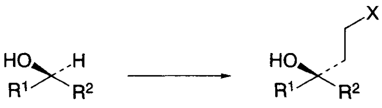
Tertiary Alcohol Synthesis from Secondary Alcohols *via* C–H Insertion

Eun Lee,* Insung Choi and Sue Yeon Song

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-742, Korea

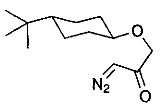
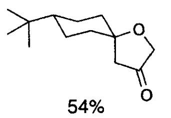
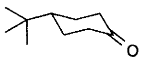
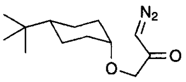
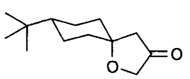
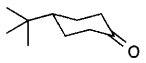
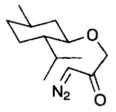
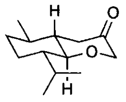
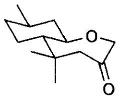
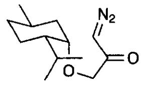
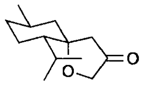
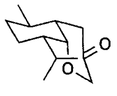
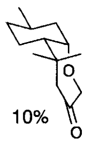
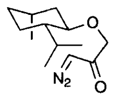
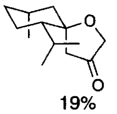
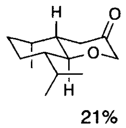
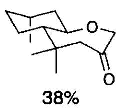
Secondary alcohols are converted into 3(2*H*)-furanone derivatives *via* C–H insertion reaction, from which tertiary alcohols are prepared with retention of stereochemistry.

The conversion of secondary carbinols into tertiary alcohols by substituting the C–H bond with a C–C bond will constitute a useful method in organic synthesis (Scheme 1). In this context, intramolecular insertion of the alkylidene carbene into the C–H bond adjacent to the protected hydroxyl group had been utilized to obtain a chiral tertiary alcohol derivative.[1] Conceptually, the hydroxyl group may be used as a handle for the insertion reaction if properly derivatized, which will lead to a more generally applicable scheme for the conversion. Our initial efforts were focused on the use of β-lactones obtained from insertion reactions of diazomalonates,[2] but further transformation of these lactones presented problems due to facile elimination of carbon dioxide. α-Alkoxy diazoketones served as good precursors in the preparation of 3(2*H*)-furanones as the insertion occurred preferentially at the C–H bonds adjacent to the ether oxygens in the dirhodium tetraacetate catalysed reactions.[3] As the known examples primarily deal with derivatives of primary alcohols, a systematic study on the selectivity of insertion reactions of α-alkoxy diazoketones prepared from secondary alcohols was undertaken.

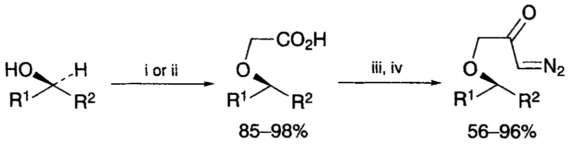


Scheme 1 Intramolecular C–H bond insertion with retention of configuration

Table 1 Insertion reactions of α-alkoxy diazoketones. *Reagents and conditions*: 0.01 equiv. $Rh_2(OAc)_4$ in CH_2Cl_2 (50 μmol dm^{-3}), room temp. Substrates added *via* a syringe pump, 10 h

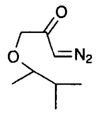
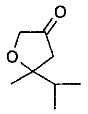
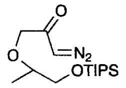
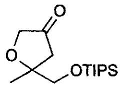
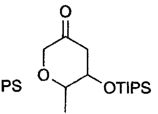
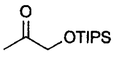
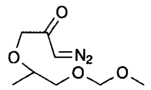
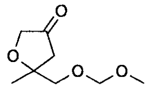
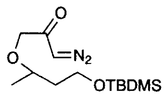
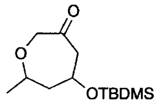
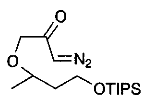
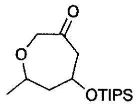
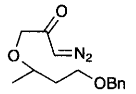
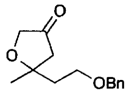
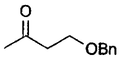
Entry	Substrate	Products		
1		 54%	 30%	
2		 46%	 17%	
3		 27%	 29%	
4		 30%	 36%	 10%
5		 19%	 21%	 38%

α-Alkoxy diazoketones were prepared from secondary alcohols *via* the corresponding α-alkoxy carboxylic acids (Scheme 2). The insertion reaction in the presence of dirhodium tetraacetate was carried out under high dilution conditions and the product distribution was studied (Table 1). Substrates derived from *trans*- and *cis*-*tert*-butylcyclohexan-4-ol were converted into the 3(2*H*)-furanone products in modest yields accompanied by *tert*-butylcyclohexan-4-one (Table 1, entries 1 and 2). Steric crowding alters the course of the reaction greatly: the menthyl derivative did not yield a noticeable amount of the 3(2*H*)-furanone product and the six- and seven-membered ring

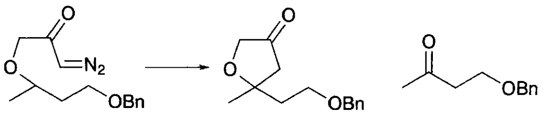


Scheme 2 *Reagents and conditions*: i, NaH, THF–DMSO, $ClCH_2CO_2Na$; ii, NaH, THF, allyl bromide then RuO_4; iii, $(COCl)_2$, benzene, room temp.; iv, CH_2N_2, Et_2O, 0 °C

