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A Strategy to Synthesize Taxol Side Chain and (−)-*epi* Cytoxazone via Chiral Brønsted Acid-$Rh_2(OAc)_4$ Co-catalyzed Enantioselective Three-Component Reactions†

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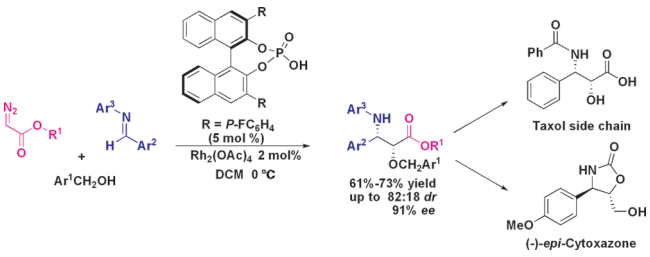
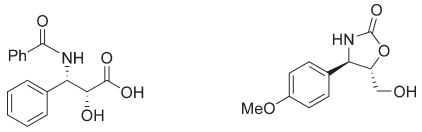


A new approach to synthesize optically active β-amino-α-hydroxyl acid derivatives via chiral Brønsted acid-$Rh_2(OAc)_4$ cocatalyzed three-component reactions of diazo acetates with alcohols and imines is reported. A matched reaction system was identified to give the products in moderate diastereoselectivity and good enantioselectivity. Application of this methodology is demonstrated in the efficient synthesis of a taxol side chain and (−)-*epi*-cytoxazone.

Chiral β-amino-α-hydroxyl acid derivatives are not only frequently used as building blocks in natural product synthesis[1] and as chiral ligands[2] in asymmetric catalysis, but also are frequently present in pharmaceutical related compounds.[1a,3] For example, a side chain of the anticancer drug Taxol[3a,b] and (−)-*epi*-cytoxazone,[3c,d] which showed potential biological activity to allergens, share the same core structure as that of chiral β-amino-α-hydroxyl acid derivatives (Scheme 1). Therefore, numerous efforts have been made to develop enantioselective methodologies to synthesize optically active β-amino-α-hydroxyl acids. Successful approaches include 1,3-dipolar cycloadditions,[4] Sharpless aminohydroxylation,[5] and the ring-opening of epoxides and aziridines[6] with appropriate nucleophiles. Furthermore, organocatalytic asymmetric Mannich-type reactions[7] toward producing chiral β-amino-α-hydroxyl acids have been developed independently by List[7a] and Córdova.[7b]

SCHEME 1. Structure of a Taxol Side Chain and (−)-*epi*-Cytoxazone



The development of highly efficient reactions that yield complex molecules from simple starting materials has received considerable attention in recent years.[8] Multicomponent reactions (MCRs)[9] are considered as powerful strategies to form multiple chemical bonds from three or more starting materials in one step with a high yield. Recently, as an effective strategy to enhance reaction selectivity and reactivity, cooperative catalysis in asymmetric tandem, multicomponent reactions has been reported to produce chiral molecules with improved synthetic efficiency.[10]

† Dedicated to Professor Albert B. C. Chan on the occasion of his 60th birthday.

