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Synthetic Methods

# Divergent Titanium-Mediated Allylations with Modulation by Nickel or Palladium**

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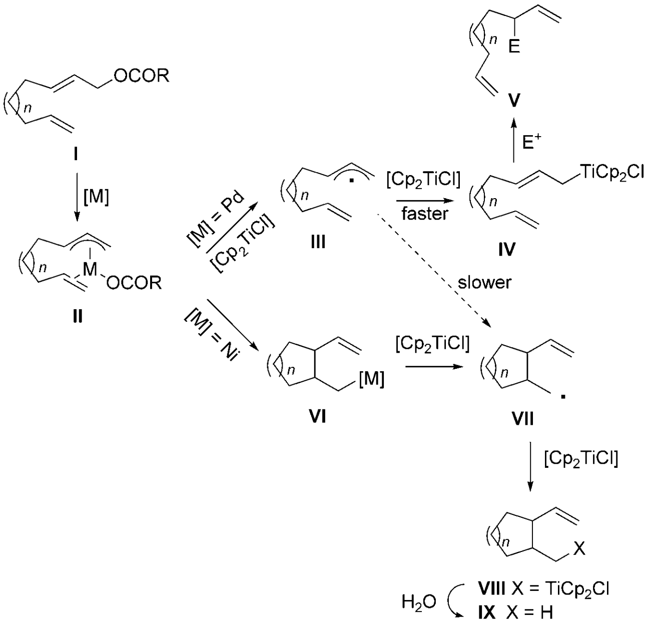
Titanocene(III)-mediated radical processes are important tools for the formation of C−C bonds under mild conditions, and are compatible with many functional groups.[1,2] Moreover, titanium(III) complexes can be used substoichiometrically,[3] which has allowed the development of enantioselective versions of these reactions.[4]

A serious limitation of these radical processes, however, derives from the fact that titanium(III)-mediated radical generation requires reactive substrates, such as allylic halides, which are often cumbersome in introduction and manipulation. Allylic carbonates and carboxylates, in contrast, are easily prepared and handled but are inert against titanocene(III) complexes. Nevertheless, it is known that nickel and palladium complexes can readily activate allylic carbonates and carboxylates **I** (Scheme 1) to form $\eta^3$-allylmetal complexes (**II**). On the basis of these results, we deemed that the combination of palladium or nickel derivatives with titanocene(III) complexes would facilitate the development of novel allylation processes using accessible allyl carbonates or carboxylates.

In the case of palladium catalysis, it is known that the Oppolzer-type cyclization of organometallic species (**II**, M = Pd, Scheme 1) to cyclic derivatives (**VI**) is relatively slow at room temperature.[5] Thus, reduction of **II** by a single-electron-transfer reagent, such as [$Cp_2TiCl$],[6] could lead to the allylic radical **III**, which might be eventually trapped by a second [$Cp_2TiCl$] species to give an allylic titanium(IV) complex **IV**. Finally, nucleophilic attack of the organometallic derivative **IV** on an aldehyde or other electrophilic reagent would provide the corresponding allylation product **V**.



*Scheme 1.* Mechanism for palladium-catalyzed, titanocene-mediated allylation of carbonyl compounds and nickel-catalyzed, titanocene-mediated carbocylization of allylic carboxylates. [M] = transition metal catalyst; Cp = cyclopentadienyl; $E^+$ = electrophilic reagent (e.g. aldehyde).R = OEt, Me, or Ph.

On the other hand, nickel-catalyzed carbocyclizations, via intermediates such as **II** (M = Ni, Scheme 1) to cyclic derivatives **VI**, are relatively fast at room temperature.[7] Once formed, **VI** might be reduced by [$Cp_2TiCl$] to a primary radical **VII**, which could be trapped by a second [$Cp_2TiCl$] species to give an alkyl titanium(IV) complex **VIII**. Hydrolysis of the organometallic derivative **VIII** would yield carbocycles **IX.** Thus, we anticipated that the use of palladium or nickel catalysts could modulate titanium(III) to drive allylation reactions with allyl carboxylates by two different pathways, either through intermolecular coupling with electrophilic reagents or to give carbocyclic derivatives by an intramolecular allylation.

