Dynamic Kinetic Resolution of Biaryl Atropisomers by Chiral Dialkylaminopyridine Catalysts

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The acylative dynamic kinetic resolution (DKR) of configurationally unstable biaryl atropisomers is achieved by using newly developed chiral dialkylaminopyridine catalysts with fluxional chirality. Various types of biaryl substrates containing phenolic structures were subjected to the DKR to obtain a range of acylated biaryl products with enantiomeric ratios up to 90:10.

Stereoselective synthesis of small organic molecules is the central focus of research in synthetic organic chemistry. Over the past few decades, methodologies aimed at controlling the relative and absolute stereochemistry of a variety of reactions have been developed.[1] These procedures make molecules that have stereogenic atoms (point chirality). In contrast, atropisomeric biaryl compounds exhibit an axis of chirality (Fig. 1(A)). Atropisomerism plays an important role in controlling the pharmacological properties of biologically active compounds.[2] Atropisomeric biaryl compounds are important building blocks in the synthesis of a wide range of natural products and biologically active compounds (Fig. 1(B)).[3] They also serve as privileged skeletons for chiral auxiliaries, ligands and catalysts for asymmetric synthesis (Fig. 1(C)).[4]

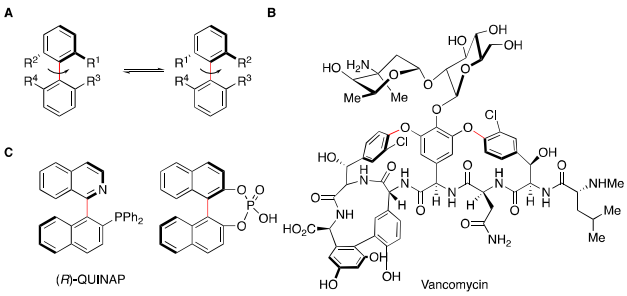

Figure 1. (A) Atropisomers with axis of chirality. (B) Glycopeptide antibiotic vancomycin, as a single atropisomer. (C) (*R*)-QUINAP, an axially chiral ligand, and a chiral phosphoric acid used in asymmetric reactions.

The inherently high rotation barriers present in hindered biaryl systems render the atropisomers stable and less amenable to racemization. Compared to the synthesis of centrally chiral molecules (such as those with chiral sp^3 centers), the introduction of axial chirality is challenging. Several methodologies are available for the synthesis of configurationally stable biaryls, such as (1) transition metal–catalyzed atropselective cross-coupling reactions[5] and (2) kinetic resolution of racemic biaryls.[6] Another simple and remarkable approach is dynamic kinetic resolution (DKR) of atropisomeric biaryls that display low rotation barriers about the axis of chirality. A major drawback of simple kinetic resolution is that the yield of the desired product is limited to 50%. A dynamic kinetic resolution (DKR) process could overcome this disadvantage by converting a racemic mixture to a single enantiomer of the product. DKR is possible when racemization of enantiomeric starting material occurs during the kinetic resolution process, resulting in the conversion of both enantiomers into a single enantiomer of the product.[7]

Due to its advantage over kinetic resolution, DKR has practical applications in organic synthesis.[8] In the past few years, significant developments to improve efficiency and applications of DKR have been reported along with an increased interest from both academia and the pharmaceutical industry. Several important reviews have been published, focusing on the theory and practical applications of DKR.[9] Dynamic kinetic resolution approaches to obtain enantiomerically pure biaryls have been investigated to a lesser extent.[10] Besides enzymatic DKR, there are very few remarkable non-enzymatic DKR approaches to synthesize stereoisomerically pure atropisomers: (a) ring-opening of configurationally unstable Bringmann's lactones[10b] and (b) peptide-catalyzed electrophilic bromination[10a] (Scheme 1).

