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Highly Enantioselective O–H Bond Insertion of α-Alkyl-α-diazoacetates and α-Alkenyl-α-diazoacetates with Water

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ABSTRACT: Catalytic asymmetric reactions in which water is a substrate are rare. Enantioselective transition-metal-catalyzed insertion of carbenes into the O–H bond of water can be used to incorporate water into the stereogenic center, but the reported chiral catalysts give good results only when α-aryl-α-diazoesters are used as the carbene precursors. Herein we report the first highly enantioselective O–H bond insertion reactions between water and α-alkyl- and α-alkenyl-α-diazoesters as carbene precursors, with catalysis by a combination of achiral dirhodium complexes and chiral phosphoric acids or chiral phosphoramides. Participation of the phosphoric acids or phosphoramides in the carbene transfer reaction markedly suppressed competing side reactions, such as β-H migration, carbene dimerization, and olefin isomerization, and thus ensured good yields of the desired products. Fine-tuning of the ester moiety facilitated enantiocontrol of the proton transfer reactions of the enol intermediates and resulted in excellent enantioselectivity. This protocol represents an efficient new method for preparation of multifunctionalized chiral α-alkyl and α-alkenyl hydroxyl esters, which readily undergo various transformations and can thus be used for the synthesis of bioactive compounds. Mechanistic studies revealed that the phosphoric acids and phosphoramides promoted highly enantioselective 1,2- and 1,3-proton transfer reactions of the enol intermediates. Maximization of molecular orbital overlap in the transition states of the proton transfer reactions was the original driving force to involving the proton shuttle catalysts in this process.

INTRODUCTION

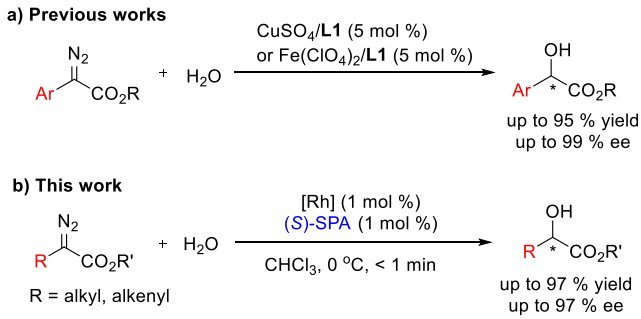
Water is a widely used chemical in industrial processes because it is inexpensive, safe, and recyclable.[1] However, even though significant progress has been made in the field of asymmetric catalysis during the past half century,[2] there have been only a few reports of the use of water as a substrate in catalytic enantioselective reactions. Notable examples of the use of water as a substrate in asymmetric catalysis include Co(salen)-catalyzed kinetic resolution of racemic epoxides by means of ring-opening reactions in which water acts as a nucleophile[3] and enantioselective palladium-catalyzed allylic substitution reactions of vinylethylene carbonates with water.[4]

Transition-metal-catalyzed carbene insertion into the O–H bond of water can be used to introduce all part of water into the insertion products and thus represents an elegant application of water.[5] However, there are only a few reported examples of asymmetric O–H insertion reactions involving water,[6] although highly enantioselective O–H insertion reactions involving alcohols, phenols, and carboxylic acids have been achieved.[6c,7] As early as 1995, Moody and coworkers[6a] reported diastereoselective O–H insertion reactions of water and α-phenyl-α-diazoacetates containing chiral ester moieties, obtaining diastereomeric excesses of up to 50%. In 1997, Landais and coworkers[6b] achieved the first enantioselective O–H bond insertion reaction of α-cinnamyl-α-diazoacetate with water by using a chiral dirhodium catalyst, but the enantiomeric excess (ee) was only 8%. In 2006, Fu and coworkers[6c] reported the first highly enantioselective O–H insertion reactions of alcohols with α-aryl-α-diazoacetates, which they accomplished by using a chiral copper catalyst; however, when water was the O–H bond donor, the enantioselectivity was poor (~15% ee). We previously realized highly enantioselective O–H bond insertion reactions of α-aryl-α-diazoacetates with water by using copper or iron catalysts bearing chiral spiro bisoxazoline ligands (Scheme 1a).[6d,e] However, these reactions gave unsatisfactory results for α-alkyl-α-diazoacetates and α-alkenyl-α-diazoacetates, which is unfortunate because such transformations would afford useful α-alkyl-α-hydroxyacetates and α-alkenyl-α-hydroxyacetates, respectively. Saito and coworkers[6f] carried out an enantioselective O–H bond insertion reaction of methyl α-phenyl-α-diazoacetate with water by using a combined catalyst consisting of an achiral dirhodium complex and quinine, but the enantioselectivity was only moderate (<50% ee). Carbene transfer reactions involving α-alkyl-α-diazoesters and α-alkenyl-α-diazoacetates are challenging because the metal carbenes generated from these compounds readily undergo a number of side reactions, including β-H migration, rearrangement, and carbene dimerization.[5,8] Besides, the challenge of the enantioselective version of O–H bond insertion reactions between water and carbenes generated from α-alkyl-α-diazoesters and α-alkenyl-α-diazoesters mainly attribute to

their elusive enantioselective determining steps. Many pioneering works indicate that reactions of rhodium carbenes with *O*-nucleophiles generate oxinium ylides or enolate intermediates[9] and the proton-transfer of these intermediates is the chiral determining step but difficult to control.

Because the diversity of products that can be obtained via O–H bond insertion reactions of water is restricted, the practical utility of this method is limited. However, we herein report a protocol for unprecedented highly enantioselective O–H bond insertion reactions between water and carbenes generated from α-alkyl-α-diazoesters and α-alkenyl-α-diazoesters with catalysis by a combination of achiral dirhodium complexes and chiral phosphoric acids or chiral phosphoramides (Scheme 1b). The phosphoric acids or phosphoramides suppressed competing β-H migration, carbene dimerization, and isomerization and thus ensured good yields of the desired products. Fine-tuning of the ester moiety facilitated enantiocontrol of proton transfer reactions of the enolate intermediates and resulted in excellent enantioselectivity.

Scheme 1. Catalytic Enantioselective O-H Bond Insertion Reactions with Water



RESULTS AND DISCUSSION

We began by exploring the reaction between water and a typical α-alkyl-α-diazoacetate, methyl 2-diazooctanoate (**1a**, Table 1). First, we evaluated transition-metal catalysts bearing chiral ligand **L1** or **L2** (Figure 1), which have been shown to efficiently catalyze enantioselective O–H bond insertion reactions of α-aryl-α-diazoesters.[6d,,7c] Unfortunately, these catalysts gave poor yields of desired O–H bond insertion product **2a**, and the enantioselectivities were low (entries 1–3). The β-H elimination product (**3a**) and dimerization products **4a** and **5a** were the main products generated under these conditions. Next, we tested several commercially available chiral dirhodium catalysts, but once again the yields of **2a** and the enantioselectivities were poor (entries 4–6). We then turned to combined catalysts. Although combinations of $Rh_2(OAc)_4$ and basic hydrogen-bond catalysts **C1** and **C2** (Figure 1) failed to improve the outcome, combining $Rh_2(OAc)_4$ with chiral spiro phosphoric acids **C3** substantially improved the yields of the desired insertion product and gave moderate ee values (entries 9–15).[10] Phosphoric acid (*S*)-**C3g**, which has 6,6′-*di*(10-phenyl-9-anthracenyl) substituents, performed the best (99% yield, 44% ee; entry 15). Further investigation revealed that both the backbone and the acidity of the phosphoric acid strongly affected its catalytic performance. Phosphoric acid **C4**, which has a binaphthyl scaffold, afforded only a moderate yield and ee (entry 16). Highly acidic phosphoramide **C5** gave an 18% ee (entry 17). The achiral rhodium complexes greatly influenced the yields as well as the enantioselectivities, with $Rh_2(esp)_2$ being the best choice (entries 18–21). Finally, we could further improve the ee by changing the ester moiety of the diazo compound (entries 23–26); the highest enantioselectivity (95% ee) was obtained with a 2-phenyl-2-propyl ester (entry 26).

