Pergamon

Tetrahedron Letters 43 (2002) 1231–1233

TETRAHEDRON LETTERS

CP_2TiCl_2-catalyzed hydroalumination of internal alkynes: an access to (*Z*)-olefins

Arnaud Parenty and Jean-Marc Campagne*

Institut de Chimie des Substances Naturelles, CNRS, F-91198 Gif-sur-Yvette, France

Received 27 November 2001; accepted 20 December 2001

Abstract—The reduction of alkynols with $LiAlH_4$ in diglyme is a long known process leading to the formation of (*E*)-alkenols. We have, by serendipity, found that, in the presence of a catalytic amount (10%) of Cp_2TiCl_2, the stereoselectivity of the reaction is reversed, leading to the selective formation of the (*Z*)-alkenols. The scope and limitations of this methodology and a postulated catalytic cycle are also discussed. © 2002 Elsevier Science Ltd. All rights reserved.

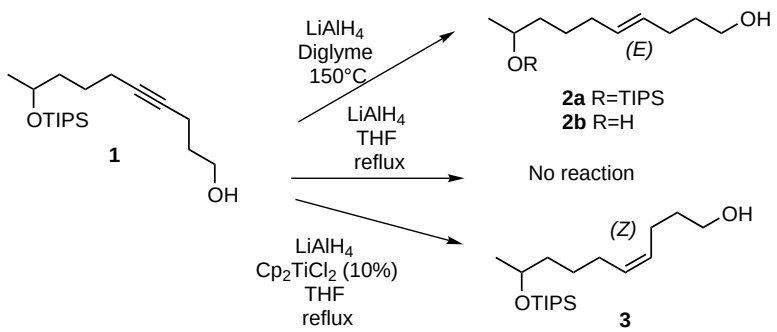
During the course of an ongoing project towards the total synthesis of dolastatin 14,[1] we were keen to reduce alkyne **1** into the corresponding (*E*)-alkene **2a**. However, the harsh standard conditions (xs. $LiAlH_4$ in diglyme at 150°C) described by Rossi and Carpita[2] resulted in the deprotection of the TIPS silyl protecting group leading to the diol **2b** in 71% yield. The same reaction in refluxing THF led to no reduction nor deprotection of the silyl group. In order to get milder reaction conditions we thought about catalyzing the hydroalumination[3] using various transition metal catalysts[4,5] such as $Ni(acac)_2$, Cp_2TiCl_2, etc.

Indeed, using 10% of Cp_2TiCl_2 in refluxing THF, the protected alcohol **3** was obtained in 52% yield, but surprisingly with the opposite (*Z*) double bond configuration (*Z*/*E* >9/1) (Scheme 1).

In order to determine the scope and limitations of this intriguing result,[6] we undertook the reduction of several internal alkynes as illustrated in Table 1.

The reduction of β and γ-alkynols (Table 1, entries 1–2) proved to be very efficient leading to the corresponding (*Z*)-alkenols in good yields 75 and 64%, respectively. The reduction of α-alkynol (Table 1, entry 3) was non stereoselective (*E*/*Z*=1/1) certainly resulting from a competition between the catalyzed and non-catalyzed processes.

The requirement of a free alcohol in the Cp_2TiCl_2-catalyzed reduction process was then questioned. Consequently, we undertook the reduction of a benzyl-protected γ-alkynol (Table 1, entry 4) which resulted in the formation of the (*Z*) reduced product in

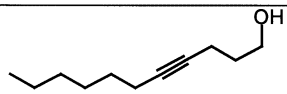
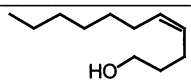
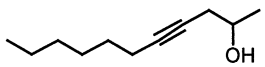
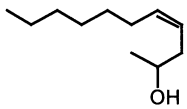
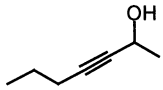
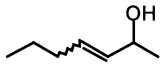
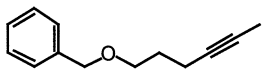
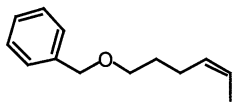
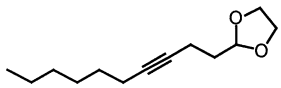
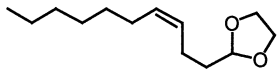
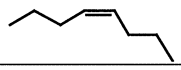


Scheme 1.

