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Anion-π Catalysts with Axial Chirality

Chao Wang and Stefan Matile*[a]

Abstract: The idea of anion-π catalysis is to stabilize anionic transition states by anion-π interactions on aromatic surfaces. For asymmetric anion-π catalysis, π-acidic surfaces have been surrounded with stereogenic centers. Here, we introduce the first anion-π catalysts that operate with axial chirality. Bifunctional catalysts with tertiary amine bases next to π-acidic naphthalenediimide planes are equipped with a bulky aromatic substituent in the imide position to produce separable atropisomers. The addition of malonic acid half thioesters to enolate acceptors is used for evaluation. In the presence of a chiral axis, the selective acceleration of the disfavored but relevant enolate addition was much better than with point chirality, and enantioselectivity could be observed for the first time for this reaction with small-molecule anion-π catalysts. Enantioselectivity increased with the π acidity of the π surface, whereas the addition of stereogenic centers around the aromatic plane did not cause further improvements. These results identify axial chirality of the active aromatic plane generated by atropisomerism as attractive strategy for asymmetric anion-π catalysis.

Introduction

Anion-π catalysis, that is the stabilization of anionic transition states and reactive intermediates on aromatic surfaces, has been introduced explicitly in 2013.[1] Since then, contributions from anion-π interactions[2] to enolate,[3-8] enamine,[9,10] iminium,[11] transamination and oxocarbenium[12] chemistry have been reported.[13] The delocalized nature of anion-π interactions has been confirmed as particularly attractive to stabilize long-distance charge displacements in cascade processes,[11,13] the first anion-π enzymes have been prepared[6,13] and electric-field-assisted anion-π catalysis has been explored.[7]

For asymmetric anion-π catalysis, π-acidic aromatic surfaces have been surrounded by stereogenic centers (Figure 1). Examples reach from chiral sulfoxides right at the edge of the aromatic plane[9,10] to fusion catalysts with classical motifs in organocatalysis from cinchona alkaloids.[13] In **1**, one of the most studied anion-π catalysts, the π-acidic aromatic plane is provided by a naphthalenediimide (NDI).[14-16] A tertiary amine base is positioned in closest possible proximity to turn on anion-π interactions as soon as proton transfer injects the negative charge into the substrate (Figure 1).[4] For asymmetric anion-π catalysis, point chirality from stereogenic centers has been

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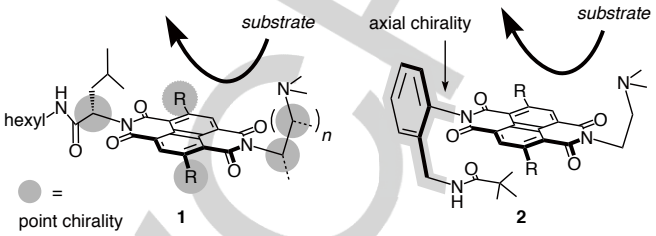


Figure 1. Anion-π catalyst **2** with axial chirality (*P* enantiomer, R = SO_2-octyl), compared to previously reported anion-π catalyst **1** with point chirality.

installed around the site of the reaction in **1**, that is the π-acidic surface of the NDI. This includes the α carbon of the leucine solubilizer on the imide opposite to the amine base and stereogenic centers in the Leonard turn between aromatic surface and amine base. The introduction of chiral sulfoxides as π-accepting substituents R in the core of the NDI at the edge of the aromatic plane has failed so far because separation of the diastereomers by chiral HPLC was unsuccessful.[4]

However, chirality within rather than around aromatic planes originates from chiral axes rather than from chiral points. This axial chirality of aromatic planes is generated with atropisomers. Atropisomerism results from hindered rotation around a single bond of highly substituted biaryls and related compounds.[15-22] Atropisomers with high enough barriers generate stable axial chirality and can be separated as enantiomers. They are ubiquitous throughout chemistry. In medicinal chemistry, atropisomers show different activity and selectivity, and atropisomerism is exploited to improve drug efficiency.[17] Atropisomeric scaffolds are also widely distributed in natural products[18] and used in organic materials, molecular machines, models, probes and so on.[15,16,19] As a result, atroposelective synthesis has recently attracted much interest.[20] Moreover, atropisomerism has been utilized in privileged chiral ligands and catalyst structures such as BINAP or chiral phosphoric acids.[21,22] To achieve asymmetric catalysis on aromatic planes, the introduction of this intrinsic axial chirality was thus most promising. Axially chiral NDIs have been prepared previously in several variations for different purposes.[15,16] Here, we report design, synthesis and evaluation of the first axially chiral anion-π catalysts.

