Ti/Pd Bimetallic Systems for the Efficient Allylation of Carbonyl Compounds and Homocoupling Reactions

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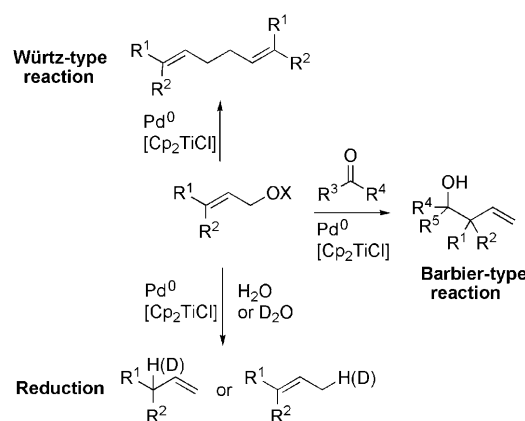
Abstract: The allylation, crotylation and prenylation of aldehydes and ketones with stable and easily handled allylic carbonates is promoted by a Ti/Pd catalytic system. This Ti/Pd bimetallic system is especially convenient for the allylation of ketones, which are infrequent substrates in other related protocols, and can be carried out intramolecularly to yield five- and six-membered cyclic products with good stereoselectivities. In addition, Ti/Pd-mediated reductions and Würtz-type dimerisation reactions can be readily carried out from allyl carbonates and carboxylates.

Introduction

Allylation of carbonyl compounds with allylmetals is an indispensable tool in total synthesis.[1] Building upon the seminal work of Barbier,[2] carbonyl compounds can now be directly transformed into homoallylic alcohols by using allylic halides as pro-nucleophiles in the presence of a metal in a low oxidation state. Nevertheless, introducing an allylic halide in the final steps of a synthetic sequence, into a highly functionalized molecule, can be cumbersome. This has led to new procedures based on the use of allylic carboxylates.[3–8] However, allylic carboxylates are not substrates for the valuable Nozaki–Hiyama–Kishi (NHK) reaction.[9] Furthermore, most of these procedures are limited to aldehyde electrophiles and are unsuccessful with ketones due to the poor nucleophilicity of the allylmetals generated in situ.[6,10]

We recently reported a catalytic bimetallic Ti/Pd-based protocol to carry out efficient and chemoselective Barbier-type allylation of carbonyl compounds from allylic carboxylate and carbonate pro-nucleophiles (Scheme 1).[11,12] In contrast with other protocols, ketones are also substrates of this reaction. The success of our strategy was based on combina-

Scheme 1. Catalytic Ti/Pd-mediated reactions.

tion of the free-radical chemistry mediated by Ti[III][13–16] with the late-transition-metal chemistry mediated by Pd. The excellent chemical profile of allyltitanium complexes towards aldehydes and ketones is at the heart of the chemoselectivity of the process.[17] We have extended these preliminary studies to broaden the scope of this allylation to new substrates. In addition, we report our results on Ti/Pd-mediated reductions and Würtz-type dimerisations (Scheme 1).

Results and Discussion

Ti/Pd-mediated Würtz-type coupling reaction: The single-electron reduction of an η^3-allylpalladium intermediate generates an allyl radical that can couple with: 1) a molecule of [Cp$_2$TiCl][18] (Cp = cyclopentadienyl) to yield a nucleophilic η^1-allyltitanocene(IV) intermediate, or 2) another allyl radical to give a Würtz-type homocoupling product. The classical experimental procedure has severe drawbacks and, therefore, it has been scarcely used in organic synthesis.[19]

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Other, more convenient, Würtz-type protocols have been developed that use different metals (such as Cu,[20] Sm,[21] Ti,[22] Fe[23] or Ni),[24] but, in all cases, allylic halides are required as starting materials. The use of allylic esters in Würtz-type reactions is rather unusual.[25] In this context, a general Würtz-type reaction of allylic carboxylates catalysed by a Ti/Pd bimetallic system may broaden the scope of this transformation.

Many interesting compounds with dimeric structures occur naturally, for example, squalene. Therefore, we focused on simple acetate and ethyl carbonate derivatives of geraniol, nerol, linalool and farnesol as starting materials. A simple solution to minimise heterocoupling processes between the allyl radical and [Cp$_2$TiCl] is to decrease the concentration of [Cp$_2$TiCl] below the concentration of the Pd catalyst. New developments in titanocene(III)-regenerating agents[26] allow reactions to be performed with [Cp$_2$TiCl$_2$] (5–40 mol %) as a pre-catalyst.[27] Especially, the combination of 2,4,6-collidine and trimethylsilyl chloride (TMSCl), developed in our lab, has proven to regenerate different titanium species (titanium alkoxides, carboxylates or hydrides).[28] Based on these precedents, we carried out the reactions by using a mixture of allylic derivative (1 mmol), palladium catalyst (20 mol %), [Cp$_2$TiCl$_2$] (10 mol %), Mn dust (8 mmol), 2,4,6-collidine (7 mmol) and TMSCl (4 mmol).

The initial experiment with geranyl carbonate **1** showed that Würtz-type coupling products were obtained when a simple mixture of PdCl$_2$ and PPh$_3$ was used (Table 1).[29] Notably, the reaction takes place smoothly at room temperature. In the absence of the phosphane ligand the starting substrate was recovered, which underlines its importance.

The head-to-head coupling of the allyl radical (α,α'-coupling product) is the main product in all cases (Table 1).[30] This regioselectivity is in accordance with previously described results for the dimerisation of geranyl bromide and geranyl acetate.[22,25] It is worth noting that the E or Z stereochemistry of the double bond in the allylic substrate was mainly retained when ethyl carbonates of trisubstituted alkenes were used (Table 1, entries 1, 2 and 6). This stereospecificity in palladium-mediated coupling reactions of allylic carbonates is known[31] and suggests that the dimerisation process is faster than isomerisation of the η^3-allylpalladium complex or the subsequent allyl radical. Good stereocontrol in the coupling process is an important goal, because stereodefined natural polyprenes are required as starting materials in the biomimetic synthesis of natural products. On the other hand, reactions of allylic acetates (Table 1, entries 3–5) led to similar regioselectivities, but poorer stereoselectivities.

To exemplify the potential of this transformation in the context of the synthesis of polyprenes, we carried out the first synthesis of squalene from readily prepared ethyl farnesyl carbonate (Table 1, entry 6). This coupling process could be also extended to other substrates to give the respective Würtz-type coupling products (Table 1, entries 7–10). The reaction is compatible with different substitution patterns in

Table 1. Ti/Pd-Mediated Würtz-type coupling.[a]

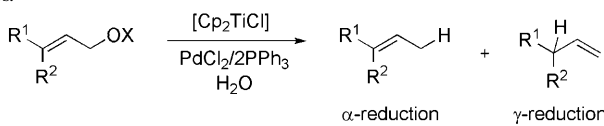| Allylic derivative	α,α' Coupling product		Yield [%]	(α,α')/(α,γ')
1	**1**	**11**	78	5.6:1[b]
2	**2**	**11**	60	4:1[c]
3	**3**	**11**	60	3:1[d]
4	**4**	**11**	72	3:1[e]
5	**5**	**11**	73	3:1[f]
6	**6**	**12**	81	4:1[g]
7	**7**	**13**	100	2:1
8	**8**	**13**	49	3:2
9	**9**	**14**	70	3:2
10	**10**	**15**	55	1:1[h]

[a] Allyl derivative (1 mmol), PdCl$_2$ (20 mol %), [Cp$_2$TiCl$_2$] (10 mol %), Mn dust (8 mmol), TMSCl (4 mmol), 2,4,6-collidine (7 mmol). [b] 4:1 mixture of E,E/E,Z stereoisomers. [c] 1:4 mixture of E,Z/Z,Z stereoisomers. [d] 1:1 mixture of E,E/E, Z stereoisomers. [E] 1:1 mixture of E,Z/Z,Z stereoisomers. [f] 1:1:1 mixture of E,E/E,Z/Z,Z stereoisomers. [g] 4:1 mixture of E,E/E,Z stereoisomers. [h] 1:1 syn/anti mixture.

the allylic carboxylate, but a decrease in substitution at the γ-position of the allylic carbonate gives lower α,α' regioselectivity.

