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Article

Rational Design of 2-Substituted DMAP-*N*-oxides as Acyl Transfer Catalysts: Dynamic Kinetic Resolution of Azlactones

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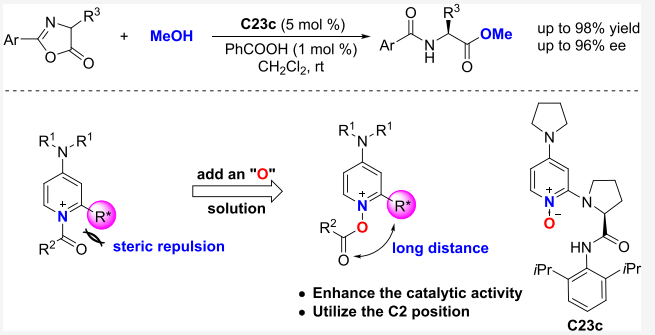
ABSTRACT: A novel concept that conversion of chiral 2-substituted DMAP into its DMAP-*N*-oxide could significantly enhance the catalytic activity and still be used as an acyl transfer catalyst is presented. A new type of chiral 2-substituted DMAP-*N*-oxides, derived from L-prolinamides, has been rationally designed, facilely synthesized, and applied in the dynamic kinetic resolution of azlactones. Using simple MeOH as the nucleophile, various L-amino acid derivatives were produced in high yields (up to 98% yield) and enantioselectivities (up to 96% ee). Furthermore, α-deuterium labeled L-phenylalanine derivative was also obtained. Experiments and DFT calculations revealed that in 2-substituted DMAP-*N*-oxide, the oxygen atom acted as the nucleophilic site and the N−H bond functioned as the H-bond donor. High enantioselectivity of the reaction was governed by steric factors, and the addition of benzoic acid reduced the activation energy by participating in the construction of a H-bond bridge. The theoretical chemical study indicated that only when attack directions of the chiral catalyst were fully considered could the correct calculation results be obtained. This work paves the way for the utilization of the C2 position of the pyridine ring and the development of chiral 2-substituted DMAP-*N*-oxides as efficient acyl transfer catalysts.



INTRODUCTION

Chiral 4-(dimethylamino)pyridine (DMAP) is recognized as a classic acyl transfer catalyst in organic synthesis,[1] with the development and generation of diverse DMAP analogues being an area of tremendous interest (Figure 1).[2] The first chiral DMAP reagent **C1** was reported by Vedejs and Chen in 1996 (Figure 1a),[3] in which a steering stereocenter was introduced at the pyridine ring's C2 position. In this seminal study, the obvious steric hindrance between the stereocontrol group at the C2 position and the *N*-acyl moiety inhibited the catalytic turnover, and the chiral 2-substituted DMAP reagent **C1** must be employed in stoichiometric amounts, resulting in less utilization of the C2 position in the further design of chiral DMAP catalysts as acyl transfer catalysts (Scheme 1a).[4−6] Soon afterward, Fu and co-workers developed the 2,3-disubstituted ferrocene-fused planar chiral DMAP catalyst **C2** (Figure 1a) and demonstrated their application in a broad array of reactions with impressive levels of stereocontrol.[4] Since the pioneering studies of Vedejs and Fu, the C3 and C4 positions, which are adequately distant from the nucleophilic site, have been extensively studied, producing diverse 3-substituted chiral DMAP,[7] 4-substituted chiral DMAP,[8] and multiple positions-substituted DMAP (Figure 1b−d).[9]

To reduce or even avoid the steric hindrance influence of the C2 substituent toward catalytic activity,[10] we envisaged that the conversion of DMAP into DMAP-*N*-oxide will make the C2 substituent far from the *O*-acyl moiety and thus enhance the activity of the catalyst and the utilization of the C2 position (Scheme 1b). Meanwhile, challenges can arise due to the introduction of an additional rotatable O−C bond in the *O*-acyl moiety, as well as changing the nucleophilic site from nitrogen to oxygen (Scheme 1b). However, until now, chiral 2-substituted DMAP-*N*-oxide was only developed in the sulfonylation of 2-substituted indolines and has not been reported in the enantioselective acyl transfer reaction.[11] It must be emphasized that there is a great difference between sulfonylation and acylation. In sulfonylation, the nucleophile's attack pathway is a S_N2 linear trajectory,[12] whereas acylation follows a Bürgi−Dunitz trajectory (Scheme 1c).[13] Herein, we will introduce an L-prolinamide at the C2 position of the pyridine ring to design a chiral 2-substituted DMAP-*N*-oxide, and we hope to achieve asymmetric acylation with the assistance of the H-bond interaction (Scheme 1c).

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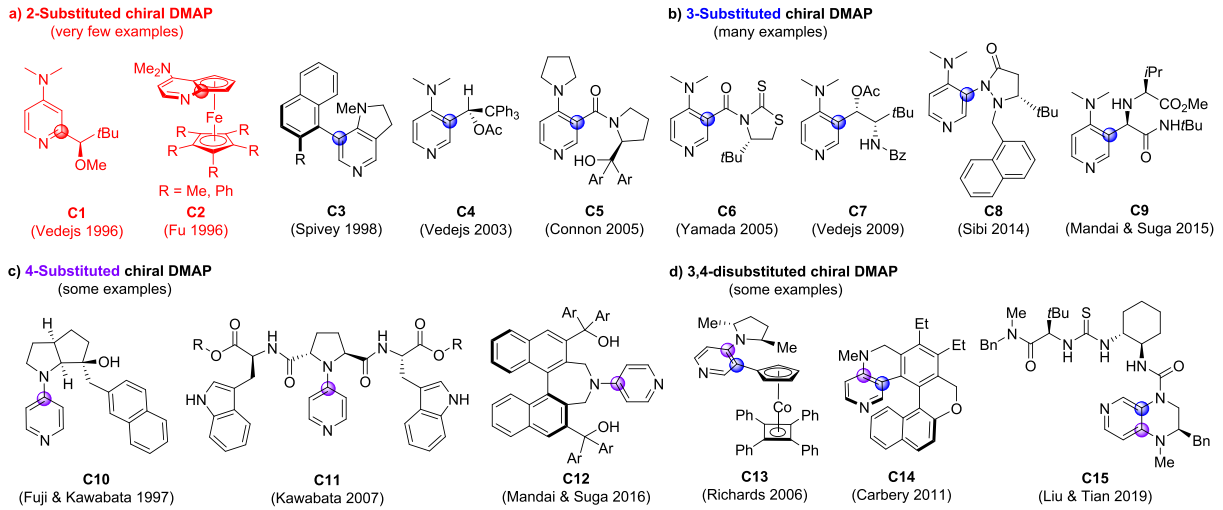
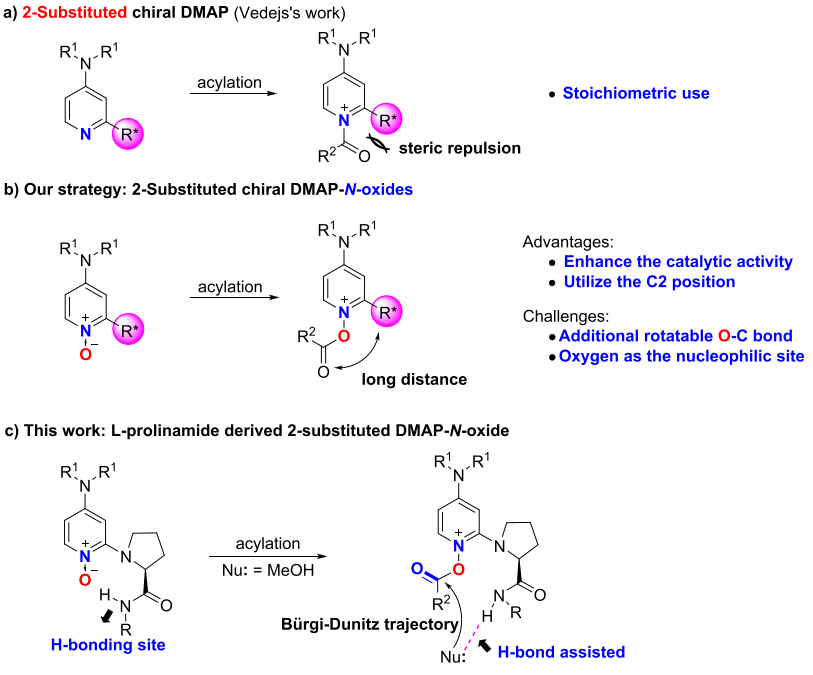


