Chiral 1,2-Dialkenyl Diaziridines: Synthesis, Enantioselective Separation, and Nitrogen Inversion Barriers

KERSTIN ZAWATZKY, MATTHIAS KAMUF, AND OLIVER TRAPP*
Organisch-Chemisches Institut, Ruprecht-Karls-Universität Heidelberg, Heidelberg, Germany

ABSTRACT *trans*-1,2-Disubstituted diaziridines form stable enantiomers at ambient conditions because of the two stereogenic pyramidal nitrogen atoms. Functionalized *trans*-1,2-disubstituted diaziridines can be utilized as a chiral switching moiety between two enantiomeric states in more complex molecular structures. However, the synthesis of functionalized diaziridines is quite challenging, because of the limited tolerance of reaction conditions that can be applied. Here we present a strategy to make *trans*-1,2-disubstituted diaziridines accessible as versatile building blocks in C-C-bond formations, i.e., the Heck reaction, and therefore introducing aryl substituents. The synthesis of *trans*-1,2-dialkenyl diaziridines with terminal alkenyl substituents and their stereodynamic properties are described. *Chirality 27:156–162, 2015*.

KEY WORDS: diaziridines; stereogenic pyramidal nitrogen atoms; stereodynamic properties

INTRODUCTION

1,2-Disubstituted diaziridines (Scheme 1) exist as stable enantiomers at room temperature due to the high stability of the two stereogenic pyramidal nitrogen atoms. As the *N*-substituents are in *trans*-orientation, first because of the repulsion of the nitrogen lone pairs,[1] second due to minimization of steric interactions, only two enantiomers in the case of achiral substituents and no *cis*-isomers are formed. In particular, 3,3-unsubstituted diaziridines are of great interest because of the unusual high stereointegrity.[2,3] The enantiomerization barrier is higher compared to diaziridines substituted at the 3-position, where repulsive interactions of the vicinal substituents destabilize the ground state.[4] More recently, Fioravanti and Pellacani and colleagues presented the stereoselective synthesis of 3,3'-bridged bisdiaziridines.[5] Aziridines can coordinate to a metal ion via the nitrogen atom and can therefore be used as chiral ligands. Transition metal complexes with different types of mono- and bisdiaziridines have successfully been synthesized. Shevtsov et al. reported a series of complexes of different transition metals with *N*-(2-aminoethyl)diaziridines,[6] while Adedapo et al. were able to prepare Pt complexes of 3,4-substituted diaziridines.[7] The same group also synthesized and characterized Rh complexes of adamantyl- and 4-*tert*-butylcyclohexyldiaziridine and studied their catalytic activity for hydrogenation and hydroformylation of alkenes.[8]

It is more attractive to use diaziridines as chiral switches in functional organic materials due to the enantiomerization properties, which can be triggered at elevated temperatures. Because the enantiomers can be easily separated at ambient temperature, it is possible to reracemize one of the enantiomers in a continuous process and therefore enrich the other enantiomer. This allows realizing degenerated states −1 and +1 in contrast to states 0 and +1 in compounds prone to *E*/*Z* isomerization. The synthesis of tailored diaziridines, which can be utilized as a switching moiety, is a prerequisite.

So far, little is known about the functionalization of diaziridines and the synthesis of more complex structures based on diaziridines. This is mainly due to the low stability of diaziridines against acids and the typically harsh reaction conditions used to prepare diaziridines starting from amines, which involves strong bases and oxidative conditions using bleach to achieve oxidative ring closing of the aminals. Therefore, there are only a few functional groups that tolerate these restrictions. Transformation of 1-unsubstituted diaziridines to their bis(2-arylcarbamoyl) derivatives[9] is only one of the few examples that were reported for diaziridines.[10] As there is no efficient method to further functionalize alkyl-substituted diaziridines, the functional group already has to be present when synthesizing the diaziridine starting from amines.

Therefore, we synthesized diaziridines with terminal double bonds, which are not affected under these reaction conditions. Furthermore, such building blocks allow performing convergent synthesis strategies, because such diaziridines can be used in a variety of reactions such as metathesis or Heck reactions.

Herein we report the synthesis of 1,2-diaziridines, substituted with terminal alkenyl groups (allyl[11] to pentenyl) and the investigation of their stereodynamic properties compared to the well-known alkyl diaziridines.[2–4,12] To determine the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, temperature-dependent measurements using enantioselective dynamic gas chromatography (DGC) were performed, because the activation energy for the nitrogen inversion in diaziridines is usually well above 90 kJ mol^{-1}.[4,13–15] In particular, the influence of the alkenyl chain length was investigated, which provides valuable data for designing novel chiral switchable structures. Furthermore, the functionalization of these building blocks by a Heck reaction to form phenyl substituted diaziridines is demonstrated.