Ti/Pd-mediated reduction of allylic carboxylates and carbonates: When the concentration of [Cp$_2$TiCl] is higher than the concentration of the Pd catalyst a heterocoupling reaction between the allyl radical and the Ti^{III} catalyst takes place. The resultant η^1-allyltitanium(IV) complexes can react with water, which leads to reduction of the allylic substrate. We validated this assumption by carrying out the re-

action of different carbonates and carboxylates in the presence of a mixture of allylic derivative (1 mmol), $PdCl_2$ (20 mol %), [Cp_2TiCl_2] (200 mol %), Mn (8 mmol) and water (10 mmol); see Table 2 for a summary of the results. In all

Table 2. Pd^0/Ti^{III}-mediated reduction of allylic carboxylates and carbonates.[a]

	Allyl carbonate	α/γ	Yield [%]
1	C_7H_{15} ⌒⌒ OCO_2Et	1.6:1[b]	60
2	C_7H_{15} ⌒⌒ OAc	1.6:1[b]	66
3	C_7H_{15} ⌒⌒ OBz	1.6:1[b]	61
4	MeO_2C ⌒⌒ OCO_2Et CO_2Me	1:1	45
5	OCO_2Et	1.5:1	100
6	OAc	1.5:1	100

[a] Allyl derivative (1 mmol), $PdCl_2$ (20 mol %), [Cp_2TiCl_2] (200 mol %), Mn dust (8 mmol), water (10 mmol). [b] 5:1 mixture of E/Z stereoisomers.

cases, the expected alkenes were obtained. This fact is remarkable when taken into account that homodimers are obtained in the titanocene(III)-mediated reactions of allylic halides, even in the presence of high amounts of water.[22] Formation of the α regioisomer as the major product is inconsistent with protonolysis of the allyltitanium(IV) complex, which would take place preferentially at the γ-position. Although protonolysis at the α-position is also possible, an explanation based on reduction of the corresponding allyl radical by titanocene(III)–aqua complexes cannot be ruled out.[32]
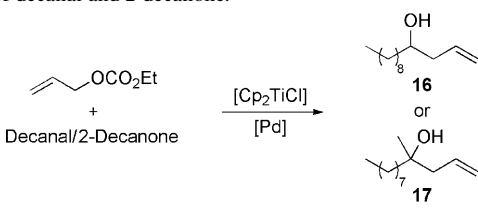
The reaction can be carried out with deuterium oxide as the electrophile, which leads to a quantitative yield of the deuterated isotopologues of the products illustrated in Table 2, entries 5 and 6. The presence of the deuterium atom was confirmed by mass spectroscopy and changes in the multiplicity of signals in the ^1H NMR spectrum. These deuterated derivatives, which present almost the same physical and chemical properties than their non-deuterated analogues, have potential applications for mechanistic studies, analysis of metabolic routes[33] and as internal standards in the analysis of complex mixtures (of great interest in the food and pharmaceutical industries).[34,35]

Ti/Pd-mediated allylation, crotylation and prenylation of aldehydes and ketones: η^1-Allyltitanium(IV) complexes are known to be good nucleophiles towards carbonyl compounds; homoallylic alcohols can be obtained by reaction

with appropriate aldehydes and ketones. Initially, we carried out experiments to find the best reaction conditions by using simple allyl ethyl carbonate as the pro-nucleophile and decanal and 2-decanone as the carbonyl compounds. In these experiments, the amount of titanium complex was high enough (200 mol %) to minimise the Würtz coupling. The results are summarised in Tables 3 and 4.

The reaction took place at room temperature with both decanal and 2-decanone as the electrophile. Interestingly, the yields with the less reactive 2-decanone are, in some
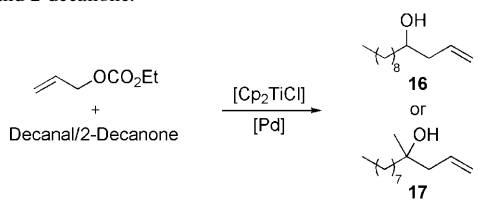
Table 3. Influence of the palladium complex in the Pd^0/Ti^{III}-catalysed allylation of decanal and 2-decanone.

	Palladium catalyst ([Pd])	16 [%]		17 [%]	
		A[a]	B[b]	A[a]	B[b]
1	$PdCl_2$	22	29	23	14
2	$PdCl_2/2PPh_3$	77	75	85	59
3	[$PdCl_2(PPh_3)_2$]	54	66	32[c]	48
4	[$Pd(PPh_3)_4$]	56	68	8	98
5	[$Pd_2(dba)_3$]·dba	26	60	55	22
6	$Pd(OAc)_2$	–	–	–	–
7	$Pd(OAc)_2+2PPh_3$	48	47	24[d]	15
8	[$PdCl_2(MeCN)_2$]	–	–	–	–
9	[$PdCl_2(MeCN)_2$]+2PPh_3	46	31	55[e]	56

[a] Method A: Allyl ethyl carbonate (4 mmol), palladium cat. (20 mol %), [Cp_2TiCl_2] (200 mol %), Mn dust (8 mmol), carbonyl compound (1 mmol). [b] Method B: Allyl ethyl carbonate (4 mmol), palladium cat. (10 mol %), [Cp_2TiCl_2] (40 mol %), Mn dust (8 mmol), TMSCl (4 mmol), 2,4,6-collidine (7 mmol), carbonyl compound (1 mmol) [c] 37 % of 2-decanone was recovered. [d] 53 % of 2-decanone was recovered. [e] 36 % of 2-decanone was recovered.

Table 4. Influence of the ligand in the Pd^0/Ti^{III}-mediated allylation of decanal and 2-decanone.[a]

	Ligand	16 [%]	17 [%]
1	PCy_3	8	51
2	$PPhCy_2$	28	53
3	$P(oTol)_3$	10	71
4	PPh_3	77	85
5	$P(Mes)_3$	33	37
6	$P(C_6F_5)_3$	28	45
7	$P(OEt)_3$	7	9
8	$P(OPh)_3$	–	33
9	dppe	26	–

[a] Allyl ethyl carbonate (4 mmol), palladium chloride (20 mol %), ligand (240 mol %), [Cp_2TiCl_2] (200 mol %), Mn dust (8 mmol), carbonyl compound (1 mmol).

cases, higher relative to those obtained with decanal. This is due to the slow transfer of one of the Cp groups of [Cp$_2$TiCl] to the aldehyde to yield the equivalent Grignard-type alcohol, a process that is especially relevant when stoichiometric amounts of [Cp$_2$TiCl] are used.

Although the phosphane ligand does not seem to be strictly required in this transformation (Table 3, entry 1), it might help in the stabilisation of low-valence palladium intermediates. Different phosphanes could also be used; however, the best yields were obtained with PPh$_3$ (Table 4, entry 4). On the other hand, phosphites were not suitable ligands for this transformation (Table 4, entries 7 and 8).[36] Interestingly, catalyst [PdCl$_2$(PPh$_3$)$_2$] gave lower yields than PdCl$_2$/PPh$_3$ (Table 3, entry 2 versus 3), which suggests that reduction of the pre-formed complex to the active Pd^0 species is disfavoured. The reaction could also be performed with [Cp$_2$TiCl$_2$] (40 mol%) in the presence of TMSCl (4 mmol), 2,4,6-collidine (7 mmol) and Mn dust (8 mmol) (Table 3, method B). For decanal, under these conditions, the combination of PdCl$_2$ and PPh$_3$ again gave the best results (Table 3, entry 2), whereas for 2-decanone an almost quantitative yield was obtained when [Pd(PPh$_3$)$_4$] was used (Table 3, entry 4).

We also tested the influence of the nature of the pro-nucleophile. The results are summarised in Table 5. A correlation between the leaving-group ability of the allylic functionality and the yield of the addition reaction was found. This suggests that the rate-determining step in the global process is oxidative addition to the allylic substrate. Although simple allylic ethyl and phenyl ethers are substrates of this reaction (Table 5, entries 1 and 2), the yields were improved when benzoates were used (Table 5, entries 4 and 5). Phenyl carbonate also gave satisfactory results (Table 5, entry 8). Nevertheless, the use of benzoates and phenyl carbonates produced benzoic acids and phenol as byproducts, whereas ethyl carbonates gave clean reactions. Therefore,

ethyl carbonates were selected to carry out the present study.

The scope of the process was studied under the optimised reaction conditions (Table 6). The allylation of a variety of aldehydes and ketones proceeded in moderate to good

Table 6. Pd^0/Ti^{III}-mediated allylation of aldehydes and ketones.

Carbonyl compound	Product	Yield[a] [%]	Yield[b] [%]
1 3-phenylpropanal	**18**	57	54
2 2-phenylpropanal	**19**	–	48[c]
3 citronelal	**20**	64	73[d]
4 adamantanone	**21**	72	79
5 acetophenone	**22**	87	74
6 cyclopropylphenyl ketone	**23**	74	63
7 α-tetralone	**24**	77	74
8 2-indanone	**25**	73	56
9 acetyl ferrocene	**26**	99	48
10 carvone	**27**	95	45
11 cyclododecanone	**28**	54	78
12 cyclodecanone	**29**	65	–
13 *tert*-butylcyclohexanone	**30**	61[e]	65[e]

[a] Method A: Allyl ethyl carbonate (4 mmol), palladium cat. (20 mol%), [Cp$_2$TiCl$_2$] (200 mol%), Mn dust (8 mmol), carbonyl compound (1 mmol). [b] Method B: Allyl ethyl carbonate (4 mmol), palladium cat. (10 mol%), [Cp$_2$TiCl$_2$] (40 mol%), Mn dust (8 mmol), TMSCl (4 mmol), 2,4,6-collidine (7 mmol), carbonyl compound (1 mmol). [c] 15:85 mixture of *syn/anti* stereoisomers. [d] Racemic mixture. [e] 2:1 mixture of *cis/trans* stereoisomers.

