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Ru-Centered Coordination Complexes as a New Phase Transfer Catalyst for Alkylation of Enolates and Michael Additions

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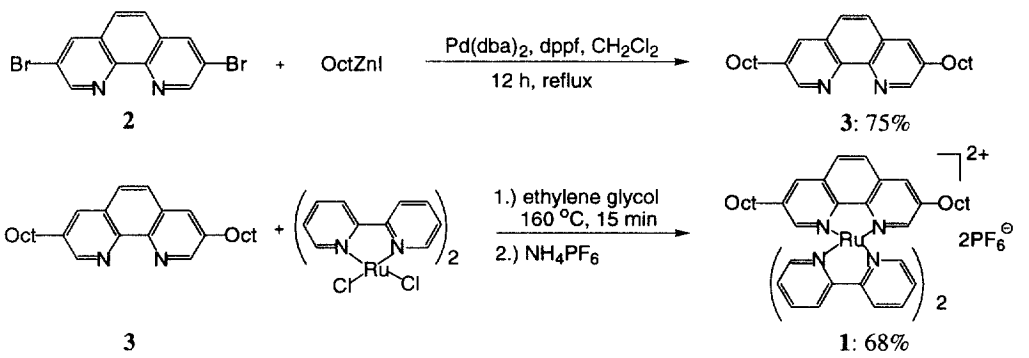
Abstract: A novel phase transfer catalysis based on a Ru(II)-polypyridyl complex **1** allows the fast alkylation of enolates and Michael additions under very mild conditions.

Phase-transfer catalysis (PTC) is an important technology for the performance of carbanionic chemistry under mild and economical conditions utilizing inexpensive reagents [1]. Currently tetraalkyl ammonium halides or tetraalkyl phosphonium halides are mostly used as phase transfer catalysts [1,2]. Although several of these catalysts have high activity [1-3] and allow enantioselective alkylations [3], there is a need for new classes of PTC, having significantly different physical properties, such as good extraction coefficient, good solubility in non-polar organic solvents and allowing an easy recovery at the end of reaction. We wish to report a new class of PTC which satisfies these criteria: tris(polypyridyl)ruthenium(II) complexes [4] of which the hexafluorophosphate complex **1** proved to have the best properties for PTC. This compound was easily prepared in 2 steps from 3,8-dibromo-1,10-phenanthroline **2** [5]. Cross-coupling with octylzinc iodide in the presence of $Pd(dba)_2$ and dppf (diphenylphosphinoferrocene) in THF



Scheme 1

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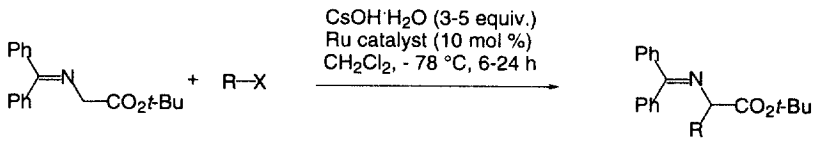
(reflux, 12 h) produces the 3,8-dioctyl-1,10-phenanthroline **3** in 75 % yield [6]. The complexation with $(bpy)_2RuCl_2$ in ethylene glycol at 160 °C for 15 min followed by the addition of an aqueous solution of NH_4PF_6 furnishes the desired complex **1** in 68 % yield (Scheme 1). The two octyl substituents give complex **1** an excellent solubility in CH_3CN, THF and CH_2Cl_2 making it ideally suited for solid-liquid PTC. Interestingly, complex **1** is insoluble in ether or pentane and this difference of solubility can be exploited to recover the catalyst after the reaction (see below).

Catalyst **1** proves to be very active for the alkylation of the glycine derived imine **4** [3]. Thus, the alkylation of **4** with primary alkyl iodides or bromides in the presence of **1** (10 mol %) and $CsOH{\cdot}H_2O$ (3-5 equiv) was complete in CH_2Cl_2 at -78 °C within 4-8 h leading to the amino-acid derivatives **5** in 71-83 % yield (Scheme 2 and Table 1). However, in the case of cyclopropylmethyl bromide, a reaction time of 24 h was required [7].

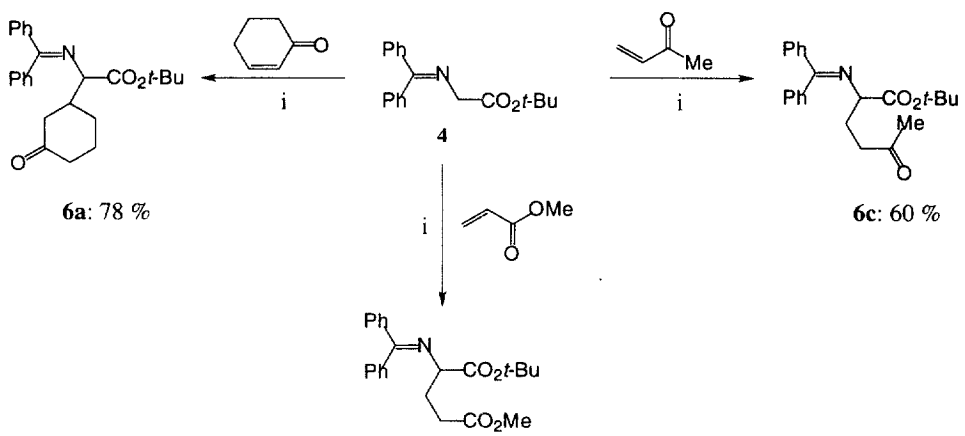


4 **5a-h**: 71-83%

Scheme 2

Interestingly compared to similar alkylations performed with quaternary ammonium salts, a significantly faster reaction is observed [3]. Typically the alkylation of **4** with methyl iodide requires 28 h at -60 °C using 10 mol % of a quarternary ammonium salt as catalyst and 10 equivalents of base whereas with catalyst **1** the reaction is complete after 7 h at -78 °C with 3-5 equivalents of base (see entry 1 of Table 1).

