One-Pot Enantioselective Synthesis of Tryptophan Derivatives via Phase-Transfer Catalytic Alkylation of Glycine Using a Cinchona-Derived Catalyst

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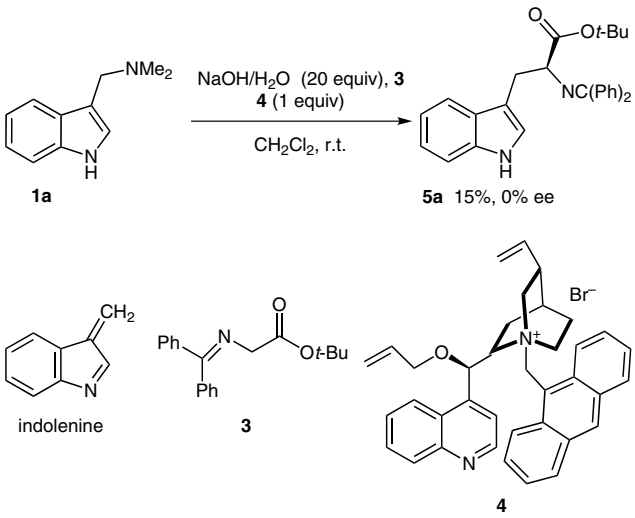
Abstract: Tryptophans are building blocks for many natural products. This paper describes the enantiospecific synthesis of ring-A substituted tryptophan derivatives from commercially available gramines using chiral phase-transfer conditions. This one-pot reaction avoids protecting/deprotecting the indolylic nitrogen of gramine by choosing a chemoselective quaternization reagent, 4-(trifluoromethoxy)benzyl bromide, to produce an electrophilic salt intermediate, which is subsequently alkylated in good yield with high enantiomeric excess.

Key words: asymmetric synthesis, one-pot, organocatalysis, phase transfer, tryptophan

Optically active tryptophans have been regarded as important components in the areas of both synthetic and medicinal chemistry.[1] Ring-A substituted tryptophans have been utilized in the design and synthesis of many biologically active compounds, including indole-based alkaloids, which have recently been receiving attention for their anti-cancer properties.[2] Several methods are known to effectively synthesize enantiopure tryptophans, but most strategies are only suitable for a particular species of tryptophan.[3] Many of these methods use stoichiometric amounts of chiral auxiliaries and extensive multistep syntheses, and often involve problematic separation of isomers obtained in the alkylation and annulation steps.[3] In recent years, asymmetric phase-transfer catalysis (PTC) has been established as a powerful tool in the synthesis of chiral mono- and di-substituted α-amino acids.[4,5] To date, the only reported asymmetric substitution of this type utilizes a relatively unstable Boc-protected indole to synthesize α-methyl tryptophan in 78% yield and 91% ee,[5e] but there has not been a general synthesis of chiral tryptophans via PTC reported. In this paper, we describe a simple, cost-effective, one-pot synthetic procedure that can be used to prepare chiral tryptophan derivatives via a phase-transfer-catalyzed (PTC) asymmetric alkylation reaction. We believe that this approach is the most economical and versatile process for synthesizing these important chiral building blocks.

In this study, a cinchona-derived phase-transfer catalyst was employed in the first reported PTC synthesis of chiral tryptophan derivatives, using a glycine Schiff base and various gramine derivatives. The first experiment, using substrate **1a**, glycine Schiff base **3**, catalyst **4**, and 50% aqueous $NaOH/CH_2Cl_2$ resulted in a disappointing racemic mixture of product with a chemical yield of 15% and reaction time of 50 hours (**5a**; Scheme 1). Such alkylation using gramine has been thoroughly studied in achiral systems, with an intermediate 3-methylene indolenine (Scheme 1) being identified.[6]



Scheme 1 Reaction of gramine **1a** with glycinate **3** in the presence of the catalyst **4** and an external base

