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Ti/Ni-Based Multimetallic System for the Efficient Allylation of Carbonyl Compounds

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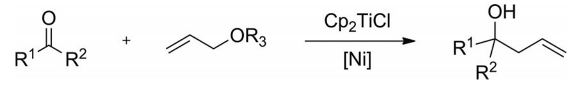
A mild method for the allylation of carbonyl compounds is presented. This methodology allows the allylation of a broad range of carbonyl compounds starting with allyl carbonates as pronucleophiles. Noteworthy is that ketones, infrequent substrates in other related protocols, are suitable substrates under these reaction conditions. Moreover, the reaction proceeds at room temperature with the use of catalytic amounts of both Ni and Ti catalysts. The success of this strategy is based on the perfect match between the late transition metal (nickel) and the radical reagent (titanium). The use of Ni instead of Pd widens the scope of this transformation and makes this method more economical.

Introduction

The substitution of palladium to nickel for the catalysis of a process is a desirable goal for economic advantages.[1] Moreover, the intrinsic differences between these two metals could lead to interesting chemoselectivities for the same process.[1] Within this context, in recent years we have been interested in the development of new Barbier-type allylations and progargylations of carbonyl compounds by using easily prepared and handled allylic carboxylates as pronucleophiles.[2–4] To this end, we have described a Ti/Pd multimetallic protocol by taking advantage of the efficient combination of the free radical chemistry mediated by $\mathrm{Ti^{III}}$[5] with the late transition metal chemistry mediated by Pd.[6,7] It is noteworthy that as far as the starting electrophiles are concerned aldehydes and ketones can be used in this transformation, which is quite unusual when unactivated pronucleophiles are used.[3f,8] Following with the study of this interesting reaction, herein we present the results obtained when Pd is replaced by Ni as the transition metal catalyst (Scheme 1).



Scheme 1. $\mathrm{Ni^0/Ti^{III}}$ catalyzed allylation of aldehydes and ketones.

In this particular case, the Ti/Ni multimetallic system retains some of the key characteristics of the parent reaction. It is able to promote the efficient allylation of aldehydes and, remarkably, ketones in yields similar to those obtained by using Pd. Nevertheless, Ni is unable to activate substituted allylic pronucleophiles in intermolecular reactions. This is a noteworthy difference which makes the Ti/Ni multimetallic system more chemoselective with respect to the starting pronucleophile. This chemoselectivity in turn makes this Ni-based multimetallic system useful with substrates incompatible with the Pd-based multimetallic system.

Results and Discussion

To set up the best reaction conditions we carried out the allylation reaction with the use of allyl ethyl carbonate as the pronucleophile and decanal and 2-decanone as the carbonyl compounds.[9] Remarkably, the reaction proceeded to give the corresponding homoallylic alcohols in good yields by using substoichiometric amounts of both $NiCl_2$ (10 mol-%) and Cp_2TiCl_2 (40 mol-%) precatalysts. In this case, the aid of a $\mathrm{Ti^{III}}$ regenerating agent was required. In preceding works, we established that for these multimetallic systems the mixture of TMSCl (4 mmol), 2,4,6-collidine (7 mmol), and Mn dust (8 mmol) gives the best results.[10] Different Ni catalysts, phosphanes, and phosphites with different electronic and steric characteristics were tested, and the results are summarized in Table 1. From those results, it seems that a simple relationship between the nature of the phosphorus ligands and the catalytic activity does not exist. Fortunately, among the different phosphanes and phosphites tested, acceptable yields were obtained by using sim-

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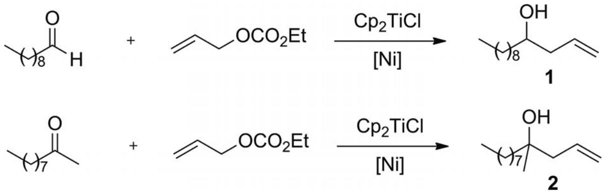
ple PPh_3 as the ligand (Table 1, Entries 1 and 2). We also found that easily prepared $Ni(PPh_3)_2Cl_2$ gave successful results for both substrates, decanal and 2-decanone, similarly to that observed with the use of Pd.[6]

Table 1. Influence of the nickel complex in the Ni^0/Ti^{III}-promoted allylation of decanal and 2-decanone.[a]