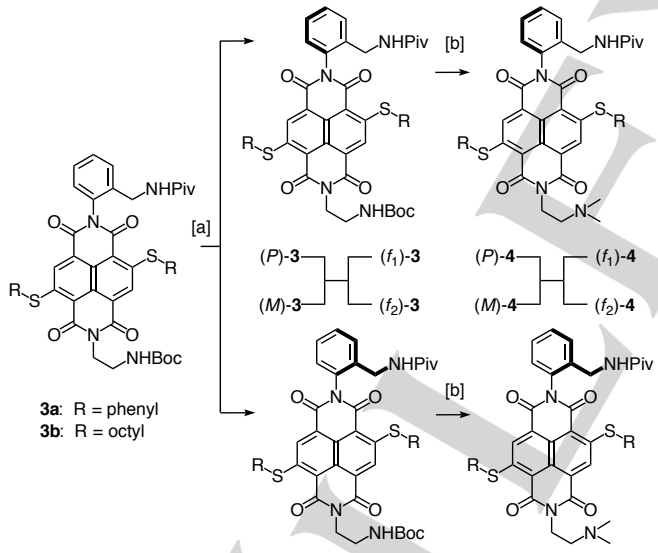
Results and Discussion

To introduce axial chirality to asymmetric anion-π catalysis, we decided to replace the leucine solubilizer in bifunctional catalyst **1** with the *ortho* substituted phenyl group in **2** (Figure 1). The axial chirality in anion-π catalyst **2** is created by the substituents R in the core of the NDI as well as the hindered rotation around the single bond that connects the NDI plane, the site of the

reaction, with the phenyl substituent in the imide opposite to the amine base (Figure 1). This rotation is blocked by the bulky pivaloyl (Piv) substituent in *ortho* position of this phenyl group. The atropisomer shown in Figure 1 introduces axial chirality with the absolute configuration *P*.

The substitution of the leucine in **1** with the *ortho* substituted phenyl in **2** turns the solubilizing alkyl group to reside below the aromatic plane rather than at the periphery. This central position of the bulky pivaloyl group was expected to direct the other substituents to the other side of the aromatic plane and thus structure the chiral space around at the site of action on the π-acidic NDI surface somehow by remote control. Although better turns are available,[4] the π surface and the amine catalyst in **2** were connected with a simple achiral Leonard turn[4] to isolate contributions from axial chirality from any interference from point chirality.

Synthetic access to axially chiral anion-π catalysts has been hindered so far by the failure to separate stereoisomers by chiral HPLC in the presence of a tertiary amine base.[4] To solve this problem, the stereoisomers should be separated before the introduction of the tertiary amine. In NDIs **3**, the tertiary amine needed in the final catalyst **2** is kept on the level of a Boc-protected primary amine (Scheme 1). NDIs **3a** and **3b** with aryl or alkyl sulfides in the core were readily available by adapting established synthetic routes (Schemes S1, S2). Details on preparation and characterization of all new compounds can be found in the Supporting Information. The two enantiomers of **3a** and **3b** appeared as very well separated peaks in the chiral HPLC (Figure 2).



Scheme 1. [a] Separation on chiral HPLC (CHIRALPAK ID, 250 mm x 10 mm, Daicel, 4 mL/min and detection at λ_{abs} = 300 nm; (f_1)-**3a**: R_t = 6-9 min, (f_2)-**3a**: R_t = 16-24 min (CH_2Cl_2/EtOAc 9:1); (f_1)-**3b**: R_t = 16-17.5 min, (f_2)-**3b**: R_t = 17.5-20 min (CH_2Cl_2/EtOAc 99:1). [b] 1. TFA, CH_2Cl_2; 2. CH_2O (aq), TFA, Et_3SiH, CH_2Cl_2, 86-90%.