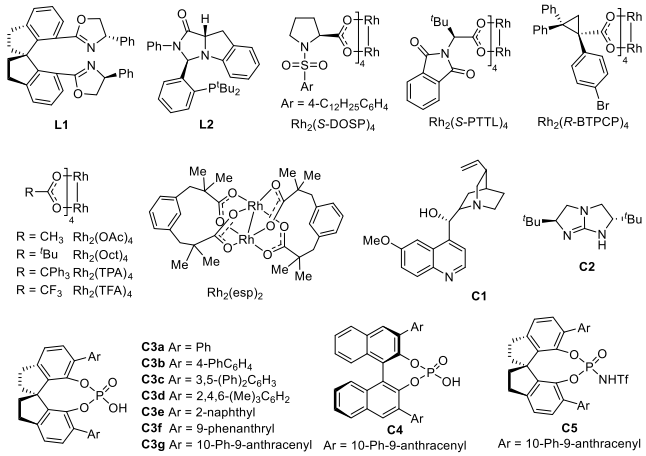
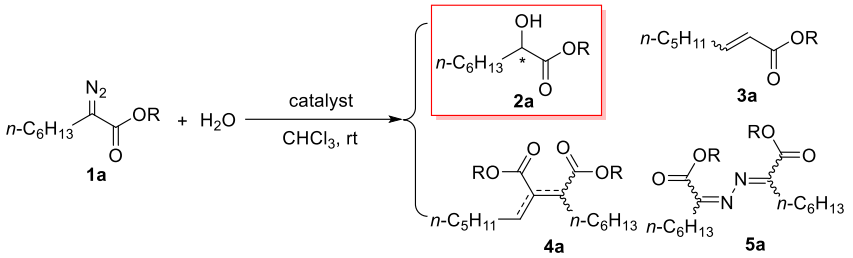


Figure 1. Chiral Ligands and Catalysts Used in This Study

Table 1. Asymmetric O–H Bond Insertion Reactions of 1-Diazooctanoates (1a) with Water: Optimizing Reaction Conditions [a]



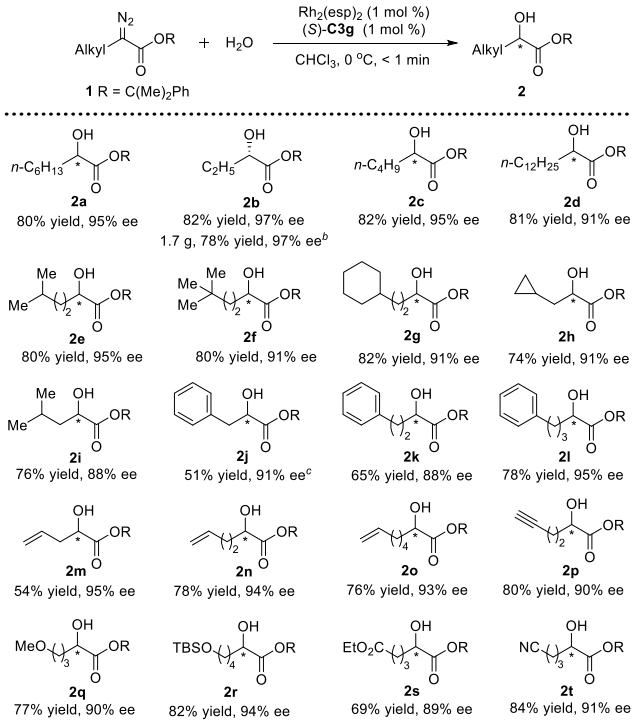
entry	catalyst	R	**2a** (yield%/ee%)[b]	**3a/4a/5a** (yield%)[b]
1	$CuSO_4$/**L1**/$NaBAr_F$	Me	ND[c]	66/15/8
2	$FeCl_2.4H_2O$/**L1**/$NaBAr_F$	Me	ND	70/10/9
3	CuOTf/**L2**	Me	ND	66/16/9
4	Rh_2(*R*-DOSP)$_4$	Me	5/4	56/12/15
5	Rh_2(*S*-PTTL)$_4$	Me	27/20	41/10/13
6	Rh_2(*R*-BDPCP)$_4$	Me	41/28	30/7/12
7	$Rh_2(OAc)_4$/**C1**	Me	45/2	37/8/7
8	$Rh_2(OAc)_4$/**C2**	Me	49/5	27/8/6
9	$Rh_2(OAc)_4$/**C3a**	Me	96/11	1/ND/1
10	$Rh_2(OAc)_4$/**C3b**	Me	92/22	5/ND/1
11	$Rh_2(OAc)_4$/**C3c**	Me	91/28	4/ND/2
12	$Rh_2(OAc)_4$/**C3d**	Me	94/21	2/ND/1
13	$Rh_2(OAc)_4$/**C3e**	Me	96/29	1/ND/1
14	$Rh_2(OAc)_4$/**C3f**	Me	98/33	1/ND/ND
15	$Rh_2(OAc)_4$/**C3g**	Me	99/44	1/ND/ND
16	$Rh_2(OAc)_4$/**C4**	Me	54/26	19/10/6
17	$Rh_2(OAc)_4$/**C5**	Me	72/21	10/10/3
18	$Rh_2(Oct)_4$/**C3g**	Me	69/44	10/7/8
19	$Rh_2(TPA)_4$/**C3g**	Me	76/78	6/5/4
20	$Rh_2(TFA)_4$/**C3g**	Me	14/17	50/14/12
21	$Rh_2(esp)_2$/**C3g**	Me	80/78	11/2/1
22[d]	$Rh_2(esp)_2$/**C3g**	Me	78/80	10/7/1
23[d]	$Rh_2(esp)_2$/**C3g**	^{t}Bu	74/76	5/8/6
24[d,e]	$Rh_2(esp)_2$/**C3g**	Bn	82/82	5/4/5
25[d,e]	$Rh_2(esp)_2$/**C3g**	$CH(Ph)_2$	80/90	4/6/5
26[d,e]	$Rh_2(esp)_2$/**C3g**	$C(Me)_2Ph$	80/95	2/4/10

[a] Reaction conditions of entries 1-3: 0.2 mmol **1a**, 1.0 mmol H_2O, 5 mol % copper or iron salts, 6 mol % **L1** or **L2**, 6 mol % $NaBAr_F$, 3 mL $CHCl_3$, at room temperature (rt). Reaction conditions of entries 4-6: 0.2 mmol **1a**, 1.0 mmol H_2O, 1 mol % chiral dirhodium catalyst, 3 mL $CHCl_3$ at rt. Reaction conditions of entries 7-26: 0.2 mmol **1a**, 1.0 mmol H_2O, 1 mol % achiral dirhodium catalyst, 1 mol % **C1**-**C5**, 3 mL $CHCl_3$ at rt. [b] Isolated yields, ee values were determined by GC using a *Beta*-325 chiral column. [c] Not detected. [d] The reaction was performed at 0 °C. [e] Yields were determined by ^{1}H NMR using 1,3,5-trimethoxy-benzene as an internal standard, ee values were determined by HPLC equipped with AD-H chiral column.

Under the optimal conditions, O–H bond insertion reactions of various α-alkyl-α-diazoacetates **1** with water were evaluated (Scheme 2). Impressively, all the reactions were complete within 1 min, and α-alkyl-α-diazoacetates with linear or branched alkyl substituents gave high or excellent enantioselectivities and good yields (**2a–2i**). Generally, the ee values decreased as the steric bulk of the alkyl group increased. When diazoesters bearing alkyl groups with a terminal phenyl group were used, high ee values were obtained, and the yields increased with alkyl chain length (**2j–2l**). Because the diazo ester with a benzyl group (**1j**) easily underwent β-H migration, we increased the amount of phosphoric acid (*S*)-**C3g** to 2 mol % to get an acceptable yield. This O–H bond insertion reaction showed

good functional group tolerance; introduction of alkenyl, alkynyl, ether, ester, and cyano groups on the alkyl chains (**1m–1t**) only slightly affected the reaction outcome. In addition, the reaction could be performed on a gram scale with negligible effect on the yield and ee (**2b**, 1.7 g scale).

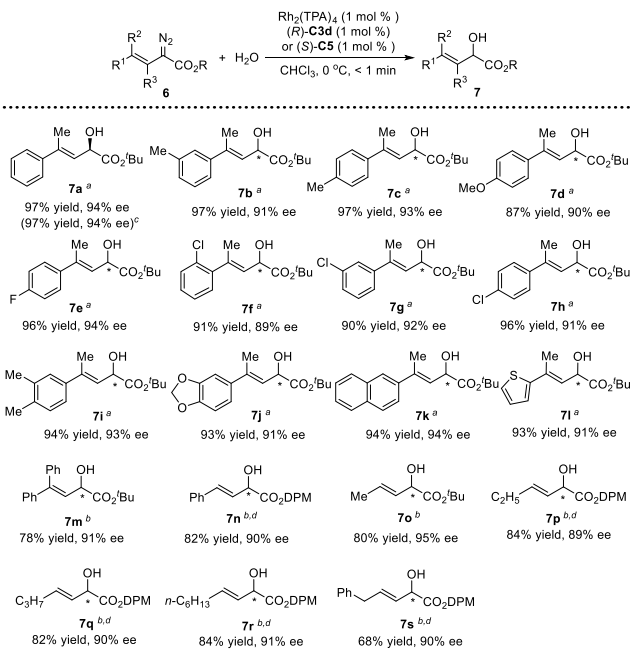
Scheme 2. Enantioselective O–H Bond Insertion Reactions of α-Alkyl-α-diazoacetates with Water: Substrate Scope [a]



[a] Reaction conditions: **1**/H_2O/$Rh_2(esp)_2$/(*S*)-**C3g** = 0.2:1.0:0.002:0.002 (mmol), in 3 mL $CHCl_3$, at 0 °C. All reactions completed in 1 min. Isolated yields were given. The ee values were determined with AS-H or OJ-3 chiral column. [b] A gram-scale experiment: **1b**/H_2O/$Rh_2(esp)_2$/(*S*)-**C3g** = 10:50:0.1:0.1 (mmol), in 150 mL $CHCl_3$. [c] Used 2 mol % (*S*)-**C3g**.

