

Catalytic enantioselective synthesis of atropisomeric biaryls by a cation-directed *O*-alkylation

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Abstract

Axially chiral biaryls, as exemplified by 1,1'-bi-2-naphthol (BINOL), are key components of catalysts, natural products and medicines. These materials are synthesized conventionally in enantioenriched form through metal-mediated cross coupling, *de novo* construction of an aromatic ring, point-to-axial chirality transfer or an atropselective transformation of an existing biaryl. Here, we report a highly enantioselective organocatalytic method for the synthesis of atropisomeric biaryls by a cation-directed *O*-alkylation. Treatment of racemic 1-aryl-2-tetralones with a chiral quinidine-derived ammonium salt under basic conditions in the presence of an alkylating agent leads to atropselective *O*-alkylation with e.r. up to 98:2. Oxidation with DDQ gives access to C_2 -symmetric and non-symmetric BINOL derivatives without compromising e.r. We propose that the chiral ammonium counterion differentiates between rapidly equilibrating atropisomeric enolates, leading to highly atropselective *O*-alkylation. This dynamic kinetic resolution process offers a general approach to the synthesis of enantioenriched atropisomeric materials.

Atropisomerism is a phenomenon whereby restricted rotation about a single bond leads to the formation of stereoisomers. Atropisomerism is a key feature of many natural products, drug molecules and catalysts, and is of increasing importance in all of those fields¹⁻⁴. Consequently, new methods for the enantioselective synthesis of atropisomeric compounds and especially biaryl derivatives are extremely valuable. The utility and importance of this class of stereoisomer is exemplified by 1,1'-bi-2-naphthol (BINOL), which represents a privileged architecture in synthetic chemistry. Conventionally, atropisomeric biaryls are synthesised in enantioenriched form through metal-mediated cross coupling,⁵ *de novo* construction of an aromatic ring,⁶ point-to-axial chirality transfer⁷ or an atropselective transformation of an existing biaryl (Figure 1a)⁸⁻¹¹. There are also a growing number of metal-free atropselective biaryl syntheses that span these strategic approaches¹²⁻²².

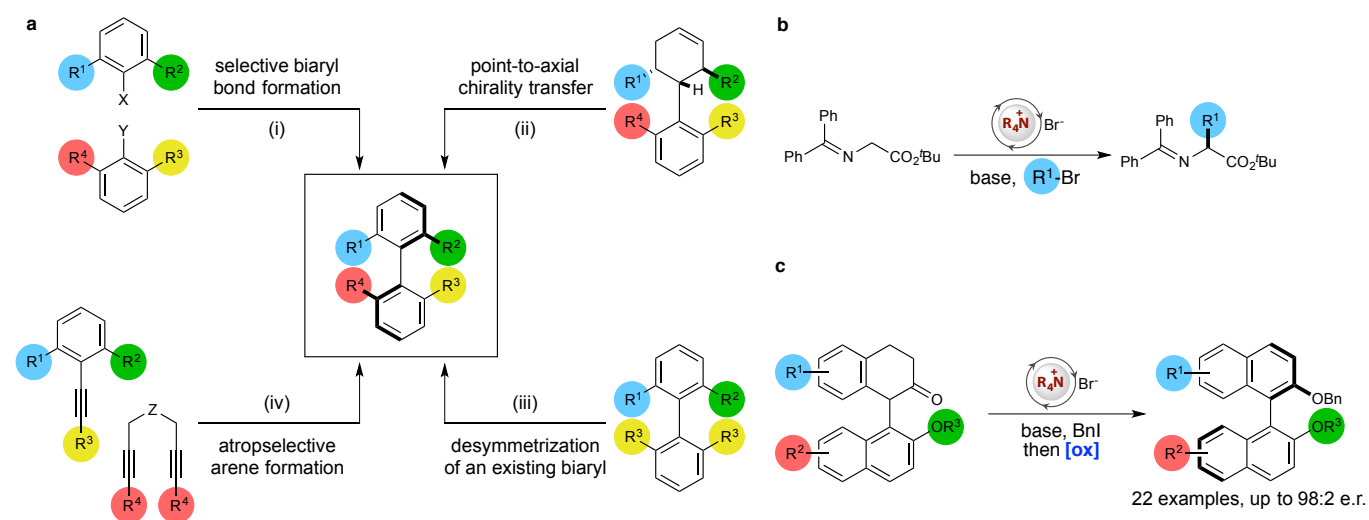
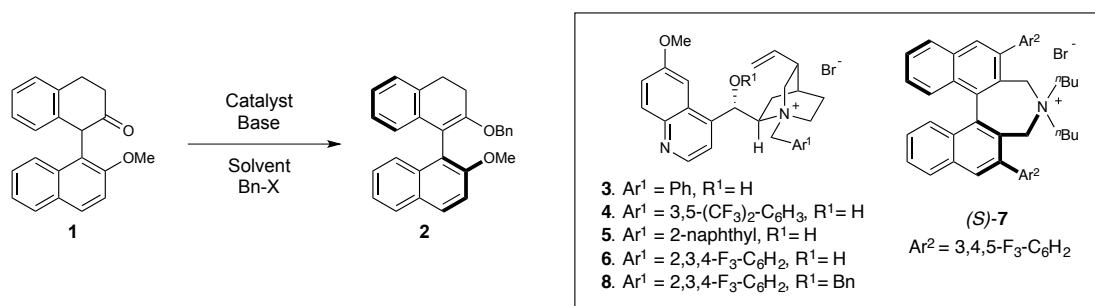


