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Angewandte Communications

**Counterion-Directed Catalysis**

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# Hydrogen bond enabled dynamic kinetic resolution of axially chiral amides mediated by a chiral counterion

*Alison J. Fugard, Antti S. K. Lahdenperä, Jaqueline S. J. Tan, Aroonroj Mekareeya, Robert S. Paton* & Martin D. Smith**

***Abstract**: Non-biaryl atropisomers are valuable in medicine, materials and catalysis but their enantioselective synthesis remains a challenge. Here we outline a counterion-mediated O-alkylation method for the generation of atropisomeric amides with er up to 99:1. This dynamic kinetic resolution is enabled by the observation that the rate of racemization of atropisomeric naphthamides is significantly increased by the presence of an intramolecular O-H···NCO hydrogen bond. Upon O-alkylation of the H-bond donor, the barrier to rotation is significantly increased. Quantum calculations demonstrate the intramolecular H-bond reduces the rotational barrier about the aryl-amide bond, stabilizing the planar transition state for racemization by approximately 40 kJ mol$^{-1}$, facilitating the observed dynamic kinetic resolution.*

Axially chiral molecules are of fundamental importance across a range of different fields including catalysis, medicine and materials. Biphenyl derivatives with restricted rotation about the biaryl axis have been intensively investigated since the seminal report of Kenner and Christie in 1922[1] and are exemplars of the field, both in their study and their applications. More recently, non-biaryl atropisomers including anilides, amides and imides have also been investigated,[2] amid a growing realization of the importance of these molecules in medicine[3] and other fields such as catalysis.[4] Appropriately substituted tertiary amides can possess significant barriers to rotation,[5] and this has been exploited for stereoselective *ortho*-functionalization reactions[6] and for long range stereocontrol.[7] Several approaches to the catalytic enantioselective synthesis of atropisomeric amides have been disclosed including metal catalysed[8] and organocatalytic methods.[9] Walsh has described an enantioselective proline-catalysed aldol reaction on a naphthamide-derived aldehyde, and Miller has demonstrated an elegant peptide catalysed atropselective bromination.[10] More recently, the Sparr group described a proline catalysed aldol-elimination procedure for the enantioselective synthesis of axially chiral aromatic amides.[11] As part of a programme focussed on the catalytic enantioselective synthesis of axially chiral molecules, we observed that the barrier to rotation of certain napthamides was dependant on the presence of a hydrogen bond donor proximal to the amide group (Figure 1). Napthamide **1**, which bears a 2-hydroxy group, has a barrier to rotation about the $C_{aryl}$-$C_{amide}$ bond of 97.5 kJ mol$^{-1}$ at 298K in $CH_2Cl_2$ solution, which is close to the boundary for atropisomerism as defined by Oki.[12] In contrast, amide **2**, in which the 2-naphthol is derivatized as a benzyl ether, has a significantly higher barrier to rotation of 129.3 kJ mol$^{-1}$ (394K in *m*-xylene), which is sufficient to essentially preclude rotation at ambient temperature. As the steric difference between an OH group and OBn group is too small to explain this

