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Organocatalytic Kinetic Resolution of N-Boc-Isoxazolidine-5-ones

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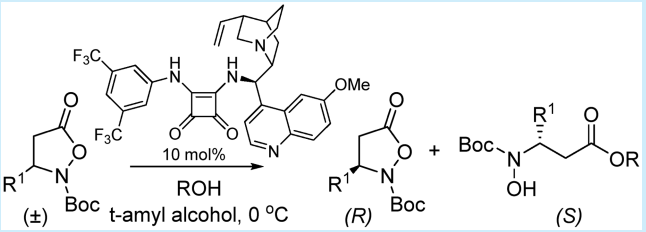
ABSTRACT: Easily accessible racemic N-Boc-isoxazolidine-5-ones undergo enantioselective alcoholysis promoted by double hydrogen bond donor amine organocatalysts, resulting in their effective kinetic resolution.



Isoxazolidinones are valuable precursors to β-amino acid derivatives, including β-peptides. As a consequence, there is considerable interest in accessing them in enantioenriched form.[1−7] Within this broad category, N-carbalkoxy-isoxazolidinones constitute an important subset, thanks to the ease of deprotecting the nitrogen atom. Several asymmetric catalytic approaches to the latter class of compounds[2−5] are illustrated in Figure 1. A few years ago, Brière et al. disclosed a

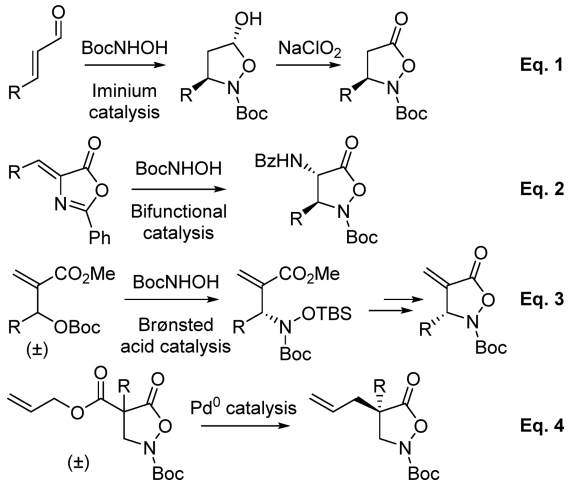


Figure 1. Asymmetric catalytic approaches.

multicomponent synthesis of racemic N-carbalkoxy-isoxazolidinones (Figure 2).[8] Although attempts to develop an asymmetric version of this process proved unsuccessful, its simplicity and flexibility make it quite attractive, especially if a method is found to resolve the racemic products. In this Letter, we report an effective kinetic resolution (KR)[9] of N-Boc-isoxazolidinones, which complements existing enantioselective approaches to these useful intermediates.

A number of cyclic acyl donors, such as N-carboxyanhydrides,[10] oxazinones,[11] and N-acyl-β-lactams,[12] have been

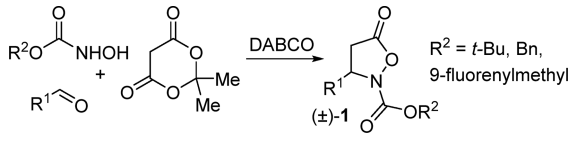


Figure 2. Brière's racemic route.

successfully resolved via organocatalyzed enantioselective alcoholysis. In addition, the conceptually related dynamic kinetic resolution (DKR)[13,14] and desymmetrization[15] have been achieved using similar methods. The overall structural similarity of N-Boc-isoxazolidinones to these compounds suggested to us that they may also be amenable to asymmetric ring opening. Furthermore, literature precedent indicated that they undergo methanolysis under fairly mild conditions.[3] However, no information could be found regarding catalytic acceleration of this process.