Similarly, the imine **4** undergoes smooth 1,4-additions with various Michael-acceptors like cyclohexenone, methyl vinyl ketone or methyl acrylate leading to the amino-acid derivatives **6a-c** in 60-78 %. Remarkably all reactions proceed at -78 °C and are complete within 1 h (Scheme 3).

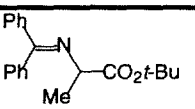
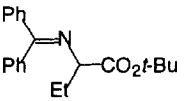
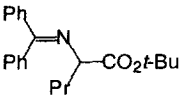
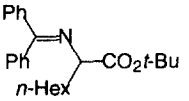
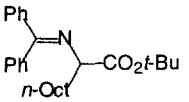
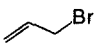
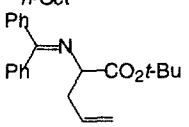
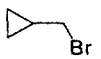
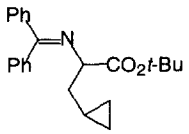
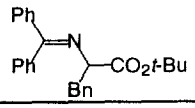


6a: 78 % **6c**: 60 %

6b: 76 %

Scheme 3. i) $CsOH{\cdot}H_2O$ (5 equiv.), [Ru]-catalyst **1** (10 mol%), CH_2Cl_2, -78 °C, 1h.

Table 1. Amino-acid derivatives **5a-h** obtained by PTC alkylation of **4** using the catalyst **1** (10 mol %)

entry	RX	product of type **5**		reaction time (h)	yield[a] (%)
1	MeI		**5a**	7	82
2	EtI		**5b**	6	72
3	PrBr		**5c**	8	71
4	*n*-Hex-I		**5d**	6	83
5	*n*-OctBr		**5e**	8	77
6			**5f**	7	83
7			**5g**	24	77
8	BnBr		**5h**	4	78

[a]Isolated yields of analytically pure products

The catalyst was recovered in 87 % yield by treating the crude reaction mixture with pentane. The precipitate was filtered and taken up in acetonitrile and recrystallized from water. The catalyst could be reused without any loss of activity.

In conclusion we have found that the [Ru]-centered coordination complex **1** is a highly active phase transfer catalyst for the alkylation of enolates and Michael-acceptors. It can also be easily recovered and reused without any significant loss of activity. Currently we are investigating the use of chiral Ru-catalysts as phase transfer catalysts.

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[7] Preparation of **3**: A mixture of 3,8-dibromo-1,10-phenanthroline (**2**; 1.0 g, 3.0 mmol), $Pd(dba)_2$ (90 mg, 0.2 mmol) and dppf (90 mg, 0.2 mmol) was treated with a solution of octylzinc iodide in THF (9.0 mL, 4.4 mmol) and heated under reflux for 12 h. The reaction mixture was poured into CH_2Cl_2 (100 mL) and washed with H_2O (50 mL), aqueous NH_4Cl (2 × 50 mL), 1M EDTA solution (50 mL) and brine (50 mL). The organic phase was dried ($MgSO_4$) and evaporated to dryness, resulting in a dark red paste, which yielded upon recrystallization in methanol a white solid (0.9 g, 75 %). ^1H NMR (300 MHz, $CDCl_3$) δ 9.01 (d, J = 2 Hz, 2H), 8.35 (d, J = 2 Hz, 2H), 7.95 (s, 2H), 2.96 (t, J = 8 Hz, 4H), 1.80 (m, 4H), 1.27 (bm, 20H), 0.82 (m, 6H). ^{13}C (75 MHz, $CDCl_3$) δ 150.2, 141.0, 139.0, 138.1, 128.4, 126.8, 33.1, 31.6, 30.7, 29.1, 28.9, 22.4, 13.9. Mp = 227-230 °C. MS(EI): = 404 (M^+)

Preparation of **1**: A mixture of **3** (800 mg, 2.0 mmol) and *cis*-dichlorobis(2,2'-dipyridyl)ruthenium(II) (480 mg, 1.0 mmol) was heated for 15 min to 160 °C in ethylene glycol. The reaction mixture was cooled on ice and the formed precipitate was filtered off and washed with H_2O (20 mL). The mother liquid was treated with a saturated aqueous NH_4PF_6 solution. The product was filtered off and recrystallized from acetonitrile and water to yield an orange solid (0.82 g, 68 % yield).

General Procedure for Alkylation. Preparation of **5a**: In a Schlenk flask *t*-butylglycine benzophenone imine **4** (360 mg, 1.2 mmol), $CsOH \cdot H_2O$ (800 mg, 4.8 mmol) and **1** (140 mg, 0.1 mmol), were suspended in CH_2Cl_2, precooled to -78 °C, and methyl iodide was added dropwise. The reaction mixture was stirred for 7 h. The mixture was poured into pentane (30 mL). The organic layer was diluted with ether and was washed with H_2O (3 × 10 mL), brine (10 mL) and dried ($MgSO_4$). The oily residue obtained after evaporation of solvents was purified by column chromatography (ethyl acetate:pentane 3:100) affording the desired product as a colorless oil (303 mg, 82 % yield). The filtrate containing **1** was taken up in acetonitrile and recrystallized from aqueous NH_4PF_6 solution to yield 121 mg of a orange solid (87 % yield). **1** was reused for the synthesis of **5a** as described above with the same reaction time and similar yield (79 % yield).