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Organocatalytic Functionalization of Carboxylic Acids: Isothiourea-Catalyzed Asymmetric Intra- and Intermolecular Michael Addition−Lactonizations

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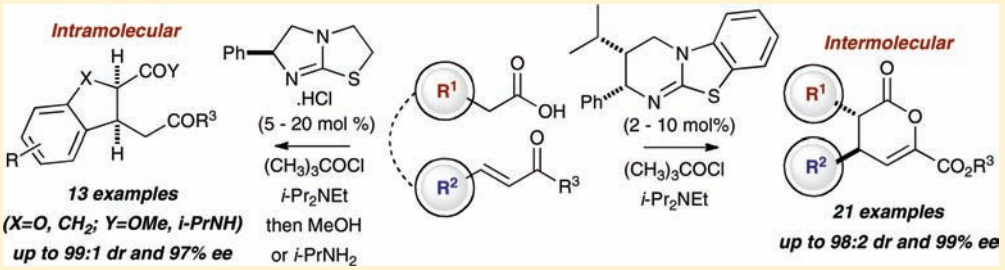
Supporting Information

ABSTRACT:



Tetramisole promotes the catalytic asymmetric intramolecular Michael addition−lactonization of a variety of enone acids, giving carbo- and heterocyclic products with high diastereo- and enantiocontrol (up to 99:1 dr, up to 99% ee) that are readily derivatized to afford functionalized indene and dihydrobenzofuran carboxylates. Chiral isothioureas also promote the catalytic asymmetric intermolecular Michael addition−lactonization of arylacetic acids and α-keto-β,γ-unsaturated esters, giving *anti*-dihydropyranones with high diastereo- and enantiocontrol (up to 98:2 dr, up to 99% ee).

INTRODUCTION

The development of methods for the catalytic generation of enolates or their equivalents is of widespread interest in asymmetric catalysis. While the use of transition metals to generate enolates is well documented,[1] a variety of organocatalytic methods, such as the use of enamines,[2] *N*-heterocyclic carbenes (NHCs),[3] and cinchona alkaloid derivatives,[4] have also been reported.[5] Lewis base catalysis encompasses a multitude of different catalyst types and reactions,[6] with the generation and reactivity of ammonium enolates,[7] typically formed from the interaction of a nucleophilic tertiary amine with either a preformed or *in situ* generated ketene, exploited for a range of asymmetric transformations.[8] Among these processes, the formal [4+2] cycloadditions of ammonium and azolium enolates, typically generated using cinchona alkaloids from acid chlorides, or from enals or α-functionalized aldehydes with NHCs, have been elegantly developed. For example, Lectka has shown that cinchona alkaloid-derived ketene enolates undergo a variety of enantioselective [4+2] cycloadditions with *o*-quinones,[9] *o*-quinone diimides[10] and quinone imides,[11] while Nelson has employed a similar pathway using *N*-thioacyl imines.[12,13] Bode has employed NHCs to catalyze asymmetric [4+2] cycloadditions, using azolium enolates generated from enals or α-chloroaldehydes to give *syn*-dihydropyranones with exquisite diastereo- and enantiocontrol,[14] while Ye has shown that NHCs promote the [4+2] cycloaddition of disubstituted ketenes with enones.[15,16] An asymmetric [4+2] approach using enamine catalysis has also been reported by Jørgensen,[17] generating *anti*-dihydropyranones after oxidation.

An alternative but synthetically appealing strategy to generate enolates in an organocatalytic fashion directly from carboxylic acids has received relatively little attention to date. In this area, Romo has elegantly shown that aldehyde- and keto-acids undergo intramolecular cyclization using either cinchona alkaloids or 4-pyrrolidinylpyridine as the Lewis base promoter, giving the corresponding β-lactones in good yields and stereoselectivities.[18] This protocol has been extended to highly enantioselective intramolecular desymmetrizing aldol-lactonization events, initially using stoichiometric tetramisole,[19] and very recently to substoichiometric homobenzotetramisole.[20] Building upon these precedents, and our own interest in Lewis base catalysis,[21] we report herein the highly diastereo- and enantioselective *intramolecular* Michael addition−lactonization process[22] of a range of enone-acid substrates using isothioureas, introduced by Birman and utilized extensively for asymmetric *O*-acylation procedures,[23] to afford indene and dihydrobenzofuran carboxylates after derivatization.[24] The further application of this methodology to an *intermolecular* Michael addition−lactonization strategy, allowing the direct asymmetric functionalization of a range of arylacetic acids with α-keto-β,γ-unsaturated esters, giving *anti*-dihydropyranones with excellent diastereo- and enantiocontrol, is also detailed herein (Figure 1).

