Aldol Reactions

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Stereoselective Arene-Forming Aldol Condensation: Synthesis of Axially Chiral Aromatic Amides

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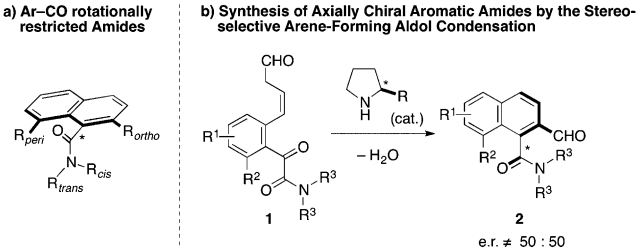
Abstract: *The increasing awareness of the importance of amide atropisomers prompts the development of novel strategies for their selective preparation. Described herein is a method for the enantioselective synthesis of atropisomeric aromatic amides by an amine-catalyzed arene-forming aldol condensation. The high reactivity of the glyoxylic amide substrates enables a remarkably efficient construction of a new aromatic ring, which proceeds within minutes at ambient temperature to afford products with excellent stereoselectivity. The high rotational barriers of the reduced products highlight the utility of this stable, spatially organized chiral scaffold.*

Aromatic amides are among the most fundamental structural entities in medicinal chemistry. Despite this pertinence, rotationally restricted aromatic amides have not been employed to their full potential, as diverse stereochemical implications are encountered upon substitution.[1] The restricted rotation about the Ar–CO, N–CO, and R–N bonds, combined with their potential interplay, contribute to the intricate conformational features of amides. Only with a detailed understanding of conformational changes and individual atropisomerization processes,[2] can the properties and the range of applications for different classes of axially chiral aromatic amides be estimated and exploited, for instance in the development of single-atropisomer drugs.[3]

The favorable structure of amide atropisomers is epitomized by naphthamides with a restricted Ar–CO bond rotation (Scheme 1 a). In the ensuing perpendicular arrangement, one side of the ring system is flanked exclusively by the carbonyl oxygen atom, while the amide residues effectively shield the other face. Pioneering studies by Clayden and coworkers demonstrated the aptitude of axially chiral amides to exert stereochemical control,[4] and chiral auxiliaries, ligands, and organocatalysts were subsequently designed based on these findings.[5]

In spite of the growing range of applications, the preparation of Ar–CO rotationally restricted amides has mainly relied on kinetic resolution, planar-to-axial chirality transfer, conglomerate crystallization, and the use of stoichiometric amounts of chiral reagents.[6] Only two strategies are reported for the synthesis of this burgeoning class of compounds by stereoselective catalysis. The group of Tanaka disclosed an elegant rhodium-catalyzed [2+2+2] cycloaddition to prepare fully substituted aromatic amides,[7] while Miller and co-workers developed an innovative tribromination of 3-hydroxyamides catalyzed by short peptides.[8]



Scheme 1. a) Structure of a Ar–CO rotationally restricted, axially chiral naphthamide. b) Stereoselective arene-forming aldol condensation to axially chiral aromatic amides: the construction of a new aromatic ring affords enantioenriched tertiary amides with a restricted rotation about the Ar–CO bond.

By considering the formation of a new aromatic ring of the *ortho*-substituted arylglyoxylic amides **1**, we became intrigued by the possibility of complementing these methods by the chiral amine-catalyzed atroposelective aldol condensation developed in our group (Scheme 1 b).[9] In particular, if the stereochemical information of the amine catalyst is transferred into the axially chiral product, the process would provide the enantioenriched aromatic amide **2** with restricted rotation about the Ar–CO bond.

To validate this notion, the naphthyl glyoxylic amide **1a** was prepared as an exploratory substrate (Scheme 2). The esterification of 2-naphtol (**3a**) with oxalyl chloride was followed by a Friedel–Crafts acylation to form naphthofurandione **4a** in 92% yield.[10] The lactone was opened with diisopropylamine[11] and a subsequent treatment with Tf_2O provided the triflate **5a** in 80% yield over two steps. After a Sonogashira cross-coupling reaction with 3-butyn-1-ol, different methods for the semi-hydrogenation were examined to prevent Z→E alkene isomerization. Palladium on charcoal, deactivated by pyridine, was found to be an optimal catalyst for the preparation of (*Z*)-**7a**, which was then oxidized with Dess–Martin periodinane (DMP). After removal of the solids from the reaction mixture, the in situ prepared **1a** in $CDCl_3$ was stable for several hours at room temperature and was used directly as a substrate for the stereoselective arene-forming aldol condensation.[12]