Figure 1. Selected chiral DMAP catalysts and their classification via different positions of the chiral group attached to the pyridine ring.

Scheme 1. Design of Chiral 2-Substituted DMAP-*N*-oxides as Acyl Transfer Catalysts



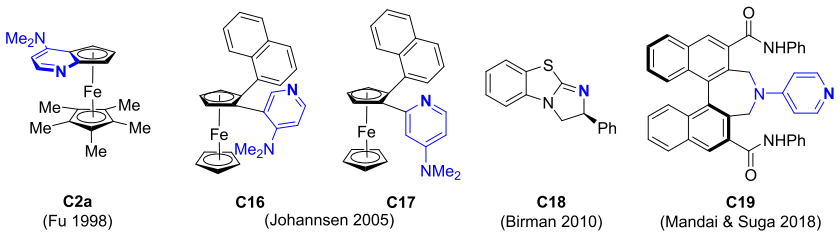


Figure 2. Chiral acyl transfer catalysts previously used in the DKR of azlactones.

The dynamic kinetic resolution (DKR) of azlactones by alcoholysis is an attractive method of generating enantioenriched protected α-amino acid derivatives.[14,15] In addition to hydrolytic enzymes[16] and transition metal complexes,[17] a variety of organocatalysts have been developed for this transformation, including chiral DMAP,[18,5a,19] diketopiperazine,[20] (thio)urea-based bifunctional catalysts,[21] cinchona alkaloid,[22] benzotetramisole,[23] phosphoric acid,[24] tetrapeptide,[25] and 1,3-ketoenol.[26] Among these organocatalysts, chiral acyl transfer catalysts are of particular interest because the first organocatalyst used in DKR of azlactones was a chiral DMAP (Figure 2).[18] In 1998, Fu's group pioneered the chiral organocatalytic DKR of azlactones by alcoholysis, by employing a planar-chiral DMAP derivative **C2a**.[18] Excellent yields

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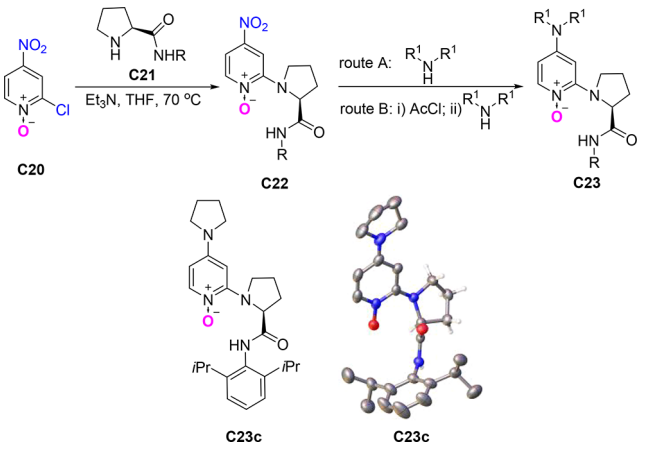
and moderate enantioselectivities (44−61% ee) were obtained using MeOH as the nucleophile, while higher enantioselectivity (78% ee) was afforded by employing the bulky ^{i}PrOH nucleophile, albeit with low reactivity. In 2005, Johannsen's group developed ferrocene-based planar chiral DMAP analogues **C16** and **C17** and found that 3-substituted DMAP **C16** produced the alcoholysis product in moderate enantioselectivities (21−42% ee), while 2-substituted DMAP catalyst **C17** was unreactive.[5a] In 2010, Birman's group reported the benzotetramisole **C18** catalyzed highly enantioselective DKR of azlactones, in which bulky di(1-naphthyl)methanol was required.[23a] In 2018, Mandai and Suga's group described a highly efficient asymmetric DKR of azlactones using binaphthyl-based DMAP derivative **C19** as the catalyst, in which bulky ^{i}PrOH was employed as the nucleophile.[19] On the basis of the aforementioned reports, it can be determined that bulky alcohols are often required as nucleophiles to achieve high enantioselectivities of alcoholysis products in the presence of chiral acyl transfer catalysts. Therefore, the development of a chiral acyl transfer catalyst to achieve excellent enantioselectivities of alcoholysis products, using simple MeOH as the nucleophile, is desirable. Herein, we described the DKR of azlactones with MeOH as the nucleophile using chiral 2-substituted DMAP-*N*-oxides as the acyl transfer catalysts.[27−29]

RESULTS AND DISCUSSION

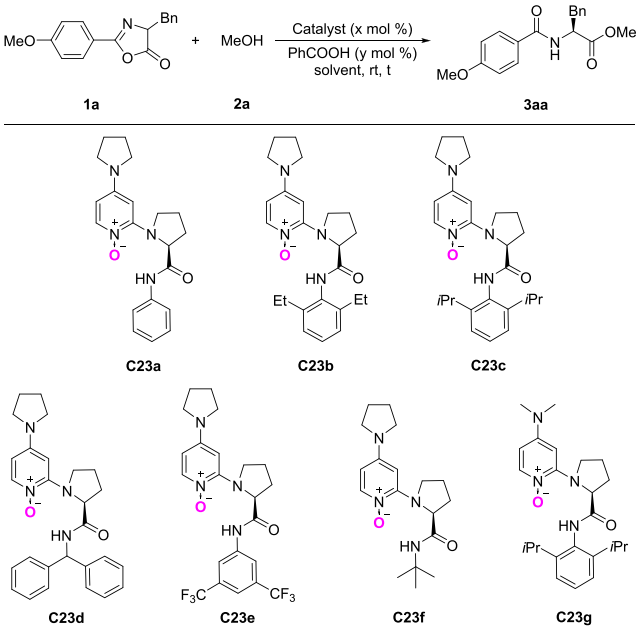
Catalyst Synthesis. Chiral 2-substituted DMAP-*N*-oxides **C23** were synthesized from 2-chloro-4-nitropyridine *N*-oxide and L-prolinamides through 2−3 steps as depicted in Scheme 2. The structure and absolute configuration of chiral 2-substituted DMAP-*N*-oxide **C23c** were determined via single-crystal X-ray diffraction analysis.

