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Development of a Cysteine-Catalyzed Enantioselective Rauhut−Currier Reaction

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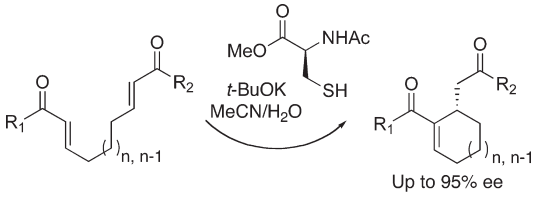

Scope, Catalyst Analogs, Mechanistic Studies

Herein, we report a full account of the development of an enantioselective Rauhut−Currier process that affords products in high yields and enantioselectivities using a cysteine-based catalyst. While traditional Morita−Baylis−Hillman catalysts were found to be essentially ineffective, various derivatives of protected cysteine were found to exhibit extraordinary reactivity and enantiotopic control. Extensive screening of reaction conditions led us to discover the enhanced effects of water as an additive and the chelating power of potassium in achieving higher enantiomer ratios. Mechanistic experiments also provided insight on the potential mechanism of the reaction in addition to possible transition states that provide the absolute stereochemistry formed in the observed products. Also included is a brief survey of the reaction scope involving different ring sizes as well as functionalized substrates.

Introduction[1]

Research efforts in our laboratory have endeavored to harness the power of biosynthetic tools in the form of small peptide-based nucleophilic catalysts for synthetic organic transformations.[2] Through study of the enantioselective Morita−Baylis−Hillman (MBH) reaction, we discovered an enantioselective cocatalytic system (pipecolinic acid/*N*-methylimidazole (NMI)) for this classic C−C bond-forming reaction.[3] Since its independent discovery in 1968 by Morita[4] and 1972 by Baylis and Hillman,[5] the MBH reaction continues to be a sought after reaction and an active area of research. Although our progress in the intramolecular MBH reaction led to improved levels of enantioselectivity, the reaction is still in its infancy. Inspired by our recent findings, we sought to expand this methodology even further to aid in the development of this class of carbon−carbon bond-forming reactions.[6] Specifically, we sought to create an enantioselective variant of the Rauhut−Currier (RC) reaction with the goal of providing a method to access highly functionalized enantioenriched ring systems.[7−9] The RC reaction, also known as the

(1) Aspects of this study are described in the doctoral thesis of C.E.A.: Aroyan, C. E. Ph.D. Thesis, Boston College, Chestnut Hill, MA, approved in 2008.

(2) For a review of the use of peptides as asymmetric catalysts, see: (a) Colby Davie, E. A.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759–5812. (b) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601-610 and references therein.

(3) Aroyan, C. E.; Vasbinder, M. E.; Miller, S. J. *Org. Lett.* **2005**, *7*, 3849–3851.

(4) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.

(5) Baylis, A. B.; Hillman, M. E. D. (Calanese Corp.) Acrylic Compounds. DE 2155113, **1972**, 16 pp.

(6) For selected reviews, see: (a) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653–4670. (b) Basavaiah, D.; Rao, P. D.; Hyma, R, S. *Tetrahedron* **1996**, *52*, 8001–8062. (c) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891.

(7) For a review, see: Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069–4084.

(8) (a) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404–2405. (b) Wang, L.-C.; Luis, A. L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402–2403.

(9) For some recent reports of RC-type processes, including several that proceed through a variety of mechanisms, see: (a) Reynolds, T. E.; Binkley, M. S.; Scheidt, K. A. *Org. Lett.* **2008**, *10*, 2449–2452. (b) Marqués-López, E.; Herrera, R. P.; Marks, T.; Wiebke, J. C.; Könning, D.; de Figueiredo, R. M.; Christmann, M. *Org. Lett.* **2009**, *11*, 4116–4119. (c) Yao, W.; Wu, Y.; Wang, G.; Zhang, Y.; Ma, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 9713–9716. (d) Qiao, Y.; Kumar, S.; Malachowski, W. P. *Tetrahedron Lett.* **2010**, *51*, 2636–2638.

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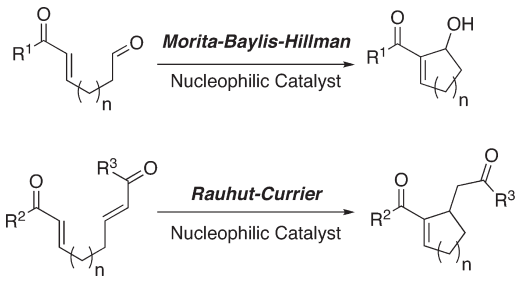


FIGURE 1. Generalized Morita−Baylis−Hillman and Rauhut−Currier reactions.

vinylogous MBH reaction,[10] involves the coupling of two activated alkenes versus the coupling of an activated alkene and an aldehyde, as in the MBH reaction (Figure 1).

The development of methods for the formation of new carbon−carbon bonds as well as functional group transformations are central to the successful synthesis of target molecules. For this reason, both of these transformations hold great potential for becoming indispensable reactions in organic synthesis. Furthermore, the MBH and RC reactions are of specific interest due to their ability to generate a new carbon−carbon bond in an atom-economical manner, while generating a new stereogenic center and densely functionalized products that have served as substrates for a variety of subsequent transformations.[11] Although this class of reactions has been known in the scientific community for over four decades, these reactions still present many opportunities for growth.[12] The development of a robust asymmetric version will require the design of highly efficient chiral catalysts, able to promote the coupling reaction of many diverse partners. Progress in the intramolecular (as well as asymmetric intramolecular) variant of both reactions will provide opportunities for the design of novel substrates leading to complex products with multiple stereogenic centers. Finally, the dense functionality present in the MBH and RC products offers many possibilities for further elaboration and the synthesis of natural products as well as nonnatural target molecules.

Importantly, until our report in 2007,[13] the asymmetric RC reaction was not well studied. Herein, we present the natural extension of the intramolecular MBH reaction to allow the use of vinylogous reaction partners in the RC reaction and demonstrate the use of a single amino acid derivative of cysteine as a highly selective catalyst to provide cyclized products in up to 70% yield and 97.5:2.5 er.[14]

(10) The definition of vinylogy is the transmission of stereoelectronic effects through conjugation. "The influence of a functional group may be felt at a distant point in the molecule when this position is connected by conjugated double bond linkages to the group...this concept allows the extension of the electrophilic or nucleophilic character of a functional group through the π-system of a carbon−carbon double bond", R. C. Fuson (1935). Although the term "vinylogous Morita−Baylis−Hillman" reaction has been used interchangeably with Rauhut−Currier in the literature, we have chosen to refer specifically to the coupling of two activated olefins through 1,4-addition as the RC reaction, whereas the MBH reaction involves 1,2-addition. We make this distinction to emphasize the multidimensional differences between the two reactions.

(11) (a) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481–1490. (b) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614–4628.

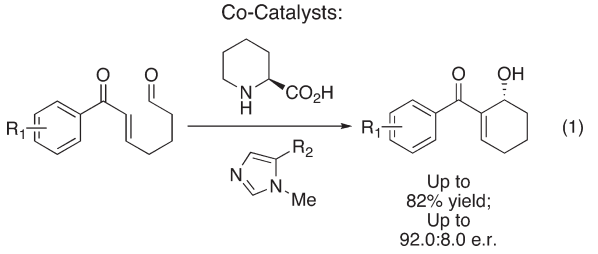
(12) Basavaiah, D.; Rao, K. V.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581–1588.

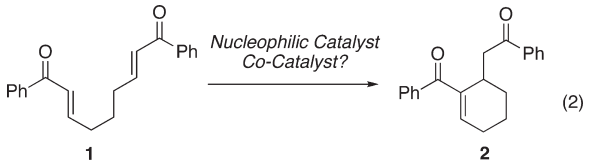
(13) Gladysz and co-workers reported an enantioselective intramolecular RC reaction later in the same year: Seidel, F.; Gladysz, J. A. *Synlett* **2007**, *6*, 986–988.

(14) Aroyan, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 256–257.

Results and Discussion

Nitrogen-Based Nucleophiles. In analogy to our findings in the MBH reaction (eq 1),[3] we were intrigued with the possibility of using our optimized cocatalytic system (pipecolinic acid/*N*-methylimidazole (NMI)) and protic reaction conditions (THF/H_2O) to extend the MBH methodology to include a vinylogous reaction partner. Our study of the intramolecular RC thus began with the anticipated conversion of **1** to **2** (eq 2).

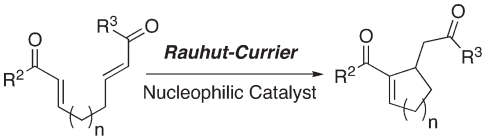




1 **2**

From previous reports in the literature, we began our investigation with the knowledge that the RC cycloisomerization differs in reactivity when compared to its MBH counterpart. For example, trialkylphosphines were reported to be sufficiently reactive to catalyze the cycloisomerization of bis(enones). On the other hand, triarylphosphines were unreactive. Additionally, nitrogen-based nucleophiles, which were traditionally successful catalysts of the MBH reaction, were incapable of catalyzing the analogous RC cyclization reaction (Table 1).

