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Traceless isoprenylation of aldehydes via *N*-Boc-*N*-(1,1dimethylallyl)hydrazones

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Abstract: A short isoprenylation protocol starting from nonconjugated *N*-Boc-*N*-(1,1-dimethylallyl)hydrazones was developed utilising Thomson's traceless bond construction. This type of [3,3]sigmatropic rearrangement is catalysed by the Brønsted acid triflimide and liberates only gaseous by-products. The required *N*-Boc-*N*allylhydrazine precursor is available in three steps starting from a known diazene using biocatalytic aldol addition and Tebbe olefination as key steps. Allylhydrazones are prepared via condensation with appropriate aldehydes. Scope and limitations of the [3,3]-sigmatropic rearrangements are analysed.

Introduction

The [3,3]-sigmatropic rearrangement is a common but impressive tool for the formation of new C-C-bonds in synthetic chemistry.^[1] In 1973 Stevens showed that N-allylhydrazones undergo such a rearrangement under release of N₂ as well, but due to very harsh reaction conditions (300 °C) and low yields, this reaction was limited in its applicability.^[2] For several decades, synthetic chemists did not see any real benefit of this unique rearrangement, until 2010, when Thomson and co-workers published the traceless bond construction (TBC), an improved variant of Stevens' [3,3]-sigmatropic rearrangement, working with N-Boc-Nallylhydrazones (A, Scheme 1a) and catalytic amounts of the Brønsted superacid triflimide (HNTf2).[3] It was now possible to lower the temperature of the rearrangement to 125 °C and the yields of the products could be increased. This pioneering work of Thomson allowed the synthesis of various 1,2-disubstituted olefins (B) and one 1,1-disubstituted olefin (Scheme 1a). Monosubstituted olefins could not be obtained by this way. Later our group extended the scope to the synthesis of 1,1-disubstituted olefins (D, Scheme 1b), bearing an isopropyl group in 1-position, which resulted in a methylene branched end, a motif which is found in the side chains of steroidal natural products, e.g. episterol.^[4] In the same year we reported the synthesis of terminal vinylsilanes (F, Scheme 1c) using TBC, which opened a new route to diversely substituted olefins.^[5]

In this work we present a protocol for the introduction of an isopentenyl (isoprenyl) residue to aldehydes (Scheme 1d). The

isoprenyl function is a common structural element in terpenoid biomolecules and natural secondary metabolites.^[6] The natural isoprene building block in terpenoid biosynthesis is dimethylallyl pyrophosphate (DMAPP).^{[7],[8]} Steroids like cholesterol as a membrane component^[9], pigments like β -carotene,^[10] or cortisone or progesterone to name a few hormones,^[11] are naturally occurring terpenoid derivatives, derived from DMAPP.

в

D







HNTf₂ (10 mol%)

b) Dittrich and Bracher (2015):^[4]

R¹ = aryl, alkyl

c) Dittrich and Bracher (2015):^[5]

$$\begin{array}{c} \xrightarrow{\text{HNTf}_2 (10 \text{ mol}\%)} \\ \xrightarrow{\text{HNTf}_2 (10 \text{ mol}\%)} \\ \xrightarrow{\text{diglyme, } 125 \ ^\circ C} \\ \xrightarrow{\text{R}^1 \otimes N^{-N} \otimes \text{Boc}} \\ \xrightarrow{\text{Pol}_2 \cap 1, \ ^\circ C \otimes 2^{\uparrow}, \ ^\circ C_4 H_8 \uparrow} \\ \end{array}$$



Scheme 1. a) Original TBC by Thomson and co-workers.^[3] b) Extension of the TBC to the synthesis of 1,1-disubstituted olefins bearing an isopropyl group.^[4] c) TBC yielding terminal vinylsilanes.^[5] d) Introduction of an isoprenyl group via TBC developed in this work.

