Phase-Transfer Catalysis

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Phosphonium Salts as Chiral Phase-Transfer Catalysts: Asymmetric Michael and Mannich Reactions of 3-Aryloxindoles**

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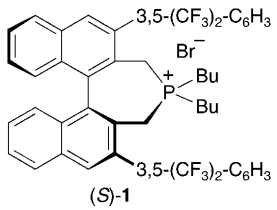
Asymmetric phase-transfer catalysis has been recognized as a powerful and convenient tool for the construction of chiral compounds over the last decade.[1,2] The majority of synthetic achievements was realized by using chiral quaternary ammonium salts as phase-transfer catalysts.[1,2] Despite the success of such ammonium salts in this field, the design and synthesis of a novel class of phase-transfer catalysts, for example, by replacing the nitrogen center with other elements is rare, and has been a challenge for a long time.[3] Recently we discovered the first successful example of a chiral quaternary phosphonium salt as phase-transfer catalyst and applied it to an asymmetric amination of β-keto esters.[3d] To additionally demonstrate the significance and generality of chiral quaternary phosphonium salts as phase-transfer catalysts, we were interested in the construction of chiral quaternary carbon centers, as it is one of the most fundamental challenges in synthetic organic chemistry.[4] Specifically, the construction of a quaternary chiral center in 3-aryloxindoles is of crucial importance and has received extensive attention as this structural motif is a prominent feature in a number of biologically and pharmaceutically active natural products and molecules.[5] Given the success of various asymmetric transformations of the prochiral 3-aryloxindoles,[6] the asymmetric Michael addition[7] of such substrates has not been reported. Herein we report a highly enantioselective Michael addition reaction of 3-aryloxindoles under very mild reaction conditions in the presence of the chiral quaternary tetraalkylphosphonium salt (*S*)-**1** as a reliable phase-transfer catalyst.

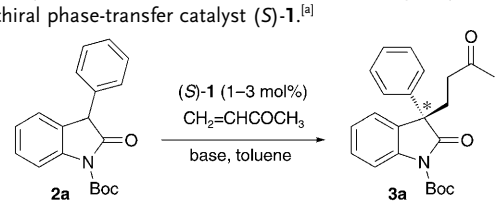
We chose 3-phenyloxindole **2a** as a donor substrate and methyl vinyl ketone (MVK) as the Michael acceptor for obtaining an optimal set of reaction conditions. In the presence of 1 mol% of chiral tetraalkylphosphonium salt (*S*)-**1**, the reaction proceeded smoothly with the mild base K_2HPO_4 to furnish conjugate adduct **3a** in high yield with a moderate *ee* value (Table 1, entry 1). After screening various weak bases, potassium benzoate was found to be among the best, providing high enantioselectivity (Table 1, entries 2–5). By lowering the reaction temperature, the enantioselectivity



(*S*)-**1**

was improved (Table 1, entries 6–8), and finally an optimal set of reaction conditions was achieved by adding 3 mol% of the catalyst (*S*)-**1** at −60 °C (Table 1, entry 9).

Table 1: Asymmetric Michael addition reactions of 3-phenyl oxindole **2a** using chiral phase-transfer catalyst (*S*)-**1**.[a]



Entry	Base (equiv)	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	K_2HPO_4 (1)	0	5	97	66
2	AcOK (1)	0	4	99	72
3	AcONa (5)	0	72	93	55
4	$PhCO_2K$ (5)	0	2	96	90
5	$KHCO_3$ (5)	0	12	95	44
6	$PhCO_2K$ (5)	0	2	97	90
7	$PhCO_2K$ (5)	−20	10	96	92
8	$PhCO_2K$ (5)	−40	15	96	98
9	$PhCO_2K$ (5)[d]	−60	18	97	99

[a] Reaction conditions (unless otherwise specified): MVK (1.2 equiv) in the presence of (*S*)-**1** (1 mol%) and base in toluene under the given reaction parameters. [b] Yield of the isolated product. [c] Enantiopurity of the products was determined by HPLC analysis using a chiral column (DAICEL Chiralcel AD-H) with hexane/isopropanol (15:1) as the eluent. [d] Used 3 mol% of (*S*)-**1**. Boc = *tert*-butoxycarbonyl.

