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Titanocene(III)-Promoted Barbier-type Crotylation of Carbonyl Compounds

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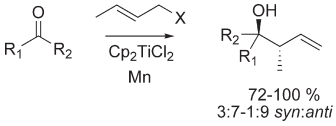
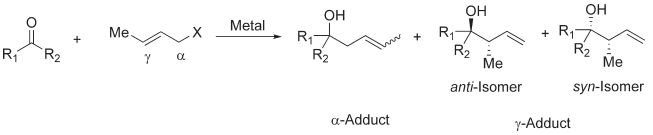


A mild, highly regio- and stereoselective method for the crotylation of aldehydes and ketones mediated/catalyzed by titanocene(III) is described. Optimized conditions permit the selective generation of γ-adducts in high yields together with high stereoselectivity, with a predominance of *anti* stereoisomers.

Regio- and stereoselective addition of crotyl metals to carbonyl compounds allows the creation of two new adjacent stereogenic centers in only one step (see Scheme 1), which is an important process in organic synthesis.[1] Within this context, Barbier-type protocols,[2] in which the crotyl metal intermediates are generated "in situ" from the crotyl halide and the corresponding metal, are attractive from a practical point of view because prior preparation of the organometallic intermediate is circumvented. Thus, for example, Barbier-type protocols based on Cr,[3] Sm,[4] Mn,[5] Zn,[6] Cd,[7] Sn,[8] or In[9] have been developed. Among them, those in which the active metal is in a homogeneous phase present some advantages derived from a better control of the reaction conditions and reproducibility. One remarkable example of this case is the *anti* stereoselective Cr(II)-mediated[3] crotyl additions, although it is restricted to aldehydes as electrophiles. Therefore, the development of a general regioselective and stereoselective Barbier-type crotyl addition under homogeneous conditions is desirable.

SCHEME 1. General Crotylation Reaction under Barbier Conditions



In this sense, we have recently described that Cp_2TiCl, a mild single-electron transfer (SET) reagent extensively studied by RajanBabu and Nugent,[10] Gansäuer,[11] and our group,[12] is able to promote mild, chemo- and regioselective

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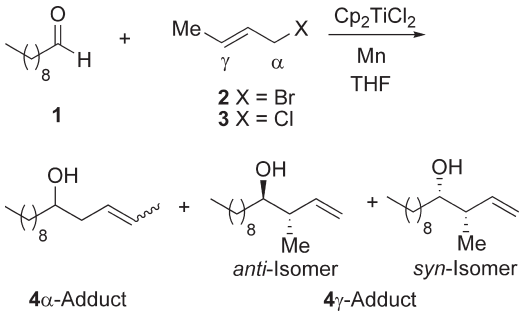
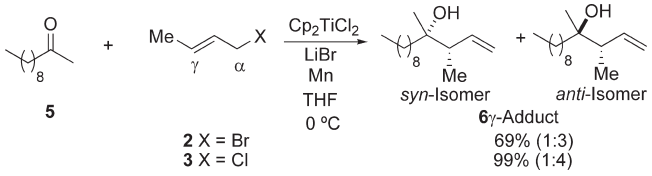
TABLE 1. Titanocene(III)-Mediated Barbier-type Crotylation of 1

entry	halide	temp	LiBr (mol %)	products, yield, (α:γ)	isomeric relationship (*syn*:*anti*)
				4α + 4γ	
1	**2**	rt		50%, (1:1)	2:3
				4α + 4γ	
2	**3**	rt		92%, (1:9)	1:3
				4α + 4γ	
3	**2**	0 °C		77% (15:85)	1:3.4
				4α + 4γ	
4	**2**	−20 °C		93%, (1:9)	1:9
				4γ	
5	**2**	rt,	150	50%	1:4
				4γ	
6	**2**	0 °C	150	99%	1:4
				4γ	
7	**2**	−20 °C	150	90%	1:4
				4α + 4γ	
8	**3**	0 °C		92%, (15:85)	3:7
9	**3**	−20 °C		N. R.	
				4γ	
10	**3**	rt	150	75%	3:7
				4γ	
11	**3**	0 °C	150	80%	1:3
				4γ	
12	**3**	−20 °C	150	75%	1:3