First, we confirmed that the background reaction of test substrate **1a** with a 10-fold excess of methanol was negligible (Table 1, entry 1). On the contrary, rapid methanolysis was observed in the presence of stoichiometric base (entry 2). Widely used enantioselective acyl transfer catalyst benzotetramisole **3**[16] (Figure 3) displayed barely detectable catalytic activity and no asymmetric induction (entry 3). A more electron-rich amidine-based catalyst H-PIP **4**[17] did promote the reaction, but the selectivity factor[18] was still negligible (entry 4). Faced with these disappointing results using the covalent mode of catalysis, we decided to test Takemoto's bifunctional catalyst **5**,[19] which had demonstrated its efficacy in the DKR of azlactones.[13b] The initial result showed some

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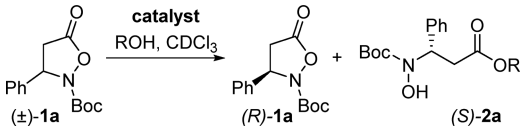
Table 1. Initial Screening of Reaction Conditions[a]



entry	catalyst (mol %)	ROH (equiv)	time (h)	% conversion	*s*
1	none	MeOH (10)	24	0[b]	N/A
2	NEt_3 (100)	MeOH (10)	0.5	100[b]	N/A
3	**3** (20)	MeOH (1)	192	45[b]	1.1
4	**4** (20)	MeOH (1)	2.5	62[b]	1.5
5	**5** (10)	MeOH (1)	5	53	5.2
6[c]	**5** (10)	MeOH (1)	8	55	5.9
7[c]	**5** (10)	BnOH (1)	16	46	16.3
8	**5** (10)	Ph_2CHOH (1)	120	25	7.7
9	**5** (10)	*i*-PrOH (1)	24	<5	N/A

[a]General conditions: 0.10 mmol of (±)-**1a**, 0.10 or 1.0 mmol of ROH, 0.010 mmol of catalyst, 500 μL of $CDCl_3$, rt. [b]Determined by ^1H NMR. [c]Carried out at 0 °C.

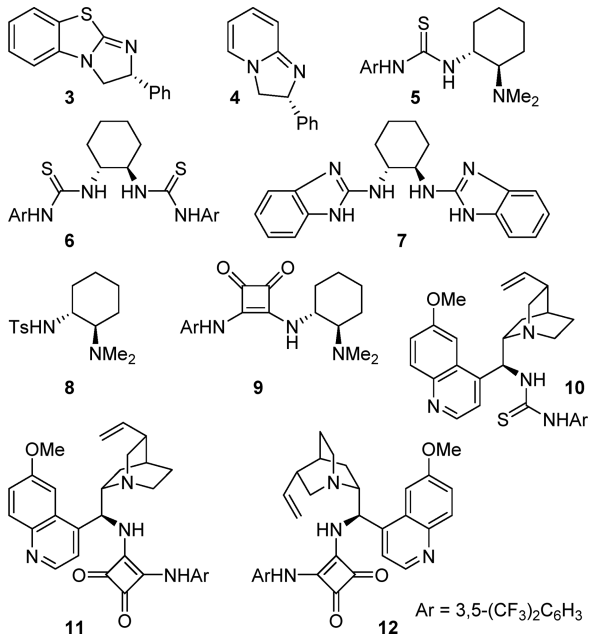
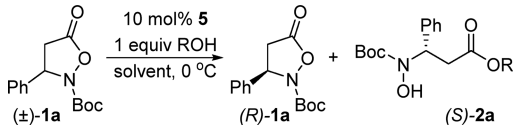


Figure 3. Catalysts used in this study.

promise (entry 5). Modest improvement was observed when the reaction was carried out at 0 °C (entry 6). At this point, we examined the effect of using more sterically demanding alcohols. Benzyl alcohol improved the selectivity factor 3-fold (entry 7). Benzhydrol reacted very slowly (entry 8). Finally, isopropanol proved to be completely unreactive (entry 9).