At the biological level, protein prenyltransferases attach terpenoid residues like farnesyl (C_{15}) or geranylgeranyl (C_{20}) groups to

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cysteinyl residues of proteins in posttranslational modifications. Due to the introduction of this hydrophobic group, the proteins can anchor in biomembranes resulting in altered biological activities.^[12] In synthetic chemistry, organometallic building blocks like 3-methyl-2-butenylmagnesium chloride are commonly used for the introduction of an isoprenyl group.^[13] Utilising inverse reactivities, 3,3-dimethylallyl bromide can be applied as an electrophilic isoprenyl building block,^[14] as exemplified by the total syntheses of natural products, e.g. (\pm)-eldanolide^[15] and (\pm)-fumagillin.^[16] Besides direct isoprenylation, eliminations can lead to the isoprenyl function by forming the thermodynamically most stable double bond, e.g. from tertiary alcohols by dehydration.^[17] An intramolecular isoprenylation, in which the group is constructed during a rearrangement, is to the best of our knowledge, not described in literature yet.

A further centrepiece of this work is the synthesis of the required, hitherto unknown, N-Boc-N-(1,1-dimethylallyl)hydrazine building block (G. Scheme 1d), bearing two geminal methyl groups in gposition to the hydrazine moiety to receive the desired isoprenylated products (I, Scheme 1d) via N-Boc-Nallvlhvdrazones (H. Scheme 1d). In our previous investigations leading to 1.1-disubstituted olefins.^[4] undesired subsequent acidcatalysed isomerisations of the formed olefinic double bond^[18] were observed, which led occasionally to isomeric mixtures of product alkenes. In the present case this is not expected to happen, since the resulting trisubstituted olefin should be the thermodynamically most stable isomer. An additional benefit of the two geminal methyl groups in precursor G is on the one hand that product I cannot be formed as mixture of E/Z isomers and on the other hand it is expected to facilitate the rearrangement due to the Thorpe-Ingold effect (gem-dimethyl effect).^[19] As a result, less drastic reaction temperatures and shortened reaction times may be employable.^[20]

Results and Discussion

The synthesis of the required N-Boc-N-(1,1dimethylallyl)hydrazine building block 8a (Scheme 2; G in Scheme 1d) started with the two-step synthesis of known N-Troc-N-Boc-protected diazene 2.[21] Conversion into aldehyde 6a was performed on two different routes. Route A used commercially available silyl enol ether 3, which was activated by LiOTf and TBAF. The idea was to achieve a controlled O-Si-bond cleavage in 3 by slow addition of the fluoride source. Simultaneously, the presence of significant amounts of lithium ions should lead to an immediate formation of the lithium enolate. However, the addition of 3 to 2 did not proceed in a regioselective manner, and a 50:50 mixture of the isomeric aldehydes 6a and its regioisomer 6b was obtained. It is noteworthy, that the regioselectivity of this reaction could not be measured in this step, hence, it was determined retrospectively after conversion into 8a/8b after the last step. Both isomers showed identical chromatographic behaviour and no distinct signals enabling quantification of the ratio of regioisomers could be observed by NMR spectroscopy until reaching 8a/8b. Because of the lack of regioselectivity, an alternative approach to intermediate 6a utilising organocatalysis^{[22],[23]} was worked out (route B). For this Aldol-type reaction with isobutyraldehyde (4), three catalysts were explored: L-proline,^[24] L-phenylalanine,^[25] and Ley's (S)-5-(pyrrolidin-2-yl)-1H-tetrazole (5).[21],[26] Tetrazole catalyst 5 gave the best result with 68% yield and the isomeric ratio could be improved to 91:9 (determined retrospectively by ¹H NMR spectroscopy) of the desired aldehyde **6a** and its regioisomer **6b**. Methylenation of the aldehyde function of **6a/6b** gave the olefins **7a** and **7b**. Different methods like Wittig,^[27] Nysted-Takai^[28] and Tebbe^[29] olefination were tested, whereby the first two methods did not result in any product. Under Tebbe conditions the desired terminal olefin **7a** and its regioisomer **7b** were obtained in an acceptable yield of 48% as an inseparable mixture.



