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Supplementary Material Available: Tables of crystal data, data collection, data reduction, refinement details, positional and thermal parameters, and bond distances and angles for the crystal structures of $C_{14}H_{16}O_3Mo$ (**25**) and $C_{16}H_{20}O_3Mo$ (**31b**) and thermal ellipsoid plot of the *Z* enantiomer of $C_{14}H_{16}O_3Mo$ (22 pages). Ordering information is given on any current masthead page.

Mechanistic Aspects on the Formation of Chiral Allenes from Propargylic Ethers and Organocopper Reagents

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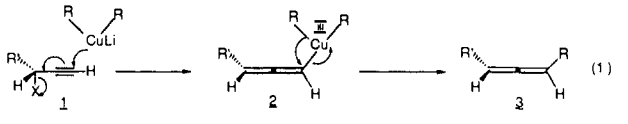
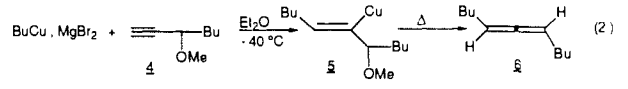
Abstract: Propargylic ethers react with organocopper reagents to afford allenes by a syn addition to the triple bond followed by a β-elimination of the resulting alkenyl copper species. With use of chiral propargylic ethers and stoichiometric organocopper reagent, it was shown that the β-elimination step is purely anti, resulting in the formation of a chiral allene with 96% optical yield. The same reaction, run with a Grignard reagent RMgX and a catalytic amount of a Cu^I salt, affords allenes through an anti or syn overall process. The crucial step is the β-elimination of the intermediate alkenyl organometallic species, which is of anti type with RMgI and of syn type with RMgCl. Propargylic acetates, which also afford allenes in this reaction, but through a Cu^{III} intermediate, are not sensitive to this "halogen effect".

Introduction

One of the most popular methods for the synthesis of allenes is the reaction of propargylic derivatives with organocopper reagents.[1] Since the first report by Crabbé et al.,[2] many authors have used modified organocopper reagents, with stoichiometric or catalytic amounts of Cu^I salt. The propargylic substrate itself varies from ethers and epoxides to various esters of more or less reactivity. The question of the mechanism and of the stereochemistry of this substitution reaction arose quickly, and chiral propargylic esters of type **1** were used to produce chiral allenes of type **3**. It is presently believed that these reactions proceed through a Cu^{III} intermediate **2** resulting from an anti S_N2' nucleophilic attack of the Cu^I atom.[3] This intermediate collapses by reductive elimination to allene **3** with *retention* of configuration. The overall result is an ANTI process (eq 1). During our work

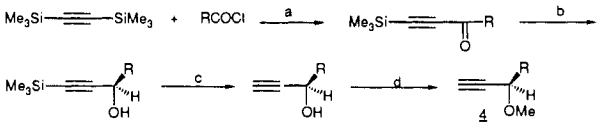


on the carbocupration of alkynes,[4] we had the opportunity to demonstrate that the formation of allene **6** from propargylic *ether* **4** follows a different path[5] (eq 2). A syn addition takes place,



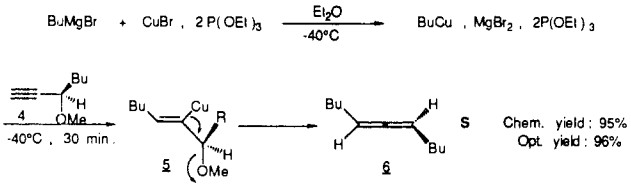
first, producing an alkenyl copper reagent **5**, which can be trapped with various electrophiles. Upon warming, **5** undergoes a β-elimination, leading to allene **6**. The nature of this β-elimination was, at that time, unknown, and the aim of this article is to report our recent results in this field.[6]

Scheme I



a) $AlCl_3$, CH_2Cl_2 ; b) $LiAlH_4$ / Darvon alcohol ; c) KF, DMF d) NaH, MeI / THF

Scheme II



Such a study requires optically active propargylic ethers, which were prepared from the corresponding alcohols by a nonracemizing etherification procedure.[7] The needed alcohols were prepared by enantioselective reduction[8] of ynones, according to the sequence in Scheme I. Many methods exist for the enantioselective reduction of ynones, but high levels of induction are obtained only with costly reagents or/and tedious preparation of chiral auxiliaries.[9] For a mechanistic study, propargylic ethers of moderate ee are acceptable, provided they can be prepared in bulk. This is the case with the $LiAlH_4$/Darvon alcohol procedure.[8b] The enantiomeric excesses range from 37% to 58%.

(1) (a) Landor, S. R. *The Chemistry of the allenes*; Academic Press: New York, 1982. (b) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Chemistry*; Wiley: New York, 1984.
(2) Rona, P.; Crabbe, P. *J. Am. Chem. Soc.* **1968**, *90*, 4733.
(3) Dollat, J. M.; Luche, J. L.; Crabbe, P. *J. Chem. Soc., Chem. Commun.* **1977**, 761.
(4) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.
(5) Alexakis, A.; Normant, J. F.; Villieras, J. *J. Mol. Catal.* **1975/76**, *1*, 43.
(6) For a preliminary account of this work see: Marek, I.; Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 5499.
(7) Barton, D.; Brown, C. A. *Synthesis* **1974**, 434.
(8) (a) Vigneron, J. P.; Bloy, V. *Tetrahedron Lett.* **1979**, *29*, 2683. (b) Brinckmeyer, R. S.; Kapoor, V. M. *J. Am. Chem. Soc.* **1977**, *99*, 8339.
(9) Grandbois, E. R.; Howard, S. I.; Morrison, J. D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, p 71.

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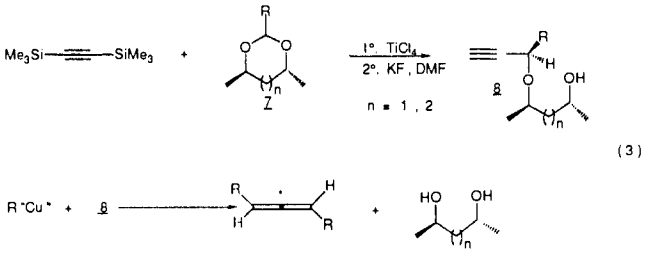
An alternative and more direct way to obtain chiral propargylic ethers was described by Johnson.[10] It has the advantage of avoiding the propargylic alcohol step. Ethers **8** are almost enantiomerically pure (95%). In addition, their use in the synthesis of allenes would allow the recovery of the chiral diol (eq 3). The last part of this paper is devoted to this approach.

