Asymmetric Catalysis Hot Paper

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Catalytic Enantioselective Synthesis of Atropisomeric Biaryls: A Cation-Directed Nucleophilic Aromatic Substitution Reaction**

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Abstract: *A catalytic enantioselective nucleophilic aromatic substitution reaction which yields axially chiral biaryl derivatives in excellent yields with e.r. values of up to 97:3 has been developed. This process uses a chiral counterion to direct the addition of thiophenolate to a prochiral dichloropyrimidine by a tandem desymmetrization/kinetic resolution mechanism. The products can be derivatized to a range of atropisomeric structures without any reduction in enantioenrichment, thus offering access to unexplored chiral biaryl architectures.*

The nucleophilic aromatic substitution reaction is a benchmark transformation within the field of synthetic organic chemistry, representing a powerful method for the construction of functionalized aromatic systems.[1] Despite the significant synthetic utility of this reaction, few methods have been reported which enable the absolute stereochemical outcome of the transformation to be controlled[2,3] and to the best of our knowledge, few catalytic asymmetric variants have been disclosed. The groups of Jørgensen[4] and Maruoka[5] have elegantly demonstrated that trisubstituted enolates can be employed as nucleophiles in aromatic substitution reactions with electron-deficient aryl fluorides. Within both of these studies, the formation of the resulting quaternary stereogenic center is controlled by a chiral phase-transfer catalyst. Zhu and co-workers have carried out an asymmetric intramolecular cycloetherification reaction catalyzed by a chiral Brønsted base.[6] The product, an enantioenriched cyclophane, is rendered chiral by virtue of restricted rotation of a linker about a plane of chirality (Figure 1). Our aim was to build on these methods and develop a synthesis of atropisomeric biaryls, axially chiral compounds whose chirality originates from restricted rotation about a σ bond.[7,8] Given the central role occupied by atropisomeric materials within the fields of asymmetric catalysis and synthesis,[9] enantioselective methods for the construction of such compounds are of great value.[10] We reasoned that a chiral catalyst could effect a desymmetrizing nucleophilic aromatic substitution through discrimination in the displacement of enantiotopic leaving groups.[11,12] It was envisaged that under asymmetric phase-transfer conditions, the tight ion pair formed in a nonpolar organic solvent between a deprotonated nucleophile and a chiral cation may allow such an event to be controlled (Figure 1).[13] For such an approach to prove successful, we rationalized that the electrophile should possess 1) a plane of symmetry containing the biaryl axis, and 2) an arene which is sufficiently electron-poor to undergo a nucleophilic aromatic substitution under mild reaction conditions. With these considerations in mind, we decided to investigate a sterically encumbered dichloropyrimidine electrophile **1** (Scheme 1),[14] which was synthesized in four steps from commercially available starting materials.[15] There is significant hindrance about the biaryl axis in this substrate, and hence we believed that substitution of one of the enantiotopic chlorine atoms would yield chiral material. Pleasingly, treatment of **1** with thiophenol in the presence of KOH and tetra-*n*-butylammonium bromide afforded racemic **2** at room temperature.[16]

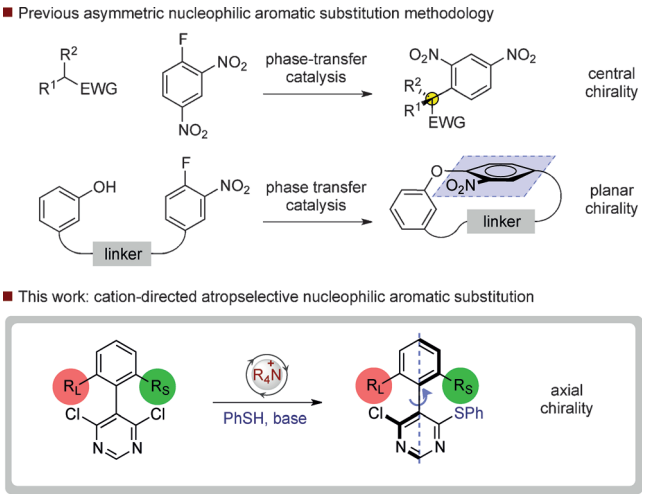
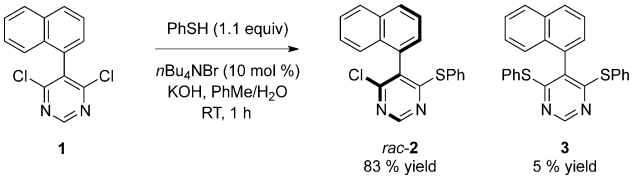


Figure 1. Previous work and strategy. EWG = electron-withdrawing group.

