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New route to optically active amine derivatives: ruthenium-catalyzed enantioselective hydrogenation of ene carbamates

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Abstract

The reaction of cyclic ketones with *tert*-butyl or benzyl carbamate under acidic conditions directly affords prochiral ene carbamates. Their enantioselective hydrogenation in the presence of a chiral ruthenium catalyst provides a new access to optically active carbamates easy to deprotect to the corresponding optically active amines.

1. Introduction

Optically active amine derivatives constitute a class of key-intermediates for human and plant health and are efficient ligands for asymmetric catalysis.[1] Many synthetic methods have been used to prepare optically active amines, most of them based on asymmetric syntheses and the utilization of stoichiometric amounts of chiral reagents.[1,2] The enantioselective reduction of prochiral imines constitutes a straightforward method, but apart from the rhodium-,[3] titanium-[4] and iridium-catalyzed[5] hydrogenation, and ruthenium-catalyzed hydrogen transfer[6] in the presence of ammonium formate, few examples have been reported[7] and deal with very specific substrates. Functionalized imines such as oximes[8] and tosylimines[9] have been hydrogenated in the presence of chiral ruthenium catalysts and the best results have been obtained from hydrazones with rhodium catalyst.[10] Enamines also represent a useful class of precursors for access to optically active amines; however, their catalytic enantioselective hydrogenation has only been successfully achieved with titanium catalysts.[11]

Up to now, the best catalytic preparations of optically active amine derivatives have been performed via enantioselective hydrogenation of simple enamides as first shown by Kagan et al. with the use of rhodium-diop catalyst precursor.[12] Then, excellent enantioselectivities were reached in the presence of ruthenium–Binap[13,14] or rhodium–duphos[15] and rhodium–BICP or –PennPhos catalysts[16] for access to biologically active compounds. An example of the catalytic hydrogenation of the exocyclic C=C bond

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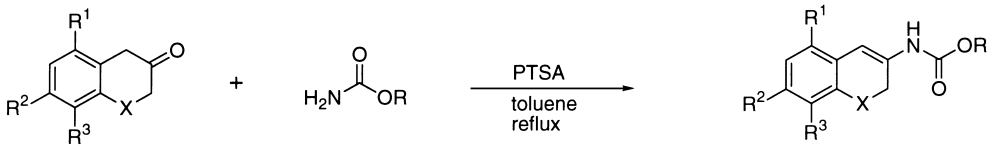
of cyclic ene carbamates, generated by carbamatation of a proline derivative with ethyl chloroformate, has just been reported.[17] The transformation of a ketone into an enamide would be an efficient way to generate an amine derivative containing a chelating functional group able to orientate the enantioselective hydrogenation, but the deprotection of the amine functionality is not always straightforward.

We now report a novel method of access to optically active amine derivatives via:

(i) an efficient preparation of ene carbamates from non-activated cyclic ketones;
(ii) their enantioselective hydrogenation in the presence of optically active ruthenium catalysts; and
(iii) the easy cleavage of *tert*-butyl and benzyl carbamates to give optically active amines.

2. Preparation of ene carbamates

The ene carbamates **3**–**6** were obtained by treatment of 10 mmol of the chromanone **1** with 25 mmol of carbamate in the presence of 1 mmol of *p*-toluenesulfonic acid (PTSA) (10 mol% with respect to the ketone) in refluxing toluene in a Dean–Stark apparatus for 20 h (Scheme 1). After purification by chromatography over silica with an ether/pentane mixture, the ene carbamates **3**–**6** were isolated in 50, 65, 50 and 65% yield, respectively.

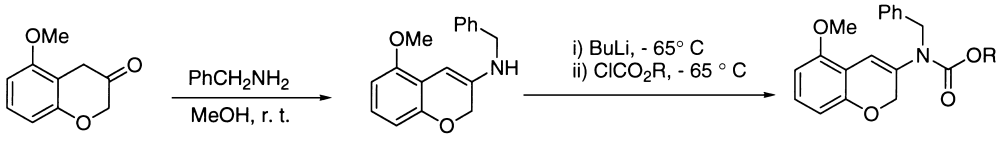


1 R^1 = OMe, R^2 = R^3 = H, X = O
2 R^1 = H, R^2 = Me, R^3 = $(CH_2)_2CO_2H$, X = CH_2

R = Et (**3**), ^{t}Bu (**4**), CH_2Ph (**5**), $CH_2CH{=}CH_2$ (**6**)
R = Et (**7**), nBu (**8**), ^{t}Bu(**9**), CH_2Ph (**10**)
R^1 = R^2 = R^3 = H, X = CH_2, R = Et (**11**)

Scheme 1.