Figure 1. Strategies for the enantioselective synthesis of biaryls. **a**, Previous approaches to the enantioselective synthesis of biaryls include (i) metal-mediated cross coupling, where enantioselectivity arises in the formation of the biaryl C-C bond, (ii) point-to-axial chirality transfer, where an existing stereocentre in the molecule influences atropselectivity, (iii) atropselective transformation of an existing biaryl by desymmetrization, kinetic resolution or dynamic kinetic resolution and (iv) [2+2+2] cycloaddition, where a chiral catalyst controls the union of two fragments to generate a new aromatic ring. **b**, Previous ammonium salt catalysed amino acid synthesis by enantioselective C-alkylation of a glycine Schiff base derivative. **c**, A new approach to the enantioselective synthesis of atropisomeric biaryls by a counterion-directed *O*-alkylation.

We reasoned that a versatile method for the synthesis of BINOL derivatives could be achieved by using a chiral counterion to achieve atropselective enolate *O*-alkylation²³. Chiral counterions have been used extensively for the synthesis of amino acid derivatives though the *C*-alkylation of enolates derived from glycine Schiff base derivatives (Figure 1b)^{24,25}. We proposed that we could reverse the polarity of this transformation²⁶ and access *O*-alkylation as an alternative mode of reactivity. This could be achieved by the use of a ketone as the enolate precursor rather than an ester,²⁷⁻³⁰ and suppression of *C*-alkylation through steric hindrance. We reasoned that this principle could be applied to the atropselective alkylation of 1-aryl-2-tetralones by a dynamic kinetic resolution process,³¹ leading to an organocatalytic synthesis of enantioenriched BINOLs (Figure 1c). This has the potential to be an especially valuable process, as it would enable access to non-*C*₂-symmetrical biaryl diols. These compounds are particularly challenging to assemble, and general catalytic enantioselective methods for their synthesis are not currently available,³² despite their value as ligands and catalysts³³.

Results

A suitable 1-aryl-2-tetralone substrate to probe the potential for atropselective *O*-alkylation was prepared on a multi-gram scale in three preparative steps. This involved a cerium(III) mediated addition of the Grignard reagent derived from 1-bromo-2-methoxynaphthalene to α -tetralone, with subsequent elimination of water on acidic workup to yield a conjugated alkene. Treatment of this material with *m*-chloroperoxybenzoic acid furnished an epoxide that underwent rearrangement to the desired ketone **1** on treatment with stoichiometric BF₃·OEt₂³⁴. Ketone **1** is racemic and point chiral, but does not demonstrate restricted rotation about the C_{u-aryl} bond. With this intermediate in hand, we examined the ammonium salt catalysed *O*-alkylation reaction. We were pleased to observe that treatment of **1** with benzyl bromide in the presence of aqueous KOH and tetra-*N*-butylammonium bromide afforded racemic enol ether **2** in 96% yield with no trace of *C*-alkylation. Analytical HPLC, using a chiral stationary phase, indicated that **2** was atropisomeric, with no interconversion between enantiomers observed at room temperature on the HPLC timescale. Consequently, we turned our attention to the possibility of an enantioselective process and were pleased to observe that upon treatment of **1** in a biphasic mixture of benzyl bromide, *N*-benzylquinidinium bromide **3**, and aqueous potassium hydroxide in toluene we obtained **2** in a moderate, but promising, 60:40 e.r. (Table 1).