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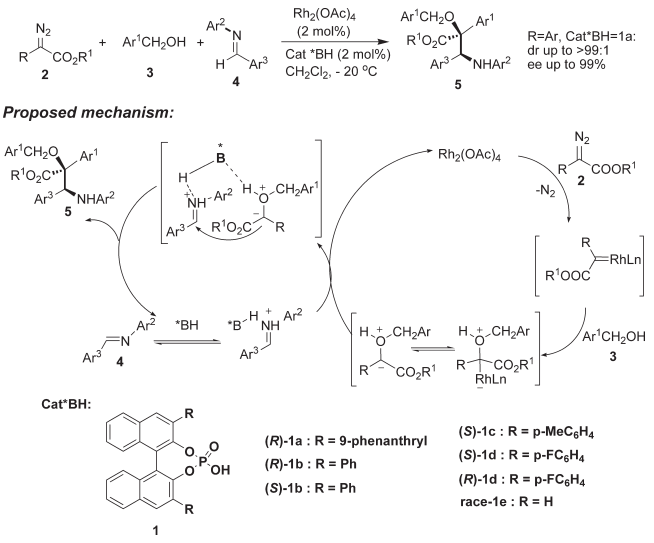
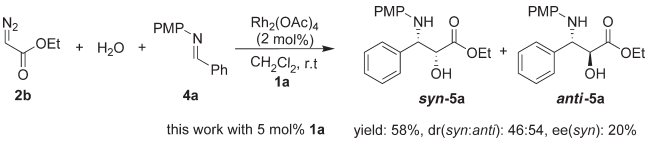
SCHEME 2. Constructing β-Amino-α-hydroxyl Acid Derivatives from Three-Component Reactions



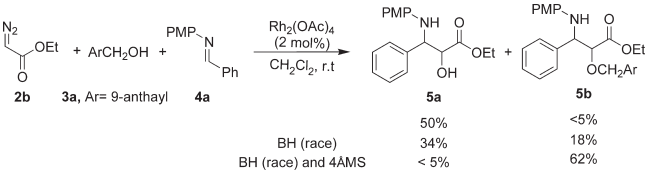
Our group recently reported Rh(II)-catalyzed three- component reactions of aryldiazoacetates, alcohols, and imines.[10a] By applying a cocatalysis strategy, using chiral Brønsted acids as a cocatalyst,[11] optically active β-amino-α-aryl-α-alkyloxy esters were obtained in excellent diastereoselectivity and enantioselectivity (Scheme 2).[10a] However, the efficient synthetic method was mostly limited to aryldiazoacetates (**2**: R = Ar), therefore, the synthetic utility was quite limited. Recently, we reported a matched system to extend the reaction scope from aryldiazoacetates to alkyldiazoacetates, and an excellent yield was obtained from the reaction by using water to replace the alcohol.[12] Our challenge now is to achieve an enantioselective version of the three-component reaction using ethyl diazoacetate (EDA) as a reaction component. In this note, we report our efforts to find a matched catalytic system to achieve high enantioselectivity of the three-component reaction with EDA. The efficient strategy is demonstrated in the total synthesis of a taxol side chain and (−)-*epi*-cytoxazone. This is the first example of the application of the ylide-trapping process to obtain pharmaceutically related molecules.

Our research started with the coupling reaction of EDA, water, and the imine **4a** in the presence of $Rh_2(OAc)_4$ and chiral Brønsted acid **1a**; the desired product **5a** was isolated in a 58% yield with a dr of 46:54. The enantioselectivity of *syn*-**5a** was found to be only 20% ee (Scheme 3). The low enantioselectivity is considered to be partially related to the background reaction caused by the high reactivity of the oxonium ylide from water. In order to enhance the enantioselectivity of the reaction, we decided to investigate the reaction by using an alcohol as a component, hoping that the lower nucleophilicity of the oxonium ylide derived from the alcohol may reduce the influence from the background reaction and therefore lead to high enantioselectivity of the reaction.

SCHEME 3. Three-Component Reaction of EDA, Water, and Imine 4a



SCHEME 4. Three-Component Reaction of EDA, Alcohol 3a, and Imine 4a



Alcohol **3a** was employed in the three-component reaction of the imine **4a** and EDA in the presence of $Rh_2(OAc)_4$ catalyst alone (Scheme 4). Unfortunately, less than 5% of the desired product **5b** was obtained. Instead, the compound **5a**, being considered from a trace amount of water in the reaction system, was isolated in a 50% yield. When a racemic Brønsted acid (BH) **1e** was added in the reaction mixture so as to activate the imine **4a**, an 18% yield of **5b** was isolated together with a 34% yield of **5a**. We understand now that an oxonium ylide derived from an alcohol and EDA can react with the imine in the presence of the cocatalyst. To totally suppress the side reaction from water, we added freshly dried 4 Å MS into the solvent. We were gratified to find that the desired product **5b** was isolated in a 62% yield. Our next effort was to find matched components and chiral Brønsted acids in the reaction to enhance the reaction selectivity.