Table 5. Influence of the allylic derivative in the Pd^0/Ti^{III}-promoted allylation of carbonyl compounds.[a]

	R	**16** [%]	**17** [%]
1	CH$_2$CH$_3$	–	43
2	Ph	40	63
3	COCH$_3$	30	39
4	COPh	40	68
5	COC$_6$F$_5$	87	79
6	CO$_2$Et	77	85
7	CO$_2$CH$_2$CCl$_3$	10	–
8	CO$_2$Ph	64	63

[a] Allyl ethyl carbonate (4 mmol), PdCl$_2$ (10 mol%), ligand (20 mol%), [Cp$_2$TiCl$_2$] (200 mol%), Mn dust (8 mmol), carbonyl compound (1 mmol).

yields. The results from the use of stoichiometric and sub-stoichiometric amounts of titanium catalyst were, in many cases, similar. The yields obtained from reactions with ketones as electrophiles are typically higher than those from the corresponding aldehydes. Notably, even ketones such as acetophenone, prone to readily undergo pinacol reaction (thus, unsuitable substrates for samarium-related transformations),[37] gave the desired allylation products.

Crotylation was also examined (Table 7). In this case, the two positions of the allyl radical intermediate are not equivalent and mixtures of regioisomers would be expected. However, the reaction is highly regioselective and exclusively favours the γ-addition product. With respect to the stereo-

chemistry, we could also observe a slight preference for formation of the *anti* isomer. This regio- and diastereoselectivity suggest the involvement of a 2-butenyltitanium(IV) intermediate, similar to that described by Sato.[38] Notably, the crotylation reaction takes place satisfactorily with ketones.

Prenylation of ketones is γ regioselective, whereas variable amounts of the α regioisomer were isolated when aldehydes were used as electrophiles (Table 8). Although the α prenylation is rather infrequent, it has been previously observed in other titanocene(III)-mediated Barbier-type reactions.[1,2b]

Intramolecular Barbier-type allylation reactions are scarce in the literature, probably a result of the synthetic effort required to introduce the labile allylic halide moiety. Nevertheless, the present protocol allowed for the efficient synthesis of six- (Table 9, entries 1–8) and five-membered (Table 9, entries 9–10) carbo- and heterocyclic products. Different substituents are tolerated in the ketone (Table 9, entries 7 and 10) and alkene moieties (Table 9, entry 8). The stereoselectivities in the formation of six-membered carbocycles are, in general, excellent; the major stereoisomer presents a *cis* configuration between the vinyl and hydroxyl groups. Although the reason for this preference is unclear, precedent from other intramolecular titanocene(III)-mediated Barbier reactions suggest that an allyl radical addition to the carbonyl group takes place instead of the expected η1-allyltitanium(IV) nucleophilic addition.[12b] Five-membered carbocycles present mainly the opposite stereochemistry, with the vinyl and hydroxyl group in a *trans* configuration.

Mechanistic studies: The results obtained by reaction with the Ti/Pd bimetallic system can be rationalised by the mechanism shown in Scheme 2.[39] Initially, an oxidative addition of the allylic electrophile **I** to Pd0 would give the corresponding η3-allyl-palladium complex **II**. Monoelectronic reduction of complex **II** could form an η3-allylpalla-
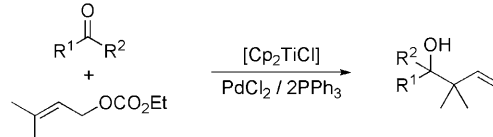
Table 7. Pd0/TiIII-mediated crotylation of aldehydes and ketones.

	Ethyl carbonate	Carbonyl compound	Product	Yield[a] [%]	Yield[b] [%]	*syn/anti*
1	OCO2Et	decanal		**31** 53	–	4:6
2	OCO2Et	2-decanone		**32** 63	75	4:6
3	OCO2Et	citronelal		**33** 46	66	4:6
4	OCO2Et	cyclocitral		**34** –	96	4:6
5	OCO2Et	geranyl acetone[c]		**35** 55	71	4:6
6	OCO2Et	acetophenone		**36** –	36	1:1
7	C7H15 OCO2Et	2-decanone		**37** 80	–	1:2
8	OCO2Et C5H11	2-decanone		**38** 52	–	1:2
9	OCO2Et Z Z=C(CO2Me)2	decanal		**39** –	52[d]	–
10	OCO2Et Z Z=C(CO2Me)2	decanal		**40** 63[d]	–	–

[a] Method A: Allyl ethyl carbonate (4 mmol), palladium cat. (20 mol%), [Cp2TiCl2] (200 mol%), Mn dust (8 mmol), carbonyl compound (1 mmol). [b] Method B: Allyl ethyl carbonate (4 mmol), palladium cat. (10 mol%), [Cp2TiCl2] (40 mol%), Mn dust (8 mmol), TMSCl (4 mmol), 2,4-collidine (7 mmol), carbonyl compound (1 mmol). [c] 1:1 mixture of *E/Z* stereoisomers. [d] Single stereoisomer, tentatively assigned as *anti* isomer.
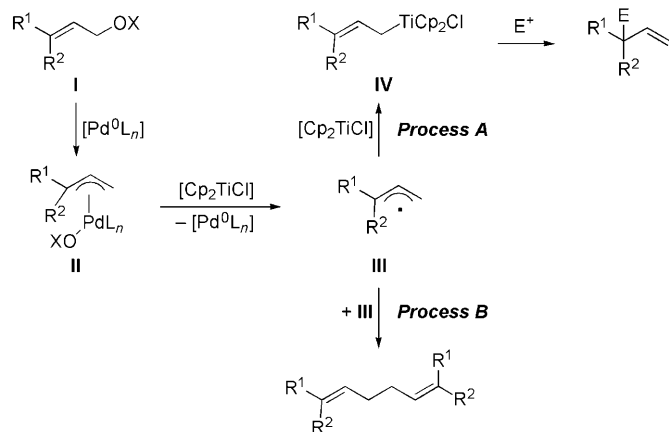
Table 8. Pd^0/Ti^{III}-mediated prenylation of aldehydes and ketones.

	Carbonate	Carbonyl compound	Product	Yield[a] [%]	Yield[b] [%]
1	OCO$_2$Et	decanal		**41** 84[c]	65[c]
2	OCO$_2$Et	2-decanone		**42** 61	53
3	OCO$_2$Et	citronelal		**43** 54[d]	61[d]
4	OCO$_2$Et	cyclocitral		**44** –	53
5	OCO$_2$Et	decanal		**45** 64[e]	–

[a] Method A: Allyl ethyl carbonate (4 mmol), palladium cat. (20 mol %), [Cp$_2$TiCl$_2$] (200 mol %), Mn dust (8 mmol), carbonyl compound (1 mmol). [b] Method B: Allyl ethyl carbonate (4 mmol), palladium cat. (10 mol %), [Cp$_2$TiCl$_2$] (40 mol %), Mn dust (8 mmol), TMSCl (4 mmol), 2,4,6-collidine (7 mmol), carbonyl compound (1 mmol). [c] 65:35 mixture of α/γ regioisomers. [d] 1:1 mixture of syn/anti regioisomers. [d] 1:10 mixture of diastereoisomers.

Scheme 2. Mechanistic hypothesis for the Ti/Pd-mediated allylation and Würtz-type coupling reactions.

Table 9. Pd^0/Ti^{III}-mediated cyclisation reactions.

