DOI: 10.1002/adsc.201300135

Organocatalytic Asymmetric Mannich Reactions of 5*H*-Oxazol-4-ones: Highly Enantio- and Diastereoselective Synthesis of Chiral α-Alkylisoserine Derivatives

Zhiqiang Han,[+a] Wenguo Yang,[+a] Choon-Hong Tan,[a,b] and Zhiyong Jiang[a,b,*]

[a] Key Laboratory of Natural Medicine and Immuno-Engineering of Henan Province, Henan University, Kaifeng, Henan 475004, People's Republic of China
E-mail: chmjzy@henu.edu.cn

[b] Division of Chemistry and Biological Chemistry, Nanyang Technological University, 21 Nanyang Link, 637371, Singapore

[+] Z. Han and W. Yang made equal contributions to this work.

Received: February 8, 2013; Published online: May 15, 2013

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300135.

Abstract: The first organocatalytic Mannich reaction of 5*H*-oxazol-4-ones with various readily prepared aryl- and alkylsulfonimides has been developed. Two commercially available pseudoenantiomeric *Cinchona* alkaloids-derived tertiary amine/ureas have been demonstrated as the most efficient catalysts to access the opposite enantiomers of the Mannich products with equally excellent enantio- and diastereoselectivities. From the Mannich adducts, important α-methyl-α-hydroxy-β-amino acid derivatives, such as the α-methylated C-13 side chain of taxol and taxotere, can be conveniently prepared.

Keywords: α-alkyl-α-hydroxy β-amino acids; asymmetric catalysis; Mannich reaction; 5*H*-oxazol-4-ones; *N*-triisopropylbenzenesulfonylimines

Non-proteinogenic α-hydroxy-β-amino acids (isoserines) are probably the most important members of the β-amino acid family that are essential scaffolds to a large number of well-known, naturally occurring products endowed with potent biological activity (Figure 1).[1] A prime example is (2*R*,3*S*)-phenylisoserine at the C-13 side chain of taxol, taxotere and derivatives, which are currently considered to be among the most promising drugs used in cancer chemotherapy for breast and ovarian cancer.[2] Following numerous synthetic efforts, biological assays carried out with the C-2′-methylated α-hydroxy-β-amino acids, namely α-hydroxy-α-methyl-β-amino acids, revealed significant enhancement of potency and reduction in toxicity compared with the parent drug.[3] Concurrently, Turos and co-workers disclosed that the incorporation of methyl group into the C-3 position of *N*-thiolated C-3-oxygenated β-lactams should increase the

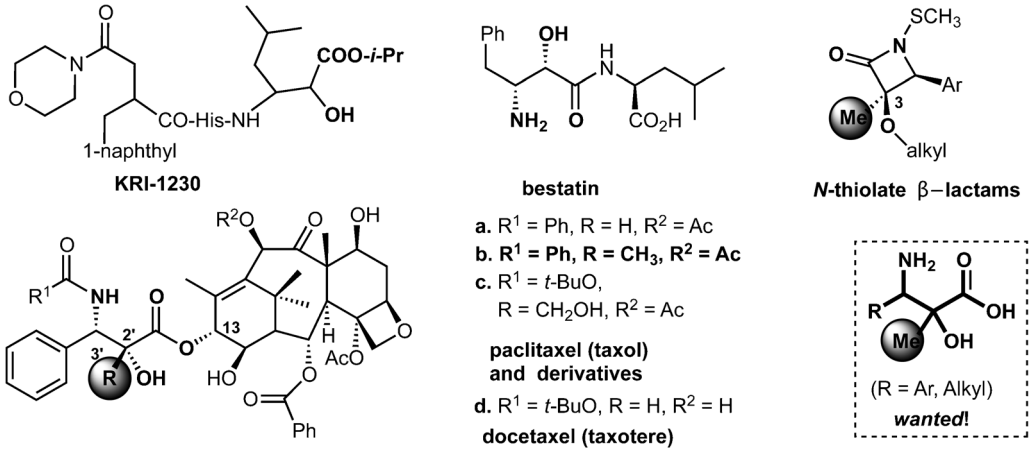


Figure 1. Representative biologically active molecules containing α-hydroxy-β-amino acids.

