Cyclizations

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Enantioselective Catalytic Carbonyl–Ene Cyclization Reactions**

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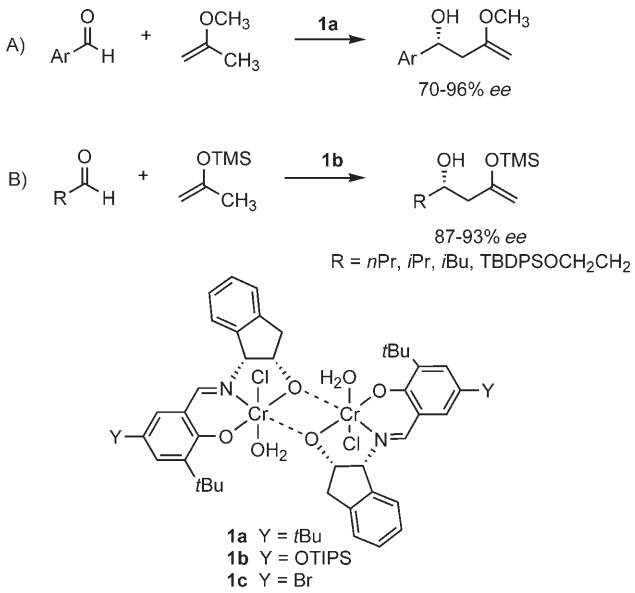
The carbonyl–ene reaction is a synthetically important method of generating homoallylic alcohols with concomitant carbon–carbon bond formation.[1–3] Substantial effort has been directed toward developing catalytic enantioselective variants, and several notable advances have been made.[3–9] However, most systems identified to date are limited to highly electrophilic aldehyde substrates bearing strongly electron-withdrawing substituents or Lewis basic substituents that allow two-point binding to the catalyst.[4,5,9] Recently, our group discovered that Cr^{III} complexes of tridentate Schiff base ligands (**1**) promote enantioselective hetero-ene reactions between electron rich enol ethers and electronically unactivated aldehydes (Scheme 1).[6b,c] We became interested

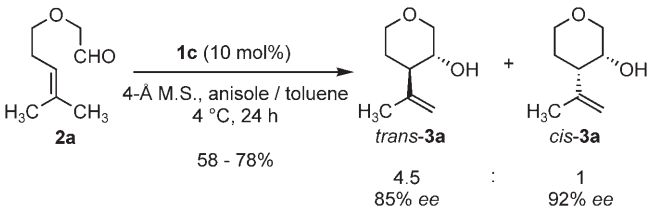


Scheme 1. (Schiff base)Cr^{III}-catalyzed enantioselective intermolecular hetero-ene reactions. TMS = trimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl, TIPS = triisopropylsilyl.

in developing an intramolecular variant of this reaction, motivated in part by the possibility that the entropic advantage conferred to such transformations might allow simultaneous use of both unactivated olefins and aldehydes. Moreover, intramolecular carbonyl–ene reactions often generate stereochemically complex cyclic structures in a straightforward manner. Herein, we report carbonyl–ene cyclization reactions of a variety of alkenyl aldehydes promoted by catalyst **1c**, resulting in the highly diastereo- and enantioselective formation of a diverse range of heterocyclic and carbocylic products.

Until now, only very limited success has been reported for intramolecular ene reactions induced by chiral catalysts.[2,3,7–10] Yamamoto and co-workers discovered the first examples that were promoted by more than stoichiometric amounts of a Zn/binol complex (binol = 2,2′-dihydroxy-1,1′-binapthyl).[7] Subsequently, Mikami and co-workers demonstrated that a Ti^{IV}/binol system is an effective catalyst for the enantio- and diastereoselective cyclization of a limited range of alkenyl aldehydes.[8] More recently, Yang and co-workers reported the highly enantioselective cyclization of pyruvate derivatives catalyzed by a Cu^{II}/bisoxazoline complex to generate functionalized cyclopentanes.[9]

Evaluation of a series of Schiff base complexes of type **1** in the ene cyclization of model substrate **2a** led to identification of complex **1c** as the optimal catalyst; the product was obtained as a 4.5:1 ratio of diastereomers and in good enantiomeric excess (Scheme 2). However, product **3a** was



Scheme 2. Preliminary result.

generated in variable yields as a result of competing enolization and poorly stereoselective aldol pathways. Undesired side reactions were avoided through the use of α,α-disubstituted aldehydes as substrates.[11] Thus, treatment of alkenyl aldehyde **2b** with 0.8 mol% catalyst **1c** at 4 °C resulted in a reproducible, highly diastereo- and enantioselective carbonyl–ene cyclization to yield tetrahydrofuran **3b** as a volatile oil in greater than 30:1 d.r., 93% *ee*, and 77% yield (Table 1, entry 1).