Furthermore, this reaction proved to be selective for single versus double addition, affording **2** and **3** in a 17:1 ratio.



Scheme 1. Racemic phase-transfer-catalyzed nucleophilic aromatic substitution reaction. Reaction conditions: **1** (1.0 equiv), PhSH (1.1 equiv), nBu$_4$NBr (10 mol %), 50% KOH (aq., w/w, 5.0 equiv), PhMe ([**1**] = 0.1 mol dm^{-3}).

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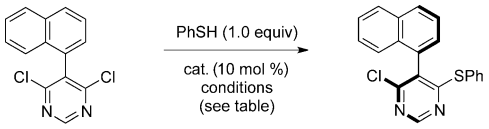
Analytical HPLC, using a chiral stationary phase, indicated that **2** was indeed atropisomeric, with no interconversion between enantiomers observed at room temperature on the HPLC timescale (Scheme 1).[17] With these initial results in hand, we turned our attention to the asymmetric nucleophilic aromatic substitution reaction. Gratifyingly, upon treatment of **1** with a biphasic mixture of thiophenol, *N*-benzylcinchonidinium chloride **4**, and aqueous potassium carbonate in toluene we obtained **2** in a moderate, but promising 58:42 e.r. (Table 1, entry 1). We next probed the efficacy of the catalysts **5** and **6**, derived from cinchonine and quinidine, respectively, but little impact on the degree of enantioinduction was observed (entries 2 and 3). We were therefore delighted to find that employing *N*-benzylquininium chloride **7** led to a significant improvement in enantioselectivity, affording the product **2** in 87:13 e.r. (entry 4). It is noteworthy that in these four examples (entries 1–4), the major enantiomer possesses the same absolute configuration, irrespective of which pseudoenantiomer of the catalyst is employed.

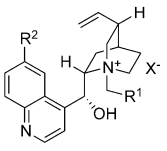
Table 1: Optimization: asymmetric nucleophilic aromatic substitution reaction.[a]



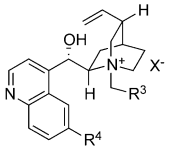
1 **2**

Entry	Catalyst	Base	e.r.[b]
1	**4**	K_2CO_3	58:42
2	**5**	K_2CO_3	61:39
3	**6**	K_2CO_3	55:45
4	**7**	K_2CO_3	87:13
5	**8**	K_2CO_3	39:61
6	**9**	K_2CO_3	46:54
7	**10**	K_2CO_3	43:57
8	**11**	K_2CO_3	43:57
9	**12**	K_2CO_3	45:55
10	**7**	Li_2CO_3	85:15
11	**7**	Cs_2CO_3	86:14
12	**7**	KOH	68:32
13[c]	**7**	K_2CO_3	36:64
14[c]	**7**	KOH	66:34
15[d]	**7**	K_2CO_3	95:5
16[d,e]	**7**	K_2CO_3	97:3

[a] Conditions: **1** (0.073 mmol), PhSH (1.0 equiv), catalyst (10 mol%), base (33% aq., w/w, 5.0 equiv), PhMe ([**1**] = 0.1 mol dm^{-3}), RT, 24 h. [b] Determined by HPLC using a chiral stationary phase. [c] Solid base (1.0 equiv) was used. [d] CCl_4 was used as the reaction solvent. [e] Used 1.1 equiv of PhSH; reaction time 48 h.



4: R^1 = Ph; R^2 = H; X = Cl
7: R^1 = Ph; R^2 = OMe; X = Cl
8: R^1 = 4-NO_2-C_6H_4; R^2 = OMe; X = Br
9: R^1 = 3,5-$(CF_3)_2$-C_6H_3; R^2 = OMe; X = Br
10: R^1 = 2,3,4-F_3-C_6H_2; R^2 = OMe; X = Br
11: R^1 = 3-Me-C_6H_4; R^2 = OMe; X = Br
12: R^1 = 2-Me-C_6H_4; R^2 = OMe; X = Br

