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Dynamically resolved *peri*-substituted 2-formyl naphthamides: a new class of atropisomeric chiral auxiliary

Jonathan Clayden,[a,*] Catherine McCarthy [a] and John G. Cumming [b]

[a] *Department of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK*
[b] *AstraZeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK*

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Abstract

2-Formyl-*N*,*N*-dialkylnaphthamides are chiral, atropisomeric compounds, provided they are substituted *peri* to the amide group. They may be obtained as single enantiomers by dynamic resolution on formation of diastereoisomeric aminal derivatives and used as chiral auxiliaries in a new addition/rearrangement strategy. Nucleophilic attack by vinyl anion equivalents in the presence of Lewis acids leads atroposelectively to single diastereoisomers of allylic alcohols, whose derivatives undergo stereospecific [3,3]-sigmatropic rearrangements. Reductive ozonolysis of the rearrangement product returns an enantiomerically pure functionalised alcohol and in principle allows recovery of the atropisomeric auxiliary.

Despite the long history of axially chiral compounds (in particular binaphthyls) as chiral ligands,[1] enantiomerically pure *non-biaryl* atropisomers have only recently found uses in asymmetric synthesis.[2] The perpendicular architecture of atropisomeric anilides, naphthamides and benzamides allows these groups to exert powerful diastereoselective control over new stereogenic centres in the racemic sense,[3,4] and recently the anilides **1** have been obtained in enantiomerically enriched form[5–8] and employed as chiral auxiliaries to asymmetric enolate alkylations and aldols,[5,6] cycloadditions[7] and iodolactonisations.[8] We[9] and others[10] have recently reported enantioselective routes to atropisomeric benzamides **2** and the related naphthamides, but uses for enantiomerically enriched atropisomeric benzamides have been confined to NADH model studies[11] and components of tachykinin NK_1 receptor agonists.[12] In this letter we describe the first use of compounds in this class as chiral auxiliaries.

To facilitate removal of the auxiliary, most chiral auxiliaries are linked to their substrates by means of an ester or amide, with the disadvantage that there are always at least three bond lengths between the source of asymmetric induction and the newly forming stereogenic centre. We have published[13] an alternative strategy (Scheme 1) in which an aldehyde **3** functions as a C–C bonded chiral auxiliary, allowing a new stereogenic centre to be formed immediately adjacent to the auxiliary's chiral influence under Felkin[14]–Anh[15] control. Diastereoselective attack by a vinyl anion equivalent **4** to give **5**, followed by

* Corresponding author.

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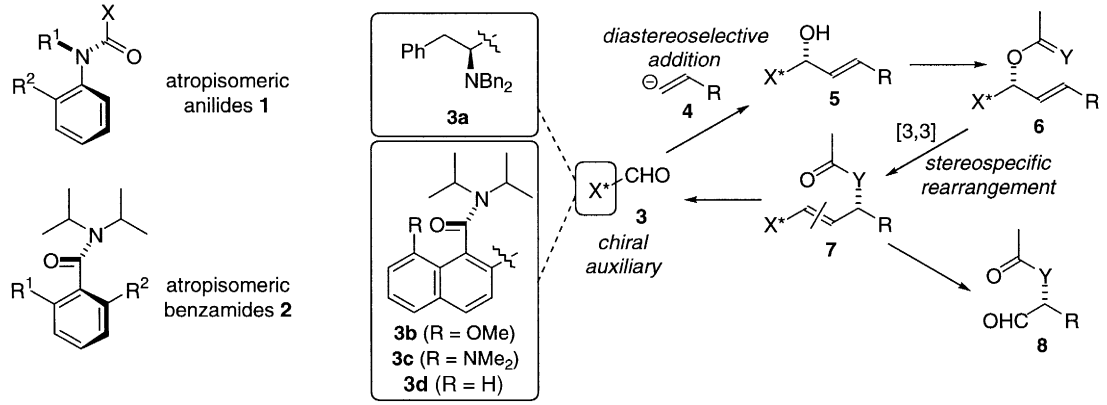
stereospecific [3,3]-sigmatropic rearrangement (or its equivalent), leads to an alkene **7** whose ozonolysis returns the aldehyde auxiliary **3** and a 2-substituted aldehyde **6** as the product.[16]



