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DyKAT by DiCat: Stereoconvergent Dienamine-Catalyzed Claisen Rearrangements

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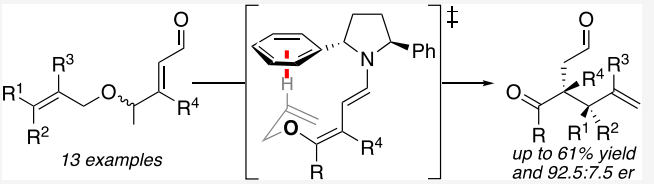
ABSTRACT: This Claisen rearrangement establishes the feasibility of DyKAT of γ-epimeric enals via dienamine formation to afford enantioenriched products. γ-Aryl and -alkyl enals, and exocyclic enals that introduce quaternary centers, are all amenable substrates. Products are readily converted into pyrrolidines or cyclopentenols. Notably, a reactive dienamine intermediate has been isolated from a catalytic reaction, fully characterized, and converted to product upon reexposure to reaction conditions. Product configuration arises from a directing C−H···π interaction in the transition state.

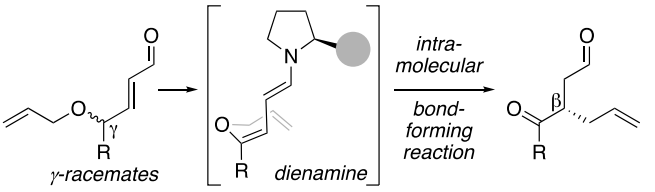


INTRODUCTION

Catalysis via vinylogous enamine and iminium ion intermediates enables direct remote functionalization of aldehydes,[1] which are among the most versatile functional groups in organic chemistry. Despite the tremendous utility of such catalytic reactions, their implementation in synthesis is nowhere near the level of their enamine and iminium ion counterparts.[2] The root of this is the multiple reactive centers on vinylogous intermediates, leading to multiple reaction outcomes and a lack of comprehensive understanding of catalyst control over outcomes, which together have precluded rational design of broadly useful synthetic transformations. Stereochemical outcomes of reactions of dienamine intermediates are rationalized by invoking dienamine conformation, alkene geometry, and/or specific interactions between catalysts and electrophiles.[3] There exists, however, no robust general model for asymmetric induction at remote centers of dienamine intermediates. Moreover, in transformations resulting in moderate product yields or in which multiple stepwise functionalizations occur, the possibility of *no remote stereocontrol* in the γ-functionalization of the dienamine intermediate, but rather racemic products become enantioenriched through resolution, has been explicitly considered by few.[4]

Based on our interest in organocascade kinetic resolution,[5] we sought to test this hypothesis through the lens of new reaction development. The dienamine-catalyzed Claisen rearrangement was thusly conceived (Scheme 1). The substrates for this rearrangement, γ-racemates, represent products of a hypothetical nonstereoselective γ-functionalization of a dienamine intermediate. A stereoconvergent Claisen rearrangement can occur if the dienamine intermediate shown in Scheme 1 is accessible from both enantiomers, either directly or via a dienamine-mediated epimerization. Collectively, and by analogy to what conceivably could occur in stepwise cycloaddition reactions, γ-racemates undergo a dynamic kinetic asymmetric transformation (DyKAT) via dienamine formation and concomitant intramolecular functionalization at a proximal carbon, generating enantiopure products.

Scheme 1. Reaction Design



In addition to providing a platform for evaluating this hypothesis, this transformation would furnish useful molecular scaffolds and be a rare example of an enantioselective sigmatropic rearrangement via enamine or iminium catalysis, or a vinylogous version thereof.[6] Given the ubiquity of enamine and iminium catalysis, it is surprising that sigmatropic rearrangements are not more firmly established in this catalytic repertoire. Organocatalytic asymmetric [3,3]-sigmatropic rearrangements using *N*-heterocyclic carbene,[7] noncovalent hydrogen bonding/Brønsted acidic,[8] and other[9] organocatalysts have emerged. By contrast, there is one isolated

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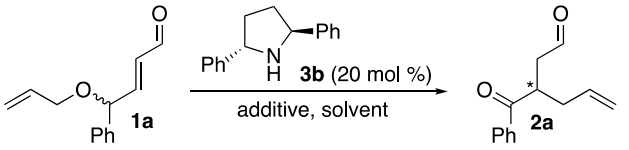
example of an asymmetric [3,3]-sigmatropic rearrangement proceeding via a catalytically generated iminium ion intermediate, in which the product is generated in 54% yield and 47% ee.[10] The few other asymmetric sigmatropic rearrangements via enamine or iminium catalysis include semipinacol rearrangements involving highly strained ring systems[11] and [2,3]-rearrangements.[12]

RESULTS AND DISCUSSION

Initial examination of a number of 2-pyrrolidine, imidazolidinone, and 2,5-diarylpyrrolidine catalysts (Table SI-1) identified **3b** as a promising catalyst for this transformation (Table 1, entry 1).[13] Preliminary control experiments indicated that the Claisen rearrangement was not being promoted by a dienol(ate) species (entry 2), suggesting that catalyst **3b** may be acting via the formation of a dienamine intermediate. While the use of BzOH was intended to enhance amine catalyst activity or possibly accelerate the Claisen rearrangement via hydrogen bonding,[8,14] nontrivial quantities (~10% yield) of allyl benzoate were observed as a byproduct. Thus, about half of the BzOH was being deactivated and, in the process, presumably, the starting material was destroyed. To circumvent this, other Brønsted acids and hydrogen bond donors were evaluated, including substituted benzoic acids, phenols, (bis)thioureas, sulfonimides, inorganic acids, water, chiral diols, and phosphoric acids (Table SI-2).[13] Among these, 4-nitrophenol and a bis-thiourea additive, **(±)-*trans*-4**, available in one step from inexpensive and widely used *trans*-diaminocyclohexane, emerged as the most effective additives for improving product yields with minimal impact on er (entries 3–4). A screen of solvents (Table SI-3) revealed that the yield doubled again in a hydrogen-bonding reaction solvent, with only slight erosion of er (entry 5). Use of **(±)-*trans*-4** additive had no impact on er or on the configuration of the major product enantiomer (entry 6), nor did the use of enantiopure (+)-(1*S*,2*S*)- and (-)-(1*R*,2*R*)-**4** (Table SI-2).[13] Lower temperatures restored the er without compromising reaction yield (entries 7 vs 5). Under these conditions, however, 4-nitrophenol was inferior to **(±)-*trans*-4**, as was the absence of additives altogether (entries 8–9). Further experimentation revealed that superstoichiometric quantities of 4-nitrophenol in toluene were required to provide the product in yields above ~30% (Table SI-5),[13] and overall, the conditions in entry 10 provided comparable results to those of entry 7.

These sets of conditions accommodated significant substrate diversity (Scheme 2), and Claisen products (**2**) were the sole aldehyde products generated. A variety of aryl R groups afforded corresponding products in good er's and moderate yields (**2a–d**). Whereas a strongly activating *para*-substituent led to a complex product mixture (**2e**), *ortho*-substitution hampered reactivity, forming trace product (**2f**). Heteroaromatic R groups were also tolerated (**2g**). Products with quaternary stereocenters (**2h–i**) were generated from cycloalkylidenals. An alkyl substrate furnished the corresponding product (**2j**), albeit in reduced er, possibly due to slightly elevated reaction temperatures. A *trans*-crotyl substrate afforded a product with vicinal stereocenters in a 4:1 dr and with an er of 89.5:10.5 for the major diastereomer (**2k**). A *cis*-crotyl substrate generated the corresponding product with an er of 92.5:7.5 for one diastereomer but without diastereoselectivity (**2l**). A substrate with R^3 = Me provided product (**2m**) in low er (vide infra).

