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Catalytic, Enantioselective N-Acylation of Lactams and Thiolactams Using Amidine-Based Catalysts

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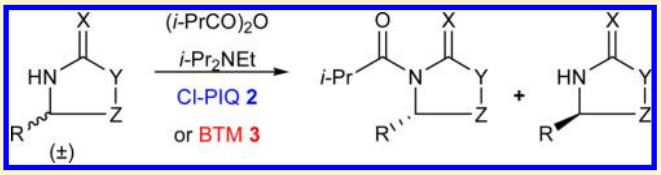
Supporting Information

ABSTRACT: In contrast to alcohols and amines, racemic lactams and thiolactams cannot be resolved directly via enzymatic acylation or classical resolution. Asymmetric N-acylation promoted by amidine-based catalysts, particularly Cl-PIQ **2** and BTM **3**, provides a convenient method for the kinetic resolution of these valuable compounds and often achieves excellent levels of enantioselectivity in this process. Density functional theory calculations indicate that the reaction occurs via N-acylation of the lactim tautomer and that cation−π interactions play a key role in the chiral recognition of lactam substrates.



INTRODUCTION

Chiral lactams (and thiolactams)[1] find numerous applications as pharmaceuticals,[2] chiral auxiliaries,[3] ligands,[4] and synthetic intermediates.[5] Many lactams can be found among bioactive natural products.[6] As a consequence, methods for their preparation in enantiopure form continue to be in high demand. Most available asymmetric catalytic methods that form the lactam ring directly from achiral precursors[7,8] deliver N-substituted lactams, which usually need to be deprotected prior to further synthetic manipulations. Most often, chiral lactams are synthesized via cyclization of enantioenriched acyclic precursors[3,6e] which simply relegates the problem of controlling the absolute configuration to an earlier step in the synthesis. However, in those cases when N-unsubstituted lactams are easily available in racemic form,[9] their resolution[10] into individual enantiomers becomes a viable alternative to asymmetric synthesis.

Since 2003, our group's efforts have been focused on the development of a new class of enantioselective amidine-based catalysts (ABCs) and their synthetic applications.[11−13] The structures of the most successful ABCs are shown in Figure 1. In 2004, having demonstrated their efficacy in the kinetic resolution (KR)[14] of benzylic secondary alcohols (Figure 2), we turned our attention to other classes of substrates. We became particularly interested in exploring the potential of ABCs in the catalytic, enantioselective acylation of nitrogen nucleophiles (Figure 3).[15] Most examples of this transformation come from the formidable body of work on enzymatic resolution of amines.[16] Enantioselective acylation of amines using non-enzymatic catalysts,[17] however, is made particularly challenging by the high nucleophilicity of these substrates, which results in their rapid background reaction with conventional acyl donors.

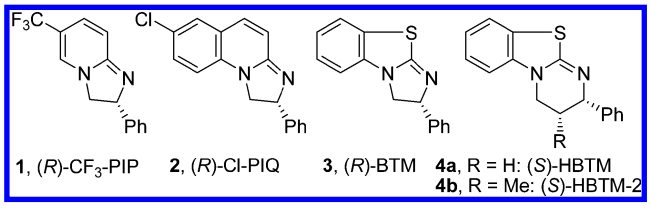


Figure 1. Amidine-based catalysts.

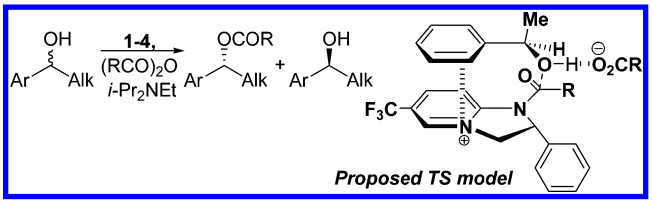


Figure 2. ABC-promoted KR of benzylic alcohols.

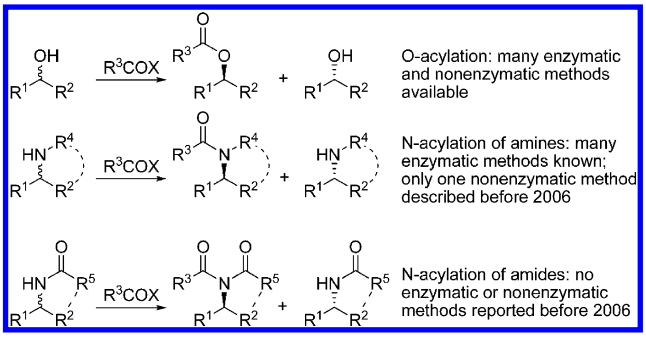


Figure 3. Scope of catalytic asymmetric acylation.