TABLE 1. Phosphine- and Nitrogen-Based Catalysis of the RC Reaction



catalyst	result
$P(alkyl)_3$	reactive
$P(aryl)_3$	unreactive
traditional MBH catalysts (DABCO, DBU, DMAP, Et_2NH)	unreactive

With these observations in mind, we examined cocatalytic systems. As shown in eq 3, MBH reaction precursor **3** could be converted to **4** in good yield and with substantial enantioselectivity (90:10 er) when a combination of *N*-methylimidiazole (NMI) and pipecolinic acid (**5**) were employed as cocatalysts. Therefore, we were prompted to examine cocatalytic amines once again with the hope that the RC cyclization would benefit from a similar heightened reactivity. Accordingly, as shown in Figure 2, bis(enone) **1** was subjected to the previously optimized reaction conditions (THF/H_2O, 3:1) employing NMI, pipecolinic acid (Pip), and the cocatalytic combination of NMI/Pip. Unfortunately, we were not able to successfully promote the cycloisomerization reaction employing these conditions, and under forcing

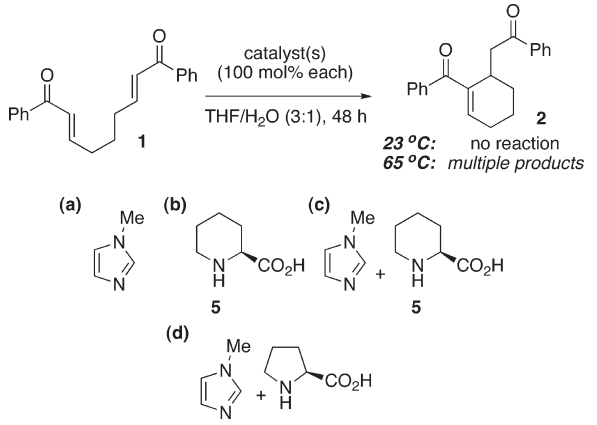
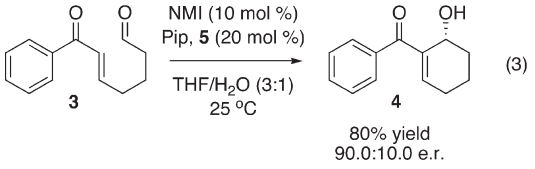


FIGURE 2. Investigation of Cocatalysis in the RC reaction.

conditions (65 °C, 48 h), we obtained significant decomposition of the starting material. The cocatalytic combination of NMI/proline[15] was examined as well; however, it provided similar results with no reaction at room temperature and decomposition upon heating.

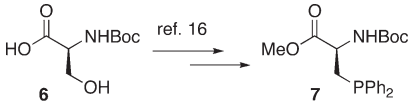


(3)

Phosphorus-Based Nucleophiles. Undaunted by the ineffectiveness of our amine-based catalysts, we turned to the more reactive phosphine-based catalysts, mindful that the steric and electronic environment would play a critical role in reactivity. Similar to previous work in our laboratory, where a nucleophilic moiety (i.e., NMI) was incorporated into small peptide-based catalysts (as a modified histidine residue) to confer high levels of enantioselectivity,[1] we were intrigued by the possibility of employing a similar chiral phosphine-based catalyst in the RC reaction. In this sense, we were interested in determining if we could use a phosphine-containing amino acid or peptide catalyst to promote an enantioselective variant of the RC reaction by taking advantage of the chiral environment provided by the amino acid or peptide secondary structure.

We began our study by focusing on diarylphosphine-containing peptides due to their relative stability (compared with trialkylphosphines). Specifically, we were interested in using the known chiral phosphine-based amino acid diphenylphosphinoserine (Pps, **7**), which contains a β-stereogenic center. Gilbertson and co-workers have pioneered the use of Pps by incorporating the amino acid into peptides used as phosphorus-based metal ligands for various transformations such as hydrogenation and alkylation.[16] Following Gilbertson's work,

SCHEME 1. Diphenylphosphinoserine Synthesis (Pps, 7)



Pps was synthesized in four steps from commercially available Boc-Ser (**6**, Scheme 1).[17]

Prior to testing the chiral amino acid (**7**), it was imperative to establish the level of reactivity of phosphines in the RC reaction. As previously described by Krische and Roush,[8] trialkylphosphines have been reported to catalyze the cycloisomerization of bis(enone) **1** to **2**, while triarylphosphines were not reactive enough and provided only recovered starting material. Therefore, methyldiphenylphosphine ($MePh_2P$), the achiral counterpart to Pps, was tested as a model catalyst to provide insight into the relative reactivity of various substituted phosphines. Bis(enone) **1** was thus subjected to $MePh_2P$ (100 mol %), providing promising results in various solvents (acetone, THF/H_2O, or ethanol); the RC reaction underwent full conversion to the desired product within 12 h (Figure 3a). Encouraged by this preliminary data, we briefly investigated the possibility of employing combination catalysis with this new phosphine-based nucleophilic moiety. Therefore, bis(enone) **1** was subjected to $MePh_2P$ in combination with pipecolinic acid (as in the MBH reaction); however, preliminary experimentation suggested the presence of pipecolinic acid was deleterious to the phosphine-promoted RC reaction and resulted in less than 50% conversion to **2** (Figure 3b).

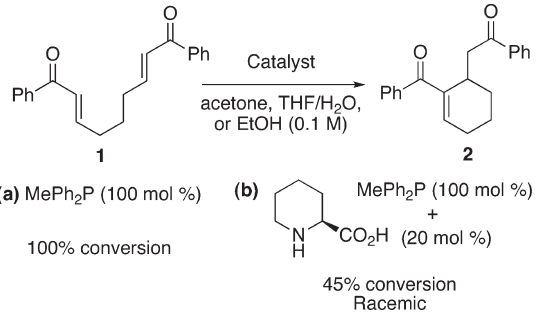
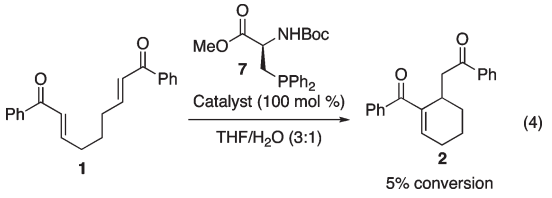


FIGURE 3. Conversion of **1** to **2** with achiral $MePh_2P$.

Having established sufficient catalysis of the desired cyclization reaction with the model catalyst methyldiphenylphosphine, we next examined catalysis employing the chiral variant amino acid **7**. Unfortunately, the reactivity of $MePh_2P$ did not translate to the amino acid and upon exposure of bis(enone) **1** to Pps at room temperature, only 5% conversion to **2** was obtained (eq 4). We hypothesized that steric demand near the phosphorus center, and the inductive electron-withdrawing affect of the amino acid group, combined to produce an ineffective catalyst. Consequently, we abandoned this approach.



(4)

Chalcogenides. During our initial investigation into the RC reaction, it became clear that the development of a

(15) For some examples of the use of NMI/proline in the MBH reaction, see: (a) Shi, M; Jiang, J.-K.; Li, C.-Q. *Tetrahedron Lett*. **2002**, *43*, 127–130. (b) Shi, M.; Jiang, J.-K. *Tetrahedron: Asymmetry* **2002**, *13*, 1941–1947. (c) Imbriglio, J. E.; Vasbinder, M. M.; Miller, S. J. *Org. Lett*. **2003**, *5*, 3741–3743. (d) Vasbinder, M. M.; Imbriglio, J. E.; Miller, S. J. *Tetrahedron* **2006**, *62*, 11450–11459.

(16) (a) Gilbertson, S. R.; Chen, G.; McLoughlin, M. *J. Am. Chem. Soc*. **1994**, *116*, 4481–4482. (b) Greenfield, S. J.; Gibertson, S. R. *Synthesis* **2001**, *15*, 2337–2340. (c) Agarkov, A.; Greenfield, S. J.; Xie, D.; Pawlick, R.; Starkey, G.; Gilbertson, S. R. *Biopolymers: Pept. Sci*. **2006**, *84*, 48–73.

(17) Pps is not as air-sensitive as trialkylphosphines; however, it was found that Pps will oxidize completely to the corresponding diphenylphosphinoserine oxide within 24 h when exposed to air.

