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Asymmetric Synthesis

Novel Asymmetric Formylation of Aromatic Compounds: Enantioselective Synthesis of Formyl 7,8-Dipropyltetrathia[7]helicenes

Julien Doulcet and G. Richard Stephenson*[a]

Abstract: Asymmetric formylation of aromatic compounds is virtually unexplored. We report the synthesis and evaluation of a library including 20 new chiral formamides in the kinetic resolution of 7,8-dipropyltetrathia[7]helicene, affording the corresponding formyl- or diformylhelicenes in up to 73% *ee*, making enantiopure compounds available by recrystallisation. With the *N*,*N*-disubstituted formamides used in this study, the best enantioselectivity has been achieved with $R^1 = i$Pr, R^2 = Me, R^3 = H, R^4 = 1-naphthyl or its 1-pyrenyl equivalent.

Introduction

In recent years, there has been rapid progress with the development of new asymmetric processes for enantioselective synthesis, yet, despite its importance as a general synthetic method, and the advantage that it introduces a simple but versatile functional group, the possibility of asymmetric formylation of aromatic substrates remains largely unexplored.[1] There are many classes of functional C_2-symmetric (*rac*)-arenes and heteroarenes such biaryls, paracyclophanes, helicenes and also metallocenes where chiral formyl donors could provide a useful strategy for access to enantiopure samples, and in this paper we report our first-generation results to develop the methodology as an approach for the kinetic resolution of helicenes. Helicenes, in particular, have been the subject of intense research in the past decade,[2] but despite many efforts to access enantiomerically pure helicenes, and some noteable individual successes,[3] there is still no generally applicable approach. Our interest in tetrathia[7]helicenes as bidentate ligands,[4] or as powerful chiral NLO-responsive chromophores (NLOphores),[5] which required an easy method to prepare enantiopure 2-formyl- or 2,13-diformyltetrathia[7]helicenes,[6] led us to investigate a novel approach based on asymmetric formylation.

We report the preparation and evaluation of 23 chiral formamides (20 synthesised for the first time for this project) in the kinetic resolution (KR) of 7,8-dipropyltetrathia[7]helicene (**5**) which was chosen because of its ease of preparation,[7] and because of the availability of efficient methods to perform lithiation at the 2-position.[8] Furthermore, conventional formylation of 2-lithio-tetrathia[7]helicenes with DMF is widely used in the racemic series.[6] This paper, however, describes the first examples of the chiral modification of this well-known reaction.

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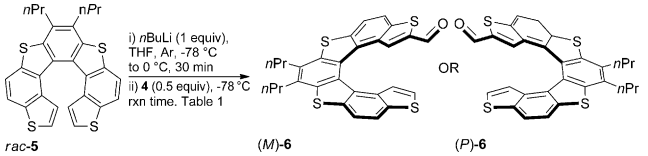
Results and Discussion

Chiral formamides[9] needed for our project were easily prepared from chiral secondary amines, by reaction with formic acetic anhydride[9a, 10] providing an initial selection of chiral formamides in excellent yields (Table 1, **3a–w** to **4a–w**). Not all the required secondary amines were commercially available, so additional examples were prepared from chiral primary amines by reductive amination of aldehydes[11] or ketones[12] (Table 1, except **3a,b,d,g** which were purchased, and **3c**,[13] **3g**[14] which were synthesised by other means).

The products were evaluated with 7,8-dipropyltetrathia[7]helicene (**5**) in a standard KR procedure (Scheme 1, Table 2). Despite relatively low enantioselectivities, early results (Table 2, **4a–f**) gave us important clues and it quickly became clear that chiral scaffolds that were prized in asymmetric deprotonation (**4a**, **4d**),[15] and organocatalysis (**4b**, **4c**[16] and **4g**[17]) gave poor results when modified for use in asymmetric formylation. Interestingly, however, formamide **4h**, which also contains only one stereogenic centre but had smaller achiral second alkyl group (Me) on the nitrogen atom ($R^3 = R^4$ = H) gave a significant improvement and (*M*)-**6** was isolated with 26% *ee*. Formamide **4i** gave (*M*)-**6** in 29% *ee* (Table 2, entry 9) and an acceptable 34% yield (50% is the highest attainable yield).

