Letter

Design of Efficient Chiral Bifunctional Phase-Transfer Cata-lysts Possessing an Amino Functionality for Asymmetric Aminations

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Design of Efficient Chiral Bifunctional Phase-Transfer Catalysts Possessing an Amino Functionality for Asymmetric Aminations

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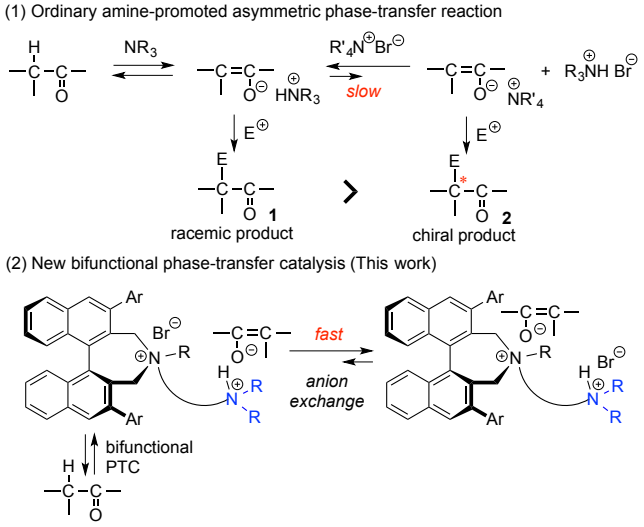
ABSTRACT: An efficient, chiral bifunctional phase-transfer catalyst with an intramolecular amino functionality has been designed, and successfully applied to highly enantioselective amination of 3-aryloxindoles and 3-arylbenzofuran-2(3H)-ones with bis(adamantyl) azodicarboxylate. Optically active amination products were generally obtained in high yield with high enantioselectivity. The origin of stereoselectivity was explained by means of the DFT calculations.

KEYWORDS: phase-transfer catalyst, bifunctional catalyst, asymmetric amination, oxindole, benzofuran-2(3H)-one

Asymmetric phase-transfer catalysis under basic conditions provides an extremely powerful and versatile means for inducing asymmetry in reactions of prochiral anionic nucleophiles through the formation of an ion pair with chiral ammonium cation, thereby producing high levels of enantioselectivity in a wide range of reactions including enolate alkylation, conjugate addition, cyclopropanation, oxidative cyclization, amination, etc.[1]

Scheme 1. Mechanistic Scenario Under Ordinary and New Bifunctional Phase-transfer Catalysis.



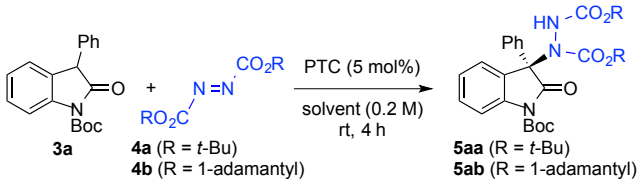
In the case of asymmetric nucleophilic reactions, strongly basic conditions would generally be required for the efficient generation of an ion pair with chiral ammonium cation,[2] and hence ordinary tertiary amine bases are not recommended for this purpose due to the unfavorable generation of an ammonium enolate via the slow ion-exchange reaction, thereby providing a racemic product **1** as a major product ((1) in Scheme 1). In this context, we are interested in the possibility of designing a new chiral bifunctional phase-transfer catalyst possessing an intramolecular amino linkage for affecting the deprotonation and subsequent facile anion-exchange reaction with an adjacent ammonium cation to furnish a chiral product **2** preferentially ((2) in Scheme 1).

Oxindoles bearing a chiral quaternary stereocenter at the 3-position are common structural motifs in various natural and bioactive products. Consequently, a significant amount of effort have been devoted to achieve this goal by the use of metal and organocatalysis.[3] Chiral phase-transfer catalysis also has made appreciable contribution in this direction by means of alkylation, conjugate addition, Mannich reaction, SNAr etc.[2a,e,g,i,4] Among the chiral 3,3-disubstituted oxindoles of particular interest are 3-amino-2-oxindole compounds which exhibit significant biological activities.[5] Procedures describing the asymmetric synthesis of this class of oxindoles utilized bischinchona alkaloid, chiral scandium complex or Schiff base as catalyst starting from 3-substituted oxindoles.[6] However, many literature procedures suffer from high catalyst loading and longer reaction times.[6d,f] Our aim was to design a new chiral bifunctional phase-transfer catalyst which can overcome above mentioned limitations.

