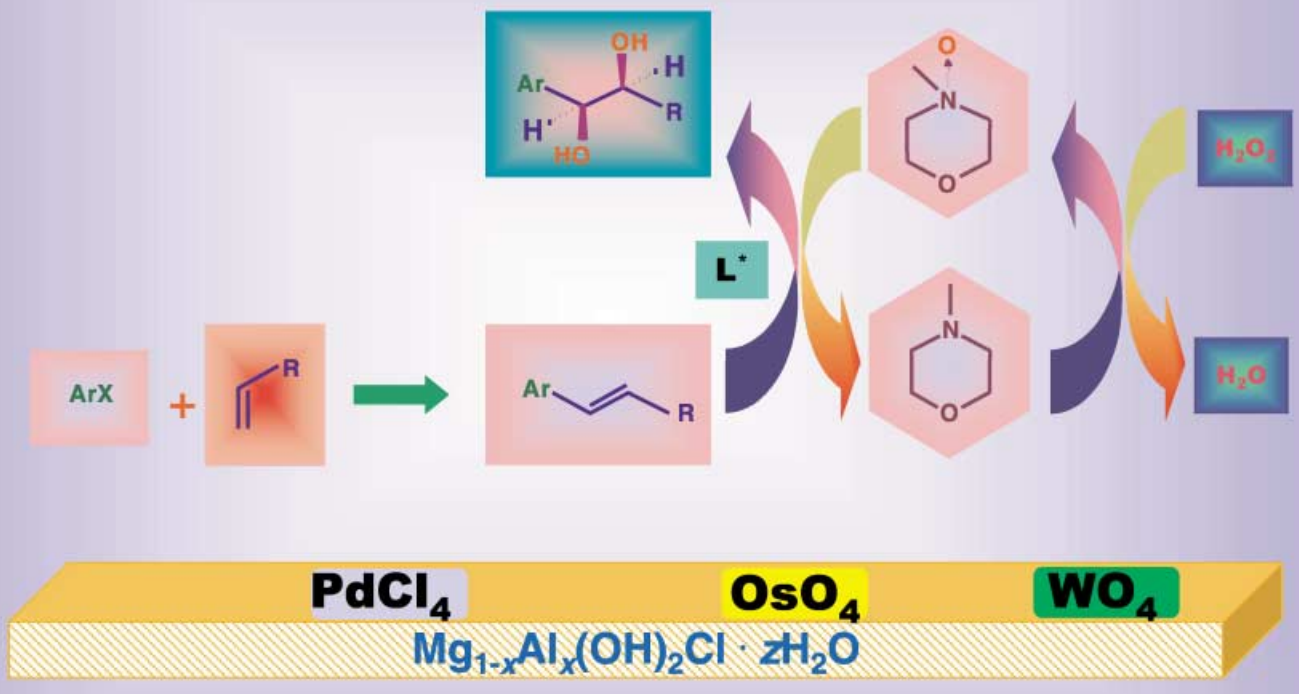
Unique biomimic multicomponent synthesis in a single pot ...



... with a trifunctional catalyst embedded in a single matrix.

For more information see the following pages.

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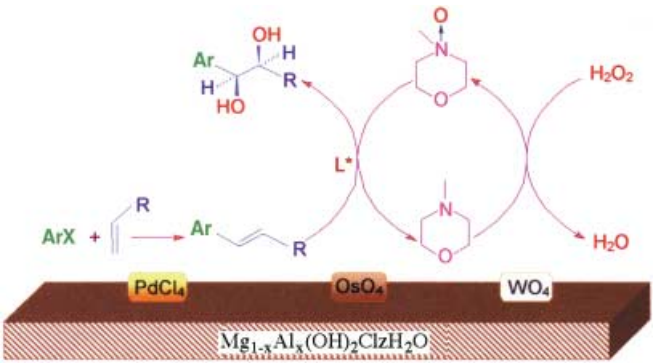
A Trifunctional Catalyst for the Synthesis of Chiral Diols**

Boyapati M. Choudary,* Naidu S. Chowdari, Sateesh Madhi, and Mannepalli L. Kantam

