Published in final edited form as:

J Am Chem Soc. 2018 February 14; 140(6): 1998–2001. doi:10.1021/jacs.7b12185.

Biomimetic Desymmetrization of a Carboxylic Acid

Matthew T. Knowe¹, Michael W. Danneman¹, Sarah Sun¹, Maren Pink², and Jeffrey N. Johnston^{1,*}

¹Department of Chemistry & Vanderbilt Institute of Chemical Biology, Vanderbilt University, Nashville, Tennessee 37235-1822, United States

²Indiana University Molecular Structure Center, Bloomington, Indiana 47405, United States

Abstract

The enantioselective desymmetrization of carboxylic acids by chiral Brønsted base catalysis is reported, leading to bridged bicyclic lactones with up to 94% ee. Crystallographic analysis of a substrate-catalyst complex suggests an origin of stereocontrol, reminiscent of functional Brønsted bases in biological settings, and enabled reaction optimization. The products contain an all-carbon quaternary stereocenter, and can be derivatized to functionalized cyclopentanes.

Graphical abstract

Carboxylic acids are robust substrates widely valued for their availability and utility in substitutions (e.g. Mitsunobu reactions) and addition reactions to activated alkenes. As a reagent, the carboxylic acid can function as a catalyst,¹ although successful chiral carboxylic acid organocatalysts² remain relatively limited. Likewise, development of asymmetric activation strategies for reactions of carboxylic acid substrates have evolved slowly.^{3,4} Cases of enzyme-mediated base activation of carboxylates are known, but a similar demonstration in small molecule catalysis is absent. Advances in chemistry have blurred the distinction between enzymatic and organic catalysis,^{5,6} and the latter has been categorized by mechanism (covalent vs. non-covalent catalysis) and functionality (hydrogen bonding). A detailed understanding of those features necessary for catalysis involving carboxylic acids,

*Corresponding Author: jeffrey.n.johnston@vanderbilt.edu.

Supporting Information.

Complete experimental details (PDF); NMR and HPLC trace data (PDF); crystallographic data for **1a-3a** (CIF).

Funding Sources

The authors declare no competing financial interest.

however, is still developing and catalyst designs trend toward confined cavities for catalysis and stereocontrol.^{3,4,7}

A variety of strategies have been employed for alkene halofunctionalization,^{8,9} yet activation of carboxylic acids by a simple Brønsted base has little precedent,^{10,11,12} preventing development of a clear picture for activation and stereocontrol. A remarkable example of carboxyl control is found in the carbamic acid nucleophile in the enzyme *dethiobiotin synthetase*, for which crystallographic evidence supports a hydrogen bond-mediated *oxygen differentiation* (Figure 1A).¹³ The hydrogen bond-accepting feature of chiral phosphoric acids were used recently to activate a carboxylic acid, with simultaneous activation of an electrophile by hydrogen-bond donation^{3,4} (Figure 1B, Etter graph sets¹⁴). Similarly, bifunctional Brønsted acid-base catalysis in the co-activation of a carboxylic acid and a halogen donor has been firmly established for enantioselective alkene haloesterification.¹⁵

We reasoned that prochiral cyclic unsaturated acids **III/1** (Figure 2) might further challenge a catalyst by decoupling Brønsted base and Brønsted acid activation of a carboxylic acid and a halonium source, respectively. In contrast to more conformationally unrestricted substrates (**I**) for which dual Brønsted base/Brønsted acid activation can be envisioned, the conformational restrictions of cyclic acids **II/III** require halonium delivery *anti* to the carboxyl, such that a catalyst hydrogen bond donor/acceptor can bind only the nucleophile *or* electrophile. Symmetric diene **II** requires only π -carbon selectivity, while unsaturated acid **III** additionally demands carboxylic acid oxygen-selectivity. Framed by this mechanistic question and existing evidence for bifunctional catalysis of π -face selective halocyclizations,¹⁶ we sought to apply BisAMi-dine (BAM) catalysis to the desymmetrization of constrained *Z*-alkenes (**1**).¹⁷ A map of stereocontrol (Figure 2) illustrates that carboxyl oxygen selectivity during nucleophilic attack, as well as orientation about the C-CO₂H bond, are equally necessary to achieve enantioselection. This report details the first enantioselective iodolactonizations of cyclopentenones **1**, evidence for Brønsted base activation of the carboxylic acid, and the X-ray crystal structure of a substrate-BAM complex. The latter suggests the role of an array of three hydrogen bonds, which we hypothesize to be the origin of enantiocontrol (Figure 1C). The overall picture is reminiscent of enzymatic hydrogen bonding where substrate conformational control and carboxyl activation play a key role in catalysis.

