Molecules 2016, 21, 713; doi:10.3390/molecules21060713 www.mdpi.com/journal/molecules

Communication
Organocatalyzed Intramolecular Carbonyl-Ene Reactions

Heidi A. Dahlmann, Amanda J. McKinney, Maria P. Santos and Lindsey O. Davis *
Department of Chemistry and Biochemistry, Berry College, P.O. Box 495016, Mt. Berry, GA 30149, USA; hdahlmann@berry.edu (H.A.D.); amanda.mckinney@vikings.berry.edu (A.J.M.); maria.santos@vikings.berry.edu (M.P.S.)
* Correspondence: ldavis@berry.edu; Tel.: +1-706-236-2237
Academic Editor: Raquel P. Herrera
Received: 2 May 2016; Accepted: 27 May 2016; Published: 31 May 2016

Abstract: An organocatalyzed intramolecular carbonyl-ene reaction was developed to produce carbocyclic and heterocyclic 5- and 6-membered rings from a citronellal-derived trifluoroketone and a variety of aldehydes. A phosphoramidite derivative was found to promote the cyclization of the trifluoroketone, whereas a less acidic phosphoric acid proved to be a superior catalyst for the aldehyde substrates.

Keywords: organocatalysis; carbonyl-ene; phosphoric acid; N-triflylphosphoramide

1. Introduction

The carbonyl-ene reaction is a well-studied transformation in organic chemistry, as it affords an atom-economical method for synthesizing homoallylic alcohols [1]. Traditionally, Lewis acids have been used to catalyze this reaction [2,3], but organocatalysis has recently emerged as a powerful means for facilitating many organic transformations [4–6], including carbonyl-ene reactions. Clarke and co-workers developed the first organocatalyzed carbonyl-ene reaction using the Schreiner catalyst [7], a thiourea derivative [8]. An asymmetric variant was then developed by Rueping et al. using a chiral N-triflylphosphoramide [9]. The reaction yielded α-hydroxyesters in good yield and enantioselectivity, but the scope was limited to intermolecular reactions and required the use of an activated enophile. Recently, List and co-workers reported an intramolecular carbonyl-ene cyclization to afford pyrrolidines, tetrahydrofurans, and cyclopentanes using a chiral imidodiphosphate catalyst [10]. While this report serves as a hallmark for Brønsted-acid-catalyzed intramolecular carbonyl-ene reactions, the scope was limited to the formation of the kinetically-favored five-membered rings [11]. The majority of these products were pyrrolidines derived from N-tosylated aminoaldehyde, the parent molecule which was known to spontaneously undergo intramolecular carbonyl-ene cyclization [12], while less activated substrates required up to 11 days to reach completion. Noting the utility of this reaction, but also the limitations of current reports, we set out to develop a Brønsted-acid-catalyzed intramolecular carbonyl-ene reaction with a complementary substrate scope and faster reaction times. Herein, we describe organocatalyzed intramolecular carbonyl-ene reactions that produced carbocyclic and heterocyclic 5- and 6-membered rings.

2. Results and Discussion

We began our investigation by screening a variety of Brønsted acids for their ability to cyclize citronellal-derived trifluoromethylketone 1 (Table 1), selecting this activated substrate based on previous reports of trifluoropyruvate derivatives serving as carbonyl-acceptors in intermolecular carbonyl-ene reactions [8,9]. Simple Brønsted acid catalysts such as H3PO4 and HCl were unable to catalyze the reaction at an acceptable rate, producing little to no product within 24 h (Table 1, Entries 1
and 2) [13]. Similarly, the phosphoric acid derivative diphenyl phosphate (Figure 1, 3a), induced very slow conversion of substrate, resulting in a low yield of ene product (Table 1, Entry 3). In contrast, the more acidic N-triflyl phosphoric amide 3b (Figure 1) catalyzed the reaction at a significantly higher rate, resulting in complete conversion and good yields in as few as 7 h (Table 1, Entries 4 and 8) [14]. Notably, we were able to decrease the catalyst loading from 0.5 to 0.2 equivalents without a significant loss in yield (Table 1, Entries 4 and 5). Decreasing the concentration of the reaction resulted in a longer reaction time with a small drop in yield (Table 1, Entries 6 and 7).

