COMMUNICATION

ChemComm
www.rsc.org/chemcomm

3-Chloropropenyl pivaloate in organic synthesis: the first asymmetric catalytic entry to *syn*-alk-1-ene-3,4-diols

Marco Lombardo,* Sebastiano Licciulli, Stefano Morganti and Claudio Trombini*
Università di Bologna, Dipartimento di Chimica "G. Ciamician", via Selmi 2, I-40126 Bologna, Italy.
E-mail: trombini@ciam.unibo.it, marlom@ciam.unibo.it; Fax: +39 051 2099456

Received (in Cambridge, UK) 25th April 2003, Accepted 4th June 2003
First published as an Advance Article on the web 18th June 2003

The first asymmetric catalytic synthesis of *syn*-alk-1-ene-3,4-diols was developed; the regio-, diastereo- and enantioselective addition of 3-chloropropenyl pivaloate to aldehydes was made possible by exploiting Salen–Cr(II) species, in a catalytic version of the Nozaki–Hiyama–Kishi reaction.

One of the most valuable routes to the alk-1-ene-3,4-diol **1** motif involves the formal nucleophilic addition of 1-hydroxyallyl anion (**2**) to carbonyl compounds. So far, molecular design has supplied a number of heterosubstituted allylic organometallic compounds **3**,[1] acting as synthetic equivalents of **2** (Scheme 1), but asymmetric catalytic solutions are still lacking.[2]

We recently reported the use of 3-halopropenyl esters **4** in Barbier–Grignard carbonyl additions using In(0)[3] or Zn(0),[4] in an efficient, practical, regioselective and environmentally friendly route to racemic *syn*- or *anti*-**1** (Scheme 2).

Simple diastereoselectivity was found to basically depend on the nature of the aldehyde, saturated aldehydes affording *anti*-adducts, and aromatic aldehydes and ketones favoring formation of *syn*-**1**.

Here, we wish to report the first catalytic asymmetric synthesis of *syn*-**1**, by applying Cr(II) chemistry[5] to 3-chloropropenyl pivaloate (**6**).

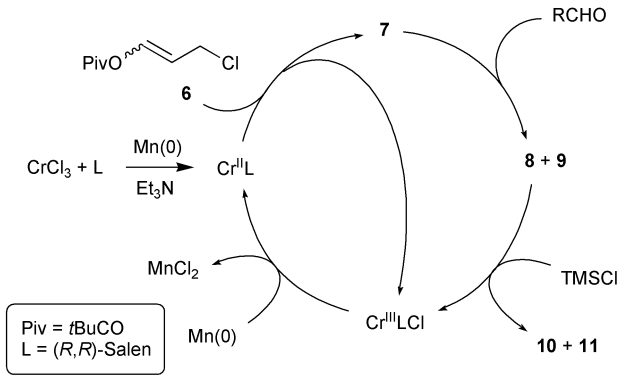
Even though the use of environmentally and toxicologically hazardous metals (chromium is listed as a priority pollutant by US EPA)[6] is discouraged by green chemistry concerns, the chromium star is not fading thanks to the availability of catalytic protocols. A very significant achievement was accomplished by Fürstner who developed a catalytic version of the Nozaki–Hiyama–Kishi reaction based on the combined use of the redox Mn(0)/Cr(III) couple and of trimethylsilyl chloride (TMSCl).[5c,7] Moreover, the integration of the Fürstner protocol with the addition of the Jacobsen's Salen [*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine] and triethylamine[8] allowed Cozzi, Umani-Ronchi *et al*. to develop a catalytic enantioselective route to homoallylic alcohols.

When we applied the Fürstner protocol to 3-chloropropenyl pivaloate (**6**) in the presence of a supplementary achiral ligand (L = Bu_4NI) in acetonitrile at 22 °C, the catalytic cycle depicted in Scheme 3 afforded (*Z*)-enolester **11a** (R = cyclohexyl) in 40% yield accompanied by 5% of **10a**, as a 4 : 1 *syn–anti* mixture.[9]

Thoroughly unexpected was the change in terms of regioselectivity when the same process was carried out in the presence of a chiral ligand [L = (*R*,*R*)-Salen] and Et_3N; under this condition *syn*-enriched adduct **10a** was obtained as the main product (Table 1, entries 1, 2).

