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Catalytic Enantioselective 1,3-Alkyl Shift in Alkyl Aryl Ethers: Efficient Synthesis of Optically Active 3,3'-Diaryloxindoles

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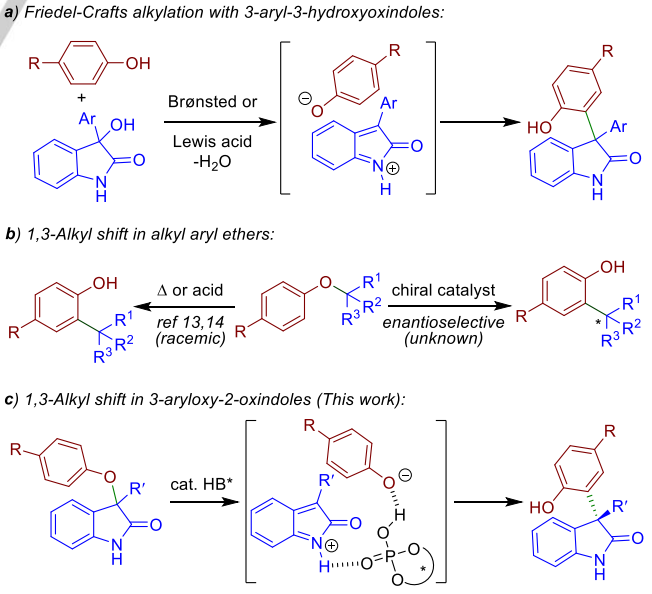
Abstract: First organocatalytic asymmetric 1,3-alkyl shift in alkyl aryl ethers for the synthesis of chiral 3,3'-diaryloxindoles as triarylmethane using a chiral Brønsted acid catalyst has been reported. Preliminary results showed that both the enantiomers of 3,3'-diaryloxindoles and racemic mixture showed different antiproliferative activities against HeLa cell lines by an MTT assay.

Triarylmethanes have been regarded as an important class of organic compounds due to their remarkable significance in natural products and medicinal chemistry research.[1] The development of catalytic methods for accessing these motifs in a enantioselective fashion has thus been the focus of substantial studies in recent years.[2] As a subset, 3,3'-diaryloxindoles represent an important class of molecules that bear all-carbon quaternary center and exhibit potent biological activities.[3] Surprisingly, there exist only one report by Maruoka and co-workers who demonstrated the synthesis of chiral 3,3'-diaryloxindoles by S_NAr reaction of 3-aryloxindoles with aryl fluorides under phase-transfer catalysis conditions.[4] However, this method was limited to the nitro-containing aryl fluorides. Given the challenges and the high value of the 3,3'-diaryloxindoles, the development of a general and robust protocol for accessing this important structural motif would be highly desirable.

In recent years, chiral phosphoric acid catalyzed reactions[5] of *in situ* generated *ortho*-quinone methides (*o*-QM) with various nucleophilic reaction partner has emerged as a new research field.[6] However, the report dealing with the chiral phosphoric acid catalyzed reactions of aza-*ortho*-quinone methides (aza-*o*-QM) are scarce. The research group of Tang reported transfer hydrogenation of 1,2-dihydroquinolines through the intermediary of aza-*o*-QM.[7] Subsequently, Rueping and co-workers reported addition of indoles,[2i] thiols and alcohols[8] on *in situ* generated aza-*ortho*-quinone methides. In yet another report, Schneider and co-workers described an interesting formal [4 + 2]-cycloaddition of enamides to aza-*o*-QM.[9] Very recently, the group of Zu has reported asymmetric aza-pinacol rearrangement involving a cyclic aza-*o*-QM intermediate.[10] In similar lines, we envisioned that the chiral Brønsted acid catalyzed Friedel–Crafts alkylation of phenols with aza-*o*-QM generated in situ from 3-aryl-3-hydroxyoxindoles would be a powerful strategy for the construction of optically active 3,3'-diaryloxindoles (Scheme 1a).[11] Unfortunately, all our efforts to make this reaction highly enantioselective failed.[12] These unsatisfactory results could be accounted on the basis of competing S_N2 pathway and high reaction temperature which facilitates racemization.

In our attempt to work out a feasible solution, a report by Turnbull and co-workers on the thermal and acid-catalyzed rearrangement of 3-aryloxy-2-oxindoles caught our attention.[13] Surprisingly, despite the synthetic utility of [1,3]-alkyl shift in alkyl aryl ethers,[14] to date, no catalytic enantioselective variant has been reported (Scheme 1b).[15] The challenges for the enantioselective alkyl shift in alkyl aryl ethers, as we identified, stems from the following reasons: The chiral catalyst must 1) avoid concerted [1,3]-alkyl shift,[16] 2) be active enough to facilitate the C-O bond cleavage and 3) be able to participate in key enantiodescriminating step. Herein, we report first catalytic enantioselective 1,3-alkyl shift in alkyl aryl ethers using chiral Brønsted acid to deliver enantioenriched 3,3'-diaryloxindoles (Scheme 1c).



