ORGANOCATALYSIS WITH AZAHELICENES: THE FIRST USE OF HELICALLY CHIRAL PYRIDINE-BASED CATALYSTS IN THE ASYMMETRIC ACYL TRANSFER REACTION

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Dedicated to Dr Alfred Bader on the occasion of his 85th birthday.

The successful utilisation of a helicene-based organocatalyst in acylative kinetic resolution of racemic secondary alcohol was described. Employing *rac*-1-phenylethanol, optically pure (–)-(*M*)-2-aza[6]helicene (5–20 mole %), isobutyric anhydride and *N*-ethyldiisopropylamine in chloroform at 22–40 °C, an asymmetric acyl transfer reaction took place overwhelming the uncatalysed background process. Moderate reactivity as well as selectivity factor (*s* = 9, 10) were observed. An effective control of the enantiodiscriminating step in acylative kinetic resolution by the helically chiral organocatalyst was proven for the first time.

Keywords: Azahelicenes; Organocatalysis; Asymmetric catalysis; Acyl transfer; Kinetic resolution.

Azahelicenes represent unique helically chiral polyaromatic heterocycles[1] but they were for decades practically unexplored. As far as pyridohelicenes, a subcategory of azahelicenes, are concerned, there are only scattered but significant studies focused on their self-assembly[2,3], basicities[4,5] and chiroptical properties controlled by metal coordination[6]. These compounds can now be synthesised not only by using the classical photodehydrocyclisation method[7–9] but also employing intramolecular [2 + 2 + 2] cycloisomerisation of triynes[10,11] or the Stille–Kelly reaction of dihalogenated *cis*-stilbene-type precursors[12]. Becoming more easily accessible in a racemic

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or nonracemic form, azahelicenes attract an increasing attention and a systematic study of their properties and a search for their promising applications has recently been commenced. In particular, remarkably high proton affinities of pyridohelicene derivatives were measured by mass spectrometric techniques[13], chiral discrimination in silver(I)-bound dimers probed by electrospray mass spectrometry demonstrated a pronounced preference for the formation of homochiral dimers[14] similarly to the solid state[10] and acid–base dissociation constants of azahelicenes were determined by capillary zone electrophoresis[15].

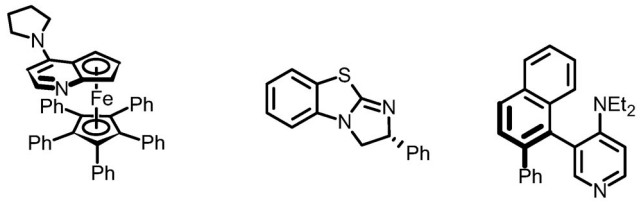
The robust helical skeleton of azahelicenes along with the presence of a basic, nucleophilic and coordinating heteroatom calls for the applications to asymmetric catalysis. The preliminary study in gas phase revealed that the interaction between protonated azahelicene and 2-alkanols, both in optically pure forms, leads to promising enantiodiscrimination[13]. Most significantly, optically pure azahelicene *N*-oxides were successfully used in desymmetrisation of *meso* epoxides achieving up to 94% ee [12]. To the best of our knowledge, this is the only example published in the literature so far, which describes the utilisation of azahelicene derivatives in enantioselective catalysis and, in particular, organocatalysis.

Herein, we report our preliminary results manifesting the first use of nonracemic azahelicenes as organocatalysts in the asymmetric acyl transfer reaction leading to kinetic resolution of racemic secondary alcohol.

RESULTS AND DISCUSSION

4-(Dimethylamino)pyridine (DMAP) is a powerful catalyst in a variety of acyl transfer reactions[16–18]. Owing to the presence of the electron-donating dimethylamino group, significantly increased nucleophilicity of the pyridine nitrogen atom leads, on reaction with carboxylic acid anhydride, to the favourable formation of the acylpyridinium–carboxylate ion pair intermediate, which serves as an effective acyl transfer-reagent in acylation reactions[16]. It goes without saying that chiral congeners of DMAP could be of outstanding utility in asymmetric acylations as, for instance, kinetic resolution of racemic secondary alcohols. Indeed, starting from the mid-nineties, myriads of chiral analogues of DMAP have emerged along with non-DMAP chiral catalyst such as fused dihydroimidazoles, imidazole-containing peptides, *N*-heterocyclic carbenes and tertiary phosphines[19]. Among them, Fu's chiral ferrocenyl DMAP catalysts[20,21] and Birman's 3,4-dihydro-2*H*-pyrimido- or 2,3-dihydroimidazo[2,1-*b*][1,3]benzothiazole catalysts[22,23] (Chart 1) have gained a privileged position due to their efficiency in asym-

