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Evaluation of titanium alkoxides and aryloxides in the Kulinkovich cyclopropanation of carboxylic esters

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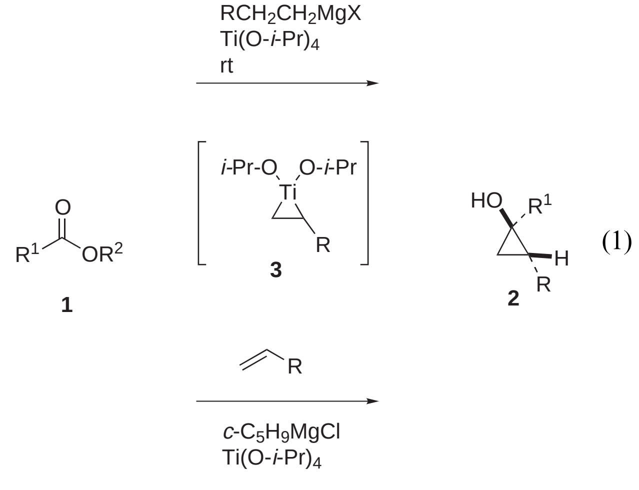
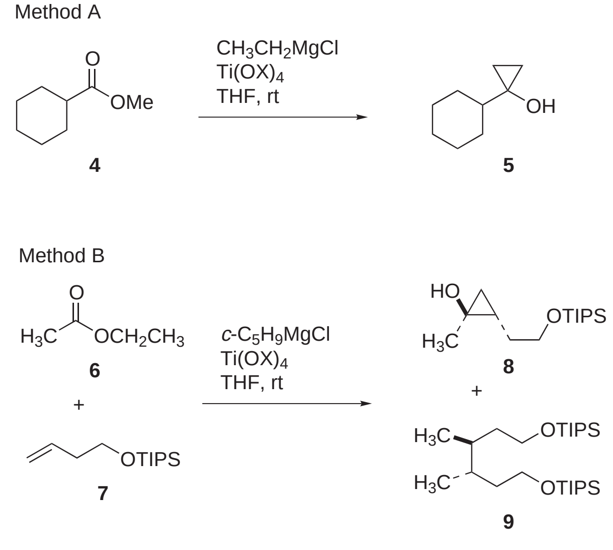
Abstract—Systematic evaluation of several titanium alkoxides and aryloxides was undertaken in the titanium-mediated cyclopropanation reactions of carboxylic esters. Chlorotitanium triisopropoxide and/or methyltitanium triisopropoxide were found to be the reagents of choice for the olefin exchange modification, whereas the original Kulinkovich process proved to be insensitive to the nature of titanium alkoxides and aryloxides. © 2001 Elsevier Science Ltd. All rights reserved.

A new, efficient preparation of hydroxycyclopropanes was developed by Kulinkovich and co-workers by treatment of carboxylic esters with a suitable Grignard reagent in the presence of Ti(O-*i*-Pr)$_4$, for which formation of the key titanacyclopropane intermediate **3** was postulated (Eq. (1)).[1,2] We have subsequently developed a convenient modification based on the notion of facile ligand exchange by an appropriate titanacyclopropane intermediate with a terminal olefin in both intermolecular[3] and intramolecular[4,5] coupling reactions of terminal olefins and esters. Extension to other acyl derivatives, as well as synthetic applications, has since been reported.[6,7] In order to gain additional mechanistic insights, we assessed the efficacy of several titanium alkoxides and aryloxides in the Kulinkovich cyclopropanation reaction of carboxylic esters.

Several titanium alkoxides and phenoxides were evaluated under both the original Kulinkovich conditions (Method A) and the olefin exchange modification (Method B). For convenience, commercially available methyl cyclohexanecarboxylate (**4**) and ethylmagnesium chloride were employed in Method A, whereas ethyl acetate (**6**) and 1-triisopropylsiloxy-3-butene (**7**) were subjected to the action of commercially available cyclopentylmagnesium chloride in Method B (Eq. (2)).



