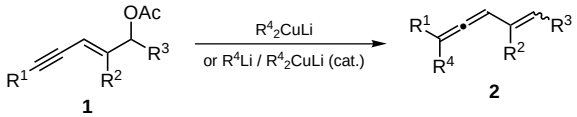
"Remote Stereocontrol" in Organocopper Chemistry: Highly Enantioselective Synthesis of Vinylallenes by 1,5-Substitution of Enyne Acetates**

Norbert Krause* and Martin Purpura

Dedicated to Professor Henning Hopf on the occasion of his 60th birthday

Vinylallenes, as a special class of allenes, are highly interesting substrates, for example in Diels–Alder reactions, because of their high reactivity and stereoselectivity.[1, 2] In contrast to ordinary 1,3-dienes, they can transfer their inherent axial chirality with high stereoselectivity to the new stereogenic centers formed during the cycloaddition;[3, 4] furthermore, due to the more favorable equilibrium between the s-*trans* and the s-*cis* conformer, they are also more reactive.[3, 5] Particularly with regard to the chirality transfer, the enantioselective synthesis of substituted vinylallenes if of high current interest.

Recently, we reported a new synthesis of vinylallenes by 1,5-(S_N'')-substitution of enyne acetates (**1**) and oxiranes with organocuprates.[6] Irrespective of the substitution pattern, these substrates react regioselectively at the triple bond. Normally, the vinylallenes **2** were formed as a mixture of the *E*/*Z* isomers; in some cases, however, one geometric isomer was obtained exclusively.



In order to study the enantioselectivity of copper-promoted 1,5-substitutions, the enyne acetates **1** were required in enantiomerically enriched or pure form. We obtained these with enantiomeric excesses of 92–99% *ee*[7] by lipase-catalyzed kinetic resolution of the racemic acetates and subsequent acylation of the alcohols (*R*)-**3** (Table 1). The absolute configuration of enyne acetate (*S*)-**1a** ($R^1 = R^3 = Me$, $R^2 = H$) was determined by correlation with mit (*S*)-ethyl lactate.[8]

The first experiments with (*R*)-**1a** (96% *ee*) were unsatisfactory. Reaction with the cyano-Gilman reagent $tBu_2CuLi \cdot LiCN$ at $-80\,^{\circ}C$ furnished vinylallene **2a** as a 25:75 mixture of the *E*/*Z* isomers with enantiomeric excesses of 8 and 68%, respectively; these could be improved slightly to 20 and 74% *ee* by lowering the reaction temperature to $-90\,^{\circ}C$. (Table 2, entries 1, 2).[6] A possible reason for these insufficient enantioselectivities is a racemization of the vinylallene by the cuprate or other reactive copper species formed in the reaction mixture. Such racemizations (which probably occur via one-electron transfer steps) have already been observed several times in copper-promoted S_N2'-substitutions of propargyl electrophiles.[9] According to Alexakis,[9a] it is possible to improve the enantioselectivity of these transformations considerably by addition of trialkylphosphanes; apparently, these ligands modify the copper intermediates which are responsible for the racemization. As a matter of fact, the reaction of (*R*)-**1a** with two equivalents of $tBu_2CuLi \cdot LiCN$ at $-80\,^{\circ}C$ in the presence of four equivalents of nBu_3P provided the vinylallene **2a** with high enantiomeric excesses of 92% *ee* for the *E* isomer and 93% *ee* for the *Z* isomer (Table 2, entry 3). Consequently, the 1,5-substitution of chiral enyne acetates is one of the few examples of efficient "remote stereocontrol" in organocopper chemistry.[10]

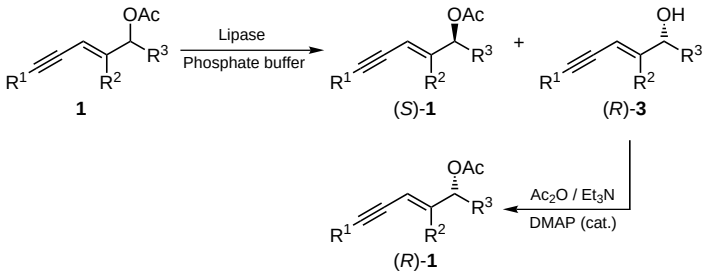


Table 1. Preparation of nonracemic enyne acetates **1** by lipase-catalyzed kinetic resolution.

