Asymmetric Synthesis of 1,3-Oxazolidines from Chiral Imines Using Rh(III) Catalyst

Seung-Han Lee* and Young-Hwan Kim

*Department of Chemistry, Kyunghee University, Yongin 449-701, Korea. *E-mail: shlee@khu.ac.kr*
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Oxazolidines and aminoalcohols have been widely used as chiral auxiliaries and as intermediates in organic synthesis.[1] Recently we reported the formation of 1,3-oxazolidines and 1,2-amino alcohols from imines and ethyl diazoacetate (EDA) using copper catalysts.[2] Although this reaction afforded 1,3-oxazolidines and 1,2-amino alcohols in high yields, the reaction with various chiral ligands gave the racemic mixture of products.[3]

Also, the same reactions between chiral *N*-benzylimines and EDA in acetone using various metal catalysts including Cu(I), Cu(II), Co(II), Ru(III), Mn(II), Zn(II), Rh(I) and Rh(II) failed to give the desired 1,3-oxazolidines. Below, we report the results which demonstrate that chiral 1,3-oxazolidines can be generated by the reaction of chiral *N*-benzylimines with EDA using Rh(III) catalyst (Scheme 1 and Table 1).

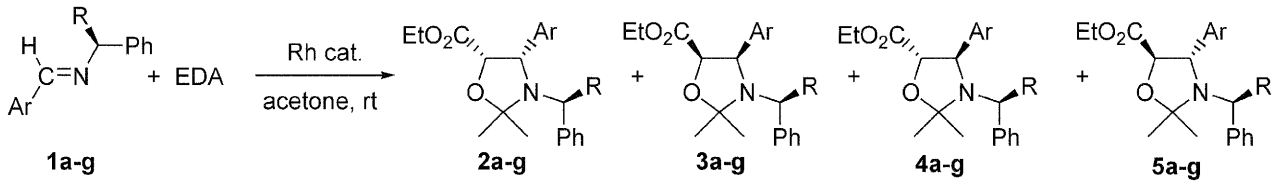
A number of experiments were performed to maximize the efficiency of the 1,3-oxazolidine forming reaction. In this effort, we found that reactions of imines with EDA (2 equivalents) using 10% of $RhCl_3(H_2O)_3$ in the presence of $AgBF_4$ in dry acetone afforded the oxazolidines in moderate yields.[4,5]

Table 1. 1,3-Oxazolidine Formation Using Rh(III) Catalyst

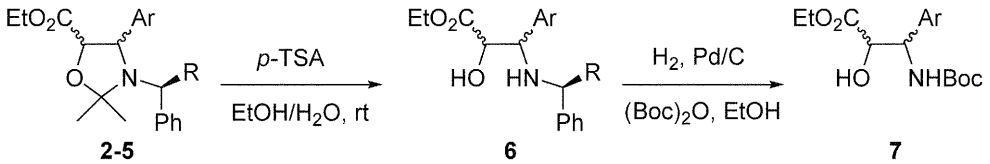
Entry	Imine	Ar	R	**2+3** (%)[a] (**2**/**3**)[b]	**4+5** (%)[a] (**5**/**4**)[b]	Total yield (%) (*cis*/*trans*)
1	**1a**	Ph	H	36	28	64 (1.3)
2	**1b**	*p*-$NO_2C_6H_4$	H	41	20	61 (2.0)
3	**1c**	*p*-ClC_6H_4	H	40	23	63 (1.7)
4	**1d**	*p*-$CH_3OC_6H_4$	H	16	15	31 (1.0)
5	**1e**	*p*-$CH_3C_6H_4$	H	12	11	23 (1.0)
6	**1f**	Ph	Me	32 (2.3)	30 (1.5)	62 (1.1)
7	**1g**	*p*-$NO_2C_6H_4$	Me	32 (2.5)	29 (1.6)	61 (1.1)

[a]Isolated yields. [b]Ratios were determined by ^{1}H NMR analysis.

