VIP Organocatalysis Very Important Paper

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An Organocatalytic Cope Rearrangement

*Dainis Kaldre and James L. Gleason**

Abstract: *The first example of an organocatalytic Cope rearrangement is reported. Acyclic and cyclic acyl hydrazides catalyze the rearrangement of 1,5-hexadiene-2-carboxaldehydes via iminium ion formation. A correlation between ring size and catalyst activity was observed for the cyclic hydrazides, with seven- and eight-membered-ring catalysts being the most active. Diazepane carboxylate* ***5c*** *(10 mol%) catalyzed the rearrangement of a range of dienes at room temperature in acetonitrile using triflic acid as a co-catalyst. Preliminary proof of principle for asymmetric catalysis was provided by rearrangement of 3,3-dimethyl-7-phenyl-1,5-heptadiene-2-carboxaldehyde in the presence of a novel 7-substituted diazepane carboxylate.*

Pericyclic reactions play a central role in the synthesis of complex natural products.[1] Whereas significant progress has been made in the catalysis of cycloadditions, most notably the Diels–Alder reaction,[2] catalytic asymmetric methods of sigmatropic and electrocyclic reactions are less well developed.[3] In both the Cope and Claisen rearrangements, transition-metal coordination to the alkenes has played a prominent role, and complexes of palladium, platinum, and nickel have all been reported to facilitate [3,3]-sigmatropic rearrangements.[4] These methods have been extended to several catalytic asymmetric Claisen rearrangements[5] and a single example of an enantioselective Cope rearrangement, the gold-catalyzed rearrangement of 1-cyclopropylidiene-1,5-hexadienes.[6] In the Claisen rearrangement, Lewis acid coordination of the oxygen atom may also accelerate the [3,3]-rearrangement by weakening the C–O bond and/or stabilizing charge on the oxygen atom in the transition state.[7] This has enabled several catalytic asymmetric Claisen rearrangements that are catalyzed by chiral Lewis acid complexes[8] and chiral protic organocatalysts.[9,10] Finally, a few sporadic reports have suggested that stoichiometric acid can promote the Cope rearrangement of acyl-1,5-dienes,[11] and the use of catalytic amounts of acid has been shown to promote the electrocyclic closure of acyl-1,3,5-hexatrienes.[3a,d,12] Herein, we expand upon the possibility of acid catalysis to report the first organocatalytic Cope rearrangement and identify a new seven-membered-ring hydrazide catalyst capable of iminium ion formation from hindered enals.

The concept of LUMO-lowering catalysis via iminium ion formation is well established for Diels–Alder cycloadditions.[13] We envisioned extending LUMO-lowering catalysis to other pericyclic reactions such as the Cope and Claisen rearrangements. We began by examining the accelerating effect on the Cope rearrangement of 1,5-hexadiene by an iminium ion substituent at the 2-position (see Figure 1). This position was chosen as it would be impervious to effects of conjugation/deconjugation and would lend itself more easily to eventual asymmetric catalysis. An inherent limitation is the significant A-1,3 strain that arises in the formation of an iminium ion from an α-substituted enal/enone with a secondary amine. Indeed, there are only a few such examples of iminium catalysis with secondary amines,[14] although primary amine catalysis is often a viable solution,[15] and thus this is an area of opportunity for new catalyst development.

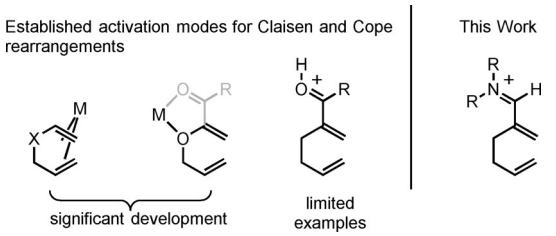

Figure 1. Activation modes for Cope and Claisen rearrangements.