One of the challenges central to asymmetric synthesis is the design and engineering of novel catalytic systems applicable to new classes of reactions. An important concept

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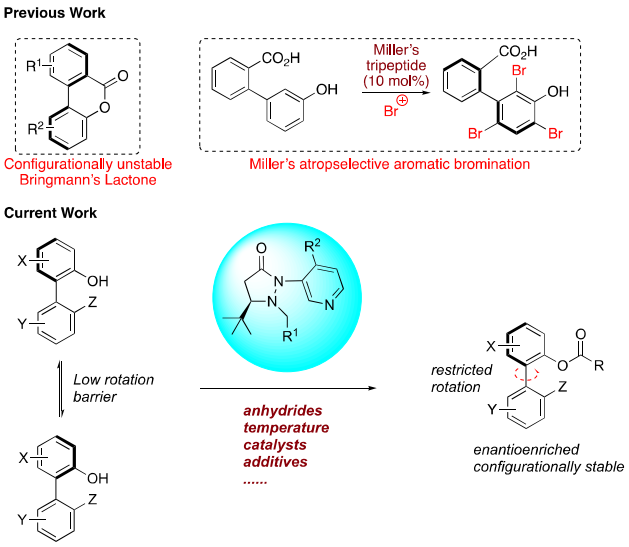
used to achieve/control stereoselectivity of reactions is the use of conformationally fluxional substituents. Our group has extensively used 3-pyrazolidinone moieties containing N-1 fluxional groups as achiral templates, ligands and additives in several asymmetric transformations.[11] As a significant extension of this strategy we recently applied the concept of *fluxional chirality* to catalyst design. This new class of modular fluxionally chiral catalysts was able to catalyze acylative kinetic resolution of secondary alcohols with high selectivity factor (up to s = 37).[6d]



Scheme 1. Illustration of Dynamic Kinetic Resolution of Atropisomeric Biphenyls

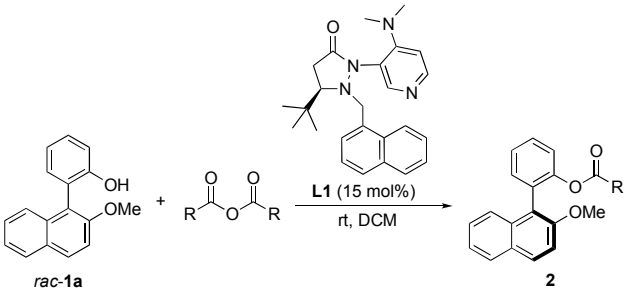
Results and Discussion

Inspired by our previous studies on kinetic resolution of secondary alcohols and dihydroxy biaryl derivatives,[6d] we decided to explore the DKR of atropisomeric biaryls using novel fluxionally chiral DMAP catalysts.[12] Our approach, shown in Scheme 1, takes advantage of the low rotation barriers in certain classes of atropisomers. In this scenario, interconversion between the less hindered starting racemic atropisomers takes place rapidly during the reaction whereas product racemization is difficult because of restricted rotation of the more hindered acylated product.[13] In the presence of a chiral 4-(dialkylamino)pyridine catalyst, the enantiomers will react with the acyl donor with different rates, and if the two enantiomers equilibrate at a rate that is faster than the reaction rate of the slow-reacting enantiomer, one enantioenriched acylated product will be produced exclusively.[14]

Effect of anhydrides on the atropselectivity

The reaction of *rac*-**1a** with different anhydrides in the presence of catalyst **L1** was carried out to identify the optimal acylating agent (Table 1, entries 1–5). Among the anhydrides tested, isobutyric anhydride was identified as the best reagent since it gave a configurationally stable product in 70% yield and 79:21 er (Table 1, entry 3). Trimethylacetic anhydride also gave the product with good enantioselectivity, but the reactivity was low (Table 1, entry 5). Notably, the isobutyrate substituted product is much more configurationally stable at room temperature than propionate or acetate substituted products.[15]