A solvent survey was performed next (Table 2). Most solvents examined displayed performance comparable to that of chloroform (entry 1). The most nonpolar (entries 3 and 4) and the most polar (entry 8) solvents were decidedly inferior to it. Most interestingly, we found that *tert*-amyl alcohol produced a selectivity factor that was higher than those of all of the aprotic solvents (entry 9). This result came as a pleasant surprise as this solvent might be expected to disrupt hydrogen bonding. Encouraged by this finding, we re-examined different alcohols. Allyl alcohol was superior to benzyl alcohol (entry 10 vs entry 9). Methanol displayed markedly improved performance compared to the results obtained earlier in chloroform

Table 2. Solvent Survey[a]



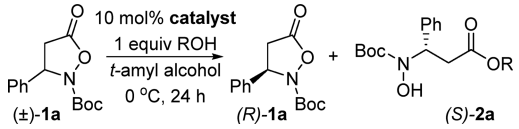
entry	solvent	ROH	time (h)	% conversion	*s*
1	$CHCl_3$	BnOH	16	46	16.3
2	CH_2Cl_2	BnOH	16	43	16.1
3	PhMe	BnOH	7	54	13.0
4	cyclohexane	BnOH	16	73	6.0
5	THF	BnOH	72	25	21.0
6	EtOAc	BnOH	22	37	18.9
7	Me_2CO	BnOH	23	24	19.3
8	MeCN	BnOH	23	37	7.4
9	$EtCMe_2OH$	BnOH	22	34	25
10	$EtCMe_2OH$	allylOH	22	36	45
11	$EtCMe_2OH$	MeOH	22	31	14.6
12	$EtCMe_2OH$	Ph_2CHOH	22	39	199
13	$EtCMe_2OH$	*i*-PrOH	22	0	ND

[a]General conditions: 0.10 mmol of (±)-**1a**, 0.10 mmol of ROH, 0.01 mmol of **5**, 500 μL of solvent.

(cf. Table 1, entry 6). Most surprisingly, benzhydrol, which reacted very poorly in chloroform (cf. entry 8 of Table 1), reproducibly gave the highest selectivity factor observed yet (Table 2, entry 12).

At this point, we decided to examine a wide variety of bifunctional organocatalysts (Table 3). C_2-symmetrical bis-

Table 3. Bifunctional Catalyst Survey[a]



entry	catalyst	ROH	% conversion	*s*
1	**6**	Ph_2CHOH	0	N/A
2[b]	7	Ph_2CHOH	35	1.4
3	**8**	Ph_2CHOH	0	N/A
4	**9**	Ph_2CHOH	41	33
5[b]	**10**	Ph_2CHOH	42	94
6[b]	**11**	Ph_2CHOH	38	123
7	**12**	Ph_2CHOH	42	419
8	**12**	MeOH	47	23
9	**12**	BnOH	47	23
10	**12**	allylOH	43	37

[a]General conditions: 0.10 mmol of (±)-**1a**, 0.10 mmol of ROH, 0.01 mmol of catalyst, 500 μL of *tert*-amyl alcohol. [b]The absolute stereochemistry of the products is the opposite of that shown.

thiourea **6**[20] gave zero conversion (entry 1), indicating the importance of a Brønsted basic moiety in the catalyst. Reasonable catalytic activity, but very little enantioselectivity, was seen with bis-benzimidazole catalyst **7**[21] (entry 2). Tosylamide **8**[22] (entry 3) was completely ineffective, which suggested the need for a double hydrogen bond donor (cf. **5**, entry 12 in Table 2). Amino-squaramide catalyst **9**[23] gave a selectivity factor (entry 4) substantially lower than that of the analogous Takemoto's amino-thiourea catalyst **5**. This result, however, may be attributable to the poor solubility of **9** in *tert*-amyl alcohol. Quinine-derived amino-thiourea **10**[24] and

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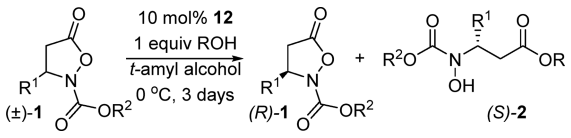
amino-squaramide **11**[25] gave comparable selectivity factors (entries 5 and 6, respectively). Surprisingly, the pseudoenantiomeric quinidine-derived amino-squaramide **12**[25] gave a superior selectivity factor (entry 7).[26] Other alcohols were briefly explored with catalyst **12**, but none proved superior to benzhydrol (entries 8−10).

