J|A|C|S
COMMUNICATIONS

Published on Web 11/13/2002

Catalytic Asymmetric Epoxidation of α,β-Unsaturated Amides: Efficient Synthesis of β-Aryl α-Hydroxy Amides Using a One-Pot Tandem Catalytic Asymmetric Epoxidation−Pd-Catalyzed Epoxide Opening Process

Tetsuhiro Nemoto, Hiroyuki Kakei, Vijay Gnanadesikan, Shin-ya Tosaki, Takashi Ohshima, and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo 113-0033, Japan

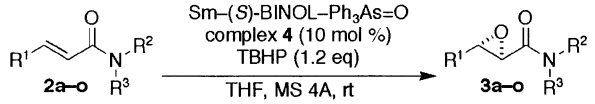
Received September 7, 2002

Catalytic asymmetric epoxidation of α,β-unsaturated amides provides chiral α,β-epoxy amides that can be converted into useful chiral building blocks such as α-hydroxy amides and β-hydroxy amides. To date, catalytic asymmetric epoxidation of enones[1] and α,β-unsaturated esters[2] have been intensively studied. There are no reports, however, of catalytic asymmetric epoxidation of α,β-unsaturated amides,[3] perhaps due to the lower reactivity. We report a general and highly enantioselective epoxidation of α,β-unsaturated amides promoted by chiral lanthanide catalysts. In addition, a one-pot tandem catalytic asymmetric epoxidation−Pd-catalyzed epoxide opening process was demonstrated. This process leads to the efficient synthesis of β-aryl α-hydroxy amides.

We previously reported that alkali-metal free lanthanide−BINOL complexes, in particular La−BINOL−Ph_3As═O complex **1**, were very useful catalysts for the asymmetric epoxidation of enones[4a,b] and α,β-unsaturated imidazolides.[4c] Although catalytic asymmetric epoxidation of α,β-unsaturated esters proceeded very sluggishly with the use of 10 mol % of **1**, α,β-unsaturated amides were epoxidized more smoothly under the same conditions.[5] This result prompted us to optimize the reaction conditions.[6] The effect of the central metal and the amount of TBHP were investigated in detail using **2a**. Sm−(*S*)-BINOL−Ph_3As═O complex **4**, generated from Sm(O-*i*-Pr)$_3$, (*S*)-BINOL, and Ph_3As═O in a ratio of 1:1:1, was found to be the best catalyst for this reaction and 1.2 equiv of TBHP to **2a** gave the best reactivity (condition A). The scope and limitations using numerous substrates was further examined. As shown in Table 1, this catalytic system had a broad generality for epoxidations of various amides **2a**−**o**. When 5−10 mol % of **4** was used, β-alkyl-substituted amides **2a**−**j**, prepared from primary amines (entries 1, 2, 4−6, 11−13), α-branched primary amines (entries 7, 8), and secondary amines (entries 9, 10), were smoothly epoxidized to afford the corresponding α,β-epoxy amides in excellent yield and in excellent enantiomeric excess. This was also effective for the epoxidation of β-aryl-substituted amides **2k**−**o**. In these cases, activation of MS 4A was necessary to improve the lower reactivity, but there was a slight decrease in enantiomeric excess (condition B). In addition, Sm−(*S*)-BINOL−Ph_3P═O complex **5** was found to be also effective, yielding the products with slightly lower selectivity (entries 3, 16).[7,8] To the best of our knowledge, this is the first example of a general catalytic asymmetric epoxidation of α,β-unsaturated amides.

Optically active β-aryl α-hydroxy amides are biologically important structural units and can be easily synthesized from β-aryl α,β-epoxy amides. To achieve efficient transformation, we planned to develop a new method: a one-pot tandem catalytic asymmetric epoxidation−Pd-catalyzed epoxide opening process.[9] Key to the success of this sequential process is whether the second catalysis is compatible with the conditions of the first epoxidation. Therefore, we first performed experiments to examine the influence of the constituents of the first reaction on the second catalysis (Table 2).[6] With the use of 5 mol % of Pd−C, an epoxide opening reaction of **3k** was investigated as a model reaction. In the absence of additives, the reaction proceeded smoothly, giving rise to a mixture of three compounds, **6k**, **7k**, and **8k** in a ratio of 100:6:3. On the other hand, when the reaction was performed in the presence of **5**,[10] the formation of **7k** was completely prevented, whereas there was a significant increase in the formation of **8k**. The formation of both **7k** and **8k** was successfully depressed in the reaction conditions including all of the reagents for the first epoxidation, affording **6k** with excellent selectivity (100:0:1). This finding suggests that beneficial modifications of the Pd catalyst are achieved by the