After treatment with excess $KHCO_3$, addition of 5.0 mol% pyrrolidinyl-tetrazole catalyst **8**[13] triggered full and selective conversion of **1a** within 60 minutes at room temperature. Analysis of the product revealed nearly complete stereoinduction, but also showed slow deterioration of

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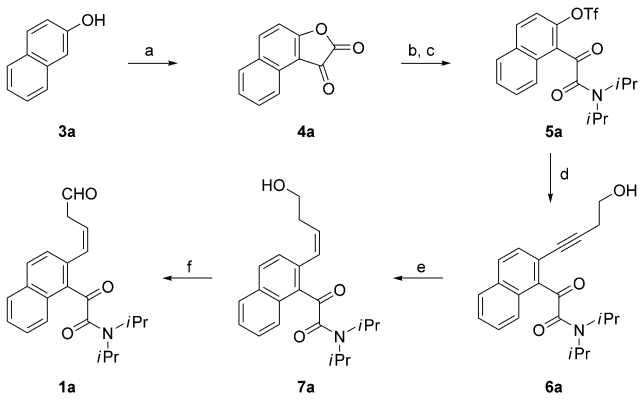


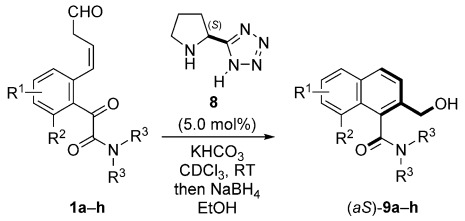
Scheme 2. Synthesis of the substrate **1a**. a) $(COCl)_2$, CH_2Cl_2, 0 °C, then $AlCl_3$, 2 h, RT, 92%; b) iPr_2NH, toluene, 16 h, RT; c) Tf_2O, Et_3N, CH_2Cl_2, 15 min, RT, 80% over two steps; d) 3-butyn-1-ol, $Pd(PPh_3)_4$, CuI, iPr_2NH, DMF, 1 h, 80 °C, 80%; e) Pd/C, H_2, pyridine, 25 min, RT; f) DMP, $CDCl_3$, 30 min, RT, 73% over two steps. The in situ prepared solution of **1a** in $CDCl_3$ was used directly for the stereoselective arene-forming aldol condensation. DMF = *N*,*N*-dimethylformamide, Tf = trifluoromethanesulfonyl.

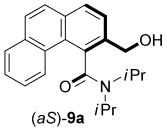
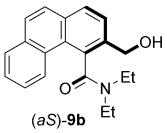
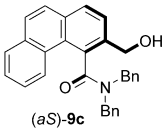
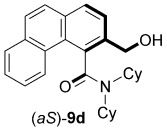
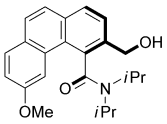
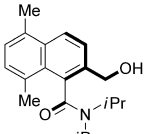
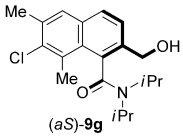
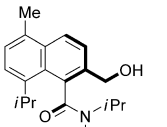
the enantiopurity upon heating. Seminal studies by the group of Clayden referred to the substantially increased barriers to rotation about the Ar–CO bond of the *ortho*-hydroxymethyl-substituted tertiary aromatic amides relative to the formyl-substituted compounds.[2c] We therefore implemented a $NaBH_4$ reduction after the atroposelective aldol condensation and the hydroxymethyl phenanthreneamide **9a** was isolated in 77% yield with a 99:1 e.r. (Table 1, entry 1).[14] As the arene formation proceeds within a short time at ambient temperature, we anticipated that the in situ reduction to configurationally more stable isolated products could expand the substrate scope of the method.

The notable efficiency of the reaction also encouraged us to investigate the minimal amount of required catalyst. At the outset of our assessment, the use of 1.0 mol% catalyst resulted in full conversion of the substrate within 2 hours at ambient temperature and an atroposelectivity of 99:1. However, incomplete conversion was observed sporadically in subsequent experiments, presumably because of catalyst deactivation pathways by small amounts of catalyst poison impurities. To maintain a facile substrate synthesis, the fully robust reaction conditions with 5.0 mol% catalyst loading were used for the remainder of the study.

