Asymmetric Synthesis

Stereoselective Construction of Acyclic Carbon Chains by a One-Pot Coupling Process Based on Alkenyloxazoline–Titanium Complexes**

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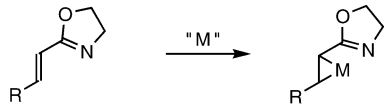
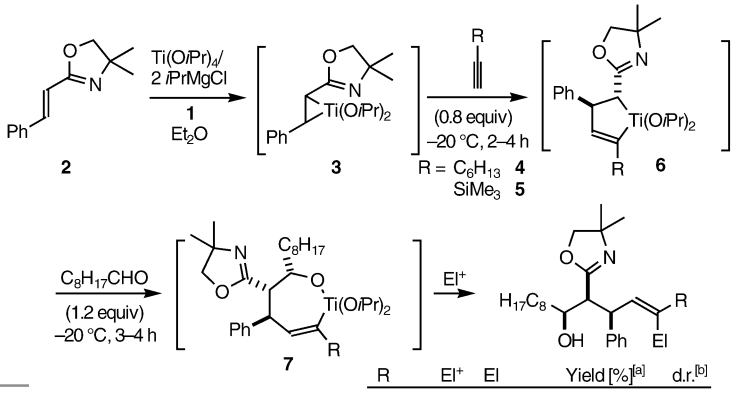
Oxazoline is known as a versatile functional group in organic synthesis for the activation of substrates and for asymmetric synthesis.[1] Complexation of organic compounds having this group with transition metals may lead to the development of unique synthetic transformations,[2] but an olefin complex such as the one in Scheme 1 (M = metal)[3] has not been investigated. We report here that titanation of alkenyloxazolines proceeds nicely to give novel olefin–titanium complexes (Scheme 1, M = Ti(O*i*Pr)$_2$), which subsequently allow for a diastereoselective multicomponent coupling process and an asymmetric coupling reaction.



Scheme 1. Generation of the olefin–metal complex.

Treatment of alkenyloxazoline **2**[4] with a titanium(II) alkoxide reagent **1** formed from Ti(O*i*Pr)$_4$ with two equivalents of *i*PrMgCl,[5] generates olefin complex **3**,[6] which underwent a coupling reaction with 1-octyne (**4**) to give titanacycle **6** (R = C_6H_{13}; Scheme 2). Intermediates **3** and **6** were identified by deuteriolysis.[7] The carbon–titanium bond α to the oxazoline (rather than the vinyl–titanium bond) of **6** selectively reacted with the octanal to give, after hydrolytic work-up, a single regioisomer **8** having exclusively an *E*-olefinic bond. Surprisingly, the crude reaction mixture contained this adduct **8** together with a very small amount of one of the four possible diastereoisomers (d.r. = 96:4) arising from the three consecutive stereogenic centers. Compound **8** could be readily separated from this minor isomer[8] by flash chromatography on silica gel to give a pure sample in 66% yield. The stereochemistry of **8** was determined (as depicted) by derivatization.[7] A stereochemical course from **2** to **8** is proposed in the Supporting Information.[7] Analogously, the sequential treatment of **2** with silylacetylene **5** and nonanal



R	El$^+$	El		Yield [%][a]	d.r.[b]
C_6H_{13}	H^+	H	**8**	66	96:4
$SiMe_3$	H^+	H	**9**	73	93:7
$SiMe_3$	D^+	D	**10**	73[c]	93:7
$SiMe_3$	I_2	I	**11**	52	93:7

[a] Pure sample. [b] In a crude mixture. [c] 96% incorporation of deuterium.

Scheme 2. Four-component coupling process.

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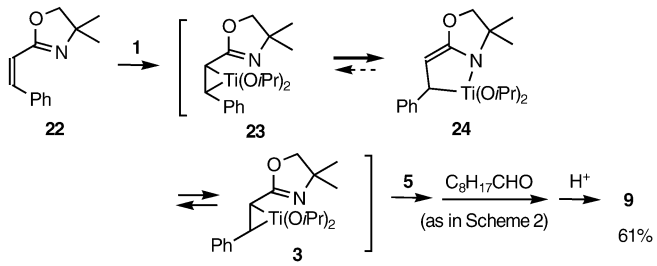
afforded the adduct **9** in good yield. In place of the simple hydrolysis, deuteriolysis or iodinolysis of the remaining vinyl–titanium bond in the intermediate **7** ($R = SiMe_3$) gave deuterium-labeled and iodinated products **10** and **11**, respectively. Thus, the four-component coupling of the unsaturated oxazoline, acetylene, aldehyde, and an electrophile proceeded in one pot with nearly complete regio-, olefinic stereo-, and diastereoselectivities to give an acyclic carbon chain of the defined structure.[9] This and the following transformations were made possible by the collaboration of the aforementioned feature of oxazolines and the behavior of the olefin–metal complex.

