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Chromium-Catalyzed Homoaldol Equivalent Reaction Employing a Nucleophilic Propenyl Acetate

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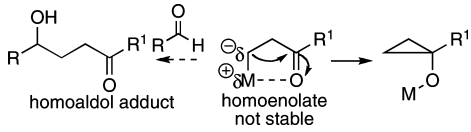
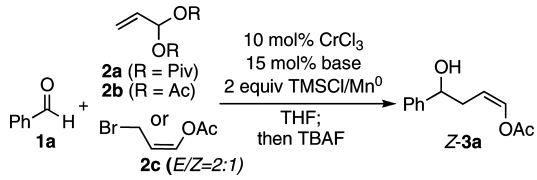
Although the first observation of a presumed homoenolate anion dates back to 1962,[1] the homoenolate retains the status of a synthon, as there are no known literal examples. Despite the utility that homoenolate addition reactions hold for C−C bond construction, as such reactions can be considered to be the polarity reversal of the venerable conjugate addition reaction, direct homoenolate formation is of little practical use due to the simultaneous presence of both nucleophilic and electrophilic sites which undergo rapid cyclization to the oxyanionic isomers.



Several strategies have emerged to access homoenolate equivalents, including the use of acetal-protected Grignard reagents,[2] stoichiometric Li(I),[3] Si(IV),[4] Ti(IV),[5] and Zn(II)[6] reagents, as well as more recent developments in the area of NHC-catalyzed transformations.[7] Separately, chromium-mediated additions of allylic nucleophiles to aldehydes, specifically the Nozaki−Hiyama−Kishi[8] and Takai−Utimoto[9] reactions, as well as the catalytic variant developed by Fürstner,[10] are well-studied processes. Here, we report efficient, catalytic generation of a chromium homoenolate equivalent and application to highly regioselective intermolecular homoaldol reactions which proceed under mild reaction conditions.

Table 1. Initial Screening Results[a]

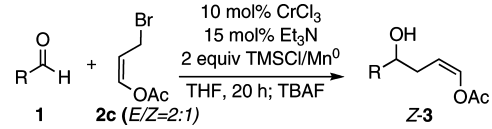


entry	reagent	base	yield (%)[b]	entry	reagent	base	yield (%)[b]
1	**2a**	*i*-Pr_2NEt	0	5	**2b**	*i*-Pr_2NEt	0
2	**2a**	Et_3N	0	6	**2c**	none	45
3	**2b**	none	0	7	**2c**	*i*-Pr_2NEt	90
4	**2b**	Et_3N	0	8	**2c**	Et_3N	99

[a] Reactions were performed using nucleophiles (**2a**, **2b**, or **2c**, 0.64 mmol), aldehyde **1a** (0.32 mmol), $CrCl_3$ (0.032 mmol), Mn^0 (0.64 mmol), Et_3N (0.048 mmol), and TMSCl (0.64 mmol) in 2 mL of THF at rt for 20 h and then quenched with sat. $NaHCO_3$ followed by 1 M TBAF. [b] Isolated yield.

Previous studies by Lombardo had shown that acetoxyallyl chlorides are poor nucleophiles in Cr-catalyzed additions to aldehydes,[11] so we chose to employ masked carbonyls **2a** and **2b** (acetals), and the presumably more reactive allyl bromide **2c** (3-bromopropenyl acetate) as nucleophiles in additions to benzaldehyde (Table 1). Nucleophiles **2a** and **2b** were not competent in the reaction (0% yield), but bromide **2c** provided the desired product in 45% yield. We surmised that the presence of an amine base would increase the reactivity of this system.[12] Notably, we observed a significant increase in the yield of the reaction in the presence of catalytic Et_3N, leading to a 99% yield of regiomerically pure **3a** (Table 1, entry 8). Other bases, including chelating diamines, were less effective.[13]