Under similar experimental conditions, the tetralone **2** was converted into the ene carbamates **7**–**10**, which were isolated as white solids in 66, 90, 60, 80 and 60% yield, respectively. The carbamates **12** and **13** were obtained in two steps, both in 72% yield, from **1** on reaction with benzylamine at room temperature followed by deprotonation with BuLi at −65°C and addition of chloroformate according to Scheme 2.



12 R = Et
13 R = CH_2Ph

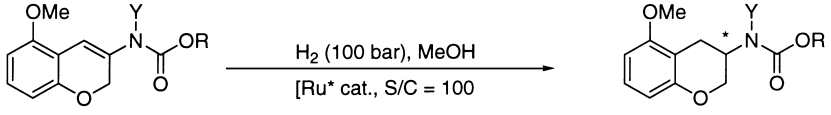
Scheme 2.

3. Enantioselective hydrogenation of ene carbamates

The direct hydrogenation of the ene carbamates **3**–**13** was attempted in the presence of catalytic amounts of optically active ruthenium complexes containing the atropoisomeric Binap ligand: ((*R*)-Binap)Ru$(O_2CCF_3)_2$ **A** and [((*S*)-Binap)$RuCl_2]_2NEt_3$ **B**. Under typical conditions, 1 mmol of ene

carbamate and 0.01 mmol of ruthenium catalyst were placed in a 125 ml autoclave in 10 ml of methanol. After degassing with hydrogen, a pressure of 100 bar of hydrogen was applied. The autoclave was stirred mechanically during 20 to 60 h and the conversion was determined by ^{1}H NMR. After isolation of the hydrogenated carbamates, the enantiomeric excesses were determined by HPLC with a chiral column (Chiralcel OD 25 cm or (*S*,*S*) WHELK 0–1 Interchim). The derivatives **3**–**5** led to moderate results, whereas the carbamates **7**–**10** bearing a pendant functional chain afforded excellent ee values.

The ene carbamates **3**–**5** and **12**, **13** obtained from the chromanone derivative **1** were hydrogenated in methanol under 100 bar of hydrogen (Scheme 3). All of them were hydrogenated and the complete conversion was obtained within 20 h at 50–60°C; a lower temperature of 25°C required 40 h reaction time (Table 1).



Scheme 3.

The catalytic activities of complexes **A** and **B** were quite similar. The enantioselectivitites resulting from hydrogenation of the secondary ene carbamates **3**–**5** were not good (<22%) whatever the conditions. Higher enantioselectivities in the range 33–45% were obtained from the tertiary ene carbamate **13** and the best result was obtained from the ethyl ene carbamate **12**, which was completely hydrogenated in methanol within 20 h (at 30–50°C) in the presence of [((*R*)-Binap)$RuCl_2$]$_2$$NEt_3$ **B** and led to an enantiomeric excess of 75%. The hydrogenation of the allyl carbamate **6** gave a total conversion into the saturated propyl carbamate and, thus, the objective of palladium-catalyzed deprotection could not be attempted.

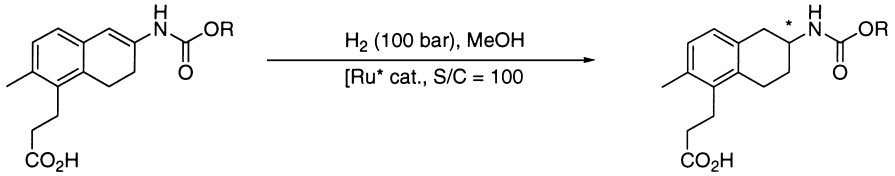
Table 1
Enantioselective hydrogenation of ene carbamates **3**–**5**, **12** and **13**

