Synthesis of chiral allylic alcohols by the reaction of chiral titanium–alkyne complexes with carbonyl compounds

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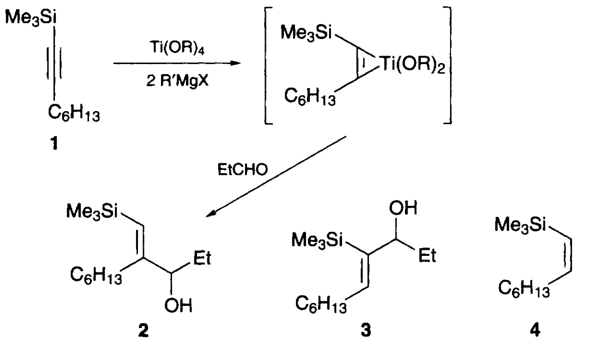
Chiral titanium–alkyne complexes derived from chlorotris[(−)-menthoxy]titanium/2 Pr^{i}MgCl and alkynes react with aldehydes to afford optically active allylic alcohols in up to 38% ee.

Recently we have reported that the titanium(II) compound (η^2-propene)Ti(OPr^i)$_2$, readily generated *in situ* by the reaction of Ti(OPr^i)$_4$ with 2 equiv. Pr^{i}MgX (X = Cl, Br), reacts with internal alkynes to give titanium–alkyne complexes in essentially quantitative yield and which, in turn, react with aldehydes and ketones to afford the corresponding allylic alcohols.[1] In view of current interest in the asymmetric addition reaction of organometallic reagents to carbonyl compounds,[2] we decided to undertake a study to determine the feasibility of performing the reaction in an enantioselective way by using a chiral titanium alkoxide. Here we report our findings.

Firstly, generation of titanium–alkyne complexes from 1-(trimethylsilyl)oct-1-yne **1** by using several achiral titanium alkoxides and their reactions with propanal were investigated to obtain guidelines for choosing the best chiral titanium alkoxide. The results are summarized in Table 1. As can be seen, the reaction was affected seriously by the nature of the alkoxy ligand. Use of Ti(OEt)$_4$ or Ti(OBu^t)$_4$[3] instead of Ti(OPr^i)$_4$ resulted in significant decrease in yield of the corresponding titanium–alkyne complex and, as a consequence, the allylic alcohol (entry 1 *vs.* 5 and 7). The combination of titanium alkoxide and the Grignard reagent used also affected the reaction considerably. When Ti(OPr^i)$_4$ was used as a titanium reagent, use of Grignard reagents other than Pr^{i}MgX lowered the yield of the titanium–alkyne complex: use of EtMgBr provided only moderate yield (entry 2), while PrMgBr or Bu^{i}MgCl resulted in a poor yield (entries 3 and 4). Noteworthy also is the fact that, in the case of Ti(OBu^t)$_4$, the use of ethyl instead of isopropyl Grignard reagent gave higher yield of the corresponding titanium–alkyne complex; however, it reacted with aldehydes sluggishly (entries 7 and 8).

Table 1 Generation of titanium–alkyne complexes from 1-(trimethylsilyl)oct-1-yne **1** and their reaction with propanal[a]

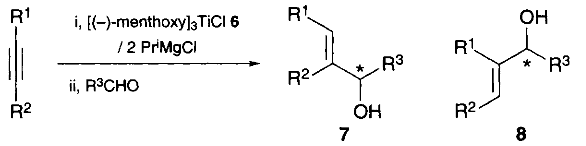


	Reaction conditions		2 + 3			
Entry	Ti(OR)$_4$	R′MgX	Yield (%)[b]	Ratio (**2**:**3**)[c]	**4** (%)	Recovery of **1** (%)
1	Ti(OPr^i)$_4$	Pr^{i}MgCl	87	79:21	9	0
2		EtMgBr	34	75:25	8	48
3		PrMgBr	4	75:25	2	81
4		Bu^{i}MgCl	0	—	0	85
5	Ti(OEt)$_4$	Pr^{i}MgCl	33	87:13	2	56
6		EtMgBr	8	68:32	< 1	21
7	Ti(OBu^t)$_4$	Pr^{i}MgCl	4	83:17	< 1	93
8		EtMgBr	16	85:15	42	31

[a] Alkyne : Ti(OR)$_4$: R′MgX : EtCHO = 0.8 : 1.0 : 2.2 : 1.0. [b] Isolated yield of a mixture of **2** and **3**. [c] Determined by ^{1}H NMR analysis.

