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Catalytic Enantioselective α,β,γ-Trioxygenation

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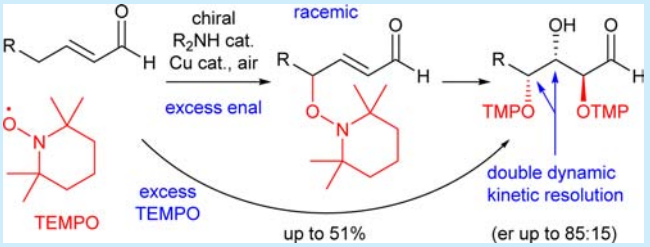
Supporting Information

ABSTRACT: Applying a catalytic enantioselective aldehyde α-oxygenation condition to an enal substrate led to the discovery of the first α,β,γ-trifunctionalization cascade of enals. Under optimal conditions, a tryptophan-derived imidazolidinone catalyst in fluorinated aromatic solvents provided α,β,γ-trioxyaldehydes in up to 51% isolated yield (average of 80% yield per oxygenation step) and 85:15 er. Substitution at the δ position was tolerated, but not at the α, β, or γ positions. The reaction proceeded through initial TEMPO incorporation at the γ position, and rapid racemization of this intermediate, reversible conjugate addition of water, followed by TEMPO incorporation at the α position to set all three stereocenters with double dynamic kinetic resolution.

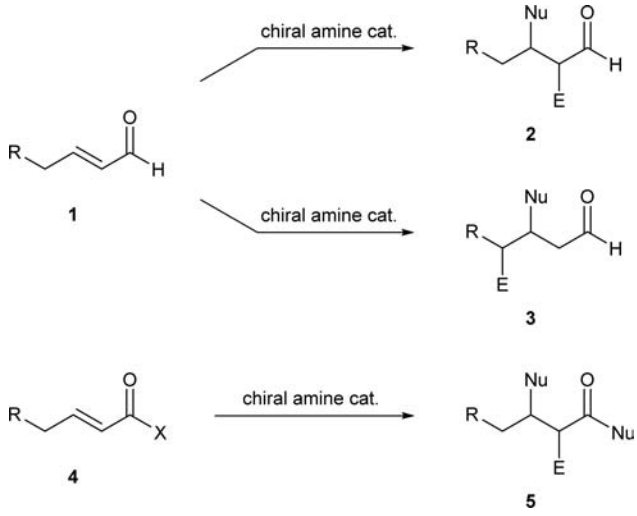


Enantioselective transformations of aldehydes and enals promoted by chiral amine catalysts have been heavily studied since 2000.[1] The most common variants of these reactions are aldehyde α-functionalizations[2] and enal β-functionalizations,[3] but reactions at more remote sites are also known.[4] α-Oxygenations have been developed using nitrosobenzene,[5] TEMPO radical,[6] or singlet oxygen[7] as the oxygen source. β-Oxygenations through conjugate addition of substituted hydroxylamines,[8] alcohols,[9] or hydrogen peroxide[10] have been described, but have found limited application due to their reversible nature.[11] A nonenantioselective γ-oxygenation using a TEMPO radical has been reported.[12]

Organocatalytic cascade reactions[13] have also been popular. Conjugate addition to an α,β-unsaturated iminium ion (generated by condensation of an enal with an amine catalyst) forms an enamine whose further reaction with an electrophile leads to α,β-difunctionalization (**1** → **2**, Scheme 1). The α and β positions may form new bonds to the same atom, generating a three-membered ring.[14] More often, the enal is coupled to two different reaction partners. Organocatalytic α,β-difunctionalizations involving oxygenation at the α[15] or β[16,9c] position have been developed, but organocatalytic α,β-dioxygenation is unknown. Some examples of enal β,γ-difunctionalization (**1** → **3**) have been reported,[17] but there is no precedent for enal α,β,γ-trifunctionalization (organocatalytic or otherwise). However, *ipso*,α,β-trifunctionalizations of activated carboxylic acid derivatives (**4** → **5**) have been described.[18]