Table 2 Insertion reactions of α-alkoxy diazoketones. *Reagents and conditions*: 0.01 equiv. $Rh_2(OAc)_4$ in CH_2Cl_2 (50 μmol dm^{-3}), room temp. Substrates added *via* a syringe pump, 10 h. (TIPS = triisopropylsilyl; TBDMS = *tert*-butyldimethylsilyl)

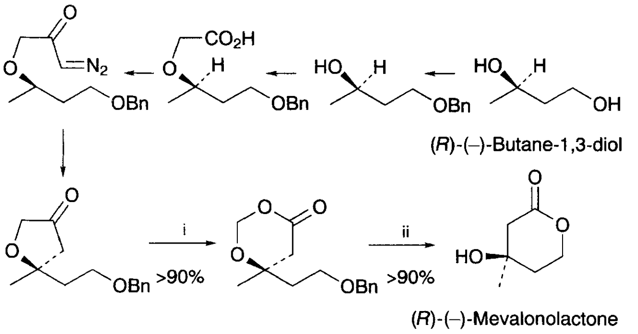
Entry	Substrate	Products		
6		 20%		
7		 37%	 33%	 Trace
8		 40%		
9		 80% (1:1)		
10		 82% (4:1)		
11		 58%	 37%	

products were isolated from the reaction (Table 1, entry 3). Substrates derived from neomenthol and isomenthol were converted into three different products: remarkably, the seven-membered ring ketone was the predominant product from the isomenthyl derivative (Table 1, entries 4 and 5). Next, acyclic secondary alcohol derivatives were investigated (Table 2). The yield of the 3(2*H*)-furanone product from the 3-methylbutan-2-ol derivative was quite low (Table 2, entry 6). The 1-triisopropylsilyloxypropan-2-ol derivative was converted into equal amounts of the five- and six-membered ring ketones but the 1-methoxymethoxypropan-2-ol derivative yielded only the 3(2*H*)-furanone product (Table 2, entries 7 and 8). From the results, it is clear that silyloxy group promotes insertion into the adjacent C–H bond. This effect is more clearly manifested in the reaction of 1-silyloxybutan-3-ol derivatives, as both 1-*tert*-butyldimethylsilyloxybutan-3-ol and 1-triisopropylsilyloxybutan-3-ol derivatives mainly yielded seven-membered ring ketones upon exposure to dirhodium tetraacetate catalyst (Table 2, entries 9 and 10). In these cases, the electronic effect of the silicon atom[4] overrode the usual conformational preference for the five-membered ring formation. In the reaction of the 1-benzyloxybutan-3-ol derivative, on the other hand, the seven-membered ring products were not isolated and the 3(2*H*)-furanone product was mainly obtained accompanied by the ketone by-product (Table 2, entry 11).



$Rh_2(acam)_4$	41 °C	35%	0%	(55% starting material recovered)
$Rh_2(oct)_4$	room temp.	28%	45%	
$Rh_2(tfa)_4$	room temp.	5%	55%	
$Rh_2(tpa)_4$	room temp.	60%	15%	
$Rh_2(OAc)_4$	room temp.	58%	37%	

Scheme 3 (acam = acetamide; oct = octanoate; tfa = trifluoroacetate; tpa = triphenylacetate)



Scheme 4 *Reagents and conditions*: i, MCPBA, $NaHCO_3$, CH_2Cl_2, room temp., 15 min, >90%; ii, H_2, Pd/C, EtOH, 4 h, >90%

In the insertion reactions of the 1-benzyloxybutan-3-ol derivative, the amount of the by-product 4-benzyloxybutan-2-one varies depending on the nature of the catalysts (Scheme 3). With dirhodium tetrakis(acetamidate), no ketone by-product was obtained, but the insertion reaction was too slow. Use of dirhodium tetrakis(trifluoroacetate) catalyst led mainly to the ketone formation. Dirhodium tetrakis(triphenylacetate)[5] was the most useful catalyst in this case.

Starting from (*R*)-(−)-butane-1,3-diol, selective protection of the primary hydroxyl group, diazoketone formation, and insertion reaction led to the chiral 3(2*H*)-furanone. Baeyer–Villiger oxidation and hydrogenolysis resulted in the formation of (*R*)-(−)-mevalonolactone† in excellent yield (Scheme 4).

We thank the Organic Chemistry Research Center (KOSEF) for financial support.

Received, 26th October 1994; Com. 4/06559J

Footnote

† $[\alpha]_D^{22}$ = −22.5 (MeOH, *c* 1.02), >98% ee; NMR analysis of (*R*)-1-(1-naphthyl)ethylamide.

References

1 S. Ohira, S. Ishi, K. Shinohara and H. Nozaki, *Tetrahedron Lett.*, 1990, **31**, 1039.
2 E. Lee, K. W. Jung and Y. S. Kim, *Tetrahedron Lett.*, 1990, **31**, 1023.
3 J. Adams, M.-A. Poupart, L. Grenier, C. Schaller, N. Ouimet and R. Frenette, *Tetrahedron Lett.*, 1989, **30**, 1749; J. Adams, M.-A. Poupart and L. Grenier, *Tetrahedron Lett.*, 1989, **30**, 1753; D. M. Spero and J. Adams, *Tetrahedron Lett.*, 1992, **33**, 1143.
4 C. G. Pitt, M. M. Bursey and D. A. Chatfield, *J. Chem. Soc., Perkin Trans. 2*, 1976, **434**.
5 S. Hashimoto, N. Watanabe and S.Ikegami, *J. Chem. Soc., Chem. Commun.*, 1992, 1508; *Tetrahedron Lett.*, 1992, **33**, 2709.