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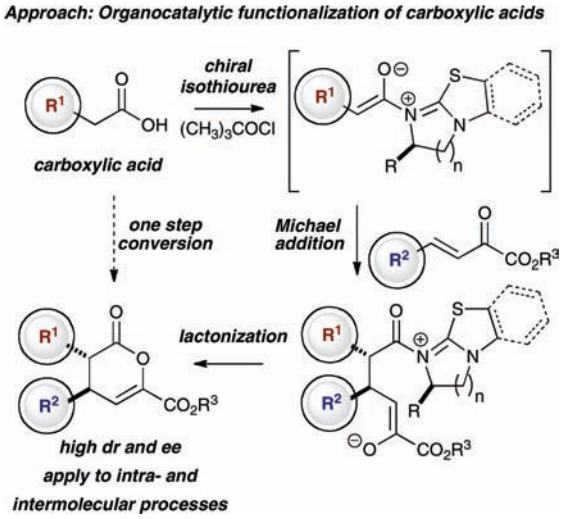


Figure 1. Proposed catalytic strategy: intra- and intermolecular Michael addition−lactonizations.

RESULTS AND DISCUSSION

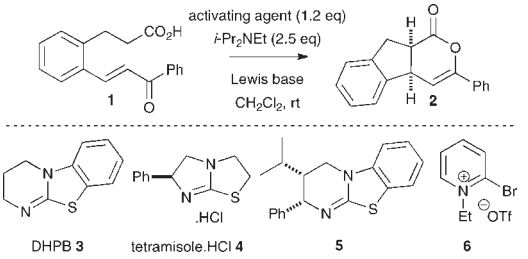
Intramolecular Michael Addition−Lactonization Reactions. Initial studies focused upon the demonstration of the intramolecular Michael addition−lactonization strategy, with this proposed reaction sequence optimized using the transformation of model enone-acid **1** to polycyclic lactone **2** (Table 1). In the racemic series, using Mukaiyama reagent **6** as the activating agent, both DMAP and isothiourea DHPB **3** proved competent catalysts for this transformation, giving **2** with high diastereocontrol (99:1 dr). Tetramisole hydrochloride **4** proved a competent enantioselective precatalyst for this transformation, giving **2** with excellent diastereo- and enantiocontrol (≥95:5 dr, 97% ee),[25] although in only modest yields unless 50 mol % of the isothiourea was used. Further optimization through variation of the activating agent showed that pivaloyl chloride allowed the synthesis of **2** using 20 mol % of precatalyst **4** in an acceptable 62% yield and high stereoselectivity (99:1 dr, 97% ee). Isothiourea **5** also proved catalytically active but gave **2** with reduced diastereo- and enantiocontrol. Consistent with the recent work of Romo and coworkers,[20] this study demonstrates the importance of the combination of activating agent and isothiourea in generating an efficient catalytic process in such transformations.

With a working protocol in place, the generality of this domino Michael addition−lactonization process was next exemplified (Table 2). Utilizing the optimized conditions delineated above, this protocol allows the incorporation of alkyl and both electron-withdrawing and -donating aryl substituents within the enone, substitution of the aromatic tether, as well as the use of aliphatic substrates, giving the desired polycyclic products **7**−**12** in good yield with high dr (up to 99:1) and ee (90−99% ee) in all cases.

To exemplify the synthetic utility of these products, lactones **2**, **7**, and **8** were readily derivatized with either methanol or isopropylamine, generating the corresponding indene carboxylate derivatives in excellent yield and ee (Scheme 1).