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

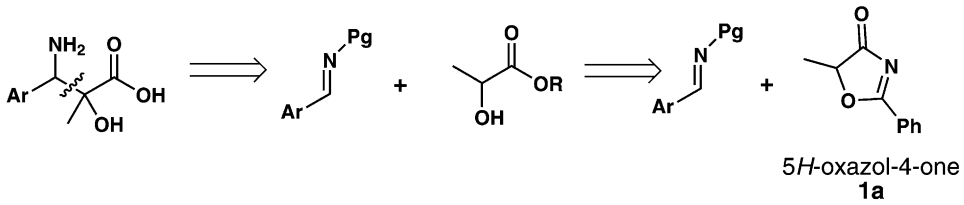


Figure 2. Retrosynthetic analysis of α-methyl-α-hydroxy-β-amino acids (Pg = protecting group).

anti-*Bacillus* activity (Figure 1).[4] The improved activities exhibited by these potential drug candidates have stimulated the development of preparative methods for α-hydroxy-α-methyl-β-amino acids.[5] However, the asymmetric strategy to access α-hydroxy-α-methyl-β-amino acids with aryl and alkyl β-substituted groups simultaneously, is still not reported and represents a formidable task, coupled with the challenge to construct a chiral tertiary alcohol.[6]

On retrosynthetic analysis, it is easy to reveal that the Mannich reaction is plausible to construct the β-amino acid with α-hydroxy esters as nucleophiles (Figure 2). However, the construction of a chiral tertiary alcohol using the Mannich reaction demands a highly reactive system for the sterically hindered donor substrates. We turned our attention to the Mannich reaction of 5*H*-oxazol-4-one **1a** bearing a methyl group at the C-5 position as the pronucleophile, by which the Mannich adduct could be readily converted into chiral α-hydroxy acids with a quaternary stereocenter.

5*H*-Oxazol-4-ones were first introduced by Trost and co-workers as useful pronucleophiles in asymmetric allylic alkylation with chiral diphosphine-molybdenum catalysts.[7] Subsequently, Misaki and Sugimura et al. described an asymmetric aldol reaction of 5*H*-oxazol-4-ones with aldehydes and 1,4-addition with terminal alkynyl carbonyl compounds catalyzed by chiral guanidine catalysts.[8] Ye and co-workers presented a 1,4-addition of 5*H*-oxazol-4-ones to α,β-unsaturated ketones using a new thiourea-tertiary amine bifunctional catalyst derived from L-*tert*-leucine.[9] Trost and co-workers reported a 1,4-addition of 5*H*-oxazol-4-ones to nitroolefins to prepare α-alkyl-α-hydroxy carboxylic acid derivatives catalyzed by a dinuclear zinc complex.[10]

Very recently, Wang and co-workers disclosed the first report on the asymmetric Mannich reaction between 5*H*-oxazol-4-ones with *N*-diphenylphophinoyl-protected imines catalyzed by a zinc complex with good to excellent enantioselectivities.[5c] Notably, the presented results with 5*H*-oxazol-4-one **1a** as nucleophile were rare, and only one example of an alkylimine was reported with a good enantioselectivity. In this context, it is still highly desirable and represents a formidable task to develop an asymmetric catalysis to afford an efficient and economical approach to access various α-hydroxy-α-methyl/alkyl-β-amino acids with excellent enantio- and diastereoselectivity and a broad substrate scope. Herein, we would like to report the first organocatalytic Mannich reaction of 5*H*-oxazol-4-ones with the readily prepared and modified aryl- as well as alkylsulfonimides in excellent enantio- and diastereoselectivities, leading to the favorable preparation of enantiopure α-methyl/alkyl-α-hydroxy-β-amino acid derivatives. Furthermore, this protocol is applicable to access the opposite enantiomers of the Mannich adducts with equally excellent stereoselectivities by replacing the catalyst with its pseudoenantiomeric pair.

To achieve the stereoselective Mannich reaction of 5*H*-oxazol-4-ones with sulfonimides, a bifunctional tertiary amine catalyst with a properly installed Brønsted acid moiety is pertinent. Therefore, we began our investigation by examining a number of thiourea and urea bifunctional catalysts derived from commercially available *Cinchona* alkaloids (**I–VI**) (Figure 3).[11] The results are summarized in Table 1. Initially, we selected the Mannich reaction of 5*H*-oxazol-4-one **1a** with *N*-Ts-imine **2a** as a model reaction in CH_2Cl_2 at 25 °C in the presence of 10 mol% cinchonine-derived thiourea **I** (Table 1, entry 1). We found that the reaction could proceed smoothly within 12 h in excellent yield with good enantioselectivity but poor diastereoselectivity. When the reaction was conducted at −10 °C (Table 1, entry 2), the *ee* value of the product **3a** increased to 94%. Further optimizations of the reaction conditions were done by screening and examination of solvents with **I** as catalyst at −10 °C (Table 1, entries 3–5). Et_2O proved optimal with regards to both diastereo- and enantioselectivity (Table 1, entry 4). We further prepared several sulfonimides[12] and explored the effects of the *N*-protective group of imines under the same reaction conditions (Table 1, entries 6–8). It was found that the steric tuning of the protective groups enhanced the diastereoselectivity greatly and sulfonimide **2c** with *N*-triisopropylbenzenesulfonyl (TIPBs)[13] as the bulkiest group gave the best results (**3c**, 96% *ee* and >19:1 *dr*). Since the adduct **3c** was very unstable in the presence of traces of moisture, the hydrolyzed product **4a** without compromising *ee* and *dr* was conveniently obtained by adding 5.0 equiv. of water into the reaction system at room temperature after the

