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Asymmetric synthesis of secondary alcohols from primary alcohols via intramolecular carbenoid C–H insertion catalyzed by rhodium(II) 3-phenylcholestane-2-carboxylate

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Chiral secondary alcohols may be prepared from primary alcohols via asymmetric C–H insertion reactions of α′-alkoxy-α-diazoketones catalyzed by rhodium(II) (2*R*,3*R*)-3-phenylcholestane-2-carboxylate.

Rhodium(II)-catalyzed C–H insertion reactions of α′-alkoxy-α-diazoketones are well known to yield 3(2*H*)-furanones as the insertion occurs at the C–H bonds adjacent to the ether oxygens.[1–4] The reaction proceeds with retention of configuration, and efficient conversion of secondary alcohols to tertiary alcohols was realized *via* oxidative transformations. This way, chiral tertiary alcohols may be prepared from chiral secondary alcohols (Scheme 1).[2]

Preparation of chiral secondary alcohols from achiral primary alcohols presents a completely different and more difficult problem. Asymmetric C–H insertion reaction of α′-alkoxy-α-diazoketones prepared from primary alcohols requires developing appropriate chiral catalysts capable of discriminating two prochiral hydrogens on the carbinol carbon (Scheme 2).

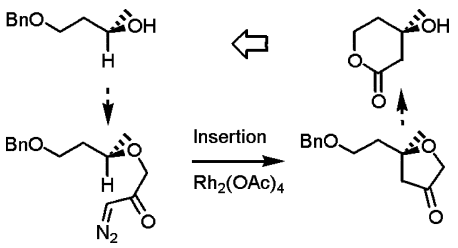
The substrate α′-octyloxy-α-diazoacetone (**3a**) was prepared from octanol (**1a**) *via* octyloxyacetic acid (**2a**). Insertion reactions were carried out and the product 3(2*H*)-furanone **4a** was converted into the cyclic acetal **5a** by treatment with *m*-chloroperoxybenzoic acid.[2] Methanolysis of **5a** under acidic conditions afforded methyl 3-hydroxydecanoate (**6a**) as the final product. Enantiomeric excess was calculated for each reaction by converting **6a** into the (*S*)-(*O*)-acetylmandelate mixture (**7a** and **8a**) and analyzing the ^{1}H-NMR spectrum (Scheme 3).

Enantioselective processes for reactive carbenoids derived from diazoketones have proved to be problematic. Among acceptor-substituted carbenoids, carbenoids derived from α-diazoketones are more reactive than those derived from α-diazoacetates and α-diazoacetamides, and C–H activation reactions with enantiopure rhodium(II) carboxylate or carboxamidate catalysts were reported to generate little asymmetric induction.[5] In our case, the insertion reaction of **3a** in dichloromethane in the presence of Rh_2[*S*-DOSP]$_4$ at room temperature proceeded to give the final product **6a** in relatively low yield (28%),[6] and the level of asymmetric induction was low (13% e.e.).[7] Use of Rh_2[*S*-TBSP]$_4$ did not much improve the chemical yield or the asymmetric induction. Use of Rh_2(5*S*-MEPY)$_4$ in dichloromethane required heating, which resulted in a low level of asymmetric induction (8% e.e.) (Table 1).

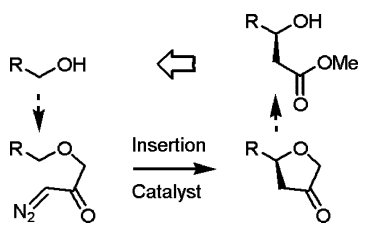
There was clearly a need for a new chiral catalyst system. We considered the chiral *trans*-2-phenylcyclohexanecarboxylate motif for construction of chiral rhodium(II) carboxylate, and decided to investigate the efficacy of rhodium(II) (2*R*,3*R*)-3-phenylcholestane-2-carboxylate (**12**, Rh_2(PCC)$_4$).