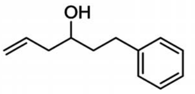
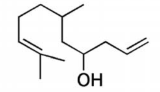
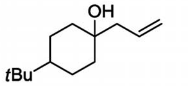
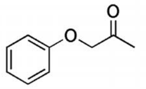
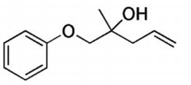
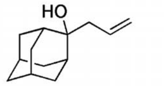
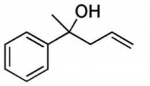
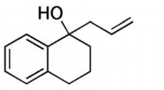
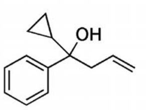
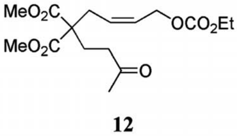
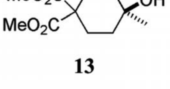
Entry	[Ni]	% Yield	
		1	2
1	$Ni(PPh_3)_2Cl_2$	69	70
2	$NiCl_2/PPh_3$	65	69
3	$NiCl_2/PCy_3$	18	23
4	$NiCl_2(glyme)/PPh_3$	0	0
5	$NiCl_2/PPhCy_2$	0	0
6	$NiCl_2/P(o\text{-}Tol)_3$	49	47
7	$NiCl_2/P(C_6F_5)_3$	0	0
8	$NiCl_2/P(OEt)_3$	70	0
9	$NiCl_2/P(OPh)_3$	5	0
10	$NiCl_2$/dppe	0	0

[a] Allyl ethyl carbonate (4 mmol), nickel catalyst (10 mol-%), Cp_2TiCl_2 (40 mol-%), Mn (8 mmol), TMSCl (4 mmol), 2,4,6-collidine (7 mmol), and carbonyl compound (1 mmol).

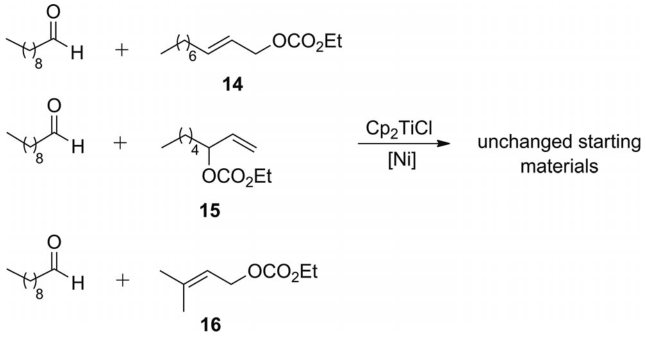
To establish the scope of the process, different aldehydes and ketones were submitted to the optimized reaction conditions (Table 2). This reaction allows the allylation of different aldehydes and ketones with different electronic and steric characteristics with moderate to good yields. Thus, the reaction works with aliphatic aldehydes (Table 2, Entries 1 and 2), unhindered aliphatic acyclic and cyclic ketones (Table 2, Entries 3 and 4), and sterically hindered adamantanone (Table 2, Entry 5). Notably, aromatic ketones (Table 2, Entries 6–8), which are prone to undergo pinacol reactions, also gave the allylation product. Interestingly, an uncommon intramolecular Barbier-type allylation was also conducted. In this case, a six-membered carbocycle could be obtained in good yield (Table 2, Entry 9) presenting the vinyl and hydroxy groups with *cis* stereochemistry. This stereoselectivity was previously observed in Ti^{III}-promoted allylations.[6,11] In summary, the allylation reaction proceeded in yields similar to those obtained with Pd. Equally, the yields obtained from reactions with ketones as electrophiles were typically higher than those from the corresponding aldehydes due to the slow transfer of a Cp group from Cp_2TiCl to the aldehyde to yield the equivalent Grignard-type alcohol.

Although the catalytic behavior of Ni and Pd is similar for the allylation reaction, this reaction does not take place intermolecularly with crotyl or prenyl derivatives as pronucleophiles. Thus, when decanal was treated with ethyl carbonates **14**–**16** under the optimized conditions the started materials were recovered unchanged (Scheme 2).

Table 2. Ni^0/Ti^{III-} vs. Pd^0/Ti^{III}-catalyzed allylation of aldehydes and ketones.

