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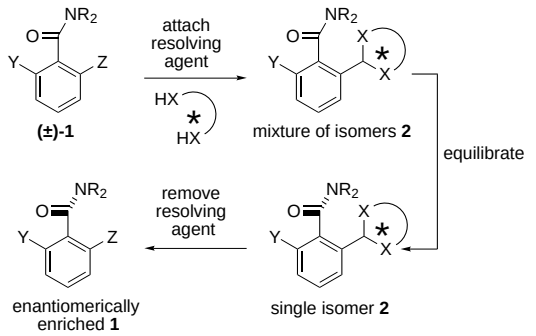
Enantioselective Synthesis of Atropisomeric Amides by Dynamic Resolution: Thermodynamic Control with a Proline-Derived Diamine Resolving Agent**

Jonathan Clayden* and Lai Wah Lai

Enantiomerically pure atropisomers, widely used as chiral ligands for metal-promoted asymmetric reactions, have generally been obtained for practical purposes by resolution and not by enantioselective synthesis.[1, 2] While there are a number of useful enantioselective routes to atropisomeric biaryls,[3] the enantioselective synthesis of non-biaryl atropisomers[4] is an unexplored area. Enantiomerically pure anilides have been derived from the chiral pool,[5, 6] and other enantiomerically pure non-biaryl atropisomers have been resolved—classically,[7, 8] by chromatography on a chiral stationary phase,[9–11] or kinetically.[12, 13] The only truly enantioselective synthesis of non-biaryl atropisomers is that of Koide and Uemura,[14] who used the desymmetrization of an arene–tricarbonylchromium complex to make aromatic amides related to **1** (see Scheme 1) in enantiomerically pure form.

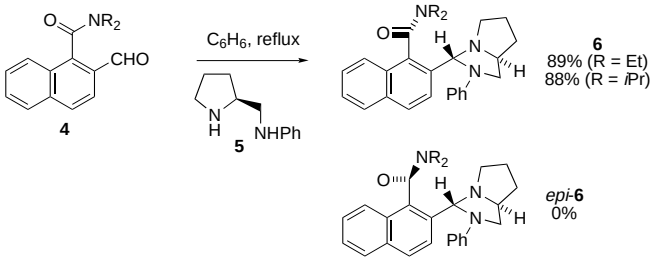
Here we describe our own enantioselective synthesis of atropisomeric aromatic amides **1**, which we have already shown to be powerful tools for the diastereoselective synthesis of racemic compounds.[15] Our strategy is outlined in Scheme 1. We aimed to start with the racemic amide (±)-**1**, to which we would attach an enantiomerically pure resolving agent to give a mixture of atropisomeric diastereoisomers **2**. We would then exploit the thermal instability of the conformation of the Ar–CO bond of **2**, equilibrating the mixture of diastereoisomers to a single isomer in a thermodynamically controlled process. The resolving agent would then be removed, leaving **1** in enantiomerically enriched form.



Scheme 1. Dynamic resolution of atropisomeric amides.

In the event, this approach proved highly successful. We chose to start with two naphthamides **4** (see Scheme 2) bearing CHO as the group Z, which led to problems later, as described below, but which allowed us to make the starting material by ortholithiation/DMF quench of the parent naphthamides.[16, 17] Furthermore, it allowed us to use, as the resolving agent, diamine **5**,[18] which is available from proline in four steps.

Refluxing **4** with **5** in benzene or toluene for 24 h gave the aminals **6** in excellent yield (Scheme 2), and quite remarkably both were formed with greater than 90:10 diastereoselectivity



Scheme 2. Atroposelective formation of aminals.

(by NMR spectroscopy). After chromatography on neutral alumina, pure diastereoisomers **6** were isolated in 88% (R = *i*Pr) and 89% yield (R = Et). The stereochemistry of **6** (R = *i*Pr) was proved by X-ray crystallography (see Figure 1).

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Since aldehydes **4** are themselves chiral, racemic compounds,[11] there are two possible explanations for the formation of the aminals as single diastereoisomers. The first is that the aminal forms initially as a mixture of diastereoisomers **6** and *epi*-**6**, but under the conditions of the reaction (which, at 80–110 °C, is warm enough to isomerize a typical 2-substituted naphthamide)[11] *epi*-**6** is epimerized to the more stable atropisomer **6**. This process would amount to a dynamic resolution of **4** under thermodynamic control. The other possibility is that a dynamic kinetic resolution is taking place: One enantiomer of the starting material gives the aminal faster than the other, and the slow-reacting enantiomer racemizes under the conditions of the reaction.[19]

To distinguish between these possibilities, we carried out the aminal-forming reaction at room temperature, simply by stirring **4** (R = *i*Pr) and **5** in C_6D_6. The reaction failed to reach completion, but the product mixture contained a 1:3 mixture of **6** and a thermally unstable compound which we identified as the atropisomer *epi*-**6**. Purified *epi*-**6** epimerized to **6** in a matter of minutes at 20 °C. The single isomers obtained in the aminal-forming reactions must therefore be due to subsequent equilibration of a first-formed mixture of atropisomers:[20] In effect we have, rather fortunately, compressed two of the steps in our strategy (Scheme 1) into one.