MATERIALS AND METHODS

General

All starting materials and deuterated solvents were obtained from commercial suppliers and were used without further purification unless otherwise stated. Anhydrous solvents were purified using a solvent purification

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*Correspondence to: Oliver Trapp, Ruprecht-Karls-Universität Heidelberg, Organisch-Chemisches Institut, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany. E-mail: trapp@oci.uni-heidelberg.de
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Scheme 1. Interconversion of diaziridines enantiomers.

system prior to distillation. Air- and moisture-sensitive reactions were conducted in oven-dried glassware by using standard Schlenk line or dry-box techniques under an inert atmosphere of N_2 or Ar. Flash column chromatography was carried out with silica gel 60 (70–230 mesh) using the indicated solvents. Thin layer chromatography (TLC) was performed on silica plates with a UV indicator and visualized using permanganate stain and/or UV light. ^{1}H nuclear magnetic resonance (NMR) spectra were recorded either on a 300 MHz or a 600 MHz spectrometer. ^{13}C NMR spectra were recorded either on a 75 MHz or 151 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) and were calibrated to the residual signals of the deuterated solvents; coupling constants (*J*) are indicated in Hz. High-resolution mass spectra (HR-MS) were acquired using electron impact ionization (EI). Enantioselective DGC was performed on a quadrupole–ion trap mass spectrometer equipped with a split injector (250°C) and a flame ionization detector (250°C). Helium was used as the inert carrier gas. Separation of the enantiomers of diaziridines **1**, **2**, **3** and stereodynamic measurements were performed on fused silica capillaries (25 m × 0.25 mm i.d. or 50 m × 0.25 mm i.d., 0.25 μm film thickness) coated with 50% (*w/w*) heptakis(2,3-di-*O*-ethyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin[23,24] dissolved in 50% (*w/w*) PS086. The dynamic measurements were repeated at least three times at each temperature.

High-performance liquid chromatography (HPLC) measurements were performed on an Agilent Technologies 1200 HPLC (Agilent Technologies, Palo Alto, CA), equipped with a binary solvent pump, an autosampler, membrane solvent degasser, DAD detector, and a quadrupole mass spectrometer Agilent 6120, equipped with an APCI source. Preparative HPLC separations were performed on an Agilent Technologies 1260 preparative HPLC (Agilent Technologies), equipped with a binary solvent pump. All operations were controlled by the Agilent ChemStation software (Agilent Technologies). Enantioselective separations were performed on a Chiralpak IA column (250 mm, i.d. 4.6 mm, particle size 5 μm), on a Chiralpak IA-3 column (150 mm, i.d. 2.1 mm, particle size 3 μm) or on Chiralpak IC column (250 mm, i.d. 4.6 mm, particle size 5 μm), from Chiral Technologies (Illkirch, France). Preparative separations were performed on a Chiralpak IA column (250 mm, i.d. 20 mm, particle size 5 μm) or on a Chiralpak IC column (250 mm, i.d. 20 mm, particle size 5 μm), from Chiral Technologies. The solvents used (n-hexane and 2-propanol) were obtained from Sigma-Aldrich (St. Louis, MO; HPLC-grade quality). Dynamic HPLC measurements were performed with solutions of 1.0 mg substance in 1.0 mL of the solvent mixture which was also used for the separation of the enantiomers.

Determination of Activation Parameters

Gibbs free activation energies $\Delta G^{\ddagger}$ of enantiomerization of the diaziridines were calculated according to the Eyring Equation (Eq. (1)) with k_B as the Boltzmann constant ($k_B = 1.380662\text{x}10^{-23}\,\text{J}\cdot\text{K}^{-1}$), T as the epimerization temperature [K], h as Planck's constant ($h = 6.62617\cdot10^{-34}\,\text{J}\cdot\text{s}$), and R as the gas constant ($R = 8.31441\,\text{J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$). The statistical factor κ was set to 0.5 for a reversible degenerated interconversion process.[16]

$$\Delta G^{\ddagger}(T) = -RT\ \ln\frac{k_1 h}{\kappa k_B T} \qquad (1)$$

1,2-Diallyldiaziridine (1). [11] Allylamine **4** (7.51 ml, 100 mmol, 1.00 eq.) was added to a solution of NaOH (4.00 g, 100 mmol, 1.00 eq.) in water (10.0 mL) at 0°C. A concentrated formaldehyde solution (3.74 mL, 50.0 mmol, 0.50 eq., 37% w/w) and subsequently sodium hypochlorite solution (21.2 mL 50.0 mmol, 0.50 eq, 14% w/w) were added dropwise over 30 min. The mixture was stirred at room temperature for 13 h, then the organic layer was separated and washed with diluted sodium thiosulfate solution and water. Flash chromatography (SiO_2, DCM/MeOH 99:1, Rf = 0.27) afforded 1,2-diallyldiaziridine **1** as a colorless oil (1.92 g, 31 %). ^{1}H NMR (300.51 MHz, $CDCl_3$) δ (ppm) 2.52 (s, 2 H) 2.94–3.14 (m, 4 H), 5.12–5.29 (m, 4 H), 5.93 (ddt, J = 17.0, 10.6, 6.1 Hz, 2 H); ^{13}C NMR (75.56 MHz, $CDCl_3$) δ (ppm) 55.8, 63.4, 117.4, 133.9; HR-MS (EI$^+$) *m/z* $[M]^+$ calcd for $C_7H_{12}N_2$ 124.1000, found 124.1020.