The low chemical yield was attributed to the difficult task of eliminating Me_2NH to generate the product. To offset this matter, **1a** was converted into a quaternary salt **2a** using iodomethane, which resulted in a much improved chemical yield of 75% (**5a**; Scheme 2), albeit with no asymmetric induction. The latter result may be due to the fact that **2a** is very soluble in water, and insoluble in dichloromethane, which are not ideal conditions for asymmetric PTC reaction.[4,5] In order to improve the asymmetric induction, we attempted to change the polarity of the quaternary salt, making it very soluble in dichloromethane and partially soluble in water. Upon introduction of a bulky hydrophobic triisopropylsilyl (TIPS) protecting group on the indolylic nitrogen of the substrate (**1b**; Scheme 2), we were able to improve the enantioselection (84% ee) of the PTC alkylation reaction using one equivalent of catalyst (**5a**; Scheme 2). In addition, the TIPS group was removed during the alkylation process.

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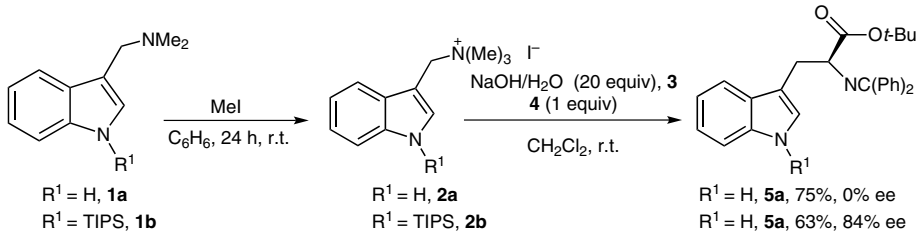
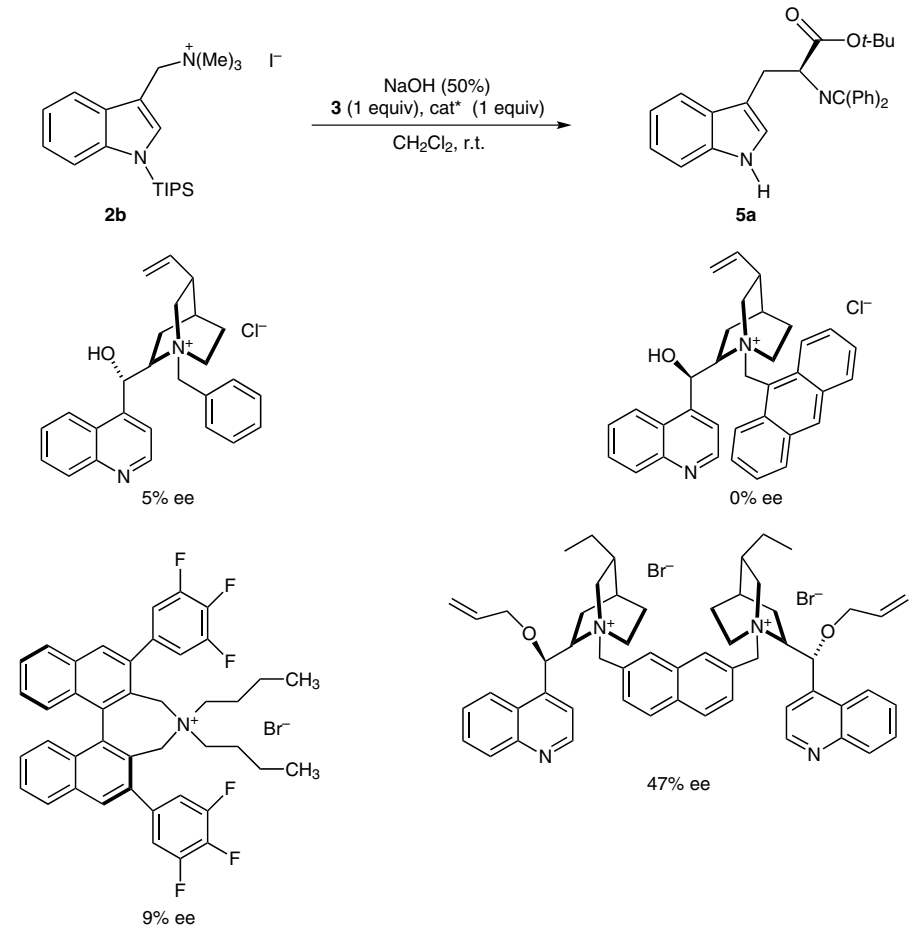