Table 1. Catalytic Asymmetric Epoxidation of α,β-Unsaturated Amides



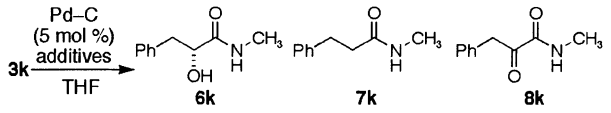
entry	substrate R^1	substrate NR^{2}R^3		conditions[a]	time (h)	yield[b] (%)	ee[c] (%)
1	$Ph(CH_2)_2$	CH_3NH	**2a**	A	8	99	>99
2[d]			**2a**	A	24	94	>99
3[e,f]			**2a**	A	24	91	97
4	$Ph(CH_2)_2$	BnNH	**2b**	A	6	97	>99
5[d]			**2b**	A	24	82	99
6	$Ph(CH_2)_2$	AllylNH	**2c**	A	4	95	98
7	$Ph(CH_2)_2$	cHexNH[g]	**2d**	A	11	97	>99
8	$Ph(CH_2)_2$	*t*-BuNH	**2e**	A	22	91	99
9	$Ph(CH_2)_2$	$(CH_3)_2N$	**2f**	A	3	96	99
10	$Ph(CH_2)_2$		**2g**	A	4	94	>99
11	$Ph(CH_2)_4$	CH_3NH	**2h**	A	8	81	>99
12	C_3H_7	BnNH	**2i**	A	9	94	94
13	cHex[g]	BnNH	**2j**	A	12	90	>99
14	Ph	CH_3NH	**2k**	A	24	89	>99
15			**2k**	B	18	95	99
16[e]			**2k**	B	9	92	97
17	Ph	BnNH	**2l**	B	18	91	>99
18	Ph	$(CH_3)_2N$	**2m**	B	9	96	>99
19	4-F-C_6H_4	CH_3NH	**2n**	B	20	94	99
20	4-Me-C_6H_4	CH_3NH	**2o**	B	21	89	>99

[a] Conditions A: TBHP in decane was used. MS 4A was not dried. Conditions B: TBHP in toluene was used. MS 4A was dried for 3 h at 180 °C under reduced pressure. [b] Isolated yield. [c] Determined by HPLC analysis. [d] 5 mol % of **4** was used. [e] Ph_3P═O (30 mol %) was used as an additive. [f] Dy was used as a central metal. [g] cHex = cyclohexyl.

* To whom correspondence should be addressed. E-mail: mshibasa@mol.f.u-tokyo.ac.jp.

10.1021/ja028454e CCC: $22.00

Table 2. Preliminary Experiments for the Pd-Catalyzed Epoxide Opening Reaction of **3k**



entry	additives	time (min)	yield[a] (%)	ratio[b] (**6k**:**7k**:**8k**)	selectivity (**6k**/**7k** + **8k**)
1		60	100	100:6:3	11
2	MeOH[c]	10	100	100:8:2	10
3	(*S*)-**5** (10 mol %)	90	100	100:0:23	4
4	(*S*)-**5** (10 mol %), MS 4A, TBHP (0.2 equiv), MeOH[c]	60	100	100:0:1	100

[a] Conversion yield. [b] The ratio was determined by ^{1}H NMR analysis of the crude sample. [c] Solvent ratio: THF/MeOH = 2/1.

Table 3. One-Pot Tandem Catalytic Asymmetric Epoxidation−Pd-Catalyzed Epoxide Opening Process

entry	substrate R^1	substrate NR^{2}R^3		time (h) step A	time (h) step B	yield[c] (%)	ee[d] (%)
1	Ph	CH_3NH	**2k**	21	2	97	97
2	Ph	BnNH	**2l**	16	2	91	98
3	Ph	$(CH_3)_2N$	**2m**	11	2	89[e]	99[e]
4	4-F-C_6H_4	CH_3NH	**2n**	18	2	90	99
5	4-Me-C_6H_4	CH_3NH	**2o**	18	2	82	97

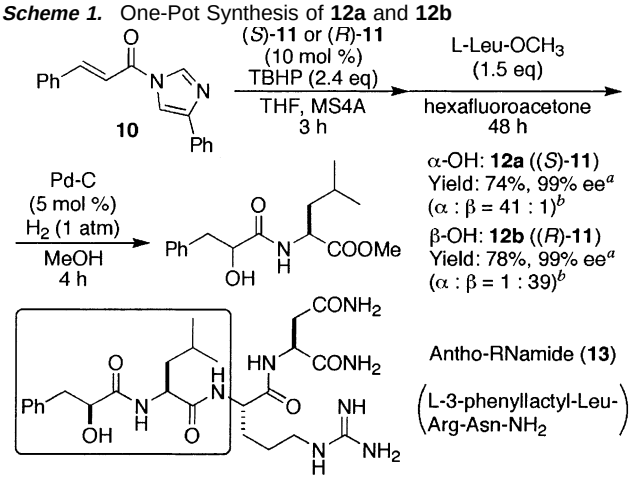
[a] Conditions: (*S*)-**5** (10 mol %), TBHP in toluene (1.2 equiv), MS 4A (dried), THF, room temperature. [b] Conditions: Pd−C (5 mol %), H_2 (1 atm), MeOH (solvent ratio: THF/MeOH = 2/1). [c] Isolated yield. [d] Determined by HPLC analysis. [e] Yield and ee were determined after converting into the corresponding triethylsilyl ether.

constituents of the first epoxidation, producing a more suitable catalyst for the second epoxide opening reaction.