The circular dichroism (CD) spectra of the separated enantiomers were exact mirror images (Figure 2b). The maximum of their first CD Cotton effect at λ_{max} = 505 nm coincided with the absorption maximum. From this induced CD, it was not possible to assign their absolute configuration. The obtained pair of enantiomers is thus described in the following as (f_1)-**3** and (f_2)-**3**, referring to fraction 1 and fraction 2 eluted from the chiral HPLC under the specified conditions. They were stable at room temperature. Racemization in DMF at 383 K occurred with t_{50} = 2.0 h (Figure S6). The corresponding k_{rac} = 9.5 10^{-5} s^{-1} calculated to a barrier of $\Delta G^{‡}$ = 105 kJ mol^{-1} (Figure S7).

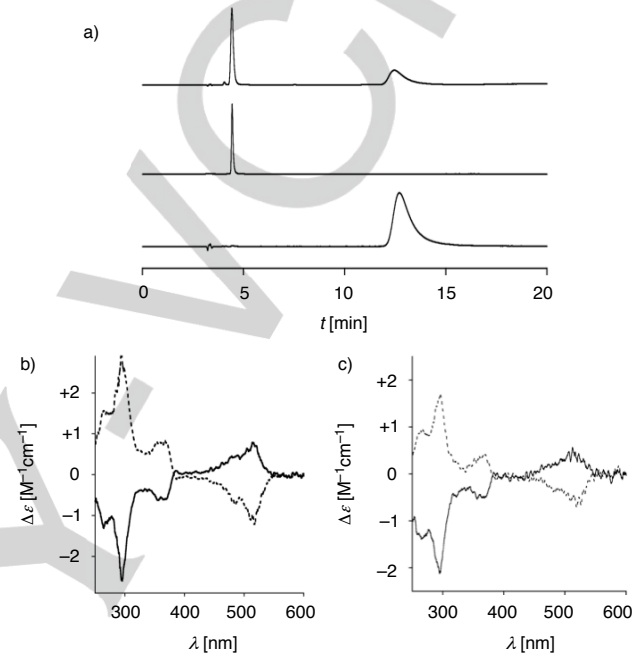
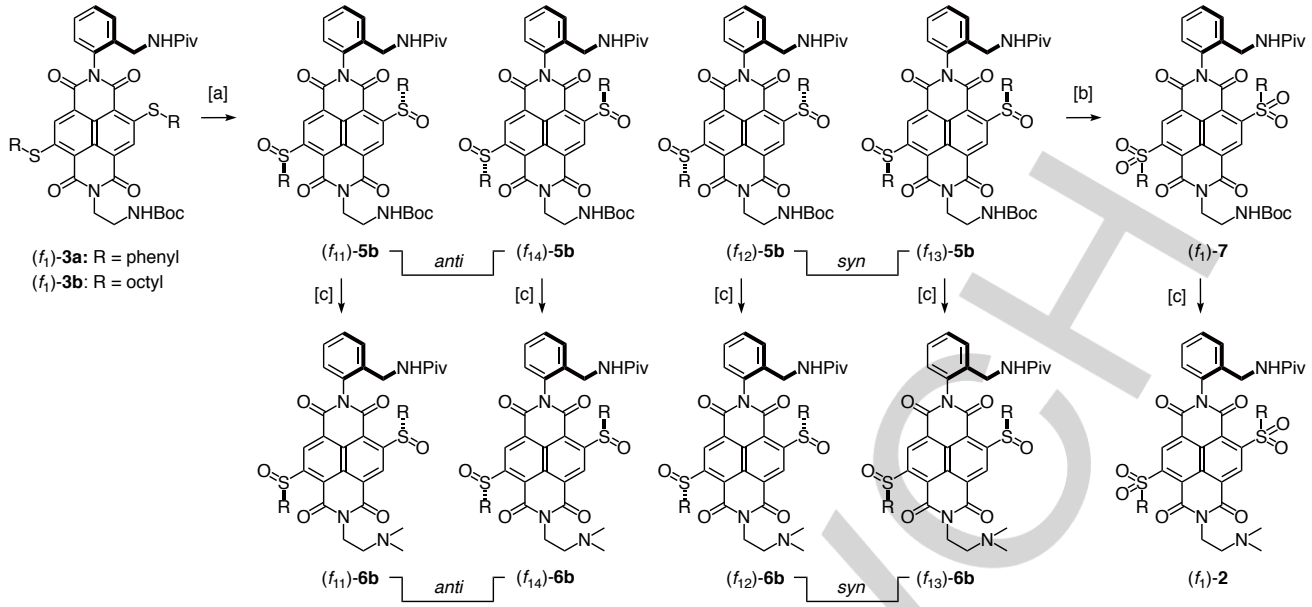


