Organocatalytic Atroposelective Aldol Condensation: Synthesis of Axially Chiral Biaryls by Arene Formation**

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Dedicated to Professor Andreas Pfaltz

Abstract: Axially chiral compounds are of significant importance in modern synthetic chemistry and particularly valuable in drug discovery and development. Nonetheless, current approaches for the preparation of pure atropisomers often prove tedious. We demonstrate here a synthetic method that efficiently transfers the stereochemical information of a secondary amine organocatalyst into the axial chirality of tri-orthosubstituted biaryls. An aromatic ring is formed during the dehydration step of the described aldol condensation cascade, leading to highly enantioenriched binaphthyl derivatives. The fundamental course of the reaction is related to the biosynthesis of aromatic polyketides.

Lyclase and aromatase proteins catalyze specific intramolecular aldol addition and dehydration reactions in aromatic polyketide biosynthesis (PKS). The acetate-derived, highly reactive poly-\beta-ketones are temporarily stabilized by PKS proteins and subsequently folded selectively into the corresponding cyclic structure to form discrete resorcinol derivatives after a dehydration step (Scheme 1a; e.g. orsellinic acid). This biocatalytic reaction cascade allows for the regulation of a striking number of polyketide natural products that participate in various biological processes.^[1] Considering this fascinating functionality, it is not surprising that analogous condensation reactions were implemented for preparative, synthetic chemistry to access aromatic compounds. In seminal work by Harris, Barrett, Yamaguchi, and others, innovative strategies for polyketide synthesis have been realized in which the intramolecular aldol addition is triggered by the formation of an enolate anion.^[2]

In this context we envisaged that the scope of application of the aldol condensation to aromatic compounds could be further extended, if the cyclization event is initiated by an alternative process, namely by formation of dienamines.^[3,4] This proposal is based on following considerations: a) the array of methods for enantioselective catalytic aldol addition

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a) Aromatic Polyketide Biosynthesis:





Scheme 1. a) Aromatic polyketide biosynthesis of orsellinic acid. CYC: cyclase, ARO: aromatase. b) Atroposelective aldol condensation to tri*ortho*-substituted biaryls catalyzed by secondary amines.

reactions by enamine activation, b) the prospect of transferring central to axial chirality during a dehydration step, and c) the large driving force and irreversibility of arene formation.^[5,6] These compelling features motivated us to undertake synthetic studies towards an organocatalytic atroposelective variant of aromatic polyketide biosynthesis.

Owing to the ideal reactivity of α -acidic aldehydes with chiral secondary amine organocatalysts, ketoaldehyde substrates that lead to axially chiral binaphthyl derivatives by an aldol condensation reaction were considered as a suitable starting point for our exploration (Scheme 1b). Archetypical poly- β -ketones exist in solution as a mixture of keto and enol tautomers. The β - and δ -keto groups were therefore replaced by an aryl and an olefin functional group to obtain a more defined synthetic model. Through the course of the reaction, the α -carbon atom is activated by dienamine formation and, as a consequence of the ortho disubstitution and the Z geometry of the olefin, positioned precisely over the keto group by the rotation depicted in Scheme 1b. An effective transfer of stereochemical information from the catalyst to the axial chirality of the product would culminate the process by giving access to enantioenriched C_1 -symmetric biaryls.

We began our studies with a modular synthesis of a model substrate precursor from readily available starting materials. The LiCl-promoted Br/Mg exchange of 1,2-dibromobenzene (1) described by Knochel was followed by the addition of

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Scheme 2. Synthesis of the substrate precursor (\pm) -4a. a) *i*PrMgBr-LiCl, THF, 1, -15 °C, then 2; b) 3-Butyn-1-ol, Cul, [Pd(PPh₃)₄], *i*Pr₂NH; c) Ni(OAc)₂·4 H₂O, NaBH₄, EtOH, H₂, then (\pm) -3a and ethylene-diamine; 73% over three steps.