We became interested in organocatalytic aldehyde α-oxygenation using stoichiometric TEMPO[6] as part of a strategy for preparing *anti*-1,2-diols from simple aldehydes.[19] The α-oxygenation proceeds through an enamine mechanism,[6c] but the optimal catalysts are imidazolidinone salts originally designed to promote enal reactions through the intermediacy of α,β-unsaturated iminium ions.[1b] This apparent mismatch led us to wonder what would happen if an enal were subjected to the α-oxygenation conditions. Would α-oxygenation proceed with transposition of the alkene? Would conjugate addition of a nucleophile occur? Or would γ-oxygenation be observed?

Scheme 1. Summary of Related Cascade Reactions



To distinguish these possibilities, we subjected enal **6** (Scheme 2) to the aldehyde α-oxygenation conditions. Enal **6** and TEMPO reacted under the influence of imidazolidinone salt **7**·HCl to give γ-oxyenal **8** and α,β,γ-trioxyaldehyde **9**, both in racemic form. Using an excess of enal **6** favored formation of γ-oxyenal **8**, and using an excess of TEMPO favored trioxyaldehyde **9**. Resubjecting γ-oxyenal **8** to the reaction conditions effected its conversion into trioxyaldehyde **9**, demonstrating that γ-oxyenal **8** likely is an intermediate in the cascade. The relative stereochemistry of trioxyaldehyde **9** was ascertained by comparing the NMR spectra of tetraacetate

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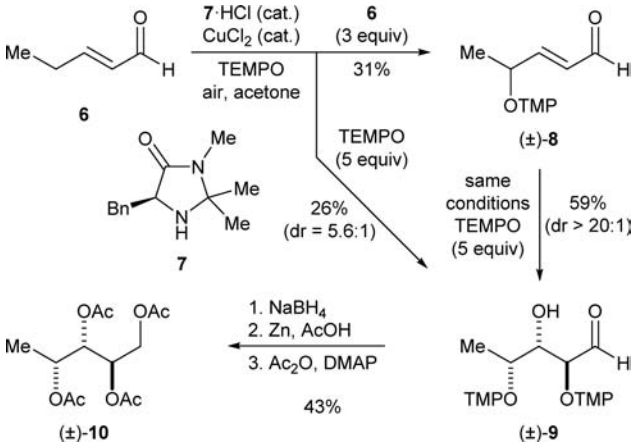
Scheme 2. Discovery of a Trioxygenation Cascade[a]



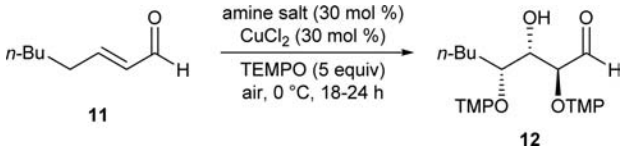
[a]TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy radical. TMP = 2,2,6,6-tetramethylpiperidinyl.

derivative **10** against the published spectra of all diastereomers of this compound.[20] Shortly after we commenced these experiments, Jang and co-workers reported the conversion of enal **6** into γ-oxyenal (±)-**8** under similar reaction conditions;[12] however, they apparently did not observe trioxyaldehyde **9** since they used TEMPO as the limiting reagent.