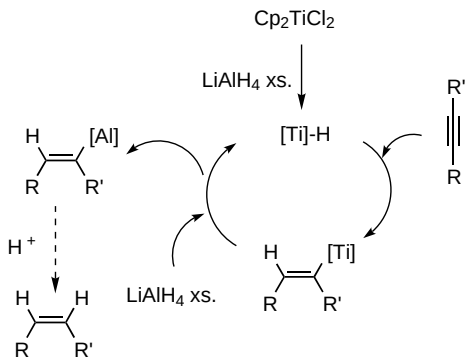
* Corresponding author. E-mail: jean-marc.campagne@icsn.cnrs-gif.fr

PII: S0040-4039(01)02402-9

Table 1. Cp_2TiCl_2-catalyzed reductions of internal alkynes[a]

Entry	Alkyne	Alkene	Isolated Yield	Z/E ratio
1			75%	10/1[b]
2			64%	10/1[b]
3			54%	1/1[b]
4			82%	20/1[b]
5			65%	11/1[b]
6			nd[c]	18/1[b]

[a] Unless otherwise specified, the reactions have been carried out in THF at reflux using 10% of Cp_2TiCl_2 and 4 Eq. of $LiAlH_4$. [b] The *E/Z* ratio was determined on the crude product by ^{13}C NMR or ^1H NMR by comparison with an authentic (*E*) sample either obtained by reduction with $LiAlH_4$[2] or with Li(0)/diaminopropane.[15] [c] The reaction was conducted at room temperature during 48 hours: on the crude product, no over-reduction product and no starting material could be detected by ^{13}C NMR.



Scheme 2.

82% yield. Since the presence of a free alcohol is not required, this process can virtually be used to the (*Z*)-reduction of any internal dialkyl-alkynes as illustrated in entries 5 and 6.

Mechanistically, this reaction could be similar to the Cp_2TiCl_2-catalyzed hydromagnezation[7,8] and hydrozincation[9] described by Sato and Eisch. The pre-catalyst Cp_2TiCl_2 is reduced into a [Ti]-H species able to hydrotitanate the triple bond. A transmetallation from titanium to aluminum regenerates the catalytic [Ti]-H species and generates the (*syn*)-hydroaluminated compound (Scheme 2).

In conclusion, we have described an efficient access to (*Z*)-alkenes based on a titanium-catalyzed hydroalumination reaction. This very simple and cheap methodology could constitute an attractive alternative to known and efficient alkynes (*Z*)-reduction procedures previously described.[7–15]

Acknowledgements

We thank Dr. Yvan Six for helpful discussions and the CNRS for financial support.

References

1. Pettit, G. R.; Kamano, Y.; Herald, C. L.; Dufresne, C.; Bates, R. B.; Schmidt, J. M.; Cerny, R. L.; Kizu, H. *J. Org. Chem.* **1990**, *55*, 2989–2990.
2. Rossi, R.; Carpita, A. *Synthesis* **1977**, 561–562.
3. For general reviews on hydroalumination, see: (a) Eisch, J. J. In *Comprehensive Organic Synthesis*; Trost, B.; Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, Chapter 3.11; (b) Zweifel, G.; Miller, J. A. In *Organic Reactions*; Dauben, W. G., Ed.; Wiley: New York, 1984; Vol. 32, Chapter 2, pp. 377–517.
4. For the transition metal-catalyzed hydroalumination of alkenes, see (and references cited therein): (a) Gagneur, S.; Makabe, H.; Negishi, E. *Tetrahedron Lett.* **2001**, *42*, 785–787; (b) Sato, F.; Sato, S.; Sato, M. *J. Organomet. Chem.* **1977**, *131*, C26–C28; (c) Isagawa, K.; Tatsumi, K.; Otsuji, Y. *Chem. Lett.* **1976**, 1145–1148.
5. For the catalytic and stoichiometric use of other transition metals in the hydroalumination of alkynes (thanks to referee 1 for bringing these references to our attention), see: (a) Ashby, E. C.; Lin, J. J. *Tetrahedron Lett.* **1977**, *18*, 4481–4484; (b) Ashby, E. C.; Lin, J. J. *J. Org. Chem.* **1978**, *43*, 2567–2572.

6. The Cp_2TiCl_2-catalyzed reduction of diphenylacetylene was previously reported to give predominantly dihydroaluminated compounds: Lee, H. S.; Kim, I. H. *J. Korean. Chem. Soc*. **1993**, *37*, 689–691.
7. (a) Sato, F. *J. Organomet. Chem*. **1985**, *285*, 53–64; (b) Gao, Y.; Sato, F. *J. Chem. Soc., Chem. Commun*. **1995**, 659–660.
8. Eisch, J. J.; Galle, J. E. *J. Organomet. Chem*. **1978**, *178*, C8–C12.
9. Gao, Y.; Harada, K.; Hata, T.; Urabe, H.; Sato, F. *J. Org. Chem*. **1995**, *60*, 290–291.
10. Larock, R. C. *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1999; pp. 405–408.
11. (a) Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett*. **1995**, *36*, 3203–3206; (b) Hungerford, N. L.; Kitching, W. *Chem. Commun*. **1996**, 1697–1698.
12. Choi, J.; Yoon, N. M. *Tetrahedron Lett*. **1996**, *37*, 1057–1060.
13. Daeuble, J. F.; McGettigan, C.; Stryker, J. M. *Tetrahedron Lett*. **1990**, *31*, 2397–2400.
14. Kini, A. D.; Nadkarni, D. V.; Fry, J. L. *Tetrahedron Lett*. **1994**, *35*, 1507–1510.
15. Kovarova, I.; Streinz, L. *Synth. Commun*. **1993**, *23*, 2397–2404.