Scheme 2. Synthetic Routes for 2-Substituted DMAP-*N*-oxides



Optimization Study. Initially, the DKR reaction of benzyl-substituted azlactone **1a** with MeOH **2a** was selected as the model reaction (Table 1). When catalyst **C23a** was employed in CH_2Cl_2 at room temperature for 4 h with PhCOOH as the additive,[18,23a,b,24] the desired ester **3aa** was afforded in 98% yield and 74% ee (Table 1, entry 1). Several other 2-substituted DMAP-*N*-oxides **C23b−C23f** of varying steric hindrance and electronic effects were evaluated (Table 1, entries 2−6). Catalyst **C23c**, bearing two bulky isopropyl groups at aniline's *ortho* positions, gave the product **3aa** with enhanced enantioselectivity as 92% ee (Table 1, entry 3).

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	*x*	solvent	*y*	*t* (h)	yield (%)[b]	ee (%)[c]
1	**C23a**	10	CH_2Cl_2	10	4	98	74
2	**C23b**	10	CH_2Cl_2	10	4	98	90
3	**C23c**	10	CH_2Cl_2	10	4	98	92
4	**C23d**	10	CH_2Cl_2	10	4	98	87
5	**C23e**	10	CH_2Cl_2	10	4	98	90
6	**C23f**	10	CH_2Cl_2	10	4	98	70
7	**C23g**	10	CH_2Cl_2	10	4	98	91
8	**C23c**	10	THF	10	4	34	90
9	**C23c**	10	$CHCl_3$	10	4	97	92
10	**C23c**	10	EtOAc	10	4	96	91
11	**C23c**	10	toluene	10	4	96	90
12	**C23c**	10	CH_2Cl_2	20	3	98	90
13	**C23c**	10	CH_2Cl_2	1	6	98	93
14	**C23c**	10	CH_2Cl_2	0	17	97	92
15	**C23c**	5	CH_2Cl_2	1	8	98	93
16	**C23c**	1	CH_2Cl_2	1	30	98	91
17	**C23c**	0.5	CH_2Cl_2	1	58	98	90
18[d]	**C23c**	5	CH_2Cl_2	1	24	98	94

[a]Unless otherwise noted, the reaction conditions are as follows: **1a** (14.1 mg, 0.05 mmol), **2a** (6.1 μL, 3.0 equiv), catalyst (*x* mol %), and PhCOOH (*y* mol %) in solvent (1.0 mL) at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]CH_2Cl_2 (2.0 mL).

When catalyst **C23g** was employed, product **3aa** was produced in 98% yield and 91% ee (Table 1, entry 7), showing that changing the pyrrolidinyl group to the dimethylamino group had no significant influence on the reactivity and selectivity (Table 1, entries 7 vs 3). Variation of the solvent did not lead to improved results (Table 1, entries 3, 8−11). Increasing the amount of benzoic acid from 10 to 20 mol % only slightly accelerated the reaction but decreased the enantioselectivity (Table 1, entries 12 vs 3). However, decreasing benzoic acid to 1 mol % gave ester **3aa** in 98% yield and 93% ee, albeit with slightly prolonged reaction time (Table 1, entries 13 vs 3). In the absence of benzoic acid, the enantioselectivity was maintained and 97% yield was obtained, while the reaction rate decreased and a prolonged time of 17 h was needed (Table 1, entries 14 vs 3). Therefore, the obtained results

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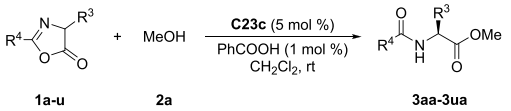
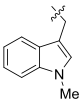
Table 2. Substrate Scope of Azlactones[a]



1a-u 2a 3aa-3ua

Entry	R^3	R^4	1	3	t (h)	Yield (%)[b]	ee (%)[c]
1	Bn	4-MeOPh	**1a**	**3aa**	24	98	94
2	Me	4-MeOPh	**1b**	**3ba**	24	97	92
3	Et	4-MeOPh	**1c**	**3ca**	24	91	91
4	*n*Pr	4-MeOPh	**1d**	**3da**	24	94	94
5	*n*Bu	4-MeOPh	**1e**	**3ea**	24	92	95
6	*i*Bu	4-MeOPh	**1f**	**3fa**	24	97	94
7	*i*Pr	4-MeOPh	**1g**	**3ga**	72	84	91
8	CH_2CH_2SMe	4-MeOPh	**1h**	**3ha**	24	96	94
9	4-$ClC_6H_4CH_2$	4-MeOPh	**1i**	**3ia**	24	95	93
10	4-$NO_2C_6H_4CH_2$	4-MeOPh	**1j**	**3ja**	24	97	93
11	4-$BnOC_6H_4CH_2$	4-MeOPh	**1k**	**3ka**	24	97	92
12		4-MeOPh	**1l**	**3la**	24	98	92
13		4-MeOPh	**1m**	**3ma**	24	96	91
14		4-MeOPh	**1n**	**3na**	24	98	91
15[d]	Ph	4-MeOPh	**1o**	**3oa**	24	90	87
16	Bn	Ph	**1p**	**3pa**	24	88	87
17	Bn	4-ClPh	**1q**	**3qa**	24	96	94
18	Bn	4-CH_3Ph	**1r**	**3ra**	24	94	91
19	Bn	3,5-$(MeO)_2C_6H_3$	**1s**	**3sa**	24	98	94
20	Bn	2-naphthyl	**1t**	**3ta**	24	97	94
21[e]	Bn	1-naphthyl	**1u**	**3ua**	24	98	96

[a]Unless otherwise noted, the reaction conditions are as follows: **1** (0.05 mmol), **2a** (3.0 equiv), **C23c** (5 mol %), and PhCOOH (1 mol %) in CH_2Cl_2 (2.0 mL) at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]**C23c** (10 mol %), PhCOOH (10 mol %). [e]**C23c** (1 mol %).

implied that the main role of benzoic acid was to accelerate the reaction (Table 1, entries 3 and 12−14). Screening of the catalytic loading demonstrated that 5 mol % of **C23c** was optimal; however, even 0.5 mol % of **C23c** still afforded product **3aa** in 98% yield and 90% ee but over prolonged time (Table 1, entries 13 and 15−17). Further evaluation of the concentration indicated that 2.0 mL of CH_2Cl_2 gave an improved result with 94% ee (Table 1, entry 18).

