Asymmetric Catalysis

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Catalytic Asymmetric Synthesis of 3,3′-Diaryloxindoles as Triarylmethanes with a Chiral All-Carbon Quaternary Center: Phase-Transfer-Catalyzed S_NAr Reaction**

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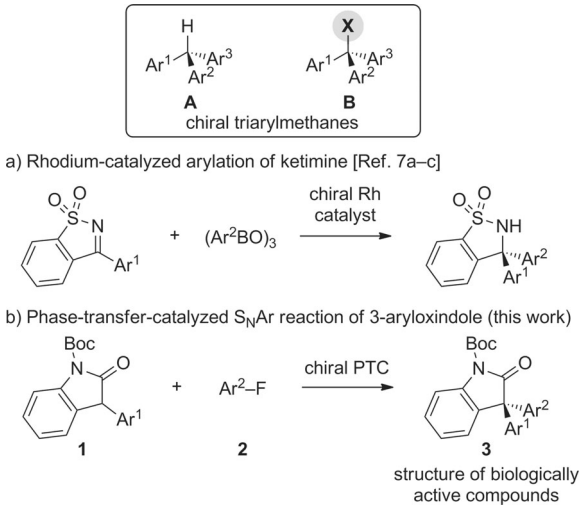
Abstract: *Catalytic asymmetric synthesis of unsymmetrical triarylmethanes with a chiral all-carbon quaternary center was achieved by using a chiral bifunctional quaternary phosphonium bromide catalyst in the S_NAr reaction of 3-aryloxindoles under phase-transfer conditions. The presence of a urea moiety in the chiral phase-transfer catalyst was important for obtaining high enantioselectivity in this reaction.*

The development of efficient synthetic methods for triarylmethanes is an important task for organic chemistry because of the utility of these compounds in materials science[1] and medicinal chemistry,[2,3] and a number of methods have been reported to date.[4,5] In particular, research in catalytic asymmetric methods for the synthesis of chiral, unsymmetrical triarylmethanes has attracted much attention in recent years.[6,7] Although several catalytic asymmetric methods for the synthesis of chiral triarylmethanes of type **A** with a tertiary carbon center have been reported (Scheme 1),[6] only one general method for the synthesis of compounds of type **B**, possessing a quaternary carbon center, has been developed and involves a rhodium-catalyzed asymmetric addition of arylboroxines to diaryl ketimines to produce chiral (triaryl)-methylamines (Scheme 1 a).[7a–c] In this context, we are interested in the development of a new approach to the synthesis of chiral triarylmethanes of type **B**. Herein we report a valuable example of the catalytic asymmetric synthesis of triarylmethanes, possessing a chiral all-carbon quaternary center, by phase-transfer-catalyzed S_NAr reaction of 3-aryloxindoles (**1**),[8–10] and it results in chiral 3,3′-diaryloxindoles (**3**) which are biologically interesting compounds (Scheme 1 b).[3]



Scheme 1. Catalytic asymmetric synthesis of triarylmethanes with a quaternary carbon center. Boc = *tert*-butoxycarbonyl, PTC = phase-transfer-catalyst.

We first examined the screening of chiral bifunctional quaternary phosphonium bromides [(*S*)-**4**–**6**] as phase-transfer catalysts,[11,12] which were developed recently by our group,[13] for the asymmetric S_NAr reaction of the 3-phenyloxindole **1a** (Table 1). Attempted reaction of **1a** and 2,4-dinitrofluorobenzene (**2a**) with solid $KHCO_3$ in toluene under the influence of the bifunctional catalyst (*S*)-**4**, which possesses a hydroxy group, at room temperature for 24 hours afforded the arylation product **3a** in high yield with low enantioselectivity (entry 1). Switching the catalyst to the benzamide-substituted (*S*)-**5** slightly improved the enantioselectivity (entry 2), and the benzenesulfonamide-substituted catalyst (*S*)-**6** gave the product **3a** in low yield with low enantioselectivity (entry 3). To further improve the enantioselectivity of this reaction, we next examined the newly designed bifuctional phosphonium bromides (*S*)-**7**, which possess a urea group.[14] It was expected that the urea moiety of (*S*)-**7** interacts with the nitroarene **2** through two hydrogen bonds, thus giving rise to a well-organized transition state which provides high stereocontrol (Figure 1).[15] Based on this hypothesis, (*S*)-**7a** was utilized in this reaction, and to our delight, **3a** was obtained in moderate enantioselectivity (entry 4). Further tuning of the catalyst structure of led to

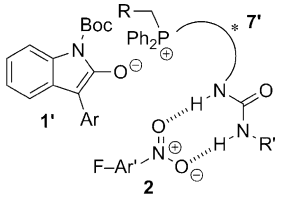


Figure 1. Proposed working model on the asymmetric arylation of 3-aryloxindole with bifunctional catalyst (*S*)-**7**.

