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Low-valent titanium(II) mediated intramolecular and regioselective alkyne/alkoxyallene reductive coupling reactions

Florent Bodinier^a, Marie-Isabelle Lannou^{*a}, Geoffroy Sorin^{*a}

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Low-valent titanium(II) complexes turned out to be suitable reagents in the promotion of alkyne/alkoxyallene coupling reactions in intramolecular fashion. The conditions developed herein led to a broad range of highly functionalized cyclic adducts with excellent regioselectivities toward the central carbon of the alkoxyallene moiety. Good yields (up to 76%) were obtained over 19 examples. One-pot late functionalization by electrophile trapping was also possible and led to excellent diastereoselectivities (up to 95/5 d.r.).

Alkoxyallenes are versatile small building blocks in organic synthesis.^[1] They are easily reachable by isomerization of propargylic ethers in the presence of a base and are fairly stable. Due to the electronic effects induced by the oxygen atom, a polarization of the alkoxyallene moiety, stronger than allenes, can be deduced through numerous studies for the last four decades. Thus, in the presence of nucleophilic species, alkoxyallenes undergo a selective addition onto their *sp*² carbons (**C**¹ and/or **C**³). However, in the presence of electrophilic species, the *sp* carbon of the alkoxyallene (**C**²) will be more prone to perform the addition this time (Fig. 1). It can thereby be considered that carbons **C**¹ and **C**³ are electrophilic centres,^[2] whereas the carbon **C**² is more nucleophilic,^[3] although these properties may be modulated by the R group.

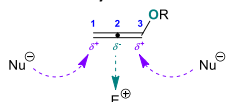


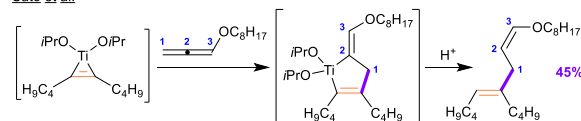
Fig.1 Polarization and reactivity of alkoxyallenes

In the field of organometallic-induced coupling reactions involving an alkoxyallene moiety, various systems have been established with palladium,^[4] cobalt,^[5] rhodium,^[6] copper^[7] and gold.^[8] To date, only two intermolecular low-valent titanium(II)^[9] mediated alkyne/alkoxyallene coupling reactions have been reported (Scheme 1).^[10]

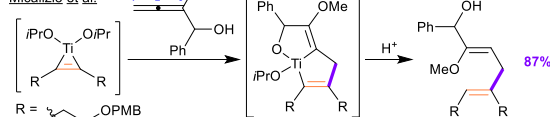
Both examples showed excellent regioselectivity in favour of an addition onto the electrophilic centre **C**¹, less hindered than **C**³. Products resulting from an addition onto the carbon **C**² were not observed. It must be mentioned that previous studies on low-

valent titanium(II) mediated intramolecular alkyne/allene reductive coupling reactions^[11] reported amazing selectivities toward an addition of the titanacyclopropene intermediate on the more electron-rich carbon **C**² of the allene moiety.^[11b] It was thus expected, through the development of titanium mediated alkyne/alkoxyallene coupling reactions in an intramolecular fashion, to overcome the electronic effects induced by the oxygen atom on the alkoxyallene moiety and orientate a selective addition onto the more electron-rich carbon **C**².

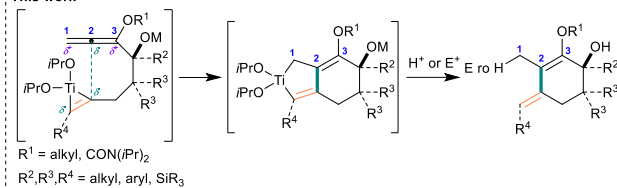
Sato et al.



Micalizio et al.



This work



Scheme 1 Titanium (II) mediated synthesis of six-membered rings

The cyclization precursor **1** was prepared in five steps with good overall yield.^[12] At first, the application of reaction conditions inspired from our previous works^[13] led to a complex mixture. However, it was possible to observe the desired compound **2** as traces. The optimization of the reaction conditions was thus performed (Table 1).