We began our investigation with 3-phenyloxindole derivative **3a** and di-tert-butyl azodicarboxylate **4a** to obtain the optimal reaction conditions (Table 1). Carrying out the reaction using 5 mol% of triethylamine without additon of any phase-transfer catalyst (PTC) gave 66% of racemic product **5aa** (entry 1). Applying commercially available Maruoka catalyst® **6** with 5 mol% organic (triehtylamine) or inorganic

(K_2CO_3) base also led to the formation of racemic product with moderate to high reactivity (entries 2 and 3). Maruoka catalyst® alone, in the absence of any basic additive gave the product in 6% yield as a racemic mixture (data not shown). In contrast, when catalyst **7** with an additional 2-(dimethylamino)ethyl moiety was employed as PTC under similar reaction conditions, product **5aa** was obtained in 70% yield and importantly 36% enantioselectivity (entry 4). With this promising result in hand, we synthesized a library of catalysts and tested them for the amination reaction. Results are delineated in Table 1. PTC **8a**, bearing pyrrolidine as the additional basic moiety attached to the chiral ammonium salt scaffold improved the enantioselectivity (entry 5). Significant improvement in the enantioselectivity was obtained when the aryl substituents at 3,3′ positions of **8** were changed to 3,5-$(CF_3)_2C_6H_3$ group. Thus, chiral bifunctional PTC **8b** gave the product **5aa** in 68% enantioselectivity (entry 6). PTC **9** with an additional carbon in the alkyl chain between ammonium and pyrrolidine moiety led to significant drop in enantioselectivity (entry 7), highlighting the importance of appropriate distance between ammonium and pyrrolidine base. Chiral bifunctional PTC **10** with piperidine also resulted in lower enantiocontrol (entry 8). Hence, PTC **8b** was selected for further optimization studies. After some more optimization, we found that application of bis(adamantyl) azodicarboxylate **4b** as electrophilic partner can improve the enantioselectivity of the product **5ab** up to 82% ee (entry 9). Addition of molecular sieves and changing the solvent to mesitylene further improved the enantioselectivity (entries 10 and 11). Finally, an optimal set of reaction conditiones were obtained by adding 2 mol% of catalyst **8b** at 0 ˚C, and the product was obtained in 96% yield and 95% of enantioselctivity (entry 13).

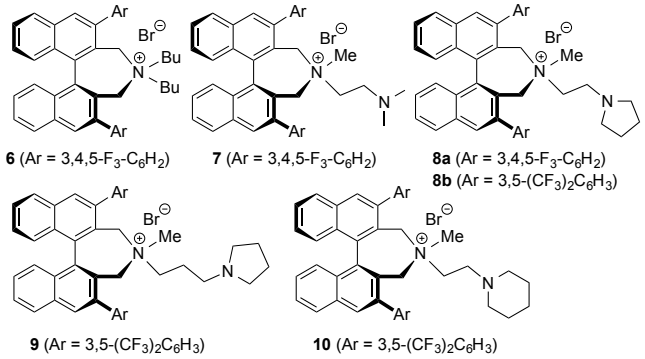
Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	4	yield (%)[b]	ee (%)[c]
1[d]	—/NEt_3	toluene	**4a**	66	0
2	**6**/NEt_3	toluene	**4a**	72	0
3	**6**/K_2CO_3	toluene	**4a**	98	0
4	**7**	toluene	**4a**	70	36
5	**8a**	toluene	**4a**	72	53
6	**8b**	toluene	**4a**	86	68
7	**9**	toluene	**4a**	82	33
8	**10**	toluene	**4a**	82	40
9	**8b**	toluene	**4b**	85	82
10[e]	**8b**	toluene	**4b**	87	88
11[e]	**8b**	mesitylene	**4b**	89	92
12[e,f]	**8b**	mesitylene	**4b**	99	95
13[e,f,g]	**8b**	mesitylene	**4b**	99 (96)[h]	95