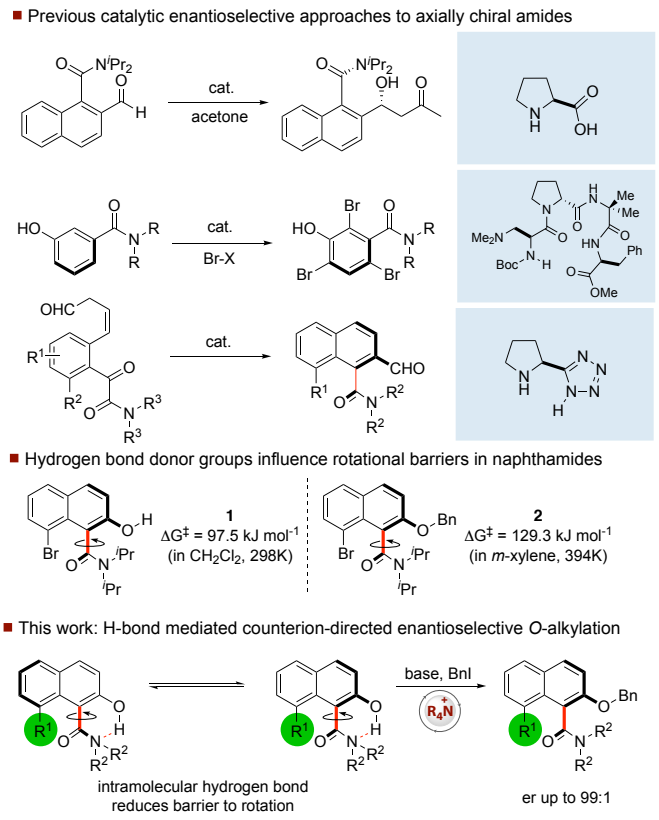


**Figure 1.** Previous work and approach to DKR of atropisomeric naphthamides

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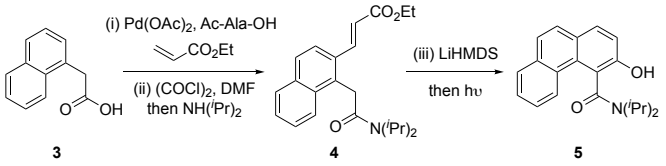
observation, we postulated that the difference in rotational barrier was likely due to the presence of an intramolecular hydrogen bond between the naphthol OH and the amide nitrogen. In principle, this could stabilize the planar transition state for interconversion of the two enantiomeric forms.[13] To probe this, we also determined the barrier to rotation of **1** about the $C_{aryl}$-$C_{amide}$ bond in isopropanol, as a hydrogen bonding solvent. The measured barrier was 113.6 kJ mol$^{-1}$ (298K), a significant increase versus the barrier in $CH_2Cl_2$. This is consistent with solvation of the phenolic group leading to disruption of the intramolecular hydrogen bond and an overall increase in size.[14] We reasoned that the presence of this hydrogen bond offered an opportunity to carry out an enantioselective synthesis of axially chiral amides via atropselective *O*-functionalization.[15,16] In this scenario, the increased barrier to rotation of *O*-functionalized materials precludes room temperature racemization and enables a dynamic kinetic resolution. To probe the feasibility of this procedure we needed access to a model atropisomeric amide, and this was synthesized through a three-step procedure from cheap and readily available 1-naphthylacetic acid using a key photo-mediated Dieckmann condensation (Scheme 1).

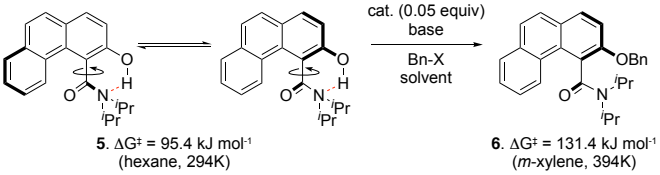



**Scheme 1.** Synthesis of atropisomeric amides. Reaction conditions: (i) $Pd(OAc)_2$ (0.1 equiv.), Ac-Ala-OH (0.2 equiv.), ethyl acrylate (2.0 equiv.), $KHCO_3$ (2.0 equiv.), 2-methyl butan-2-ol, 90˚C. (ii) $(COCl)_2$ (2.0 equiv.), DMF (0.1 equiv.), $CH_2Cl_2$; then $NH(^iPr)_2$ (2 equiv.). (iii) LiHMDS, (2.1 equiv.), THF, 0˚C, 5 mins; then 12 W blue LED, RT, 30 mins. Yields are for isolated and purified materials.

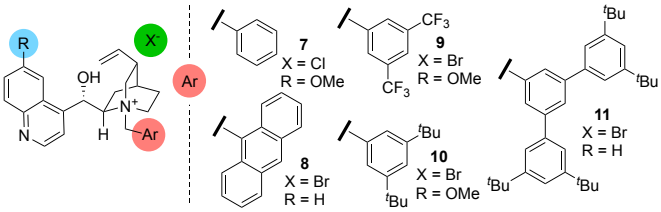
A palladium(II) mediated oxidative Heck reaction using the method disclosed by Yu[17] enabled selective C-2 functionalization of **3** in 92% yield, and this was transformed into amide **4** via the intermediacy of an acid chloride in 63% yield. The alkene in **4** is incorrectly configured for the Dieckmann reaction, but we reasoned that a cascade energy transfer[18] isomerization-cyclization process could be effective.[19] Treatment of **4** with 2.1 equivalents LiHMDS in THF followed by irradiation with blue LED light afforded 2-naphthol **5** in 77% yield. This is a scalable and operationally simple procedure and demonstrates the compatibility of visible light isomerization with strong anionic bases.