Our efforts to find matched components and catalysts started with the use of *tert*-butyl diazoacetate, **2c**. As compared to ethyl diazoacetate, **2c** is considered to be a bulkier diazo compound. The reaction gave a slightly better result than that from using EDA, the ratio to the desired syn diastereomer slightly improved from 37:73 (*syn*-**5**:*anti*-**5**) to 45:55 with a higher ee (49% vs 35%) of the syn isomer (Table 1, entry 2 vs 3). The ee of *syn*-**5d** was improved to 52% when we changed the catalyst (*R*)-**1a** to (*R*)-**1b**, but at the expense of diastereoselectivity for the desired syn isomer (Table 1, entry 4). We were gratified to find that the alcohol component has significant effect on the reaction. When the less sterically hindered benzyl alcohol **3b** was used, the ee of *syn*-**5e** improved significantly to 84% (Table 1, entry 5). Based on the above reaction results, various substituted benzyl alcohols were screened, and it was found that 2,6-dichlorophenyl methanol **3e** was the best among the alcohols tested to give the product **5h** in 88% ee and dr of 47:53 (entries 6−8). Further evaluation of various chiral phosphoric acid catalysts revealed that the *p*-fluorophenyl derived BINOL phosphoric

(11) Selected examples of chiral Brønsted acid-catalyzed reactions: (a) Lu, M; Zhu, D.; Lu, Y.; Zeng, X.; Tan, B.; Xu, Z.; Zhong, G. F. *J. Am. Chem. Soc.* **2009**, *131*, 4562. (b) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336. (c) Han, Z.; Xiao, H.; Chen, X.; Gong, L. *J. Am. Chem. Soc.* **2009**, *131*, 9182. (d) Lu, M; Lu, Y.; Zhu, D.; Zeng, X.; Li, X.; Zhong, G. F. *Angew. Chem., Int. Ed.* **2010**, *49*, DOI: 10.1002/anie.201002640. (e) Zeng, X.; Xu, Z.; Lu, M.; Zhong, G. *Org. Lett.* **2009**, *11*, 3036. (f) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566. For representative reviews: (g) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (h) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713.

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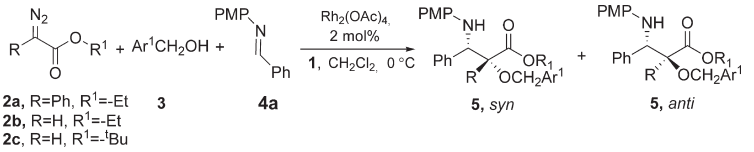
TABLE 1. Catalyst Screening and Optimization of Reaction Conditions[a]

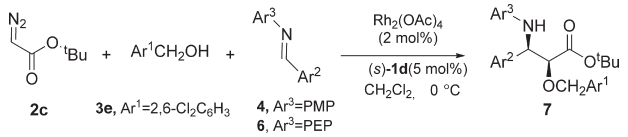


2a, R=Ph, R^1=-Et **2b**, R=H, R^1=-Et **2c**, R=H, R^1=-^{t}Bu | **3** | **4a** | **5**, *syn* | **5**, *anti*