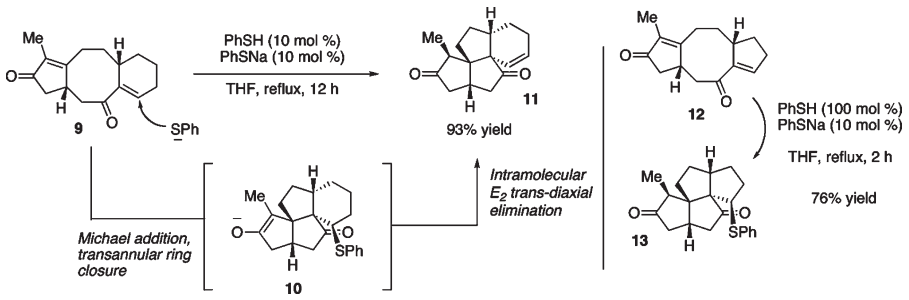
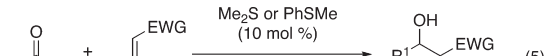
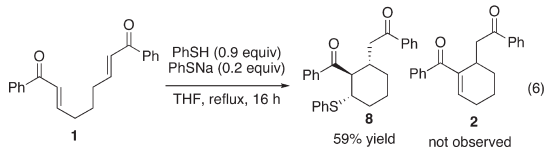


FIGURE 4. Catalysis of the RC reaction thiophenol and thiophenolate in natural product synthesis.

powerful catalyst would require an entirely new methodological study and that our previous work in the MBH reaction would not be applicable here. Hence, during the study of nitrogen- and phosphorus-based catalysts, we simultaneously investigated the possibility of a thiolate-promoted cycloisomerization. Various chalcogenides have been reported as catalysts in MBH-type reactions; however, dialkyl chalcogenides require Lewis acid activation to overcome their low reactivity,[2] and reactions catalyzed by monoalkyl chalcogenides terminate without elimination of the catalyst.[18] For example, the intermolecular MBH reaction can be promoted with catalytic dimethyl sulfide or thioanisole by employing stoichiometric amounts of titanium tetrachloride to provide the desired products in up to 88% yield (eq 5). Additionally, Murphy and co-workers demonstrated the cyclization of bis(enone) **1** catalyzed by thiophenol and sodium thiophenolate; however, they obtained cyclized addition adduct **8** instead of the desired RC product, **2** (eq 6).





In a unique example by Moore and co-workers,[19] the cycloisomerization of tricyclic bis(enone) **9** was promoted by combination of thiophenol and sodium thiophenolate (Figure 4). This intriguing transformation was proposed to proceed through the conjugate addition of thiolate to substrate **9**, which then underwent a transannular Michael reaction to provide intermediate **10**. From molecular modeling, they determined that the three-dimensional conformation of the molecule placed the generated enolate in close proximity to the β-proton of the thiophenolate leaving group. Thus, the enolate induces an intramolecular E_2 *trans*-diaxial elimination to produce desired product **11** and regenerate the thiophenolate catalyst. Interestingly, and more representative of general thiol catalysis, in a very similar transformation involving homologue **12** (containing a five-membered ring versus a six-membered ring), the requisite intermediate was no longer in proper alignment for the elimination reaction and product **13** was isolated when a stoichiometric quantity of thiophenol was employed.

Examination of Cysteine-Based Catalysts. We began our study of the thiolate-promoted RC cycloisomerization with derivatives of cysteine (Cys), hoping that upon sufficient reactivity, the amino acid could be embedded into a peptide to induce substantial enantioselectivity. However, unlike catalysis with nitrogen- or phosphorus-based catalysts, our new study began with many basic questions. Would cysteine be reactive enough to catalyze the desired RC transformation without the use of a Lewis acid? If we could catalyze the initial conjugate addition and cyclization steps, would our system be capable of promoting the final elimination step to regenerate the catalyst and deliver the desired cyclization products? And finally, would we be able to catalyze the transformation with discernible levels of stereoinduction using a cysteine nucleophile embedded into a peptide?

We were encouraged to find that the simple protected amino acid **14** catalyzed the reaction (Figure 5a). However, as anticipated, catalyst elimination was a problem, and intermediate **15** was isolated in addition to recovered starting material. Furthermore, Boc-Cys-OMe (**14**) in combination with various amine bases (such as triethyl amine, Hünig's base, diaza(1,3)bicyclo[5.4.0]undecane (DBU), and 2,6-lutidine) was not able to promote the elimination reaction in order to generate desired product **2** (Figure 5b). However, we determined that by incorporating a stronger base, NaH, in combination with the Cys-based catalyst we were able to promote the full transformation of bis(enone) **1** to provide **2** (Figure 5c). Most importantly, we were able not only to catalyze the cyclization but also to determine that this simple protected amino acid was able to promote the desired transformation with 40.0:60.0 er. Although the enantioselectivity was modest, we hypothesized that *a more elaborate secondary structure would not be needed to separate the energetics of diastereomeric transition states*. Thus, we decided to proceed in our study with the investigation of diverse reaction parameters using a single amino acid derivative as the catalyst.

Realizing that the choice of base was critical to product distribution, we first performed a base screen in the RC reaction promoted by **14**. In addition to the amine bases already tested in combination with **14**, Na_2CO_3 and NaOH were examined in the cyclization of bis(enone) **1** (Table 2).

(18) (a) Dinon, F.; Richards, E.; Murphy, P. J.; Hibbs, D. E.; Hursthouse, M. B.; Malik, K. M. A. *Tetrahedron Lett*. **1999**, *40*, 3279–3282. (b) Brown, P. M.; Käppel, N.; Murphy, P. J. *Tetrahedron Lett*. **2002**, *43*, 8707–8710. (c) Brown, P. M.; Käppel, N.; Murphy, P. J.; Coles, S. J.; Hursthouse, M. B. *Tetrahedron* **2007**, *63*, 1100–1106.

(19) Erguden, J. K.; Moore, H. W. *Org. Lett*. **1999**, *1*, 375–377.

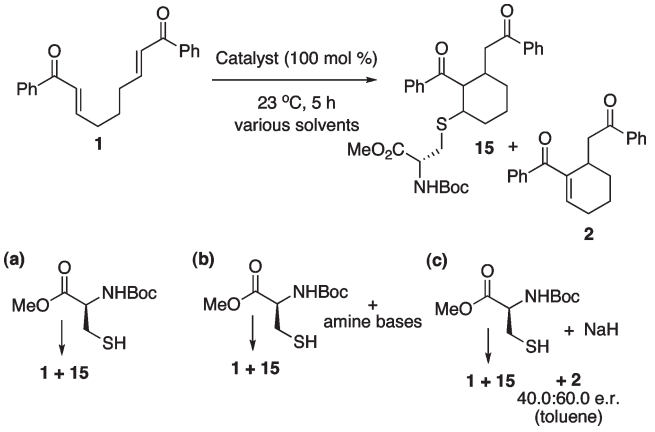
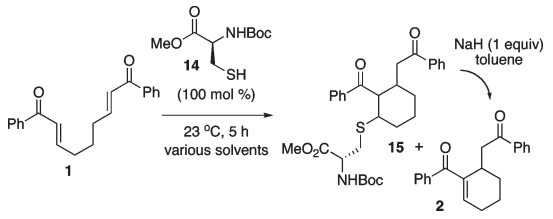


FIGURE 5. Catalysis of the RC reaction with catalyst **14**.

TABLE 2. Base Screen in the RC Reaction



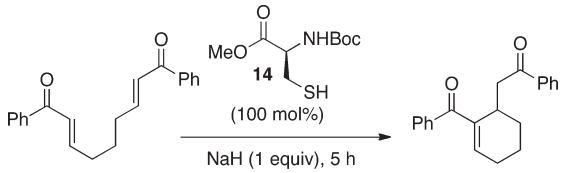
entry	base (1 equiv)	result
1	Na_2CO_3	**1** + **15**
2	NaOH	multiple products
3	*t*-BuONa	**2** + byproduct
4	*t*-BuOK	**2** + byproduct
5	KH	**2** + byproduct
6	LDA	multiple products
7	LHMDS	multiple products
8	*n*-BuLi	multiple products

The results were similar to those obtained when using amine bases, such that we obtained a mixture of starting material and cyclized addition product **15**, without production of the desired product. Importantly, NaH, KH, and *t*-BuOK provided the cleanest transformations while the stronger bases, LDA and *n*-BuLi (thiolate was preformed to avoid conjugate addition), led mainly to decomposition. It is interesting to note that **15** can be converted to **2** upon isolation and subjection to NaH, suggesting that it is indeed an intermediate en route to desired product **2**. This proved to be important in the following studies, as it required the fine-tuning of reaction conditions to promote cyclization followed by final elimination of the catalyst.

As in the case of the intramolecular MBH reaction, solvent was found to affect the RC reaction (Table 3). Catalysis of the RC reaction with **14** (1 equiv) and NaH (1 equiv) in various solvents (THF, ether, acetonitrile, *N*,*N*-dimethylformamide, hexanes, toluene, CH_2Cl_2, and acetone) produced the desired product with varying degrees of enantioselectivity and byproduct formation. Notably, acetonitrile and acetone provided the cleanest reactions with the highest levels of stereoinduction (30.5:69.5 er, entry 3, and 31.0:69.0 er, entry 8, respectively).