Table 1. Survey of Different Anhydrides in DKR



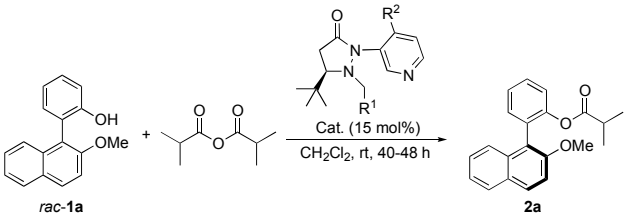
entry[a]	R	Time	Yield, %[a]	er[b]
1	methyl	12 h	85	74:26
2	ethyl	24 h	93	78:22
3	isopropyl	24 h	70	79:21
4	phenyl	5 d	82	72:28
5[c]	*tert*-butyl	10 d	66	83:17

[a]Conditions: racemic biaryl substrate *rac*-**1a** (1 equiv.) and anhydride (1.2 equiv.) in the presence of catalyst **L1** (15 mol%), DCM (2 mL), at room temperature; [b]Determined by chiral HPLC analysis. [c]Reaction was conducted at 40 °C.

Effect of catalyst structure on the atropselectivity of the DKR

The next part of our study was to evaluate the novel 4-(dialkylamino)pyridine catalysts to determine if the size of the N-1 fluxional group impacts enantioselectivity (Table 2).

Table 2. Survey of Chiral 4-(Dialkylamino)pyridine Catalysts



entry	Cat.	R^1	R^2	Yield, %[a]	er[b]
1	**L1**	1-naphthyl	dimethylamino	91	79:21
2	**L2**	phenyl	dimethylamino	86	62:38
3	**L3**	2-naphthyl	dimethylamino	89	61:39
4	**L4**	mesityl	dimethylamino	93	65:35
5	**L5**	9-anthracenyl	dimethylamino	80	79:21
6	**L6**	1-naphthyl	di-*n*-butylamino	86	70:30

[a] Conditions: racemic biaryl substrate *rac*-**1** (1 equiv.) and isobutyric anhydride (1.2 equiv.) in the presence of catalyst (15 mol%), CH_2Cl_2 (2 mL), at rt. [b] Determined by chiral HPLC analysis.

Six chiral DMAP catalysts were evaluated (Table 2, entries 1–6). Catalyst **L2** bearing a *t*-butyl chiral group at the C-5 position and a benzyl fluxional group gave low selectivity (Table 2, entry 2; 62:38 er). Similar results were observed with the 2-naphthylmethyl substituted catalyst **L3** (Table 2, entry 3; 61:39 er) and mesityl substituted catalyst **L4** (Table 2, entry 4; 65:35 er). Increasing the size of the fluxional group to 1-naphthylmethyl (**L1**) provided the best result (Table 2, entry 1; 79:21 er and 91% yield). Installing a larger 9-anthracenylmethyl fluxional group (**L5**) gave similar selectivity compared to **L1** (compare entry 1 with 5). These results suggested that the effective size of fluxional substituent has a dramatic effect on the enantioselectivity. The larger fluxional group can provide effective steric shielding only if its effective size matches the high selectivity chiral environment. The dialkylamino group on the pyridine unit of the catalyst was also investigated and found to impact selectivity: catalyst **L1** bearing the dimethylamino group gave much higher selectivity (79:21 er) than catalyst **L5** with di-*n*-butylamino substituent (70:30 er; compare entry 1 with 6). This result demonstrated that a large amino substituent is less selective. Results of catalyst screening demonstrate that **L1** is the best catalyst for the DKR of *rac*-**1a**.