Ene-carbamate	Catalyst	Temperature (°C)	Reaction time (h)	product	Yield [a] (%)	ee (%)
3	**A**	50	20	**14**	90	22 (+)
3	**B**	50	20	**14**	90	5 (-)
4	**B**	50	20	**15**	95	9 (-)
4	**B**	25	40	**15**	96	8 (-)
5	**B**	50	20	**16**	95	16 (-)
12	**B**	50	20	**17**	85	75 (+)
13	**A**	40	20	**18**	50	45 (-)
13	**A**	60	20	**18**	98	34 (-)
13	**B**	60	20	**18**	98	33 (+)

General conditions : H_2 (100 bar), MeOH (10 ml), substrate/catalyst = 100, total conversion of the ene carbamate, [a] isolated yield. **A**: ((R)-Binap)$Ru(O_2CCF_3)_2$, **B**: [((S)-Binap)$RuCl_2$]$_2$$NEt_3$.

The ene carbamates **7**–**11** were hydrogenated under 100 bar H_2 at 50–80°C in the presence of ((*R*)-Binap)$Ru(O_2CCF_3)_2$ **A** as catalyst (Scheme 4).

At 50°C, the hydrogenation of 0.75 mmol of ene carbamate was completed within 20 h from the ethyl and *n*-butyl ene carbamates **7** and **8**, whereas 48 h and 60 h were necessary to obtain a total conversion



Scheme 4.

of *tert*-butyl and benzyl ene carbamates **9** and **10**, respectively (Table 2). These results indicate that the reactivities of the different ene carbamates increased in the order of benzyl<*tert*-butyl<*n*-butyl, ethyl groups. When the hydrogenation reactions were carried out at 50°C, the enantiomeric excesses obtained from the four carbamates were in the range 65–92%. Increasing the temperature to 80°C led to a faster reaction but the enantiomeric excesses decreased from 65 to 54% for **9** and from 88 to 70% for **10**. It is noteworthy that no conversion was obtained when the carbamate **11** was treated at 50°C for 60 h in the presence of 1 mol% of **A** under 100 bar of H_2. Thus the presence of either the methoxy group or the oxygenated heterocycle in the chromanone series **3**–**6**, **12**, **13** and a carboxylic acid functionality in carbamates **7**–**10** probably favours the coordination of the substrate to the ruthenium centre, thus promoting their hydrogenation.

Table 2
Enantioselective hydrogenation of ene carbamates **7**–**10**

Ene-carbamate	Temperature (°C)	Reaction time (h)	product	Yield [a] (%)	ee (%)
7	50	20	**19**	80	75
8	50	20	**20**	70	92
9	80	20	**21**	95	54
9	50	48	**21**	94	65
10	80	20	**22**	95	70
10	50	60	**22**	95	88

General conditions : H_2 (100 bar), MeOH (10 ml), catalyst : ((R)-Binap)Ru(O_2CCF_3)$_2$, substrate/catalyst = 100, total conversion of the carbamate, [a]: isolated yield.

4. Deprotection of *t*-butyl and benzyl carbamates

Based on classical methods used in peptide synthesis for the removal of protecting groups without racemization, the deprotections of the hydrogenated *tert*-butyl carbamates **15**, **21** and benzylcarbamates **16**, **18**, **22** were attempted. The treatment of 0.75 mmol **15** and **21** with trifluoroacetic acid at room temperature for 1.5 h followed, after evaporation of TFA, by acidification with 1N HCl led to the corresponding amine hydrochlorides in 77 and 80% yield, respectively. Under 40 bar of hydrogen, the hydrogenolysis of **16**, **18** and **22** in methanol at 25°C in the presence of 10% of palladium on charcoal (10%) followed by treatment with 1N HCl gave the corresponding amine hydrochlorides in 80, 94 and 83% yield, respectively.

5. Conclusion

We have shown that the direct hydrogenation of ene carbamates containing an intracyclic C=C bond arising from a cyclic ketone, in the presence of Binap–ruthenium catalysts, leads to a complete conversion into saturated carbamates when an additional coordinating functionality is present in the starting molecule. The resulting enantiomeric excesses obtained strongly depend on both the structure of the substrate and the nature of the carbamate.

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