Temperature appeared to be a crucial parameter (entries 1 to 5) since 58% ¹H NMR yield was reached when the reaction was performed from -40°C to -30°C (entry 5). Higher temperatures (entries 1 to 3) led to significant degradation. Grignard reagent was thus modulated to increase the reactivity of the corresponding low-valent titanium intermediate complex toward ligand exchange with the alkyne moiety of **1**.^[9b]

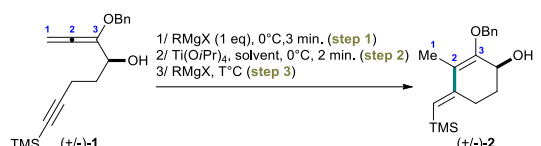
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However, disappointing results were obtained (entries 6 and 7) and *i*PrMgCl^[14] was kept as the best reagent (entry 5) for this reaction.

Table 1 Optimization of reaction parameters



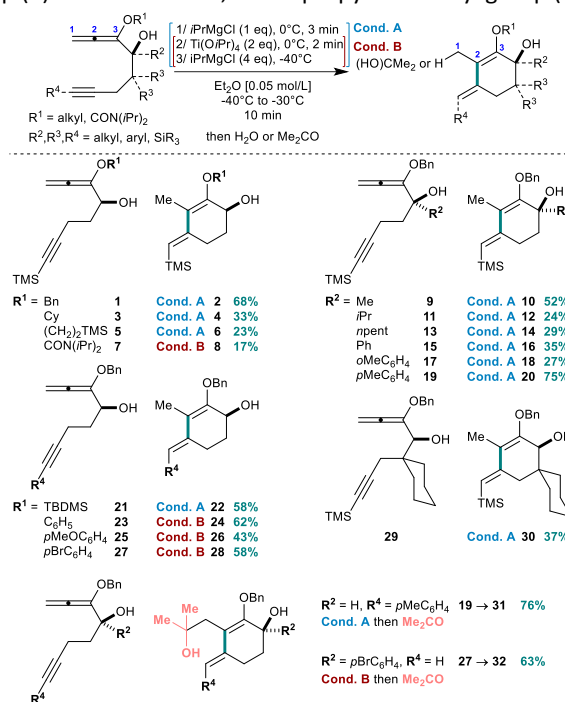
Entr y	Temp.	RMgX	Solvent	Ti(O <i>i</i> Pr) ₄	2 ^(a)
1	RT	<i>i</i> PrMgCl	Toluene	2.5 eq	Trace
2	0°C	<i>i</i> PrMgCl	Toluene	2.5 eq	s
3	-20°C	<i>i</i> PrMgCl	Toluene	2.5 eq	s
4	-40°C	<i>i</i> PrMgCl	Toluene	2.5 eq	51%
5	-30°C ^(b)	<i>i</i> PrMgCl	Toluene	2.5 eq	58%
6	-30°C ^(b)	<i>c</i> -pentMgCl	Toluene	2.5 eq	44%
7	-30°C ^(b)	<i>c</i> -hexylMgCl	Toluene	2.5 eq	0%
8	-30°C ^(b)	<i>i</i> PrMgCl	Toluene	2.5 eq	58%
9	-30°C ^(b)	<i>i</i> PrMgCl	THF	2.5 eq	29%
10	-30°C ^(b)	<i>i</i> PrMgCl	MeTHF	2.5 eq	53%
11	-30°C ^(b)	<i>i</i> PrMgCl	Et ₂ O	2.5 eq	74%
12	-30°C ^(b)	<i>i</i> PrMgCl	MTBE	2.5 eq	56%
13	-30°C ^(b)	<i>i</i> PrMgCl	Et ₂ O	1.5 eq	65%
14	-30°C ^(b)	<i>i</i> PrMgCl	Et ₂ O	2.0 eq	74%
15 ^(c)	-30°C ^(b)	<i>i</i> PrMgCl	Et ₂ O	2.0 eq	64%
16	-30°C ^(b)	<i>i</i> PrMgCl	Et ₂ O	2.5 eq	74%
17	-30°C ^(b)	<i>i</i> PrMgCl	Et ₂ O	3.5 eq	57%

^(a) ¹H NMR yield was determined from 1,3,5-trimethoxybenzene as internal standard. ^(b) Starting from -40°C, this solution was allowed to warm up to -30°C over 10 minutes. ^(c) Deprotonation step (step 1) was suppressed. Step 2 then step 3 were directly carried out.