Many enzymes partake in the intricate construction of complex structures of fascinating stereochemistry from very small molecules in biological systems. The biomimic approach to realize the multistep reactions, composed of multicomponent systems in a single-pot synthesis[1, 2] has been confined to a few examples that include the synthesis of corrin and α-acylaminocarbonamides. Sharpless asymmetric dihydroxylation of olefins offers one of the most efficient methods for the preparation of chiral diols, the key intermediates for many biologically active compounds.[3–5] However, additional upstream operations are required to obtain the desired prochiral olefin, the substrate, and *N*-methylmorpholine *N*-oxide (NMO), the oxidant, employed in molar ratio in asymmetric dihydroxylation. We herein describe an unique single-pot biomimic synthesis of chiral diols mediated by a newly developed trifunctional solid catalyst consisting of active palladium, tungsten, and osmium species embedded in a single layered double-hydroxide matrix to provide the desired prochiral olefins and NMO in situ in a most economical way by Heck coupling and *N*-oxidation of *N*-methylmorpholine (NMM), respectively, for the asymmetric dihydroxylation in a low-cost process (Scheme 1).



Scheme 1. The catalytic cycle in the LDH-PdOsW-catalyzed synthesis of chiral diols using H_2O_2 as the terminal oxidant.

Layered double-hydroxides (LDHs) consist of alternating cationic $M^{II}_{1-x}M^{III}_x(OH)_2^{x+}$ and anionic $A^{n-}\cdot z\,H_2O$ layers.[6] The positively charged layers contain edge-shared metal M^{II} and M^{III} hydroxide octahedra, with charges balanced by A^{n-} ions located in the interlayer spacing or at edges of the lamellae. LDHs have recently received much attention in view of their potential as adsorbents, anion exchangers, and more importantly as catalysts.[7, 8] Small hexagonal LDH crystals of composition $Mg_{1-x}Al_x(OH)_2(Cl)_x\cdot z\,H_2O$ were synthesized following existing procedures ($x = 0.25$; the crystals are 50–100 nm with external surface area of $\sim 100\ m^2\,g^{-1}$).[6] The $PdCl_4^{2-}$ and OsO_4^{2-} ions in the form of Na_2PdCl_4 and K_2OsO_4, respectively, and OsO_4^{2-} and WO_4^{2-} ions as K_2OsO_4 and Na_2WO_4, respectively, are co-exchanged concomitantly onto chloride saturated LDH to obtain bifunctional catalysts, LDH-[$PdCl_4$, OsO_4] (abbreviated as LDH-PdOs) and LDH-[OsO_4, WO_4] (LDH-OsW), respectively. Finally, these bivalent anions are simultaneously exchanged onto a single LDH matrix to yield LDH-[$PdCl_4$,OsO_4,WO_4] (LDH-PdOsW) on interaction with the combined aqueous salt solution. X-ray powder-diffraction patterns of the initial LDH and of the exchanged catalysts hardly differ in the range $2\theta = 3–65°$. The observed basal spacings remain unchanged after the anion exchange, which indicates the position of divalent anions in edge positions of the LDH.

In the FT infrared (IR) spectra of these catalysts, broad absorption bands appear near 830–860 cm^{-1}, assigned to the vibrational asymmetric O=M=O (M = Os and/or W) stretching in contrast to the sharp bands at 819 cm^{-1} in K_2OsO_4 and 831, 857 cm^{-1} in the spectrum of Na_2WO_4. The observation of broad bands in the same region for the catalysts indicates that the osmate and tungstate units are unaffected by exchange onto the support but experience very weak interactions with the support. The Pd–Cl stretching band of the $PdCl_4^{2-}$ ion is observed at 335 cm^{-1} for catalysts LDH-PdOs and LDH-PdOsW. The diffuse reflectance UV/Vis spectra of the catalysts show broad bands with absorption maxima that indicate the presence of related divalent anions in trifunctional and bifunctional catalysts (253 nm WO_4^{2-}, 280 nm $PdCl_4^{2-}$, and 293 nm OsO_4^{2-}). No shift in absorption maxima for these multifunctional catalysts is observed, when compared to the spectra of the pure LDH-complexes (Figure 1). All these studies indicate the retention of the coordination geometries of the specific divalent anions anchored to the LDH matrix in their monomeric form. The Brunauer–Emmet–Teller (BET) surface areas of LDH-PdOs, LDH-OsW, and LDH-PdOsW are found to be 88, 60 and 68 $m^2\,g^{-1}$, respectively.