Having demonstrated the suitability of this process for the preparation of carbocyclic products, we further applied this process to the synthesis of dihydrobenzofuran derivatives (Table 3). A range of substituted aryloxyacetic acids, readily prepared from salicylaldehyde derivatives,[26] proved susceptible to the tetramisole-catalyzed intramolecular Michael addition−lactonization process. Substituent variation within the enone and the aromatic tether was readily tolerated, with short reaction times employed. In each case, *in situ*

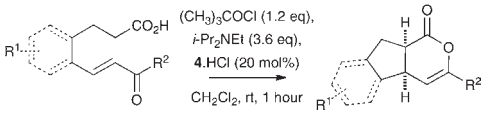
Table 1. Intramolecular Michael Addition−Lactonization: Optimization Studies

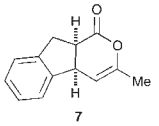
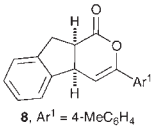
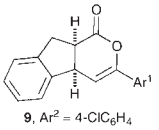
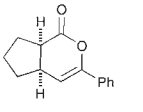
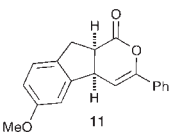
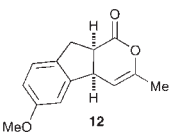


entry	activating agent	Lewis base (equiv)	yield (%)[a]	dr[b]	ee (%)[c]
1	**6**	DMAP (1.0)	40	≥95:5	–
2	**6**	DHPB (1.0)	87	≥95:5	–
3	**6**	DHPB (0.5)	95	≥95:5	–
4	**6**	DHPB (0.2)	53	≥95:5	–
5	**6**	**4**·HCl (0.5)	73	≥95:5	97
6	**6**	**4**·HCl (0.2)	43	≥95:5	97
7	EDCI	**4**·HCl (0.2)	47	99:1	92
8	PyBOP	**4**·HCl (0.2)	36	99:1	97
9	DCC	**4**·HCl (0.2)	28	99:1	96
10	$(CH_3)_3COCl$[d]	**4**·HCl (0.2)	62	99:1	97
11	$(CH_3)_3COCl$[d]	**5** (0.2)	72	80:20	70 (ent)

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [c] Determined by HPLC analysis. [d] *i*-Pr_2NEt (3.6 equiv) was used.

Table 2. Scope of the Intramolecular Michael Addition−Lactonization Process



Product	Yield,[a] dr,[b] ee[c]	Product	Yield,[a] dr,[b] ee[c]
 **7**	81% 99:1 dr 95% ee	 **8**, Ar^1 = 4-MeC_6H_4	74% 99:1 dr 97% ee
 **9**, Ar^2 = 4-ClC_6H_4	71% 99:1 dr 95% ee	 **10**	99% 99:1 dr 99% ee
 **11**	94%[d] 99:1 dr 90% ee	 **12**	43%[d] 99:1 dr 96% ee

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [c] Determined by HPLC analysis. [d] Reaction time 16 h.

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Scheme 1. Lactone Derivatizations To Give Indene Carboxylates

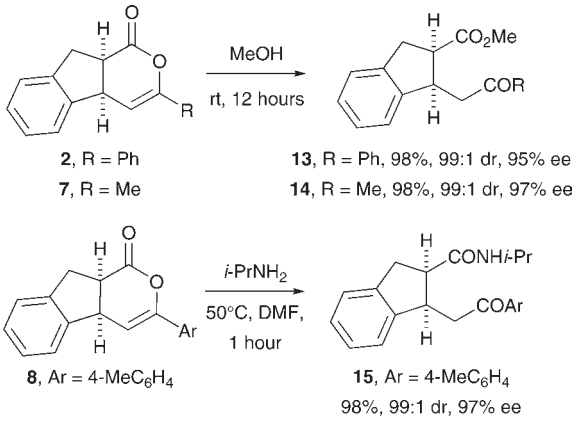
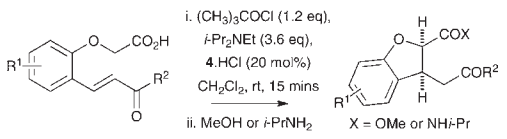
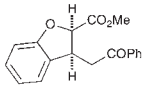
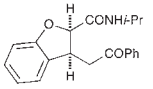
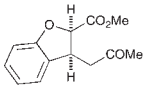
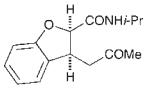
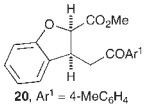
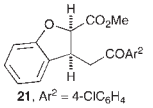
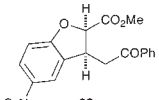
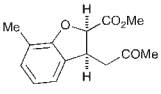
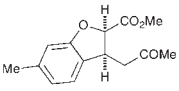
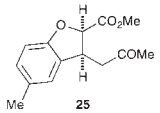