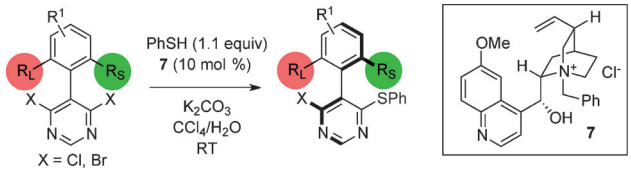


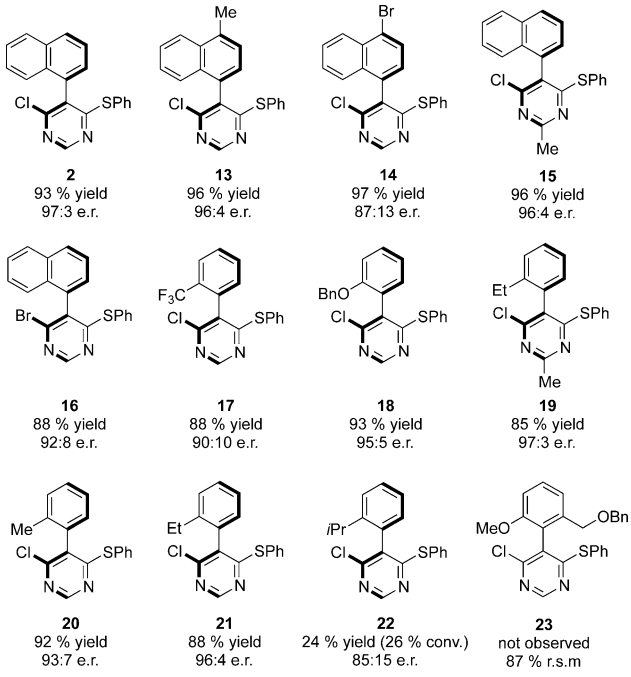
5: R^3 = Ph; R^4 = H; X = Cl
6: R^3 = Ph; R^4 = OMe; X = Cl

Variation of the steric and electronic nature of the N-pendant group of the catalyst had a significant impact upon selectivity, reversing the absolute configuration of the major enantiomeric product (relative to that for entries 1–4 in Table 1), along with significantly reduced enantioselectivities (entries 5–9). A range of aqueous carbonate bases proved equally effective at promoting the reaction, although aqueous hydroxide and solid bases generated **2** with inferior stereoselectivity (entries 10–14). The use of carbon tetrachloride, which has previously been demonstrated to be an effective solvent for asymmetric phase-transfer-catalyzed reactions of thiol nucleophiles, led to a further increase in enantioselectivity to 95:5 e.r. (entry 15).[18] We found that increasing the number of equivalents of thiophenol from 1.0 to 1.1 also led to increased enantioenrichment, affording **3** in 97:3 e.r. (entry 16).

With conditions for a highly enantioselective asymmetric nucleophilic aromatic substitution reaction established, we set out to examine the generality of the process by varying the electrophile (Table 2). Substitution of the naphthyl group in the 4-position was well tolerated in the case of a methyl group, affording **13** in 96:4 e.r., and subsequently the absolute configuration of **13** was established by X-ray crystallography.[19] When a bromine substituent was incorporated into the

Table 2: Asymmetric nucleophilic aromatic substitution reaction.[a]





2 93 % yield 97:3 e.r. | **13** 96 % yield 96:4 e.r. | **14** 97 % yield 87:13 e.r. | **15** 96 % yield 96:4 e.r.

16 88 % yield 92:8 e.r. | **17** 88 % yield 90:10 e.r. | **18** 93 % yield 95:5 e.r. | **19** 85 % yield 97:3 e.r.

20 92 % yield 93:7 e.r. | **21** 88 % yield 96:4 e.r. | **22** 24 % yield (26 % conv.) 85:15 e.r. | **23** not observed 87 % r.s.m

[a] Reaction conditions: PhSH (1.1 equiv), **7** (10 mol%), 50% K_2CO_3 (aq., w/w, 5.0 equiv), CCl_4 ([electrophile] = 0.1 mol dm^{-3}), 48 h. Yields refer to isolated materials. The e.r. value was determined by HPLC using a chiral stationary phase. r.s.m. = recovered starting material.

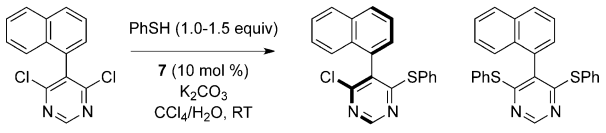
same position, the selectivity was somewhat diminished, and the product **14** was isolated in 87:13 e.r.