The combination of achiral dirhodium complexes and chiral Brønsted acids could also be extended to O–H bond insertion reactions of α-alkenyl-α-diazoacetates with water (Scheme 3). Systematic study of the reaction conditions revealed that combining $Rh_2(esp)_2$ with chiral spiro phosphoric acid (*R*)-**C3d** promoted O–H bond insertion reactions of γ-aryl-γ-methyl-α-vinyldiazoesters with water, affording products **7a–7l** in high yields with high enantioselectivities (see SI for details regarding optimization of the reaction conditions). Like the reactions of α-alkyl-α-diazoacetates, the reactions of α-alkenyl-α-diazoacetates were very fast (going to completion in <1 min). The electronic and steric properties of substituents on the phenyl groups of the diazo compounds had little effect on the reaction outcome. For γ,γ-diaryl- and γ,γ-dialkyl-α-vinyldiazoesters (**7m**), we used chiral spiro phosphoramide (*S*)-**C5**, which has higher acidity and gave better results than (*S*)-**C3d**. The same catalysis system was also successfully used for highly enantioselective O–H bond insertion reactions between water and (*E*)-γ-alkyl- and (*E*)-γ-aryl-α-vinyl-α-diazoacetates (**7n**–**7s**). Finally, **7a** could be obtained on a gram scale at a catalyst loading as low as 0.5 mol %. Under standard reaction conditions, the reaction of methyl α-diazophenylacetate with water smoothly afforded desired O-H bond insertion product with high yield (92%) but very modest enantioselectivity (34%). These results imply that the method developed in this study is complementary to the previously reported methods.[6d,e]

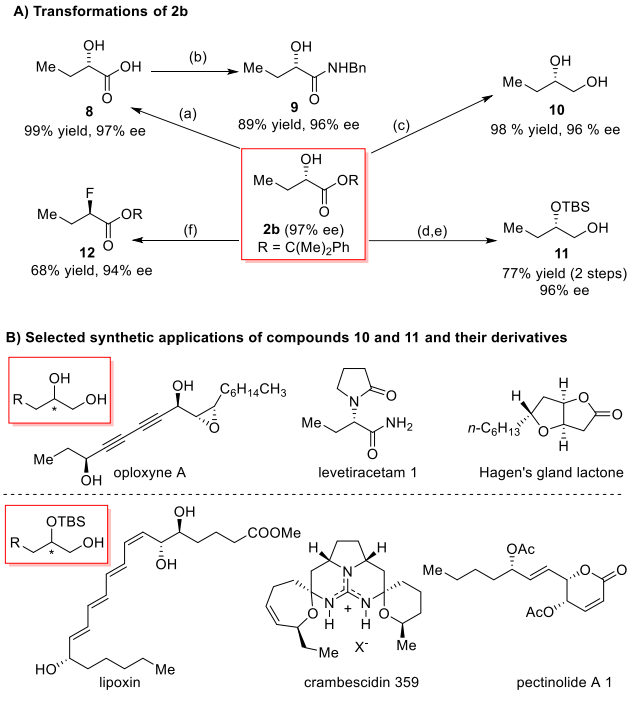
Scheme 3. Enantioselective O–H insertion Reactions of α-Alkenyl-α-diazoacetates with Water: Substrate Scope [a]



[a] Reaction conditions: **6**/H_2O/$Rh_2(TPA)_4$/(*R*)-**C3d** = 0.2:1.0:0.002:0.002 (mmol), in 3 mL $CHCl_3$, at 0 °C. All reactions completed within 1 min. Isolated yields were given. [b] Reaction conditions: **6**/H_2O/$Rh_2(TPA)_4$/(*S*)-**C5** = 0.2:1.0:0.002:0.002 (mmol), in 3 mL $CHCl_3$, at 0 °C. All reactions completed in 1 min. Isolated yields were given. [c] The data in parenthesis are of the reaction performed at a gram-scale: **6a**/H_2O/$Rh_2(TPA)_4$/(*R*)-**C3d** = 3.7:18.5:0.019:0.019 (mmol), in 30 mL $CHCl_3$. [d] DPM = $CH(Ph)_2$

The O–H insertion reactions of α-alkyl-α-diazoacetates with water provide a new route to multifunctionalized chiral α-alkyl-α-hydroxyesters, which are useful building blocks in organic synthesis and can undergo a wide variety of transformations (Scheme 4A). For instance, insertion product **2b** could be transformed to corresponding acid **8** in nearly quantitative yield by means of acidic hydrolysis (eq a), and amidation of **8** with benzyl amine produced **9** in good yield with retained ee (eq b).[11] Chiral 1,2-diols **10** and **11** were prepared in high yields and retained ee values by reduction of **2a** (eqs c–e). Notably, **10** and **11** and derivatives with different alkyl chains have been used in syntheses of chiral natural products (Scheme 4B).[12] α-Fluoro carboxylic ester **12** was prepared by means of stereochemistry-inverse fluorination of the hydroxy group of **2a** (Scheme 4A, eq f).[13] Chiral α-fluoro carboxylic esters have been used to synthesize bioactive compounds.[14]

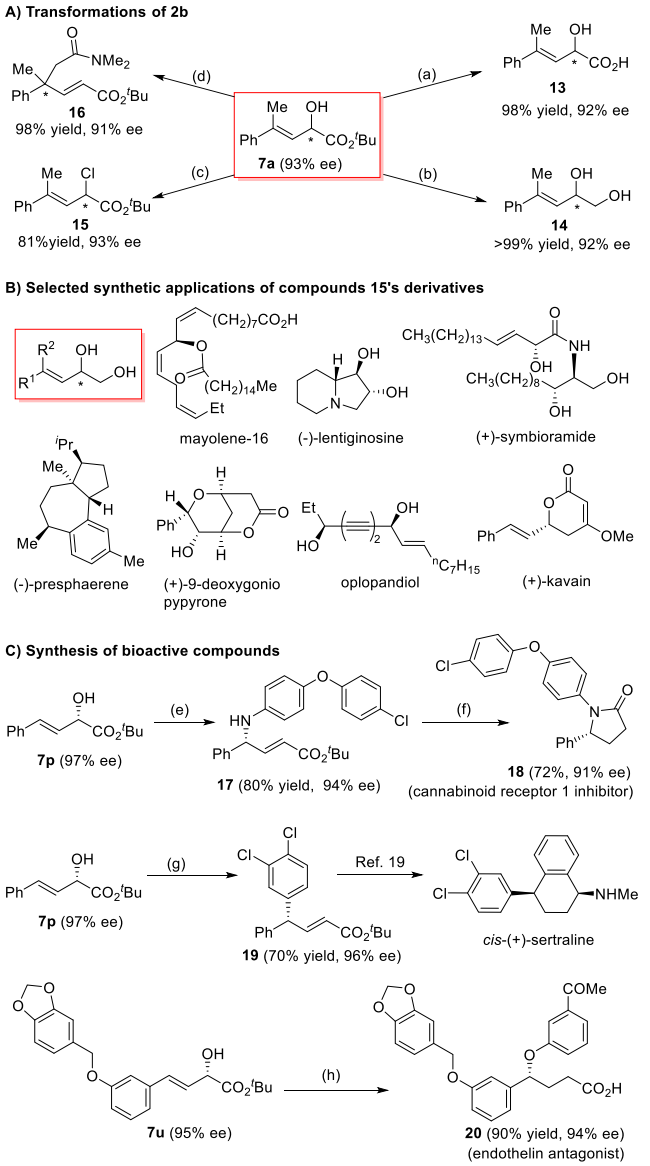
Scheme 4. Transformations and Potential Synthetic Applications of the Insertion Products of α-Alkyl-α-diazoesters with Water



Reaction conditions: (a) HCl, MeOH, 60 °C, 2 h. (b) $BnNH_2$, $MeB(OH)_2$, $PhCO_2H$, toluene, 10 h. (c) $LiAlH_4$, THF, rt, 2 h. (d) Chloro(1,1-dimethylethyl)dimethyl-silane, imidazole, DMF, rt, 1 h. (e) H_2, $Pd(OH)_2/C$, rt, 2 h. (f) *N,N*-diethylamino)sulfurtrifluoride, DCM, -78 °C to rt, 10 h.