	Allyl carbonate	Product	Yield[a] [%]	Yield[b] [%]
1	Z = C(CO$_2$Me)$_2$		**46** 73[c]	–
2	Z = C(CO$_2$Me)$_2$		**47** 74[c]	–
3	Z = C(CO$_2$Me)$_2$		**48** –	95
4	Z = C(CO$_2$Me)$_2$	**48**	–	92
5	Z = NTs		**49** 71	62
6	Z = C(SO$_2$Ph)$_2$		**50** 78	67
7	Z = C(SO$_2$Ph)$_2$		**51** 63	60
8	Z = C(CO$_2$Me)$_2$		**52** 53[c]	56[c]
9	Z = C(CO$_2$Me)$_2$		**53** 83[d]	46[d]
10	Z = C(CO$_2$Me)$_2$		**54** –	46

[a] Method A: Allyl ethyl carbonate (4 mmol), palladium cat. (20 mol %), [Cp$_2$TiCl$_2$] (200 mol %), Mn dust (8 mmol), carbonyl compound (1 mmol). [b] Method B: Allyl ethyl carbonate (4 mmol), palladium cat. (10 mol %), [Cp$_2$TiCl$_2$] (40 mol %), Mn dust (8 mmol), TMSCl (4 mmol), 2,4,6-collidine (7 mmol), carbonyl compound (1 mmol). [c] 1:1 mixture of diastereoisomers. [d] 4:1 mixture of diastereoisomers.

dium(I) intermediate, which apparently fragments to three new species: 1) the corresponding carbon-centred allyl radical **III**, 2) a Pd^0 complex, which is reintroduced into the catalytic cycle and 3) a Ti^{IV} ethyl carbonate. Although we initially assigned the role of single-electron-transfer (SET) reagent to [Cp$_2$TiCl], despite its relatively low reduction potential ($E^0 = -0.8$ V vs. Fc/Fc$^+$), we should take into account that Mn dust is also present in the reaction media. Therefore, we carried out some control experiments. The reaction takes place when a mixture of Pd^0 complexes, such as [Pd(PPh$_3$)$_4$] and pre-generated [Cp$_2$TiCl]$_2$, are used.[40] Nevertheless, the reaction is highly accelerated in the presence of Mn dust. It is also worth noting that in the absence of [Cp$_2$TiCl] the reaction does not take place. One possible explanation for this is that [Cp$_2$TiCl] is not only acting as a SET reagent, but also as a pre-activator for the reduction of the η^3-allylpalladium complex. Coordination with the ethyl carbonate anionic ligand could favour a Mn^0-mediated SET. This hypothesis is supported by the previously reported Lewis acidic character of [Cp$_2$TiCl].[41]

Homocoupling between two allyl radicals **III** generates the Würtz-type products (Scheme 2, Process B). A hetero-

coupling process between the resulting allyl radical **III** and the titanocene(III) complex would yield a nucleophilic η^1-allyl titanocene(IV) complex **IV** (Scheme 2, Process A),[17] which is able to react with different electrophiles. Titanocene(III) regenerators (2,4,6-trimethyl-1-trimethylsilylpiridinium chloride/Mn dust or 2,4,6-collidine·HCl/Mn dust) then reintroduce [Cp$_2$TiCl] into the catalytic cycle. Alternative mechanisms based on pre-coordination of the Ti^{III} complex to aldehydes and ketones[42] or nucleophilic palladium complexes[43,44] cannot be ruled out.

Conclusion

We have demonstrated that Ti^{III} can catalyse allylation, crotylation and prenylation of carbonyl compounds, Würtz-type coupling and reduction reactions, in the presence of palladium complexes, from stable and easily handled allylic carboxylate starting materials. The addition reaction can also be carried out intramolecularly to yield five- and six-membered cyclic products with good stereoselectivities. Notably, this Ti/Pd bimetallic system is especially convenient for the allylation of ketones, which are infrequent substrates in other related protocols. From a mechanistic point of view, the role of all the involved metallic species must be clarified to develop an enantioselective version of this reaction. In this sense, Ti^{III} intermediates seem to play a key role in the Barbier-type reactions and the development of chiral titanocene(III) complexes compatible with our catalytic conditions is underway.

Experimental Section

General details: For all reactions that involved titanocene, solvents and additives were strictly deoxygenated prior to use. THF was distilled over sodium/benzophenone ketyl radical under argon. The following known compounds were isolated as pure samples and NMR spectra matched those previously reported: **28**;[9c] **17**, **20**, **21**, **32**, **39–42**, **46–48**;[11] **23**, **29**, **49**, **50**;[12b] **11**;[22] **13–16**;[45–48] **18**;[49] **19**;[50] **22**;[51] **25**;[52] **24**, **26**;[53] **27**;[54] **30–33**;[55–57] **36**.[58]

General procedure for the synthesis of allyl, crotyl and prenyl carbonates from alcohols (GP 1): Ethylchloroformate (2.0 mmol) was slowly added to a mixture of 4-dimethylaminopyridine (0.3 mmol), pyridine (3.0 mmol) and alcohol (1.0 mmol) in dry CH$_2$Cl$_2$ (25 mL). The reaction mixture was stirred for 3 h and subsequently washed with 10% aqueous HCl solution, 10% aqueous NaOH solution and brine. The organic phase was dried over anhydrous NaSO$_4$ and the solvent was removed in vacuo. The residue was purified by flash chromatography (EtOAc/hexane) to give the carbonate.

General procedure for Pd^0/Ti^{III}-mediated Würtz-type coupling reaction of allylic derivatives (GP 2): Rigorously dried and deoxygenated THF (20 mL) was added to a mixture of [Cp$_2$TiCl$_2$] (0.1 mmol), PdCl$_2$ (0.2 mmol), PPh$_3$ (0.4 mmol) and Mn dust (8.0 mmol) under an Ar atmosphere and the suspension was stirred at RT until it turned dark green (about 15 min). A solution of allylic derivative (1.0 mmol) and 2,4,6-collidine (7.0 mmol) in THF (2 mL) and Me$_3$SiCl (4.0 mmol) was then added. The mixture was stirred for 16 h and then diluted with EtOAc and washed with 10% aqueous HCl solution and brine. The organic phase was dried over anhydrous NaSO$_4$ and the solvent was removed in vacuo. Products were purified by flash chromatography on silica gel (hexane)

and characterised by spectroscopic techniques. The yields obtained are reported in Table 1.

General procedure for Pd^0/Ti^{III}-mediated reduction of allylic carboxylates and carbonates (GP 3): Rigorously deoxygenated THF (20 mL) was added to a mixture of [Cp$_2$TiCl$_2$] (2.0 mmol), PdCl$_2$ (0.1 mmol), PPh$_3$ (0.2 mmol) and Mn dust (8.0 mmol) under an Ar atmosphere and the suspension was stirred at RT until it turned dark green (about 15 min). A solution of carbonate (1.0 mmol) and water (10 mmol) in THF (2 mL) was then added. The mixture was stirred for 6 h and then diluted with EtOAc and washed with brine. The organic phase was dried over anhydrous NaSO$_4$ and the solvent was removed in vacuo. Products were purified by flash chromatography on silica gel (hexane) and characterised by spectroscopic techniques. The yields obtained are reported in Table 2.

General procedure for Pd^0/Ti^{III}-mediated allylation, crotylation and prenylation of carbonyl compounds with carbonates (GP 4)

Method A: Rigorously dried and deoxygenated THF (20 mL) was added to a mixture of [Cp$_2$TiCl$_2$] (2.0 mmol), PdCl$_2$ (0.1 mmol), PPh$_3$ (0.2 mmol) and Mn dust (8.0 mmol) under an Ar atmosphere and the suspension was stirred at RT until it turned dark green (about 15 min). A solution of carbonyl compound (1.0 mmol) and carbonate (4.0 mmol) in THF (2 mL) was then added. The mixture was stirred for 6 h and then diluted with EtOAc and washed with brine. The organic phase was dried over anhydrous NaSO$_4$ and the solvent was removed in vacuo. The residue was purified by flash chromatography (EtOAc/hexane).

Method B: Rigorously dried and deoxygenated THF (20 mL) was added to a mixture of [Cp$_2$TiCl$_2$] (0.4 mmol), PdCl$_2$ (0.2 mmol), PPh$_3$ (0.4 mmol) and Mn dust (8.0 mmol) under an Ar atmosphere and the suspension was stirred at RT until it turned dark green (about 15 min). A solution of carbonyl compound (1.0 mmol), carbonate (4.0 mmol) and 2,4,6-collidine (7.0 mmol) in THF (2 mL) and Me$_3$SiCl (4.0 mmol) were then added. The mixture was stirred for 16 h and then diluted with EtOAc and washed with 10% aqueous HCl solution and brine. The organic phase was dried over anhydrous NaSO$_4$ and the solvent was removed in vacuo. The residue was purified by flash chromatography (EtOAc/hexane).

General procedure for Pd^0/Ti^{III}-mediated cyclisation reactions (GP 5)

Method A: Rigorously dried and deoxygenated THF (15 mL) was added to a mixture of [Cp$_2$TiCl$_2$] (2.0 mmol), PdCl$_2$ (0.1 mmol), PPh$_3$ (0.2 mmol) and Mn dust (8.0 mmol) under an Ar atmosphere and the suspension was stirred at RT until it turned dark green (about 15 min). A solution of acyclic compound (1.0 mmol) in THF (1 mL) was then added. The mixture was stirred for 16 h and then diluted with EtOAc and washed with brine. The organic phase was dried over anhydrous NaSO$_4$ and the solvent was removed in vacuo. The residue was purified by flash chromatography (EtOAc/hexane).