entry	2	3(Ar^1)	5	catalyst (mol %)	yield (%)[b]	dr[c] (syn:anti)	ee[d] (%) (syn)
1	**2a**	**3a**(9-anthayl)	**5c**	(*R*)-**1a**(2)	98	>99:1	>99
2	**2b**	**3a**(9-anthayl)	**5b**	(*R*)-**1a**(5)	62	37:63	35
3	**2c**	**3a**(9-anthayl)	**5d**	(*R*)-**1a**(5)	55	45:55	49
4	**2c**	**3a**(9-anthayl)	**5d**	(*R*)-**1b**(5)	70	32:68	52
5	**2c**	**3b**(Ph)	**5e**	(*R*)-**1b**(5)	56	54:46	84
6	**2c**	**3c**(*p*-OMeC_6H_4)	**5f**	(*R*)-**1b**(5)	45	47:53	86
7	**2c**	**3d**(*o*-BrC_6H_4)	**5g**	(*R*)-**1b**(5)	52	52:48	86
8	**2c**	**3e**(2,6-$Cl_2C_6H_3$)	**5h**	(*R*)-**1b**(5)	64	47:53	88
9	**2c**	**3e**(2,6-$Cl_2C_6H_3$)	**5h**	(*S*)-**1b**(5)	51	72:28	77
10	**2c**	**3e**(2,6-$Cl_2C_6H_3$)	**5h**	(*S*)-**1c**(5)	48	67:33	87
11	**2c**	**3e**(**2,6-$Cl_2C_6H_3$**)	**5h**	(***S***)-**1d**(**5**)	**68**	**68:32**	**88**
12	**2c**	**3e**(2,6-$Cl_2C_6H_3$)	**5h**	(*S*)-**1d**(10)	65	67:33	86
13[e]	**2c**	**3e**(2,6-$Cl_2C_6H_3$)	**5h**	(*S*)-**1d**(5)	71	66:34	84
14[f]	**2c**	**3e**(2,6-$Cl_2C_6H_3$)	**5h**	(*S*)-**1d**(5)	55	69:31	86
15	**2c**	**3e**(2,6-$Cl_2C_6H_3$)	**5h**	(*S*)-**1d**(2)	48	66:34	85

[a]For reaction conditions, see Experimental Section in Supporting Information. [b]Isolated yield. [c]Determined by 1H NMR spectroscopy from the unpurified reaction mixture. [d]Determined by chiral HPLC with IA column. [e]Reaction temperature of 30 °C. [f]Reaction temperature of −20 °C.

TABLE 2. Enantioselective three-component reaction of alcohol 3e with diazo compound 2c and imines[a]



2c | **3e**, Ar^1=2,6-$Cl_2C_6H_3$ | **4**, Ar^3=PMP **6**, Ar^3=PEP | **7**

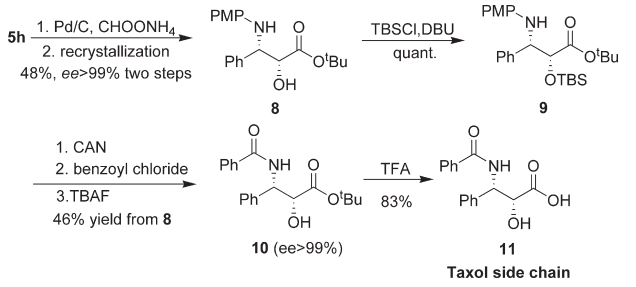
entry	**4** or **6** (Ar^2)	**7**	yield (%)[b]	dr (syn:anti)[c]	ee[d] (syn)
1	**6a**(C_6H_5)	**7a**	73	64:36	87
2	**4b**(*p*-ClC_6H_4)	**7b**	64 (26)[h]	62:38	82 (>99)[g]
3	**4c**(*p*-BrC_6H_4)	**7c**	72 (30)[h]	61:32	83 (>99)[g]
4	**4d**(*p*-$CF_3C_6H_4$)	**7d**	70 (26)[h]	52:48	91 (>99)[g]
5	**4e**(*p*-FC_6H_4)	**7e**	61	54:46	81
6	**4f**(*m*-BrC_6H_4)	**7f**	65	61:39	70
7	**4g**(*p*-MeC_6H_4)	**7g**	63 (29)[h]	66:34	86 (>99)[g]
8	**4h**(*p*-OMeC_6H_4)	**7h**	61 (28)[h]	76:24	82 (>99)[g]
9	**4i**(3,4-$(OMe)_2$-C_6H_4)	**7i**	67	82:18	80
10[e]	**4a**(C_6H_5)	**5h**	72	55:45	−84
11[f]	**4h**(*p*-OMeC_6H_4)	**7h**	68	57:43	80