Scheme 1. Conceptualization of catalytic enantioselective 1,3-alkyl shift.

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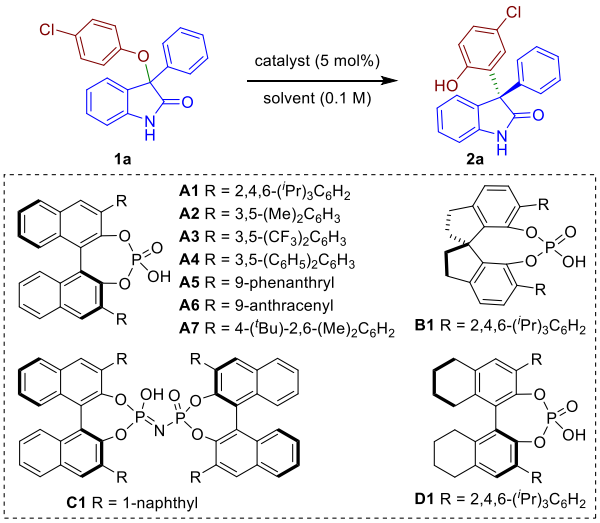
Table 1. Optimization of reaction.[a]



entry	catalyst	solvent	yield [%][b]	ee [%][c]
1	**A1**	DCE	22	12
2	**A2**	DCE	67	18
3	**A3**	DCE	83	54
4	**A4**	DCE	61	56
5	**A5**	DCE	72	66
6	**A6**	DCE	78	85
7	**A7**	DCE	74	91
8	**B1**	DCE	40	63
9	**C1**	DCE	75	10
10	**D1**	DCE	73	61
11	**A7**	toluene	76	84
12	**A7**	benzene	79	85
13	**A7**	DCM	75	89
14	**A7**	$CHCl_3$	80	80
15[d]	**A7**	DCE	77	72

[a] Reaction conditions: 0.2 mmol **1a,** 5 mol% catalyst, solvent (0.1 M), 40 °C for 48 h. [b] Isolated yields. [c] The ee values were determined by chiral-phase HPLC. [d] Reaction was performed at 70 °C for 12 h.

At the beginning of our investigation, we employed 3-(4-chlorophenoxy)-3-phenylindolin-2-one (**1a**) as model substrate for enantioselective [1,3]-alkyl shift in chiral phosphoric acid catalysis (Table 1). The reaction fruitfully led to the formation of rearranged product **2a** when (*S*)-**A1** (TRIP) was used as catalyst; albeit, in low yield and enantioselectivity (Table 1, entry 1). Interestingly, increase in yield was noted when **A2** was employed as catalyst, but ee was unperturbed (entry 2). Next, Slightly more acidic phosphoric acid **A3** pleasingly delivers **2a** in 83% yield and 54% ee (entry 3). Further screening of other BINOL-based phosphoric acids gave encouraging results and identified that **A7** is the superior catalyst providing **2a** in promising yield with good enantioselectivity (91% ee) (entries 4-7). When we examined other chiral phosphoric acids **B1**, **C1** and **D1**, reduced the enantioselectivity (entries 8-10) was noticed. Thereafter a short solvent screen was evaluated (entries 11-14); unfortunately, increase in the enantioselectivity was not observed. Increase in the reaction temperature speed up the reaction; however, deleterious effect on the enantioselectivity was observed (entry 15). The results in Table 1, entry 7 imply the best condition for enantioselective [1,3]-alkyl shift in **1a**.

With the optimized conditions in hand, we explored the scope of the catalytic enantioselective 1,3-alkyl shift in alkyl aryl ethers. At first, variation in aryl part of alkyl aryl ether was investigated (Table 2). Several different aryl groups were well tolerated regardless of their electronic properties. Halo- substituent on aryl moiety furnished the corresponding 3,3'-diaryloxindoles **2a**-**2d** in good yields and enantioselectivities (91-98% ee). It was observed that the size of the substituents on aromatic rings have a significant effect on the stereoselectivity of the process. For example, methyl substituted alkyl aryl ether reacted efficiently to afford corresponding product **2e** in 96% ee, whereas bulky ^{t}Bu substituent results into comparatively less enantioselectivity (**2f**, 81% ee). Interestingly, compound **2f** can be further enantioenriched up to 96% ee by recrystallization from ethyl acetate and hexane. However, in the case of phenyl substitution, the yield and enantioselectivity of product **2g** was unperturbed (67% yield, 93% ee). Electron-withdrawing substituents, such as cyano and acetyl groups, provided the desired products **2h** and **2i** with excellent ee; albeit, after prolonged reaction time. However, the reaction failed to give satisfactory ee when 2-naphthalenyl alkyl ether was employed under the standard reaction conditions.[12]

