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3-Halopropenyl esters as precursors of a new class of oxygen-substituted allylic organometallic compounds: Applications in organic synthesis*

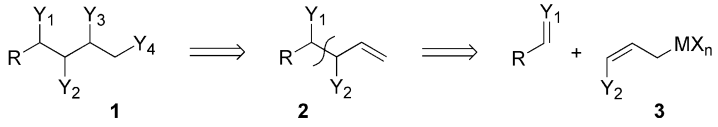
Marco Lombardo, Sebastiano Licciulli, and Claudio Trombini‡

Dipartimento di Chimica "G. Ciamician", University of Bologna, Bologna, Italy

Abstract: 3-halopropenyl esters, readily prepared by the addition of acyl halides to acrolein, react with zinc, indium, and chromium(II), thus opening a route to a new class of oxygen-substituted allylic organometallic compounds. Indium and zinc reagents smoothly add to carbonyl compounds, affording alk-1-en-3,4-diol derivatives in a variety of synthetic procedures which include typical Grignard stepwise conditions as well as Barbier one-pot protocols. Using zinc and indium in water or aprotic solvents, simple diastereoselectivity was found to depend on the nature of the carbonyl compound; conjugated aldehydes favor formation of *syn*-adducts while unconjugated aldehydes favor *anti*-adducts. Moving to chromium, a reversal of regioselectivity was observed in favor of (*Z*)-4-hydroxy-enolacetates, flexible protected forms of homoaldols. Chromium complexes are generated in a catalytic cycle based on the combined use of the redox Mn(0)/Cr(III) couple and of TMSCl. When the Cr-catalyzed reaction is carried out in the presence of Jacobsen's *Salen* ligand, the regiochemical outcome of the reaction is again reversed, and *syn*-alk-1-en-3,4-diols are formed in high ee's.

INTRODUCTION

A challenge for synthetic chemists is offered by open chain systems containing sequences of contiguous heterosubstituted stereocenters, which are present in a number of naturally occurring compounds as well as in important families of natural and synthetic drugs (e.g., monosaccharide derivatives). In terms of synthetic efficiency, formation of carbon–carbon bonds and creation of stereocenters with the correct functionality should occur in the most limited number of steps. An example of a densely functionalized carbon chain is offered by structure **1**, where Y_1–Y_4 substituents are oxygen or nitrogen groups: a straightforward access to **1** is represented in Scheme 1. The availability of a great arsenal of tools to functionalize carbon–carbon double bonds, appoints species **2** as an attractive precursor of **1**. In turn, **2** is accessible via stereocontrolled addition of a γ-heterofunctionalized allylic organometallic reagent **3** to a carbonyl compound or to an azomethine derivative [1].



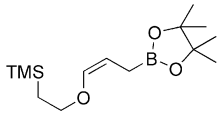
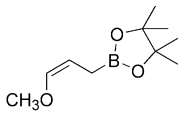
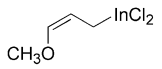
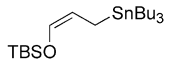
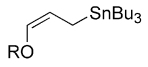
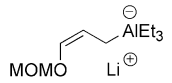
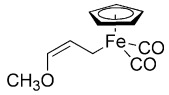
Scheme 1

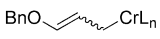
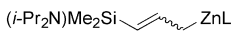
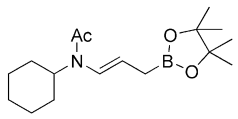
*Plenary and invited lectures presented at the 12th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-12), Toronto, Ontario, Canada, 6–10 July 2003. Other presentations are published in this issue, pp. 453–695.

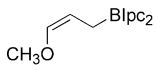
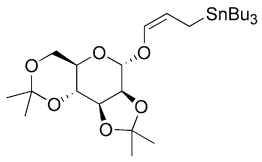
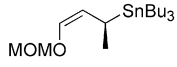
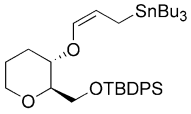
‡Corresponding author

A representative list of organometallic reagents **3** is reported in Table 1. They are classified on the basis of two criteria: (i) achiral or enantiomerically pure complexes **3**, and (ii) simple diastereoselectivity exhibited in the addition of **3** to aldehydes.

Table 1 Selected γ-heterofunctionalized allylic organometallic reagents **3**.