Concurrently, we screened Brønsted acids for their ability to catalyze the cyclization of citronellal (4a). While citronellal is less activated than the corresponding trifluoromethyl ketone, it serves as the prototypical substrate for a Type I carbonyl-ene cyclization, as it is commercially available [15–17]. Surprisingly, the use of phosphoramidate 3b resulted in the isolation of a complex mixture of products with only a trace yield of ene product 5a and no starting material recovery (Table 2, Entry 1). Diethyl phosphate (3c) successfully promoted the reaction, albeit slowly, resulting in a low yield and a 77% recovery of starting material after 24 h (Table 2, Entry 2). We were pleased to find a significant increase in reaction rate and yield after 24 h when phosphoric acid derivative 3a was used as a catalyst. Under these mild reaction conditions [18], isopulegol (5a) was the primary diastereomer isolated from the reaction mixture in addition to a small amount of neoisopulegol (5a'), typically in a 2:1 ratio (Entries 3–5). A similar yield of product 5a was obtained when only 0.06 equivalents of catalyst were used at a higher concentration (0.5 M) compared to 0.5 equivalents at 0.1 M, but a decreased selectivity was observed in the isolated products (compare Entries 3 and 4) [19]. At an even higher substrate concentration (2 M), additional uncharacterized products were formed and the yield of 5a decreased considerably (Table 2, Entry 5).

![Figure 1. Brønsted acids screened for carbonyl-ene reaction.](image)

Table 1. Optimization of carbonyl-ene cyclization of trifluoroketone 1.

| Entry | Catalyst | Equiv. of Catalyst | [1] (M) | t (h) | Yield 2 (%) | d.r. (2a:2a') 3 |
|-------|----------|-------------------|--------|-------|-------------|-----------------|
| 1     | H3PO4    | 1                 | 24     | 0     | 13          | -               |
| 2     | HCl      | 1                 | 24     | 13    | 2:1         | -               |
| 3     | 3a       | 0.5               | 24     | 25    | 2:1         | -               |
| 4     | 3b       | 0.5               | 24     | 25    | 2:1         | -               |
| 5     | 3b       | 0.2               | 24     | 25    | 2:1         | -               |
| 6     | 3b       | 0.1               | 24     | 25    | 2:1         | -               |
| 7     | 3b       | 0.1               | 48     | 75    | 2:1         | -               |
| 8     | 3b       | 0.5               | 7      | 79    | 2:2:1       | -               |

1 All reactions were run in anhydrous dichloromethane at 25 °C. 2 The yield is reported as a mixture of diastereomers 2a/2a'; however, products 2a and 2a' can be separated using column chromatography (see Material and Methods Section). 3 The diastereomeric ratios (2a:2a') were determined using 1H-NMR integration of isolated products.

Concurrently, we screened Brønsted acids for their ability to catalyze the cyclization of citronellal (4a). While citronellal is less activated than the corresponding trifluoromethyl ketone, it serves as the prototypical substrate for a Type I carbonyl-ene cyclization, as it is commercially available [15–17]. Surprisingly, the use of phosphoramidate 3b resulted in the isolation of a complex mixture of products with only a trace yield of ene product 5a and no starting material recovery (Table 2, Entry 1). Diethyl phosphate (3c) successfully promoted the reaction, albeit slowly, resulting in a low yield and a 77% recovery of starting material after 24 h (Table 2, Entry 2). We were pleased to find a significant increase in reaction rate and yield after 24 h when phosphoric acid derivative 3a was used as a catalyst. Under these mild reaction conditions [18], isopulegol (5a) was the primary diastereomer isolated from the reaction mixture in addition to a small amount of neoisopulegol (5a'), typically in a 2:1 ratio (Entries 3–5). A similar yield of product 5a was obtained when only 0.06 equivalents of catalyst were used at a higher concentration (0.5 M) compared to 0.5 equivalents at 0.1 M, but a decreased selectivity was observed in the isolated products (compare Entries 3 and 4) [19]. At an even higher substrate concentration (2 M), additional uncharacterized products were formed and the yield of 5a decreased considerably (Table 2, Entry 5).
Table 2. Optimization of carbonyl-ene cyclization of citronellal 4a.

![Chemical Structure]  

| Entry  | Catalyst | Equiv. of Catalyst | [4a] (M) | t (h) | Yield 5a (%) | d.r. (5a:5a′) |
|--------|----------|-------------------|---------|-------|--------------|---------------|
| 1      | 3b       | 1                 | 0.1     | 24    | trace        | -             |
| 2      | 3c       | 0.5               | 0.1     | 24    | 14           | 1:1           |
| 3      | 3a       | 0.5               | 0.1     | 22    | 61           | 2.4:1         |
| 4      | 3a       | 0.06              | 0.6     | 24    | 65           | 1.5:1         |
| 5      | 3a       | 0.1               | 2       | 18    | 31           | 2:1           |

1 All reactions were run in anhydrous dichloromethane at 25 °C. 2 The yield is reported as a mixture of diastereomers 5a/5a′; however, products 5a and 5a′ can be separated using column chromatography (see Material and Methods section). 3 The diastereomeric ratios (5a:5a′) were determined using 1H-NMR integration of isolated products.