With this material in hand we examined the catalytic enantioselective *O*-alkylation of **5** with a range of different conditions and ammonium salts (table 1).[20] Upon exposure of **5** to tetrabutylammonium bromide (TBAB) and 50% aqueous cesium carbonate in toluene at room temperature, we observed *O*-alkylation to afford **6**. Use of *N*-benzyl quininium chloride **7** and aqueous cesium carbonate gave good conversion to the desired product with er of 77:23 (Table 1, entry 1), and we subsequently explored a range of different *N*-aryl groups on this catalyst scaffold. *N*-Anthracenylmethyl catalyst **8** was less selective (72:28 er) but bistrifluoromethylaryl catalyst **9** afforded augmented er (82:18). Based on this, we explored the effect of substitution in the 3- and 5-positions on the aryl ring. 3,5-Bis-*tert*-butyl catalyst **10** was incrementally more selective, which may reflect increased solubility in the organic phase. To explore this further, catalyst **11**, which bears three aryl groups and four *tert*-butyl groups was evaluated; this afforded *O*-benzylated product **6** with 83:17 er (Table 1, entry 5).

**Table 1.** Optimization: atropselective *O*-alkylation of naphthamides[a]




| Entry | Cat. | Base[b] | Solvent | Bn-X | er[c] |
|---|---|---|---|---|---|
| 1 | **7** | $Cs_2CO_3$ (50% aq.) | toluene | BnBr | 77:23 |
| 2 | **8** | $Cs_2CO_3$ (50% aq.) | toluene | BnBr | 72:28 |
| 3 | **9** | $Cs_2CO_3$ (50% aq.) | toluene | BnBr | 82:18 |
| 4 | **10** | $Cs_2CO_3$ (50% aq.) | toluene | BnBr | 87:13 |
| 5 | **11** | $Cs_2CO_3$ (50% aq.) | toluene | BnBr | 83:17 |
| 6 | **11** | KF (25% aq.) | toluene | BnBr | 93:7 |
| 7 | **11** | KF (25% aq.) | benzene | BnBr | 94:6 |
| 8 | **11** | KF (25% aq.) | benzene | BnI | 95:5 |
| 9 | **11** | $Cs_2CO_3$ (50% aq.) | benzene | BnI | 96:4[d] |
| 10 | **11** | $Cs_2CO_3$ (50% aq.) | benzene | BnI | 97:3[e] |




[a] Conditions: substrate **5** (0.02 mmol), catalyst (0.1 equiv.), base (1.0 equiv.), solvent ([substrate] = 0.1 mol dm$^{-3}$), rt, 48 h. [b] base: 50 % aq., w/w (10.0 equiv.) [c] er determined by chiral stationary phase HPLC. [d] [substrate] = 0.025 mol dm$^{-3}$. [e] [substrate] = 0.01 mol dm$^{-3}$.

A change of base to KF afforded higher er with catalyst **11** (93:7, entry 6); screening solvents demonstrated that KF in benzene could lead to significantly higher enantioselectivity (er 94:6, entry 7), and a switch to benzyl iodide as electrophile continued the aggregation of marginal gains (to 95:5 er). We reasoned that slowing the rate of alkylation vs the rate of racemisation of the substrate through dilution could also be effective; ultimately this led to an increase in selectivity to 97:3 er (entry 10). With optimized conditions for the *O*-alkylation established, we examined the scope of the reaction (Table 2). Clayden has demonstrated that 1- and 8-substituted naphthamides can be axially chiral, and we focussed on variations in these positions.[21] Substrate **5** can be *O*-alkylated to afford **6** in 93% yield and 97:3 er. Changing the *N*-alkyl group from *iso*-propyl to cyclohexyl as in **12** is well tolerated (87% yield, 98:2 er).[22] Substituting the 4-position of the phenanthrenyl system with a methyl group as in **13** maintained selectivity (at 97:3 er and 83% yield). 8-Substituted naphthyl systems are also well tolerated: substrates bearing electron donating substituents such as 8-methoxy (**14**, 96:4 er, 80% yield), 8-methyl (**15**, 98:2 er, 72% yield) and 5,8-dimethyl (**16**, 99:1 er and 85% yield)