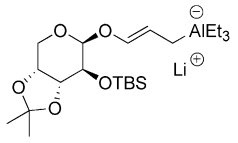
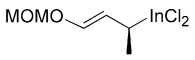
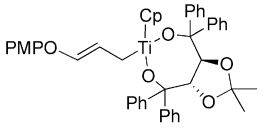
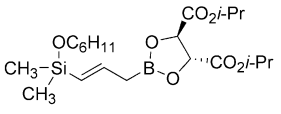
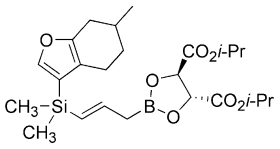
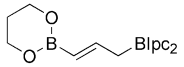
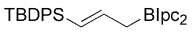
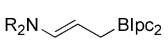
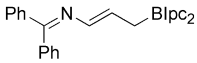
Achiral *syn* selective reagents 3		
 **3a,** [2]	 **3b**, [3]	 **3c**, [4]
 **3d**, [5]	 **3e**, [6]	 **3f**, [7]
 **3g**, [8]		

Achiral *anti* selective reagents 3		
 **3h,** [9]	 **3i**, [10]	 **3j**, [11]

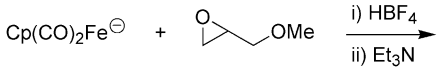
Optically active *syn* selective reagents 3		
 **3k**, [12]	 **3l**, [13]	 **3m**, [14]
 **3n**, [15]		

(*continues on next page*)

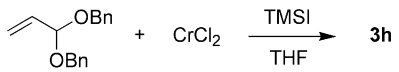
Table 1 (*Continued*).

Optically active *anti* selective reagents 3		
		
3o, [16]	**3p**, [17]	**3q**, [18]
		
3r, [19]	**3s**, [20]	**3t**, [21]
		
3u, [22]	**3v**, [23]	**3w**, [24]

With the exception of **3g**, **3h**, and **3t**, prepared according to eqs. 1–3, formation of **3** invariably requires a two-step procedure involving lithiation of the corresponding substrate **4** (allyl ether, allyl silane, etc.) followed by transmetallation of **5** with the suitable metal halide derivative (eq. 4).



(1)



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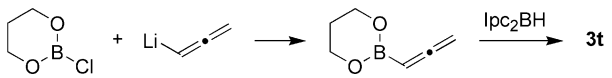
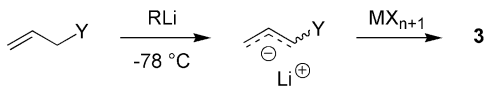


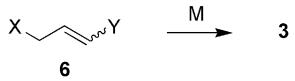
(3)



(4)

Y = heteroatom bearing groups

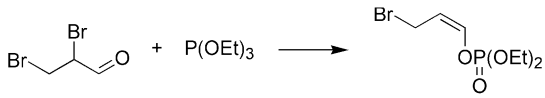
We investigated the possibility to approach species **3** by exploiting the oxidative addition of a low-valent metal M into the carbon–halogen bond of a properly tailored 3-halopropenyl derivative **6** (eq. 5). Compared to the lithiation/transmetallation protocol, advantages of an oxidative addition process, particularly using indium and zinc in water, are apparent in terms of economic and environmental costs.



(5)

A first literature survey revealed an extremely limited number of routes to synthons **6**, enol derivatives of 3-halopropanal; they include the Perkow reaction [Y = $PO(OEt_2)$] (eq. 6) [25], the addition of gaseous HCl or HBr to methoxypropadiene (Y = OMe) (eq. 7) [26], the addition of TMSI to propenal (Y = OTMS) (eq. 8) [27], and the radical bromination of a sugar-derived allylic ether (Y = O-sugar)

(eq. 9) [28]. Attempts in our lab to expand to other allylic ethers (CH_2=CH-CH_2-O*P*, where *P* = SiR_3, COR) the radical route to **6** via allylic bromination with NBS failed, with the exception of an allylic carbamate (*P* = $CONR_2$) (eq. 10) [29]. We also investigated the dehydroalogenation of *vic*-dibromo-ethers, but the regioselective formation of the undesired vinylic bromide was observed (eq. 11) [29]. Eventually, an exceptionally simple solution was devised in an almost forgotten reaction, the halo-acylation of acrolein [30], which affords 3-halopropenyl esters **7** (eq. 12) in multigram scale and in very good yields.



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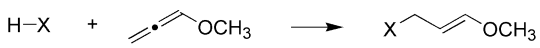

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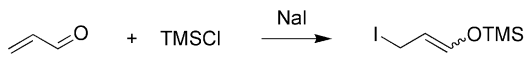

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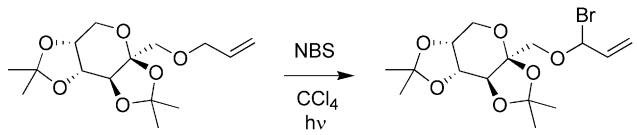

