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Enantioselective Base-Free Phase-Transfer Reaction in Water-Rich Solvent

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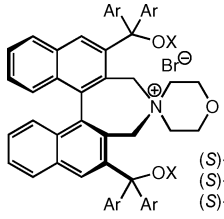
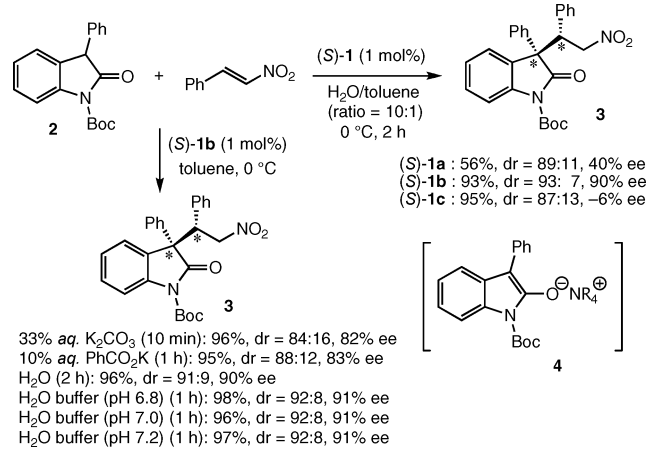
Enantioselective organocatalysis has emerged as a powerful and promising synthetic field that is complementary to metal-catalyzed transformations and has accelerated the development of new methodologies for synthesizing diverse chiral molecules.[1] The operational simplicity, ready availability of catalysts, and low toxicity associated with organocatalysis provides highly attractive synthetic methods that would compete with ordinary biocatalyzed approaches. However, although many biocatalyzed reactions proceed under neutral conditions in water, both organo- and metal-catalyzed reactions generally require either acids or bases as reaction promoters.[1] Accordingly, as in biocatalyzed transformations, the development of certain organocatalytic reactions that would proceed in water under essentially neutral conditions without any promoters is quite attractive and challenging in terms of environmental consciousness. In this context, we are interested in the possibility of developing an enantioselective conjugate addition of 3-substituted oxindoles under neutral conditions in water-rich solvent in the presence of certain chiral phase-transfer catalysts,[2] since an enantioselective conjugate addition of 3-substituted oxindoles to Michael acceptors is currently one of the hot topics in catalytic asymmetric synthesis,[3,4] as oxindoles are important building blocks in numerous natural alkaloids and in many pharmaceuticals.[5] Very recently, two enantioselective conjugate additions of 3-alkyloxindoles to nitroolefins by either an organocatalytic or organometallic pathway have been independently reported,[4] but the utility of 3-aryloxindoles as substrates for enantioselective conjugate additions is still found to be difficult.[3] Here we report a first example of this project by demonstrating a hitherto-unknown enantioselective base-free conjugate addition of 3-aryloxindoles to nitrostyrenes under neutral conditions in water-rich solvent in the presence of optically pure quaternary ammonium salts of type **1** as chiral bifunctional phase-transfer catalysts.



(*S*)-**1a** (Ar = Ph; X = H)
(*S*)-**1b** (Ar = 3,5-$(CF_3)_2C_6H_3$; X = H)
(*S*)-**1c** (Ar = 3,5-$(CF_3)_2C_6H_3$; X = Me)

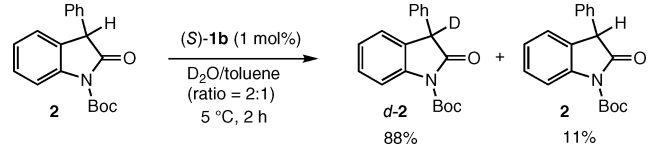
Conjugate addition of 3-phenyloxindole **2** to β-nitrostyrene catalyzed by Bu_4NBr as the phase-transfer catalyst proceeded smoothly with aqueous K_2CO_3 in toluene at 0 °C for 10 min to furnish the corresponding conjugate adduct *rac*-**3** in 95% yield (diastereomeric ratio = 61:39) (Scheme 1). Use of aqueous $PhCO_2K$ as a mild base, however, gave only 5% yield under phase-transfer conditions with a much longer reaction time (24 h). In marked contrast, our newly designed chiral bis(3,5-bis(trifluoromethyl)phenyl)hydroxymethyl-substituted phase-transfer catalyst (*S*)-**1b** with bifunctional properties exhibited a high reactivity compared with