Table 3. Further Scope of the Intramolecular Michael Addition−Lactonization Process

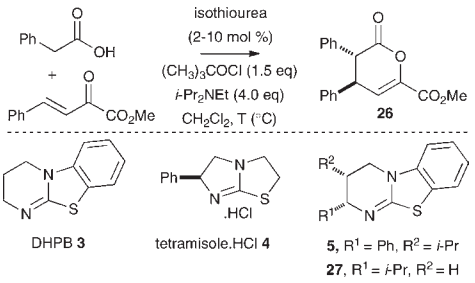


Product	Yield,[a] dr,[b] ee[c]	Product	Yield,[a] dr,[b] ee[c]
 16	98% (67%)[d] 99:1 dr 94% ee	 17	65% 99:1 dr 94% ee
 18	87% 99:1 dr 95% ee	 19	51% 99:1 dr 96% ee
 20, Ar[1] = 4-MeC6H4	95% 99:1 dr 94% ee	 21, Ar[2] = 4-ClC6H4	63% 99:1 dr 84% ee
 22	73% 99:1 dr 92% ee	 23	75% 98:2 dr 95% ee
 24	79% 96:4 dr 96% ee	 25	62% 99:1 dr 94% ee

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [c] Determined by HPLC analysis. [d] Using 5 mol % **4**·HCl, reaction time 15 min.

methanolysis or amidation was used to directly generate the corresponding dihydrobenzofuran esters and amides **16**−**25** in good to excellent yields and with high stereocontrol (dr up to 99:1, up to 96% ee).[27,28] While 20 mol % of **4**·HCl is necessary in the carbocyclic series for optimal reactivity and to avoid long reaction times, in this series the catalyst loading could be readily reduced to 5 mol % without compromising diastereo- and enantioselectivity while maintaining a short reaction time.

Table 4. Intermolecular Michael Addition−Lactonization: Optimization Studies



entry	isothiourea (mol %)	T (°C)	time (h)	yield (%)[a]	dr[b]	ee (%)[c]
1	**3** (20)	rt	1	64	95:5	−
2	**4** (20)	rt	3	60	94:6	86 (ent)
3	**27** (20)	rt	3	55	96:4	83
4	**5** (20)	rt	3	52	96:4	91
5	**5** (20)	−10	3	55	95:5	93
6	**5** (20)	−30	3	60	94:6	97
7	**5** (20)	−50	3	55	96:4	95
8	**5** (20)	−78	3	60	98:2	96
9	**5** (10)	−30	16	68	95:5	97
10	**5** (5)	−30	24	68	95:5	96
11	**5** (2)	−30	72	55	94:6	96

[a] Isolated yield of major diastereoisomer of **1** (>98:2 dr) unless otherwise stated. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [c] Determined by HPLC analysis.

Intermolecular Michael Addition−Lactonization Reactions. Subsequent studies focused upon demonstrating the challenging intermolecular Michael addition−lactonization strategy, with this reaction sequence optimized using phenylacetic acid (Table 4). In the racemic series, using pivaloyl chloride, i-Pr$_2$NEt, isothiourea DHPB **3**, and chalcone as the Michael acceptor gave no conversion to the desired product, while the use of an α-keto-β,γ-unsaturated ester readily gave *anti*-dihydropyranone **26** with high diastereocontrol (95:5 dr). Tetramisole hydrochloride **4** proved a competent enantioselective precatalyst for this transformation, giving **26** in promising diastereo- and enantioselectivity (94:6 dr, 86% ee). Variation of the isothiourea showed that **5** offered the highest levels of enantiocontrol at room temperature (96:4 dr, 91% ee), although for optimal enantioselectivity lowering the temperature was necessary, giving **26** with excellent enantiocontrol (up to 97% ee). The catalyst loading of **5** could also be lowered to 2 mol % without compromising the diastereo- and enantiocontrol of this transformation, although longer reaction times were required.