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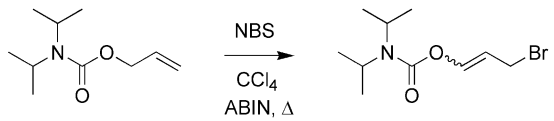
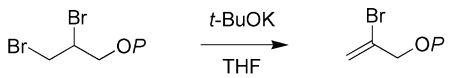
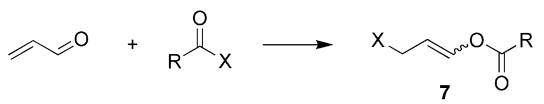


(10)



P = SiR_3, COR, Ms
(11)

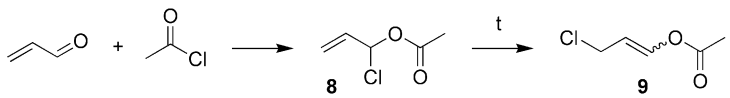


(12)

PREPARATION OF 3-HALOPROPENYL ESTERS

The reaction of acyl halides (RCOX) with aldehydes (R′CHO), formerly observed by Wurtz [31] and Simpson [32], was correctly elucidated by Schiff [33] in 1876 to give 1-halo-alkyl esters R′CHXOCOR. The scope of the reaction was examined in 1918 [34], but only in the 1970s the haloacylation of carbonyl compounds was retrieved by Neuenschwander [35] and successively exploited by Knochel [36] as a tool for the preparation of carbenoid species. Haloformates similarly add to aldehydes to give 1-haloalkyl carbonates [37].

In 1938, the reaction of acrolein with acetyl chloride was reported [30] to give the expected 1,2-adduct **8** which, upon standing for several weeks, slowly rearranged into 3-chloropropenyl acetate (**9**), the formal 1,4-addition product (eq. 13). Later on, Neuenschwander [38] demonstrated that conversion of **8** into **9** is almost complete in a few hours when the reaction is carried out in the presence of



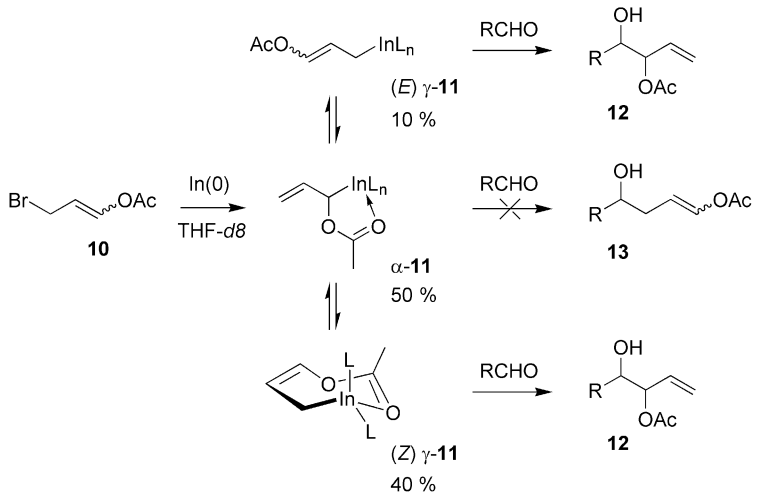
(13)

anhydrous $ZnCl_2$ (5–10 % at 0 °C). Even more rapid is the formation of 3-bromopropenyl acetate (**10**) using acetyl bromide at –20 °C.

OXIDATIVE ADDITION OF INDIUM TO 3-BROMOPROPENYL ACETATE

The oxidative addition of In(0) to allyl bromide gives rise to discrete organoindium species both in water and in organic solvents, as evidenced by Chan and Yang in an elegant NMR study [39]. In particular, allylindium(I) is the only organometallic species observed in D_2O, while in DMF solution allylindium(I) undergoes conversion into a second complex, likely an allylindium(III) species which does not correspond to the generally proposed sesquibromide structure.

When 3-bromopropenyl acetate (**10**) reacts with indium in THF-d_8, the initial enolic signals of **10** ebb and new signals, attributed to allylic indium intermediates (*E*) γ–**11**, (*Z*) γ–**11**, and α-**11**, appear, reach a maximum after 0.5 h, and then keep almost constant for the following 20 h (Scheme 2). Intermediates **11** should correspond to In(III) species, since allylic In(I) complexes should be short-lived species according to Chan [39] and their signals should disappear after a few hours. Since the same α-**11**/(*Z*) γ–**11**/(*E*) γ–**11** ratio was observed using either (*E*-) or (*Z*)-enriched **10**, the composition of allylindium species observed at the NMR is supposed to be the result of a thermodynamic equilibration [40].