The likely destabilization suffered by α-**7** due to the proximity of two sterically encumbered groups, namely the pivaloate ester and the chiral chromium–ligand unit, could account for this dramatic effect on regioselectivity.

Increasing the amount of Salen and Et_3N from 10 and 20% (Table 1, entry 1), to 20 and 40% (Table 1, entry 2),

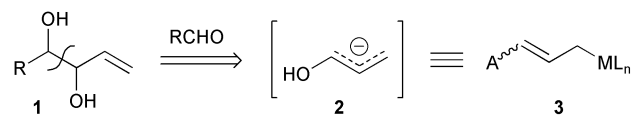


Scheme 3

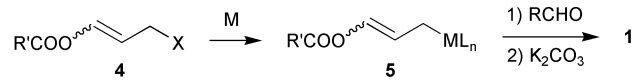
Table 1 (*R*,*R*)-Salen–Cr(II) catalysed reactions of **6** with a few representative aldehydes[a]

Entry	R of RCHO	**10**, Yield (%)	*syn* : *anti*[b]	*syn* e.e. (%)[c]	*anti* e.e. (%)[c]
1[d]	Cyclohexyl	**10a**, 47	82 : 18	84	48
2	Cyclohexyl	**10a**, 68	83 : 17	94	67
3	Pentyl	**10b**, 50	83 : 17	93	65
4	2-Phenylethyl	**10c**, 78	85 : 15	99	85
5	Isopropyl	**10d**, 42	72 : 28	92	77
6	2-Methylpropyl	**10e**, 55	80 : 20	92	60
7	Phenyl[e]	**10f**, 77	71 : 29	64	43
8	4-Methoxyphenyl	**10g**, 82	74 : 26	65	51
9	2-Naphthyl	**10h**, 60	78 : 22	73[f]	23[f]

[a] Reactions were carried out at 20–25 °C for 18 h using 20% Salen and 10% $CrCl_3$. See ref. 10. [b] Determined by GC-MS analysis of adducts **10** in the crude reaction mixture. [c] E.e.'s were determined by chiral GC analysis of 1,3-dioxolanes **12** (see ref. 11). [d] 10% Salen and 10% $CrCl_3$ were used; **11a** was isolated in 17% yield. [e] Extending the reaction time to 66 h, no change in chemical yield and stereoisomer composition was observed. [f] E.e. values were obtained by chiral HPLC analysis (Chiralcel OD, hexane–isopropanol) of *syn*- and *anti*-**1**.

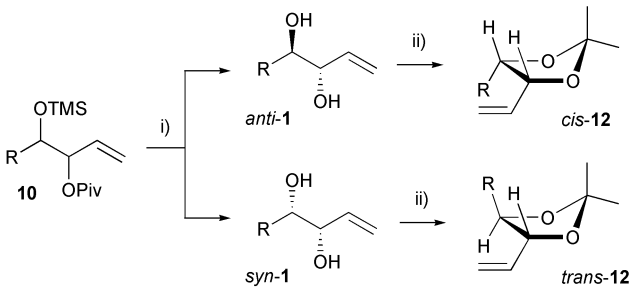


Scheme 1 A = OR, BR_2, SiR_3.



Scheme 2 R′ = CH_3, Ph; X = Cl, Br; M = In(0), Zn(0).

DOI: 10.1039/b304485h



Scheme 4 i) $LiAlH_4$, THF; ii) $Me_2C(OMe)_2$, Amberlyst® 15H, CH_2Cl_2.

respectively, made regioselectivity virtually complete in favour of **10a**. Even more exciting was the effect of increasing the relative amount of Salen and Et_3N on relative and absolute stereocontrol exhibited by the pivaloate ester **6**; while simple *syn*-diastereoselectivity increased to 64% d.e., 94% e.e. was obtained for the major *syn*-isomer, and 67% e.e. for *anti*-**10a** (Table 1, entry 2).

In order to evaluate the scope of the reaction, experiments were performed with **6** using a few representative aldehydes and adopting a carefully controlled synthetic protocol;[10] the results are collected in Table 1.

Products **10** are obtained in good yield and excellent enantiomeric purity, particularly when aliphatic aldehydes are involved (Table 1, entries 2–6), while a lower control of the absolute stereochemistry is displayed by aromatic aldehydes (Table 1, entries 7–9).