A variety of alkenyl aldehydes bearing heteroatom substitution proved to be suitable substrates for this method, providing access to a diverse array of substituted heterocyclic products (Table 1). Geranyl aldehyde **2c** underwent regioselective cyclization to yield tetrahydrofuran **3c** in 20:1 d.r. and 96% *ee* (Table 1, entry 2). Although slightly higher catalyst loadings were required to promote the reaction of tetrasubstituted alkene **2d**, tetrahydrofuran **3d**

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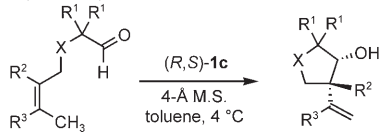
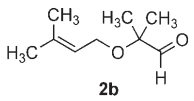
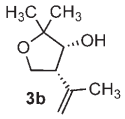
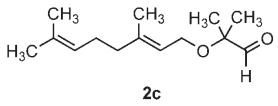
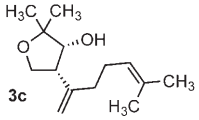
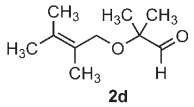
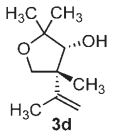
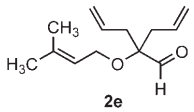
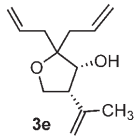
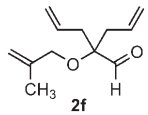
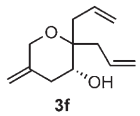
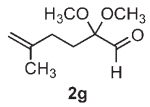
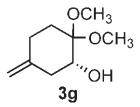
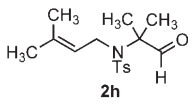
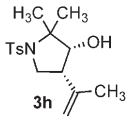
Table 1: Enantioselective carbonyl–ene cyclizations.



Entry	Aldehyde	Product	(*R*,*S*)-**1c** [mol%]	d.r.[a]	*ee* [%][b]	Yield [%][c]
1	 **2b**	 **3b**	0.8	>30:1	93	77
2	 **2c**	 **3c**	1	20:1	96	94
3	 **2d**	 **3d**	5	>30:1	75	78
4	 **2e**	 **3e**	1	>30:1	96	96
5	 **2f**	 **3f**	5	–	93	72
6	 **2g**	 **3g**	2.5	–	94	88
7	 **2h**	 **3h**	2	>30:1	95	98

[a] Ratios determined by ^{1}H NMR spectroscopy or GC analysis of the crude reaction mixtures. The relative stereochemistry was determined by NOE spectroscopy. [b] Determined by chiral GC or HPLC analysis. The absolute stereochemistry of **3h** was determined by X-ray crystallographic analysis of the *p*-bromobenzoyl ester[13] and those of the other products were inferred from this result. [c] Yield of the indicated diastereomer isolated after purification by column chromatography.

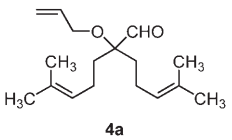
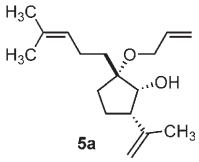
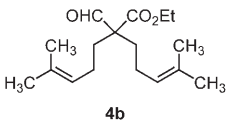
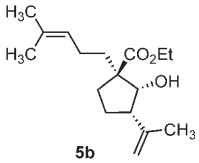
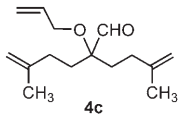
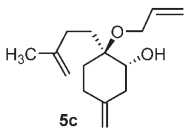
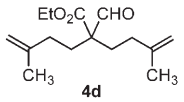
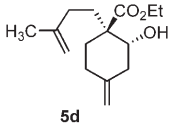
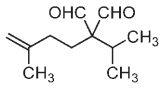
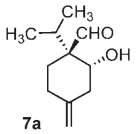
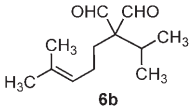
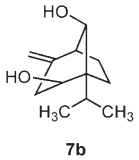
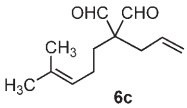
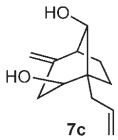
was obtained in high diastereoselectivity with concomitant formation of a quaternary stereocenter (Table 1, entry 3). Prenylated aldehyde **2e**, which bears geminal diallyl substitution at the α-carbon atom, was an excellent substrate, undergoing cyclization in nearly quantitative yield and 96% *ee* (Table 1, entry 4). Six-membered rings resulted from the cyclization of terminal olefin containing substrates, such as **2f**, affording tetrahydropyran **3f** in 93% *ee* (Table 1, entry 5).[12] The protected 2-hydroxycyclohexanone **3g** was generated in 93% *ee* by cyclization of the corresponding protected α-ketoaldehyde **2g** (Table 1, entry 6). Treatment of α-amino aldehyde **2h** with 2 mol% **1c** afforded tosyl-protected pyrrolidine **3h** as a single diastereomer in 95% *ee* and 98% yield (Table 1, entry 7).