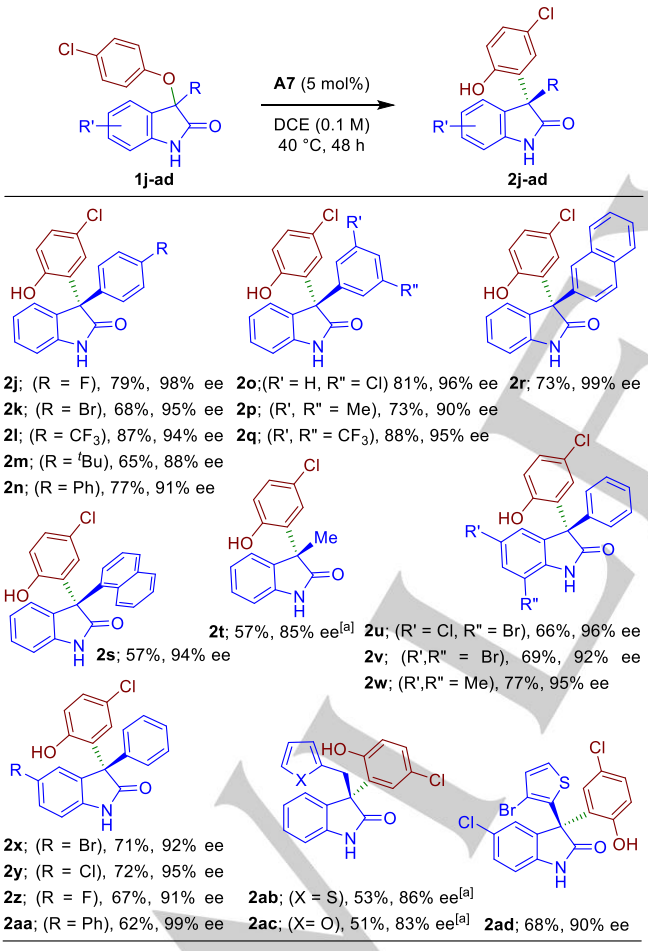
Table 2. Scope with aryl groups.[a]

entry	R	product	yield [%][b]	ee [%][c]
1	Cl	**2a**	80	91
2	Br	**2b**	72	95
3	I	**2c**	61	98
4	F	**2d**	75	96
5	Me	**2e**	79	96
6	^{t}Bu	**2f**	64	81 (96)[d]
7	Ph	**2g**	67	93
8[e]	CN	**2h**	53	86
9[e]	COMe	**2i**	58	96

[a] Reaction conditions: 0.2 mmol **1,** 5 mol% catalyst (**A7**), DCE (0.1 M), 40 °C for 48 h. [b] Isolated yields. [c] The ee values were determined by chiral-phase HPLC. [d] The values in parenthesis indicates ee after single crystallization in ethyl acetate and hexane (1:3); CCDC 1583134. [e] Reaction time 4 days.

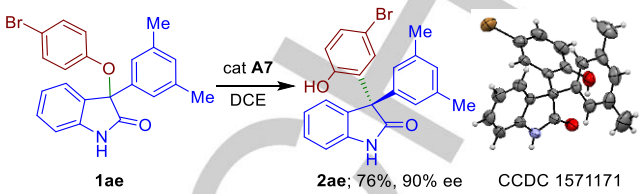
To further expand the scope of reaction, variation in alkyl group of alkyl aryl ethers was examined (Scheme 2). Accordingly, a range of variously substituted substrates were treated under standard reaction conditions. The introduction of substituents on both the 3-aryl group and oxindole core uniformly afforded products with excellent enantioselectivities.

For instance, *p*-substituted C3-aryl group bearing alkyl, aryl, halogen substituents gave corresponding 3,3'-diaryloxindoles **2j**-**2n** with good enantioselectivities (88-98% ee). Further, when *m*-substituted C3-aryl group were used as a substrate, the reaction furnished **2o**-**2q** in good yields and excellent ees. Interestingly, substrate having β-naphthyl subtituent at C3 position of oxindole produced **2r** with highest enantioselectivity (99% ee).The substrate bearing sterically bulky α-naphthyl group gave **2s** in low yield but with promising enantioselectivity (94% ee). Notably, substrate having methyl substituent at C3 position reacted slowly and resulted in the formation of **2t** with slightly lower enantioselectivity (85% ee). The scope of the reaction was further extended with a diverse set of substituents on aryl ring of oxindole core. To our delight, 3,3'-diaryloxindoles **2u**-**2aa** were obtained in decent yields and good enantioselectivities (91-99% ee). Interestingly, heteroaryl substituents is also well tolerated under the reaction conditions, furnishing **2ab**-**2ad** in 83-90% ees. Next, we demonstrated the scalability of our approach by performing the reaction on a gram scale (3 mmol of **1a**). Notably, the yield and ee remained unaffected and the product **2a** was isolated in 82% yield and 91% ee.[12]