To explore the range of applications for the method, the amide nitrogen substitution was varied to probe the steric interactions of the *ortho* and *peri* substituents.[15] With a smaller diethylamide substrate, the reaction rate increased and the conversion of the substrate was complete after 30 minutes (Table 1, entry 2). The product (*aS*)-**9b** was isolated in 83% yield with 97:3 stereocontrol, thus demonstrating that enantioenriched amides with primary alkyl substituents are also feasible with this procedure. We subsequently examined N-dibenzyl-substituted substrates and a similarly high reaction rate and selectivity was observed (entry 3). With cycloalkane residues, the enantioselection and catalytic performance was excellent (entry 4), and the methoxy-substituted

Table 1: Scope of the stereoselective arene-forming aldol condensation to form axially chiral aromatic amides.[a]



Entry	Product	*t*	Yield [%][b]	$[\alpha]_D$[c]	e.r.[d]
1	 (*aS*)-**9a**	1 h	77	+180.9	99:1
2	 (*aS*)-**9b**	30 min	83	+159.2	97:3
3	 (*aS*)-**9c**	30 min	78	+162.5	94:6
4	 (*aS*)-**9d**	30 min	75	+111.7	99:1
5	 (*aS*)-**9e**	30 min	68	+232.3	99:1
6	 (*aS*)-**9f**	30 min	81	+58.6	99:1
7	 (*aS*)-**9g**	2 h	57	+90.9	97:3
8	 (*aS*)-**9h**	30 min	71	+142.6	99:1

[a] The reactions were performed with 150 μmol substrate (**1a–h**) and 5.0 mol% **8** in $CDCl_3$ at RT with 30 mmolL^{-1} concentration. Reduction of the resulting arylcarbaldehydes (**2a–h**) with $NaBH_4$ in EtOH [b] Yield of the isolated products **9a–h** over two steps. [c] Measured at RT in $CHCl_3$ (*c* 1.00). [d] Determined by HPLC on a chiral stationary phase.

phenanthrene (*aS*)-**9e** could also be prepared within 30 minutes at ambient temperature with 99:1 e.r. (entry 5). We next turned our attention to the synthesis of the naphthamides **9f–h** with alkyl *peri* substituents. The transformation of the methyl-substituted phenylglyoxylic amide **1f** into the naphthamide (*aS*)-**9f** compared well to the previous conversions of naphthyl substrates into the corresponding phenanthrene products (entry 6). Contrastingly, the consumption of the chlorodimethyl-substituted substrate **1g** required 2 hours and a compromised yield was obtained (entry 7). To our delight, expedient product formation was achieved within 30 minutes with a larger isopropyl substituent at the *peri*-position, thus giving the naphthamide (*aS*)-**9h** with nearly complete stereoinduction in 71% yield (entry 8).

The optical rotation values for the phenanthrene and naphthamides were in the range of +58.6 to +232.3 and the absolute configuration was established by X-ray crystallographic analysis of (*aS*)-**9a**, (*aS*)-**9c**, and (*aS*)-**9g**.[16] In the solid state, a minimal deviation of the Ar–CO torsion angle from perpendicularity was determined (Figure 1). The exo-

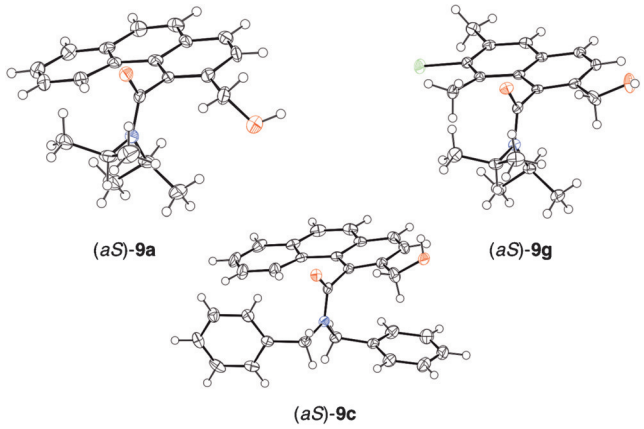


Figure 1. X-ray crystal structures of the hydroxymethyl amides (*aS*)-**9a**, (*aS*)-**9c**, and (*aS*)-**9g**, having a perpendicular arrangement of the amide and arene. Thermal ellipsoids are drawn at the 50% probability level.[16]

cyclic bond angle distortions and elongated distances between the amide and the *peri* substituents indicate that steric interactions of the parallel aligned substituents dominantly characterize the atropisomerism.[17]