Having thus completed our optimization studies, we proceeded to explore the substrate scope of the new methodology (Table 4). In several cases, we encountered substrates that were poorly soluble in pure *tert*-amyl alcohol, which would be detrimental to their KR. To remedy this problem, we had to employ *tert*-amyl alcohol/chloroform mixtures and occasionally pure chloroform. The addition of chloroform did not have any negative effect on the selectivity factor with substrate **1a** (cf. entries 1 and 2). Substrates bearing variously substituted aromatic and heteroaromatic groups were resolved with excellent selectivity factors (entries 1−10). Diminished but still useful levels of enantioselectivity were observed with a styryl and alkyl group (entries 11−13). However, branching at the α-position of the alkyl substituent greatly diminished the reactivity, as one can see in the case of the isopropyl group (entry 13). Fortunately, replacing benzhydrol with benzyl or allyl alcohol improved the conversion somewhat while producing enantioselectivities higher than that obtained previously with the phenyl substrate (cf. entries 14 and 15 in Table 4 vs entries 9 and 10 in Table 3). Alas, the *tert*-butyl substituent rendered the substrate completely unreactive with benzhydrol and produced barely detectable conversion with allyl alcohol (entries 16 and 17, respectively). Surprisingly, replacing the Boc group with a Cbz group also rendered the substrate unreactive toward benzhydrol (entry 18). Once again, however, less sterically demanding alcohols gave practically useful results (entries 19−21). The reaction scale was easily increased 10-fold (cf. entry 22 vs entry 6). Finally, we confirmed that Takemoto's catalyst **5** produces lower but still practically useful selectivity factors with representative aryl- and alkyl-substituted substrates under the same conditions (entries 23 and 24, respectively).

Various ester products obtained in the KR studies described above underwent quantitative transesterification with methanol under mild conditions (see, e.g., eq 1 in Figure 4), which proved to be useful for their HPLC analysis (see the Supporting Information). Nevertheless, most of the esters were stable and did not undergo spontaneous recyclization upon storage or exposure to silica gel. One notable exception was *tert*-butyl derivative **2m**-Me: although its formation could be observed on treating **1m** with methanol, it reverted to the starting isoxazolidinone even at room temperature (eq 2). This thermodynamic instability explains the lack of success in its KR (entries 16 and 17, Table 4). Other methyl esters could be easily cyclized back to isoxazolidinones by heating in the presence of catalytic dibutyltin oxide[4,27] (see, e.g., eq 1). The synthetic utility of resolved N-Boc-isoxazolidinones was demonstrated by the quantitative hydrogenolysis of the N−O bond giving rise to the N-protected β-amino acid (eq 3).[2a]

In conclusion, we have demonstrated that N-carbalkoxy-isoxazolidin-5-ones are effectively activated toward enantioselective alcoholysis by bifunctional organocatalysts. In fact, some of the selectivity factors recorded in this study are among the highest ever obtained in this type of transformation, thus highlighting the potential of these underexplored acyl donors in asymmetric catalysis. From a practical standpoint, the new methodology is expected to offer a mechanistically different alternative to existing asymmetric approaches to isoxazolidinones and can be used to upgrade their level of enantiomeric enrichment.

Table 4. Substrate Scope[a]