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Fortunately, several creative solutions to this problem have been found over the past decade, most notably by the groups of Fu,[18] Seidel,[19] and Bode.[20] In addition, noncatalytic methods are available for the resolution of racemic amines, such as classical resolution and related methods, i.e., crystallization of their diastereomeric salts with chiral acids,[10,21] and acylation with stoichiometric chiral acylating agents.[22]

We realized that the enantioselective N-acylation of secondary amides with simple anhydrides should be inherently less problematic than that of amines, due to the lower nucleophilicity of the former. Surprisingly, prior to our first publication in this area in 2006,[12a] there had been no reports of this transformation achieved using either enzymes or nonenzymatic catalysts. At the same time, we reasoned, it would be even more practically valuable than the enantioselective N-acylation of amines, because, in contrast to the latter, amides cannot be resolved via classical resolution.

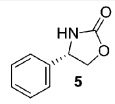
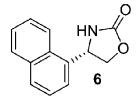
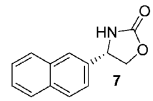
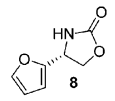
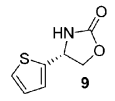
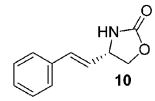
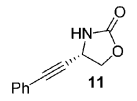
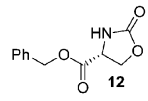
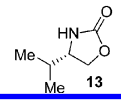
Generally speaking, resolution of amides—both acyclic and cyclic ones (lactams)—is underdeveloped and relies mostly on the use of stoichiometric resolving agents or indirect methods. For example, Kuneida et al. reported in 1992 that racemic oxazolidinones could be resolved by chromatographic separation of their diastereomeric *N*-camphanoyl derivatives.[23a] Later, the same group achieved catalytic KR of *N*-acyl-oxazolidinones and *N*-acyl-imidazolidinones via enantioselective reductive deacylation mediated by CBS.[23b] Transformation of secondary amides into their *N*-hydroxymethyl derivatives followed by enzymatic O-acylation and deprotection has been reported by several groups.[24] Acyclic amides and *β*-lactams have been resolved via enzymatic hydrolysis of the amide bond.[25] An analogous nonenzymatic transformation, enantioselective alcoholysis of *N*-acyl-*β*-lactams, was recently developed in our group using catalyst **3**.[13d] Apart from our studies in this area described below, Miller et al. reported KR of formamides and thioformamides in 2010.[26] Their study has provided the first successful examples of catalytic, enantioselective N-acylation of *acyclic* amides.

In the present Article, we provide a detailed account of our studies on the KR of lactams and thiolactams promoted by ABCs. Our focus shall be on the correlation between the structures of our substrates and catalysts and their reactivity and enantioselectivity in KR. Therefore, the discussion of varying reaction parameters (solvent, concentration, temperature, time, acylating agent, base, etc.) shall be kept to a minimum. The results shown in Tables 1−5 are the best obtained for each given substrate−catalyst combination. We also provide the first density functional theory (DFT) study on the mechanism of ABC-catalyzed N-acylation of lactams and the origins of enantioselectivity in this process.

RESULTS AND DISCUSSION

Oxazolidinones. In 2006, we disclosed the first examples of KR of oxazolidinones via enantioselective N-acylation.[12a] Our inspiration came from prior reports[27] that N-acylation of oxazolidinones with anhydrides is effectively promoted by DMAP, the classical achiral acyl transfer catalyst.[28] The results of our initial investigation of this class of substrates, as well as subsequent, previously unpublished findings are summarized in Tables 1 and 2. Generally speaking, benzotetramisole (BTM) **3**[11c] has emerged as the catalyst of choice for most of the oxazolidinones studied, due to its outstanding enantioselectivity and the convenience of the optimal reaction conditions (chloroform at room temperature). 7-Chloro-1,2-dihydro-2-phenyl-imidazo[1,2-*a*]quinoline (Cl-PIQ) **2**,[11b] on the other hand, typically produces lower selectivity factors[29] and besides, reaches its peak performance in *tert*-amyl alcohol, which is less than ideal from the practical standpoint. The efficacy of KR depends on the presence of all of the fast-reacting enantiomer of the substrate in solution. Therefore, it is usually critical to ensure complete dissolution of the racemic substrate prior to the start of the reaction. For example, oxazolidinone **21**, which is singularly insoluble in *tert*-amyl alcohol, could not be resolved at all using Cl-PIQ in this solvent. Fortunately, it dissolved relatively easily in chloroform at room temperature, which permitted its successful KR using BTM (Table 2, entry 8). This is not to suggest, however, that Cl-PIQ can be dismissed in favor of BTM. In fact, we have found a number of oxazolidinone substrates that fail under BTM catalysis, but produce respectable results using Cl-PIQ (Table 1, entries 6a and 6b, Table 2, entries 9a and 9b). Some enhancement of enantioselectivity in Cl-PIQ-catalyzed reactions is observed at