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

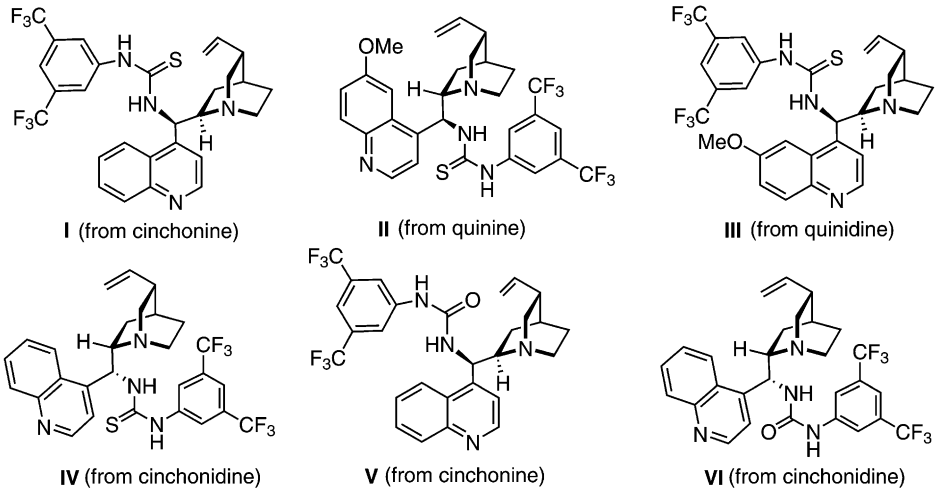
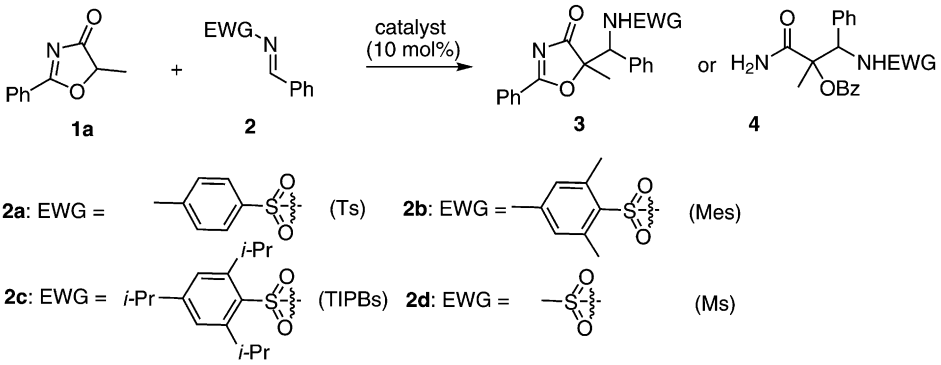


Figure 3. Structures of various *Cinchona* alkaloid-derived bifunctional organocatalysts **I–VI**.

Table 1. Screening studies.[a]

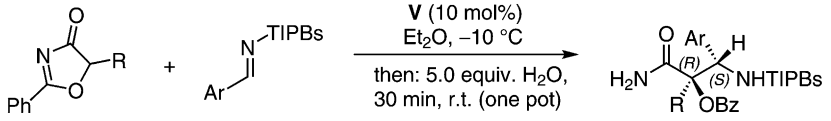


Entry	**2**	Catalyst	Solvent	Temp. [°C]	Time [h]	**3/4**	Yield [%][b]	*ee* [%][c]	*dr*[d]
1	**2a**	**I**	CH_2Cl_2	25	12	**3a**	90	77, 31	1.5:1
2	**2a**	**I**	CH_2Cl_2	−10	12	**3a**	43	94, 48	2.5:1
3	**2a**	**I**	toluene	−10	12	**3a**	87	96, 74	2.0:1
4	**2a**	**I**	Et_2O	−10	12	**3a**	82	96, 57	4.0:1
5	**2a**	**I**	THF	−10	12	**3a**	39	82, 45	3.0:1
6	**2b**	**I**	Et_2O	−10	28	**3b**	76	96, 87	13:1
7[e]	**2c**	**I**	Et_2O	−10	28	**4a**	87	96	>19:1
8	**2d**	**I**	Et_2O	−10	28	**3d**	76	99, 99	1:1
9[e]	**2c**	**II**	Et_2O	−10	72	*ent*-**4a**	80	96	>19:1
10[e]	**2c**	**III**	Et_2O	−10	72	**4a**	79	98	>19:1
11[e]	**2c**	**IV**	Et_2O	−10	72	**4a**	76	95	>19:1
12[e,f]	**2c**	**V**	Et_2O	−10	72	**4a**	87	99[g]	>19:1
13[e,h]	**2c**	**VI**	Et_2O	−10	72	*ent*-**4a**	83	97	>19:1