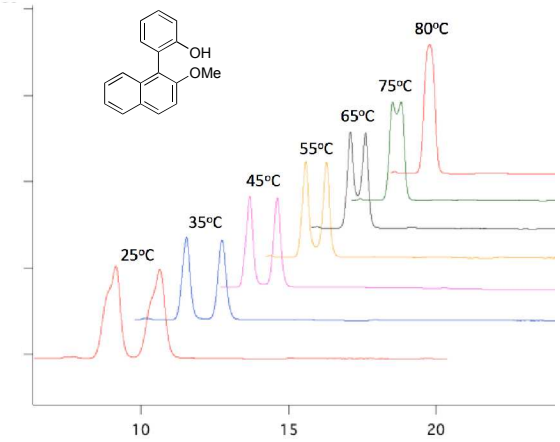
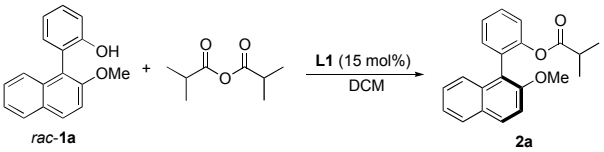


Figure 2. Temperature gradient HPLC analysis of *rac*-**1a**.

Effect of temperature on the atropselectivity of the DKR process

Previous investigation has shown that during the DKR process, a lower temperature enhances the proper recognition of each enantiomer whereas a higher temperature causes a fast equilibrium between them but also leads to more background reaction, which can decrease the enantioselectivity.[16] Temperature gradient HPLC analysis of biaryl *rac*-**1a** is shown in Figure 2. At higher temperatures (>55 °C) the peaks due to the two enantiomers started to overlap and coalesce to a single peak at about 80 °C, suggesting that at higher temperatures, lesser resolution occurred. At room temperature, two clear peaks were assigned to the two enantiomers of *rac*-**1a**. Upon increasing the temperature to 45 °C there is no considerable change in the resolution. Hence, we thought the temperature could play an important role in the DKR process of biaryl systems. The temperature of the resolution could play an important role in tuning the enantioselectivity; thus the reaction temperature was examined, and these results are shown in Table 3.

Table 3. Impact of Temperature on Selectivity



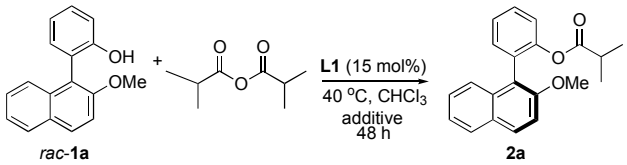
rac-**1a** **2a**

entry	T (°C)	Time	Yield, %[a]	er[b]
1	0	5 d	77	59:41
2	rt	48 h	91	79:21
3	35	48 h	94	87:13
4	45	48 h	93	86:14
5	55	48 h	93	82:18
6	75	24 h	96	75:25
7	40	48 h	95	87:13

[a] Conditions: racemic biaryl substrate *rac*-**1a** (1 equiv.) and anhydride (1.2 equiv.) in the presence of catalyst **L1** (15 mol%), DCM (2 mL), at different temperatures. [b] Determined by chiral HPLC analysis.

When the reaction was carried out at a low temperature (0 °C), the reaction time was long, and the acylated biaryl **2a** was obtained with low enantioselectivity (Table 3, entry 1). When conducted at room temperature, the reaction led to substantially higher enantioselectivity for the product (79:21 er) and showed improved reactivity (Table 3, entry 2). To our delight, the reaction at 35 °C gave the biaryls in 87:13 er (Table 3, entry 3). DKR at a slightly elevated temperature of 45 °C was successful without loss of enantioselectivity (Table 3, entry 4). Further increase in reaction temperature to 55 °C was detrimental to the selectivity (Table 3, entry 5). The loss of selectivity is likely due to the increased background reaction at higher temperature. The reaction conducted at 75 °C showed remarkable reduction of enantioselectivity (Table 3, entry 6). Finally, it was found that 40 °C was the best reaction temperature for the catalytic atropselective acylation of *rac*-**1a,** and the product was obtained with good enantioselectivity and high yield (Table 3, entry 7). Solvent also played a role in the overall efficiency. Better results were observed with halogenated solvents, and reactions in chloroform gave slightly higher selectivity (see SI).