Table 1. KR of 4-Substituted Oxazolidinones

entry	(±)-substrate[a]	catalyst (mol%)	time (h)	%C	s
1a	 5	**2** (4)	19	44	24
1b[a]		**2** (4)	24	41	41
1c[b]		**3** (8)	5.0	48	170
1d[c,d]		**4a** (10)	24	44	45
2a	 6	**2** (4)	17	46	38
2b		**3** (4)	21	42	450
3a	 7	**2** (4)	19	44	44
3b		**3** (4)	14	47	260
4a	 8	**2** (4)	17	50	25
4b		**3** (4)	9.0	42	96
5a	 9	**2** (4)	15	47	16
5b		**3** (4)	6.0	49	430
6a	 10	**2** (4)	24	43	92
6b[e]		**3** (4)	24	~15	ND
7	 11	**3** (4)	1.5	45	58
8	 12	**3** (4)	2.0	52	95
9a[d]	 13	**2** (10)	24	0	ND
9b		**3** (10)	24	0	ND

General conditions: 0.2 M (±)-substrate concentration, 0.75 equiv (*i*-PrCO)$_2$O, 0.75 equiv *i*-Pr$_2$NEt, (*R*)-**2** was used at in *tert*-amyl alcohol at 0° C; (*R*)-**3** was used in chloroform at rt (23° C), unless specified otherwise. Absolute configuration of the fast-reacting enantiomer is shown. [a]0.05 M substrate. [b]1.5 equiv (*i*-PrCO)$_2$O. [c]0.1 M substrate, *tert*-amyl alcohol [d]At rt. [e]Conversion estimated by ^{1}H NMR.

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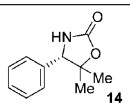
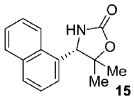
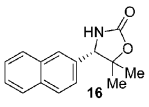
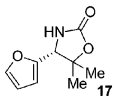
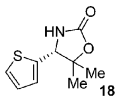
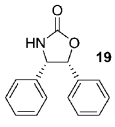
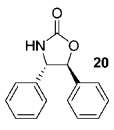
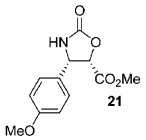
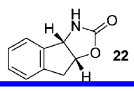
Table 2. KR of 4,5-Substituted Oxazolidinones

entry	(±)-substrate	catalyst (mol%)	time (h)	%C	s
1a	 14	**2** (8)	22	43	55
1b[a]		**3** (8)	12	33	340
2a[b]	 15	**2** (4)	10	40	110
2b[a]		**3** (8)	7.0	45	520
3a	 16	**2** (4)	10	49	70
3b[a]		**3** (8)	9.0	37	200
4a	 17	**2** (4)	28	50	28
4b[a]		**3** (8)	7.0	43	88
5a	 18	**2** (4)	19	49	18
5b[a]		**3** (8)	7.0	50	390
6a[b]	 19	**2** (4)	24	43	26
6b		**3** (4)	6.0	43	300
7a	 20	**2** (4)	15	48	19
7b		**3** (4)	6.0	44	50
8	 21	**3** (4)	6.0	51	110
9a[c]	 22	**2** (10)	30	36	36
9b		**3** (10)	24	0	ND

General conditions: same as Table 1, except as noted. [a]1.5 equiv $(i\text{-PrCO})_2O$. [b]Substrate incompletely dissolved at 0.1 M. [c]0.05 M substrate.

low substrate concentrations (Table 1, entries 1a vs 1b, 0.2 and 0.05 M, respectively). Homobenzotetramisole (HBTM) **4a**, which was developed a few years later,[11d] also produced a respectable selectivity factor when used in *tert*-amyl alcohol (Table 1, entry 1d). However, it proved to be less active than either **2** or **3** and therefore was not pursued further.