Once the cyclization of the aldehyde substrate was optimized (0.5 equiv of 3a, 0.1 M, 24 h, rt), the scope of the reaction was explored. The carbonyl-ene reaction proceeds with excellent yield to give 3,4-disubstituted piperidine product 5b (Table 3, Entry 1), favoring the trans diastereomer. Aryl aldehyde 4c, which required a full equivalent of 3a to undergo complete conversion within 24 h, afforded a moderate yield of the carbonyl-ene product 5c (again with the trans product favored over the cis product) as well as a substantial amount (≈17%) of the conjugated diene, 3-isopropenyl-1,2-dihydronaphthalene, that resulted from an elimination reaction (Table 3, Entry 2).

Lastly, the cyclization of commercially available 2,6-dimethyl-5-heptenal (4d) resulted in the formation of five-membered ring 5d with great diastereoselectivity, albeit in only moderate yield (Entry 3). The reaction conditions have been modified in an attempt to increase the yield of the carbonyl-ene product; however, in each case, a complex mixture of products was isolated with no starting material recovered.

Table 3. Scope of the carbonyl-ene reaction of aldehydes.

| Entry  | Aldehyde | Product | Yield (%) (d.r.) |
|--------|----------|---------|------------------|
| 1      | ![Chemical Structure] | ![Chemical Structure] | 89 (2.7:1) |
| 2      | ![Chemical Structure] | ![Chemical Structure] | 44 (3.3:1) |
| 3      | ![Chemical Structure] | ![Chemical Structure] | 37 (>10:1) |

1 Unless otherwise noted, reactions were run in anhydrous dichloromethane at 25 °C for 19–24 h with [4] = 0.1 M and 0.5 equivalents of 3a. 2 The yield is reported as a mixture of diastereomers 5/5′; however, the diastereomeric products of 5b and 5c can be separated using column chromatography (see Material and Methods section). 3 The diastereomeric ratios (trans/cis; 5/5′) were determined using 1H-NMR integration of isolated products. The methyl group of the minor diastereomer 5d′ is cis to the hydroxyl group. 4 One molar equivalent of 3a was used.
3. Materials and Methods

3.1. General

Citronellal (93%) was obtained from Acros and was purified with normal-phase column chromatography. 2,4-dimethylheptenal (80%) was purchased from Aldrich and was purified via normal phase chromatography before use. Diphenyl phosphate (3a) was purchased from Aldrich. Trifluoromethyl ketone (1) was prepared from citronellic acid as previously described [20]. Diphenylphosphoramide (3b) was prepared as previously described [21]; following chromatographic purification, catalyst 3b was washed with 6 M of HCl and extracted with chloroform to ensure protonation of the catalyst, as discussed for the preparation of related N-triflylphosphoramide catalysts [22]. 2-(4-methyl-3-pentenyl)benzaldehyde [23] and 4-methyl-N-(3-methylbut-2-enyl)-N-(3-oxopropyl)benzenesulfonamide [24] were prepared as previously described. Anhydrous dichloromethane was obtained from a solvent system purchased by Pure Process Technology. Normal-phase flash-chromatography was carried out manually on silica gel (Mallinckrodt Chemicals, 60 Å, 40–63 micron) or with a Combi-flash MPLC system equipped with Redi-Sep Gold chromatography cartridges. $^1$H-NMR spectra were obtained by using a Jeol 400 MHz spectrometer (Jeol USA, Inc., Peabody, MA, USA). Chemical shifts are reported in parts per million relative to TMS. Coupling constants were reported in Hertz, and multiplicities were indicated using the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), ddd (doublet of doublets of doublets), etc. $^{13}$C-NMR data was obtained using Jeol 400 MHz NMR operating at 100 MHz. All products were characterized by $^1$H-NMR and $^{13}$C-NMR and compared with available literature data. High-resolution mass spectra (HRMS) of 2a/a’ were obtained on a Thermo LTQ-FTMS instrument (ThermoFisher Scientific, Waltham, MA, USA).