Scheme 2

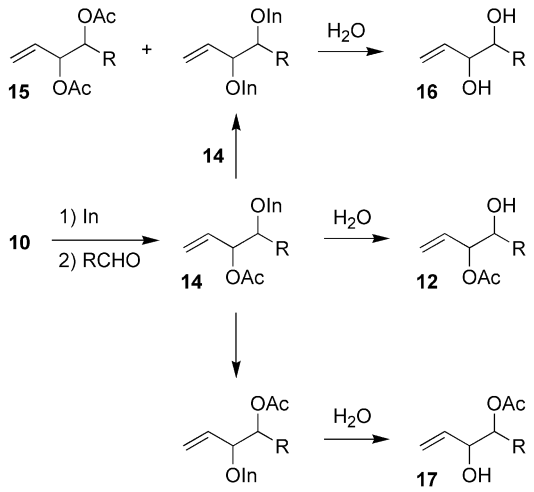
Trapping experiments (^{1}H NMR) of indium species **11** with a submolar amount of cyclohexanecarboxaldehyde proved that: (i) (*Z*) γ–**11** is ten times more reactive than (*E*) γ–**11**, (ii) the rate of addition both of (*E*) γ–**11** and (*Z*) γ–**11** to the aldehyde is faster than the haptotropic rearrangement (*E*) γ–**11** ⇔ (*Z*) γ–**11**, and (iii) addition of α-**11** to the aldehydes does not occur, since traces of the expected enolacetates **13** have been never detected (Scheme 2).

Regarding the oxidative addition mechanism there is no conclusive evidence about the predominance either of two-electron mechanisms or of one-electron mechanisms involving free-radical intermediates [41]; however, the presence of minor amounts of Wurtz-type dimers makes the latter mechanism more plausible.

Water was also examined as reaction medium for detecting allylic indium species. Following by ^{1}H NMR the reaction of an equimolar amount of **10** and indium in D_2O, two doublets are observed after 5 min at 6.55 (J = 6.0 Hz, 1H) and 1.57 ppm (J = 9.6 Hz, 2H); they can be assigned to a discrete (*Z*) γ–**11** allylic indium(I) species, which rapidly decomposes to Wurtz coupling products.

INDIUM- AND ZINC-PROMOTED α-HYDROXYALLYLATION OF CARBONYL COMPOUNDS IN ORGANIC SOLVENTS (GRIGNARD PROTOCOL)

Once established that allylindium species can be easily formed in THF and that they are stable for several hours, the first synthetic protocol to alk-1-en-3,4-diols we have developed was a classical two-step Grignard reaction: **10** is first reacted with indium, then an aldehyde is added to the preformed organoindium derivative [40,42]. Temperature of both steps can be adjusted in the 0–25 °C interval. Careful analysis of the reaction of **11** with cyclohexanecarboxaldehyde reveals the occurrence of acetyl scrambling reactions leading to formation of diesters **15**, monoesters **12** and **17**, and diols **16**, as shown in Scheme 3. Isolation of **17** reveals that it consists of a virtually pure *syn*-adduct, able to adopt a sterically acceptable eclipsed conformation required by the intramolecular acyl transfer reaction. On the other hand, both diesters **15** and diols **16**, coming from intermolecular acyl transfer processes, correspond to *anti*-enriched adducts.



Scheme 3

Water is not suited for Grignard protocols for the instability of **11** in this medium, however, water can be added as cosolvent in the second step because nucleophilic addition of **11** to the carbonyl group was found to be faster than hydrolysis. The presence of water completely inhibits the intermolecular acetyl transfer reactions, while it does not affect the intramolecular rearrangement to **17**.

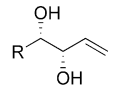
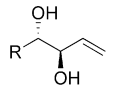
Complexity of the reaction mixture does not represent a drawback, since a simple alkaline workup (K_2CO_3 in H_2O/MeOH) quantitatively converts esters **12**, **15**, and **17** into a *syn/anti* mixture of alk-1-en-3,4-diols **16**.

A list of selected results is reported in Table 2.

Even though simple diastereoselectivity does not reach high levels, the stereochemical outcome of these reactions deserves attention. Indeed, *syn/anti* simple diastereoselectivity was found to depend on the nature of the carbonyl compound, in particular saturated aldehydes favor formation of *anti*-adducts and conjugated aldehydes formation of *syn*-adducts. Conversely, *syn/anti* diastereoselectivities exhibited by organometallic species **3** (Table 1) can be mainly charged to the metal and to the C–C double bond configuration.