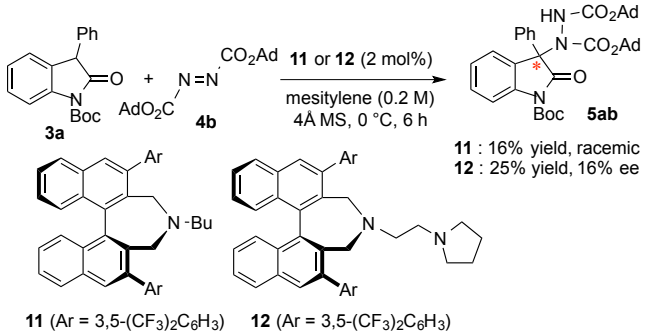
[a]Reaction conditions (unless otherwise specified): 3-phenyloxindole **3a** (0.05 mmol), azodicarboxylate **4** (1.2 equiv) in the presence of PTC (5 mol%). [b]The yield was determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c]Determined by HPLC analysis using a chiral column. [d]With only NEt_3 (5 mol%). [e]4 Å molecular sieves (20 mg) was added. [f]At 0 °C. [g]With 2 mol% of PTC **8b**. [h]Isolated yield.

Scheme 2. Chiral Binaphthyl-Modified Phase-Transfer Catalysts 6~10.



It should be noted that in the presence of amine **11**, the reaction of oxindole **3a** with azodicarboxylate **4b** afforded amination product **5ab** in 16% yield as a racemate, whereas chiral diamine catalyst **12** afforded **5ab** in 25% yield with 16% enantioselectivity (Scheme 3). This result suggests the importance of the bifunctional groups in a suitable position on the rational design of chiral phase-transfer catalysts of type **8** possessing an amino functionality.

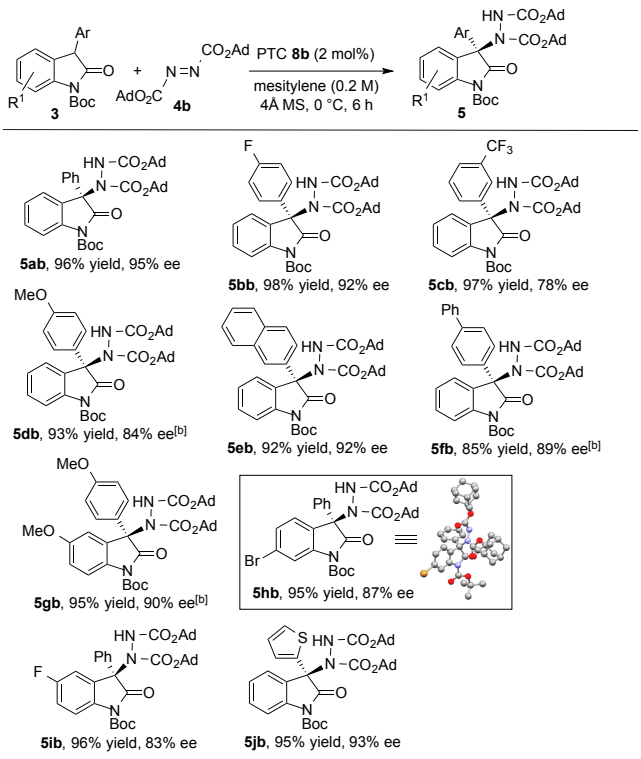
Scheme 3. Control Experiments



With optimal reaction conditions in hand, we studied the substrate generality for this amination reaction with respect to oxindole substrates (Table 2). To make it general, all the reactions were carried out for 6 hours before work up. Amination of **3a**, when carried out in 1 mmol-scale, gave the final product **5aa** in similar yield and enantioselectivity to those of small-scale reaction, thereby demonstrating the scalability of this amination protocol. Substrates with electron withdrawing groups on the 3-aryl ring proceeded with high efficiency and high (**5bb**) to moderate (**5cb**) enantioselectivity. An electron donating methoxy substituent at 4-position of the 3-aryl ring

had no impact on reactivity but lowered the enantioselectivity of the product **5db**. Aryl substituent other than phenyl also well tolerated (**5eb**, **5fb**). Methoxy substituent at the 5-position of the oxindole ring proceeded with high efficiency and selectivity (**5gb**). Halogen substitution at the 6-position of the oxindole ring proceeded smoothly to give **5hb** in high yield with high enantioselectivity. The absolute configuration of **5hb** was determined to be *R* by X-ray diffraction analysis.[7]