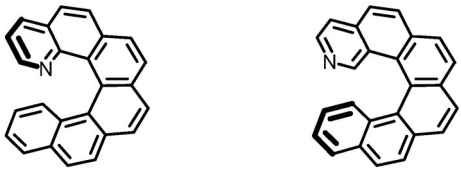
metric acylative kinetic resolution of secondary alcohols. Moreover, the Fu's catalyst **1** [24] is commercially available and the Birman's catalyst **2** [22] can be prepared in only two steps from catalogue chemicals. Classifying acyl transfer catalysts according to the type of chirality, elements of central[22], axial[25] and planar chirality have been explored exemplified by **1**–**3** (Chart 1). To the best of our knowledge, no helically chiral catalyst has so far been used in this regard.



1 Fu **2** Birman **3** Spivey

CHART 1

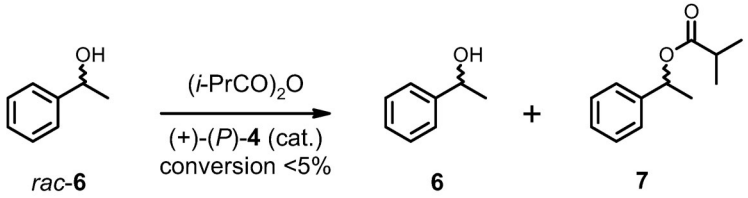
To understand the role of helical chirality in asymmetric acyl transfer reactions, we decided to explore 1-aza[6]helicene **4** and 2-aza[6]helicene **5** (Chart 2) as organocatalysts in kinetic resolution of secondary alcohols. We described earlier such azahelicenes are accessible within a reasonable number of synthetic steps to receive them in optically pure forms such as (*M*) and (*P*) enantiomers[10]. We were aware that DMAP and its derivatives, compared to parent pyridine, are approximately 10^4 times more active when used as acylation catalysts[18]. Regardless of the absence of the activating dialkylamino group in the *para* position to nitrogen in the annulated pyridine ring, we speculated that azahelicenes **4** and **5** might still be reactive enough to promote the acylation reaction possibly with enantiodiscrimination.



(+)-(*P*)-**4** (-)-(*M*)-**5**

CHART 2

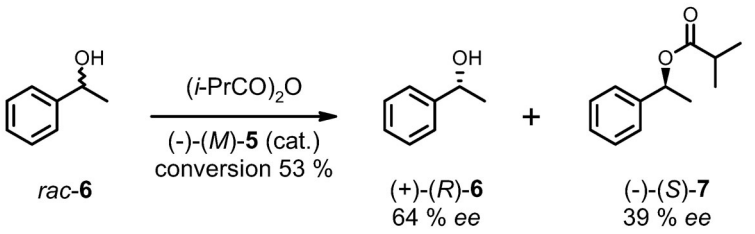
First, we examined the acyl transfer capability at (+)-(*P*)-1-aza[6]helicene **4** (Eq. (*1*)). Racemic 1-phenylethanol **6** was treated with isobutyric anhydride in the presence of a catalytic amount of (+)-(*P*)-**4** and *N*-ethyldiisopropylamine as a base in chloroform at room temperature. However, to our discouragement, even after a prolonged reaction period (20 h) we detected only a negligible amount of the acylated product **7** (<5%), whose formation could be ascribed to an uncatalysed background reaction. We reasoned that the catalytic inefficiency of (+)-(*P*)-**4** could be ascribed to a limited accessibility of the nitrogen atom in the most sterically congested position 1 rather than to its low nucleophilicity. Thus, the catalytic activity of (+)-(*P*)-**4** was not further studied.