Figure 2. a) Analytical chiral HPLC of the mixture of (f_1)-**3a** (R_t = 4.4 min) and (f_2)-**3a** (R_t = 12.7 min, top), and the purified enantiomers (f_1)-**3a** (middle) and (f_2)-**3a** (bottom). b) CD spectra of (f_1)-**3a** (solid) and (f_2)-**3a** (dashed). c) CD spectra of (f_1)-**4a** (solid) and (f_2)-**4a** (dashed).

The pure enantiomers (f_1)-**3** and (f_2)-**3** were transformed into the active catalysts (f_1)-**4** and (f_2)-**4** by removing the Boc protecting groups with TFA in CH_2Cl_2, followed by reductive amination of the liberated primary amines with formaldehyde. The CD spectra of the obtained catalyst (f_1)-**4** and (f_2)-**4** remained mirror images (Figure 2c). Preserved CD Cotton effects demonstrated that the axial chirality remained intact during the introduction of the tertiary amine. Further support of this conclusion was obtained with sulfoxide instead of sulfide substituents in the NDI core (see below).

The redox switch[23] in the NDI core was turned on only for (f_1)-**3** because the preparation of the complementary set of enantiomers from (f_2)-**3** was considered redundant. Controlled oxidation under routine conditions with ~1 equivalent of mCPBA per sulfide at –20 ºC afforded sulfoxides **5** as a mixture of four diastereomers. The four diastereomers were separable by chiral HPLC (Figures S1, S2). With octylsulfoxides **5b**, the circular dichroism (CD) spectra of the fractions eluting second



Scheme 2. [a] 1. 2.4 equivalent mCPBA, CH_2Cl_2, –20 to –10 °C, 78%. 2. Separation on silicagel: ($f_{11,12,14}$)-**5b**: R_f (CH_2Cl_2/EtOAc 4:1): 0.20; (f_{13})-**5b**: R_f (CH_2Cl_2/EtOAc 4:1): 0.10; and chiral HPLC: CHIRALPAK ID, 250 mm x 10 mm, Daicel, CH_2Cl_2/EtOAc 9:1, 4 mL/min and detection at λ_{abs} = 300 nm; (f_{11})-**5b**: R_t = 6.4-8.6 min, (f_{12})-**5b**: R_t = 8.8-11.6 min, (f_{14})-**5b**: R_t = 15-24 min. *Syn* and *anti* configurations were assigned according to CD (Figure 3). [b] 1. 10 equivalent mCPBA, CH_2Cl_2, rt, 90%. [c] 1. TFA, CH_2Cl_2; 2. CH_2O (aq), TFA, Et_3SiH, CH_2Cl_2, 85-92%. Note, absolute configurations are unknown, stereoisomers are differentiated from their elution from HPLC.