Insertion products **7**, generated by O–H bond insertion reactions of α-alkenyl-α-diazoacetates with water, are also useful building blocks because of the presence of the ester, hydroxy, and alkenyl groups on these molecules (Scheme 5). For instance, reduction of **7a** smoothly afforded corresponding carboxylic acid **13**, and hydrolysis generated 1,2-diol **14** (Scheme 5A, eqs a and b), with excellent yields and ee values in both cases. Derivatives of 1,2-diols such as these have been used for the synthesis of various natural products (Scheme 5B).[15] In the presence of PPh_3 and CCl_4, the hydroxy group of **7a** could be smoothly replaced with a chlorine atom, affording **15** with retained ee (Scheme 5A, eq c). In addition, **7a** underwent an Eschenmoser–Claisen rearrangement to produce **16**, which has a chiral quaternary carbon center, in 98% yield with 91% ee (eq d).[16] Moreover, we used insertion products **7p** and **7u** to synthesize bioactive compounds (Scheme 5C). Specifically, cannabinoid receptor 1 inhibitor **18**, which has a pyrrolidin-2-one core structure, was prepared from **7p** by means of an allylic rearrangement–cyclization sequence (eqs e and f),[17] demonstrating the potential utility of our protocol for the synthesis of important chiral pyrrolidine-2-ones.[18] In addition, a formal synthesis of the chiral drug sertraline was realized by subjecting **7p** to a palladium-catalyzed stereospecific allylic arylation (eq f).[19] Finally, endothelin antagonist **20** was obtained through a stereospecific allylic etherification reaction of insertion product **7u**.[20]

Scheme 5 Transformations and Potential Synthetic Applications of the Insertion Products of α-Alkenyl-α-diazoesters with Water



Reaction conditions: (a) HCl, MeOH, reflux. (b) $LiAlH_4$, THF, reflux. (c) PPh_3, CCl_4, reflux. (d) $CH_3C(OMe)_2NMe_2$, xylene, 140 °C, reflux. (e) ArNCO, DCM, reflux, then $Pd(OAc)_2$, Xantphos, rt. (f) H_2, Pd/C, then ^{t}BuOK. (g) $ClCO_2Et$, then 3,4-dichlorophenylboronic acid, $Pd(OAc)_2$, 1,10-phenanthroline, AgOTf. (h) $ClCO_2Et$, then methyl 3-hydroxybenzoate, $Pd(PPh_3)_4$, DCM, rt.

MECHANISTIC STUDIES

We carried out density functional theory calculations to elucidate the mechanism of this rhodium(II)-catalyzed O–H insertion reaction and to show how the spiro phosphoric acids induced O–H insertion and regulated its chemoselectivity and enantioselectivity. To reduce the computational costs, we used the $Rh_2(OAc)_4$-catalyzed O–H insertion reaction between methyl α-diazobutyrate and water as a model. In the presence of $(PhO)_2P(O)OH$ (1 mol %), the model reaction gave insertion product methyl 2-hydroxybutanoate in 85% yield along with β-H migration

side-product methyl (*Z*)-but-2-enoate in 9% yield; in the absence of the phosphoric acid, the corresponding yields were 30% and 40% (see SI for details). We performed the calculations by means of the B3LYP-D3(BJ)/def2TZVP//B3LYP/def2SVP method in chloroform solution (using the SMD model) with the Gaussian 09 program package (see SI for details). Because the dirhodium-complex-catalyzed decomposition of α-diazoacetates has been reported previously in other O–H bond insertion reactions,[5] we started our calculations with a simplified rhodium carbene (**CB**). Once formed, **CB** can insert into the O–H bond of water (Figure 2, right) or undergo side reactions, such as β-H migration (Figure 2, left). The calculated transition states for β-H migration, which gives *E*-**BP** and *Z*-**BP**, are designated **TS1** and **TS2** and are 11.7 and 9.6 kcal/mol higher in energy than **CB**. The calculations also showed that nucleophilic attack by water on **CB** is very facile, having an activation free energy of only 6.9 kcal/mol via transition state **TS3** and giving rhodium-associated oxonium ylide **INT1**. Formation of **INT1** is followed by a quick intramolecular [1,3]-proton shift via **TS4** to generate rhodium-associated enol **INT2**. Dissociation of the dirhodium complex from **INT2** liberates free enol **INT3**, a process that is not energetically difficult because it is uphill by only 3.5 kcal/mol. The process of free enol formation in O–H insertion reactions is consistent with previous DFT calculations.[7j,7m,7l,21] From free enol **INT3**, several possible proton shift processes lead to the final product (**Pdt**): a water-assisted [1,3]-proton shift via **TS5** (ΔG_{sol} = 23.8 kcal/mol) or via **TS6** (ΔG_{sol} = 17.6 kcal/mol) or an enol intermediate self-catalyzed [1,3]-proton shift via **TS5** (ΔG_{sol} = 14.3 kcal/mol). Other possible proton shift processes that do not involve the phosphoric acid (**PA**) are considered in the SI. The energy barriers to these proton-shift processes are much higher than the energy barrier to β-H migration. However, two **PA**-assisted keto–enol tautomerization processes with much lower activation energies are also possible. Specifically, our calculations indicated that **INT3** and **PA** can participate in a [1,2]- or [1,3]-proton shift via seven-membered transition state **TS9** or eight-membered transition state **TS8**, with activation free energies of 3.2 and 3.5 kcal/mol, respectively. In addition, the less bulky dirhodium catalyst $Rh_2(OAc)_4$ might be involved in a **PA**-promoted [1,3]-proton shift that proceeds via **TS10** (ΔG_{sol} = −2.1 kcal/mol), which is consistent with the effect of varying the rhodium complex on enantioselectivity (Table 1). The stepwise acid-base process, which was proposed in a Morita-Ballis-Hillman reaction,[22] was also considered, but such process exhibited much higher energy barrier ($\Delta\Delta G_{sol}$ = 4.1 kcal/mol) than that of proton-shuttle process according to the calculation (Figure S8). By comparing the energy barriers of β-H migration and O–H insertion, we concluded that reduction of the activation energy for transforming **INT2** to **Pdt** is the mechanism by which the chiral phosphoric acids suppress side reactions. The fast reaction rate of the O–H bond insertion might attribute to the high activity of dirhodium catalyst as well as the efficient proton transfer promoted by the phosphoric acid.

To explain how the chiral phosphoric acid controlled the enantioselectivity, we propose a chiral control model based on a [1,2]- or [1,3]-proton shift reaction of an enol species (Figure 3). As a model reaction for density functional theory calculations, we used the insertion reaction between water and diazoester **1b** with catalysis by $Rh_2(esp)_2$ and (*S*)-**C3g** to afford (*S*)-**2b**. In this case, the proton shift most likely involves a free enol species rather than a rhodium-associated enol, because bulky phosphoric acid (*S*)-**C3g** can be expected to prevent the bulky $Rh_2(esp)_2$ catalyst from approaching the enol intermediate. Our calculations showed that the most favorable pathway for the formation of (*R*)-**2b** involves an (*S*)-**C3g**-promoted [1,3]-proton shift reaction of an enol intermediate with *cis*-hydroxy via transition state **TSII-*R***, whereas the most favorable pathway for the formation of (*S*)-**2b** involves an (*S*)-**C3g**-promoted [1,2]-proton shift reaction of the enol intermediate via transition state **TSI-*S***. The energy of **TSI-*S*** is 3.4 kcal/mol lower than that of **TSII-*R***, which is in agreement with results of the corresponding experiments. Because the energy difference between *cis*- and *trans*-enol is small ($\Delta\Delta G_{sol}$ = 0.2 kcal/mol, Figure S5), we also calculated the (*S*)-**C3g**-promoted [1,3]-proton shift reaction of an enol intermediate with *trans*-hydroxy (Figures S6 and S7). The calculation once again supports the pathway affording (*S*)-**2b**. The [1,2]-proton shift is not allowed in this case. Moreover, we tried a lot but failed to add $Rh_2(esp)_2$ into the **TS-I** and **TS-II** shown in Figure 3 during the DFT calculation.

We found that the energy difference between **TSI-*S*** and **TSII-*R*** depends strongly on the O7-H8-O9 angle and the H4-O5-C6-C7 dihedral angle (Figure 4). The former determines the extent of overlap between the p orbital of C7 and the σ* orbital of O9–H8, which in turn determines the strength of the interaction between the enol and the phosphoric acid; the latter correlates to the stability of the enol moiety. This conclusion can be supported by comparing the geometries of **TSI-*S*** and **TSII-*R***: in the former, the O7-H8-O9 angle is 171° and the H4-O5-C6-C7 dihedral angle is −8.7°; whereas the corresponding angles for the latter are 163° and −24.4°. The angles for **TSI-*S*** are clearly much closer to the ideal angles (180° for O7-H8-O9 and 0° for H4-O5-C6-C7). This observation is consistent with previous calculations on proton shift processes of other enol intermediates.[23]