1-naphthaldehyde (2; Scheme 2).^[7] A subsequent Sonogashira cross-coupling reaction with 3-butyn-1-ol and a fully Z-selective hydrogenation of (\pm) -**3a** on colloidal nickel resulted in a 73 % yield over three steps.^[8] This short reaction sequence allowed for the efficient preparation of substrate precursor(\pm)-**4a**, poised for later conversion to the ζ -ketoal-dehyde **5a** by a double oxidation process.

Oxidation using Dess-Martin periodinane (DMP) provided substrate **5a** in 91% yield (Table 1).^[9] When investigating the stability of compound **5a**, we found that the ζ -ketoaldehyde is stable as a solution in CDCl₃ over an extended period of time, but slowly decomposes in isolated form. Gratifyingly, the reaction mixture after the oxidation step was amenable to purification over poly-4-vinylpyridine to furnish **5a** as a CDCl₃ solution of high purity.

Having established the in situ generation of the substrate, we embarked on the key experiments by using privileged secondary amine catalysts (Table 1). Intriguingly, when L-proline 7 was used, the desired binaphthalene carbaldehyde (aS)-6a could be isolated and a promising enantiomeric ratio was measured (entry 1; e.r. 88:12). Product formation was also observed when MacMillan imidazolidinones 8-10 were employed. In this case, the absence of atroposelectivity suggests that competing general-base catalysis is operational (entries 2-4). Additionally, the performance of TMS-diarylprolinol catalysts 11 and 12 was assessed (entries 5 and 6). These experiments also indicated lack of stereoinduction and we therefore turned our attention to proline derivatives 13 and 14 (entries 7 and 8).^[10,11] After catalyst 13 proved inefficient, excellent atroposelectivity was achieved by employing pyrrolidinyl-tetrazole catalyst 14 (entry 8; e.r. 99:1). In quest of optimal reaction parameters, we evaluated the effect of substrate concentration and solvent mixtures. A high substrate concentration was found to be advantageous (entries 8-10), while solvent mixtures resulted in slightly lower selectivity (entries 11 and 12). However, dilution with CD₃OD had only a marginal effect on the efficiency of the process (entry 12 versus entry 8).

An indication for the configurational stability of the product was obtained by heating a solution of (aS)-**6a** (95 °C, 3 h). HPLC analysis showed an unaffected enantiomeric ratio; considerable thermal atropisomerization is therefore not expected even at elongated reaction times. Moreover, we

Table 1: In situ generation of substrate $5 a^{[a]}$ and optimization of reaction parameters of the atroposelective aldol condensation.^[b]



[a] 3.0 equiv DMP, 3.0 equiv D₂O for 14 h at RT; filtration over poly-4vinylpyridine; 91%. [b] The reactions were performed with 10 mol% **7–14** at a concentration of 40 mmol L⁻¹. [c] Determined by HPLC. [d] 10 mmol L⁻¹. [e] 5.0 mmol L⁻¹.

examined the response to increased reaction temperatures by measuring the corresponding enantioselectivity (entries 13– 16). A remarkably linear temperature dependence of stereocontrol was observed in this series of experiments. It is noteworthy that an unusually high atroposelectivity could be sustained at temperatures of up to 60 °C (entry 16; e.r. 94:6). Nonetheless, to combine enantiocontrol and practicality, we continued our investigations with reactions at room temperature.

In order to determine the optimal catalyst loading, we compared the data obtained after a reaction time of 46 h (Table 2). The highest atroposelectivity was observed at 5 and 10 mol % catalyst loading, while conversion to **6a** was similar for both cases (entries 3 and 4). The required catalyst loading

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Table 2: Influence of the catalyst loading on conversion and selectivity.^[a]

Entry	14	Conversion to $\mathbf{6a}^{[b]}$	e.r. ^[c]
1	1.0 mol%	27%	97:3
2	2.5 mol%	48 %	98:2
3	5.0 mol%	69%	99:1
4	10 mol %	71 %	99:1
5	20 mol %	87%	98:2

[a] The reactions were performed at RT and 50 mmol L^{-1} in CDCl₃ for 46 h. [b] Determined by NMR spectroscopy. [c] Determined by HPLC.

could therefore be reduced by half for the remainder of the studies.

