Practical Synthesis of a Soluble Schiff Base Catalyst for the Asymmetric Strecker Reaction

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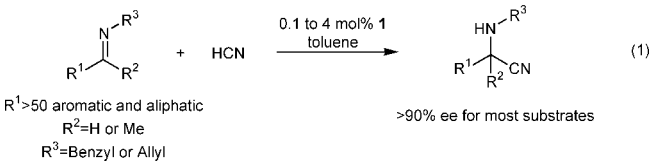
We reported recently that Schiff base **1** (Figure 1) is a remarkably general catalyst for the hydrocyanation of aldimines[1] and ketoimines,[2] producing Strecker adducts in >90% ee for most substrates examined (Equation 1).[5] This catalyst was identified and optimized from a parallel library of Schiff base derivatives that was synthesized and screened on solid phase.[1,4]



Resin-bound catalyst **1a** was identified as affording optimal enantioselectivity for a model imine hydrocyanation reaction, and was applied successfully to the enantioselective synthesis of Strecker adducts on preparative scale. This polymer-supported catalyst displayed important practical features, as it could be reisolated readily by simple filtration and recycled repeatedly.[1,2] On the other hand, the homogeneous analogue **1b** was found to display substantially higher reactivity and to induce slightly improved enantioselectivity (1–3% ee) in the hydrocyanation of most substrates, even if used at substantially lower loadings.[5] These advantages were offset, however, by the fact that **1b** was more difficult to prepare than resin-bound **1a**.[6] Our previously reported synthesis[2] provided **1b** in 53% overall yield and included three chromatographic purifications (Scheme 1).

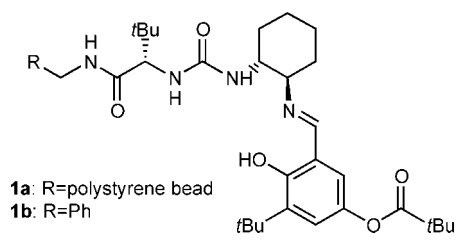


Figure 1. Structure of catalyst **1**.

In this Update, we report a significantly improved synthesis of **1b**. Through careful optimization and judicious modification of the synthetic route, we have improved the yield of the overall process to 80%. More important, all of the chromatographic purification steps have been circumvented, thus rendering possible the practical synthesis of **1b** on a large scale.

The original route to **1b** was adapted directly from the procedure we had developed for the preparation of resin-bound **1a** (Scheme 1). As is generally the case in solid phase synthesis, the method used for the preparation of **1a** relies on the attainment of high yields through the use of excess soluble reagents, and on operationally simple purification by filtration and thorough rinsing of the resin-bound intermediates and product. Without the benefit of a resin support in the synthesis of soluble catalyst **1b**, we had resorted to column chromatography for purification of **1b** as well as intermediates **4** and **5**. With an eye toward a practical synthesis, we sought in particular to avoid chromatographic purifications and to render the procedure as streamlined and high-yielding as possible.[7]

The lowest-yielding step of the original sequence was deprotection of intermediate **3a** by Fmoc removal (70% yield, Scheme 1). It was observed that the corresponding product **4** underwent degradation in the presence of diethylamine during solvent removal. In addition, chromatography on silica gel was necessary to remove the dibenzofulvene byproduct. In order to circumvent these problems, we opted to use Boc instead of Fmoc as a protecting group in the initial amidation step. Reaction of Boc-*tert*-leucine[8] with benzylamine proceeded in quantitative yield, affording **3b** as a mixture with the tetramethylurea byproduct generated by hydrolysis of HBTU (Scheme 2). The Boc group was subsequently cleaved by treatment with trifluoroacetic acid in dichloromethane to provide **4** in 99% yield. Since the only contaminant, tetramethylurea, was judged to be sufficiently inert