But-3-ene-1-amine hydrochloride (6a).[20] A suspension of $LiAlH_4$ (8.72 g, 230 mmol, 1.10 eq.) in anhydrous Et_2O (280 mL) was cooled to 0°C and $AlCl_3$ (27.8 g, 209 mmol, 1.00 eq.) was added. Allylcyanide **5** (14.0 g, 16.9 mL, 209 mmol, 1.00 eq.) in dry Et_2O (80.0 mL) was added dropwise. The mixture was stirred for 2 h at 0°C and 1 h at room temperature. The mixture was quenched with 30%-NaOH (150 mL) at 0°C and extracted with Et_2O (3 x 100 mL). Combined organic extracts were extracted with 6 M HCl (3 x 50 mL) and concentrated in vacuo. But-3-ene-1-amine hydrochloride **6a** was obtained as a colorless solid (21.6 g, 201 mmol, 96 %). ^{1}H NMR (300.19 MHz, D_2O) δ (ppm) 2.48 (q, J = 6.7 Hz, 2 H), 3.14 (t, J = 6.7 Hz, 2 H), 5.22-5.35 (m, 2 H), 5.77-5.95 (m, 1 H). ^{13}C NMR (75.56 MHz, D_2O): δ (ppm) 31.0, 38.8, 119.0, 133.2. MS (EI$^+$) *m/z* 71.08 $[M\text{-}HCl]^+$.

1,2-Di(but-3-en-1-yl)diaziridine (2). But-3-enyl-1-amine hydrochloride **6a** (7.54 g, 70.0 mmol) was added to a solution of NaOH (5.60 g, 140 mmol, 2.00 eq.) in water (7.60 mL) at 0°C. First, a concentrated formaldehyde solution (1.05 g, 2.80 mL, 35.0 mmol, 0.50 eq., 37% w/w) and then sodium hypochlorite solution (2.61 g, 18.6 mL, 35.0 mmol, 0.50 eq., 14% w/w) were added dropwise over 30 min. The mixture was stirred at room temperature for 13 h, the organic layer was separated, and washed with diluted sodium thiosulfate solution and water. Flash chromatography (SiO_2, DCM/MeOH 99:1, R_f = 0.36) afforded 1,2-di(but-3-en-1-yl)diaziridine **2** as a clear oil (1.76 g, 33 %). ^{1}H NMR (300.51 MHz, $CDCl_3$) δ (ppm) 2.26–2.41 (m, 6 H), 2.48 (s, 2 H), 2.52-2.62 (m, 2 H), 4.98–5.15 (m, 4 H), 5.77-5.95 (m, 2 H); ^{13}C NMR (75.56 MHz, $CDCl_3$): δ (ppm) 33.2, 57.0, 60.6, 116.0, 136.1; GC-MS: *m/z* 55.2 $[C_4H_7]^+$, 84.1 $[M\text{-}C_5H_8]^+$, 97.1 $[M\text{-}C_4H_7]^+$,. 111.1 $[M\text{-}C_3H_5]^+$, 125.1 $[M\text{-}C_2H_3]^+$, 151.2 $[M\text{-}H]^+$; HR-MS (EI$^+$) *m/z* calcd for $C_9H_{16}N_2$ 152.1308, found 152.1297.

N-(Pent-4-en-1-yl)phthalimide. [17] Pentene-1-ol (6.00 g, 7.20 mL, 69.7 mmol), phthalimide (11.3 g, 76.7 mmol, 1.10 eq.) and triphenylphosphine (20.1 g, 76.7 mmol, 1.10 eq.) were dissolved in dry THF (40.0 mL) and cooled to 0°C. Di*iso*propyl azodicarboxylate (15.5 g, 15.1 mL, 76.7 mmol, 1.10 eq.) was added dropwise. The mixture was stirred for 3 h at 0°C. The solvent was removed under reduced pressure and the mixture loaded directly onto a silica column and subjected to flash chromatography (SiO_2, petroleum ether/ethyl acetate 6:1, R_f = 0.50) to furnish *N*-(Pent-4-en-1-yl)phthalimide as a colorless oil (14.6 g, 97%). ^{1}H NMR (300.51 MHz, $CDCl_3$): δ (ppm) 1.80 (quin, J = 7.4 Hz, 2 H), 2.08–2.20 (m, 2 H), 3.71 (t, J = 7.4 Hz, 2 H), 4.94–5.12 (m, 2 H), 5.83 (ddt, J = 17.0, 10.3, 6.6 Hz, 1 H), 7.67-7.77 (m, 2 H), 7.80-7.91 (m, 2 H); ^{13}C NMR (75.56 MHz, $CDCl_3$): δ (ppm) 27.6, 31.0, 37.6, 115.3, 123.2, 132.2, 133.9, 137.3, 168.4; MS (EI$^+$) *m/z* (%) 215.12 (20) $[M]^+$, 160.06 (100) $[M\text{-}C_4H_7]^+$.