SCHEME 2. Barbier-type Crotylation of Aldehyde 1 Mediated by Titanocene(III) under Different Conditions



SCHEME 3. Barbier-type Crotylation of 2-Decanone (5) Mediated by Titanocene(III) under Different Conditions



allylation, prenylation, and propargylation reactions of aldehydes and also ketones using the corresponding activated halides as pronucleophiles.[13] The efficiency of this protocol seems to be based in the in situ generation of the corresponding nucleophilic titanocene(IV) complexes. Taking into account that it is known that crotyl titanium complexes have shown excellent γ-regio- and *anti* stereoselectivity when they are added to carbonyl compounds,[14] we wonder if the previously reported Ti-based procedures[13] could be extended to the corresponding regio- and stereoselective crotylation reaction. Herein, we want to communicate a novel and mild Cp_2TiCl-promoted method for the crotylation of aldehydes and ketones with complete regioselectivity and interesting *anti* stereoselectivities. Additionally, this method can be carried out using substoichiometric amounts of Cp_2TiCl.

We began the study of this reaction using decanal (**1**) as model aldehyde (Table 1 and Scheme 2). In this case, stoichiometric amounts of Cp_2TiCl (2.5 mmol), generated in situ by stirring of commercial Cp_2TiCl_2 (2.5 mmol) and Mn dust (8 mmol), and crotyl halides **2** and **3** (2 mmol) in THF, were first tried at different temperatures. At room temperature, mixtures of α- and γ-regioisomers were obtained, although in different ratios (Table 1, entries 1 and 2). When the temperature was decreased to 0 °C, we could observe in the case of crotyl halide **2** an improvement in yield and regioselectivity (entry 3). At −20 °C, an even better yield and regioselectivity could be obtained (entry 4). On the other hand, Cp_2TiCl is unable to promote the homolytic dissociation of the C−Cl bond at that temperature, and therefore, no reaction takes place when crotyl chloride **3** was used (entry 9). Although a 9:1 mixture of regioisomers could be considered acceptable if both isomers can be separated by column chromatography, as it is the case, we fortunately found that the addition of LiBr (1.5 mmol) was able to remove the undesirable α-regioisomer (entries 5−7 and 10−12). In agreement with the previous results, the better yield was obtained at 0 °C using crotyl bromide **2** as a pronucleophile (entry 6) with a minor reduction of stereoselectivity.

With these precedents in mind, we used these optimized reaction conditions (0 °C and LiBr) in the crotylation of a model ketone, 2-decanone (**5**). To our delight, regioisomer **6γ** was exclusively obtained using both crotyl halides **2** (69%) and **3** (99%) as pronucleophiles (Scheme 3). Regarding the stereoselectivity, an interesting 1:3 and 1:4 mixture of *syn*:*anti* stereoisomers was obtained (Scheme 3). It is worth noting that stereoselective reaction of the γ-substituted allylic metals with simple ketones instead of aldehydes has been rarely reported.[15] This fact is probably due to the difference in steric demand between two substituents on the carbonyl carbon, which leads to smaller stereoselection in ketones than in aldehydes.

This result shows that the better conditions for the selective crotylation of ketones were identical to those used above

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(14) *anti* selectivity: (a) Reetz, M. T.; Steinbach, R.; Westermann, J.; Peter, R.; Wenderoth, B. *Chem. Ber.* **1985**, *118*, 1441–1454. (b) Sato, F.; Iida, K.; Iijima, S.; Moriya, H.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1981**, 1140–1141. (c) Sato, F.; Uchiyama, H.; Iida, K.; Kobayashi, Y.; Sato, M. *J. Chem. Soc., Chem. Commun.* **1983**, 921–922. (d) Collins, S.; Dean, W. P.; Ward, D. G. *Organometallics* **1988**, *7*, 2289–2293. (e) Collins, S.; Kuntz, B. A.; Hong, Y. *J. Org. Chem.* **1989**, *54*, 4154–4158. (f) Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881–3882. (g) *syn* selectivity: Reetz, M. T.; Saurwald, M. *J. Org. Chem.* **1984**, *49*, 2292–2293. (h) Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691–1694.

