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Enantioselective Rauhut−Currier Reactions Promoted by Protected Cysteine

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Proteinogenic amino acids have received renewed attention as catalysts and promoters of enantioselective reactions.[1] Most prominent among them is perhaps proline, which is now known to catalyze a wide array of reactions.[2] The mechanistic rubric under which amino acid-catalyzed reactions can operate may be expanded if additional amino acids, either proteinogenic or nonproteinogenic, could be induced to be catalysts. Among the more prominent biochemical nucleophiles, the thiol associated with cysteine (Cys) or coenzyme A has evolved as a workhorse of enzymes operating through nucleophilic mechanisms.[3] Could cysteine's thiol be induced to mediate a synthetically useful process? We report our findings in this regard in the context of a cycloisomerization reaction, the intramolecular Rauhut−Currier cyclization reaction shown in Scheme 1.[4]

To date, pioneering methodological studies of Rauhut−Currier-type reactions by Krische and Roush have largely emphasized phosphine-based catalysts.[5,6] Related metal-mediated cycloreductions and cycloisomerizations have been reported.[7] Also known are variants mediated by thiolates reported by Murphy and Moore.[8] To our knowledge, no enantioselective variants of this process have yet been reported. Consequently, we began an investigation of thiolate-promoted cycloisomerization of **1** to deliver **2**. With an eye toward enantioselective catalysis, we began our study with Cys and its derivatives as a potential catalyst. In analogy to the phosphine-catalyzed reactions, thiolate could undergo 1,4-addition to **1** to form enolate **3**; cyclization via Michael addition would then afford **4**, which would undergo proton transfer and elimination to give product **2** along with regeneration of the Cys-derived anion.

Upon exposure of **1** to Cys derivative **5** and *t*-BuOK (1.5 equiv) in CH_3CN at room temperature, we observed clean conversion to **2**, with the intriguing observation that **2** exhibited 32% ee (Table 1, entry 1). Furthermore, the addition of varying quantities of water leads to a dramatic increase in enantioselectivity.[9] As shown in Table 1 (entries 2 and 3), there is an optimum quantity of water that leads to an increased selectivity from 42% ee (1 equiv of H_2O, entry 2) to 81% ee (20 equiv of H_2O, entry 3). Quantities in excess of 20 equiv have a deleterious effect (entries 4 and 5). The water effect stimulated us to examine alternative hydroxylic additives. In the presence of MeOH (9 equiv), the reaction leads to **2** with 40% ee (entry 6; cf. 70% ee with 9 equiv of H_2O). *iso*-Propanol and *t*-BuOH were also examined, but each leads to diminished selectivity (entries 7 and 8). Alternative bases (e.g., Et_3N, NaH, KH) were also examined but were found to be less effective. We also performed a study of catalyst structure. Notably, *N*-functionalization of Cys is key. Whereas *N*-isobutyryl catalyst **6** leads to modest loss in product ee (78%, entry 9), *N*-pivaloyl (**7**) and *N*-benzoyl (**8**) substitution lead to more pronounced loss of ee (43 and 41% ee, entries 10 and 11).

Optimization of the reaction conditions led to a dramatic increase in product ee (Table 2). For example, simply cooling the reaction mixture to −20 °C leads to the formation of the product with 92% ee, but the rate is slow when only 1.5 equiv of *t*-BuOK is employed (15% isolated yield of **2** after 5 h, entry 1). However, increasing the stoichiometry of the base, while reducing the overall concentration, leads to excellent results. Of note, increasing the quantity of base alone (from 1.5 to 6 equiv) leads to an improvement in yield but at the expense of ee (entries 2 and 3). Yet, good ee can be preserved by dropping the concentration from 0.1 to 0.07 M (85% ee with 70% isolated yield, entry 4). Under these conditions, the temperature may be dropped further without substantial loss of yield.