Scheme 2. Route A leading to an equimolar mixture of 8a/8b starting from silyl enolether 3. Route B provides 8a, contaminated with 9% of isomer 6b starting from aldehyde 4. *The ratios of the isomers were determined retrospectively by NMR spectroscopy of the product 8a/8b. The X-ray crystal structure of the desired isomer 8a is shown on the left. Diazene 2 was synthesised according to literature.^[21]

Chemoselective reductive Troc cleavage with zinc powder gave a still inseparable mixture of the desired olefin 8a and its constitutional isomer 8b in excellent yield. However, at this stage NMR spectroscopy enabled determination of the ratio of isomers (route A 50:50, route B 91:9). The structure of the desired N-Boc-N-allylhydrazine 8a was unambiguously confirmed by X-ray crystal structure analysis (see Supporting Information). The enriched isomeric mixture of building block 8a and 8b could be used for the next step without further purification, since exclusively 8a undergoes condensation with the employed aldehydes to give the N-Boc-N-allylhydrazones 9, whereas the isomer 8b remains unreacted. Scheme 3 shows the prepared allylhydrazones 9a-q. Aliphatic (9a-d, 9f, 9g, 9p), allylic (9h, 9q) and aromatic (9i-9o) and ester-bearing (9e) allylhydrazones were synthesised by reacting the appropriate aldehydes with building block mixture 8a/b in ethanol (yields 33-95%). Especially nonconjugated allylhydrazones slowly decomposed during the purification process, which is reflected in the yields. Before we studied the capability of our N-Boc-N-allylhydrazine building block 8a, we identified the optimum reaction conditions for the

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rearrangement utilising cyclohexanecarboxaldehyde-derived hydrazone 9g as a model compound. Overall, 33 test reactions were performed with variations of temperature (23 to 125 °C), time (15 to 75 min) and solvents (THF and diglyme) (see Supporting Information). Significant rearrangement was only accomplished at temperatures of 75 °C and above. Besides HNTf₂ (pK_a -12.0, measured in DCE),^[30] triflic acid (TfOH, pK_a -11.3, measured in DCE)^[30] and trifluoroacetic acid (TFA, pK_a 0.23)^[31] were tested. All in all, the hitherto used conditions of Thomson^[3] (HNTf₂, diglyme, 125 °C) gave the best results for this conversion, closely followed by the rearrangement with triflic acid in diglyme at 125 °C, which would be a rewarding alternative to HNTf₂, which decomposes immediately in air and requires extremely dry reaction conditions. As the main side product, and even right at the beginning of the reaction, the corresponding Boc-deprotected allylhydrazone was observed, a compound which does not undergo the rearrangement. This is in accordance with the observations of Thomson and could not be prevented.^[3] This prompted us to further investigate an alternative carbamate residue, which might be less prone to premature acidic cleavage. We prepared the ethyl carbamate analogue S5a of 8a starting from ethyl carbazate on a route analogous to route B shown in Scheme 2 (for details, see Supporting Information). Two N-Boc-N-allylhydrazones S6g and S6i derived thereof were subjected to the previously determined best reaction conditions for rearrangement (HNTf₂, diglyme, 125 °C), but though the starting materials were fully consumed, none of the expected rearrangement products could be identified by GC/MS analysis. Consequently, the Boc group cannot be replaced in this protocol by the smaller ethoxycarbonyl group.



Scheme 3. *N*-Boc-*N*-allylhydrazones **9a-q** prepared via condensation reaction between *N*-Boc-*N*-allylhydrazine **8a** and appropriate aldehydes. The yields refer to the content of *N*-Boc-*N*-allylhydrazine **8a** in the applied **8a/8b** mixture.

Scheme 4 shows the following rearrangement of substrates 9. The allylhydrazones 9a-c derived from *n*-alkanals underwent

sigmatropic rearrangement providing the appropriate olefins **10a**c in 20-21% isolated yields. The poor yields are in part due to the high volatility of the olefinic products, as demonstrated by an increased yield (25%) of **10g** on a larger scale (3 mmol). The rearrangement product **10d** of isobutyraldehyde-derived *N*-allylhydrazone **9d** could be detected by GC/MS, but could not be isolated due to its very high volatility (b.p. 135-136 °C^[32]). Ester **9e** did not undergo rearrangement to the corresponding olefin and only the Boc-deprotected allylhydrazone was found.



Scheme 4. Successful rearrangements of *N*-Boc-*N*-allyhydrazones using the standard conditions of the TBC. The reactions were performed at least in a 0.5 mmol scale. Isolated yields are given.

