Alkylation

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Stereoselective Alkylation of Allylic Alcohols: Tandem Ethylation and Functionalization**

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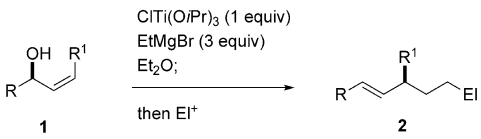
Transition metal catalyzed allylic substitution is used frequently in organic synthesis. A high level of regio- and stereocontrol of asymmetric allylic alkylation is made possible by a judicious choice of substrates, late-transition-metal catalysts, and chiral ligands.[1,2] Outside the domain of late transition metal catalyzed reactions the use of group IVA metals can also be effective for allylic substitution of readily available allylic alcohols.[3] For example, treatment of acyclic and cyclic allylic alcohols with the ethyl Grignard reagent in the presence of titanium isopropoxide provides stereoselective S_N2'-type ethylation products [Eq. (1); El = H].[4–6] The



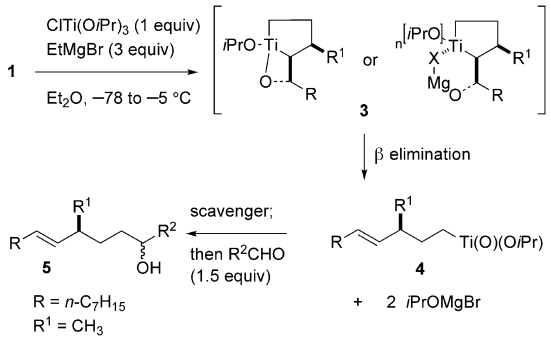
(1)

synthetic utility of the low-valent titanium (Kulinkovich reagent)[4] mediated alkylation would be greatly enhanced by an in situ introduction of a functionalized side chain (El ≠ H). We report herein a stereoselective alkylation reaction of allylic alcohols by trapping of the presumed alkyltitanium intermediates with suitable electrophiles.

This formal S_N2' ethylation reaction by the ethyl Grignard reagent was first reported by the Kulinkovich group,[5] and the stereochemical studies revealed the overall suprafacial stereochemical outcome is due to *syn* addition of the Kulinkovich reagent through a Ti–O tether and subsequent *syn* β elimination.[5d,e,6] Our mechanistic analysis implicated the generation of an alkyltitanium intermediate **4** by way of β elimination of **3** at the penultimate stage, which prompted us to investigate in situ elaboration of **4** to broaden the scope of this allylation reaction (Table 1).[7] In light of the known instability of alkyl homologues of $MeTi(OiPr)_3$,[8] the temperature control of the reaction was first examined, and it was optimal to warm the reaction mixture from −78 °C up to −10 or −5 °C, to set the stage of the trapping step. The presence of a scavenger for magnesium alkoxides in the reaction mixture was necessary prior to addition of an aldehyde to prevent an aldol condensation. Among three scavengers [TMSCl, $TiCl_4$, and $ClTi(OiPr)_3$] examined, $ClTi(OiPr)_3$ afforded the most satisfactory yields of the products. The reaction conditions were found to be general for aliphatic, unsaturated, and aromatic aldehydes. Halogenation and oxidation of the alkyl–titanium bond of **4** were also effected by electrophilic halogenation reagents (I_2 and CF_3SO_2Cl) and O_2, respectively, to provide **6**, **7**, and **8** (Scheme 1).

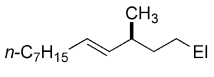
As expected, cyclic substrates are also well suited for allylic ethylation and in situ functionalization (Table 2 and Scheme 2).

Table 1: Titanium-mediated ethylation of acyclic allylic alcohols and in situ functionalization using three different scavengers.