Scope of the Reaction. Under optimized reaction conditions (Table 1, entry 18), the substrate scope of azlactones was explored (Table 2). The DKR of several C(4)-primary alkyl-substituted azlactones **1b−f** afforded α-amino acid derivatives **3ba−3fa** in 91−97% yields and 91−95% ee (Table 2, entries 2−6). In the case of azlactone **1g** bearing an α-branched alkyl group (^{i}Pr), a known challenging substrate for reported chiral acyl transfer catalysts,[19,23a,24] the corresponding L-valine methyl ester **3ga** was obtained in 84% yield and 91% ee (Table 2, entry 7). Next, methionine-derived azlactone **1h** and α-arylalanine-derived azlactones **1i−l** were evaluated, and they generated protected α-amino acid derivatives **3ha−3la** in 95−98% yields and 92−94% ee (Table 2, entries 8−12). In the case of *N*-Me tryptophan-derived azlactone **1m** or tryptophan-derived azlactone **1n** bearing a free N−H bond, the DKR reaction proceeded well (Table 2, entries 13 and 14). C(4)-Phenyl-substituted azlactone **1o** produced good enantioselectivity for the L-phenylglycine derivative **3oa**, but an increase in catalytic loading was required (Table 2, entry 15). Variation of C(2)-aryl-substituted azlactones **1p−u** gave the desired protected α-

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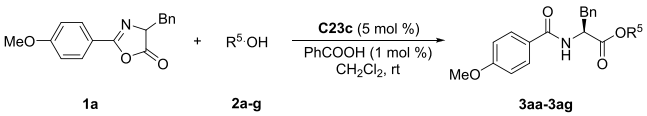
amino acid derivatives **3pa**−**3ua** in 88−98% yields and 87−96% ee (Table 2, entries 16−21).

Subsequently, the substrate scope of alcohols was explored (Table 3). When straight chain alcohols **2b**−**e** were employed,

Table 3. Substrate Scope of Alcohols[a]



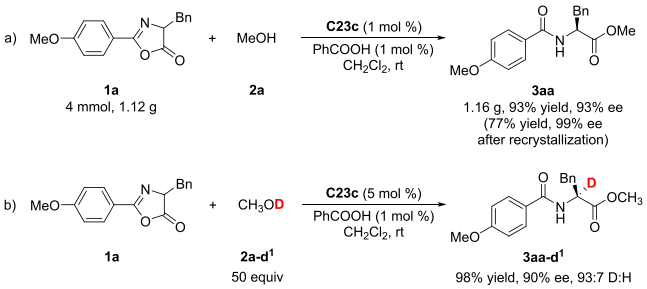
entry	R^5	2	3	t (h)	yield (%)[b]	ee (%)[c]
1	Me	**2a**	**3aa**	24	98	94
2	Et	**2b**	**3ab**	48	95	94
3[d]	Et	**2b**	**3ab**	24	97	94
4	^{n}Pr	**2c**	**3ac**	48	92	95
5	^{n}Bu	**2d**	**3ad**	48	94	93
6	^{n}Pent	**2e**	**3ae**	48	96	93
7[e]	^{i}Pr	**2f**	**3af**	72	94	94
8	1-NpCH$_2$CH$_2$	**2g**	**3ag**	48	84	90

[a]Unless otherwise noted, the reaction conditions are as follows: **1a** (0.05 mmol), **2** (3.0 equiv), **C23c** (5 mol %), and PhCOOH (1 mol %) in CH_2Cl_2 (2.0 mL) at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]**2b** (5 equiv). [e]**C23c** (10 mol %).

the enantioselectivities of the alcoholysis products **3ab**−**3ae** were 93−95% ee (Table 3, entries 2−6). However, the reaction rates of these alcohols were slow as compared to that of MeOH (Table 3, entries 2, 4−6 vs 1). In the case of ethanol, the DKR reaction activity was enhanced by increasing the amount of ethanol, while maintaining enantioselectivity (Table 3, entries 2 and 3). When bulky ^{i}PrOH was used, the enantioselectivity of ester **3af** was maintained, but the rate of reactivity significantly decreased (Table 3, entries 7 vs 1). Upon using 1-naphthylethanol **2g** as the nucleophile, the enantioselectivity of product **3ag** decreased slightly (Table 3, entries 8 vs 1).

Scale-Up Reaction and Application. To further evaluate the synthetic utility of the current methodology, gram-scale synthesis of L-phenylalanine derivative **3aa** was performed (Scheme 3a). Using 1 mol % of catalyst **C23c**, 4 mmol of azlactone **1a** reacted smoothly with methanol **2a** and generated 1.16 g (93% yield) of the desired L-phenylalanine derivative **3aa** with 93% ee. After recrystallization, the corresponding **3aa** was obtained as a pure enantiomer (77% yield, 99% ee). Considering that α-deuterated amino acids are widely used in mechanistic studies of bioorganic chemistry,[22b] the enantioselective synthesis of α-deuterium labeled L-phenylalanine derivative was carried out as a representative. By utilizing low-cost, commercially available CH_3OD as the reactant, the DKR reaction of azlactone **1a** afforded the desired α-deuterium derivative **3aa-d**^{1} in 98% yield, 90% ee, and a 93:7 D/H ratio (Scheme 3b). On the other hand, this deuterium labeling experiment also proved that azlactone **1a** could be racemized rapidly. It should be noted that the H/D exchange in the PhCOOH/CH_3OD mixture will lead to the H/D exchange in unreacted azlactone **1a**, but this effect could be ignored when only 1 mol % PhCOOH was employed (see Table S5 for details).

Scheme 3. (a) Gram-Scale Synthesis of L-Phenylalanine Derivative 3aa; and (b) Synthesis of α-Deuterium Labeled L-Phenylalanine Derivative 3aa-d^1



Mechanistic Studies. To gain insight into the reaction's mechanism catalyzed by chiral 2-substituted DMAP-*N*-oxides, several control experiments were conducted (Figure 3). When 2-substituted DMAP **C24c**, the reduced product of DMAP-*N*-oxide **C23c**, was employed, product **3aa** was obtained in only 9% yield and 80% ee. Through this comparative experiment, it could be concluded that (i) the proximity of the chiral L-prolinamide moiety on catalyst **C24c** was too close to the nucleophilic site, which had a dramatic influence on reaction reactivity but only slightly altered the enantioselectivity; and (ii) the *N*-oxide group was vital to the chiral induction for chiral 2-substituted DMAP-*N*-oxide **C23c**. Evaluation of DMAP-*N*-oxide **C23h**, the *N*-Me derivative of **C23a**, revealed that product **3aa** was obtained in its racemic form (0% ee) and in lower yield, and this indicated that the N−H proton on the amide framework was important for reactivity and enantioselectivity. Insertion of the C═O double bond between the pyridine ring and L-prolinamide moiety generated catalyst **C25c**, which produced product **3aa** in only 5% yield and 10% ee. Therefore, catalysts **C23c** and **C25c** were compared carefully. In terms of structure, **C23c** had a donor substituent at the C2 position, while **C25c** had an acceptor substituent at the C2 position. Through natural bond orbital (NBO) theory analysis, the natural atomic charge (Q) on the oxygen atom in *N*-oxide groups of **C23c** and **C25c** was −0.722 and −0.692, respectively (see Scheme S6 for detail). Thus, the oxygen atom of the *N*-oxide group in **C23c** exhibited more negative charge than that in **C25c**, and this resulted in a stronger nucleophilicity and catalytic activity of catalyst **C23c**. On the other hand, in **C25c**, the distance between the L-prolinamide moiety and the pyridine ring became longer than that in **C23c**, which might affect the catalyst configuration and the H-bonding interaction, thus having an adverse effect on the reaction selectivity. When 3-substituted DMAP-*N*-oxide **C26c** was used,[28g] product **3aa** was generated in 36% yield and −15% ee. It was speculated that the L-prolinamide moiety in **C26c** was relatively far from the nucleophilic site, which impeded H-bond formation with the substrate and only exhibited a steric hindrance effect.