N-Allylhydrazones derived from cycloalkane carboxaldehydes (9f, 9g) underwent rearrangement to olefins 10f and 10g with a yield of 20% for both compounds (Scheme 4). In contrast, allylhydrazone 9h derived from an a,b-unsaturated aldehyde did not undergo rearrangement and again only Boc-deprotected allylhydrazone was isolated. The attempted rearrangements of variously substituted arylidene hydrazones failed as well (9i-m). During the purification process of the attempted rearrangements of 9i and 9j crystalline solids were obtained, which were identified as the symmetric bis-hydrazones 12a/b (Scheme 5).



 $\label{eq:Scheme 5.} Scheme 5. Attempted rearrangements of allylhydrazones 9i and 9j leading to deprotected allylhydrazons 11a/b and bis-hydrazones 12a/b.$

Obviously, acid-mediated removal of both the Boc and the dimethylallyl residue took place in these experiments. Next to those, once again Boc-deprotected allylhydrazones **11a/b** were formed. Introduction of both electron-donating (methoxy compound **9I**) and electron-withdrawing groups (nitro compound **9m**) did not lead to successful rearrangements, and the same holds for hydrazones derived from heteroaromatic aldehydes (thiophene **9n** and pyridine **9o**). After these experiments it became evident which type of allylhydrazones would undergo the attempted acid-catalysed rearrangement. Non-conjugated allylhydrazones, like aliphatic systems **9a-d**, **9f**, and **9g** form the

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corresponding olefins, in contrast to allylhydrazones conjugated with aryl or ester groups, which do not show any rearrangement. The following experiments supported this assumption: Nonconjugated N-allylhydrazone 9p derived from phenylpropanal showed a successful rearrangement with 19% yield, whereas its cinnamaldehyde-derived congener (9q) did not give the desired alkene 10q and only Boc-deprotected allylhydrazone was obtained. Thomson also reported on problems during the development of methods for hydrazone rearrangements, but with aliphatic systems,^{[3],[33]} which resulted in unidentified decomposition products. However, the rearrangement of aryl substituted allylhydrazones worked well in his setup. Bocdeprotected allylhydrazones were observed in every reaction as by-products by GC/MS analysis, but no rearrangement takes place with these deprotected forms under our conditions. The deprotection reaction outcompetes the rearrangement and is a possible reason for the observed yields. This finding validates computational studies towards the mechanism of the triflimidecatalysed [3,3]-sigmatropic rearrangement by Gutierrez et al. indicating that conversion of deprotected allylhydrazones does not proceed well or not at all.^[34]

Conclusion

In summary, we present a unique method for traceless isoprenylation of aliphatic aldehydes *via* triflimide-catalysed [3,3]-sigmatropic rearrangement of *N*-Boc-*N*-allylhydrazones. The central *N*-Boc-*N*-allylhydrazine building block **8a** is available in four steps utilising organocatalysis and Tebbe methylenation. This method opens a new route to isoprenyl compounds. This novel protocol is compromised by poor yields in the final step and its limitation to non-conjugated systems. Nevertheless, it broadens the scope of Stevens-type traceless bond constructions and represents the first example of a TBC for the introduction of an isoprenyl group into readily available aliphatic aldehydes. Therefore, this work extends the repertoire of methods for the total synthesis of isoprenoid natural products.