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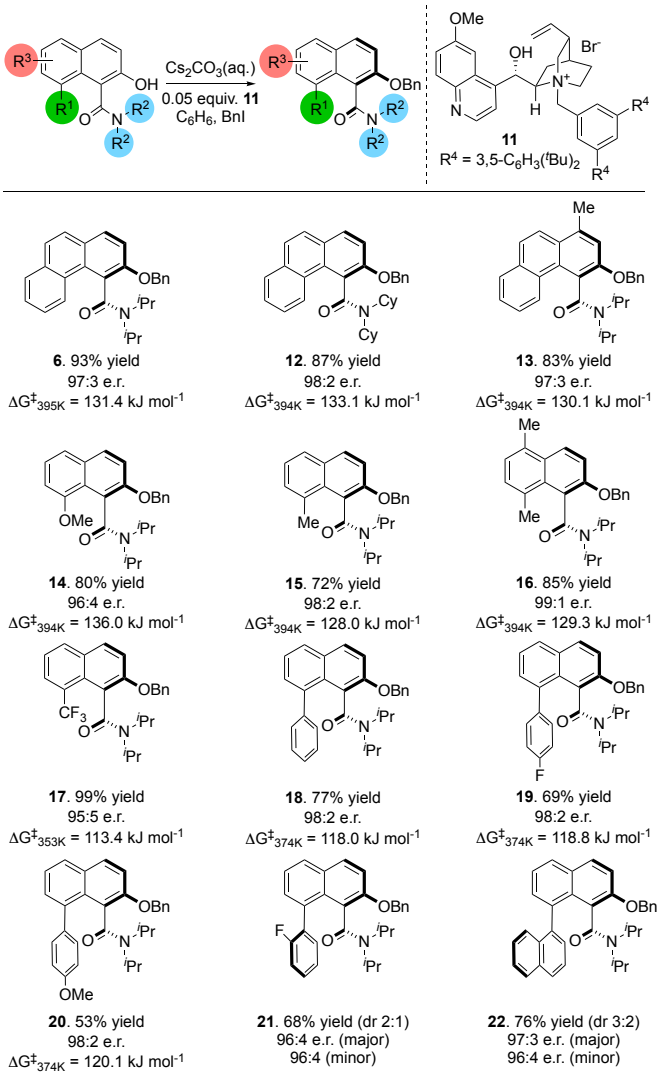
are all alkylated in good enantioselectivities and yields throughout. Substrates bearing electron withdrawing groups such as 8-trifluoromethyl (**17**, 96:4, 99% yield) are also *O*-alkylated in high enantioselectivity. 8-Aryl systems such as **18** (98:2 er, 77% yield) are similarly tolerated with high yield and high enantioselectivity. Substitution on this arene is also possible and substrates bearing *para*-electron withdrawing groups such as fluorine (**19**, 69% yield, 98:2 er) and electron donating groups such as methoxy (**20**, 53% yield, 98:2 er) are also accommodated well.

**Table 2.** Enantioselective *O*-alkylation of axially chiral amides[a]

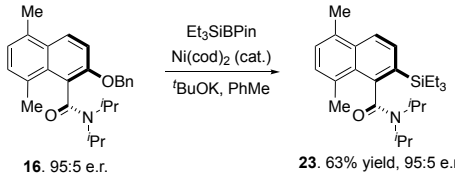



[a] Conditions: substrate (0.1-0.2 mmol), catalyst (0.05 equiv.) $Cs_2CO_3$ (50% aq., 5.0 equiv.), solvent ([substrate] = 0.01 mol $dm^{-3}$), rt, 48 h. er determined by chiral stationary phase HPLC. Yields are for isolated and purified materials. Rotational barriers measured in *m*-xylene, at temperature stated; see SI for full details.

The ability to incorporate substituents in the *ortho*-position on this arene also enables the generation of compounds that possess multiple rotational axes.[23] The *ortho*-fluoro substituent in **21** restricts rotation about the biaryl axis to close to Oki's definition,[12] so this material equilibrates relatively rapidly leading to a 2:1 diastereoisomeric mixture (96:4 er for both diastereoisomers). We also examined the *O*-alkylation of a substrate bearing a second rotational axis with a significantly higher barrier. The 8-(1-naphthyl) starting naphthol exists as a 2:1 mixture of racemic diastereoisomers. Treatment under our standard alkylation conditions led to **22**, a 3:2 mixture of diastereoisomers, in 97:3 er for the major diastereoisomer, and 96:4 er for the minor diastereoisomer. These two diastereoisomers do not interconvert at ambient temperature. The enantioselective synthesis of **21** and **22** demonstrates that the restricted rotation about the biaryl axis has little impact on the ability of the ammonium salt to effect the enantioselective *O*-alkylation.

The value of axially chiral amides is most likely to be realised in their utility as building blocks for other purposes. To this end we have demonstrated that the benzyl ether in **16** can be directly transformed to aryl silane **23** without loss of enantiopurity (Scheme 2).[24]

**Scheme 2.** Direct functionalization of benzyl ether to aryl silane[a]




[a] Conditions: substrate (0.1 mmol), $Et_3SiBPin$ (1.3 equiv.), $Ni(cod)_2$ (0.1 equiv.), $^tBuOK$ (2.2 equiv.), toluene ([substrate] = 0.1 mol $dm^{-3}$), rt, 3 h. er determined by chiral stationary phase HPLC. Yields are for isolated and purified materials.