Table 2. Scope of Homoaldol Equivalent Reaction[a]



entry	SM	R	product	yield (%)[b]
1	**1a**	Ph	**3a**	99
2	**1b**	*p*-$MeOC6H_4$	**3b**	90
3	**1c**	*p*-$CF3C6H_4$	**3c**	91
4	**1d**	*o*-MeC_6H_4	**3d**	82
5	**1e**	*o*-BrC_6H_4	**3e**	78
6	**1f**	PhCHCH	**3f**	85
7	**1g**	$PhCH_2$	**3g**	75
8	**1h**	$PhCH_2CH_2$	**3h**	80
9	**1i**	C_6H_{11}	**3i**	96
10	**1j**	*p*-$CH_3COC_6H_4$	**3j**	70
11	**1k**	*p*-$CH_3O_2CC_6H_4$	**3k**	71
12	**1l**	*p*-NCC_6H_4	**3l**	75
13[c]	**1m**	*p*-$TBSOC_6H_4$	**3m**	99
14	**1n**	*m, p*-$(OCH_2O)C_6H_4$	**3n**	96

[a] Reactions were performed using **2c** (0.64 mmol), aldehydes **1** (0.32 mmol), $CrCl_3$ (0.032 mmol), Mn^0 (0.64 mmol), Et_3N (0.048 mmol), and TMSCl (0.64 mmol) in 2 mL of THF at rt for 20 h, quenched with sat. $NaHCO_3$ and deprotected with TBAF. [b] Isolated yield. [c] 24 h reaction.

With these catalytic reaction conditions in hand, we explored the scope of the reaction of various aldehydes with nucleophile **2c**. The results are summarized in Table 2. Aromatic, aliphatic, and α,β-unsaturated aldehydes undergo clean reaction to provide the desired products in good to excellent yields after 20 h at room temperature. It appears that steric effects are more important than electronic effects in modulating aldehyde reactivity. For instance, the bulkier *o*-substituted aldehydes 2-methylbenzaldehyde (**1d**) (entry 4) and 2-bromobenzaldehyde (**1e**) (entry 5) provide somewhat lower but still acceptable product yields (82% and 78% yields, respectively) compared to the high yields (approximately 90%) obtained from the electronically differentiated *p*-substituted aldehydes (*p*-OMe vs *p*-CF_3) **1b**/**1c**. Potentially reactive functionalities including ketone (**1j**), ester (**1k**), nitrile (**1l**), and acetal (**1n**) are compatible with the desired reaction.

In all cases, none of the potential 1,2-oxygenated regioisomeric product is observed, and none of the *trans*-vinyl acetate product is observed. We preliminarily attribute these observations to the formation of a 5-membered ring chelate between a proximal acetate and the chromium center as part of a well-established 6-membered ring transition state arrangement for the C−C bond-forming reaction. This arrangement correctly rationalizes the product's *cis*-

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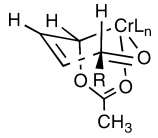
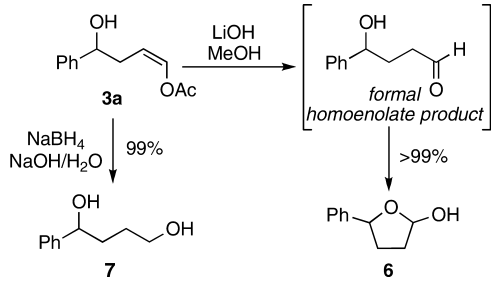
alkene geometry as well as the observed regiochemistry of the addition reaction.



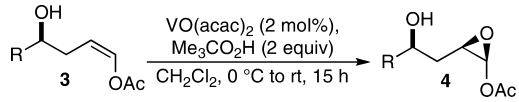
Because of the potential utility of this process for creating chiral building blocks applicable to total synthesis, we investigated larger-scale reactions. Upon utilizing 2 mmol of benzaldehyde, we still were able to isolate a 99% yield of product **3a**. On even larger scales, care must be taken to use Mn^0 which has been freshly washed with HCl to obtain high yields. On 5 or 20 mmol scale, the isolated yield of product **3a** is 90% or 85%, respectively.