The absolute sense of enantioselection and the general structure-selectivity trends noted in this study were consistent with the cation–π interaction model proposed earlier in the context of enantioselective O-acylation.[11a,e] As we had expected, an aryl or heteroaryl group next to the nitrogen of the substrates was important not only for the enantioselectivity, but even reactivity. Thus, isopropyl-substituted oxazolidinone **13** simply failed to react under our standard reaction conditions (entry 9). Later, we demonstrated that nonaromatic substituents, e.g., an alkene, alkyne, or ester group can also be quite effective as chiral recognition elements (Table 1, entries 6–8), which, again, is in accord with the successful KR of the analogous alcohols by the same catalysts.[11f,30]

There are, however, several notable differences between oxazolidinones and alcohols.[11f] For example, increasing the size of the a-alkyl group on benzylic alcohol substrates (Me→ Et→*i*-Pr→*t*-Bu) leads to progressively higher selectivity factors. In the case of oxazolidinones, the trend is not so clear. Although *gem*-dimethyl substitution of C5 usually increases enantioselectivities when C4 substituent is an aryl (phenyl, 1-naphthyl or 2-naphthyl), it makes little difference when R is heteroaryl (2-furyl or 2-thienyl). Furthermore, KR of 1-thienylethanol is much less enantioselective than that of 1-phenylethanol (s = 19 vs 80 under similar conditions). In contrast, BTM-catalyzed KR of 2-thienyl-oxazolidinone yielded one of the highest selectivity factors obtained in this series, considerably outperforming that of its phenyl counterpart (Table 1, entries 5b vs 1c, s = 430 vs 170). An even more intriguing difference is found in the following example. The ring constrained benzylic alcohol 1-indanol has proved to be an unsuitable substrate for our catalysts. Its lack of reactivity has been explained by its inability to adopt the reactive conformation, which would allow the benzene ring to stack on top of the N-acylated catalyst. However, its oxazolidinone counterpart, the indane-fused substrate **22**, produced fairly good enantioselectivity when acylated in the presence of 10 mol % of Cl-PIQ (BTM was completely ineffective in this case). The mechanistic origin of the differences noted above is not clear. The only definite conclusion they point to is that the structure-selectivity trends observed for one class of substrates cannot be extrapolated reliably to another one.

Survey of Structurally Related Lactams and Acyclic Amides. Upon completion of our initial study of oxazolidinones, we decided to map out the substrate scope of our new enantioselective N-acylation methodology. We were disappointed to find that pyrrolidinone **23** and imidazolidinone **24**, despite being close structural analogues of 4-phenyl-oxazolidin-2-one **5**, are completely unreactive in the presence of 10 mol % catalyst loadings of either BTM or Cl-PIQ (Table 3, entries 1 and 2). On the other hand, benzyl (±)-pyroglutamate **25** did react, albeit very slowly, in the presence of 10 mol % of Cl-PIQ and afforded excellent enantioselectivity (entry 3).

Comparison of the results obtained in the oxazolidinone and pyrrolidinone series (Table 1, entries 1 and 8; Table 3, entries 2 and 3, respectively) suggested that the reactivity of lactams toward N-acylation might be dependent on the pK_a of the N–H bond.[31] Indeed, while substrate **23** was totally unreactive, replacing the amide moiety in its structure with a carbamate (cf. **5**), or even the α-phenyl with the more electron-withdrawing ester group (cf. **25**), was sufficient to permit acylation. Combination of the two, as expected, resulted in the higher reactivity of substrate **12** (Table 1, entry 8). With this in mind, we turned our attention to another structural type of 5-membered lactams bearing an additional heteroatom in the ring and thus predicted to have increased N–H acidity: oxazolidin-4-one **26**, thiazolidin-4-one **27**, and imidazolidin-4-one **28**. Gratifyingly, all three of them underwent acylation in the presence of BTM with excellent selectivity factors and, pleasingly, much higher reaction rates than their oxazolidin-2-one prototype **5**. It is noteworthy that these three compounds are closely related to Seebach's chiral enolate precursors.[5] Although they are easily obtained in racemic form via acid-catalyzed condensation of benzaldehyde, their asymmetric synthesis would not be trivial. Therefore, the KR procedure described herein should be of practical value for their preparation in enantiopure form. We also examined 6-phenyl-

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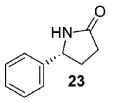
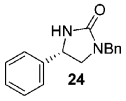
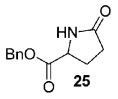
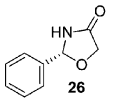
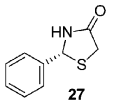
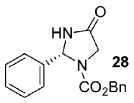
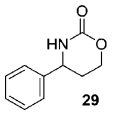
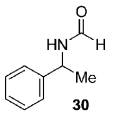
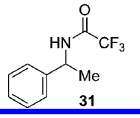
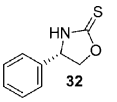
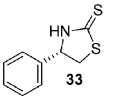
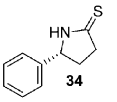
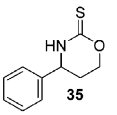
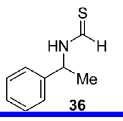
Table 3. KR of Related Lactams and Amides