With the optimal reaction conditions in hand, we studied the generality of the asymmetric Michael addition of various 3-aryloxindoles **2** under the influence of chiral quaternary tetraalkylphosphonium bromide (*S*)-**1** as shown in Table 2. The introduction of electron-donating and electron-withdrawing substituents on both the oxindole core and the 3-aryl group uniformly gave excellent enantioselectivity by using MVK as the Michael acceptor (Table 2, entries 1–15). In most cases, the products were obtained with *ee* values of 99% except for one example (Table 2, entry 9). Notably, in many reported enantioselective reactions of the 3-aryloxindoles, the substituents on aryl groups led to differences in the enantio-

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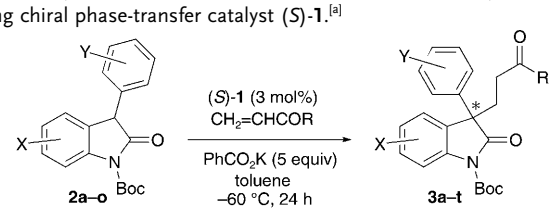
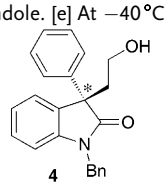
Table 2: Asymmetric Michael addition reactions of 3-aryloxindole **2** using chiral phase-transfer catalyst (*S*)-**1**.[a]



Entry	3-Aryloxindole **2** (X, Y)	Acceptor (R)	Product, yield [%][b]	*ee* [%][c]
1	**2a** (H, H)	Me	**3a**, 97	99
2	**2b** (H, 4-F)	Me	**3b**, 99	99
3	**2c** (H, 3-Cl)	Me	**3c**, 98	98
4	**2d** (H, 4-Cl)	Me	**3d**, 99	98
5	**2e** (H, 4-Ph)	Me	**3e**, 95	96
6	**2f** (H, [2-Np])[d]	Me	**3f**, 99	99
7	**2g** (H, 3-Me)	Me	**3g**, 99	98
8	**2h** (H, 4-Me)	Me	**3h**, 94	99
9	**2i** (H, 4-MeO)	Me	**3i**, 96[e]	94
10	**2j** (5-F, H)	Me	**3j**, 99	>99
11	**2k** (7-F, H)	Me	**3k**, 96	96
12	**2l** (6-Cl, H)	Me	**3l**, 99	98
13	**2m** (6-CF_3, H)	Me	**3m**, 91	98
14	**2n** (5-Me, H)	Me	**3n**, 99	99
15	**2o** (5-MeO, H)	Me	**3o**, 95	>99
16	**2a** (H, H)	Et	**3p**, 97[e]	96
17	**2c** (H, 3-Cl)	Et	**3q**, 98[e]	96
18	**2a** (H, H)	H	**3r**, 93	90
19	**2j** (5-F, H)	H	**3s**, 99	90
20	**2l** (6-Cl, H)	H	**3t**, 98	90

[a] Reaction conditions (unless otherwise specified): MVK or acrolein (1.2 equiv) in the presence of (*S*)-**1** (3 mol%) and $PhCO_2K$ (5 equiv) in toluene at −60°C for 24 h. [b] Yield of isolated product. [c] Enantiopurity of the products was determined by HPLC analysis using a chiral column (DAICEL Chiralcel AD-H) with hexane/isopropanol (15:1) as the eluent. [d] Used 3-(2-naphthyl)oxindole. [e] At −40°C for 45 h.



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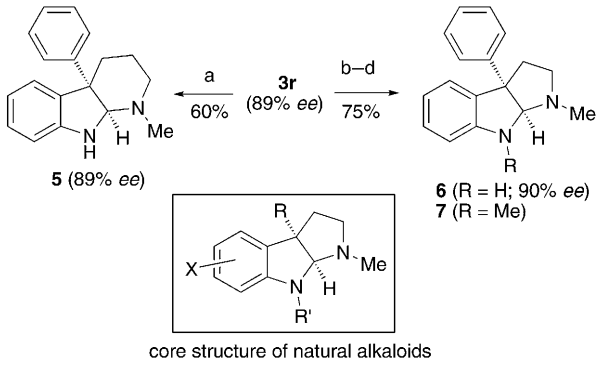
selectivity of the reaction.[6] The asymmetric Michael addition of **2** to ethyl vinyl ketone appears feasible (Table 2, entries 16 and 17). Acrolein can also be used as reactive Michael acceptor, giving acceptable enantioselectivity (Table 2, entries 18–20).

