Pergamon

Tetrahedron Letters 41 (2000) 3187–3191

TETRAHEDRON LETTERS

A novel asymmetric route to 2-amino-1,2,3,4-tetrahydronaphthalenes

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Received 2 February 2000; accepted 21 February 2000

Abstract

A novel asymmetric route to 2-amino-1,2,3,4-tetrahydronaphthalenes has been demonstrated starting from phthalimidovinylglycinol (PVG). Functionalisation of PVG via Heck reaction, olefin hydrogenation and cyclisation provides the title products. © 2000 Elsevier Science Ltd. All rights reserved.

The pharmacological activity of 2-amino-1,2,3,4-tetrahydronaphthalenes (2-aminotetralins) is well known.[1] The 2-aminotetralin structure is most commonly accessed from the corresponding 2-tetralone either via reductive amination[2] or oxime reduction.[3] Two asymmetric routes have been reported, namely the hydrogenation of an enamide derived from a 2-tetralone,[4] and the cyclisation of homo-phenylalanine derivatives.[5] Here we report an alternative asymmetric route to 2-aminotetralins using readily available and inexpensive starting materials.

The key starting material is phthalimidovinylglycinol (PVG) **1**, readily available from racemic 3,4-epoxy-1-butene by a palladium(0)-catalysed allylic substitution as described by Trost (Scheme 1).[6] All of the substrate is converted into optically enriched product, therefore, a mechanism for the equilibration of the diastereoisomeric π-allyl intermediates is required. Two mechanisms for this equilibration have been suggested, Pd–Pd substitution and an η^3–η^1–η^3 process,[7] however, we have no evidence as to which is operational in this reaction. High enantiomeric excess product is obtained at high catalyst loading (5 mol%),[6] but both the enantiomeric excess and the rate of reaction drops as the catalyst loading is decreased to 0.1 mol% (Table 1, entry 1).[8] Recent literature reports have demonstrated that halides can be added to increase regio-[9] and enantioselectivity[9,10] in palladium catalysed allylic substitution reactions. We chose to study the effect of using a mild, soluble fluoride additive, tetrabutylammonium (triphenylsilyl)difluorosilicate (TBAT)[9,11] in the synthesis of PVG **1** (Table 1).

In order to achieve high conversion in dichloromethane with 0.1 mol% of catalyst prolonged heating at reflux was required (Table 1, entry 1). Upon the addition of TBAT, both the rate and the enantioselectivity of the reaction were increased (entry 2). Changing to the more environmentally responsible solvent,

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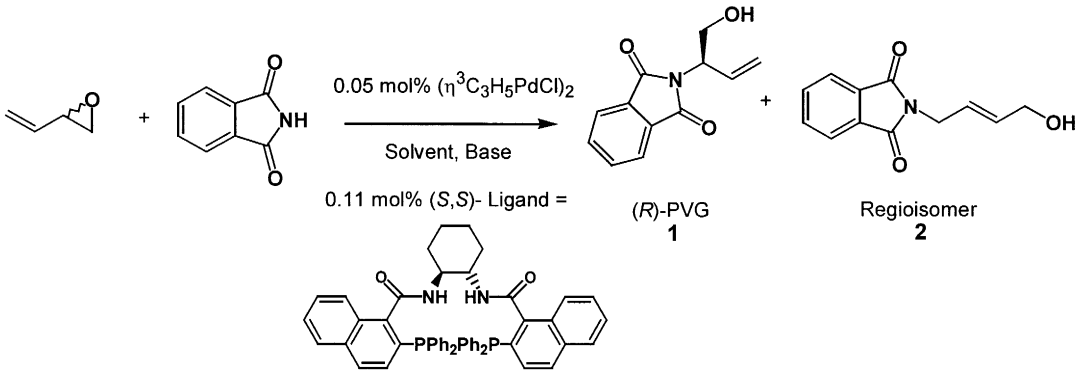
PII: S0040-4039(00)00327-0