Cat.	Base	Solvent	Temp.	Electrophile	e.r. ^a
3	KOH (aq.)	toluene	r.t.	BnBr	60 : 40
3	CsOH (aq.)	toluene	r.t.	BnBr	73 : 27
4	CsOH (aq.)	toluene	r.t.	BnBr	80 : 20
5	CsOH (aq.)	toluene	r.t.	BnBr	83 : 17
6	CsOH (aq.)	toluene	r.t.	BnBr	88 : 12
7	CsOH (aq.)	toluene	r.t.	BnBr	53 : 47
6	K ₂ CO ₃ (s)	toluene	r.t.	BnBr	89 : 11
6	K ₃ PO ₄ (s)	toluene	r.t.	BnBr	90 : 10
6	K ₃ PO ₄ (s)	C ₆ H ₆	r.t.	BnBr	92 : 8
8	K ₃ PO ₄ (s)	C ₆ H ₆	r.t.	BnBr	66 : 34
6	K ₃ PO ₄ (s)	C ₆ H ₆	r.t.	BnI	94 : 6
6	K ₃ PO ₄ (s)	C ₆ H ₆ /CH ₂ Cl ₂ ^b	0 °C	BnI	96 : 4

Table 1. Optimization of atropselective *O*-alkylation. ^aDetermined by chiral HPLC analysis. ^bRatio of solvents is 4:1.

62 Changing the base to aqueous cesium hydroxide afforded an increase in enantioselectivity (to 73:27 e.r.). We
63 subsequently explored >30 catalysts for this transformation in combination with a range of solvents and bases; for a
64 full account of the optimization process employed, see supplementary information page 6. We particularly focused
65 on how the nature of the *N*-pendant group on the quinidine-derived catalyst could influence enantioselectivity.
66 Changing from *N*-benzyl (in **3**) to *N*-3,5-bis(trifluoromethyl)benzyl (in **4**) led to an incremental increase in
67 atropselectivity (to 80:20 e.r.), and applying 2-naphthyl derivative **5** increased selectivity further (to 83:17 e.r.). A
68 further increase in selectivity (to 88:12 e.r.) was observed when *N*-2,3,4-trifluorobenzyl containing catalyst **6** was
69 used. Assessment of the architecturally distinct phase-transfer catalyst **7**, introduced by Maruoka,³⁵ led to a
70 significant drop in enantioselectivity (53:47 e.r.) and so this class of catalyst was not investigated further. With this
71 catalyst in hand, we subsequently examined a series of base and solvent combinations, which established that an
72 increase in enantioselectivity (to 92:8 e.r.) could be attained by switching the solvent to benzene and the base to
73 solid potassium phosphate³⁶. To establish whether the free OH group in **6** was playing a role in the performance of
74 this catalyst, we generated **8** in which this functional group is capped as a benzyl ether. This catalyst delivered
75 product in significantly lower enantioselectivity (66:34 e.r.), consistent with observations from us³⁷ and others³⁸
76 that Brønsted acidic groups can play a key role in both catalytic activity and selectivity of phase transfer catalysts.
77 We finally considered whether the reactivity of the electrophile could play a role in this process, which
78 demonstrated that the use of benzyl iodide increased selectivity further (to 94:6 e.r.), which could be augmented (to
79 96:4 e.r.) by running the reaction at 0 °C using a benzene/dichloromethane solvent mixture. By employing a
80 pseudoenantiomeric quinine-derived catalyst, the opposite absolute configuration could be produced with only a
81 small drop in e.r. (4:96 e.r., see supplementary information). Using this highly enantioenriched material, we
82 decided to probe the barrier to rotation in enol ether **2** by refluxing in *m*-xylene (139 °C) and measuring the erosion
83 in e.r. over time. This demonstrated that $t_{1/2rac}$ (in solution at 139 °C) is 64 mins, which corresponds to a barrier to
84 rotation of 134 kJ mol⁻¹ at 139° C. A barrier to rotation of this magnitude is sufficiently high to essentially
85 preclude any room temperature racemization.