Pent-4-enyl-1-amine hydrochloride (8a). [18] *N*-(Pent-4-en-1-yl)phthalimide (14.6 g, 67.9 mmol, 1.00 eq.) was dissolved in dry EtOH (300 mL) and heated to 50°C. Hydrazine-monohydrate (7.49 g, 7.27 mL, 150 mmol, 2.20 eq.) was added and refluxed for 1 h. The mixture was quenched with concentrated HCl (80.0 mL) and stirred for 10 min. The white solid was filtered off and washed with EtOH. EtOH was removed under reduced pressure and the remaining aqueous solution was made basic by dropwise addition of NaOH (30% w/w). The solution is extracted with Et_2O (3 x 50.0 mL). Combined organic extracts were extracted with 1 M HCl (3 x 50.0 mL) and aqueous extracts concentrated in vacuo to afford pent-4-enyl-1-amine hydrochloride **8a** as white solid (7.60 g, 62.5 mmol, 92 %). ^{1}H NMR (300.51 MHz, D_2O): δ (ppm) 1.70 (d, J = 7.57 Hz, 2 H), 2.08 (q, J = 6.97 Hz, 2 H), 2.93 (t, J = 7.4 Hz, 2 H), 4.95-5.11 (m, 2 H), 5.80 (ddt, J = 17.0, 10.3, 6.6 Hz, 1 H)); ^{13}C NMR (75.56 MHz, D_2O) δ (ppm) 25.8, 29.7, 39.0, 115.7, 137.4; MS (EI$^+$) *m/z* (%): 86.10 (3) $[M\text{-}Cl]^+$.

1,2-Di(pent-4-en-1-yl)diaziridine (3). Pent-4-enyl-1-amine hydrochloride **8a** (7.76 g, 63.8 mmol) was added to a solution of NaOH (5.10 g, 127 mmol, 2.00 eq.) in water (7.50 mL) at 0°C. First, a concentrated formaldehyde solution (2.38 mL, 31.9 mmol, 0.50 eq., 37% w/w)

and then sodium hypochlorite solution (14.1 mL, 31.9 mmol, 0.50 eq., 14% w/w) were added dropwise over 30 min. The mixture was stirred at room temperature for 13 h, then the organic layer was separated and washed with diluted sodium thiosulfate solution and water. Flash chromatography (SiO_2, DCM/MeOH 99:1, R_f = 0.26) afforded 1,2-di(pent-4-en-1-yl) diaziridine **3** as a clear oil (1.44 g,25 %).[1]H NMR (300.51 MHz, $CDCl_3$) δ (ppm) 1.70 (quin, J = 7.43 Hz, 4 H), 2.08 - 2.30 (m, 6 H), 2.45 (s, 2 H), 2.51 (dt, J = 11.93, 7.6 Hz, 2 H), 4.93–5.08 (m, 4 H) 5.82 (ddt, J = 17.0, 10.3, 6.6 Hz, 2 H); ^{13}C NMR (75.56 MHz, $CDCl_3$) δ (ppm) 27.9, 31.4, 56.8, 60.7, 114.7, 138.3; GC-MS (EI$^+$) *m/z* = 55.2 $[C_4H_7]^+$, 84.1 $[M\text{-}C_4H_7\text{-}C_3H_5]^+$, 98.1 $[M\text{-}C_4H_7\text{-}C_2H_3]^+$,. 111.1 $[M\text{-}C_3H_5]^+$, 125.1 $[M\text{-}C_4H_7]^+$, 179.1 $[M\text{-}H]^+$; HRMS (EI$^+$) *m/z* calcd for $C_{11}H_{20}N_2$ 180.1621, found 180.1607.

1,2-Dicinnamyldiaziridine (9). Under argon K_2CO_3 (49.0 mg, 0.35 mmol, 5.54 eq.) and NBu_4Br (47.0 mg, 0.15 mmol, 2.28 eq.) were added to dry MeCN (2 mL). 1,2-Diallyldiaziridine **1** (8.00 mg, 0.06 mmol, 1.00 eq.), iodobenzene (39.4 mg, 0.19 mmol, 3.00 eq.) and $Pd(OAc)_2$ (5 mol%, 3.20 μmol, 0.72 mg) were added subsequently. The mixture was stirred at 83°C for 24 h. After cooling to room temperature the mixture was loaded directly onto a silica column (pentane/diethylether 4:1, R_f = 0.16) to afford the product as a colorless oil (6.00 mg, 34%). ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 2.65 (s, 2 H) 3.14–3.32 (m, 4 H) 6.34 (dt, J = 15.9, 6.5 Hz, 2 H) 6.60 (d, J = 15.9 Hz, 2 H) 7.21-7.37 (m, 10 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) 56.2, 62.9, 125.5, 126.4, 127.5, 128.5, 132.7, 136.9; HRMS (EI$^+$) *m/z* calcd for $C_{19}H_{20}N_2$ 276.1621, found 276.1641. **R_f** (Chiralpak IC, 25 cm 4.6 mm, Hex/IPA 98/2, 1.0 mL/min, 20°C) 7.6 min and 8.8 min.