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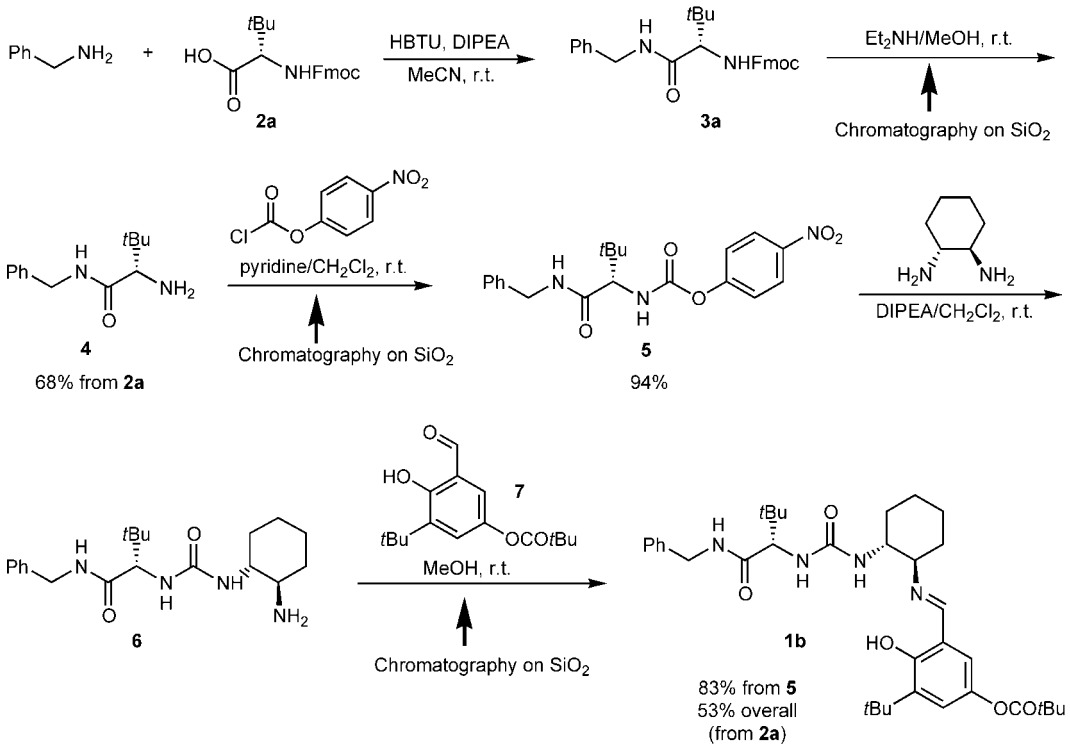
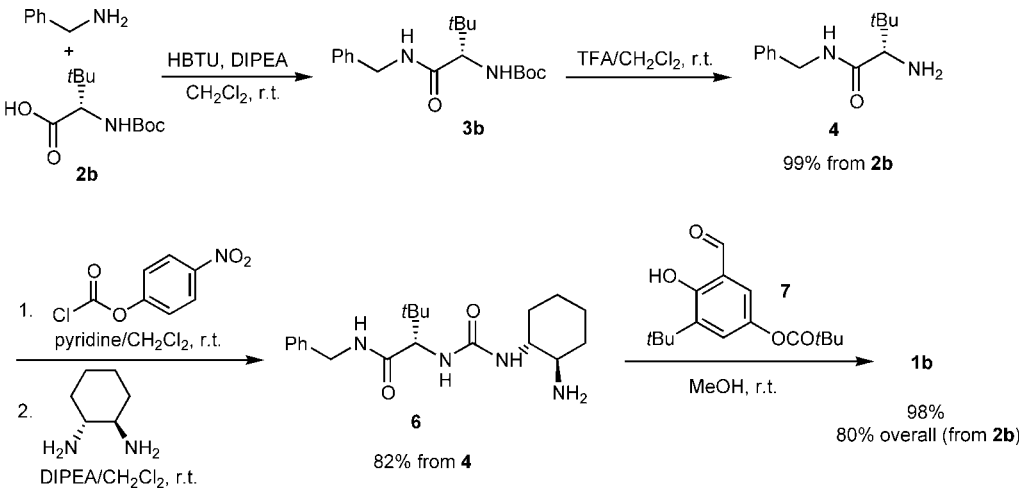


Scheme 1. Original synthesis of **1b**.

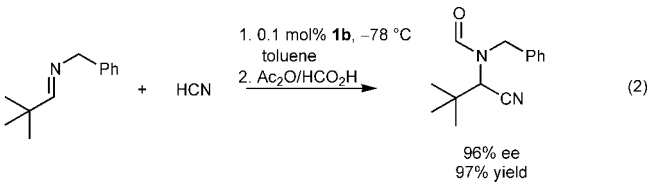


Scheme 2. Optimized synthesis of **1b**.

to be carried to later stages of the synthesis, no additional purification was effected.