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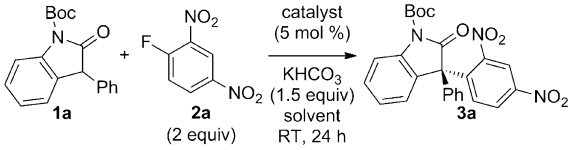
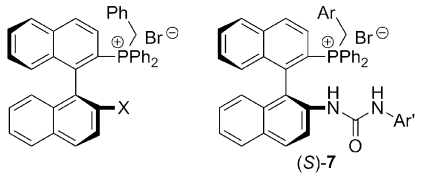
Table 1: Optimization of the reaction conditions.[a]





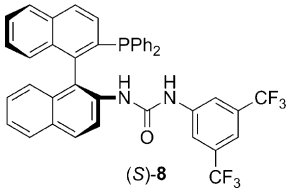
(*S*)-**7**

(*S*)-**4**: X = OH
(*S*)-**5**: X = NHBz
(*S*)-**6**: X = $NHSO_2Ph$

(*S*)-**7a**: Ar = Ph, Ar' = Ph
(*S*)-**7b**: Ar = Ph, Ar' = 3,5-$(CF_3)_2$-C_6H_3
(*S*)-**7c**: Ar = Ph, Ar' = 3,5-$(MeO)_2$-C_6H_3
(*S*)-**7d**: Ar = 3,5-$(CF_3)_2$-C_6H_3, Ar' = 3,5-$(CF_3)_2$-C_6H_3
(*S*)-**7e**: Ar = 3,5-$(t\text{Bu})_2$-C_6H_3, Ar' = 3,5-$(CF_3)_2$-C_6H_3
(*S*)-**7f**: Ar = 3,5-$(t\text{Bu})_2$-C_6H_3, Ar' = 3,5-$(MeO)_2$-C_6H_3

Entry	Catalyst	Solvent	Yield [%][b]	*ee* [%][c]
1	(*S*)-**4**	toluene	98	−17
2	(*S*)-**5**	toluene	89	35
3	(*S*)-**6**	toluene	36	3
4	(*S*)-**7a**	toluene	46	64
5	(*S*)-**7b**	toluene	42	79
6	(*S*)-**7c**	toluene	49	76
7	(*S*)-**7d**	toluene	30	76
8	(*S*)-**7e**	toluene	50	87
9	(*S*)-**7f**	toluene	85	84
10	(*S*)-**7e**	CCl_4	80	87
11	(*S*)-**7e**	Et_2O	88	88
12	(*S*)-**7e**	iPr_2O	90	88
13	(*S*)-**7f**	iPr_2O	97	85
14[d]	(*S*)-**7e**	iPr_2O	99	91