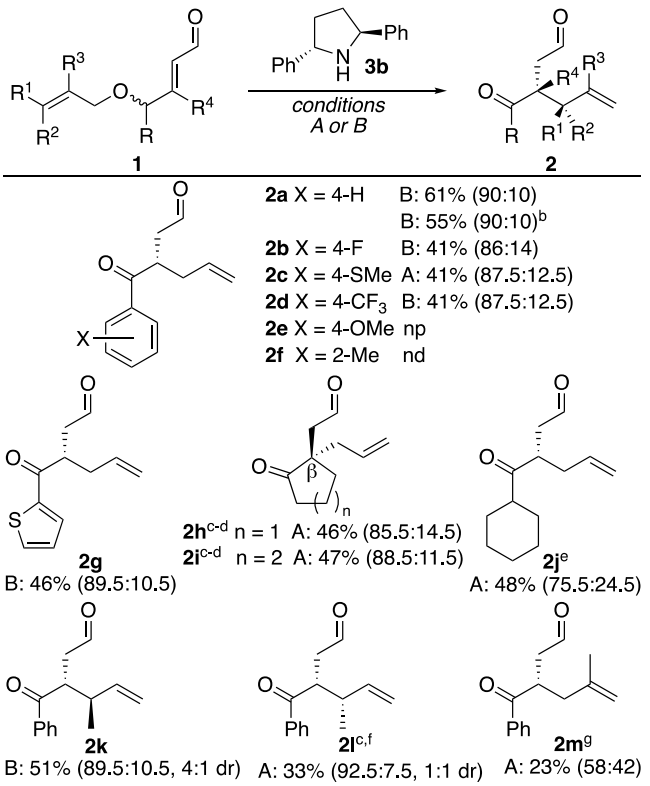
Table 1. Key Reaction Optimizations



entry	additive (20 mol %)	solvent (0.2 M)	temp (°C)	yield (%)[a]	er[b]
1	BzOH	toluene	rt	14	90:10
2[c]	BzOH	toluene	rt	–	–
3	*p*-$NO_2C_6H_4OH$	toluene	rt	23	91.5:8.5
4	**(±)-*trans*-4**	toluene	rt	29	87.5:12.5
5[d]	**(±)-*trans*-4**	TFE	rt	50	85:15
6[d]	–	TFE	rt	62	84:16
7[d]	**(±)-*trans*-4**	TFE	0	50	88.5:11.5
8[d]	–	TFE	0	16[e]	86:14
9	*p*-$NO_2C_6H_4OH$	TFE	0	12	87.5:12.5
10[f]	*p*-$NO_2C_6H_4OH$	toluene	rt	61	90:10

[a]Isolated yield. [b]er determined by chiral phase HPLC. [c]DBU (20 mol %) used instead of **3b**; same results with and without BzOH. [d]reaction time = 48 h. [e]Average of two experiments. [f]*p*-$NO_2C_6H_4OH$ (5 equiv) used.

Scheme 2. Substrate Scope[a]



[a]Conditions: A: **3b** (20 mol %), **(±)-*trans*-4** (20 mol %), CF_3CH_2OH (0.2 M), 0 °C, 24 h; B: **3b** (20 mol %), *p*-$NO_2C_6H_4OH$ (5 equiv), toluene (0.2 M), rt, overnight; yields are isolated yields, and the number in parentheses is er, which was determined by chiral phase HPLC. [b]1 mmol scale. [c]Temp = 35 °C. [d]Yield and er determined after further transformation (see Scheme 3). [e]Temp = 40 °C; time = 5 h; ee determined after derivitization. [f]Time = 6 h. [g]Time = 6 days. np = no product; nd = not determined (i.e., trace).

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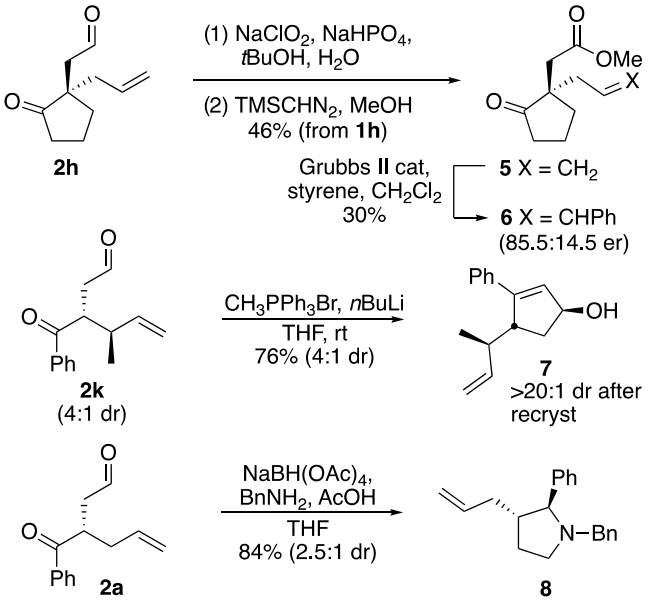
Subsequent elaboration of products helped to establish both their configuration and synthetic utility (Scheme 3). The

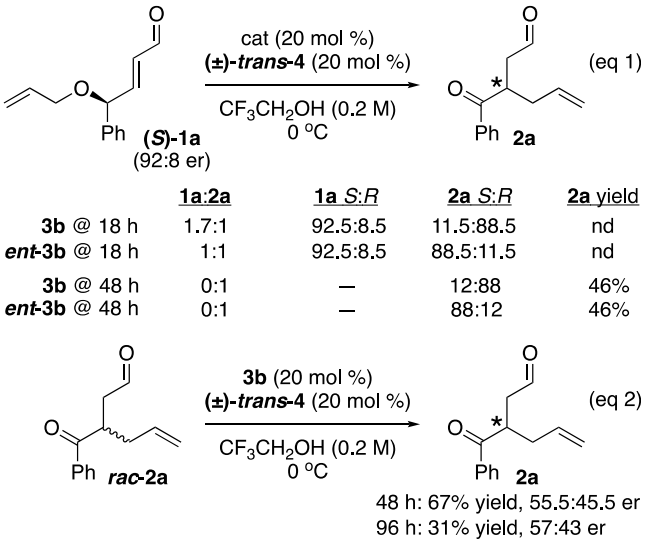
Scheme 3. Elaboration of Products



absolute configuration at the β-stereocenter was determined by transformation of **2h** into ester **5**, an intermediate in the synthesis of the complex alkaloid (−)-isoschizogamine.[15] In this synthesis, the quaternary chiral center in **5** was used to set the remaining three chiral centers in the natural product. A comparison of optical rotation data for **6** against that reported revealed that the *S* configuration had been generated by catalyst **3b** in the Claisen rearrangement. The corresponding stereocenter in all other products (**2**) was assumed by analogy. We were pleasantly surprised when product **2k** was subjected to Wittig olefination conditions and directly produced a cyclopentenol (**7**). This product is presumed to form via the initial addition of the phosphonium ylide to the aldehyde, regeneration of a phosphonium ylide species by proton transfer to the resulting alkoxide, followed by intramolecular olefination of the ketone. The addition of the phosphonium ylide to both the ketone and the aldehyde is seemingly reversible, leading to the exclusive formation of the thermodynamic, 1,3-*trans* product. Cyclopentenol **7** was crystalline, facilitating the configurational assignment of its stereocenters.[16] Reductive amination of **2a** directly generated 2,3-disubstituted pyrrolidine **8** in a ∼3:1 *trans*:*cis* ratio. Relative configuration was determined by NOESY.[13]