Entry	**5** (R^2)	TMSCl[b]	Yield [%][a] $TiCl_4$[c]	$ClTi(OiPr)_3$[d]
1	**5a** (*i*Pr)	52	58	70
2	**5b** (Ph)	56	60	73
3	**5c** (PhCH=CH)	52	n.d.	n.d.
4	**5d** (CH_2=CH)	56	n.d.	n.d.
5	**5e** (CH_2=CMe)	48	n.d.	69
6	**5f** (MeCH=CH)	52	n.d.	73
7	**5g** (H)	45	n.d.	48

[a] Yields of the isolated products are given for each of the three scavengers used. [b] Used 3 equiv. [c] Used 0.75 equiv. [d] Used 3 equiv. n.d. = not determined.



Products	El	Yield [%]
6	I	69[a] (59)[b]
7	Cl	72[a] (52)[b]
8	OH	65[a] (55)[b]

Scheme 1. Halogenation and oxidation of the alkyl–titanium bond of **4**. [a] Yields of the isolated products when using 3 equiv $ClTi(OiPr)_3$. [b] Yields of the isolated products in absence of $ClTi(OiPr)_3$.

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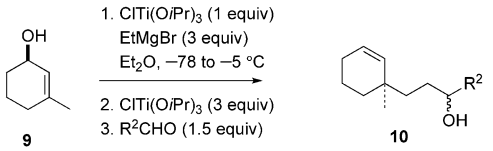
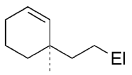
Table 2: Titanium-mediated ethylation of cyclic allylic alcohols and in situ functionalization.



9 10

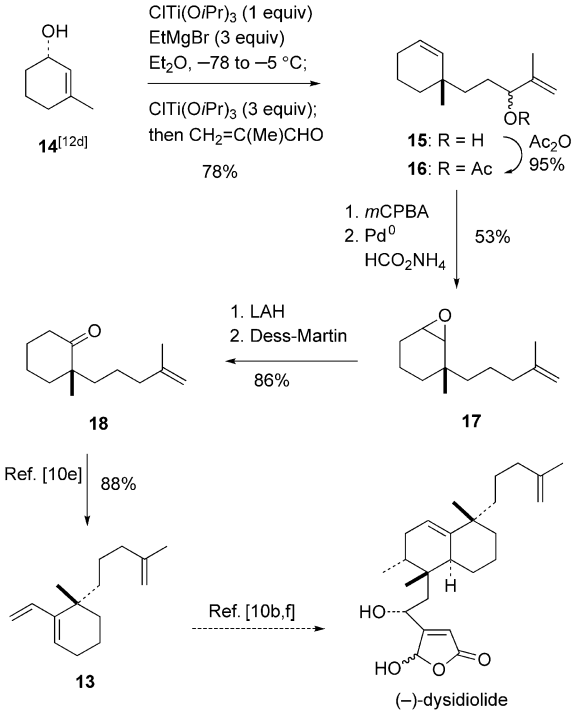
Entry	**10** (R^2)	Yield [%][a] TMSCl[b]	$ClTi(OiPr)_3$[b]
1	**10a** (*i*Pr)	42	71
2	**10b** (PhCH=CH)	58	76
3	**10c** (CH_2=CH)	n.d.	70
4	**10d** (CH_2=CMe)	70	78
5	**10e** (H)	45	56

[a] Yields of the isolated products are given for each of the three scavengers used. [b] Used 3 equiv.



Products	El	Yield [%]
11	I	62[a] (52)[b]
12	OH	68[a] (59)[b]