entry	R^1	R^2	ROH	% conversion	*s*
1	Ph	*t*-Bu	Ph_2CHOH	45	361
2[b]	Ph	*t*-Bu	Ph_2CHOH	45	487
3[b]	4-ClC_6H_4	*t*-Bu	Ph_2CHOH	37	344
4[b]	4-$MeOC_6H_4$	*t*-Bu	Ph_2CHOH	41	301
5[c]	4-NO_2Ph	*t*-Bu	Ph_2CHOH	31	127
6	2-ClC_6H_4	*t*-Bu	Ph_2CHOH	44	107
7	3-$MeOC_6H_4$	*t*-Bu	Ph_2CHOH	45	430
8[d]	1-naphthyl	*t*-Bu	Ph_2CHOH	29	171
9[d]	2-naphthyl	*t*-Bu	Ph_2CHOH	42	334
10	2-thienyl	*t*-Bu	Ph_2CHOH	48	352
11	styryl	*t*-Bu	Ph_2CHOH	50	80
12	isobutyl	*t*-Bu	Ph_2CHOH	40	67
13	isopropyl	*t*-Bu	Ph_2CHOH	24	151
14	isopropyl	*t*-Bu	BnOH	35	144
15	isopropyl	*t*-Bu	allylOH	37	92
16	*tert*-butyl	*t*-Bu	Ph_2CHOH	N/A	N/A
17	*tert*-butyl	*t*-Bu	allylOH	<5%	N/A
18[c]	Ph	Bn	Ph_2CHOH	N/A	N/A
19[c]	Ph	Bn	MeOH	54	27
20[c]	Ph	Bn	BnOH	50	40
21[c]	Ph	Bn	allylOH	49	50
22[e]	2-ClC_6H_4	*t*-Bu	Ph_2CHOH	44	80
23[d,f]	2-naphthyl	*t*-Bu	Ph_2CHOH	41	118
24[f]	isobutyl	*t*-Bu	Ph_2CHOH	27	21

[a]General conditions: 0.10 mmol of substrate, 0.10 mmol of alcohol, 0.01 mmol of **12**, 500 μL of *tert*-amyl alcohol. [b]A 4:1 *tert*-amyl alcohol/$CHCl_3$ mixture was used as the solvent. [c]$CHCl_3$ was used as the solvent. [d]A 3:2 *tert*-amyl alcohol/$CHCl_3$ mixture was used as the solvent. [e]Performed on 1.0 mmol of substrate. [f]Catalyst **5** was used.

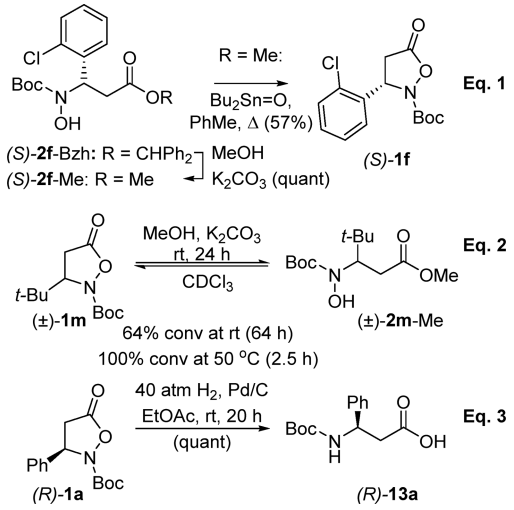


Figure 4. Transformations of the products.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04196.

Experimental procedures, NMR spectra, and HPLC data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For a comprehensive review of catalytic enantioselective syntheses of isoxazolidine-5-ones, see: Annibaletto, J.; Oudeyer, S.; Levacher, V.; Brière, J.-F. Catalytic Enantioselective Syntheses of Isoxazolidin-5-ones. *Synthesis* **2017**, *49*, 2117−2128.

(2) (a) Ibrahem, I.; Rios, R.; Vesely, J.; Zhao, G.-L.; Cordova, A. Organocatalytic asymmetric 5-hydroxyisoxazolidine synthesis: a highly enantioselective route to beta-amino acids. *Chem. Commun.* **2007**, 849−851. (b) Ibrahem, I.; Rios, R.; Vesely, J.; Zhao, G.-L.; Cordova, A. Catalytic enantioselective 5-hydroxyisoxazolidine synthesis: an asymmetric entry to β-amino acids. *Synthesis* **2008**, *2008*, 1153−1157.

(3) Izumi, S.; Kobayashi, Y.; Takemoto, Y. Catalytic Asymmetric Synthesis of anti-α,β-Diamino Acid Derivatives. *Org. Lett.* **2016**, *18*, 696−699.

(4) Kamlar, M.; Cisarova, I.; Hybelbauerova, S.; Vesely, J. Asymmetric Allylic Amination of Morita-Baylis-Hillman Carbonates with Silylated tert-Butylhydroxycarbamate Derivatives. *Eur. J. Org. Chem.* **2017**, *2017*, 1926−1930.