entry	(±)-substrate	catalyst (mol%)	time (h)	%C	s
1a	 23	**2** (10)	24	0	ND
1b		**3** (10)	24	0	ND
2a	 24	**2** (10)	24	0	ND
2b		**3** (10)	24	0	ND
3a[a]	 25	**2** (10)	72	46	131
3b		**3** (10)	24	0	ND
4	 26	**3** (4)	0.25	41	113
5	 27	**3** (4)	0.66	47	294
6[b]	 28	**3** (4)	0.25	42	151
7a	 29	**2** (10)	24	0	ND
7b		**3** (10)	24	0	ND
8a	 30	**2** (10)	24	0	ND
8b		**3** (10)	24	0	ND
9a	 31	**2** (10)	24	0	ND
9b		**3** (10)	24	0	ND

General conditions: same as Table 1, except as noted. [a]At rt. [b]0.1 M substrate.

Table 4. KR of Thiolactams

entry	(±)-substrate	catalyst (mol%)	time (h)	%C	s
1[a]	 32	**3** (4)	1.0	49	82
2[a,b]	 33	**3** (4)	4.0	47	30
3	 34	**3** (8)	4.0	44	140
4[c,d]	 35	**2** (10)	24	~14	1.2
5[c]	 36	**2** (10)	48	~24	1.2

General conditions: same as Table 1, except as noted. [a]0.1 M substrate. [b]Substrate incompletely dissolved. [c]Conversion estimated by ^{1}H NMR. [d]Product decomposed during chromatography.

oxazinone **29**, the ring-expanded analogue of **5**, as well as acyclic secondary amides, *N*-(α-phenethyl)-formamide **30** and -trifluoroacetamide **31**. Unfortunately, all of these failed to react under our standard conditions.

Thiolactams. The apparent correlation between pK_a and reactivity noted above suggested that thiolactams, known to be more acidic than the analogous lactams, might display enhanced activity. Indeed, 4-phenyloxazolidine-2-thione **32** (Table 4, entry 1) underwent more rapid acylation than its oxygen counterpart **5** (Table 1, entry 1c). Although the enantioselectivity was reduced relative to the latter, it was still amply sufficient for practical purposes. The corresponding dithio derivative **33**, unfortunately, proved to be virtually insoluble in chloroform and other suitable reaction solvents and dissolved only gradually in the course of acylation. Thus, the calculated values for the selectivity factor and the conversion may not reflect the true enantioselectivity and rate of the reaction. We were especially pleased to find that **34**, the thio analogue of the completely unreactive pyrrolidinone **23**, underwent BTM-catalyzed KR smoothly and with an excellent selectivity factor. Oxazine-2-thione **35**, on the other hand, reached only low conversions during acylation. Furthermore, the acylated product proved to decompose easily on silica gel. Similarly slow reaction was observed in the case of *N*-(α-phenethyl)thioformamide **36**. Ee's of the products in both of these cases were low, which suggested that further efforts in this direction were unlikely to produce a practically useful result.

***β*-Lactams.** In a recent parallel development in our group, we demonstrated that *N*-aroyl-*β*-lactams could be efficiently resolved via BTM-catalyzed enantioselective alcoholysis.[13d] While this method produced good to excellent enantioselectivities and displayed a broad substrate scope, we were aware that the N-benzoyl group could not be removed without opening the four-membered ring. Therefore, it was not suitable for producing N-unsubstituted *β*-lactams themselves in enantiopure form. This consideration prompted us to revisit the N-acylation chemistry. We were worried, of course, that, by analogy with 5-phenylpyrrolidinone mentioned above, the pK_a of the amide moiety of *β*-lactams might be too high to permit acylation with ABCs. Indeed, both BTM and HBTM, proved to be ineffective. Fortunately, Cl-PIQ lived up to our expectations (Table 5). After some optimization of the reaction conditions, we were able to obtain modest to good selectivity factors with a range of substrates bearing an aryl or heteroaryl group at C4. Additional alkyl substituents at C3 were tolerated, although the enantioselectivity and the reaction rates were diminished in these cases (cf. entries 8 vs 1a, 9 vs 6). Indene-derived substrate **46** (entry 10) produced an encouraging selectivity factor 13, which is in line with the result obtained in the oxazolidinone series (cf. **22**, Table 2) and in contrast to the corresponding alcohol, 1-indanol.[11f] At the same time, substrate **47** failed to undergo acylation completely, which again suggests the importance of π-interactions (entry 11). Finally, we explored the possibility of rendering this class of substrates more reactive by replacing the lactam oxygen with sulfur (cf. Table 4). Indeed, thio-*β*-lactam **48** (Table 5, entry 12) reacted very