Through careful optimization of solvent and base, we began to reveal an efficient catalytic system for the promotion of an enantioselective variant of the RC reaction. Due to

TABLE 3. Solvent Screen in the RC Cyclization



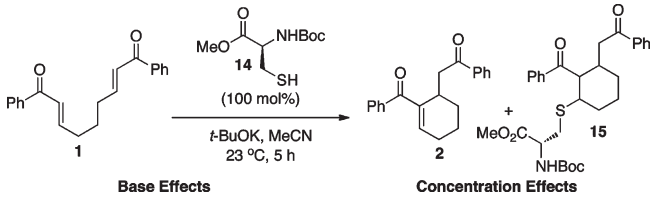
entry	solvent (0.6 M)	er
1	THF	36.5:63.5
2	Et_2O	41.0:59.0
3	MeCN	30.5:69.5
4	DMF	35.5:64.5
5	hexanes	41.5:58:5
6	toluene	40.0:60.0
7	CH_2Cl_2	37.0:63.0
8	acetone	31.0:69.0

inconsistencies in results when employing NaH, we decided to proceed in our optimization studies using *t*-BuOK, which provided results indistinguishable from those obtained when using NaH. Accordingly, further investigation of reaction conditions revealed that the stoichiometry of catalyst and base was extremely critical to product distribution and levels of stereoinduction in the cyclization. As illustrated in Table 4, the optimal ratio of catalyst/base was found to be 1:1.5. Using fewer equivalents of base, the reaction terminated prematurely, leading to intermediate **15** as well as unidentifiable byproduct. Alternatively, an excess of base furnished the desired product with varying degrees of decomposition. Additionally, greater dilution of the reaction concentration (0.1 versus 0.9 M) provided the cleanest transformation of **1** to **2** with the highest levels of enantioselectivity. Therefore, the initial optimization of base, solvent, stoichiometry, and reaction concentration led to an exciting entry into enantioselective catalysis of the RC reaction, addressing our first two questions of (1) sufficient reactivity employing a Cys-based catalyst and (2) control of product formation through final elimination and regeneration of the catalyst. Exposure of bis(enone) **1** to catalyst **14** along with *t*-BuOK (1.5 equiv) in acetonitrile (0.1 M) at room temperature afforded the desired product **2** with 32.0:68.0 er (Table 4).

Cystine Catalysis. Our next goal was to address the third question that we initially posed: would we be able to catalyze the desired transformation with discernible levels of stereoinduction using a cysteine-based nucleophile embedded in a peptide? In turning to answer this question and investigate optimization of the cysteine moiety, we remained enthusiastic that such a simple catalyst (**14**) was able to show measurable levels of stereoinduction, and we were therefore optimistic that an elaborate secondary structure may not ultimately be required to achieve high levels of enantioselectivity.

Although cysteine is stable, it is known that dipeptides containing a cysteine residue are readily oxidized to the corresponding disulfide dimer. Therefore, before synthesizing various dipeptides to examine the Cys amino acid embedded into more complex secondary structures, we were interested in the possibility of catalyzing the transformation with the corresponding dimer of the protected cysteine catalyst, **16**, even perhaps as a precatalyst. Interestingly, Boc-protected cystine catalyst (i.e., the dimer of cysteine; Figure 6b, **16**), in the presence of *t*-BuOK, also promoted cyclization of bis(enone) **1** to **2** with enantioselectivity (41.5:58.5 er)

TABLE 4. Effects of Base Stoichiometry and Reaction Concentration



base effects		concentration effects	
t-BuOK (equiv)	result[a]	conc (M)	result[b]
0.5	**2**, **15**, multiple products	0.1	32.0:68.0 er **2**, byproduct
1.0	**2**, **15**, dec	0.3	32.5:67.5 er **2**, byproduct
1.5	32.5:67.5 er **2**	0.6	37.5:62.5 er **2**, **15**, byproduct
2.0	32.5:67.5 er **2**, byproduct	0.9	44.5:55.5 er **2**, **15**, byproduct

[a]Reactions performed at 0.1 M. [b]Reactions performed with 1.5 equiv of *t*-BuOK.

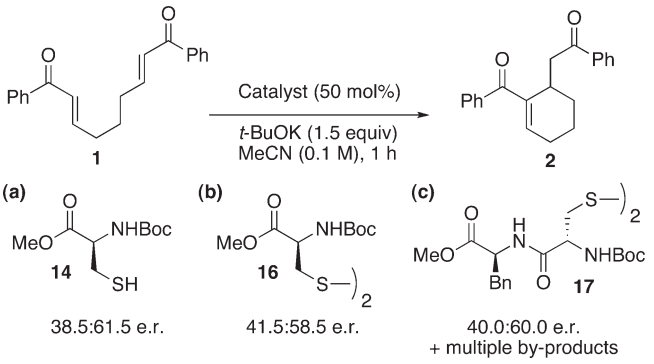


FIGURE 6. Catalysis of the RC reaction with cystine derivatives.

comparable to that of monomeric Boc-protected cysteine (**14**, 38.5:61.5 er), using *substoichiometric* catalyst loading (Figure 6a). One dipeptide (**17**) was synthesized using solution-phase peptide synthesis and tested in the analogous reaction. Although stereoinduction was similar (40.0:60.0 er), the reaction suffered from poor chemoselectivity compared to that of catalyst **14** or **16** and led to the formation of multiple byproducts (Figure 6c). The mechanism by which cystine-based precatalysts might undergo conversion to the monomeric form of the catalyst is unclear and could serve as the basis of a future study.

Development of Cysteine Derivatives. While the incorporation of Cys into an oligopeptide was just beginning, we were very interested in maintaining the simplicity of our catalyst. Therefore, we simultaneously began an optimization study of the cysteine component by considering structural changes. The exploration of simple SAR (structure−activity relationship) around the monoamino acid led to intriguing results. Changing the nitrogen protecting group from a carbamate to an amide caused a complete reversal in the sense of asymmetric induction. Under the optimized conditions, Boc-protected (**14**) and Fmoc-protected (**18**) cysteine promoted the cyclization of **1**, providing **2** with 34.0:66.0 and 36.0:64.0 er, respectively (Figure 7). Amide-protected compounds **19** and **20** led to similar levels of stereoselectivity (66.0:34.0, 65.5:34.5 er) but, however, provided the opposite enantiomer.

Protic Additives in the RC Reaction. Research efforts in MBH-type reactions from other groups have demonstrated the potential of protic additives to accelerate the reaction and

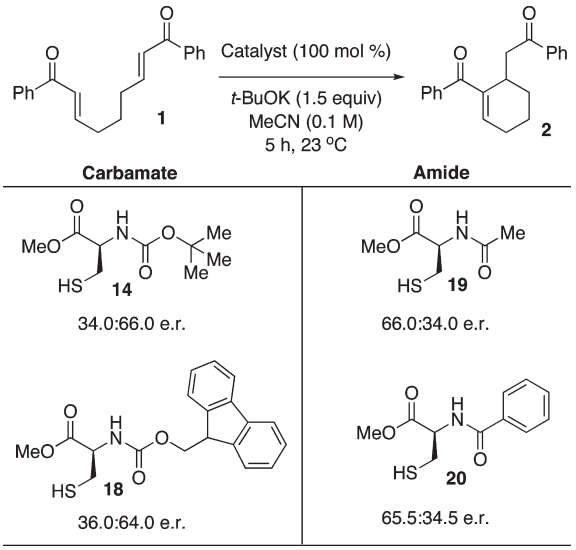


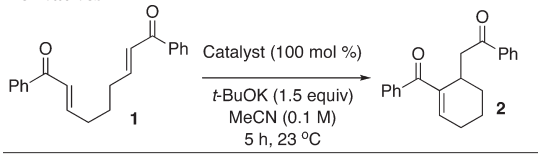
FIGURE 7. Simple SAR of the nitrogen protecting group.

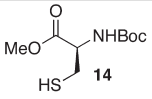
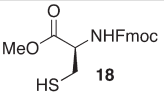
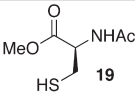
affect product distribution.[20] In our investigation of the MBH reaction, we learned that protic additives had a dramatic effect not only on the reaction rate and product distribution but also, importantly, on the enantioselectivity of the desired transformation.[20] Although the MBH and RC reactions have proven to be highly distinct from one another in our laboratory, we were nonetheless interested in exploring the possibility of employing protic additives in this transformation as well.

Interestingly, we discovered that the incorporation of a protic additive did indeed have a dramatic effect on enantioselectivity in the RC reaction, with the outcome strictly dependent upon the catalyst employed. For example, in the catalysis of **1** to **2** employing carbamate-protected catalysts **14** and **18**, the incorporation of water (9 equiv) was completely deleterious to stereoinduction and provided only racemic product (Table 5). *Most importantly, when water was incorporated in the reaction with amide-protected catalyst **19**, we observed a dramatic increase in enantioselectivity to 85.5:14.5 er.*

(20) (a) Methot, J. L.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4223–4226. (b) Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510–514. (c) Keck, G. E.; Welch, D. S. *Org. Lett.* **2002**, *4*, 3687–3690 and references cited therein.

TABLE 5. Effects of Protic Additives by Various Cys-Protected Derivatives



Water (equiv)	 14	 18	 19
0	34.0:66.0 e.r.	36.0:64.0 e.r.	66.0:34.0 e.r.
9	< 47.5:52.5 e.r.	< 47.5:52.5 e.r.	85.5:14.5 e.r.

Hence, we discovered that we could promote the RC reaction with good levels of stereoinduction using a single amino acid catalyst, lending credence to our hypothesis that a more complex secondary structure would not be critical to obtaining a highly stereoselective reaction.