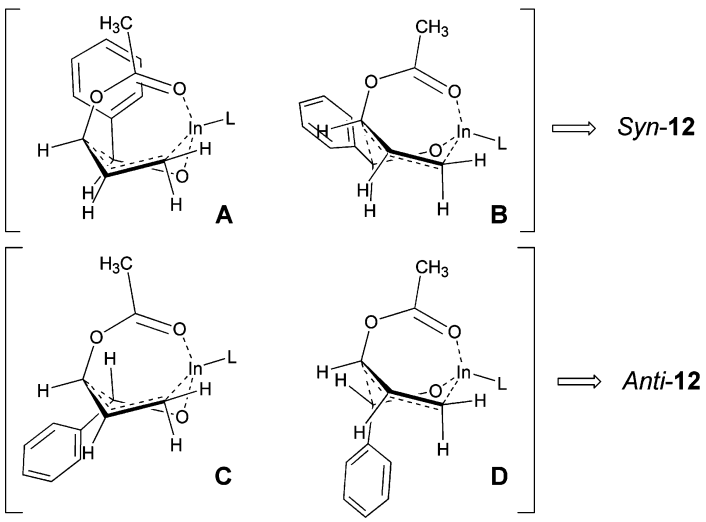
Such a stereochemical behavior, unprecedented in the chemistry of oxygen or nitrogen-substituted allylic organometallic compounds **3**, was demonstrated not to depend on thermodynamic control. Indeed, quenching experiments at different reaction times both with cyclohexanecarboxaldehyde and benzaldehyde (chosen as prototypes of a saturated and a conjugated aldehyde, respectively), did not re-

Table 2 In-promoted synthesis of *syn*-**16** and *anti*-**16** under Grignard conditions.

 ***Syn*-16**			 ***Anti*-16**		
R	**Y (%)**	***Syn*:*Anti***	**R**	**Y (%)**	***Syn*:*Anti***
Ph	86	75:25	$c\mathrm{C_6H_{11}}$	88	10:90
PhCH=CH-	96	70:30	$(\mathrm{CH_3})_2\mathrm{CH\text{-}CH_2}$-	83	35:65
2-Furyl	72	90:10	$\mathrm{PhCH_2CH_2}$-	95	30:70
$\mathrm{CH_2{=}(CH_3)CH}$-	79	85:15	$n\mathrm{C_{10}H_{21}}$	75	35:65

veal any change in stereoadducts composition from 5 min to 20 h. Furthermore, bringing samples of *syn* or *anti*-**12** into contact with **11** under typical reaction conditions, did not affect the original stereoadduct composition, thus ruling out any role of thermodynamic equilibration on the observed diastereoselectivity.

A kinetic rationale was proposed for the hydroxyallylation of aldehydes in THF using indium, on the basis of two assumptions: (i) the stereochemical outcome is mainly due to (*Z*) γ–**11**, the major reactive allylic indium species present in solution, and (ii) six-membered cyclic transition states are adopted. If chair-like transition states (TSs) were involved, according to the classical Zimmermann–Traxler theory, *syn*-**12** should always prevail owing to the (*Z*) C=C bond configuration of γ–**11**. Our rationale is based on the assumption that twist-boat TS enjoy stabilization with respect to chair TS due to intramolecular chelation of the carbonyl oxygen to indium. Four possible bicyclo[3.2.2]nonane-type TS structures are depicted in Scheme 4; **A** and **B** consider the approach of benzaldehyde *si* face to the *si* face of (*Z*) γ–**11** , while **C** and **D** refer to the alternative approach of benzaldehyde *re* face to the *si* face of (*Z*) γ–**11**.



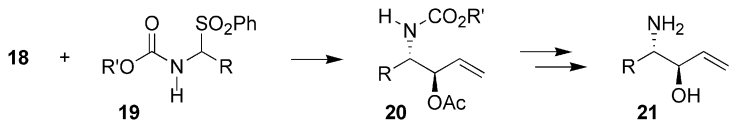
Scheme 4

On pure steric grounds, the less congested site is found by the phenyl substituent in TS-**C**, so formation of *anti*-**12** should be expected. On the other hand, when a conjugated aldehyde is involved, TS-**A** offers the unsaturated group, e.g., the phenyl ring, the opportunity of approaching face to face the ester

carbonyl group, thus developing an attractive π–π stabilizing interaction. Thus, stereocrossover in the reaction of (*Z*) γ–**11** with aldehydes could be explained as primarily due to steric repulsions, when saturated aldehydes are involved (*anti* diastereoselectivity), and to π staking interactions [43] when conjugated aldehydes are used (*syn* diastereoselectivity).

Even though indium applications in organic synthesis are rapidly accelerating in the last years [44], replacement of indium with zinc, whenever possible, is advantageous for the much lower cost of the latter. Thus, we applied the same Grignard-type protocol to zinc; the oxidative addition step in anhydrous THF requires longer reaction times (10–12 h vs. 1–2 h using indium), and chemical yields are almost a half of those reported in Table 2. However, the addition of 20 % of DMSO as cosolvent has a beneficial effect on the oxidative addition rate, as well as in the reactivity of the corresponding organozinc species $AcOCH{=}CHCH_2ZnBr$ (**18**). With this simple modification of the reaction medium, ketones too (benzalacetone and pinacolone) can be forced to react [45], affording the corresponding adducts in 83 and 35 % yield, respectively.