The high spatial organization of the axially chiral aromatic amides is also apparent by the strong ring current effects observed in the ^{1}H NMR spectra. The signals of the amide substituents are particularly well resolved and the large shifts of up to 1.4 ppm [$\Delta\delta_{Me}$ of (*aS*)-**9a**] underscore the distinct architecture of Ar–CO rotationally restricted amides.

We next determined the configurational stability of the formyl amides **2a–h** and the corresponding hydroxymethyl derivatives **9a–h** by HPLC after thermal atropisomerization.[18] The rotational barriers of the diisopropyl, dibenzyl, and dicyclohexyl formylamides (*aS*)-**2a**,**2c–h** were in the range of 111 to 118 kJ mol^{-1} ($\Delta G^{\ddagger}_{334\,K}$), whereas that of the diethyl amide (*aS*)-**2b** amounted to 103 kJ mol^{-1} ($\Delta G^{\ddagger}_{298\,K}$) (Table 2).[18] The high enantiopurity of (*aS*)-**9b**, prepared via

Table 2: Configurational stability of the formylamides **2a–h** and hydroxymethyl amides **9a–h**.[a]

Entry	Formyl-amides **2**	$\Delta G^{\ddagger}_{334\,K}$[b] [kJ mol^{-1}]	Hydroxymethyl amides **9**	$\Delta G^{\ddagger}_{381\,K}$[c] [kJ mol^{-1}]
1	(*aS*)-**2a**	114	(*aS*)-**9a**	135
2	(*aS*)-**2b**	103[d]	(*aS*)-**9b**	131
3	(*aS*)-**2c**	116	(*aS*)-**9c**	132
4	(*aS*)-**2d**	118	(*aS*)-**9d**	140
5	(*aS*)-**2e**	112	(*aS*)-**9e**	133
6	(*aS*)-**2f**	115	(*aS*)-**9f**	135
7	(*aS*)-**2g**	111	(*aS*)-**9g**	129
8	(*aS*)-**2h**	113	(*aS*)-**9h**	131

[a] Rotational barriers determined by HPLC.[18] [b] DMP oxidation of **9** to **2**, thermal atropisomerization at 61 °C in $CDCl_3$ for more than three half-lives with $NaBH_4$ reduction of aliquots (**2** back to **9**), and HPLC measurement of the partially racemized **9** on a chiral stationary phase (Chiralcel OD-H or AD-H, *i*PrOH/ n-Hexane). [c] Heated to 108 °C in *i*BuOH. [d] Determined at 25 °C in $CDCl_3$ ($\Delta G^{\ddagger}_{298\,K}$).

intermediate (*aS*)-**2b**, illustrates the broader scope of the method obtained by combining the expeditious aldol condensation with a subsequent in situ reduction. On the other hand, the corresponding hydroxymethyl amides **9a–h** are considerably more configurationally stable ($\Delta G^{\ddagger}_{381\,K}$ = 129–140 kJ mol^{-1}) and emphasize the value of axially chiral aromatic amides as structural component.

In conclusion, we report the efficient and stereoselective synthesis of configurationally stable axially chiral aromatic amides. With optimized reaction conditions involving an in situ reduction, the substrate scope was significantly extended and the generality of the stereoselective arene-forming aldol condensation as a synthetic concept was confirmed. The high rotational barriers of the hydroxymethyl amides underline the value of tertiary aromatic amides as stable chiral scaffold. With the emergence of stereoselective catalytic methods and the increasing understanding of atropisomerization processes, we expect that the favorable architecture of axially chiral aromatic amides will be of significant utility to induce stereoselectivity, or as structural component of pharmaceuticals, agrochemicals, or functional materials. We are currently investigating the stereoselective arene-forming aldol condensation as a platform to study the atropisomerism and the diastereoselective synthesis of Ar–CO, N–CO, and R–N rotationally restricted aromatic amides.[8b,15]

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