Although the starting material was consumed in all reactions, moderate product yields raised the possibility of a kinetic resolution (KR) instead of a DyKAT. To test this, enantioenriched **1a** was synthesized[13] and independently subjected to each enantiomer of catalyst (eq 1, Scheme 4). While there was a rate difference within the initial 18 h, **2a** was obtained in identical isolated yield and equal but opposite enantioselectivities after 48 h (compare to entry 7, Table 1). The recovered **1a** from both reactions after 18 h retained its original enantioenrichment. Additionally, racemic **2a** was resubjected to reaction conditions (eq 2). After 48 h, nearly racemic **2a** was recovered in 67% yield. These results exclude the possibility that enantioenrichment in this reaction arises from a KR of substrates or products.

Scheme 4. Evidence for Dienamine-Catalyzed DyKAT[a]



	1a:2a	1a *S*:*R*	2a *S*:*R*	2a yield
3b @ 18 h	1.7:1	92.5:8.5	11.5:88.5	nd
***ent*-3b** @ 18 h	1:1	92.5:8.5	88.5:11.5	nd
3b @ 48 h	0:1	—	12:88	46%
***ent*-3b** @ 48 h	0:1	—	88:12	46%

[a]**1a**:**2a** determined by relative integrations of corresponding aldehyde peaks in ^{1}H NMR.

Further corroborating the involvement of a dienamine of the type illustrated in Scheme 1, the dienamine was visible by ^{1}H NMR of crude reaction mixtures and could be isolated and fully characterized (Figure 1).[13] The 2,5-disubstitution of the catalyst, which was crucial for stereoselectivity,[13] might facilitate the persistence of the dienamine by hindering reactions at the α- and carbonyl carbons, while geminal disubstitution hampers such reactions at the γ-position. Upon resubjection to CF_3CH_2OH and (±)-***trans*-4** at rt, the isolated dienamine converted to a Claisen product in 70% yield and 83.5:16.5 er (compare to entry 5, Table 1), and the formation of **1d** was not observed. While [2,3]-rearrangement of this dienamine is possible, as occurs with enamine species,[12a,b] there is no evidence of this pathway. NOESY (i.e., C) revealed that the β,γ-olefin of the dienamine is *Z*. This is consistent with the reactivity of cycloalkylidenals **1h**−**i** (Scheme 2), which can form only dienamines with (*Z*)-β,γ-olefins. Notably, while similar chiral dienamine intermediates have been observed in situ by ^{1}H NMR[3,17] and similar dienamine substrates (i.e., dienes for Diels-Alder cycloadditions) have been isolated,[17] to the best of our knowledge, this is the first time a chiral dienamine reactive intermediate has been isolated from a catalytic asymmetric reaction. Collectively, these data suggest that the *E*,*Z*-dienamine required for the Claisen rearrangement can be accessed from both enantiomers of the starting material, confirming the plausibility of DyKAT in dienamine-catalyzed reactions and the mechanism in Scheme 1.

Finally, computations illuminated the stereocontrol. All geometry optimizations were performed at the wB97xd/6-31G(d) level of theory with thermal corrections computed at 0 °C. Single-point solvation energy refinements were performed at the wB97xd/6-311++G(2df,p) using SMD with trifluoroethanol. Conformational searches[18] yielded 16 different transition structures (TSs) for the Claisen of **1h** catalyzed by **3b**. All computations were performed with Gaussian 16[19] and visualized with CYLview.[20] The thiourea cocatalyst was not included, since it did not affect the selectivity.

Chair-like Claisen TSs were more stable than boat-like TSs by >1.7 kcal/mol. The *s-trans* diene was universally more stable

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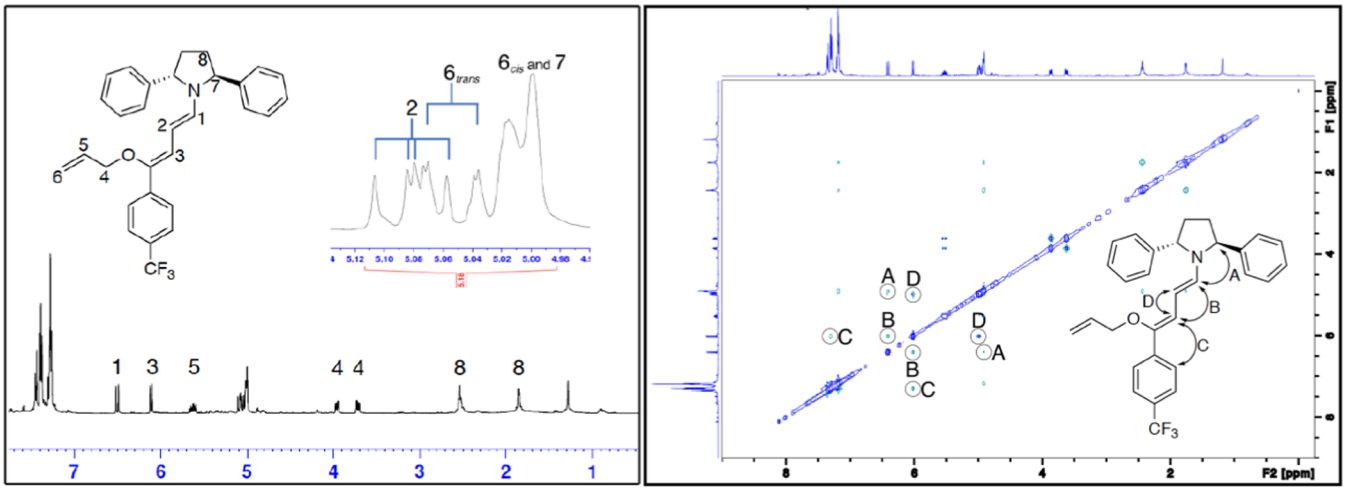

Figure 1. [1]H NMR and NOESY spectra of isolated dienamine intermediate.

than the *s-cis* in the TS by >1.4 kcal/mol. In the favorable ***Syn*-TS**, the allyl is undergoing the Claisen on the same face as the catalyst phenyl with a stabilizing C−H···π interaction between the catalyst phenyl and the central C−H of the allyl (Figure 2).

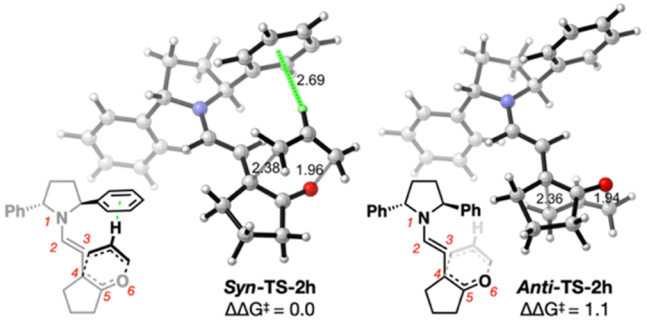

Figure 2. Claisen rearrangement transition structures of **1h** to **2h**. The dienamine atoms 1−6 is 34° off-planarity in the ***Syn*-TS-2h** ($\angle_{1234}$ = 175°, $\angle_{2345}$ = 169°, $\angle_{3456}$ = 18°).