The generality of this intermolecular Michael addition−lactonization process catalyzed by isothiourea **5** was first exemplified through variation of the arylacetic acid component (Table 5).[29] Under optimized conditions this protocol tolerates 2-, 3-, and 4-aryl substitution and allows the incorporation of electron-withdrawing and -donating substituents on the aryl unit, as well as heteroaryl substituents within the arylacetic acid,[30] giving the *anti*-dihydropyranones **28**−**36** in good yield with high dr (up to 96:4 after chromatography) and ee (up to 99% ee).[31,32]

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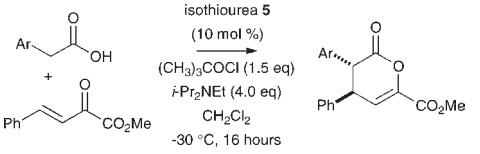
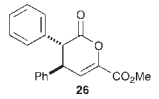
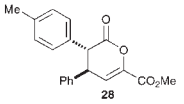
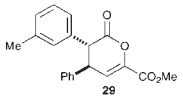
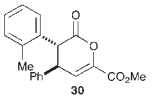
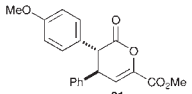
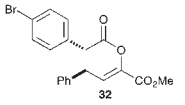
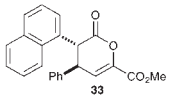
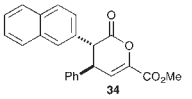
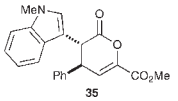
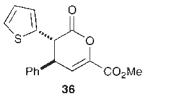
Table 5. Scope of the Intermolecular Michael Addition−Lactonization: Variation of the Acid Component



Product	Yield,[a] dr,[b] ee[c]	Product	Yield,[a] dr,[b] ee[c]
 **26**	68% 95:5 dr 97% ee	 **28**	81%[d] 95:5 dr 99% ee
 **29**	67% 95:5 dr 97% ee	 **30**	66% 95:5 dr 87% ee
 **31**	76% 92:8 dr 98% ee	 **32**	62% 90:10 dr 93% ee
 **33**	72%[d] 96:4 dr 86% ee	 **34**	73% 93:7 dr 97% ee
 **35**	66% 91:9 dr 97% ee	 **36**	65%[e] 80:20 dr 83% ee

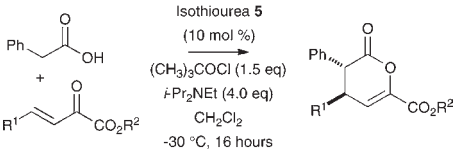
[a] Isolated yield of major diastereoisomer (>98:2 dr) unless otherwise stated. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [c] Determined by HPLC analysis. [d] isolated yield of product of 97:3 dr. [e] isolated yield of product of 95:5 dr.

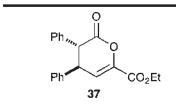
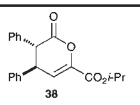
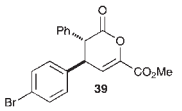
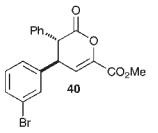
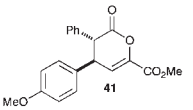
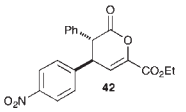
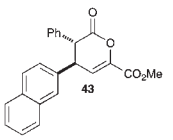
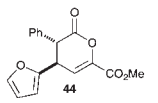
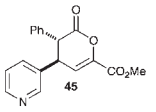
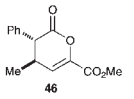
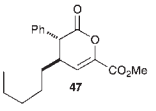
To further demonstrate the generality of this procedure, phenylacetic acid was functionalized using a range of γ-alkyl- and γ-aryl-substituted α-keto-β,γ-unsaturated esters (Table 6). Variation of the ester group is readily tolerated in this Michael addition−lactonization process, as is substitution of the γ-aryl unit with electron-withdrawing and -donating substituents as well as γ-heteroaryl substituents, giving *anti*-dihydropyranones **37**−**45** with high dr (up to 98:2) and ee (up to 99% ee). γ-Alkyl-substituted α-keto-β,γ-unsaturated esters are also readily incorporated, albeit with reduced diastereoselectivity, generating *anti*-dihydropyranones **46** and **47** with excellent enantioselectivity.

