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1,3-Diethynylallenes (DEAs): Enantioselective Synthesis, Absolute Configuration, and Chiral Induction in 1,1,4,4-Tetracyanobuta-1,3-dienes (TCBDs)

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Dedicated to Professor Javier de Mendoza on the occasion of his 65th birthday

In 1875 van't Hoff predicted that in cumulenes with an even number of double bonds the four substituents must be arranged in two perpendicular planes.[1] Van't Hoff's proposal implied that allenes must be chiral when appropriately substituted.[2] The predictions were confirmed when the first optically active allenes were described in 1935.[3] For 1,3-dimethylallene, the activation enthalpy for rotational isomerism leading to racemization was determined by Roth et al. as $\Delta H^{\neq} = 45.07\ \mathrm{kcal\,mol^{-1}}$.[4]

In 1952, Celmer and Solomons recognized that optically active allenes also occur in nature.[5] Since then, a number of natural chiral allenes have been found. Today, allenes are versatile starting materials and intermediates in organic synthesis because their double bonds participate in all types of addition processes, their terminal, acidic C−H bonds are easily replaced by functional groups, and their axial chirality is increasingly exploited in stereoselective synthesis.[6]

We have been involved in the preparation of ethynylated allenes[7a–c] as building blocks for the construction of linear[8] and macrocyclic[7d,9] carbon-rich scaffolds through oxidative acetylenic coupling. Following the synthesis of a first series of stable 1,3-diethynylallenes (DEAs), we proceeded with the preparation of shape-persistent macrocycles with allenoacetylenic carbon backbones.[7d] Although DEAs are axially chiral, racemic mixtures were previously used in our group for acetylenic scaffolding. Recently, we reported the synthesis of optically enriched DEA **1a** in 25% yield and with an enantiomer ratio (e.r.)[10] of 89:11 by Pd-mediated S_N2'-type cross-coupling of alkyne **2a** with the optically pure bispropargylic ester (*S*)-**3**.[8] The absolute configuration of the allene was tentatively assigned as (*P*) on the basis of an *anti*-S_N2'-type addition of **2a** to (*S*)-**3**, as previously reported for enantioselective[11] and diastereoselective[12] Pd-mediated S_N2'-type cross-coupling reactions.

Here, we give X-ray crystallographic evidence that the enantioselective Pd-mediated addition of alkynes **2** to (*S*)-**3** actually proceeds under opposite stereocontrol, leading to (*M*)-**1**, thereby providing the first example for a Pd-mediated enantioselective *syn*-S_N2'-type cross-coupling reaction. We show that 4-*N*,*N*-dimethylanilino (DMA) donor-substituted optically active DEAs undergo photoisomerization leading to racemization. They also react in a facile [2+2] cycloaddition with tetracyanoethene (TCNE)[13] to form, after retrocycloaddition, optically active, photostable 1,1,4,4-tetracyanobuta-1,3-diene (TCBD) derivatives. In these compounds, chiral induction from the optically active allene moiety in the TCBD chromophore is observed by circular dichroism (CD) spectroscopy.

First, we undertook further studies to improve both the yield and the enantioselectivity of the previously reported synthesis of optically active DEAs.[8] Alkynes **2a,b** with different protecting groups were used to enable selective deprotection, providing subsequent access to oligomers in a controlled manner (Scheme 1, Table 1). The e.r. of Me_3Si-protected DEA **1a** was determined after derivatization with the Mosher acid chloride[8] and the e.r. of **1b** by recycling HPLC on the chiral stationary phase (CSP) WHELK-O1 (hexane/0.25% *i*PrOH) after removal of the iPr_3Si group with nBu_4NF/THF (see Supporting Information).