Reaction of **4** with 4-nitrophenyl chloroformate proceeded with high selectivity and the crude product **5** was shown to be >94% pure by ^{1}H NMR analysis. Since both this and the subsequent urea-forming reaction are conducted under basic conditions, we investigated the possibility of carrying out the reactions sequentially in one pot, ideally with the same base for both reactions. We ultimately observed that the one-pot procedure was indeed possible, although best results were obtained using pyridine for formation of carbamate **5** and DIPEA for generation of urea **6**. Combining both reactions into a one-pot arrangement made it possible to avoid isolation and purification of the sensitive intermediate **5** (Scheme 2). The crude product mixture was washed with aqueous sodium hydroxide to remove the 4-nitrophenol byproduct, leaving behind the product **6** contaminated with DIPEA, pyridine, unreacted excess diamine, and tetramethylurea. All of the components except **6** proved to be soluble in hexanes. Thus, after solvent removal, the crude solid residue was washed with hexanes to afford **6** in high purity and in 82% yield. With pure **6**

in hand, formation of Schiff base **1b** by condensation with salicylaldehyde derivative **7** proceeded in quantitative yield with no detectable byproducts. Catalyst **1b** was tested in a representative Strecker reaction of an aldimine, and the corresponding Strecker adduct was isolated in 96% ee and 97% yield (Equation 2).[9]



(2)

In summary, we have developed an optimized procedure for the synthesis of **1b** in 5 steps from commercially available Boc-*tert*-leucine and in 80–83% overall yield (Scheme 2). We have found that a first-time practitioner can execute the entire synthesis within one day and in the indicated yield range. The improved route should make possible the synthesis of **1b** on a commercial scale. In light of the considerable synthetic utility of this Strecker catalyst, we hope this will open the door to its broad application in asymmetric synthesis.

Experimental Section

General

All commercial reagents were used as received unless noted otherwise. Boc-L-*tert*-leucine was purchased from Fluka; HBTU and diisopropylethylamine from Advanced ChemTech; and 4-nitrophenyl chloroformate and benzylamine from Aldrich. (*S*,*S*)-1,2-Diaminocyclohexane was resolved by literature methods.[10] Aldehyde **7** was synthesized according to our published procedure.[2]

Coupling of Boc-L-tert-leucine with Benzylamine Followed by Deprotection (2b → 3b → 4)
A 1000-mL, round-bottomed flask equipped with a stirbar was charged with 5.00 g (21.6 mmol) of Boc-L-*tert*-leucine (**2b**). Dichloromethane (170 mL) and HBTU (8.21 g, 1.0 equiv.) were added with stirring. After 2 minutes, DIPEA (7.55 ml, 2 equiv.) and benzylamine (2.37 mL, 1.0 equiv.) were added sequentially and the reaction was stirred for 90 minutes. The mixture was combined with dichloromethane (250 mL) and water (250 mL) and the organic layer was separated, washed three times with 1 M hydrochloric acid (250 mL), and dried over sodium sulfate. Solvents were removed in vacuo to afford crude **3b** as a colorless oil. The oil was dissolved in dichloromethane (110 mL); then trifluoroacetic acid (25 mL, 15 equiv.) was added in one portion and the mixture was stirred at room temperature for 1 hour. The reaction mixture was then cooled to 0 °C and a 20% aqueous solution of sodium carbonate (250 mL) was added slowly. The resulting biphasic mixture was transferred to a separatory funnel, diluted with chloroform (140 mL), and the organic and aqueous layers were separated. The organic layer was washed with a 20% aqueous solution of sodium carbonate (250 mL). The combined aqueous layers were washed with chloroform (3×150 mL). All organic phases were combined, dried over sodium sulfate and concentrated to afford a mixture of **4** and tetramethylurea as a white solid (4.71 g, 21.4 mmol, 99% yield of **4** over two steps based on crude mass and ^{1}H NMR analysis). The mixture was carried on to the next step without further purification.

Carbamate and Urea Formation (4 → 5 → 6)
A 500-mL, round-bottomed flask equipped with a stirbar was flame-dried and charged with the entire amount of crude **4** obtained from the previous step (4.71 g, 21.4 mmol of **4**) dissolved in freshly distilled dichloromethane (50 mL). Freshly distilled pyridine (3.49 mL, 2 equiv.) was added via syringe to the stirred solution; after 2 minutes, 4-nitrophenyl chloroformate (4.44 g, 1.02 equiv.) was added in one portion. After the reaction was stirred for 10 minutes, (*S*,*S*)-1,2-diaminocyclohexane (7.40 g, 3 equiv.) was added in one portion, followed by addition of DIPEA (4.2 mL, 1.1 equiv.) via syringe, and the reaction mixture was stirred for an additional 10 minutes. The resulting mixture was then combined with dichloromethane (500 mL) and 0.5 M sodium hydroxide solution (120 mL). The organic layer was separated, washed with another portion of 0.5 M sodium hydroxide solution (120 mL), and dried over sodium sulfate. The organic layer was concentrated by rotary evaporation to afford a viscous oil which was suspended in hexanes (500 mL). The resulting mixture was allowed to stand for 30 minutes, and then filtered, with the collected solids then washed with (3×125 mL) hexanes. The white powder thus obtained (6.25 g, 17.3 mmol, 82% yield over 2 steps) was identified as **6** with no impurities detectable by ^{1}H NMR analysis: IR (thin film): ν = 3284, 2934, 2858, 1631, 1555 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (m, 5H), 7.08 (s, 1H), 6.11 (s, 1H), 5.31 (s, 1H), 4.48 (dd, J_1 = 14.9 Hz, J_2 = 6.1 Hz, 1H), 4.26 (dd, J_1 = 14.9 Hz, J_2 = 5.1 Hz, 1H), 4.20 (d, J = 8.8 Hz, 1H), 3.20 (m, 1H), 2.31 (m, 1H), 1.98 (d, J = 11.7 Hz, 1H), 1.85 (m, 2H), 1.68 (d, J = 11.2 Hz, 2H), 1.16 (m, 5H), 1.03 (s, 9H); ^{13}C NMR {^{1}H} (400 MHz, $CDCl_3$): δ = 172.7, 159.0, 138.5, 128.5, 127.5, 127.1, 61.3, 57.0, 55.1, 43.1, 35.0, 34.7, 33.4, 27.1, 25.3, 25.1.