Scheme 2 Synthesis of quaternary salt **2** by reaction of gramine **1** with MeI, followed by alkylation with glycinate **3** under phase-transfer conditions using catalyst **4** and external base

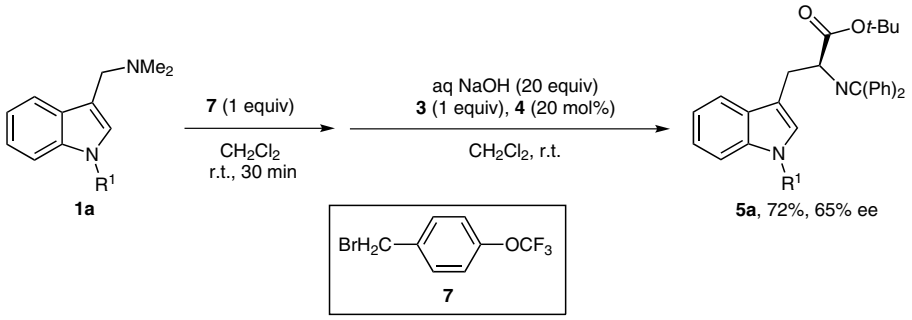
We screened other commercially available catalysts to determine if any were more effective than catalyst **4** for this alkylation reaction. From our results, summarized in Scheme 3, it was revealed that catalyst **4** (Scheme 2) was the catalyst of choice for best enantioselection.

Further studies revealed that changing the quaternization reagent from iodomethane to 4-(trifluoromethoxy)benzyl bromide (**7**) eliminated the need for protection/deprotection steps, allowing for the quaternization and chiral alkylation steps to be carried out in one pot (Scheme 4). The one-pot asymmetric alkylation was a success because the salt formed from **7** and gramine **1a** was found to be insoluble in water, similar to salt **2b**. Changing quaternization reagents from iodomethane to 4-(trifluoromethoxy)benzyl bromide (**7**; Scheme 4), not only rendered a one-pot transformation feasible, but also resulted in both an increase in yield and a reduction in the reaction time (<1 h; Scheme 5).

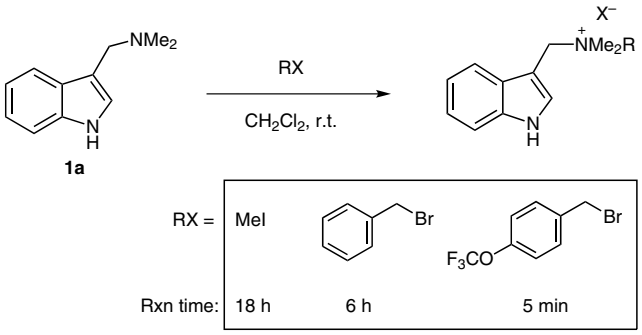
In order to further improve the chemical and enantioselection, a number of variables were studied for the alkylation reaction in dichloromethane. Increasing the concentration of aqueous NaOH from 10 to 50% resulted in an increase in enantioselection. Changing base from 50% aqueous NaOH to 45% aqueous KOH resulted in an increase in enantioselection from 65 to 80% ee. The use of other common bases such as CsOH or $Ba(OH)_2$ did not improve the chemical or enantioselection of the product. Further screening of solvents such as tetrahydrofuran (THF) (6% ee), dioxane (84% ee) and toluene (71% ee) showed that similar results were obtained with dichloromethane and