Increasing the amount of base from 0.4 to 2.1 equiv was essential to improve the yield considerably without affecting the enantioselectivity (entries 1 and 2, Table 1). When the acetonide-protected acetylene **2b** was used, a lower reactivity was observed. Raising the temperature from 30 to 50 °C

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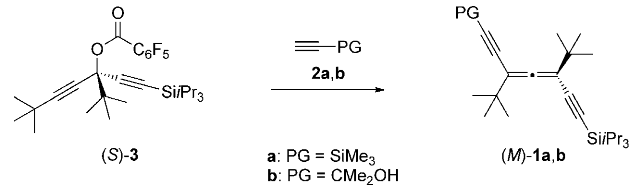
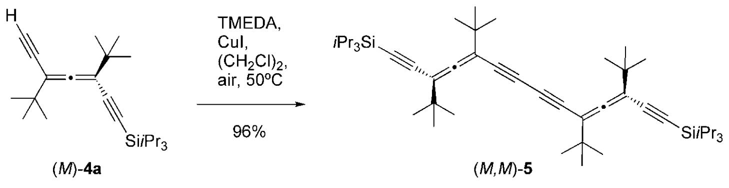


Scheme 1. Enantioselective synthesis of DEAs (*M*)-**1a**/**b** starting from optically pure (*S*)-**3**.[8] For reaction conditions, see Table 1.



Scheme 2. Synthesis of (*M*,*M*)-**5**. A diastereomeric ratio (d.r.) of 90.25 ((*M*,*M*)-**5**):9.5 ((*M*,*P*)-**5**):0.25 ((*P*,*P*)-**5**) is expected for an unselective homo-coupling reaction of **4a** (e.r. 95:5). TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine. (*M*)-**4a** (e.r. 95:5) was obtained by deprotection of (*M*)-**1a** (e.r. 95:5) with K_2CO_3, THF/MeOH 1:1 as previously reported.[8]

Table 1. Enantioselective synthesis of DEAs by Pd-mediated *syn*-S_N2' substitution of **2a**/**b** to (*S*)-**3** or (*R*)-**3**.

Entry	PG	Base	*T* [°C]/*t* [h]	Yield [%]/e.r. *M*:*P*
1[a,b][8]	Me_3Si	Cy_2NMe	20/24	25/89:11[e]
2[a,b]			30/5	61/90:10[f]
3[a,b]	CMe_2OH		30/96	69/96:4[g]
4[a,b]			50/72	93/74:26[g]
5[a,c]	Me_3Si	$i$$Pr_2NH$	20/14	53/6:94[f]
6[c,d]			20/20	90/5:95[e]
7[c,d]	CMe_2OH		20/96	49/7:93[g]
8[b,d]			30/16	70/71:29[g]
9[b,d]			50/6	86/69:31[g]

[a] Solvent: toluene. [b] Starting material (*S*)-**3** was used. [c] Starting material (*R*)-**3** was used. [d] Solvent: $(ClCH_2)_2$. [e] The enantiomeric ratio (e.r.) was determined by derivatization with the Mosher acid chloride as previously reported.[8] [f] The e.r. was estimated from the optical rotation. [g] The e.r. was determined by recycling HPLC on the CSP WHELK-O1 (hexane/0.25% *i*PrOH) after removal of the iPr_3Si group with nBu_4NF/THF. In general, 2.1 equiv of base were used in the reaction, except for entry 1 where only 0.4 equiv were used. Cy = cyclohexyl.

increased the yield but a loss in stereoselectivity occurred (entries 3 and 4, Table 1). The enantioselectivity was very sensitive to the nature of the base used. With iPr_2NH, the e.r. was improved for **1a**, but the yield was only moderate (entry 5, Table 1). When the solvent was changed from toluene to 1,2-dichloroethane, the yield became excellent without any loss in enantioselectivity (entry 6, Table 1). Under the same conditions, the acetonide-protected DEA **1b** was obtained in moderate yield and with good e.r. The yield was increased when the temperature was changed to 30 or 50 °C, however, at the cost of stereoselectivity (entries 7–9, Table 1). Enantiopure (*M*)-**4b** and (*P*)-**4b** were obtained by resolution of (±)-**4b**, using recycling HPLC on the CSP WHELK-O1 (hexane/0.25 % *i*PrOH; see Supporting Information).