Alternatively, stereochemically complex carbocycles could be prepared by this method from achiral alkenyl aldehydes bearing either enantiotopic alkene or aldehyde groups (Table 2). Bis(alkenyl) aldehydes proved to be superb cyclization substrates, affording products with a variety of structural motifs in high yields and enantioselectivities (Table 2, entries 1–4). Aldehyde **4a**, which contains prochiral prenyl moieties, underwent cyclization to generate a cyclopentanol ring with three contiguous stereogenic centers in 7:1 d.r. The major diastereomer of the differentially protected diol, **5a**, was isolated in 87% yield and 99% *ee* (Table 2, entry 1). Desymmetrization of aldehyde ester **4b** (Table 2, entry 2) afforded β-hydroxy ester **5b** as a single diastereomer in 95% yield and 98% *ee*. The stereochemically complex cyclopentane products **5a** and **5b** contain useful handles for further synthetic elaboration, including multiple olefin moieties with distinct steric and electronic properties. Cyclization of aldehydes containing prochiral terminal olefin substituents, such as **4c** and **4d**, led to formation of cyclohexanol rings with two contiguous stereogenic centers in high enantio- and diastereoselectivity (Table 2, entries 3 and 4).

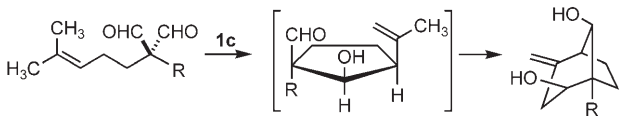
Catalyst **1c** also proved to be applicable to the desymmetrization of dialdehyde substrates (Table 2, entries 5–7).[10] Treatment of **6a** with 1 mol% **1c** afforded cyclized product **7a** in 2.2:1 d.r. (Table 2, entry 5). Despite the moderate diastereoselectivity obtained in this reaction, the major isomer could be isolated after purification by column chromatography in 57% yield and 91% *ee*.

Upon treatment with catalyst **1c**, prenylated 1,3-dialdehydes **6b** and **6c** undergo tandem ene cyclizations to yield bicyclo[3.2.1]octanes **7b** and **7c** as single diastereomers in 92 and 93% *ee*, respectively (Table 2, entries 6 and 7). The first ene cyclization generates a transient cyclopentane intermediate that contains an olefin and aldehyde in a 1,3-*syn* orientation. This intermediate is poised to undergo a second intramolecular ene reaction, resulting in the observed bicyclic product (Scheme 3). Although **7b** and **7c** were isolated in moderate yield, the precursor dialdehydes **6b** and **6c** are accessible in only three steps from commercially available starting materials, and the double ene cyclization imparts a significant increase in both structural and stereochemical complexity. In principle, bicyclo[3.2.1]octanes with a wide

Table 2: Desymmetrizations of bis(alkenyl) aldehydes and alkenyl dialdehydes.[a]

Entry	Aldehyde	Product	(*R*,*S*)-**1c** [mol%]	d.r.[b]	*ee* [%][c]	Yield [%][d]
1	 **4a**	 **5a**	2	7:1	99	87
2	 **4b**	 **5b**	2	>30:1	98	95
3	 **4c**	 **5c**	2	>30:1	97	89
4	 **4d**	 **5d**	1	>30:1	99	99
5	 **6a**	 **7a**	1	2.2:1	91	57
6	 **6b**	 **7b**	10	>30:1	92	46
7	 **6c**	 **7c**	10	>30:1	93	42

[a] Reactions were carried out in toluene (8 M), in the presence of 4-Å molecular sieves, and at ambient temperature, except for entries 4 and 5, which were run at 4 °C. [b] Diastereomeric ratios determined by ^{1}H NMR spectroscopy or GC analysis of the crude reaction mixtures. The relative stereochemistry was determined by NOE spectroscopy. [c] Determined by chiral GC or HPLC analysis. [d] Yield of the indicated diastereomer isolated after column chromatography.



