ORGANIC LETTERS

2005
Vol. 7, No. 10
1931−1934

Efficient Synthesis of an Imidazole-Substituted δ-Amino Acid by the Integration of Chiral Technologies

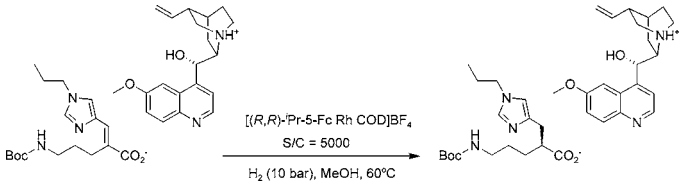
Ian Appleby,[†] Lee T. Boulton,[‡] Christopher J. Cobley,[‡] Catherine Hill,[‡] Mike L. Hughes,[†] Pieter D. de Koning,[‡,§] Ian C. Lennon,*[,‡] Céline Praquin,[‡] James A. Ramsden,[‡] Helen J. Samuel,[‡] and Niamh Willis[†]

Dowpharma, Chirotech Technology, Ltd., A Subsidiary of The Dow Chemical Company, Unit 321, Cambridge Science Park, Milton Road, Cambridge, CB4 0WG, UK, and Chemical Research and Development, Pfizer Global Research and Development, Pfizer, Ltd., Ramsgate Road, Sandwich, Kent CT13 9NJ, UK

ilennon@dow.com

Received February 14, 2005

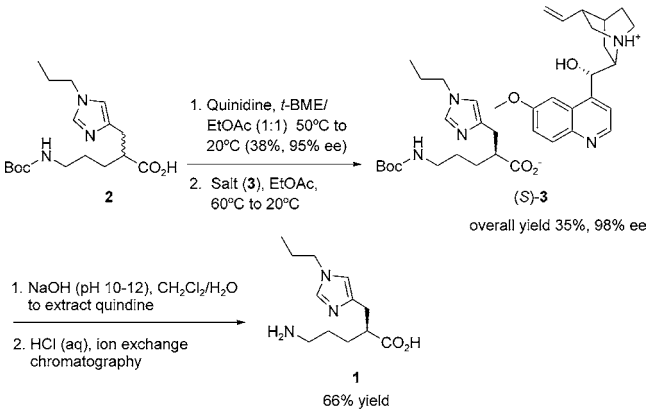
ABSTRACT



Two methods to produce (2*S*)-5-amino-2-(1-*n*-propyl-1*H*-imidazol-4-ylmethyl)-pentanoic acid were investigated. Diastereoisomeric salt resolution, using the quinidine salt, gave the desired intermediate in 98% ee and 33% yield. Asymmetric hydrogenation of various substrates gave high conversions, with up to 83% ee. Integration of these two approaches via asymmetric hydrogenation of a quinidine salt substrate followed by crystallization provided the desired intermediate in 94% ee and 76% yield.

Pfizer is currently developing a series of substituted imidazole compounds as thrombin activatable fibrinolysis inhibitors for use in the treatment of conditions such as thrombosis, cancer, and inflammatory diseases.[1] To support ongoing investigations an efficient method to synthesize (2*S*)-5-amino-2-(1-*n*-propyl-1*H*-imidazol-4-ylmethyl)-pentanoic acid **1** was required (Scheme 1). The first route to be investigated was a diastereoisomeric salt resolution.[2] Racemic **2**[1] was screened against 48 chiral amines, and 16 crystalline salts were isolated. The salts derived from cinchonidine and quinidine were identified as the most promising, giving the highest enantiomeric excess and yield. After further optimization, examining the effects of concentration and solvents on isolated yield and de, the salt derived from quinidine was

Scheme 1. Diastereoisomeric Salt Resolution



[†] Pfizer, Ltd.
[‡] Dowpharma.
[§] Current address: Pfizer, Ltd., Ramsgate Road, Sandwich, Kent, UK.

(1) Allerton, C. M. N.; Blagg, J.; Bunnage, M. E.; Steele, J. W.O. Pat. Appl. 2002014285, 2002; *Chem. Abstr.* **2002**, *136*, 184120.
(2) Jacques, J.; Collet, A.; Wilden, S. H. *Enantiomers, Racemates and Resolutions*; Krieger Publishing Company: Malabar, FL, 1991; Chapter 5, pp 251−368.