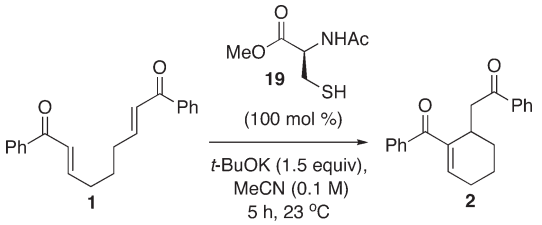
To determine if this effect was unique to water, we were prompted to examine various alternative hydroxylic additives in the transformation of **1** to **2** catalyzed by **19**. As illustrated in Table 6, the addition of methanol, ethanol, and 2-propanol (9 equiv) led to a modest enhancement in selectivity, providing product **2** with approximately a 10% increase in er over the analogous reaction with no additive (entries 1−3, 70.0:30.0, 68.5:31.5, and 68.0:32.0 er, respectively; cf. 66.0:34.0 er with no protic additive). The addition of 2,2,2-trifluoroethanol provided a further enhancement in enantioselectivity (72.5:27:5 er, entry 5), while incorporation of *tert*-butyl alcohol led to a slight decrease in enantioselectivity (77.0:23.0 er, entry 4).

With water demonstrating the most dramatic effect as a protic additive, we next explored the exact requirements of the system. As expected, we determined that a precise quantity of water was required. Notably, selectivity increased from 71.0:29.0 er (1 equiv of water, entry 2, Table 7) to 90.5:9.5 er with the addition of 20 equiv of water to the acetonitrile solvent. A further increase in the number of equivalents of water was deleterious, with a 2:1 mixture of MeCN/H_2O providing the desired product with only 55.0:45.0 er (entry 11).

Once we uncovered the dramatic effects of water on enantioselectivity in the RC cyclization, we looked at other conditions and catalysts to optimize the cysteine-based catalyst. With the new reaction conditions in hand (20 equiv of water in bulk acetonitrile), we examined a series of *N*-amide-protected cysteine derivatives. As shown in Figure 8, when *N*-benzoyl-protected catalyst **20** was employed in the cyclization of **1** to **2**, a considerable decrease in enantioselectivity was seen (70.5:29.5 er) as compared with catalyst **19** (90.5:9.5 er). *N*-Isobutyryl catalyst **21** provided comparable results (89.0:11.0 er), whereas a further increase in steric bulk of the protecting group led to a significant decrease in enantioselectivity (*N*-pivaloyl catalyst **22**, 71.5:28.5 er).

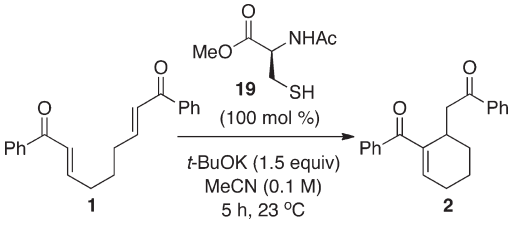
At this point, we also became curious about effects the *C*-terminus of the catalyst may have on the er of the product. In other words, we wanted to know whether or not the mixture of *t*-BuOK and H_2O was resulting in hydrolysis of the methyl ester moiety of the catalyst. Surprisingly, we found that when catalyst **23** was used, no reaction took place (eq 7). This result suggests that either partial or no hydrolysis

TABLE 6. Effect of Various Additives in the RC Reaction Catalyzed by 19



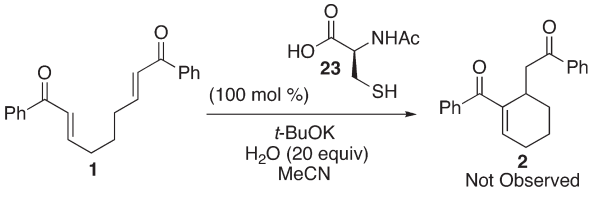
entry	additive (9 equiv)	er
1	MeOH	70.0:30.0
2	EtOH	68.5:31.5
3	*i*-PrOH	68.0:32.0
4	*t*-BuOH	77.0:23.0
5	CF_3CH_2OH	72.5:27.5
6	H_2O	85.5:14.5

TABLE 7. Effect of Water Additive in the RC Reaction



entry	water (equiv)	er
1		66:0:34:0
2	1	71.0:29.0
3	3	78.5:21.5
4	9	85.5:14.5
5	20	90.5:9.5
6	25	90.5:9.5
7	30	87.0:13.0
8	40	84.5:15.5
9	50	86.0:14.0
10	100	71.5:38.5
11	275	55.0:45.0

of our catalysts is taking place. Further studies are needed but were not pursued at this time.



(7)

A brief study of solvent effects was revisited under the optimized aqueous reaction conditions (20 equiv of H_2O in MeCN) in the cyclization reaction promoted by the optimal catalyst, **19**, which mainly led to eroded product enantioselectivity and resulted in the formation of byproduct (Table 8). Propionitrile led to a modest decrease in enantioselectivity (88.5:11.5 er, entry 2), while deleterious results with THF were more pronounced (77.5:22.5 er, entry 1).

Importantly, because we were able to develop a highly reactive catalytic system that was able to promote the conversion of **1** to **2** within 5 h at 23 °C, we believed there was an opportunity to use temperature control to further enhance

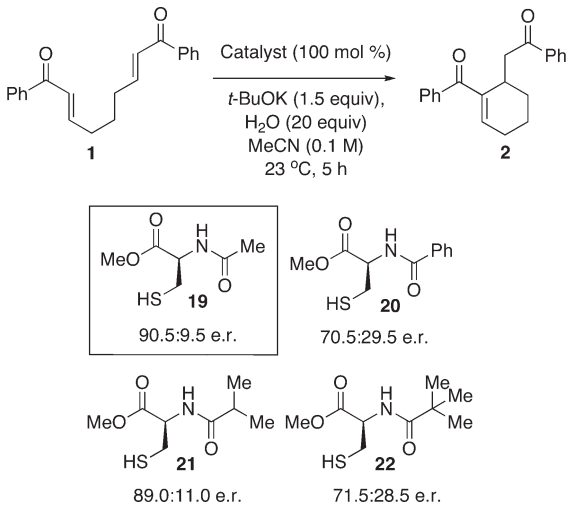
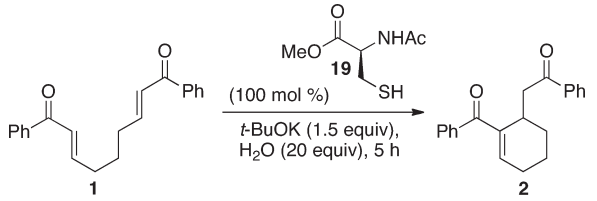


FIGURE 8. Effects of various amide protecting groups on cysteine in the RC cyclization.

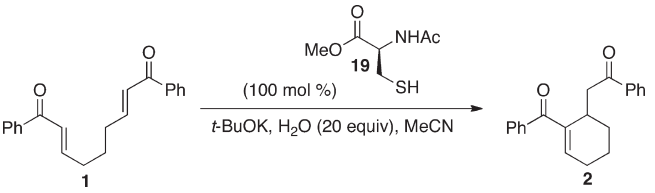
TABLE 8. Solvent Effect with Water Additive in the RC Cyclization



entry	solvent (0.1 M)	er
1	THF	77.5:22.5
2	propionitrile	88.5:11.5
3	MeCN	90.5:9.5

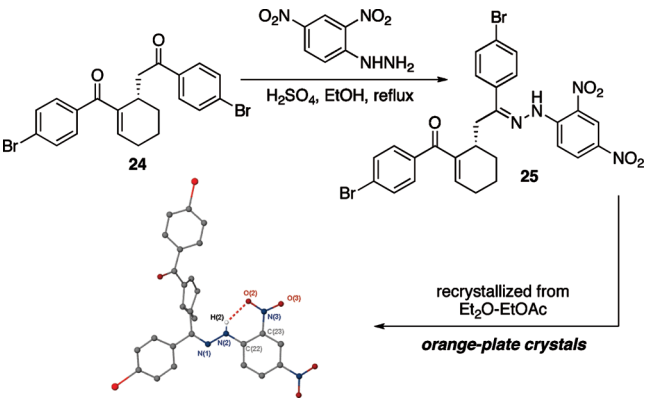
the enantioselectivity. In beginning our investigation of temperature effects, we quickly learned there was a delicate balance required between the stoichiometry of the base, the reaction concentration, and the temperature of the reaction. For example, in cooling the reaction to −20 °C, we observed an increase in the level of stereoinduction (96.0:4.0 er, entry 1, Table 9), albeit with a major decrease in the isolated yield (15%). At this reduced temperature, the final elimination step was prohibitive, and the major isolated product was intermediate **15**. By fine-tuning the stoichiometry of the base and overall concentration, we were able to obtain excellent results. Consequently, increasing the quantity of *t*-BuOK led to higher conversions and thus higher isolated yields (4 equiv, 47%, entry 2; 6 equiv, 57%, entry 3). This was demonstrated previously (Table 2) in the independent conversion of intermediate **15** to desired product **2** by isolation and subjection to the appropriate base. However, this also led to a simultaneous decrease in the enantioselectivity of the reaction (92.0:8:0 and 88.5:11.5 er, respectively). Nevertheless, by lowering the reaction concentration while maintaining a moderate quantity of base, we were able to preserve the enantioselectivity while obtaining high yield. This trend continued as we decreased the temperature further. For example, in going from −20 to −30 °C (entries 5 and 6, Table 9) and finally to −40 °C (entries 7−10), we observed a continual improvement in enantioselectivity to 97.5:2.5 er, however, with a reduced yield of 39% (6 equiv of *t*-BuOK,

TABLE 9. Optimization of the Reaction Conditions of the RC Cyclization Reaction



entry	*T* (°C)	conc (M)	*t*-BuOK (equiv)	time (h)	yield (%)	er
1	−20	0.1	1.5	5	15	96.0:4.0
2	−20	0.1	4	5	47	92.0:8.0
3	−20	0.1	6	5	57	88.5:11.5
4	−20	0.07	4	5	70	92.5:7.5
5	−30	0.07	4	5	27	97.0:3.0
6	−30	0.07	5	5	67	95.5:4.5
7	−40	0.05	6	5	39	97.5:2.5
8	−40	0.05	8	5	54	96.0:4.0
9	−40	0.05	9	5	74	91.5:8.5
10	**−40**	**0.05**	**6**	**24**	**70**	**97.5:2.5**

SCHEME 2. Formation of Hydrazone 25 for Crystallization



entry 7). Increasing the amount of base to 9 equiv provided good conversion to product **2** (74% yield, entry 9), again at the cost of selectivity (91.5:8.5 er). Excitingly, by simply running the reaction for a longer amount of time, 24 h versus 5 h, we were delighted to find that we were able to catalyze the RC reaction with high levels of enantioselectivity (97.5:2.5 er) and synthetically useful yields (70%, entry 10).