Scheme 1. Phase-Transfer Conjugate Addition of 3-Phenyloxindole



Bu_4NBr, and both aqueous K_2CO_3 and $PhCO_2K$ as mild bases work well for the enantioselective conjugate addition of **2** with high enantioselectivity (82−83% ee) (Scheme 1). *Very surprisingly, we discovered that even without any basic additives, the reaction proceeds smoothly in the presence of chiral phase-transfer catalyst (S)-**1b** in 1:2 toluene/water at 0 °C for 2 h to furnish **3** with 90% ee*,[7,8] implying the intervention of intermediary chiral ion pair **4**. Indeed, treatment of **2** with catalyst (*S*)-**1b** in 1:2 toluene/D_2O at 5 °C for 2 h gave rise to deuterated *d*-**2** in 88% yield with recovery of **2** in 11% yield, indicating the facile enolization of **2** with the aid of (*S*)-**1b** in water solvent (Scheme 2). In the absence of (*S*)-**1b** or in the presence of Bu_4NBr, none of the deuterated product *d*-**2** was formed. It should be noted that water is essential for the promotion of the reaction, and the reaction in toluene without water does not proceed at all. *Since quaternary ammonium salts as phase-transfer catalysts are generally believed to require base additives,*[6] *the present reaction involving catalyst (S)-**1b** solely without any base is regarded as a rare example under essentially neutral conditions*. The enantioselective conjugate addition of **2** to β-nitrostyrene is also found to be catalyzed by (*S*)-**1b** in buffer solutions in the pH range 6.8−7.2 (Scheme 1).[9]

Scheme 2. Deuteration of 3-Phenyloxindole **2**



With this information at hand, we further carried out the enantioselective conjugate addition of 3-phenyloxindole **2** to β-nitrostyrene under neutral conditions in water-rich solvent (10:1 water/toluene)[10] in the presence of chiral phase-transfer catalyst

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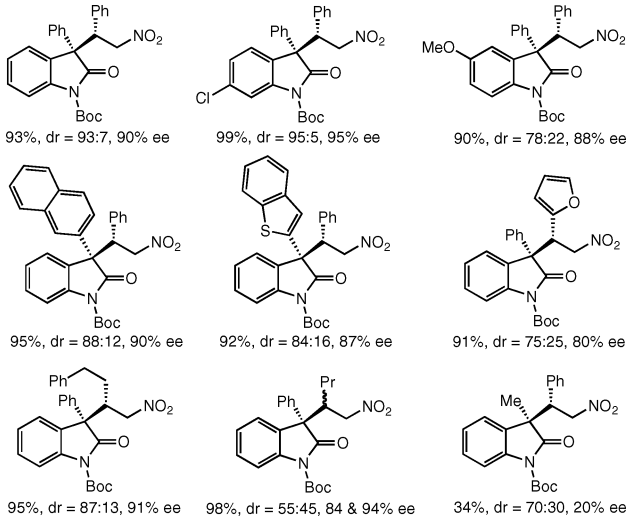
(*S*)-**1b** with both high diastereo- and enantioselectivity (Scheme 1). In contrast, chiral diphenylhydroxymethyl-substituted phase-transfer catalyst (*S*)-**1a**, the structure of which was confirmed by X-ray analysis,[11] exhibited moderate enantioselectivity (40% ee). Because methyl-protected (*S*)-**1c** showed only a low enantioselectivity (−6% ee), the presence of hydroxy groups in catalyst (*S*)-**1b** is crucially important, implying the bifunctional nature of this catalyst.[12,13]