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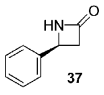
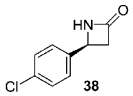
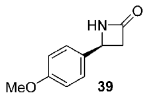
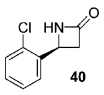
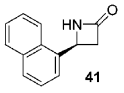
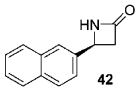
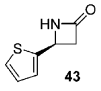
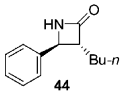
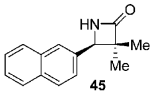
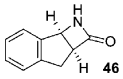
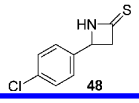
Table 5. KR of β-Lactams

entry	(±)-substrate	catalyst (mol%)	time (h)	%C	s
1a	 37	(*S*)-**2** (10)	24	43	22
1b[a]		(*S*)-**3** (10)	24	0	ND
1c[a,b]		**4a** (10)	48	~10	ND
2	 38	(*S*)-**2** (10)	30	54	30
3	 39	(*S*)-**2** (10)	30	42	38
4	 40	(*S*)-**2** (10)	30	14	3.1
5[c]	 41	(*S*)-**2** (10)	72	41	19
6	 42	(*S*)-**2** (10)	30	53	54
7	 43	(*S*)-**2** (10)	30	59	17
8[c]	 44	(*S*)-**2** (10)	72	38	16
9[c]	 45	(*S*)-**2** (10)	72	26	13
10	 46	(*S*)-**2** (10)	30	42	14
11[a]	 47	(*S*)-**2** (10)	24	0	ND
12[a,b]	 48	(*S*)-**3** (4)	0.25	~75	1.1

General conditions: 0.05 M (±)-substrate concentration, 2.0 equiv $(i\text{-PrCO})_2O$, 2.0 equiv $i\text{-Pr}_2NEt$, *tert*-amyl alcohol at 0 °C, unless specified otherwise. [a]In $CDCl_3$ at rt. [b]Conversion estimated by ^1H NMR. [c]4.0 equiv $(i\text{-PrCO})_2O$, 4.0 equiv $i\text{-Pr}_2NEt$.

rapidly under BTM catalysis. Alas, virtually no enantioselectivity was observed in this reaction.

Computational Studies. Taking into account that the N-acylation project was initially conceived by analogy with KR of alcohols, it is not surprising that we interpreted all our experimental data in accord with the previously proposed transition state model for the latter process[11a,e] (Figure 2). Indeed, all successfully resolved lactam substrates exhibited the same absolute sense of enantioselection as their alcohol counterparts. This general observation was consistent with π-interactions playing a major role in the transition states leading to the N-acylation of 5- and 4-membered lactams. However, finer details of the reaction mechanism and transition state geometry in this process still remained unclear.

In the acylation of alcohols, the hydroxyl attacking the acyl carbonyl is hydrogen-bound to the carboxylate counterion, which acts as a general base. Thus, the C−O bond formation and the O−H bond cleavage occur in a concerted fashion. Does the N-acylation of lactam substrates also happen in the same way?

We have considered three possible pathways illustrated schematically in Figure 4 for 4-phenyloxazolidinone **5**: (a) N-

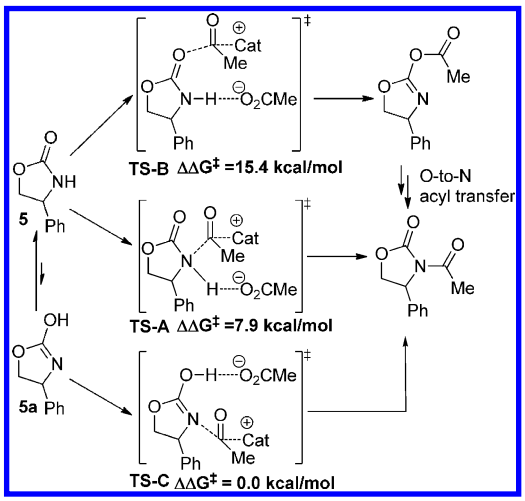


Figure 4. Three possible pathways of catalytic N-acylation of **5**.

acylation proceeding via concerted deprotonation of the lactam nitrogen by the carboxylate anion, in direct analogy to the acylation of alcohols; (b) Initial acylation of the lactam oxygen with subsequent O-to-N acyl transfer, and (c) N-acylation of the lactim tautomer **5a** hydrogen-bound to the carboxylate anion. M06-2X calculations[32,33] on a simplified model (using des-phenyl-BTM as catalyst and acetic anhydride) indicate that the transition states **TS-A** and **TS-B** representing the first two scenarios are 7.9 and 15.4 kcal/mol higher in energy, respectively, than the isomeric transition state **TS-C**. The latter is favored by the higher nucleophilicity of the lactim nitrogen than of either the nitrogen or the oxygen of the lactam form.[34]