Our initial studies with **1a** indicated that the free base of organocatalyst **3a** was moderately active and selective while the 1:1 Brønsted acid salt (Table 1, entries 1–2) was essentially inactive.¹⁸ This result stood in striking contrast to all other alkene iodofunctionalizations with BAMs,¹⁶ and was interpreted as evidence for monofunctional activation. At this point, a single crystal of catalyst **3a** with **1a** was successfully prepared and analyzed by X-ray

diffraction (Figure 3). Two features were evident: 1) the amidinium-carboxylate salt effectively bound the substrate close to the catalyst's chiral cavity, assisted by a third hydrogen bond donor, and 2) the second quinoline ring is oriented such that its 4-substituent (pyrrolidine) is positioned near the substrate binding pocket.

We undertook a broader investigation of catalysts, resulting in the discovery that *N*-aryl BAM **3b** provided competitive levels of selectivity and significantly improved reactivity (Table 1, entry 3). We hypothesized that a substituent at the quinoline 6-position might buttress the aniline in **3b**, deterring a conformation that places the aromatic ring away from the binding site.¹⁹ The effect of a 6-*tert*-butyl was explored with **3c** providing selectivity to 73% (ee at -20 °C (Table 1, entry 4) and 85% ee at -50 °C Table 1, entry 6).

Investigation of iodonium sources found *N*-iodophthalimide increased enantioselectivity to 89% ee (Table 1, entry 6). Other halogen sources provided lower selectivity and reactivity. Investigation of aniline derivatives identified **3d** as a catalyst with optimal selectivity and reactivity (Table 1, entry 7). The influence of the 6-*tert*-butyl substituent does not translate to the original findings with **3a** (c.f. Table 1, entries 4, 8). Several commercially available chiral phosphoric acids and thioureas were evaluated, but provided only racemic bridged lactones.¹⁹

The structure in Figure 3 provides a reasonable basis to further refine our hypothesis for stereocontrol (*vide supra*), proposing that the three hydrogen bond contacts between the catalyst and carboxylic acid may be responsible for enantioselection.²⁰ Two hydrogen bonds from one amidine and a third hydrogen bond from the ancillary amidine effectively desymmetrize the carboxylate by diminishing the nucleophilicity of the doubly bonded oxygen relative to the singly bonded carboxylate oxygen. Catalyst-substrate binding in solution was investigated by isothermal titration calorimetry,²¹ and found to be driven by strong hydrogen bonding ($K_A = 2.52 \times 10^5 \text{ M}^{-1}$).¹⁹ The role of the quinoline 4-substituent (pyrrolidine (**3a**) → *p*-toluidine (**3d**)) may be critical to achieve the second criterion for selectivity – restricted rotation about the cyclopentene-CO₂H bond – by a steric interaction.¹⁹ Importantly, this hypothesis suggests that this second quinoline may not be important for binding and activation (i.e. to NIP).

The reaction scope was evaluated using catalyst **3d**, and exploratory substrate **1a** (Table 2, entry 1) was completed on 1 mmol scale with good yield (66%) and 94% ee (Table 2, entry 2). 2-Naphthyl derivative **1b** reacted well and with good selectivity (Table 2, entry 3), while the sterically demanding 1-naphthyl **1c** provided good yield and moderate enantioselection (Table 2, entry 4). Halophenyl substrates were also tolerated (Table 2, entries 5–6). The electronic nature of the aromatic ring exhibited some generality, with **1f–1h** converting to product in moderate to good yields and with high enantioselectivity (Table 2, entries 7–10), although **1g** required an extended reaction time. Isopropyl-, benzyl-, and methyl-substituents are well tolerated, reacting with slightly lower selectivity relative to aryl substrates (Table 2, entries 11–13). Malonate half-ester **1m** and thioester **1n** provide additional versatility for applications of the lactone products, albeit with some depression of enantioselection. α -Unsubstituted carboxylic acid **1o** failed to convert under these conditions (Table 2, entry 16),

suggesting ground state destabilization, provided by compression of the carboxylic acid-alkene distance, may be needed.