Scheme 1

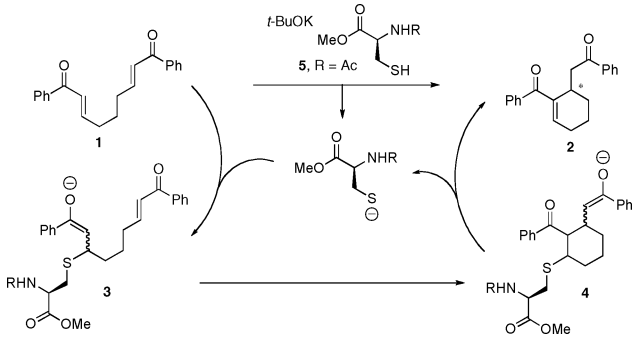

Table 1. Enantioselective RC Reactions of **1** to Afford **2** Promoted by **5**[a]

entry	catalyst	additive	equiv	ee[b]
1	**5**, R = Ac	−	−	32
2	**5**	H_2O	1	42
3	**5**	H_2O	20	81
4	**5**	H_2O	40	69
5	**5**	H_2O	100	33
6	**5**	methanol	9	40
7	**5**	*i*-PrOH	9	36
8	**5**	*t*-BuOH	9	26
9	**6**, R = C(O)*i*-Pr	H_2O	20	78
10	**7**, R = C(O)*t*-Bu	H_2O	20	43
11	**8**, R = C(O)Ph	H_2O	20	41

[a] All reactions were run at 23 °C in the presence of catalyst (1 equiv) with *t*-BuOK (1.5 equiv) for 5 h. [b] All enantiomeric excesses were measured using chiral HPLC.

Table 2. Optimization of Reaction Conditions[a]

entry	temperature (°C)	concentration (M)	base (equiv)	isolated yield[b]	ee[c]
1	−20	0.1	1.5	15	92
2	−20	0.1	4	47	84
3	−20	0.1	6	57	77
4	−20	0.07	4	70	85
5	−40	0.05	6	39	95
6	−40	0.05	9	74	83
7	−40	0.05	6	70	95[d]

[a] All reactions were run in MeCN in the presence of AcCysOMe (1 equiv) and water (20 equiv) for 5 h (see Supporting Information for reaction details). [b] Yields refer to the mass isolated after silica gel chromatography. [c] All enantiomeric excesses were measured using chiral HPLC. [d] Reaction was run for 24 h.

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Table 3. Substrate Scope[a]

entry	substrate	product	time	loading of catalyst **5**	isolated yield[b]	ee[c]
1	**1a**, R = H	**2a**, R = H	24 h	100 mol%	70	95
2			24 h	20 mol%	75	92
3			24 h	10 mol%	41	91
4	**1b**, R = OMe	**2b**, R = OMe	24 h	100 mol%	73	90
5			24 h	20 mol%	57	90
6	**1c**, R = Br	**2c**, R = Br	24 h	100 mol%	70	93
7	**1d**, R = NO_2	**2d**, R = NO_2	4 h	100 mol%	71	84
8	**9**	**10**	40 h	100 mol%	55	90
9	**11**	**12**	40 h	100 mol%	54	92
10	**13**	**14**	24 h	100 mol%	66	67

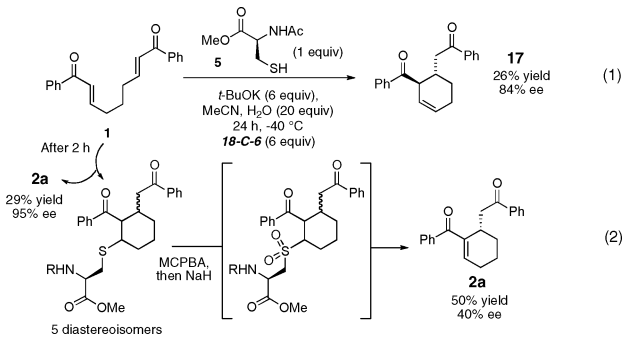
[a] Reactions were run at −40 °C (see Supporting Information for reaction details). [b] Yields refer to the mass isolated after silica gel chromatography. [c] All enantiomeric excesses were measured using chiral HPLC. The absolute configuration of **2c** was determined by X-ray crystallography of the corresponding hydrazone. See Supporting Information for details. The other products were assigned by analogy.