Besides carbonyl compounds, organozinc species **18** have been shown by Petrini et al. to react with α-amidoalkyl phenylsulphones **19** to give *anti*-adducts **20**, synthetic precursors of the alk-1-en-4-amino-3-ols **21** (Scheme 5) [46]. In this case, simple *anti* diastereoselectivity is independent of the nature of the R group.



Scheme 5

ONE-POT INDIUM- AND ZINC-PROMOTED α-HYDROXYALLYLATION OF CARBONYL COMPOUNDS (BARBIER PROTOCOL)

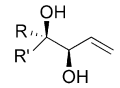
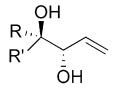
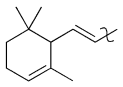
It is customary to designate as Barbier protocol [47] a one-pot process where a carbonyl compound, a metal, and an alkyl halide are combined in situ to give a substituted alcohol. From an operational point of view, a one-pot Barbier protocol is more practical than a two-step Grignard reaction. Barbier conditions can be applied, if side reactions such as reduction of carbonyl compound or pinacol coupling do not compete with the desired oxidative addition of the metal to the organic halide and the subsequent coupling of the organometallic species to the aldehyde or ketone. On the other hand, Barbier protocols represent the unique solution when the organometallic species is not stable in the reaction medium, for example, it undergoes protonation or Wurtz coupling; in these cases, it is essential to produce the reactive intermediate in the presence of the desired trapping agent, for example, a carbonyl compound. This is the case of water used as reaction medium, a solvent which favors formation of allylic indium species, but rapidly protonates them and speeds up Wurtz coupling.

Considering green chemistry encouragements to develop organometallic reactions in water [48], we studied the direct coupling of 3-bromopropenyl esters with aldehydes and ketones in aqueous solvents. The first experiments were carried out by mixing indium, 3-bromopropenyl acetate (**10**), and an aldehyde (benzaldehyde or cyclohexanecarboxaldehyde) in H_2O or H_2O/THF. Chemical yields were in the 75–85 % range, and, even more interesting, the same trend in stereopreference observed in Grignard reactions (previous section) was confirmed. However we were delighted by the observation that an even more efficient Barbier protocol could be developed by using the cheaper zinc in aqueous (aq) NH_4Cl solutions [40,45,49]; when the aldehyde, **10** and zinc are subsequently added to a sat. aq NH_4Cl solution at room temperature, an exothermic reaction takes place and the reaction can be worked-up after 15 min. When the same Barbier protocol in aq NH_4Cl is applied to ketones [45], reactions are quite

more sluggish. Since this drawback is mainly due to the lower solubility of ketones in aq. solvents, it is sufficient to add THF as cosolvent (20 %) to get very high conversions at room temperature in 30 min.

A few representative examples are reported in Table 3.

Table 3 Zinc-promoted coupling of 3-bromopropenyl esters with aldehydes and ketones in aq. NH_4Cl/THF solutions under Barbier conditions.

 ***Syn*-16**				 ***Anti*-16**			
R	**R'**	**Y (%)**	***Syn*:*Anti***	**R**	**R'**	**Y (%)**	***Syn*:*Anti***
Ph	H	90	70:30	Ph	C_2H_5	87	75:25
2-Furyl	H	80	80:20		CH_3	98	70:30
4-Tolyl	H	60	60:40	*c*C_6H_{11}	H	80	15:85
4-Anisyl	H	72	70:30	*n*C_6H_{13}	H	84	30:70
PhCH=CH-	H	80	60:40	$PhCH_2CH_2$-	H	81	30:70
Ph	CH_3	87	70:30	$(CH_3)_2CHCH_2$-	H	76	30:70
2-Naphthyl	CH_3	98	70:30	*n*C_6H_{13}	CH_3	84	40:60
4-Anisyl	CH_3	98	80:20	-$CH_2(CH_2)_3CH_2$-		87	-

Again, the previously discussed general stereochemical trend is retained.