In the disfavored ***Anti*-TS**, the Claisen occurs on the face opposite the catalyst phenyl, and the loss of this interaction raises the energy by 1.1 kcal/mol, matching the experimentally observed 85.5:14.5 er (**2h**, $\Delta G^{\ddagger}$ = 1.0 kcal/mol). Model systems reveal that C−H···π interactions, similar to those in the ***Syn*-TS**, are enthalpically favorable ($\Delta H \sim -1$ to 3 kcal/mol).[13]

To evaluate the magnitude of the C−H···π interaction, a methyl was substituted for the central hydrogen of the allyl to disrupt the C−H···π. The selectivity was noticeably diminished to 0.4 kcal/mol (Figure 3). Indeed, under optimized conditions, related substrate **1m** resulted in 58:42 er, or $\Delta G^{\ddagger}$ = 0.2 kcal/mol, (**2m**, Scheme 2), a reasonable match to the DFT predictions.

Upon closer examination, we discovered that while the addition of a methyl does lead to a reduction in selectivity, this reduction does not stem from disruption of the C−H···π interaction. Indeed, the model systems reveal that methylated allyl can also exhibit stabilizing C−H···π interactions. The origins of the marked decrease in selectivity instead arise from the disruption of the ideal C−H···π distances found in the ***Syn*-TS-2h** by the methyl group in the ***Syn*-TS-2h-methallyl**. The catalyst needs to distort to accommodate the additional space required by the allyl methyl in the ***Syn*-TS-2h-methallyl**, leading to destabilization of the transition structure with respect to the ***Anti*-TS-2h-methallyl** which does not experience such distortions. Indeed, examination of the atoms representative of the dienamine in ***Syn*-TS-2h** is a total of 34° off-planarity, whereas in the ***Syn*-TS-2h-methallyl**, the distortion off-planarity is larger at 43°.

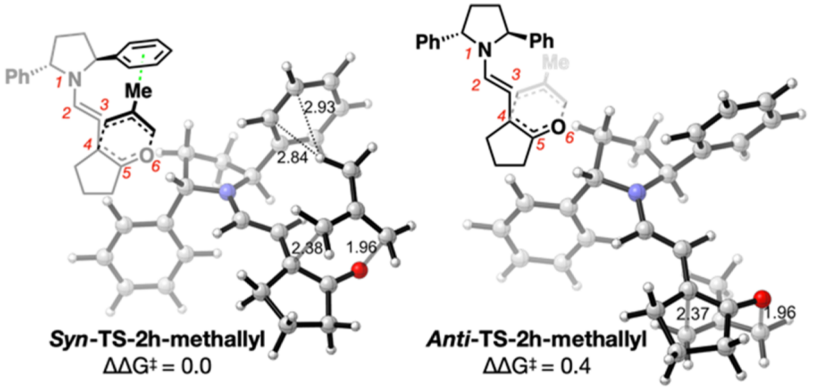

Figure 3. Claisen rearrangement transition structures of methylated analogue **1h-methallyl** to **2h-methallyl**. The dienamine atoms 1−6 is 43° off-planarity in the ***Syn*-TS-2h-methallyl** ($\angle_{1234}$ = 176°, $\angle_{2345}$ = 164°, $\angle_{3456}$ = 23°).

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CONCLUSIONS

In conclusion, we have developed a dienamine-catalyzed enantioconvergent Claisen rearrangement. This transformation tolerates diverse γ-allyloxy enals and can install quaternary chiral centers and thus complex structures should be amenable. Products are converted in one step into pyrrolidines or cyclopentenols. Computations revealed that the transition state stereocontrol arises from a stabilizing C−H···π interaction, suggesting that this mode of asymmetric induction may be operative more so than previously attributed to **3b**[21] and is ripe for harnessing in reaction development. Also of note is that a chiral dienamine intermediate was isolated from a catalytic reaction, fully characterized, and shown to convert to a product upon reexposure to reaction conditions. This, in conjunction with mechanistic studies, supports a DyKAT occurring via this dienamine intermediate, which was the initial hypothesis motivating this research. The ability of dienamine catalysis to generate enantioenriched products from γ-epimeric enals, which in turn can arise from nonstereoselective dienamine-catalyzed γ-functionalizations of enals, has powerful implications for organocascade reaction development and is presently being explored.

EXPERIMENTAL SECTION

General Methods. All NMR data were acquired on a Bruker Avance III HD 500 MHz NMR spectrometer and processed via TopSpin 4.0.9 software. All column chromatography was carried out with F60, 40−63 mm, 60 Å silica gel, and EMD silica 60 F_{254} glass TLC plates. Solvents were dried and kept air-free in a solvent purification unit and were evaporated using a standard rotovapor and high vacuum. Chemicals were used as store-bought unless specified otherwise. All reactions were performed in oven-dried glassware and under an Argon atmosphere unless otherwise stated. Reactions involving lower temperatures were cooled to 0 °C under an ice bath/cold room. Reactions carried out at room temperature were performed at 20−25 °C. Reactions involving higher temperatures were heated in an oil bath using a Corning laboratory stirrer/heat plate. HPLC samples and spectra were analyzed using a Flexar HPLC system with Totalchrom processing software. All mass spectrometry samples and HRMS spectra were acquired via high-resolution electrospray (ESI) technique with Q-TOF mass analyzer by The School of Chemical Sciences Mass Spectrometry Laboratory (MSL) in the University of Illinois at Urbana-Champaign. The specific rotation ($[\alpha]_D^X$) was determined for all characterized chiral compounds using a JASCO P-2000 digital polarimeter. Melting points of all solids were determined using an Electrothermal Mel-Temp melting point apparatus.

Representative Procedures for Claisen Rearrangements. Method A: To a 5 ml round-bottom flask equipped with a stir bar and septum containing enal **1a** (25 mg, 0.12 mmol) were added catalyst **3b** (5.4 mg, 0.024 mmol), (±)-*trans*-**4** (15.8 mg, 0.024 mmol), and TFE (600 μL). The reaction was stirred at °C under an Ar atmosphere until the complete consumption of aldehyde **1a**, as determined by ^{1}H NMR. The reaction mixture was then loaded onto silica gel and purified by flash column chromatography (3% EtOAc/petroleum ether). The pure fractions were collected and reduced under pressure to yield product **2a** (12.1 mg, 50% yield). Racemic samples for HPLC analysis were prepared on the same scale by weighing out and combining identical quantities of catalyst **3b** (2.7 mg, 0.012 mmol) and catalyst ***ent*-3b** (2.7 mg, 0.012 mmol).

Method B: To a 5 ml round-bottom flask equipped with a stir bar and septum containing enal **1a** (25 mg, 0.12 mmol) were added catalyst **3b** (5.4 mg, 0.024 mmol), 4-nitrophenol (83.5 mg, 0.6 mmol), and toluene (600 μL). The reaction was stirred overnight at rt under an Ar atmosphere and then loaded onto silica gel and purified by flash column chromatography (8% EtOAc/petroleum ether). The pure fractions were collected and reduced under pressure to yield product **2a** (15.3 mg, 61% yield).