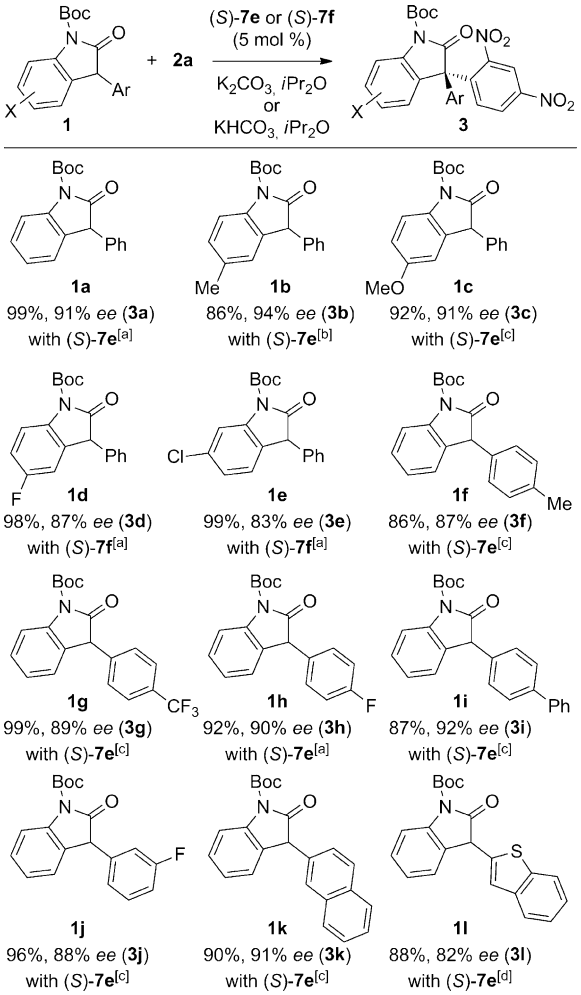
[a] Reaction conditions: **1a** (0.050 mmol), **2a** (0.10 mmol), and $KHCO_3$ (0.075 mmol) in the presence of the chiral phase-transfer catalyst (5 mol%) in solvent (1.0 mL) at room temperature (25 °C) for 24 h. [b] Enantiomeric excess (*ee*) was determined by HPLC analysis using a chiral stationary phase. [c] Yield of isolated product. [d] The reaction was performed at −20 °C with K_2CO_3 (0.038 mmol) as a base. Bz = benzoyl.



(*S*)-**8**

improved enantioselectivity (entries 5–9), and the arylation product **3a** was obtained with good enantioselectivity by using the catalysts (*S*)-**7e** and (*S*)-**7f** (entries 8 and 9). The screening of solvents led to improved yields (entries 10–13), and the highest yield and enantioselectivity were obtained at a lower temperature (−20 °C) with K_2CO_3 in diisopropylether in the presence of (*S*)-**7e** (entry 14). Notably, the reaction with the triarylphosphine catalyst (*S*)-**8** gave the product **3a** with low enantioselectivity (< 5% *ee*), that is, the quaternary phosphonium bromide moiety of (*S*)-**7e** was essential to obtaining high enantioselectivity.

With the effective chiral bifunctional quaternary phosphonium bromides (*S*)-**7e** and (*S*)-**7f** in hand, we studied the substrate generality of the asymmetric arylation of various 3-aryloxindoles (**1**) with **2a** (Scheme 2). The introduction of electron-donating and electron-withdrawing substituents on both the oxindole core and the 3-aryl group uniformly gave the products (**3a**–**k**) in good to high enantioselectivities (83–94% *ee*). 3-Heteroaryl-substituted oxindole could also be used in this reaction, thus providing the product **3l** with good enantioselectivity (82% *ee*).[16]



Scheme 2. Asymmetric arylation of the 3-aryloxindoles **1** with 2,4-dinitrofluorobenzene (**2a**). [a] Run with K_2CO_3 (0.75 equiv) at −20 °C for 24 h. [b] Run with K_2CO_3 (0.75 equiv) at −20 °C for 48 h. [c] Run with $KHCO_3$ (1.5 equiv) at RT for 24 h. [d] Run with $KHCO_3$ (1.5 equiv) at 0 °C for 48 h.

Other electron-deficient aryl fluorides could also be employed in the S_NAr reaction (Scheme 3). The asymmetric arylation of **1a** with 1-bromo-5-fluoro-2,4-dinitrobenzene and 1,5-difluoro-2,4-dinitrobenzene in the presence of (*S*)-**7e** gave the corresponding arylation products **3m** and **3n**, respectively, with high enantioselectivities. Pentafluoronitrobenzene was also used in the reaction, thus giving the product **3o** as a single regioisomer with good enantioselectivity. The reaction with 2,4,6-trifluoropyrimidine as a heteroaryl fluoride was also promoted by (*S*)-**7e** to afford the product **3p** as a single regioisomer with good enantioselectivity.[17] The absolute configuration of the arylation products **3** was determined by X-ray diffraction analysis of **3m** (Figure 2).[18]

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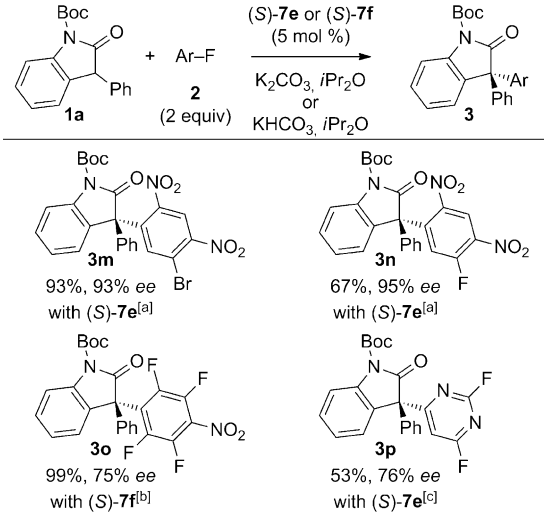