To further probe the mechanism of the reaction, the kinetic order of each reaction component was determined through studying initial rates of the reaction (Figure 4). The rate showed approximately first-order dependence on the concentration of MeOH **2a** (Figure 4, top), which indicated that the alcohol is involved in the rate-determining step and the nucleophilic attack of alcohol might be the rate-determining step of the reaction. For catalyst **C23c**, the rate also showed approximately first-order dependence on the concentration of catalyst **C23c** (Figure 4, top). Meanwhile, azlactone **1a** and PhCOOH exhibited approximately first-order rate dependence but with saturation at higher concentration (Figure 4, bottom).

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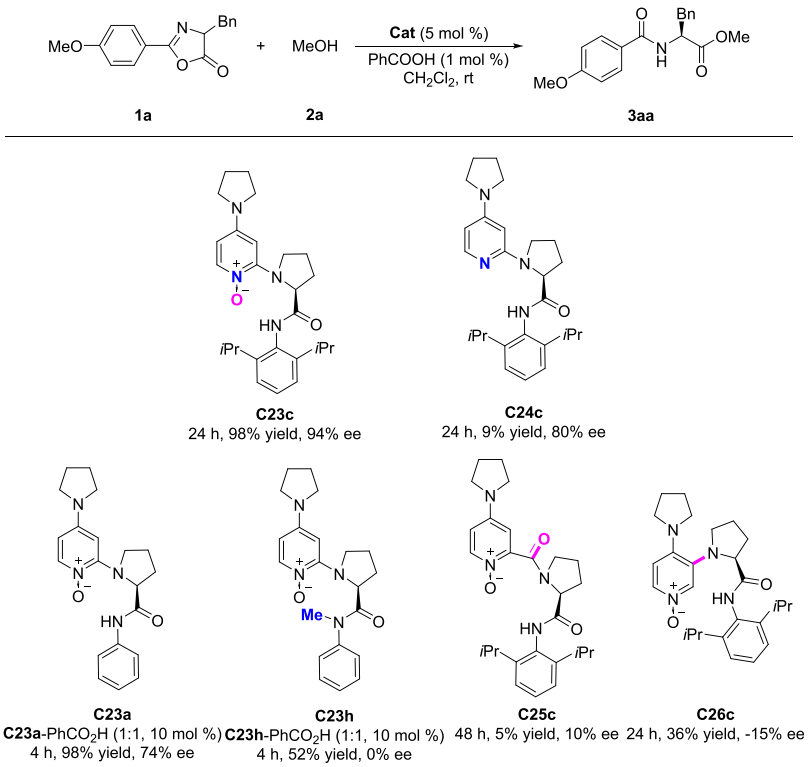

Figure 3. Control experiments.

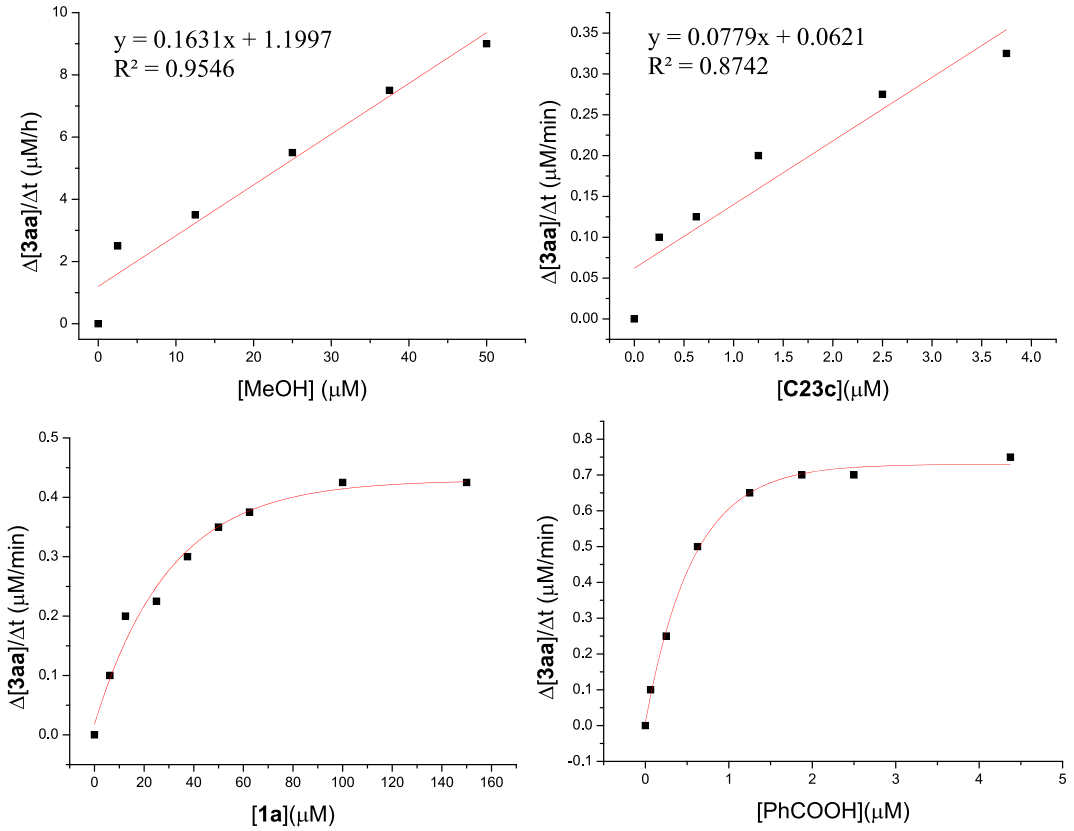

Figure 4. Kinetic order of each reaction component.