Scheme 1. Hydrolysis and Reduction of Homoaldol Equivalent Product



We next focused on the manipulation of the homoaldol equivalent products to demonstrate the value of the proximal hydroxyl and vinyl acetate groups. Hydrolysis of adduct **3a** under mild conditions (LiOH/MeOH/rt) provides the formal homoaldol product, which is isolated after spontaneous cyclization to lactol **6** (Scheme 1) in quantitative yield, as expected.[11] Alternatively, reduction of **3a** with $NaBH_4$ in $NaOH/H_2O$ provides 1,4-diol **7** in excellent yield (99%).

Table 3. Hydroxyl-Directed Epoxidation of Vinyl Acetates[a]



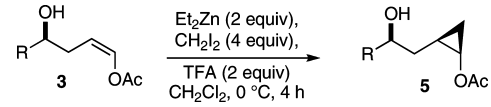
entry	SM	R	product	yield (%)[b]	dr[c]
1	**3a**	Ph	**4a**	82	13:1
2	**3e**	*o*-BrC_6H_4	**4e**	80	>15:1
3	**3i**	C_6H_{11}	**4i**	82	10:1

[a] Reagents: $VO(acac)_2$ (2 mol %), adducts **3** (1 mmol), TBHP (5.5 M solution) (2 mmol) in CH_2Cl_2 at rt for 15 h. [b] Isolated yield. [c] dr (syn:anti) was determined by ^1H NMR spectroscopy; see Supporting Information.

Surprisingly, hydroxyl-directed[14] epoxidations and cyclopropanations of vinyl acetates have not been previously reported. We were hopeful that the proximal acetate would not interfere with the directing ability of the homoallylic alcohol. Gratifyingly, directed epoxidation (2 mol % $VO(acac)_2$, *t*-BuOOH) of **3a** installed the epoxide/acetal, providing the 1,2,4-oxygenated α-acetoxy-δ-hydroxy α,β-epoxide in 82% yield as primarily the syn diastereomer (dr = 13:1, entry 1, Table 3). Diastereoselectivity was slightly better in the case of the bulkier *o*-substituted alcohol **3e** but slightly lower in the case of the aliphatic alcohol **3i**.

Treatment of **3a** with Shi's cyclopropanation reagent ($CF_3CO_2ZnCH_2I$)[15] afforded the desired cyclopropane (dr = 6.6:1) in excellent yield (95%) with diastereoselectivity consistent with hydroxyl direction. Several other substrates underwent cyclopropanation with good yields and diastereoselectivities (Table 4), again indicating that the proximal acetate does not interfere with this directed reaction.

Table 4. Hydroxyl-Directed Cyclopropanation of Vinyl Acetates[a]



entry	SM	R	product	yield (%)[b]	dr[c]
1	**3a**	Ph	**5a**	95	6.6:1
2	**3d**	*o*-MeC_6H_4	**5d**	84	5:1
3	**3i**	C_6H_{11}	**5i**	88	6:1
4	**3e**	*o*-BrC_6H_4	**5e**	80	3.8:1

[a] All reactions were performed using Et_2Zn (1 mmol), CH_2I_2 (2 mmol), TFA (1 mmol), olefin **3** (0.5 mmol) in CH_2Cl_2 at 0 °C for 4 h. [b] Isolated yield. [c] dr (syn:anti) was determined by HPLC; see Supporting Information.

In summary, we have reported a scalable, highly regioselective, catalytic homoaldol equivalent reaction employing 3-bromopropenyl acetate as a masked homoenolate nucleophile under mild Cr/Mn redox conditions. This reaction allows rapid access to stereo- and regiochemically enriched 1,4-oxygenated compounds which can be further manipulated to a variety of synthetically valuable compounds.

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Supporting Information Available: Experimental procedures, ^1H and ^{13}C NMR spectra of new compounds, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

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