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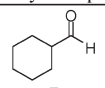
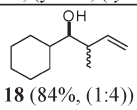
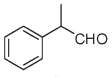
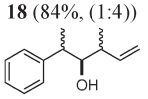
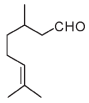
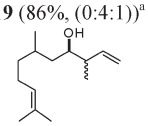
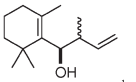
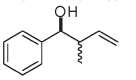
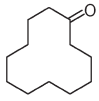
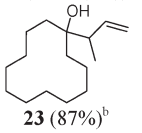
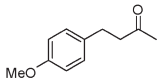
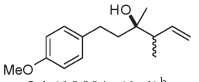
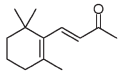
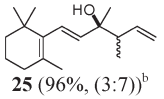
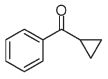
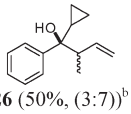
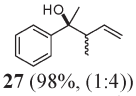
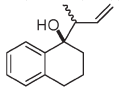
TABLE 2. Titanocene(III)-Mediated Barbier-type Crotylation of Carbonyl Compounds 7−17

Entry	Carbonyl compound	halide	Products, (yields, (*syn*:*anti*))
1	 **7**	**2**	 **18** (84%, (1:4))
2	 **8**	**2**	 **19** (86%, (0:4:1))[a]
3	 **9**	**2**	 **20** (75%, (1:4))
4	 **10**	**2**	 **21** (72%, (1:4))[b]
5	 **11**	**2**	 **22** (34%, (3:7))[c]
6	 **12**	**3**	 **23** (87%)[b]
7	 **13**	**3**	 **24** (100%, (1:4)[b]
8	 **14**	**3**	 **25** (96%, (3:7))[b]
9	 **15**	**3**	 **26** (50%, (3:7))[b]
10	 **16**	**3**	 **27** (98%, (1:4))
11	 **17**	**3**	 **28** (84%, (3:7))

[a]Isomer proportions refer to 1,2-*syn*:1,2-*anti*:2,3-*anti*. [b]Stereochemistry has been tentatively assigned based on the known compounds **4γ**, **18**−**20,** and **27**−**28**. [c]1:1 mixture of α:γ regioisomers.

for aldehydes, but using chloride **3** instead of bromide **2**. This halide preference has been observed and explained by us in precedent papers.[13b,c,16]

We then decided to extend our study to other carbonyl compounds with different substitution patterns. We submitted these carbonyl compounds to the optimized reaction conditions mentioned above. The results are listed in Table 2.

We obtained good to excellent yields (50−100%) for crotylation products **18**−**28**, with complete regioselectivity to the γ-isomers, and, in general, with good stereoselectivities (entries 1−4, 7, and 10). The reaction took place with

(16) Moreover, it is known that the nature of the halide coordinated to titanocene(III) also affects the *syn*:*anti* stereoselection; see ref 14b.

TABLE 3. Titanocene(III)-Catalyzed Barbier-type Crotylation of Carbonyl Compounds 1, 5, 12, 14, 16, and 17

entry	carbonyl compound	halide	products, (yields, (*syn*:*anti*))
1	**1**	**2**	**4γ** (92%, (1:4))
2	**5**	**3**	**6γ** (93%, (3:7))
3	**12**	**3**	**23** (70%)
4	**14**	**3**	**25** (100%, (3:7))
5	**16**	**3**	**27** (90%, (3:7))
6	**17**	**3**	**28** (100%, (3:7))

aliphatic, aromatic, and α,β-unsaturated aldehydes and ketones, which are normally unreactive in Cr(II)-mediated reactions,[3] showing the versatility and usefulness of our method. Interestingly, the absence of cyclopropane-opening compounds in the crotylation of ketone **15** (entry 9) suggests that ketyl radical intermediates are not involved in this reaction.[13b,c] One exception to this excellent behavior is constituted by benzaldehyde (**11**) (entry 5). In this case, a mixture of α:γ regioisomers and pinacol coupling products[17] was obtained. Interestingly, the addition of crotyl bromide to benzaldehyde (**11**) has been described under similar conditions by Roy et al., obtaining exclusively the γ-regioisomer as a 1:1 mixture of *syn*:*anti* stereoisomers.[18] The only difference between the protocols is the use of different metals, Zn dust instead Mn dust, for the reduction of Cp_2TiCl_2 to generate the active complex Cp_2TiCl. A control reaction pointed out that the use of Zn dust in the absence of Cp_2TiCl_2 gives the same results in yield and stereochemistry (*syn*:*anti* 1:1) as those reported by Roy. Noteworthily, similar control reactions using Mn dust showed that, in our reaction conditions, this metal is unable to promote Barbier-type reactions.