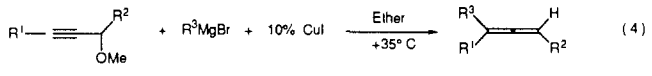


(3)

Results and Discussion

When chiral propargylic ether **4** of *R* configuration was reacted with $BuCu{\cdot}MgBr_2$ under the previously reported conditions, optically active dibutylallene **6** of *S* configuration was obtained (Scheme II). The optimum experimental conditions, for both the chemical and optical yield, involve the use of 2 equiv of $P(OEt)_3$ as ligand (its necessity will be discussed below). The absolute configuration of the starting ether and the final allene implies that the intermediate alkenyl–copper reagent **5**, obtained by a syn addition, undergoes an anti elimination. Thus the overall process (syn addition–anti elimination) is an anti S_N' displacement of the methoxy moiety.

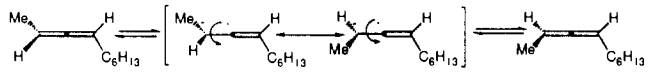
In 1976, Gaudemar reported that allenes can also be obtained by the reaction of propargylic ethers with Grignard reagents and catalytic amounts (10%) of Cu(I)[11] (eq 4). Since no alkenyl–metal intermediate could be quenched, it was not known whether this reaction proceeded through a Cu^{III} intermediate (as in eq 1), where the alkenyl–metal intermediate would be too unstable to be detected (eq 4). The same reaction was, later on, performed with



(4)

a chiral propargylic ether by Claesson.[12] A chiral allene was obtained albeit with a very low optical yield, 16%. The overall process was an anti S_N' displacement, and the exact mechanism could not be ascertained. As for the low optical yield, two explanations can be given: (1) an intrinsic low transfer of chirality due to a possible multiplicity of involved mechanisms or (2) a highly selective reaction with extensive racemization of the final allene.

This last explanation might be corroborated by the fact that allenes are racemized by organocopper and cuprate reagents[13a] or by Cu^0,[13b] which might arise from the decomposition of organocopper species. The postulated mechanism by Claesson involves a reversible single-electron-transfer process (eq 5). This

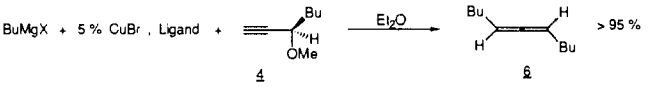


(5)

process is not very fast, but in a slow reaction it may predominate, leading to a racemized allene.

On the basis of the idea that a good ligand to copper could avoid the formation of Cu^0 by decomposition of the organocopper species, and therefore the racemization process, we undertook a systematic study of the catalytic reaction shown in eq 4 using complexed copper salts. The results are compiled in Table I. In contrast

Table I. Effect of the Ligands on the Anti Process.

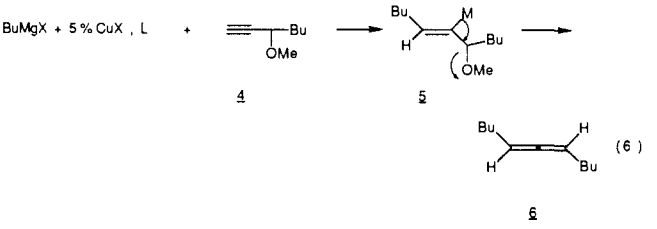


4 6

entry	X in RMgX	ligand	$[\alpha]^{25}_D$ [c]	optical yield, %
1	Br		+4° (1.50)	16[a]
2	Br	$2P(OEt)_3$	+11° (2.13)	43[a]
3	Br	$P(NMe_2)_3$	+18° (3.02)	55[b]
4	Br	$2P(NMe_2)_3$	+24° (4.01)	72[b]
5	Br	PBu_3	+26° (2.88)	80[b]
6	Br	$2PBu_3$	+30° (2.64)	90[b]
7	I	$2P(OEt)_3$	+20° (2.16)	80[a]
8	I	$2PBu_3$	+27° (0.68)	88[b]

[a] *R* propargylic ether of 37% enantiomeric purity. [b] *R* propargylic ether of 48% enantiomeric purity. [c] All rotations were taken in $CHCl_3$. The maximum reported rotation for dibutylallene is $[\alpha]^{25}_D$ 68° (ref 14).

to previous results, the reaction could be run at low temperature (instead of refluxing Et_2O). Starting at −40 °C, the stirred mixture was allowed to warm slowly to 0 °C and carefully followed by GC by hydrolyzing aliquots. We were, thus, able to detect an intermediate (up to 30% yield), which was characterized as the addition product **5** (eq 6). This alkenyl–metal intermediate

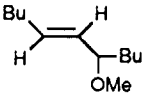


4 5

(6)

6

disappears in favor of the allene, which is obtained in quantitative yield. Thus, this catalytic reaction proceeds through an *addition–elimination* mechanism exactly as the stoichiometric one, and not through a Cu^{III} intermediate (Scheme II). Hydrolysis of the reaction mixture at an intermediate stage allows the isolation (in 30% yield) of the allylic ether



The coupling constant of the vinylic protons (J: 15.4 Hz) clearly corresponds to an *E* double bond, which indicates that the addition occurred by a syn mode.

The stereochemical results reported in Table I fulfill our expectations. In all these experiments an anti overall process is observed, corresponding to an anti mode of β-elimination in the intermediate alkenyl–metal species. Without any ligand a very low optical yield is obtained (entry 1). With increasingly strong ligand ($P(OEt)_3$, $P(NMe_2)_3$, PBu_3) the optical yield increases correspondingly (entries 2, 3, and 5), reaching 90% with 2 equiv of PBu_3 (entry 6).

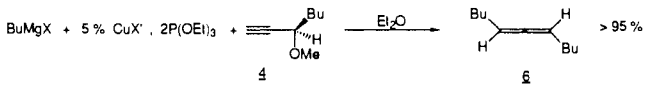
Thus, with an appropriate ligand, chiral propargylic ethers can afford optically active allenes in synthetically very good enantiomeric excesses.

Entry 7 points to another phenomenon that is the nature of the halogen in RMgX. Comparing entries 2 and 7, a higher value of optical yield is obtained with BuMgBr. We were, thus, led to study in more detail this effect, and the results were quite unexpected! It appears that X in RMgX plays a crucial role that not only affects the optical yield but also the sense of the overall process syn or anti. Table II summarizes these results (Table II).