Treatment of benzyl ether **16** with triethylsilyl pinacol borane in the presence of a nickel(0) catalyst and *tert*-butoxide afforded aryl silane **23** in 63% yield and without any erosion of er.

To probe the influence of hydrogen bonding on the rate of racemization we turned to quantum calculations. We modelled compounds **24** and **25** (which bear a dimethyl- rather than a diisopropylamide) and quantified the effect of *O*-alkylation upon the rotational barrier (Figure 2).

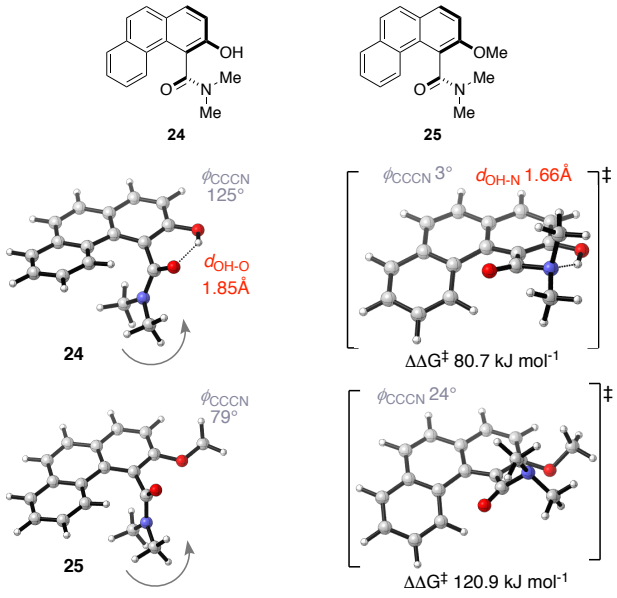



**Figure 2.** Optimized ground and transition state structures for model napthamides **24** and **25**.

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Calculations were performed at the DLPNO-CCSD(T)/def2-TZPD//M062X/6-31G(d) level, with SMD solvation for toluene and $CH_2Cl_2$. The increase in activation barrier, $\Delta\Delta G^{\ddagger}$, from *O*-alkylation of **24** is 39.7 kJ mol$^{-1}$, which compares favourably with experiment (36.0 kJ mol$^{-1}$).[25] An intramolecular OH—O H-bond (1.85Å) is present in the ground state structure of napthamide **24**. Rotation about the exocyclic C-C bond results in a transition structure with a non-planar amide. In this structure, the pyramidalized nitrogen atom is in very close contact with the hydroxyl proton (1.66 Å). In the absence of a free naphthol, rotation proceeds *via* a transition structure in which the non-planar amide cannot be similarly stabilized. Amide pyramidalization (a consequence of steric demands) enhances the nitrogen atom's hydrogen-bond basicity, leading to a *stronger* hydrogen bond in the transition structure than in the ground state, and contributes to a pronounced reduction in barrier height.

In conclusion we have developed a highly enantioselective route to axially chiral napthamides. This approach relies on a transition-state hydrogen bond to mediate substrate racemization that enables a dynamic kinetic resolution via *O*-alkylation. These molecules may find application in supramolecular chemistry, catalysis and medicinal chemistry programmes.

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### Conflict of Interest

The authors declare no conflict of interest.

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[25] We also examined related naphthol substrates bearing 8-methoxy and 8-trifluoromethyl substituents. Similar results were obtained, with even larger differences in $\Delta\Delta G^{\ddagger}$ predicted (51.5 and 44.1 kJ mol$^{-1}$, respectively). See SI for full details.

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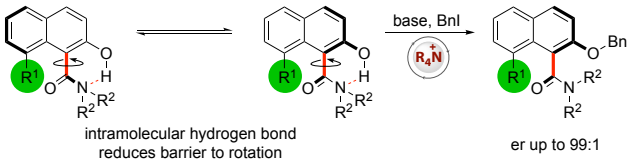


Non-biaryl atropisomers are valuable in medicine, materials and catalysis but their enantioselective synthesis remains a challenge. Here we outline a counterion-mediated *O*-alkylation method for the generation of atropisomeric amides with er up to 99:1. This dynamic kinetic resolution is enabled by the observation that the rate of racemization of atropisomeric naphthamides is significantly increased by the presence of an intramolecular O-H···NCO hydrogen bond. Upon *O*-alkylation of the H-bond donor, the barrier to rotation is significantly increased. Quantum calculations demonstrate the intramolecular H-bond reduces the rotational barrier about the aryl-amide bond, stabilizing the planar transition state for racemization by approximately. 40 kJ $mol^{-1}$, facilitating the observed dynamic kinetic resolution.