Method B (1 mmol scale): To a 25 mL round-bottom flask equipped with a stir bar and septum containing enal **1a** (202.25 mg, 1 mmol) were added catalyst **3b** (45 mg, 0.2 mmol), 4-nitrophenol (696 mg, 5 mmol), and toluene (5 mL). The reaction was stirred overnight at rt under an Ar atmosphere and then loaded onto silica gel and purified by flash column chromatography (8% EtOAc/petroleum ether). The pure fractions were collected and reduced under pressure to yield product **2a** (112 mg, 55% yield).

*(S)-3-Benzoylhex-5-enal (**2a**).* Yellow oil. Method A: 12.4 mg, 50% yield (48 h), 88.5:11.5 er. Method B: 15.3 mg, 61% yield, 90:10 er; $[\alpha]_D^{22} = -23.9$ (c = 0.5 in CH_2Cl_2, 88.5:11.5 er); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.98 (dd, J = 8.5, 1.23 Hz, 2H), 7.60−7.57 (m, 1H), 7.50−7.47 (m, 2H), 5.73−5.65 (m, 1H), 5.07 (s, 1H), 5.05−5.03 (m, 1 H), 4.03 (m, 1H), 3.14 (dd, J = 18.9, 8.8 Hz, 1H), 2.69 (dd, J = 18.8, 4.5 Hz, 1H), 2.52−2.47 (m, 1H), 2.22 (dt, J = 14.8, 10 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 201.6, 200.4, 136.1, 134.3, 133.2, 128.8, 128.5, 118.0, 44.8, 39.8, 36.3. HPLC with an AS-H column (*n*-hexane/*i*-PrOH= 99:1 at 1.0 mL/min for 40 min); major enantiomer t_R = 16.49 min, minor enantiomer t_R = 15.76 min; HRMS (ESI) m/z $[M + H]^+$ calcd for $[C_{13}H_{15}O_2]$ 203.1068, found 203.1072.

*(S)-3-(4-Fluorobenzoyl)hex-5-enal (**2b**).* Purified by column chromatography (petroleum ether/ EtOAc 97:3) and isolated as a pale yellow oil. Method A: 7 mg, 26% yield (96 h), 85.5:14.5 er. Method B: 11 mg, 41% yield, 86:14 er; $[\alpha]_D^{22} = -19.0$ (c = 0.6 in CH_2Cl_2, 85.5:14.5 er); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.01 (dd, J = 8.7, 5.5 Hz, 2H), 7.17−7.14 (m, 2H), 5.72−5.64 (m, 1H), 5.07 (s, 1H), 5.04 (d, J = 5.8 Hz, 1H), 4.01−3.96 (m, 1 H), 3.15 (dd, J = 18.8, 9.1 Hz, 1H), 2.70 (dd, J = 18.9, 4.1 Hz, 1H), 2.48−2.44 (m, 1H), 2.24−2.18 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 200.4, 200.1, 166.9, 164.8, 134.1, 132.6, 132.5, 131.2, 131.1, 118.2, 116.0, 115.8, 45.0, 39.7, 36.4. HPLC with an AS-H column (*n*-hexane/*i*-PrOH= 99:1 at 1.0 mL/min for 40 min); major enantiomer t_R = 16.42 min, minor enantiomer t_R = 18.08 min; HRMS (ESI) m/z $[M + H]^+$ calcd for $[C_{13}H_{14}FO_2]$ 221.0975, found 221.0978.

*(S)-3-(4-(Methylthio)benzoyl)hex-5-enal (**2c**).* Purified by column chromatography (petroleum ether/EtOAc 97:3) and isolated as a pale yellow oil. Method A: 12.3 mg, 41% yield, 87.5:12.5 er; $[\alpha]_D^{22} = -25.9$ (c = 0.08 in CH_2Cl_2, 87.5:12.5 er); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.81 (s, 1H), 7.93 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 5.71 (ddd, J = 17.2, 14.2, 7.6 Hz, 1H), 5.09−5.08 (d, J = 12.6 Hz, 2H), 4.01 (tt, J = 8.9, 4.9 Hz, 1H), 3.16 (dd, J = 18.6, 8.8 Hz, 1H), 2.70 (dd, J = 18.6, 4.4 Hz, 1H), 2.56 (s, 3H), 2.50 (dt, J = 12.9, 6.2 Hz, 1H), 2.24 (dt, J = 14.9, 7.9 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 202.1, 194.9, 140.7, 135.5, 132.5, 129.2, 128.2, 119.0, 47.0, 42.0 38.1, 17.1. HPLC with an AS-H column (*n*-hexane/*i*-PrOH= 99:1 at 1.0 mL/min for 40 min); major enantiomer t_R = 24.11, minor enantiomer t_R = 20.86; HRMS (ESI) m/z $[M + H]^+$ calcd for $[C_{14}H_{17}O_2S]$ 249.0949, found 249.0943.

*(S)-3-(4-(Trifluoromethyl)benzoyl)hex-5-enal (**2d**).* Purified by column chromatography (petroleum ether/EtOAc 97:3) and isolated as a yellow oil. Method A: 11.2 mg, 32% yield (48 h), 86.5:13.5 er. Method B: 14 mg, 41% yield, 87.5:12.5 er; $[\alpha]_D^{22} = -21.4$ (c = 0.11 In CH_2Cl_2, 86.5:13.5 er); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.10 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 8.1 Hz, 2H), 5.74−5.63 (m, 1H), 5.11−5.04 (m, 2H), 4.02 (tdd, J = 9.4, 4.7, 2.7 Hz, 1H), 3.22 (dd, J = 19.0, 9.3 Hz, 1H), 2.77 (dd, J = 19.0, 4.0 Hz, 1H), 2.52−2.43 (m, 1H), 2.28−2.17 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 200.9, 200.1, 171.2, 139.1, 133.8, 128.7, 125.8, 125.8, 118.4, 60.4, 45.0, 40.0, 36.1. HPLC with an AS-H column (*n*-hexane/*i*-PrOH= 99:1 at 1.0 mL/min for 40 min); major enantiomer t_R = 12.19, minor enantiomer t_R = 11.4; HRMS (ESI) m/z $[M + H]^+$ calcd for $[C_{14}H_{14}F_3O_2]$ 271.0946, found 271.0938.

*(S)-3-(Thiophene-2-carbonyl)hex-5-enal (**2g**).* Purified by column chromatography (petroleum ether/EtOAc 97:3) and isolated as a yellow oil. Method A: 13.3 mg, 38% yield (48 h), 11.5:88.5 er (***ent*-3b** used). Method B: 16.1 mg, 46% yield, 89.5:10.5 er; $[\alpha]_D^{22} = +9.5$ (c = 0.1 in CH_2Cl_2, 11.5:88.5 er); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (s,

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1H), 7.74 (dd, J = 3.8, 1.1 Hz, 1H), 7.60 (dd, J = 5.0, 1.1 Hz, 1H), 7.09 (dd, J = 4.9, 3.8 Hz, 1H), 5.65 (ddt, J = 17.1, 10.1, 7.1 Hz, 1H), 5.07−4.97 (m, 2H), 3.77 (ddd, J = 13.5, 8.5, 5.1 Hz, 1H), 3.05 (dd, J = 18.7, 8.8 Hz, 1H), 2.62 (dd, J = 18.7, 4.5 Hz, 1H), 2.47 (dt, J = 14.1, 6.2 Hz, 1H), 2.22 (dt, J = 14.8, 7.7 Hz, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 200.1, 194.2, 143.3, 134.2, 134.1, 132.3, 128.2, 118.1, 44.9, 41.5, 36.9. HPLC with an AS-H column (*n*-hexane/*i*-PrOH= 99:1 at 0.8 mL/min for 50 min); major enantiomer t_R = 30.26, minor enantiomer t_R = 32.81; HRMS (ESI) m/z $[M + H]^+$ calcd for $[C_{11}H_{13}O_2S]$ 209.0636, found 209.0627.