Scheme 1. The strategy

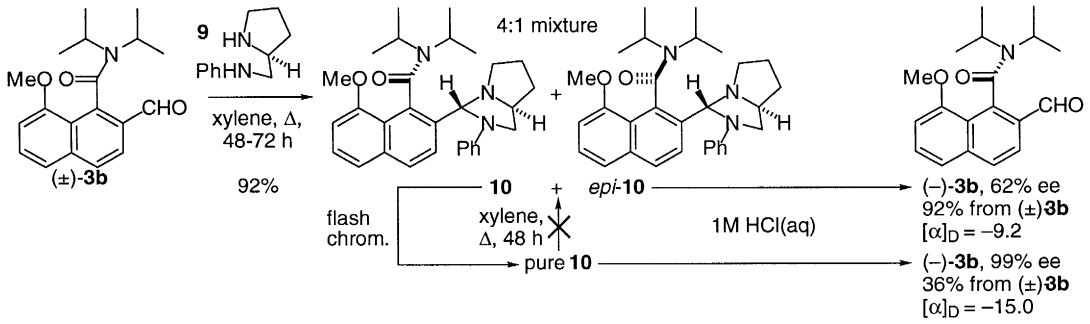
The key step is the diastereoselective addition to the aldehyde: originally, we used phenylalanine-derived **3a** because of its highly selective, non-chelation controlled reactions with organolithiums and Grignard reagents.[17] We have recently discovered[18] that, in the presence of certain Lewis acids, additions to 2-formyl-*N*,*N*-dialkyl-1-naphthamides **3d** (R=H) are among the most diastereoselective additions to aldehydes known, and we now describe the use of related compounds as chiral auxiliaries in a similar strategy.

Aldehyde **3d** (R=H) is barely atropisomeric and racemises with a half-life of only 12 min at 20°C, making it unsuitable as a chiral auxiliary.[19] However, in a recent study of *peri*-substituted naphthamides[20] we found that heteroatomic 8-substituents (R=NMe_2, OMe) provide highly effective barriers to racemisation by incipient donation into the C=O π* orbital. The half life for racemisation of **3c** (R=NMe_2) is estimated as 80 days at 20°C; that for **3b** (R=OMe) is >10 years at 20°C.[21]

We decided to use the most stable chiral aldehyde **3b** (R=OMe) as the auxiliary. It was made in racemic form in multi-gram quantities from naphthalic anhydride by a published high-yielding route,[22] and was resolved by chromatographic purification of one of a pair of diastereoisomeric aminals **10** and *epi*-**10** (Scheme 2).[23] The aminals were made by refluxing **3b** with the diamine **9** (available in four steps from proline[24]) in xylene.[9] Some interconversion of the atropisomers must have taken place during the formation of the aminal, because the two diastereoisomers **10** and *epi*-**10** were formed as a 4:1 mixture in 92% yield. Simply hydrolysing the crude mixture of aminals returned (–)-**3b** quantitatively, with 62% ee. Alternatively, **10** could be purified on basic alumina and hydrolysed (HCl, H_2O) to give the aldehyde (–)-**3b** in 99% ee and 36% overall yield from the racemate. It proved impossible to isolate a pure sample of the unstable *epi*-**10**.

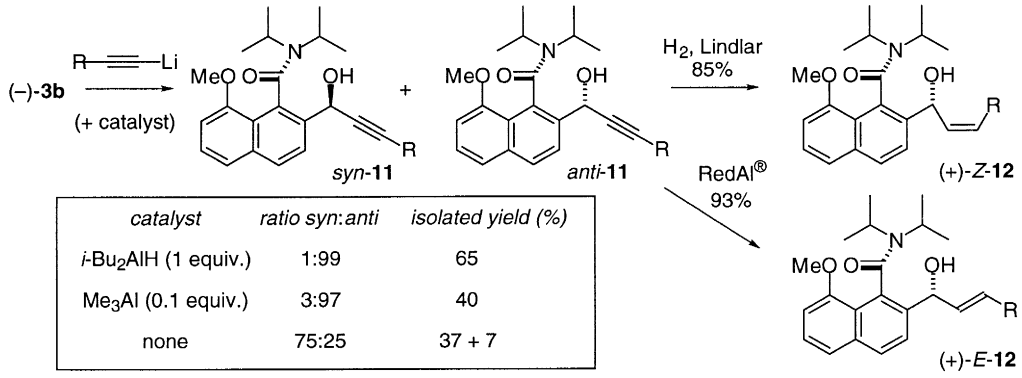
A similar, but complete, interconversion of atropisomers accompanies the formation of homologous aminals from **3b** (R=H). In that case, it is the aminal products which equilibrate, a process which amounts to a dynamic *thermodynamic* resolution. However, re-subjecting purified **10** to the conditions of the reaction gave no *epi*-**10**, so the atropisomeric enrichment of **10** in this case appears to represent instead a dynamic *kinetic* resolution of **3b**, whose racemisation at the temperature of the reaction is estimated to take place over a matter of a few hours.[21,25]

For the next step, stereoselective addition of a vinyl anion equivalent, we decided to use the strategy employed previously[13] of adding a lithiated alkyne and reducing the product to an allylic alcohol. Lithiated octyne added to (–)-**3b** to give *syn*-**11** (whose relative stereochemistry was proved by an



Scheme 2. Dynamic resolution of the aldehyde

X-ray crystal structure) relatively unselectively, but in the presence of *i*-Bu_2AlH or Me_3Al the same nucleophile gave *anti*-**11** with >97:3 selectivity (Scheme 3). Alkylaluminiums appear to coordinate to the aldehyde oxygen, fixing it *s-trans* to the amide, prevent chelation of the two carbonyls by a metal ion, and encouraging *anti*-selective nucleophilic attack.[18] The *anti* product *anti*-**11** was reduced either to the *E*-allylic alcohol (+)-*E*-**12** with RedAl® [$NaAlH_2(OCH_2CH_2OMe)_2$] or to the *Z*-allylic alcohol (+)-*Z*-**12** by hydrogenation over Lindlar's catalyst.