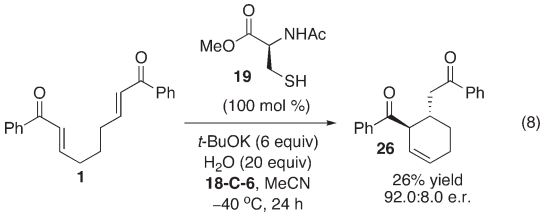
Determination of Absolute Stereochemistry. The absolute configuration of cyclization product **24** from the intramolecular RC reaction was determined by X-ray diffraction analysis of crystalline hydrazone derivative **25** following Brady's method.[21] As illustrated in Scheme 2, optically enriched *para*-bromo-substituted compound **24** (96.5:3.5 er) was treated with a solution of 2,4-dinitrophenylhydrazine in ethanol and sulfuric acid to provide hydrazone **25** (45% yield), followed by recrystallization of the orange precipitate from diethyl ether and ethyl acetate to provide X-ray quality crystals.

Mechanistic Studies. Insofar as we had been able to use a single amino acid to catalyze a uniquely enantioselective RC reaction, we wished to learn about the mechanism. Although the simplicity of our catalytic system was empirically determined,

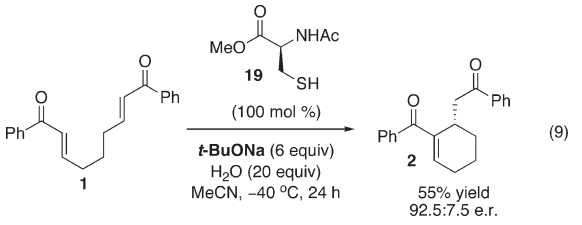
(21) (a) Behforouz, M.; Bolan, J. L.; Flynt, M. S. *J. Org. Chem.* **1985**, *50*, 1186–1189. (b) Brady, O. L. *J. Chem. Soc.* **1931**, 756–759.

it was initially unexpected, as we believed incorporation of the cysteine moiety into a more elaborate secondary structure would be necessary. Therefore, in order to provide a plausible mechanism of stereoinduction, two key experiments were performed.

First, the cycloisomerization of bis(enone) **1** was run under optimized conditions in the presence of 18-crown-6 in order to sequester the potassium ion and determine its role in the reaction (eq 8). Expected product **2** was not observed; however, unconjugated cyclized product **26** was found to be the predominant product, albeit in low yield (26%) and with attenuated enantioselectivity (92.0:8.0 er). Therefore, these results suggest that potassium ion chelation was essential to both product distribution and stereoselectivity.

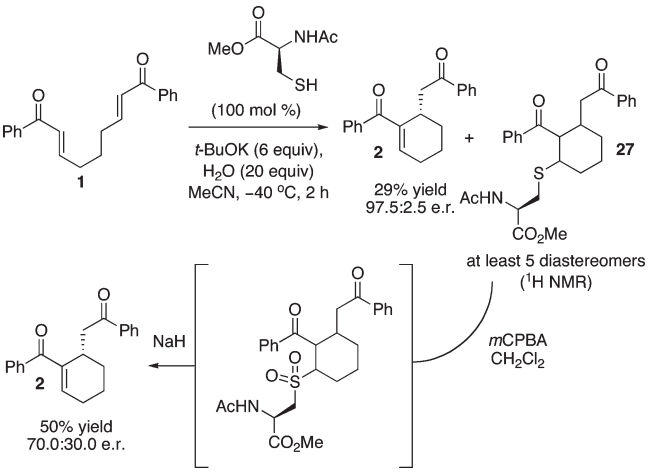


In support of this hypothesis, the RC cycloisomerization was performed with catalyst **19** in the presence of *t*-BuONa versus the optimized conditions including *t*-BuOK (eq 9). Under otherwise identical reaction conditions, substitution of potassium with sodium afforded product **2** with attenuated yield (55%) as well as enantioselectivity (92.5:7.5 er), further demonstrating the importance of the potassium counterion in promoting a highly efficient transformation.

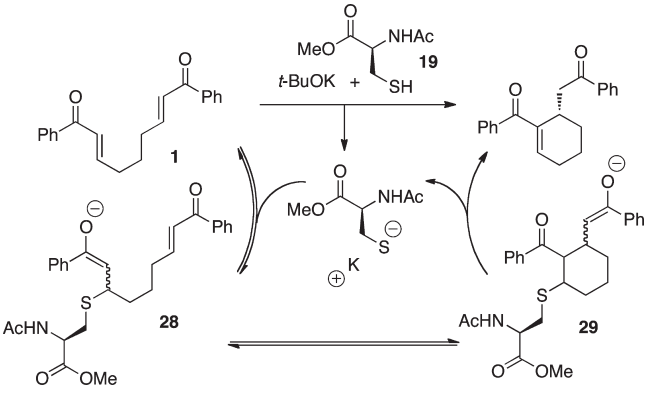


In the second experiment, bis(enone) **1** was subjected to the optimized cycloisomerization reaction conditions; however, the reaction was stopped after only 2 h instead of 24 h (Scheme 3). As expected, we obtained the desired product (**2**) with high enantioselectivity (97.5:2.5 er) and in reduced yield (29%) due to the short reaction time. Additionally, a mixture of five diastereomers of intermediate **27** was isolated, as determined by ^{1}H NMR. We then subjected intermediate **27** to oxidation and elimination under irreversible conditions ((i) *m*-CPBA, (ii) NaH) to determine the enantioselectivity of the desired stereogenic center prior to any potential equilibration. Unlike the outcome under our optimized conditions, product **2** was isolated with reduced enantioselectivity of only 70.0:30.0 er, which suggested that *carbon*−*carbon*

SCHEME 3. Isolation of Intermediate 27 and Resubjection to Irreversible Elimination



SCHEME 4. Proposed Mechanism for the Cys-Catalyzed RC Reaction



bond formation was reversible under the optimized conditions and that abstraction of the α*-H atom and extrusion of the catalyst that was the stereodetermining step*. These data are in agreement with the most recent mechanistic studies of MBH-type processes by the groups of Aggarwal and McQuade, who have also proposed proton transfer/catalyst elimination to be rate-determining.[22]

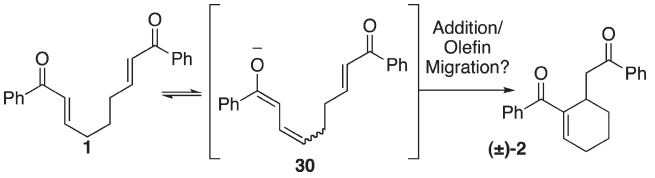
As in our studies of the MBH reaction, the mechanism of the RC reaction is not definitively known. However, based on these experiments and in analogy to the phosphine-catalyzed reactions,[23] we proposed that the mechanism of the reaction involved conjugate addition of the cysteine-based thiolate to bis(enone) **1** to form enolate **28** (Scheme 4). Reversible intramolecular Michael addition would then afford cyclized intermediate **29**, followed by irreversible proton transfer and extrusion of the catalyst to generate the RC cyclization product **2** with regeneration of the catalyst. The final step, proceeding from intermediate **29** to the desired product **2**, would therefore be the rate-determining and stereodetermining step.

As previously disclosed, a significant decrease in enantioselectivity was observed in the cyclization reaction when excess base was employed. We have determined that the integrity of product er was not diminished by resubjection of

(22) For mechanistic studies regarding the MBH reaction, see: (a) Aggarwal, V. K.; Fulford, S.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 1706–1708. (b) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980–3987. (c) Price, K. E.; Broadwater, S. J.; Jung, H. M.; McQuade, D. T. *Org. Lett.* **2005**, *7*, 147–150. For mechanistic studies regarding the related aza-MBH reaction, see: (d) Buskens, P.; Klankermayer, J.; Leitner, W. *J. Am. Chem. Soc.* **2005**, *127*, 16762–16763. (e) Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701–1708.

(23) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050.