3.2. General Procedure for Intramolecular Carbonyl-Ene Reactions

Aldehyde or CF$_3$-ketone substrate (0.4–2 mmol), catalyst 3 (0.1–1 equivalents), and anhydrous dichloromethane (0.1–2 M with respect to aldehyde) were added to a small glass vial containing a stir bar. After stirring at room temperature for 24–48 h, the reaction was concentrated and purified by column chromatography.

3.2.1. Synthesis of Compounds 2a/a’

Compounds 2a/a’ were prepared according to the above-described general procedure by stirring CF$_3$ ketone 1 (208 mg, 1 mmol) and diphenylphosphoramide 3b (76 mg, 0.2 mmol) in anhydrous dichloromethane (0.5 mL) at room temperature for 24 h to provide a mixture of diastereomers as a colorless oil in 86% yield (flash-chromatography: 20% diethyl ether in petroleum ether). Retention factor of 2a/2a’ = 0.3 (5% ethyl acetate: 95% hexanes). The relative stereochemical assignments of 2a/2a’ were made on the basis of coupling constants for H$_2$ and H$_6$ $^{ax}$[25]. For 2a, the coupling constants for H$_2$ = 3.6 and 12.8 Hz indicated axial orientation, and the coupling constants for H$_6$ $^{ax}$ = 12.4 and 14.0 Hz indicated axial-axial splitting with H$_5$ and germinal coupling. Therefore, H$_5$ must be in the axial position and trans to H$_2$. For 2a’, H$_2$ had a coupling constant of 13.2 Hz, indicating axial orientation, and one of the coupling constants for H$_6$ $^{ax}$ = 4.5 Hz indicated axial-equatorial splitting with H$_5$. Therefore, H$_5$ must be in the equatorial position and cis to H$_2$. $^1$H-NMR of 2a (400 MHz, CDCl$_3$): $\delta$ 4.94 (s, 1H, vinylic H); 4.83 (s, 1H, vinylic H); 2.37 (s, 1H, -OH); 2.25 (dd, $J = 3.7, 12.7$ Hz, 1H, H$_2$); 1.96 (ddd, $J = 1.8, 3.2, 13.9$ Hz, 1H, H$_6$ $^{eq}$); 1.84 (m, 1H, H$_5$ $^{eq}$); 1.83 (s, 3H, vinylic Me); 1.80 (m, 1H, H$_3$ $^{eq}$); 1.73 (m, 1H, H$_4$ $^{eq}$); 1.55 (m, 1H, H$_3$ $^{ax}$); 1.18 (ddd, $J = 1.9, 12.4, 13.9$ Hz, H$_6$ $^{ax}$); 0.94 (m, 1H, H$_4$ $^{ax}$); 0.93 (d, $J = 8.0$ Hz, 3H, C$_5$-Me). $^{13}$C-NMR (100 MHz): $\delta$ 147.6 (vinylic C); 126.1 (q, $J = 290$ Hz, -CF$_3$); 112.2 (vinylic C); 74.3 (q, $J = 26$ Hz, C$_1$); 46.3 (C$_2$); 39.0 (C$_6$); 34.3 (C$_4$); 28.5 (C$_5$); 24.2 (vinylic Me); 21.9 (C$_5$-Me). HRMS, APCI: Calcd. for C$_{11}$H$_{17}$F$_3$O (M+): 222.12315; found: 223.13509. $^1$H-NMR of 2a’ (400 MHz): $\delta$ 5.01 (m, 1H, vinylic H); 4.90 (m, 1H, vinylic H); 2.92 (s, 1H, -OH); 2.31 (m, 1H, H$_2$); 2.25 (ddd, $J = 1.9, 3.4, 13.6$ Hz, 1H, H$_6$ $^{eq}$); 1.89 (m, 1H, H$_5$ $^{eq}$); 1.82 (m, 1H, H$_4$ $^{eq}$); 1.75 (s,
3H, vinylic Me); 1.73 (m, 1H, H5); 1.66 (m, 1H, H3a); 1.125 (tq, J = 2.4, 2.4, 2.4, 13.6, 13.6 Hz, H6); 1.00 (m, 1H, H4a); 0.94 (d, J = 6.5 Hz, 3H, C5-Me). 13C-NMR (100 MHz, CDCl3): δ 144.1 (vinyl C); 126.6 (q, J = 286 Hz, -CF3); 115.7 (vinyl C); 73.0 (q, J = 27 Hz, C1); 53.2 (C2); 42.2 (C6); 34.1 (C4); 28.2 (C5); 26.3 (C3); 22.4 (C5-Me); 19.7 (vinyl Me). HRMS, ESI: Calcd. for C11H18F3O+ (M + H+): 223.13043; found: 223.13041.