4-Phenyl-1,5-hexadiene-2-carboxaldehyde (**1a**) was chosen as the model substrate as the Cope equilibrium was expected to favor the conjugated product **2a**. Indeed, thermolysis of **1a** in toluene for 24 h at 110 °C proceeded to completion and resulted in the isolation of **2a** in 94% yield. Potential catalysts were initially screened in [D_4]methanol at 60 °C, conditions under which the uncatalyzed rearrangement of **1a** was observed to proceed in only 21% yield over 24 h (Table 1). The addition of proline (50 mol%) slightly increased the conversion (29%) whereas other simple secondary amines, such as pyrrolidine, proline methyl ester, and MacMillan's second-generation catalyst (**3**),[16] each as the hydrochloride salt, did not afford any observable catalysis. As noted above, the negligible levels of catalysis were presumed to result from significant A-1,3 strain in the iminium ion; indeed, we did not observe any iminium ion formation by ^{1}H NMR spectroscopy with simple secondary amine catalysts. We reasoned that a more nucleophilic amine might increase the rate of iminium ion formation. *N*-Acyl hydrazides have been found to form iminium ions at high rates in the Diels–Alder reaction, with the higher reactivity

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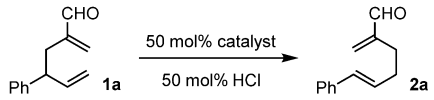
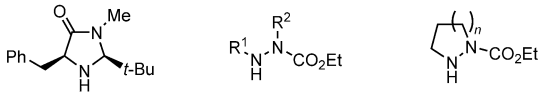
Table 1: Catalyst screen.



Entry	Catalyst	Solvent	*T* [°C]	Yield [%][a]
1	–[b]	CD_3OD	60	21
2	proline[b]	CD_3OD	60	29
3	pyrrolidine	CD_3OD	60	21
4	**3**	CD_3OD	60	16
5	**4a**	CD_3OD	60	34
6	**4b**	CD_3OD	60	45
7	**5a**	CD_3OD	60	18
8	**5b**	CD_3OD	60	35[c]
9	**4b**	CD_3CN	23	19
10	**5a**	CD_3CN	23	6
11	**5b**	CD_3CN	23	28
12	**5c**	**CD_3CN**	**23**	**83**
13	**5d**	**CD_3CN**	**23**	**89**

[a] Determined by ^{1}H NMR spectroscopy with mesitylene as the internal standard. All reactions were run for 24 h unless otherwise noted. [b] Without an acid co-catalyst. [c] Acetal and oxa-Michael products observed.



initially ascribed to the α-effect.[14a,17] We were pleased to find that several acyl hydrazides afforded a measurable improvement in catalytic activity. For instance, cyclic hydrazides **4a** and **4b** afforded modest yields, with conversions up to 45% (Table 1, entries 5 and 6).

Examination of cyclic hydrazides showed that whereas a five-membered-ring hydrazide (**5a**) was inferior to acyclic hydrazides, the corresponding six-membered-ring catalyst **5b** was significantly more active, with the starting material being fully consumed within 24 h (Table 1, entries 7 and 8). However, the mass balance of the reaction was negatively affected by the formation of a mixture of acetal and oxa-Michael addition products that result from addition of the solvent, [D_4]methanol. Switching to [D_3]acetonitrile alleviated this problem, and at room temperature, conditions under which the uncatalyzed reaction does not proceed to any measureable extent, six-membered-ring catalyst **5b** afforded the product in 28%, a definite advantage over the smaller catalyst **5a**, which was largely ineffective under these conditions (Table 1, entries 10 and 11). Given the higher reactivity of the larger-ring catalyst, we extended our study to the seven-membered diazepane carboxylate **5c** and were pleased to observe a significant improvement in reactivity along with a yield of 83% (Table 2, entry 12). Given the continued trend towards higher reactivity with increasing ring size, we also prepared eight-membered-ring catalyst **5d**. Whereas a slight increase in reactivity was noted (89% yield), its inherently more difficult synthesis discouraged further development. It is important to note that primary amines, such as aniline, benzylamine, 1,2-cyclohexanediamine, *O*-methyl hydroxylamine, alanine, and glycine methyl ester, all failed to afford any rearrangement product at 23 °C, highlighting the unique reactivity of the cyclic hydrazide catalysts.

Table 2: Optimization of the acid co-catalyst.

Entry	Catalyst	Co-catalyst (mol%)	Yield [%][b]
1	**5b**	TsOH (50)	25
2	**5b**	HCl (50)	28
3	**5b**	HBr (50)	38
4	**5b**	**$HClO_4$ (50)**	**94**
5	**5b**	**TfOH (50)**	**96**
6	**5b**	TfOH (20)	75
7	**5b**	TfOH (10)	43
8	**5c**	**TfOH (10)**	**95**

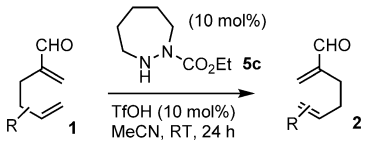
[a] General reaction conditions: **1a**, catalyst as noted in equivalent mol% to acid, CD_3CN, 23 °C. [b] Determined by ^{1}H NMR spectroscopy with mesitylene as the internal standard. Tf = trifluoromethanesulfonyl, Ts = *para*-toluenesulfonyl.