Other selected examples are listed in Scheme 3. 3-Phenyloxindole possessing an electron-withdrawing chloro substituent gave higher enantioselectivity, while introduction of an electron-donating methoxy group resulted in the decrease of both the diastereo- and enantioselectivity. 3-(*β*-naphthyl)oxindole, 3-benzothiophen-2-yloxindole, 1-(2-furyl)-2-nitroethene, and 1-nitro-4-phenyl-1-butene exhibited good diastereoselectivity and high enantioselectivity. In case of the 1-nitro-1-pentene substrate, high enantioselectivities were observed for both diastereomers in spite of low diastereoselectivity. Unfortunately, 3-methyloxindole gave low reactivity and selectivity.[14]

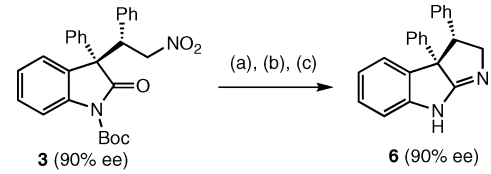
Scheme 3. Selected Examples of Enantioselective Conjugate Addition of 3-Substituted Oxindoles



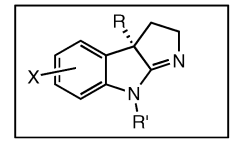
Importantly, both racemic and optically active conjugate adducts derived from 3-aryloxindoles can be readily transformed into valuable natural products and their analogues. For example, the optically active conjugate adduct **3** (90% ee) was subjected to catalytic hydrogenation over Pd/C in EtOAc/MeOH, removal of the Boc protecting group with trifluoroacetic acid in CH_2Cl_2, and treatment with $LiAlH_4$ in THF (Scheme 4) to furnish the corresponding cyclization product **6**, which has a core structure similar to those of many important natural products such as flustramines and flustramides, etc.[15] These natural product analogues might possess important biological activity and hence are valuable for drug discovery.

In conclusion, we have developed the enantioselective conjugate addition of 3-aryloxindoles to *β*-nitrostyrene under neutral conditions in water-rich solvent in the presence of chiral phase-transfer catalyst (*S*)-**1b** without base additives. The reaction proceeds in a highly diastereo- and enantioselective manner. We are continuing to explore the enormous synthetic potential of chiral bifunctional phase-transfer catalysts to realize various enantioselective base-free organic transformations in water solvent under neutral conditions. The results of these studies will be reported in due course.

Scheme 4. Transformation of Conjugate Adduct **3**



(a) Pd/C, H_2 (1 atm), EtOAc/MeOH, 0 °C, 24 h;
(b) CF_3CO_2H, CH_2Cl_2, r.t., 0.5 h;
(c) $LiAlH_4$ (10 eq.), THF, 75 °C, 2 h. (21% overall yield)



core structure of natural alkaloids

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Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) *Phase-Transfer Catalysis: Fundamentals, Applications and Industrial Perspectives*; Starks, C., Liotta, C., Halpern, M., Eds.; Chapman & Hall: New York, 1994; Chapter 16.
(7) The BF_4^- salt of (*S*)-**1b** showed results similar to those for the corresponding bromide salt (97%, dr = 92:8, 90% ee).
(8) For the stereochemical determination of **3**, see the Supporting Information.
(9) Buffer solutions were prepared from NaH_2PO_4/Na_2HPO_4 by the Sigma-Aldrich Buffer Reference Center.
(10) We used a small amount of toluene to dissolve solid **2**, *β*-nitrostyrene, and (*S*)-**1**.
(11) See the Supporting Information.
(12) Chiral 3,3′-diarylbinaphthyl-modified ammonium salts (ref 13) also exhibited low enantioselectivity. For details, see the Supporting Information.
(13) (a) Wang, X.; Kitamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 1038. (b) Wang, Y.-G.; Kumano, T.; Kano, T.; Maruoka, K. *Org. Lett.* **2009**, *11*, 2027.
(14) Only a low yield (34%) was obtained after 24 h at 0 °C.
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