More results regarding the transformation of Scheme 2 are summarized in Table 1. The combination of oxazoline **2**, acetylene **4** or **5**, and a variety of aldehydes always showed high diastereoselectivities (entries 1–6). The structure of product **18** (entry 6) was also confirmed by X-ray crystallographic analysis.[7,10] The aryl-substituted vinyloxazolines **12** and **13** also participated in the reaction (entries 7 and 8). Entry 9 illustrates the diastereoselective preparation of functionalized allylsilane **21**[11] from (silylvinyl)oxazoline **14**.[12]

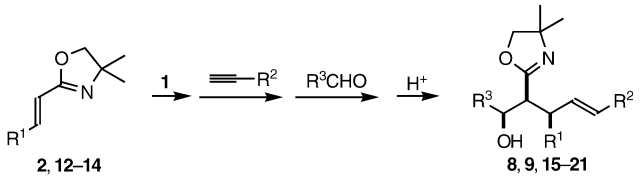
While all reactions described above started with *E*-alkenyloxazolines, *Z*-alkenyloxazolines such as **22**[13] in Scheme 3 gave the same product **9** previously obtained from the *E*-oxazoline **2** (see Scheme 2). Rapid isomerization of the initially formed olefin complex **23** to less sterically congested **3** via the azatitanacyclopentene **24** should account for this phenomenon. The *E*-olefinic oxazolines are more readily available than the *Z* isomers, and hence the former are, synthetically, the substrates of choice.



Scheme 3. Stereochemistry of the starting alkenyloxazoline.

Oxazoline is a potential chiral auxiliary,[1] so we next pursued the possibility of an asymmetric coupling reaction between the oxazoline–titanium complex and acetylene (Table 2). Oxazolines **25**–**27**[4] ($R = Et$, *t*Bu, and *i*Pr groups, respectively) were used in the reaction (entries 1–3) to evaluate the chiral induction by the oxazoline substituent R. Of these substrates, oxazoline **27** ($R = iPr$) prepared from (*S*)-valinol showed the most satisfactory result (entry 3). High chiral induction of 92:8–96:4 was uniformly observed with the valinol-derived oxazolines **27**–**30** to give coupling products **34**–**38** in good yields (entries 4–8).[14] The stereochemistry of the products **31** and **33** was unambiguously determined as depicted by derivatization to a known compound.[7] Optically active allylsilane **38**[11] was easily prepared

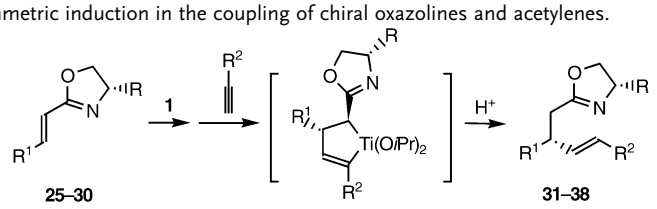
Table 1: Diastereoselective coupling reaction of oxazolines, acetylenes, and aldehydes according to Scheme 2.



Entry	Oxazoline		Acetylene		Aldehyde		Product	
	R^1		R^2		R^3		Yield [%][a]	d.r.[b]
1	Ph	**2**	C_6H_{13}	**4**	C_8H_{17}	**8**	66	96:4
2	Ph	**2**	C_6H_{13}	**4**	(*E*)-$C_5H_{11}CH{=}CH-$	**15**	54	88:12
3	Ph	**2**	C_6H_{13}	**4**	Ph	**16**	68	92:8
4	Ph	**2**	$SiMe_3$	**5**	C_8H_{17}	**9**	73	93:7
5	Ph	**2**	$SiMe_3$	**5**	*i*Pr	**17**	72	90:10
6	Ph	**2**	$SiMe_3$	**5**	Ph	**18**	70	95:5
7	*p*-ClC_6H_4	**12**	$SiMe_3$	**5**	C_8H_{17}	**20**	62	96:4
8	1-$C_{10}H_7$[c]	**13**	$SiMe_3$	**5**	C_8H_{17}	**21**	60	95:5
9	$SiMe_3$	**14**	$SiMe_3$	**5**	C_8H_{17}	**8**	48	89:11

[a] Yield of the isolated pure major isomer after chromatographic separation on silica gel. [b] Diastereoselectivity of a crude sample. Two stereoisomers were detected in the crude reaction mixture. [c] 1-Naphthyl.