To check our hypothesis, we chose allylic carbonate *E*-**1** as a model allylation reagent. Thus, reaction of decanal with carbonate *E*-**1** and an excess of [$Cp_2TiCl$] (2.0 equiv),[8] in the presence of $PdCl_2$ (20 mol %) and triphenylphosphine,[9] gave the expected coupling product **2** as a single stereoisomer in 76 % yield (Scheme 2).[10] In contrast, when carbonate *E*-**1** was treated with an excess of [$Cp_2TiCl$] (2.0 equiv) in the presence of [$NiCl_2(PPh_3)_2$] (20 mol %), a mixture of carbocycles **3** and **4** (4:1 ratio) was obtained in almost quantitative

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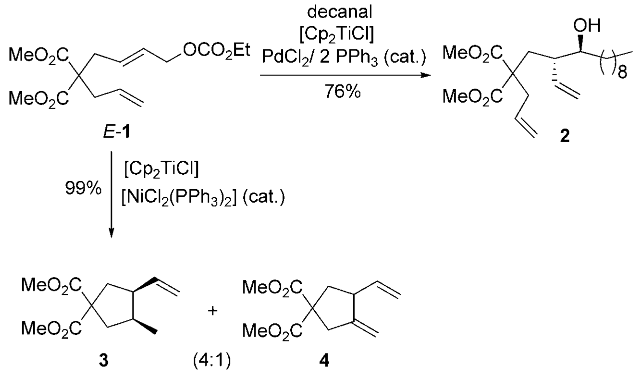


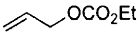
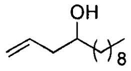
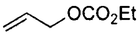
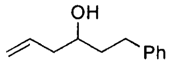
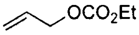
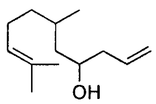
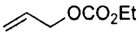
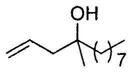
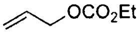
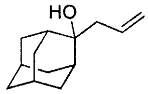
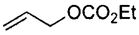
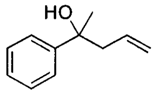
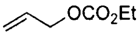
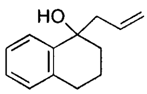
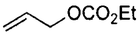
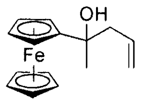
**Scheme 2.** Palladium-catalyzed formation of coupling product **2** and nickel-catalyzed formation of carbocycles **3** and **4** from *E*-**1**

yield. The *cis*-configuration of **3** was in accordance with that previously described for Oppolzer cyclizations mediated by nickel.[11] When we repeated this experiment in the presence of decanal (2.0 equiv), we obtained similar results (4:1 mixture of **3** and **4**, 94% yield), whereas decanal was recovered unchanged. Moreover, control experiments showed that, in the absence of either the transition metal or the titanium complex, the above reactions did not occur, strongly supporting our hypothesis.

We subsequently assayed the palladium-catalyzed allylation of different carbonyl compounds with allylic carbonates and stoichiometric (method A) or substoichiometric (method B) amounts of titanium (Table 1).[8] The titanocene-regenerating agent used in method B and developed in our laboratory, was a combination of manganese dust, 2,4,6-collidine and trimethylsilyl chloride.[12] Thus, we achieved the allylation of different aldehydes and ketones with allyl carbonates, obtaining moderate to excellent yields of the expected homoallylic alcohols. It is worth noting that, although palladium-based methods for the allylation of aldehydes with allyl carboxylates are known,[13] the allylation of ketones is less common and usually requires very long reaction times.[13a,14] In this case, however, ketone allylation proceeded in a few hours at room temperature and even ketones prone to undergo pinacol coupling, such as acetophenone and tetralone, proved to be suitable substrates. Moreover, alkyl substitution at the allylic carbonate was well-tolerated, yielding the corresponding γ-addition products (Table 1, entries 11–19). It should be noted that both isomers *E*-**1** and *Z*-**1**, as well as *E*-**22** and *Z*-**22**, led to the same stereoisomer (**2** and **23** respectively), thus demonstrating the stereoconvergent nature of the process. The reaction is also chemoselective: esters (ethyl benzoate) and nitriles (benzonitrile) were both inert under our conditions. Moreover, yields obtained from palladium/titanium-catalyzed allylations (method B) were similar and, in some cases, even better than those from the process using stoichiometric titanium.[8] Stereoselectivity was also comparable for both methods, suggesting closely related reaction mechanisms for both procedures.