Table 4. Evaluation of Base Additives



entry	Additive	Yield, %[a]	er[b]
1	pyridine	89	86:14
2	DABCO	95	84:16
3	Et_3N	89	87:13
4	proton sponge	87	88:12
5[c]	proton sponge	81	90:10
6	Na_2CO_3	91	86:13

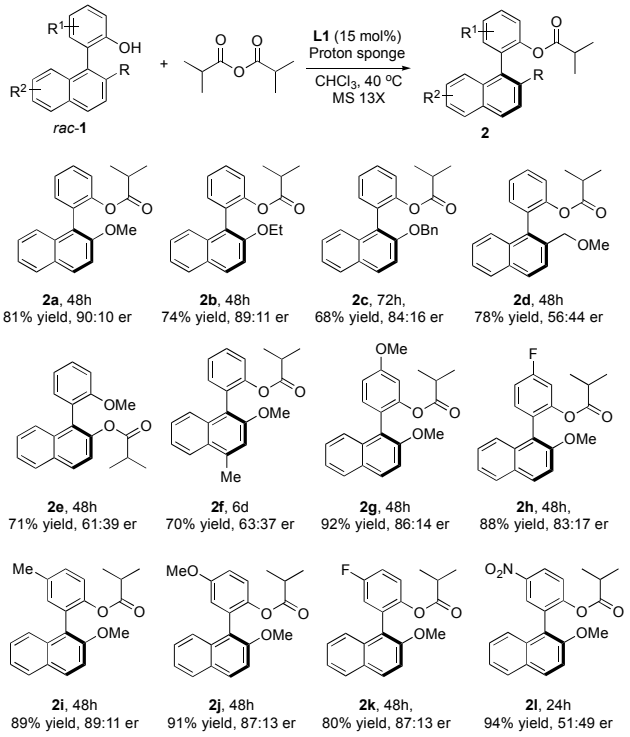
[a] Conditions: racemic biaryl substrate *rac*-**1a** (1 equiv.) and isobutyric anhydride (1.2 equiv.) in the presence of catalyst **L1** (15 mol%), Additive (1.2 equiv.), $CHCl_3$ (2 mL), at 40 °C. [b] Determined by chiral HPLC analysis; [c] with MS 13X.

Effect of base additives on the DKR process

In order to further improve the reaction, we were interested in evaluating the impact of additives on selectivity. Potentially, a basic additive could remove the acid byproduct, thus preventing deactivation of the catalyst. Additionally, base may promote proton transfer during acylation. Reaction with pyridine as the base provided the product in good yield and selectivity (Table 4, entry 1). Alkylamines as additives were also evaluated. A small loss in enantioselectivity was observed with DABCO (1,4-diazabicyclo[2.2.2]octane) as the base (Table 4, entry 2). Use of triethylamine as an additive did not improve the selectivity (Table 4, entry 3). To our delight, addition of proton sponge (1,8-bis(dimethylamino)naphthalene) improved the enantiomeric ratio slightly to 88:12 er (Table 4, entry 4). It was found that molecular sieves could further improve the selectivity (Table 4, entry 5). By adding molecular sieve 13X, the enantiomeric ratio improved slightly to 90:10 er. We were also interested in studying the effectiveness of an inorganic base in the DKR. The anion of the inorganic additive functions as a Lewis base to promote the proton transfer. In order to avoid the Lewis acidity of metal salts, an alkali metal carbonate was selected. Sodium carbonate gave selectivity comparable to that obtained with triethylamine in the DKR (Table 4, entry 6).