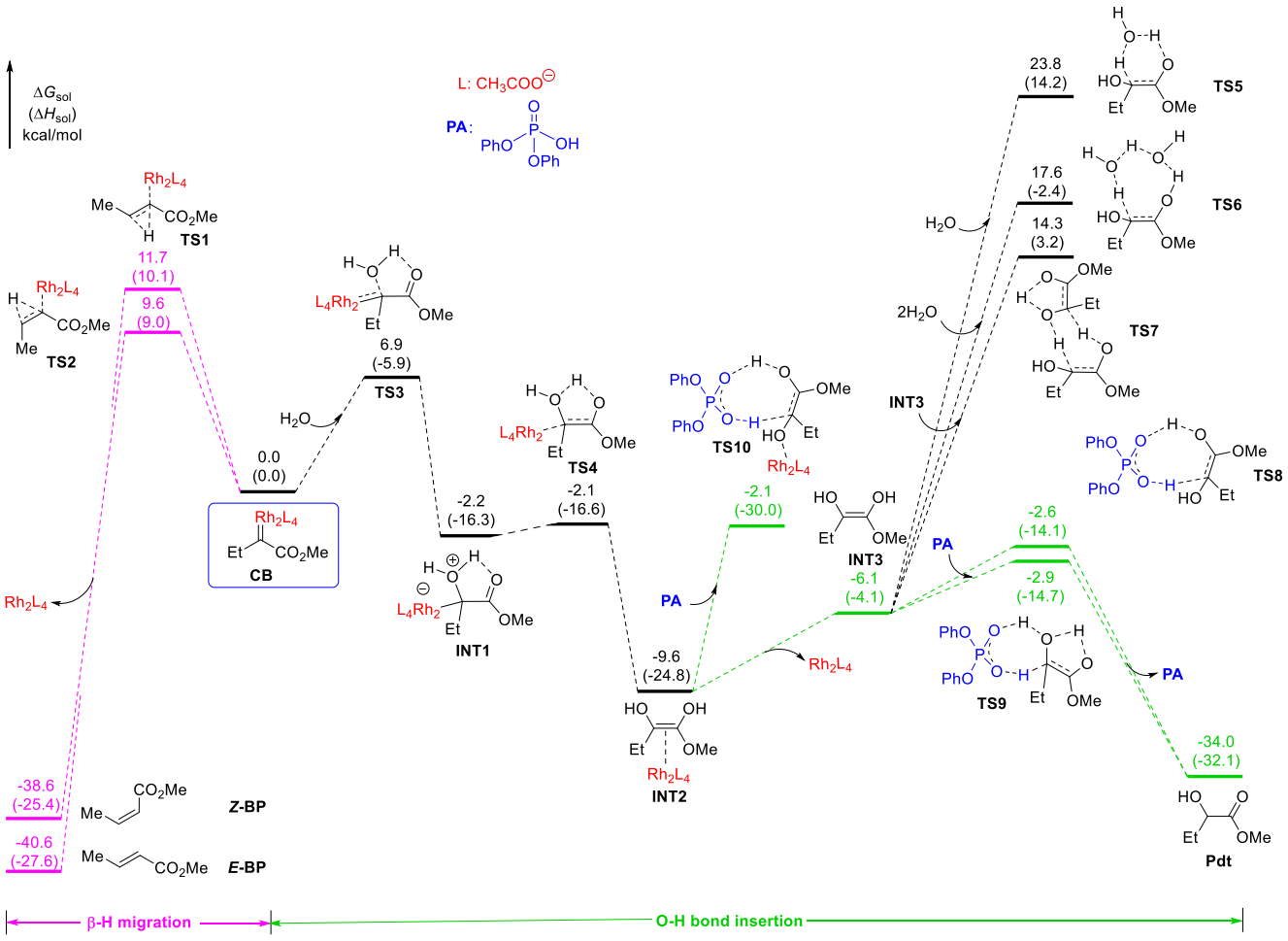


Figure 2. Computed Energy Surfaces for O–H Bond Insertion and β-H Migration

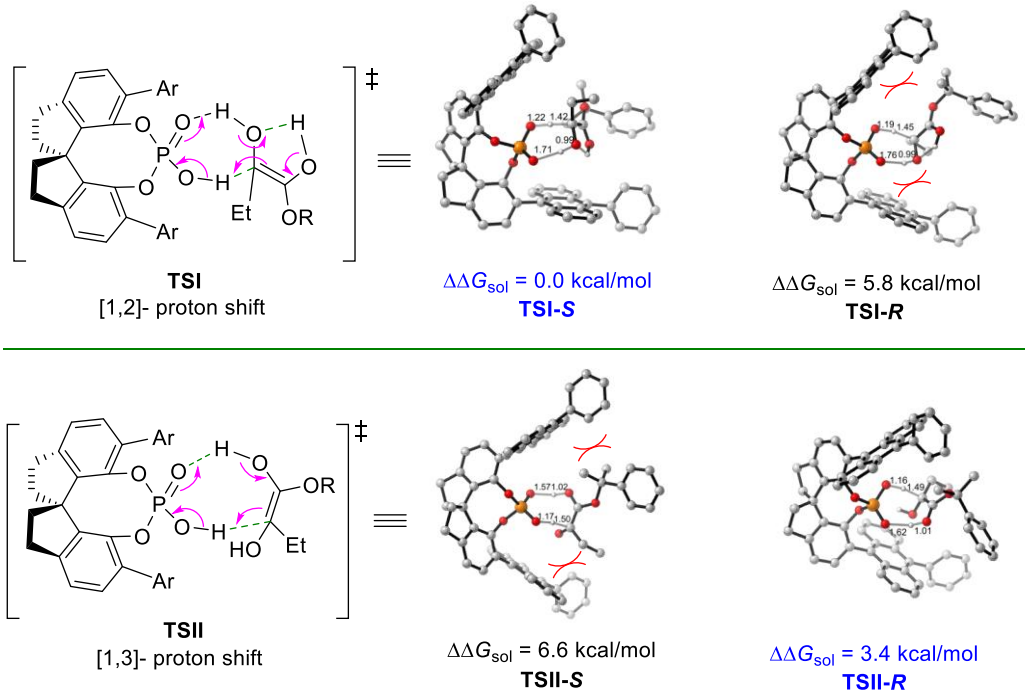


Figure 3. The Model of Chiral Control of Spiro Phosphoric Acid (*S*)-**C3g**

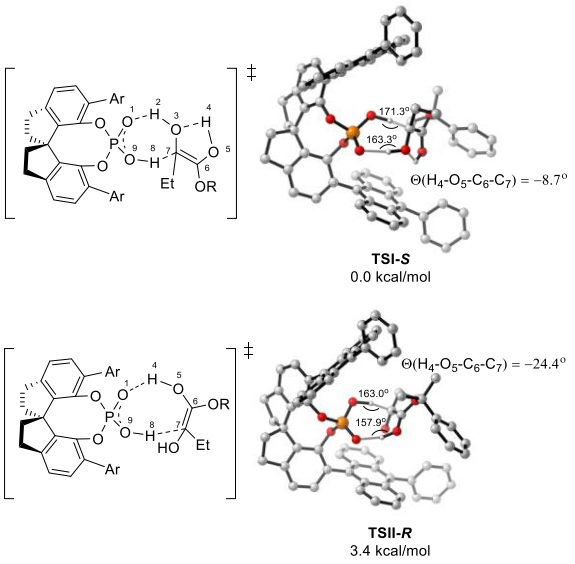
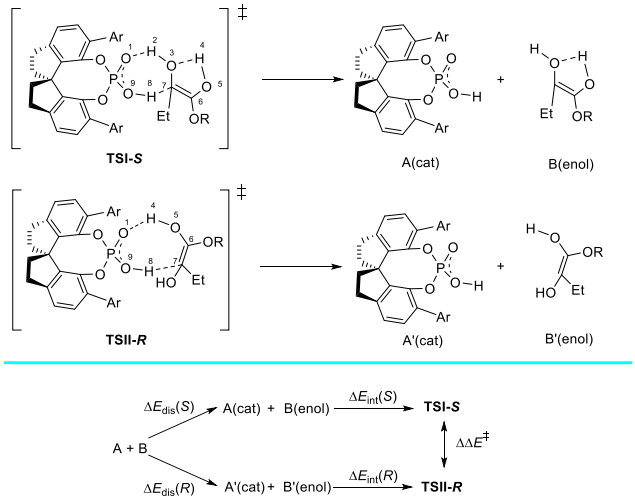


Figure 4. Difference between **TSI-*S*** and **TSII-*R***



	ΔE_{dis}	ΔE_{dis}(enol)	ΔE_{dis}(cat)	ΔE_{int}	$\Delta E^{‡}$
TSI-*S*	34.3	9.6	24.7	-51.4	-17.1
TSII-*R*	30.9	12.7	18.2	-43.9	-13.0
	$\Delta\Delta E_{dis}$	$\Delta\Delta E_{dis}$(enol)	$\Delta\Delta E_{dis}$(cat)	$\Delta\Delta E_{int}$	$\Delta\Delta E^{‡}$
	-3.4	3.0	-6.5	7.5	4.1

Figure 5. Distortion/Interaction Analysis of **TSI-*S*** and **TSII-*R***. A(cat) and B(enol) are the catalyst and the enol moieties in the **TSI-*S***, while A'(cat) and B'(enol) are the catalyst and the enol moieties in the **TSII-*R***. A is the optimized structure of the catalyst, and B is the optimized structure of enol. All energetics in this figure are in kcal/mol.