With the optimized reaction conditions in hand, we focused on the scope and limitations of the reaction (Table 3). Binaphthalene carbaldehyde (aS)-6a was obtained in 74% yield and 99:1 atroposelectivity after 68 h reaction time (entry 1). It bears mentioning that the Z-E isomerization of the dienamine can be sufficiently prevented under these reaction conditions.^[13] The corresponding phenanthrylnaphthaldehyde (aS)-6b could also be prepared by the described method in comparable yield and excellent selectivity (entry 2; e.r. 99:1). However, substrates with substituents at the 2- or 8-position of the naphthalene moiety were not converted to the corresponding binaphthalene carbaldehydes and represent the limitations of the reaction.^[14] The electronwithdrawing propensity of the difluorophenyl group was reflected by a shorter reaction time and an improved yield, while a satisfyingly high level of stereocontrol was retained (entry 3; 89%, e.r. 98:2). This is in contrast to the reduced reaction rate and the perceivable reduction of atroposelectivity for the tetrafluoro derivative (*aS*)-6d (entry 4; e.r. 96:4). Moreover, electron-rich aryls were also efficiently annulated, albeit extended reaction times were required (entries 5 and 6). Again, a remarkable degree of stereoinduction was attained, demonstrating the generality of the method. The absolute configuration of the products was established by derivatization to known compounds and X-ray crystallographic studies. Using (S)-pyrrolidinyl-tetrazole catalyst 14, these determinations are in accordance with an (aS) configuration.^[15]

In summary, we report a novel synthetic strategy for the atroposelective preparation of unsymmetrically substituted 1,1'-binaphthalene-2-carbaldehydes. The excellent enantiocontrol of the process stems from the efficient transfer of stereochemical information of the catalyst into the axis of chirality of biaryl products. To the best of our knowledge, this is the first example of atroposelective secondary amine catalysis. Furthermore, we describe an unprecedented initiation of the aldol condensation to aromatic compounds, which are not readily accessible otherwise. The application of this strategy to other substrate classes and mechanistic investigations addressing the intricacies of the chirality transfer are currently in progress in our group and will be reported in due course.

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Table 3: Scope of the atroposelective aldol condensation under the optimized reaction conditions.^[a]



[a] The reactions were performed with 150 μ mol **5 a**–**f** and 5.0 mol% **14** at RT and 25 mmol L⁻¹ dilution. [b] Yield of isolated product. [c] Measured at RT in CHCl₃ (*c* 1.00). [d] Determined by HPLC.

Keywords: aldol reaction \cdot atropisomerism \cdot enantioselectivity \cdot organocatalysis \cdot polyketides

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a) C. Hertweck, Angew. Chem. 2009, 121, 4782-4811; Angew. Chem. Int. Ed. 2009, 48, 4688-4716; b) A. Das, C. Khosla, Acc. Chem. Res. 2009, 42, 631-639; c) J. M. Crawford, C. A. Townsend, Nat. Rev. Microbiol. 2010, 8, 879-889; d) T. P. Korman, B. Ames, S.-C. Tsai, Comprehensive Natural Products II (Eds.: L. Mander, H.-W. Liu), Elsevier, Kidlington, 2010, pp. 305-345;

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e) J. Staunton, K. J. Weissman, Nat. Prod. Rep. 2001, 18, 380-416.

