Hetero-Ene Reaction

Asymmetric Hetero-Ene Reactions of Trimethylsilyl Enol Ethers Catalyzed by Tridentate Schiff Base Chromium(III) Complexes**

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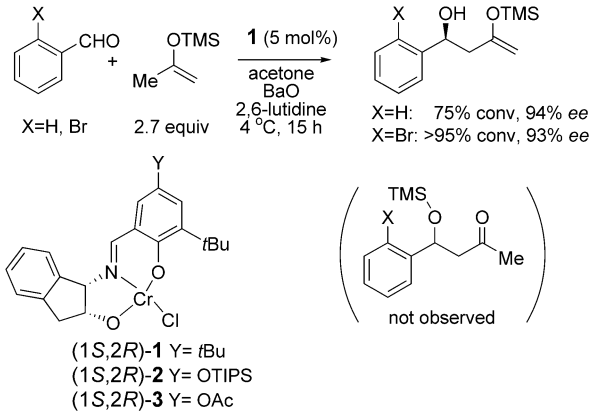
Asymmetric hetero-ene reactions between aldehydes and enol ethers provide convenient access to a wide variety of chiral β-hydroxycarbonyl derivatives from stable, readily available precursors. Recently, we demonstrated that the tridentate Schiff base chromium(III) complex **1** catalyzes hetero-ene reactions between 2-methoxypropene and benzaldehyde derivatives to provide the corresponding β-aryl β-hydroxymethylenol ether products in high enantioselectivities and yields.[1] Promising reactivity and enantioselectivity were also uncovered in reactions of 2-trimethylsilyloxyproprene with aromatic aldehydes to generate highly enantioenriched β-hydroxytrimethylsilyl enol ether products (Scheme 1).



Scheme 1. TIPS = triisopropylsilyl, TMS = trimethylsilyl.

None of the corresponding β-silyloxyketone products attributable to Mukaiyama aldol pathways were detected in the latter case, suggesting a concerted pericyclic reaction mechanism.[2] Intrigued by the potential of this unusual silyl enol ether ene methodology,[3] we have investigated it more deeply and discovered it to be far more broadly applicable than the corresponding alkyl enol ether methodology first reported.

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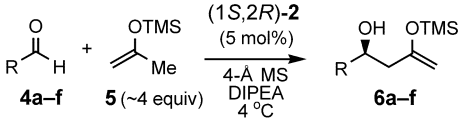
We report here its successful application to highly enantioselective and diastereoselective reactions of prochiral and chiral aliphatic aldehydes.

Aliphatic aldehydes **4a–f** proved to be excellent substrates for enantioselective hetero-ene reactions catalyzed by Cr^{III} complex **2**, undergoing reaction with 2-trimethylsilyloxypropene to generate the β-hydroxytrimethylsilyl enol ether products **6a–f** in high yields and enantioselectivities (Table 1).



(1)

Table 1: Hetero-ene reactions between aliphatic aldehydes and 2-trimethylsilyloxypropene [Eq. (1)].[a,b]

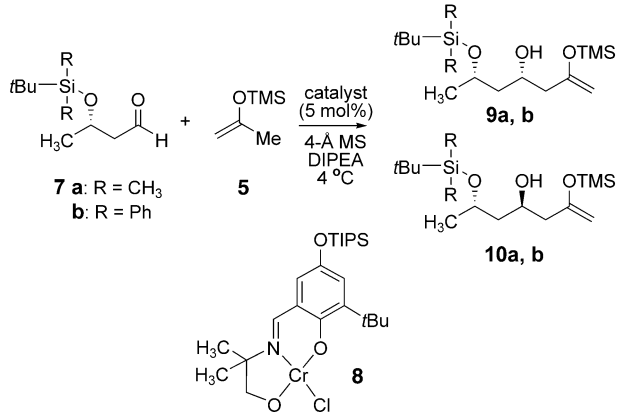
Product	R	*t* [h]	Yield [%][c]	*ee* [%]
6a	*n*Pr	65	87	89[e]
6b	*i*Pr	72	83	90[e]
6c	*i*Bu	72	77	87[e]
6d	cyclopropyl	72	47[f]	93[e]
6e	$TBDPSOCH_2CH_2$[d]	20	90	93[g]
6f	$TBDPSOCH_2CH_2CH_2$[d]	40	87	90[g]