Acetate	R^1	R^2	R^3	Lipase	(*S*)-**1**		(*R*)-**1**	
					Yield [%]	*ee* [%]	Yield [%]	*ee* [%]
1a	Me	H	Me	*Ps. fluorescens*	53	94	37	96
1b	*n*Bu	H	Me	*Ps. fluorescens*	48	98	39	94
1c	Ph	H	Me	*Ps. cepacia*	51	99	42	92
1d	Me_3Si	H	Me	*Ps. fluorescens*	51	99	43	99
1e	*n*Bu	-$(CH_2)_4$-		*Ps. fluorescens*	51	98	47	99

Further examples examined by us impressively prove the general applicability of this method. Thus, the moderate stereoselectivities found in the reaction of the *n*-butyl-substituted enyne acetate (*S*)-**1b** with lithium di-*tert*-butylcyanocuprate were again raised to high values of 94 (*E* isomer) and 96% *ee* (*Z* isomer) by addition of nBu_3P (Table 2, entries 4–6). The same holds for the 1,5-substitution of the aromatic substrate (*S*)-**1c** (92/95% *ee*; Table 2, entry 7, 8). Moreover, the method is not limited to the *tert*-butyl cuprate, as is demonstrated by the reaction of (*R*)-**1d** with $nBu_2CuLi \cdot LiCN$ in the presence of tri-*n*-butylphosphane (99/99% *ee*; Table 2, entry 9, 10). The transformations of the cyclic enyne acetate (*S*)-**1e** with the methyl cuprates $Me_2CuLi \cdot LiX$ (X = CN, I) revealed that the enantioselectivity of the 1,5-substitution is hardly affected by the copper salt used for the preparation of the cuprate (76 and 74% *ee*; Table 2, entry 11, 12); again, addition of the ligand nBu_3P caused a pronounced improvement of the stereoselectivity to 95% *ee* (Table 2, entry 13). In contrast to this, addition of the phosphane led to a decrease of the selectivity from 72 to 46% *ee* in the reaction of (*S*)-**1e** with $tBu_2CuLi \cdot LiCN$ (Table 2, entry 14, 15). This surprising effect could not be explained rationally, but it is of no practical relevance since a

[*] Prof. Dr. N. Krause, Dr. M. Purpura
Lehrstuhl für Organische Chemie II der Universität
44221 Dortmund (Germany)
Fax: (+49) 231-755-3884
E-mail: nkrause@pop.uni-dortmund.de

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Table 2. Synthesis of nonracemic vinylallenes **2** by 1,5-substitution of enyne acetates **1** with organocuprates.