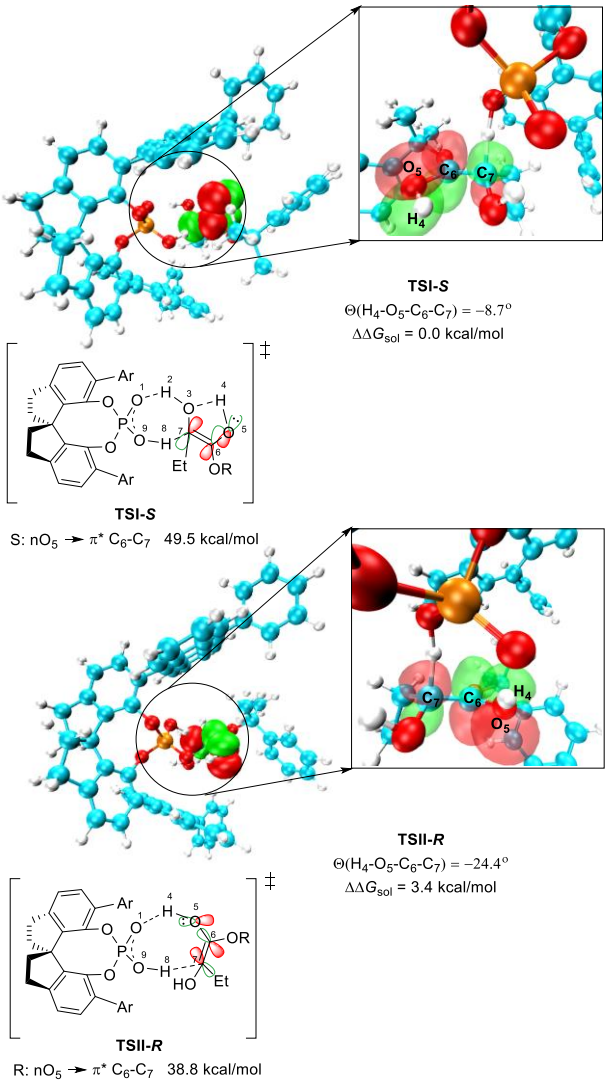


Figure 6. Natural Bond Orbital Analysis of **TSI-*S*** and **TSII-*R***. Multiwfn and VMD were employed for visualization of the results of natural bond orbital analysis.

We also used distortion/interaction analysis to quantify the difference between **TSI-*S*** and **TSII-*R*** (Figure 5). Activation energy $\Delta E^{‡}$ can be written as $\Delta E^{‡} = \Delta E_{dis} + \Delta E_{int}$, where ΔE_{dis} is the energy difference that arises from structural changes leading to **TS** formation, and interaction energy ΔE_{int} corresponds to the energy difference between the distorted catalyst plus the enol and the complex in the **TS** structures. Our calculations show that the interaction energy is stronger in **TSI-*S*** than in **TSII-*R*** ($\Delta\Delta E_{int}$ = 7.5 kcal/mol), which is consistent with the fact that the O7-H8-O9 angle in **TSI-*S*** is closer to 180°. In addition, **TSI-*S*** has a lower distortion energy in the enol than that of **TSII-*R*** ($\Delta\Delta E_{dis}$(enol) = 3.0 kcal/mol), because the planarity of the enol is maintained during formation of **TSI-*S***. Furthermore, natural bond orbital analysis shows that the nO5 → π* C6–C7 interaction in **TSI-*S*** is about 10.7 kcal/mol stronger than that in **TSII-*R*** (Figure 6). This difference indicates that in **TSI-*S***, conjugation between the lone pairs at O5 (nO5) and the π antibonding orbital of the C6–C7 double bond (π* C6–

C7) is more efficient, owing to the more planar geometry of the enol moiety relative to that in **TSII-*R***.

SUMMARY

In summary, we have realized the first highly enantioselective O–H bond insertion reactions between water and α-alkyl-α-diazoacetates and α-alkenyl-α-diazoacetates, with combined catalysis by achiral rhodium(II) carboxylates and chiral spiro phosphoric catalysts. These mild reactions proceed rapidly and show high yields, high to excellent enantioselectivities, and very good functional group tolerance. The multifunctionalized chiral α-alkyl- and α-alkenyl-α-hydroxyester products readily undergo a variety of transformations and are valuable synthons for bioactive compounds. Mechanistic studies suggest that the addition of phosphoric acid is key to the success of the reactions; the phosphoric acid not only suppresses major side reactions involving the active carbene species by accelerating proton transfer reactions of the active intermediates but also exerts chiral control during proton transfer reactions of the enol intermediates. Our results can be expected to inspire other studies on enantioselective reactions with water as a reagent.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, spectroscopic traces for mechanistic studies and characterization data for products.

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Notes

The authors declare no competing financial interests.

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REFERENCES

1 For reviews, see: (a) Pratt, L. R. Introduction: Water, an Editorial for the Special Issue of Water. *Chem. Rev.* **2002**, *102*, 2625. (b) Robinson, G. W.; Zhu, S. B.; Singh, S.; Evans, M. W. *Water in Biology, Chemistry*, and Physics, World Scientific, Singapore, **1996**. (c) Li, C.-J.; Chen, T.-H. *Organic Reactions in Aqueous Media,* Klewer Academic Publisher, Dordrecht, **1997**.

2 (a) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. Eds, *Comprehensive Asymmetric Catalysis, Springer,* Heidelberg, **1999** & Supplement 1, **2004**. (b) Ojima, I. Ed, *Catalytic Asymmetric Synthesis*, 3rd Edition, Wiley, New Jersey, **2010**.

3 (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. Asymmetric Catalysis with Water: Efficient Kinetic Resolution of Terminal Epoxides by Means of Catalytic Hydrolysis. *Science* **1997**, *277*, 936. (b) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. Highly Selective Hydrolytic Kinetic Resolution of Terminal Epoxides Catalyzed by Chiral (Salen)CoIII Complexes. Practical Synthesis of Enantioenriched Terminal Epoxides and 1,2-Diols. *J. Am. Chem. Soc.* **2002**, *124*, 1307. (c) Rossbach, B. M.; Leopold, K.; Weberskirh, R. Self-assembled Nanoreactors as Highly Active Catalysts in the Hydrolytic Kinetic Resolution (HKR) of Epoxides in Water. *Angew. Chem. Int. Ed.* **2006**, *45*, 1309.

4 Khan, A.; Khan, S.; Khan, I.; Zhao, C.; Mao, Y.; Chen,Y.; Zhang, Y. J. Enantioselective Construction of Tertiary C-O Bond via Allylic Substitution of Vinylethylene Carbonates with Water and Alcohols. *J. Am. Chem. Soc.* **2017**, *139*, 10733.

5 For selected reviews, see: (a) Doyle, M. P.; McKervey, M. A.; Ye, T. Modern Catalytic Methods for Organic Synthesis with Diazo Compounds, Wiley, New York, **1998**, chap. 8. (b) Miller, D. J.; Moody, C. J. Synthetic Applications of the O-H Insertion Reactions of Carbenes and Carbenoids derived from Diazocarbonyl and Related Diazo Compounds. *Tetrahedron* **1995**, *51*, 10811. (c) Zhu, S.-F.; Zhou, Q.-L. Transition-Metal-Catalyzed Enantioselective Heteroatom-Hydrogen Bond Insertion Reactions. *Acc. Chem. Res.* **2012**, *45*, 1365. (d) Gillingham, D.; Fei N. Catalytic X–H Insertion Reactions Based on Carbenoids. *Chem. Soc. Rev.* **2013**, *42*, 4918. (e) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. Modern Organic Synthesis with α-Diazocarbonyl Compounds. *Chem. Rev*. **2015**, *115,* 9981.

6 For a diastereoselective O-H bond insertion with water, see: (a) Aller, E.; Brown, D. S.; Cox, G. G.; Miller, D. J.; Moody, C. J. Diastereoselectivity in the O-H Insertion Reactions of Rhodium Carbenoids Derived from Phenyldiazoacetates of Chiral Alcohols. Preparation of α-Hydroxy and α-Alkoxy Esters. *J. Org. Chem.* **1995**, *60*, 4449. For enantioselective O-H bond insertion with water, see: (b) Bulugahapitiya, P.; Landais, Y.; Parra-Rapado, L.; Planchenault, D.; Weber, V. A Stereospecific Access to Allylic Systems Using Rhodium(II)-Vinyl Carbenoid Insertion into Si-H, O-H, and N-H Bonds. *J. Org. Chem.* **1997**, *62*, 1630. (c) Maier, T. C.; Fu, G. C. Catalytic Enantioselective O-H Insertion Reactions. *J. Am. Chem. Soc.* **2006**, *128*, 4594. (d) Zhu, S.-F.; Chen, C.; Cai, Y.; Zhou, Q.-L. Catalytic Asymmetric Reaction with Water: Enantioselective Synthesis of α-Hydroxyesters by a Copper-Carbenoid O-H Insertion Reaction. *Angew. Chem. Int. Ed*. **2008**, *47*, 932. (e) Zhu, S.-F.; Cai, Y.; Mao, H.-X.; Xie, J.-H.; Zhou, Q.-L. Enantioselective Iron-Catalysed O-H Bond Insertions. *Nat. Chem*. **2010**, *2*, 546. (f) Saito, H.; Iwai, R.; Uchiyama, T.; Miyake, S. Chiral Induction by Cinchona Alkaloids in the Rhodium(II) Catalyzed O-H Insertion Reaction. *Chem. Pharm. Bull.* **2010**, *58*, 872.