As a general rule, with BuMgCl, a syn overall process is always obtained, whereas with BuMgI an anti process invariably occurs. With BuMgBr, the 5% of CuX′ can affect the selectivity from 41% syn (CuCN) to 43% anti (CuBr)! It should be recalled that, in organocopper chemistry, a *syn* substitution process is quite exceptional.[15] Moreover, from a synthetic point of view it is very

(10) Johnson, W. S.; Elliot, R.; Elliot, J. D. *J. Am. Chem. Soc.* **1983**, *105*, 2904.
(11) Moreau, J. L.; Gaudemar, M. *J. Organomet. Chem.* **1976**, *108*, 159.
(12) Claesson, A.; Olsson, L. I. *Acta Chem. Scand. Ser. B* **1979**, *33*, 679.
(13) (a) Claesson, A.; Olsson, L. I. *J. Chem. Soc., Chem. Commun.* **1979**, 524. (b) Chenser, J. H. B.; Howard, J. A.; Mile, B. *J. Am. Chem. Soc.* **1985**, *107*, 4190.
(14) Pirckle, W. H.; Boeder, C. W. *J. Org. Chem.* **1978**, *43*, 1950.

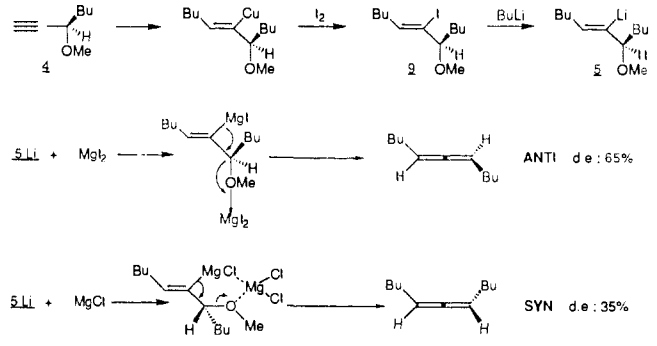
Table II. Effect of the Halogens on the Stereochemical Course of the Formation of **6**



entry	X in RMgX	CuX'	$[\alpha]^{25}_D$ [d]	optical yield, %	allene config	overall process
9	Cl	Cl	−13° (3.39)	33[c]	R	syn
10	Cl	CN	−16° (3.17)	49[c]	*R*	syn
11	Cl	I	−21° (3.3)	54[c]	*R*	syn
12	Cl	Br	−15° (3.5)	60[a]	*R*	syn
13	Br	CN	−13° (1.57)	41[b]	*R*	syn
14	Br	Cl	−7° (2.56)	22[b]	*R*	syn
15	Br	I	−5° (2.8)	13[c]	*R*	syn
16	Br	Br	+11° (2.13)	43[a]	S	anti
17	I	Cl	+20° (2.5)	51[c]	*S*	anti
18	I	CN	+23° (0.9)	58[c]	*S*	anti
19	I	I	+16° (3.1)	63[a]	*S*	anti
20	I	Br	+20° (2.16)	80[a]	*S*	anti
21	Bu_2Mg	Br	+2.5 (2.6)	10[a]	*S*	anti

[a] *R* propargylic ether of 37% enantiomeric purity. [b] *R* propargylic ether of 48% enantiomeric purity. [c] *R* propargylic ether of 58% enantiomeric purity. [d] All rotations were taken in $CHCl_3$. The maximum reported value for dibutylallene is $[\alpha]^{25}_D$ 68° (ref 14).

Scheme III



important to be able to change the stereochemical course of a reaction with the same substrate. From a mechanistic point of view it is harder to rationalize the above results.

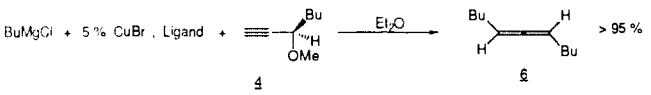
We have shown that these reactions proceed through an addition–elimination mechanism. We have checked that the addition is still syn. Therefore it is the type of β-elimination of the alkenyl–metal intermediate that determines the overall sterochemistry. Since we have at least 30% of this intermediate with only 5% CuX, it seems that this intermediate is mainly an alkenyl Grignard reagent. We were, thus, led to study the nature of the β-elimination of alkenyl Grignard reagents of type **5** in the absence of any copper salt. That was done in the following manner.

Carbocupration of the propargylic ether **4** followed by iodinolysis gave the alkenyl iodide **9**[5] in 70% yield. Metal–halogen exchange affords the alkenyllithium reagent **5Li**, from which it is possible to transmetalate to the Grignard reagent by addition of MgI_2 or $MgCl_2$, respectively. Although the optical yield is not very high, its sense clearly shows that an alkenylmagnesium iodide prefers an anti elimination whereas an alkenylmagnesium chloride favors a syn elimination. In a simplified view it may be admitted that the small size and the electronegativity of the chlorine atom allow a cyclic transition state where the greater Lewis acidity of $MgCl_2$[16] plays a role in favor of a syn elimination. On the other hand the size of the iodine atom does not allow such a cyclic arrangement and the elimination becomes predominantly anti (Scheme III).

(15) For the most notable exception see: (a) Gallina, C.; Ciattini, P. G. *J. Am. Chem. Soc.* **1979**, *101*, 1035. (b) Goering, H. L.; Kantner, S. S.; Tseng, C. C. *J. Org. Chem.* **1983**, *48*, 715.

(16) Lindsell, W. E. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon: New York, 1982; Vol. 1, p 155.