(1)



(2)

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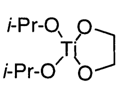
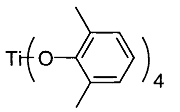
Table 1. [a]

entry	titanium reagent	Method A	Method B	
		5	**8**	**9**
1	$\mathrm{Ti(O\text{-}}i\mathrm{\text{-}Pr)_4}$	81%	71%	12%
2	$\mathrm{ClTi(O\text{-}}i\mathrm{\text{-}Pr)_3}$	76%	78%	12%
3	$\mathrm{MeTi(O\text{-}}i\mathrm{\text{-}Pr)_3}$	79%[7]	84%	3%
4		87%	61%	25%
5	$\mathrm{Ti(OPh)_4}$	82%	55%	18%
6	$\mathrm{Cl_2Ti(OPh)_2}$	*b*	38%	25%
7	$\mathrm{Ti(OC_6H_4\text{-}}p\mathrm{\text{-}OMe)_4}$	93%	53%	18%
8		*b*	45%	31%
9	$\mathrm{Ti(OCH_2CF_3)_4}$	68%	25%	3%
10	$\mathrm{Ti[OCH(CF_3)_2]_4}$	82%	9%	2%
11	$\mathrm{Ti(OSi\text{-}}t\mathrm{\text{-}BuMe_2)_4}$	86%	53%	16%

[a] Conditions for Method A: **4** (1 equiv.), titanium reagent (1.1 equiv.), EtMgCl (xs), THF, rt; conditions for Method B: **6** (1 equiv.), **7** (1 equiv.), titanium reagent (1.1 equiv.), $c\text{-}\mathrm{C_5H_9MgCl}$ (xs), THF, rt. *b*. Not determined.

Although the resulting products **5** and **8** were not identical in these two methods, the above-mentioned combinations of the reactants were chosen to avoid the formation of volatile cyclopropanols so as to facilitate handling and analysis of the products.

As summarized in Table 1, several trends were apparent in these cyclopropanation reactions of esters.[8,9] Method A proved to be insensitive to the nature of titanium alkoxides and aryloxides. All the titanium reagents examined afforded the cyclopropanol **5** in good to excellent yields. In Method B, however, the product yields depended on the reagent employed, where the desired cyclopropanation of **6** was accompanied by the titanium-mediated dimerization of **7** to yield the by-product **9**.[10] Titanium alkoxides (entries 1–4) were uniformly more effective than titanium aryloxides (entries 5–8),[11] although the overall material balance (i.e. **8**+**9**) was comparable for both types of the titanium reagents. Chlorotitanium triisopropoxide (entry 2) and methyltitanium triisopropoxide[12] (entry 3) appeared to be the reagents of choice for Method B. The latter reagent, in particular, offers the additional advantage of requiring only one equivalent of the Grignard reagent.[7b]

The divergence in yields between Methods A and B became more pronounced when an electron-withdrawing substituent was introduced into the alkoxy moiety (entries 9 and 10). In the resulting electron-deficient titanacyclopropane intermediates, the titanium metal is believed to be more tightly held by the π-electrons. Consequently, the subsequent olefin exchange step would likely become sluggish, resulting in poor yields of the cyclopropanol. On the other hand, use of an electropositive (e.g. trialkylsilanol) group did not provide a beneficial effect (entry 11).

In summary, systematic evaluation of several titanium alkoxides and aryloxides was undertaken under both the original Kulinkovich cyclopropanation conditions of carboxylic esters and the olefin exchange modification. The present study should be useful in the development of a catalytic asymmetric process.[13]

Acknowledgements

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8. The titanium alkoxides and aryloxides were prepared by the literature methods: (a) Durfee, L. D.; Latesky, S. L.; Rothwell, I. P.; Huffman, J. C.; Folting, K. *Inorg. Chem.* **1985**, *24*, 4569; (b) Yoshino, N.; Tomita, J.; Hirai, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2208; (c) Campbell, C.; Bott, S. G.; Larsen, R.; Van Der Sluys, W. G. *Inorg. Chem.* **1994**, *33*, 4950; (d) Johnson, E. S.; Balaich, G. J.; Rothwell, I. P. *J. Am. Chem. Soc.* **1997**, *119*, 7685.
9. General procedure: *Method A*. A 2.0 M solution of ethylmagnesium chloride (excess) in THF was added dropwise over 30 min at room temperature to a solution of ester **4** (1 mmol) and a titanium reagent (1.1 mmol) in THF (6 mL). After the mixture had been stirred for 30 min, it was quenched by addition of water. The product **5** was isolated by normal workup processing and purified by silica gel chromatography. *Method B*. A 2.0 M solution of cyclopentylmagnesium chloride (excess) in ether was added dropwise over 30 min at room temperature to a solution of ester **6** (1 mmol), olefin **7** (1 mmol), and a titanium reagent (1.1 mmol) in THF (6 mL). After the mixture had been stirred for 30 min, it was quenched by addition of water. The products **8** and **9** were isolated by normal workup processing and purified by silica gel chromatography.
10. In Method B, use of titanium tetraisopropoxide and titanium tetraphenoxide afforded 70 and 72% yields of **9**, respectively, in the absence of ethyl acetate.
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