7 For selected examples, see: (a) Chen, C.; Zhu, S.-F.; Liu, B.; Wang, L.-X.; Zhou, Q.-L. Highly Enantioselective Insertion of Carbenoids into O-H Bonds of Phenols: An Efficient Approach to Chiral α-Aryloxycarboxylic Esters. *J. Am. Chem. Soc.* **2007**, *129*, 12616. (b) Zhu, S.-F.; Song, X.-G.; Li, Y.; Cai, Y.; Zhou, Q.-L. Enantioselective Copper-Catalyzed Intramolecular O-H Insertion: An Efficient Approach to Chiral 2-Carboxy Cyclic Ethers. *J. Am. Chem. Soc.* **2010**, *132*, 16374. (c) Osako, T.; Panichakul, D.; Uozumi, Y. Enantioselective Carbenoid Insertion into Phenolic O-H Bonds with a Chiral Copper(I) Imidazoindolephosphine Complex. *Org. Lett.* **2012**, *14*, 194. (d) Song, X.-G.; Zhu, S.-F.; Xie, X.-L.; Zhou, Q.-L. Enantioselective Copper-Catalyzed Intramolecular Phenolic O-H Bond Insertion: Synthesis of Chiral 2-Carboxy Dihydrobenzofurans, Dihydrobenzopyrans, and Tetrahydrobenzooxepines. *Angew. Chem. Int. Ed.* **2013**, *52*, 2555. (e) Xie, X.-L.; Zhu, S.-F.; Guo, J.-X.; Cai, Y.; Zhou, Q.-L. Enantioselective Palladium-Catalyzed Insertion of α-Aryl-α-diazoacetates into the O-H Bonds of Phenols. *Angew. Chem. Int. Ed.* **2014**, *53*, 2978. (f) Gao, X.; Wu, B.; Huang, W.-X.; Chen, M.-W.; Zhou, Y.-G. Enantioselective Palladium-Catalyzed C-H Functionalization of Indoles Using an Axially Chiral 2,2'-Bipyridine Ligand. *Angew. Chem. Int. Ed.* **2015**, *54*, 11956. (g) Kitagaki, S.; Sugisaka, K.; Mukai, C. Synthesis of Planar Chiral [2.2]Paracyclophane Based Bisoxazoline Ligands Bearing No

Central Chirality and Application to Cu-Catalyzed Asymmetric O–H Insertion Reaction. *Org. Biomol. Chem.* **2015**, *13*, 4833. (h) Tan, F.; Liu, X.; Hao, X.; Tang, Y.; Lin, L.; Feng, X. Asymmetric Catalytic Insertion of α-Diazo Carbonyl Compounds into O–H Bonds of Carboxylic Acids. *ACS Catal.* **2016**, *6*, 6930. (i) Le Maux, P.; Carrié, D.; Jéhan, P.; Simonneaux, G. Asymmetric O-H Insertion Reaction of Carbenoids Catalyzed by Chiral Bicyclo Bisoxazoline Copper(I) and (II) Complexes. *Tetrahedron* **2016**, *72*, 4671. (j) Zhang, Y.; Yao, Y.; He, L.; Liu, Y.; Shi, L. Rhodium(II)/Chiral Phosphoric Acid-Cocatalyzed Enantioselective O–H Bond Insertion of α-Diazo Esters. *Adv. Synth. Catal.* **2017**, *359*, 2754. (k) Huang, D.-R.; Xu, G.-Y.; Peng, S.-Y.; Sun, J.-T. Gold-Catalyzed Highly Regio- and Enantioselective Vinylcarbene Insertion into O–H Bonds of 2-Pyridones. *Chem. Commun.* **2017**, *53*, 3197. (l) Li, M.-L.; Chen, M.-Q.; Xu, B.; Zhu, S.-F.; Zhou, Q.-L. Enantioselective O–H Bond Insertion of α-Diazoketones with Alcohols Cooperatively Catalyzed by Achiral Dirhodium Complexes and Chiral Spiro Phosphoric Acids. *Acta Chim. Sinica* **2018**, *76*, 883. (m) Harada, S.; Tanikawa, K.; Homma, H.; Sakai, C.; Ito, T.; Nemoto, T. Silver-Catalyzed Asymmetric Insertion into Phenolic O–H Bonds using Aryl Diazoacetates and Theoretical Mechanistic Studies. *Chem. Eur. J.* **2019**, *25*, 12058.

8 For reviews, see: (a) Zhu S.-F.; Zhou, Q.-L. Iron-Catalyzed Transformations of Diazo Compounds. *Nat. Sci. Rev*. **2014**, *1*, 580. (b) DeAngelis, A.; Panish, R.; Fox, J. M. Rh-Catalyzed Intermolecular Reactions of α-Alkyl-α-Diazo Carbonyl Compounds with Selectivity over β-Hydride Migration. *Acc. Chem. Res*. **2016**, *49*, 115. (c) Xia, Y.; Qiu, D.; Wang, J. Transition-Metal-Catalyzed Cross-Couplings through Carbene Migratory Insertion. *Chem. Rev.* **2017**, *117*, 13810.

9 For a review, see: (a) Guo, X.; Hu, W. Novel Multicomponent Reactions via Trapping of Protic Onium Ylides with Electrophiles. *Acc. Chem. Res.* **2013**, *46*, 2427. For selected examples, see: (b) Wood, J. L.; Moniz, G. A. Rhodium Carbenoid-Initiated Claisen Rearrangement: Scope and Mechanistic Observations. *Org. Lett.* **1999**, *1*, 371. (c) Wood, J. L.; Holubec, A. A.; Stoltz, B. M.; Weiss, M. M.; Dixon, J. A.; Doan, B. D.; Shamji, M. F.; Chen, J. M.; Heffron, T. P. Application of Reactive Enols in Synthesis: A Versatile, Efficient, and Stereoselective Construction of the Welwitindolinone Carbon Skeleton. *J. Am. Chem. Soc.* **1999**, *121*, 6326. (d) Zhang, X.; Huang, H.; Guo, X.; Guan, X.; Yang, L.; Hu, W. Catalytic Enantioselective Trapping of an Alcoholic Oxonium Ylide with Aldehydes: Rh^{II} /Zr^{IV}-Co-Catalyzed Three-Component Reactions of Aryl Diazoacetates, Benzyl Alcohol, and Aldehydes. *Angew. Chem. Int. Ed.* **2008**, *47*, 6647. (e) Li, Z.; Davies, H. M. L. Enantioselective C-C Bond Formation by Rhodium-Catalyzed Tandem Ylide Formation/[2,3]-Sigmatropic Rearrangement between Donor/Acceptor Carbenoids and Allylic Alcohols. *J. Am. Chem. Soc.* **2010**, *132*, 396. (f) Parr, B. T.; Li, Z.; Davies, H. M. L. Asymmetric Synthesis of Highly Functionalized Cyclopentanes by a Rhodium- and Scandium-Catalyzed Five-step Domino Sequence. *Chem. Sci.* **2011,** *2,* 2378. (g) Jiang, J.; Guan, X.; Liu, S.; Ren, B.; Ma, X.; Guo, X.; Lv, F.; Wu, X.; Hu, W. Highly Diastereoselective Multicomponent Cascade Reactions: Efficient Synthesis of Functionalized 1-Indanols. *Angew. Chem. Int. Ed.* **2012,** *51*, 1539. (h) Li, Z.; Parr, B. T.; Davies, H. M. L. Highly Stereoselective C-C Bond Formation by Rhodium-Catalyzed Tandem Ylide Formation/[2,3]-Sigmatropic Rearrangement between Donor/Acceptor Carbenoids and Chiral Allylic Alcohols. *J. Am. Chem. Soc.* **2012**, *134*, 10942. (i) Parr, B. T.; Davies, H. M. L. Highly Stereoselective Synthesis of Cyclopentanes Bearing Four Stereocentres by a Rhodium Carbene-Initiated Domino Sequence. *Nat. Commun*. **2014**, *5*, 4455.

10 For the applications of chiral phosphoric acids in other asymmetric carbene insertion reactions, see: Ren, Y.-Y.; Zhu, S.-F.; Zhou, Q.-L. Chiral Proton-Transfer Shuttle Catalysts for Carbene Insertion Reactions. *Org. Biomol. Chem*. **2018**, *16*, 3087.

11 Yamashita, R.; Sakakura, A.; Ishihara, K. Primary Alkylboronic Acids as Highly Active Catalysts for the Dehydrative Amide Condensation of α-Hydroxycarboxylic Acids. *Org. Lett.* **2013**, *15*, 3654.

12 (a) Reddy, B. V. S.; Rao, R. N.; Kumaraswamy, B.; Yadav, J. S. Stereoselective Total Synthesis of Oplopandiol, Oploxyne A, and Oploxyne B. *Tetrahedron Letters* **2014**, *55*, 4590. (b) Kotkar, S. P.; Sudalai, A. A Short Enantioselective Synthesis of the Antiepileptic Agent Levetiracetam Based on Proline-Catalyzed Asymmetric α-Aminooxylation. *Tetrahedron Letters* **2006**, *47*, 6813. (c) Gharpure, S. J.; Nanda, L. N.; Shukla, M. K. Enantioselective Total Synthesis of (+)-Hagen's Gland Lactones. *Eur. J. Org. Chem.* **2011**, *33,* 6632. (d) Nicolaou, K. C.; Marrón, B. E.; Veale, C. A.; Webber, S. E.; Serhan, C. N. Total Synthesis of Novel Geometric Isomers of Lipoxin A4 and Lipoxin B4. *J. Org. Chem*. **1989**, *54*, 5527. (e) Nagasawa, K.; Georgieva, A.; Koshino, H.; Nakata, T.; Kita, T.; Hashimoto, Y. Total Synthesis of Crambescidin 359. *Org. Lett*. **2002**, *4*, 177. (f) Ramulu, U.; Ramesh, D.; Reddy, S. P.; Rajaram, S. Babu, K, S. The Stereoselective Total Syntheses of Pectinolides A, B, and C. *Tetrahedron: Asymmetry* **2014**, *25*, 1409.