It was also possible to introduce a substituent onto the pyrimidine ring. A substrate with a 2-methyl group participated in the desired reaction, forming **15** in high yield with excellent enantioselectivity (Table 2). We also found that the leaving group could be varied from chlorine to bromine, affording **16** in 88% yield and 92:8 e.r. Substrates with a single *ortho*-substituted aromatic ring are also interesting synthetic targets, provided that the barrier to rotation about the aryl–aryl bond is sufficiently high to avoid racemization of the product. We synthesized a series of compounds with increasingly bulky *ortho* groups and were pleased to find that under our previously optimized reaction conditions **17**, **18**, **19**, **20**, and **21** were all formed in high yields with good to excellent enantioselectivities. The steric nature of the electrophile appears to have some impact upon reactivity. The extremely hindered *ortho*-isopropyl-substituted example **22** only reached 26% conversion after 48 hours, albeit still with good enantioselectivity. This trend continues, with more hindered 2,6-disubstituted electrophiles as exemplified by **23**, which proved unreactive under the reaction conditions. All compounds in Table 2 display a remarkably high barrier to rotation about the aryl–aryl bond. For instance, **19** racemizes in solution with a $\tau_{1/2} > 0.6$ years. A solid sample of **19** exhibited showed no racemization after several months at room temperature.[20]

During reaction optimization, we had noted that employing a slight excess of thiophenol led to increased levels of enantioselectivity. We investigated this effect further by subjecting **1** to various loadings of thiol (Table 3). A clear trend was observed: an increased excess of thiophenol led to **2** in improved enantioselectivity along with a corresponding increase in the amount of double addition product **3**.

We were interested in the origin of this effect, speculating that the excess nucleophile remaining after the first addition may preferentially scavenge the minor enantiomer of the product *ent*-**2** from the system in a kinetic resolution.[21] To test this hypothesis, we subjected *rac*-**2** to the optimized asymmetric conditions and observed 17% conversion to **3**.

Table 3: Increased thiol loading in asymmetric nucleophilic aromatic substitution reaction.[a]

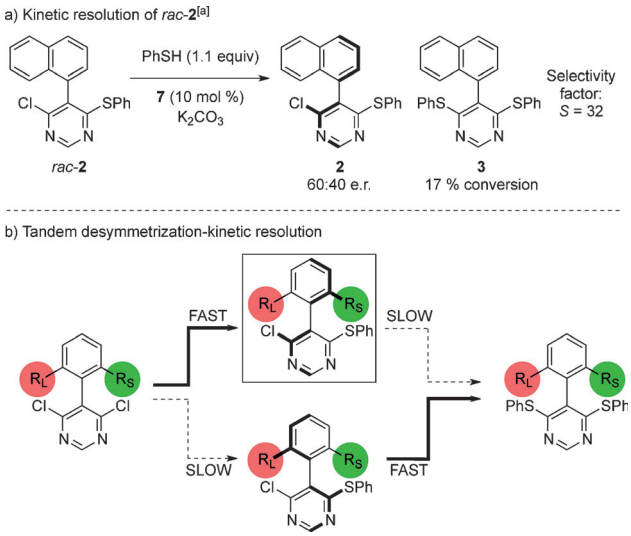


1 2 3

Entry	PhSH (equiv)	2 Yield [%]	2 e.r.	3 Yield [%]
1	1.0	98[b]	95:5	–
2	1.1	93	97:3	6
3	1.3	90	98:2	8
4	1.5	93	98:2	7

[a] Reaction conditions: **1** (0.18 mmol), PhSH, **7** (10 mol%), 50% K_2CO_3 (aq., w/w, 5.0 equiv), CCl_4 ([**1**] = 0.1 mol dm^{-3}), 48 h. Yields refer to isolated material. The e.r. value was determined by HPLC using a chiral stationary phase. [b] 94% conversion of starting material.

The starting material **2** was found to be enantioenriched (60:40 e.r.), and the major enantiomer was *R* configured, as obtained previously (Scheme 2a). This observation strongly suggests that a desymmetrization kinetic resolution effect is responsible for the enhanced enantioselectivity observed with excess thiol (Scheme 2b),[22] and is consistent with the seminal

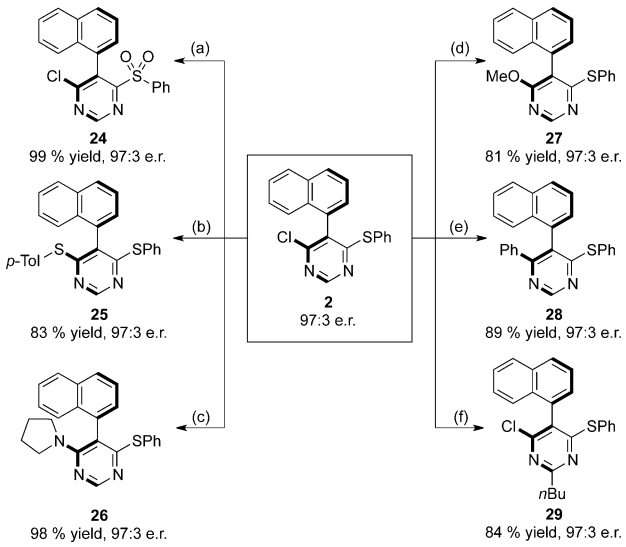


Scheme 2. Kinetic resolution. [a] Reaction conditions: *rac*-**2** (1.0 equiv), PhSH (1.1 equiv), **7** (10 mol%), 50% K_2CO_3 (aq., w/w, 5.0 equiv), CCl_4 ([*rac*-**2**] = 0.1 mol dm^{-3}), RT, 6 d. Conversion and e.r. determined by HPLC using a chiral stationary phase.