In order to assign the absolute configuration of the DEAs, the dimer (*M*,*M*)-**5** was synthesized from (*M*)-**4a** (e.r. 95:5) (Scheme 2).[8]

Suitable single crystals of (*M*,*M*)-**5** were grown for X-ray crystallographic analysis. The presence of the silicon heavy atoms enabled the unambiguous assignment of the absolute configuration of the allene moieties as (*M*), disproving the previously proposed assignment (Figure 1).[8] These results suggest that a *syn*-S_N2'-type substitution of **2a**,**b** to ester (*S*)-**3** had taken place. To the best of our knowledge this is the first reported enantioselective Pd-mediated *syn*-S_N2'-type cross-coupling reaction.[11,12] As a note, Molander and Sommers recently reported a *syn*-carbometallation/*syn*-elimination of propargyl substrates to form allenes using chiral cationic Cr^{III} catalysts.[13]

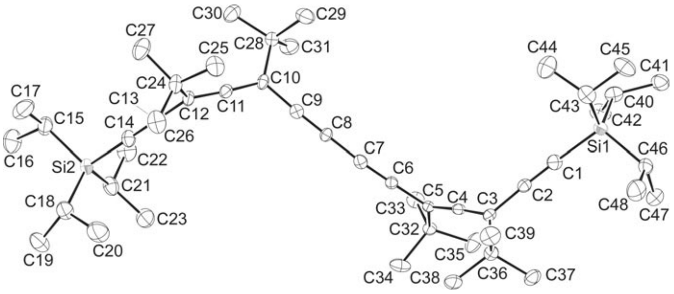
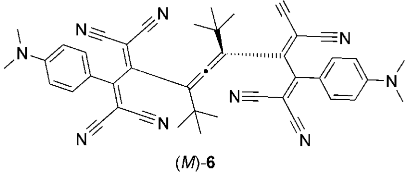


Figure 1. ORTEP plot of (*M*,*M*)-**5** with vibrational ellipsoids shown at the 30% probability level. *T* = 160 K. Arbitrary numbering (see Supporting Information). Flack parameter: 0.03(18).

The enantioselective synthesis of DEAs opens access to novel chromophores with interesting optical properties. Recently, we introduced a new class of intramolecular charge transfer (CT) chromophores, DMA donor-substituted TCBDs, accessible in excellent yields in an atom-economic synthesis by [2+2] cycloadditions between tetracyanoethylene (TCNE) and DMA-substituted alkynes, followed by electrocyclic ring-opening of the initially formed cyclobutenes.[14] We were interested in exploring whether the stereogenic allene moiety in compounds such as (*M*)-**6** (Figure 2) would induce conformational preferences and a sense of chirality in the adjacent, nonplanar donor-substituted TCBD moieties.[15]

Starting from (*M*)-**4a** (e.r. 95:5), Sonogashira cross-coupling with 4-iodo-*N*,*N*-dimethylaniline gave DEA (*M*)-**7** in



(*M*)-**6**

Figure 2. Bis-TCBD-substituted allene (*M*)-**6**.

71 % yield. Deprotection with nBu$_4$NF in THF to give (*M*)-**8**, followed by another Sonogashira cross-coupling, afforded (*M*)-**9** in good yield along with the side product (*M*,*M*)-**10** resulting from homo-coupling (Scheme 3). The e.r. of (*M*)-**7**, (*M*)-**8** and (*M*)-**9** was determined to be ≥91:9 based on the e.r. measured for (*M*)-**6** (see Scheme 4) by HPLC on the CSP WHELK-O1 (hexane/ethanol/methanol 65:30:5). The d.r. of (*M*,*M*)-**10** was determined to be ≥78 ((*M*,*M*)-**10**):20 ((*M*,*P*)-**10**):2 ((*P*,*P*)-**10**) based on the d.r. measured for (*M*,*M*)-**11** (see Scheme 4) by recycling HPLC on the CSP WHELK-O1 (hexane/55 % CH_2Cl_2).

Since we had previously observed that DEAs attached to electron-rich chromophores undergo photoisomerization,[7d] (*M*)-**9** and analogously obtained (*P*)-**9** were synthesized and characterized in the dark. This way reproducible mirror-image CD spectra of both enantiomers with consistent molar ellipticities were obtained (Figure 3).