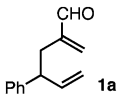
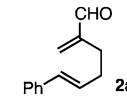
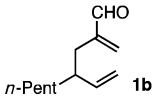
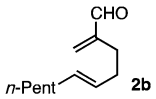
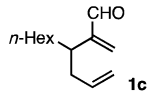
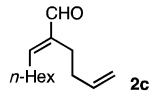
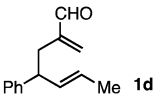
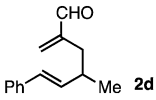
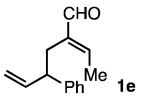
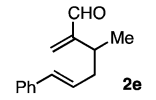
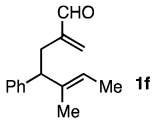
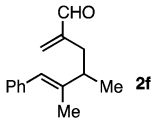
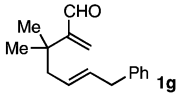
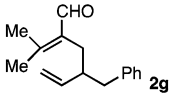
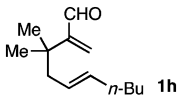
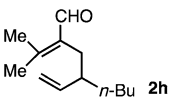
The acid co-catalyst was optimized using the less reactive six-membered-ring catalyst **5b**. We found that stronger acids afforded significantly improved reaction rates (Table 2). Using either triflic or perchloric acid with **5b**, each at 50 mol% loading, the reaction proceeded to completion within 24 h. Although reducing the catalyst loading with less reactive catalyst **5b** resulted in a significant diminution in yield, applying these conditions with 10 mol% of the more active diazepane carboxylate **5c** allowed the rearrangement to proceed to completion within 24 h and afforded the Cope product in 95% yield (isolated in 90% yield; Table 3).

Diazepane catalyst **5c** is highly effective with a range of 1,5-diene-2-carboxaldehydes (Table 3). Good yield was observed for *n*-pentyl-substituted substrate **1b**, indicating that alkene conjugation with a phenyl group, as in product **2a**, is not required for reactivity. Substituents were also tolerated at the 3- and 6-positions (entries 3 and 4). *E* Substitution was also tolerated at the 1-position (entry 5), but the reaction was slower, which is presumably due to the presence of an axial methyl group in a probable chair-like transition state.[18] Intriguingly, substitution at the 5-position was not tolerated (**1f**, entry 6) under the standard reaction conditions, and decomposition was observed with higher loadings. In contrast, **1f** does undergo rearrangement under standard thermal conditions (toluene, 110 °C, 24 h) to afford **2f** in 64% yield. Finally, we found that geminal dimethyl substitution was surprisingly well tolerated at the 3-position (entries 7 and 8), again demonstrating the unique reactivity of the diazepane carboxylate in forming highly hindered α-substituted iminium ions.

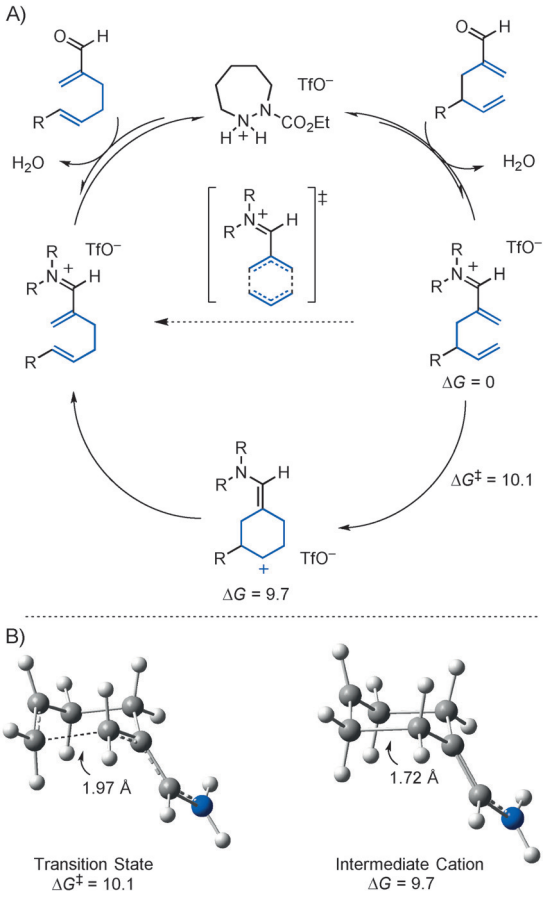
We initially envisioned a simple catalytic cycle in which iminium ion formation would facilitate the Cope rearrangement through simple LUMO lowering (dashed arrow, Scheme 1). DFT calculations (B3LYP/6-31G*)[19] clearly indicated an accelerating effect of electron-withdrawing substituents on the Cope rearrangement. The rearrangement of 1,5-hexadiene was predicted to have an activation energy of 35.8 kcal mol^{-1}. Incorporating an aldehyde at the 2-position lowered the predicted barrier to 30.5 kcal mol^{-1}, and formation of a simple iminium (R = H in Scheme 1) reduced this