13 Baskakis, C.; Magrioti,V.; Cotton, N.; Stephens, D.; Constantinou-Kokotou, V.; Dennis, E. A.; Kokotos, G. Synthesis of Polyfluoro Ketones for Selective Inhibition of Human Phospholipase A2 Enzymes. *J. Med. Chem.* **2008**, *51,* 8027.

14 Kalaritis, P.; Regenye, R. W.; Partridge, J. J.; Coffen, D. L. Kinetic Resolution of 2-Substituted Esters Catalyzed by a Lipase Ex. Pseudomonas Fluorescens. *J. Org. Chem.* **1990**, *55*, 812.

15 (a) Weibel, D. B.; Shevy, L. E.; Schroeder, F. C.; Meinwald, J. Synthesis of Mayolene-16 and Mayolene-18: Larval Defensive Lipids from the European Cabbage Butterfly. *J. Org. Chem.* **2002**, *67*, 5896. (b) Chandrasekhar, S. Vijaykumar, B. V. D.; Pratap, T. V. Total Synthesis of (-)-Lentiginosine. *Tetrahedron: Asymmetry* **2008**, *19*, 746. (c) Hess, L. C.; Posner, G. H. Asymmetric, Organocatalytic, Three-Step Synthesis of α-Hydroxy-(*E*)-β,γ-unsaturated Esters. *Org. Lett.* **2010**, *12*, 2120. (d) Bejjanki, N. K.; Venkatesham, A.; Balraju, K.; Nagaiah, K. First Stereoselective Total Synthesis of Oplopandiol. *Helv. Chim. Acta* **2013**, *96*, 1571. (e) Chen, J.; Lin, G.-Q.; Wang, Z.-M.; Liu, H.-Q. A Short and General Approach to the Synthesis of Styryllactones: (+)-Goniodiol, Its Acetates and α-Trifluoromethyl Derivative, (+)-7-*epi* Goniodiol and (+)-9-Deoxygoniopypyrone. *Synlett* **2002**, *8*, 1265. (f) Lee, J.; Hong, J. First Synthesis and Structural Elucidation of (-)-Presphaerene. *J. Org. Chem.* **2004**, *69,* 6433. (g) Wang, F.-D.; Yue, J.-M. Total Synthesis of (R)-(+)-Kavain via $(MeCN)_2PdCl_2$-Catalyzed Isomerization of a *cis* Double Bond and Sonochemical Blaise Reaction. *Synlett* **2005**, *13*, 2077. (h) Bose, D. S.; Reddy, A. V. N.; Srikanth, B. A Concise Enantioselective Strategy to (+)-(*R*)-Goniothalamin and (+)-(*R*)-Goniothalamin Oxide by Employing Hydrolytic Kinetic Resolution and Ring-Closing Metathesis as Key Steps. *Synthesis* **2008**, *15*, 2323.

16 Findlay, A. D.; Banwell, M. D. A Chemoenzymatic Total Synthesis of (+)-Amabiline. *Org. Lett*. **2009,** *11,* 3160.

17 Kondoh, A.; Kamata, Y.; Terada, M. Synthesis of Enantioenriched γ-Amino-α,β-unsaturated Esters Utilizing Palladium-Catalyzed Rearrangement of Allylic Carbamates for Direct Application to Formal [3 + 2] Cycloaddition. *Org. Lett*. **2017**, *19*, 1682.

18 (a) Ghosh, A. K.; Brindisi, M.; Tang, J. Developing β-Secretase Inhibitors for Treatment of Alzheimer's Disease. *J. Neurochem*. **2012**, *120*, 71. (b) Bregman, H.; Chakka, N.; Guzman-Perez, A.; Gunaydin, H.; Gu, Y.; Huang, X.; Berry, V.; Liu, J.; Teffera, Y.; Huang, L.; Egge, B.; Mullady, E. L.; Schneider, S.; Andrews, P. S.; Mishra, A.; Newcomb, J.; Serafino, R.; Strathdee, C. A.; Turci, S. M.; Wilson, C.; DiMauro, E. F. Discovery of Novel, Induced-Pocket Binding Oxazolidinones as Potent, Selective, and Orally Bioavailable Tankyrase Inhibitors. *J. Med. Chem.* **2013**, *56*, 4320.

19 (a) Ohmiya, H.; Makida, Y.; Li, D.; Tanabe, M.; Sawamura M. Palladium-Catalyzed γ-Selective and Stereospecific Allyl-Aryl Coupling between Acyclic Allylic Esters and Arylboronic Acids. *J. Am. Chem. Soc.* **2010**, *132*, 879. (b) Kamble, R. B.; Devalankarc, D.; Suryavanshi, G. Two Stereocentered HKR of Anti-β,β'-diphenylpropanoxirane and *anti*-3-phenylethyloxiranes Catalyzed by Co(III)(salen)-OAc Complex: Enantioselective

Synthesis of (+)-Sertraline and (+)-Naproxen. *New J. Chem*. **2018**, *42*, 10414.

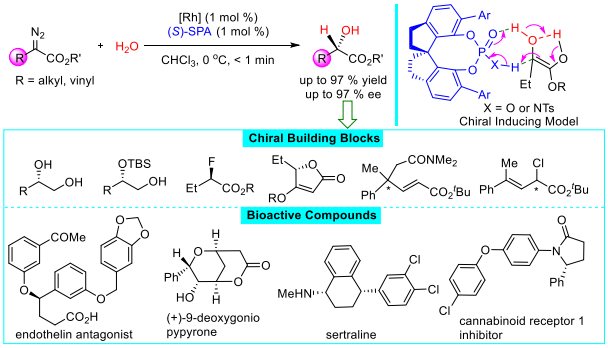
20 Discolo, C. A.; Graves, A. G.; Deardorff, D. R. Regio- and Stereospecific C- and O-Allylation of Phenols via π-Allyl Pd Complexes Derived from Allylic Ester Carbonates. *J. Org. Chem*. **2017**, *82*, 1034.

21 (a) Liang, Y.; Zhou, H.; Yu, Z.-X. Why Is Copper(I) Complex More Competent Than Dirhodium(II) Complex in Catalytic Asymmetric O-H Insertion Reactions? A Computational Study of the Metal Carbenoid O-H Insertion into Water. *J. Am. Chem. Soc.* **2009**, *131*, 17783. (b) Xie, Z.-Z.; Liao, W.-J.; Cao, J.; Guo, L.-P.; Verpoort, F.; Fang, W. Mechanistic Insight into the Rhodium-Catalyzed O–H Insertion Reaction: A DFT Study. *Organometallics* **2014**, *33*, 2448. (c) Liu, Y; Luo, Z.; Zhang, J. Z.; Xia, F. DFT Calculations on the Mechanism of Transition-Metal-Catalyzed Reaction of Diazo Compounds with Phenols: O–H Insertion versus C–H Insertion. *J. Phy. Chem. A* **2016**, *120*, 6485. (d) Wu, J.; Li, X.; Qi, X.; Duan, X.; Cracraft, W. L.; Guzei, I. A.; Liu, P.; Tang, W. Site-Selective and Stereoselective O-Alkylation of Glycosides by Rh(II)-Catalyzed Carbenoid Insertion. *J. Am. Chem. Soc.* **2019**, *141*, 19902.

22 Plata, R. E.; Singleton, D. A. A Case Study of the Mechanism of Alcohol-Mediated Morita Baylis–Hillman Reactions. The Importance of Experimental Observations. *J. Am. Chem. Soc.* **2015**, *137*, 3811.

23 (a) Li, M.-L.; Yu, J.-H.; Li, Y.-H.; Zhu, S.-F.; Zhou, Q.-L. Highly Enantioselective Carbene Insertion into N–H Bonds of Aliphatic Amines. *Science* **2019**, *366*, 990. (b) Li, Y.-P.; Li, Z.-Q.; Zhou, B.; Li, M.-L.; Xue, X.-S.; Zhu, S.-F.; Zhou, Q.-L. Chiral Spiro Phosphoric Acid-Catalyzed Friedel–Crafts Conjugate Addition/Enantioselective Protonation Reactions. *ACS Catal.* **2019**, *9*, 6522.

TOC


[Rh] (1 mol %)
(S)-SPA (1 mol %)
CHCl3, 0 °C, < 1 min
R = alkyl, vinyl
up to 97 % yield
up to 97 % ee
X = O or NTs
Chiral Inducing Model
Chiral Building Blocks
Bioactive Compounds
endothelin antagonist
(+)-9-deoxygonio pypyrone
sertraline
cannabinoid receptor 1 inhibitor