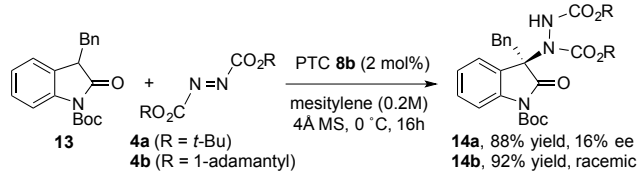
Table 2. Scope of 3-Aryloxindoles (3)[a]



[a]Reaction conditions (unless otherwise specified): 3-aryloxindole (0.05 mmol), azodicarboxylate **4b** (1.2 equiv) in the presence of PTC **8b** (2 mol%) with 4Å MS (20 mg). [b]The reaction was carried out at room temperature.

Unfortunately, attempted use of 3-alkyloxindoles as pronucleophiles was unsuccessful. 3-Benzyloxindole **13**, gave the product **14a** in high yield with low enantioselectivity when di-tert-butyl azodicarboxylate **4a** was used as electrophile (Scheme 4). In case of bis(adamantly) azodicarboxylate **4b**, the product **14b** was obtained as racemate. The observed low or no enantioselectivity can be attributed to the lack of π–π interaction between aryl ring at the C3 carbon of oxindole and binaphthyl ring of the chiral PTC, which is believed to be crucial to achieve high enantiocontrol for such kind of amination reactions.[6f]

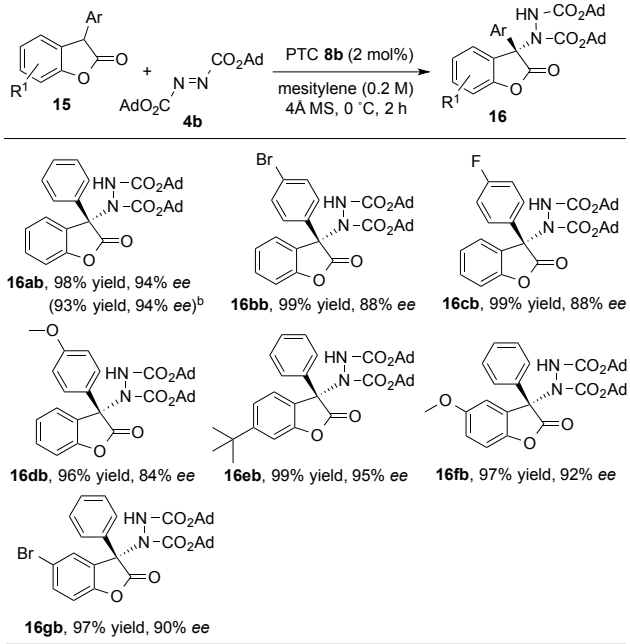
Scheme 4. 3-Alkyl Oxindole as Pronucleophile.



Having established the substrate scope for the amination of 3-aryloxindoles **3**, we sought to identify another class of nucelophile amenable to our bifunctional PTC system for this amination reaction. We selected benzofuran-2(3H)-ones **15** as pronucleophiles because benzofuranones with a chiral quaternary stereocenter at 3 position are important for their potential applications in medicinal chemistry and can be found in various natural products.[8]

Under the similar reaction conditions as for the amination of 3-aryloxindoles **3**, a wide range of 3-arylbenzofuran-2(3H)-ones **15** underwent amination to furnish **16** with high efficiency and stereo fidelity (Table 3). This methodology should also be noted for the very short reaction time (typically two hours) compared to other literature procedures for amination reactions with similar nucleophiles (24~48 hours).[9] The absolute configuaration of the newly formed stereocenter was determined to be *S* by comparison with known benzofuranone derivative of **16ab** (see supporting information).