Taking into account that organometallic catalysis plays an important role in both laboratory and industrial organic synthesis,[19] we decided to assay a Ti-catalyzed version of our crotylation process. To this end, we require a Ti(III)-regenerating agent able to reintroduce the final Ti(IV) species in the catalytic cycle. In this case, a simple mixture of Mn dust (8 equiv), Me_3SiCl (4 equiv), and 2,4,6-collidine (7 equiv) as a regenerating agent allows the use of substoichiometric amounts of Cp_2TiCl_2 (0.2 equiv).[12,13,20] Under these reaction conditions, we treated carbonyl compounds **1**, **5**, **12**, **14**, **16**, and **17** with halides **2** or **3**, obtaining in excellent yields the corresponding alcohols **4γ**, **6γ**, **23**, **25**, **27**, and **28**, respectively (Table 3), retaining the *anti* stereoselectivity. These results support the viability of the catalytic version, using titanocene amounts 1 order of magnitude lower than in the stoichiometric procedure, and point out the potential synthetic value of the Ti-catalyzed Barbier-type crotylation process for a wide range of substrates, as aliphatic, aromatic, and α,β-unsaturated carbonyl compounds.

From a mechanistic point of view, the isolation of two different regioisomers can be correlated with the existence of

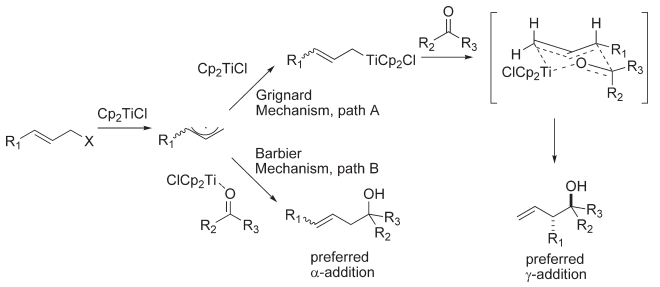
(17) (a) Gansäuer, A. *Chem. Commun.* **1997**, 457–458. (b) Paradas, M.; Campaña, A. G.; Estévez, R. E.; Álvarez de Cienfuegos, L.; Jiménez, T.; Robles, R.; Cuerva, J. M.; Oltra, J. E. *J. Org. Chem.* **2009**, *74*, 3616–3619.

(18) Jana, S.; Guin, C.; Roy, S. C. *Tetrahedron Lett.* **2004**, *45*, 6575–6577.

(19) For recent overviews on organometallic catalysts, see: (a) Shibasaki, M., Yamamoto, Y., Eds. *Multimetallic Catalysts in Organic Synthesis*; Wiley VCH: Weinheim, Germany, 2004. (b) Roberts, S. M., Xiao, J., Whittall, J., Pickett, T. E., Eds. *Catalysts for Fine Chemical Synthesis. Metal Catalysed Carbon*−*Carbon Bond-Forming Reactions*; Wiley: New York, 2004; Vol. 3.

(20) The excess of Mn and 2,4,6-collidine can be recovered at the end of the experiments by filtering and simple acid−base extraction. Subsequently, both recovered collidine and Mn dust can be used in further experiments.

SCHEME 4. Barbier-type Crotylation of Aldehydes and Ketones with Crotyl Halides



two main mechanistic pathways. After the initial Cp_2TiCl-promoted SET event, a crotyl radical is generated from the corresponding crotyl halide. A subsequent trapping of this radical by Cp_2TiCl yields a crotyltitanocene(IV) complex, which can undergo the corresponding γ-regioselective Grignard-type addition to the carbonyl compound via a chair-like transition state (Scheme 4, path A).[21] This mechanism also justifies the high *anti* selectivity observed in the final products. On the other hand, α-regioisomers are proposed to derive from the direct addition of the transient crotyl radical[22] to Cp_2TiCl-coordinated carbonyl compound[23] (Scheme 4, path B). Moreover, our experimental observations can be also correlated with this assumption. Thus, for example, a decrease in temperature would only affect mechanism B, owing to the fact that the formation of crotyltitanocene(IV) by combination of two radicals has a small energy of activation.[13b,24] Therefore, an increase of γ-regioisomers was observed. Additionally, the use of Li^+ as an additive to avoid the generation of the α-regioisomer can be related to its Lewis acidity. It can compete with titanium species for the coordination with the carbonyl group, disfavoring the mechanism B. Moreover, the counteranion (Cl^-) can also coordinate with the titanocene(III), generating a coordinatively saturated complex unable to interact with the carbonyl compound.[25,26]