Scheme 3. Asymmetric arylation of 3-phenyloxindole (**1a**). [a] Run with K_2CO_3 (0.75 equiv) at −20 °C for 24 h. [b] Run with $KHCO_3$ (1.5 equiv) at RT for 24 h. [c] Run with $KHCO_3$ (1.5 equiv) at RT for 48 h.

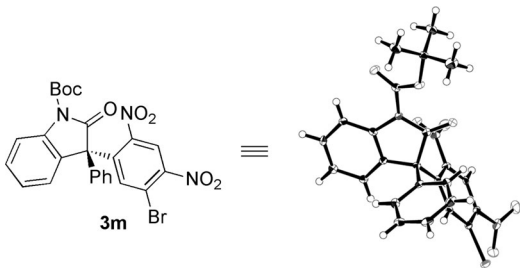
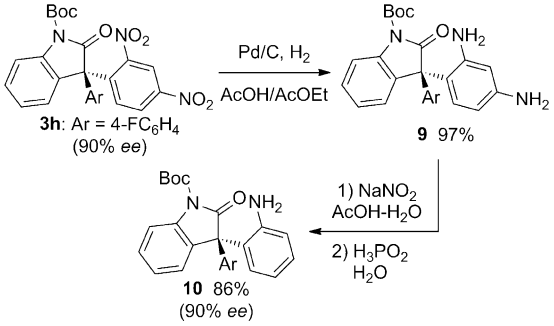


Figure 2. X-ray crystal structure of **3m**. Thermal ellipsoids shown at 50% probability.



Scheme 4. Transformation of the product **3h**.

The nitro groups in the products **3** can be readily transformed into other functionalities (Scheme 4). For example, the nitro groups of **3h** were reduced to amino groups by hydrogenation in the presence of Pd/C to give the compound **9**. The regioselective removal of an amino group at the *para*-position of **9** was performed via the formation of the corresponding diazonium salt and subsequent treatment with H_3PO_2 to give the *ortho*-amino compound **10** in good yield without any loss of stereoinformation.

In summary, we have successfully developed an efficient method for the synthesis of chiral triarylmethanes possessing an all-carbon quaternary center by S_NAr reaction of 3-aryloxindoles under phase-transfer conditions. The reactions were efficiently promoted by newly-designed chiral bifunctional quaternary phosphonium bromides possessing a urea moiety to give chiral triarylmethanes with good to high enantioselectivities. Further studies will be directed toward expansion of the reaction scope.

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[16] The *tert*-butoxycarbonyl group on the nitrogen atom of the 3-aryloxindoles **1** was important for promoting the reaction efficiently.

[17] In the case of reaction with 2,4,6-trifluoropyrimidine, the urea moiety of catalyst (*S*)-**7e** may interact with basic nitrogen atoms in the pyrimidine heterocycle.

[18] CCDC 985318 (**3m**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Communications

Asymmetric Catalysis

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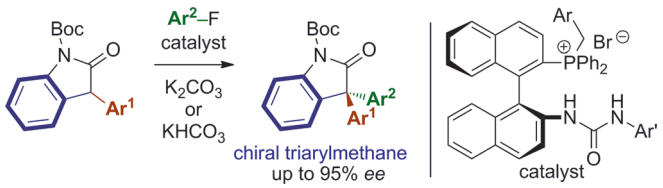
Catalytic Asymmetric Synthesis of 3,3′-Diaryloxindoles as Triarylmethanes with a Chiral All-Carbon Quaternary Center: Phase-Transfer-Catalyzed S_NAr Reaction



Going through a phase: Catalytic asymmetric synthesis of unsymmetrical triarylmethanes, with a chiral all-carbon quaternary center, was achieved by using a chiral bifunctional quaternary phosphonium bromide catalyst in the S_NAr reaction of 3-aryloxindoles. The reactions proceeded under phase-transfer conditions. Boc = *tert*-butoxycarbonyl.

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