[a] The reaction was carried out with 0.02 mmol of **1a**, 0.03 mmol of **2**, and 0.002 mmol of catalyst in 0.2 mL solvent.
[b] Isolated yield.
[c] Determined by HPLC methods.
[d] Determined by ^{1}H NMR analysis.
[e] After **1a** was exhausted, 5 equiv. of H_2O was added at room temperature and the hydrolyzed product **4a** was obtained within 30 min.
[f] 0.1 mmol of **1a**, 0.15 mmol of **2**, and 0.01 mmol of **V** in 1.0 mL Et_2O at −10 °C.
[g] Temp. = 0 °C, time = 48 h, yield = 93%, *ee* = 93%, *dr* = 19:1; temp. = 25 °C, time = 12 h, yield = 85%, *ee* = 79%, *dr* = 19:1.
[h] 0.1 mmol of **1a**, 0.15 mmol of **2**, and 0.01 mmol of **VI** in 1.0 mL Et_2O at −10 °C. Bz = benzoyl.

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 2. Asymmetric Mannich reaction of 5*H*-oxazol-4-ones **1** with *N*-TIPBs-arylimines **2** catalyzed by **V**.[a]



1 **2** **4**

Entry	R	Ar	Time [h]	**4**	Yield [%][b]	*ee* [%][c]	*dr*[d]
1	Me (**1a**)	4-$CF_3C_6H_4$ (**2e**)	82	**4b**	87	99	>19:1
2	Me (**1a**)	4-ClC_6H_4 (**2f**)	72	**4c**	81	96	>19:1
3	Me (**1a**)	3-FC_6H_4 (**2g**)	92	**4d**	83	99	>19:1
4	Me (**1a**)	4-MeC_6H_4 (**2h**)	78	**4e**	84	96	>19:1
5	Me (**1a**)	4-*i*PrC_6H_4 (**2i**)	89	**4f**	78	99	>19:1
6	Me (**1a**)	4-$MeOC_6H_4$ (**2j**)	84	**4g**	87	96	>19:1
7	Me (**1a**)	2-$MeOC_6H_4$ (**2k**)	82	**4h**	72	94	>19:1
8	Me (**1a**)	1-naphthyl (**2l**)	88	**4i**	83	98	>19:1
9	Me (**1a**)	2-furyl (**2m**)	72	**4j**	81	94	>19:1
10	Me (**1a**)	2-thienyl (**2n**)	79	**4k**	80	94	>19:1
11	Et (**1b**)	Ph (**2c**)	94	**4l**	69	97	>19:1
12	*n*-Bu (**1c**)	Ph (**2c**)	96	**4m**	77	99	>19:1
13[e]	Me (**1a**)	4-ClC_6H_4 (**2f**)	89	*ent*-**4c**	81	95	>19:1
14[e]	Me (**1a**)	4-MeC_6H_4 (**2h**)	86	*ent*-**4e**	90	96	>19:1
15[e]	Me (**1a**)	4-*i*PrC_6H_4 (**2i**)	92	*ent*-**4f**	81	98	>19:1
16[e]	Me (**1a**)	4-$MeOC_6H_4$ (**2j**)	86	*ent*-**4g**	78	96	>19:1
17[e]	Me (**1a**)	1-naphthyl (**2l**)	88	*ent*-**4i**	83	97	>19:1
18[e]	Me (**1a**)	2-thienyl (**2n**)	88	*ent*-**4k**	80	90	>19:1
19[e]	Et (**1b**)	Ph (**2c**)	96	*ent*-**4l**	72	99	>19:1
20[e]	*n*-Bu (**1c**)	Ph (**2c**)	96	*ent*-**4m**	82	98	>19:1

[a] The reaction was carried out with 0.1 mmol of **1**, 0.15 mmol of **2**, and 0.01 mmol of **V** in 1.0 mL Et_2O at −10 °C.
[b] Isolated yield.
[c] Determined by HPLC methods.
[d] Determined by ^1H NMR analysis.
[e] The reaction was carried out with 0.1 mmol of **1**, 0.15 mmol of **2**, and 0.01 mmol of **VI** in 1.0 mL Et_2O at −10 °C. Bz = benzoyl.

5*H*-oxazol-4-one **1a** had been exhausted (Table 1, entry 7).