To exemplify the synthetic utility of this intermolecular reaction protocol, a domino Michael addition−lactonization followed by *in situ* ring opening with MeOH was developed. Preparation of **26** using isothiourea **5** under standard conditions, followed by direct addition of MeOH to the crude reaction mixture, gave **48** directly in 92% isolated yield, 95:5 dr, and 96% ee (Scheme 2).

We assume that both of these transformations proceed via related catalytic pathways, involving the initial *in situ* formation of a transient mixed anhydride, **49** or **54**, from the corresponding acid,[33] with *N*-acylation of the isothiourea with this activated carboxylate giving an acyl ammonium species, **50** or **55**. Deprotonation is expected to generate the (*Z*)-ammonium enolate **51** or **56**,[34] with subsequent intra- or intermolecular asymmetric Michael addition to the relevant acceptor in the *s-cis* conformation,[35] followed by lactonization, giving the desired product in high dr and ee and regenerating the isothiourea (Figure 2). We currently favor a stepwise Michael addition−lactonization mechanism over a concerted [4+2] hetero-Diels−Alder reaction

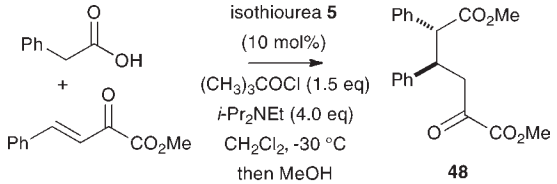
Table 6. Further Scope of the Intermolecular Michael Addition−Lactonization: Variation of the α-Keto-β,γ-unsaturated Ester Component



Product	Yield,[a] dr,[b] ee[c]	Product	Yield,[a] dr,[b] ee[c]
 **37**	74% 85:15 dr 98% ee	 **38**	77%[d] 87:13 dr 99% ee
 **39**	71% 94:6 dr 98% ee	 **40**	64% 97:3 dr 97% ee
 **41**	74%[e,f] 92:8 dr 99% ee	 **42**	63%[g,h] 91:9 dr 90% ee
 **43**	82% 95:5 dr 99% ee	 **44**	72% 98:2 dr 98% ee
 **45**	87%[d] 94:6 dr 97% ee	 **46**	80%[d] 88:12 dr 96% ee
 **47**	76%[i] 80:20 dr 95% ee		

[a] Isolated yield of major diastereoisomer (>98:2 dr) unless otherwise stated. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude reaction product. [c] Determined by HPLC analysis. [d] isolated yield of product of 97:3 dr. [e] isolated yield of product of 92:8 dr. [f] Reaction time 40 h. [g] 91:9 dr. [h] Reaction temperature −78 °C. [i] 90:10 dr.