(5) (a) Yu, J.-S.; Noda, H.; Shibasaki, M. Quaternary β2,2-amino acids: Catalytic asymmetric synthesis and incorporation into peptides by Fmoc-based solid-phase peptide synthesis. *Angew. Chem., Int. Ed.* **2018**, *57*, 818−822. See also: (b) Cadart, T.; Berthonneau, C.; Levacher, V.; Perrio, S.; Brière, J.-F. Enantioselective Phase-Transfer Catalyzed α-Sulfanylation of Isoxazolidin-5-ones: An Entry to β2,2-Amino Acid Derivatives. *Chem. - Eur. J.* **2016**, *22*, 15261−15264. (c) Tite, T.; Sabbah, M.; Levacher, V.; Briere, J.-F. Organocatalysed decarboxylative protonation process from Meldrum's acid: enantioselective synthesis of isoxazolidinones. *Chem. Commun.* **2013**, *49*, 11569−11571, DOI: 10.1039/c3cc47695b. (d) Capaccio, V.; Zielke, K.; Eitzinger, A.; Massa, A.; Palombi, L.; Faust, K.; Waser, M. Asymmetric phase-transfer catalyzed β-addition of isoxazolidin-5-ones to MBH carbonates. *Org. Chem. Front.* **2018**, *5*, 3336−3340. (e) Eitzinger, A.; Winter, M.; Schoergenhumer, J.; Waser, M. Quaternary $\beta^{2,2}$-amino acid derivatives by asymmetric addition of isoxazolidin-5-ones to para-quinone methides. *Chem. Commun.* **2020**, *56*, 579−582. (f) Capaccio, V.; Sicignano, M.; Rodriguez, R. I.; Della Sala, G.; Aleman, J. Asymmetric Synthesis of α-Trifluoromethylthio-β-Amino Acids under Phase Transfer Catalysis. *Org. Lett.* **2020**, *22*, 219−223.

(6) For asymmetric catalytic approaches to N-alkylisoxazolidinones, see: (a) Sibi, M. P.; Liu, M. Enantioselective conjugate addition of hydroxylamines to pyrazolidinone acrylamides. *Org. Lett.* **2001**, *3*, 4181−4184. (b) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. Enantioselective Synthesis of α,β-Disubstituted-β-amino Acids. *J. Am. Chem. Soc.* **2003**, *125*, 11796−11797.

(7) For select noncatalytic approaches to enantioenriched isoxazolidinones, see: (a) Ishikawa, T.; Nagai, K.; Kudoh, T.; Saito, S. Asymmetric synthesis of substituted isoxazolidinone from α,β-unsaturated esters and hydroxylamines by means of double stereodifferentiation. *Synlett* **1995**, *1995*, 1171−1173. (b) Juarez-Garcia, M.; Yu, S.; Bode, J. W.un Asymmetric synthesis of enantiopure isoxazolidinone monomers for the synthesis of β^3-oligopeptides by chemoselective amide ligation. *Tetrahedron* **2010**, *66*, 4841−4853. (c) Frazier, C. P.; Engelking, J. R.; Read de Alaniz, J. Copper-Catalyzed Aerobic Oxidation of Hydroxamic Acids Leads to a Mild and Versatile Acylnitroso Ene Reaction. *J. Am. Chem. Soc.* **2011**, *133*, 10430−10433.

(8) (a) Berini, C.; Sebban, M.; Oulyadi, H.; Sanselme, M.; Levacher, V.; Briere, J.-F. Organocatalyzed Multicomponent Synthesis of Isoxazolidin-5-ones. *Org. Lett.* **2015**, *17*, 5408−5411. See also: (b) Le Foll Devaux, A.; Deau, E.; Corrot, E.; Bischoff, L.; Levacher, V.; Briere, J.-F. A Meldrum's Acid Based Multicomponent Synthesis of N-Fmoc-isoxazolidin-5-ones: Entry to N-Fmoc-β-amino Acids. *Eur. J. Org. Chem.* **2017**, *2017*, 3265−3273. See also: (c) Martzel, T.; Annibaletto, J.; Millet, P.; Pair, E.; Sanselme, M.; Oudeyer, S.; Levacher, V.; Briere, J.-F. Organocatalytic multicomponent synthesis of α/β-dipeptide derivatives. *Chem. - Eur. J.* **2020**, *26*, 8541−8545.