Derivatization of the bicyclic lactone products (Scheme 1) was readily achieved, each with conservation of enantiomeric excess. Reduction of **2a** with lithium aluminum hydride at low temperature leads to iododiol **4** in 42% yield and at room temperature facilitates reduction followed by etherification to bicyclic alcohol **5** in 59% yield. Reductive deiodination and allylation proceeded in good yield, providing **6** and **7** (5:1 dr) respectively. Finally, aminolysis of lactone **6** afforded *syn*- γ -hydroxy amide **8** in good yield (70%), to give a functionalized cyclopentane core common to carbocyclic nucleosides,²² providing novel approaches towards accessing this type of therapeutic.²³

In conclusion, monofunctional Brønsted base catalysis of a unique iodolactonization has been discovered using a substrate that deconstructs the normal bifunctional activation mode of chiral hydrogen bond catalysts. Structural studies reveal a network of three hydrogen bonds that desymmetrizes the bound carboxylate, while a distant *N*-aryl substituent influences the cyclopentene ring's conformation. Both of these effects are necessary for enantioselection and are achieved using a C_2 -symmetric Brønsted basic catalyst. Broader use of this strategy for carboxylic acid activation may lead to an expansion of their utility in enantioselective transformations, and an improved understanding of the essential characteristics of enzymatic reactions using carboxyl nucleophiles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

S. S. was supported by the Vanderbilt University Summer Research Program. We are grateful to the National Institute of General Medical Sciences (NIH GM 084333) for financial support.

References

1. Min C, Seidel D. Chem Soc Rev. 2017;5889. [PubMed: 28730207]
2. (a) Hashimoto T, Maruoka K. J Am Chem Soc. 2007; 129:10054. [PubMed: 17655298] (b) Momiyama N, Yamamoto H. J Am Chem Soc. 2005; 127:1080. [PubMed: 15669829] (c) Hashimoto T, Maruoka K. Synthesis. 2008; 2008:3703. (d) Hashimoto T, Hirose M, Maruoka K. J Am Chem Soc. 2008; 130:7556. [PubMed: 18491901] (d) Hashimoto T, Nakatsu H, Takiguchi Y, Maruoka K. J Am Chem Soc. 2013; 135:16010. [PubMed: 24128304]
3. (a) Monaco MR, Fazzi D, Tsuji N, Leutzsch M, Liao S, Thiel W, List B. J Am Chem Soc. 2016; 138:14740. [PubMed: 27779872] (b) Monaco MR, Poladura B, Diaz de Los Bernardos M, Leutzsch M, Goddard R, List B. Angew Chem Int Ed. 2014; 53:7063.
4. Zhang J, Lin SX, Cheng DJ, Liu XY, Tan B. J Am Chem Soc. 2015; 137:14039. [PubMed: 26488384]
5. (a) MacMillan DWC. Nature. 2008; 455:304. [PubMed: 18800128] (b) Dalko PI, Moisan L. Angew Chem Int Ed. 2001; 40:3726. (c) Seayad J, List B. Org Biomol Chem. 2005; 3:719. [PubMed: 15731852] (d) Akiyama T, Itoh J, Fuchibe K. Adv Synth Catal. 2006; 348:999. (e) Terada M. Chem Commun. 2008:4097.
6. (a) Nakamura S, Ishihara K, Yamamoto H. J Am Chem Soc. 2000; 122:8131. (b) Sakakura A, Ukai A, Ishihara K. Nature. 2007; 445:900. [PubMed: 17314976]