3.2.2. Synthesis of Compounds 5a/a’

Compounds 5a/a’ were prepared according to the above-described general procedure by stirring citronellal (101.5 mg, 0.658 mmol) and diphenyl phosphate (3a) (82.0 mg, 0.328 mmol) in anhydrous dichloromethane (6.6 mL) at room temperature for 22 h to provide a colorless oil in a 61% yield (products were purified by flash-chromatography with 10% diethyl ether in petroleum ether). The NMR spectra of isopulegol (5a) and neoisopulegol (5a’) matched those previously reported [26]. 1H-NMR of isopulegol ((1α, 2x,5β)-5-methyl-2-(1-methylethenyl)cyclohexanol, 5a) (400 MHz, CDCl3): δ 4.91 (m, 1H); 4.86 (br s, 1H); 3.46 (dt, J = 4.4, 10.8, 10.8 Hz, 1H); 2.40 (s, 1H); 1.89 (qq, J = 3.4, 10.0, 12.8 Hz, 1H); 1.71 (d, J = 1.0 Hz, 3H); 1.65 (m, 2H); 1.48 (m, 2H); 1.34 (d, J = 3.4, 12.4, 12.4 Hz, 1H); 0.96 (m, 2H); 0.95 (d, J = 6.5 Hz, 3H). 1H-NMR of neoisopulegol ((1α, 2x, 5β)-5-methyl-2-(1-methylethenyl)cyclohexanol, 5a’) (400 MHz, CDCl3): δ 4.95 (br s, 1H); 2.64 (br s, 1H); 2.98 (m, 1H); 1.98 (m, 2H); 1.79 (s, 3H); 1.73 (m, 2H); 1.55 (br s, 1H); 1.45 (m, 1H); 1.12 (m, 1H); 0.95 (m, 2H); 0.88 (d, J = 6.4 Hz, 3H).

3.2.3. Synthesis of Compounds 5b/b’

Compounds 5b/b’ were prepared according to the above-described general procedure by using 4-methyl-N-(3-methylbut-2-enyl)-N-(3-oxopropyl)benzenesulfonamide (106.3 mg, 0.378 mmol) and diphenyl phosphate (3a) (48 mg, 0.192 mmol) in anhydrous dichloromethane (3.8 mL) at room temperature for 24 h to provide an oil in a 89% yield (products were purified by flash-chromatography with a stepwise gradient of 20%-30% ethyl acetate in hexanes). The NMR spectra of isolated piperidines matched those previously reported [13]. 1H-NMR of trans-3-isopropenyl-1-(toluene-4-sulfonyl)piperidin-4-ol, 5b (400 MHz, CDCl3): δ 7.64 (d, J = 8.0 Hz, 2H); 7.32 (d, J = 8.0 Hz, 2H); 5.01 (s, 1H); 4.89 (s, 1H); 3.84 (m, 1H); 3.76 (m, 1H); 3.44 (d, J = 4.5, 4.5, 10.1, 10.1 Hz, 1H); 2.44 (s, 3H); 2.37 (dt, J = 2.8, 12.4, 12.4 Hz, 1H); 2.26 (dt, J = 3.4, 11, 11 Hz, 1H); 2.17 (t, J = 11 Hz); 2.04 (m, 1H); 1.71 (s, 3H); 1.64 (m, 1H). 1H-NMR of cis-3-isopropenyl-1-(toluene-4-sulfonyl)piperidin-4-ol, 5b’ (400 MHz, CDCl3): δ 7.66 (d, J = 8.1 Hz, 2H); 7.32 (d, J = 8.1 Hz, 2H); 4.99 (s, 1H); 4.59 (s, 1H); 3.97 (m, 1H); 3.59 (m, 2H); 2.60 (dt, J = 3.1, 12, 12 Hz, 1H); 2.57 (t, J = 11.5 Hz, 1H); 2.42 (s, 3H); 2.37 (d, J = 12.1 Hz, 1H); 1.96 (dq, J = 2.8, 2.8, 2.8, 13.9 Hz, 1H); 1.87 (m, 1H); 1.77 (s, 3H).

