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Highly selective directed hydrogenation of enantiopure 4-(*tert*-butoxycarbonylamino)cyclopent-1-enecarboxylic acid methyl esters

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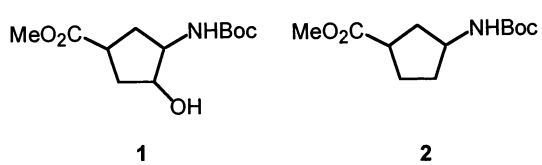
Abstract—The use of both *N*-*tert*-butoxycarbonylamino- and hydroxyl-directed hydrogenation methodology to yield essentially single diastereomers of 3-(*tert*-butoxycarbonylamino)-4-hydroxycyclopentanecarboxylic acid methyl esters and 3-(*tert*-butoxycarbonylamino)cyclopentanecarboxylic acid methyl esters is described. These results incorporate the first reported carbamate-directed hydrogenations of functionalised cyclopentenes. © 2001 Published by Elsevier Science Ltd.

The use of substrate-directed, homogeneous catalytic hydrogenation of olefins as a methodology for the creation of new, defined stereocentres in molecules is well documented but its potential, as yet, has not been fully realised. During the reaction, functional groups of defined stereochemistry present in the hydrogenation substrate chelate to the catalyst, typically a transition metal–phosphine catalyst, to create the desired directing effect. Amide[1,2] and hydroxyl[3–9] groups have been shown to be particularly useful directing groups in the reduction of both acyclic and cyclic olefins. In addition, the successful carbamate-directed hydrogenation of acyclic systems[1,10] has been reported but to our knowledge there are no previous examples demonstrating such hydrogenation in cyclic systems.

In our efforts towards making all eight stereoisomers of 3-(*tert*-butoxycarbonylamino)-4-hydroxycyclopentanecarboxylic acid methyl ester **1** and the four possible stereoisomers of 3-(*tert*-butoxycarbonylamino)cyclopentanecarboxylic acid methyl ester **2** (see Fig. 1), as potentially valuable scaffolds for pharmaceutical discovery,[11] we anticipated that this methodology would be extremely useful in the control of formation of the stereocentre α- to the carboxyl group.

We reasoned that alkene **5** and allylic alcohols **7** and **9** would make excellent precursors for the synthesis of many of the diastereoisomers of **1** and **2** (see Scheme 1). Alkene **5** contains only a single directing group whereas allylic alcohols **7** and **9** contain *N*-*tert*-butoxycarbonylamino and hydroxyl groups both of which could in theory direct a hydrogenation reaction. In the case of allylic alcohol **9**, where the relationship of carbamate and hydroxyl functions is trans, judicious choice of catalyst could, in theory, allow selective hydrogenation of either face of the olefinic bond, depending upon which functionality in the substrate determines the approach of the catalyst. Alkene **5** and allylic alcohols **7** and **9** were synthesised as illustrated in Scheme 1. The common, single enantiomer, starting material (−)-2-azabicyclo[2.2.1]hept-5-ene-3-one **3** was obtained as previously described.[12] Likewise, starting with the similarly available (+)-2-azabicyclo[2.2.1]hept-5-ene-3-one gave the opposite enantiomeric series of compounds.[12]

Treatment of lactam **3** with thionyl chloride (2.2 equiv.) in methanol yielded the amino acid methyl ester hydrochloride salt in quantitative yield. Without purification,



1 **2**

Figure 1.

Abbreviations: BPE, 1,2-bis-phospholanoethane; DUPHOS, 1,2-bis-phospholanobenzene; DiPFc, 1,1′-bis(diisopropylphosphino)ferrocene; PCy_3, tricyclohexylphosphine; 1,4-dppb, 1,4-bis-(diphenylphosphino)butane; COD, cyclooctadiene.