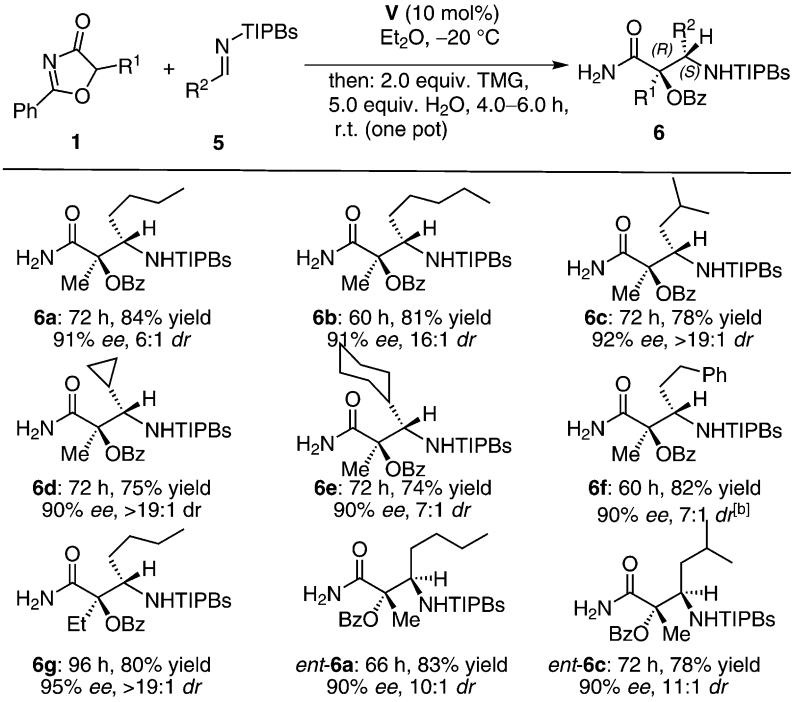
We next utilized other *Cinchona* alkaloids-derived thioureas and ureas (**II–VI**) to catalyze the Mannich reaction of 5*H*-oxazol-4-one **1a** with *N*-TIPBs-imine **2c** in Et_2O at −10 °C (Table 1, entries 9–13). The survey revealed that both of enantio- and diastereoselectivities were excellent in all of the reaction conditions, and cinchonine-derived urea **V** was the best catalyst (Table 1, entry 12). We were delighted to find that cinchonidine-derived urea **VI**, the pseudoenantiomeric pair of **V**, provided *ent*-**4a**, the enantiomer of **4a**, with 97% *ee* and >19:1 *dr* (Table 1, entry 13).

With a set of optimized reaction conditions on hand (10 mol% **V** in Et_2O at −10 °C, then 5.0 equiv. of H_2O at room temperature for 30 min), as shown in Table 2, the Mannich reaction with 5*H*-oxazol-4-ones **1a** as the nucleophiles could be extended to a wide variety of *N*-TIPBs-arylimines (**2e–n**) to afford the desired products **4b–k** in 72–87% yield with 94–99% *ee* and >19:1 *dr* (Table 2, entries 1–10). The results disclosed that the reaction rate and enantioselectivity of the reaction were not affected by the electronic effects of substituted groups on the aromatic rings of imines (Table 2, entries 1–7). Excellent *ee*s were also obtained when the phenyl group of imines is replaced by other aromatic groups such as furyl and thienyl (Table 2, entries 9 and 10). Other 5*H*-oxazol-4-ones **1b** and **1c**, containing 5-substituted *n*-butyl and ethyl, also gave the corresponding adducts **3l** and **3m** in good yields with 97% and 99% *ee* in >19:1 *dr* (Table 2, entries 11 **and** 12), indicating that more hindered substituent at the C-5 position of 5*H*-oxazol-4-one should help increase the enantioselectivity of the reaction. Subsequently, we evaluated the generality of the reaction by utilizing the catalyst **VI** to generate the enantiomers of **4** (*ent*-**4**, Table 2, entries 13–20). It was found that the desired enantiomers could be obtained in 72–90% yield and 90–99% *ee* with >19:1 *dr*.

Next we endeavored to prepare the equally important β-alkyl-substituted α-hydroxy-β-amino acid derivatives *via* Mannich reaction of 5*H*-oxazol-4-ones **1** with *N*-TIPBs-alkylimines **5** under the established reaction conditions. We believe that it is difficult to

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

Table 3. Asymmetric Mannich reaction of 5*H*-oxazol-4-ones **1** with *N*-TIPBs-alkylimines **5** catalyzed by **VI**.[a]