The absolute configuration of the Michael adduct **3a**, after conversion into compound **4**, was determined to be *S* by comparison with the reported compound.[8]

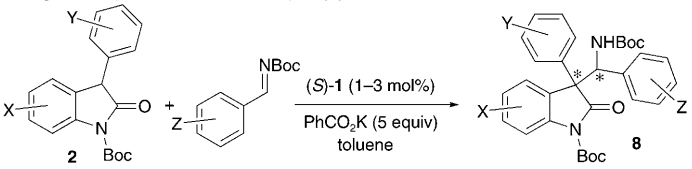
Importantly, the optically active Michael adducts derived from 3-aryloxindoles can be readily transformed into valuable natural products and their analogues. For example, Michael adduct **3r** was treated with $Me_2NH{\cdot}HCl/LiAlH_4$ to furnish the corresponding cyclization product **5** (Scheme 1). Furthermore, a three-step transformation of **3r** was realized to afford, after only a single purification step, compounds **6** and **7**, which have a core structure similar to important natural products such as CPC-1, (−)-physostigmine, (−)-pseudophrynaminol, etc.[9,10] These natural product analogues might possess important biological activity and are therefore valuable for the drug discovery.



Scheme 1. Transformation of conjugate adducts into valuable compounds. Reagents and conditions: a) $MeNH_2{\cdot}HCl$ (10 equiv), TEA (10 equiv), $MgSO_4$ (20 equiv), RT, 2 h, then $LiAlH_4$ (10 equiv), 70°C, 2 h. b) $NaClO_2$, 2-methyl-2-butene (20 equiv), $NaH_2PO_4{\cdot}H_2O$ (2 equiv), *t*BuOH/H_2O (3:1, v/v), RT, overnight). c) $(PhO)_2PON_3$ (1.1 equiv), TEA (2 equiv), toluene, 100°C, 1 h. d) $LiAlH_4$ (10 equiv), THF, 80°C, 3 h. TEA = triethylamine.

The asymmetric Mannich reaction of prochiral 3-aryloxindoles **2** is a very challenging transformation because of the molecular complexity induced by the concurrent creation of adjacent quaternary and tertiary chiral centers.[11] However, only low enantioselectivity has been observed for this substrate.[6k] Fortunately, chiral phosphonium salt (*S*)-**1** was found to catalyze the asymmetric Mannich reaction of 3-aryloxindoles **2** with activated imines at low temperature with

Table 3: Asymmetric Mannich addition reactions of 3-aryloxindole **2** using chiral phase-transfer catalyst (*S*)-**1**.[a]



Entry	Substrate (X, Y, Z)	*T* [°C]	*t* [h]	Yield[b] of **8** [%]	d.r.[c]	*ee* [%][c]
1	H, H, H	−20	24	97	96:4	56
2	H, H, H	−40	24	97	98:2	75
3	H, H, H	−60	60	95	99:1	60
4	H, H, H	−40	24[d]	96	>99:1	81
5	H, H, 4-F	−40	24[d]	99	99:1	85
6	H, 4-F, H	−40	24[d]	99	98:2	75
7	5-Me, H, H	−40	24[d]	99	>99:1	88

[a] Reaction conditions (unless otherwise specified): activated imine (1.2 equiv) in the presence of (*S*)-**1** (1 mol%) and $PhCO_2K$ (5 equiv) in toluene under the given reaction parameters. [b] Yield of isolated product. [c] Diastereoselectivity and enantiopurity of the products were determined by HPLC analysis using a chiral column (DAICEL Chiralcel OD-H or AD-H) with hexane/isopropanol (15:1 or 30:1) as the eluent. [d] Use of 3 mol% of (*S*)-**1**.

excellent diastereoselectivity and high enantioselectivity as shown in Table 3.

In conclusion, we have successfully developed a highly efficient, enantioselective Michael addition of 3-aryloxindoles with exceptionally high enantioselectivity in the presence of chiral phosphonium salt (*S*)-**1** under phase-transfer conditions. This reliable chiral phosphonium catalyst (*S*)-**1** is also found to be effective in the asymmetric Mannich reaction of 3-aryloxindoles and activated imines with excellent diastereoselectivity and high enantioselectivity.

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