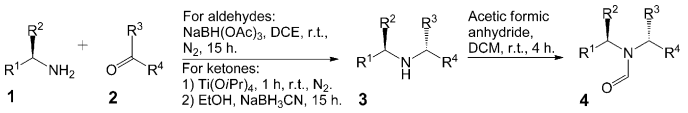
Later results (Table 2, **4j–l**) established that R^1 = isopropyl worked best (e.g. **4j**, Table 2, entry 11, 30% yield, 40% *ee*).



rac-**5** (*M*)-**6** (*P*)-**6**

Scheme 1. Initial examination of the kinetic resolution of helicene **5**.

Table 1. Synthesis of chiral formamides.



1 2 3 4

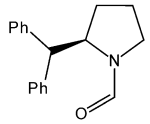
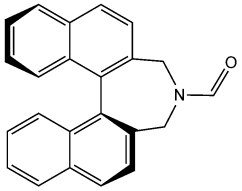
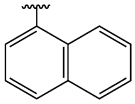
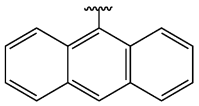
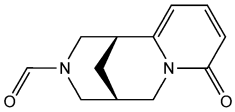
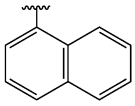
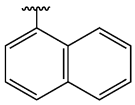
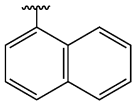
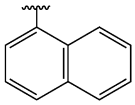
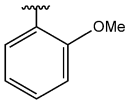
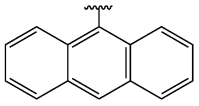
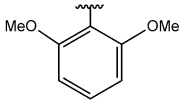
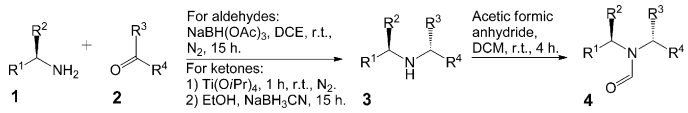
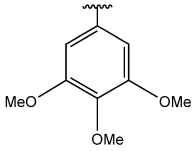
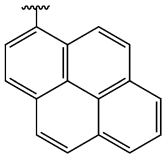
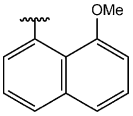
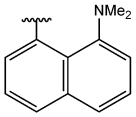
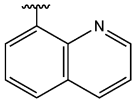
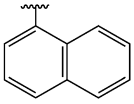
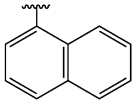
Entry	R^1	R^2	R^3	R^4	Yield **3** [%]	yield **4** [%]
a	Ph	Me	Me	Ph	–	100[a]
b					–	90[a]
c					–	99[13]
d	Me	Ph	H	Ph	–	99[a]
e	Ph	Et	H		63	79
f	Ph	Et	H		–	29[b]
g					–	79[14]
h	Me	Ph	H	H	–	89[a]
i	Cy	Me	H		71	77
j	*i*Pr	Me	H		–	73[b]
k	*t*Bu	Me	H		77	63
l	Et	Me	H		–	50[b]
m	*i*Pr	Me	H		50	77
n	*i*Pr	Me	H		75	99
o	*i*Pr	Me	H		45	71

Table 1. (Continued)



1 2 3 4

Entry	R^1	R^2	R^3	R^4	Yield **3** [%]	yield **4** [%]
p	*i*Pr	Me	H		52	100
q	*i*Pr	Me	H		–	55[b]
r	*i*Pr	Me	H		–	70[b]
s	*i*Pr	Me	H		–	71[b]
t	*i*Pr	Me	H		–	71[b]
u	*i*Pr	Me	Ph	Ph	33	89
v		Me	H	*i*Pr	–	84[b]
w	Me	*i*Pr	H		–	65[b]

[a] Commercially available secondary amine. [b] Over two steps (amine not isolated).

Modifying R^3 and R^4 (Table 2, **4m–u**), while keeping R^1 as isopropyl, showed that Lewis basic arenes (**4m**, **4o**, **4p**, **4r**, **4s**, **4t**) did not improve the efficiency of the KR, and of the bulky examples, only pyrenyl (**4q**) gave good results, providing the formylhelicene (*M*)-**6** in 32% yield and 42% *ee* (Table 2, entry 18).