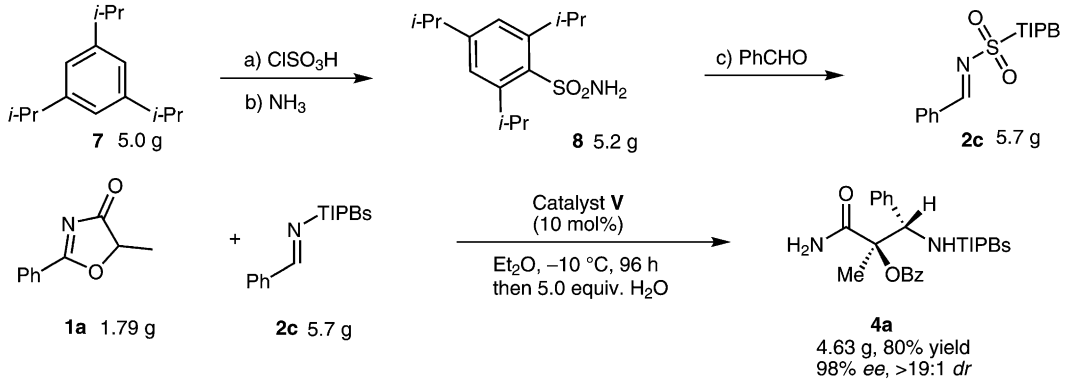


[a] The reaction was carried out with 0.1 mmol of **1**, 0.15 mmol of **5**, and 0.01 mmol of **V** in 1.0 mL Et_2O at −20 °C; yield of isolated product; *ee*s were determined by HPLC methods; *dr*s were determined by ^1H NMR analysis.

[b] The reaction was conducted at −10 °C. Bz = benzoyl, TMG = 1,1,3,3-tetramethylguanidine.

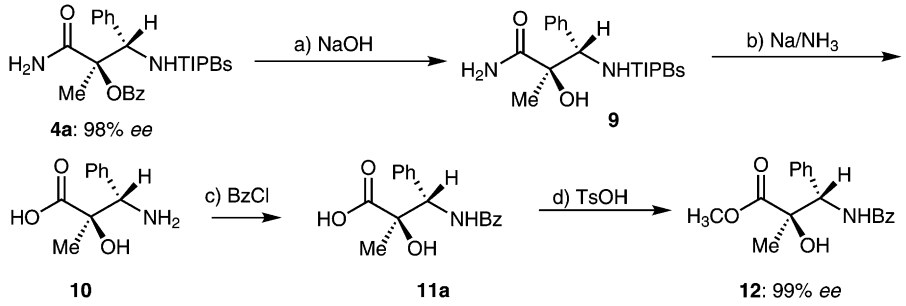
introduce both aryl- and alkylimines under the same conditions,[14] but by lowering the temperature to −20 °C, the Mannich reactions could be accomplished with good to excellent diastereoselectivities and excellent enantioselectivities (6:1 to 19:1 *dr* and 90–95% *ee*, Table 3, entries 1–7). Since the Mannich adducts are stable in the presence of H_2O, 2.0 equiv. of TMG (1,1,3,3-tetramethylguanidine) were necessary for the hydrolysis process. Moreover, the enantiomer of **6** (*ent*-**6**) could be obtained with similar enantio- and diastereoselectivities (Table 3, entries 8 and 9).

To verify the synthetic value of this work, we attempted to prepare the Mannich adducts on a gram scale (Scheme 1). From commercially available 1,3,5-



Scheme 1. Gram-scale preparation of Mannich adduct **4a**: a) $ClSO_3H$ (4.0 equiv.), CH_2Cl_2, 0 °C to room temperature, 45 min; b) NH_3 (aq.), CH_2Cl_2, room temperature, 12 h, 74% yield (two steps); c) PhCHO (1.0 equiv.), neat, 160 °C, 16 h, 83% yield. Bz = benzoyl.

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 2. Synthesis of α-methyl-α-hydroxy-β-amino acids: a) NaOH (aq., 5.0 equiv.), EtOH, 0 °C to room temperature, 98% yield; b) Na/NH_3, −78 °C, 0.5 h, 81% yield; c) BzCl (1.1 equiv.), Et_3N (4.0 equiv.), CH_2Cl_2, room temperature, 12 h, 84% yield; d) TsOH (2.0 equiv.), MeOH, 95 °C in sealed tube, 7 d, 66% yield, 99% *ee*. Bz = benzoyl.

tris(1-methylethyl)-benzene **7** (5.0 g), the corresponding sulfonamide **8** could be readily prepared with 74% yield (5.2 g) after reaction with chlorosulfuric acid and ammonia.[12] 5.7 g of *N*-TIPBs-phenylimine **2c** were then obtained from **8** and benzaldehyde with 83% yield. In the presence of catalyst **V** at −10 °C after 96 h, the Mannich reaction of **2c** with **1a** afforded the adduct **4a** in a 4.63 g (80%) yield in 98% *ee* and >19:1 *dr*.