SCHEME 5. Possible Base-Promoted Cyclization To Provide Racemic Product



the product to reaction conditions. Therefore, the decrease in enantioselectivity was not due to racemization of the product, but possibly due to an alternative mechanism, as shown in Scheme 5. In the presence of excess base, γ-deprotonation could lead to intermediate **30**, which in turn could undergo cyclization and olefin isomerization to provide (±)-**2**.[24]

In order to explain the formation of the observed enantiomer, we have proposed favored (**31**) and disfavored (**32**) transition-state models (Figure 9). While both models benefit from minimization of allylic strain between the catalyst and cyclohexanone-derived enolate, we believe the configuration allowing for a more stable potassium chelate between the enolate oxygen and the amide carbonyl on the catalyst would be favored (**31**) versus the analogous ester chelation,[25] **32**. The greater stability of structure **31** could then lead to a faster rate of elimination with subsequent formation of **2** in a high enantiomeric ratio. Such models remain speculative but allow rationalization of the observed major and minor enantiomers.

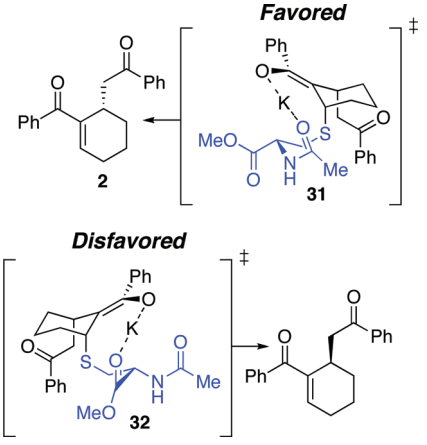


FIGURE 9. Transition-state models to explain formation of the observed enantiomer.

Reaction Scope. Traditionally, MBH- and RC-type reactions have been plagued with reactivity and selectivity issues, only to be resolved or partially solved for specific cases and narrow substrate scope. Therefore, it was our desire to develop not only a reactive system that was able to produce a highly enantiomerically enriched product but also a set of conditions that were amenable to a broad class of substrates providing structurally complex products. Thus, with our set of optimized reaction conditions, we were eager to explore the full scope of this developed methodology.

All the studies presented thus far have included stoichiometric loading of the cysteine-based catalyst. An examination

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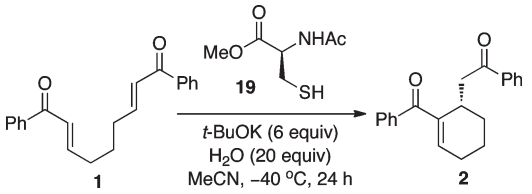
TABLE 10. Effect of Catalyst Loading on the RC Reaction



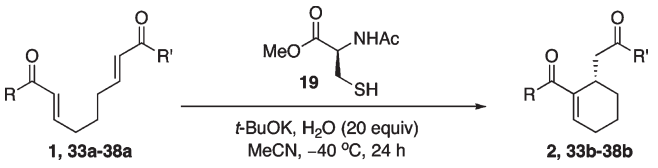
entry	catalyst (mol %)	yield (%)	er
1	100	70	97.5:2.5
2	20	75	96.0:4.0
3	10	41	95.5:4.5

of catalyst loading effects showed that a substoichiometric amount of catalyst was well tolerated. The cyclization of bis(enone) **1** underwent efficient cyclization with 20 mol % of catalyst **19** to provide **2** with 96.0:4.0 er in 75% yield after 24 h (entry 2, Table 10). While lowering the catalyst loading further to 10 mol % maintained high enantioselectivity in the transformation (95.5:4.5 er), the efficiency of the reaction was dramatically sacrificed, as the isolated yield was only 41% within the same time frame (entry 3). In light of the rate reduction from decreased catalyst loading, and because our Cys-based catalyst was simple and commercially available, we decided to perform the following study of reaction scope employing a full equivalent of **19** to ensure high efficiency and enantioselectivity within a useful time frame.

In terms of substrate scope we were first excited to find that the RC cycloisomerization could be extended to include electron-deficient and electron-rich aryl symmetrical bis(enones) as well as aliphatic and heteroaromatic bis(enones) while maintaining high levels of enantioselectivity (Table 11).[7] As previously demonstrated and reiterated in the following discussion, a delicate balance existed between the amount of base and the concentration of the reaction. RC cyclization leading to *p*-bromo-substituted compound **33a** was performed using 5 equiv of *t*-BuOK at a slightly higher dilution (0.03 M) to provide 70% yield and 96.5:3.5 er (entry 2). Unlike the case with bis(phenyl) compound **1**, a decrease in catalyst loading (20 mol %) was deleterious to enantioselectivity, providing **33b** with 87.0:13.0 er and 81% yield in the same time frame (entry 3). Analogous *p*-methoxy substitution of symmetrical bis(phenyl) compound **1** was also well tolerated, producing compound **34b** with 95.0:5.0 er in 73% yield (7 equiv *t*-BuOK, 0.01 M, entry 4). Performing this cyclization with lowered catalyst loading (20 mol %) provided comparable enantioselectivity (95.0:5.0 er), yet with reduced efficiency (57% yield, entry 5). A slight decrease in stereoinduction was observed in the cyclization leading to *p*-NO_2-substituted compound **35b** with 92.0:8.0 er and 71% yield within 4 h (2 equiv of *t*-BuOK, 0.01 M, entry 6). Heteroaromatic furan-substituted **36b** was delivered with 96.0:4.0 er and modest yield (54%) in 48 h (entry 7). Fine-tuning of the reaction conditions provided aliphatic bis(methyl ketone) **37b** with high selectivity and moderate yield (95.0:5.0 er, 55% yield, entry 8) or slightly decreased enantioselectivity (90.5:9.5 er) and higher yield (68%, entry 9). Finally, unsymmetrical keto ester **38b** showed a decrease in enantioselectivity (83.5:16.5 er, entry 10).

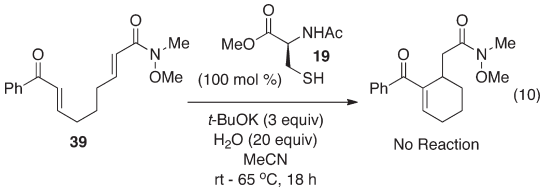
In the case of unsymmetrical substrates, we saw the opportunity to embed functional groups (i.e., Weinreb amides or thioesters) that had the advantage of being manipulated after RC cyclization. Unfortunately, substrate **39** was completely

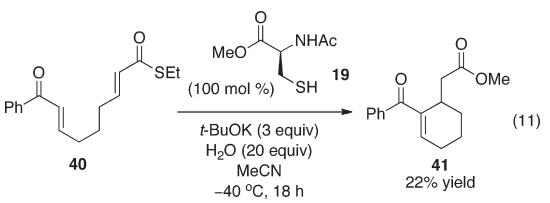
TABLE 11. Substrate Scope for Six-Membered Rings in the RC Reaction



Entry	Product	Catalyst (mol %)	Concentration (M)	*t*-BuOK (equiv)	Time (h)	Yield (%)	e.r.
1	R = R' = Ph **2**	100	0.05	6	24	70	97.5:2.5
2	R = R' = **33b**	100	0.03	5	24	70	96.5:3.5
3	R = R' = **33b**	20	0.03	5	24	81	87.0:13.0
4	R = R' = **34b**	100	0.01	7	24	73	95.0:5.0
5	R = R' = **34b**	20	0.01	7	24	57	95.0:5.0
6	R = R' = **35b**	100	0.01	2	4	71	92.0:8.0
7	R = R' = **36b**	100	0.05	6	48	54	96.0:4.0
8	R = R' = Me **37b**	100	0.008	4	40	55	95.0:5.0
9		100	0.01	4	40	68	90.5:9.5
10	R = Ph, R' = OEt **38b**	100	0.05	6	24	66	83.5:16.5

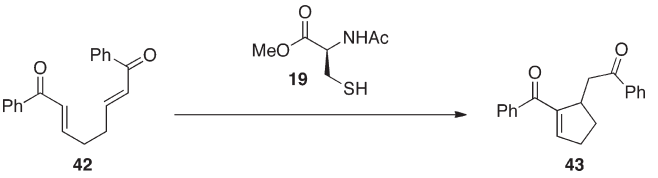
unreactive under the optimal conditions and even upon heating to 65 °C (eq 10). On the other hand, substrate **40** did show reactivity, albeit in low yield to produce compound **41** (eq 11). Transformation of the thioester into a methyl ester suggests generation of methoxide anion during the course of the reaction, which is possible by hydrolysis of the methyl ester moiety of the catalyst. It is also possible that the source of methoxide is slow decomposition of acetonitrile. As mentioned previously, the free acid form of the catalysts in unreactive (vide supra). These results together support the idea that only partial hydrolysis of the catalyst may be occurring.