[a]For reaction conditions, see Experimental Section in Supporting Information. [b]Isolated yield. [c]Determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture. [d]Determined by chiral HPLC with IA column. [e]Reaction was performed on 2.5 mmol scale with $Rh_2(OAc)_4$ (0.5 mol %) and (*R*)-**1d** (1 mol %). [f]Reaction was performed on 2 mmol scale with $Rh_2(OAc)_4$ (0.5 mol %) and (*S*)-**1d** (2 mol %). [g]The result in parentheses was obtained after a single recrystallization. [h]Yield of the syn isomer after the recrystallization.

acid (*s*)-**1d** improved the dr to 68:32 without compromising the ee value (entry 11). Similar results were obtained when increasing the catalyst loading to 10 mol % or increasing the reaction temperature to 30 °C (entries 12 and 13). A lower yield was obtained by decreasing the cocatalyst loading to 2 mol % or lowering the reaction temperature to −20 °C (entries 14 and 15).

With the optimized reaction conditions in hand, the matched system with the components **2c** and **3e** and the catalyst (*s*)-**1d** was extended to various imines; the results obtained are summarized in Table 2. In most cases, the reaction proceeded smoothly to give the desired products **7** in a good yield (61%−73%) and a moderate dr (up to 82:18) and a high enantioselectivity of the desired syn isomer (>80% ee). In general, the electronic-donating imine substrate resulted in a higher diastereoselectivity of the corresponding product than did the electronic-withdrawing one (entries 7−9 vs entries 2−6). Notably, some products were recrystallized once to give the single syn isomer with an ee exceeding 99% (entries 2−4, 7−11).

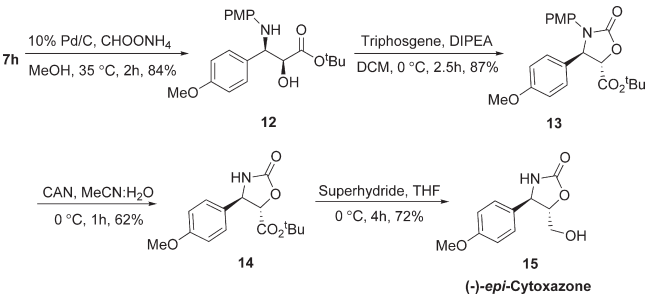
SCHEME 5. Total Synthesis of a Taxol Side Chain



For further demonstrating the synthetic utility of the novel reaction, the product **5h** was selected to undergo additional transformations so as to complete the formal total synthesis of taxol. Thus, hydrogenation of **5h** with ammonium formate in the presence of a 10% Pd/C catalyst gave the free alcohol **8** in a 48% yield with a 99% ee after recrystallization in the solvent of EtOAc:*n*-Hex = 1:50 (Scheme 5). After reprotection of the alcohol with TBSCl, oxidative cleavage of the PMP protection group, benzoylation, and deprotection with TBAF, the intermediate α-hydroxyl ester **10** was synthesized in a yield of 46% (four steps) without any loss of ee. Finally, the optically pure taxol side chain **11** was synthesized after hydrolysis. The characterization data of **11** were found to be in agreement with those reported in the literature.[13]

The advantage of an MCR in efficiently generating structurally diversified compounds is demonstrated here. Under a