(*1*)

(*i*-PrCO)$_2$O (0.75 equiv.), (+)-(*P*)-**4** (10 mole %), *N*-ethyldiisopropylamine (0.75 equiv.), chloroform, r.t., 20 h, **6**:**7** = >95:<5 (GC)

Accordingly, we turned our attention to isomeric (–)-(*M*)-2-aza[6]helicene **5**, which exhibited different behaviour. We found that, under analogous conditions, (–)-(*M*)-**5** served as an organocatalyst promoting the acyl transfer reaction (Eq. (*2*)). When achieving ca. 50% conversion, we could detect encouraging enantiomeric excess both of alcohol **6** and ester **7** by means of HPLC on a Chiralcel OD-H column (ee of ester determined after saponification).



(*2*)

(*i*-PrCO)$_2$O (1.0 equiv.), (–)-(*M*)-**5** (5 mole %), *N*-ethyldiisopropylamine (0.75 equiv.), chloroform, r.t., 110 h, **6**:**7** = 47:53 (GC)

For the first time, we observed an asymmetric acyl transfer process catalysed by a helicene molecule. Hence, we decided to explore the effects of the organocatalyst loading, temperature, solvents, bases and anhydrides on enantiomeric excess of (+)-(*R*)-**6** as well as selectivity of the reaction.

Obviously, the longer reaction period, the higher ee of (+)-(*R*)-**6** was observed (Table I, entries 1–4). The moderate selectivity factor *s* ranged between 5 and 9. However, at the same time, we observed minor uncatalysed background acylation, which negatively influenced the values of selectivity factor. Unfortunately, we were unable to extract the background reaction numerically as the selectivity factor was highly sensitive to conversion and, in this case, we found it too diffusive due to subtracting two values affected by an experimental error. A higher catalyst loading (Table I, entries 5 and 6) led to a faster reaction but selectivity factor was practically unchanged. Similarly, kinetic resolution performed at slightly elevated temperature (Table I, entry 5) resulted in analogous selectivity factor (*s* = 10).

TABLE I
Acylative kinetic resolution of racemic alcohol **6** employing (–)-(*M*)-**5** as organocatalyst[a]

Entry	(–)-(*M*)-**5** mole %	Temp. °C	Time h	Conversion %[b]	ee (%) of (+)-(*R*)-**6**[c]	ee (%) of (–)-(*S*)-**7**[d]	Selectivity factor[e] *s*
1	5	30	37	20.3 (3.4)[f]	19.1	nd	9
2	5	30	62	42.2 (8.6)[f]	50.4	nd	9
3	5	30	84	46.9 (10.5)[f]	53.1	nd	7
4	5	30	146	69.2 (27.6)[f]	84.3	nd	5
5	10	40	112	72.0 (19.0)[f]	99.0	nd	10
6	20	22	68	65.0	92.0	50.0	9

[a] Isobutyric anhydride (0.75 equiv.), *N*-ethyldiisopropylamine (0.75 equiv.), chloroform, unless stated otherwise. [b] Determined by GC-MS. [c] Determined by HPLC on a Chiralcel OD-H column. [d] Determined by HPLC on a Chiralcel OD-H column after saponification of the ester (nd: not determined). [e] Not corrected to the uncatalysed background reaction. [f] Conversion of uncatalysed reaction (the values in parentheses are related to the blank experiments without (–)-(*M*)-**5** under otherwise identical conditions). [g] Isobutyric anhydride (1.25 equiv.) added in two portions: 0.75 equiv. at the beginning and 0.5 equiv. after 84 h. [h] Isobutyric anhydride (1.0 equiv.). [i] Isobutyric anhydride (2.3 equiv.), *N*-ethyldiisopropylamine (2.3 equiv.).

We reasoned conversion as well as selectivity factor might have been solvent-dependent and, therefore, we performed acylative kinetic resolution of racemic alcohol **6** under (–)-(*M*)-**5** catalysis in a series of solvents (Table II). Accordingly, we monitored the highest reactivity in solvents with a low dielectric constant ($\varepsilon < 5$) such as toluene and chloroform (Table II, entries 1 and 2). Similarly, the highest selectivity factor we observed in chloroform ($s = 9$; Table II, entry 2).