Experimental Section

General information. All reactions were carried out in oven-dried Schlenk flasks equipped with a septum and a magnetic stirring bar which were evacuated and back filled with dry nitrogen. Solvents were dried according to standard methods by distillation over drying agents. Thin layer chromatography (TLC) was performed using polyester sheets polygram SIL G/UV254 covered with SiO_2 (layer thickness 0.2 mm, 40 x 80 mm) from Macherey-Nagel. Spots were visualized with a CAM (ceric ammonium molybdate) solution followed by heating. Flash column chromatography was performed using SiO₂ 60 (0.040-0.063 mm, 230-400 mesh ASTM) from Merck. For chromatography distilled solvents were used. NMR spectra were recorded on JNM-Eclipse 400 (400 MHz), JNM-Eclipse 500 (500 MHz), Avance III HD 400 MHz Bruker Biospin (400 MHz) and Avance III HD 500 MHz Bruker Biospin (500 MHz) with CrvoProbe™ Prodigy. Chemical shifts δ are reported as δ values in ppm relative to the deuterated solvent peak. The chemical shifts are reported in parts per million [ppm] and refer to the δ scala. Coupling constants J are indicated in hertz [Hz]. For the characterization of the observed signal multiplicities the following abbreviations were applied: s (singlet), d (doublet), dd (doublet of doublet), dt (doublet of triplet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad). Infrared spectra were recorded from 4000-650 cm⁻¹ on a PERKIN ELMER Spectrum BX-59343 FT-IR instrument. For detection a Smiths Detection DuraSamp IR II Diamond ATR sensor was used. The absorption bands are reported in wave numbers (cm⁻¹). High resolution mass spectra (HRMS) were recorded on a Jeol Mstation 700 (Fa. Jeol, Peabody, USA) or JMS GCmate II Jeol instrument for electron impact ionisation (EI) equipped with a quadrupole doublet based lens system. Thermo Finnigan LTQ FT (Fa. Thermo Electron Corporation, Bremen, Germany) was used for electrospray ionization (ESI) equipped with an ion trap. Melting points were measured with a Büchi apparatus B-540 (Büchi, Flawill, Switzerland) and are reported in °C and are not corrected. Gas chromatography (GC) was performed on a Varian 3800 gas chromatograph coupled to a Saturn 2200 ion trap from Varian (Darmstadt, Germany). The autosampler was from CTC Analytics (Zwingen, Switzerland) and the split/splitless injector was a Varian 1177 (Darmstadt, Germany). Instrument control and data analysis were carried out with Varian Workstation 6.9 SP1 software (Darmstadt, Germany). A Varian VF-5-ms capillary column of 30 m length, 0.25 mm i.d. and 0.25 µm film thickness (Darmstadt, Germany) was used at a constant flow rate of 1.4 mL/min. Carrier gas was helium 99.999% from Air Liquide (Düsseldorf, Germany). The inlet temperature was kept at 300 °C and injection volume was 1 μ L with splitless time 1.0 min. The initial column temperature was 50 °C and was held for 1.0 min. Then the temperature was ramped up to 250 °C with 50 °C/min. Then the products were eluted at a rate of 5 °C/min until 310 °C (hold time 3 min). Total run time was 20 min. Transfer line temperature was 300 °C and the ion trap temperature was 150 °C. The jon trap was operated with electron jonization (EI) at 70 eV in scan mode (m/z 50 - 650) with a solvent delay of 6.3 min.

Crystallography. All X-ray intensity data were measured on a Bruker D8 Venture TXS system equipped with a multilayer mirror optics monochromator and a Mo K α rotating-anode X-ray tube ($\lambda = 0.71073$ Å). The data collections were performed at 103 K. The frames were integrated with the Bruker SAINT Software package^[35]. Data were corrected for absorption effects using the Multi-Scan method (SADABS)[36]. The structures were solved and refined using the Bruker SHELXTL Software Package^[37]. All C-bound hydrogen atoms were calculated in positions having ideal geometry riding on their parent atoms. The data have been deposited with the Cambridge Crystallographic Data Centre (CCDC) and obtained free charge can be of from: https://www.ccdc.cam.ac.uk/structures/. The deposition number for compound 8a is CCDC 1907495.

Synthesis of Compounds.

Diazene **2** was synthesised according to a literature $protocol^{[21]}$ in two steps and a total yield of 81%.