(9) (a) Pellissier, H. Catalytic Non-Enzymatic Kinetic Resolution. *Adv. Synth. Catal.* **2011**, *353*, 1613−1666. (b) Vedejs, E.; Jure, M. Efficiency in nonenzymatic kinetic resolution. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974−4001. (c) Kagan, H. B.; Fiaud, J. C. Kinetic resolution. *Top. Stereochem.* **2007**, *18*, 249−330.

(10) (a) Hang, J.; Tian, S.-K.; Tang, L.; Deng, L. Asymmetric Synthesis of α-Amino Acids via Cinchona Alkaloid-Catalyzed Kinetic Resolution of Urethane-Protected α-Amino Acid N-Carboxyanhydrides. *J. Am. Chem. Soc.* **2001**, *123*, 12696−12697. (b) Chen, Y.; Deng, L. Parallel Kinetic Resolutions of Monosubstituted Succinic Anhydrides Catalyzed by a Modified Cinchona Alkaloid. *J. Am. Chem. Soc.* **2001**, *123*, 11302−11303. (c) Chen, Y.; McDaid, P.; Deng, L. Asymmetric Alcoholysis of Cyclic Anhydrides. *Chem. Rev.* **2003**, *103*, 2965−2983.

(11) Berkessel, A.; Cleemann, F.; Mukherjee, S. Kinetic resolution of oxazinones: An organocatalytic approach to enantiomerically pure β-amino acids. *Angew. Chem., Int. Ed.* **2005**, *44*, 7466−7469.

(12) Bumbu, V. D.; Birman, V. B. Kinetic Resolution of N-Acyl-β-Lactams via Benzotetramisole-Catalyzed Enantioselective Alcoholysis. *J. Am. Chem. Soc.* **2011**, *133*, 13902−13905.

(13) (a) Liang, J.; Ruble, J. C.; Fu, G. C. Dynamic Kinetic Resolutions Catalyzed by a Planar-Chiral Derivative of DMAP: Enantioselective Synthesis of Protected α-Amino Acids from Racemic Azalactones. *J. Org. Chem.* **1998**, *63*, 3154−3155. (b) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Mueller, T. N.; Lex, J. Highly efficient dynamic kinetic resolution of azlactones by urea-based bifunctional organocatalysts. *Angew. Chem., Int. Ed.* **2005**, *44*, 807−811. (c) Lee, J. W.; Ryu, T. H.; Oh, J. S.; Bae, H. Y.; Jang, H. B.; Song, C. E. Self-association-free dimeric cinchona alkaloid organocatalysts: unprecedented catalytic activity, enantioselectivity and catalyst recyclability in dynamic kinetic resolution of racemic azlactones. *Chem. Commun.* **2009**, 7224−7226. (d) Yang, X.; Lu, G.; Birman, V. B. Benzotetramisole-Catalyzed Dynamic Kinetic Resolution of Azlactones. *Org. Lett.* **2010**, *12*, 892. (e) Lu, G.; Birman, V. B. Dynamic Kinetic Resolution of Azlactones Catalyzed by Chiral Brønsted Acids. *Org. Lett.* **2011**, *13*, 356.