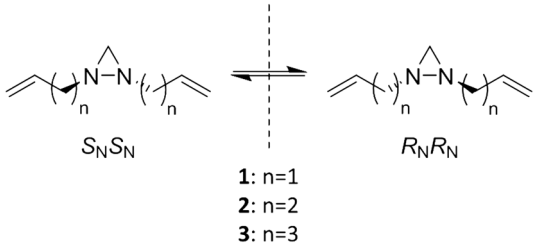
5,5'-Dipent-4,4'-enyldiaziridine-2,2'-diacetoxybiphenyl (10). 2,2'-Acetoxy-5,5'-diiodobiphenyl (145 mg, 277 μmol, 1.00 eq.) was dissolved in anhydrous MeCN (16 mL) under argon. 1,2-Di(pent-4-en-1-yl) diaziridine (3) (50.0 mg, 277 μmol, 1.00 eq.), PPh_3 (14.5 mg, 60 μmol, 20 mol%), $Pd(OAc)_2$ (6.20 mg, 30.0 μmol, 10 mol%), NEt_3 (76.0 μl, 554 μmol, 2.00 eq.) and Ag_2CO_3 (76.4 mg, 277 μmol, 1.00 eq.) were added subsequently. The mixture was stirred at 83°C for 24 h. The crude mixture was concentrated in vacuo and loaded on a silica column eluting with EtOAc. The crude mixture was purified by preparative HPLC (26 mg, 21%). **R_f** (Chiralpak IA, 25 cm 4.6 mm, Hex/IPA 98/2, 1.0 mL/min, 20°C) 18.2 min and 22.6 min. ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 1.60 - 1.69 (m, 4 H), 2.12 (s, 3 H) 2.13 (s, 3 H) 2.19–2.40 (m, 6 H) 2.48 (bs, 2 H) 2.63–2.90 (m, 2 H), 6.08–6.32 (m, 2 H), 6.33–6.49 (m, 2 H), 7.04–7.15 (m, 4 H) 7.40–7.56 (m, 2 H); ^{13}C NMR (151 MHz, $CDCl_3$) δ (ppm) 20.89, 20.92, 27.16, 27.41, 31.33, 32.14, 57.10, 61.66, 62.02, 122.48, 122.51, 127.55, 127.82, 127.90, 127.97, 128.68, 128.91, 128.98, 129.20, 130.84, 131.46, 131.84, 132.25, 146.63, 146.70, 169.45, 169.48. HRMS (ESI$^+$) *m/z* calcd for $C_{27}H_{31}N_2O_4$ 447.2278 found 447.2279.

RESULTS AND DISCUSSION

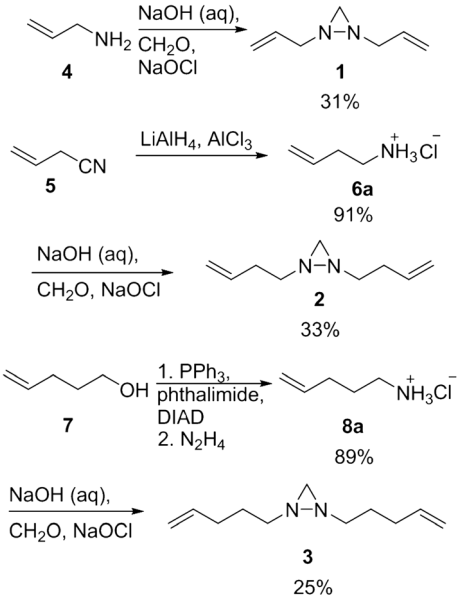
The synthesis of the 1,2-dialkenyl diaziridines **1–3** (Scheme 2) is based on a modified protocol developed by Ohme et al.[19] and Makhova et al.[11] where amines are treated with formaldehyde to form the aminal followed by in situ mono N-chlorination and nucleophilic ring closing.

1,2-Diallyldiaziridine **1** was obtained from allylamine **4** (cf. Scheme 3).[11]

To prepare 1,2-dibutenyl- and 1,2-dipentenyldiaziridine **2** and **3** (Scheme 3), respectively, the corresponding amines 3-butenylamine and 4-pentenylamine were synthesized according to procedures described in the literature. 3-Butenylamine **6b** was obtained by reduction of allylcyanide **5** with $LiAlH_4$.[20] Since isolation from the organic layer proved to be inconvenient due to the volatility of the free amine **6b**, it was isolated as its corresponding ammonium salt **6a** in 91% yield (cf. Scheme 1). 4-Pentenylamine **8b** was obtained by Mitsunobu reaction of 4-pentenol **7** with phthalimide followed by reduction with hydrazine.[20,21] Again, isolation of the corresponding ammonium salt **8a** proved to be method of choice (cf. Scheme 3).



Scheme 2. Structures of the synthesized and investigated 1,2-dialkenyl diaziridines.



Scheme 3. Synthesis of 1,2-alkenylsubstituted diaziridines **1**, **2,** and **3**.

The ammonium salts were reacted with formaldehyde and sodium hypochlorite under basic conditions using two equivalents of NaOH to release the free amines in situ. The diaziridines were obtained in moderate yields between 25 and 32% (cf. Scheme 3). Attempts to distill the crude reaction product failed; however, flash chromatography provided the reaction products in high purity without decomposition.