Scheme 3 Results obtained by using some commercially available phase-transfer catalysts in the alkylation reaction



Scheme 4 One-pot synthesis of chiral tryptophanate **5a** by reaction of gramines **1a** with glycinate **3** and catalyst **4**, using quaternization reagent **7** under ambient conditions



Scheme 5 Screening of quaternization reagents using gramine **1a** under ambient conditions

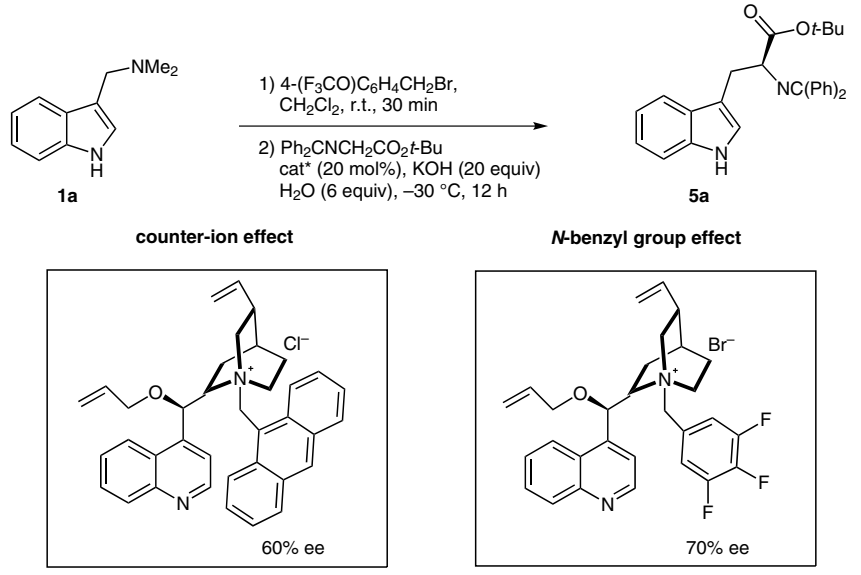
dioxane, leading to slightly higher enantioselectivity. Lowering the reaction temperature from 25 to –30 °C resulted in a further increase in enantioselection (80% ee after 2 h at 25 °C, 84% ee after 8 h at –30 °C). However, further cooling (–78 °C) increased the reaction time to 15 h but gave no additional improvement in enantioselection. The low temperature reactions were run in dichloromethane because of the relatively high freezing point of dioxane. Although we had determined that increased reaction rates and selectivity were achieved with higher base concentrations, the effect of water on the enantioselectivity was also studied (Table 1).[7] We discovered that a minimum of six equivalents of water was needed to achieve excellent enantioselection of the product (Table 1, entry 2). In these reactions, a minimum 20 mol% of catalyst **4** was required for optimal chemical and enantioselection.[8]

Once the alkylation variables were optimized, we began structure–activity relationship (SAR) studies of catalyst **4** (Scheme 6) in the asymmetric one-pot alkylation of **1a**