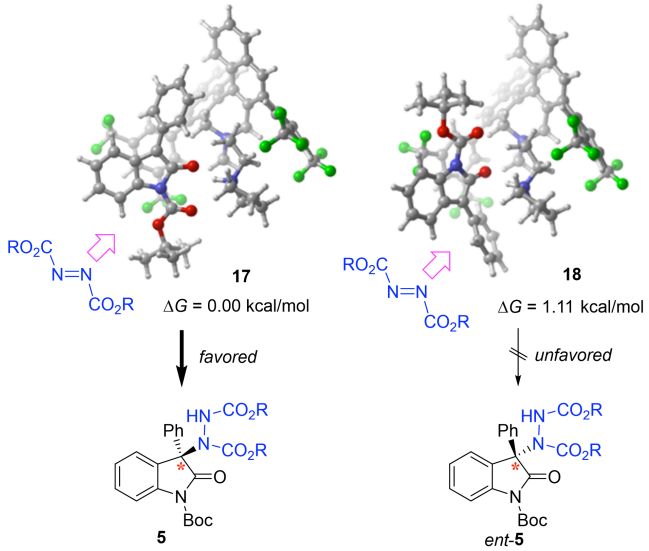
Table 3. Scope of 3-arylbenzofuran-2(3H)-ones (15)[a]



[a]Reaction conditions (unless otherwise specified): 3-arylbenzofuran-2(3H)-one (0.05 mmol), azodicarboxylate **4b** (1.2 equiv) in the presence of PTC **8b** (2 mol%) with 4Å MS (20 mg). [b]The reaction was carried out in 1 mmol scale.

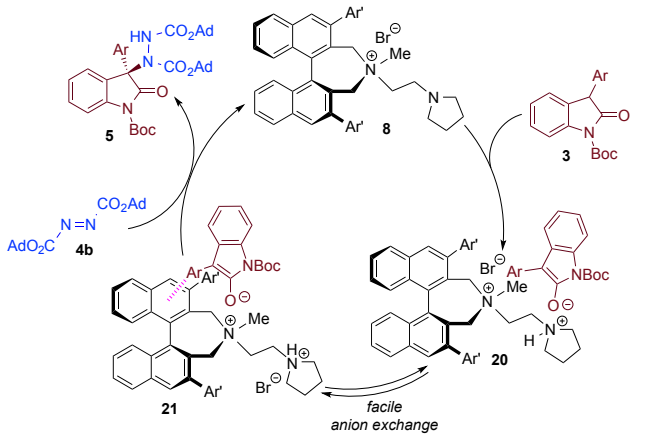
To gain more insight into the origin on the enantioselectivity of asymmetric amination reaction, we performed the density functional theory (DFT) calculations combined with the automated reaction path search strategy, called the Global Reaction Route Mapping (GRRM)[20] (see Supporting Information for details). Scheme 5 shows the energetically lowest and second lowest ammonium enolate structures **17** and **18**, respectively. Only the *Re*-face of **17** is open for the amination, whilst the *Re*- and *Si*-faces of **18** is partly blocked by the 3,5-$(CF_3)C_6H_3$ and pyrrolidine moieties, respectively. Then, dialkyl azodicarboxylate **4** approaches **17** from the front side to furnish amination product **5** with the desired absolute configuration.

Scheme 5. The Structures and Gibbs Free Energy Differences Δ*G* (in kcal/mol) of Ammonium Enolates 17 and 18 Optimized at the B3LYP-D3/6-31G(d) Level Including the Solvation Effect by the Polarized Continuum Model.



A plausible reaction mechanism for asymmetric amination reaction is depicted in Scheme 6. The basic pyrrolidine moiety of the bifunctional PTC **8** deprotonates **3** to generate ion-pair **20**. A rapid anion exchange between the two ammonium centers brings the enolate to the chiral environment of the bifunctional PTC, resulting in ion-pair **21**. Effective shielding of one face of the enolate with PTC by the π–π interaction between Ar and binaphthyl groups implies that azocarboxylate **4b** can approach the enolate by only *Re*-face preferentially over the *Si*-face leading to enantio-rich amination product **5**.

Scheme 6. Plausible reaction mechanism.



In conclusion, we have successfully developed a new class of bifunctional phase-transfer catalytic system with additional basic amino moiety attached to the chiral backbone of binaphthyl derived quaternary ammonium salt. This catalytic system was found to be superior to its parent binaphthyl ammonium scaffold for hitherto difficult enantioselective amination of 3-aryloxindoles. This reliable catalyst was also found to be effective for the enantioselective amination of 3-arylbenzofuran-2(3H)-ones. Further application of this catalytic system is currently undergoing in our group.

ASSOCIATED CONTENT

Supporting Information. The Supporting Material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no conflict of interest.

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