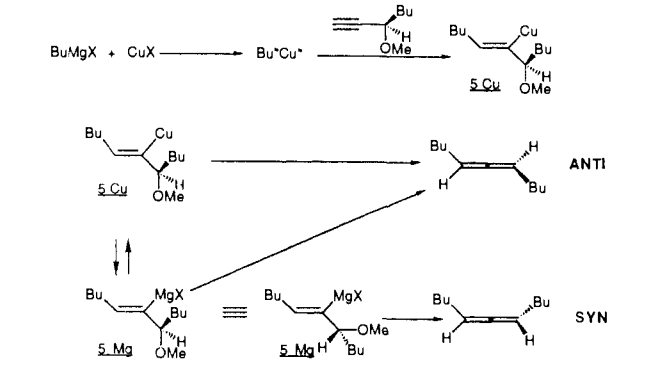
Table III. Effect of the Ligands or Additives on the Syn Process



entry	ligand	cosolvent or additive	$[\alpha]^{25}_D$ [d]	optical yield, %
22			−13° (3.44)	41[b]
23	$2PBu_3$		−8° (2.08)	24[b]
24	$2P(OEt)_3$		−15° (3.56)	60[a]
25	$2P(OEt)_3$	1 equiv of Me_3SiCl	−26° (2.43)	65[c]
26		1 equiv of Me_3SiCl	−26° (1.79)	66[c]
27		1 equiv of Me_3SiCl pentane/Et_2O 50/50	−27° (1.15)	76[b]

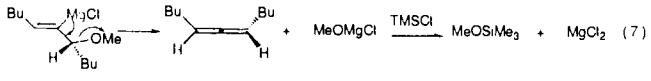
[a] *R* propargylic ether of 37% enantiomeric purity. [b] *R* propargylic ether of 48% enantiomeric purity. [c] *R* propargylic ether of 58% enantiomeric purity. [d] All rotations were taken in $CHCl_3$. The maximum reported value for dibutylallene is $[\alpha]^{25}_D$ 68° (ref 14).

Scheme IV



We have also checked the type of elimination of the vinyllithium reagent **5Li**. An anti elimination occurs in Et_2O (40% optical yield) as well as in THF (25% optical yield). Whatever the case, the synthetic interest of the syn process led us to try to improve its optical yield. The results are compiled in Table III. Without any ligand a 41% optical yield was obtained (entry 22). With $P(OEt)_3$ it raises to 60%. However, a stronger ligand such as PBu_3 does not improve it (entry 23). Thus the effect of PBu_3 was not, as we initially thought, to prevent the racemization of the formed allene; it intrinsically favors an anti elimination. On the other hand, the addition of 1 equiv of trimethylchlorosilane (TMSCl) was done by reference to Corey's work where TMSCl prevents the isomerization of *Z* enones by organocopper reagents.[17]

In fact, in our case the improved optical yield in the syn elimination may simply be due to an increased concentration of $MgCl_2$ generated in situ[29] and/or by the quenching of the alcoholate by TMSCl (eq 7). A last improvement (76% optical yield) was

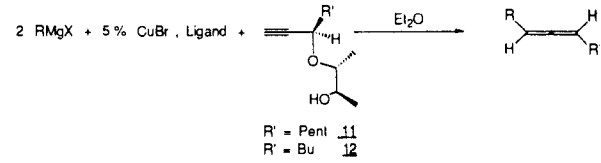


obtained when the reaction was conducted with pentane as cosolvent (entry 27). It was thus possible to attain synthetically interesting levels of stereoselection for both the anti and the syn processes, starting always with the same chiral propargylic ether.

Considering the various aspects of all the factors that affect the stereochemical course of this reaction, the following general explanation may account for all the above results. The Grignard reagent undergoes first a transmetalation to a copper species which adds to the triple bond of the propargylic ether leading to an alkenylcopper complex **5Cu** (Scheme IV). This copper intermediate **5Cu** may undergo a β-elimination which is of anti type as shown in the stoichiometric case (Scheme II). However, this intermediate **5Cu** must also transmetalate to an alkenyl Grignard species **5Mg** since at an intermediate stage of the reaction **5Cu**

(17) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015.

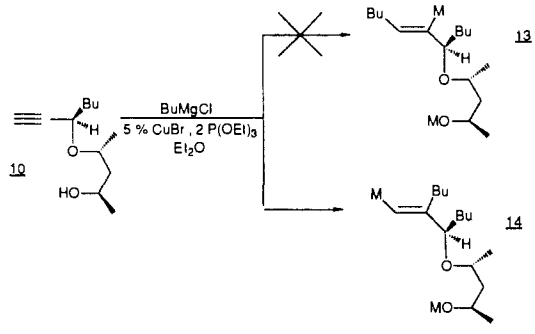
Table IV. Formation of Allenes from Propargylic Ethers **11** and **12**



entry	propargylic ether	RMgX	ligand	solvent	yield,[a] %	$[\alpha]^{25}_D$	optical yield,[b] %	allene config	overall process
28	**11**	PentMgCl	$2P(OEt)_3$	Et_2O	85	−37° (0.89)[c]	91	*R*	syn
29	**11**	PentMgBr	$2P(OEt)_3$	Et_2O	80	−24° (1.78)[c]	54	*R*	syn
30	**11**	PentMgBr	$2P(OEt)_3$	Et_2O/pentane 1/1	80	−39° (1.13)[c]	93	*R*	syn
31	**12**	BuMgBr	$2P(OEt)_3$	Et_2O	66	−56° (2.28)[d]	89	*R*	syn
32	**12**	EtMgBr	$2P(OEt)_3$	Et_2O	60	−52° (2.87)[e]	72	*R*	syn
33	**12**	$tBuO(CH_2)_4MgBr$	$2P(OEt)_3$	Et_2O	65	−24° (0.18)[f]	*f*	*R*	syn
34	**11**	tBuMgBr	$2P(OEt)_3$	Et_2O/pentane 1/1	60	+47° (0.46)[g]	64	*S*	anti
35	**11**	tBuMgBr	$2PBu_3$	Et_2O	62	+50° (0.85)[g]	67	*S*	anti
36	**11**	tBuMgBr	$2PBu_3$	Et_2O	65	+52° (0.91)[g]	70	*S*	anti

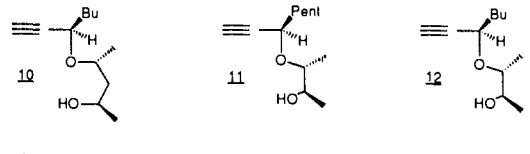
[a] Yield of isolated allene. [b] Based on the d.e. of propargylic ethers **11** and **12**: 92%. [c] Taken in CH_2Cl_2. Maximum reported value: $[\alpha]^{25}_D$ 47.7° (ref 19). [d] Taken in $CHCl_3$. Maximum reported value: $[\alpha]^{25}_D$ 68° (ref 14). [e] Taken in $CHCl_3$. Maximum reported value: $[\alpha]^{25}_D$ 80.3° (ref 14). [f] Taken in $CHCl_3$. The maximum $[\alpha]$ value is unknown. [g] Taken in CH_2Cl_2. The maximum reported value is $[\alpha]^{25}_D$ 80° (ref 19).

