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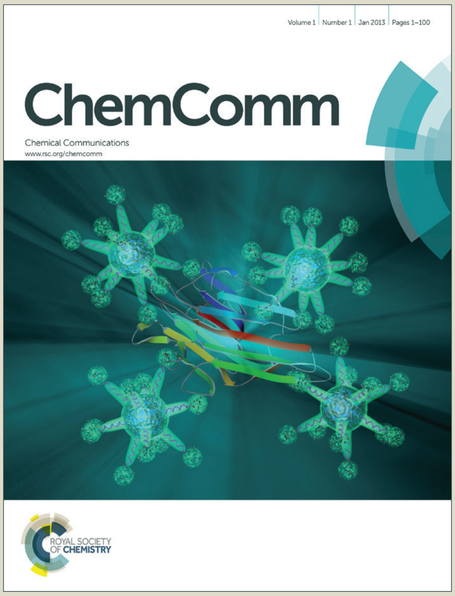

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ARTICLE TYPE

Highly regioselective and chemoselective titanocene mediated Barbier-type allylations

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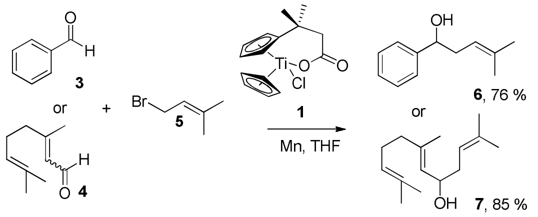
Titanocene carboxylate 1 is an excellent chemoselective reagent for unprecedented α-regioselective Barbier-type reactions. It constitutes the first titanocene(III) to tolerate epoxides and readily reduced carbonyl compounds, such as aromatic and α,β-unsaturated aldehydes.

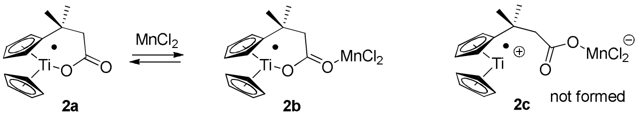
Titanocene(III) complexes are useful tools for mediating and catalyzing a number of useful transformations,[1] such as homolytic epoxide opening,[2] pinacol coupling reactions,[3] and Barbier-type additions of allylic and propargylic halides or carbonates to carbonyl compounds.[4] A drawback of these procedures is the lack of chemoselectivity in the electron transfer step. For that reason, aromatic and α,β-unsaturated carbonyl compounds are usually unsuitable substrates in Barbier-type reactions.[4] Here, we demonstrate that this shortcoming can be resolved with complex **1** (Scheme 1) in the presence of Mn dust via complex **2a** (Figure 1).[5,6]



Scheme 1. Ti-mediated regioselective α-prenylation of benzaldehyde (**3**) and citral (**4**).

Gratifyingly, **3** and **4**, model compounds for aromatic and α,β-unsaturated aldehydes, reacted with **5** in the presence of complex **1** and Mn dust to exclusively yield α-prenylated compounds **6** and **7**. Thus, the highly useful α-regioselectivity of prenylation noted earlier could be maintained.[4a,6] Remarkably, in the absence of **5**, no pinacol products are formed.[7] Further exploring of this new reactivity concluded that epoxides were also tolerated by this reagent. This suggests that the aldehydes or epoxides can not bind to Mn-**1**.

To rationalize these findings, cyclic voltammograms (CVs) of **1** and Mn-**1** in THF were recorded (Figure 1). The oxidation of electrochemically reduced **1** reveals the presence of two species. **1**$^-$ (E_{pc} = -1.38 V vs Fc$^+$/Fc) is formed via electron transfer at the electrode. The process is irreversible due to the formation of **2a** (E_{pa1} = -1.00 V) through loss of chloride. For Mn-**1**, **2a** (E_{pa1} = -0.95 V) is formed as expected, due to the more efficient abstraction of the chloride and formation of MnCl$_2$. The more negative value of E_{pa1} compared to Cp$_2$TiCl (E_{pa1} = -0.83 V) is in line with the carboxylate is a better donor ligand than chloride. The second peak (E_{pa2} = -0.65 V) is also observed at higher sweep rates (ν = 1 – 50 V s^{-1}). Thus, the species being oxidized is an initial component[8] of Mn-**1** in THF and is not formed during the sweep. We suggest that **2b** and not the cationic **2c** is the second component of Mn-**1** for a number of reasons. **2c** should have a potential similar to that of [Cp(C$_5$H$_4$^{t}Bu)Ti]$^+$ (E_{pa} = -0.47 V). It has been recently shown that cationic titanocene(III) complexes open epoxides.[9] Both findings are in contradiction to the behavior of Mn-**1**. In agreement with the observations, **2b** is more difficult to oxidize than **2a** because electron density is withdrawn from Ti through carboxylate coordination. The steric shielding of Ti in **2b** will be similar to **2a** and thus epoxide and aldehyde binding as difficult for **2b** as for **2a**.