The finding that the use of titanium compounds having a sterically different alkoxy group compared with isopropoxy did not afford good results prompted us to use chiral titanium alkoxides derived from a secondary chiral alcohol. We thus selected tetra[(−)-menthoxy]titanium **5** prepared from Ti(OPr^i)$_4$ and (−)-menthol *via* azeotropic removal of propan-2-ol.[4] Reagent **5**/2 Pr^{i}MgX, however, afforded the corresponding chiral titanium–alkyne complex in rather low yield by reaction with an alkyne; moreover, the alkyne complex thus generated did not provide the addition product with an aldehyde. Thus, reaction of **5**/2 Pr^{i}MgX with dodec-6-yne followed by treatment with cyclohexanecarboxaldehyde provided only (*Z*)-dodec-6-ene and the starting dodec-6-yne in 20 and 70% yields, respectively. However, we found that the use of chlorotris[(−)-menthoxy]titanium **6**[4,5] instead of **5** provided the expected allylic alcohols with the yield and the regioisomeric ratio comparable to those obtained using Ti(OPr^i)$_4$.[1]

Table 2 Reaction of an optically active titanium–acetylene complex derived from **6** with carbonyl compounds[a]



Entry	R^1	R^2	R^{3}CHO	Yield[b] (%)	Ratio (**7**:**8**)[c]	Enantiomeric excess of **7**[d,e] (%)
1	C$_5$H$_{11}$	C$_5$H$_{11}$	EtCHO	81	—	26
2			Pr^{i}CHO	77	—	25
3			Hex^{c}CHO	78	—	38
4			PivCHO	53	—	36
5	Me$_3$Si	C$_6$H$_{13}$	Hex^{c}CHO	73	89:11	18
6	Me$_3$Si	Ph	Hex^{c}CHO	63	95:5	25

[a] Reactant ratio; **6** : Pr^{i}MgCl : acetylene : aldehyde = 1.0 : 2.3 : 0.6 : 1.5.†. [b] Isolated yield of a mixture of **7** and **8**. [c] Determined by ^{1}H NMR analysis. [d] Determined by ^{1}H NMR analysis of the corresponding MTPA esters. [e] Configuration was determined to be *R* (see ref. 6).

As can be seen from Table 2 which summarizes the results of the reaction using **6**/2 Pr^{i}MgCl reagent, chiral titanium–alkyne complexes having an optically active menthoxy ligand react with aldehydes to afford allylic alcohols in up to 38% ee. To the best of our knowledge, this is the first example of asymmetric addition of metal–alkyne complexes with aldehydes.[7] Although the enantiomeric excess attained here is not satisfactory, the results show that the reaction can potentially be carried out in an asymmetric way and further work on the development of more efficient chiral titanium alkoxides is in progress.

Footnote

† The following procedure is typical. To a stirred solution of dodec-6-yne (0.127 ml, 0.6 mmol) and chloro-tris[(−)-menthoxy]titanium (0.770 ml, 1.30 mol dm^{-3} in Et$_2$O, 1.0 mmol) in Et$_2$O (5 ml) was added Pr^{i}MgCl (1.89 ml, 1.22 mol dm^{-3} in Et$_2$O, 2.3 mmol) at −78 °C, and the mixture warmed to −35 °C for 1.5 h. After stirring for 2 h at the same temperature, propionaldehyde (0.108 ml, 1.5 mmol) was added at −78 °C and the stirring continued for 1 h at −78 °C. The reaction mixture was then quenched with 1 mol dm^{-3} HCl aq. and allowed to warm to room temperature. The organic and aqueous layers were extracted with Et$_2$O and the combined organic layers were dried over MgSO$_4$ and then concentrated *in vacuo*. The resulting oil was purified by column chromatography on silica gel to give (*E*)-4-pentyldec-4-ene-3-ol (110 mg, 0.486 mmol) in 81% yield.

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