Investigation of the stereodynamic properties of the three diaziridines was carried out using enantioselective DGC.[15,22–33] Excellent separation of the enantiomers of these three diaziridines was achieved by gas chromatography using the chiral stationary phase heptakis(6-O-*tert.*-butyldimethylsilyl-2,3-di-O-ethyl)-β-cyclodextrin.[34,35] To determine the reaction rate constants, the activation parameters $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ of the enantiomerization of the diaziridines temperature-dependent DGC experiments were performed between 80 and 170°C. Representative gas chromatograms of the temperature-dependent separation of the enantiomers of 1,2-diallyldiazirine are depicted in Figure 1. At 100°C separation of the enantiomers of **1** was achieved without notable interconversion. Higher temperatures lead to characteristic plateau formations. Peak coalescence was observed for 1,2-diallyldiaziridine **1** at 170°C. The reaction rate constant of enantiomerization k_1 were determined by unified equation of chromatography,[36–41] which allows a direct, fast and precise evaluation of the experimental peak profiles.

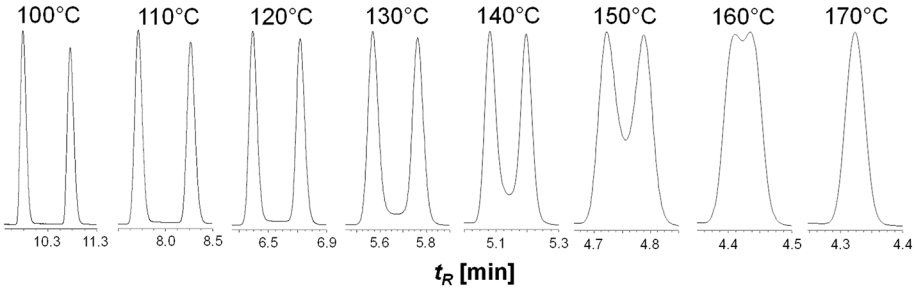


Fig. 1. Chromatograms of 1,2-diallyldiaziridine between 100 and 170°C. Separation conditions: 50 m × 250 μm i.d. fused-silica capillary coated with 250 nm heptakis(6-O-*tert*.-butyldimethylsilyl-2,3-di-O-ethyl)-β-cyclodextrin dissolved in polydimethylsiloxane PS086 (50% w/w), He as inert carrier gas.

For the evaluation of the activation parameters of enantiomerization of 1,2-diallyldiaziridine **1** experiments between 105 and 145°C (5°C steps) were considered.

Gibbs free activation energies $\Delta G^{\ddagger}$ of enantiomerization of the diaziridines was calculated according to the Eyring Equation. The activation enthalpies $\Delta H^{\ddagger}$ and activation entropies $\Delta S^{\ddagger}$ were obtained by temperature-dependent measurements and plotting $\ln(k/T)$ as a function of T. The activation enthalpy $\Delta H^{\ddagger}$ of the enantiomerization process was obtained from the slope and the activation entropy $\Delta S^{\ddagger}$ from the intercept of the Eyring plot. Figure 2 shows the Eyring plot for interconversion of 1,2-diallyldiaziridine **1**. Deviations of the activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated by error band analysis of the linear regression.

The enantiomerization of 1,2-di(but-3-enyl) diaziridine **2** and 1,2-di(pent-4-enyl)diaziridine **3** were also investigated by enantioselective DGC. Also, dynamic elution profiles with characteristic plateau formations were obtained for 1,2-di(but-3-enyl)diaziridine **2** and 1,2-di(pent-4-enyl)diaziridine **3**.

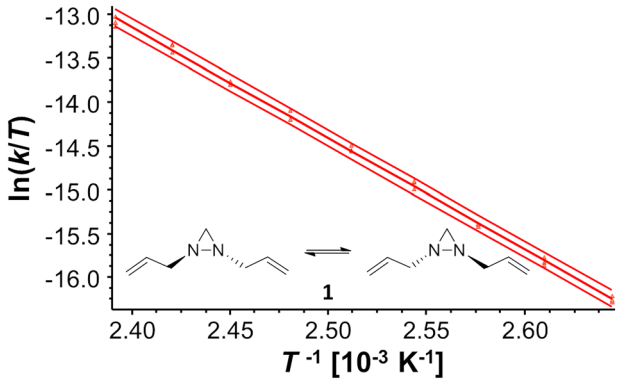


Fig. 2. Eyring plot of 1,2-diallyldiaziridine **1** obtained by enantioselective DGC to determine the activation parameters of enantiomerization. The upper and lower curves represent the error bands of the linear regression with a level of confidence of 95%. For the linear regression, three measurements for each temperature were considered.

These two diaziridines show very similar stereodynamic behavior compared to 1,2-diallyldiaziridine **1**. At 100°C, baseline separation of the two enantiomers is achieved and at 160°C peak coalescence due to rapid interconversion occurs. The elevated temperature leads to increased peak plateau formation. Peak coalescence is observed at 160°C compared to 170°C for the 1,2-diallyl analog. This is attributed to slightly lower separation factors, so that peak coalescence already at lower temperatures occurs. The separation of 1,2-di(pent-4-enyl) analog **3** was improved by using a shorter separation column (25 m), improving the quality of the separation profiles. For evaluation of the kinetic data experiments between 110 and 140°C in 5°C steps were considered for 1,2-di(but-3-enyl)diaziridines **2**.