Table 2: Asymmetric induction in the coupling of chiral oxazolines and acetylenes.

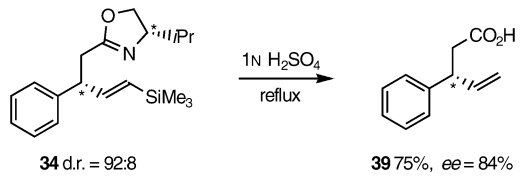


Entry		Oxazoline			Acetylene			Product	
	R	R^1			R^2			Yield [%][a]	d.r.[b]
1	Et	Ph	**25**		C_6H_{13}	**4**	**31**	65	75:25[b,c]
2	*t*Bu	Ph	**26**		C_6H_{13}	**4**	**32**	52	92:8[d]
3	*i*Pr	Ph	**27**		C_6H_{13}	**4**	**33**	72	93:7[b]
4	*i*Pr	Ph	**27**		$SiMe_3$	**5**	**34**	73	92:8[b,d]
5	*i*Pr	*p*-ClC_6H_4	**28**		C_6H_{13}	**4**	**35**	67	96:4[d]
6	*i*Pr	*p*-ClC_6H_4	**28**		$SiMe_3$	**5**	**36**	74	94:6[d]
7	*i*Pr	1-$C_{10}H_7$[e]	**29**		$SiMe_3$	**5**	**37**	54	95:5[d]
8	*i*Pr	$SiMe_3$	**30**		$SiMe_3$	**5**	**38**	63	95:5[d]

[a] Yield of isolated product. [b] Enantioselectivity of the carboxylic acid produced after hydrolysis of the oxazoline. [c] In practice, the antipode of **25** was used. [d] Diastereoselectivity of a crude sample. [e] 1-Naphthyl.

from (silylvinyl)oxazoline **30** with a high chiral induction (entry 8).

The oxazoline moiety of the above products should be useful for further transformations.[1] For example, hydrolysis of **34** with dilute aqueous acid effected concomitant desilylation (Scheme 4) to give a 3-aryl-4-pentenoic acid **39**, which is a known precursor for the synthesis of neurokinin receptor antagonists.[15]



34 d.r. = 92:8 **39** 75%, *ee* = 84%

Scheme 4. Synthetic application.

In conclusion, the novel alkenyloxazoline–titanium complexes proved to be a versatile template for diastereoselective and asymmetric coupling reactions. Further investigation on the utility of these functionalized olefin–titanium complexes and the synthetic application of the products obtained here is in progress.

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Keywords: asymmetric synthesis · C-C coupling · diastereoselectivity · metallacycles · oxazolines

[1] For reviews, see: a) K. A. Lutomski, A. I. Meyers in *Asymmetric Synthesis*, *Vol. 3*, *Part B* (Ed.: J. D. Morrison), Academic, Orlando, **1984**, pp. 213–274; b) T. G. Gant, A. I. Meyers, *Tetrahedron* **1994**, *50*, 2297–2360; c) A. I. Meyers, *J. Heterocycl. Chem.* **1998**, *35*, 991–1002.

[2] Aryloxazoline–transition metal complexes have found useful applications; see ref. [1b] and A. R. Pape, K. P. Kaliappan, E. P. Kündig, *Chem. Rev.* **2000**, *100*, 2917–2940.

[3] The olefin complex could be depicted by a few limiting structures involving **24**, but all of these are represented by the general form of the metallacyclopropane shown in Scheme 1.

[4] For their preparation, see: M. C. Elliott, E. Kruiswijk, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3157–3166.

[5] F. Sato, H. Urabe in *Titanium and Zirconium in Organic Synthesis* (Ed.: I. Marek), Wiley-VCH, Weinheim, **2002**, pp. 319–354; F. Sato, S. Okamoto, *Adv. Synth. Catal.* **2001**, *343*, 759–784; J. J. Eisch, *J. Organomet. Chem.* **2001**, *617–*618, 148–157; F. Sato, H. Urabe, S. Okamoto, *Chem. Rev.* **2000**, *100*, 2835–2886; O. G. Kulinkovich, A. de Meijere, *Chem. Rev.* **2000**, *100*, 2789–2834.