10.1021/ol0503081 CCC: $30.25
Published on Web 04/20/2005

selected for further scale-up. Treatment of racemic **2** with quinidine in a mixture of *tert*-butyl methyl ether and EtOAc gave salt **3** in 38% yield (76% of theory) and 95% ee.[3] A slurry in hot EtOAc upgraded the optical purity to 98% with an overall yield of 33% (Scheme 1). Alternatively, the resolution and upgrade could be carried out using only EtOAc providing **3** in an overall yield of 27% and 97% ee. This procedure was satisfactory to prepare early kilogram quantities of **1**, but as a resolution can only provide a maximum of 50% yield, we sought to identify an asymmetric route to **1** for future manufacturing needs.

In the synthesis of racemic **2**, acrylic acid **4** is hydrogenated using Pd/C catalyst.[1] Since considerable literature precedent exists for the asymmetric hydrogenation of substituted acrylates,[4] we were hopeful that a suitable catalyst/substrate combination could be found to prepare optically pure **1**. Several possible substrates derived from **4** are shown in Figure 1. It is worth noting, however, that asymmetric

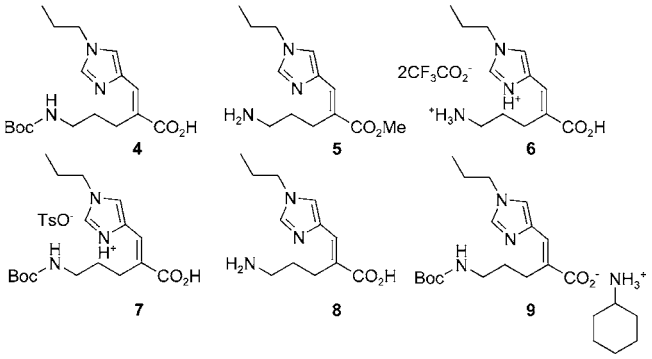


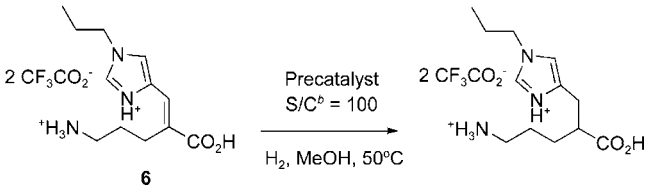
Figure 1. Substrates for asymmetric hydrogenation.

hydrogenation of an acrylate in the presence of a potentially coordinating imidazole moiety has not been previously reported.

Initial investigations into the asymmetric hydrogenation of **4** with both rhodium and iridium catalysts gave very low conversions under a variety of conditions.[5] Several ruthenium catalysts gave full conversion but provided very low levels of enantiomeric excess. The highest enantioselectivity was obtained with [(*R*,*R*)-^{i}Pr-FerroTANE Ru (methallyl)$_2$] (40% ee), but only in 20% conversion.[6] Although we envisaged that the imidazole functionality might be binding to the metal, addition of borate additives[7] gave no improvement. Next we examined the amino methyl ester **5** and found a similar pattern of low conversion. Here [(*R*)-BINAP RuCl]Cl[8] gave 60% conversion with only 14% ee.

As modification of the acid had no positive effect, we looked at making acidic salts of the imidazole unit to temper its basicity. Treatment of **4** with trifluoroacetic acid removed the Boc group and provided the bis-TFA salt **6**. Again, rhodium and iridium catalysts gave very poor conversion, but for a number of ruthenium catalysts, full conversion and high ee were obtained (Table 1). As the product of the hydrogenation could not be isolated as a solid, we could not upgrade the enantiomeric excess of this material by crystallization.

Table 1. Asymmetric Hydrogenation of the Bis TFA Salt **6**[a,5]

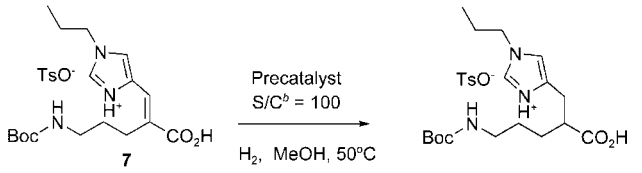


entry	precatalyst	ee (%)[c]
1	[(*R*,*R*)-^{i}Pr-DuPhos Ru (OCOCF$_3$)$_2$]	83 (*R*)
2	[(*R*,*R*)-^{i}Pr-BPE Ru (methallyl)$_2$]	71 (*R*)
3	[(*R*)-Tol-BINAP Ru(C$_6$H$_6$)Cl]Cl	79 (*S*)
4	[(*R*,*R*)-Et-BPE Ru (methallyl)$_2$]	49 (*S*)

[a] Reactions were performed in a 50 mL Parr pressure vessel with 0.1 M solutions of substrate in MeOH at 50 °C and 10 bar hydrogen pressure. All reactions gave full conversion after 18 h. [b] Molar substrate-to-catalyst ratio. [c] Enantiomeric excess was determined by chiral CE.

In an attempt to retain the Boc group after hydrogenation, with the expectation that salts of the product might be crystalline, we investigated the asymmetric hydrogenation of the *p*-toluenesulfonic acid salt **7** (Table 2). Although we were gratified to obtain good selectivities with several

Table 2. Asymmetric Hydrogenation of the TsOH Salt **7**[a,5]



entry	precatalyst	ee (%)[c]
1	[(*R*)-Tol-BINAP Ru (C$_6$H$_6$)Cl]Cl	77 (*S*)
2	[(*R*,*R*)-^{i}Pr-FerroTANE Ru (methallyl)$_2$]	33 (*R*)
3	[(*R*,*R*)-Me-DuPhos Ru (OCOCF$_3$)$_2$]	49 (*R*)
4	[(*R*)-PhanePhos Rh COD]BF$_4$	60 (*S*)
5	[(*R*,*R*)-^{i}Pr-5-Fc Rh COD]BF$_4$	34 (*R*)

[a] Reactions were performed in a 50 mL Parr pressure vessel with 0.1 M solutions of substrate in MeOH at 50 °C and 10 bar hydrogen pressure. All reactions gave full conversion after 18 h. [b] Molar substrate-to-catalyst ratio. [c] Enantiomeric excess was determined by chiral CE.

(3) Enantiomeric excess of **1** was determined using chiral capillary electrophoresis (CE). Details can be found in Supporting Information.

(4) (a) Sturm, T.; Weissensteiner, W.; Spindler, F. *Adv. Synth. Catal.* **2003**, *345*, 160. (b) Benincori, T.; Cesarotti, E.; Piccolo, O.; Sannicolò, F. *J. Org. Chem.* **2000**, *65*, 2043. (c) Crameri, Y.; Foricher, J.; Scalone, M.; Schmid, R. *Tetrahedron: Asymmetry* **1997**, *8*, 3617. (d) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029 and references therein.

(5) Full screening data are given in Supporting Information.

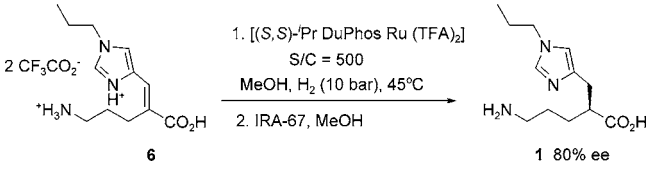
(6) For synthesis of FerroTANE ligands, see: Berens, U.; Burk, M. J.; Gerlach, A.; Hems, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 1981.

(7) Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett.* **2000**, *2*, 1749.

ruthenium and rhodium catalysts, significant levels of Boc group loss were observed (25% for ruthenium catalysts and 70% for rhodium catalysts). Therefore, this did not provide a viable approach to **1**.

A salt screen was conducted to determine if any achiral or chiral acidic or basic salts would be suitable for upgrading the enantiomeric purity of **1**. To provide material for the screen, we carried out the hydrogenation of **6** using [(*R*,*R*)-^{i}Pr-DuPhos Ru ($OCOCF_3$)$_2$] (S/C 500) on a 22 g scale.[9] This afforded the amino acid **1** in 80% ee after neutralization (Scheme 2). Only the D-(+)-galacturonic acid salt afforded

Scheme 2. Synthesis of **1** for Salt Screen



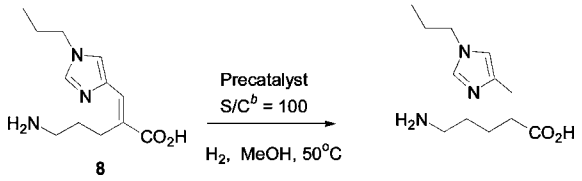
6 **1** 80% ee

a reasonable upgrade, giving >94% ee salt in 46% yield; however, this low yield was unacceptable for our purposes.

Removal of the Boc group from **4** provided substrate **8**. Achiral (TsOH, HCl, $PhCO_2H$) and chiral (L- and D-tartaric acid) salts were prepared and screened for asymmetric hydrogenation. Despite high conversions in several cases, none of the corresponding products were crystalline and the ee values were all less than those obtained for the bis-TFA salt **6**. However, we did note that strong acids such as TFA, toluenesulfonic acid, and HCl formed bis-salts, whereas weaker acids such as benzoic and tartaric acid only formed monosalts. The fact that these monosalts could be hydrogenated suggested that the imidazole functionality was not interfering with the hydrogenation reaction.

This prompted an investigation into the asymmetric hydrogenation of the free amino acid **8** (Table 3). For this substrate, only moderate selectivities were obtained (44−

Table 3. Asymmetric Hydrogenation of Compound **8**[a,5]



8

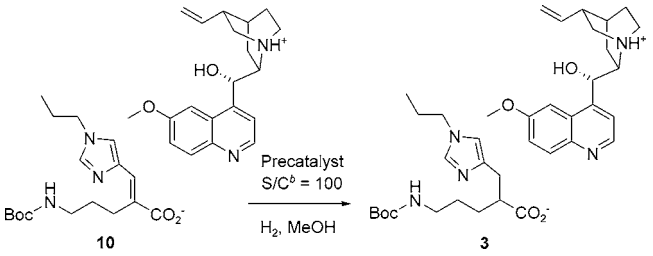
entry	precatalyst	ee (%)[c]
1	[(*R*,*R*)-^{i}Pr-DuPhos Ru ($OCOCF_3$)$_2$]	53 (*S*)
2	[(*S*,*S*)-^{i}Pr-FerroTANE Ru (methallyl)$_2$]	56 (*R*)
3	[(*R*,*R*)-Me-DuPhos Rh COD]BF_4	53 (*S*)
4	[(*R*,*R*)-Me-5-Fc Rh COD]BF_4	44 (*R*)

[a] Reactions were performed in a 50 mL Parr pressure vessel with 0.2 M solutions of substrate in MeOH at 50 °C and 10 bar hydrogen pressure. All reactions gave full conversion after 18 h. [b] Molar substrate-to-catalyst ratio. [c] Enantiomeric excess was determined by chiral CE.

56% ee), with both rhodium and ruthenium catalysts. Further development of this process would require the identification of a suitable salt to enable an ee upgrade. Experience from our previous screen of chiral acids and amines of **1** led us to believe that this would not be readily achieved. However, performing the asymmetric hydrogenation on a salt that could upgrade the ee in situ would provide a more streamlined process.

The next logical step was to examine amine salts of the Boc-protected substrate. In the first instance, we examined the cyclohexylamine salt **9**, but only low ee was obtained (26% ee, using [(*R*,*R*)-^{i}Pr-DuPhos Ru ($OCOCF_3$)$_2$]). Recrystallization of the product salt afforded racemic material. It had already been demonstrated that the quinidine salt of **2** gave an effective resolution; therefore, we investigated the asymmetric hydrogenation of the quinidine salt **10**, made in situ from **4** (Table 4).

Table 4. Asymmetric Hydrogenation of the Quinidine Salt **10**[a,5]



10 **3**

entry	precatalyst	ee (%)[f]
1[c]	[(*R*,*R*)-^{i}Pr-DuPhos Ru (C_6H_6)Cl]OTf	29 (*S*)
2[d]	[(*S*)-Xyl-PhanePhos Rh COD]BF_4	70 (*R*)
3[d]	[(*R*,*R*)-Me-5-Fc Rh COD]BF_4	18 (*R*)
4[d]	[(*R*,*R*)-Et-5-Fc Rh COD]BF_4	28 (*R*)
5[d]	[(*R*,*R*)-^{i}Pr-5-Fc Rh COD]BF_4	62 (*S*)
6[d]	[(*S*)-MeOXyl-PhanePhos Rh COD]BF_4	73 (*R*)
7[e]	[(*R*,*R*)-^{t}Bu-FerroTANE Rh COD]BF_4	82 (*R*)

[a] Reactions were performed in a 50 mL Parr pressure vessel with 0.2 M solutions of substrate in MeOH and 10 bar hydrogen pressure. [b] Molar substrate-to-catalyst ratio. [c] Reaction performed at 65 °C, full conversion after 18 h. [d] Reaction performed at 55 °C, full conversion after 18 h. [e] Reaction performed at 45 °C, full conversion after 44 h. [f] Enantiomeric excess was determined by chiral CE.

Quite surprisingly, ruthenium catalysts gave poor activity and low ee (Table 4, entry 1); however, rhodium catalysts were highly reactive and provided excellent selectivity. Of note were [(*R*,*R*)-^{t}Bu-FerroTANE Rh COD]BF_4 (Table 4, entry 7) and [(*S*)-MeOXyl-PhanePhos Rh COD]BF_4 (Table 4, entry 6).[10] This is the first reported olefin hydrogenation using the rhodium ^{t}Bu-FerroTANE catalyst that provides a practical enantiomeric excess. Upon reduction of the catalyst

(8) Noyori, R.; Ohkuma, T.; Kitamura, M.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.

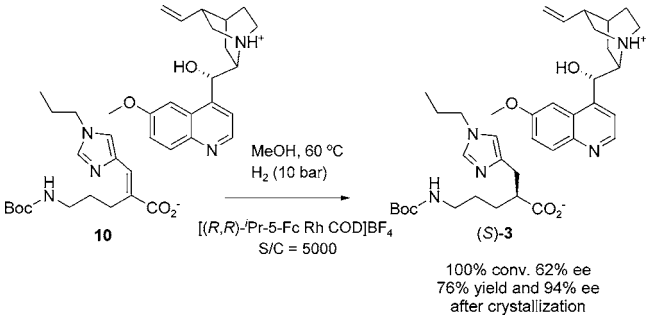
(9) For synthesis of the ^{i}Pr-DuPhos ligand, see: Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125.

(10) For synthesis of PhanePhos ligands, see: Pye, P. J.; Rossen, K,; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207.

loading toward economical levels, however, both ^{t}Bu-FerroTANE-Rh and MeOXyl-PhanePhos-Rh catalysts were insufficiently reactive. ^{t}Bu-FerroTANE-Rh took 40 h to provide complete reaction at a substrate-to-catalyst ratio (S/C) of 1000, and MeOXyl-PhanePhos-Rh required 44 h to give complete reaction at a S/C of 1000.

A prerequisite for the development of an economic chemocatalytic process is high catalyst activity,[11] rather than excellent stereoselectivity, as long as the product ee can be readily enhanced. In this case, [(*R*,*R*)-^{i}Pr-5-Fc Rh COD]BF_4 (Table 4, entry 5) was the most active catalyst,[12] providing complete reaction in 24 h at S/C 1000, albeit with moderate ee (62%). Crucially, the ^{i}Pr-5-Fc-Rh catalyst displayed high activity and reliable ee values over a wide range of experimental conditions, with only a slight reduction in ee upon raising the temperature to 70 °C. This allowed the development of a robust asymmetric hydrogenation process for the synthesis of **1** (Scheme 3). Thus, a quantitative yield

Scheme 3. Scale-up of the Quinidine Salt Hydrogenation



of the quinidine salt **3** (62% ee) was obtained from the hydrogenation reaction after 20 h at 60 °C, using a catalyst loading of 0.02 mol % (S/C 5000). After crystallization from EtOAc, the product was obtained in 76% yield (94% ee), providing a 120% increase in the yield over the classical resolution route.

It is noteworthy that in most cases, a significantly different catalyst was found to be optimal for each hydrogenation substrate studied, even though the substrates are all structurally similar. Thus, the nature of the salt and the protecting groups employed has a significant and unpredictable[13] effect on catalyst selection, once again demonstrating that there is "*no panacea for asymmetric hydrogenation, no universal catalyst*".[14] Our work suggests that in addition to screening catalysts against a given substrate, screening variants of the substrate should also be considered to identify the optimal process.

In conclusion, we have developed a scalable diastereoisomeric salt resolution, using the quinidine salt **3** to produce kilogram quantities of **1** for early clinical trials. Efforts to identify an efficient asymmetric hydrogenation process led to the use of a quinidine salt of the olefin **10** as the substrate of choice. Integration of two chiral technologies led to a doubling of the throughput and the ability to manufacture multiple kilogram quantities of **1**. Full details of the process development, optimization of the asymmetric hydrogenation step, and large-scale manufacture of **1** will be published separately.

Acknowledgment. This work was carried out in collaboration with Pfizer, Ltd., Chemical Research and Development, Sandwich, Kent, CT13 9NJ, UK.

Supporting Information Available: Details of the analytical assays, experimental procedures, characterization data, tables of hydrogenation screening data, and tables of salt screens. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0503081

(11) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40.
(12) 5-Fc = 1,1′-bis(2,5-dialkylphospholano)ferrocene: Burk, M. J.; Gross, M. F. *Tetrahedron Lett.* **1994**, *35*, 9363.
(13) Yue, T.-Y.; Nugent, W. A. *J. Am. Chem. Soc.* **2002**, *124*, 13692.
(14) Lennon, I. C.; Pilkington, C. J. *Synthesis* **2003**, 1639.