, the stirring was continued for an additional 1 h and the catalyst was filtered and washed with ethyl acetate (10 mL). The combined filtrates were extracted with 1 N HCl (2 × 5 mL) to recover the chiral ligand from the aqueous layer. The resulting organic phase was further washed with brine solution (5 mL) and the solvent was removed. The crude material thus obtained was chromatographed on silica gel using hexane/ethyl acetate (2:1) as an eluant to afford the corresponding *cis*-diol.

**Preparation of *cis*-(+)-3-(Acetyloxy)-2,3-dihydo-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one Hydrochloride (Diltiazem Hydrochloride).** LDH−PdOsW (0.4 g, 0.1 mmol), 4-iodoanisole (10 mmol), ethyl acrylate (10 mmol), and $Et_3N$ (11 mmol) were stirred at 70 °C for 16 h under nitrogen atmosphere. After completion of the Heck coupling, the heating was stopped and the reaction was allowed to reach room temperature. A mixture of $(DHQ)_2$PHAL (78 mg, 0.1 mmol) and NMM (0.5 g, 5 mmol) in $^t$BuOH−$H_2O$ (5:1, 50 mL) was added in one portion to the reaction flask under stirring. $H_2O_2$ (30% aqueous, 15 mmol) was then slowly added over 15 h using a syringe pump. After the addition was complete, the stirring was continued for an additional 1 h and the catalyst was filtered and washed with ethyl acetate (100 mL). After removal of the solvent, the thus obtained crude material was chromatographed on silica gel using hexane/ethyl acetate (1:1) as an eluant to afford ethyl (2*R*,3*S*)-2,3-dihydroxy-3-(4-methoxyphenyl)propionate (92% yield): $[\alpha]^{25}_D$ 5.98 (*c* 1.0, $CHCl_3$) [lit.[37] $[\alpha]^{25}_D$ 6.0 (*c* 0.84, $CHCl_3$)]; $^1$H NMR $\delta$ 1.29 (t, $J$ = 7.3 Hz, 3H), 2.75 (brs, 2H), 3.80 (s, 3H), 4.23 (q, $J$ = 7.3 Hz, 2H), 4.34 (dd, $J$ = 3.3, 6.6 Hz, 1H), 4.89 (dd, $J$ = 3.3, 6.6 Hz, 1H), 6.90 (d, $J$ = 8.6 Hz, 2H), 7.36 (d, $J$ = 8.6 Hz, 2H); HPLC (Daicel Chiralcel OJ, 10% $^i$PrOH in hexane, flow rate 1.0 mL/min) $t_R$ = 23.2 (major), $t_R$ = 26.0 (minor).

The diol (1.2 mmol) was dissolved in dry pyridine (2 mL) under argon. The reaction mixture was cooled to 0 °C, and freshly distilled thionyl chloride (1.3 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h and poured onto crushed ice containing dilute HCl. The reaction mixture was extracted with ether, washed with dilute HCl, aqueous $NaHCO_3$, and brine, dried ($Na_2SO_4$), and evaporated under reduced pressure to give a pale yellow oil that was chromatographed over silica gel to furnish 4(*S*)-(*p*-methoxyphenyl)-5(*R*)-(carboxyethyl)-1,3-dioxathiolane 2-oxide (98% yield).