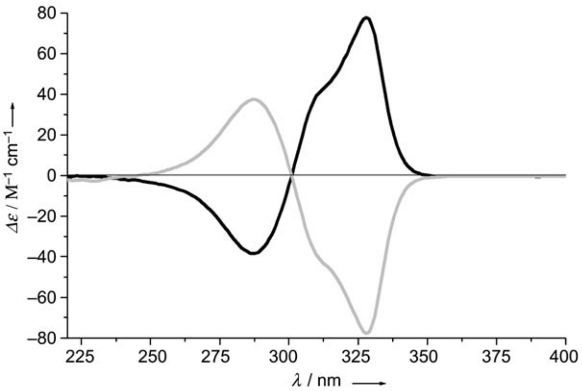
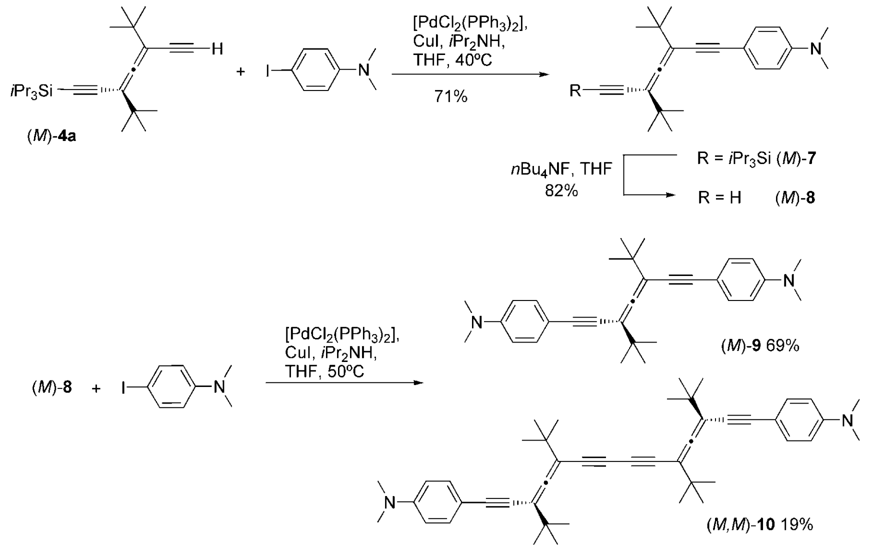
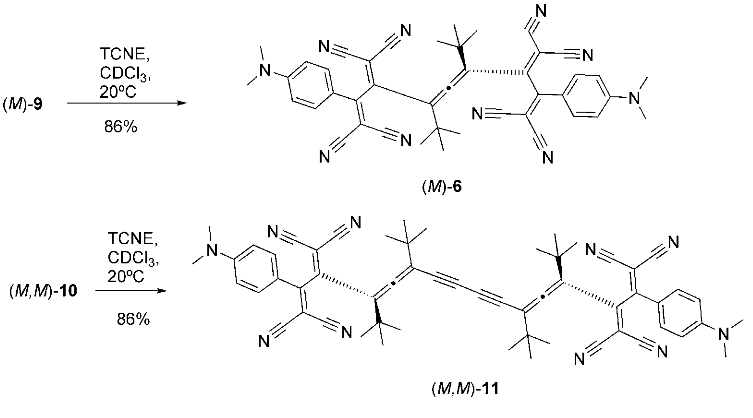


Figure 3. CD spectra of (*M*)-**9** (gray line) and (*P*)-**9** (black line) recorded in hexane at 298 K. The e.r. was determined to be ≥91:9 based on the e.r. measured for (*M*)-**6** (see Scheme 4) by HPLC on the CSP WHELK-O1 (hexane/ethanol/methanol 65:30:5).



Scheme 3. Synthesis of (*M*)-**9** (e.r. determined to be ≥91:9 based on the e.r. measured for (*M*)-**6**)) and (*M*,*M*)-**10** (e.r. was determined to be ≥78 ((*M*,*M*)-**10**):20 ((*M*,*P*)-**10**):2 ((*P*,*P*)-**10**) based on the e.r. measured for (*M*,*M*)-**11** (see Scheme 4)).



Scheme 4. Synthesis of (*M*)-**6** (e.r. determined as 91:9 by HPLC on the CSP WHELK-O1 (hexane/ethanol/methanol 65:30:5)) and (*M*,*M*)-**11** (d.r. determined as 78 ((*M*,*M*)-**11**):20 ((*M*,*P*)-**11**):2 ((*P*,*P*)-**11**) by recycling HPLC on the CSP WHELK-O1 (hexane/55 % CH_2Cl_2)).

Photoracemization was confirmed when (*M*)-**9** was exposed to daylight and CD spectra were recorded at given time intervals (Figure 4).