To understand the in-depth profile of the reactivity of the diversified reaction sequence, the bifunctional catalysts (LDH-PdOs and LDH-OsW) were evaluated in a tandem Heck-asymmetric dihydroxylation reaction and a simultaneous asymmetric dihydroxylation-*N*-oxidation reaction. The tandem Heck-dihydroxylation reaction involved stirring iodobenzene, styrene, and Et_3N at 70 °C for 8 h in the presence of 1 mol% of LDH-PdOs to obtain *trans*-stilbene. After completion of the reaction, as monitored by thin-layer chromatography (TLC), the heating was stopped and a mixture of 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine ($(DHQD)_2PHAL$; 1 mol%) and NMO in *t*BuOH/H_2O (5:1) was introduced and the mixture stirred at room temperature for 6 h to obtain the desired diol in 91% yield with 99% *ee* [Eq. (1)]. The Heck reaction[9] of styrene and iodobenzene in the presence of LDH-PdOs was carried out as above or in acetonitrile or water. The most convenient system to prepare prochiral olefin was the one without any solvent. The

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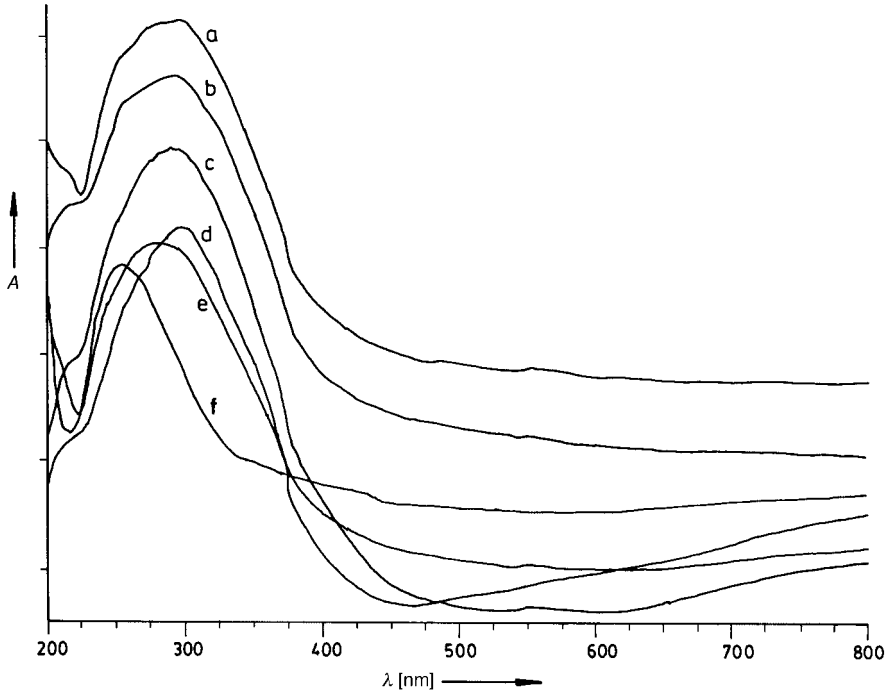
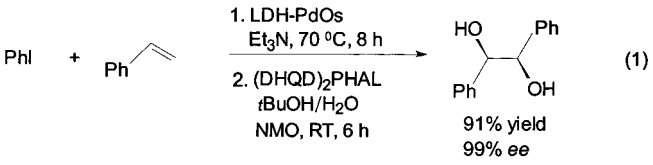


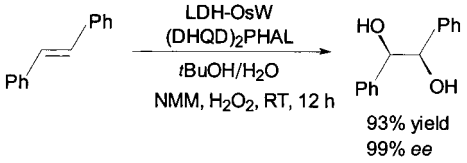
Figure 1. Diffuse-reflectance UV/Vis spectra of a) LDH-PdOsW, b) LDH-OsW, c) LDH-PdOs, d) LDH-Os, e) LDH-Pd, and f) LDH-W.