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A flame-dried two-necked 25 mL round-bottomed flask was charged with cyclic sulfite (1 mmol), $Fe^{3+}$−clay (100 mg), and dry xylene (5 mL) and stirred under nitrogen. Freshly distilled 2-aminothiophenol (0.9 mmol) was added dropwise, and the reaction mixture was refluxed for 12 h. The crude compound was chromatographed to get the *cis*-(+)-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(*5H*)-one (50% yield). The hydroxy lactam (0.54 mmol) was dissolved in ethyl acetate (5 mL), and 2-(dimethylamino)ethyl chloride hydrochloride (0.694 mmol) was added followed by the addition of finely ground $K_2CO_3$ (2.16 mmol) and a drop of water. The heterogeneous mixture was stirred at reflux for 12 h. The solvent was removed, and the crude product was chromatographed to obtain N-alkylated product (88%). The N-alkylated lactam (0.317 mmol), $Ac_2O$ (1 mmol), $Et_3N$ (2 mmol), and DMAP (0.03 mmol) taken in $CH_2Cl_2$ (5 mL) were heated at reflux under $N_2$ for 3 h. The mixture was poured into ice−water, and brine was added. The organic layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$ (10 mL). The combined organic layers were washed with 5% $NH_4OH$ (5 mL) solution, dried ($Na_2SO_4$), and evaporated. The residue was dissolved in MeOH (2 mL) and treated with anhydrous HCl until the pH was 2. Ether (3 mL) was added to the resulting solution. The precipitated solids were collected by filtration and washed with 10% MeOH−ether to afford diltiazem hydrochloride (92% yield): $[\alpha]^{25}_D$ 102.0 (*c* 1.0, MeOH) [lit.[30c] $[\alpha]^{25}_D$ 102.0 (*c* 1.0, MeOH)]; $^1$H NMR $\delta$ 1.90 (*s*, 3H, $COCH_3$), 2.85−2.94 (dd, $J$ = 4.9 Hz, 6H, $NCH_3$), 3.20−3.58 (m, 2H, $NCH_2$), 3.83 (s, 2H, $OCH_3$), 4.37−4.62 (m, 2H, $NCH_2$), 5.02 (d, $J$ = 7.8 Hz, 1H, $CHOCOCH_3$), 5.13 (d, $J$ = 7.8 Hz, 1 H, SCHAr), 6.90−7.73 (m, 8H, ArH); MS *m*/*z* 415 ($M^+ + 1$).

**Preparation of (2*R*,3*S*)-*N*-Benzoyl-3-phenylisoserine Methyl Ester (Taxol Side Chain).** LDH−PdOsW (0.4 g, 0.1 mmol), bromobenzene (10 mmol), methyl acrylate (10 mmol), and $Et_3N$ (11 mmol) were stirred at 70 °C for 16 h under nitrogen atmosphere. After completion of the Heck coupling, the heating was stopped and the reaction was allowed to reach room temperature. A mixture of $(DHQ)_2PHAL$ (78 mg, 0.1 mmol) and NMM (0.5 g, 5 mmol) in $^t$BuOH−$H_2O$ (5:1, 50 mL) was added in one portion to the reaction flask under stirring. $H_2O_2$ (30% aqueous, 15 mmol) was then slowly added over 15 h using a syringe pump. After the addition was complete, stirring was continued for an additional 1 h and the catalyst was filtered and washed with ethyl acetate (100 mL). After removal of the solvent, the thus obtained crude material was chromatographed on silica gel using hexane/ethyl acetate (1:1) as an eluant to afford methyl (2*R*,3*S*)-2,3-dihydroxy-3-phenylpropionate (90% yield): $[\alpha]^{25}_D$ 10.71 (*c* 1.0 $CHCl_3$) [Lit.[33b] $[\alpha]^{25}_D$ 10.70 (*c* 1.0, $CHCl_3$)]; $^1$H NMR $\delta$ 3.32 (br, 2H), 3.81 (s, 3H), 4.36 (d, $J$ = 2.8 Hz, 1H), 5.01 (d, $J$ = 2.8 Hz,1H), 7.36 (m, 5H); $^{13}$C NMR $\delta$ 52.8, 74.4, 74.7, 126.2, 128.1, 128.4, 139.9, 173.1; HPLC (Daicel Chiralcel OJ, 10% $^i$PrOH in hexane, flow rate 1.0 mL/min) $t_R$ = 19.1 (major), $t_R$ = 26.7 (minor).

The diol (2 mmol) was placed in a 25 mL single-necked round-bottomed flask followed by adddition of 2.9 mL of 30 wt % HBr−AcOH (13.2 mmol). The reaction mixture was heated at 45 °C for 30 min. Upon quenching with $NaHCO_3$ solution and extraction with ether, the methyl (2*R*,3*S*)-2-acetoxy-3-bromo-3-phenylpropionate was obtained with 96% yield.

The acetoxy bromoester (1 mmol) and $NaN_3$ (1.5 mmol) in DMF (5 mL) were stirred at 50 °C for 12 h. After completion of the reaction, the solvent was removed, suspended in methanol, and filtered through a pad of silica gel. The filtrate was stirred with AcONa (10 mol %) for 12 h to afford methyl (2*R*,3*S*)-3-azido-2-hydroxy-3-phenylpropionate (85% yield).