1-(tert-Butyl) 2-(2,2,2-trichloroethyl) 1-(2-methyl-1-oxopropan-2yl)hydrazine-1,2-dicarboxylate (6a) and 2-(tert-Butyl) 1-(2,2,2trichloroethyl) 1-(2-methyl-1-oxopropan-2-yl)hydrazine-1,2dicarboxylate (6b). Route A: A suspension of LiOTf (875 mg, 5.61 mmol, 1.52 eq) in dry CHCl₃ (20 mL) was cooled to - 50 °C. A solution of diazene 2 (1.70 g, 5.56 mmol, 1.5 eq) in CHCl₃ (10 mL), 2-methyl-1-(trimethylsilyloxy)-1-propen (3) (533 mg, 3.70 mmol, 1.0 eq) in CHCl₃ (10 mL) was added, followed by TBAF (1M in THF, 3.7 mL, 3.7 mmol, 1.0 eq). The resulting reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was stopped with aq. sat. NH₄Cl solution (10 mL) and the lavers were separated. The organic laver was washed with aq. sat. NaHCO3 solution (10 mL), dried over MgSO4, filtered and the solvent was removed in vacuo. The title compound was purified by flash column chromatography (hexanes/EtOAc 8:1). An inseparable mixture of aldehydes 6a/6b (911 mg, 2.43 mmol, 66%) were obtained as a colourless solid in an isomeric mixture of 50:50 (determined retrospectively via ¹H NMR). Route B: Diazene 2 (690 mg, 2.26 mmol, 1.0 eq) and (S)-5-(pyrrolidin-2-yl)-1H-tetrazole (5) (31.4 mg, 0.226 mmol, 10 mol %) were dissolved in dry methylene chloride (15 mL) and the solution was cooled to 0 °C. Isobutyraldehyde (4) (0.25 mL, 2.71 mmol, 1.2 eq) was added slowly and the reaction mixture was allowed to warm to room temperature. After completion of the reaction, the solvent was removed in

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vacuo and the product was purified by flash column chromatography (hexanes/EtOAc 8:1). An inseparable mixture of aldehydes **6a/6b** (580 mg, 1.53 mmol, 68%) were obtained as a colourless solid in an isomeric mixture of 91:9 (determined retrospectively via ¹H NMR): $R_f = 0.17$ (hexanes/EtOAc 8:1); m.p. 128 – 129 °C; ¹H NMR (500 MHz, chloroform-*d*) δ /ppm = 9.49 (s, 1H), 6.70 (s, 1H), 4.93 – 4.51 (m, 2H), 1.44 (s, 9H), 1.36 (s, 3H), 1.29 (s, 3H); ¹³C NMR (101 MHz, chloroform-*d* δ /ppm = 198.1, 155.4, 154.3, 94.9, 84.3, 75.2, 67.4, 28.2, 20.5; IR (ATR) $\tilde{\nu}$ /cm⁻¹ = 3255, 3013, 2980, 2936, 1771, 1723, 1694, 1528, 1457, 1391, 1380, 1365, 1358, 1287, 1254, 1220, 1161, 1108, 1054, 992, 945, 916, 882, 858, 834, 817, 799, 763, 750, 724, 709, 658; HRMS (ESI): *m*/*z* calcd for C₁₂H₁₈Cl₃N₂O₅ [M-H]⁻ 375.0287, found: 375.0287.

1-(tert-Butyl) 2-(2,2,2-trichloroethyl) 1-(2-methylbut-3-en-2yl)hydrazine-1,2-di-carboxylate (7a) and 2-(tert-Butyl) 1-(2,2,2trichloroethyl) 1-(2-methylbut-3-en-2-yl)hydrazine-1,2-dicarboxylate (7b). The isomeric mixture of aldehydes 6a/6b (569 mg, 1.51 mmol, 1.0 eq) and pyridine (0.22 mL, 2.7 mmol, 1.8 eq) were added to a flame dried flask and the mixture was blended to a gel via ultrasound bath. The suspension was cooled to -80 °C and Tebbe reagent (0.5M in toluene, 3.92 mL, 1.96 mmol, 1.3 eq) was added carefully by adding it along the flask. The reaction mixture was allowed to warm to 0 °C and stirred 48 h. The reaction was quenched with a saturated aqueous NaHCO3 solution (6 mL) at -80 °C and extracted with methylene chloride (3 x 10 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed in vacuo. Purification by flash column chromatography (hexanes/EtOAc 9:1) gave an inseparable mixture of olefines 7a/7b (270 mg, 0.719 mmol, 48%) as a colourless solid in an isomeric mixture of 91:9 (determined retrospectively via ¹H NMR): $R_f = 0.29$ (hexanes/EtOAc 9:1); m.p. 103 – 104 °C; ¹H NMR (500 MHz, chloroform-d) δ/ppm = 6.68 (s, 1H), 6.10 (dd, ${}^{3}J_{H,H}$ = 17.4, 11.0 Hz, 1H), 5.08 (d, ${}^{3}J_{H,H}$ = 17.1 Hz, 1H), 5.00 (d, ³J_{H,H} = 10.9 Hz, 1H), 4.87 (d, ²J_{H,H} = 11.5 Hz, 1H), 4.68 (d, ²J_{H,H} = 11.8 Hz, 1H), 1.50 (s, 3H), 1.44 (s, 9H), 1.42 (s, 3H); ¹³C NMR (126 MHz, chloroform-*d*) δ/ppm = 155.4, 154.5, 144.6, 111.2, 95.2, 82.1, 75.1, 62.9, 28.4, 26.6, 26.4; IR (ATR) V/cm⁻¹ = 3323, 2924, 2854, 1733, 1706, 1644, 1522, 1456, 1414, 1386, 1359, 1274, 1253, 1233, 1156, 1101, 1078, 1044, 1011, 990, 967, 922, 907, 851, 815, 759, 741, 724, 688; HRMS (ESI): m/z calcd for $C_{13}H_{20}O_4N_2CI_3$ [M-H]⁻ 373.0494, found: 373.0499.