Table 3: Reaction scope.



Entry	Substrate	Product	Yield [%][a]
1	 1a	 2a	90
2	 1b	 2b	66
3	 1c	 2c	93
4[b]	 1d	 2d	86
5[c]	 1e	 2e	49
6[d]	 1f	 2f	NR[e]
7[f]	 1g	 2g	88
8[f]	 1h	 2h	90

[a] Yield of isolated product. [b] Substrate **1d** was used as a 72:28 *E*/*Z* mixture. [c] At 40 °C for 96 h. [d] Substrate **1f** was used as a 69:31 *E*/*Z* mixture. [e] Use of 50 mol% **5c**/25 mol% TfOH led to significant decomposition. [f] Run for 48 h.



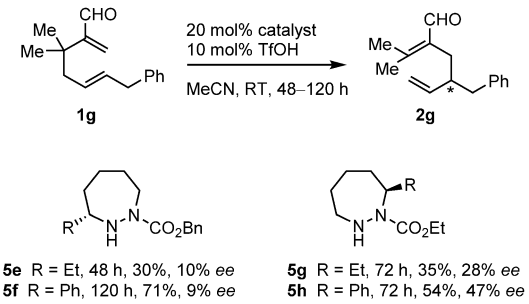
Scheme 1. A) Proposed catalytic cycle. Energies computed at the B3LYP/6-31G* level of theory for R = H. ΔG values given in kcal mol^{-1}. B) Structures of the computed transition state and the intermediate cation.

barrier even further to 10.1 kcal mol^{-1}. However, while the predicted transition states for 1,5-hexadiene and 1,5-hexadiene-2-carboxaldehyde correspond to an archetypical concerted sigmatropic rearrangement, the iminium ion is predicted to proceed through a shallow-energy intermediate ($\Delta G = 9.7$ kcal mol^{-1}) that bears a positive charge on the 5-position. Thus the reaction might be viewed as a conjugate addition of the alkene to the α,β-unsaturated iminium ion, followed by fragmentation of the cation to complete the rearrangement; in many ways, the transformation would be similar to the palladium-catalyzed Cope rearrangements originally described by Overman and co-workers.[4a,b] Thus far, the only evidence for a stepwise reaction is computational, and it is noteworthy that the rearrangement of **1f**, which bears a methyl group at the 5-position and would thus be expected to stabilize the intermediate cation, does not afford any rearranged product. Although stabilizing the cation might allow it to follow an alternative pathway, we did not identify any side products with this particular substrate.

Whereas detailed mechanistic work remains to be done, we have not been able to observe the iminium ion intermediates directly, suggesting that iminium ion formation is rate-limiting. Importantly, we have found that the *N*-methyl analogue of **5c** does not catalyze the Cope rearrangement, which is consistent with iminium ion formation and suggests that simple proton catalysis of the Cope rearrangement is not operative under our conditions.[20] It was presumed that the high catalytic activity of **5c**/**5d** arises from faster iminium ion formation relative to their smaller-ring congeners. Owing to the increased A-1,3 strain resulting from the larger bond angles in the seven-membered ring, the stability of the iminium intermediates is predicted to decrease as the ring size increases,[21] which is opposite to the observed reactivity trend. As suggested by Tomkinson and co-workers, the higher reactivity of **5c** may result from the reduced proton affinity of the amine, facilitating easier protonation of the oxygen atom during iminium ion formation.[17f,22]