Scheme 1. Synthesis of PVG using Trost palladium catalyst

Table 1
Effect of additives in PVG synthesis

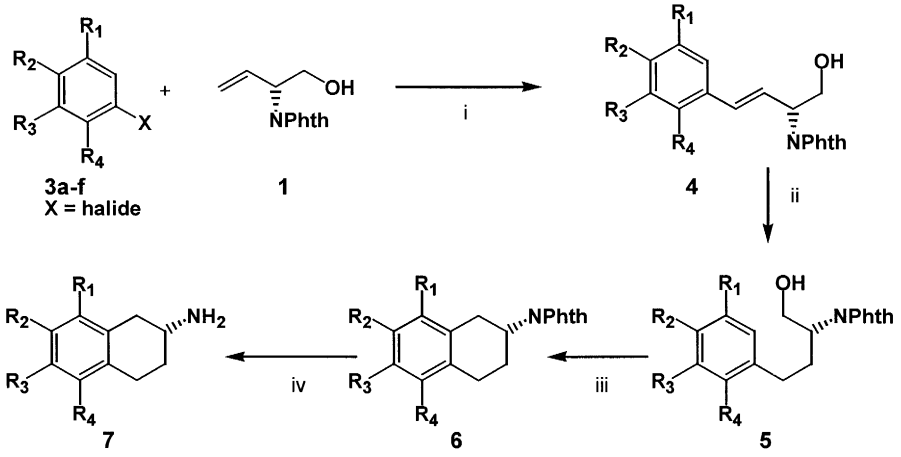
Entry	Catalyst Loading	Conv.	ee[8]	% regio-isomer **2**	Notes
1	1000:1	98%	81%	5.4%	DCM, Na_2CO_3 (5 mol%), reflux, 40h
2	1000:1	100%	91%	4.7%	DCM, Na_2CO_3 (5 mol%), reflux, 16h, TBAT (0.045 mol%)
3	500:1	96%	63%	8.5%	PhMe, Na_2CO_3 (5 mol%), 40°C, 17h
4	1000:1	100%	74%	7.1%	PhMe, Na_2CO_3 (5 mol%), 40°C, 17h, TBAT (0.045 mol%)
5	1000:1	92%	88-93%	2.0%	PhMe, Li_2CO_3 (0.25 mol%), 40°C, 40h, TBAT (0.045 mol%)
6	1000:1	100%	88%	2.0%	PhMe, Li_2CO_3 (0.25 mol%), 40°C, 40h, TBAC (0.25 mol%)

toluene, clearly demonstrated the positive effect of the additive. The standard conditions in toluene gave poor selectivity (entry 3), whereas addition of TBAT increased the enantiomeric excess by more than 10% (entry 4).

After further process optimisation we found that catalytic lithium carbonate was superior to sodium carbonate when toluene was used as the solvent. A dramatic increase in enantioselectivity was observed (entry 5) and the amount of regioisomer **2** was significantly reduced. These conditions have been used to prepare kilogram quantities of PVG **1** and are reproducible giving high yields and ee. Replacement of TBAT with tetrabutylammonium chloride (TBAC) provides a cheaper alternative with a similar reaction profile (entry 6).

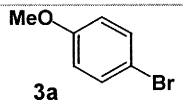
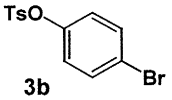
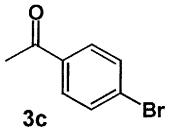
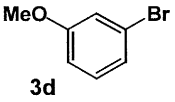
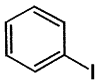
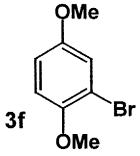
Our synthetic route to aminotetralins from PVG **1** is shown in Scheme 2. The Heck reaction was found to proceed best when catalysed by palladium acetate and tri(*o*-tolyl)phosphine.[12] Significant amounts of phenyl addition product[13] were observed when triphenylphosphine was employed and palladium precipitated prior to completion of the reaction. Triethylamine was found to be the optimal base. Upon heating PVG **1** in the presence of a carbonate base significant ring opening of the phthalimide was observed. A range of aromatic halides were used in the Heck coupling, giving access to several unsaturated *N*-protected amino alcohols **4a**–**f** (Table 2).[14]

Hydrogenation of the double bond proceeded smoothly over palladium on carbon provided that the Heck product had been purified by crystallisation, otherwise the more robust 1,1′-bis(diisopropylphosphino)ferrocenyl rhodium catalyst[15] was used. Cyclisation of the electron rich substrates proceeded readily upon heating in the presence of trifluoromethanesulfonic acid.[16] Unexpectedly, cyclisation of the *p*-methoxy compound **5a** did not give the 7-methoxy-2-aminotetralin.