[6] For reviews on olefin complexes of Group 4 metals, see: ref. [5]; E. Negishi, T. Takahashi, *Acc. Chem. Res.* **1994**, *27*, 124–130; E. Negishi in *Comprehensive Organic Synthesis*, *Vol. 5* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 1163–1184; and S. L. Buchwald, R. B. Nielsen, *Chem. Rev.* **1988**, *88*, 1047–1058.

[7] For details, see the Supporting Information.

[8] The stereochemistry of the minor isomer has not been determined.

[9] Multicomponent coupling of the ethylene—Group 4 metal complex, acetylene, and aldehyde (or ketone) was reported: B. H. Lipshutz, M. Segi, *Tetrahedron* **1995**, *51*, 4407–4420; C. Copéret, E. Negishi, Z. Xi, T. Takahashi, *Tetrahedron Lett.* **1994**, *35*, 695–698; C. Zhao, T. Yu, Z. Xi, *Chem. Commun.* **2002**, 142–143; M. G. Thorn, J. E. Hill, S. A. Waratuke, E. S. Johnson, P. E. Fanwick, I. P. Rothwell, *J. Am. Chem. Soc.* **1997**, *119*, 8630–8641. However, in these cases, the notion of diastereoselective synthesis is not applicable. In contrast, (*internal* olefin)–metal complexes could be used for diastereoselective transformations as described in the text, but their generation and the subsequent reactions appear to be retarded because of the enhanced steric hindrance around the olefin portion. Indeed, few examples of their generation and monoaddition to ketones were reported, and the double addition has not been achieved: D. Enders, M. Kroll, G. Raabe, J. Runsink, *Angew. Chem.* **1998**, *110*, 1770–1773; *Angew. Chem. Int. Ed.* **1998**, *37*, 1673–1675; J. Scholz, S. Kahlert, H. Görls, *Organometallics* **1998**, *17*, 2876–2884; J. Scholz, M. Nolte, C. Krüger, *Chem. Ber.* **1993**, *126*, 803–809. See also: B. H. Edwards, R. D. Rogers, D. J. Sikora, J. L. Atwood, M. D. Rausch, *J. Am. Chem. Soc.* **1983**, *105*, 416–426; J. M. Davis, R. J. Whitby, A. Jaxa-Chamiec, *J. Chem. Soc. Chem. Commun.* **1991**, 1743–1745; S. Kahlert, H. Görls, J. Scholz, *Angew. Chem.* **1998**, *110*, 1958–1962; *Angew. Chem. Int. Ed.* **1998**, *37*, 1857–1861.

[10] CCDC-218515 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[11] For reviews, see: T. K. Sarkar in *Science of Synthesis*, *Vol. 4*, *Organometallic Compounds of As*, *Sb*, *Bi and Si* (Ed.: I. Fleming), Georg Thieme, Stuttgart, **2002**, pp. 837–925; I. Fleming, A. Barbero, D. Walter, *Chem. Rev.* **1997**, *97*, 2063–2192; T. K. Sarkar, *Synthesis* **1990**, 969–983; T. K. Sarkar, *Synthesis* **1990**, 1101–1111.

[12] When the aryl or silyl substituent of vinyloxazolines is replaced with an alkyl group, the desired coupling product was not formed. For silicon-assisted stabilization of olefin–titanium alkoxide complexes, see R. Mizojiri, H. Urabe, F. Sato, *Tetrahedron Lett.* **1999**, *40*, 2557–2560; R. Mizojiri, H. Urabe, F. Sato, *J. Org. Chem.* **2000**, *65*, 6217–6222.

[13] The pure *Z* isomer was prepared by the treatment of the (phenylethynyl)oxazoline with **1** followed by hydrolysis. The generation and utility of the intermediate alkynyloxazoline–titanium alkoxide complex will be reported in due course.

[14] The further addition of benzaldehyde to the intermediate titanacyclopentene generated according to entry 4 in Table 2 afforded most likely an 82:13:5 mixture of three isomeric products in 67% yield, which nearly appears to be the sum of the observations of Tables 1 and 2.

[15] N.-Y. Shih, M. Albanese, J. C. Anthes, N. I. Carruthers, C. A. Grice, L. Lin, P. Mangiaracina, G. A. Reichard, J. Schwerdt, V. Seidl, S.-C. Wong, J. J. Piwinski, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 141–145.