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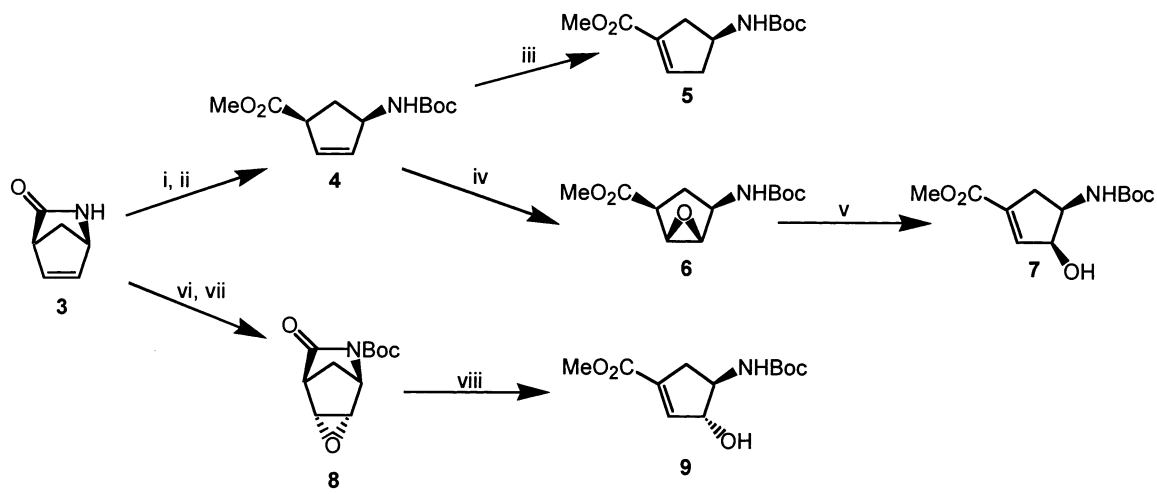


Scheme 1. (i) $SOCl_2$, MeOH, 0°C, 2 h, quantitative; (ii) Boc_2O, TEA, DCM, 0°C to rt, 2 h, 97%; (iii) DBU, DCM, rt, 3 days, 92%; (iv) Oxone®, Na_2EDTA, Bu_4NHSO_4, Me_2CO, KH_2PO_4 (aq., pH 7), 5 h, 38%; (v) DBU, DCM, 16 h, quantitative; (vi) Oxone®, H_2O, pH 6, 7 h, 33%; (vii) Boc_2O, DMAP, DCM, 0°C to rt, 5 h, 67%; (viii) NaOMe, MeOH, 0°C then rt, 16 h, quantitative.

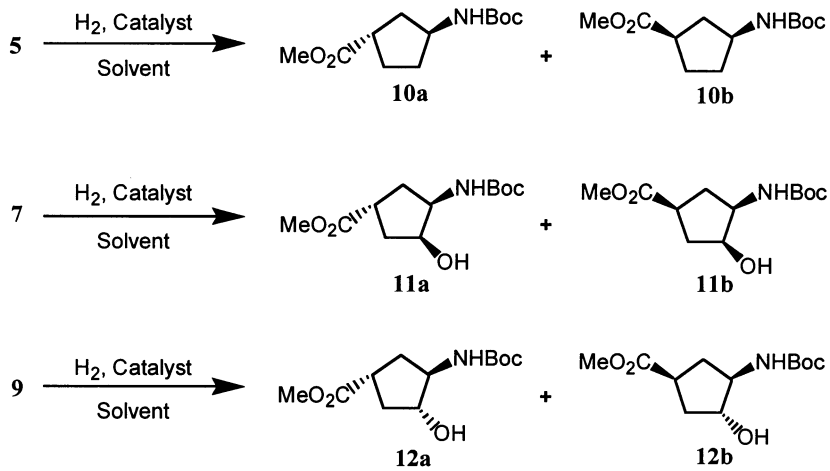
this white solid was suspended in DCM and treated firstly with TEA then Boc_2O to give *N*-Boc ester **4** as a waxy, white solid in 97% yield. Again without purification, **4** was treated with 1 equivalent of DBU in DCM to generate crude alkene **5**. Recrystallisation from ethyl acetate and heptane yielded pure alkene **5** in 92% yield. Alternatively, treatment of *N*-Boc ester **4** with Oxone® gave the crude *cis*-epoxide **6** which was crystallised to purity from *tert*-butyl methyl ether (MTBE) to give the desired product, albeit in only 38% yield. Facile rearrangement of epoxide **6** with DBU in DCM gave the desired allylic alcohol **7** as a white solid in quantitative yield. Treatment of lactam **3** with Oxone® gave crude *trans*-epoxide **8** as a 10:1 mixture of diastereomers. The mixture was crystallised to purity from MTBE and treated with Boc_2O in the presence of DMAP to give epoxide **8** in 33% yield (overall yield for two steps). A methanolic solution of **8** was treated with catalytic sodium methoxide. The initial formation of epoxide methyl ester was exothermic and required cooling. The subsequent rearrangement to allylic alcohol **9** was slower requiring the reaction temperature to be elevated to room temperature to give complete reaction. Allylic alcohol **9** was isolated as a white solid in quantitative yield. Both allylic alcohols **7** and **9** could be recrystallised from a range of solvents but in our experience purification at this stage was not necessary.