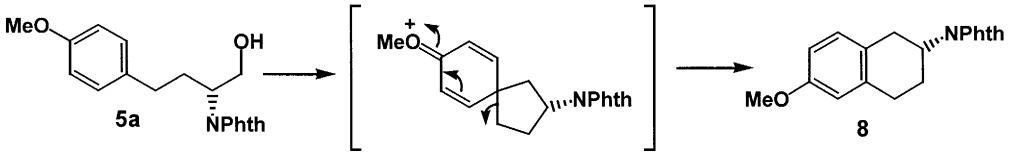
Scheme 2. (i) 1 mol% $Pd(OAc)_2$, 3 mol% P(*o*-tol)$_3$, Et_3N, DMF, 100–130°C; (ii) H_2, Pd/C or [DiPFc]Rh[COD]BF_4; (iii) CF_3SO_3H, PhCl, 80°C; (iv) H_2NNH_2, EtOH

Table 2
Synthesis of aminotetralins from PVG

Aryl halide	Heck yield (%)	Hydrogenation (%)	Cyclisation (%)	Deprotection (%)
 3a	79	95	83	95
 3b	93[a]	68	-	-
 3c	76[b]	80[c]	-	-
 3d	Quant.[a]	58	Quant.[a,d]	-
 3e	66[e]	93	52	95
 3f	78	95	51	99

[a] Crude yield; [b] only 0.2 mol% $Pd(OAc)_2$ required, [c] product contains 5% over reduced benzylic alcohol,
[d] 3:1 mixture of 6- and 8-methoxy-2-aminotetralins, [e] no phosphine required.

Instead 6-methoxy-2-aminotetralin **8** was obtained, presumably via ipso attack and rearrangement (Scheme 3).



Scheme 3. Cyclisation of *para* methoxy compound

The unexpected product was confirmed by preparation of the authentic 6- and 7-methoxy-2-aminotetralins from the corresponding 2-tetralones.[3] This rearrangement appears to be limited to the cyclisation of the alcohols, as the corresponding acid[17] and amino acid[18] gave the expected 7-methoxy product. Cyclisation of the *m*-methoxy compound **5d** afforded a 3:1 mixture of the 6- and 8-methoxy-2-aminotetralins resulting from cyclisation at both the *ortho* and *para* positions. No cyclised product was observed with electron deficient aromatics **5b** and **5c**. The parent compound **7e** (R_1–R_4=H) was readily obtained from iodobenzene.

The aminotetralins were obtained in high enantiomeric excess (>97%)[19] despite the PVG being only 88–93% ee. Presumably recystallisation of the Heck product **4** and the phthalimide protected aminotetralin **6**, enhanced the enantiomeric excess of these intermediates, and there was no degradation of optical purity in the cyclodehydration step.

To conclude we have demonstrated a short, novel and economic asymmetric synthesis of 2-aminotetralins from PVG, which can be synthesised using the optimised conditions outlined in this communication. In addition both enantiomers of vinylglycinol are readily available, >98% ee,[20] from PVG by hydrazinolysis, formation of the benzoic acid salt and crystallisation. Studies in the use of these versatile building blocks are currently ongoing.

Acknowledgements

This work was carried out as part of a collaboration with Eastman Fine Chemicals. We would like to thank Professor B. M. Trost for useful discussions. We are grateful to Catherine Rippé and Will Spearing for the development of analytical methods.

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19. GC method, Chiralsil Dex CB column: (*R*)-6-methoxy-2-aminotetralin, ee>98%, compound derivatised with trifluoroacetic anhydride, 155°C for 25 mins, ramp to 200°C at 10°C/min, hold for 5 mins, RT (*R*)=24.0 min, RT (*S*)=23.5 min; (*R*)-2-aminotetralin, ee 97%, compound derivatised with propionic anhydride, 165°C for 25 mins, ramp to 200°C at 10°C/min, hold for 5 mins, RT (*R*)=24.6 min, RT (*S*)=23.8 min.
20. GC method, Chiraldex BTA, vinylglycinol was derivatised with acetic anhydride, 150°C for 20 mins, RT (*S*)=9.9 min, RT (*R*)=10.2 min.