Schiff Base Formation (6 → 1b)
A 1000-mL, round-bottomed flask equipped with a stirbar was charged with 6.25 g of **6** and anhydrous methanol (40 mL) was added with stirring. Once the solution became homogeneous, sodium sulfate (10 g) was added. In a separate flask, aldehyde **7** (4.73 g, 0.98 equiv.) was dissolved in anhydrous methanol (40 mL), then transferred to the reaction mixture. An additional 30 mL of methanol was used to effect quantitative transfer of aldehyde **7** into the reaction mixture. The reaction mixture was stirred for 90 minutes, then concentrated under reduced pressure with the sodium sulfate still present. The resulting mixture was combined with hexanes (250 mL) and filtered through a Buchner funnel, and the solids were rinsed with hexanes (250 mL). The filtrate was concentrated under reduced pressure to yield 10.55 g of **1b** as a yellow solid (17.0 mmol, 98% yield, 80% overall yield from **2b**) with spectral and physical properties identical to those reported previously.[1,2]

Acknowledgements

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Notes and References

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[2] P. Vachal, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 867–870.

[3] For other methods for the asymmetric catalytic Strecker reaction, see: (a) M. S. Iyer, K. M. Gigstad, N. D. Namdev, M. Lipton, *J. Am. Chem. Soc.* **1996**, *118*, 4910–4911; (b) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 5315–5316; (c) H. Ishitani, S. Komiyama, S. Kobayashi, *Angew. Chem. Int. Ed.* **1998**, *37*, 3186–3188; (d) E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, *1*, 157–160; (e) C. A. Krueger, K. W. Kuntz, C. D. Dzierba, W. G. Wirschun, J. D. Gleason, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **1999**, *121*, 4284–4285; (f) J. R. Porter, W. G. Wirschun, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 2657–2658; (g) S. Kobayashi, H. Ishitani, *Chirality* **2000**, *12*, 540–543; (h) M. Takamura, Y. Hamashima, U. Yoshitaka, H. Usuda, M. Kanai, M. Shibisaki, *Angew. Chem. Int. Ed.* **2000**, *39*, 1650–1652; (i) H. Ishitani, S. Komiyama, Y. Hasegawa, S. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 762–766; (j) M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6327–6328; (k) J. J. Byrne, M. Chavarot, P. Y. Chavant, Y. Vallee *Tetrahedron Lett.* **2000**, *41*, 873–876.

[4] M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 4901–4902.

[5] For example, in the reaction of 2,2-dimethylpropylidenebenzylamine, use of 4.0 mol % of **1a** at –70 °C yielded the corresponding Strecker adduct in 93% ee in 15 h. Use of 0.1 mol% of **1b** under the same conditions yielded the Strecker adduct in 96% ee in 5 h.

[6] Full experimental data for the preparation of **1a** are given in refs. [1,2]. Catalyst **1a** has been prepared successfully in our labs on 400 g scale following the same procedure.

[7] For a lucid discussion of purification strategies in a practical context, see: N. G. Anderson *Practical Process Research & Development*; Academic Press: New York; 2000, Chapter 11.

[8] Both enantiomers of Boc-*tert*-leucine are available commercially (Fluka).

[9] The result is identical to that previously reported; see ref. [1] for experimental details.

[10] (a) J. F. Larrow, E. N. Jacobsen, Y. Gao, Y. Hong, X. Nie, C. M. Zepp, *J. Org. Chem.* **1994**, *59*, 1939; (b) J. F. Larrow, E. N. Jacobsen, *Org. Synth.*, Vol. 75. **1997**, 1–11.