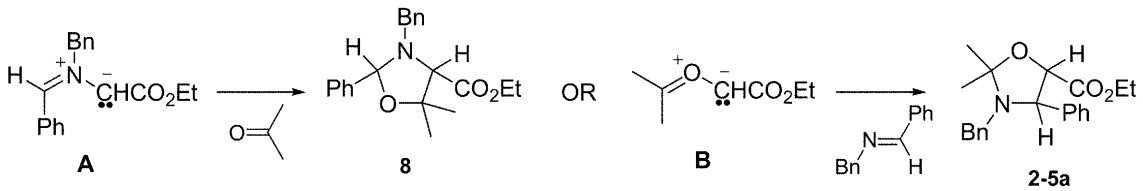
We observed the substituent effects that the imines with electron-withdrawing substituent at -Ar gave the higher yields than the imines with the electron-donating substituent at -Ar (Table 1, entry 2, 3 *vs* 4, 5). The ratios of *cis*- to *trans*-oxazolidines produced in these reactions were found to vary from 1 to 2. Unfortunately, the use of lower temperature, *e.g.*, 0 °C, to enhance stereoselectivity gave no reaction.



Scheme 1



Scheme 2



Scheme 3

Table 2. Preparation of *N*-Boc-protected 1,2-Amino Alcohols

Entry	Oxazolidine	Ar	R	**6** (%)[a]	**7** (%)[a]
1	**2**, **3a**	Ph	H	96	91
2	**4**, **5a**	Ph	H	90	95
3	**2**, **3b**	*p*-$NO_2C_6H_4$	H	98	92
4	**4**, **5b**	*p*-$NO_2C_6H_4$	H	90	90
5	**2**, **3c**	*p*-ClC_6H_4	H	92	–[b]
6	**4**, **5c**	*p*-ClC_6H_4	H	87	–[b]
7	**2**, **3d**	*p*-$CH_3OC_6H_4$	H	87	91
8	**4**, **5d**	*p*-$CH_3OC_6H_4$	H	85	94
9	**4**, **5f**	Ph	Me	85	99
10	**2**, **3g**	*p*-$NO_2C_6H_4$	Me	84	91
11	**4**, **5g**	*p*-$NO_2C_6H_4$	Me	93	95

[a]Isolated yields. [b]Yields were not determined.

The reactions of chiral imines gave four possible oxazolidine diastereomers which were separated by column chromatography and purified by recrystallization. The structures of 1,3-oxazolidine products were determined by using ^{1}H-, ^{13}C-NMR spectroscopy and elemental analysis. The absolute stereochemistry of chiral oxazolidine was determined by the transformation of oxazolidine to the corresponding aziridine which was converted to known phenylalanine derivative.[6,7]

The amino alcohols **6** were prepared by hydrolysis of *N*-benzyl-1,3-oxazolidines using *p*-toluenesulfonic acid in aqueous ethanol in high yields (Scheme 2 and Table 2). The use of stronger acids (6 N HCl or HBr) gave the lower yields.[2] Debenzylation of *N*-benzyl-1,2-amino alcohols **6** and subsequent protection of free amino group with *tert*-Boc could be achieved using Pd/C catalyst in the presence of $(Boc)_2O$ to afford the *N*-Boc-protected 1,2-amino alcohols **7** in high yields.[8]

It is interesting to speculate about the mechanism of this 1,3-oxazolidine forming reaction. Since the reaction gives the diethyl maleate and fumarate as side products, the reaction involves the intermediacy of metal carbene (Scheme 3).[2] If the reaction proceeds *via* azomethine ylide intermediate **A**, different structural isomer, 2-aryl-3-benzyl-4-(ethyloxycarbonyl)-5,5-dimethyl-1,3-oxazolidine **8** would be formed.[9] The ^{1}H NMR spectra of these substances would characteristically show the two singlets corresponding to the ring protons. And the hydrolysis of **8** would give the different amino alcohols from **6**. On the other hand, initially formed carbonyl ylide **B** undergoes 1,3-dipolar addition with imines to give 2,2-dimethyl-1,3-oxazolidines **2-5a** which are the products actually generated in the rhodium catalyzed reactions.[10] Therefore, the reaction would proceed *via* carbonyl ylide intermediate **B**.