86 With optimized conditions for the enantioselective generation of enol ether **2** in hand, we examined its *in situ*
87 oxidation to a differentially protected BINOL. Our attempts to telescope the oxidation process directly using DDQ
88 were successful, but the process was slow and conversion was inconsistent. Consequently, we switched solvents to
89 dichloromethane for the oxidation, and under these conditions a clean reaction was observed in under two hours at
90 room temperature, leading to the synthesis of 2-*O*-methyl-2'-*O*-benzyl-BINOL **9** in 95% yield and 96:4 e.r.,
91 demonstrating that there was no erosion of e.r. during the oxidation process (Table 2).

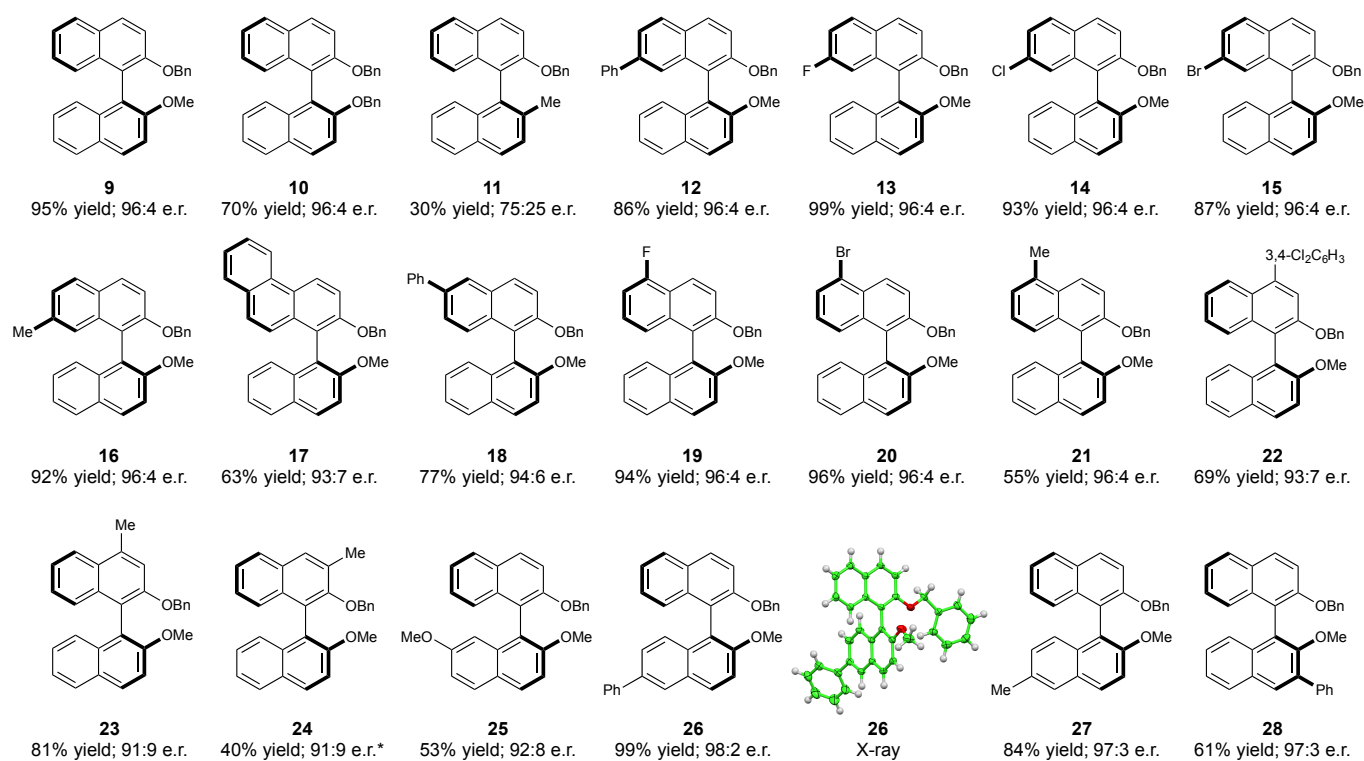
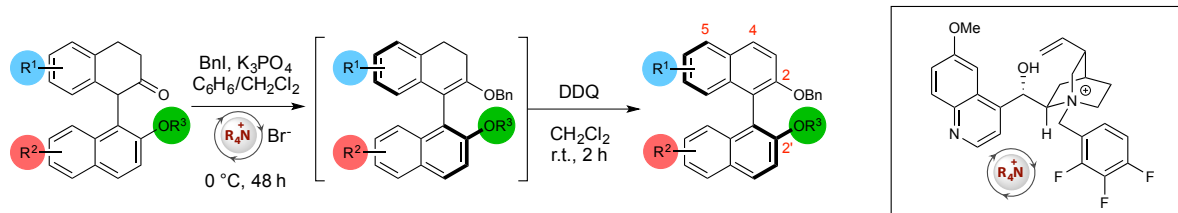