The X-ray crystal structure of **6** (R = *i*Pr) in Figure 1 shows that the more stable atropisomer is the one in which the phenyl ring of the auxiliary and the NR_2 lie on opposite sides

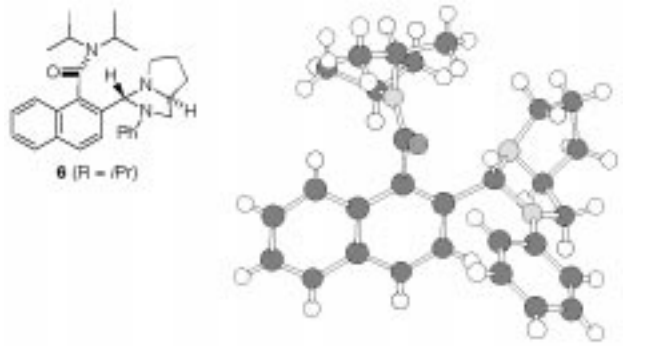
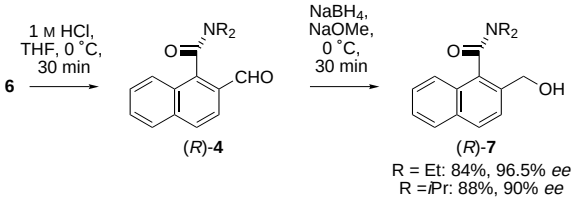


Figure 1. X-ray crystal structure of **6** (R = *i*Pr).

of the naphthalene ring. We presume that it is steric repulsion which makes one atropisomer so much more stable than the other. There are now several examples of atropisomeric amides bearing chiral *ortho* substituents which exhibit a strong thermodynamic preference for one of the two diastereoisomeric Ar–CO conformations.[11, 21]

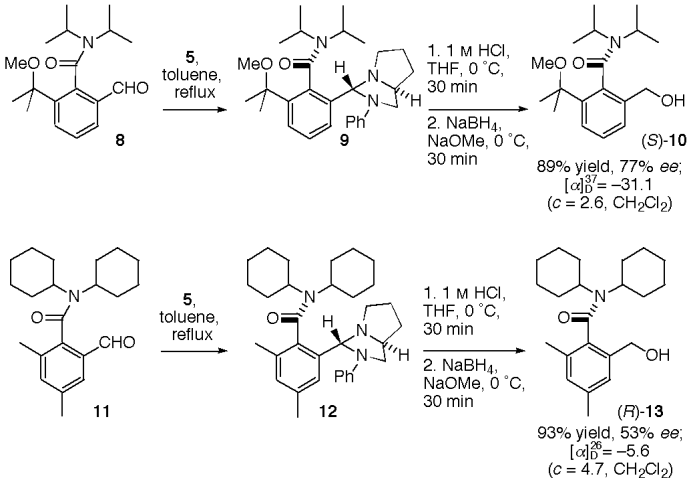
The rate of racemization of **4**, in common with other atropisomers with freely rotating trigonal blocking substituents,[11, 22] is fast: The half-life for racemization of **4** (R = *i*Pr) is only 12 min at 20 °C, or 3 h at 0 °C.[11] This poses problems for the removal of the auxiliary since hydrolyzing the aminal produces a conformationally unstable product. However, while a trigonal CHO group provides a hopeless barrier to rotation about the Ar–CO bond, a tetrahedral CH_2OH group is much more effective.[11] By carrying out the hydrolysis at 0 °C and limiting the reaction time to 30 min, we were able to retain most of the enantiomeric enrichment of the aldehydes (*R*)-**4** until they could be "fixed" by reduction to the alcohols (*R*)-**7**, still at low temperature (Scheme 3). The alcohols (*R*)-**7** are stable, chiral compounds at room temperature, and their enantiomeric excesses were determined (by



Scheme 3. In situ hydrolysis and reduction of aminals to atropisomeric alcohols. (*R*)-**7**: R = Et: $[\alpha]_D^{26} = -1.2$ ($c = 0.93$, CH_2Cl_2); R = *i*Pr: $[\alpha]_D^{26} = -10.5$ ($c = 2.3$, CH_2Cl_2).

analytical HPLC on Chiralpak-AD stationary phase) to be 90% (R = *i*Pr) and 96.5% (R = Et) after this in situ hydrolysis–reduction sequence. The overall yields of (*R*)-**7** from (±)-**4** are 77% (R = *i*Pr) and 75% (R = Et).

