Asymmetric Organocatalysis

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Fluxionally Chiral DMAP Catalysts: Kinetic Resolution of Axially Chiral Biaryl Compounds**

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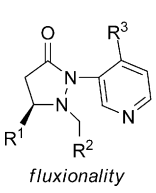
Abstract: *Can organocatalysts that incorporate fluxional groups provide enhanced selectivity in asymmetric transformations? To address this issue, we have designed chiral 4-dimethylaminopyridine (DMAP) catalysts with fluxional chirality. These catalysts were found to be efficient in promoting the acylative kinetic resolution of secondary alcohols and axially chiral biaryl compounds with selectivity factors of up to 37 and 51, respectively.*

Over the past two decades, acylative kinetic resolution through the use of non-enzymatic catalysts has become important.[1] Research in this field has focused on the development of nucleophilic catalysts, such as chiral 4-dimethylaminopyridines (DMAPs)[2] and others,[3] for the kinetic resolution of alcohols and amines with high catalytic activity and enantioselectivity. Chiral biaryl skeletons are prolific among useful organic molecules, such as biologically active natural compounds,[4] chiral ligands,[5] and chiral Brønsted acid catalysts.[6] C_2-symmetric dihydroxy-substituted biaryl derivatives have been applied extensively in a variety of enantioselective catalysts.[6] Thus, the development of catalysts which can resolve a variety of biaryl compounds efficiently is significant. Several research groups have reported the catalytic kinetic resolution of biaryl compounds, mostly by the use of biaryl-derived catalysts.[7] There is only one example of the acylative kinetic resolution of 1,1′-binaphthyl derivatives with a chiral DMAP catalyst, and the reaction proceeded with only modest selectivity ($s = 1.4$–4.4).[8]

Our research group has designed useful templates, ligands, and additives with fluxional groups to control and/or enhance stereoselectivity in a variety of asymmetric transformations.[9] A key feature of this strategy is that the size of the fluxional substituent can be varied readily. As an extension of this strategy, we became interested in developing efficient, broadly applicable, and tunable DMAP catalysts. In our design, we surmised that a fluxional group would be effective in relaying stereochemical information from the fixed stereogenic center to the catalytic center of DMAP. We report herein the synthesis of novel fluxionally chiral DMAP catalysts and their application in the acylative kinetic resolution of secondary alcohols and axially chiral biaryl compounds.

The design of our chiral DMAP catalysts is highly modular and consists of three components: a 4-(*N*,*N*-dialkylamino)pyridine (DMAP analogue) as the catalytic site, a chiral pyrazolidinone as a chirality element, and a fluxional substituent whose size can readily be varied as a blocking group (Scheme 1). Conceptually, the R^1 group dictates the orientation of the CH_2R^2 group, which in turn both influences the orientation of the DMAP group and provides steric discrimination during acylation. The 4-(*N*,*N*-dialkylamino)-pyridine is connected to the chiral pyrazolidinone at the *meta* position. Additionally, the nucleophilicity of the pyridine can be tuned by varying the dialkylamino substituent. The synthesis of these catalysts was straightforward (see the Supporting Information for details). Six novel chiral DMAP catalysts were prepared.



L1 R^1 = *i*Pr, R^2 = phenyl, R^3 = dimethylamino
L2 R^1 = *t*Bu, R^2 = phenyl, R^3 = dimethylamino
L3 R^1 = *t*Bu, R^2 = 1-naphthyl, R^3 = dimethylamino
L4 R^1 = *t*Bu, R^2 = 9-anthracenyl, R^3 = dimethylamino
L5 R^1 = *t*Bu, R^2 = 1-naphthyl, R^3 = pyrrolidine
L6 R^1 = *t*Bu, R^2 = 1-naphthyl, R^3 = di-*n*-butylamino

Scheme 1. Novel fluxionally chiral DMAP catalysts.

