

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 -diazoketone (**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 ¹H-NMR spectrum (Scheme 3).

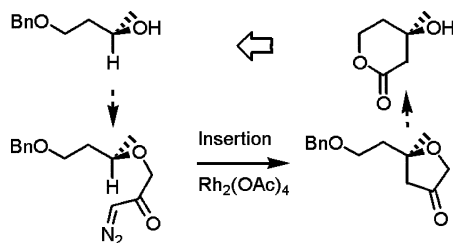
Enantioselective processes for reactive carbenoids derived from diazoketones have proved to be problematic. Among acceptor-substituted carbenoids, carbenoids derived from α -diazoketones are more reactive than those derived from α -diazocetates and α -diazocetamides, and C–H activation reactions with 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 Rh₂[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 Rh₂[S-TBSP]₄ did not much improve the chemical yield or the asymmetric induction. Use of Rh₂(5*S*-MEPY)₄ in dichloromethane required heating, which resulted in a low level of asymmetric induction (8% e.e.) (Table 1).

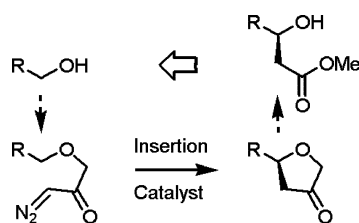
There was clearly a need for a new chiral catalyst system. We considered the chiral *trans*-2-phenylcyclohexanecarboxylate motif for construction of chiral rhodium(II) carboxylate, and decided to investigate the efficacy of rhodium(II) (2*R*,3*R*)-3-phenylcholestane-2-carboxylate (**12**, Rh₂(PCC)₄).

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 Rh₂[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

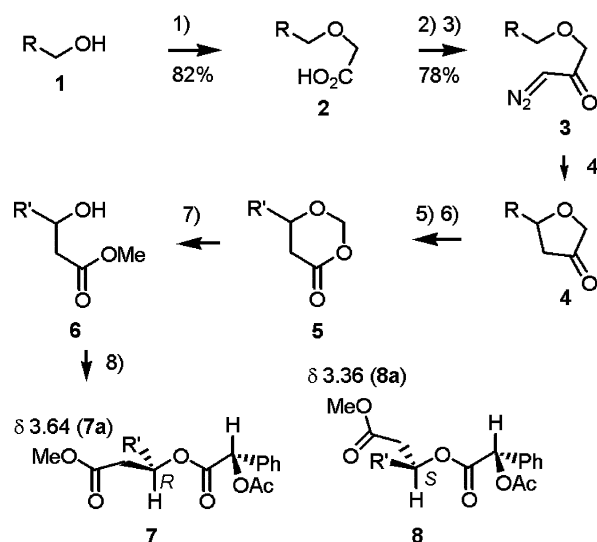


Scheme 1 Chiral tertiary alcohol preparation via C–H insertion reaction.



Scheme 2 Chiral secondary alcohols from primary alcohols

- a R = *n*-C₇H₁₅
b R = (Z)-CH₃(CH₂)₇CHCH(CH₂)₇
c R = (Z,Z)-CH₃(CH₂)₄CHCHCH₂CHCH(CH₂)₇
d R = *c*-C₆H₁₁



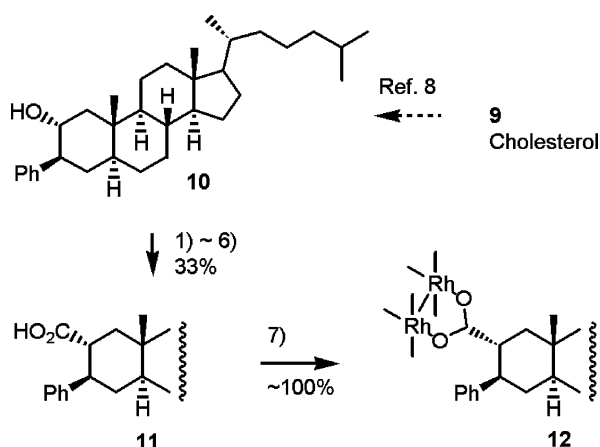
Scheme 3 Insertion reaction of the substrates. Reagents and conditions: 1) NaH, THF; 2) (COCl)₂, benzene; 3) CH₂N₂, ether; 4) see Table 1; 5) H₂, Pd/C (this step is omitted for **4a** and **4d**. R' = R in **5a–8a** and **5d–8d**, and R' = *n*-C₁₇H₃₅ in **5b–8b** and **5c–8c**); 6) mCPBA, DCM; 7) *p*-TsOH, MeOH; 8) (*S*)-(*O*)-acetylmandeloyl chloride, pyridine, DCM.

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 [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)
	Rh ₂ [S-DOSP] ₄ (1)	DCM	0 °C	31	23(R)
	Rh ₂ [S-PTPA] ₄ (1)	DCM	0 °C	67	16(R)
3b	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 Rh₂(PCC)₄. Reagents and conditions: 1) PCC, 4 Å MS, DCM; 2) Cp₂TiMe₂, THF, reflux; 3) BH₃·THF; H₂O₂, NaOH; 4) PCC, 4 Å MS, DCM; 5) 2 M NaOH, THF, reflux; 6) 5 mol% RuO₂, NaIO₄, MeCN–CCl₄–H₂O (2 : 2 : 3); 7) Rh₂(OAc)₄, PhCl, reflux, 48 h, Soxhlet (Na₂CO₃ 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 Rh₂[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 Rh₂[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 Rh₂[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 Rh₂(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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