As shown in entries 5−7, optimized conditions were found such that, within 24 h, product **2** is isolated in 70% yield with 95% ee (entry 7).

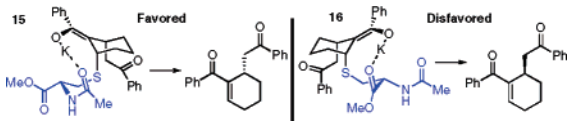
As is inherent in Scheme 1, the reaction may be run with a substoichiometric quantity of catalyst. Cyclization of **1a** to give **2a** may be conducted with 20 mol % of **5**, leading to 75% isolated yield with 92% ee after 24 h (Table 3, entry 2). Further reduction of catalyst loading (10 mol %) leads to **2a** with nearly identical ee, but with a reduced yield of 41% within this time frame (entry 3). A modest rate reduction was also observed in the conversion of **1b** to **2b** with 20 mol % of catalyst **5** (entry 4 versus 5). As a result, since such a simple and commercially available catalyst mediates this transformation, we elected to perform a preliminary study of reaction scope with a full equivalent of **5** to maintain convenient reaction rates and useful yields for a range of substrates.

As shown in Table 3, the reaction of symmetrical bis(enones) is relatively insensitive to electronic effects. For example, *para*-methoxy substitution (**1b**) and *para*-bromo substitution (**1c**) lead to similar results. Products **2b** and **2c** are isolated with 90 and 93% ee, respectively (entries 4 and 6). The *para*-NO_2-substituted compound **1d** delivers **2d** within 4 h, but with a modest drop in selectivity (84% ee, entry 7). Aliphatic compounds are also substrates for the process. Bis(methylketone) **9** undergoes the cyclization to give **10** in 90% ee, with an isolated yield of 55% after 40 h (entry 8). Furan-substituted bis(enone) **11** also results in a selective reaction (**12**, 92% ee, 54% yield, entry 9). Finally, unsymmetrical keto ester **13** forms **14** in 66% yield, with a reduced ee of 67% (entry 10).

The basis of the enantioselectivity induced by a single amino acid warrants mechanistic speculation. Two experimental observations have guided our thinking. First, we note that conducting the reaction in the presence of 18-crown-6 does not lead to **2a** as the major product, and instead deconjugated **17** dominates (26% yield, 84% ee, eq 1). Thus, we believe that K ion chelation is operative in the selective reactions. Second, we have observed that, after only 2 h under normal conditions, in addition to **2a** (29% yield, 95% ee), the cyclized cysteine-substituted diketone derivative of **4** is isolated, but it appears as a mixture of five diastereomers (eq 2). Upon oxidation and elimination under irreversible conditions, **2a** is isolated with only 40% ee. These facts raise the possibility that elimination of Cys may be the irreversible and stereochemistry-determining step. By analogy, we note that elimination of catalyst through α-proton abstraction has also been shown to be rate-determining in variants of the Morita−Baylis−Hillman reaction.[10]



Thus, we have derived models **15** and **16** that may explain the formation of the observed enantiomer, in light of reversible ring-forming C−C bond formation. Each model benefits from stable arrangements of the cyclohexanone-derived enolates that minimize allylic strain. Furthermore, each maintains π-overlap of the enolate with the σ^*-C−S orbital of the bond that is to be cleaved. The differential rates of elimination therefore may derive from the more stable *amide*-chelated enolate **15** in comparison to the *ester*-chelated enolate **16** in plausible conformers of the Cys adducts.[11]



Further studies of the scope and mechanism of this catalytic reaction are in progress.

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Supporting Information Available: Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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