Comparing the 9-anthracenylmethylformamide **4n** which performed very poorly, giving **6** in only 3% *ee* (Table 2, entry 15), and the corresponding 1-naphthylmethyl analogue **4j**, which was one of the best chiral formamides (40% *ee*, Table 2, entry 11) suggests that with a naphthalene substituent, the steric bias is offset from the point of attachment to the centre of the formamide structure, but an anthracene attached at C-9 is too symmetrical (see Figure 1 and Supporting Information).

Table 2. KR results.

Entry	Formamide	Rxn time [h]	Yield [%]	*ee*[a] [%] of **6**	*ee*[a] [%] of **5**
1	**4a**	6	NR	–	–
2	**4b**	6	22	7 (*P*)	1 (*M*)
3	**4c**	7	26	13 (*M*)	5 (*P*)
4	**4d**	6	29	14 (*M*)	4 (*P*)
5	**4e**	7	19	13 (*M*)	5.5 (*P*)
6	**4f**	6	15	9 (*M*)	1 (*P*)
7	**4g**	18	41	*rac*	*rac*
8	**4h**	6	25	26 (*P*)	9 (*M*)
9	**4i**	6	34	29 (*M*)	7 (*P*)
10	**4j**	6	23	42 (*M*)	8 (*P*)
11	**4j**	18	30	40 (*M*)	10 (*P*)
12	**4k**	6	29	17 (*M*)	3 (*P*)
13	**4l**	6	30	13 (*P*)	7 (*M*)
14	**4m**	6	15	25 (*M*)	5 (*P*)
15	**4n**	18	20	3 (*P*)	1 (*M*)
16	**4o**	6	NR	–	–
17	**4p**	6	9	28 (*M*)	3 (*P*)
18	**4q**	18	32	42 (*M*)	11 (*P*)
19	**4r**	18	11	10 (*P*)	2 (*M*)
20	**4s**	18	NR	–	–
21	**4t**	18	6	19 (*M*)	1 (*P*)
22	**4u**	18	NR	–	–
23	**4v**	18	35	7 (*P*)	2.5 (*M*)

[a] Measured by HPLC, ChiralPak IA column, for further information see the Supporting Information.

We propose that the fast reacting enantiomer in the kinetic resolution experiments will be determined by the difference in the steric interactions between the two enantiomers of the lithiohelicene and the *si*/*re* face of the formamide exposed for reaction to take place (see Supporting Information).

A further comparison reveals that installing the naphthyl group in R^1 (Figure 1: formamide **4v**) does not provide the same advantage that is observed when it is at position R^4. Although (*P*)-formylhelicene **6** was obtained in 35% yield, the *ee* was only 7%. It appears from this result that steric bias introduced by the 1-naphthalenylmethyl group is most beneficial when directly attached as a substituent on the formamide nitrogen. Based on these considerations, our currently preferred design for chiral formyl donors is: R^1 = *i*Pr, R^2 = Me, R^3 = H, R^4 = 1-naphthyl or its 1-pyrenyl equivalent and this sytem was examined under varied reaction conditions (Table 3).

Solvent effects are important in asymmetric organolithium chemistry. Due to the low solubility of helicene **5** in Et_2O, toluene was used as a co-solvent (1:4 mixture) and afforded formylhelicene **6** in 35% yield but only 3% *ee* (Table 4, entry 2). Methyl *tert*-butyl ether (MTBE) also performed poorly (1% *ee*; Table 4, entry 3) but 2-MeTHF gave (*M*)-**6** in 16% *ee* (Table 4, entry 4), a significant improvement on entries 2 and 3. DME[19] did not follow the trend observed with Et_2O, MTBE, 2-MeTHF and THF, where the most coordinating solvents gave the best results, in contrast to the standard conditions for the widely studied (−)-sparteine-mediated asymmetric lithiation chemistry, where THF is almost always avoided.[20]