Scheme 2. Tandem Michael Addition−Lactonization and Ring Opening



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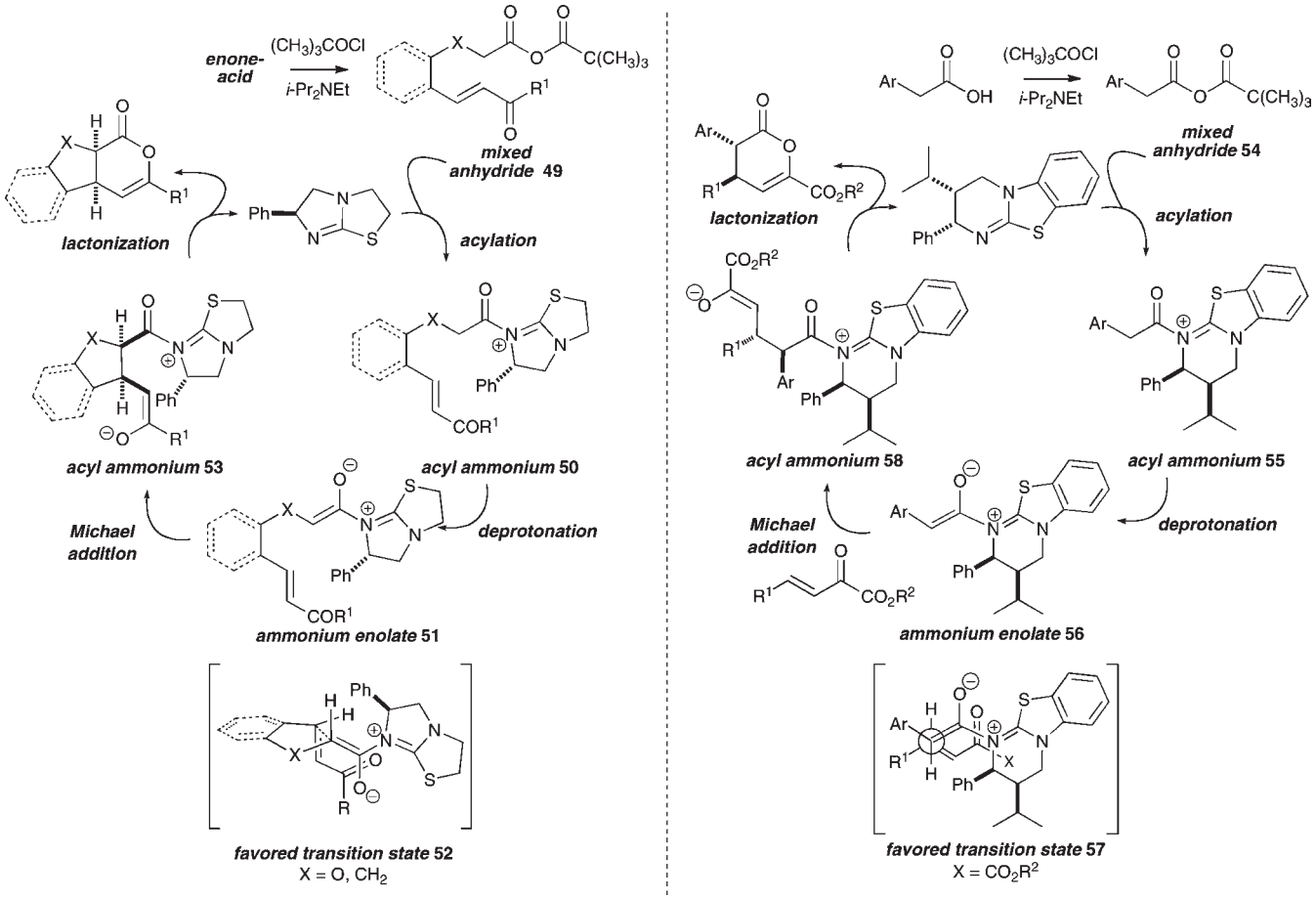

Figure 2. Proposed catalytic pathways and transition states.

pathway, although at the moment we cannot distinguish these mechanistic possibilities. Assuming the Michael addition−lactonization pathway, a simplistic rationale consistent with the observed absolute configurations of the products for these transformations can be achieved by assuming that the Michael addition proceeds with the two prostereogenic centers adopting an approximately staggered array in order to minimize unfavorable nonbonding interactions. In the intramolecular manifold, this leads to a preferred transition state such as **52**, while in the intermolecular process, Michael addition proceeds preferentially via transition state **57** by analogy to Heathcock's model.[36] Notably, both of these proposed transition-state arrangements place the enolate oxygen *syn* to the S atom within the isothiourea, possibly allowing a stabilizing n_o-to-σ^*_{C-S} interaction. Such interactions have previously been envoked by Nagao and co-workers in (acylimino)thiadiazoline derivatives,[37] and also by both Birman[38] and Romo[20] in reaction processes utilizing isothioureas.

In summary, tetramisole catalyzes the highly diastereo- and enantioselective intramolecular Michael addition−lactonization of enone-acids, generating carbo- and heterocyclic products that are readily derivatized to functionalized indene and dihydrobenzofuran carboxylates. Isothiourea **5** promotes the highly diastereo- and enantioselective intermolecular Michael addition−lactonization of arylacetic acids and α-keto-β,γ-unsaturated esters, generating *anti*-dihydropyranones with good diastereoselectivity (up to 98:2 dr) and enantioselectivity (up to 99% ee). Ongoing studies within this laboratory are currently directed toward demonstrating alternative uses of isothioureas in asymmetric catalysis.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures; X-ray structural data for **21** and **32** (CIF); spectral and HPLC data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The absolute configuration of **2** was assigned by comparison of the HPLC and specific rotation data with that contained in ref 24a. Ring opening of **2** with MeOH to give **14**, and comparison of its specific rotation contained in ref 24b, also confirmed the absolute configuration and stereochemical integrity of the products of this transformation (see SI for full details).