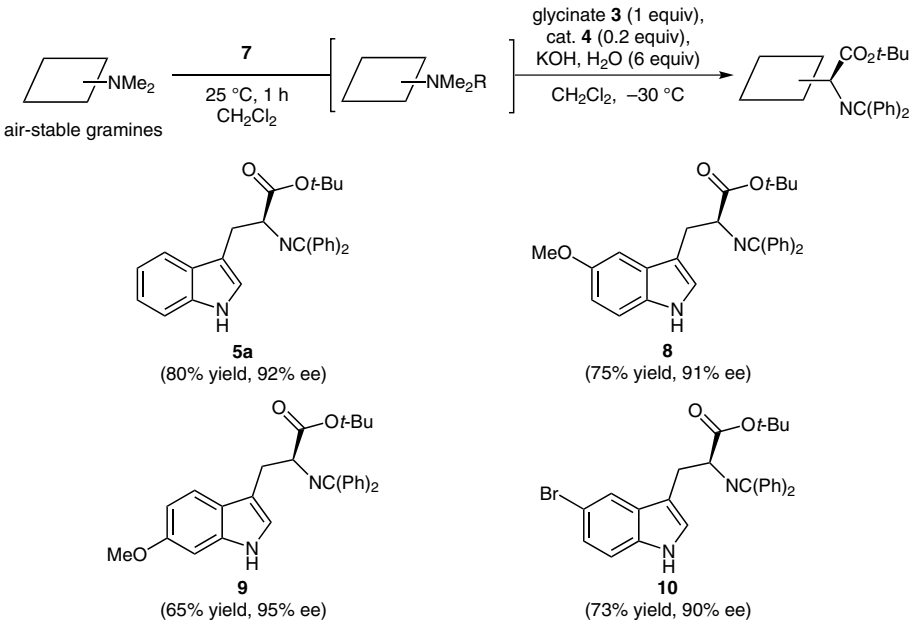
Table 1 Effect of Varying the Amount of Water on the Reaction

Entry	H_2O (equiv)	Time (h)	Yield (%)[a]	ee (%)[b]
1	100	8	80	85
2	6	18	80	92
3	3	19	>95	83

[a] Yield determined by HPLC analysis.
[b] Determined by chiral HPLC analysis (Chiralcel OD column; IPA–heptane, 5%; 254 nm DAD; 1 mL/min flow rate; 40 °C column temperature).



Scheme 6 Structure–activity relationship studies in the asymmetric alkylation of gramine **1a** with glycinate **3** with external base in a one-pot reaction



Scheme 7 Optimal asymmetric alkylation conditions of various gramines

and **3** in dichloromethane at –30 °C using solid KOH with six equivalents of water. The study revealed that both the bromide counter-anion and the *N*-anthracenyl group play an intimate role in the ability of catalyst **4** to induce high enantioselection. Changing the counter-anion from bromide to chloride resulted in a decrease in enantioselection to 60% (Scheme 6), which may be due to increased solubility of the catalyst in water. Substituting the anthracenyl group with a less bulky 3,4,5-trifluorobenzyl group also resulted in a decrease in enantioselection to 70% (Scheme 6). Steric influences were believed to be a contributing factor toward increasing enantiodifferentiation.[4,5]

After optimizing the reaction with gramine **1a**, which resulted in a good yield and excellent enantiomeric excess, we expanded the scope of our study to other gramine-type substrates, specifically ring-A substituted gramines such as 5-methoxy, 6-methoxy, and 5-bromogramine (Scheme 7).[8] All the gramines tested are commercially available and provided good yields with excellent optical purity.

In conclusion, a systematic study of substrate, catalyst, reagents, and reaction conditions led to a simple, enantioselective synthesis of L-tryptophan derivatives using chiral phase-transfer catalysis in a one-pot fashion.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(8) **Synthesis of *tert*-Butyl 2-(Diphenylmethyleneamino)-3-(1*H*-indol-3-yl)propanoate (Scheme 6; Compound 5a); Typical Procedure:** To a solution of gramine (0.300 g, 1.7 mmol, 1 equiv) in CH_2Cl_2 (10 mL) was added 4-(trifluoromethoxy)benzyl bromide (0.430 g, 1.7 mmol, 1 equiv) and the mixture was stirred for 30 min. *N*-(Diphenylmethylene)glycine *tert*-butyl ester (0.502 g, 1.7 mmol, 1 equiv) and *O*-allyl-*N*-(9-anthracenylmethyl)cinchoninium bromide (0.209 g, 0.3 mmol, 0.2 equiv) were added to the solution. The reaction mixture was then cooled to –30 °C. While stirring, solid KOH (2.0 g, 36 mmol, 20 equiv) and deionized H_2O (0.2 mL, 11.1 mmol, 6 equiv) were added to the reaction mixture, which was stirred for an additional 12 h at –30 °C. The reaction mixture was concentrated by rotary evaporation and the products were isolated by column chromatography (silica gel; EtOAc–pentane, 10%) providing **5a** (0.580 g, 80% yield) as a yellow oil. The identity of **5a** was confirmed by comparing its spectra to those of ^{1}H NMR spectra from authentic samples.[9]