Subsequently, we prepared α-methyl-α-hydroxy-β-amino acids from the Mannich adducts (Scheme 2). In the presence of NaOH in EtOH, **4a** could be hydrolyzed to afford the corresponding tertiary alcohol **9** in excellent yield. After treating compound **9** with Na/NH_3 at −78 °C, α-methylated (2*R*, 3*S*)-phenylisoserine **10** was conveniently attained. The amine group of **10** was then protected by a benzoyl group (Bz) to furnish compound **11a**. The absolute configurations of the Mannich products were assigned based on X-ray crystallographic analysis of a single crystal of **11b**, prepared from **10** and 2-chlorobenzoyl chloride.[15] Next, the esterification of **11a** by using 2.0 equiv. of *p*-toluenesulfonic acid successfully generated the optical pure compound **12**, which is the α-methylated C-13 side chain of taxol and taxotere.

In summary, we have developed the first organocatalytic Mannich reaction of 5*H*-oxazol-4-ones with easily prepared *N*-TIPBs-aryl- and alkylimines in excellent enantio- and diastereoselectivities. A pair of bifunctional tertiary amine/ureas, derived from two commercially available pseudoenantiomeric *Cinchona* alkaloids provide the optimal catalyst to access the opposite enantiomers of the Mannich products with equally excellent stereoselectivities. The Mannich reaction could be conveniently scaled up to the gram scale without compromising the enantioselectivity. Demonstrating the synthetic utility, we have successfully prepared an important α-methyl-α-hydroxy-β-amino acid derivative, the α-methylated C-13 side chain of taxol and taxotere, from the Mannich adduct. We believe that this protocol can be applied to prepare a variety of α-methyl/alkyl-α-hydroxy-β-amino acid derivatives with an extensive scope and excellent results. Further work is ongoing to prepare another pair of diastereomers through this protocol and will be reported in due course.

Experimental Section

Representative Procedure for the Synthesis of 4a

5H-Oxazol-4-one **1a** (1.79 g, 10.23 mmol, 1.0 equiv.) and *N*-TIPBs-phenylimine **2c** (5.7 g, 15.34 mmol, 1.5 equiv.) were dissolved in diethyl ether (90 mL). After stirring at −10 °C for 30 min, a pre-cooled solution of catalyst **V** (1.023 mmol, 0.1 equiv., 561 mg in 10 mL Et_2O) was added. The reaction mixture was stirred at −10 °C and monitored by TLC. After 96 h, the reaction was completed and warmed up to room temperature. H_2O (0.92 mL, 51.15 mmol, 5.0 equiv.) was added and monitored by TLC. For about 30 min, the hydrolysis was completed. After extraction using Et_2O and brine for three time, flash chromatography afforded product **4a** as a colorless oil; yield: 4.63 g (80%).

Supporting Information

Experimental procedures, characterization and spectroscopic data (PDF) are available in the Supporting Information.

Acknowledgements

We are grateful for financial support from the NSFC (21072044), Excellent Youth Foundation of Henan Scientific Committee (114100510003), Specialized Research Fund for the Doctoral Program of Higher Education (20104103120002) and International Cooperation Foundation of Henan Province (104300510062).

References

[1] For selected reviews and a book, see: a) G. Cardillo, C. Tomasini, *Chem. Soc. Rev.* **1996**, *25*, 117; b) D. Seebach, J. L. Mattews, *Chem. Commun.* **1997**, 2015; c) S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173; d) *Enantiose-*

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

lective Synthesis of β-Amino Acids, (Eds.: E. Juaristi, V. A. Soloshonok), John Wiley & Sons, Inc., Hoboken, New Jersey, **2005**. For selected examples, see: e) K. Iizuka, T. Kamijo, T. Kubota, K. Akahane, H. Umeyama, Y. Kiso, *J. Med. Chem.* **1988**, *31*, 701; f) F. Fringuelli, F. Pizzo, M. Rucci, L. Vaccaro, *J. Org. Chem.* **2003**, *68*, 7041; g) S. Weik, T. Luksch, A. Evers, J. Böttcher, C. A. Sotriffer, A. Hasilik, H.-G. Löffler, G. Klebe, J. Rademaan, *ChemMedChem* **2006**, *1*, 445.

[2] K. C. Nicolaou, W.-M. Dai, R. K. Guy, *Angew. Chem.* **1994**, *106*, 38; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15, and references cited therein.