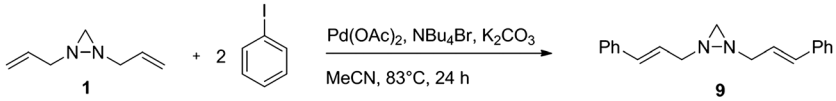
For 1,2-di(pent-4-enyl)diaziridine **3** at elevated temperatures peak coalescence was observed, so only measurements within the temperature range between 100 and 110°C were considered to obtain kinetic data.

In Table 1 the results are summarized and compared to saturated analogs. Overall, a very good agreement between the saturated analogs 1,2-di-*n*-propyl- and 1,2-di-*n*-butyldiaziridine can be observed. The interconversion barrier of the diaziridines slightly decreases with increasing chain length. These data allow predicting barriers in more complex systems where the diaziridine moiety is used as dominating a chiral switching unit.

To further investigate the applicability of the synthesized alkenyl substituted diaziridines in building more complex ligand systems, 1,2-diallyldiaziridine **1** was used as the substrate for a Heck reaction (Scheme 4).[42] Because of the sensitivity of diaziridines, mild phosphine-free conditions, namely, an aromatic iodide, NBu_4Br and $Pd(OAc)_2$ and K_2CO_3 as additional base were chosen.[43] Heck reactions often require high temperatures, between 110 and 140°C for

TABLE 1. Activation parameter for the enantiomerization of 1,2-diallyldiaziridine **1**, 1,2-di(but-3-enyl)diaziridine **2**, 1,2-di(pent-4-enyl)diaziridine **3**, 1,2-dicinnamyldiaziridine **9**, and diaziridine **10** obtained by enantioselective dynamic gas chromatography or racemization studies after preparative HPLC separation of compounds **9** and **10**

Compound	R	$\Delta G^{\ddagger}_{298K}$ [kJ mol^{-1}]	$\Delta H^{\ddagger}$ [kJ mol^{-1}]	$\Delta S^{\ddagger}$ [J mol^{-1} K^{-1}]
1	$CH_2CH=CH_2$	119.7	105.2 ± 0.9	−49 ± 1
2	$(CH_2)_2CH=CH_2$	119.5	102.3 ± 1.9	−58 ± 2
3	$(CH_2)_3CH=CH_2$	114.9	106.7 ± 8.9	−29 ± 2
	$(CH_2)_2CH_3$ [3]	118.7	100.7 ± 2.1	−60 ± 3
	$(CH_2)_3CH_3$ [4]	119.8	103.4 ± 2.6	−55 ± 3
9	$CH_2CH=CH$-Ph	124.4	111.3 ± 3.7	−44 ± 3
10	-[$(CH_2)_3CH=CH$-Ph(OAc)]$_2$	122.9	111.8 ± 12.4	−36 ± 8



Scheme 4. Double Heck reaction of 1,2-diallyldiaziridine **1** with iodobenzene.

satisfactory conversions. Due to potential decomposition of diaziridines at high temperatures, refluxing acetonitrile was used, limiting the temperature to 83°C. A Heck reaction was performed with 1,2-diallyldiaziridine **1** and iodobenzene refluxing 24 h in acetonitrile. After flash chromatography, 1,2-dicinnamyldiaziridine **9** was isolated in 34% yield.

Since the starting material could be reisolated, it is most likely that complete conversion to the desired product did not occur due to decomposition of the Pd catalyst (formation of palladium black), but not due to decomposition of the diaziridine. Therefore, a complete conversion can be achieved by successive reaction of the nonconverted reactants. This demonstrates that diaziridines are stable under Pd catalysis and can be applied to more complex systems. Next, we investigated the stereodynamics of 1,2-dicinnamyldiaziridine **9** to obtain further insight into the influence on the interconversion barrier of the remote phenyl groups. Due to the decreased volatility of this product, enantioselective HPLC was the method of choice to achieve enantiomer separation. Because of the high interconversion barrier of diaziridine **9** and the limited temperature range of HPLC, dynamic interconversion experiments could not be performed. Therefore, compound **9** was separated into its enantiomers by preparative enantioselective HPLC using the Okamoto type chiral stationary phase (CSP) Chiralpak IC. One of the enantiomerically pure samples was then heated to different temperatures for 2 h and the composition of enantiomers analyzed (cf. Fig. 3).

From the de novo peak areas the enantiomerization rate constants k_{enant} were calculated according to Eq. (2), where A represents the area, t the reaction time:

$$k_{enant} = \frac{In\frac{A_{major}+A_{minor}}{A_{major}}}{2t} \quad (2)$$

$\Delta G^{\ddagger}$ of enantiomerization was calculated according to the Eyring equation, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were obtained from the corresponding Eyring plot (cf. Fig. 4), which are in very good agreement with the experimental data of the 1,2-dialkenyl diaziridines (cf. Table 1). The enantiomerization barrier of **9** compared to the barrier of **1** is slightly increased, which can be explained by the increased rigidity of the cinnamyl system

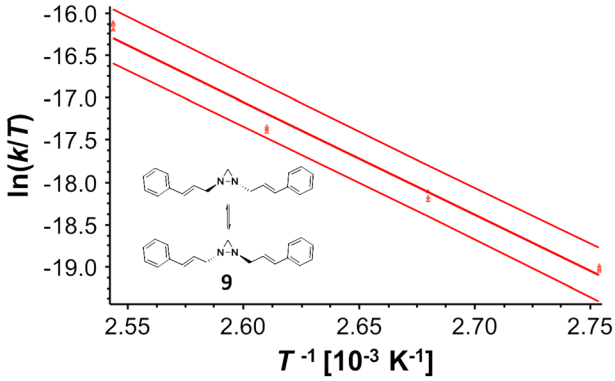


Fig. 4. Eyring plot of 1,2-dicinnamyldiaziridine **9** to determine the activation parameters of enantiomerization. The upper and lower curves represent the error bands of the linear regression with a level of confidence of 95%. For the linear regression, three measurements for each temperature were considered.