Biaryl scope in the DKR process

With an optimized set of reaction conditions at hand, we set out to investigate biaryl substrates in the newly developed DKR strategy (Scheme 2). The size of the R group in **1** was found to affect enantioselectivity, and a larger R group decreased reaction efficiency. The reaction with methoxy substituted biaryl *rac*-**1a** (R = OMe) gave the best result. Replacing the methoxy group with an ethoxy group (*rac*-**1b**, R = OEt) lowered the enantioselectivity. Similarly, lower enantioselectivity was observed for the reaction with the benzyloxy group (**2c**, 84:16 er). These results suggest that a small alkoxy substituent R is essential for higher selectivity in the DKR. For example, methoxymethyl substituted biaryl substrate (*rac*-**1d**) experienced a remarkable decrease in enantioselectivity. We also evaluated the impact of switching the 2-substituent with the 2'-substituent in *rac*-**1a**. Compound *rac*-**1e**, with a phenolic group on the naphthalene ring, gave a low level of enantioselectivity compared to *rac*-**1a**. To further extend the scope of the methodology, we varied the substitution pattern in the substrate. It was found that substitution on the naphthyl ring in *rac*-**1** had a detrimental effect on enantioselectivity. Resolution of compound *rac*-**1f** with a 4'-methyl substituent was slow and gave the product with a 63:37 er. In contrast, substitution on the phenol ring displayed much more interesting results. The corresponding products were obtained with comparable enantioselectivities to *rac*-**1a**.



Scheme 2. Substrate Scope for DKR of Biaryls Catalyzed by Chiral DMAP Catalyst

Additionally, substrates containing electron-donating or mildly electron-withdrawing substituents on the phenol ring were well tolerated in the DKR process. Reaction of substrates with substitution at the 5-position of the phenyl ring showed good enantioselectivity and reactivity (*rac*-**1g** and *rac*-**1h**). Similarly, reactions of substrates with an electron-donating substituent at the 4-position, 4-methyl (*rac*-**1i**) and 4-methoxy (*rac*-**1j**), gave the products with 89:11 er and 87:13 er, respectively. In contrast, substrates with an electron-withdrawing group at the 4-position showed different outcomes. Biaryl *rac*-**1k** with an electron-withdrawing fluoro group gave good selectivity. However, *rac*-**1l** with a strong electron-withdrawing nitro group showed poor

selectivity, presumably because of the uncatalyzed background reaction.

Stereochemical model for explaining atropselectivity

The results described above suggest that the naphthalene ring of the substrate has much stronger interaction with the catalyst than the phenol ring. We propose a stereochemical model for the DKR as shown in Figure 3. The DMAP ring and the acyl group of the acylpyridinium ion lie approximately in a single plane. The naphthalene ring with a methoxy group approaches the N-acyl group from the top face due to the intervention of attractive π–π interaction between the N-acyl and OMe groups and also the steric interaction with the fluxional group. The hydroxyl group on the phenol ring will stay at the bottom and attack the acyl group to generate the *S*-isomer.[17] When the 2'-alkoxy group of the substrate is large, the approach from the top face to the pyridine ring becomes difficult (**1b**, **1c**, **1d**). Furthermore, additional substituents on the naphthalene ring impact steric hindrance to the π□π□interaction (**1f**). When switching the hydroxyl group with a methoxy group like **1e**, the less sterically demanding methoxyphenyl group can probably approach the catalyst from both faces and lead to less stereochemical control.

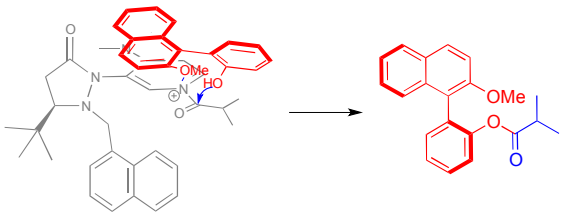


Figure 3. Proposed stereochemical model

In this work, we have demonstrated that novel fluxionally chiral 4-(dialkylamino)pyridines can serve as effective acylation catalysts for the DKR of biaryl compounds. The rapid racemization of the atropisomeric biaryl substrates was demonstrated from chiral HPLC analysis. Good yields and enantioselectivities were obtained for configurationally stable biaryl products. Our work provides a new DKR approach for the preparation of optically active biaryl compounds. Mechanistic and computational studies are underway to better understand the basis for the stereochemical outcome in this catalytic process.

Conflicts of interest

The authors declare no competing financial interest.

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