[a] Reactions were carried out with 1.0 mmol of aldehyde, ~4 mmol of **5** (480 μL of 93–94% purity), 0.05 mmol of **2** (28.4 mg), powdered 4-Å molecular sieves (400 mg), and DIPEA (25 μL) at 4°C. [b] Absolute stereochemistry was determined by hydrolysis of **6c** to the β-hydroxyketone and comparison of the optical rotation to the known literature value.[5] [c] Net yield of crude product contaminated with residual catalyst (see text). [d] TBDPS = *tert*-butyldiphenylsilyl. [e] Enantiomeric excess was determined by hydrolysis to the β-hydroxyketone and analysis by chiral GC (γ-TA) or HPLC (Whelk-01). [f] This reaction proceeded only to 55% conv. of substrate. [g] Enantiomeric excess determined for the TMS enol ether, which was analyzed by chiral HPLC on a Whelk-01 column.

Catalysts **1** and **2** afforded similar enantioselectivities, but rates were 1.5–2 times faster with the more soluble complex **2**. Reactions were conducted under solvent-free conditions in the presence of 4-Å molecular sieves, with 2-trimethylsilyloxypropene and aldehyde in a 4:1 molar ratio. Addition of substoichiometric amounts of diisopropylethylamine (DIPEA) served to inhibit an unselective pathway promoted, most likely, by trace amounts of Brønsted acid associated to the catalyst.[4] The β-hydroxytrimethylsilyl enol ether products were unreactive as ene partners under the reaction conditions.

The enantioselectivity and rate of the ene reactions displayed little dependence on the steric properties of the aldehydes, except in the extreme case of pivalaldehyde, which proved almost completely unreactive. Butyraldehyde (**4a**) underwent catalyst-induced trimerization under standard reaction conditions, but this could be avoided by slow addition of **4a** to a solution of the other reaction components, with no deleterious effect on enantioselectivity or reaction rate. Reaction of β- or γ-silyloxy-substituted aldehydes (**4e, 4f**) proceeded with similar enantioselectivities but measurably faster rates than the unfunctionalized counterparts.[6]

The high reactivity and enantioselectivity observed with aldehyde **4e** suggested that chiral β-silyloxyaldehydes might serve as useful substrates for doubly diastereoselective ene reactions to generate monoprotected *syn*- or *anti*-1,3-diols. Enantiopure 3-hydroxybutyraldehyde derivatives **7a** and **7b** were both subjected to ene reactions with 2-trimethylsilyloxypropene (**5**), and the selectivities obtained with each enantiomer of catalyst **2** were compared with those generated with the achiral variant **8** (Scheme 2, Table 2). Achiral catalyst **8**



Scheme 2.

Table 2: Doubly diastereoselective ene reactions.

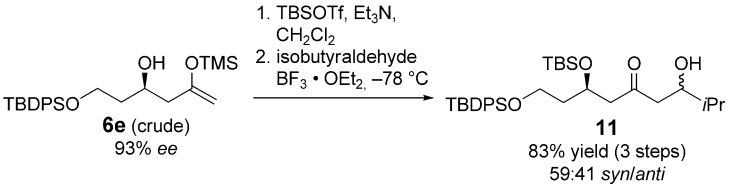
Aldehyde	Catalyst	**9**:**10**[a]	Conv. [%][b]
7a	**8**	2.8:1	n.d.
7a	(*R*,*S*)-**2**	>46:1	92
7a	(*S*,*R*)-**2**	1:14.4	92
7b	**8**	1:2.6	n.d.
7b	(*R*,*S*)-**2**	3.8:1	51
7b	(*S*,*R*)-**2**	1:>160	91

[a] *Syn*:*anti* ratios were determined by GC analysis. [b] Conversions determined by ^{1}H NMR spectroscopy; n.d. = not determined.