TABLE II
Solvent-dependent acylative kinetic resolution of racemic alcohol **6** employing (–)-(*M*)-**5** as organocatalyst[a]

Entry	Solvent	Dielectric constant[b]	Conversion %[c]	ee (%) of (+)-(*R*)-**6**[d]	Selectivity factor[e] *s*
1	toluene	2.4	37.3	36.2	6
2	chloroform	4.8	25.9	26.1	9
3	2-methyl-2-butanol	5.8	13.2	10.8	7
4	ethyl acetate	6.1	16.1	8.4	3
5	THF	7.5	5.4	3.2	4
6	dichloromethane	8.9	16.4	10.2	4
7	acetone	21.0	4.5	2.1	3
8	acetonitrile	36.6	6.5	2.6	2

[a] Isobutyric anhydride (1.0 equiv.), *N*-ethyldiisopropylamine (0.75 equiv.), (–)-(*M*)-**5** (5 mole %), r.t., 48 h. [b] For ε, see ref.[31] [c] Determined by GC-MS. [d] Determined by HPLC on a Chiralcel OD-H column. [e] Not corrected to the uncatalysed background reaction.

Since carrying out acylative kinetic resolution of racemic alcohol **6** catalysed by (–)-(*M*)-**5** in chloroform resulted in the highest selectivity factor and good reactivity, we examined the role of the base and anhydride nature under such conditions (Table III). The experiments showed selectivity factor was practically invariant to the base added but the presence of *N*-ethyldiisopropylamine led to the highest conversion (Table III, entries 1–3). A direct comparison of various anhydrides revealed that the use of acetanhydride led to the highest conversion while the addition of isobutyric anhydride resulted in the highest selectivity factor in this series (Table III, entries 4–7).

TABLE III
Base- and anhydride-dependent acylative kinetic resolution of racemic alcohol **6** employing (–)-(*M*)-**5** as organocatalyst[a]

Entry	Base	Anhydride	Conversion %[b]	ee (%) of (+)-(*R*)-**6**[c]	Selectivity factor[d] *s*
1	Et_3N	$(i\text{-PrCO})_2O$	16.6	14.4	7
2	$i\text{-Pr}_2NH$	$(i\text{-PrCO})_2O$	14.5	12.2	7
3	$i\text{-Pr}_2NEt$	$(i\text{-PrCO})_2O$	21.5	19.7	7
4	$i\text{-Pr}_2NEt$	$(i\text{-PrCO})_2O$[e]	25.9	26.1	9
5	$i\text{-Pr}_2NEt$	$(EtCO)_2O$[e]	32.9	19.6	3
6	$i\text{-Pr}_2NEt$	$(PhCO)_2O$[e]	0.6	nd	nd
7	$i\text{-Pr}_2NEt$	$(CH_3CO)_2O$[e]	61.6	48.8	3

[a] Anhydride (0.75 equiv.), base (0.75 equiv.), (–)-(*M*)-**5** (5 mole %), r.t., 48 h. [b] Determined by GC-MS. [c] Determined by HPLC on a Chiralcel OD-H column (nd: not determined). [d] Not corrected to the uncatalysed background reaction (nd: not determined). [e] Anhydride (1.0 equiv.).

METHODS

Conversion *C* (%) was calculated from enantiomeric excesses of unreacted alcohol (ee_A, %) and formed ester (ee_E, %; estimated after its saponification) according to the equation[26,27] $C = 100 \times ee_A/(ee_A + ee_E)$ or, in most cases, from the alcohol/ester relative ratio obtained by GC-MS analyses (corrected to the alcohol/ester calibration line). Acylative kinetic resolution of racemic secondary alcohol was treated as simple first-order kinetics for the substrate in the absence of nonlinear effects involving the catalyst[28]. Selectivity factor *s* was calculated from conversion (*C*, %) and enantiomeric excess of unreacted alcohol (ee_A, %) according to the equation $s = \ln [(1 - 0.01C) \times (1 - 0.01ee_A)] / \ln [(1 - 0.01C) \times (1 + 0.01ee_A)]$ or enantiomeric excess of formed ester (ee_E, %) according to the equation $s = \ln [(1 - 0.01C) \times (1 + 0.01ee_A)] / \ln [1 - 0.01C \times (1 + 0.01ee_A)]$ [28,29].

