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# ENANTIOSELECTIVE ALKYLATION OF REISSERT COMPOUNDS IN PHASE TRANSFER CATALYSED REACTIONS[#]

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**Abstract** - Isoquinoline Reissert compounds were alkylated under phase-transfer reaction conditions using chiral quaternary ammonium salts derived from *Cinchona* alkaloids as catalysts. The best stereoselectivity (ee up to 65%) was achieved in the alkylation of 1-cyano-2-phenoxycarbonyl-1.2-dihydroisoquinoline (**1d**), catalysed by *N*-benzylcynchoninium bromide (**3a**), carried in toluene/50% NaOH biphasic system.

The synthesis of chiral nonracemic compounds from prochiral substrates under phase-transfer catalysis (PTC),[1] catalysed by chiral quaternary ammonium salts, has been applied to versatile enantioselective reactions, affording products of high enantiomeric purity.[2,3] The asymmetric C-α functionalization of glycine iminoesters, pioneered by O`Donell and co-workers,[4] has been by far the most intensively studied asymmetric PTC process and used as a powerful tool for the preparation of α-mono- and α,α-disubstituted α-amino acids.[5-7] Among the many factors influencing the outcome of the asymmetric PTC reactions, the nature and structure of the quaternary ammonium salt has been proven to be a very important one. In this respect, quaternary salts derived from *Cinchona* alkaloids have been found to be the catalysts of choice.[8]

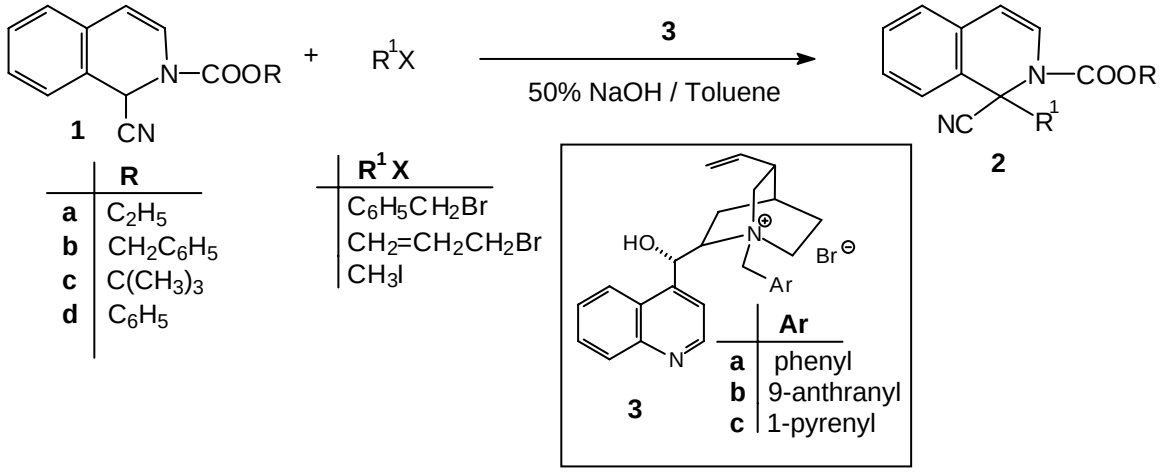
Herein we wish to report results of our preliminary experiments on the first enantioselective alkylation of isoquinoline Reissert compounds in toluene/50% NaOH biphasic system, catalysed by chiral quaternary ammonium salts, a reaction which may be potentially useful for the synthesis of unnatural heterocyclic α-amino acids as well as isoquinoline alkaloids bearing a C-1 stereocenter.[9,10]

The synthesis of chiral nonracemic Reissert compounds has not been reported until quite recently. In 2000, Shibasaki and co-workers[11-14] described a highly efficient catalytic enantioselective Reissert-type reaction with various nitrogen heteroaromatics using BINOL two-center catalysts to control the steric course of the TMSCN addition step. Later, Liebscher *et al.*[15] and Guingant *et al.*[16] have performed diastereoselective syntheses, applying chiral acylating agents to introduce chirality into the intermediate

[#] *Dedicated to professor Barry M. Trost on the occasion of his 65th birthday.*

*N*-acyliminium salts. The asymmetric Reissert reaction has been successfully extended to the synthesis of C-1 alkylated isoquinoline Reissert derivatives, bearing a quaternary C-1 stereocenter. Thus, the Japan group[13] applying their synthetic strategy to a broad range of C-1 substituted isoquinoline derivatives obtained products with enantioselectivity up to 95% ee. The German team[15] performed diastereoselective C-1 methylation (LDA/$CH_3I$) of chiral *N*-menthyloxycarbonyl Reissert compound in excellent yield and stereoselectivity.

Our approach to enantioselective synthesis of C-1 alkylated isoquinoline Reissert compounds (**2**) involved two other modifications: enantioselective alkylation of racemic Reissert compounds (**1a-d**) and application of the PTC conditions of the reaction, using chiral quaternary ammonium salts (**3a-c**) as catalysts and 50% sodium hydroxide as the base (Scheme 1).

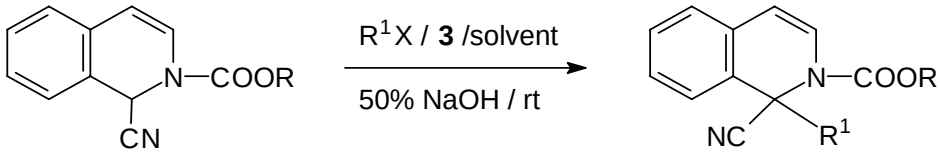



**Scheme 1**

The known starting Reissert derivatives (**1a, b, d**[18]) as well as (**1c**[19]) were prepared according to the standard procedure, in $CH_2Cl_2/H_2O$/TEBA two-phase system using isoquinoline, potassium cyanide and the corresponding acylating agent.