work of Hayashi et al., who observed a similar phenomenon in the transition-metal-catalyzed enantioselective desymmetrization of pro-stereogenic biaryls.[12]

To further expand the synthetic utility of the reaction, we wished to demonstrate that the products of the reaction (as exemplified by **2**) can be selectively manipulated (Scheme 3). The aryl sulfide in **2** could be oxidized with *meta*-chloroperbenzoic acid to the corresponding sulfone **24** in 99% yield with no erosion of enantiomeric purity. The products of the nucleophilic aromatic substitution reaction (**13**–**22**) contain an activated aryl chloride, which serves as a useful handle for further functionalization. A range of S, N, and O nucleophiles were able to undergo nucleophilic aromatic substitution at this position, leading to the corresponding products **25**, **26**, and **27**, with no change in enantiomeric ratio.[23] We were also able to carry out a Suzuki–Miyaura cross-coupling reaction with phenylboronic acid to afford the product **28** in 96% yield, again with no loss of stereochemical integrity. We found that organolithium reagents add selectively to the 2-position of the pyrimidine. Treatment with *n*BuLi followed by in situ oxidation with DDQ, afforded **29** in excellent yield, with no reduction in enantioenrichment.

From a mechanistic perspective, we believe that the asymmetric nucleophilic aromatic substitution reaction occurs by an interfacial process, as described by Mąkosza and Bialecka.[24] Deprotonation of the thiol at the interface followed by ion exchange with the catalyst generates a lipophilic ion pair which moves into the organic phase to react with the dichloropyrimidine. The nucleophilic substitution



Scheme 3. Derivatization of substituted products. Reaction conditions: a) *m*CPBA (5.0 equiv), CH_2Cl_2, RT, 16 h. b) *p*-thiocresol (1.3 equiv), 50% KOH (aq., w/w, 10 equiv), nBu_4NBr (10 mol%), PhMe, RT, 16 h. c) pyrrolidine (5.0 equiv), $NEtiPr_2$ (5.0 equiv), DMF, RT, 3 h. d) MeOH (5.0 equiv), $CsOH.H_2O$(s) (2.0 equiv), nBu_4NHSO_4 (10 mol%), PhMe, RT. 24 h. e) $PhB(OH)_2$ (1.5 equiv), $[Pd(PPh_3)_4]$ (10 mol%), K_2CO_3 (2.0 equiv), PhMe, 75 °C, 16 h. f) *n*BuLi (1.1 equiv), THF, −78 °C, 10 min, then H_2O, DDQ (1.1 equiv), −78 °C to RT, 5 min. DMF = *N*,*N*-dimethylformamide, *m*CPBA = *m*-chloroperbenzoic acid, THF = tetrahydrofuran.

event itself likely takes place by a two-step process involving formation and subsequent collapse of a Meisenheimer complex.[25] It is intriguing to consider whether the formation of such a complex, which possesses both a stereogenic center and axis, occurs diastereoselectively. We are currently investigating this possibility.

In conclusion, we have developed a selective and efficient approach to the asymmetric synthesis of axially chiral biaryls through a desymmetrizing nucleophilic aromatic substitution process. We have identified that the enantioselectivity of this process is reinforced by a kinetic resolution event which transforms the minor enantiomer into an achiral species. The resulting chiral biaryl products contain a second reactive aryl halide which can be readily derivatized to afford a range of new atropisomeric biaryl compounds.

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[16] Reaction of **1** with a range of N, O, and C nucleophiles proved relatively sluggish.

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[19] CCDC 1019025 (**13**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre www.ccdc.cam.ac.uk/data_request/cif. We tentatively speculate that the absolute configuration of the major enantiomer of substrates in Table 2 is the same as that for **13**. This configuration is consistent with the order of elution of the major enantiomer for **13**–**22** when using HPLC with a chiral stationary phase. However, absolute configuration of **14**–**22** cannot be unequivocally demonstrated with the data we possess.
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