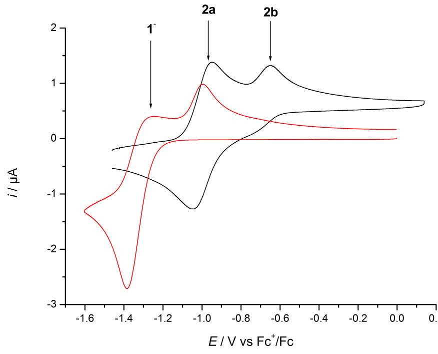


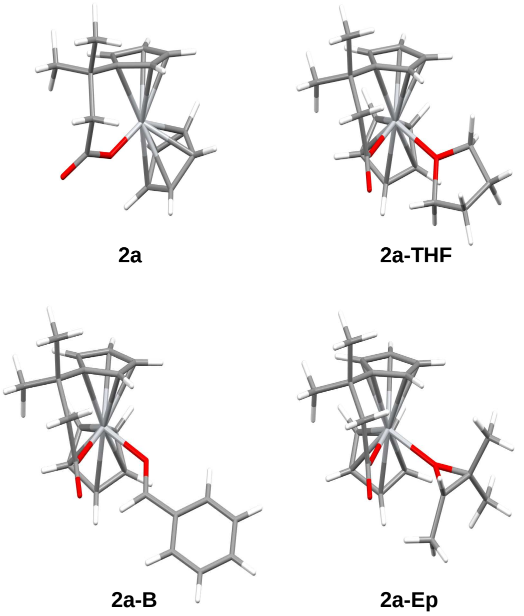
Fig. 1 CV of 2 mM solution of **1** (red) and Mn/**1** (black) recorded at ν = 100 mV s^{-1} in 0.2 M TBAPF$_6$/THF.

To understand the unprecedented chemoselectivity, we carried out the model reactions with Mn-reduced Cp$_2$TiCl(OMe),[10] Cp$_2$TiCl(OAc),[11] and Cp$_2$TiCl(OBz).[12]

Unselective electron transfer reactions as with the Cp_2TiCl_2 were observed. This suggests that the tethering of the carboxylate to the ligand is essential.

To highlight this point, the coordination of **2a** to THF, benzaldehyde, and trimethyloxirane was studied by DFT calculations (Table 1).[7]

Table 1: Structures and Energies of the interactions of THF, benzaldehyde (**B**), and trimethyloxirane (**Ep**) with **2a** (For Computational Details see Supporting Information, Energies are in kcal mol^{-1}).

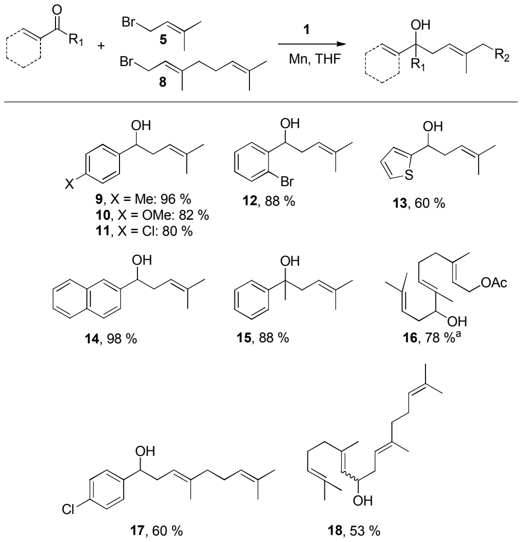


Complex	Δ*H*	−TΔ*S*	Δ*G*
2a	0.0	0.0	0.0
2a-THF	-2.8	+13.7	+10.9
2a-B	-4.2	+12.5	+8.3
2a-Ep	-0.5	+12.5	+12.0

The generation of these coordination complexes is characterized by: (a) an only slightly negative enthaply of formation and (b) a highly unfavorable entropy of formation. This results in ΔG values of about +8 to +12 kcal mol^{-1}.[13] Therefore, aldehyde and epoxide complexation seems to be precluded as observed experimentally.

Next, we explored the chemoselectivity of electron transfer further (Scheme 2 and Table 2). Gratifyingly, our Barbier-type reactions using activated halides as pronucleophiles are general and take place with moderate to excellent yields.[7] A variety of aromatic and α,β-unsaturated aldehydes are suitable. Even acetophenone, as an example for aromatic ketones, is an excellent substrate (Scheme 2). All products are valuable building blocks for terpene synthesis.[1d] Even more interesting and demanding are Barbier-type reactions with electrophiles (**19-20**) or nucleophiles as **23**, incorporating epoxides (Table 2).