The results summarized in Table 1 are consistent with the mechanism depicted in Scheme 1, starting with the oxidative addition of the palladium complex to the allylic carbonate to give an η$^3$-allyl palladium intermediate, which undergoes subsequent reduction to an allyl radical (such as **III**) by single-electron transfer from [Cp$_2$TiCl].[15] Another [Cp$_2$TiCl] species then captures the allyl radical to form a nucleophilic allyl titanium(IV) complex, which reacts with the carbonyl compound.[4b,16] This mechanistic hypothesis was strongly sup-

**Table 1:** Palladium/titanium-promoted (method A) and catalyzed (method B) allylation of carbonyl compounds with allylic carbonates.[a]

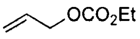
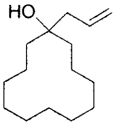
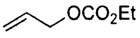
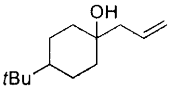
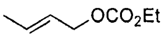
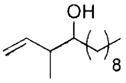
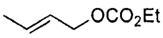
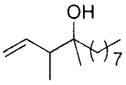
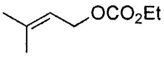
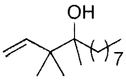
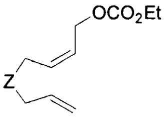
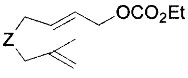
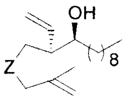
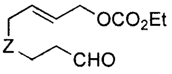
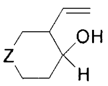
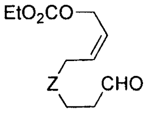
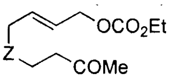
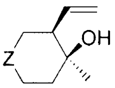
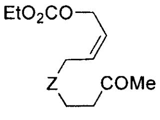
| Entry | Allyl carbonate | Carbonyl compound | Product | Method, Yield [%] |
|---|---|---|---|---|
| 1 |  | decanal |  **5** | B, 75 |
| 2 |  | 3-phenyl propanal |  **6** | B, 54 |
| 3 |  | citronellal |  **7** | B, 73[b] |
| 4 |  | 2-decanone |  **8** | A, 85 |
| 5 |  | adamantanone |  **9** | B, 79 |
| 6 |  | acetophenone |  **10** | B, 74 |
| 7 |  | tetralone |  **11** | B, 74 |
| 8 |  | acetyl ferrocene |  **12** | A, 99 |

ported by the formation of product **2** when the previously prepared palladium complex **24**[5b] was treated with decanal in the presence of $PPh_3$ and $[Cp_2TiCl]$ (Scheme 3).[17] Moreover, in the absence of either titanium or phosphines, the allylation reaction did not occur.