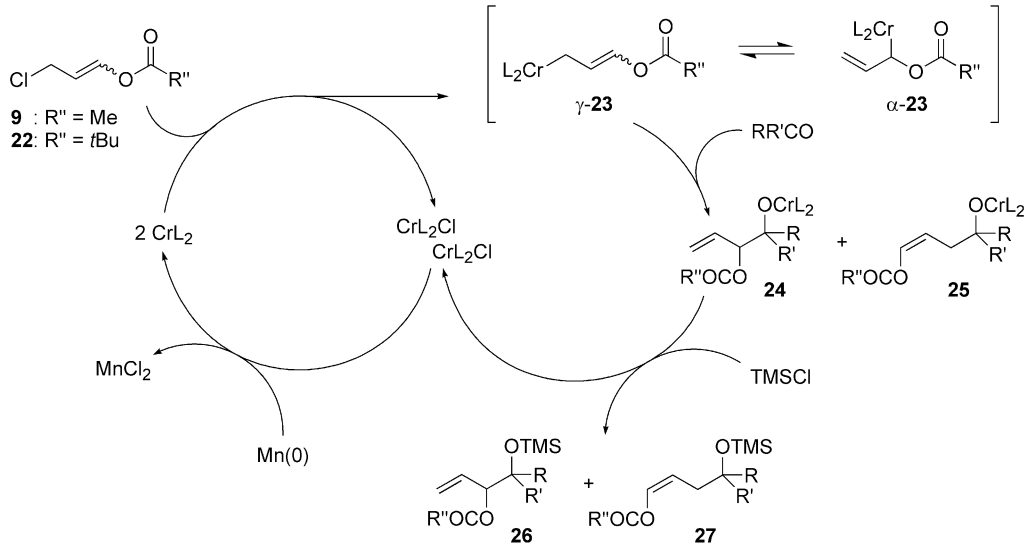
In the case of less reactive (benzalacetone) or unreactive ketones (pinacolone), the recourse to Grignard protocols in THF/DMSO represents the solution of choice to get the desired products (previous section).

CHROMIUM-CATALYZED COUPLING OF 3-CHLOROPROPENYL ESTERS WITH CARBONYL COMPOUNDS

Organometallic reactions requiring the use of stoichiometric amounts of toxic, ecotoxic, or expensive metals should be avoided on the grounds of basic environmental and/or economic concerns. However, it could be arduous to forgo chemical advantages offered by a metal, for example, in terms of reactivity, selectivity, etc. Catalysis may offer a way out, if conditions are found able to generate in situ the desired reactive species in catalytic amount. When an oxidative addition of a low valent metal species M_1 into an organic halide R-X is responsible for the generation of the key reactive species R-M_1-X, a catalytic cycle may be developed if a suitable redox couple M_1/M_2 is available. The stoichiometric metal M_2 (possibly cheap, safe, and environmentally acceptable) besides being able to reduce oxidized forms of M_1 to the desired oxidation state, must display the lowest reactivity toward R-X.

A milestone in the framework of this research area is offered by Fürstner studies [50] directed to develop a catalytic version of the Nozaki–Hiyama–Kishi coupling of organic halides to aldehydes promoted by Cr(II) salts [51]. Fürstner exploits the Cr(III)/Mn(0) redox couple and trimethylsilyl chloride (TMSCl) as a trapping agent of the intermediate Cr(III)alkoxide; the role of TMSCl is to free Cr(III) salts, thus making easier the restoration of the reactive Cr(II) species. The same strategy allowed Boeckman and Hudack to develop a catalytic version [52] of the Takai–Utimoto reaction; γ-alkoxyallyl chromium reagents **3h** (see Table 1) are generated from acrolein acetals by exploiting the Cr(III)/Mn(0) couple in the presence of NaI and TMSCl, and trapped in situ with aldehydes to give *anti*-adducts in good yields and with an improved diastereoselectivity compared to the original stoichiometric procedure [9].

3-Halopropenyl esters were supposed to be excellent candidates for a similar catalytic approach to γ-carbalkoxyallyl chromium reagents **23**. The catalytic cycle depicted in Scheme 6 works indeed, and the best results were obtained with 3-chloropropenyl esters in the presence of an additional anionic ligand L^-.



Scheme 6

A first set of reactions was carried out with 3-chloropropenyl acetate (**9**) and 3-chloropropenyl pivaloate (**22**) in the presence of a source of iodide ions (Bu_4NI) in catalytic amount (20 %) [53]. The main difference observed with respect to zinc and indium-mediated procedures, inheres reaction regiochemistry. The $CrCl_3$/Mn/TMSCl/Bu_4NI system catalyzes the formation of both compounds **26** and **27**, and conditions were found favoring formation of the homoaldol derivative **27**. In particular, two factors affect regioselectivity in favor of 4-hydroxy enolesters **27**, temperature, and the ester steric bulk. Table 4 collects a few examples obtained using pivaloate **22** and carbonyl compounds at 65 °C in acetonitrile as solvent; under these conditions, enolesters **27** are formed in pure *Z* configuration.