Substrates **5**, **7** and **9** were then subjected to a hydrogenation screen using various chiral and achiral hydrogenation catalysts as illustrated in Scheme 2 with the results displayed in Table 1. All reactions were performed according to the example experimental procedure provided,[13] and were seen to proceed to completion with crude products isolated in quantitative yields unless specified otherwise. All diastereomeric excesses quoted were measured on crude reaction products.

The absolute stereochemistry of **10a**, **10b**, **11a**, **11b**, **12a** and **12b** is assumed to be related to that of lactam **3**.[14] The relative stereochemistry of products **10a** and **10b** was assigned via the synthesis of pure methyl ester **10b** for which the assignment is unambiguous (Scheme 3). The relative stereochemistry of **11a** and **11b** was determined via NOE experiments performed on the related *O*-acetylated derivatives. The relative stereochemistry of **12a** and **12b** was determined via previously reported physical data for **12b**[15] and NOE experiments performed on the related *O*-acetylated derivatives. Diastereomeric ratios were determined using gas chromatography using a Chirasil Dex CB column.

Hydrogenation of substrate **5** to product **10a** was achieved in high yield and excellent selectivity (92% d.e.) using [(*R*,*R*)MeBPE]Rh (**A**). The catalysts [(*R*,*R*)-MeDuPHOS]Rh (**C**) and [(*S*,*S*)MeDuPHOS]Rh (**D**) were also seen to give reasonable selectivities. However, selectivity using catalyst [(*S*,*S*)MeBPE]Rh (**B**), which is the opposite enantiomer of **A**, was poor presumably due to a mismatching effect. Interestingly, both Crabtree's catalyst (**F**) and [1,4-dppb]Rh (**G**) gave **10b** as the predominant product highlighting that carbamate-directed reaction had not occurred in these cases, although the latter catalyst had been successfully employed in the carbamate-directed hydrogenation of acyclic substrates.[1]

For substrate **7**, where both carbamate and hydroxyl groups can potentially direct hydrogenation to the same alkene face, conversion to **11a** was achieved in excellent yield and selectivity by catalysts **A**, **B** and **C**. Catalyst **C** gave an exceptionally selective transformation yielding crude product of 98% d.e. A directed hydrogenation was also obtained with catalyst **E** but with poor selectivity. Catalyst **G** gave a predominance of **11b** and catalyst **F** gave no reaction at all. We found that the synthesis of **11b** was best achieved by using palladium on carbon as catalyst, giving the desired



Scheme 2.

product in quantitative yield with 76% d.e. The selectivity obtained was presumably sterically driven by addition of hydrogen to the less hindered face.

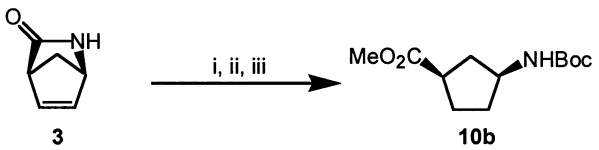
Hydrogenation of substrate **9** with catalysts **A**, **B** and **C** gave **12a**, the product obtained from carbamate-direction, in excellent yields and selectivities. Catalyst **B** gave marginally superior selectivity generating product of 94% d.e. Pleasingly, hydrogenation with catalysts **E** and **F** gave **12b**, the product obtained from hydroxyl direction, in equally gratifying yield and selectivity. Catalyst **F** has been successfully employed in hydroxyl-directed hydrogenations[7,8] previously but this is the first report to highlight the efficacy of catalyst **E** in mediating such transformations.

To conclude, we have successfully applied *N*-*tert*-butoxycarbonylamino- and hydroxyl-directed hydrogenation methodology in obtaining both hydroxylated and non-hydroxylated 3-(*tert*-butoxycarbonylamino)cyclopentanecarboxylic methyl esters in high yields and excellent selectivities. When the two directing groups have a *trans* relationship in the hydrogenation substrate, we have also demonstrated that judicious selection of catalyst allows selective hydrogenation to either face of the double bond. In addition, the study has revealed matching/mismatching effects for certain combinations of substrates and catalysts. Further work is required to develop a complete rationale for these observations.