In summary, chiral 1,3-oxazolidines were prepared in moderate yields from chiral *N*-benzylimines and EDA using Rh(III) catalyst in acetone. Also, *N*-Boc protected 1,2-amino alcohols were prepared in high yields by hydrolysis of *N*-benzyloxazolidines and followed by subsequent hydrogenolysis of *N*-benzyl-1,2-amino alcohols in the presence of $(Boc)_2O$.

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References

1. (a) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835. (b) Gordon, K.; Bolger, M.; Khan, N.; Balasubramanian, S. *Tetrahedron Lett.* **2000**, *41*, 8621. (c) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1997**, *62*, 3770. (d) Dai, W.-M.; Zhu, H. J.; Hao, X.-J. *Tetrahedron: Asymmetry* **1996**, *7*, 1245. (e) Heaney, H.; Papageorgiou, G.; Wilkins, R. F. *Tetrahedron* **1997**, *53*, 14381. (f) Le Bail, M.; Perard, J.; Aitken, D. J.; Bonin, M.; Husson, H.-P. *Tetrahedron Lett.* **1997**, *38*, 7177.
2. Lee, S.-H.; Yang, J.; Han, T.-D. *Tetrahedron Lett.* **2001**, *42*, 3487.
3. (a) Hansen, K. B.; Finney, N. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 676. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.
4. Acetone distilled from molecular sieve under nitrogen was used.
5. General procedure for the three-component coupling of imine, EDA, and acetone catalyzed by rhodium catalyst: Under a nitrogen atmosphere, to a stirred solution of $RhCl_3(H_2O)_3$ (0.05 mmol, 0.1 equiv) in acetone (3 mL) was added $AgBF_4$ (0.15 mmol, 0.3 equiv) in acetone (3 mL) at room temperature. After 5 min, imine (0.5 mmol, 1.0 equiv) in acetone (3 mL) and ethyl diazoacetate (1.0 mmol, 2.0 equiv) were added. After stirring for 30-40 min, the reaction mixture was concentrated, dissolved in ether, and filtered through celite. The ethereal solution was concentrated *in vacuo* and chromatographed on silica gel (EA : hexane = 1 : 5).
(4*R*,5*R*)-5-Ethyloxycarbonyl-2,2-dimethyl-3((*S*)-α-methylbenzyl)-4-(*p*-nitrophenyl)-1,3-oxazolidine (3g): mp 115-117 °C; $[\alpha]_D^{21}$ = +17 (c 0.10, CH_2Cl_2); IR (KBr) 3491, 2980, 2935, 1758, 1520, 1347, 1206, 1123, 854, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.5 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.18-7.13 (m, 5H), 4.90 (d, *J* = 8.3 Hz, 1H), 4.72 (d, *J* = 8.3 Hz, 1H), 4.04 (q, *J* = 6.8 Hz, 1H), 3.79 (dq, *J* = 10.9, 7.1 Hz, 1H), 3.57 (dq, *J* = 10.9, 7.1 Hz, 1H), 1.44 (s, 3H), 1.26 (s, 3H), 1.22 (d, *J* = 6.6 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.30, 149.63, 147.13, 144.27, 129.23, 128.03, 127.52, 127.12, 122.75, 97.51, 77.21, 64.82, 60.87, 56.85, 28.89, 22.50, 21.70, 13.69.; Anal. calcd: C, 66.32; H, 6.58; N, 7.03. Found C, 66.50; H, 6.73; N, 7.07.
6. Xie, W.; Fang, J.; Wang, P. G. *Tetrahedron* **1999**, *55*, 12929.
7. Park, C. S.; Choi, H. G.; Lee, H. J.; Lee, W. G.; Ha, H. J. *Tetrahedron: Asymmetry* **2000**, *11*, 3283.
8. Chang, J.-W.; Bae, J. H.; Shin, S.-H.; Park, C. S.; Choi, D.; Lee, W. K. *Tetrahedron Lett.* **1998**, *39*, 9193.
9. (a) Doyle, M. P.; Yan, M.; Hu, W.; Gronenberg, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 4692. (b) Rasmussen, K. G.; Jφrgensen, K. A. *J. Chem. Soc. Perkin Trans. 1* **1997**, 1287.
10. (a) Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50. (b) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett.* **2001**, *3*, 933. (c) Doyle, M. P.; Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* **1997**, *62*, 7210.