Not only 2-substituted naphthamides, but also unsymmetrically 2,6-disubstituted benzamides are chiral compounds.[9, 11] The synthesis of (*S*)-**10** and (*R*)-**13** from racemic aldehydes **8** and **11** (Scheme 4) demonstrates the generality of our strategy. The purified aminals **9** and **12** were hydrolyzed and reduced to alcohols (*S*)-**10** and (*R*)-**13** with 77% *ee* (NMR spectroscopy in the presence of (*R*)-2,2,2-trifluoro-1-(9-an-



Scheme 4. Enantioselective synthesis of atropisomeric benzamides.

thryl)ethanol[23]) and 53% *ee* (HPLC on Chiralpak-AD), respectively. The lower barrier to rotation about the Ar–CO bond in 2,6-disubstituted benzamides compared with their more rigid 2-substituted naphthamide counterparts[11] is reflected in the lower enantiomeric excesses observed in these reactions. The alcohol **10** lost only 20% *ee* over 24 h at 40 °C, so the loss of enantiomeric purity must have occurred at the aldehyde stage of the hydrolysis–reduction sequence.

Dynamic resolution processes allow, in principle, racemic compounds to be converted in quantitative yield into single enantiomers. The inherent conformational mobility of atropisomeric compounds makes them exceptionally suitable

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candidates for dynamic resolution, yet to our knowledge this is the first general synthesis of a class of atropisomeric compounds by a dynamic resolution using a recyclable resolving agent.

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[20] The fact that the mixture of atropisomeric aminals formed at room temperature contains more *epi*-**6** than **6** suggests that there is in fact some degree of dynamic kinetic resolution taking place during the initial formation of the aminals, ironically favoring *epi*-**6**. Stereocontrol at the aminal center is precedented: T. Mukaiyama, Y. Sakito, M. Asami, *Chem. Lett.* **1978**, 1253.
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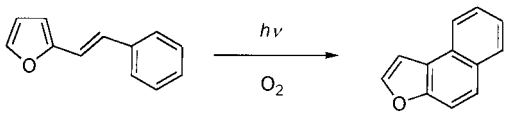
Novel Photochemical Rearrangement of Styrylfurans**

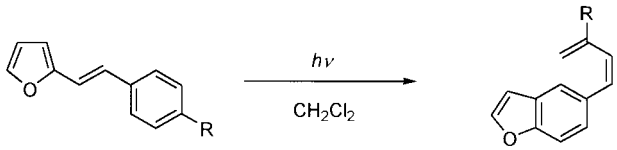
Tong-Ing Ho,* Jin-Yi Wu, and Shun-Li Wang

Rearrangement reactions are ubiquitous and they can occur both in the ground state as well as in the excited state.[1] The photochemical properties of stilbene-type compounds are well-documented[2–4] and major reactions include *cis*–*trans* isomerization, exciplex reactions, addition, and oxidative cyclization to phenanthrene. The mechanism for the oxidative cyclization involves a photochemically allowed six-electron conrotatory process to form a *trans*-dihydrophenanthrene intermediate;[4b] oxidation of this intermediate then affords the phenanthrene product. Styrylfuran is also known to undergo photochemical isomerization, and in the presence of oxygen or iodine it affords cyclized products [Eq. (1)].[5]



(1)

We have prepared several styrylfurans **1** – **11** with substituents in the *para* position of the benzene ring and now report a novel skeletal rearrangement of the styrylfurans (Scheme 1). The starting materials were prepared from 2-furaldehyde and



1 – **11** **12** – **19**

1, **12**, R = CH_3
2, **13**, R = CH_2CH_3
3, **14**, R = $CH(CH_3)_2$
4, **15**, R = $CH_2CH_2CH_3$
5, **16**, R = $C(CH_3)_3$
6, **17**, R = CH_2Ph
7, **18**, R = F
8, **19**, R = Cl
9, R = CN
10, R = NO_2
11, R = $N(CH_3)_2$

Scheme 1. Photochemical rearrangement of the styrylfuran derivatives **1** – **11**.

the corresponding benzyl chloride through a Wittig reaction. When N_2-degassed *p*-methylstyrylfuran **1** (1×10^{-2} M in CH_2Cl_2) was irradiated (350 nm) in a Rayonet reactor for 4 h the only product isolated was the 5-(3-methylbuta-1,3-dienyl)benzo[*b*]furan **12** (96% yield).[6] The presence of a 3-substituted 1,3-butadienyl group could be clearly identified

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