Method B: Rigorously dry and deoxygenated THF (15 mL) was added to a mixture of [Cp$_2$TiCl$_2$] (0.4 mmol), PdCl$_2$ (0.2 mmol), PPh$_3$ (0.4 mmol) and Mn dust (8.0 mmol) under an Ar atmosphere and the suspension was stirred at RT until it turned dark green (about 15 min). A solution of acyclic compound (1.0 mmol) and 2,4,6-collidine (7.0 mmol) in THF (1 mL) and Me$_3$SiCl (4.0 mmol) were then added. The mixture was stirred for 24 h and then diluted with EtOAc and washed with 10% aqueous HCl solution and brine. The organic phase was dried over anhydrous NaSO$_4$ and the solvent was removed in vacuo. The residue was purified by flash chromatography (EtOAc/hexane).

Compound 34: Following GP 4, compound **34** was obtained as a colourless oil. ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): $\delta = 5.85–5.73$ (m, 1H), 5.19–5.11 (m, 1H), 3.94 (d, $J = 9.9$ Hz, 1H), 2.90–2.73 (m, 1H), 1.99–1.90 (m, 2H), 1.81 (s, 3H), 1.73–1.32 (m, 4H), 1.17 (d, $J = 6.5$ Hz, 3H), 1.06 (m, 3H), 1.01–0.94 (s, 3H), 0.90 ppm (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$, 25 °C): $\delta = 143.3$ (CH), 141.7 (CH isom), 133.3 (C), 132.5 (C), 115.8 (CH$_2$), 113.3 (CH$_2$ isom), 75.4 (CH), 73.7 (CH isom), 44.3 (CH), 43.0 (CH isom), 40.4 (CH$_2$), 34.8 (C), 34.6 (CH$_2$), 34.4 (CH$_2$ isom), 29.1 (2× CH$_3$), 21.5 (CH$_3$), 19.5 (CH$_2$), 17.8 (CH$_3$), 17.3 ppm (CH$_3$ isom); HRMS (FAB): m/z calcd for C$_{14}$H$_{24}$ONa [M+Na]$^+$: 231.1725; found: 231.1719.

Compound 35: Following GP 4, compound **35** was obtained as a colourless oil. ^{1}H NMR (500 MHz, CDCl$_3$, 25 °C): $\delta = 5.91–5.79$ (m, 1H), 5.15–5.03 (m, 4H), 2.31–2.20 (m, 1H), 2.13–2.01 (m, 4H), 2.02–1.95 (m, 2H),

1.68 (s, 6H), 1.60 (s, 3H), 1.54–1.44 (m, 2H), 1.10 (s, 3H), 1.03–0.97 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$, 25°C): $\delta = 139.5$ (CH), 134.3 (C), 130.5 (C), 124.3 (CH), 123.3 (CH), 114.8 (CH$_2$), 72.7 (C), 46.3 (CH), 38.6 (CH$_2$), 30.9 (CH$_2$), 25.6 (CH$_2$), 24.7 (CH$_3$), 22.6 (CH$_3$), 20.8 (CH$_2$), 16.7 (CH$_3$), 15.0 (CH$_3$), 13.9 ppm (CH$_3$).

Compound 37: Following GP 4, compound **37** was obtained as colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$, 25°C): $\delta = 5.60$ (m, 1H), 5.17 (d, $J = 10.2$ Hz, 1H), 5.08 (d, $J = 17.0$ Hz, 1H), 2.06–2.05 (m, 1H), 1.51–1.16 (m, 26H), 1.07 (s, 3H), 0.87 ppm (t, $J = 6.3$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$, 25°C): $\delta = 139.1$ (CH), 118.4 (CH$_2$), 73.4 (C), 54.2 (CH), 39.8 (CH$_2$), 31.9 (2×CH$_2$), 30.3 (CH$_2$), 30.2 (CH$_2$), 29.6 (CH$_2$), 29.5 (CH$_2$), 29.3 (2×CH$_2$), 28.9 (CH$_2$), 28.1 (CH$_2$), 28.0 (CH$_2$), 24.2 (CH$_3$), 23.1 (CH$_2$), 22.6 (CH$_2$), 14.1 ppm (2×CH$_3$); HRMS (EI): m/z calcd for C$_{20}$H$_{40}$ONa [M+Na]$^+$: 319.2977; found: 319.2979.

Compound 38: Following GP 4, compound **38** was obtained as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$, 25°C): $\delta = 5.70$–5.47 (m, 1H), 5.16 (d, $J = 10.2$ Hz, 1H), 5.07 (d, $J = 17.1$ Hz, 1H), 2.02–1.94 (m, 1H), 1.64–1.11 (m, 22H), 1.06 (s, 3H), 0.86 ppm (t, $J = 6.3$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$, 25°C): $\delta = 139.1$ (CH), 118.4 (CH$_2$), 73.4 (C), 54.2 (CH), 39.8 (CH$_2$), 31.8 (2×CH$_2$), 30.3 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 28.9 (CH$_2$), 27.7 (CH$_2$), 24.2 (CH$_3$), 23.13 (CH$_2$), 23.09 (CH$_2$), 22.7 (CH$_2$), 22.6 (CH$_2$), 14.1 (CH$_3$), 14.0 ppm (CH$_3$); HRMS (EI): m/z calcd for C$_{18}$H$_{36}$ONa [M+Na]$^+$: 291.2664; found: 291.2676.

Compound 43: Following GP 4, compound **43** was obtained as a colourless oil. ^{1}H NMR (500 MHz, CDCl$_3$, 25°C): $\delta = 5.80$ (ddd, $J = 17.5$, 10.8, 2.5 Hz, 1H), 5.13–4.98 (m, 3H), 3.36 (br s, 1H, one isomer), 3.32 (br s, 1H, other isomer), 2.09–1.88 (m, 2H), 1.67 (s, 3H), 1.60 (m, 3H), 1.52–1.36 (m, 2H), 1.33–1.24 (m, 1H), 1.21–1.11 (m, 2H), 0.97 (d, $J = 6.2$ Hz, 6H), 0.93 (d, $J = 6.7$ Hz, 3H, one isomer), 0.88 ppm (d, $J = 6.6$ Hz, 3H, other isomer); ^{13}C NMR (125 MHz, CDCl$_3$, 25°C): $\delta = 145.5$ (CH), 124.9 (C), 124.8 (CH), 113.1 (CH$_2$), 76.0 (CH), 75.6 (CH), 41.6 (C), 39.0 (CH$_2$), 38.7 (CH$_2$), 38.33 (CH$_2$), 35.7 (CH$_2$), 29.8 (CH) 29.2 (CH), 25.6 (2×CH$_3$), 25.2 (CH$_2$), 23.0 (CH$_3$), 22.0 (CH$_3$), 20.8 (CH$_3$), 18.8 (CH$_3$), 17.6 ppm (CH$_3$); HRMS (FAB): m/z calcd for C$_{15}$H$_{28}$ONa [M+Na]$^+$: 247.2037; found: 247.2029.

Compound 44: Following GP 4, compound **44** was obtained as a colourless oil. ^{1}H NMR (500 MHz, CDCl$_3$, 25°C): $\delta = 6.08$ (dd, $J = 17.6$, 10.8 Hz, 1H), 5.03–4.93 (m, 2H), 4.12 (br s, 1H), 2.03–1.95 (m, 2H), 1.77 (s, 3H), 1.63–1.42 (m, 2H), 1.42–1.31 (m, 2H), 1.11 (s, 6H), 1.07 ppm (s, 6H); ^{13}C NMR (100 MHz, CDCl$_3$, 25°C): $\delta = 147.8$ (CH), 138.6 (C), 133.8 (C), 111.0 (CH$_2$), 77.6 (CH), 42.8 (CH$_2$), 40.6 (C), 34.8 (CH$_2$), 29.8 (C), 28.0 (4×CH$_3$), 25.3 (CH), 19.2 ppm (CH$_2$); HRMS (EI) m/z calcd for C$_{15}$H$_{26}$O [M−OH]$^+$: 205.1956; found: 205.1958.