7. Coric I, List B. *Nature*. 2012; 483:315. [PubMed: 22422266]
8. Asymmetric halocyclization reviews:(a) Denmark SE, Kuester WE, Burk MT. *Angew Chem Int Ed*. 2012; 51:10938.(b) Chen J, Zhou L. *Synthesis*. 2014; 46:586.(c) Fujioka H, Murai K. *Heterocycles*. 2013; 87:763.(d) Cheng Y, Yu W, Yeung YY. *Org Biomol Chem*. 2014; 12:2333. [PubMed: 24595745] (e) Tan C, Zhou L, Yeung YY. *Synlett*. 2011:1335.(f) French AN, Bissmire S, Wirth T. *Chem Soc Rev*. 2004; 33:354. [PubMed: 15280968] (g) Haas J, Piguel S, Wirth T. *Org Lett*. 2002; 4:297. [PubMed: 11796074] (h) Hennecke U. *Chem - Asian J*. 2012; 7:456. [PubMed: 22315237]
9. (a) Veitch GE, Jacobsen EN. *Angew Chem Int Ed*. 2010; 49:7332.(b) Whitehead DC, Yousefi R, Jaganathan A, Borhan B. *J Am Chem Soc*. 2010; 132:3298. [PubMed: 20170118] (c) Yousefi R, Ashtekar KD, Whitehead DC, Jackson JE, Borhan B. *J Am Chem Soc*. 2013; 135:14524. [PubMed: 24025085]
10. Brønsted base catalysis review:(a) Palomo C, Oiarbide M, Lopez R. *Chem Soc Rev*. 2009; 38:632. [PubMed: 19169469] (b) Ashtekar KD, Vetticatt M, Yousefi R, Jackson JE, Borhan B. *J Am Chem Soc*. 2016; 138:8114. [PubMed: 27284808]
11. Related study of catalyst/substrate complex in solution:Wilking M, Daniliuc CG, Hennecke U. *Chem Eur J*. 2016; 22:18601. [PubMed: 27727486]
12. (a) Murai K, Matsushita T, Nakamura A, Fukushima S, Shimura M, Fujioka H. *Angew Chem Int Ed*. 2010; 49:9174.(b) Murai K, Nakamura A, Matsushita T, Shimura M, Fujioka H. *Chem Eur J*. 2012; 18:8448. [PubMed: 22623128] (c) Murai K, Nakajima J, Nakamura A, Hyogo N, Fujioka H. *Chem - Asian J*. 2014; 9:3511. [PubMed: 25256170] (d) Paull DH, Fang C, Donald JR, Pansick AD, Martin SF. *J Am Chem Soc*. 2012; 134:11128. [PubMed: 22726214] (e) Zhou L, Tan C, Jiang X, Chen F, Yeung YY. *J Am Chem Soc*. 2010; 132:15474. [PubMed: 20945837] (f) Jaganathan A, Garzan A, Whitehead DC, Staples RJ, Borhan B. *Angew Chem Int Ed*. 2011; 50:2593.(g) Zhang W, Xu H, Xu H, Tang W. *J Am Chem Soc*. 2009; 131:3832. [PubMed: 19245198]
13. Huang W, Jia J, Gibson KJ, Taylor WS, Rendina AR, Schneider G, Lindqvist Y. *Biochemistry*. 1995; 34:10985. [PubMed: 7669756]
14. (a) Etter MC. *Acc Chem Res*. 1990; 23:120.(b) Lynch DE, Jones GD. *Acta Crystallogr, Sect B: Struct Sci*. 2004; 60:748.
15. Nolsøe MJ, Hansen TV. *Eur J Org Chem*. 2014:3051.
16. (a) Dobish MC, Johnston JN. *J Am Chem Soc*. 2012; 134:6068. [PubMed: 22463391] (b) Vara BA, Struble TJ, Wang W, Dobish MC, Johnston JN. *J Am Chem Soc*. 2015; 137:7302. [PubMed: 26039818] (c) Toda Y, Pink M, Johnston JN. *J Am Chem Soc*. 2014; 136:14734. [PubMed: 25336273]
17. (a) Ikeuchi K, Ido S, Yoshimura S, Asakawa T, Inai M, Hamashima Y, Kan T. *Org Lett*. 2012; 14:6016. [PubMed: 23148461] (b) Wilking M, Mück-Lichtenfeld C, Daniliuc CG, Hennecke U. *J Am Chem Soc*. 2013; 135:8133. [PubMed: 23679927] (c) Hennecke U, Wilking M. *Synlett*. 2014; 25:1633.(d) Zeng XP, Cao ZY, Wang YH, Zhou F, Zhou J. *Chem Rev*. 2016; 116:7330. [PubMed: 27251100] (e) Borissov A, Davies TQ, Ellis SR, Fleming TA, Richardson MSW, Dixon DJ. *Chem Soc Rev*. 2016; 45:5474. [PubMed: 27347567] (f) Petersen KS. *Tetrahedron Lett*. 2015; 56:6523. [PubMed: 26834295] (g) C Willis M. *J Chem Soc, Perkin Trans*. 1999; 1:1765.(h) Champagne PA, Houk KN. *J Am Chem Soc*. 2016; 138:12356. [PubMed: 27629045]
18. Benzoic acid additive tests revealed that yield and selectivity begin to lower when 8 equivalents of (substrate) acid are present (see supporting information). Separately, selectivity was monitored at low conversions without detection of a significant effect. Therefore, although catalyst protonation state can affect reactivity and selectivity, these BAM catalysts are not affected by the hindered, weak carboxylic acid substrates.
19. See supporting information.
20. (a) Barrow GM. *J Am Chem Soc*. 1956; 78:5802.(b) Kinbara K, Hashimoto Y, Sukegawa M, Nohira H, Saigo K. *J Am Chem Soc*. 1996; 118:3441.(c) Braga D, Maini L, Grepioni F, De Cian A, Felix O, Fischer J, Hosseini MW. *New J Chem*. 2000; 24:547.(d) Taylor R, Kennard O, Versichel W. *J Am Chem Soc*. 1983; 105:5761.(e) Taylor R, Kennard O. *Acc Chem Res*. 1984; 17:320.(f) Bis JA, Zaworotko MJ. *Cryst Growth Des*. 2005; 5:1169.
21. Lah J, Maier NM, Lindner W, Vesnaver G. *J Phys Chem B*. 2001; 105:1670.
22. (a) Wisniewski T, Bayne E, Flanagan J, Shao Q, Wnek R, Matheravidathu S, Fischer P, Forrest MJ, Peterson L, Song X, Yang L, DeMartino JA, Struthers M. *J Immunol Methods*. 2010; 352:101.