*(S)-3-(Cyclohexanecarbonyl)hex-5-enal (**2j**).* Purified by column chromatography (petroleum ether/EtOAc 97:3) and isolated as a clear oil. Method A: 16.8 mg, 48% yield; ^1H NMR (500 MHz, $CDCl_3$) δ 9.72 (s, 1H), 5.72−5.60 (m, 1H), 5.10−5.03 (m, 2H), 3.25 (dq, J = 9.1, 4.6 Hz, 1H), 2.93 (dd, J = 18.5, 9.2 Hz, 1H), 2.58 (d, J = 7.8 Hz, 1H), 2.48 (dd, J = 18.5, 4.2 Hz, 1H), 2.43−2.34 (m, 1H), 2.16−2.05 (m, 1H), 1.85−1.69 (m, 3H), 1.31−1.20 (m, 4H);$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 214.6, 200.5, 134.5, 117.9, 49.8, 44.2, 43.3, 35.4, 29.2, 27.9, 25.9, 25.8, 25.4. HRMS (ESI) m/z $[M + H]^+$ calcd for $[C_{13}H_{21}O_2]$ 209.1542, found 209.1540.

*(3R,4R)-3-Benzoyl-4-methylhex-5-enal (**2k**).* Purified by column chromatography (petroleum ether/EtOAc 97:3) and isolated as a pale yellow oil. Method A: 14 mg, 40% yield (24 h), 4:1 dr, 86.5:13.5 er (92.5:7.5 *minor*). Method B: 18 mg, 51% yield, 4:1 dr, 89.5:10.5 er (82.5:17.5 *minor*); $[\alpha]_D^{22}$ = −44.6 (c = 0.8 in CH_2Cl_2, 86.5:13.5 er); ^1H NMR (500 MHz $CDCl_3$) δ 9.82 (s, 1H)*, 9.78 (s, 1H), 8.05−7.98 (m, 3H), 7.63−7.57 (m, 1H), 7.51 (t, J = 7.6 Hz, 3H), 5.83 (ddd, J = 17.0, 10.0, 6.4 Hz, 1H)*, 5.61 (ddd, J = 16.7, 10.3, 8.2 Hz, 1H), 5.11−4.96 (m, 3H), 4.08 (dt, J = 10.1, 3.7 Hz, 1H)*, 3.94 (ddd, J = 10.1, 6.9, 3.7 Hz, 1H), 3.24 (dd, J = 18.7, 10.2 Hz, 1H)*, 3.14 (dd, J = 18.8, 9.5 Hz, 1H), 2.73 (dd, J = 18.8, 3.6 Hz, 1H), 2.66−2.55 (m, 1H), 1.04 (d, J = 6.8 Hz, 3H), 0.92 (dd, J = 7.0, 1.6 Hz, 3H)* (*denotes diastereomer);$^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 202.4, 200.7, 139.9, 137.3, 133.1, 133.1, 128.7, 128.4, 115.9, 115.0, 44.8, 44.3, 43.8, 40.2, 38.2, 19.4. 18.6. HPLC with an AS-H column (*n*-hexane/*i*-PrOH= 99.5:0.5 at 1.0 mL/min for 40 min); major enantiomer t_R = 12.74, minor enantiomer t_R = 14.18; HRMS (ESI) m/z $[M + H]^+$ calcd for $[C_{14}H_{17}O_2]$ 217.1229, found 217.1224.

*(3R,4S)-3-Benzoyl-4-methylhex-5-enal (**2l**).* Purified by column chromatography (petroleum ether/EtOAc 97:3) and isolated as a pale yellow oil. Method A: 11.5 mg, 33% yield, 1:1 dr, 92.5:7.5 er (86.5:13.5 *minor*). $[\alpha]_D^{22}$ = −7.54 (c = 0.2 in CH_2Cl_2, 92.5:7.5 er); ^1H NMR (500 MHz $CDCl_3$) δ 9.73 (s, 1H), 9.69 (s, 1H)*, 7.94 (t, J = 8.4 Hz, 4H), 7.51−7.49 (m, 2H), 7.43 (t, J = 7.7 Hz, 4H), 5.78 (ddd, J = 17.1, 10.0, 6.4 Hz, 1H), 5.52 (ddd, J = 16.9, 10.3, 8.2 Hz, 1H)*, 5.00−4.89 (m, 4H), 4.00 (dt, J = 10.2, 3.7 Hz, 1H), 3.86 (ddd, J = 10.1, 6.9, 3.6 Hz, 1H)*, 3.18 (dd, J = 18.6, 10.2 Hz, 1H), 3.12 (dd, J = 18.8, 9.5 Hz, 1H)*, 2.65 (dd, J = 18.7, 3.8 Hz, 2H), 2.52−2.47 (m, 2H), 0.96 (d, J = 6.8 Hz, 3H)*, 0.83 (d, J = 6.9 Hz, 3H) (*denotes diastereomer); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 202.3, 201.3, 200.7, 200.6, 140.6, 139.9, 137.3, 136.7, 133.1, 133.0, 128.7, 128.7, 128.4, 128.4, 115.9, 115.0, 44.7, 44.3, 43.8, 41.2, 40.2, 38.2, 18.6, 14.4. HPLC with an AS-H column (*n*-hexane/*i*-PrOH= 99.5:0.5 at 1.0 mL/min for 40 min); major enantiomer t_R = 12.59, minor enantiomer t_R = 14.06; HRMS (ESI) m/z $[M + H]^+$ calcd for $[C_{14}H_{17}O_2]$ 217.1229, found 217.1223.

*(S)-3-Benzoyl-5-methylhex-5-enal (**2m**).* Purified by column chromatography (petroleum ether/EtOAc 97:3) and isolated as a colorless oil. Method A: 18.4 mg, 23% yield, 58:42 er; $[\alpha]_D^{22}$ = −13.0 (c = 0.1 in CH_2Cl_2, 58:42 er); ^1H NMR (500 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.99 (d, J = 8 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.8 Hz, 3H), 4.83 (s, 1H), 4.75 (s, 1H), 4.16−4.10 (m, 1 H), 3.12 (dd, J = 18.7, 9.0 Hz, 1H), 2.68 (dd, J = 18.7, 3.9 Hz, 1H), 2.45 (dd, J = 14.1, 4.5 Hz, 1H), 2.08 (dd, J = 14.0, 9.9 Hz, 1H), 1.75 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 202.0, 200.5, 198.6, 141.8, 133.2, 128.8, 128.4, 113.7, 44.8, 40.4, 38.4, 22.1. HPLC with an AS-H column (*n*-hexane/*i*-PrOH= 99:1 at 1.0 mL/min for 40 min); major enantiomer t_R = 13.45 min, minor enantiomer t_R = 11.5 min; HRMS (ESI) m/z $[M + H]^+$ calcd for $[C_{14}H_{17}O_2]$ 217.1225, found 217.1229.