It should be noted that no background reaction occurred in the absence of catalyst **C23c**, MeOH **2a**, or azlactone **1a**. These kinetic studies suggested that a four-component transition state including MeOH **2a**, catalyst **C23c**, azlactone **1a**, and PhCOOH might be involved in the rate-determining step of the reaction. After that, HRMS experiments were carried out to

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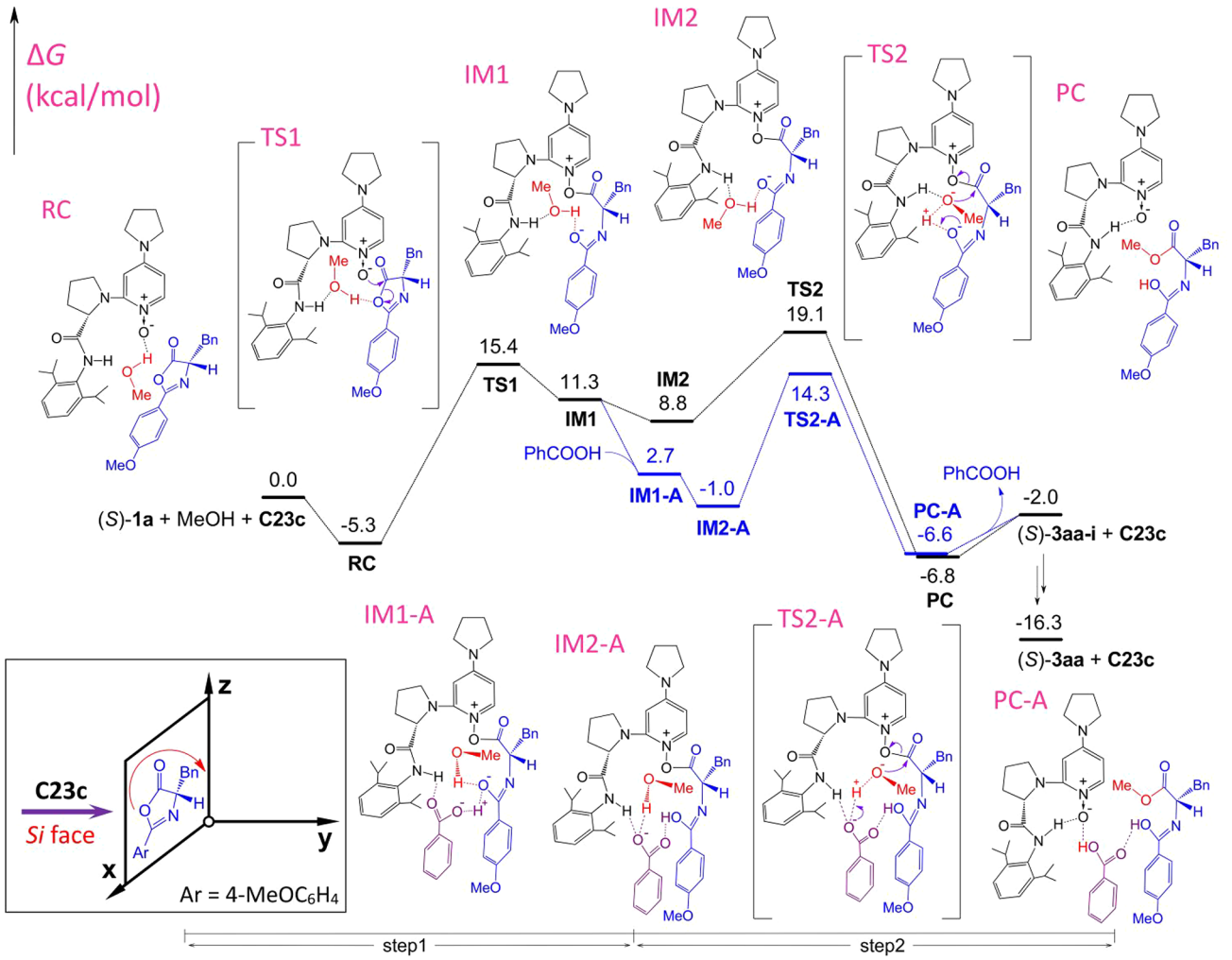

Figure 5. Relative energy profiles (in kcal/mol) of nucleophilic addition along the *Si* face of the azlactone ring plane obtained via the M08-HX/6-311G(d,p)/CPCM(DCM) method.

shed light on the mechanism of the reaction. In the mixture of **C23c**, azlactone **1a**, and PhCOOH, a peak at *m*/*z* 718.3930 was found, which corresponded to the intermediate [**C23c**+**1a** +H^+]$^+$, and confirmed the generation of *O*-acylated intermediate from catalyst **C23c** and azlactone **1a** (see Figure S11 for details). Afterward, in the reaction mixture of **C23c**, azlactone **1a**, MeOH **2a**, and PhCOOH, an ion at *m*/*z* 559.3276 was probed, which might correspond to the intermediate [**C23c**+PhCOOH+H^+]$^+$, and suggested that there might be a weak interaction between catalyst **C23c** and PhCOOH (see Figure S12 for details). Furthermore, in the reaction mixture of **C23c**, azlactone **1g**, MeOH, and PhCOOH, an ion at *m*/*z* 824.4600 was observed, which might correspond to the intermediate [**C23c**+**1g**+MeOH +PhCOOH+H^+]$^+$, and suggested a four-component transition state might be involved in the reaction (see Figure S13 for details). Subsequently, the relationship between the enantioselectivity of the catalyst **C23c** and the product **3aa** was studied (see Figure S14 for details). There was no nonlinear effect in this catalytic reaction, which indicated that only one chiral catalyst might be involved in the rate-determining step of the reaction.

In light of the above experimental findings, to further elaborate on the nucleophilic addition mechanism and the origins of stereoselectivity, density functional theory (DFT) was utilized to explore and analyze the reaction process. As described in Figure 5, the mechanism consists of a two-step process: ring-opening and nucleophilic addition. In step 1, the reaction starts from the free catalyst **C23c** and substrate (*S*)-**1a**, followed by the hydrogen-bonded reactant complex (RC) formed between catalyst **C23c** and MeOH, and then the nucleophilic oxygen in the *N*-oxide group of catalyst **C23c** attacks the electrophilic carbonyl carbon of azlactone (*S*)-**1a** from the *Si* face of the azlactone ring plane. Simultaneously, the C−O ester single bond of azlactone (*S*)-**1a** is broken. In intermediate IM1, the oxygen anion generated from ring-opened azlactone is trapped through the H-bond from MeOH and N−H in the amide framework.