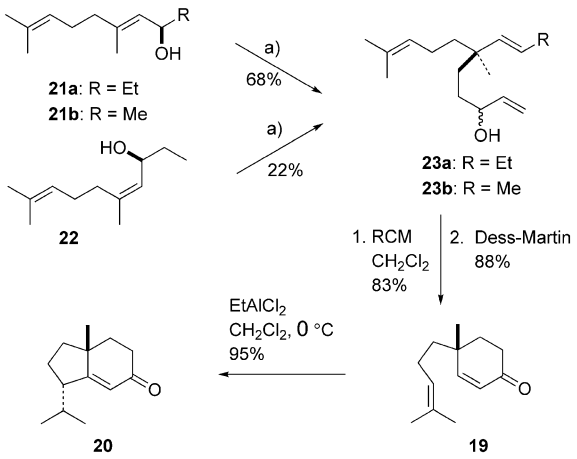
Scheme 2. Halogenation and oxidation of the alkyl–titanium to give products **11** and **12**, respectively. [a] Yields of the isolated products when using 3 equiv $ClTi(OiPr)_3$. [b] Yields of the isolated products in absence of $ClTi(OiPr)_3$.



Scheme 3. Formal synthesis of (−)-dysidiolide.

The construction of all-carbon quaternary stereocenters in the context of natural product synthesis was next undertaken to showcase the utility of the in situ functionalization of the presumed alkyltitanium intermediates. The enantioselective formation of quaternary stereocenters has been an active area of research.[9] Toward this end, **13** was selected as a target molecule, which had been converted by Danishefsky and coworkers into dysidiolide,[10f] a bioactive sesterterpene (Scheme 3).[10,11] Starting from the known and readily available (*S*)-seudenol (**14**),[12] the stereoselective ethylation and subsequent in situ trapping with methacrolein, provided easy access to the alcohol **15** bearing a quaternary stereocenter in 78% yield. Acetylation of alcohol **15** with subsequent chemoselective epoxidation and Pd^0-catalyzed allylic deoxygenation,[13] afforded the epoxide **17** as an inconsequential mixture of two diastereomers. The epoxide was next converted into the ketone **18** by standard methods. The diene **13** was then prepared by known procedures.[10b,e] As **13** had already been converted into dysidiolide,[10b,f] this work represents its formal synthesis.

The enone **19** was selected as the second target as a prototype of 4,4-dialkyl-2-cyclohexenones (Scheme 4). There is a paucity of general methods for enantioselectively preparing 4,4-dialkyl-2-cyclohexenones, which stands in marked contrast to more readily accessible 4-alkyl-2-cyclohexenones.[14] Additionally, treatment of **19** with $EtAlCl_2$ was documented to deliver an attractive route to bicyclic ketone **20**,[15] which has found applications in natural product synthesis.[16,17] Under our standard reaction conditions an S_N2'-type alkylation of the enantiomerically enriched **21a**[18a] and **21b**[18b] and subsequent trapping with acrolein gave **23a** and



Scheme 4. Enantioselective synthesis of a 4,4-dialkyl-2-cyclohexenone. a) $ClTi(OiPr)_3$ (1 equiv), EtMgBr (3 equiv), Et2O, −78→−5 °C; then $ClTi(OiPr)_3$ (3 equiv); CH_2=CHCHO.

23b, respectively, in 68% yield and with little loss in the *ee* value. The *Z*-alcohol **22** was prepared from nerol for comparison, and its parallel reaction proceeded unexpectedly in poor (22%) yield. Ring-closing metathesis of **23a** or **23b** with Grubbs' second-generation catalyst, followed by Dess–Martin oxidation, provided the cyclohexenone **19** cleanly. Finally, a short enantioselective synthesis of **20** was achieved by the method reported by Snider et al.[15]

In conclusion, a straightforward, yet valuable functionalization of the primary C–Ti bond with suitable electrophiles has been incorporated into the S_N2'-type reaction of acyclic

and cyclic allylic alcohols with the ethyl Grignard reagent in the presence of a titanium alkoxide. The stereospecific and convenient introduction of a functionalized side chain by the use of inexpensive reagents is notable and broadens the scope of this alkylation. Additionally, the present method offers direct use of allylic alcohols without preactivation or derivatization. This also represents formal cross-coupling reactions between allylic alcohols and terminal olefins bearing useful functional groups with concomitant 1,3-transposition.[3,6]

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