Entry	Acetate	Cuprate	T [°C]	Additive	Product	R^1	R^2	R^3	R^4	E:Z	$ee(E)$ [%]	$ee(Z)$ [%]
1	(*R*)-**1a**	tBu$_2$CuLi · LiCN	−80	—	**2a**	Me	H	Me	tBu	25:75	8	68
2	(*R*)-**1a**	tBu$_2$CuLi · LiCN	−90	—	**2a**	Me	H	Me	tBu	25:75	20	74
3	(*R*)-**1a**	tBu$_2$CuLi · LiCN	−80	nBu$_3$P	**2a**	Me	H	Me	tBu	25:75	**92**	**93**
4	(*S*)-**1b**	tBu$_2$CuLi · LiCN	−80	—	**2b**	nBu	H	Me	tBu	33:67	6	72
5	(*S*)-**1b**	tBu$_2$CuLi · LiCN	−90	—	**2b**	nBu	H	Me	tBu	33:67	36	86
6	(*S*)-**1b**	tBu$_2$CuLi · LiCN	−80	nBu$_3$P	**2b**	nBu	H	Me	tBu	33:67	**94**	**96**
7	(*S*)-**1c**	tBu$_2$CuLi · LiCN	−80	—	**2c**	Ph	H	Me	tBu	40:60	74	95
8	(*S*)-**1c**	tBu$_2$CuLi · LiCN	−80	nBu$_3$P	**2c**	Ph	H	Me	tBu	40:60	**92**	**95**
9	(*R*)-**1d**	nBu$_2$CuLi · LiCN	−80	—	**2d**	Me$_3$Si	H	Me	nBu	60:40	8	28
10	(*R*)-**1d**	nBu$_2$CuLi · LiCN	−80	nBu$_3$P	**2d**	Me$_3$Si	H	Me	nBu	60:40	**99**	**99**
11	(*S*)-**1e**	Me$_2$CuLi · LiCN	−80	—	**2e**	nBu	-(CH$_2$)$_4$-		Me	—	76	
12	(*S*)-**1e**	Me$_2$CuLi · LiI	−80	—	**2e**	nBu	-(CH$_2$)$_4$-		Me	—	74	
13	(*S*)-**1e**	Me$_2$CuLi · LiI	−80	nBu$_3$P	**2e**	nBu	-(CH$_2$)$_4$-		Me	—	**95**	
14	(*S*)-**1e**	tBu$_2$CuLi · LiCN	−80	—	**2f**	nBu	-(CH$_2$)$_4$-		tBu	—	72	
15	(*S*)-**1e**	tBu$_2$CuLi · LiCN	−80	nBu$_3$P	**2f**	nBu	-(CH$_2$)$_4$-		tBu	—	46	
16	(*R*)-**1e**	tBu$_2$CuLi · LiCN	−80	(EtO)$_3$P	**2f**	nBu	-(CH$_2$)$_4$-		tBu	—	**91**	

value of 91% *ee* could be obtained in this case by addition of triethylphosphite.

We have already demonstrated that the 1,5-substitution can also be achieved efficiently with catalytic amounts of copper salts.[6] These reaction conditions could also be applied to chiral, nonracemic substrates without problems. For example, slow addition of one equivalent of (*R*)-**1b** (94% *ee*) and one equivalent of *t*BuLi to 10 mol% of tBu$_2$CuLi · LiCN · 2nBu$_3$P at −50 °C gave vinylallene **2b** as a 33:67 *E*/*Z* mixture with 90% *ee* for both isomers (80% chemical yield). Thus, also this catalytic reaction takes place with efficient "remote stereocontrol". We are currently examining the absolute configuration of the vinylallenes formed in enantioselective 1,5-substitutions and their application in organic synthesis.

Experimental Section

(EtO)$_3$P (2.0 g, 12.0 mmol) was added to a suspension of CuCN (537 mg, 6.0 mmol) in diethyl ether (30 mL) at 0 °C, and the mixture was allowed to warm to room temperature. After complete dissolution of the copper salt, the solution was cooled to −30 °C, and *t*BuLi (7.1 mL of a 1.7 M solution in pentane) was added dropwise. The cuprate solution was stirred for 15 min at −30 °C, then cooled to −80 °C, and (*R*)-**1e** (703 mg, 3.0 mmol; 99% *ee*) in diethyl ether (30 mL) was added dropwise. After the mixture had been stirred for 1 h at −80 °C, saturated NH_4Cl solution (15 mL) was added and the mixture was filtered through Celite. In order to remove the phosphite, the filtrate was washed several times with 1N sulfuric acid and then dried with $MgSO_4$. Removal of the solvent by distillation in vacuum and chromatography with silica gel (cyclohexane) furnished vinylallene **2f** (577 mg; 80%) with $[\alpha]_D^{20} = +26$ ($c = 0.1$, Et_2O). An enantiomeric excess of 91% *ee* was determined by gas chromatography with octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin.