- [PubMed: 19913021] (b) Vilums M, Zweemer AJM, Yu Z, de Vries H, Hillger JM, Wapenaar H, Bollen IAE, Barmare F, Gross R, Clemens J, Krenitsky P, Brussee J, Stamos D, Saunders J, Heitman LH, Ijzerman AP. *J Med Chem.* 2013; 56:7706. [PubMed: 24028535]
23. (a) Boutureira O, Matheu MI, Diaz Y, Castillon S. *Chem Soc Rev.* 2013; 42:5056. [PubMed: 23471263] (b) Marquez VE, Lim MI. *Med Res Rev.* 1986; 6:1. [PubMed: 3512934]

Figure 1.

Hydrogen Bond-Driven Activation A) double hydrogen bond donation to one oxygen, and Brønsted base activation of the other, leading to enhancement of an oxygen's nucleophilicity in dethiobiotin synthetase; B) model for simultaneous electrophile and carboxylic acid activation by a chiral phosphoric acid (proposed); C) carboxyl oxygen desymmetrization using an array of three hydrogen bonds (proposed). *For Etter graph set nomenclature see ref. ¹⁴.

Figure 2. Prior approaches to alkene functionalization (**I**, **II**) and this approach (**III**) requiring simultaneous control of nucleophilic carboxyl oxygen and carbon-CO₂H bond conformation by a chiral base (*B:).

Figure 3.
Key features of the X-ray cocrystal structure of **1a·(R,R)-3a**

Scheme 1.
Conversions of Lactone **2a**^a

Table 1

Discovery and Development of an Enantioselective Synthesis of a Bridged Lactone

Entry ^a	catalyst	I^+ source ^b	temp. (°C)	time (h)	yield (%) ^c	ee (%) ^d
1	3a-HNTf ₂	NIS	-20	48	<5	–
2	3a	NIS	-20	48	50	62
3	3b	NIS	-20	24	64	61
4	3c	NIS	-20	24	79	73
5	3c	NIS	-50	48	74	85
6	3c	NIP	-50	48	86	89
7 ^e	3d	NIP	-50	24	83	94
8	3e	NIP	-20	24	36	69

^a All reactions were performed on a 0.05 mmol scale.

^b NIS = *N*-iodosuccinimide, NIP = *N*-iodophthalimide.

^c Yield determined by ¹H NMR analysis relative to an internal standard (CH₂Br₂).

^d Enantiomeric ratios were measured using HPLC with a chiral stationary phase. See SI for complete details.

^e Reaction stirred in a 2–5 mL round bottomed microwave vial.

Table 2

Enantioselective Iodolactonizations Cat-alyzed by BAM 3d: Scope and Limitations

Entry	R	1/2	time (h)	yield (%) ^b	ee (%) ^c
1	C ₆ H ₅	a	24	87	93
2	C ₆ H ₅ (1.0 mmol scale)	a	48	66	94
3	² Np	b	72	78	90
4	¹ Np	c	72	72	67
5	^m ClC ₆ H ₄	d	24	69	89
6	^p BrC ₆ H ₄	e	24	74	89
7	^t (MeO)C ₆ H ₄	f	48	65	91
8	^t (O ₂ N)C ₆ H ₄	g	120	78	86
9	^p PhC ₆ H ₄	h	72	55	94
10	2-thiophene	i	24	69	92
11	ⁱ Pr	j	24	74	87
12	Bn	k	48	66	87
13	Me	l	72	66	86
14	CO ₂ tBu	m	72	64	64
15	C(O)S <i>t</i> Bu	n	72	66	74
16	H	o	72	<5	-

^a All reactions were performed on a 0.10 mmol scale using 1 equivalent of the carboxylic acid, 10 mol% catalyst, and 1.04 equiv NIP in toluene (0.05 M).

^b Isolated yield.

^c Enantiomeric ratios were measured using HPLC and a chiral stationary phase. See SI for details.