We initiated the evaluation of these novel chiral DMAP catalysts **L1**–**L6** for the kinetic resolution of secondary alcohols by using 1-(2-naphthyl)ethanol (*rac*-**1a**) as a test substrate and isobutyric anhydride as the acylation reagent (Table 1). Catalyst **L1** bearing an isopropyl group at the asymmetric C5 position and a benzyl fluxional group gave low selectivity for the resolution ($s = 4$; Table 1, entry 1). The selectivity factor (s) was considerably influenced by the substituent at the asymmetric center; the replacement of the isopropyl group in **L1** with a larger *tert*-butyl group (catalyst **L2**) raised the s factor from 4 to 15 (Table 1, entry 2). An increase in the size of the relay group from benzyl to 1-naphthylmethyl (in **L3**) gave the best result: $s = 23$ (Table 1, entry 3). However, an even larger 9-methylanthracenyl fluxional group (in **L4**) reduced the selectivity from that observed with **L3** ($s = 14$; Table 1, entry 4). The dialkylamino group on the pyridine unit of the catalyst was also investigated and found to impact selectivity: **L3** bearing a dimethylamino group gave higher selectivity ($s = 23$) than **L5** ($s = 11$) and **L6**

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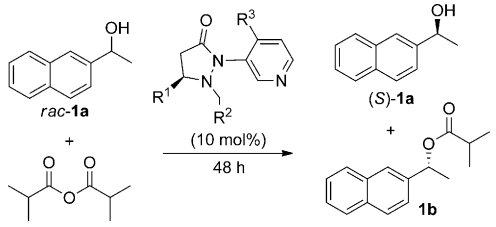
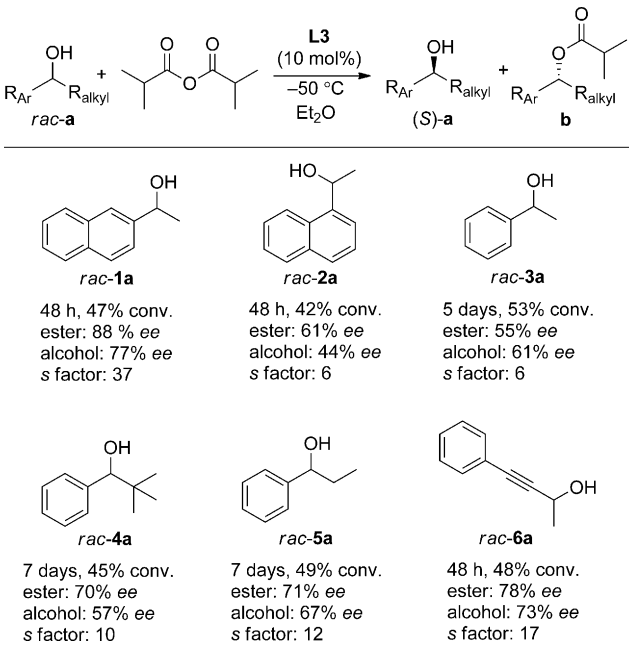
Table 1: Optimization of the reaction conditions for the resolution of 1-(2-naphthyl)ethanol.[a]



Entry	Catalyst	*T* [°C]	Conv. [%][b]	*s* factor[b–d]
1	**L1**	0	53	4
2	**L2**	0	54	15
3	**L3**	0	56	23
4	**L4**	0	49	14
5	**L5**	0	52	11
6	**L6**	0	51	9
7	**L3**	−10	57	24
8	**L3**	−50	47	37
9[e]	**L3**	−50	47	22

[a] Reaction conditions: racemic alcohol (0.1 mmol, 1 equiv), isobutyric anhydride (0.06 mmol, 0.6 equiv), chiral catalyst (10 mol%), Et_2O (2 mL), 48 h. [b] The following equations were used to calculate conversion and selectivity factors:[1a] $conv = ee_{alcohol}/(ee_{ester}+ee_{alcohol})$; $s\ factor = \ln[1-conv(1+ee_{ester})]/\ln[1-conv(1-ee_{ester})]$. [c] The *ee* value was determined by HPLC analysis. [d] The absolute configuration was assigned by comparison with literature data.[10] [e] 2,6-Di-*tert*-butylpyridine (0.06 mmol, 0.6 equiv) was added.



Scheme 2. Substrate scope for the kinetic resolution of secondary alcohols. For reaction conditions, see the Supporting Information. See Table 1 for the calculation of the conversion and *s* factor. The *ee* values were determined by HPLC analysis. Absolute configurations were assigned by comparison with literature data.[10]

($s = 9$) with a pyrrolidine and di-*n*-butylamino substituent, respectively (Table 1, entries 3, 5, and 6). The results of catalyst screening thus demonstrate that **L3** is the best catalyst for the kinetic resolution of *rac*-**1a**.