- [2] a) T. M. Harris, C. M. Harris, *Tetrahedron* 1977, 33, 2159–2185;
 b) J. S. Hubbard, T. M. Harris, *J. Org. Chem.* 1981, 46, 2566–2570;
 c) T. M. Harris, C. M. Harris, *Pure Appl. Chem.* 1986, 58, 283–294;
 d) H. Miyatake-Ondozabal, A. G. M. Barrett, *Org. Lett.* 2010, 12, 5573–5575;
 e) M. Yamaguchi, T. Okuma, A. Horiguchi, C. Ikeura, T. Minami, *J. Org. Chem.* 1992, 57, 1647–1649.
- [3] For examples of enamine activation, see: a) Z. G. Hajos, D. R. Parrish, J. Org. Chem. 1974, 39, 1615-1621; b) U. Eder, G. Sauer, R. Wiechert, Angew. Chem. 1971, 83, 492-493; Angew. Chem. Int. Ed. Engl. 1971, 10, 496-497; c) B. List, R. A. Lerner, C. F. Barbas III, J. Am. Chem. Soc. 2000, 122, 2395-2396; d) A. B. Northrup, D. W. C. MacMillan, J. Am. Chem. Soc. 2002, 124, 6798-6799; e) A. Bøgevig, N. Kumaragurubaran, K. A. Jørgensen, Chem. Commun. 2002, 620-621; for intramolecular aldolizations, see: f) J. Zhou, V. Wakchaure, P. Kraft, B. List, Angew. Chem. 2008, 120, 7768-7771; Angew. Chem. Int. Ed. 2008, 47, 7656-7658; for asymmetric organocatalytic domino reactions, see: g) D. Enders, C. Grondal, M. R. M. Hüttl, Angew. Chem. 2007, 119, 1590-1601; Angew. Chem. Int. Ed. 2007, 46, 1570-1581; for asymmetric dienamine activation, see: h) M. Christmann in Asymmetric Synthesis II, More Methods and Applications (Eds.: M. Christmann, S. Bräse), Wiley-VCH, Weinheim, 2012, pp. 45-48.
- [4] For seminal mechanistic studies of organocatalytic processes, see: a) H. Mayr, S. Lakhdar, B. Maji, A. Ofial, *Beilstein J. Org. Chem.* 2012, *8*, 1458–1478; b) P. H.-Y. Cheong, C. Y. Legault, J. M. Um, N. Çelebi-Ölçüm, K. N. Houk, *Chem. Rev.* 2011, *111*, 5042–5137; c) D. Seebach, A. K. Beck, D. M. Badine, M. Limbach, A. Eschenmoser, A. M. Treasurywala, R. Hobi, W. Prikoszovich, B. Linder, *Helv. Chim. Acta* 2007, *90*, 425–471.
- [5] For examples of central-to-axial chirality transfer, see: a) A. I. Meyers, D. G. Wettlaufer, J. Am. Chem. Soc. 1984, 106, 1135–1136; b) M. Shindo, K. Koga, K. Tomioka, J. Am. Chem. Soc. 1992, 114, 8732–8733; c) T. Hattori, H. Hotta, T. Suzuki, S. Miyano, Bull. Chem. Soc. Jpn. 1993, 66, 613–622; d) F. Guo, L. C. Konkol, R. J. Thomson, J. Am. Chem. Soc. 2011, 133, 18–20.
- [6] For review articles and examples of atroposelective synthesis, see: a) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* 2005, *117*, 5518–5563; *Angew. Chem. Int. Ed.* 2005, *44*, 5384–5427; b) J. Clayden, W. J. Moran, P. J. Edwards, S. R. LaPlante, *Angew. Chem.* 2009, *121*, 6516–6520; *Angew. Chem. Int. Ed.* 2009, *48*, 6398–6401;