To unambiguously ascertain the *syn*/*anti* stereorelationships, adducts **10** were deprotected to alk-1-ene-3,4-diols **1** with $LiAlH_4$, and compared with authentic specimens obtained in racemic form using the zinc-promoted acetoxyallylation of the same aldehydes with **4** (R′ = CH_3, X = Br).[3,4] Diols **1** were transformed into 1,3-dioxolanes **12** and e.e.'s were determined for **12** by chiral GC (Scheme 4).[11]

The stereopreference of (*R*,*R*)-Salen–chromium complex **7**, invariably used in all the experiments, for the attack to the *si* face of the aldehyde, was unambiguously established in three cases;[12] this observation was in agreement with the stereopreference exhibited by other allylic complexes.[8]

In conclusion, only a limited number of stoichiometric diastereo- and enantioselective routes to *syn*-**1**[13] or *anti*-**1**[14] *via* nucleophilic addition of chiral heterofunctionalized allylic complexes **3** to aldehydes are available.

The asymmetric synthesis of *syn*-**1** proposed here represents the first enantioselective catalytic route to this class of molecules, and provides a new highly competitive synthetic opportunity to address the synthesis of densely functionalized intermediates, thanks to the synthetic flexibility of the carbon–carbon double bond.

This work was supported by MIUR-Rome (National Project "Stereoselezione in Sintesi Organica. Metodologie e Applicazioni" and FIRB funds to CT, 2002).

Notes and references

1 A. R. Katritzky, M. Piffl, H. Lang and E. Anders, *Chem. Rev.*, 1999, **99**, 665.

2 A catalytic version of the Utimoto reaction leading to (±)-*anti*-**1** has been recently reported: R. K. Boeckman, Jr. and R. A. Hudack, *J. Org. Chem.*, 1998, **63**, 3524.

3 M. Lombardo, R. Girotti, S. Morganti and C. Trombini, *Org. Lett.*, 2001, **3**, 2981.

4 (*a*) M. Lombardo, S. Morganti, F. d'Ambrosio and C. Trombini, *Tetrahedron Lett.*, 2003, **44**, 2823; (*b*) M. Lombardo, S. Morganti and C. Trombini, *J. Org. Chem.*, 2003, **68**, 997; (*c*) M. Lombardo, R. Girotti, S. Morganti and C. Trombini, *Chem. Commun.*, 2001, 2310.

5 Low-valent chromium species have attracted the attention of synthetic chemists for the last three decades since they offer chemo-, regio- and stereoselective solutions to carbon–carbon bond-forming reactions, as highlighted by three recent review articles: (*a*) M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez and J. C. Palacios, *Chem. Soc. Rev.*, 1999, **28**, 169; (*b*) L. A. Wessjohann and G. Scheid, *Synthesis*, 1999, 1; (*c*) A. Fürstner, *Chem. Rev.*, 1999, **99**, 991.

6 S. Sasnett, T. Murray, S. Canavan, J. Alter, K. Davey and P. Matthai, *ACS Symp. Ser.*, 2001, **773** (Persistent, Bioaccumulative, and Toxic Chemicals II), 114. See also the US EPA web site: http://oaspub.epa-.gov/wqsdatabase/wqsi_epa_criteria.rep_parameter.

7 A. Fürstner and N. Shi, *J. Am. Chem. Soc.*, 1996, **118**, 12349.

8 (*a*) M. Bandini, P. G. Cozzi, P. Melchiorre and A. Umani-Ronchi, *Angew. Chem., Int. Ed.*, 1999, **38**, 3357; (*b*) M. Bandini, P. G. Cozzi and A. Umani-Ronchi, *Angew. Chem., Int. Ed.*, 2000, **39**, 2327; (*c*) M. Bandini, P. G. Cozzi and A. Umani-Ronchi, *Tetrahedron*, 2001, **57**, 835.