3.2.4. Synthesis of Compounds 5c/c’

Compounds 5c/c’ were prepared according to the above-described general procedure by using 2-(4-methyl-3-pentenyl)benzaldehyde (123.6 mg, 0.656 mmol) and diphenyl phosphate (3a) (183.0 mg, 0.656 mmol) in anhydrous dichloromethane (7.3 mL) at room temperature for 24 h to provide a mixture of diastereomers in a 44% yield (products were purified by flash-chromatography with a stepwise gradient of 0%-1% diethyl ether in petroleum ether). The NMR spectra of alcohol products (5c and 5c’) [27], and the elimination product [28] matched those previously reported. 1H-NMR of trans-2-isopropenyl-1,2,3,4-tetrahydro-1-naphthalenol, 5c (400 MHz, CDCl3): δ 7.61 (d, J = 7.6 Hz, 1H); 7.23 (m, 1H); 7.19 (m, 1H); 7.09 (d, J = 7.2 Hz, 1H); 4.96 (m, 1H); 4.89 (m, 1H); 4.70 (d, J = 9.5 Hz, 1H); 2.89 (ddd, J = 5.5, 11.2, 16.7 Hz, 1H); 2.82 (ddd, J = 3.2, 5.4, 16.7 Hz, 1H); 2.39 (ddd, J = 3.1, 9.5, 11.8 Hz, 1H); 2.07 (br s, 1H); 1.93 (m, 1H); 1.83 (m, 1H); 1.81 (s, 3H). 1H-NMR of cis-2-isopropenyl-1,2,3,4-tetrahydro-1-naphthalenol, 5c’ (400 MHz, CDCl3): δ 7.38(dd, J = 2.1, 7.0 Hz, 1H); 7.23 (m, 1H); 7.22 (m, 1H); 7.16 (m, 1H); 5.08 (m, 1H); 4.91 (m, 1H); 4.76 (m, 1H); 2.95 (ddd, J = 2.0, 5.4, 17.0 Hz, 1H); 2.81 (ddd, J = 5.9, 12.3, 17.0 Hz, 1H); 2.40 (m, 1H); 2.06 (dq, J = 5.4, 12.7, 12.7 Hz, 1H); 1.91 (s, 3H); 1.79 (m, 2H). 1H-NMR of 3-isopropenyl-1,2-dihyronaphthalene (400 MHz, CDCl3): δ 7.11 (m, 4H); 6.57 (s, 1H); 5.22 (s, 1H); 5.04 (s, 1H); 2.85 (t, J = 8 Hz, 2H); 2.53 (t, J = 8 Hz, 2H); 2.05 (s, 3H).
3.2.5. Synthesis of Compounds 5d/d′

Compounds 5d/d′ were prepared according to the above-described general procedure by using 2, 6-dimethyl-5-heptenal (280 mg, 2 mmol) and diphenyl phosphate (3a) (250 mg, 1 mmol) in anhydrous dichloromethane (20 mL) at room temperature for 19 h to provide a mixture of diastereomers in a 37% yield (products were purified by flash-chromatography with a stepwise gradient of 5–20% diethyl ether in petroleum ether). 1H-NMR of 5d (major isomer), (400 MHz, CDCl₃): δ 4.81 (d, J = 6.2 Hz, 2H); 3.4 (t, J = 9.3 Hz, 1H); 2.38 (q, J = 9.3 Hz, 1H); 1.78–1.95 (m, 3H); 1.74 (bs, 1H, -OH); 1.73 (s, 3H); 1.5 (m, 1H); 1.15 (m, 1H); 1.08 (d, J = 6.5 Hz, 3H). 13C-NMR (100 MHz): δ 146.3, 110.8, 81.8, 55.0, 41.0, 29.3, 26.0, 19.7, 18.1. The NMR spectra of 5d/d′ match those previously reported for an analogous compound [29]. The protons of 5d′ overlapped with the major isomer (5d) except for H1, which appeared at 3.93 ppm, and the β-methyl group at 1.00 ppm.

NMR spectra for products 2a/a′ and 5d/d′ can be found in the Supplementary Materials.

4. Conclusions

In summary, we have reported organocatalyzed intramolecular carbonyl-ene cyclizations of a citronellal-derived trifluoroketone and several aldehydes. The scope of this reaction is more general than previous reports and produces various trans-configured carbocyclic and heterocyclic 5- and 6-membered rings in moderate-to-good yield. In addition, these reactions are complete within 7–24 h. Further exploration of the scope of the reaction as well as screening enantioselective catalysts are ongoing in our laboratory.