Our initial experiments, which involved C-1 benzylation of Reissert compound (**1a**), carried out in the presence of various quaternary ammonium salts derived from (–)-ephedrine, (+)-thiomicamine and Chirald®, were unsuccessful (ee 0-16%). Next, we turned our attention to catalysts (**3a-c**), derived from *Cinchona* alkaloids. In one of our first experiments, in which the classic *N*-benzylcinchoninium bromide (**3a**) was applied for benzylation of compound (**1a**) in benzene, the benzylation product ((–)-**2a**), showing negative rotation, was obtained in high yield and with enantioselectivity up to 62%. This prompted us to undertake experiments to optimize the reaction conditions. Thus, several factors that might influence the steric course of this reaction have been examined and the results are shown in the Table.

**Table**. Enantioselective alkylation of Reissert compounds




**1** **2**

| Entry | **1** | R | **3** (equiv) | Solvent | T (h) | Alkylation Product **2**[19] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | **2** | $R^1$ | Y (%) | ee (%)[a,b] |
| 1 | **1a** | Et | **3a** (1.0) | benzene | 3.5 | **2a** | Bn | 98 | 59[c] |
| 2 | **1a** | Et | **3a** (0.1) | benzene | 1.5 | **2a** | Bn | 95 | 62 |
| 3 | **1a** | Et | **3a** (0,01) | benzene | 24 | **2a** | Bn | 93 | 58 |
| 4 | **1a** | Et[d] | **3a** (0.1) | benzene | 1.5 | **2a** | Bn | 94 | 63 |
| 5 | **1a** | Et[d,e] | **3a** (0.1) | benzene | 20 | **2a** | Bn | 68 | 50 |
| 6 | **1a** | Et | **3a** (0.1) | toluene | 1.5 | **2a** | Bn | 98 | 56 |
| 7 | **1a** | Et | **3a** (0.1) | toluene/ $CHCl_3$ | 1.5 | **2a** | Bn | 92 | 36 |
| 8 | **1b** | Bn | **3a** (0.1) | toluene | 5 | **2b** | Bn | 74 | 37 |
| 9 | **1c** | *t*-Bu | **3a** (0.1) | toluene | 4.5 | **2c** | Bn | 89 | 20[c] |
| 10 | **1d** | Ph | **3a** (0.1) | toluene | 4 | **2d** | Bn | 73 | 65[c] |
| 11 | **1a** | Et | **3b** (0.1) | toluene | 5 | **2a** | Bn | 84 | 48 |
| 12 | **1a** | Et | **3c** (0.1) | benzene | 5.5 | **2a** | Bn | 91 | 50 |
| 13 | **1a** | Et | **3a** (0.1) | toluene | 6 | **2a** | Allyl | 36 | 42 |
| 14 | **1b** | Bn | **3a** (0.1) | toluene | 6 | **2b** | Allyl | 47 | 24 |
| 15 | **1c** | *t*-Bu | **3a** (0.1) | toluene | 4.5 | **2c** | Allyl | 35 | 27 |
| 16 | **1d** | Ph | **3a** (0.1) | toluene | 4.5 | **2d** | Allyl | 45 | 65 |
| 17 | **1a** | Et | **3a** (0.1) | benzene | 8 | **2a** | Me | 86 | 36 |

[a] ee of crude reaction product after filtration through a pad of silicagel, determined by chiral HPLC (Chiralcel OD-H column), [b] negative rotation of all products, [c] determined by $^1$H-NMR spectrum using DNBA as shift reagent, [d] solid KOH used as the base, [e] run at 0° C.
*Alkylation conditions:* A two-phase system composed of Reissert compound (**1**) (0.5 mmol) in a given solvent (3 mL), 50% sodium hydroxide (1.5 mL), quaternary ammonium salt (0.05 mmol) and the acylating agent (0.5 mmol) was stirred vigorously at rt, under the argon atmosphere for a time indicated in the Table. Phases were separated, the aqueous one extracted with the solvent (10 mL), the combined organic extracts were washed with water, dried and the solvent evaporated. The remainder was filtered through a pad of silicagel, and the crude product HPLC-analyzed, then recrystallized from 96% ethanol.

As shown in the Table, 0.1 equiv. of *N*-benzylcinchoninium bromide (**3a**) was found to be a more effective catalytic system, affording products with ee up to 65% (Entries 10, 16). Reactions carried in either benzene or toluene showed better enantioselectivity then that in the more polar toluene/$CHCl_3$ (7:3) solvent mixture (Entries 2, 6 and 7). No difference in the outcome of the reaction was observed when the liquid/liquid was substituted with the solid/liquid biphasic system (Entries 3, 4). Lowering the temperature from rt to 0ºC caused decrease in the yield and ee, while extending the reaction time from 1.5

h to 20 h (Entries 4, 5). The influence of the structure of the acyl substituent at the nitrogen was evaluated as well. Our experiments on benzylation and alkylation of **1d** confirmed the observation made by the Shibasaki team[13] that compounds containing the phenyloxycarbonyl group seem to be better substrates in the Reissert reactions (Entries 10, 16) then those with Cbz and Boc substituents (Entries 8, 9).
In summary, we have developed a simple procedure for enantioselective C-1 alkylation of racemic Reissert compounds in a two-phase catalytic system using 50% NaOH as the base and chiral quaternary ammonium salts derived from *Cinchona* alkaloids to control the steric course of the reaction.

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