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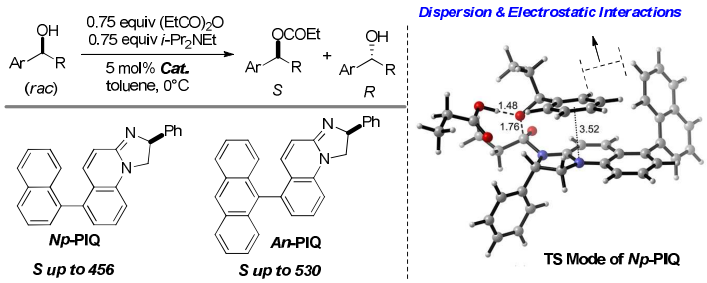

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Bi-Aryl Rotation in Phenyl-dihydroimidazoquinoline Catalysts for Kinetic Resolution of Arylalkyl Carbinols

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Chiral nucleophilic catalysts, 6-aryl-phenyl-dihydroimidazoquinolines (PIQs), were designed, synthesised and applied to the kinetic resolution of arylalkyl carbinols with very high selectivity (*S*) factors (up to 530). Density functional theory calculations indicate that multiple noncovalent interactions play a key role in chiral recognition between 6-aryl-PIQ catalyst and chiral secondary alcohol substrates.

Introduction

Nucleophilic acyl transfer catalysts,[1] such as chiral phosphines and chiral DMAP derivatives, have attracted much attention since the early work of Vedejs[2] on catalytic, nonenzymatic secondary alcohol kinetic resolution (KR). Fu and co-workers introduced planar chiral DMAP equivalents (*p*-DMAP) delivering a step changing effectiveness with selectivity factors (*S*) ranging from 32 to 200.[3] Thereafter, numerous scalemic DMAP-like catalysts integrating elements of central,[4,5] axial,[6] helical[7] and planar[8] chirality have been developed showing similar selectivity factors to those of ferrocene-containing planar chiral DMAP derivatives. Birman and coworkers[9] have described a class of amidine-based nucleophiles[10], such as CF_3-PIP,[9a] Cl-PIQ[9b] and BTM,[9c] offering higher selectivity factors (*S* up to 355). The higher selectivity factors were rationalised as resulting from π-π and π-cation interactions between the aromatic ring of the *N*-acylated catalysts and the aromatic rings of the arylalcohol substrates.

In 2010, we reported a new class of hybrid planar chiral ferrocene nucleophilic catalyst Fc-PIP (Fig. 1),[11] which combines aspects from Fu's and Birman's catalysts to deliver high selectivity factors in the kinetic resolution of bulky alkyl-containing arylalkyl carbinols (*S* up to >1800). However, our Fc-PIP system did not give such impressive selectivity factors for arylalkyl carbinols with less sterically demanding alkyl groups. In order to overcome this shortcoming, a new catalyst design concept is required.

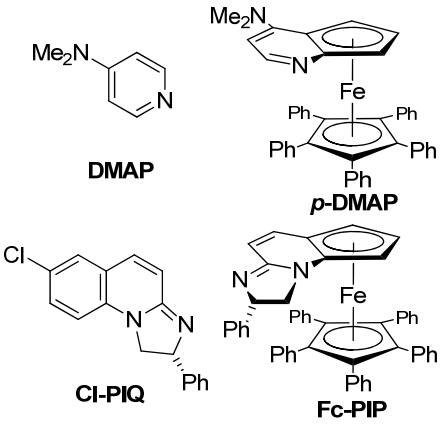


Fig. 1 DMAP and examples of previously reported chiral nucleophilic catalysts for secondary alcohol kinetic resolution

Herein, we report a variant of the PIQ core structure with aryl groups at position 6 of PIQ backbone (Fig. 2). Through comparing phenyl, naphthyl and anthracenyl derivatives, the role of semi-stable atropisomers was revealed, permitting access to greatly improved selectivity factors for most arylalkyl carbinols (*S* up to 530).

The catalytically active Fc-PIP diastereoisomer utilises matched central and planar chiral stereochemical elements with phenyl and metallocene fragments on the same face of the molecule, to create a highly selective catalyst. Whereas the alternative diastereoisomer

with the opposite sense of planar chirality (not drawn) was completely inactive as a kinetic resolution catalyst.[12]