Supplementary Materials: Supplementary materials can be accessed at: http://www.mdpi.com/1420-3049/21/6/713/s1.

Acknowledgments: Acknowledgement for financial support is made to Berry College (start-up funds and Faculty Development Grant) and the National Science Foundation (CHE-1125616). M.P.S. would like to thank the Richards family for partial support of this project.

Author Contributions: This project was developed and designed by L.O.D. Undergraduate co-authors A.J.M. and M.P.S. contributed equally to the experimentation and result analysis under the direction of both L.O.D. and H.A.D. H.A.D. contributed to experimentation, analysis of results, and manuscript preparation.

Conflicts of Interest: The founding sponsors had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

References and Notes

1. Clarke, M.L.; France, M.B. The carbonyl ene reaction. Tetrahedron 2008, 64, 9003–9031. [CrossRef]
2. Carlos Dias, L. Chiral Lewis Acid Catalyzed Ene-Reactions. Curr. Org. Chem. 2000, 4, 305–342. [CrossRef]
3. Snider, B.B. Lewis-acid catalyzed ene reactions. Acc. Chem. Res. 1980, 13, 426–432. [CrossRef]
4. Pihko, P.M. Activation of Carbonyl Compounds by Double Hydrogen Bonding: An Emerging Tool in Asymmetric Catalysis. Angew. Chem. Int. Ed. 2004, 43, 2062–2064. [CrossRef] [PubMed]
5. Doyle, A.G.; Jacobsen, E.N. Small-Molecule H-Bond Donors in Asymmetric Catalysis. Chem. Rev. 2007, 107, 5713–5743. [CrossRef] [PubMed]
6. Bolm, C.; Rantanen, T.; Schifflers, I.; Zani, L. Protonated Chiral Catalysts: Versatile Tools for Asymmetric Synthesis. Angew. Chem. Int. Ed. 2005, 44, 1758–1763. [CrossRef] [PubMed]
7. Wittkopf, A.; Schreiner, P.R. Metal-Free, Noncovalent Catalysis of Diels-Alder Reactions by Neutral Hydrogen Bond Donors in Organic Solvents and in Water. Chem. Eur. J. 2003, 9, 407–414. [CrossRef] [PubMed]
8. Clarke, M.L.; Jones, C.E.; France, M.B. The first organocatalytic carbonyl-ene reaction: Isomerisation-free C-C bond formations catalysed by H-bonding thio-ureas. Beilstein J. Org. Chem. 2007, 3, 24. [CrossRef] [PubMed]
9. Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R.M. Highly Enantioselective Organocatalytic Carbonyl-Ene Reaction with Strongly Acidic, Chiral Brønsted Acids as Efficient Catalysts. Angew. Chem. Int. Ed. 2008, 47, 6798–6801. [CrossRef] [PubMed]
10. Liu, L.; Leutzsch, M.; Zheng, Y.; Alachraf, M.W.; Thiel, W.; List, B. Confined Acid-Catalyzed Asymmetric Carbonyl–Ene Cyclization. J. Am. Chem. Soc. 2015, 137, 13268–13271. [CrossRef] [PubMed]
11. Baldwin, J.E.; Thomas, R.C.; Kruse, L.I.; Silberman, L. Rules for ring closure: Ring formation by conjugate addition of oxygen nucleophiles. J. Org. Chem. 1977, 42, 3846–3852. [CrossRef]
12. Grachan, M.L.; Tudge, M.T.; Jacobsen, E.N. Enantioselective Catalytic Carbonyl–Ene Cyclization Reactions. Angew. Chem. Int. Ed. 2008, 47, 1469–1472. [CrossRef] [PubMed]
13. Williams, J.T.; Bahia, P.S.; Kariuki, B.M.; Spencer, N.; Philip, D.; Snaith, J.S. Synthesis of 3,4-Disubstituted Piperidines by Carbonyl Ene and Prins Cyclizations: Switching between Kinetic and Thermodynamic Control with Brønsted and Lewis Acid Catalysts. J. Org. Chem. 2006, 71, 2460–2471. [CrossRef] [PubMed]
14. Christ, P.; Lindsay, A.G.; Vormittag, S.S.; Neudörfl, J.-M.; Berkessel, A.; O’Donoghue, A.C. pKa Values of Chiral Brønsted Acid Catalysts: Phosphoric Acids/Amides, Sulfonyl/Sulfuryl Imides, and Perfluorinated TADDOLs (TTFDDOLs). Chem. Eur. J. 2011, 17, 8524–8528. [CrossRef] [PubMed]