A similar photoisomerization was observed for (*P*,*P*)-**10** (see Supporting Information). Accordingly, the "click-type" synthesis of the TCBD derivatives (*M*)-**6** and (*M*,*M*)-**11** by TCNE addition to (*M*)-**9** and (*M*,*M*)-**10**, respectively, followed by retro-electrocyclization was carried out in the absence of light (Scheme 4).

The conversions were performed in $CDCl_3$ to allow monitoring of the reaction progress by ^{1}H NMR spectroscopy. Fortunately, these new charge-transfer chromophores showed no photoisomerization.

Enantiomerically pure (*M*)-**6** and (*P*)-**6** were obtained by resolution of (±)-**6**, using HPLC on the CSP WHELK-O1 (hexane/ethanol/methanol 65:30:5; see Supporting Information) as well as enantiopure (*M*,*M*)-**11** and (*P*,*P*)-**11** by recycling HPLC on the same CSP (hexane/55 % CH_2Cl_2; see Supporting Information). Single crystal X-ray crystallographic analysis of (±)-**6** and (*M*,*M*)-**11** showed that in the solid state, the bulky *tert*-butyl groups on the allene moieties force the

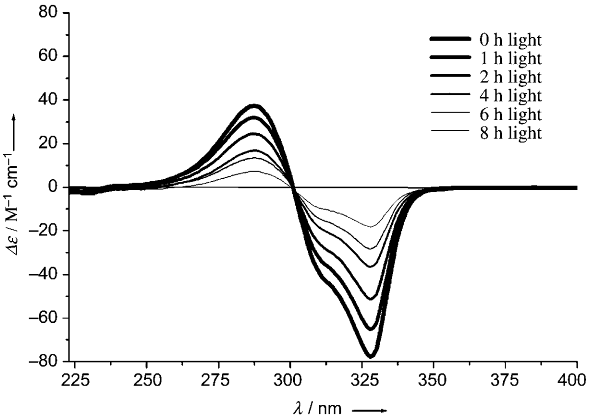


Figure 4. Photoracemization of (*M*)-**9** in hexane upon exposure to daylight at 298 K, as monitored over time by CD spectroscopy. The e.r. at the initial time was determined to be ≥91:9 based on the e.r. measured for (*M*)-**6** (see Scheme 4) by HPLC on the CSP WHELK-O1 (hexane/ethanol/methanol 65:30:5).