The effect of temperature was also investigated (Table 1). Lowering of the temperature from 0 ($s = 23$) to −10 °C ($s = 24$) showed limited improvement. However, when the reaction was carried out at −50 °C, the *s* factor increased dramatically to 37 (Table 1, entry 8). The addition of a base, such as 2,6-di-*tert*-butylpyridine, was detrimental to the selectivity ($s = 22$; Table 1, entry 9). Further reaction screening included different acylation reagents and solvents (see the Supporting Information).

On the basis of these investigations, we conducted the kinetic resolution of various racemic secondary alcohols with isobutyric anhydride (0.6 equiv) and **L3** (10 mol%) at −50 °C (Scheme 2). The 2-naphthyl-substituted and propargylic alcohols *rac*-**1a** and *rac*-**6a**, respectively, could be efficiently resolved within 48 h with $s = 17$–37. In contrast, resolution of 1-naphthyl-substituted alcohol **2a** proceeded with lower selectivity ($s = 6$). The steric bulk of the alkyl group on secondary alcohols **3a**–**5a** had a significant impact on the selectivity factor. The presence of bulkier *tert*-butyl and ethyl groups led to higher *s* factors of 10 and 12, respectively, than that observed for methyl-substituted benzyl alcohol ($s = 6$).

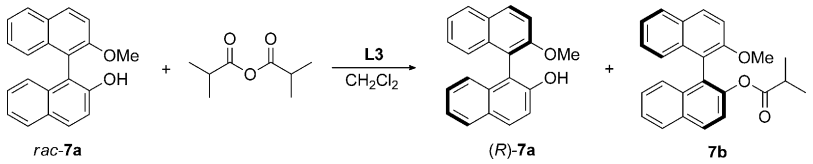
Encouraged by the results of the kinetic resolution of secondary alcohols, we proceeded to study the kinetic resolution of biaryl compounds. Our investigation started with the acylation of derivatives of dihydroxy aryl compounds. Optically active 2,2′-dihydroxy-1,1′-biaryls have received significant attention, as they are highly effective as ligands and also serve as precursors for the synthesis of many important biaryl compounds.[11]

We examined the kinetic resolution of monomethylated bi-2-naphthol (binol), *rac*-**7a**, under various conditions with catalyst **L3** and isobutyric anhydride (0.6 equiv). In the presence of 5 mol% of the catalyst at room temperature, after 72 h, *rac*-**7a** was resolved with an *s* factor of 9. Lowering of the reaction temperature led to increased selectivity (Table 2, entries 1–3), and at −50 °C, catalytic resolution gave $s = 33$, although the acylation proceeded slowly with 24% conversion. The use of higher amounts of the catalyst improved conversion (Table 2, entries 3–5). With 15 mol% of **L3**, (*R*)-**7a** was produced with increased selectivity ($s = 38$, 49% conversion; Table 2, entry 5).

We speculated that the addition of a base might lead to a higher acylation rate, because a base could remove the by-product isobutyric acid and thus prevent deactivation of the catalyst. Bulky 2,6-di-*tert*-butylpyridine was the most effective of the tested bases (Table 2, entries 6–9), and provided sufficient selectivity ($s = 36$) and 41% conversion in 84 h with 15 mol% of **L3**. We observed a diminished *s* value with 1,8-bis(dimethylamino)naphthalene (proton sponge). The absolute configuration of the product alcohol was assigned by comparison of the HPLC trace of an authentic sample of monomethylated enantiomerically pure binol.

The scope of the kinetic resolution was investigated under the optimal conditions (Scheme 3). A variety of substrates (*rac*-**7a**–*rac*-**16a**) were resolved effectively. A number of 2-hydroxy-1,1′-biaryl analogues were resolved with good to excellent selectivity ($s = 10$–51). The biaryl compound *rac*-**8a** without a substituent at the β′-position gave a reduced *s* factor