15. Aggarwal, V.K.; Vennall, G.P.; Davey, P.N.; Newman, C. Scandium trifluoromethanesulfonate, an efficient catalyst for the intermolecular carbonyl-ene reaction and the intramolecular cyclisation of citronellal. Tetrahedron Lett. 1998, 39, 1997–2000. [CrossRef]
16. Nakatani, Y.; Kawashima, K. A Highly Stereoselective Preparation of 1-Isopulegol. Synthesis 1978, 1978, 147–148. [CrossRef]
17. Kočovský, P.; Ahmed, G.; Šrogl, J.; Malkov, A.V.; Steele, J. New Lewis-Acidic Molybdenum(II) and Tungsten(II) Catalysts for Intramolecular Carbonyl Ene and Prins Reactions. Reversal of the Stereoselectivity of Cyclization of Citronellal. J. Org. Chem. 1999, 64, 2765–2775. [CrossRef] [PubMed]
18. Cheon, C.-H.; Yamamoto, H. Synthesis of N,N-Bis( nonafluor) Squaric Acid Diamide and its Application to Organic Reactions. Bull. Korean Chem. Soc. 2010, 31, 539–540. [CrossRef]
19. At 24 h, the reaction described in entry 4 had only reached 85% conversion.
20. Reeves, J.T.; Song, J.J.; Tan, Z.; Lee, H.; Yee, N.K.; Senanayake, C.H. Trifluoromethyl Ketones from Enolizable Carboxylic Acids via Enediolate Trifluoroacetylation/Decarboxylation. J. Org. Chem. 2008, 73, 9476–9478. [CrossRef] [PubMed]
21. Tomooka, K.; Suzuki, M.; Shimada, M.; Ni, R.; Uehara, K. Stereoselective Multimodal Transformations of Planar Chiral 9-Membered Diallylic Amides. Org. Lett. 2011, 13, 4926–4929. [CrossRef] [PubMed]
22. Rueping, M.; Nachtsheim, B.J.; Koenigs, R.M.; Ieawsuwan, W. Synthesis and Structural Aspects of N-Triflylphosphoramides and Their Calcium Salts—Highly Acidic and Effective Brønsted Acids. Chem. Eur. J. 2010, 16, 13116–13126. [CrossRef] [PubMed]
23. Denmark, S.E.; Kesler, B.S.; Moon, Y.C. Inter- and intramolecular [4 + 2] cycloadditions of nitroalkenes with oleins. 2-Nitrostyrenes. J. Org. Chem. 1992, 57, 4912–4924. [CrossRef]
24. Gandon, L.A.; Enggist, P. A Chemical Study of Virginia Tobacco Flavour (Nicotiana tabacum L.) II. Isolation and synthesis of cis-2-isopropenyl-8-methyl-1,2,3,4-tetrahydro-1-naphthalenol and 3-isopropenyl-5-methyl-1,2-dihyronaphthalene. Helv. Chim. Acta 1978, 61, 1335–1341. [CrossRef]
25. Shirakawa, E.; Imazaki, Y.; Hayashi, T. Cobalt-catalyzed Coupling of Alkenyl Triflates with Aryl and Alkenyl Grignard Reagents. Chem. Lett. 2008, 37, 654–655. [CrossRef]
26. Kropp, P.J.; Breton, G.W.; Crawford, S.D.; Durland, W.F.; Jones, J.E.; Raleigh, J.S. Surface-Mediated Reactions. 6. Effects of Silica Gel and Alumina on Acid-Catalyzed Reactions. J. Org. Chem. 1995, 60, 4146–4152. [CrossRef]
27. Demole, E.; Enggist, P. A Chemical Study of Virginia Tobacco Flavour (Nicotiana tabacum L.) II. Isolation and synthesis of cis-2-isopropenyl-8-methyl-1,2,3,4-tetrahydro-1-naphthalenol and 3-isopropenyl-5-methyl-1,2-dihyronaphthalene. Helv. Chim. Acta 1978, 61, 1335–1341. [CrossRef]
28. Snider, B.B.; Karras, M.; Price, R.T.; Rodini, D.J. Alkylaluminum halide induced cyclization of unsaturated carbonyl compounds. J. Org. Chem. 1982, 47, 4538–4545. [CrossRef]

**Sample Availability:** Samples of the Compounds 2 and 5b–d are available from the authors.

© 2016 by the authors; licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC-BY) license (http://creativecommons.org/licenses/by/4.0/).