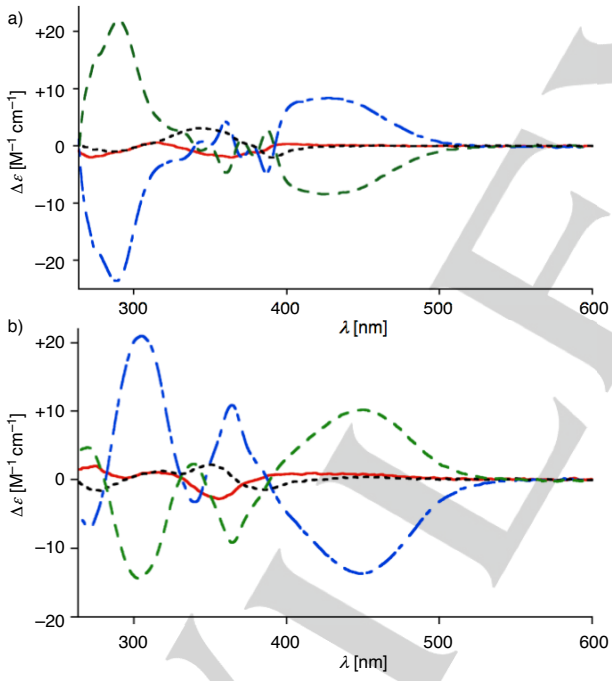


Figure 3. a) CD spectra of **5a** in CH_2Cl_2 separated into HPLC fractions f_{11} (red, *anti*), f_{12} (blue, *syn*), f_{13} (green, *syn*) and f_{14} (black, *anti*). b) CD spectra of f_{11} (red, *anti*), f_{12} (blue, *syn*), f_{13} (green, *syn*) and f_{14} (black, *anti*) for **5b** in CH_2Cl_2.

and third, i.e., (f_{12})-**5b** and (f_{13})-**5b** were almost perfect mirror images with strong broad CD Cotton effects also at long wavelength, maximizing around 450 nm (Figure 3b). Previous comparison with crystal structures of other NDIs with two sulfoxides in the core have shown that CD active isomers can be assigned to *syn* configuration.[16] With the S-O bond oriented in plane toward the naphthalene core, *syn* isomers have both alkyl tails on the same side of the aromatic plane (Scheme 2). The nearly CD silent *anti* isomers eluted as (f_{11})-**5b** and (f_{14})-**5b** (Scheme 2, Figure 3b). The order of elution was the same also with aryl substituents. The first and the last eluting diastereomers (f_{11})-**5a** and (f_{14})-**5a** were almost CD silent and therefore *anti*, whereas (f_{12})-**5a** and (f_{13})-**5a** were CD active, that is *syn* (Figure 3a). As already described for (f_1)-**4**, deprotection and reductive amination of both sets of diastereomeric pre-catalysts afforded complementary collection of catalysts (f_1)-**6**. The absence of detectable diastereomeric products provided compelling evidence for the lack of axial epimerization during these two steps.

Complete oxidation of precatalyst (f_1)-**3** with excess mCPBA gave precatalyst (f_1)-**7** with two achiral sulfone acceptors in the core (Scheme 2). Conversion into catalyst (f_1)-**2** followed the procedure introduced above.

The addition of malonic acid half thioester **8** to enolate acceptor **9** was selected to elaborate on asymmetric anion–π catalysis on axially chiral π surfaces (Figure 4). This reaction is emerging as a useful model to probe for anion-π catalysis. So far, enantioselectivity has been achieved with conventional organocatalysts[24] and anion-π enzymes[6] but neither with small-molecule anion-π catalysts, including NDI tweezers,[3]

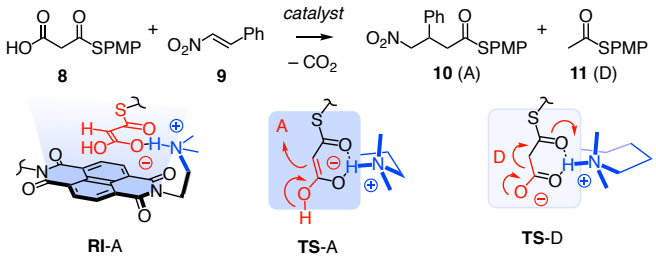


Figure 4. Anion-π catalysts accelerate the addition (A) of **8** to **9**, yielding **10**, and decelerate the intrinsically favored decarboxylation (D) of **8**, yielding **11**, presumably by discriminating the planar reactive intermediate **RI**-A and transition state **TS**-A from the twisted **TS**-D on their π-acidic aromatic surface.

NDIs[4] and PDIs[5] with rigidified chiral Leonard turns, nor with electric-field-assisted anion-π catalysis with NDIs on conducting solid surfaces.[7] This failure contrasts sharply with excellent results reported for other reactions in asymmetric anion-π catalysts, which overall proved competitive with conventional catalysts.[9-13] Moreover, this reaction is of central importance in chemistry and biology. However, without enzymes, the formation of the chiral enolate addition product **10** (or A) is disfavored, decarboxylation product **11** (or D) dominates instead.[3-7] Under routine conditions, the intrinsic selectivity observed in the presence of TEA and related base catalyst is A/D = 0.7. Catalyst **1** with a Leonard turn as in **2** and ethyl sulfides in the core inverts this selectivity to A/D = 1.9.[4] Oxidation of the sulfide donor to sulfoxide and sulfone acceptors further increases the selective acceleration of the disfavored but useful enolate addition to A/D = 2.5 and A/D = 2.8, respectively.[4]