(1)

methodology described herein uses bulk chemicals such as styrene and acrylates as starting materials to prepare prochiral substrates, stilbenes, and cinnamates in situ and upon dihydroxylation gives chiral diols in a single-pot reaction (Table 1).

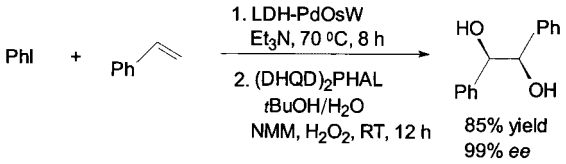
The bifunctional catalyst LDH-OsW was tested in the simultaneous asymmetric dihydroxylation of *trans*-stilbene and *N*-oxidation of NMM in the presence of H_2O_2. The H_2O_2 was added slowly over 12 h to a mixture of 1 mol% of LDH-OsW, $(DHQD)_2PHAL$, *trans*-stilbene, and NMM in *t*BuOH/H_2O (5:1), to afford the desired diol in 93% yield with 99% *ee* [Eq. (2)]. This novel method gave chiral diols by using



(2)

NMM in catalytic amounts and a cheaper oxidant H_2O_2, instead of the NMO currently used in stoichiometric amounts in asymmetric dihydroxylations. This process rivals the one employed by Bäckvall and co-workers, by using flavine, in a biomolecule-induced catalytic oxidation of NMM to NMO in a homogeneous asymmetric dihydroxylation.[4] The homogenous flavine-based process suffers from the problem of difficult catalyst recovery, while the basic advantage of our LDH-OsW process is the recyclability of the catalyst.

The trifunctional catalyst LDH-PdOsW was tested in a Heck-*N*-oxidation-asymmetric dihydroxylation, a multicomponent system in a single-pot reaction. The continuous supply of NMO was ensured in situ though the oxidative cycle of NMM by H_2O_2 as shown in Scheme 1. A mixture of iodobenzene, styrene, and Et_3N in the presence of 1 mol% of LDH-PdOsW was stirred without solvent at 70 °C for 8 h. The heating was stopped and a mixture of $(DHQD)_2PHAL$ (1 mol%) and NMM in *t*BuOH/H_2O (5:1) was added. Subsequently, H_2O_2 was added slowly over 12 h to afford the desired diol in 85% yield with 99% *ee* [Eq. (3)]. In all these multifunctional approaches [Eqs. (1)–(3)], the chiral diols are obtained in good yields with high enantioselectivities (Table 1). Employment of the cheaper raw materials and reduction of number of operations thus favorably influence the economics of the process.

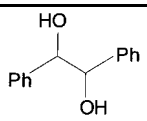
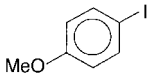
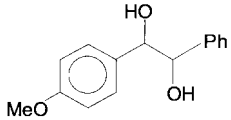
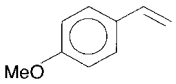
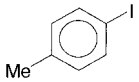
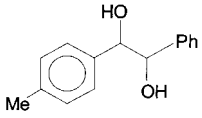
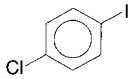
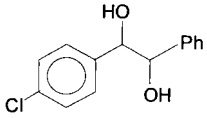
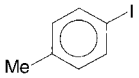
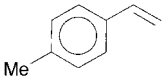
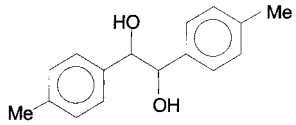
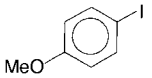
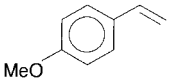
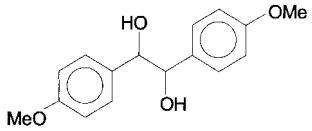
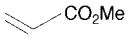
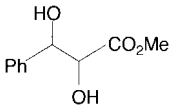
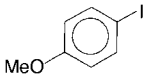
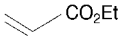
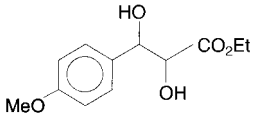