A mixture of azido alcohol (0.5 mmol), benzoyl chloride, (1 mmol), $Et_3N$ (2 mmol), and DMAP (0.03 mmol) in 5 mL of ethyl acetate was stirred at room temperature for 4 h, whereupon 1.4 mL of methanol was added. After being stirred for 3 h, the reaction mixture was treated with 10 mg of 10% Pd/C and stirred for 2 days under hydrogen atmosphere. Upon evaporation of the solvent, the crude product was purified by column chromatography to give (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine methyl ester (92% yield): $[\alpha]^{25}_D$ −48.7 (*c* 1.0 MeOH) [lit.[33a] $[\alpha]^{25}_D$ −48.0 (*c* 1.0, MeOH)]; $^1$H NMR $\delta$ 2.98 (d, 1H), 3.75 (s, 3H), 4.67 (m, 1H) 5.58 (dd, 1H), 7.06 (d, 1H), 7.20−7.56 (m, 8H), 7.80 (d, 2H); $^{13}$C NMR $\delta$ 52.3, 55.6, 73.2, 127.3, 128.2, 129.0, 132.1, 134.6, 137.0, 167.1, 172.5; MS *m*/*z* 300 ($M^+ + 1$), 281 ($M^+ - H_2O$).

**Characterization of Diols. 1-Phenyl-1,2-ethanediol (Table 5, entry 1):**[13b] $^1$H NMR $\delta$ 2.04 (brs, 1H), 2.46 (brs,-1H), 3.63 (dd, 1H, $J$ = 8.2, 11.4 Hz), 3.72 (dd, 1H, $J$ = 3.6, 11.4 Hz), 4.79 (dd, 1H, $J$ = 3.6, 8.2 Hz), 7.28−7.34 (m, 5H); $^{13}$C NMR $\delta$ 68.0, 74.7, 126.0, 128.0, 128.5, 140.4; HPLC (Daicel Chiralcel OD-H, 5% $^i$PrOH in hexane, flow rate 0.5 mL/min) $t_R$ = 34.7 (major), $t_R$ =38.9 (minor).

**2-Phenyl-1,2-propanediol (Table 5, entry 2):**[13b] $^1$H NMR $\delta$ 1.50 (s, 3H), 3.15 (brs, 2H), 3.60 (d, 1H, $J$ = 11.2 Hz), 3.75 (d, 1H, $J$ = 11.2 Hz), 7.24−7.44 (m, 5H); $^{13}$C NMR $\delta$ 26.0, 70.9, 74.8, 125.0, 127.1, 128.4, 145.0; HPLC (Daicel Chiralcel OJ, 10% $^i$PrOH in hexane, flow rate 1.0 mL/min) $t_R$ = 9.2 (minor), $t_R$ =12.5 (major).

**1-Phenyl-1,2-propanediol (Table 5, entry 3):**[13b] $^1$H NMR $\delta$ 0.97 (d, 3H, $J$ = 6.3 Hz), 2.65 (brs, 2H), 3.79 (dq, 1H, $J$ = 6.3, 7.6 Hz), 4.28 (dd, 1H, $J$ = 7.6 Hz), 7.25−7,3.4 (m, 5H); $^{13}$C NMR $\delta$ 18.6, 72.1, 79.4, 126.8, 127.9, 128.3, 141.0; HPLC (Daicel Chiralcel OD, 5% $^i$PrOH in hexane, flow rate 1.0 mL/min) $t_R$ = 15.0 (major), $t_R$ =16.28 (minor).

**2-Methyl-1-phenyl-1,2-propanediol (Table 5, entry 4):**[13b] $^1$H NMR $\delta$ 1.03 (s, 3H), 1.15 (s, 3H), 2.78 (brs, 2H), 4.43 (d, 1H), 7.23−7.35 (m, 5H); $^{13}$C NMR $\delta$ 23.4, 26.4, 73.4, 80.7, 127.4, 127.6, 127.8, 140.6; HPLC (Daicel Chiralcel OD, 2.5% $^i$PrOH in hexane, flow rate 1.0 mL/min) $t_R$ = 22.8 (major), $t_R$ = 27.1 (minor).

**1-Phenyl-1,2-cyclohexanediol (Table 5, entry 5):**[13b] $^1$H NMR $\delta$ 1.35−1.89 (m, 9H), 2.51 (s, 1H), 3.96 (dd, 1H, $J$ = 4.7, 11.1 Hz), 7.21−7.53 (m, 5H); $^{13}$C NMR $\delta$ 21.1, 24.3, 30.9, 38.5, 74.5, 75.7, 125.1, 127.0, 128.5, 146.3; HPLC (Daicel Chiralcel OJ, 5% $^i$PrOH in hexane, flow rate 1.0 mL/min) $t_R$ = 17.6 (minor), $t_R$ = 21.9 (major).

**1,2-Diphenyl-1,2-ethanediol (Table 6, entry 1):**[13b] $^1$H NMR $\delta$ 2.73 (brs, 2H), 4.69 (s, 2H), 7.09−7.22 (m, 10H); $^{13}$C NMR $\delta$ 79.1, 126.9, 127.9, 128.1, 139.8; HPLC (Daicel Chiralcel OJ, 10% $^i$PrOH in hexane, flow rate 1.0 mL/min) $t_R$= 12.1 (minor), $t_R$ = 13.3 (major).

**Methyl 2,3-dihydroxy-3-pheylpropionate (Table 6, entry 5):** $^1$H NMR $\delta$ 3.32 (br, 2H), 3.81 (s, 3H), 4.36 (d, $J$ = 2.8 Hz, 1H) 5.01 (d, $J$ = 2.8 Hz, 1H), 7.36 (m, 5H); $^{13}$C NMR $\delta$ 52.8, 74.4, 74.7, 126.2, 128.1, 128.4, 139.9, 173.1; HPLC (Daicel Chiralcel OJ, 10% $^i$PrOH in hexane, flow rate 1.0 mL/min) $t_R$ = 19.1 (minor), $t_R$ = 26.7 (major).

**Ethyl 2,3-dihydroxy-3-(4-methoxyphenyl)propionate (Table 6, entry 6):** $^1$H NMR $\delta$ 1.29 (t, $J$ = 7.3 Hz, 3H), 2.75 (brs, 2H), 3.80 (s, 3H), 4.23 (q, $J$ = 7.3 Hz, 2H), 4.34 (dd, $J$ = 3.3, 6.6 Hz, 1H), 4.89 (dd, $J$ = 3.3, 6.6 Hz, 1H), 6.90 (d, $J$ = 8.6 Hz, 2H), 7.36 (d, $J$ = 8.6 Hz, 2H); HPLC (Daicel Chiralcel OJ, 10% $^i$PrOH in hexane, flow rate 1.0 mL/min) $t_R$ = 23.2 (major), $t_R$ = 26.0 (minor).

**Methyl 2,3-dihydroxy-2-methyl-3-phenylpropanoate (Table 6, entry 7):**[27c] $^1$H NMR $\delta$ 1.56 (s, 3H), 3.0 (d, 2H), 3.64 (s, 3H), 4.74 (d, 1H), 7.2−7.4 (m, 5H); $^{13}$C NMR $\delta$ 22.4, 52.5, 77.3, 78.0, 126.8, 128.1, 128.3, 139.1, 175.0; HPLC (Daicel Chiralcel OJ, 10% $^i$PrOH in hexane, flow rate 1.0 mL/min) $t_R$ = 20.04 (minor), $t_R$ = 20.96 (major).

**1-Methyl 1,2-Diphenyl-1,2-ethanediol (Table 6, entry 8):**[27a] $^1$H NMR $\delta$ 1.35 (s, 3H), 2.5 (d, 1H), 2.60 (s, 1H), 4.8 (d, 1H), 7.05−7.40 (m, 10H). A ketal derivative of the diol was made as described: To 15 mL $CHCl_3$, in a 100 mL round-bottomed flask, was added 0.29 mmol of diol, 0.1 mL of 2,2′-dimethoxypropane, and traces of 4-toluenesulfonic acid. After 3 h of reflux, the heat was removed and the reaction mixture was transferred to a separating funnel and washed subsequently with 10% aqueous $NaHCO_3$ and water. The organic

layer was dried over $Na_2SO_4$ and then concentrated to get 2,2′,4-trimethyl-4,5-diphenyl-1,3-dioxolane (95% yield): $^1$H NMR $\delta$ 7.4−7.2 (m, 10H), 4.96 (s, 1H), 1.72 (s, 3H), 1.62 (s, 3H), 1.25 (s, 3H); HPLC (Daicel Chiralcel OD, 2% $^i$PrOH in hexane, flow rate 0.5 mL/min) $t_R$ = 8.66 (minor), $t_R$ = 10.03 (major).

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