Synthesis of **12** started from the known alcohol **10**[8] prepared from cholesterol (**9**). PCC oxidation afforded the corresponding ketone, which was mainly converted into the 3*S*-carboxaldehyde *via* methylenation, hydroboration, and oxidation. The requisite 3*R*-carboxaldehyde was obtained under basic equilibrating conditions, and ruthenium catalyzed oxidation provided the carboxylic acid **11**. The catalyst **12** was then synthesized *via* ligand exchange reaction with rhodium(II) acetate (Scheme 4).

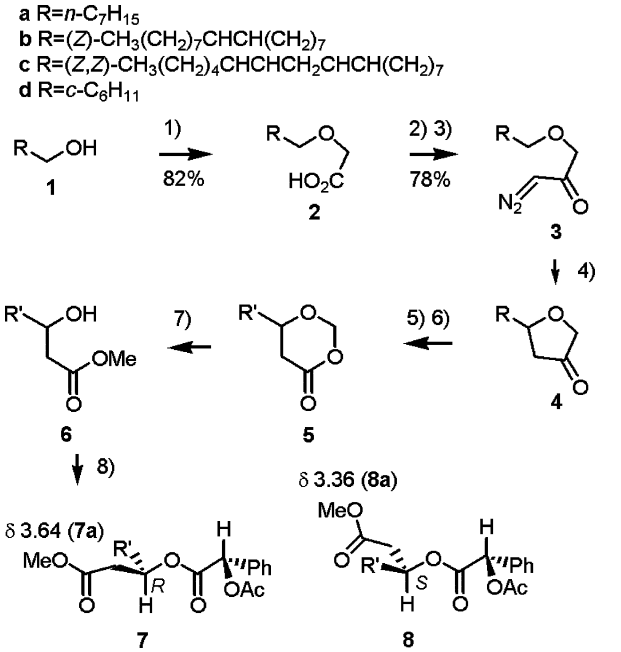
The insertion reaction of **3a** in dichloromethane at room temperature in the presence of Rh_2[PCC]$_4$ (**12**) proceeded to yield the product **6a** in higher enantiomeric excess (80% yield, 37% e.e.) (Table 1). Different solvent systems were tested aiming at more efficient asymmetric induction using the catalyst **12**, but the situation did not improve in dichloromethane–pentane (1 : 10, −78 °C), in fluorobenzene (−40 °C), and in pentane (r.t.). The insertion reaction in pentane at −45 °C was found to yield the product **6a** in 71% e.e. Further lowering the temperature was not practical as the



Scheme 1 Chiral tertiary alcohol preparation *via* C–H insertion reaction.



Scheme 2 Chiral secondary alcohols from primary alcohols



Scheme 3 Insertion reaction of the substrates. *Reagents and conditions*: 1) NaH, THF; $ClCH_2CO_2Na$, HMPA, reflux; 2) $(COCl)_2$, benzene; 3) CH_2N_2, ether; 4) see Table 1; 5) H_2, Pd/C (this step is omitted for **4a** and **4d**. R′ = R in **5a**–**8a** and **5d**–**8d**, and R′ = *n*-$C_{17}H_{35}$ in **5b**–**8b** and **5c**–**8c**); 6) mCPBA, DCM; 7) *p*-TsOH, MeOH; 8) (*S*)-(*O*)-acetylmandeloyl chloride, pyridine, DCM.

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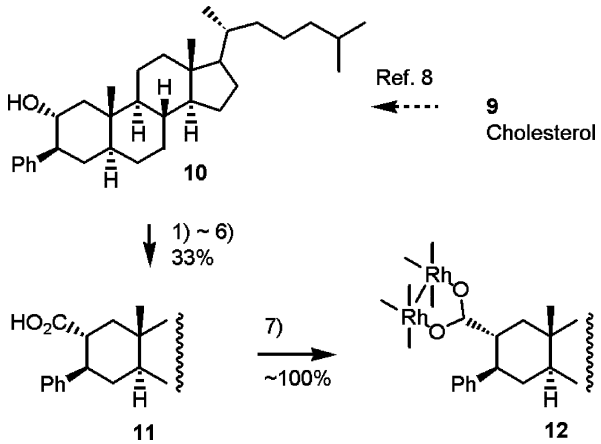
Table 1 Results of insertion reactions