C_5 enal **6** is difficult to observe by TLC analysis due to its moderate volatility, so reaction optimization was conducted on C_8 enal **11** (Table 1). Aldol and Michael reaction products were observed, so enal **11** was added portionwise in order to suppress its self-dimerization. The reaction was sluggish, and thus it was run at high concentration (500 μL of solvent for a 1 mmol reaction) in order to increase the reaction rate. At this concentration, TEMPO became a significant contributor to reaction volume; to further enhance the initial rate, TEMPO was added in two portions. Under these conditions, imidazolidinone salt **7**·AcOH delivered trioxyaldehyde **12** in higher yield and with superior stereoselectivity as compared with the hydrochloride salt (Table 1, entries 1 and 2). A solvent screen revealed improved enantioselectivity in toluene, but at the expense of yield (Table 1, entries 3–6). Copper(II) chloride was poorly dissolved in toluene, and so we speculated that more polar fluorinated aromatic solvents may better dissolve the copper salt and, thus, rescue the reaction yield while retaining the improved stereoselectivity (Table 1, entries 7–10). This proved to be the case; use of pentafluorobenzene delivered a higher yield of the major diastereomer than that obtained in acetone (albeit with a lower yield of the combined diastereomers) and an enantiomeric ratio comparable to that achieved in toluene. The anion of the amine salt was then varied, but no improvements were forthcoming (Table 1, entries 11 and 12).

Believing that use of a sterically more demanding catalyst would improve enantioselectivity, we switched to tryptophan-derived catalyst **13**·AcOH (Figure 1 and Table 1, entries 13–15).[21] The desired trioxygenation did not proceed in acetone using the bulkier catalyst; only aldol and Michael addition products were observed. However, use of the bulkier catalyst improved the enantiomeric ratio to 85:15 when the reaction was conducted in pentafluorobenzene. Unfortunately, this change also slowed the conversion of the intermediate γ-oxyenal into trioxyaldehyde **12**. The γ-oxyenal was present in 21% yield after 24 h, but the yield of trioxyaldehyde **12** peaked at this time since the product slowly decomposed under the reaction conditions. Nonetheless, a 59% combined yield of two diastereomers of **12** was obtained. After aldehyde reduction to facilitate chromatographic separation, the major diastereomer was isolated in 51% overall yield (i.e., average of 80% yield per oxygenation).

Table 1. Trioxygenation Cascade Optimization



entry	amine salt	solvent	yield (%)[a]	dr[b]	er[c]
1	7·HCl	acetone	47	2.7:1	43:57
2	7·AcOH	acetone	78 (57)	4.1:1	61:39
3	7·AcOH	THF	39	9.0:1	66:34
4	7·AcOH	DMSO	0	ND	ND
5	7·AcOH	$CHCl_3$	0	ND	ND
6	7·AcOH	PhMe	42	5.5:1	73:27
7	7·AcOH	$PhCF_3$	69 (52)	5.0:1	71:29
8	7·AcOH	$C_6H_3F_3$[d]	54	6.8:1	72:28
9	7·AcOH	C_6HF_5	66 (59)	>20:1	70:30
10	7·AcOH	C_6F_6	48	3.5:1	75:25
11	7·TFA	C_6HF_5	67	6.2:1	68:32
12	7·HCl	C_6HF_5	58	5.7:1	71:29
13	**13**·AcOH	acetone	0	ND	ND
14	**13**·AcOH	$PhCF_3$	45 (36)	6.4:1	84:16
15	**13**·AcOH	C_6HF_5	59 (51)	8.9:1	85:15

[a]Combined yield of two major diastereomers, determined by crude NMR in the presence of an internal standard. Yields in parentheses refer to the isolated yield of the major diastereomer after $NaBH_4$-mediated reduction. [b]Determined by crude NMR. [c]Determined by chiral HPLC for the major diastereomer. [d]1,3,5-Trifluorobenzene. ND = not determined.

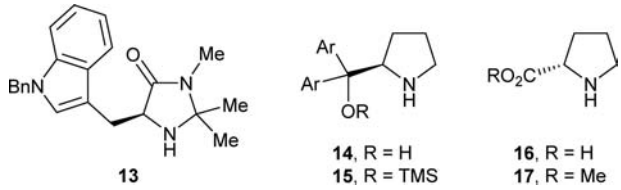


Figure 1. Other secondary amine catalysts screened.