provided a modest 2.8:1 diastereoselectivity in the ene reaction between **7a** and **5**, favoring the enantiopure *syn*-diol derivative **9a**. This substrate-based selectivity was enhanced to a significant extent with "matched" catalyst (1*R*,2*S*)-**2** (>46:1). The "mismatched" catalyst (1*S*,2*R*)-**2** provided a synthetically useful diastereoselectivity of 14.4:1 in favor of the enantiopure *anti*-diol derivative **10a**. The substrate-induced selectivity with the bulkier aldehyde **7b** reversed to favor *anti*-diol derivative **10b** in a 2.6:1 ratio. The now-"matched" catalyst (1*S*,2*R*)-**2** provided a >160:1 d.r. in favor of the *anti* product **10b**, whereas "mismatched" catalyst (1*R*,2*S*)-**2** afforded a modest 3.8:1 selectivity favoring the *syn* isomer **9b**. Thus, the highly selective generation of either *syn*- or *anti*-1,3-diol derivatives was possible through appropriate choice of catalyst enantiomer and silyl protecting group.

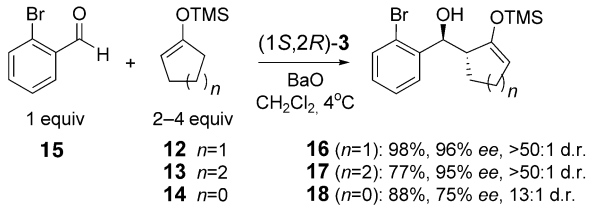
The crude β-hydroxytrimethylsilylenol ether products were obtained by filtration of the reaction mixtures through Celite to remove the 4-Å molecular sieves followed by concentration in vacuo.[7] Analysis of the brown residue by ^{1}H NMR spectroscopy indicated the presence of ene adduct as the only diamagnetic component. Yields were calculated

assuming that the crude product retains 100% of the catalyst by subtracting the mass of catalyst **2** used from the mass of crude product obtained. Purification by chromatography led to significant losses due to product decomposition, and clean products were obtained by flash chromatography in only ca. 35% yield.[8] However, we found that the crude mixture of catalyst and product could be employed in a variety of useful transformations. For example, crude β-hydroxytrimethylsilyl enol ether **6e** was protected as the *tert*-butyldimethylsilyl (TBS) ether,[9] and then a Mukaiyama aldol reaction was carried out with isobutyraldehyde in the presence of $BF_3 \cdot OEt_2$ to generate enantiopure adduct **11** in 83% yield over three steps and a 59:41 *syn*/*anti* ratio of diastereomers (Scheme 3).[10]



Scheme 3.

More sterically hindered silyl enol ether derivatives were also found to undergo asymmetric ene reactions, albeit with significant limitations on the scope of useful aldehyde substrates. While aliphatic aldehydes were unreactive in ene reactions with trimethylsilylenol ethers derived from cyclopentanone (**12**) or cyclohexanone (**13**), 2-bromobenzaldehyde (**15**) underwent clean and highly stereoselective reactions with these enophiles in the presence of catalyst **3** (Scheme 4).[11] High *anti* diastereoselectivity was observed in



Scheme 4.

both reactions, indicating that the ene reaction of the cyclic (*E*)-enol ether proceeds selectively through an endo transition state, as is the case in Cr^{III}-catalyzed hetero-Diels–Alder reactions.[2] Reaction of 2-bromobenzaldehyde (**15a**) with 1-trimethylsilyloxycyclobutene (**14**) as the ene component was also catalyzed by **3**, although the product (**18**) was generated with only moderate enantio- and diastereoselectivity. The trisubstituted trimethylsilyl enol ether products displayed increased stability toward silica gel chromatography, and their purification and full characterization was accomplished after simple filtration of the crude reaction mixture through a small pad of silica gel to remove catalyst.

In summary, tridentate Schiff base chromium(III) complexes **1**–**3** catalyze a wide range of hetero-ene reactions between aromatic or aliphatic aldehydes and silyl enol ether derivatives to generate β-hydroxytrimethylsilyl enol ethers in high enantioselectivities and yields. Current efforts are directed toward elucidation of the mechanism of this process and toward synthetic extensions and applications of this promising methodology.

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[7] The crude β-hydroxytrimethylsilyl enol ether products listed in Table 1 were characterized by ^1H NMR spectroscopy; the purified β-hydroxyketone hydrolysis products were fully characterized.
[8] Separation of the products from the nonpolar catalyst was difficult and required careful chromatography. The low recovery of the silyl enol ether products is attributable to partial hydrolysis due to prolonged exposure to the chromatographic support.
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