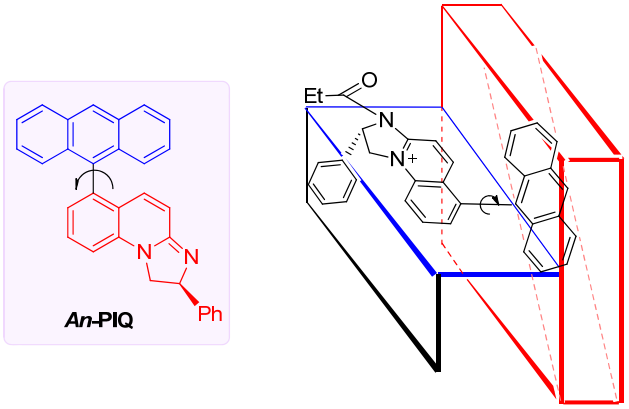
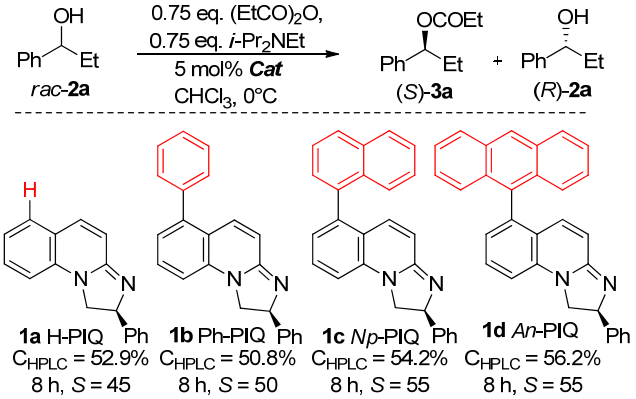


Fig. 2 Design of Ar-Ar PIQ derivatives

Results and discussion

We wished to investigate the potential for metallocene-free (organo) catalysts and drawing on knowledge learned from our earlier investigations we hypothesised that a group orthogonal to the catalyst plane may be required for the improvement of enantioselectivity. By introducing phenyl, 1-naphthyl and 9-anthryl groups at the 6-position of the catalyst core we could observe the effects of small, medium and large orthogonal aryl groups (see ESI for details of the synthesis of these 6-aryl-PIQs). A 1-naphthyl substituent offers a diversity potential in that rotational diastereoisomers, perhaps *via* a chiral relay effect,[13] may be exploited in catalysis.

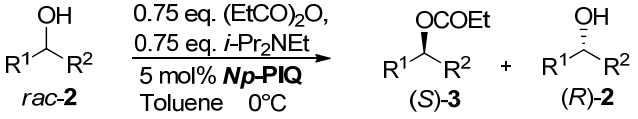
Racemic **2a** was then chosen as model substrate to investigate the catalytic asymmetric resolution capability[14] of different PIQ catalysts (**1a-d**) under a previously reported regime[9b] (Scheme 1). Interestingly, the *Np*-PIQ was found to give one set of ^{1}H NMR, however the chiral HPLC gave two diastereoisomeric peaks in 1:1 ratio. Further preparative chiral HPLC separation gave two diastereoisomers in high diastereomeric purities, but they can slowly epimerize in the HPLC eluent as well as during the evaporation under reduced pressure. Further investigation showed **1c** can also slowly epimerize under optimized reaction condition (in toluene at 0 °C). Therefore, the 1:1 ratio of diastereoisomers of *Np*-PIQ were used for the KR of secondary alcohols. (see ESI for details)



Scheme 1 Comparison of different PIQ catalysts for the KR of rac-**2a**

Encouraged by the good stereoselectivity factors obtained when using *Np*-PIQ as catalyst, we further screened the reaction condition with *Np*-PIQ (see ESI for full screening). Gratifyingly, the KR proceeded smoothly with a selectivity factor of S = 89 under optimal resolution conditions (Table 1, entry 1; *versus* S = 41 obtained with Cl-PIQ).

Table 1 Scope and generality of the *Np*-PIQ Catalysed KR[a]



Entry	R^1/R^2	C_{HPLC} (%)[b] /t (h)	S	Fc-PIP[c]	Cl-PIQ[d]
1[e]	Ph / Et (**2a**)	48.9/10	89	53	41
2	Ph / Me (**2b**)	47.4/10	43	31	33
3[e]	Ph / *i*Pr (**2c**)	49.1/15	124	84	59
4[e]	Ph / *t*Bu (**2d**)	40.6/35	450	534	117
5	2-MePh / Me (**2e**)	45.1/12	95	-	60
6	3-MeOPh / Me (**2f**)	49.8/10	70	44	-
7	4-MeOPh / Me (**2g**)	42.3/10	68	35	-
8	4-ClPh / Me (**2h**)	50.0/10	73	41	-
9	4-BrPh / Me (**2i**)	51.0/10	85	37	-
10	4-NO_2Ph / Me (**2j**)	53.9/10	95	-	-
11	4-MePh / Me (**2k**)	49.5/10	91	-	-
12	2,4-DimethylPh / Me (**2l**)	49.0/10	95	-	-
13	1-Naphthyl / Me (**2m**)	49.8/10	88	47	55
14	2-Naphthyl / Me (**2n**)	49.9/10	113	-	74
15	4-ClPh / *t*Bu (**2o**)	51.5/48	152	118	-
16	4-MePh / *t*Bu (**2p**)	43.3/48	456	61	-
17	2-Naphthyl / *t*Bu (**2q**)	49.9/50	258	142	-
18	4-(2-ClPy) / *t*Bu (**2r**)	52.5/51	118	74	-