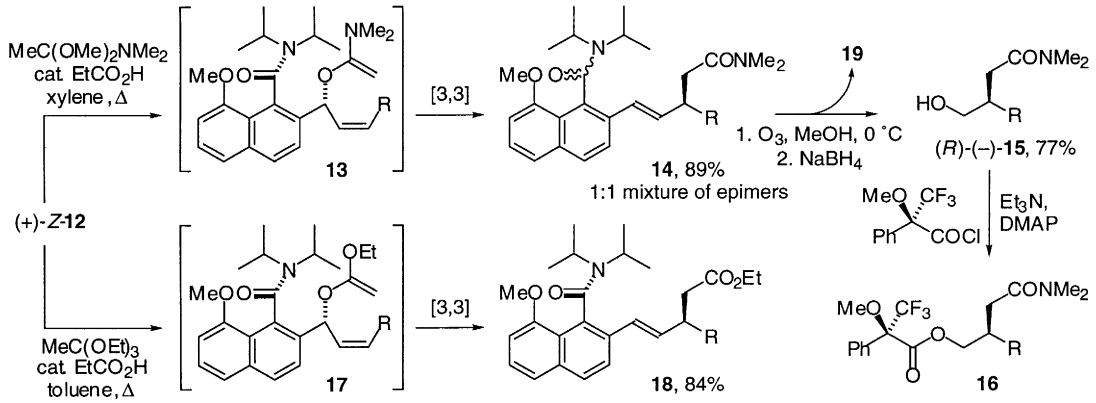


catalyst	*ratio syn*:*anti*	*isolated yield (%)*
i-Bu_2AlH (1 equiv.)	1:99	65
Me_3Al (0.1 equiv.)	3:97	40
none	75:25	37 + 7

Scheme 3. Stereoselective construction of allylic alcohols (R=*n*-hexyl)

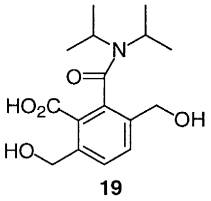
The next step in the strategy requires stereospecific allylic rearrangement of **12** to transfer stereochemistry to the stereogenic centre which will remain once the auxiliary is recovered. We chose to use two variants of the [3,3]-sigmatropic Claisen rearrangement of known stereospecificity. Allylic alcohol *Z*-**12** was heated with trimethyl orthoacetate to give the ketene acetal **17** which underwent a stereospecific Johnson–Claisen rearrangement[26] in 12 h at 110°C (Scheme 4). The product ester **18** was isolated as a single diastereoisomer in 84% yield. By contrast, Eschenmoser–Claisen rearrangement[27] of *Z*-**12** with dimethylacetamide dimethoxy acetal in refluxing xylene at 130°C for 20 h gave a mixture of epimers of the product amide **14**. The most reasonable explanation for this is that the higher temperature allows equilibration of the atropisomeric epimers, particularly in the rearranged product which has a small, trigonal substituent (a *trans* double bond) adjacent to the amide axis. The newly formed centre was nonetheless evidently formed with high stereospecificity, because ozonolysis of **14** with reductive work-up yielded an optically active alcohol (*R*)-(–)-**15** whose Mosher ester[28] **16** (formed from (+)-MTPACl) contained less than 5% of the diastereoisomer formed from the known[13] (*S*)-(+)-**15**.

Unfortunately, it proved impossible to recover the auxiliary (in its reduced form) from the ozonolysis step: the only other product turned out to be a benzamide **19** derived from further oxidation of the naphthalene's more electron-rich ring.



Scheme 4. Stereospecific rearrangements and cleavage (R=*n*-hexyl)

In summary, we have shown that atropisomeric amides may be dynamically resolved by formation of epimeric aminals, and we have illustrated their use as a new class of chiral auxiliaries by making a chiral amidoalcohol using an unusual stereoselective addition–stereospecific rearrangement strategy. In principle, a variety of 2-substituted (including 2-heterosubstituted) alcohols and aldehydes should be available using this route simply by variation of the nature of the allylic rearrangement. We would hope that optimisation of the oxidative cleavage step could also allow recovery of the auxiliary.



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Acknowledgements

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