The axially chiral catalyst (f_1)-**4a** with phenylsulfide substituents in the core was evaluated first (Scheme 1). The obtained A/D = 3.9 (Table 1, entry 1) revealed that already at lowest π acidity produced by sulfide donors, anion-π catalysts with axial chirality selectively accelerate the disfavored but relevant enolate addition to an extent that has never been reached with point chirality.

In the aryl series, oxidation of sulfides **4a** to sulfoxides **6a** and sulfones produced catalysts of increasingly poor solubility. Replacement of the aryl sulfides with alkyl sulfides solved this problem. The diastereomeric catalysts **6b** with sulfoxides in the core gave selectivities reaching from A/D = 2.9 to A/D = 6.1 (Table 1, entries 3-6). These significant differences, reaching from the best to the worst, confirmed that the point chirality at the edge of the π surface retains high importance also in the presence of axial chirality in the catalysts. Further increase of π acidity in catalyst **2b** with sulfones did not improve the selectivity (A/D = 4.3) compared to that with sulfides **4b** (A/D = 4.2, Table 1, entries 2, 7).

Modification of reaction conditions allowed to increase selectivities significantly. For instance, sulfoxide (f_{12})-**6b** reached A/D = 7.8 in C_6F_6/$CDCl_3$ 1:1 and A/D = 11.5 in *tert*-butyl methyl ether (TBME) at 20 °C (Table 1, entries 12, 9). Best results were obtained at low temperature. The highest selectivity A/D = 20.4 was observed for sulfone (f_1)-**2b** in TBME/$CDCl_3$ 1:1 at 0 °C (Table 1, entry 23). Reduction of the π acidity in the best sulfoxide (f_{12})-**6b** and in sulfide (f_1)-**4b** caused the respective

Table 1. Catalyst Characterization.[a]

Entry	Catalyst[b]	Conditions[c]	A/D [d]	*er*[e]
1	(f_1)-**4a**(S)	$CDCl_3$/THF-d_8 1:1	3.9	50:50
2	(f_1)-**4b** (S)	$CDCl_3$/THF-d_8 1:1	4.2	50:50
3	(f_{11})-**6b** (SO)	$CDCl_3$/THF-d_8 1:1	6.1	54:46
4	(f_{12})-**6b** (SO)	$CDCl_3$/THF-d_8 1:1	5.9	56:44
5	(f_{13})-**6b** (SO)	$CDCl_3$/THF-d_8 1:1	2.9	52:48
6	(f_{14})-**6b** (SO)	$CDCl_3$/THF-d_8 1:1	4.0	52:48
7	(f_1)-**2b** (SO_2)	$CDCl_3$/THF-d_8 1:1	4.3	57:43
8	(f_{12})-**6b**(SO)	CD_2Cl_2	7.2	57:43
9	(f_{12})-**6b**(SO)	TBME	11.5	57:43
10	(f_{12})-**6b**(SO)	C_6D_6	4.1	59:41
11	(f_{12})-**6b**(SO)	Toluene-d_8	4.7	58:42
12	(f_{12})-**6b**(SO)	C_6F_6/$CDCl_3$ 1:1	7.8	57:43
13	(f_{12})-**6b**(SO)	1,3-DMB	3.5	60:40
14	(f_1)-**4b** (S)	1,3-DMB, 0 °C	4.8	50:50
15	(f_{11})-**6b** (SO)	1,3-DMB, 0 °C	3.5	56:44
16	(f_{12})-**6b** (SO)	1,3-DMB, 0 °C	7.1	61:39
17	(f_{13})-**6b** (SO)	1,3-DMB, 0 °C	3.4	47:53
18	(f_{14})-**6b** (SO)	1,3-DMB, 0 °C	5.6	55:45
19	(f_1)-**2b** (SO_2)	1,3-DMB, 0 °C	7.0	60:40
20	(f_{12})-**6b** (SO)	TBME, 0 °C	12.1	59:41
21	(f_1)-**4b** (S)	TBME/$CDCl_3$ 1:1, 0 °C	16.4	50:50
22	(f_{12})-**6b** (SO)	TBME/$CDCl_3$ 1:1, 0 °C	17.7	61:39
23	(f_1)-**2b** (SO_2)	TBME/$CDCl_3$ 1:1, 0 °C	20.4	61:39