Table 2: Optimization of the reaction conditions for the resolution of monomethylated bi-2-naphthol.[a]



rac-**7a** (*R*)-**7a** **7b**

Entry	**L3** [mol%]	*T* [°C]	Additive (0.6 equiv)	*t* [h]	Conv. [%][b]	*ee* [%][c] (ester)	*ee* [%][c] (alcohol)	*s* factor[b,d]
1	5	RT	–	72	44	69	54	9
2	5	−30	–	72	46	82	71	20
3	5	−50	–	144	24	92	30	33
4	10	−50	–	120	39	90	56	34
5	15	−50	–	120	49	87	84	38
6	15	−50	2,6-di-*tert*-butylpyridine	84	41	90	62	36
7	15	−50	2,6-lutidine	60	45	88	71	34
8	15	−50	pyridine	60	50	84	84	31
9	15	−50	proton sponge	60	50	81	79	21

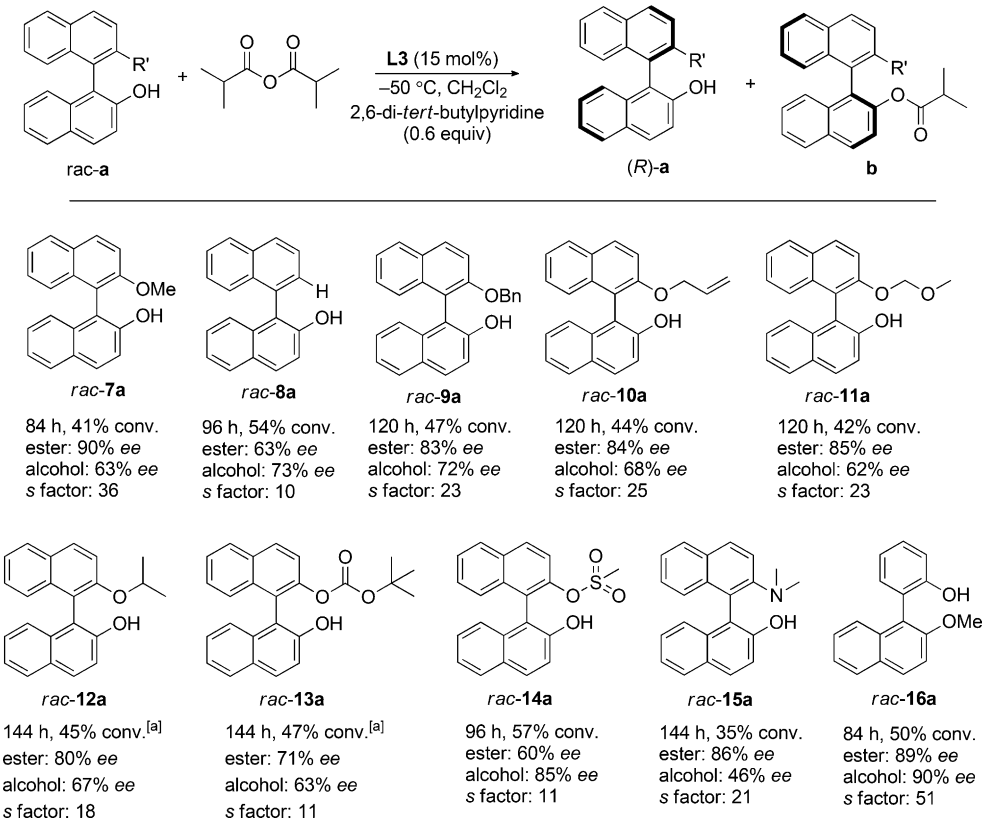
[a] Reaction conditions: racemic alcohol (0.1 mmol, 1 equiv), anhydride (0.06 mmol, 0.6 equiv), **L3**, CH_2Cl_2 (2 mL), with or without an additive. The effects of different catalysts, acylation reagents, and solvents are shown in the Supporting Information. [b,c] See Table 1. [d] The absolute configuration was assigned by comparison with HPLC data of authentic samples.

substrates with bulkier substituents, such as *rac*-**12a** and *rac*-**13a**, to increase conversion.

The catalytic kinetic resolution of 2-amino-2′-hydroxy-1,1′-binaphthyl (nobin) derivatives remains a challenging problem, and only limited examples have been reported.[7c,8] Among them, the reported chiral DMAP acylation showed only modest selectivity.[8] To expand the utility of our DMAP catalysts, we synthesized and resolved nobin derivative *rac*-**15a**. To our surprise, the kinetic resolution afforded the acylation product with 35% conversion and a high *s* factor ($s = 21$). Remarkably, substrate *rac*-**16a** with a biaryl structure was resolved with very high selectivity and an *s* factor of 51 with 50% conversion.