In step 2, in the absence of PhCOOH, relatively stable intermediate IM2 is formed, in which a less crowded 15-membered ring H-bond emerges with the release of 2.5 kcal/mol from IM1. The nucleophilic MeOH molecule, activated by the N−H bond in the amide framework, then attacks the carbonyl carbon and allows its labile proton to transfer into the oxygen anion in the ring-opened azlactone. Simultaneously, the C−O bond between the carbonyl carbon of the azlactone (*S*)-**1a** and nucleophilic oxygen of catalyst **C23c** is broken. As shown in Figure 5, the DFT calculation indicates that the relative free energy of TS1 (15.4 kcal/mol) is lower than that of TS2 (19.1 kcal/mol), which suggests that the latter is the

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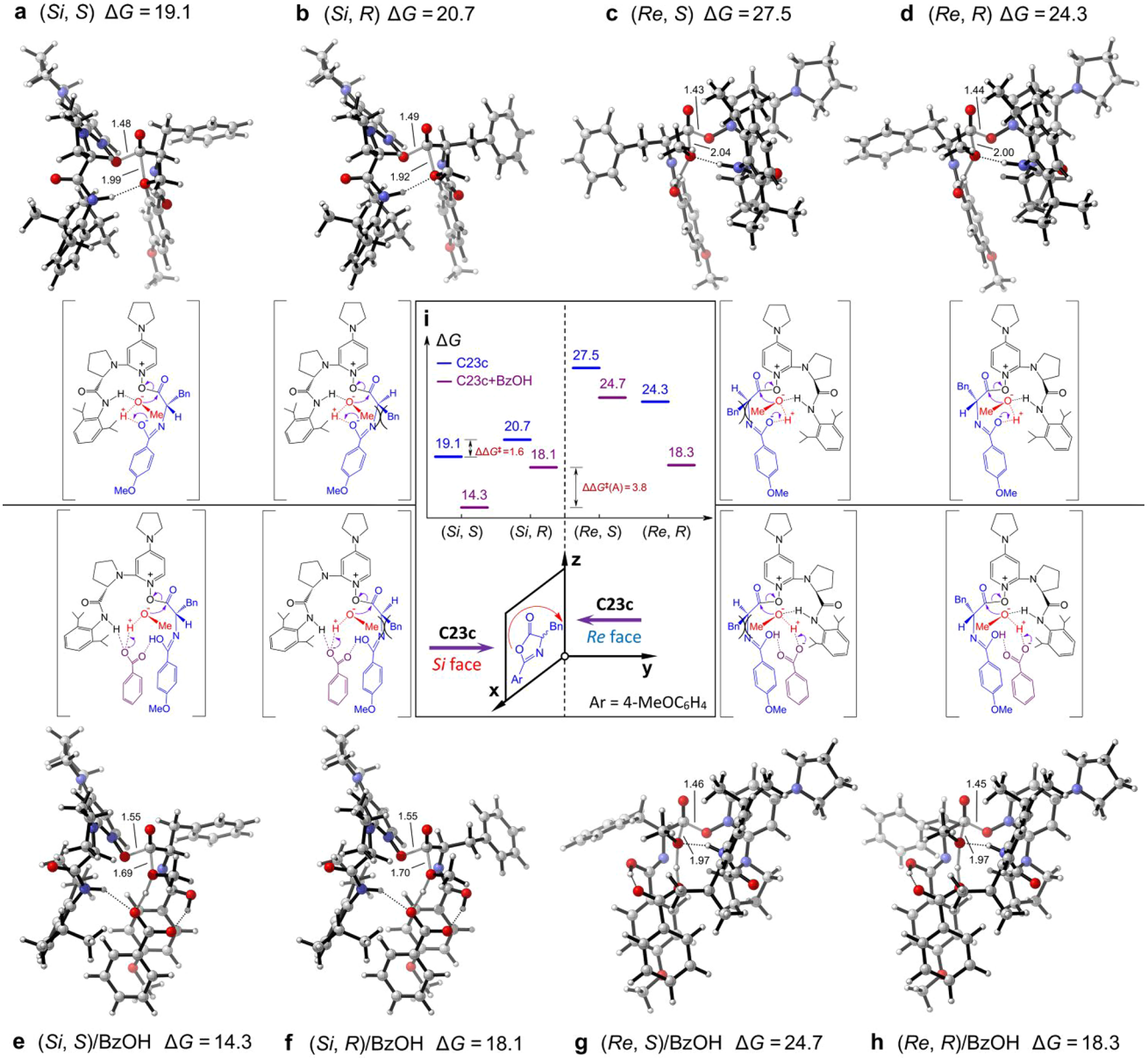

Figure 6. Optimized structures (bond lengths, Å) and relative free energies (Δ*G*, kcal/mol) of the enantio-determining transition state along two attack pathways obtained by the M08-HX/6-311G(d,p)/CPCM(DCM) method. The **C23c** catalyst was optimized on the basis of the single-crystal structure, and the crystal conformation of **C23c** was utilized to explore the catalyzed reaction pathway.

rate-determining step. Finally, the product complex (PC) releases catalyst **C23c** and tautomer (*S*)-**3aa-i**, which undergoes exothermic isomerization to generate the corresponding (*S*)-**3aa** with 14.3 kcal/mol. The isomerization mechanism is described in Scheme S3.

In the presence of PhCOOH (Figure 5), more stable intermediate IM2-A is formed with the release of up to 12.3 kcal/mol from IM1, in which the PhCOOH participates in the formation of the H-bond. The relative free energy of the resulting IM2-A is 9.8 kcal/mol lower than that of IM2, which can be attributed to the large H-bond bridge contributed by PhCOOH. In the following nucleophilic substitution step through TS2-A, due to the high acidity of PhCOOH, which serves as a bridge to aid hydrogen transfer, the MeOH is activated by PhCOOH, and the oxygen anion in ring-opened azlactone also generates a H-bond with PhCOOH. The energy barrier of this step is 14.3 kcal/mol, which is lower than that of TS2 and shows that the addition of PhCOOH reduces the reaction energy barrier, thus accelerating the reaction rate. Product complex PC-A then is produced and releases the PhCOOH to give catalyst **C23c** and tautomer (*S*)-**3aa-i**.

When the attack direction of catalyst **C23c** to reactant (*S*)-**1a** is reversed, as shown in Scheme S4, catalyst **C23c** attacks reactant (*S*)-**1a** from the *Re* face of the azlactone ring plane via transition state TS1. In the following TS2 or TS2-A, whether PhCOOH is added or not, the energy barriers of the step are higher than 24 kcal/mol. Therefore, when the attack direction of the chiral catalyst to reactant is reversed, the energy profiles might be different, which can be due to the asymmetry of chiral catalyst **C23c** and the whole transition state.[30]

To understand the origin of enantioselectivity, the geometry information on transition states in the rate-determining step leading to final product (*S*)-**3aa** and its enantiomer was carefully explored and displayed in Figure 6. In the absence of