Table 2. Scope of enantioselective cation-directed O-alkylation. Reaction conditions: (i) 0.2 mmol ketone, 3 eq. BnI, 10 eq. K_3PO_4 (s), 10 mol% catalyst **6**, 4:1 C_6H_6/CH_2Cl_2 (v/v), 0 °C, 48 h; then 3 eq. DDQ, CH_2Cl_2 , 2 h. e.r. determined by chiral HPLC analysis. Yields are for isolated material and are quoted over two steps from ketone starting materials. Positions around the BINOL core are indicated with red numerals. * DDQ oxidation required 24 h.

We were able to establish that the absolute configuration of **9** is (*S*)- through comparison with both literature optical rotation and with an authentic sample prepared from (*S*)-BINOL. With an optimal procedure in hand, we assessed the scope of this catalytic enantioselective reaction. Changing the phenolic group from a methyl ether to a benzyl ether (as in **10**) did not impact on the selectivity of the overall process (70% yield and 96:4 e.r.). We were interested whether the 2' oxygen substituent was essential for reactivity and enantioselectivity, and replaced it with a methyl group. This substrate led to biaryl **11** in moderate enantioselectivity (75:25 e.r.) and only poor conversion to product (25%). This is indicative of the oxygen substituent playing an important role for both reactivity and selectivity. We subsequently examined the impact of introducing substituents in the BINOL 7-position. 7-Phenyl compound **12** was generated in 96:4 e.r. and 86% yield, implying that introducing steric bulk at this position was unlikely to be deleterious to the reaction. This was confirmed by the reaction of substrates with halogens in the 7-position, which proceeded smoothly and with high levels of enantioselectivity to afford 7-fluoro (**13**, 96:4 e.r.), 7-chloro (**14**, 96:4 e.r.) and 7-bromo derivatives (**15**, 96:4 e.r.). Introduction of an alkyl group at this position was also tolerated; 7-methyl BINOL derivative **16** was generated in 92% yield and 96:4 e.r. Exchanging one hemisphere of the BINOL core from 2-naphthol to 2-phenanthrenol (as in **17**) had only a minor impact on enantioselectivity (93:7 e.r.) but this demonstrates that the introduction of sterically demanding substituents in this position is possible. We next examined substitution in the 5-position, and were pleased to observe that halogens such as fluorine (**19**, 96:4 e.r., 94% yield), and bromine (**20**, 96:4 e.r., 96% yield) could be introduced whilst maintaining high levels of enantioselectivity and reaction yield. A 5-methyl derivative **21** was also generated in high enantiomeric purity (96:4 e.r.) and good yield. Introduction of groups in the 4-position is also possible: 4-aryl substituted compound **22** was synthesized in 93:7 e.r. and 69% yield, and 4-methyl derivative **23** was generated in

91:9 e.r. and 81% yield. Installing a substituent in the 3-position is also possible; **24** can be synthesized in 91:9 e.r. and 40% yield. The relatively low yield in this case is likely a consequence of slow reaction during the DDQ oxidation; the prolonged reactions times required to consume both diastereoisomers of the intermediate enol ether led to deleterious side reactions (see Supplementary Information page 100). Introduction of a substituent at the 7' position is possible, as demonstrated by methoxy derivative **25** (53% yield; 92:8 e.r.), and groups such as phenyl and methyl can also be introduced in the 6' position (**26**: 99% yield; 98:2 e.r. and **27**: 84% yield and 97:3 e.r.). The formation of 7' aryl derivative **26** could also be performed on a gram scale without significantly compromising yield or e.r. (96% yield, 98:2 e.r.). We were also able to crystallize **26** and confirm absolute stereochemistry through single crystal X-ray diffraction (see Supplementary Information page 122). Installation of a 3'substituent was also possible; we were able to synthesize **28** in 61% yield and 97:3 e.r.

With an enantioselective route to enol ether **2** and BINOL derivative **9** in hand, we examined whether these intermediates could be derivatized chemoselectively (Figure 2).