In conclusion, we have described a novel procedure for the crotylation of a wide range of aldehydes and ketones promoted by the titanocene(III) complex under mild reaction conditions that is compatible with many functional groups. Mixtures of α- and γ-adducts in different proportions were obtained under standard conditions. Interestingly, a single change in the reaction conditions (temperature and addition of LiBr) allowed the selective production of γ-adducts in high yield and stereoselectivity. The *anti* isomer was formed predominantly. The use of substoichiometric amounts of titanocene(III) was also studied, yielding similar results. This method constitutes an excellent alternative for other well-known crotylation processes, such as the Nozaki–Hiyama–Kishi reaction, which do not work with ketones as electrophiles.

Experimental Section

General Procedure for Ti^{III}-Mediated Barbier-type Crotylation of Carbonyl Compounds. Strictly deoxygenated THF (20 mL) was added to a mixture of Cp_2TiCl_2 (2.5 mmol) and Mn dust (8 mmol) under an Ar atmosphere, and the suspension was stirred at room temperature until it turned lime green (after about 15 min). A solution of carbonyl compound (1 mmol), allylic halide (2 mmol), and LiBr (1.5 mmol when indicated) in THF (1 mL) was then added dropwise for 5 min, and the mixture was stirred for a further 6 h at room temperature, 0 °C, or −20 °C (when indicated). The reaction was quenched with brine and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4) and the solvent removed. Products **4**, **6**, and **18**–**28** were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopic techniques.[27] The yields are listed in Tables 1 and 2.

General Procedure for Ti^{III}-Catalyzed Barbier-type Crotylation of Carbonyl Compounds. Strictly deoxygenated THF (20 mL) was added to a mixture of Cp_2TiCl_2 (0.2 mmol) and Mn dust (8 mmol) under an Ar atmosphere, and the suspension was stirred at room temperature until it turned lime green (after about 15 min). A solution of carbonyl compound (1 mmol), allylic halide (2 mmol), LiBr (1.5 mmol), and 2,4,6-collidine (7 mmol) in THF (1 mL) was then added dropwise for 5 min, and finally, Me_3SiCl (4 mmol) was added. The mixture was stirred for a further 6 h at 0 °C. The reaction was quenched with a saturated solution of $KHSO_4$ and extracted with EtOAc. The organic layer was washed with brine and dried (anhyd Na_2SO_4) and the solvent removed. Products **4**γ, **6**, **23**, **25**, **27**, and **28**, were purified by flash chromatography on silica gel (hexane/EtOAc) and characterized by spectroscopic techniques.[27] The yields are listed in Table 3.

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Supporting Information Available: General experimental details and ^1H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Sato, F.; Iijima, S.; Sato, M. *Tetrahedron Lett*. **1981**, *22*, 243–246.

(22) The existence of crotyl radicals as intermediates in this reaction was confirmed by carrying out some experiments with 3-chloro-1-butene as a pronucleophile. The results were identical to those obtained from crotyl chloride.

(23) Fernández-Mateos, A.; Herrero Teijón, P.; Mateos Burón, L.; Rabanedo Clemente, R.; Rubio González, R. *J. Org. Chem*. **2007**, *72*, 9973–9982.

(24) It is generally assumed that coupling reactions between free radicals do not require any activation energy because new bonds are formed rather than existing ones broken; see: Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; p 738.

(25) This assumption is supported by the fact that $LiBF_4$ cannot completely drive the reaction to the γ-isomer.

(26) Enemærke, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *J. Am. Chem. Soc*. **2004**, *126*, 7853–7864.

(27) All new compounds are fully described in the Supporting Information.