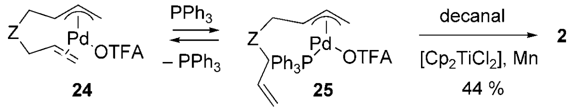
The nickel/titanium-based procedure afforded Oppolzer-type cyclizations (Table 2) at room temperature, under conditions substantially milder than those previously reported for this type of cyclization.[5a] We also found that the ratio of carbocycles **3** and **4** obtained was dependent on the relative ratio of titanium and nickel catalysts employed.[8] Cyclic compound **3** probably derives from the reduction of alkyl nickel **VI** by $[Cp_2TiCl]$ (see Scheme 1), which is faster that any potential β-hydride elimination process. Thus, its production is maximized in the presence of high ratios of $[Cp_2TiCl]$. In fact, using 4 equivalents of $[Cp_2TiCl]$ and only 0.1 equivalents of $[NiCl_2(PPh_3)_2]$, we obtained almost exclusively cyclopentane **3** (**3**:**4** = 97:3) in good yield (75 %) (Table 2, entry 2). On the other hand, using substoichiometrically $[Cp_2TiCl]$ (0.1 equiv) and $[NiCl_2(PPh_3)_2]$ (0.2 equiv) substantially increased the proportion of exocyclic alkene **4** (**3**/**4**, 30:70; 60 % overall yield).[8,18]

Different carbocycles and heterocycles were obtained in moderate to good yield by this method, with complete regiochemical control (Table 2). Excellent stereoselectivity was also obtained, affording exclusively products with *cis* configuration, with the only exception being **38** (9:1 *cis*/*trans*). Nickel/titanium-promoted cyclization of carbonates **37** and **39** stereoselectively led to **38** and **40** respectively, both products containing three stereogenic centers (Table 2, entries 9 and 10).[19] Allylic acetates assayed under our conditions (Table 2, entries 3, 7, and 8) showed similar behavior to that of carbonates. In fact, nickel/titanium-induced cyclizations of acetate **27** (Table 2,

***Table 1:*** (Continued)

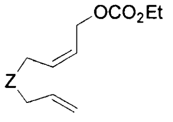
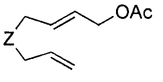
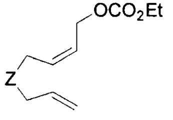
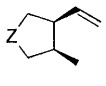
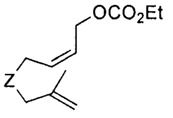
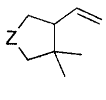
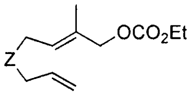
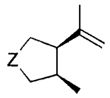
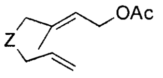
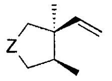
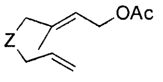
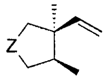
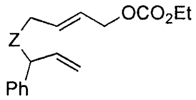
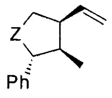
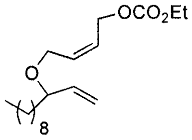
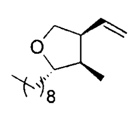
| Entry | Allyl carbonate | Carbonyl compound | Product | Method, Yield [%] |
|---|---|---|---|---|
| 9 |  | cyclododecanone |  **13** | B, 78 |
| 10 |  | *t*Butyl-cyclohexanone |  | B, 65[c] |
| 11 |  | decanal |  **15** | B, 58[d] |
| 12 |  | 2-decanone |  **16** | B, 75[e] |
| 13 |  | 2-decanone |  **17** | B, 55 |
| 14 |  *Z*-**1** Z = C($CO_2Me$)$_2$ | decanal | **2** | B, 52 |
| 15 |  **18** Z = C($CO_2Me$)$_2$ | decanal |  **19** | A, 63[f] |
| 16 |  *E*-**20** Z = C($CO_2Me$)$_2$ | – |  **21** | A, 73[b] |
| 17 |  *Z*-**20** Z = C($CO_2Me$)$_2$ | – | **21** | A, 74[b] |
| 18 |  *E*-**22** Z = C($CO_2Me$)$_2$ | – |  **23** | B, 95 |
| 19 |  *Z*-**22** Z = C($CO_2Me$)$_2$ | | **23** | B, 92 |

[a] Method A: Carbonyl compound (1 mmol), allyl carbonate (4 mmol), $[Cp_2TiCl_2]$ (2 mmol), $PdCl_2$ (0.2 mmol), $PPh_3$ (0.4 mmol), Mn (8 mmol). Method B: Carbonyl compound (1 mmol), allyl carbonate (4 mmol), $[Cp_2TiCl_2]$ (0.4 mmol), $PdCl_2$ (0.2 mol), $PPh_3$ (0.4 mmol), Mn (8 mmol), $Me_3SiCl$ (4 mmol), and 2,4,6-collidine (7 mmol). [b] 1:1 mixture of stereoisomers. [c] 2:1 mixture of *cis:trans* stereoisomers. [d] 3:7 mixture of *syn:anti* stereoisomers. [e] 3:2 mixture of stereoisomers. [f] single stereoisomer, tentatively assigned as the *anti* stereoisomer.