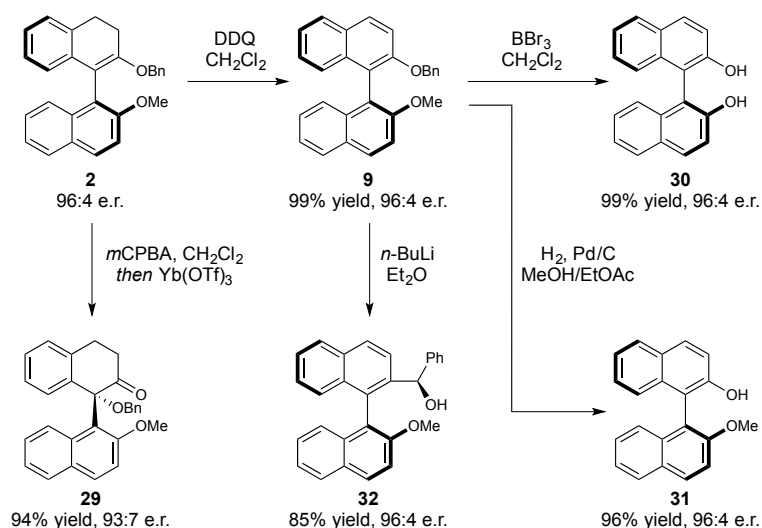


Figure 2. Chemoselective derivatization of axially chiral enol ether intermediate and BINOL products. Orthogonal functional groups lead to chemo- and stereoselective derivatization.

Axially chiral enol ether **2** (96:4 e.r.) underwent diastereoselective oxidation with *m*-chloroperoxybenzoic acid to afford an intermediate epoxide that rearranged to point chiral 1-alkoxy-2-tetralone **29** (93:7 e.r.) in the presence of catalytic ytterbium triflate. The absolute configuration of **29** was confirmed by single crystal X-ray diffraction (see supplementary information page 123). The BINOL derivative **9** could be globally dealkylated with boron tribromide to afford **30** (99% yield, 96:4 e.r.) or selectively debenzylated by hydrogenolysis in the presence of palladium on carbon yielding **31** (96% yield, 96:4 e.r.). Treatment of BINOL **9** with *n*-butyllithium in diethyl ether led to a diastereoselective [1,2]-Wittig rearrangement, affording **32** as a single diastereoisomer without compromising enantioselectivity (96:4 e.r.)³⁸.

Mechanistic considerations: a counterion-directed dynamic kinetic resolution

The reaction likely proceeds by initial interfacial deprotonation of the racemic 2-tetralone **1** with solid potassium phosphate to generate axially chiral and racemic potassium enolates (figure 2). These stereoisomeric potassium enolates can interconvert through rapid and reversible protonation and deprotonation of tetralone **1**. We expect that counterion metathesis with the chiral ammonium salt generates soluble diastereoisomeric ion pairs **33** and **34** that are alkylated at different rates to give the observed atropselectivity, with **2** as the major enantiomer (and **35** as the minor enantiomer).