9 M. Lombardo, S. Morganti, S. Licciulli and C. Trombini, *Synlett*, 2003, 43.

10 In a typical experimental procedure, anhydrous CH_3CN (2.5 ml) is poured under argon into a reaction flask where $CrCl_3$ (16 mg, 0.1 mmol) was previously heated at about 300 °C with a heat gun for 5 min. To this suspension freshly crushed manganese (110 mg, 2 mmol) is added, the mixture is left undisturbed for 5 min and then vigorously stirred for 2 h at 20–25 °C. The following chemicals are consecutively added at precise time intervals, while maintaining an efficient stirring at 20–25 °C: i) Salen (110 mg, 0.2 mmol) and anhydrous triethylamine (56 µl, 0.4 mmol), 1 h (the mixture turns dark red-brown); ii) 3-chloropropenyl pivaloate **6** (245 µl, 1.5 mmol), 1 h; iii) aldehyde (1 mmol) and trimethylsilyl chloride (152 µl, 1.2 mmol), 18 h (the reaction mixture slowly turns yellow-brown and becomes thicker). Quenching is performed with sat. aq. $NaHCO_3$, the resulting mixture is filtered over Celite®, extracted with ether, and flash-chromatographed on silica-gel. Two fractions are collected, corresponding to *syn*/*anti* **10** and to desilylated **10**, respectively. The following tricks need to be considered to achieve good results: i) crushing manganese chips (Aldrich, 99.98%) in a mortar invariably affords a much more reactive metal with respect to the use of commercial manganese powder of the same purity; ii) immediately before use, trimethylsilyl chloride is purified by elution through a short column packed with basic alumina.

11 Derivatisation of diols **1** into 1,3-dioxolanes **12** was carried out as reported in ref. 4*b*; GC analysis was performed using a β-cyclodextrin Megadex5 column (length 25 m, internal diameter 0.25 mm, film thickness 0.25 µm) using hydrogen as carrier gas (1 ml min^{-1}).

12 The 3*S*,4*S* configuration of *syn*-**10b** deriving from hexanal (Table 1, entry 3) was confirmed by direct comparison of the optical properties of the known compound: found $[\alpha]_D^{20} = -22.5°$ (*c* = 1, $CHCl_3$) lit. $[\alpha]_D^{20} = -23.3°$ (*c* = 1, $CHCl_3$), see T. Matsumoto, Y. Kitano and F. Sato, *Tetrahedron Lett.*, 1988, **29**, 5685. The 3*S*,4*S* configuration of *syn*-**10f** and the 3*R*,4*S* configuration of *anti*-**10f** (Table 1, entry 7) were also unambiguously established by the enhancement of the GC peaks of *trans*- **12f** and *cis*-**12f**, obtained from *syn*-**10f** and *anti*-**10f**, respectively, with authentic 4*S*,5*S trans*-**12f** and 4*S*,5*R cis*-**12f** obtained after vinylation of (*S*)-*O*-TBS-mandelic aldehyde (CH_2=CH–MgCl, THF, 0 °C, 90%, 60% d.e. in favour of the *anti*-adduct), desilylation (Bu_4NF, THF, 20 °C) and protection as the dioxolanes **12f**.

13 (*a*) P. V. Ramachandran, J. S. Chandra and M. V. R. Reddy, *J. Org. Chem.*, 2002, **67**, 7547 and references therein (*b*) R. S. Coleman and J.-S. Kong, *J. Am. Chem. Soc.*, 1998, **120**, 3538; (*c*) J.-I. Chika and H. Takei, *Tetrahedron Lett.*, 1998, **39**, 605; (*d*) P. Ganesh and K. M. Nicholas, *J. Org. Chem.*, 1997, **62**, 1737; (*e*) I. Kadota, K. Kobayashi, H. Okano, N. Asao and Y. Yamamoto, *Bull. Chim. Soc. Fr.*, 1995, 615; (*f*) W. R. Roush and M. S. VanNieuwenhze, *J. Am. Chem. Soc.*, 1994, **116**, 8536.

14 (*a*) J. Cossy, C. Willis, V. Bellosta and L. Saint-Jalmes, *Synthesis*, 2002, 951; (*b*) W. R. Roush, A. N. Pinchuk and G. C. Micalizio, *J. Org. Chem.*, 2000, **65**, 8730; (*c*) H. C. Brown and G. Narla, *J. Org. Chem.*, 1995, **60**, 4686; (*d*) J. A. Hunt and W. R. Roush, *Tetrahedron Lett.*, 1995, **36**, 501; (*e*) W. R. Roush, P. T. Grover and X. Lin, *Tetrahedron Lett.*, 1990, **31**, 7563.