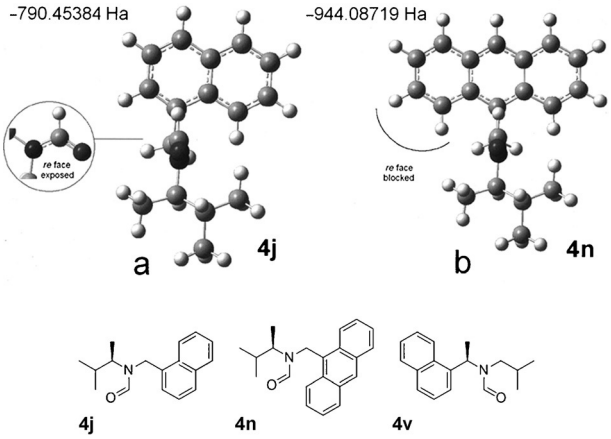
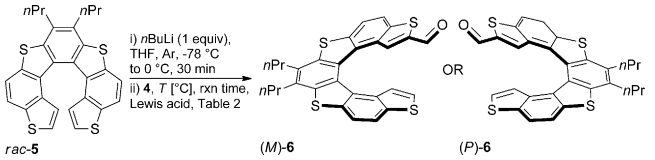


Figure 1. Comparison of steric effects: (a) **4j** and (b) **4n**; illustration of the reversed positions of alkyl and naphthyl groups in **4v**.

Double kinetic resolution (double-KR) is a much underused synthetic strategy but with C_2-symmetric substrates such as helicenes, a novel and convenient one-pot variant is possible. The first examples of double-KR were reported many years ago,[21] but even after the development of the method by Vänttinen and Kanerva in 1997,[22] the advantages have been largely ignored by synthetic chemists. With suitable chiral formamides in hand we had an ideal opportunity to test the double-KR principle in this important practical situation.[23] Helicene **5** was treated with two equivalents of *n*BuLi to form the *rac*-2,13-dilithiohelicene and, in separate experiments, our two best formamides **4j** or **4q** were added at −78 °C in THF (Scheme 2). The significantly higher *ee* values measured for (*M*)-**7** (68% and 73%, respectively; Scheme 2), compared to

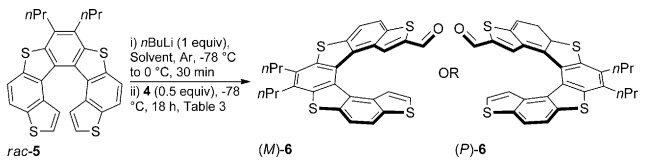
Table 3. KR results using modified reaction conditions.



Entry	**4** (equiv)	Lewis acid	*T* [°C]	Rxn time [h]	Yield [%]	*ee*[a] [%] of **6**	*ee*[a] [%] of **5**
1	**4j** (0.5)	–	−78	18	30	40 (*M*)	10 (*P*)
2	**4j** (0.5)	–	−63	2	9	34 (*M*)	7 (*P*)
3	**4j** (0.35)	–	−42	2	29	25 (*M*)	9 (*P*)
4	**4j** (1)	–	−78	6	29	17 (*M*)	5 (*P*)
5	**4w**[b] (0.5)	BF_3·Et_2O	−78	3.5	37	10 (*P*)	6 (*M*)
6	**4u** (0.5)	BF_3·Et_2O	−78	3.5	20	4.5 (*P*)	1.5 (*M*)

[a] Measured by HPLC, ChiralPak IA column, for further information see the Supporting Information. [b] **4w** = (*S*)-**4j**.

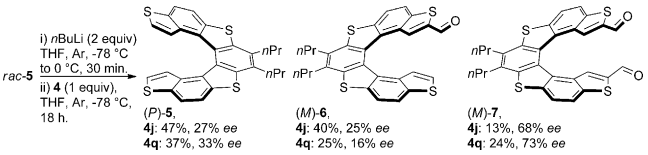
Table 4. Kinetic resolution: solvent screening results.



Entry	4	Solvent	Yield [%]	*ee*[a] [%] of **6**	*ee*[a] [%] of **5**
1	**4j**	THF	30	40 (*M*)	10 (*P*)
2	**4j**	Et_2O/toluene	35	3 (*M*)	1.5 (*P*)
3	**4j**	MTBE[b]	32	1 (*P*)	*rac*
4	**4q**	2-MeTHF	26	16 (*M*)	5 (*P*)
5	**4j**	DME/THF[c]	28	30 (*M*)	7 (*P*)

[a] Measured by HPLC, ChiralPak IA column, for further information see the Supporting Information. [b] Helicene dissolved in MTBE (9.6 mmol L^{-1}). [c] Helicene dissolved in DME/THF (21 mmol L^{-1}).

the best *ee* values for **6** (40–42%), indicate the substantial improvement possible when a double-KR one-pot reaction is performed. Using ethyl acetate, (*M*)-**7** was recrystallised to enantiopurity (28% recovery). The success of the double-KR approach described here will bring a renewed focus to this underused strategy and is the first report of a deliberate and effective one-pot application of a multi-KR approach in an actual synthetic sequence.