Using transition state **TS-C** as the starting point, we analyzed the origin of enantioselectivity in the acylation of 4-phenyloxazolidinone **5** using M06-2X. The geometries of the competing diastereomeric transition states with *(R)*-BTM are shown in Figure 5. Both transition states involve a concerted C−N bond formation and deprotonation by the acetate

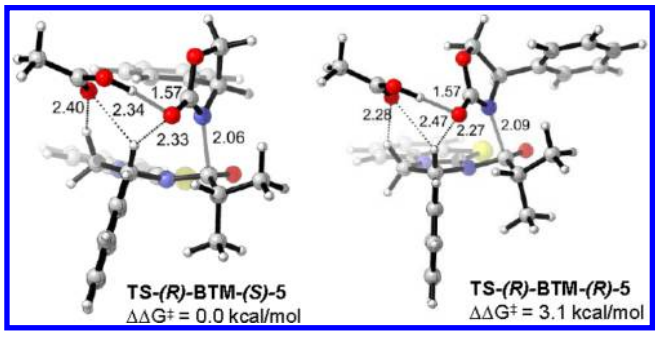


Figure 5. Transition states of BTM-catalyzed acylation of **5** (in $CHCl_3$).

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counterion (representing the isobutyrate anion in the actual reaction). In both structures shown, the oxazolidinone oxygen forms a weak hydrogen bond to the C2-position of the catalyst (O−H distances are both ~2.3 Å). The acetate counterion also forms additional hydrogen bonds to the C2 and C3 of the catalyst. In the fast-reacting diastereomer, the phenyl ring of the substrate is stacked over the thiazolium moiety of the catalyst due to the cation-π interactions, as expected by analogy with the acylation of alcohols. The computed free energy difference was in a good agreement with the experimental result (selectivity factor s = 170 at room temperature corresponds to ΔG_{298K} = 3.0 kcal/mol).

With this result in hand, we proceeded to analyze the transition states for the Cl-PIQ-catalyzed KR of three representative lactams: 4-phenyloxazolidinone **5**, its ring-constrained analogue, the Indane-fused oxazolidinone **22**, and 4-phenylazetidinone **37** (Figures 6−8, respectively). Qualitatively similar results were obtained in each of these cases, except that the acyl carbonyls were twisted markedly out of the plane of the catalyst and pyramidalized in both diastereomeric transition states. Strong cation-π interactions clearly contributed to the stabilization of all the fast-reacting enantiomers, even **22**, despite the rigidly constrained orientation of its benzene ring (Figure 7). In fact, our calculations overestimated the free energy differences for all Cl-PIQ-based structures, especially the one with 4-phenyloxazolidin-2-one **5** (Figure 6), in contrast to the good agreement obtained for the BTM-based transition states (Figure 5). In the actual Cl-PIQ-catalyzed KR, substrate **5** produced s = 17 in $CHCl_3$ and s = 41 in *tert*-amyl alcohol at 0 °C, i.e., ΔG_{273K} = 1.5 or 2.0 kcal/mol, respectively. The reason for this discrepancy is unclear at present.

We speculate that the ease of tautomerization is likely to be one of the key factors determining the rate of acylation. What we do know is that the more acidic substrates generally get acylated faster. Since experimental pK_a values for many of these compounds have not been reported, we have used instead the M06-2X computed proton affinities of the corresponding anions relative to the 4-phenyl-oxazolidinone anion (Figure 9).

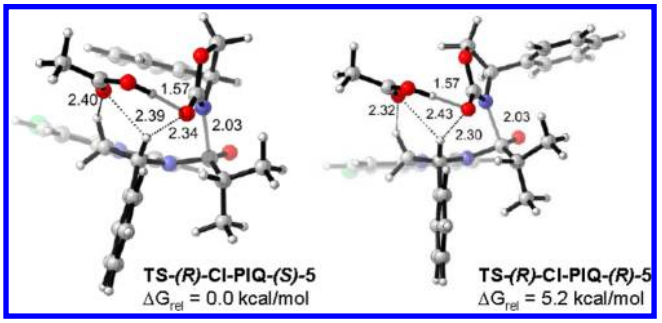

Figure 6. Transition states of Cl-PIQ-catalyzed acylation of **5** (in $CHCl_3$).