Preparation of (*S,E*)-Methyl 2-(1-cinnamyl-2-oxocyclopentyl)acetate (6). Product **2h** was inseparable from (±)-***trans*-4** and required further modification to obtain yield, er data, and establish its absolute configuration. To a solution of **2h** (37.2 mg) in *t*-BuOH (5 mL) were added $NaClO_2$ (124 mg, 0.90 mmol), $NaHPO_4$ (124 mg, 0.90 mmol), and H_2O (2.5 mL). The reaction was stirred at rt overnight until complete consumption of starting aldehyde was observed by ^1H NMR. The reaction was diluted with brine (3.0 mL) and extracted with EtOAc (3 × 7.5 mL), then dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude acid, which was used directly in the next step.

To a solution of the crude acid dissolved in anhydrous MeOH (1 mL), which had been cooled to 0 °C, was added $TMSCHN_2$ (460 μL, 0.92 mmol) dropwise until a yellow color persisted. The reaction was warmed to rt and stirred overnight. The crude reaction was poured into a separatory funnel containing brine, which was then extracted with EtOAc (3 × 7.5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Crude methyl ester **5** was flashed through a silica plug (10% EtOAc/petroleum ether) to obtain 10.1 mg (46% yield from **1h**) of a colorless oil.

6 was prepared from **5** using a known procedure,[15] and the characterization was in agreement with the experimental data.[15] Compound **6** was purified by column chromatography (petroleum ether/ EtOAc 5:1) and isolated as a colorless oil (4.9 mg, 30% yield from **5**); $[\alpha]_D^{22}$ = −21.2 (c = 0.11 in CH_2Cl_2, 85.5:14.5 er); Literature $[\alpha]_D^{22}$ = +40.0 (c = 1.0 in $CHCl_3$, 8.5:91.5 er);[15] ^1H NMR (500 MHz, $CDCl_3$): δ 7.28−7.22 (m, 4H), 7.17−7.14 (m, 1H), 6.6 (d, J = 15.7 Hz, 1H), 6.01 (dt, J = 15.5, 7.6 Hz, 1H), 3.56 (s, 3H), 2.65, 2.45 (ABq, J = 16.4 Hz, 1H × 2), 2.41−2.35 (m, 1H), 2.30−2.17 (m, 3H), 2.01−1.89 (m, 3H), 1.86−1.77 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 221.4, 171.9, 137.0, 134.2, 128.6, 127.5, 126.2, 124.2, 51.6, 50.0, 39.9, 39.3, 37.6, 32.2, 18.8. HPLC with an AS-H column (*n*-hexane/*i*-PrOH= 99.5:0.5 at 1.0 mL/min for 40 min); major enantiomer t_R = 16.98 min, minor enantiomer t_R = 24.32 min; HRMS m/z (ESI) $[M + Na]^+$ calcd for $[C_{17}H_{20}O_3Na]$ 295.1305, found 295.1302.

Modification of 2i for Chiral Phase HPLC Analysis to Form (*S,E*)-Methyl 2-(1-Cinnamyl-2-oxocyclohexyl)acetate. Product **2i** was inseparable from (±)-***trans*-4** and required further modification to obtain yield and er data. Product **2i** was subjected to the same three-step sequence described above for the preparation of **6** from **2h**. The corresponding derivative of **2i** was purified by column chromatography (petroleum ether/ EtOAc 5:1) and isolated as colorless oil (9.5 mg, 37% yield from methyl ester precursor; methyl ester precursor generated in 22 mg, 47% yield from **1i**); $[\alpha]_D^{22}$ = −39.3 (c = 0.15 in CH_2Cl_2, 88.5:11.5 er); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.17 (m, 5H), 6.43 (d, J = 15.7 Hz, 1H), 6.04 (dt, J = 15.5, 7.6 Hz, 1H), 3.63 (s, 3H), 2.72 (d, J = 16.0 Hz, 1H), 2.59 (dd, J = 7.3, 1.4 Hz, 1H), 2.55−2.41 (m, 4H), 2.06−1.94 (m, 1H), 1.95−1.75 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 212.9, 172.2, 137.0, 133.9, 128.5, 128.5, 127.4, 126.2, 124.2, 51.4, 50.9, 39.6, 39.0, 39.0, 35.7, 26.5, 21.0. HPLC with an OD-H column (*n*-hexane/*i*-PrOH= 90:10 at 1.0 mL/min for 40 min); major enantiomer t_R = 9.72 min, minor enantiomer t_R = 14.23 min; HRMS m/z (ESI) $[M + H]^+$ calcd for $[C_{18}H_{23}O_3]$ 287.1647, found 287.1641.

Modification of 2j for Chiral Phase HPLC Analysis to Form (*S,E*)-3-(Cyclohexanecarbonyl)-6-phenylhex-5-enal. To a solution **2j** (29.3 mg, 0.14 mmol, 1 equiv) and styrene (32 μL, 0.28 mmol, 2 equiv) in dry CH_2Cl_2 (7.2 mL) was added Grubbs 2nd generation catalyst (8.5 mg, 0.01 mmol, 0.1 equiv) under an Ar atmosphere. The reaction mixture was stirred at rt overnight. The solvent was then concentrated in *vacuo*, and the crude mixture was subjected to flash chromatography (10% EtOAc/petroleum ether) to afford the derivative of **2j** as a colorless oil (18.5 mg, 86% yield); $[\alpha]_D^{22}$ = −26.4 (c = 0.5 in CH_2Cl_2, 75.5:24.5 er); ^1H NMR (500 MHz, $CDCl_3$): δ 9.65 (s, 1H), 7.25−7.23 (m, 4H), 7.17−7.16 (m, 1H), 6.36 (dd, J = 15.9, 1.6 Hz, 1H), 6.00 (dt, J = 15.3, 7.4 Hz, 1H), 3.28 (tt, J = 9.0, 4.7 Hz, 1H), 2.93 (dd, J = 18.6, 9.1 Hz, 1H), 2.44−2.46 (m, 3H), 2.23 (dtd, J = 14.1, 8.0, 1.3 Hz, 1H), 1.94−1.93 (m, 1H), 1.72−1.70 (m, 4H), 1.62−1.60 (m, 1H), 1.26−1.20 (m, 5H), 1.43−1.17 (m,

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1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 214.7, 200.5, 136.8, 133.0, 128.6, 127.5, 126.1, 126.0, 50.0, 44.4, 43.7, 34.8, 27.9, 25.9, 25.8, 25.5. HPLC with an AS-H column (*n*-hexane/*i*-PrOH= 97:3 at 1.0 mL/min for 20 min); major enantiomer t_R = 9.42 min, minor enantiomer t_R = 10.24 min; HRMS *m/z* (ESI) $[M + Na]^+$ calcd. for $[C_{19}H_{24}O_2Na]$ 307.1674 found 307.1670.