***Scheme 3.*** Formation of adduct **2** from palladium complex **24** (Z = C(CO$_2$Me)$_2$, OTFA = trifluoroacetate).

***Table 2:*** Nickel/titanium-promoted intramolecular allylation of alkenes (Oppolzer-type cyclization) with allylic carbonates.[a]

| Entry | Allylic substrate | Product | Yield [%] |
|---|---|---|---|
| 1 | <br>*Z*-**1** Z = C(CO$_2$Me) | **3** + **4** (4:1) | 98 |
| 2 | *Z*-**1** | **3** + **4** (97:3) | 75[c] |
| 3 | <br>**26** Z = C(CO$_2$Me) | **3** + **4** (4:1) | 98 |
| 4 | <br>**27** Z = NSO$_2$Ph | <br>**28** | 95 |
| 5 | <br>**29** Z = NSO$_2$Ph | <br>**30** | 59 |
| 6 | <br>**31** Z = NTs | <br>**32** | 69[d] |
| 7 | <br>**33** Z = C(CO$_2$Me) | <br>**34** | 75 |
| 8[b] | <br>**35** Z = NSO$_2$Ph | <br>**36** | 71 |
| 9 | <br>**37** Z = NSO$_2$Ph | <br>**38** | 83[e] |
| 10 | <br>**39** | <br>**40** | 81 |

[a] Allyl carbonate or acetate (1 mmol), [Cp$_2$TiCl$_2$] (2 mmol), NiCl$_2$(PPh$_3$)$_2$ (0.2 mmol), Mn (8 mmol). [b] **33** is a 5.4:1 mixture of *E*:*Z* diastereoisomers. [c] [Cp$_2$TiCl$_2$] (4.0 mmol) was used. [d] Up to 50% of the related product derived from a β-hydride elimination process was obtained. [e] 10% of the product obtained was the stereoisomer with the opposite configuration of the vinyl group.

entry 3) and both stereoisomers *E*-**1** (Scheme 2) and *Z*-**1** (Table 2, entry 1) led to the same products, confirming the versatility of this method and revealing the stereoconvergent nature of the process. Additionally, the reaction proved to be compatible with different functional groups, including esters, ethers, and sulfonamides and permitted different substitution patterns in the involved alkenes.[20] However, six-membered rings were not obtained under these reaction conditions.

In summary, we have demonstrated for the first time that late transition metals palladium and nickel are capable of modulating titanium(III) reactivity to achieve selective allylations of either carbonyl compounds or alkenes respectively, using allylic carbonates and carboxylates, instead of cumbersome allyl halides, as allylation reagents. The palladium/titanium-catalyzed allylation of ketones (method B) is an especially convenient procedure, as evidenced by the excellent diastereoselectivity obtained under mild conditions. The catalytic nature of this process should facilitate the development of enantioselective versions. Nickel/titanium-promoted Oppolzer-type cyclizations provided polyalkyl substituted carbo- and heterocycles at room temperature, under conditions compatible with several functional groups, and with excellent stereoselectivity. Moreover, by modifying the relative ratios of nickel and titanium employed, the final step of the cyclization process can be either a reductive (*cis*-substituted products)[21] or a nonreductive (exocyclic alkenes) process. A more in-depth study of the reaction mechanisms involved in these processes and the development of enantioselective versions are underway.

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[9] Addition of triphenylphosphine considerably increased the yields, possibly stabilizing palladium intermediates.

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