Table 4 Chromium-catalyzed coupling of 3-chloropropenyl pivaloate with carbonyl compounds in the $CrCl_3$/Mn/TMSCl/Bu_4NI reaction system. Acetonitrile as solvent at 65 °C.

R	R′	Y (%)	27:26	R	R′	Y (%)	27:26
Ph	H	61	82:18	cC_6H_{11}	H	66	90:10
2-Naphthyl	H	53	72:28	$PhCH_2CH_2$–	H	64	83:17
Ph	CH_3	55	73:27	nC_5H_{11}	H	72	83:17
–$CH_2(CH_2)_3CH_2$–		55	91:9	$BnOCH_2$–	H	53	90:10

The last set of experiments reported in this section was again carried out with pivaloate **22** using the $CrCl_3$/Mn/TMSCl catalytic system, in the presence of Jacobsen's *Salen* as supplementary ligand, as recently reported by Cozzi, Umani-Ronchi, et al. in an asymmetric version of the Fürstner reaction [54]. Reactions are carried out at 20–25 °C by sequentially adding to a stirred mixture of $CrCl_3$ (10 %) and manganese in acetonitrile the following reactants: Salen (20 %), Et_3N (40 %), pivaloate **22**, an aldehyde, and TMSCl. The catalytic cycle shown in Scheme 6 again accounts for the observed transforma-

tions, the anionic ligand L^- being now represented by the dianion of Salen, deriving from an acid-base reaction with Et_3N [55].

The most striking features arising from this new catalytic system are here summarized.

- A dramatic inversion of regioselectivity in favor of alk-1-en-3,4-diol derivative **26** is observed. A possible rationale involves the destabilization of α-**23** with respect to γ-**23** due to the proximity in the former of the sterically demanding L_2 and R″ groups, corresponding to Salen and the pivaloate group, respectively.
- Simple diastereoselectivity favours formation of *syn*-adducts independently of the nature of the aldehyde. Conversely, substituted allylic chromium reagents generally stereoconverge to *anti*-adducts [51].
- *Syn*-adducts are formed in excellent enantiomeric excesses, particularly when aliphatic aldehydes are used. In particular, (*R,R*)-Salen complexed chromium species **23** display a stereopreference for the attack to the *si* face of the aldehyde.

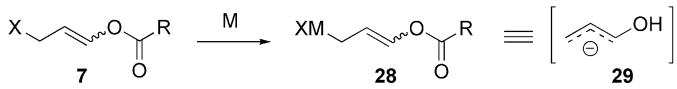
Selected examples are reported in Table 5.

Table 5 Chromium-catalyzed asymmetric synthesis of *syn*-alk-1-en-3,4-diol derivative **26** (R′ = H) in the presence of *Salen*.

R	Y (%)	*Syn*:*Anti*	*Syn*-**26** ee (%)	R	Y (%)	*Syn*:*Anti*	*Syn*-**26** ee (%)
cC_6H_{11}	68	83:17	94	iC_4H_9	55	80:20	92
nC_5H_{11}	50	83:17	93	Ph	77	71:29	64
$PhCH_2CH_2$–	78	85:15	99	4-Anisyl	82	74:26	65
iC_3H_7	42	72:28	92	2-Naphthyl	60	78:22	73

CONCLUSIONS

A new family of synthetic equivalents **28** of the formal 1-hydroxy allyl anion **29** is now available from the oxidative addition of zinc, indium, and chromium(II) to the carbon–halogen bond of 3-halopropenyl esters **7** (eq. 14).



(14)

Oxygen-substituted allylic organometallic compounds **28** not only enrich the list of heterofunctionalized complexes **3** collected in Table 1, but even offer notable practical benefits:

- Precursors **7** are easily prepared in good yield and multigram scale.
- Very mild conditions are required both for the oxidative addition step and for the nucleophilic addition to the carbonyl derivative, generally carried out at room temperature.
- Environmental concerns are clearly addressed, particularly when water is used as solvent in zinc-promoted Barbier procedures.
- Simple chromium-based catalytic cycles may be applied to achieve the coupling of 3-halopropenyl esters with carbonyl compounds. The exploitation of chromium allowed us to develop a racemic version of the homoaldol reaction, as well as the first asymmetric catalytic entry to *syn* alk-1-en-3,4-diols **16**.
- The variety of experimental conditions which can be adopted in terms of solvents and of Barbier or Grignard protocols makes very likely the chance of success when organometallics **28** are applied to new substrates.

- The use of azomethine derivatives or their synthetic equivalents such as **19** (Scheme 5) will broaden further on the applications of **7** to the synthesis of alk-1-en-3-amino-4-ols **21**.

ACKNOWLEDGMENTS

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