Compound 45: Following GP 4, compound **45** was obtained as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$, 25°C): $\delta = 5.74$–5.63 (m, 1H), 5.13 (dd, $J = 10.9$, 1.3 Hz, 1H), 5.06–5.01 (m, 1H), 5.01–4.95 (m, 1H), 3.19 (m, 1H), 1.89–1.69 (m, 2H), 1.60 (s, 3H), 1.51 (s, 3H), 1.43–1.08 (m, 18H), 0.88 (s, 3H), 0.81 ppm (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$, 25°C): $\delta = 144.3$ (CH), 131.2 (C), 124.8 (CH), 115.0 (CH$_2$), 77.1 (CH), 45.0 (C), 37.4 (CH$_2$), 31.9 (CH$_2$), 30.9 (CH$_2$), 29.8 (CH$_2$), 29.7 (CH$_2$), 29.6 (CH$_2$), 29.3 (CH$_2$), 27.1 (CH$_2$), 25.6 (CH$_3$), 22.8 (CH$_2$), 22.7 (CH$_2$), 17.5 (CH$_3$), 16.6 (CH$_3$), 14.1 ppm (CH$_3$); HRMS (ESI$^+$): m/z calcd for C$_{20}$H$_{39}$O [M+H]$^+$: 295.3001; found: 295.3000.

Compound 51: Following GP 5, compound **51** was obtained as a colourless oil. ^{1}H NMR (500 MHz, CDCl$_3$, 25°C): $\delta = 8.09$ (d, $J = 7.5$ Hz, 2H), 8.00 (d, $J = 7.6$ Hz, 2H), 7.76–7.63 (m, 2H), 7.58 (dt, $J = 17.3$, 7.8 Hz, 4H), 5.86–5.65 (m, 1H), 5.15 (t, $J = 14.4$ Hz, 1H), 3.01 (ddd, $J = 12.6$, 8.5, 4.0 Hz, 1H), 2.69–2.58 (m, 1H), 2.27 (tdd, $J = 8.5$, 6.9, 2.4 Hz, 1H), 2.11–1.99 (m, 1H), 1.72–1.62 (m, 1H), 1.54 (ddd, $J = 14.7$, 7.3, 3.4 Hz, 1H), 0.89 ppm (t, $J = 7.6$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$, 25°C): $\delta = 137.0$ (CH), 136.7 (C), 136.2 (C), 134.4 (CH), 134.3 (CH), 131.5 (C), 131.1(CH), 131.1 (CH), 128.6 (CH), 118.0 (CH$_2$), 87.7 (C), 70.8 (C) , 43.6 (CH), 33.7 (CH$_2$), 30.9 (CH$_2$), 27.4 (CH$_2$), 22.2 (CH$_2$), 7.50 ppm (CH$_3$); HRMS (EI): m/z calcd for C$_{22}$H$_{26}$O$_5$S$_2$Na [M+Na]$^+$: 457.1119; found: 457.1126.

Compound 52: Following GP 5, compound **52** was obtained as a colourless oil. ^{1}H NMR (500 MHz, CDCl$_3$, 25°C): $\delta = 5.01$ (s, 1H), 4.79 (s, 1H), 3.76 (s, 3H), 3.71 (s, 3H), 2.42–2.22 (m, 3H), 1.88 (t, $J = 13.6$ Hz, 1H),

1.85–1.78 (m, 1H), 1.81 (s, 3H), 1.73 (dt, $J = 13.4$, 3.5 Hz, 1H), 1.64–1.55 (m, 1H), 1.17 ppm (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$, 25°C): $\delta = 172.6$ (C), 171.2 (C), 144.8 (C), 114.8 (CH$_2$), 71.6 (C), 55.30 (C), 52.9 (CH$_3$), 52.7 (CH$_3$), 50.8 (CH), 38.2 (CH$_2$), 33.4 (CH$_2$), 29.0 (CH$_2$), 23.01 (CH$_3$), 22.0 ppm (CH$_3$); HRMS (EI): m/z calcd for C$_{14}$H$_{22}$O$_5$Na [M+Na]$^+$: 293.1365; found: 293.1374.

Compound 53: Following GP 5, compound **53** was obtained as a colourless oil. ^{1}H NMR major isomer (500 MHz, CDCl$_3$, 25°C): $\delta = 5.68$ (ddd, $J = 17.2$, 10.4, 2.2 Hz, 1H), 5.07 (d, $J = 8.8$ Hz, 1H), 5.05 (d, $J = 1.2$ Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 2.66–2.55 (m, 2H), 2.45 (d, $J = 14.3$ Hz, 1H), 2.34 (d, $J = 14.3$ Hz, 1H), 2.17–2.13 (m, 2H), 1.43 ppm (s, 3H); ^{13}C NMR major isomer (100 MHz, CDCl$_3$, 25°C): $\delta = 173.5$ (C), 168.5 (C), 136.8 (CH), 118.7 (CH$_2$), 91.1 (C), 57.1 (C), 52.7 (CH$_3$), 49.8 (CH$_3$), 48.1 (CH), 45.1 (CH$_2$), 34.4 (CH$_2$), 17.3 ppm (CH$_3$); ^{1}H NMR minor isomer (500 MHz, CDCl$_3$, 25°C): $\delta = 5.72$ (ddd, $J = 17.2$, 10.4, 2.2 Hz, 1H), 5.07 (d, $J = 8.8$ Hz, 1H), 5.05 (d, $J = 1.2$ Hz, 1H), 3.74 (s, 3H), 3.72 (s, 3H), 2.66–2.55 (m, 2H), 2.45 (d, $J = 14.3$ Hz, 1H), 2.34 (d, $J = 14.3$ Hz, 1H), 2.17–2.13 (m, 2H), 1.44 ppm (s, 3H); ^{13}C NMR minor isomer (100 MHz, CDCl$_3$, 25°C): $\delta = 173.3$ (C), 168.3 (C), 135.1 (CH), 119.1 (CH$_2$), 90.3 (C), 57.8 (C), 52.7 (CH$_3$), 49.9 (CH$_3$), 48.1 (CH), 45.1 (CH$_2$), 34.1 (CH$_2$), 16.9 ppm (CH$_3$); HRMS (EI): m/z calcd for C$_{12}$H$_{18}$O$_5$Na [M+Na]$^+$: 265.1052; found: 265.1060.

Compound 54: Following GP 5, compound **54** was obtained as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$, 25°C): $\delta = 7.43$–7.28 (m, 5H), 5.74 (dt, $J = 18.0$, 9.1 Hz, 1H), 5.10 (d, $J = 10.2$ Hz, 1H), 4.96 (d, $J = 17.0$ Hz, 1H), 3.85 (s, 6H), 3.21–3.14 (m, 1H), 2.79–2.70 (m, 1H), 2.66 (d, $J = 11.0$ Hz, 1H), 2.58 (d, $J = 10.6$ Hz, 1H), 2.08 ppm (ddd, $J = 13.4$, 4.5, 2.3 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$, 25°C): $\delta = 167.8$ (C), 163.3 (C), 130.1 (C), 129.2 (CH), 123.7 (2×CH), 120.4 (2×CH), 123.4 (CH), 114.3 (CH$_2$), 87.8 (C), 53.1 (C), 48.0 (2×CH$_3$), 46.1 (CH), 43.8 (CH$_2$), 29.2 ppm (CH$_2$); HRMS (EI): m/z calcd for C$_{17}$H$_{20}$O$_5$Na [M+Na]$^+$: 327.1208; found: 327.1210.

Acknowledgements

[1] Selected reviews: a) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207–2293; b) C. E. Masse, J. S. Panek, *Chem. Rev.* **1995**, *95*, 1293–1316; c) B. W. Gung, *Org. React.* **2004**, *64*, 1–112; d) Z. Lu, S. Ma, *Angew. Chem.* **2008**, *120*, 264–303; *Angew. Chem. Int. Ed.* **2008**, *47*, 258–297; e) L. F. Tietze, T. Kinzel, C. C. Brazel, *Acc. Chem. Res.* **2009**, *42*, 367–378.

[2] P. Barbier, *C. R. Hebd. Seances Acad. Sci.* **1899**, *128*, 110.

[3] J. A. Marshall, *Chem. Rev.* **2000**, *100*, 3163–3185.

[4] Zn and B: a) J. P. Takahara, Y. Masuyama, Y. Kurusu, *J. Am. Chem. Soc.* **1992**, *114*, 2577–2586; b) S. Sebelius, O. A. Wallner, K. J. Szabó, *Org. Lett.* **2003**, *5*, 3065–3068; c) S.-F. Zhu, Y. Yang, L.-X. Wang, B. Liu, Q.-L. Zhou, *Org. Lett.* **2005**, *7*, 2333–2335.

[5] Pd and Sn: a) Y. Masuyama, N. Kinugawa, Y. Kurusu, *J. Org. Chem.* **1987**, *52*, 3702–3704; b) W. Qui, Z. Wang, *J. Chem. Soc. Chem. Commun.* **1989**, 356–357.

[6] Sm^{II}: T. Tabuchi, J. Inanaga, M. Yamaguchi, *Tetrahedron Lett.* **1986**, *27*, 1195–1196.

[7] Rh: M. Vasylyev, H. Alper, *J. Org. Chem.* **2010**, *75*, 2710–2713.