[a] Conditions: Substrate concentration 0.1 M, $(EtCO)_2O$ 0.75 equiv., iPr_2NEt 0.75 equiv., catalyst 5 mol%. [b] Calculated from the ee of the ester and unreacted alcohol, see ref 15. [c] The S factors given by Fc-PIP in previous reports. [d] The S factors given by Birman and co-workers. [e] The experiment was carried out in duplication and relative lower S values were reported herein(see ESI for details).

Next, the generality and scope of substrates were examined, the results are summarised in Table 1. The newly developed catalyst **1c** displayed its excellent chiral recognition ability. The kinetic resolution proceeded smoothly under the optimal reaction condition for all arylalkyl carbinols tested. Selectivity factors[15] ranged from 43 to 456 and ee values for the corresponding unreacted alcohols were up to > 99.5% (see ESI). The S factors for arylalkyl carbinols with small alkyl groups were higher than those achieved with Cl-PIQ and Fc-PIP (Table 1, entries 1-3, 5-9, 13-14). Notably, bulky (hetero) arylalkyl carbinols were also well accommodated as substrates, and *Np*-PIQ also exhibited a wider substrate scope, with higher S values in many cases (entries 4, 15-18). The highest S factor (S = 456) was observed in the case of using a *p*-methyl phenyl butyl carbinol (**2p**), much higher than that achieved with Fc-PIP (entry 16).

Density functional theory (DFT) calculations were performed to better understand the role of naphthyl group appended to PIQ catalyst. At first, the origin of enantioselectivity in the acylation of 1-phenyl-1-propanol (**2a**) was analysed using B97D/TZVP[16]. Two competing diastereomeric transition states were constructed and optimised for each catalyst examined.[17] Corresponding transition state geometries were verified by frequency analysis and intrinsic reaction coordinate (IRC) calculation. Since a mixture of diastereoisomers exists under equilibrium due to a somewhat hindered rotation about an Ar-Ar bond, *N*-acetyl-6-naphthyl-PIQ was divided into two categories, one with naphthyl group on the upper

face of PIQ, and the other with the naphthyl group under the plane of PIQ, marked respectively as **1c-2a-A** and **1c-2a-B**.

For all calculated transition state structures, the free energy for the reaction with the (*S*)-enantiomer of alcohol was lower than its (*R*)-enantiomer counterpart, consistent absolute sense of enantioselection of KR. Unexpectedly, the free energy differences between stacked and splayed transition states of **1c-2a-A** and **1c-2a-B** were 5.22 kcal mol^{-1} and 3.65 kcal mol^{-1} respectively, which indicated the naphthyl group points towards the same face as the approaching arylalkyl carbinol substrates in the energetically favoured transition state. Interestingly, it was found that the transition state geometries of the fast-reacting enantiomer were stabilised by dispersion and electrostatic interactions between the naphthyl group and phenyl ring of alcohol substrates when the naphthyl group was located at the upper face of PIQ (Fig. 3, TS-1a-(*S*)-2a-A, see ESI for details).

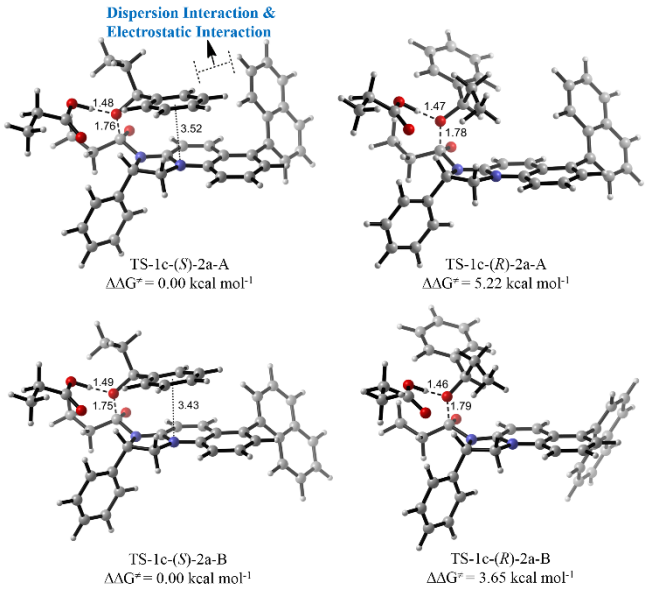


Fig. 3 Free energy calculation for possible transition states of *Np*-PIQ (**1c**)-catalysed acylation of 1-phenylpropanol (*rac*-**2a**).