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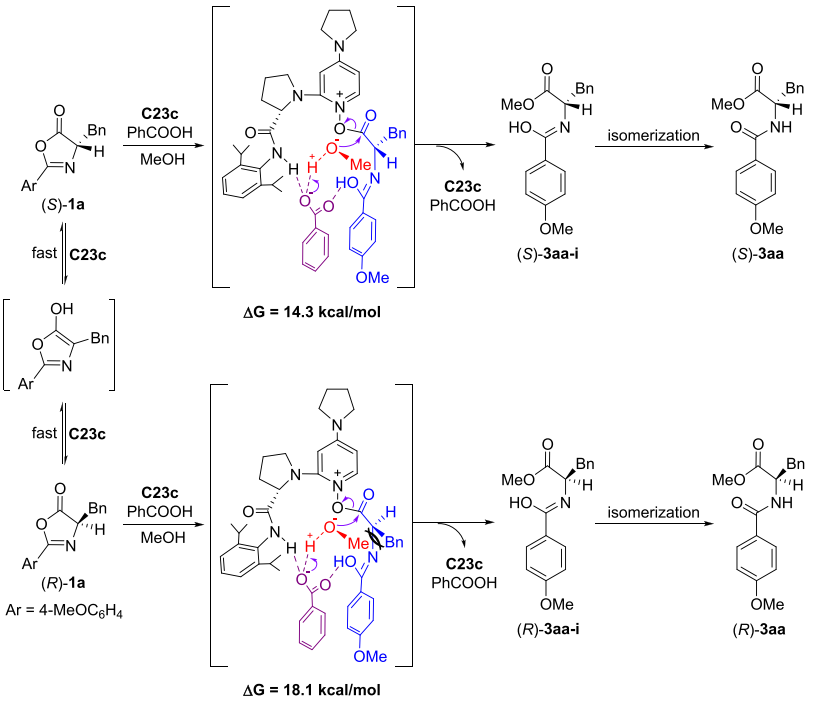

Figure 7. Proposed DKR mechanism.

PhCOOH, as shown in Figure 6a and b, the relative free energy of (*Si*,*S*)-TS2 (ΔG = 19.1 kcal/mol, leading to product (*S*)-**3aa**) is 1.6 kcal/mol ($\Delta\Delta G^{\ddagger}$) lower than that of (*Si*,*R*)-TS2 (ΔG = 20.7 kcal/mol, leading to product (*R*)-**3aa**), which corresponds to the dominant (*S*)-configuration alcoholysis product. In transition state (*Si*,*R*)-TS2, enhancement of the energy barrier is mainly due to the significant steric repulsion between the Me group in MeOH and the Bn group in ring-opened azlactone.

When catalyst **C23c** attacks azlactone **1a** from the *Re* face of the azlactone ring plane (Figure 6c and d), (*Re*,*R*)-TS2 (leading to product (*R*)-**3aa**) is energetically more favored than (*Re*,*S*)-TS2, which corresponds to the predominance of the (*R*)-configuration alcoholysis product. It should be noted that the relative free energies of transition states (*Re*,*S*)-TS2 and (*Re*,*R*)-TS2 are higher than those of (*Si*,*S*)-TS2 and (*Si*,*R*)-TS2, leading to that the attack pathway from the *Re* face of the azlactone ring plane is not the dominant. In the presence of PhCOOH, as shown in Figure 6e and f, the transition state (*Si*,*S*)/PhCOOH-TS2, which leads to product (*S*)-**3aa**, is energetically more favored than (*Si*,*R*)/PhCOOH-TS2 by 3.8 kcal/mol. As mentioned above, when the catalyst attacks the azlactone from the *Re* face of the azlactone ring plane (Figure 6g and h), the relative free energies of (*Re*,*S*)/PhCOOH-TS2 and (*Re*,*R*)/PhCOOH-TS2 are higher than those of (*Si*,*S*)/PhCOOH-TS2 and (*Si*,*R*)/PhCOOH-TS2, which indicate that the *Si* face attack is favorable. Therefore, only when the attack directions of the chiral catalyst are fully considered can the correct calculation results be obtained.

More delicately, as shown in Figure 6i, for the chiral catalyst to interact with the reactant through the *Si* face and *Re* face, the reverse attack direction and asymmetry of chiral catalyst directly lead to differences in the chemical microenvironment between transition state *Si*-TS2 and *Re*-TS2. More importantly, the relative free energy of transition state (*Si*,*S*)-TS2 is the lowest, which corresponds to the major enantiomer and key enantio-determining step.

Furthermore, other possible transition states are also proposed and calculated in Scheme S5. In the transition state (*Si*,*S*)-TS, as shown in Scheme S5a, the C═O double bond in *O*-acylated pyridinium cation is locked by the N−H in the amide framework through the H-bond. The H atom in OH group of MeOH is activated by the oxygen anion in ring-opened azlactone. The energy barrier for this transition state is 21.9 kcal/mol, which is higher than that mentioned in Figure 6a. Similarly, the attack direction of the chiral catalyst and steric repulsion factors can also affect the energy barrier of these transition states (Scheme S5b−d).

On the basis of the experiments and DFT calculations, a possible DKR mechanism was proposed in Figure 7. First, azlactone **1a** could be racemized rapidly due to their configurational lability.[31] For azlactone (*S*)-**1a**, in the presence of catalyst **C23c** and PhCOOH, the alcoholysis of MeOH underwent a four-component transition state with a low relative free energy of 14.3 kcal/mol. The ring-opened tautomer (*S*)-**3aa-i** then was produced, which underwent exothermic isomerization to generate the corresponding (*S*)-**3aa**. For azlactone (*R*)-**1a**, due to the significant steric repulsion between the Me group in MeOH and the Bn group in the ring-opened azlactone, the corresponding transition state exhibited a higher relative free energy with 18.1 kcal/mol. As a result, the rate of alcoholysis step became slow and (*R*)-**3aa** was a minor enantiomer. Finally, most (*R*)-**1a** converted into (*S*)-**1a** through in situ racemization and participated in the alcoholysis step, and this made (*S*)-**3aa** a major enantiomer.

In conclusion, we present a novel concept in that conversion of chiral 2-substituted DMAP into its DMAP-*N*-oxide could significantly enhance the catalytic activity and still be used as an acyl transfer catalyst. A new type of chiral 2-substituted DMAP-*N*-oxides has been rationally designed, facilely

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synthesized, and applied as acyl transfer catalysts in the DKR of azlactones with MeOH. Using simple MeOH as the nucleophile, a variety of L-protected amino acid derivatives were obtained in 88−98% yields and 87−96% ee. Other alcohols were also suitable nucleophiles. In the presence of 1 mol % of catalyst loading, the DKR reaction was performed on the gram-scale with excellent results. The mechanism experiments and DFT calculations revealed that in 2-substituted DMAP-*N*-oxide **C23c**, the oxygen atom was the nucleophilic site and the N−H bond in L-prolinamide moiety was the H-bond donor. The high enantioselectivity of the reaction is governed by steric factors, and the addition of benzoic acid reduces the activation energy by participating in the construction of the H-bond bridge. The theoretical calculation study shows that only when the attack directions of chiral catalyst are fully considered can the correct calculation results be obtained. This work will open the door for the utilization of the C2 position of the pyridine ring and the development of chiral 2-substituted DMAP-*N*-oxides as efficient acyl transfer organocatalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09075.

Experimental procedures, catalyst synthesis and characterization, mechanism experiments, computational data, and copies of NMR and HPLC spectra (PDF)

Crystallographic data for **1a** (CIF)

Crystallographic data for **C22c** (CIF)

Crystallographic data for **C23c** (CIF)

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Notes

The authors declare no competing financial interest.

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