[3] a) I. Ojima, C. M. Sun, M. Zucco, Y. H. Park, O. Duclo, S. Kuduk, *Tetrahedron Lett.* **1993**, *34*, 4149; b) S. H. Chen, V. Farina, *Paclitaxel (Taxol) – Chemistry and Structure-Activity Relationships*, in: *The Chemistry and Pharmacology of Taxol and its Derivatives*, (Ed.: V. Farina), Elsevier, Amsterdam, **1995**, p. 165; c) J.-H. Denis, A. Fkyerat, Y. Gimbert, C. Coutterez, P. Mantellier, S. Jost, A. E. Greene, *J. Chem. Soc. Perkin Trans. 1* **1995**, 1811; d) J. Kant, W. S. Schwartz, C. Fairchild, Q. Gao, S. Huang, B. H. Long, J. F. Kadow, D. R. Langley, V. Farina, D. Vyas, *Tetrahedron Lett.* **1996**, *37*, 6495; e) I. Ojima, T. Wang, F. Delaloge, *Tetrahedron Lett.* **1998**, *39*, 3663; f) G. Cardillo, L. Gentilucci, A. Tolomelli, C. Tomasini, *J. Org. Chem.* **1998**, *63*, 2351; g) A. M. Nocioni, C. Papa, C. Tomasini, *Tetrahedron Lett.* **1999**, *40*, 8453; h) G. Cardillo, A. Tolomelli, C. Tomasini, *Eur. J. Org. Chem.* **1999**, 155; i) Y. Takeda, T. Yoshino, K. Uoto, J. Chiba, T. Ishiyama, M. Iwahana, T. Jimbo, N. Tanaka, H. Terasawa, T. Soga, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 185.

[4] E. Turos, T. E. Long, B. Heldreth, J. M. Leslie, G. S. K. Reddy, Y. Wang, C. Coates, M. Konaklieva, S. Dickey, D. V. Lim, E. Alonso, J. Gonzalez, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2084.

[5] a) M.-X. Wang, G. Deng, D.-X. Wang, Q.-Y. Zheng, *J. Org. Chem.* **2005**, *70*, 2439; b) N. C. Giampietro, J. P. Wolf, *Angew. Chem.* **2010**, *122*, 2984; *Angew. Chem. Int. Ed.* **2010**, *49*, 2922; c) D. Zhao, L. Wang, D. Yang, Y. Zhang, R. Wang, *Angew. Chem.* **2012**, *124*, 7641; *Angew. Chem. Int. Ed.* **2012**, *51*, 7523.

[6] For selected examples of catalytic construction of chiral tertiary alcohols, see: a) J. Luo, H. Wang, X. Han, L.-W. Xu, J. Kwiatkowski, K.-W. Huang, Y. Lu, *Angew. Chem.* **2011**, *123*, 1901; *Angew. Chem. Int. Ed.* **2011**, *50*, 1861; b) C. Liu, X. Dou, Y. Lu, *Org. Lett.* **2011**, *13*, 5248. For our recent examples, see: c) Y. Yang, F. Moinodeen, W. Chin, T. Ma, Z. Jiang, C.-H. Tan, *Org. Lett.* **2012**, *14*, 4762; d) W. Zhang, D. Tan, R. Lee, G. Tong, W. Chen, B. Qi, K.-W. Huang, C.-H. Tan, Z. Jiang, *Angew. Chem.* **2012**, *124*, 10216; *Angew. Chem. Int. Ed.* **2012**, *51*, 10069.

[7] B. M. Trost, K. Dogra, M. Franzini, *J. Am. Chem. Soc.* **2004**, *126*, 1944.

[8] a) T. Misaki, G. Takimoto, T. Sugimura, *J. Am. Chem. Soc.* **2010**, *132*, 6286; b) T. Misaki, K. Kawano, T. Sugimura, *J. Am. Chem. Soc.* **2011**, *133*, 5695.

[9] H. Huang, K. Zhu, W. Wu, Z. Jin, J. Ye, *Chem. Commun.* **2012**, *48*, 461.

[10] B. M. Trost, K. Hirano, *Angew. Chem.* **2012**, *124*, 6586; *Angew. Chem. Int. Ed.* **2012**, *51*, 6480.

[11] For reviews, see: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289; b) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999; c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; d) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713; e) S. J. Connon, *Chem. Commun.* **2008**, 2499; f) X. Yu, W. Wang, *Chem. Asian J.* **2008**, *3*, 516. For our recent example using *Cinchona* alkaloid thiourea bifunctional catalyst, see: g) F. Zhao, W. Zhang, Y. Yang, Y. Pan, W. Chen, H. Liu, L. Yan, C.-H. Tan, Z. Jiang, *Adv. Synth. Catal.* **2011**, *353*, 2624.

[12] J. R. Reid, R. F. Dufresne, J. J. Chapman, *Organic Syntheses* **1998**, *9*, 281.

[13] T. Hayashi, M. Kawai, N. Tokunaga, *Angew. Chem.* **2004**, *116*, 6251; *Angew. Chem. Int. Ed.* **2004**, *43*, 6125.

[14] a) T. Akiyama, Y. Honma, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2008**, *350*, 399; b) Y. Zhang, Y.-K. Liu, T.-R. Kang, Z.-K. Hu, Y.-C. Chen, *J. Am. Chem. Soc.* **2008**, *130*, 2456.

[15] In the presence of 2-Cl-BzCl (1.1 equiv.) and Et_3N (4.0 equiv) in CH_2Cl_2 at room temperature within 12 hours, 84% yield of **11b** was obtained. CCDC 917270 (**11b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

 © 2013 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim