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Communications to the Editor

Synthesis of 4-Fluoro-β-(4-fluorophenyl)-L-phenylalanine by an Asymmetric Phase-Transfer Catalyzed Alkylation: Synthesis on Scale and Catalyst Stability

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Abstract:

4-Fluoro-β-(4-fluorophenyl)-L-phenylalanine 1 was synthesized by the asymmetric phase-transfer catalyzed alkylation of *tert*-butyl glycinate-benzophenone Schiff base using the cinchona alkaloid derived catalyst 6. Upon scaling, it was observed that to achieve high levels of enantioselectivity, it was necessary to add the catalyst or base last. From these studies, insight into the stability of the catalyst 6 under the reaction conditions was gained.

Asymmetric phase transfer catalysis (PTC) has been successfully applied to a number of important synthetic transformations.[1,2] This method has been particularly valuable for the synthesis of natural and unnatural α-amino acids by the alkylation of glycinate ester Schiff bases.[3,4] The most successful examples of syntheses of amino acids using PTC have used catalysts derived from cinchona alkaloids.[3,4] Use of PTC for the synthesis of amino acids has several advantages over alternative methods, especially for synthesis on large scale. There is no need for a stoichiometric chiral auxiliary, which lowers costs and minimizes waste. In addition, the typical reaction conditions are mild, do not require the use of metal catalyst, and utilize only inexpensive and readily available reagents.

Unnatural amino acid 4-fluoro-β-(4-fluorophenyl)-L-phenylalanine **1** is a key intermediate in the synthesis of a lead drug candidate in development. Initial supplies of this compound were synthesized by employing, as the key step, an asymmetric azidation mediated by a chiral auxiliary.[5] Subsequent hydrolysis of the chiral auxiliary, followed by reduction of the azide gave amino acid **1**. This route to **1** was deemed unacceptable for larger-scale synthesis both because of its length as well as safety issues related to the stability of azide intermediates on scale. For this reason, it was necessary to develop a new route to **1** that would be safe and amenable to scale-up. Several synthetic strategies were considered, including resolution[6] and hydrogenation[7] routes, but it was decided to initially investigate the use of asymmetric PTC[1] using a cinchonidine-derived chiral catalyst to synthesize the desired amino acid because this route could be quickly assessed and offered rapid access to the desired structure.[4f] Using the asymmetric PTC route, the synthesis of **1** could be achieved by reaction of *t*ert-butyl glycinate-benzophenone Schiff base **2** with bromide **3** in the presence of a cinchonidine-derived chiral catalyst, which, after hydrolysis of the product, would give the desired amino acid **1** (Scheme 1).

In order to investigate the asymmetric PTC alkylation route to **1**, it was first necessary to synthesize the requisite bromide **3**.[8] For initial lab-scale experiments, the bromide was prepared by treating 4,4′-difluorobenzhydrol **4** with a solution of boron tribromide in methylene chloride. Although this method was effective, the workup was highly exothermic, and the large excess of base needed to quench the reaction would lower the throughput in larger equipment. As an alternative, **4** was treated with 48% hydrobromic acid

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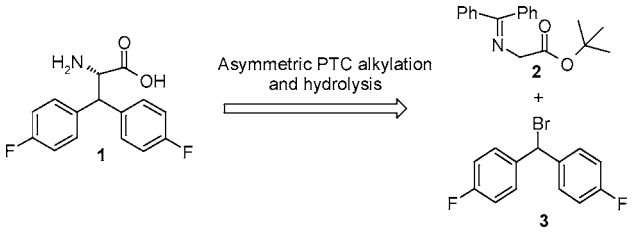
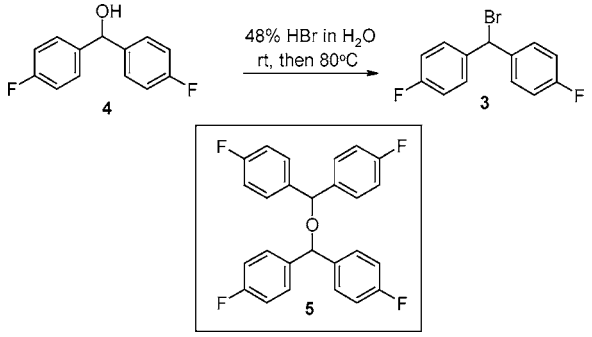
Scheme 1. **Retrosynthesis of 4-fluoro-β-(4-fluorophenyl)-L-phenylalanine 1**



Scheme 2. **Synthesis of 4,4′-difluorobenzhydrylbromide 3**



in water at room temperature to give the desired product **3**. Unfortunately, this material was contaminated with approximately 25% of the dibenzyl ether byproduct **5**. This byproduct could easily be converted to the desired bromide by heating to 80 °C in 48% aqueous HBr. In practice, the bromide was synthesized by treating 4,4′-difluorobenzhydrol **4** with 48% aqueous HBr for 1 h at room temperature, followed by 2 h at 80 °C (Scheme 2). A simple extractive workup provided a dichloromethane solution of **3**, which was carried directly into the PTC.

With a synthesis of bromide **3** in hand, the alkylation of *tert*-butyl glycinate-benzophenone Schiff base **2** with bromide **3** was examined using the cinchonidine-derived chiral phase transfer catalyst **6**.[4e,9] Using literature conditions (10 mol % catalyst, CsOH as base, in DCM at −78 °C),[4f] the alkylation of **2** with bromide **3** resulted in the isolation of racemic product **7**.[10] Further experimentation showed that when the reaction was carried out using the same catalyst under modified conditions[4f] (biphasic mixture of dichloromethane and 45% potassium hydroxide), the desired product **7** was formed in 80:20 enantiomeric ratio.[10−12] The product **7** could be crystallized out of the reaction mixture in >99% ee from ethyl acetate and heptane. The reaction was carried out by dissolving **2** and 10 mol % of the catalyst **6** in dichloromethane, followed by addition of 10 equiv of 45% aqueous potassium hydroxide. The reaction was then cooled to 0 °C, and bromide **3** was added. The reaction was stirred until completion as determined by TLC, and then extractive

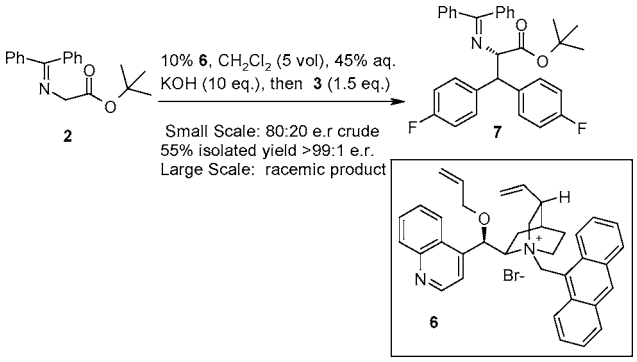
(9) The catalyst was either bought from Aldrich or, for larger-scale studies, was synthesized in two steps from cinchonidine.

(10) The enantiomeric ratio was determined by chiral HPLC.

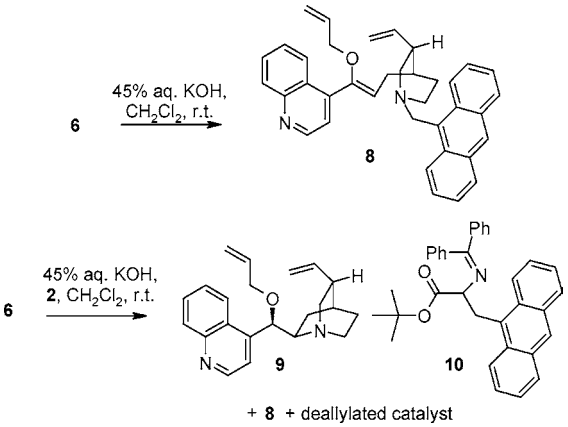
(11) Several other cinchonidine-derived phase transfer catalysts were investigated, but **6** gave the highest selectivities.

(12) A solvent screen showed that 1,2-dichloroethane gave higher levels of enantioselectivity (>90:10 er) versus dichloromethane; however dichloromethane was used based on ease of removal by distillation and due to the fact that 1,2-dichloroethane is not a green solvent of choice and presents some toxicity issues versus dichloromethane.

Scheme 3. **PTC Alkylation of *tert*-butyl glycinate benzophenone Schiff base 2**



Scheme 4. **Catalyst decomposition studies**

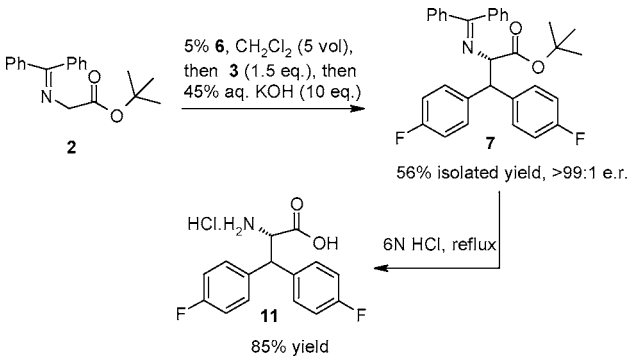


workup followed by crystallization from 20% ethyl acetate/heptane provided up to 55% yield of optically pure **7** as a white crystalline solid (Scheme 3).

When the PTC reaction was run on kilogram scale, the reaction proceeded sluggishly, and surprisingly, the product **7** was isolated in racemic form (65% yield)! At this point, it was necessary to determine why the reaction deviated so much from lab scale to large scale and to devise conditions that would be amenable to running on large scale. One significant difference between small and large scale was the rate of cooling to 0 °C prior to addition of the bromide. The cooling time was 5−10 min on lab scale to upwards of 30−60 min on larger batches. We hypothesized that during the extended cooling down period, prior to the addition of the bromide **3**, the catalyst might be completely decomposing to an unselective catalyst.

This hypothesis was confirmed when a test reaction in the lab was cooled to 0 °C over 45 min prior to the addition of bromide **3**, and only racemic product was obtained. To further confirm the decomposition of the catalyst, the phase transfer catalyst **6** was dissolved in dichloromethane and treated with 45% KOH. Under these conditions, the catalyst was quantitatively converted to a new product, which was identified to be enol ether **8** by LC−MS ($M^+ = 524$) and NMR analysis (Scheme 4). Enol ether **8** arises by base-catalyzed Hoffman elimination of the catalyst, a decomposition pathway that has been observed for related catalysts.[2b] In a second study, a mixture of the catalyst **6**, imine **2**, and 45% KOH in dichloromethane was stirred at room temperature for 1 h. Analysis of the reaction mixture by LC-MS

Scheme 5. **Synthesis of 4-fluoro-β-(4-fluorophenyl)-L-phenylalanine 1**



showed that the catalyst had been converted into enol ether **8**, alkylation product **10** ($M^+ = 485$), and byproduct **9** ($M^+ = 334$), as well as the deallylated catalyst ($M^+ = 484$). These results led to the conclusion that in the absence of a reactive halide, the catalyst reacts with base or with the nucleophile to degrade the PTC catalyst. Tertiary amines **8** and **9** could, on addition of an alkyl halide, be alkylated to form a new quarternary ammonium salt that could catalyze the reaction with little or no selectivity.

The degradation studies described above suggest that good selectivity should still be attainable on large scale if all reactants were added in a defined sequence. Addition of the catalyst or base last should lead to good selectivity.[13] For convenience, and in order to avoid adding a solid to the reaction last, it was decided to charge the base last. Under these conditions, the reaction proceeded smoothly to completion to give the desired alkylated product with a crude enantiomeric ratio of 80:20. The reaction was observed to be faster (5 h) and to require less catalyst than it previously did. For scaling purposes, 5 mol % catalyst was used, but subsequent experiments showed that the reaction proceeds with the same level of selectivity with as low as 2% catalyst. Interestingly, when the catalyst was monitored during the reaction, it was observed that the catalyst did not decompose as long as the starting materials were present, but as soon as the reaction was complete, the catalyst quickly decomposed by the Hoffman elimination pathway. This observation implies that catalyst recycling would be very tenuous, especially if the reaction is allowed to go to completion at the temperature range used in these reactions.

From our experiments, the preferred conditions for the alkylation on scale, are 5 mol % catalyst, 1.2 equiv of the bromide **3**, followed by addition of the base (10 equiv of 45% aqueous KOH) last. On 6 mole scale, the reaction proceeded smoothly to completion in 5 h (80:20 er), and workup and crystallization gave the product in >99% ee (56% yield) as shown in Scheme 5.

The alkylated product **7** can be hydrolyzed to the desired amino acid by refluxing the product in 6 N hydrochloric acid for several hours. After removal of the benzophenone by extraction with methyl *tert*-butyl ether, the amino acid is crystallized from the aqueous layer in 85% yield as the hydrochloric acid salt **11** (Scheme 5).

4-Fluoro-β-(4-fluorophenyl)-L-phenylalanine **1** was synthesized as its HCl salt in enantiomerically pure form in two steps from the commercially available *tert*-butyl glycinate-benzophenone Schiff base **2** in 48% overall yield via an asymmetric phase transfer alkylation followed by hydrolysis. This represents only the second example of the use of secondary alkyl halides in this type of PTC alkylation.[4f] Studies of this reaction show that the chiral catalyst **6** is very sensitive to base-catalyzed decomposition in the absence of either the nucleophile or the electrophile. For this reason it is important to add the base or catalyst last in order to achieve high levels of enantioselectivity. The asymmetric phase-transfer catalyzed alkylation is a powerful method for the synthesis of chiral amino acids, but a good understanding of the catalyst stability is important to successfully use this method, especially on kilogram scale. Further studies on improving enantioselectivity and on extending the alkylation to other secondary alkyl halides is proceeding and will be reported in due course.

Experimental Section

General. All commercial chemicals were used as received. Combustion analyses were performed by the Atlantic Microlab, Inc. All reactions were performed under a nitrogen atmosphere unless otherwise stated. TLC analysis was performed on silica gel plate, eluted with 10% ethyl acetate in hexane. The enantiomeric excess of **7** was determined by chiral HPLC: column, Bakerbond DNBPG (covalent), 250 cm × 4.6 mm, 5 μm; mobile phase (isocratic) 0.1% methanol in heptane; flow rate 1.0 mL/min; detection, 250 nm; temperature 35 °C; retention times, **7**: 13.73 min, ent-**7**: 16.53 min. The enantiomeric excess of **11** was determined by derivitization with Marfey's reagent, followed by HPLC analysis: column, Zorbax Eclipse XDB C18, 150 cm × 4.6 mm, 3.5 μm; Mobile phase (isocratic) 0.5% TFA in water; flow rate 1.0 mL/min; detection, 340 nm, 8 nm bandwidth; temperature 40 °C; retention times, desired diastereomer: 17.1 min, undesired: 17.9 min.

Synthesis of 4-Fluoro-β-(4-fluorophenyl)-L-*tert*-butylphenylalanine Benzophenone Imine 7. A reactor was charged with 4,4′-difluorobenzhydrol **4** (1.7 kg, 7.72 mol), followed by 48% HBr in water (5.1 L). The resulting slurry was stirred for 1 h at 25 °C. The reaction was heated to 80 °C and was stirred at this temperature for 2 h. The reaction was cooled to 25 °C and water (6.8 L) was added, followed by dichloromethane (8.5L). The biphasic mixture was stirred, and the layers were separated. The organic layer was washed successively with water (5.1 L) and 5% aq sodium bicarbonate (5.1 L). The organic layer was returned to the reactor and was concentrated under atmospheric pressure to 9.5 L (5.5 vol). To the above solution of 4,4′difluorobenzhydryl bromide **3** in dichloromethane was added the *tert*-butyl glycinate-benzophenone Schiff base **2** (1.8 kg, 6.10 mol), followed by the catalyst **6** (0.185 kg, 0.30 mol). Dichloromethane (1.8 L) was added (rinse). The reaction was cooled to 0 °C over 30 min, and 45% aqueous KOH (7.6 kg, 60.9 mol) was added over 15−30 min while maintaining the

(13) Another possibility that could be envisioned to avoid catalyst decomposition was to simply reduce the concentration of the base, but experiments using lower base concentration (15% KOH) still showed significant catalyst decomposition, while slowing the rate of the desired reaction.

temperature at 0−5 °C. The biphasic reaction was stirred until complete by TLC (approximately 5 h). The reactor was then charged with water (1.8 L), and the layers were separated. The organic layer was washed with brine (5.4 L). The organic layer was returned to the reactor (rinse with 1.8 L of dichloromethane). The organic solution was concentrated at atmospheric pressure to 10 L. The reactor was then charged with 23% ethyl acetate in heptane (9.1 L) and was concentrated under vacuum to 14.5 L. The reaction was then seeded. The vacuum distillation was continued to a final volume of 12.5 L. The vacuum was removed, the reaction was cooled to 20 °C and held at this temperature for 1−2 h. The solids were collected by filtration and were washed with 10% ethyl acetate in heptane (3.6 L). The solids were dried in a 50 °C vacuum oven to constant weight. The product **7** is an off-white solid (1.72 kg, 56%, >99% ee). $[\alpha]_D = -206.1°$ ($c = 2.0$, $CHCl_3$). Mp = 168−171 °C. IR 3100, 2974, 2870, 1724, 1710, 1620, 1601, 1576, 1508, 1392, 1368, 1222, 1161, 1150, 825 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 9H), 4.58 (d, $J = 8.3$ Hz, 1H), 4.76 (d, $J = 8.3$ Hz, 1H), 6.74 (m, 2H), 6.93 (t, $J = 8.8$ Hz, 4H), 7.14 (m, 2H), 7.28−7.44 (m, 8H), 7.53 (d, $J = 6.7$ Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.0, 53.6, 71.3, 81.6, 115.1, 115.3, 115.5, 128.3, 129.1, 130.5, 131.2, 136.3, 137.7, 139.8, 160.3, 163.5, 170.0, 171.3. Anal. Calcd For $C_{32}H_{29}F_2NO_{-2}$: C, 76.86; H, 5.82; N, 2.89. Found: C, 76.75; H, 5.76; N, 2.85.

Synthesis of 4-Fluoro-β-(4-fluorophenyl)-L-phenylalanine Hydrochloride 11. A reactor was charged with water (9.0 L) followed by concentrated hydrochloric acid (9.0 L). The reactor was then charged with **7** (2.0 kg, 4.02 mol) over 5−10 min. The resulting slurry was heated at reflux for 3−4 h. The reaction was cooled to room temperature and washed with MTBE (2 × 20 L). The aqueous layer was concentrated under vacuum to 6 L (3 vol), and was cooled at 5 °C for 1 h. Filtration, washing with heptane (3.0 L), and drying at 50 °C afforded the product **11** as an off-white solid (1.07 kg, 85% yield, >99% ee). $[\alpha]_D = +56.3°$ ($c = 2.0$, CH_3OH). Mp = 149 °C dec. IR 3180, 3137, 2820, 2645, 2564, 2462, 1715, 1606, 1589, 1536, 1503, 1232, 1192, 827 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ 4.47 (d, $J = 10.3$ Hz, 1H), 4.85 (d, $J = 10.3$ Hz, 1H), 7.07 (t, $J = 8.8$ Hz, 2H), 7.16 (t, $J = 8.8$ Hz, 2H), 7.44 (dd, $J = 5.2$, 8.8 Hz, 2H), 7.56 (dd, $J = 5.2$, 8.8 Hz, 2H). ^{13}C NMR (300 MHz, DMSO-d_6) δ 169.5, 162.4, 162.2, 160.5, 160.2, 135.6, 135.0, 55.3, 51.2. Anal. Calcd For $C_{15}H_{14}ClF_2NO_2$: C, 57.43; H, 4.50; N, 4.46. Found: C, 57.22; H, 4.48; N, 4.41.

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