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[1] a) *The Chemistry of Ketenes, Allenes and Related Compounds* (Ed.: S. Patai), Wiley, New York, **1980**; b) H. Hopf in *The Chemistry of the Allenes* (Ed.: S. R. Landor), Academic Press, London, **1982**, pp. 563–577; c) H. F. Schuster, G. M. Coppola, *Allenes in Organic Synthesis*, Wiley, New York, **1984**.

[2] a) J. Kleinschroth, H. Hopf, *Angew. Chem.* **1982**, *94*, 485–496; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 469–480; b) H. Siegel, H. Hopf, A. Germer, P. Binger, *Chem. Ber.* **1978**, *111*, 3112–3118; c) H. Bross, R. Schneider, H. Hopf, *Tetrahedron Lett.* **1979**, 2129–2132; d) G. Schön, H. Hopf, *Liebigs Ann. Chem.* **1981**, 165–180; e) R. Schneider, H. Siegel, H. Hopf, *Liebigs Ann. Chem.* **1981**, 1812–1825.

[3] Intermolecular Diels–Alder reactions: a) H. J. Reich, E. K. Eisenhart, W. L. Whipple, M. J. Kelly, *J. Am. Chem. Soc.* **1988**, *110*, 6432–6442; b) U. Koop, G. Handke, N. Krause, *Liebigs Ann.* **1996**, 1487–1499.

[4] Intramolecular Diels–Alder reactions: a) R. A. Gibbs, K. Bartels, R. W. K. Lee, W. H. Okamura, *J. Am. Chem. Soc.* **1989**, *111*, 3717–3725; b) N. Krause, *Liebigs Ann. Chem.* **1993**, 521–525.

[5] D. Bond, *J. Org. Chem.* **1990**, *55*, 661–665.

[6] M. Purpura, N. Krause, *Eur. J. Org. Chem.* **1999**, 267–275.

[7] The enantiomeric excesses were determined by gas chromatography with octakis(2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin.

[8] Wittig reaction of (*S*)-2-trimethylsilyloxypropanal (obtained from (*S*)-ethyl lactate) with 2-butyn-1-yl-triphenylphosphorane, desilylation and acylation gave (*S*)-2-acetoxy-3-hepten-5-yne as a 2:1 *E*/*Z* mixture; the *E* isomer was identical with the less reactive enantiomer in the kinetic resolution of **1a** with the lipase from *Pseudomonas fluorescens*. In all cases, the less reactive enantiomer of the enyne acetates **1a–e** is levorotatory ($[\alpha]_D^{20} = -159$ to -211 ($c = 0.1$, Et_2O)).

[9] a) Review: A. Alexakis, *Pure Appl. Chem.* **1992**, *64*, 387–392; b) A. Claesson, L. I. Olsson, *J. Chem. Soc. Chem. Commun.* **1979**, 524–525; c) C. J. Elsevier, P. Vermeer, *J. Org. Chem.* **1989**, *54*, 3726–3730; d) A. Alexakis, P. Mangeney, A. Ghribi, I. Marek, R. Sedrani, C. Guir, J. F. Normant, *Pure Appl. Chem.* **1988**, *60*, 49–56; e) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *J. Am. Chem. Soc.* **1990**, *112*, 8042–8047.

[10] Here, the term "remote stereocontrol" applies only to the enantioselectivity and not to the *E*/*Z* selectivity. Previous examples for "remote stereocontrol" in organocopper chemistry: a) S. E. Denmark, L. K. Marble, *J. Org. Chem.* **1990**, *55*, 1984–1986; b) H. Rakotoarisoa, R. G. Perez, P. Mangeney, A. Alexakis, *Organometallics* **1996**, *8*, 1957–1959; c) L. F. Captain, X. Xia, D. C. Liotta, *Tetrahedron Lett.* **1996**, 37, 4293–4296; d) V. Caló, A. Nacci, V. Fiandanese, *Tetrahedron* **1996**, *52*, 10799–10810; e) B. Breit, *Angew. Chem.* **1998**, *110*, 535–538; *Angew. Chem. Int. Ed.* **1998**, 37, 525–527.

  1433-7851/00/3923-4356 $ 17.50+.50/0