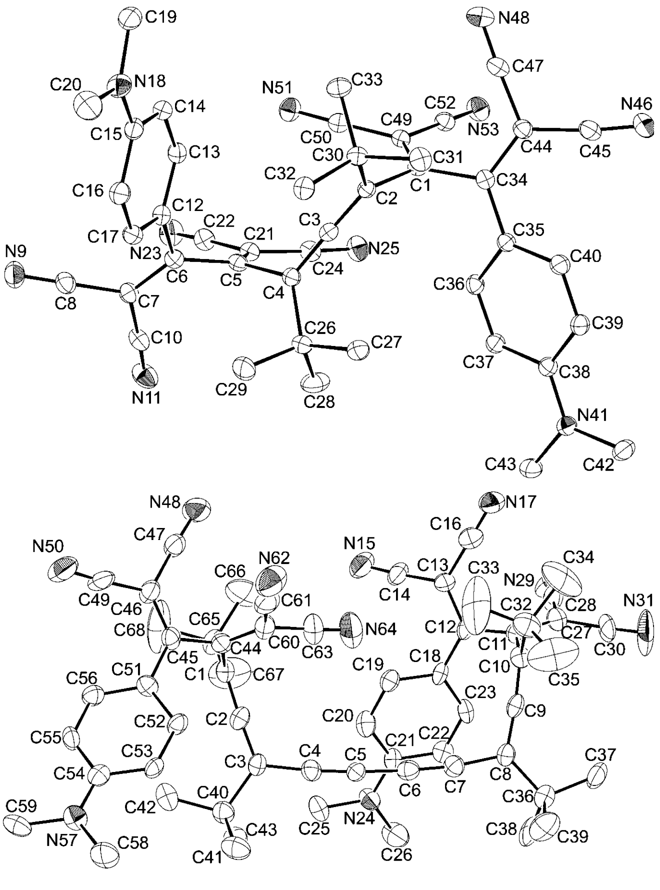


Figure 5. ORTEP plot of (±)-**6** (top, $T = 170$ K) and (*M*,*M*)-**11** (bottom, $T = 220$ K) with vibrational ellipsoids shown at the 30 % probability level. Arbitrary numbering. Selected dihedral angles [°]: (±)-**6**: C3-C4-C5-C21 71.9(3), C3-C4-C5-C6 −106.0(2), C21-C5-C6-C7 58.4(3), C12-C6-C7-C8 8.7(4), C49-C1-C2-C3 65.8(3), C34-C1-C2-C3 −113.2(2), C49-C1-C34-C44 65.4(3), C35-C34-C44-C45 3.6(4); (*M*,*M*)-**11**: C2-C1-C44-C60 −77.6(12), C2-C1-C44-C45 98.4(10), C60-C44-C45-C46 −70.2(14), C51-C45-C46-C49 −0.6(16), C9-C10-C11-C27 101.8(12), C9-C10-C11-C12 −74.1(11), C27-C11-C12-C13 73.3(13), C18-C12-C13-C14 7.4(14) (see Supporting Information).

adjacent dicyanovinyl residues to adopt dihedral angles around 90° (C49-C1-C2-C3 and C3-C4-C5-C21 in (±)-**6** or C2-C1-C44-C60 and C9-C10-C11-C27 in (*M*,*M*)-**11**, Figure 5). In solution, this could also induce chirality in the non-planar TCBD chromophores which feature central dihedral angles between 58° and 75°.

UV/Vis spectroscopy studies of (*P*)-**6** and (*M*)-**6** revealed two CT absorptions at 390 nm and 520 nm in CH_2Cl_2. The absorptions in the region between 350 and 700 nm disappeared to a large extent upon acidification with CF_3COOH and were fully recovered after neutralization with Et_3N (see Supporting Information). The CD spectra show Cotton effects associated with the CT absorptions. This clearly indicates chiral induction[15] from the allene into the TCBD moieties (Figure 6).

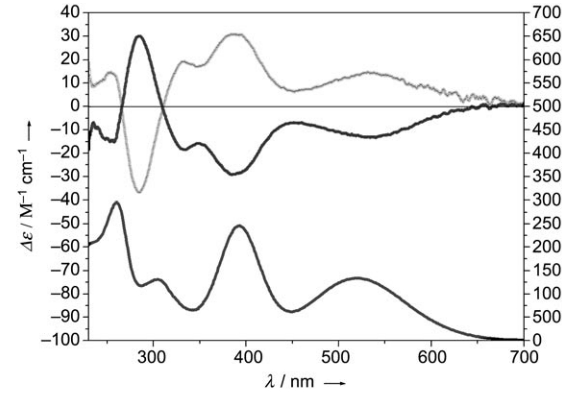


Figure 6. CD spectra (top) of (*M*)-**6** (e.r. 100:0, black line) and (*P*)-**6** (e.r. 100:0, gray line) and UV/Vis spectra (bottom) recorded in CH_2Cl_2.

In conclusion, we performed the enantioselective synthesis of differently protected (*M*) and (*P*)-DEAs **1a**,**b** in good to excellent yields with high enantioselectivity. Unambiguous assignment of the absolute configuration by X-ray crystallographic analysis led us to confirm the first enantioselective Pd-mediated *syn*-S_N2'-type cross-coupling reaction. CD spectroscopy revealed chiral induction in TCBDs when they are directly attached to optically pure allenes. Further studies on chiral induction in TCBDs are currently under way, using a combination of CD spectroscopy and theoretical calculations. Furthermore, the availability of optically pure DEAs opens the way to new chiral, non-racemic helical foldamers and allenoacetylenic macrocycles.

Experimental Section

General procedure for the synthesis of 1: Two solutions A and B were prepared. A) A solution of enantiomerically pure **3** and base (2.1 equiv) in the corresponding solvent (0.05 M); B) A solution of $[PdCl_2(PPh_3)_2]$ (0.09 equiv) in the corresponding solvent (0.05 M). Both solutions were degassed with Ar. Acetylene **2a**,**b** (2.05 equiv) was added to solution A, CuI (0.10 equiv) to solution B and both were degassed again. Solution B was added to A and the reaction stirred at the corresponding temperature. Purification by FC on silica gel (hexane for **1a** and hexane/10% AcOEt for **1b**) gave colorless oils.

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Keywords: allenes · chirality · circular dichroism · configuration determination · enantioselectivity

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