($s = 10$). Notably, compounds with an electron-rich group at the β′-position gave higher *s* factors: The resolution of substrates *rac*-**7a**, *rac*-**9a**, *rac*-**10a**, *rac*-**11a**, and *rac*-**12a** proceeded with *s* values higher than 18. In contrast, compounds with electron-deficient groups at the β′-position gave lower selectivities (*rac*-**13a**, *rac*-**14a**). Pyridine was used for

To get insight into the origin of the catalytic activity and stereoselectivity, we obtained the single-crystal X-ray structure of catalyst **L3** (Figure 1).[12] According to the X-ray crystal structure, the pyridine ring lies at the top of the fluxional naphthalene ring. In analogy with our prior observation, the *tert*-butyl group and the fluxional naphthylmethyl substituent are on opposite faces of the five-membered ring owing to steric interactions. The fluxional group blocks the back side as well as the bottom side of the pyridine ring. Thus, on the basis of the experimental results and structure analysis, we propose a stereochemical model for selectivity as shown Scheme 4. The DMAP ring and the acyl group of the acylpyridinium ion lie approximately in a single plane. Naphthalene ring A with the hydroxy group attacks the *N*-acyl group from the top face, and the other ring, B, approaches from the back side. To minimize steric repulsion between the naphthylmethyl group of **L3** and the B ring, the OR′ side of the B ring prefers to approach the catalyst; thus, the (*S*)-binol derivative is more favored than (*R*)-binol derivative to afford the acylation product. However,



Scheme 3. Substrate scope for the resolution of binol derivatives. For conditions, see the Supporting Information. See Table 1 for the calculation of the conversion and *s* factor. Configurations were assigned by comparing HPLC data with those of authentic samples; see the Supporting Information. [a] Pyridine (0.6 equiv) was used instead of 2,6-di-*tert*-butylpyridine. Bn = benzyl.

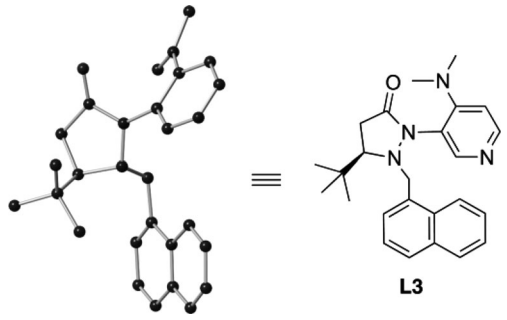
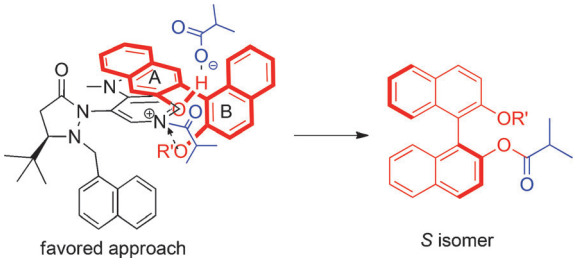


Figure 1. X-ray crystallographic analysis of **L3**.



Scheme 4. Stereochemical model for the kinetic resolution of biaryl compounds.

bulky substituents on the B ring show relatively strong repulsion and therefore decreased selectivity. The high selectivity exhibited by β′-OR′-substituted biaryl compounds possibly results from the intervention of an attractive π–π interaction between the *N*-acyl and OR′ groups.

In summary, we have established that novel fluxionally chiral DMAP molecules serve as effective acylation catalysts for the kinetic resolution of racemic secondary alcohols and biaryl compounds. This study adds a new family of DMAP-based organocatalysts to the field of nucleophilic acylation catalysis. Biaryl substrates were resolved with *s* factors of up to 51 by using this catalyst system. To the best of our knowledge, the selectivities observed for the kinetic resolution of biaryl compounds are better than those for previously reported asymmetric acylation catalysts. We have proposed a stereochemical model to explain the enantioselectivity observed in this process. Further applications of the chiral DMAP catalysts in other asymmetric transformations are under investigation.

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