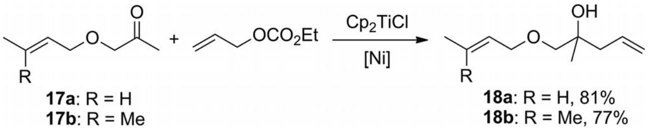
Entry	Carbonyl compound	Product	% Yield[a]
1	3-phenylpropanal	 **3**	A: 53 B: 54
2	citronellal	 **4**	A: 61[b] B: 73[b]
3	*t*-butylcyclohexanone	 **5**	A: 50[c] B: 65[c]
4	 **6**	 **7**	A: 67 B: 56
5	adamantanone	 **8**	A: 66 B: 79
6	acetophenone	 **9**	A: 65 B: 74
7	tetralone	 **10**	A: 95 B: 74
8	cyclopropylphenyl ketone	 **11**	A: 68 B: 33
9	 **12**	 **13**	A: 68 B: 73

[a] Method A: carbonyl compound (1 mmol), allyl carbonate (4 mmol), $[Cp_2TiCl_2]$ (0.4 mmol), $PdCl_2$ (0.2 mmol), PPh_3 (0.4 mmol), Mn (8 mmol), Me_3SiCl (4 mmol), and 2,4,6-collidine (7 mmol). Method B: carbonyl compound (1 mmol), allyl carbonate (4 mmol), $[Cp_2TiCl_2]$ (0.4 mmol), $Ni(PPh_3)_2Cl_2$ (0.1 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.



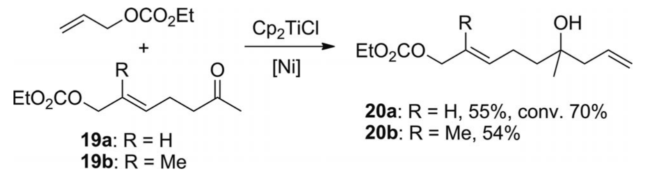
Scheme 2. Ni^0/Ti^{III} system is unable to promote the crotylation and prenylation reactions.

Therefore, substrates containing such functionalities (crotyl or prenyl ether) could now be used as starting electrophiles. To verify this hypothesis we selected some acceptors which failed in the allylation reaction when Pd was used. Firstly, we tried the allylation of different substituted α-hydroxy ketones **17** with different substitution patterns. When Ni was used the corresponding homoallylic alcohols were obtained in good yields (Scheme 3). On the other hand, when the reactions were carried out with the use of Pd instead of Ni no allylation product was obtained.



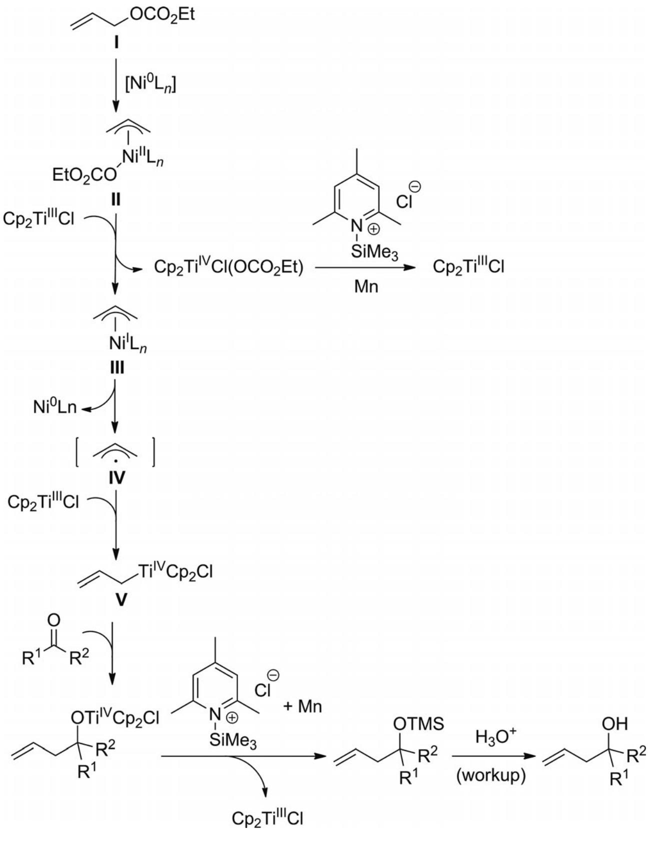
Scheme 3. Ni^0/Ti^{III}-catalyzed allylation reaction of compounds **17**.

In a similar way, this chemoselectivity can be extended to other substrates. For example, ketones presenting mono- and disubstituted allyl carbonates **19** are also suitable electrophiles for the Ni/Ti-catalyzed Barbier-type allylation reaction (Scheme 4). Homoallylic alcohols **20** could be obtained with the remaining allylic functionality intact. However, the Pd/Ti-catalyzed reactions yielded a mixture of products with no carbonate in their structures.



Scheme 4. Ni^0/Ti^{III}-catalyzed allylation reaction of compounds **19**.