One-pot tandem reactions were further examined using **2k**−**o** as substrates (Table 3). After completion of the epoxidation, both 5 mol % of Pd−C and MeOH were directly added to the reaction mixture and the resulting mixture was stirred under a hydrogen atmosphere. As expected, the sequential process functioned efficiently, affording the corresponding **6k**−**o** in excellent overall yield and in enentiomeric excess. The fact that **6k** was obtained in 97% ee indicates that no racemization occurred in this tandem process.

β-Aryllactyl-Leu sequences are found in various biologically active peptides.[11] The developed process can be utilized for the construction of these dipeptide fragments. Unfortunately, catalytic asymmetric epoxidation of *N*-cinnamoyl L-leucine methyl ester **9** did not proceed at all. However, tandem catalytic asymmetric epoxidation of the α,*β*-unsaturated imidazolides−peptide coupling-Pd-catalyzed epoxide opening process made these fragments easily accessible in a single pot reaction. After completion of the first epoxidation of **10** using (*S*)- or (*R*)-La−BINOL−Ph_3P═O complex **11**, 1.5 equiv of L-leucine methyl ester was added and the reaction was stirred for 48 h in the presence of hexafluoroacetone.[12] Finally, a Pd-catalyzed epoxide opening reaction was performed sequentially to provide the desired fragments **12a** and **12b** in optically pure forms, which can be utilized for the synthesis of a neuropeptide, Antho-RNamide **13** (Scheme 1).[11a]

Scheme 1. One-Pot Synthesis of **12a** and **12b**



[a] Determined by HPLC analysis. [b]Determined by ^{1}H NMR analysis.

In summary, the catalytic asymmetric epoxidation of α,*β*-unsaturated amides with broad generality was developed. Moreover, this reaction was successfully applied to the synthesis of *β*-aryl α-hydroxy amides using a novel one-pot tandem process. Further studies are currently under investigation in our group.

Acknowledgment. Financial support was provided by RFTF of Japan Society for the Promotion of Sciences. T. Nemoto thanks the Japan Society for the Promotion of Science (JSPS) for a research fellowship.

Supporting Information Available: Experimental procedures and characterization of the products; other detailed results and discussion (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a recent review, see: Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 94.
(2) (a) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martínez, L. E. *Tetrahedron* **1994**, *50*, 4323. (b) Armstrong, A.; Hayter, B. R. *Chem. Commun.* **1998**, 621. (c) Soladié-Cavallo, A.; Bouérat, L. *Org. Lett.* **2000**, *2*, 3531. (d) Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8792.
(3) Recently, asymmetric synthesis of α,*β*-epoxy amides using a highly enantioselective Darzens reaction of a camphor-derived sulfonium amide was reported, see: Aggarwal, V. K.; Hynd, G.; Picoul, W.; Vasse, J.-L. *J. Am. Chem. Soc.* **2002**, *124*, 9964.
(4) (a) Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 2329. (b) Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2725, and references therein. (c) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9474.
(5) Preliminary experiments suggested that unfavorable complexation between the catalyst and α,*β*-unsaturated ester might occur, resulting in decreased in the catalyst activity. See Supporting Information for the data.
(6) See Supporting Information for details.
(7) Daikai, M.; Kamaura, M.; Inanaga, J. *Tetrahedron Lett.* **1998**, *39*, 7321.
(8) Absolute configurations of **3a**−**b**, **3f**, and **3j**−**m** were determined to be 2*R*,3*S*. For the detailed data, see the Supporting Information.
(9) For recent examples of tandem catalytic processes, see: (a) Jeong, N.; Seo, S.-D.; Shin, J.-Y. *J. Am. Chem. Soc.* **2000**, *122*, 10220. (b) Yamasaki, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 1256. (c) Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609. (d) Louie, J.; Bielawski, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 11312. (e) Choudary, B. M.; Chowdari, N. S.; Madhi, S.; Kantam, M. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 4620. (f) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700.
(10) Addition of Ph_3As═O retarded the epoxide opening reaction.
(11) (a) Grimmelikhuijzen, C. J. P.; Rinehart, K. L.; Jacob, E.; Graff, D.; Reinscheid, H.-P.; Staley, A. L. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 5410. (b) Ishida, K.; Okita, Y.; Matsuda, H.; Okino, T.; Murakami, M. *Tetrahedron* **1999**, *55*, 10971.
(12) Even with use of 3 equiv of L-leucine methyl ester, the peptide coupling reaction did not complete in 8 d in the absence of hexafluoroacetone. For the detailed data and discussion, see the Supporting Information.

JA028454E