(3)

The LDH-PdOsW was recovered quantitatively by filtration while the chiral ligand was recovered by acid/base extraction (>95% recovery). The recovered catalyst was reused in the multicomponent reaction and following replenishment of the chiral ligand (to make-up 1 mol%) at the appropriate stage, consistent activity was noticed even after 5th cycle. When the reaction was conducted with filtrate obtained by washing of the catalyst with solvent, no product formation was observed. These results and others indicate that the Os and W oxides on the LDH matrix remained bound throughout the reaction, while Pd leached from the support into solution during the reaction and redeposited on the support at the end of the reaction.

The bifunctional and trifunctional catalysts comprising Pd, Os/W performed Heck coupling, *N*-oxidation, and asymmetric dihydroxylation reactions and demonstrated characteristic features of the metal centers in the diverse multifunctional activities of the catalysts. These results substantiate the retention of the coordination geometries of the metal complexes in their monomeric form, a proposal supported by IR and UV/DRS (DRS = diffuse reflectance spectroscopy) spec-

Table 1. The synthesis of chiral diols using heterogeneous multifunctional catalysts LDH-PdOs and LDH-PdOsW.[a]

Entry	Aryl halide	Olefin	Product	Method	Yield	*ee*[b]	Config.[c]
1	PhBr			A	90	99	*R*,*R*
2	PhI			A	91	99	*R*,*R*
3				B	85	99	*R*,*R*
4				A	95	99	*R*,*R*
5				B	85	99	*R*,*R*
6	PhI			A	94	99	*R*,*R*
7				B	88	99	*R*,*R*
8				A	93	99	*R*,*R*
9				B	91	99	*R*,*R*
10				A	90	97	*R*,*R*
11				B	89	97	*R*,*R*
12				A	91	99	*R*,*R*
13				B	86	99	*R*,*R*
14				A	89	99	*R*,*R*
15				B	83	99	*R*,*R*
16	PhI			A	92	95	2*S*,3*R*
17				B	90	98	2*S*,3*R*
18				A	94	95	2*S*,3*R*
19				B	93	96	2*S*,3*R*

[a] Method A and Method B: see Experimental Section. [b] *ee* determined by HPLC analysis on Chiralcel OJ column with 10% isopropanol in hexane as an eluant; flow rate 1 mL min^{-1}; detection UV 220 nm. [c] The absolute configuration was determined by comparison of specific rotations with literature values.[10]

tral data which rule out the formation of bi- or tri-heterometallic species during the exchange process or the dihydroxylation reaction. The superior performance of these catalysts in providing chiral diols with higher yields is ascribed to the large positive electric potential and spatial organization of LDH-PdOs and LDH-PdOsW. These results are in accord with LDH-WO_4 catalyzed oxidative bromination.[8a] The present system composed of new variants, LDH support, Et_3NHX coupled with slow addition of H_2O_2, facilitates the hydrolysis of osmium monogylcolate ester to subdue the formation of bisglycolate ester and thus achieve higher *ee* values.[3d] Further, the higher *ee* values obtained using a bulky chiral ligand, $(DHQD)_2PHAL$ suggest that the OsO_4^{2-} ion is only present on the surface, since the diffusion of the chiral ligand to interact with OsO_4^{2-} ions located in the very small interlamellar space (3 Å) of LDH is very unlikely. This result concurs with the evidence obtained by X-ray diffraction data that the OsO_4^{2-} ions are located at edge positions.

In summary, we have designed and developed a recoverable and reusable LDH-PdOsW trifunctional solid catalyst for the synthesis of chiral diols. The catalyst consists of active palladium, osmium, and tungsten species embedded in a single LDH matrix. This method provides the desired prochiral olefins in situ and chiral diols (which are very valuable intermediates for drugs, such as diltiazem and taxol) from cheaper precursors and NMO by in situ oxidation thus minimizing the number of operations that need to be performed. The high cost and toxicity of osmium, a major obstruction to the use of homogeneous catalysis in industry are addressed by our heterogeneous catalyst.

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Experimental Section

The LDH (Mg-Al-Cl) was obtained using a reported procedure.[8c]

LDH-PdOs: LDH (1 g) was suspended in an aqueous solution (100 mL) of Na_2PdCl_4 and $K_2OsO_4 \cdot 2H_2O$ (0.4 mmol each) and stirred at 25 °C for 12 h under nitrogen atmosphere. The solid catalyst was collected by filtration, washed thoroughly with water (500 mL), and vacuum dried to obtain LDH-PdOs (1.158 g; 0.34 mmol g^{-1} of each Pd and Os).

LDH-OsW: LDH (1 g) was suspended in an aqueous solution (100 mL) of $K_2OsO_4 \cdot 2H_2O$ 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 collected by filtration, washed thoroughly with water (500 mL), and vacuum dried to obtain of LDH-OsW (1.172 g; 0.34 mmol g^{-1} of each Os and W).

LDH-PdOsW: LDH (1 g) was suspended in an aqueous solution (100 mL) of 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 collected by filtration, washed thoroughly with water (500 mL), and vacuum dried to obtain LDH-PdOsW (1.181 g; 0.25 mmol g^{-1} of each Pd, Os, and W).

General procedure for the synthesis of chiral diols: Method A: LDH-PdOs (29 mg, 0.01 mmol), arylhalide (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 mixture was allowed to reach room temperature. A mixture of $(DHQD)_2PHAL$ (7.8 mg, 0.01 mmol) and NMO (175 mg, 1.3 mmol) in *t*BuOH/H_2O (5:1, 5 mL) was added to the reaction mixture and stirred at room temperature. After completion of the diol formation (4–6 h, as monitored by TLC), the catalyst was collected by filtration and washed with ethyl acetate (10 mL). The combined filtrates were extracted with 1N 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 under reduced pressure. The crude material thus obtained was purified by chromatography on silica gel using hexane/ethyl acetate (2:1) as an eluant to afford the corresponding *cis*-diol.

Method B: LDH-PdOsW (40 mg, 0.01 mmol), arylhalide (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 a 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 $(DHQD)_2PHAL$ (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 μL, 30% aqueous, 1.5 mmol) was then slowly added over 12 h using a syringe pump. After the addition was complete, the stirring was continued for an additional 1 h and the catalyst was collected by filtration 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 under reduced pressure. The crude material thus obtained was purified by chromatography on silica gel using hexane/ethyl acetate (2:1) as an eluant to afford the corresponding *cis*-diol.

Specific rotations of the diols obtained in method B: entry 3: $[\alpha]_D^{25} = 91.2$ ($c = 1.0$, EtOH) [ref.[10a] 91.0 ($c = 1.11$, EtOH)]; entry 5: $[\alpha]_D^{25} = 93.1$ ($c = 1.0$, EtOH) [ref.[10a] 94.0 ($c = 1.32$, EtOH)]; entry 9: $[\alpha]_D^{25} = 99.2$ (c = 1.0, EtOH) [ref.[10a] 100.0 ($c = 1.11$, EtOH)]; entry 11: $[\alpha]_D^{25} = 119.3$ ($c = 1.0$, EtOH) [ref.[10a] 123.0 ($c = 1.4$, EtOH)]; entry 13: $[\alpha]_D^{25} = 105.8$ ($c = 1.0$, EtOH) [ref.[10a] 107.0 ($c = 1.16$, EtOH)]; entry 15: $[\alpha]_D^{25} = 100.5$ ($c = 1.0$, EtOH) [ref.[10a] 101.0 ($c = 1.15$, EtOH)]; entry 17: $[\alpha]_D^{25} = -10.3$ ($c = 1.0$ $CHCl_3$) [ref.[10b] −10.7 ($c = 1.1$, $CHCl_3$)]; entry 19: $[\alpha]_D^{25} = -5.8$ ($c = 1.0$, $CHCl_3$) [ref.[10c] −6.0 ($c = 0.84$, $CHCl_3$)].

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