Modulation of the solvent was next regarded. Replacing toluene (entry 8) by THF conducted to a low ¹H NMR yield of 29% whereas MeTHF and MTBE afforded satisfying ¹H NMR yields (entries 10 and 12), respectively 53% and 56%. However, it was possible to reach 74% ¹H NMR yield when the reaction was carried out in Et₂O (entry 11). Finally, decreasing the amount of Ti(O*i*Pr)₄ to 2.0 eq provided **2** in 74% ¹H NMR yield (entry 14). It must be underlined that the preliminary deprotonation of the alcohol group of **1** (step 1) seems preferable but not mandatory. Indeed, the direct introduction of Ti(O*i*Pr)₄ (step 2) to generate the low-valent titanium complex (step 3) led to a satisfying ¹H NMR yield of 64% (entry 15). We thus decided to elect both **Conditions A** with a preliminary deprotonation of the hydroxyl group and **Conditions B** without this deprotonation for a case to case optimization if required.

With our optimized conditions in hand, we investigated the scope and limitations of this cyclization reaction (**Scheme 2**). Product **2** was isolated in 68% yield under **Conditions A** (50% on 3.33 mmol scale). The modulation of R¹ group at the alkoxyallene moiety (**1**, **3**, **5**, **7**) was possible but conducted to

low yields: 33% with cyclohexyl group (**4**), 23% with CH₂CH₂TMS group (**6**) and 17% with *N,N*-diisopropylcarbamoyl group (**8**).



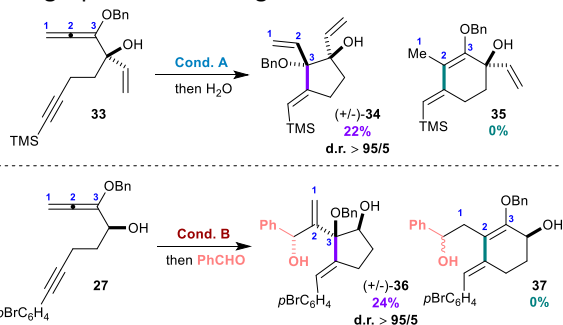
Scheme 2 Titanium(II) mediated alkyne/alkoxyallene intramolecular coupling reactions

Conditions B were mandatory in the case of compound **7** in order to prevent the side-migration of the carbamoyl group.^[15] Based on these results, it was thereby decided to fix the benzyl group for the rest of the survey. A broad range of tertiary alcohols was obtained thanks to **Conditions A** but led to disparate yields due to the steric hindrance induced by R² on the carbon next to the alkoxyallene moiety. The cyclic adduct **10** bearing a methyl group was obtained in 52% however, yields dropped when bulkier isopropyl and *n*pentyl groups were introduced, affording the corresponding adducts **12** and **14** in respectively 24% and 29% isolated yields. Noteworthy, the reduced product was isolated as the major compound in 35% yield from the reaction with **11**, showing thus that high steric hindrance only affects the reaction between alkoxyallene and titanacyclopropene. In the case of unsubstituted aromatic substituents, the cyclization of the precursor **15** led to the corresponding product **16** in 35% yield. When the aromatic ring was ortho-substituted (**18**), the yield slightly decreased to 27% due to steric effects. However, 75% yield was reached in the case of product **20**, functionalized with a *para*-tolyl group. The same reaction was carried out on 1.5 mmol scale and afforded a similar yield (71%). In compound **20**. Further investigations were dedicated to electrophile trapping. Using acetone provided the diol **31** in very good yield (76%). **Conditions A** were also suitable for the synthesis of the spiro-adduct **30** which was however obtained in moderate yield (37%). At last, the substitution of the alkyne moiety (R⁴) was regarded. Bulky TBDMS group was suitable to reach the corresponding cyclized product in 58% yield following **Conditions A**. Three cyclic adducts bearing an aromatic ring (**24**, **26** and **28**) were also

obtained in good yields, respectively 62% with phenyl group (**24**), 43% with *para*-methoxyphenyl group (**26**) and 58% with *para*-bromophenyl group (**28**). Once again, **Conditions B** were found mandatory in these cases since the corresponding magnesium alkoxide resulting from the preliminary deprotonation of the alcohol group (**step 1**) following **Conditions A** was not soluble and did not allow the reaction to proceed. It must be mentioned that the five-membered ring adduct resulting from addition on centre **C³** was observed by ¹H NMR before purification in the reaction involving compound **27**. However, this side-product could not be isolated. Trapping of the corresponding metallated intermediate resulting from the cyclization of **27** led to the diol **32** in 63% yield.