Scheme V



+ 5Mg amount to 30% of the reaction products with only 5% of Cu^I salt present. This was quite unexpected since transmetalation from a vinylcopper to vinyl grignard is highly contrathermodynamic. According to the nature of the halogen of the Grignard intermediate **5Mg** a syn or an anti β-elimination takes place. The rate of the exchanges **5Cu** → **5Mg** and the kinetics of the β-elimination (the irreversible step) of **5Cu** or **5Mg** determine the final proportion of the syn or the anti allene. We have already noted the accelerating effect of a good ligand in the β-elimination of the alkenyl–copper intermediate **5Cu**.[18] Thus a good ligand such as PBu_3 will favor the β-elimination of **5Cu** and therefore the anti process, rather than the transmetalation to **5Mg** which, with Cl as halogen, would favor the syn process.

Having established the best conditions for the obtention of *R* or *S* dibutylallene **6** starting from the same enantiomer of propargylic ether **4**, we applied these conditions to the almost enantiomerically pure ethers **10**, **11**, and **12**. However, compounds

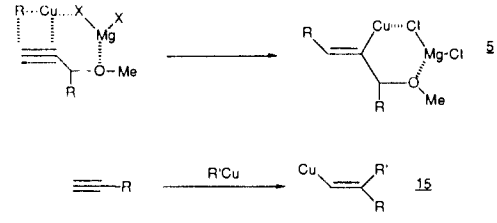


10, **11**, and **12** differ from 3-methoxy-1-heptyne (**4**) in that the ether functionality was linked to two substituted carbons and also in that they possess an additional alcohol functionality. Thus, with **10** the reaction underwent a completely different course: the carbocupration step took place with a reverse regioselectivity affording product **14** (Scheme V). The desired regioisomer **13**

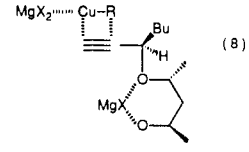
(18) Alexakis, A. Thèse de Doctorat d'Etat. Université P. et M. Curie, Paris, 1975.

(19) Mannschrek, P.; Munninger, W.; Burgemeister, T.; Gore, J.; Cazes, B. *Tetrahedron* **1986**, *42*, 399.

Scheme VI



and intermediate **5** (eq 6) are chelation-controlled regioisomers, whereas nonfunctionalized alkynes react to afford the Markovnikov regioisomer **15**[4] (Scheme VI). In propargylic ether **10** the two oxygens serve to chelate MgX_2 and a cyclic transition state, as stated above, could not be operative (eq 8). In contrast to **10**,

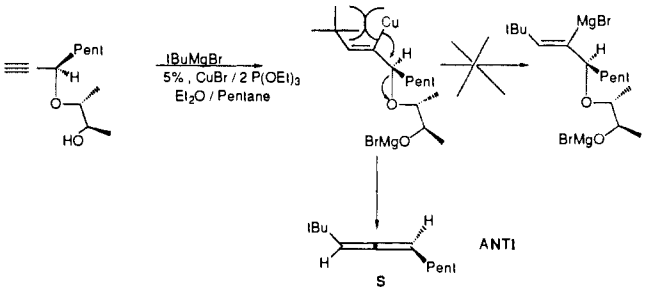


propargylic ether **11** and **12** react to afford mainly the desired allene. The Markovnikov regioisomer was found in only 10–35%. The results with various Grignard reagents are quoted in Table IV. In all these experiments, the reaction rate was slowed down, taking place only around −10 to 0 °C. Although the intermediate addition product could not be isolated, the presence of the undesired regioisomer is an indication that indeed an addition–elimination process is involved. The stereochemical course of the reaction with primary alkyl Grignard reagents (entries 28–33) shows that the syn process predominates, whatever the reaction conditions! Under the best conditions we were able to obtain dipentylallene in up to 93% optical yield (entry 30). In a similar manner with **12**, dibutylallene and butyl-*tert*-butoxybutylallene (entries 31, 32, and 33) were obtained. This last compound is unknown, and by analogy to the other results we ascribe to it the *R* configuration.

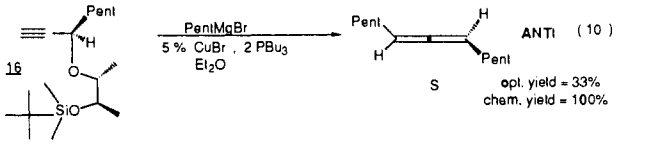
The predominance of the syn process may be due to the second oxygen of the substrate, which serves, now, to maintain a tight cyclic transition state (eq 9). The protection of the free alcohol

of **11** as a bulky silyl ether, in **16**, does not prevent completely the formation of such a cyclic complex. Even under the best anti conditions, only a moderate optical yield of "anti" allene was

Scheme VII



obtained (eq 10). In this case, however, the wrong regioisomer was not formed.

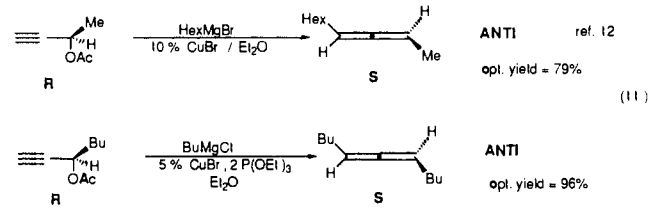


(10)

The reaction of propargylic ether **11** with tBuMgBr was surprising in this context. It steadily affords the allene arising from an anti process. It seems that the bulkiness of the tBu group destabilizes the intermediate adduct. This intermediate alkenylcopper eliminates through an anti process faster than it transmetalates to the alkenyl Grignard species (Scheme VII). It seems, thus, that with chiral propargylic ethers, such as **11** and **12**, it is possible, with primary Grignard reagents, to reach high syn selectivity. The best optical yield (93%) of the allene is the highest for a syn process (see Table IV, entry 30) and is of real synthetic value. Moreover the chiral auxiliary, viz (*R*,*R*)-pentanediol, can be recovered throughout the whole process (see eq 3).

Finally, it was interesting to study the behavior of propargylic acetates toward this "halogen effect" of the Grignard reagent. Propargylic acetates, as well as other propargylic substrates having a good leaving group, are known to afford allenes through a Cu^{III} intermediate[3] (eq 1) following an overall anti process. The reaction was also known to occur with a catalytic amount of Cu^{I} salt.[12]

We performed the same reaction under our best syn conditions, as they were determined for propargylic ethers. Due to the solubility of copper salt the reaction was exceedingly fast, the allene being formed at −70 °C (eq 11). The stereochemical result is



(11)

an unambiguous ANTI process with an excellent optical yield. Thus a reaction that proceeds through a Cu^{III} intermediate is always an anti substitution, whatever the halogen of the Grignard reagent RMgX. This different behavior of the two mechanisms (addition-elimination of Cu^{III} intermediate) can be used for the determination of the mechanism of other reactions in organocopper and organomagnesium chemistry.[12]

Conclusion

The formation of allenes from propargylic ethers is sensitive to many factors, of which the nature of the halogen of the Grignard reagent plays a key role. Depending on the kind of ether, variation from the basic scheme can affect the stereochemical course of the reaction by complexations of the intermediate alkenyl copper and the alkenyl Grignard reagent.