SCHEME 6. Total synthesis of (−)-*epi*-cytoxazone



similar reaction situation, with a simple change to the imine **4h**, the chiral amino alcohol **7h** bearing two stereogenic centers was constructed in moderate dr and high ee. From **7h**, (−)-*epi*-cytoxazone was synthesized in several steps (Scheme 6). Thus, the recrystallized **7h** was hydrolyzed with ammonium formate in the presence of a 10% Pd/C catalyst so as to afford the *syn*-aminol **12** in an 84% yield. After treatment of **12** with triphosgene and DIPEA in dichloromethane, the oxazolidinone **3** was obtained in an 87% yield. With the oxidation of the ceric ammonium nitrate in acetonitrile and water, the *N*-methoxyphenyl moiety on the oxazolidinone ring was cleaved to the compound **14** in a 62% yield. The subsequent reduction with superhydride gave the (4*R*,5*S*)-*epi*-cytoxazone **15** in a 72% yield. The compound **15** has spectroscopic properties identical to those described in the literature.[3d]

In conclusion, we report a new strategy to synthesize chiral β-amino-α-hydroxyl acid derivatives bearing two stereogenic centers in one step from three simple starting materials in a highly efficient manner. The strategy of cooperative catalysis is applied to the three-component reactions to produce the target products in a good yield with moderate diastereoselectivity and high enantioselectivity. The key to the success is to find a matched system among the components and the catalysts. The efficient synthetic method was demonstrated in the synthesis of a taxol side chain and (−)-epi-cytoxazone. This is the first time that the highly efficient ylide-trapping process is applied for the synthesis of pharmaceutically interesting molecules. The application of this strategy in the efficient synthesis of additional biologically active compounds is currently underway in our lab.

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Experimental Section

General Procedure for the Enantioselective Three-Component Reactions. A suspension of $Rh_2(OAc)_4$ (2.2 mg, 2.0 mol %), chiral phosphoric acid **1** (5.0 mol %), alcohol **3** (0.28 mmol, 1.1 equiv), imine **4** or **6** (0.25 mmol, 1.0 equiv) and 4 Å MS (0.1 g) in 2.0 mL CH_2Cl_2 under argon atmosphere was cooled to 0 °C, and then diazo compound **2** (0.30 mmol, 1.2 equiv) in 1.0 mL CH_2Cl_2 was added over 1 h via a syringe pump. After completion of the addition, the reaction was stirred for another 0.5 h and followed by addition of saturated aqueous $NaHCO_3$ (0.1 mL) to quench the reaction. The crude products were subjected to ^1H NMR spectroscopy analysis for the determination of diastereoselectivity. The reaction mixtures were purified by flash chromatography on silica gel (eluent: EtOAc/light petroleum ether = 1:40−1:20) to give the three-component reaction products.

(2*S*,3*R*)-*tert*-Butyl2-(2,6-dichlorobenzyloxy)-3-(4-methoxyphenylamino)-3-phenylpropanoate (*syn*-5h): 68% yield; 88% ee, determined by HPLC (Daicel Chirapak IA, flow rate 1.0 mL/min, hexane/isopropanol = 20: 1, 254 nm, Retention time: t_{minor} = 7.6 min, t_{major} = 12.7 min.); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9H), 3.57 (s, 3H), 3.99 (d, J = 4.0 Hz, 1H), 4.62 (m, 2H), 4.87 (d, J = 8.0 Hz, 1H), 6.37 (d, J = 8.0 Hz, 2H), 6.54 (d, J = 8.0 Hz, 2H), 7.01−7.05 (m, 1H), 7.08−7.16 (m, 5H), 7.19−7.21 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.9, 55.6, 60.5, 66.8, 82.0, 82.2, 114.5, 114.9, 127.1, 127.2, 128.1, 128.2, 130.0, 132.2, 136.9, 139.5, 141.3, 151.9, 169.3; HRMS (ESI) calcd for $C_{27}H_{29}Cl_2NNaO_4$ $[M + Na]^+$ = 524.1371, found 524.1362.

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Supporting Information Available: Experimental procedures, characterization data, copies of ^1H and ^{13}C NMR, HPLC of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.