In addition to the formation of six-membered ring RC products, we wanted to test the usefulness of this methodology in forming different ring sizes. As shown in Table 12, cycloisomerization of substrate **42** using catalyst **19** under optimal conditions produced the desired product **43** in 59% yield but in lower er (72.5:27.5, entry 1) as compared to the six-membered variant (97.5:2.5 er). Extending the reaction time to 12 h resulted in increased yield (81%) and reduced er (58.5:41.5, entry 2). Keeping the reaction time the same (12 h) but decreasing the amount of base to 2 equiv lowered the yield to 40% and boosted the er up to 84.0:16.0 (entry 3). A similar set of results was obtained in the following experiments (entries 4−6) where increasing either temperature or equivalents of base provided higher yields but at the expense of er. A quick solvent

TABLE 12. Various Conditions for Five-Membered Ring Formation in the RC Reaction



entry	solvent	conc (M)	*T* (°C)	*t*-BuOK (equiv)	time (h)	yield (%)	er
1	MeCN	0.05	−40	6	3	59	72.5:27.5
2	MeCN	0.05	−40	6	12	81	58.5:41.5
3	MeCN	0.05	−40	2	12	40	84.0:16.0
4	MeCN	0.05	−40	1	24	12	87.0:13.0
5	MeCN	0.05	−15	6	3	86	55.0:45.0
6	MeCN	0.05	−15	2	3	53	75.0:25.0
7	THF	0.05	−40	6	3	55	70.5:29.5
8	CH_2Cl_2	0.05	−40	6	3	58	54.0:46.0
9	MeCN	0.025	−40	2	24	20	86.0:14.0

screen (entries 7 and 8) seemed to show no improvement in er or yield, and diluting the reaction (entry 9) essentially gave the same result as entry 3.

Conclusion

The RC reaction is a powerful transformation with the capability of providing structurally complex enantioenriched compounds through the generation of a new carbon−carbon bond. Although progress in the development of this 45-year-old reaction has been slow due to difficulties in controlling reactivity, it has recently become a more prominent reaction with the development of the intramolecular version. We have been able to contribute to the further advancement of this transformation by establishing a method to perform the first enantioselective intramolecular RC reaction in high yield and enantioselectivity using convenient reagents and conditions. Moreover, our report documents the first use of a simple cysteine derivative as an asymmetric catalyst. An initial substrate scope was examined, and we determined that electron-deficient and electron-rich aryl symmetrical bis(enones) as well as aliphatic and heteroaromatic bis(enones) were viable substrates under this catalytic system. Unsymmetrical substrates and differing ring-sizes proved to be more difficult and will be the subject of further explorations.

Experimental Section

General Procedure A: Preparation of Intramolecular RC Substrates. Compound 36a. Cyclopentene (0.52 mL, 5.9 mmol) was dissolved in CH_2Cl_2 (8.7 mL) and cooled to −78 °C, and ozone was bubbled through the reaction until the clear solution turned blue. Nitrogen was then bubbled through the solution until the blue color disappeared to remove excess ozone. Triphenylphosphine (2.3 g, 8.9 mmol) was added, and the reaction was allowed to stir for 1 h at −78 °C. 1-(2-Furanyl)-2-(triphenylphosphoranylidene)ethanone[26] (4.6 g, 12.4 mmol) was added at room temperature, and the pale yellow solution was allowed to stir for 24 h and then concentrated under reduced pressure. Flash chromatography (hexanes−EtOAc, 5:1) provided **38a** as a pale yellow oil (790 mg, 2.8 mmol, 47%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63−7.62 (m, 2H), 7.27−7.24 (m, 2H), 7.15 (dt, J = 15.4, 7.2 Hz, 2H), 6.84 (d, J = 15.6 Hz, 2H), 6.56 (dd, J = 3.5, 1.8 Hz, 2H), 2.38 (q, J = 6.8 Hz, 4H), 1.78 (q, J = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.3, 153.7, 148.1, 146.9, 125.9, 118.0, 112.7, 32.4, 26.9; IR (film, cm^{-1}) 3124, 2933, 1664, 1620, 1564, 1465, 1392, 1297, 1010; TLC R_f 0.25 (2:1 hexanes−EtOAc); HRMS (ESI) m/z 285.1137 (285.1127 calcd for $C_{17}H_{17}O_4$ [M + H]$^+$). Compounds **1**, **34a**, **33a**, **35a**, and **37a**, were prepared by analogous methodology. See the Supporting Information for details.

General Procedure B: Preparation of Intramolecular Unsymmetrical RC Substrates. Compound 38a. 2-(Triphenylphosphanylidene)acetophenone[26] (9.1 g, 24 mmol) was added to a solution of 5,5-dimethoxypentanal[27] (2.5 g, 17 mmol) in CH_2Cl_2 (43 mL). After being stirred for 24 h at ambient temperature, the reaction mixture was concentrated under reduced pressure and purified via silica gel chromatography (hexanes−EtOAc, 5:1) to afford the (*E*) Wittig product. This material was then dissolved in THF (60 mL) and 1 N HCl (20 mL) and stirred at 23 °C. After 2 h, THF was removed in vacuo from the yellow solution and the resultant residue was diluted with Et_2O (100 mL) and washed with water (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and saturated aqueous NaCl (50 mL). The aqueous layers were extracted with ether (2 × 50 mL), and the combined organic layers were then dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (toluene−EtOAc, 5:1) provided the product as a pale yellow oil (960 mg, 4.7 mmol, 28%). The spectral data for the product matched that which had been previously reported.[28] The product (300 mg, 1.5 mmol) and ethyl 2-(triphenylphosphoranylidene)acetate (680 mg, 1.95 mmol) were dissolved in CH_2Cl_2 (3.7 mL) and stirred overnight at ambient temperature. The reaction was concentrated under reduced pressure and purified via flash chromatography (hexanes−EtOAc, 5:1) to yield compound **38a** in 61% yield (250 mg, 1.01 mmol): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 (d, J = 7.0 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.07−6.89 (m, 3H), 5.85 (dt, J = 15.8, 1.5 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 2.36 (q, J = 6.9 Hz, 2H), 2.28 (q, J = 6.9 Hz, 2H), 1.72 (quintet, J = 7.3 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 191.0, 166.9, 148.9, 148.4, 138.2, 133.1, 128.9, 128.9, 126.8, 122.4, 60.6, 32.4, 31.9, 26.9, 14.6; IR (film, cm^{-1}) 2980, 2936, 1715, 1672, 1652, 1616, 1442, 1264, 1178; TLC R_f 0.28 (3:1 hexanes−EtOAc); HRMS (ESI) m/z 295.1310 (295.1310 calcd for $C_{17}H_{20}O_3Na$ [M + Na]$^+$). Compounds **39** and **40** were prepared by analogous methodology. See the Supporting Information for details.

General Procedure C: Catalytic Intramolecular RC Reactions. Compound 2. Bisenone **1** (30.0 mg, 0.10 mmol) was dissolved in acetonitrile (2.0 mL) and water (36 μL, 2.0 mmol) and cooled to −40 °C. AcCysOMe (**19**) (17.6 mg, 0.10 mmol) and *t*-BuOK (67.0 mg, 0.59 mmol) were added sequentially, and the reaction was allowed to stir for 24 h at −40 °C. The reaction mixture was then filtered through a short plug of silica (hexanes−EtOAc, 1:1), concentrated under reduced pressure, and purified by silica gel chromatography (hexanes−EtOAc, 5:1) to afford **2** as a pale yellow oil (21 mg, 0.069 mmol, 70%). The characterization data for this compound matched that which has previously been reported:[13] $[\alpha]_D$ −38.6 (*c* 0.76, $CHCl_3$, 95% ee). Assay of enantiomeric purity: Enantiomers of product were separated by chiral HPLC employing a Chiralcel AD column (Daicel). Conditions: 96:4 hexanes−2-propanol. Flow rate 0.75 mL/min; 15.1 min (major ent), 20.5 min (minor ent). Compounds **33b**, **34b**, **35b**, **36b**, **37b**, and **38b** were prepared by analogous methodology. See the Supporting Information for details. **Note:** In order to ensure high efficiency and enantioselectivity, the reaction concentration and equivalents of *t*-BuOK must be as described for each respective substrate. For runs employing less than 100 mol % of catalyst, reaction parameters other than catalyst loading remain constant.

General Procedure D: Preparation of RC Catalysts. Compound 19. A white heterogeneous mixture of CysOMe·HCl (1.00 g, 5.82 mmol) in acetonitrile (58 mL) was cooled to 0 °C. *N*,*N*-Diisopropylethylamine (935 μL, 5.24 mmol) and acetyl chloride (374 μL, 5.24 mmol) were added, and the reaction was allowed to stir for 20 min. Saturated aqueous NH_4Cl (50 mL) was added at 0 °C, and the reaction mixture was extracted with EtOAc (2 × 100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL) and saturated aqueous NaCl (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography on silica gel (hexanes−EtOAc, 1:2) yielded **19** as a white fluffy solid (422 mg, 2.38 mmol, 41%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.41−6.33 (bs, 1H), 4.90 (dt, J = 7.9, 3.8 Hz, 1H), 3.80 (s, 3H), 3.07−2.98 (m, 2H), 2.08 (s, 3H), 1.34 (t, J = 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0, 170.1, 53.9, 53.2, 27.2, 23.5; IR (film, cm^{-1}) 3276, 2952, 1748, 1652, 1532, 1437, 1369, 1213; TLC

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R_f 0.21 (1:2 hexanes−EtOAc); $[\alpha]_D$ +71 (*c* 1.0, $CHCl_3$); HRMS (ESI) *m*/*z* 200.0363 (200.0357 calcd for $C_6H_{11}NO_3SNa$ $[M + Na]^+$).

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for compounds and X-ray data for compound **25** (CIF). This material is provided free of charge via the Internet at http://pubs.acs.org.