Scheme 3. Tandem carbonyl–ene cyclizations of prenylated dialdehydes.

range of substituents at the quaternary carbon stereogenic center (**7b**, R = isopropyl; **7c**, R = allyl) can be accessed by this methodology.[14]

In conclusion, catalyst **1c** promotes highly diastereo- and enantioselective carbonyl–ene cyclizations of a variety of alkenyl aldehydes to afford densely functionalized hetero- and carbocycles bearing up to three contiguous stereocenters. We anticipate that this methodology will prove to be enabling in a variety of synthetic contexts.

Experimental Section

General procedure for enantioselective ene cyclizations catalyzed by **1c**: (3*R*,4*R*)-2,2-dimethyl-4-(prop-1-en-2-yl)tetrahydrofuran-3-ol (Table 1, entry 1): Toluene (25 μL) and aldehyde **2b** (0.2 mmol) were added to a cooled (0 °C), stirred mixture of 4-Å molecular sieves (40 mg) and catalyst **1c** (1.6 mg, 1.6 μmol), contained in a flame-dried 0.5-dram reaction vial and under a N_2 atmosphere, was added The reaction mixture was warmed to 4 °C and allowed to stir until conversion of **2b** was deemed complete by TLC (ca. 30 h). The mixture was diluted with 50% Et_2O/hexanes (0.5 mL) and loaded onto a silica gel column. Purification by flash column chromatography, eluting with 10% Et_2O/hexanes, afforded **3b** (24 mg, 77%) as a volatile, colorless oil in >30:1 d.r. by ^{1}H NMR spectroscopy and 93% *ee* by chiral GC (γ-TA, 85 °C isothermal, t_r (minor) 19.5 min, t_r (major) 27.1). $R_f = 0.15$ (10% EtOAc/hexanes); $[\alpha]_D^{20} = -11.3\ cm^3 g^{-1} dm^{-1}$ ($c = 0.36\ g cm^{-3}$ in CH_2Cl_2); IR (film): $\tilde{\nu}_{max} = 3429$ (s), 2972 (s), 2934 (m), 2884 (w), 1650 (w), 1451 cm^{-1} (w); ^{1}H NMR (500 MHz, $CDCl_3$) $\delta = 5.07$ (1H, br.s, CH), 4.77 (1H, brs, CH), 3.98–3.92 (2H, m, OCH_2), 3.83 (1H, app t, $J = 4$, HOC*H*), 3.09–3.05 (1H, m, CH), 1.84 (3H, s, CH_3), 1.62 (1H, d, $J = 4$, OH), 1.31 (3H, s, CH_3), 1.22 ppm (3H, s, CH_3); ^{13}C NMR (125.6 MHz, $CDCl_3$) $\delta = 141.1$, 113.8, 84.7, 76.6, 67.6, 51.1, 27.7, 23.9, 22.7 ppm; *m*/*z* (*CI*, NH_4^+) 174 [$M + NH_4$].

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[1] For a selection of recent reports of carbonyl–ene and related cyclizations in stereoselective syntheses of biologically active molecules, see: a) B. Alcaide, C. Pardo, C. Rodriguez-Ranera, A. Rodriquez-Vicente, *Org. Lett.* **2001**, *3*, 4205–4208; b) T. Okano, K. Nakagawa, N. Kubodera, K. Ozono, A. Isaka, A. Osawa, M. Terada, K. Mikami *Chem. Biol.* **2000**, *7*, 173–184; c) K. Mikami, S. Ohba, H. Ohmura, N. Kubodera, K. Nakagawa, T. Okano, *Chirality* **2001**, *13*, 366–371; d) Q. Xia, B. Ganem, *Org. Lett.* **2001**, *3*, 485–487.

[2] For reviews of the ene reaction, including the carbonyl–ene reaction and cyclization, see: a) H. M. R. Hoffmann, *Angew. Chem.* **1969**, *81*, 597–618; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 556–577; b) B. Snider, *Acc. Chem. Res.* **1980**, *13*, 426–432; c) W.

Carruthers in *Tetrahedron Organic Chemistry Series, Vol. 8: Cycloaddition Reactions in Organic Synthesis* (Eds.: J. E. Baldwin, P. D. Magnus), Pergamon, Oxford, **1990**, chap. 5; d) W. Oppolzer, V. Sniekus, *Angew. Chem.* **1978**, *90*, 506 – 516; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 476 – 486.

[3] For a review of advances in enantioselective catalytic ene reactions, see: a) K. Mikami, M. Terrada in *Comprehensive Asymmetric Catalysis, Vol. 3* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, chap. 32.3; b) K. Mikami, M. Shimizu, *Chem. Rev.* **1992**, *92*, 1021 – 1050.