[8] The group of Krische reported new allylations that use iridium complexes and a source of hydrogen but the procedure seems to be limited to simple allyl and α-methyl allyl acetate as pro-nucleophiles and aldehydes as electrophiles: a) I. S. Kim, M.-Y. Ngai, M. J. Krische, *J. Am. Chem. Soc.* **2008**, *130*, 14891–14899; b) I. S. Kim, M.-Y. Ngai, M. J. Krische, *J. Am. Chem. Soc.* **2009**, *131*, 2514–2520;

c) S. B. Han, H. Han, M. J. Krische, *J. Am. Chem. Soc.* **2010**, *132*, 1760–1761; d) Y. J. Zhang, J. H. Yang, S. H. Kim, M. J. Krische, *J. Am. Chem. Soc.* **2010**, *132*, 4562–4563.

[9] R. E. Taylor, J. P. Ciavarri, *Org. Lett.* **1999**, *1*, 467–469.

[10] a) W. Qiu, Z. Wang, *J. Chem. Soc. Chem. Commun.* **1989**, 356–357; b) J. P. Takahara, Y. Masuyama, Y. Kurusu, *J. Am. Chem. Soc.* **1992**, *114*, 2577–2586; c) H. Nakamura, N. Asao, Y. Yamamoto, *J. Chem. Soc. Chem. Commun.* **1995**, 1273–1274.

[11] A. G. Campaña, B. Bazdi, N. Fuentes, R. Robles, J. M. Cuerva, J. E. Oltra, S. Porcel, A. M. Echavarren, *Angew. Chem.* **2008**, *120*, 7625–7629; *Angew. Chem. Int. Ed.* **2008**, *47*, 7515–7519.

[12] We have also described Ti^III-mediated Barbier-type reactions from allylic halide starting materials with a regioselectivity which diverges from the NHK reaction, a) A. Rosales, J. L. Oller-Lopez, J. Justicia, A. Gansäuer, J. E. Oltra, J. M. Cuerva, *Chem. Commun.* **2004**, 2628–2629; b) R. E. Estévez, J. Justicia, B. Bazdi, N. Fuentes, M. Paradas, D. Choquesillo-Lazarte, J. M. García-Ruiz, R. Robles, A. Gansäuer, J. M. Cuerva, J. E. Oltra, *Chem. Eur. J.* **2009**, *15*, 2774–2791; c) J. Justicia, I. Sancho-Sanz, E. Alvarez-Manzaneda, J. E. Oltra, J. M. Cuerva, *Adv. Synth. Catal.* **2009**, *351*, 2295–2300; J. E. Oltra, J. M. Cuerva, *Adv. Synth. Catal.* **2009**, *351*, 2295–2300.

[13] For seminal works in titanocene(III) chemistry, see: a) T. V. Rajan-Babu, W. A. Nugent, *J. Am. Chem. Soc.* **1994**, *116*, 986–997; b) A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859.

[14] For recent reviews, see: a) A. Gansäuer, T. Lauterbach, S. Narayan, *Angew. Chem.* **2003**, *115*, 5714–5731; *Angew. Chem. Int. Ed.* **2003**, *42*, 5556–5573; b) J. M. Cuerva, J. Justicia, J. L. Oller-López, J. E. Oltra, *Top. Curr. Chem.* **2006**, *264*, 63–91.

[15] a) J. Justicia, A. Rosales, E. Buñuel, J. L. Oller-López, M. Valdivia, A. Haïdour, A.; J. E. Oltra, A. F. Barrero, D. J. Cárdenas, J. M. Cuerva, *Chem. Eur. J.* **2004**, *10*, 1778–1788; J. E. Oltra, A. F. Barrero, D. J. Cárdenas, J. M. Cuerva, *Chem. Eur. J.* **2004**, *10*, 1778–1788; b) J. Justicia, J. L. Oller-López, A. G. Campaña, J. E. Oltra, J. M. Cuerva, E. Buñuel, D. J. Cárdenas, *J. Am. Chem. Soc.* **2005**, *127*, 14911–14921; c) J. M. Cuerva, A. G. Campaña, J. L. Oller-López, J. Justicia, A. Rosales, R. Robles, E. Buñuel, D. J. Cárdenas, J. E. Oltra, *Angew. Chem.* **2006**, *118*, 5648–5652; *Angew. Chem. Int. Ed.* **2006**, *45*, 5522–5526; d) R. E. Estévez, J. L. Oller-López, R. Robles, C. R. Melgarejo, A. Gansäuer, J. M. Cuerva, J. E. Oltra, *Org. Lett.* **2006**, *8*, 5433–5436.

[16] For a review of the advantages of these mixed systems, see: L. Ford, U. Jahn, *Angew. Chem.* **2009**, *121*, 6504–6507; *Angew. Chem. Int. Ed.* **2009**, *48*, 6386–6389.

[17] For selected references of closely related nucleophiles: a) A. Kasatkin, T. Nakagawa, S. Okamoto, F. Sato, *J. Am. Chem. Soc.* **1995**, *117*, 3881–3882; b) F. Sato, S. Iijima, M. Sato, *Tetrahedron Lett.* **1981**, *22*, 243–246.

[18] Bis(cyclopentadienyl)titanium(III) chloride is usually generated in situ by stirring commercial [Cp$_2$TiCl$_2$] with Zn or Mn dust in THF, and exists as an equilibrium mixture of the monomer [Cp$_2$TiCl] and the dinuclear species [(Cp$_2$TiCl)$_2$]; see: a) R. J. Enemærke, J. Larsen, T. Skrydstrup, K. Daasbjerg, *J. Am. Chem. Soc.* **2004**, *126*, 7853–7864; b) K. Daasbjerg, H. Svith, S. Grimme, M. Gerenkamp, C. Mück-Lichtenfeld, A. Gansäuer, A. Barchuck, F. Keller, *Angew. Chem.* **2006**, *118*, 2095–2098; *Angew. Chem. Int. Ed.* **2006**, *45*, 2041–2044; c) A. Gansäuer, A. Barchuk, F. Keller, M. Schmitt, S. Grimme, M. Gerenkamp, C. Mück-Lichtenfeld, K. Daasbjerg, H. Svith, *J. Am. Chem. Soc.* **2007**, *129*, 1359–1371; for the sake of clarity, we usually represent this complex herein as [Cp$_2$TiCl].

[19] For a review, see: D. C. Billington, in *Comprehensive Organic Synthesis* Ed. B. M. Trost, I. Fleming, Chapter 2.1, Vol. 3, Pergamon Press, Oxford, **1991**. For a selected reference in the field of natural product synthesis: N. H. Chishti, S. M. Coppell, R. Ramage, *Tetrahedron Lett.* **1975**, *16*, 1025.

[20] a) G. W. Ebert, R. D. Rieke, *J. Org. Chem.* **1988**, *53*, 4482–4488; b) F. O. Ginah, T. A. Donovan, Jr., S. D. Suchan, D. R. Pfennig, G. W. Ebert, *J. Org. Chem.* **1990**, *55*, 584; c) J. Ma, T.-H. Chan, *Tetrahedron Lett.* **1998**, *39*, 2499.

[21] a) P. Girard, J. L. Namy, H. B. Kagan, *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698; b) Cr. Y. Okude, T. Hiyama, H. Nozaki, *Tetrahedron Lett.* **1977**, *18*, 3829–3830.

[22] A. F. Barrero, M. M. Herrador, J. F. Quilez del Moral, P. Arteaga, J. F. Arteaga, M. Piedra, E. M. Sanchez, *Org. Lett.* **2005**, *7*, 2301–2304.

[23] D. H. Hill, M. A. Parvez, A. Sen, *J. Am. Chem. Soc.* **1994**, *116*, 2889–2901.

[24] a) W. G. Dauben, G. H. Beasly, M. D. Broadhurst, B. Muller, D. J. Peppard, P. Pesnelle, C. Suter, *J. Am. Chem. Soc.* **1974**, *96*, 4724–4726; b) E. J. Corey, *J. Am. Chem. Soc.* **1972**, *94*, 667–668; c) E. J. Corey, E. Hamanaka, *J. Am. Chem. Soc.* **1967**, *89*, 2758–2759; d) E. J. Corey, E. A. Broger, *Tetrahedron Lett.* **1969**, *10*, 1779–1782.

[25] For other Würtz-type couplings of allylic carboxylates, see: a) B. M. Trost, K. M. Pietrusiewicz, *Tetrahedron Lett.* **1985**, *26*, 4039; b) S.-I. Sasaoka, T. Yamamoto, H. Kinoshita, K. Inomata, H. Kotake, *Chem. Lett.* **1985**, 315–318; c) Y. Masuyama, K. Otake, Y. Kurusu, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1527–1528.