c) M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193–3207; d) C. Bolm, J. P. Hildebrand, K. Muñiz, N. Hermanns, *Angew. Chem.* **2001**, *113*, 3382–3407; *Angew. Chem. Int. Ed.* **2001**, *40*, 3284–3308; e) J. L. Gustafson, D. Lim, S. J. Miller, *Science* **2010**, *328*, 1251–1255; f) K. Yamaguchi, J. Yamaguchi, A. Studer, K. Itami, *Chem. Sci.* **2012**, *3*, 2165–2169; g) T. Bach, J. Schröder, K. Harms, *Tetrahedron Lett.* **1999**, *40*, 9003–9004; a Ferrier-type rearrangement via an enolate anion with a chiral guanidinium counterion to a biaryl with 12% *ee* was recently reported: h) M. Terada, K. Dan, *Chem. Commun.* **2012**, *48*, 5781–5783.

- [7] A. Krasovskiy, P. Knochel, Angew. Chem. 2004, 116, 3396–3399; Angew. Chem. Int. Ed. 2004, 43, 3333–3336: aryne formation from ortho-bromophenylmagnesiumchlorid LiCl could be sufficiently prevented by cooling the reaction mixture to -15°C.
- [8] a) C. A. Brown, V. K. Ahuja, J. Chem. Soc. Chem. Commun. 1973, 553–554; b) C. Hulot, G. Blond, J. Suffert, J. Am. Chem. Soc. 2008, 130, 5046–5047.
- [9] The addition of water significantly accelerates the Dess-Martinoxidation: S. D. Meyer, S. L. Schreiber, J. Org. Chem. 1994, 59, 7549-7552. The reaction was monitored by NMR spectroscopy.
- [10] Z. Tang, F. Jiang, L.-T. Yu, X. Cui, L.-Z. Gong, A.-Q. Mi, Y.-Z. Jiang, Y.-D. Wu, J. Am. Chem. Soc. 2003, 125, 5262-5263.
- [11] a) A. J. A. Cobb, D. M. Shaw, S. V. Ley, *Synlett* 2004, 558-560;
 D. A. Longbottom, V. Franckevičius, S. Kumarn, A. J. Oelke, V. Wascholowski, S. V. Ley, *Aldrichimica Acta* 2008, 41, 3-11;
 b) H. Torii, M. Nakadai, K. Ishihara, S. Saito, H. Yamamoto, *Angew. Chem.* 2004, 116, 2017-2020; *Angew. Chem. Int. Ed.* 2004, 43, 1983-1986; c) A. Hartikka, P. I. Arvidsson, *Tetrahedron: Asymmetry* 2004, 15, 1831-1834.
- [12] Owing to the high reactivity of substrates 5a-f, NMR spectroscopy is the method of choice for monitoring the reactions.
- [13] The conversion rate of the corresponding *E*-isomer to binaphthalene carbaldehyde (aS)-**6a** is drastically reduced.
- [14] See the Supporting Information for details.
- [15] CCDC 988866 [(-)-(aS)-**6a**] and CCDC 988867 [(-)-(aS)-**6d**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The specific rotation of (-)-(aS)-**6a** is in agreement with the literature value of the enantiomer with opposite sign.^[5b] The absolute configuration of (+)-(aS)-**6b** was determined after aldehyde reduction by NaBH₄ and comparison with the reported optical rotation value: N. Harada, T. Hattori, T. Suzuki, A. Okamura, H. Ono, S. Miyano, H. Uda, *Tetrahedron: Asymmetry* **1993**, *4*, 1789–1792.

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Communications



Organocatalytic Atroposelective Aldol Condensation: Synthesis of Axially Chiral Biaryls by Arene Formation



Head-turning! An organocatalytic atroposelective aldol condensation to triortho-substituted biaryls is described. Key to the process is an efficient transfer of the stereochemical information of a secondary amine catalyst into the axis of chirality of binaphthyl products. The reaction proceeds analogous to the aromatic polyketide biosynthesis and is distinct in its initiation by virtue of dienamine formation. This method allows for the synthesis of axially chiral biaryls with remarkable atroposelectivity of up to e.r. 99:1.