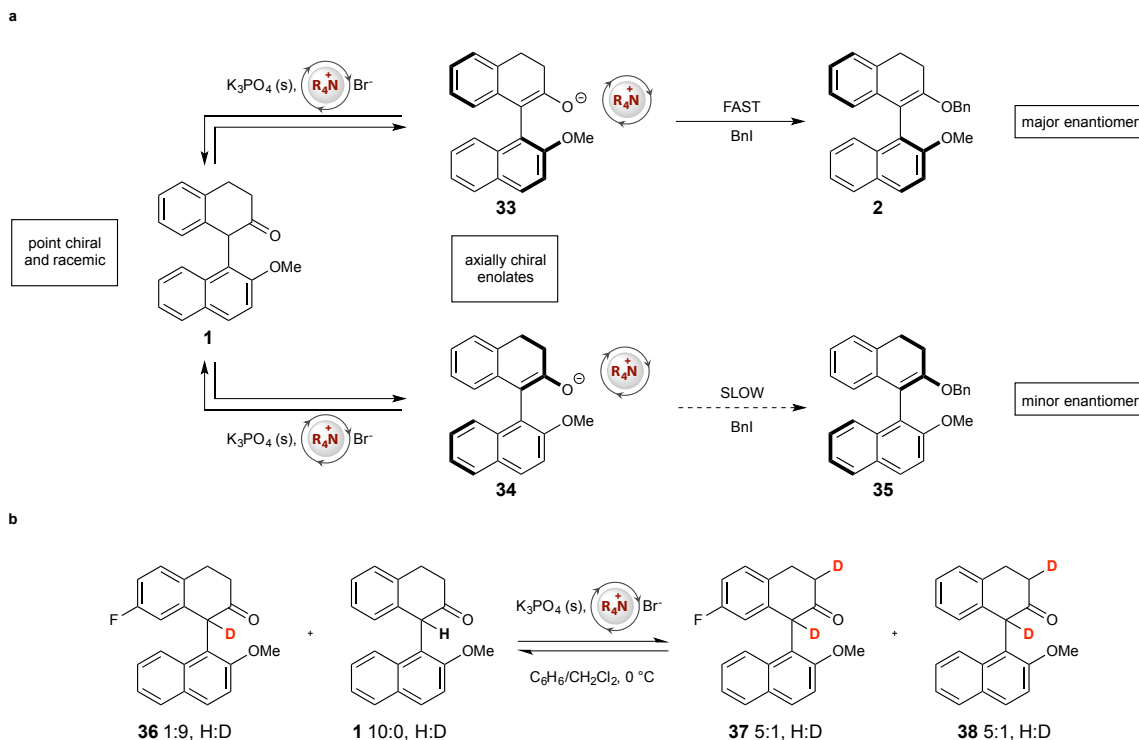


Figure 3. Proposed mechanism for observed enantioselectivity by variable rates of *O*-alkylation. **a** Rapid and reversible interconversion of the point chiral and racemic 2-tetralone to axially chiral diastereoisomeric ammonium enolates, which are then *O*-alkylated at different rates, is proposed. Biased populations of diastereoisomeric ammonium enolates **33** and **34** could be generated under these conditions. **b** Transfer of deuterium between substrates under the basic reaction conditions is consistent with enolate equilibration. Ratios for **37** and **38** reflect total deuteration across C-1 and C-3.

This selectivity could be augmented through selective transport to the solution phase of one enantiomer of the axially chiral potassium enolate by the ammonium salt to generate **33** (in a higher concentration than **34**), which is subsequently alkylated. It has been previously observed in the enantioselective alkylation of Schiff bases that the phase-transfer catalyst becomes alkylated during the reaction, and that this is the active catalytic species¹⁹. Alkylation of catalyst **6** to give **8** is slow under the reaction conditions, and the e.r. of the product is constant throughout, indicating that the active catalyst does not change during the reaction. Running the reaction at different concentrations of electrophile (over a 40-fold concentration change) does not change the enantioselectivity of the process, consistent with the rate of alkylation being slow relative to interconversion of the axially chiral enolates. To probe whether enolate equilibration occurs under the reaction conditions, we prepared deuterated compound **36** (90% D). Treatment of a 3:1 mixture of **36** and non-deuterated 2-tetralone **1** in the presence of catalyst **6** and solid potassium phosphate base led to distribution of the deuterium label across both tetralones, leading to **37** and **38**, in which deuterium is predominantly present at C-3 (see supplementary information page 120 for full details). This is consistent with reversible enolate exchange via deprotonation and protonation of tetralone starting substrates, as outlined above (Figure 3).

Conclusion

A catalytic enantioselective synthesis of non-*C*₂ symmetric atropisomeric BINOL derivatives from a chiral but racemic ketone precursor has been achieved. In this process, the chiral quinidine-derived ammonium salt likely discriminates between axially chiral enolates, leading to highly enantioselective *O*-alkylation. This dynamic kinetic resolution offers a general enantioselective organocatalytic approach to the synthesis of biaryls, and will likely find application in synthesis of a range of atropisomeric materials.

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Authorship

M.D.S., J.D.J. and R.J.A. conceived and designed the study; J.D.J. and R.J.A. performed the synthetic experiments and analyzed data for all compounds; M.D.S., J.D.J. and R.J.A. co-wrote the paper.

Data Availability

Crystallographic data for compounds **26** and **29** have been deposited with the Cambridge Crystallographic Data Centre under deposition numbers CCDC 1476066 and CCDC 1476099 respectively. These data can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif. Any relevant data not present in the manuscript or supplementary information are available from the authors.

Additional Information

Supplementary information, X-ray data (CIF) for compound **26** and **29** and chemical compound information are available in the [online version](#) of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to M.D.S.

Competing Financial Interests

The authors declare no competing financial interests.

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