In addition to the excellent regioselectivities of this process in favour of a selective addition onto the more electron-rich centre **C²**, few counter-examples have been identified, again with excellent diastereoselectivities (**Scheme 3**).

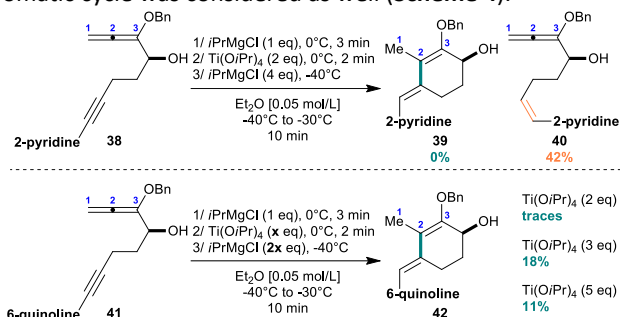
In the field of tertiary alcohol comportsing substrates, the cyclization of **33** led to interesting results since the expected compound **35** was not observed in the crude mixture, but the five-membered ring **34** was obtained and isolated in 24% yield as the single product following **Conditions A**.



Scheme 3 Specific regioselectivities toward the centre **C³**

However, the generation of **35** as the major but unstable product cannot be ruled out. Due to the preliminary deprotonation of the hydroxyl group (**step 1**) and the introduction of 2 eq of Ti(O*i*Pr)₄ (**step 2**), the formation of a titanium alkoxide intermediate may be assumed.^[11a] It can therefore be proposed that a partial complexation of the double bond next to the alkoxy occurred with the low-valent titanium complex, allowing an addition onto the **C³** carbon of the alkoxyallene moiety.^[16] The diastereoselectivity could be explained by a conformation which minimises unfavourable steric interactions between the benzyloxy group and the titanium alkoxide intermediate. Trapping of the metallated intermediate resulting from the cyclization of **27** with benzaldehyde led to the five-membered ring **36** as unique product of the reaction in 24% yield, along with degradation since the expected diol **37** was not observed. No explanation about the partial addition onto the carbon **C³** could be given so far in that case, but the opposite configuration of this centre compared to product **34** may be correlated to **Conditions B** (without preliminary deprotonation **step 1**)^[17] which did not allow the titanium alkoxide intermediate to be generated. In addition to the good diastereocontrol of the cyclization, benzaldehyde trapping proved to be diastereoselective, leading to the formation of a second chiral centre in a single synthetic

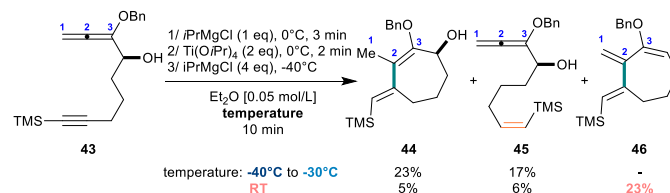
step. An extension to frameworks functionalized with a hetero-aromatic cycle was considered as well (**Scheme 4**).



Scheme 4 Titanium(II) mediated alkyne/alkoxyallene intramolecular coupling reactions involving a hetero-aromatic group