($\Delta G^{\ddagger}(298.15\,K) = 124.4\,kJ{\cdot}mol^{-1}$, $\Delta H^{\ddagger} = 111.3 \pm 3.7\,kJ{\cdot}mol^{-1}$, $\Delta S^{\ddagger} = -44 \pm 3\,J{\cdot}(K{\cdot}mol)^{-1}$).

In a very similar approach, we used 1,2-di(pent-4-en-1-yl) diaziridine **3** to bridge 2,2'-diacetoxybiphenyl with a diaziridine in the backbone (Scheme 5). Quantum chemical calculations indicated that at least a chain of five carbon atoms is needed on both sides of the diaziridine moiety to achieve an efficient cyclization. Furthermore, quantum chemical calculations at the DFT B3LYP 6-31G* level of theory predicted that the interconversion barrier should be around $120\,kJ{\cdot}mol^{-1}$, which means that the stereodynamics is solely dominated by the diaziridine ring and therefore the tropos biphenyl unit will align according to the stereochemistry of the diaziridine ring.

The interconversion barrier was determined by temperature-dependent racemization measurements after separation of the enantiomers by preparative HPLC in the presence of the CSP Chiralpak IA with a good separation factor α of 1.24. The activation parameters were obtained by Eyring plot analysis and determined to be $\Delta G^{\ddagger}(298.15\,K) = 122.9\,kJ{\cdot}mol^{-1}$, $\Delta H^{\ddagger} = 111.8 \pm 12.4\,kJ{\cdot}mol^{-1}$, and $\Delta S^{\ddagger} = -36 \pm 8\,J{\cdot}(K{\cdot}mol)^{-1}$, which are in very good agreement with the quantum chemical calculations and the barriers of the other compounds determined in this study.

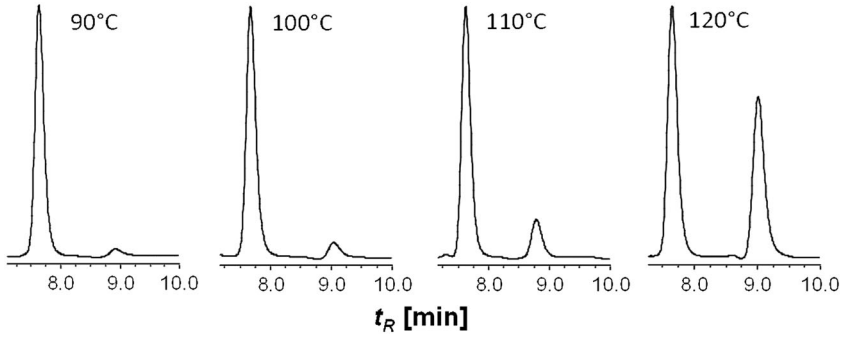
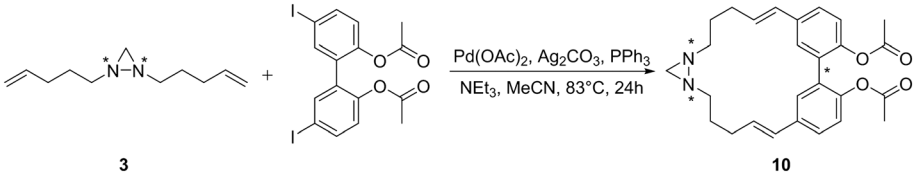


Fig. 3. Chromatograms of 1,2-dicinnamyldiaziridine **9** after heating an enantiomerically pure sample to 90–120°C for 2 h.



Scheme 5. Synthesis of 5,5'-dipent-4,4'-enyldiaziridine-2,2'-diacetoxybiphenyl **10** by a double Heck reaction.

CONCLUSION

We successfully synthesized alkenyl substituted diaziridines and investigated their dynamic behavior by enantioselective DGC and classical racemization analysis. The unified equation gives access to kinetic parameters (rate constants) and in combination with the Eyring equation activation parameters $\Delta G^{\ddagger}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ for the enantiomerization of the here investigated compounds were obtained. Increasing chain length of the alkenyl substituents results in no remarkable difference of the activation barrier $\Delta G^{\ddagger}$ for the interconversion process between enantiomeric diaziridines. We also demonstrated that alkenyl substituted diaziridines can be used as versatile building blocks in Pd-mediated catalytic reactions, e.g., the Heck reaction, which was shown for the functionalization of 1,2-diallyldiaziridine and 1,2-di(pent-4-en-1-yl)diaziridine. Furthermore, we have shown that this method is expandable to more complex substrates and thus be able to build ligands containing a chiral switch for various metal catalyzed reactions.

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