Amine salts of α,α-diarylprolinols **14** and related silyl ethers **15** also catalyzed the formation of trioxyaldehyde **12**. However, the reactions became even more sluggish when using these catalysts, and neither yield nor stereoselectivity was improved. Proline **16**, proline methyl ester **17**, and their salts did not catalyze the trioxygenation cascade. However, proline hydrochloride (**16**·HCl) proved to be a good catalyst for γ-oxygenation. The 71% isolated yield of γ-oxyenal **18** (Scheme 3) using enal **11** as the limiting reagent is comparable to the best γ-oxygenation yields reported by Jang and co-workers using TEMPO as the limiting reagent.[12]

As shown in Scheme 4, the optimized reaction of C_5 enal **6** gave chiral trioxyaldehyde **9**, but with an inferior enantiomeric ratio than that achieved in the reaction of C_8 enal **11**. The absolute configuration of trioxyaldehyde **9** (and, by extension, the other trioxyaldehydes) was determined by comparing the

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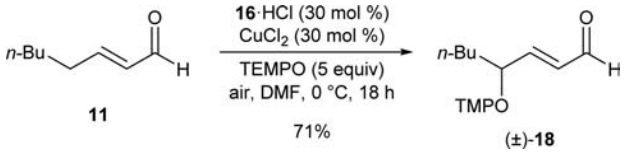
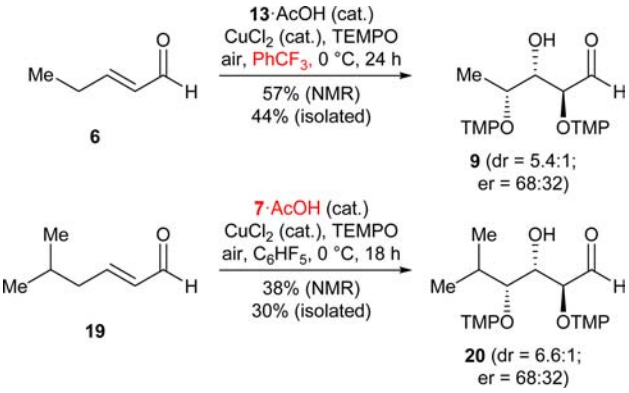
Scheme 3. Proline-Catalyzed γ-Oxygenation



Scheme 4. Trioxygenation of Other Substrates[a]

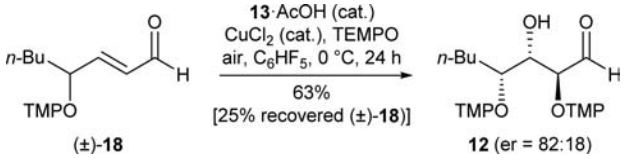


[a]NMR yields refer to the combined yield of two diastereomers, determined by crude NMR in the presence of an internal standard. Isolated yields refer to the yield of the major diastereomer after $NaBH_4$-mediated reduction.

optical rotation of optically active tetraacetate **10** (Scheme 2) against that of the known carbohydrate-derived tetraacetate.[22] Since the functional group tolerance of the reaction conditions has already been demonstrated in the context of α-oxygenation,[6] we investigated whether the cascade reaction tolerated branching on or near the enal. Substrates with branching at the α, β, or γ position did not undergo α,β,γ-trioxygenation or even γ-oxygenation. Cinnamaldehyde was similarly unreactive. δ-Branching was tolerated (see **19** → **20**), but with poor kinetics. Use of the less bulky catalyst **7**·AcOH delivered a 38% yield of the combined diastereomers, but the enantiomeric ratio suffered.

We probed the reaction mechanism of the transformation since such knowledge might assist in the design of improved enal α,β,γ-trifunctionalizations. As shown in Scheme 5, racemic