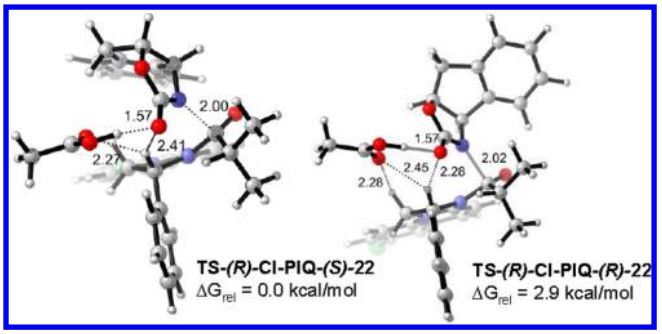

Figure 7. Transition states of Cl-PIQ-catalyzed acylation of **22** (in $CHCl_3$).

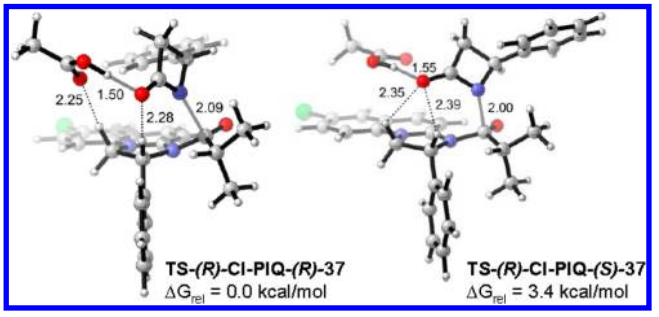

Figure 8. Transition states of Cl-PIQ-catalyzed acylation of **37** (in $CHCl_3$).

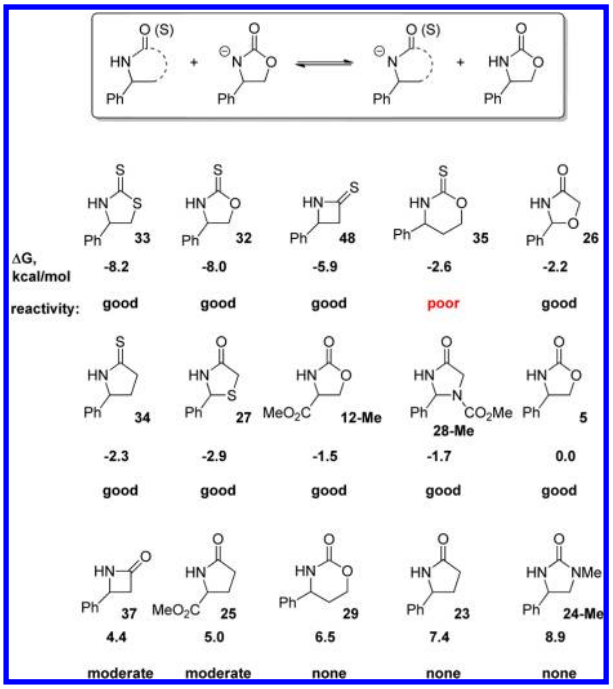

Figure 9. Computed relative proton affinities of conjugate bases of lactams and thiolactams. Negative values indicate that the N−H bond is more acidic than the N−H bond in **5**.

A qualitative correlation between the acidity and the reactivity of the substrates was observed. The only obvious outlier in the series displayed in Figure 9 is the oxazine-2-thione **35**, which displays poor reactivity despite its high acidity, apparently due to its different geometry. Even though this approach provides only a rough estimate of reactivity, it does allow us to predict with some confidence the likelihood of success in the acylation of new substrates.

■ CONCLUSION

Our studies described above demonstrate that several classes of 4- and 5-membered lactams and thiolactams are amenable to catalytic enantioselective N-acylation using amidine-based catalysts. This methodology provides a means for achieving their kinetic resolution under simple experimental conditions, using only inexpensive reagents, and often with excellent

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selectivity factors.[35] The presence of an aryl, alkenyl, alkynyl or ester moiety adjacent to the NH group is apparently critical for the enantioselectivity. Computational studies indicate that cation-π interactions play a key role in the chiral recognition of lactam substrates. There is no simple answer to the question "which catalyst is the best?" Based on available data, Cl-PIQ has broader substrate scope (see results with substrates **10**, **22**, **25**, and **37**), while BTM exhibits higher enantioselectivity in the KR of those substrates where a direct comparison has been made (see Tables 1 and 2). As a rule, we have given priority to BTM when exploring new substrates with proton affinities equal to or lower than that of the conjugate base of 4-phenyl-oxazolidin-2-one **5**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental details, previously unreported kinetic resolution data, characterization and preparation data for previously unreported compounds, details of computational studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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