[26] For recent reviews, see: a) A. Gansäuer, B. Rinker in *Titanium and Zirconium in Organic Synthesis* (Ed.: I. Marek), Wiley-VCH, Weinheim, Germany, **2002**, pp. 435–450; b) A. Gansäuer, S. Narayan, *Adv. Synth. Catal.* **2002**, *344*, 465–475; c) A. Gansäuer, B. Rinker, *Tetrahedron* **2002**, *58*, 7017–7026; d) A. Gansäuer, M. Pierobon in *Radicals in Organic Synthesis, Vol. 2* (Eds.: P. Renaud, M. P. Sibi), Wiley-VCH, Weinheim, Germany, **2001**, pp. 207–220; e) A. Gansäuer, H. Bluhm, *Chem. Rev.* **2000**, *100*, 2771–2788.

[27] a) A. Gansäuer, M. Pierobon, H. Bluhm, *Angew. Chem.* **1998**, *110*, 107–109; *Angew. Chem. Int. Ed.* **1998**, *37*, 101–103; b) A. Gansäuer, H. Bluhm, *Chem. Commun.* **1998**, 2143–2144; c) S. Fuse, M. Hanochi, T. Doi, T. Takahashi, *Tetrahedron Lett.* **2004**, *45*, 1961.

[28] A. F. Barrero, A. Rosales, J. M. Cuerva, J. E. Oltra, *Org. Lett.* **2003**, *5*, 1935–1938.

[29] The pre-generated [PdCl$_2$(PPh$_3$)$_2$] catalyst was also able to carry out the reaction but with lower yield and stereoselectivities.

[30] We have only detected the γ,γ′-coupling product in trace amounts.

[31] a) J. Justicia, J. E. Oltra, J. M. Cuerva, *J. Org. Chem.* **2004**, *69*, 5803–5806; b) A. M. Castaño, A. M. Echavarren, *Tetrahedron Lett.* **1996**, *37*, 6587; c) A. M. Castaño, M. Mendez, M. Ruano, A. M. Echavarren, *J. Org. Chem.* **2001**, *66*, 589.

[32] M. Paradas, A. G. Campaña, T. Jiménez, R. Robles, J. E. Oltra, E. Buñuel, J. Justicia, D. J. Cardenas, J. M. Cuerva, *J. Am. Chem. Soc.* **2010**, *132*, 12748–12756.

[33] a) D. J. Porter, F. L. Boyd, *J. Biol. Chem.* **1992**, *267*, 3205–3213; b) K. H. Gardner, L. E. Kay, *J. Am. Chem. Soc.* **1997**, *119*, 7599–7600; c) T. Junk, W. J. Catallo, *Chem. Soc. Rev.* **1997**, *26*, 401–406; d) H. Nakazawa, S. Ino, K. Kato, T. Watanabe, Y. Ito, H. Oka, *J. Chromatogr. B: Biomed Sci. Appl.* **1999**, *732*, 55–64; e) D. M. Marcus, M. J. Hayman, Y. M. Blau, D. R. Guenther, J. O. Ehresmann, P. W. Kletnieks, J. F. Haw, *Angew. Chem.* **2006**, *118*, 1967–1969; *Angew. Chem. Int. Ed.* **2006**, *45*, 1933–1935; f) J. Atzrodt, V. Derdau, T. Fey, J. Zimmermann, *Angew. Chem.* **2007**, *119*, 7890–7911; *Angew. Chem. Int. Ed.* **2007**, *46*, 7744–7765.

[34] a) R. A. Rudel, D. E. Camann, J. D. Spengler, L. R. Korn, J. G. Brody, *Environ. Sci. Technol.* **2003**, *37*, 4543–4553; b) E. Stokvis, H. Rosing, J. H. Beijnen, *Rapid Commun. Mass Spectrom.* **2005**, *19*, 401–407; c) Y. Suzuki, T. Korenaga, Y. Chikaraishi, *Chem. Lett.* **2006**, *35*, 532–533.

[35] A proof of principle of such an analysis used deuterated products, derived from titanocene(III)-mediated deuterations: T. Jiménez, A. G. Campaña, B. Bazdi, M. Paradas, D. Arráez-Román, A. Segura-Carretero, A. Fernández-Gutiérrez, J. E. Oltra, R. Robles, J. Justicia, J. M. Cuerva, *Eur. J. Org. Chem.* **2010**, 4288–4295.

[36] Although the reason is not clear without considering the electronic effects, it is known that phosphites are in some cases unstable in the presence of radicals: M. Bietti, A. Calcagni, M. Salamone, *J. Org. Chem.* **2010**, *75*, 4514–4520.

[37] T. Tabuchi, J. Inanaga, M. Yamaguchi, *Tetrahedron Lett.* **1986**, *27*, 1195–1196; one of the main limitations in Sm^II chemistry is the high atomic weight of Sm, which requires the use of a large amount of re-

agent with respect to the organic substrate—moreover, Sm is a relatively expensive metal: H. B. Kagan, *Tetrahedron* **2003**, *59*, 10351–10372; recently a catalytic version in Sm has been described but with limited success: S. Médégan, F. Hélion, J.-L. Namy, *Eur. J. Org. Chem.* **2005**, 4715–4722.

[38] a) F. Sato, S. Iijima, M. Sato, *Tetrahedron Lett.* **1981**, *22*, 243–246; b) F. Sato, K. Iida, S. Iijima, H. Moriya, M. Sato, *J. Chem. Soc. Chem. Commun.* **1981**, 1140–1141; c) F. Sato, H. Uchiyama, K. Iida, Y. Kobayashi, M. Sato, *J. Chem. Soc. Chem. Commun.* **1983**, 921–922.

[39] In some cases, a previous step for the generation of the Pd^0-active species from the palladium(II) pre-catalyst is required.

[40] The synthesis of highly air sensitive $[Cp_2TiCl]_2$ has been described: R. S. P. Coutts, P. C. Wailes, R. L. Martin, *J. Organomet. Chem.* **1973**, *47*, 375–382.

[41] M. Paradas, A. G. Campaña, R. E. Estévez, L. Álvarez de Cienfuegos, T. Jiménez, R. Robles, J. M. Cuerva, J. E. Oltra, *J. Org. Chem.* **2009**, *74*, 3616–3619.

[42] A. Fernandez-Mateos, P. Herrero-Teijoón, L. Mateo Burón, R. Rabanedo-Clemente, R. Rubio-Gonzalez, *J. Org. Chem.* **2007**, *72*, 9973–9982.

[43] Bis(η^3-allyl)palladium complexes derived from a transmetallation step between species **II** and **IV** could also explain the experimental results: H. Nakamura, H. Iwama, Y. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 6641–6647.

[44] η^1-Allylpalladium complexes: a) O. A. Wallner, K. J. Szabó, *J. Org. Chem.* **2003**, *68*, 2934–2943; b) N. Solin, J. Kjellgren, K. Szabo, *J.*

[45] A. Yanagisawa, H. Hibino, S. Habaue, Y. Hisada, H. Yamamoto, *J. Org. Chem.* **1992**, *57*, 6386–6389.

[46] W. v. E. Doering, L. Birladeanu, K. Sarma, J. H. Teles, F.-G. Klärner, J.-S. Gehrke, *J. Am. Chem. Soc.* **1994**, *116*, 4289–4297.

[47] C. K. Lau, C. Dufresne, P. C. Bélanger, S. Piètrè, J. Scheigetz, *J. Org. Chem.* **1986**, *51*, 3038–3043.

[48] A. Dommisse, J. Wirtz, K. Koch, W. Barthlott, J. Kolter, *Eur. J. Org. Chem.* **2007**, 3508–3511.

[49] S. Kobayashi, K. Nishio, *J. Org. Chem.* **1994**, *59*, 6620–6628.

[50] R. Guyon, P. Villa, *Bull. Soc. Chim. Fr.* **1972**, 1375–1384.

[51] S. Casolari, D. D′Addario, E. Tagliavini, *Org. Lett.* **1999**, *1*, 1061–1063.

[52] J. G. Kim, K. W. Waltz, I. F. García, D. Kwiatkowski, J. P. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 12580–12585.

[53] S. J. Jong, J. M. Fang, *J. Org. Chem.* **2001**, *66*, 3533–3537.

[54] L. Zhao, D. J. Burnell, *Tetrahedron Lett.* **2006**, *47*, 3291–3294.

[55] L. A. Paquette, P. C. Lobben, *J. Org. Chem.* **1998**, *63*, 5604–5616.

[56] S.-I. Sumida, M. Ohga, J. Mitani, J. Nokami, *J. Am. Chem. Soc.* **2000**, *122*, 1310–1313.

[57] D. Furlani, D. Marton, G. Taglianni, M. Zordan, *J. Organomet. Chem.* **1988**, *341*, 345–346.

[58] R. Wada, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8910–8911.