Scheme 2. Double KR by asymmetric diformylation.

Conclusions

As a result of the work described here, previously unexplored chiral formamides are now readily available, providing an important range of structurally varied new chiral auxiliaries. The practicality of enantioselective formylation has been established for the first time as a kinetic resolution procedure with (*rac*)-7,8-dipropyltetrathia[7]helicene, and we have identified a preferential substitution pattern ($R^1 = i$Pr, R^2 = Me, R^3 = H, R^4 = aryl) surrounding the *N*-formyl centre, with R^4 = naphthyl (**4j**) and pyrenyl (**4q**) giving the best results, affording (*M*)-2-formyl-7,8-dipropyltetrathia[7]helicene (**6**) respectively in 30% and 32% yields, and 40% and 42% *ee* from the single-KR version of the reaction. This process has been applied in a one-pot double-KR which gave improved *ee* values (68–73%) and established practical access to optically pure helicenes by this method. As new generations of chiral formyl donors become available the final crystallisation to achieve enantiomeric purity will be far more efficient when starting for a higher initial *ee* The 2,13-diformyl-7,8-dipropyltetrathia[7]helicene (**7**) obtained using double-KR offers an excellent building block for the construction of innovative (A)-(chiral π)-(A) NLO-phores which conform to the novel and recently reported 'double-dipole half-turn' design.[5]

Experimental Section

General methods

Aldehydes **2r**[24] and **2s**[25] and secondary amines **3c**[26] and **3g**[14] were prepared according to literature procedures. Organolithium reagents were titrated according to the procedure reported by Burchat,[27] using *N*-benzylbenzamide. Further details are given in the Supporting Information.

Synthetic procedures for the synthesis of chiral formamides

Method 1: General procedure for reductive amination of aldehydes: Amine (1 equiv) and aldehyde (1 equiv) were mixed in 1,2-dichloroethane (about 5 mL $mmol^{-1}$ of amine) before sodium triacetoxyborohydride (1.4 equiv) was added. The mixture was stirred at room temperature under nitrogen overnight. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with dichloromethane. The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration, the solvent was evaporated to give the crude material which was generally purified by silica gel column chromatography.

Amines **3e**, **3i**, **3k**, **3m**, **3n**, **3o** and **3p** were prepared using Method 1 (for full characterisation data, see Supporting Information). (*R*)-(+)-*N*-(naphthalen-1-ylmethyl)-1-phenylpropan-1-amine, **3u**. In a 50 mL flame-dried round-bottomed flask filled with nitrogen, (*R*)-(−)-3-methyl-2-butylamine (0.4 g, 4.6 mmol, 1 equiv), benzophenone (0.84 g, 4.6 mmol, 1 equiv) and $Ti(OiPr)_4$ (1.7 mL, 5.75 mmol, 1.25 equiv) were mixed and stirred at room temperature for 1 h. Then, EtOH (15 mL) was added to dissolve the mixture and $NaBH_3CN$ (193 mg, 3.1 mmol, 0.67 equiv) was added and the mixture was stirred at room temperature under nitrogen for 15 h. Water (2 mL) was added, the mixture filtered and the precipitate was washed with EtOH (30 mL). The filtrate was concentrated and the crude product was extracted into EtOAc (50 mL), washed with brine (50 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated to give the crude material which was purified by silica gel column chromatography (10 g silica, hexanes/EtOAc gradient 10/1 to 3/1 v/v) affording **3u** (390 mg, 33%; for full characterisation data, see Supporting Information) as a colourless oil.

Method 2: General procedure for the *N*-formylation of secondary amines: To a solution of secondary amine in dichloromethane under nitrogen, was added acetic formic anhydride (2.5 equiv). The resulting solution was stirred overnight at room temperature. Saturated aqueous $NaHCO_3$ was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over $MgSO_4$, filtered and evaporated. The crude material was then purified by silica gel column chromatography affording the desired formamide.