***tert*-Butyl 2-(Diphenylmethyleneamino)-3-(5-methoxy-1*H*-indol-3-yl)propanoate (Scheme 6; Compound 8):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19 (s, 1 H), 7.59 (d, *J* = 7.9 Hz, 2 H), 7.27–7.43 (m, 4 H), 7.15–7.20 (m, 3 H), 6.93 (s, 1 H), 6.78–6.83 (m, 2 H), 6.61 (d, *J* = 7.5 Hz, 2 H), 4.33 (dd, *J* = 8.7, 4.5 Hz, 1 H), 3.69 (s, 3 H), 3.44 (dd, *J* = 14.1, 4.5 Hz, 1 H), 3.30 (dd, *J* = 14.1, 8.7 Hz, 1 H), 1.47 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.4, 170.1, 153.6, 139.6, 136.1, 131.1, 130.0, 128.7, 128.3, 128.0, 127.9, 127.6, 124.0, 112.0, 111.8, 111.6, 100.5, 81.0, 66.6, 55.7, 45.2, 29.3, 28.0. HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{29}H_{30}N_2O_3$: 455.2335; found: 455.2353.

***tert*-Butyl 2-(Diphenylmethyleneamino)-3-(6-methoxy-1*H*-indol-3-yl)propanoate (Scheme 6; Compound 9):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.39 (s, 1 H), 7.63–7.71 (d, *J* = 7.9 Hz, 2 H), 7.28–7.41 (m, 4 H), 7.18–7.25 (m, 3 H), 6.84 (d, *J* = 2.4 Hz, 2 H), 6.67–6.80 (m, 3 H), 4.36 (dd, *J* = 8.4, 4.8 Hz, 1 H), 3.82 (s 3 H), 3.46 (dd, *J* = 14.1, 4.8 Hz, 1 H), 3.27 (dd, *J* = 14.1, 8.4 Hz, 1 H), 1.48 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.5, 170.2, 156.1, 139.6, 136.7, 136.2, 130.1, 128.7, 128.1, 128.0, 127.9, 127.6, 122.0, 119.4, 111.7, 109.0, 94.4, 80.9, 66.8, 55.6, 45.2, 29.4, 28.0. HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{29}H_{30}N_2O_3$: 455.2335; found: 455.2349.

***tert*-Butyl 3-(5-Bromo-1*H*-indol-3-yl)-2-(diphenylmethyleneamino)propanoate (Scheme 6; Compound 10):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 7.80–7.90 (d, *J* = 7.9 Hz, 2 H), 7.60–7.70 (m, 3 H), 7.18–7.41 (m, 9 H), 7.00 (s, 1 H), 6.65 (d, *J* = 3.32 Hz, 2 H), 4.24 (dd, *J* = 8.4, 4.8 Hz, 1 H), 3.36 (dd, *J* = 14.1, 4.8 Hz, 1 H), 3.21 (dd, *J* = 14.1, 8.4 Hz, 1 H), 1.45 (s, 9 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 170.2, 135.9, 134.5, 130.0, 129.9, 128.6, 128.3, 128.2, 128.0, 127.9, 127.4, 124.4, 124.3, 121.6, 112.4, 112.2, 112.0, 81.0, 66.4, 28.9, 28.0. HRMS: *m*/*z* $[M + H]^+$ calcd. for $C_{28}H_{27}BrN_2O_2$: 503.1334; found: 503.1297.

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