In agreement with our DFT calculations, epoxides are readily tolerated by Mn-**1**.[7] Thus, functionalized epoxypolyprenes that are highly attractive intermediates for natural products synthesis[1d] can be prepared from either epoxide containing carbonyl compounds or activated halides. As an attractive additional feature, our novel method allows the elimination of the often difficult regioselective epoxidation step of the polyprenic starting materials.



Scheme 2. Ti-mediated regioselective α-prenylation of aromatic and α,β-unsaturated carbonyl compounds. Conditions: For aromatic aldehydes: **1** (1 mmol), Mn dust (8 mmol), aldehyde (1 mmol), and activated halide (2 mmol) in THF. Otherwise: **1** (1.5 mmol), Mn dust (8 mmol), carbonyl compound (1 mmol), and activated halide (3 mmol) in THF. [a] Prenyl chloride can be used with similar yield (77 %).

An important aspect of this study is the regioselectivity of the addition of the allylic nucleophile. In contrast to the numerous γ-selective additions, α-regioselective additions are considerably less common.[14] Here, we obtained the α-regioisomers in very high selectivity (>92:<8) when prenyl derivatives **5**, **8** and **23** were used as pronucleophiles. Moreover, commercially available Mn dust could be used at room temperature.

Finally, we also investigated Wurtz-type couplings mediated by Mn-**1**. Such reactions can be carried out in the presence of Cp_2TiCl.[15] However, the chemoselectivity of these reactions is low. This is not the case in our system and, hence, epoxide containing substrates can be readily coupled (Table 2, entry 8). The reaction took place with excellent yield and also with a high α,α-regioselectivity (86:14).

In summary, we have demonstrated that Mn-**1** is a reagent for Barbier-type allylation reactions delivering the α-addition products with almost complete regioselectivity. The reactions proceed with an unprecedented chemoselectivity because epoxides and readily reduced carbonyl compounds, such as aromatic and α,β-unsaturated aldehydes, are tolerated. The compounds obtained are difficult to prepare using other methodologies and are valuable substrates in terpene synthesis. Moreover, the reactions can be perfomed at room temperature and no preformed organometallic reagents (B or Li) or especially activated metals (Ba) have to employed.

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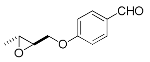
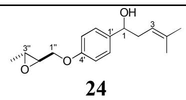
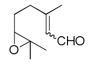
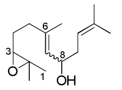
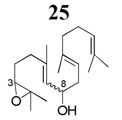
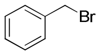
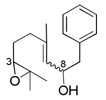
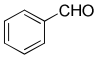
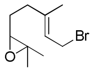
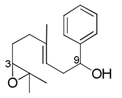
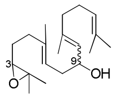
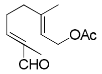
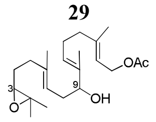
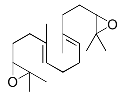
Table 2 Regioselective Barbier-type reactions of electrophiles and nucleophiles presenting an oxirane ring mediated by Mn-**1**.[a]

Entry	Carbonyl compound	Halide	Product	Yield (%)
1	 **19**	**5**	 **24**	76
2	 **20**	**5**	 **25**	68
3	**20**	**8**	 **26**	42
4	**20**	 **22**	 **27**	63
5	 **3**	 **23**	 **28**	77
6	**4**	**23**	 **29**	68
7	 **21**	**23**	 **30**	72
8	-	**23**	 **31**	99[b]

[a] Complex **1** (1.5 mmol), Mn dust (8 mmol), carbonyl compound (1 mmol), and activated halide (3 mmol) in THF. [b] This compound was obtained as a 6:1 mixture of α,α and α,γ-regioisomers

Notes and references

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† Electronic Supplementary Information (ESI) available: [Experimental Methods and characterisation of new compounds]. See DOI: 10.1039/b000000x/

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13 A direct comparison of the binding capabilities of complex **2a** with parent Cp_2TiCl is not simple owing to it is known that chloride anion dissociates in THF solution generating cationic species (ref. 9). Such effect cannot take place with tethering ligand in complex **2**. Related zwitterionic species **2c** were calculated and the results showed that in absence of a ligand (L) the zwitterion is too high in energy to be a real intermediate, as CV experiments suggest. In the presence of a ligand, cationic complexes **2c**-L also showed to be thermodynamically highly disfavoured species.

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