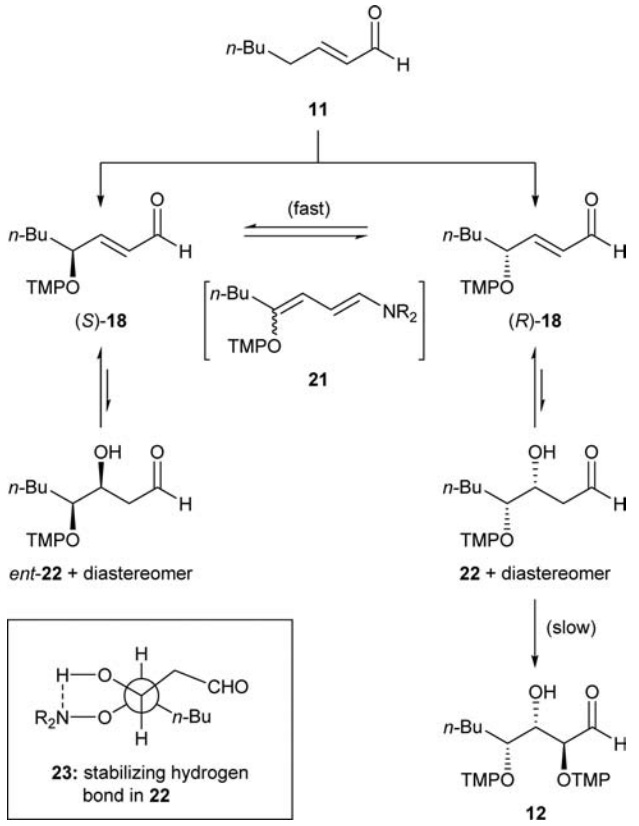
Scheme 5. Evidence for Dynamic Kinetic Resolution



γ-oxyenal **18** reacted under the optimized trioxygenation conditions to afford trioxyaldehyde **12** in 63% isolated yield (single diastereomer after aldehyde reduction) with 82:18 er and racemic recovered starting material (±)-**18** in 25% isolated yield. The 64% combined yield of compounds with the (*R*) configuration at the γ position (12% (*R*)-**18** + 52% major enantiomer of **12**) proves that the enantiomers of γ-oxyenal **18** interconvert under the reaction conditions to afford dynamic kinetic resolution.[16f,h]

The above data lead to a clear mechanistic overview of the cascade, outlined in Scheme 6 using enal **11** as a model

Scheme 6. Proposed Trioxygenation Mechanism



substrate. The reaction proceeds through initial formation of γ-oxyenal **18**, a compound that undergoes rapid racemization through the intermediacy of dienamine **21**. β,γ-Dioxyaldehyde **22** is not detected, suggesting that consistent with the nonaqueous reaction conditions, conjugate addition of water is thermodynamically unfavorable.[11] Our recent computational study on 2,2,6,6-piperidinyl-masked vicinal diols[23] reveals a thermodynamic preference for the *syn* diastereomer of **22**, which adopts a six-membered ring hydrogen bond between the β-hydroxyl proton and the piperidinyl nitrogen of the masked γ-hydroxyl group (see **23**). The stability conferred by this hydrogen bond may play a role in achieving a sufficiently high concentration of β,γ-dioxyaldehyde **22** for the subsequent α-oxygenation to proceed at a viable rate; recall that cinnamaldehyde is unreactive. Since water addition is reversible and the enantiomers of γ-oxyenal **18** equilibrate, α-oxygenation sets all three stereocenters with double dynamic kinetic resolution. The configuration of the masked α-hydroxyl group is consistent with that observed in the α-oxygenation of simple aldehydes.[6]

In conclusion, we discovered the first enal α,β,γ-trifunctionalization cascade. The reported trioxygenation is of limited synthetic utility due to moderate enantioselectivity, but the mechanistic insight gained is expected to be useful for the design of improved polyfunctionalization cascades. For example, using a tethered nucleophile or a nucleophile that adds irreversibly should enhance the overall reaction rate by improving the thermodynamic driving force for the β-functionalization step. The latter change might also enhance enantioselectivity since the catalyst would be able to exert its influence at two steps (α- and β-functionalization). Efforts to translate these ideas into improved cascades are underway.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03050.

Experimental details, graphical NMR spectra, and chiral HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

The footnote text for Scheme 4 was moved from the text to the scheme; the correct version reposted December 10, 2015.

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