On the basis of our previous studies using a Ti/Pd bimetallic system[6] and the results obtained in this work, we propose a similar mechanism for the Ti/Ni-promoted allylation reaction, which is shown in Scheme 5. Initially, oxidative addition of allylic electrophile **I** to Ni^0 {generated from $[Ni(PPh_3)_2Cl_2]$ and Ti^{III}/Mn}[12] would give the corresponding η^3-allylnickel complex **II**. Monoelectronic reduction of complex **II** could form η^3-allylnickel(I) intermediate **III**,[13] which apparently fragments into three new species: (a) the corresponding carbon-centered allyl radicals **IV**, (b) a Ni^0 complex, which is reintroduced into the catalytic cycle, and (c) a Ti^{IV} ethyl carbonate. A heterocoupling process between resulting allyl radical **IV** and the Ti^{III} complex would yield nucleophilic η^1-allyl Ti^{IV} complex **V**, which is able to react with different electrophiles. Additional experiments to verify which is the catalytic species involved in the C–C bond-forming reaction were carried out by using a $NiCl_2$ catalyst with a chiral phosphorus ligand [(*R*)-monophos] and the Ti^{III} Riant[14] chiral complex.[15] Therefore, when 3-phenyl propanal[16] was allylated by using the chiral $NiCl_2$/[(*R*)-monophos] catalyst no chiral induction was observed. However, when the Ti^{III} Riant chiral complex was used a moderate *ee* (32 %) of the corresponding homoallylic alcohol was obtained, thus supporting that the reaction pathway proceeds through the formation of η^1-allyl Ti^{IV} complex **V** as the nucleophile.



Scheme 5. Mechanistic hypothesis for the Ni^0/Ti^{III}-catalyzed allylation.

A common intermediate to Pd/Ti and Ni/Ti multimetallic systems is also supported by the fact that both methods gave the same diastereoisomeric ratio of products in Entries 2 and 3 of Table 2. The different reactivity is then related with the apparent reluctance of Ni^0 complexes to add to crotyl and prenyl derivatives as previous works with allyl halides[17] and acetates[18] had shown.[19]

Conclusions

In summary, we have demonstrated that the combination of Ni and Ti catalysts is also a valid method for the efficient allylation of aldehydes and ketones starting with allyl carbonates as pronucleophiles. This protocol is restricted to allyl donors and therefore useful when acceptors incompatible with Pd are used. It is worth noting that the reaction takes place at room temperature and under mild conditions to give the corresponding homoallylic alcohols in moderate to good yields. Notably, as far as we know this is the first example that uses Ni for the catalysis of Barbier-type allylations of simple ketones starting with unactivated allyl carbonates as pronucleophiles.[20] From a mechanistic point of view, it seems that Ti^{III} intermediates are involved in the C–C bond-forming reaction and therefore are responsible for the enantioselectivity of the process. In this sense, future work will be conducted to the development of novel chiral Ti^{III} complexes to allow a full enantioselective version of this reaction.

Experimental Section

General Procedure for the Ni^0/Ti^{III}-Catalyzed Allylation of Carbonyl Compounds with Carbonates: Rigorously dried and deoxygenated THF (20 mL) was added to a mixture of Cp_2TiCl_2 (0.4 mmol), $Ni(PPh_3)_2Cl_2$ (0.1 mmol), and Mn dust (8.0 mmol) under an Ar atmosphere, and the suspension was stirred at room temperature until it turned dark green (about 5 min). A solution of the carbonyl compound (1.0 mmol), the allyl carbonate (4.0 mmol), and 2,4,6-collidine (7.0 mmol) in THF (2 mL) and Me_3SiCl (4.0 mmol) were then added. The mixture was stirred at room temperature for 48 h and then diluted with EtOAc and washed with 10% aqueous HCl solution and brine. The organic phase was dried with anhydrous $NaSO_4$, and the solvent was removed in vacuo. The residue was purified by flash chromatography (EtOAc/hexane).

Supporting Information (see footnote on the first page of this article): Synthesis of the precursors for the allylation reactions, influence of the pronucleophile in the Ni^0/Ti^{III}-promoted allylation of carbonyl compounds, influence of the chiral phosphorous ligand (*R*)-monophos and Ti-Riant catalyst in the enantioselectivity of the allylation of 3-phenylpropanal, general procedures for the Pd^0/Ti^{III}- and Ni^0/Ti^{III}-catalyzed allylation of aldehydes and ketones, characterization data for synthesized compounds, copies of the ^1H NMR and ^{13}C NMR spectra of selected compounds..

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