Nevertheless, these reactions are of synthetic value for the obtention, at will, of chiral allenes of either configuration starting from the same enantiomeric propargylic ether.

Experimental Section

Starting Materials. 3(*R*)-Methoxy-1-heptyne. To a suspension of NaH (50% in mineral oil, 8.16 g, 170 mmol) in THF (70 mL) were added, at 40 °C, MeI (5.93 mmol) and then dropwise 1-heptyn-3-ol (9.7 g, 86 mmol, $[\alpha]^{25}_D$ +15.15° (*c* = 1.66, Et_2O), ee 58%), prepared according to literature procedure,[20,22,23] in THF (30 mL). After 2 h at +50 °C, the reaction was completed. Saturated aqueous NH_4Cl (50 mL) was carefully added, at 0 °C, and then Et_2O (200 mL). The aqueous phase was extracted with Et_2O (2 × 50 mL) and the combined organic phases were dried over $MgSO_4$. The solvents were removed at atmospheric pressure and the residue distilled to afford 7.6 g (70% yield) of pure material: bp 135 °C (760 mm); $[\alpha]^{25}_D$ +55.4° (*c* = 3.39, Et_2O), ee 58%; IR 3300, 2110; ^1H NMR 4.0 (dt, 1 H, *J* = 7, 2.1 Hz), 3.5 (s, 3 H), 2.5 (d, 1 H, *J* = 2.1 Hz), 1.8–1.2 (m, 6 H), 1.0 (t, 3 H, *J* = 7.3 Hz); ^{13}C NMR 82.9, 74, 71, 56, 35.5, 27.6, 22.6, 14. Anal. Calcd for $C_8H_{14}O$: C, 79.97; H, 6.71. Found: C, 79.88; H, 6.81.

3(*R*)-Acetoxy-1-heptyne.[25] To 1(*R*)-heptyn-3-ol (3.8 g, 25 mmol, 28% ee) in pyridine (25 mL) was successively added (dimethylamino)-pyridine (DMAP) (300 mg, 2.5 mmol). After 2 h, at room temperature, the reaction was completed, and saturated aqueous NH_4Cl (20 mL) followed by 100 mL of Et_2O were added. The organic phase was washed with aqueous 1 N HCl (4 × 100 mL) and then dried over $MgSO_4$ and the solvents were removed in vacuo. The residue was chromatographed through SiO_2 (eluant: cyclohexane/Et_2O 70/30). Yield of pure acetate 94%; $[\alpha]^{25}_D$ +19.6° (*c* = 2.1, Et_2O), ee 28% (lit[25] +11.1° (*c* = 2.97, Et_2O), ee 16%); IR 3300, 2120, 1750; ^1H NMR 4.8 (dt, 1 H, *J* = 7.5, 2 Hz), 2.12 (s, 3 H), 2.08 (d, 1 H, *J* = 2 Hz), 2.0–1.1 (m, 6 H), 0.92 (t, 3 H, *J* = 7 Hz); ^{13}C NMR 169.4, 81.4, 75.5, 63.7, 34.7, 27.2, 27.1, 22.4, 13.9.

4(*R*),6(*R*)-Dimethyl-2-butyl-1,3-dioxanne.[26] A solution of pentanal (2.6 g, 30 mmol) and 2(*R*),4(*R*)-pentanediol (3.12 g, 30 mmol) in benzene (50 mL) with a catalytic amount of PTSA was refluxed in a Dean-Stark apparatus. After 15 h, the reaction was completed and saturated aqueous $NaHCO_3$ (10 mL) was added, at room temperature. The aqueous phase was extracted with Et_2O (50 mL) and the combined organic phases were dried over Na_2CO_3 and then concentrated in vacuo. The residue was distilled to afford 4.6 g (89% yield) of pure material: bp 79 °C (0.7 mm) (lit.[26] 98–99 °C (30 mm)); $[\alpha]^{25}_D$ +22° (*c* = 1.4, Et_2O); IR 2950, 2850, 1150; ^1H NMR 4.87 (t, 1 H, *J* = 4 Hz), 4.25 (m, 1 H), 4.0 (m, 1 H), 1.8 (m, 2 H), 1.6–1.2 (m, 6 H), 1.4 (d, 3 H, *J* = 6.4 Hz), 1.15 (d, 3 H, *J* = 6.4 Hz), 0.92 (t, 3 H, *J* = 7 Hz); ^{13}C NMR 93.05, 67.96, 67.38, 34.7, 32.0, 22.41 (2C), 21.76, 17.1, 13.87.

4(*R*),5(*R*)-Dimethyl-2-pentyl-1,3-dioxolane. The same procedure as above was used with hexanal (3 g, 30 mmol) and 2(*R*),3(*R*)-butanediol (2.7 g, 30 mmol). The crude residue was distilled: 4.7 g (91% yield); bp 77 °C (0.8 mm); $[\alpha]^{25}_D$ −10.23° (*c* = 2.81, Et_2O); IR 2950, 2850, 1200; ^1H NMR 5.08 (t, 1 H, *J* = 4 Hz), 3.60 (m, 2H), 1.8–1.1 (m, 14 H), 0.9 (t, 3 H, *J* = 7 Hz); ^{13}C NMR 103.4, 79.7, 78.1, 34.9, 32, 27.7, 23.7, 17.3, 17.1, 14. Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.91; H, 11.82.

4(*R*),5(*R*)-Dimethyl-2-butyl-1,3-dioxolane. The same procedure as above was used with pentanal (2.6 g, 30 mmol) and 2(*R*),3(*R*)-butanediol (2.7 g, 30 mmol). The crude residue was distilled: 4.31 g (91% yield); bp 60 °C (14 mm); $[\alpha]^{25}_D$ −16.75° (*c* = 4.8, CCl_4); IR 2950, 2850, 1200; ^1H NMR 5.08 (t, 1 H, *J* = 4 Hz), 3.60 (m, 2 H), 1.8–1.1 (m, 12 H), 0.9 (t, 3 H, *J* = 7 Hz); ^{13}C NMR 103.4, 79.8, 78.1, 34.6, 26.2, 22.8, 17.4, 17.1, 14.1. Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.46. Found: C, 68.24; H, 11.61.