(14) (a) Tang, L.; Deng, L. Dynamic Kinetic Resolution via Dual-Function Catalysis of Modified Cinchona Alkaloids: Asymmetric Synthesis of α-Hydroxy Carboxylic Acids. *J. Am. Chem. Soc.* **2002**, *124*, 2870−2871. (b) Hang, J.; Li, H.; Deng, L. Development of a Rapid, Room-Temperature Dynamic Kinetic Resolution for Efficient Asymmetric Synthesis of α-Aryl Amino Acids. *Org. Lett.* **2002**, *4*, 3321−3324.
(15) (a) Chen, Y.; Tian, S.-K.; Deng, L. A Highly Enantioselective Catalytic Desymmetrization of Cyclic Anhydrides with Modified Cinchona Alkaloids. *J. Am. Chem. Soc.* **2000**, *122*, 9542−9543. (b) Chen, Y.; McDaid, P.; Deng, L. Asymmetric Alcoholysis of Cyclic Anhydrides. *Chem. Rev.* **2003**, *103*, 2965−2983. (c) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. Asymmetric Organic Catalysis with Modified Cinchona Alkaloids. *Acc. Chem. Res.* **2004**, *37*, 621−631.
(16) Birman, V. B.; Li, X. Benzotetramisole: A Remarkably Enantioselective Acyl Transfer Catalyst. *Org. Lett.* **2006**, *8*, 1351−1354.
(17) (a) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. 2,3-Dihydroimidazo[1,2-a]pyridines: A New Class of Enantioselective Acyl Transfer Catalysts and Their Use in Kinetic Resolution of Alcohols. *J. Am. Chem. Soc.* **2004**, *126*, 12226−12227. (b) Ahlemeyer, N. A.; Streff, E. V.; Muthupandi, P.; Birman, V. B. Dramatic Acceleration of an Acyl Transfer-Initiated Cascade by Using Electron-Rich Amidine-Based Catalysts. *Org. Lett.* **2017**, *19*, 6486−6489.
(18) The selectivity factor is defined as $s = k$(fast-reacting enantiomer)/k(slow-reacting enantiomer). The % conversion and selectivity factor are both calculated from ees of the product and the recovered starting material.
(19) Okino, T.; Hoashi, Y.; Takemoto, Y. Enantioselective Michael Reaction of Malonates to Nitroolefins Catalyzed by Bifunctional Organocatalysts. *J. Am. Chem. Soc.* **2003**, *125*, 12672−12673.
(20) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. Development of bis-thiourea-type organocatalyst for asymmetric Baylis-Hillman reaction. *Tetrahedron Lett.* **2004**, *45*, 5589−5592.
(21) Gomez-Torres, E.; Alonso, D. A.; Gomez-Bengoa, E.; Najera, C. Conjugate Addition of 1,3-Dicarbonyl Compounds to Maleimides Using a Chiral C2-Symmetric Bis(2-aminobenzimidazole) as Recyclable Organocatalyst. *Org. Lett.* **2011**, *13*, 6106.
(22) Azuma, T.; Murata, A.; Kobayashi, Y.; Inokuma, T.; Takemoto, Y. A Dual Arylboronic Acid-Aminothiourea Catalytic System for the Asymmetric Intramolecular Hetero-Michael Reaction of α,β-Unsaturated Carboxylic Acids. *Org. Lett.* **2014**, *16*, 4256−4259.
(23) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. Enantioselective α-Amination of 1,3-Dicarbonyl Compounds Using Squaramide Derivatives as Hydrogen Bonding Catalysts. *Org. Lett.* **2010**, *12*, 2028−2031.
(24) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. Highly enantioselective conjugate addition of nitromethane to chalcones using bifunctional cinchona organocatalysts. *Org. Lett.* **2005**, *7*, 1967−1969.
(25) Yang, W.; Du, D.-M. Highly enantioselective Michael addition of nitroalkanes to chalcones using chiral squaramides as hydrogen bonding organocatalysts. *Org. Lett.* **2010**, *12*, 5450−5453.
(26) Differences in the activity and enantioselectivity of Cinchona-derived pseudoenantiomeric catalysts have been documented. See, e.g.: Hu, B.; Bezpalko, M. W.; Fei, C.; Dickie, D. A.; Foxman, B. M.; Deng, L. Origin of and a Solution for Uneven Efficiency by Cinchona Alkaloid-Derived, Pseudoenantiomeric Catalysts for Asymmetric Reactions. *J. Am. Chem. Soc.* **2018**, *140*, 13913−13920.
(27) Lee, H.-S.; Park, J.-S.; Kim, B. M.; Gellman, S. H. Efficient Synthesis of Enantiomerically Pure β2-Amino Acids via Chiral Isoxazolidinones. *J. Org. Chem.* **2003**, *68*, 1575−1578.

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