[a] Reactions were conducted with 200 mM **8**, 20 mol% catalyst and 2 M acceptor **9** at 20 °C if not indicated otherwise, and monitored by ^{1}H NMR spectroscopy. Total conversion (A + D) was always almost quantitative (>90%). [b] Catalysts, see Schemes 1 and 2 for structures (S, SO and SO_2 refer to the oxidation level of the redox switch in the NDI core). [c] Different conditions tested (TBME: *tert*-butyl methyl ether. [d] Chemoselectivity: Yield of addition (**10**) / yield of decarboxylation (**11**). [e] Enantiomeric ratio.

decrease in selectivity also under these highly optimized conditions (Table 1, entries 21–23). Overall, these results indicated that for anion-π catalysts with axial chirality, increasing π acidity is more important than additional point chirality at the edge of the π surface, at least for "tortoise-and-hare"[4] catalysis, that is the selective acceleration of the intrinsically disfavored reaction.

With regard to enantioselectivity under routine conditions, the sulfide catalyst (f_1)-**4a** afforded racemic product **10** (Figure 4, Table 1, entry 1). However, among the diastereomers **6b**, the

emergence of enantioselectivity could be observed (Table 1, entries 3-6). Best enantiomeric ratios *er* = 56:44 for sulfoxide diastereomer (f_{12})-**6b** coincided with high A/D = 5.9 (Table 1, entry 4). Interestingly, further oxidized sulfone (f_1)-**2b** without sulfur point chirality gave preserved *er* = 57:43 (Table 1, entry 7). Thus, the axial chirality is apparently dominant in determining the enantioselectivity under these conditions. Solvent screening afforded the highest enantioselectivity *er* = 60:40 for sulfoxide (f_{12})-**6b** in 1,3-dimethoxybenzene (1,3-DMB), albeit with low A/D = 3.5 (Table 1, entry 13). Although this chemoselectivity could be improved by using more π-acidic sulfone catalyst (f_1)-**2b** under optimized conditions up to A/D = 20.4 (Table 1, entry 23), the enantioselectivity was found difficult to surpass. Nevertheless, the most important finding here is the highest chemo- and enantioselectivities were obtained with sulfone catalyst (f_1)-**2b** without point chirality. These results supported the precious conclusion that for asymmetric anion-π catalysis, axial chirality is more important than point chirality.

Conclusions

Anion-π catalysis occurs on aromatic planes. To break the symmetry of these planes, axial chirality is required. For asymmetric anion-π catalysis, axial chirality should thus be more effective than point chirality installed around the active aromatic plane. This study, introducing the first anion-π catalysts with axial chirality, provides direct experimental support for these expectations. The synthetic strategy developed to realize axial chirality also in the presence of tertiary amine catalysts is particularly valuable because it opens new perspectives to integrate anion-π catalysts into more complex systems. Current interest focuses on remote control of such advanced anion-π catalysts.[25,14b,10,6]

Experimental Section

See Supporting Information.

Acknowledgements

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Keywords: Anion-π interactions • axial chirality • atropisomers • catalysis • enolate chemistry

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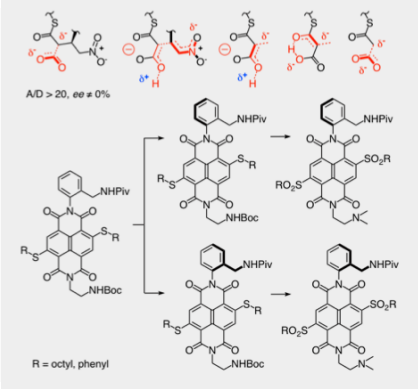
Chiral planes: To stabilize anionic transition states by anion-π interactions on aromatic surfaces stereoselectively, symmetry breaking of this active plane with axial chirality is more powerful than the accumulation of point chirality around the same active plane.



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