The catalyst system reported here will open up new avenues for reaction discovery. In particular, the high reactivity of the diazepane carboxylates with α-substituted enals has a wide range of possible applications in catalysis and

makes them an intriguing platform for chiral catalyst development. To this end, we assessed the potential for asymmetric catalysis using substrate **1g**. This is a challenging substrate as the new stereocenter is remote to the positioning of the catalyst (see the TS structure in Scheme 1). We examined two catalyst architectures, one with a stereocenter adjacent to the nucleophilic nitrogen atom (**5e**/**5f**; Scheme 2) and one with the stereocenter adjacent to the carbamate (**5g**/**5h**; Scheme 2). To our surprise, catalysts bearing the substituent



Scheme 2. Asymmetric variant of the Cope rearrangement.

adjacent to the nucleophilic nitrogen atom gave minimal enantioinduction. In contrast, **5g** and **5h**, with substitution adjacent to the carbamate nitrogen atom, afforded the desired product in 28 and 47% *ee*, respectively.[23,24] The observation that substitution further from the reactive site was more effective was unexpected and may result from gearing of the carbamate by the adjacent stereocenter. This is an intriguing control element for asymmetric catalysis that should enable the rational development of catalysts for reactions that involve α-substituted iminium ions.

In conclusion, we have developed the first organocatalytic Cope rearrangement and identified diazepane carboxylates as unique catalysts for the activation of α-substituted enals. The method is viable with a range of 1,5-hexadienyl-2-carboxyaldehydes. Computational evidence suggests a possible stepwise mechanism, and preliminary examination of chiral catalysts revealed that remote stereocontrol elements are effective through gearing of the hydrazide carboxylate. The diazepane catalysts represent an intriguing platform for future development in iminium catalysis of α-substituted enals.

Experimental Section

To a solution of ethyl 1,2-diazepane-1-carboxylate (**5c**; 1.3 mg, 75 μmol, 10 mol%) in 275 μL MeCN were added 26.5 μM of a stock solution of TfOH (0.283 M, 7.5 μmol, 10 mol%) and mesitylene (internal standard). After 5 min, the mixture was added to neat 2-methylene-4-phenylhex-5-enal (**1a**; 14.0 mg, 0.075 mmol, 1 equiv). The reaction was mixed for 2 min and monitored by ^{1}H NMR spectroscopy for 24 h. The reaction was diluted with EtOAc (2 mL), washed with saturated $NaHCO_3$ (2 mL), extracted with EtOAc (2 × 5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by flash chromatography on silica gel (hexanes/EtOAc 95:5), providing **2a** as an oil (12.6 mg, 0.065 mmol, 90%). IR (film): $\tilde{\nu}$ =3028, 2925, 1689, 964 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.56 (s, 1H), 7.34–7.26 (m, 4H), 7.21 (t, J = 6.9 Hz, 1H), 6.40 (d, J = 15.9 Hz, 1H), 6.30 (s, 1H), 6.18 (dt, J = 15.6, 6.4 Hz, 1H), 6.04 (s, 1H), 2.46–2.36 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.62, 149.28, 137.48, 134.70, 130.74, 129.25, 128.50, 127.04, 125.98, 31.10, 27.65 ppm. HRMS: m/z calcd for $C_{13}H_{14}ONa^+$: 209.0937 $[M+Na]^+$; found: 209.0929.

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Keywords: allylic strain · Cope rearrangements · hydrazides · iminium ions · organocatalysis

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[20] Use of triflic acid alone led to decomposition, and a combination of triethylamine and triflic acid did not result in any catalysis.

[21] DFT calculations at the B3LYP/6-31G* level of theory suggested that the six- and seven-membered-ring iminium ions are about 2.5 and 3.7 kcal mol^{-1} less stable, respectively, than the five-membered ring.

[22] DFT-computed proton affinities: **5a**: 220.3 kcal mol^{-1}; **5b**: 219.5 kcal mol^{-1}; **5c**: 218.9 kcal mol^{-1}; **5d**: 218.4 kcal mol^{-1}.

[23] Note that catalysts **5g** and **5h** afforded the opposite major enantiomer relative to catalysts **5e** and **5f**. The absolute stereochemistry of **2g** was not assigned.

[24] We found that camphor-based sulfonyl hydrazide, CaSH (see H. He, B. J. Pei, H.-H. Chou, T. Tian, W.-H. Chan, A. W. M. Lee, *Org. Lett.* **2008**, *10*, 2421 – 2424), which is effective in Diels – Alder reactions of α-unsubstituted enals, was inactive in the Cope rearrangement.

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