Table 1. Directed hydrogenation of cyclopentenes **5**, **7** and **9**

Substrate	Catalyst	Diastereomeric excess (d.e.)
5	{[(*R*,*R*)-MeBPE]Rh(COD)}OTf (**A**)	92 (**10a**)
5	{[(*S*,*S*)-MeBPE]Rh(COD)}OTf (**B**)	9 (**10a**)
5	{[(*R*,*R*)-MeDuPHOS]Rh(COD)}BF_4 (**C**)	60 (**10a**)
5	{[(*S*,*S*)-MeDuPHOS]Rh(COD)}BF_4 (**D**)	82 (**10a**)
5[a]	[Ir(COD)py(PCy_3)]PF_6 (**F**)	85 (**10b**)
5	[1,4-dppb-Rh(COD)]BF_4 (**G**)	57 (**10b**)
7	{[(*R*,*R*)-MeBPE]Rh(COD)}OTf (**A**)	95 (**11a**)
7	{[(*S*,*S*)-MeBPE]Rh(COD)}OTf (**B**)	95 (**11a**)
7	{[(*R*,*R*)-MeDuPHOS]Rh(COD)}BF_4 (**C**)	98 (**11a**)
7	{[(*S*,*S*)-MeDuPHOS]Rh(COD)}BF_4 (**D**)	64 (**11b**)
7	[DiPFc-Rh(COD)]BF_4 (**E**)	33 (**11a**)
7[a]	[Ir(COD)py(PCy_3)]PF_6 (**F**)	–
7	[1,4-dppb-Rh(COD)]BF_4 (**G**)	13 (**11b**)[b]
9	{[(*R*,*R*)-MeBPE]Rh(COD)}OTf (**A**)	92 (**12a**)
9	{[(*S*,*S*)-MeBPE]Rh(COD)}OTf (**B**)	94 (**12a**)
9	{[(*R*,*R*)-MeDuPHOS]Rh(COD)}BF_4 (**C**)	92 (**12a**)
9	{[(*S*,*S*)-MeDuPHOS]Rh(COD)}BF_4 (**D**)	33 (**12a**)[c]
9	[DiPFc-Rh(COD)]BF_4 (**E**)	94 (**12b**)
9[a]	[Ir(COD)py(PCy_3)]PF_6 (**F**)	94 (**12b**)
9	[1,4-dppb-Rh(COD)]BF_4 (**G**)	60 (**12b**)

[a] DCM used as solvent.
[b] Reaction proceeds to 95% completion.
[c] Reaction proceeds to 31% completion.



3 10b

Scheme 3. (i) Boc_2O, DMAP, DCM; (ii) H_2, Pd/C, MeOH; (iii) NaOMe, MeOH.

Acknowledgements

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13. *Experimental procedure*: (1*R*,3*R*,4*S*)-3-*tert*-Butoxycarbonylamino-4-hydroxy-cyclopentanecarboxylic acid methyl ester **11a**: [(1,2-bis(2*R*,5*R*)-2,5-Dimethylphospholano)benzene](cyclooctadiene)rhodium(I) tetrafluoroborate (23 mg, 1 mol%) was added to a degassed solution of (3*R*,4*S*)-4-*tert*-butoxycarbonylamino-3-hydroxy-cyclopent-1-enecarboxylic acid methyl ester (1 g, 3.9 mmol) **7** in methanol (5 ml). The reaction mixture was transferred to a bomb and after purging with nitrogen and then hydrogen, a hydrogen pressure of 5 bars was applied and the reaction stirred for 14 h. The pressure was released and the bomb purged with nitrogen. Concentration of the reaction mixture gave a residue which was redissolved in dichloromethane (5 ml). Addition of silica (0.5 g) with stirring removed the catalyst from the reaction and filtration and concentration of the organic gave the title compound as an off-white solid of 98% d.e. in quantitative yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (9H, s, CH_3 Boc), 1.77 (1H, bs, OH), 1.85 (1H, dt, *J* 13, 10 Hz, 2-H), 2.05 (2H, m, 5-H), 2.26 (1H, m, 2-H), 3.10 (1H, m, 1-H), 3.67 (3H, s, CH_3 ester), 3.99 (1H, bs, 3-H), 4.27 (1H, m, 4-H), 4.91 (1H, d, *J* 7 Hz, NH).
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