(26) See SI for full experimental details.

(27) The relative and absolute configuration of **21** was confirmed by X-ray crystal structure analysis, with all other dihydrobenzofuran derivatives assigned by analogy. See SI for further details. Crystallographic data for **21** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 799331.

(28) The lactone products arising from Michael addition−lactonization in this series proved susceptible to degradation upon attempted isolation by chromatography, so direct ring opening with MeOH or *i*-PrNH$_2$ was followed.

(29) Preliminary unoptimized experiments show only modest conversion (around 30%) using hydrocinnamic acid as the acid component.

(30) Dihydropyranone **36** proved susceptible to isomerization upon extended exposure to isothioureas DHPB or **5**. See SI for further information.

(31) The relative and absolute configuration of **32** was confirmed by X-ray crystal structure analysis, with all other derivatives assigned by analogy. See SI for further details. Crystallographic data for **32** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 799871.

(32) Although this intermolecular process was routinely carried out on an analytical scale (0.2 mmol), this reaction process has been scaled to a 2 mmol scale, giving **26** in 66% yield and 99% ee. This reaction can also be performed in an open flask using bench-grade solvents without degradation of reactivity and enantioselectivity.

(33) Shiina and co-workers have utilised a *trans*-acylation procedure to generate reactive mixed anhydrides from acids and anhydrides for applications in kinetic resolutions catalyzed by isothioureas. See ref 23g and also the following: (a) Shiina, I.; Nakata, K. *Tetrahedron. Lett.* **2007**, *48*, 8314–8317. (b) Shiina, I.; Nakata, K.; Sugimoto, M.; Onda, Y.; Iizumi, T.; Ono, K. *Heterocycles* **2009**, *77*, 801–810. (c) Shiina, I.; Nakata, K. *Heterocycles* **2010**, *80*, 169–175. (d) Shiina, I.; Nakata, K.; Onda, Y. *Eur. J. Org. Chem.* **2008**, 5887–5890. (e) Shiina, I.; Nakata, K.; Ono, K.; Sugimoto, M.; Sekiguchi, A. *Chem. Eur. J.* **2010**, *16*, 167–172. (f) Nakata, K.; Onda, Y.; Ono, K.; Shiina, I. *Tetrahedron. Lett.* **2010**, *51*, 5666–5669.

(34) We have considered the possibility that these reaction processes proceed via the enol tautomer of the acyl ammonium species, rather than the ammonium enolate, although we currently favor the enolate pathway due to the assumed attenuated nucleophilicity of the enol. An alternative reaction process, involving the *in situ* generation of a ketene from the mixed anhydride, followed by nucleophilic addition of an isothiourea to generate the ammonium enolate, cannot be ruled out at this time, although we favor the mechanisms depicted in Figure 2. Further mechanistic investigations of these reaction pathways are currently under investigation. We thank a reviewer for helpful comments on this matter.

(35) Using the assumption of a stepwise Michael addition−lactonization pathway over a concerted [4+2] hetero-Diels−Alder reaction manifold, the high observed diastereoselectivity in these processes may arise due to reversible Michael addition, followed by an irreversible lactonization process occurring preferentially through one diastereoisomer.

(36) For an excellent overview of this area see: (a) Oare, D. A.; Heathcock, C. H. *Topics Stereochem.* **1989**, *19*, 227–407. For select representative examples of enolate additions to Michael acceptors see: (b) Heathcock, C. H.; Henderson, M. A.; Oare, D. A.; Sanner, M. A. *J. Org. Chem.* **1985**, *50*, 3019–3022. (c) Oare, D. A.; Henderson, M. A.; Sanner, M. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 132–157. (d) Yamaguchi, M.; Tsukamoto, M.; Tanaka, S.; Hirao, I. *Tetrahedron Lett.* **1984**, *25*, 5661–5664. For a recent computational investigation of intermolecular Michael reactions see: (e) Kwan, E. E.; Evans, D. A. *Org. Lett.* **2010**, *12*, 5124–5127.

(37) Nagao, Y.; Hirata, T.; Goto, S.; Sano, S.; Kakehi, A.; Iizuka, K.; Shiro, M. *J. Am. Chem. Soc.* **1998**, *120*, 3104–3310.

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