Synthesis of Ether 10.[10] $TiCl_4$ (0.18 mL, 1.7 mmol) was injected to a cooled (−78 °C) solution of 4(*R*),6(*R*)-dimethyl-2-butyl-1,3-dioxane (205 mg, 1.2 mmol) and bis(trimethylsilyl)acetylene (510 mg, 3 mmol) in CH_2Cl_2 (25 mL). The solution turned red, and after 20 min the reaction was completed. MeOH (1 mL) was injected, at −78 °C, and the stirred mixture was allowed to warm to 0 °C and then hydrolyzed with aqueous HCl 1 N (5 mL). The organic phase, to which 50 mL of CH_2Cl_2 were added, was washed with aqueous HCl 1 N (3 × 20 mL) and then concentrated, without drying, in vacuo. The residue was desilylated with KF in DMF. After the usual workup the residue was

(20) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron Lett.* **1989**, *30*, 2387.
(21) Bourelle-Wargnier, F.; Vincent, M.; Chuche, J. *J. Org. Chem.* **1980**, *45*, 428.
(22) Walton, D. R. M.; Wuagh, F. *J. Organomet. Chem.* **1972**, *37*, 45.
(23) (a) Colobert, F.; Genet, J. P. *Tetrahedron Lett.* **1985**, *26*, 2779. (b) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192.
(24) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1971.
(25) Vigneron, J. P.; Bloy, Y. *Tetrahedron Lett.* **1979**, 2683.
(26) Mori, K.; Akao, H. *Tetrahedron* **1980**, *36*, 91.

chromatographed on silica gel (eluent: cyclohexane/Et_2O 90/10). Yield 193 mg (81%). The diastereomeric purity was determined by GC on capillary column (OV 101, 50 m): de 93%; IR 3400, 3300, 2110, 1150; ^1H NMR 3.9 (dt, 1 H, J = 6.4, 2 Hz), 3.4 (m, 1 H), 3.1 (m, 1 H), 2.1 (d, 1 H, J = 2 Hz), 1.8–1.1 (m, 14 H), 0.9 (t, 3 H, J = 6.6 Hz); ^{13}C NMR 84.1, 73 (2C), 68.5, 64.3, 44.9, 35.9, 27.3, 23.9, 22.4, 20.8, 13.9.

Synthesis of Ether 11.[10] The same procedure as for the synthesis of **10** was used, starting with 4(*R*),5(*R*)-dimethyl-2-pentyl-1,3-dioxolane (205 mg, 1.2 mmol). After purification on SiO_2 (eluent: cyclohexane-/Et_2O 90/10), 202 mg of pure **11** was obtained (85% yield): de 92%; IR 3400, 3300, 2100, 1150; ^1H NMR 4.0 (dt, 1 H, J = 6.4, 2 Hz), 3.4 (m, 1 H), 3.25 (m, 1 H), 2.3 (d, 1 H, J = 2 Hz), 1.6–1.1 (m, 8 H), 1.1 (d, 3 H, J = 6.3 Hz), 1.0 (d, 3 H, J = 6.3 Hz) 0.82 (t, 3 H, J = 6.4 Hz); ^{13}C NMR 84.2, 80.0, 73.3, 70.5, 69.6, 36.2, 31.6, 24.9, 22.6, 18.4, 16.7, 14.

Synthesis of Ether 12.[10] The same procedure as above was used, starting with 4(*R*),5(*R*)-dimethyl-2-butyl-1,3-dioxolane (2.37 g, 15 mmol). Yield 2.4 g (87%); de 92%; IR 3300, 2100, 1100; ^1H NMR 4.02 (dt, 1 H, J = 6.4, 2 Hz), 3.4 (m, 1 H), 3.25 (m, 1 H), 2.34 (d, 1 H, J = 2 Hz), 1.6–1.1 (m, 6 H), 1.1 (d, 3 H, J = 6.3 Hz), 1.0 (d, 3 H, J = 6.3 Hz), 0.84 (t, 3 H, J = 6.4 Hz); ^{13}C NMR 84.1, 80.3, 73.3, 70.8, 69.7, 35.9, 27.5, 22.5, 18.5, 16.8, 14.0.

Ether 15. A stirred solution of *tert*-butyldimethylchlorosilane (300 mg, 2 mmol), ether **11** (300 mg, 1.5 mmol), and triethylamine (2 mL) in acetonitrile (8 mL) was refluxed for 12 h. After cooling to room temperature aqueous HCl 1 N (2 mL) in Et_2O (20 mL) were added. The organic phase was washed with 1 N HCl (2 × 5 mL), dried over Na_2SO_4, and then concentrated in vacuo. The residue was chromatographed on SiO_2 (eluent: cyclohexane/Et_2O 90/10). Yield 374 mg (80% yield); ^1H NMR 4.15 (dt, 1 H, J = 6.6, 2.1 Hz), 3.85 (m, 1 H), 3.65 (m, 1 H), 2.38 (d, 1 H, J = 2.1 Hz), 1.8–1.2 (m, 8 H), 1.2 (d, 3 H, J = 6.2 Hz), 1.1 (d, 3 H, J = 6.2 Hz), 0.9 (br s, 12 H), 0.1 (s, 6 H); ^{13}C NMR 84.3, 77.7, 72.8, 69.7, 68.9, 36.3, 31.7, 26, 25, 22.7, 18.2, 17.9, 15.1, 14.1, –0.5.