[4] For examples of enantioselective intermolecular carbonyl–ene reactions of electron-deficient aldehydes, such as chloral and fluoral, see: a) K. Maruoka, Y. Hoshino, T. Shirasaka, H. Yamamoto, *Tetrahedron Lett.* **1988**, *29*, 3967 – 3970; b) K. Mikami, T. Yajima, T. Takasaki, S. Matsukawa, M. Terada, T. Uchimaru, M. Maruta, *Tetrahedron* **1996**, *52*, 85 – 98.

[5] For examples of enantioselective intermolecular carbonyl–ene reactions of glyoxalate and pyruvate derivatives, see: a) K. Aikawa, S. Kainuma, M. Hatano, K. Mikami, *Tetrahedron Lett.* **2004**, *45*, 183 – 185; b) K. Mikami, M. Terada, T. Nakai, *J. Am. Chem. Soc.* **1989**, *111*, 1940 – 1941; c) K. Mikami, M. Terada, T. Nakai, *J. Am. Chem. Soc.* **1990**, *112*, 3949 – 3954; d) K. Mikami, S. Matsukawa, *J. Am. Chem. Soc.* **1993**, *115*, 7039 – 7040; e) S. Pandiaraju, G. Chen, A. Lough, A. K. Yudin, *J. Am. Chem. Soc.* **2001**, *123*, 3850 – 3851; f) G. Manickam, G. Sundararajan, *Tetrahedron: Asymmetry* **1999**, *10*, 2913 – 2925; g) S. Kezuka, T. Ikeno, T. Yamada, *Org. Lett.* **2001**, *3*, 1937 – 1939; h) J. Hao, M. Hatano, K. Mikami, *Org. Lett.* **2000**, *2*, 4059 – 4062; i) J. H. Koh, A. O. Larsen, M. R. Gagne, *Org. Lett.* **2001**, *3*, 1233 – 1236; j) D. A. Evans, C. S. Burgey, N. A. Paras, T. Vojkovsky, S. W. Tregay, *J. Am. Chem. Soc.* **1998**, *120*, 5824 – 5825; k) D. A. Evans, S. W. Tregay, C. S. Burgey, N. A. Paras, T. Vojkovsky, *J. Am. Chem. Soc.* **2000**, *122*, 7936 – 7943; l) D. A. Evans, J. Wu, *J. Am. Chem. Soc.* **2005**, *127*, 8006 – 8007.

[6] For examples of enantioselective catalytic intermolecular carbonyl–ene reactions of unactivated aldehydes see: a) E. M. Carreira, W. Lee, R. A. Singer, *J. Am. Chem. Soc.* **1995**, *117*, 3649 – 3650; b) R. T. Ruck, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 2882 – 2883; c) R. T. Ruck, E. N. Jacobsen, *Angew. Chem.* **2003**, *115*, 4919 – 4922; *Angew. Chem. Int. Ed.* **2003**, *42*, 4771 – 4774.

[7] For enantioselective carbonyl–ene cyclizations promoted by a more than stoichiometric amount of Zn/binol system, see: S. Sakane, K. Maruoka, H. Yamamoto, *Tetrahedron* **1986**, *42*, 2203 – 2209.

[8] For enantioselective catalysis of carbonyl–ene cyclizations by Ti complexes, see: a) K. Mikami, E. Sawa, M. Terada, *Tetrahedron: Asymmetry* **1991**, *2*, 1403 – 1412; b) K. Mikami, Y. Koizumi, A. Osawa, M. Terada, H. Takayama, K. Nakagawa, T. Okano, *Synlett* **1999**, *11*, 1899 – 1902.

[9] For Cu^{II}-catalyzed enantioselective cyclizations of α-keto esters, see: D. Yang, M. Yang, N. Zhu, *Org. Lett.* **2003**, *5*, 3749 – 3752.

[10] The desymmetrization of dialdehydes by ene cyclization has been investigated by Ziegler and Sobolov in an approach to the synthesis of the natural product anguidine: F. E. Ziegler, S. B. Sobolov, *J. Am. Chem. Soc.* **1990**, *112*, 2749 – 2758.

[11] Intramolecular reactions of these substrates presumably also benefit from a Thorpe–Ingold effect. For a recent review, see: M. E. Jung, G. Piizi, *Chem. Rev.* **2005**, *105*, 1735 – 1766.

[12] For a recent review of approaches to tetrahydropyran frameworks, see: P. A. Clarke, S. Santos, *Eur. J. Org. Chem.* **2006**, 2045 – 2053.

[13] See the Supporting Information for X-ray crystallographic data.

[14] See the Supporting Information for substrate preparation.