Preparation of (1*S*,4*R*)-4-((*R*)-but-3-en-2-yl)-3-phenylcyclopent-2-en-1-ol (7). To an oven-dried Schlenk flask were added methyltriphenylphosphonium bromide (64 mg, 0.18 mmol) and dry THF (1 mL). The reaction was cooled to 0 °C, and *n*-BuLi (0.113 mL, 1.6 M in hexanes, 0.18 mmol) was added dropwise. The mixture was stirred for 20 min, and then a solution of the aldehyde **2k** (32 mg, 0.15 mmol, a 4:1 diastereomeric mixture) in THF (1 mL) was added slowly. Additional THF (0.3 mL) was taken up in the syringe and transferred to the reaction flask, and the reaction was stirred for 3 h at 0 °C. The reaction was quenched with saturated aq NH_4Cl, diluted with H_2O, and extracted with CH_2Cl_2 (×3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography (20% EtOAc/hexanes) to afford **7** as a white crystalline solid (24 mg, 76% yield, 4:1 dr). Clear needle-shaped crystals were obtained via vacuum sublimation (>20:1 dr). mp: 94−95 °C; $[\alpha]_D^{22}$ = −43.8 (*c* = 0.48 in CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.47−7.40 (m, 2H), 7.40−7.33 (m, 2H), 7.33−7.27 (m, 1H), 6.11 (t, *J* = 1.8 Hz, 1H)*, 6.07 (t, *J* = 1.8 Hz, 1H), 5.96−5.76 (m, 1H)*, 5.56 (ddd, *J* = 17.1, 10.5, 6.3 Hz, 1H), 5.07−4.98 (m, 3H)*, 4.94 (dt, *J* = 10.6, 1.6 Hz, 2H), 4.80 (dt, *J* = 17.3, 1.7 Hz, 2H), 3.62 (dd, *J* = 7.0, 3.7 Hz, 1H)*, 3.56−3.40 (m, 1H), 2.53 (ddt, *J* = 6.7, 3.6, 1.7 Hz, 1H), 2.29 (ddd, *J* = 14.0, 7.5, 3.3 Hz, 1H), 1.85 (ddd, *J* = 14.0, 8.6, 4.5 Hz, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.70 (d, *J* = 6.9 Hz, 3H)* (*denotes diastereomer); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 149.0, 143.2, 138.9, 135.7, 130.1, 129.8, 128.5, 128.4, 127.9, 127.8, 126.6, 126.6, 114.9, 113.2, 49.8, 48.5, 37.4, 37.3, 36.0, 35.9, 18.0, 12.2. HRMS (ESI) *m/z* $[M]^+$ calcd for $[C_{15}H_{18}O]$ 214.1358, found 214.1354.

Preparation of 3-Allyl-1-benzyl-2-phenylpyrrolidine (8). To a solution of **2a** (80 mg, 0.40 mmol) in THF (6.5 mL) at 0 °C were added $NaBH(OAc)_3$ (258 mg, 1.2 mmol), benzylamine (66.5 μL, 0.61 mmol), and AcOH (22.61 μL, 0.4 mmol). After stirring for 1 h at 0 °C and 16 h at rt, the reaction was quenched with aqueous $NaHCO_3$ and extracted with EtOAc (x3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a residue, which was purified by preparative thin layer chromatography (15% EtOAc/hexane) to yield the *trans*- and *cis*-product diastereomers as colorless oils. (2*S*,3*S*)-3-allyl-1-benzyl-2-phenylpyrrolidine (***trans*-8**): 66.5 mg, 60% yield; $[\alpha]_D^{22}$ = 1.0 (*c* = 0.1 in CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.3 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.34−7.29 (m, 4H), 7.24 (dd, *J* = 5.9, 2.2 Hz, 1H), 5.76−5.68 (m, 1H), 5.01 (d, *J* = 17.1 Hz, 1H), 4.97 (d, *J* = 10.1 Hz, 1H), 3.81 (d, *J* = 7.2 Hz, 1H), 3.14−3.08 (m, 1H), 3.03−2.99 (m, 2H), 2.29−2.24 (m, 2H), 2.13−1.98 (m, 3H), 1.67−1.52 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 142.7, 139.7, 137.1, 128.7,128.4, 128.1, 128.1, 127.2, 126.7, 115.7, 75.7, 58.2, 52.1, 47.2, 37.4, 28.5. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $[C_{20}H_{24}N]$ 278.1909, found 278.1908. (2*R*,3*S*)-3-allyl-1-benzyl-2-phenylpyrrolidine (***cis*-8**): 26.6 mg, 24% yield; $[\alpha]_D^{22}$ = −1.0 (*c* = 0.11 in CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.37−7.30 (m, 6H), 7.27−7.24 (m, 2H), 5.62−5.54 (m, 1H), 4.88 (ddd, *J* = 6.6, 4.0, 1.5 Hz, 1H), 4.86 (t, *J* = 1.3, 1H), 3.94 (d, *J* = 13.3 Hz, 1H), 3.70 (d, *J* = 8.5 Hz, 1H), 3.13− 3.07 (m, 2H), 2.39−2.31 (m, 1H), 2.24 (td, *J* = 9.4, 9.3 Hz, 1H), 2.00−1.94 (m, 1H), 1.69−1.59 (m, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 141.0, 137.9, 128.7, 128.6, 128.1, 128.0, 126.8, 126.6, 115.2, 71.9, 58.5, 52.5, 42.1, 37.3, 29.9. HRMS (ESI) *m/z* $[M + H]^+$ calcd for $[C_{20}H_{24}N]$ 278.1909, found 278.1908.

Preparation and Isolation of Corresponding Dienamine of 1d, (2*S*,5*S*)-1-((1*E*,3*Z*)-4-(allyloxy)-4-(4-(trifluoromethyl)-phenyl)buta-1,3-dien-1-yl)-2,5-diphenylpyrrolidine. The dienamine was isolated from standard Method A conditions. To a 5 ml round-bottom flask equipped with a stir bar and septum containing enal **1d** (35 mg, 0.13 mmol) were added catalyst **3b** (5.8 mg, 0.026 mmol), (±)-***trans*-4** (17 mg, 0.026 mmol), and TFE (650 μL). After 48 h of stirring at °C under an Ar atmosphere, the crude reaction mixture was loaded directly onto a column and purified by column chromatography (petroleum ether/EtOAc 97:3). The dienamine was isolated as a yellow oil (7 mg, 100% yield). $[\alpha]_D^{22}$ = −11.4 (*c* = 0.12 in CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.5 Hz, 2H), 7.33−7.26 (m, 6H), 7.28−7.08 (m, 6H), 6.41 (d, *J* = 13.6 Hz, 1H), 6.02 (d, *J* = 11.0 Hz, 1H), 5.58−5.47 (m, 1H), 5.03−4.88 (m, 5H), 3.90−3.82 (m, 1H), 3.62 (ddt, *J* = 12.4, 6.1, 1.4 Hz, 1H), 2.50−2.41 (m, 2H), 1.89−1.70 (m, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 161.9, 143.8, 140.4, 137.5, 134.1, 128.6, 127.1, 126.2, 125.1, 123.4, 118.4, 117.0, 97.5, 71.8, 33.1. HRMS (ESI) *m/z* $[M]^+$ calcd for $[C_{30}H_{28}F_3NO]$ 475.2123, found 475.2121.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c01079.

Full details of reaction optimization, preparation of enal substrates and characterization data, and copies of ^1H, $^{13}C\{^1H\}$, COSY, NOESY, and HPLC spectra (PDF)

Full computational details (PDF)

Accession Codes

CCDC 2128632 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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