Synthesis of Allenes from Propargylic Ethers. Stoichiometric Procedure. A 1 N solution of $CuBr{\cdot}2P(OEt)_3$ in Et_2O (5.7 mL, 5.7 mmol) was introduced into a flask containing 30 mL of Et_2O. After cooling to –40 °C, an ethereal solution of nBuMgBr (1 N, 5.7 mL, 5.7 mmol) was added. A yellow precipitate appeared immediately. The temperature was kept at –30 °C for 30 min. After cooling to –60 °C, 3(*R*)-methoxy-1-heptyne (58% ee, 600 mg, 4.76 mmol) in Et_2O (10 mL) was added. The mixture was stirred at –40 °C for 1 h and 30 min and the quantitative formation of the adduct **5** was checked by GC. For the elimination step, the mixture was allowed to warm slowly (90 min) to +5 °C. The quantitative elimination to the allene was checked by GC. The hydrolysis was done with a mixture of aqueous NH_3 (1 part) and saturated aqueous NH_4Cl (4 parts) (50 mL). The aqueous phase was extracted twice with ether (2 × 50 mL), and the combined organic phases were washed with a mixture of NH_3/NH_4Cl (3 × 50 mL) and then dried over $MgSO_4$ and concentrated in vacuo (with a *cold* water bath). The residue was chromatographed on SiO_2 (eluent: pentane only). Yield of 5,6-undecadiene 688 mg (95%); $[\alpha]^{25}_D$ 37.9° (c = 2.43, $CHCl_3$); ee 56%; optical yield 96%.

Procedure through Alkenyl Iodide 9. The alkenyl copper reagent **5** was prepared as described above for the stoichiometric procedure (with 3-(*R*)-methoxy-1-heptyne of 28% ee). Instead to allow it undergo β-elimination, it is quenched by portionwise addition, at –40 °C, of finely ground iodine (1.45 g, 5.7 mmol). After completion of this addition, the mixture was warmed to 0 °C and hydrolyzed with the above 1:4 mixture of aqueous NH_3/NH_4Cl (50 mL). The organic phase was washed over $MgSO_4$ and concentrated in vacuo, and the residue was chromatographed on SiO_2 (eluent: cyclohexane/Et_2O 95/5). Yield of (*Z*)-6-iodo-5(*R*)-methoxy-6-undecene (**9**) 1.03 g (70%); $[\alpha]^{25}_D$ +11.73° (c = 0.77, Et_2O), ee 28%; IR 1640, 1100, 840; ^1H NMR 6.0 (t, 1 H, J = 11 Hz), 3.3 (s, 3 H), 3.2 (t, 1 H, J = 8 Hz), 2.3 (m, 2 H), 1.9–1.2 (m, 10 H), 1.0 (t, 6 H, J = 7.6 Hz); ^{13}C NMR 137.8, 114.1, 87.2, 55.7, 35.2, 35.1, 30.5, 27.4, 27.0, 22.6, 22.3, 14.0. Anal. Calcd for $C_{12}H_{23}IO$: C, 46.46; H, 7.47. Found: C, 46.31; H, 7.55.

To a solution of alkenyl iodide **9** (500 mg, 1.61 mmol) in Et_2O (30 mL) was added, at –78 °C, 1.1 equiv of nBuLi (1.6 M solution in hexane, 1.1 mL, 1.77 mmol). This solution was warmed to –65 °C for 10 min to complete the lithium–iodine exchange, and then at –78 °C the needed magnesium salt MgX_2 (1.8 mmol) was added at once. The mixture was stirred 15 min at –78 °C and then warmed slowly. The elimination to the allene occurs around –50 °C. The hydrolysis, workup, and isolation of the allene was performed as described above, for the stoichiometric case.

Catalytic Procedure with Ethers 4 and 10–16. To a solution of propargylic ether (3.17 mmol) in Et_2O (20 mL) was added a solution of CuX·L (1 N solution in Et_2O, 0.16 mL, 0.16 mmol). The mixture is cooled to –78 °C and the Grignard reagent RMgX (6.3 mmol; twice that amount for **11**) was rapidly introduced. The cooling bath was removed and the reaction was followed by GC. With **4** the allene was formed around –40 to –30 °C, whereas with **11** and **15** the reaction was completed only at room temperature. The mixture was hydrolyzed, worked up, and purified as described for the stoichiometric procedure.

3,4-Nonadiene:[14,27] n^{20}_D 1.4159; IR 2980, 1955, 1450, 1370; ^1H NMR 5.0 (m, 2 H), 1.98 (m, 4 H), 1.35 (m, 4 H), 0.97 (t, 6 H, J = 7 Hz); ^{13}C NMR 203.7, 92.6, 91.6, 31.6, 28.9, 22.9, 22.2, 13.9, 13.5.

5,6-Undecadiene:[14,27] Bp 177 °C (760 mm); n^{20}_D 1.4295; IR 2980, 1960, 1450, 1370; ^1H NMR 5.2 (m, 2 H, J = 10 Hz), 2.0 (t, 4 H, J = 10 Hz), 1.6–1.44 (m, 8 H), 1.0 (t, 6 H, J = 8 Hz); ^{13}C NMR 204, 90.8, 31.5, 28.8, 22.2, 13.9.

5,6-Tridecadiene:[19] IR 2980, 1955, 1450, 1370; ^1H NMR 5.2 (m, 2 H, J = 10 Hz), 2.0 (t, 4 H, J = 10 Hz), 1.6–1.4 (m, 12 H), 0.98 (t, 6 H, J = 8 Hz); ^{13}C NMR 204, 91.1, 31.6, 29.3, 29.2, 22.8, 14.2.

2,2-Dimethyl-3,4-decadiene:[19] IR 2970, 1930, 1450, 1350; ^1H NMR 5.1 (m, 2 H), 2.0 (m, 2 H), 1.5–1.1 (m, 6 H), 1.0 (s, 9 H), 0.92 (t, 3 H, J = 7 Hz); ^{13}C NMR 201.4, 103.2, 93.1, 31.7, 30.5, 30.0, 29.5, 22.8, 14.3.

1-*tert*-Butoxy-5,6-undecadiene: n^{20}_D 1.4542; IR 1960, 1700, 1200; ^1H NMR 5.08 (m, 2 H), 3.04 (t, 2 H, J = 6.8 Hz), 2.0 (t, 4 H, J = 6.7 Hz), 1.2–1.4 (m, 8 H), 1.1 (s, 9 H), 0.92 (t, 3 H, J = 7 Hz); ^{13}C NMR 204.0, 90.9, 90.7, 72.3, 61.4, 31.5, 30.2, 29.0, 28.8, 27.6, 26.0, 22.2, 13.9. Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.15; H, 12.65.

(27) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *J. Organomet. Chem.* **1985**, *285*, 83.

(28) Walerick, J. M.; Wilson, J. W., Jr.; Jones, W. M. *J. Am. Chem. Soc.* **1968**, *90*, 2895.

(29) A control experiment run with preformed $MgCl_2$ gave a slightly lower optical yield (58%). However, in these conditions, the concentration of $MgCl_2$ in ether is very low. In contrast, in situ generated $MgCl_2$ should be more dispersed and therefore more efficient.