CONCLUSION

We described, for the first time, the successful utilisation of a helicene-based organocatalyst in acylative kinetic resolution of racemic alcohol. Employing *rac*-**6**, (–)-(*M*)-**5** (5–20 mole %), isobutyric anhydride and *N*-ethyldiiso-

propylamine in chloroform at 22–40 °C, we could monitor an asymmetric catalytic acyl transfer reaction overwhelming the uncatalysed background process. Furthermore, we recorded moderate selectivity factor (s = 9, 10). Although other organocatalysts known to date exhibited higher catalytic activities as well as selectivity factors, we succeeded in applying a bare pyridohelicene molecule without the activating dimethylamino group. We proved the helically chiral organocatalyst could effectively control the enantiodiscriminating acyl transfer step achieving up to 99% ee of (+)-(*R*)-**6** at 72% conversion. Further studies on the application of other nonracemic azahelicenes to organocatalysis are in progress.

EXPERIMENTAL

^{1}H NMR spectra were measured at 499.8 or 500.13 MHz, ^{13}C NMR spectra at 125.7 MHz, in $CDCl_3$ with TMS as an internal standard. Compounds (+)-(*P*)-**4** and (–)-(*M*)-**5** were prepared earlier in the authors' laboratory[10]. Commercially available reagent grade materials were used as received. Toluene, dichloromethane, ethyl acetate, acetone, acetonitrile, *N*-ethyldiisopropylamine, diisopropylamine and triethylamine were distilled from CaH_2 under nitrogen (acetone was quickly distilled to minimise its decomposition). Chloroform stabilised with ethanol (1 vol.%) was washed with water (3 ×), dried over anhydrous $CaCl_2$ overnight, distilled from fresh anhydrous $CaCl_2$ and redistilled from CaH_2 under argon (dry chloroform was stored over 3Å molecular sieves in refrigerator). THF was freshly distilled from sodium/benzophenone under nitrogen. 2-Methyl-2-butanol (ReagentPlus®) was used as purchased. TLC was performed on Silica gel 60 F_{254}-coated aluminium sheets (Merck) and spots were detected with a solution of $Ce(SO_4)_2 \cdot 4H_2O$ (1%) and $H_3P(Mo_3O_{10})_4$ (2%) in sulfuric acid (10%).

Enantiomeric excess of alcohol **6** was determined by chiral HPLC on a Chiralcel OD-H column (250 × 4.6 mm, *n*-heptane–isopropanol 95:5, 0.6 ml/min, 18 °C) using UV (254 nm) and polarimetric detectors; retention times: 16 min for (+)-(*R*)-**6**, 19 min for (–)-(*S*)-**6**. The (*R*) absolute configuration of (+)-enantiomer and (*S*) configuration of (–)-enantiomer were assigned according to literature data[30]. Conversion (the alcohol **6** to ester **7** ratio) was determined by GC-MS using an Agilent 19091s-443 column (HP-5MS, 5% phenylmethylsiloxane; nominal length, diameter and film thickness: 30 m × 250 μm × 0.25 μm).

General procedure: A Schlenk flask was charged with (–)-(*M*)-2-aza[6]helicene **5** (4.1 mg, 0.013 mmol, 5 mole %) and flushed with argon. Dry chloroform (1 ml), racemic 1-phenylethanol **6** (30 μl, 0.25 mmol) and *N*-ethyldiisopropylamine (32 μl, 0.19 mmol, 0.75 equiv.) were added and the solution was treated with isobutyric anhydride (31 μl, 0.19 mmol, 0.75 equiv.). The reaction mixture was stirred under argon at 30 °C for a period specified in Tables I–III. Samples were continuously taken up and analysed by GC-MS and chiral HPLC.

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