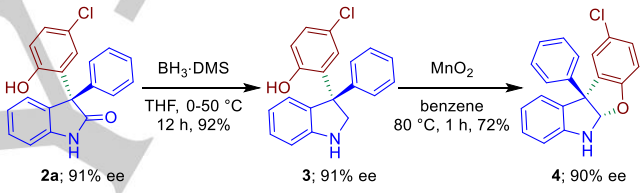
Scheme 2. Scope with alkyl groups. Reaction conditions: 0.2 mmol **1,** 5 mol% catalyst (**A7**), DCE (0.1 M), 40 °C for 48 h. [a] Reaction time 4 days.

Similarly, alkyl aryl ether **1ae** under optimized reaction conditions produced crystalline 3,3'-diaryloxindole **2ae** in 76% yield and 90% ee (Scheme 3). The absolute configuration of the product **2ae** was determined by x-ray crystallographic analysis and that of other products was assigned by analogy. In addition, DFT studies also indicated that the *re*-face addition of nucleophillic species is kinetically preferred over the *si*-face addition by 2.1 kcal/mol (ΔG) and 0.8 kcal/mol (ΔE).[12]



Scheme 3. Determination of absolute configuration

As a preliminary investigation on the application of this methodology, we demonstrated enantioselective synthesis of benzofuroindoline core **4** (Scheme 4). Initial attempts for reductive cyclization[17] of **2a** was failed to produce benzofuroindoline **4**. Instead, over-reduction product **3** was detected at higher temperature. When 3,3'-diarylindoline (**3**) was treated with excess of MnO_2 in benzene at reflux, benzofuroindoline **4** was obtained in 72% yield with 90% ee. [18]



Scheme 4. Synthesis of benzofuroindoline core

Next, based on thorough survey,[3e,3f] we selected **2f** and 2**m** as a potential lead compounds for *in vitro* cytotoxicity studies. Towards this end, both enantiomers and racemic mixture of **2f** and 2**m** were tested against HeLa cell lines by an MTT assay (Figure S1).[12] The study revealed that enantiomerically pure compound **2f** and **2m** has higher cytotoxicity than racemic forms. More specifically, the study revealed that both enantiomers of **2m** showed higher inhibition compared to (±)-**2m**; while, inhibitory effect of (–)-**2f** was slightly higher than its antipod and (±)-**2f**.

In summary, we have disclosed the first catalytic enantioselective 1,3-alkyl shift in alkyl aryl ethers for the efficient synthesis of optically active 3,3'-diaryloxindoles. This reaction represents efficient and general approach for the construction of triarylmethanes with all carbon quaternary stereocenter with high optical purity. Given the importance of 3,3'-diaryloxindoles in medicinal chemistry, the method reported herein is of high importance as it provides access to hitherto unknown enantiomers whose biological investigation is highly warranted. Our preliminary result showed that pure enantiomers exhibit higher cytotoxicity than the racemic 3,3'-diaryloxindoles. Detailed investigations on the synthesis of both the enantiomers of 3,3'-diaryloxindoles and understanding their anti-proliferative activities with various cell lines is currently ongoing in our laboratories.

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Keywords: Brønsted acid • aza-*ortho*-quinone methides • rearrangement • 3,3'-diaryloxindoles • synthetic methods

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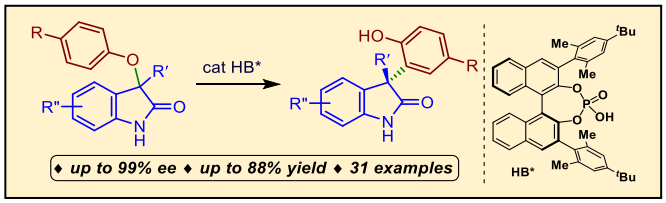

First organocatalytic asymmetric 1,3-alkyl shift in alkyl aryl ethers for the synthesis of chiral 3,3'-diaryloxindoles as triarylmethene using a chiral Brønsted acid catalyst has been reported.

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Catalytic Enantioselective 1,3-Alkyl Shift in alkyl aryl ethers: Efficient Synthesis of Optically Active 3,3'-Diaryloxindoles