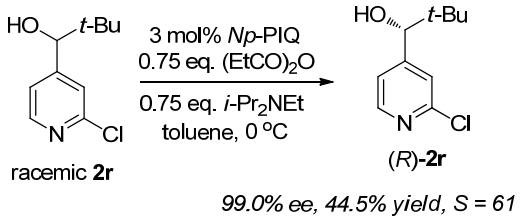
Table 2 KR of secondary alcohols using *An*-PIQ **1d**[a]

Entry	R^1/R^2	t (h)	C_{HPLC} (%)[a]	*S*	*S* (*Np*-PIQ)
1	Ph / Et (**2a**)	10	46.4	118	89
2	Ph / Me (**2b**)	10	46.2	76	43
3	Ph / *i*Pr (**2c**)	17	51.1	174	124
4[b]	Ph / *t*Bu (**2d**)	46	48.0	530	450
5	2-MePh / Me (**2e**)	13	49.2	178	95
6	3-MeOPh / Me (**2f**)	10	48.4	102	70
7	4-MeOPh / Me (**2g**)	10	48.4	105	68
8	4-BrPh / Me (**2i**)	10	51.7	110	85
9	2,4-DimethylPh/Me (**2l**)	10	46.6	114	95
10	1-Naphthyl / Me (**2m**)	10	43.5	54	88
11	2-Naphthyl / Me (**2n**)	10	52.0	72	113

[a] Conditions: 0.1 M of substrate concentration, 0.75 equiv. $(EtCO)_2O$, 0.75 equiv.iPr_2NEt, 5 mol% *An*-PIQ **1d**. [b] The experiment was carried out in duplication and relative lower *S* values were reported herein (see ESI for details).

Based on this finding, we further speculated that the selectivity factors of KR could be further improved by using the 6-anthryl-PIQ (*An*-PIQ). To our delight, *An*-PIQ catalysed KR of phenyl alkyl carbinols proceeded smoothly with higher *S* values up to 530 under the optimal condition (Table 2, entries 1-9). However, a dramatic drop of *S* value was found when naphthyl methyl carbinol (**2m** and **2n,** entries 10-11) was employed, compared with those catalysed by *Np*-PIQ. This observation might be ascribed to the steric repulsion between the extended aromatic ring of substrates with anthryl group in the favoured transition state.

In order to demonstrate the utility of 6-aryl-PIQ catalysts, catalyst *Np*-PIQ (3 mol%) was applied to the kinetic resolution on a reasonable scale (800 mg) of substrate **2r.** The reaction was proceeding smoothly to afford unreacted alcohol **2r** in 99.0% ee with good selectivity factor *S* = 61 and in 44.5% yield (Scheme 2). Besides, the catalyst could be readily recovered (88%).



Scheme 2 Larger scale catalytic KR of racemic **2r**

Conclusions

In conclusion, we have developed remarkably effective chiral 6-aryl PIQ catalysts (*Np*-PIQ/*An*-PIQ) for the enantioselective acyl transfer of secondary alcohols to achieve selectivity factors up to *S* = 530. Notably, the newly designed catalysts *Np*-PIQ/*An*-PIQ is useful for the catalytic KR of arylalkyl carbinols with both small alkyl and bulky groups with excellent *S* factors much higher than those achived with the parent Cl-PIQ and our previously reported Fc-PIP catalyst. Theoretical calculations supported the hypothesis that selectivity in kinetic resolution is induced by a *chiral relay effect* of PIQ catalysts through multiple noncovalent interactions.[18] Besides classic cation-π[19] and π-π interactions, secondary interactions, majorly dispersion and electrostatic interactions, are complimentary to each other to further enhance enantiodiscrimination, which is evident in a calculated favoured transition state between aromatic substituent and phenyl fragment of alcohol.

Acknowledgements

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† Electronic Supplementary Information (ESI) available: Synthetic procedures and characterisation for nucleophilic catalysts **1**; HPLC data analysis for all kinetic resolutions of *rac*-**2**; Computational Studies. See DOI: 10.1039/b000000x/.

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15 Due to the calculation error associated with high ee's, large *S* values should be viewed as approximate.

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17 Transition state structures of **1a** were also calculated (see ESI) and the free energy differences was 3.19 kcal mol^{-1}, indicating the asymmetric induction ability of **1c** should be much better than that of **1a**, which was exactly in accord with the experimental finding.

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