Substrate	Catalyst (mol%)	Solvent[a]	Temp.	Yield (%)[b]	e.e. (%)
3a	Rh_2[*S*-DOSP]$_4$ (2)	DCM	r.t.	28	13(*R*)
	Rh_2[*S*-TBSP]$_4$ (2)	DCM	r.t.	31	14(*R*)
	Rh_2[5*S*-MEPY]$_4$ (2)	DCM	reflux	84	8(*R*)
	Rh_2[PCC]$_4$ (**12**) (2)	DCM	r.t.	80	37(*R*)
	(1)	DCM–pentane (1 : 10)	−78 °C	87	36(*R*)
	(1)	PhF	−40 °C	65	30(*R*)
	(2)	pentane	r.t.	79	33(*R*)
	(2)	pentane	−45 °C	72	71(*R*)
3b	Rh_2[*S*-DOSP]$_4$ (1)	DCM	0 °C	31	23(*R*)
	Rh_2[*S*-PTPA]$_4$ (1)	DCM	0 °C	67	16(*R*)
	Rh_2[PCC]$_2$ (**12**) (1)	pentane	0 °C	60	47(*R*)
	(1)	pentane	−78 °C	62	83(*R*)
3c	(1)	pentane	−78 °C	71	80(*R*)
3d	(1)	pentane	−78 °C	52	67(*R*)

[a] Slow addition of the substrate *via* syringe pump for 4–6 h into the solution containing the catalyst (1 mol% at 0.2–0.5 mM or 2 mol% at 0.8–0.9 mM). [b] Three-step yield of **6a** from **3a** and **6d** from **3d**. Yield of **4b** from **3b** and **4c** from **3c**.



Scheme 4 Synthesis of $Rh_2(PCC)_4$. *Reagents and conditions*: 1) PCC, 4 Å MS, DCM; 2) Cp_2TiMe_2, THF, reflux; 3) BH_3·THF; H_2O_2, NaOH; 4) PCC, 4 Å MS, DCM; 5) 2 M NaOH, THF, reflux; 6) 5 mol% RuO_2, $NaIO_4$, MeCN–CCl_4–H_2O (2 : 2 : 3); 7) $Rh_2(OAc)_4$, PhCl, reflux, 48 h, Soxhlet (Na_2CO_3 trap).

substrate diazoketone **3a** crystallized out in pentane at lower temperature.

A new α-diazoketone substrate **3b** was prepared from oleyl alcohol (**1b**), and the C–H insertion product **4b** was analyzed after conversion to **6b** *via* hydrogenation, mCPBA oxidation, and methanolysis. The result obtained from the insertion reaction in the presence of Rh_2[*S*-DOSP]$_4$ in dichloromethane at 0 °C was comparable to the result obtained for the reaction of **3a**. Insertion reaction in the presence of Rh_2[*S*-PTPA]$_4$ in dichloromethane at 0 °C gave a higher yield of **4b**, but the enantiomeric excess did not improve. The reaction of **3b** in the presence of Rh_2[PCC]$_4$ (**12**) in pentane at 0 °C proceeded to yield **4b** in 47% e.e., and eventually at −78 °C in 83% e.e.

In the presence of the catalyst **12** in pentane at −78 °C, the furanone **4c** was obtained from the α-diazoketone substrate **3c** (prepared from linoleyl alcohol (**1c**)) in 80% e.e. The C–H insertion reaction of the substrate **3d** prepared from cyclohexanemethanol (**1d**) proceeded in 67% e.e.

The present studies show that $Rh_2(PCC)_4$ is an efficient chiral catalyst in asymmetric C–H insertion reaction of α′-alkoxy-α-diazoketones. Due to its lipophilic character, we were able to carry out insertion reactions in non-polar solvents at low temperature. Further applications of this catalyst in related carbenoid reactions will be the subject of future communications.

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