Conditions B were required again to ensure the solubility of the metallated intermediates. However, the precursor **38** bearing a 2-pyridyl group did not undergo the cyclization leading to the desired adduct **39**. The reduced product **40** was isolated in 42% yield and the starting material **38** was recovered in 35% yield. This result could be explained by interactions between the nitrogen atom of the pyridine ring and Ti(O*i*Pr)₄,^[18] leading to unsuitable conformations or huge steric hindrance next to the titanacyclopropene intermediate which did not allow the approach of the alkoxyallene moiety. To overcome the side effects induced by these interactions, compound **41** bearing a 6-quinoline moiety was prepared. The addition of Ti(O*i*Pr)₄ (2 eq) following **Conditions B** led to rapid precipitation of the substrate, which only afforded **42** as traces and recovery of **41** in 70% yield. Increasing the amount of Ti(O*i*Pr)₄ to 3 eq delivered the product **42** in 18% yield and the starting material was only recovered in 25% yield. At last, 5 eq of Ti(O*i*Pr)₄ ensured a full conversion of **41** but provided **42** in 11% yield. Despite the low yields, it was possible to run the first titanium(II) mediated alkyne/alkoxyallene coupling reactions involving a hetero-aromatic ring in an intramolecular fashion.

In line with our previous works,^[13] we investigated the formation of seven-membered ring frameworks. Reaction **Conditions A** were thus applied to the precursor **43**, affording a mixture of the desired seven-membered ring **44** and the reduced product **45** which could not be separated (respectively 23 and 17% ¹H NMR yield) (**Scheme 5**). Increasing the reaction time led to similar results.

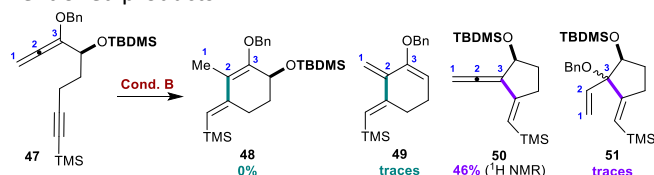


Scheme 5 Titanium(II) mediated alkyne/alkoxyallene coupling reaction for seven-membered ring framework synthesis

In order to push forward the conversion of the titanacyclopropene intermediate into cyclized adducts, and considering that seven-membered ring synthesis requires higher temperature than that of five- and six-membered rings, the reaction was performed at room temperature.^[13,17] Both products **44** and **45** were observed as traces. However, a new

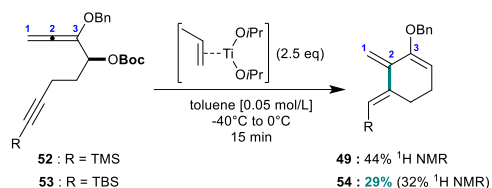
seven-membered ring **46** was obtained as the major product of the reaction in 23% yield along with degradation. In addition to the selectivity in favour of an addition onto the more electron-rich carbon **C**², it appeared that temperature allowed a spontaneous domino deoxygenation.^[16]

Finally, the cyclization of substrates bearing a protected alcohol was investigated.^[6b] First the alcohol was protected as a silyl ether with a bulky TBDMS group (**Scheme 6**). However, the desired product **48** was not observed and the reaction led to a complex mixture of **49**, **50** and **51**.^[16] Similarly, other silyl ethers (TMS, TIPS) also led to mixtures of the three previously mentioned products.



Scheme 6 Investigation on protected alcohol

However, it was possible to obtain the six-membered ring **49** as the single product of the reaction when the TBDMS group was replaced by a Boc group. Other leaving groups (OCONEt₂, OAc) mostly led to degradation. Interestingly, the amount of degradation dropped when the low-valent titanium(II) complex was generated preliminarily. After tuning of the conditions, a conversion of 44% (determined by ¹H NMR) was reached but **49** proved to be highly unstable and could not be isolated (**Scheme 7**).



Scheme 7 Toward deoxygenated six-membered ring adducts

Conclusion

In summary, we highlighted an unprecedented low-valent titanium(II) mediated intramolecular alkyne/alkoxyallene coupling reaction. The conditions developed herein are easy to set up and use inexpensive Ti(OiPr)₄ and Grignard reagent. Highly functionalized six- and seven-membered ring adducts were thus obtained in moderate to excellent yields (up to 76% yield over 19 examples). The reaction showed very good and atypical regioselectivities with a preferential addition of the titanacyclopropene intermediate onto “the more electron-rich” carbon of the alkoxyallene moiety. Only a few counter-examples are reported leading to five-membered ring adducts in modest yields but with excellent diastereoselectivities (up to 95/5 d.r.). The presence of the hydroxy group proved to be crucial and led to several unexpected original frameworks.

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Conflicts of interest

There is no conflict to declare.

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