Formamides **4a**,[9a] **4b**, **4c**, **4d**,[9c] **4e**, **4g**, **4h**,[9b] **4i**, **4k**, **4m**, **4n**, **4o**, **4p** and **4u** were prepared using Method 2 (for full characterisation data, see Supporting Information).

Method 3: General procedure for the *N*-formylation of crude secondary amines obtained by reductive amination of aldehydes: Amine (1 equiv) and aldehyde (1 equiv) were mixed in 1,2-dichloroethane (about 5 mL $mmol^{-1}$ of amine) before sodium triacetoxyborohydride (1.4 equiv) was added. The mixture was stirred at room temperature under nitrogen overnight. Saturated aqueous $NaHCO_3$ was added and the mixture was extracted with dichloro-

methane. The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration, the solvent was evaporated to give the crude material which was dissolved in dichloromethane and stirred under nitrogen. Acetic formic anhydride (2.5 equiv) was then added and the resulting solution was stirred overnight at room temperature, after which, saturated aqueous $NaHCO_3$ was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane and the combined organic layers were dried over $MgSO_4$, filtered and evaporated. The crude material was then purified by silica gel column chromatography affording the desired formamide.

The following formamides **4f**, **4j**, **4l**, **4q**, **4r**, **4s**, **4t**, **4v** and **4w** were prepared using Method 3 (for full characterisation data, see Supporting Information).

Synthetic procedures for kinetic resolution using chiral formamides

Method 4: General procedure for the asymmetric formylation of 7,8-dipropyltetrathia[7]helicene (5), using chiral formamides: In a 10 mL flame-dried round-bottomed flask filled with argon, to a solution of 7,8-dipropyltetrathia[7]helicene (**5**, 70 mg, 0.14 mmol, 1 equiv) in distilled solvent (5 mL) cooled at −78 °C, was added dropwise *n*BuLi (0.14 mmol, 1 equiv). After stirring for 5 min at −78 °C, the yellow solution was allowed to reach 0 °C over 30 min, and then was cooled again at −78 °C. Then, a solution of chiral formamide (0.071 mmol, 0.5 equiv) in distilled solvent (1 mL) was added dropwise (when using Lewis acid, $BF_3{\cdot}Et_2O$ was added dropwise to the formamide solution at 0 °C and stirred for 15 min at 0 °C before the mixture was added dropwise to the lithiohelicene). The reaction mixtures were stirred at the temperature and for the time reported in Tables 1, 2 and 3. Then, saturated aqueous NH_4Cl (1 mL) was added, and the resulting mixture was extracted with EtOAc (2×20 mL), dried over $MgSO_4$, filtered and evaporated. The crude material was then purified by column chromatography (4 g silica, hexanes/EtOAc gradient 100/0 to 50/1 v/v) affording 7,8-dipropyl-2-formyltetrathia[7]helicene as a yellow solid (**6**, yields and *ee* values are reported in Tables 1, 2 and 3).

Method 5: General procedure for the asymmetric diformylation of 7,8-dipropyltetrathia[7]helicene (5), using chiral formamides: In a 10 mL flame-dried round-bottomed flask filled with argon, to a solution of 7,8-dipropyltetrathia[7]helicene (5, 70 mg, 0.14 mmol, 1 equiv) in distilled THF (5 mL) cooled at −78 °C, was added dropwise *n*BuLi (0.29 mmol, 2 equiv). After stirring for 5 min at −78 °C, the yellow solution was allowed to reach 0 °C over 30 min, and then was cooled again at −78 °C. Then, a solution of the chiral formamide (0.14 mmol, 1 equiv) in distilled THF (2 mL) was added dropwise before stirring at −78 °C for 18 h. Next, saturated aqueous NH_4Cl (1 mL) was added, and the resulting mixture was extracted with EtOAc (2×20 mL), dried over $MgSO_4$ filtered and evaporated. The crude material was purified by column chromatography (4 g silica, hexanes/EtOAc gradient 100/0 to 50/1 v/v) affording 7,8-dipropyl-2-formyltetrathia[7]helicene (**6**, yields and *ee* values are reported in Scheme 2) and 2,13-bis(formyl)-7,8-dipropyltetrathia[7]helicene as a yellow solid (**7**, yields and *ee* values are reported in Scheme 2).

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Keywords: asymmetric synthesis · chiral formamides · double-kinetic resolution · enantioselective formylation · kinetic resolution

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