tert-Butyl 1-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (8a) and tert-Butyl 2-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (8b). The mixture of olefins 7a/7b (95.6 mg, 0.254 mmol, 1.0 eq) was dissolved in a mixture of ethanol (0.3 mL), water (0.3 mL) and acetic acid (0.3 mL). Zinc powder (582 mg, 8.91 mmol, 35.0 eq) was added and the reaction mixture was stirred for 10 minutes at room temperature. After filtration of the reaction mixture, the filtrate was extracted with methylene chloride (3 x 3 mL) and the residue was extracted. The combined organic layers were washed was saturated aqueous NaHCO3 solution (5 mL) and the organic layer was dried over MgSO₄, filtered and the solvent was removed in vacuo. The product was used without purification. 8a/8b (57 mg, 0.28 mmol, quantitative) was obtained as a colourless oil in an isomeric mixture of 91:9: Rf = 0.15 (hexanes/EtOAc 8:2); ¹H NMR (8a) (400 MHz, DMSO-d₆) δ /ppm = 6.00 (dd, ³J_{H,H} = 17.5, 10.7 Hz, 1H), 4.87 (dd, ³J_{H,H} = 17.5, 10.8, 2H), 4.24 (s, 2H), 1.38 (s, 9H), 1.33 (s, 6H); ¹³C NMR (8a) (126 MHz, DMSO-d₆) δ /ppm = 156.4, 146.2, 108.8, 79.3, 60.6, 28.1, 26.5; ¹H NMR (8b) (500 MHz, DMSO- d_6) δ /ppm = 7.95 (s, 1H), 5.81 (dd, ${}^{3}J_{H,H}$ = 17.6, 10.8 Hz, 1H), 5.08 - 4.92 (m, 2H), 4.07 (s, 1H), 1.38 (s, 9H), 1.03 (s, 6H); ¹³C NMR (**8b**) (126 MHz, DMSO-*d*₆) δ/ppm = 155.6, 145.0, 112.2, 78.1, 57.8, 28.2, 24.8; IR (ATR) v/cm⁻¹ = 3334, 2977, 2932, 1679, 1477, 1455, 1412, 1365, 1249, 1163, 1101, 1005, 994, 948, 907, 868, 766, 724, 687; HRMS (ESI): *m*/*z* calcd for C₁₀H₂₁N₂O₂ [M+H]⁺ 201.1597, found: 201.1597.

General procedure 1 (GP1) for the synthesis of *N*-Boc-*N*-(1,1-dimethylallyl)hydrazones 9a-q:

The mixture of N-(1,1-dimethylallyl)hydrazines **8a/8b** (1.0 eq) was dissolved in absolute EtOH and the appropriate aldehyde (1.0 eq) was added. The reaction mixture was stirred at room temperature for 15 h, then

the solvent was removed *in vacuo* and the crude product was purified by flash column chromatography. Isolated yields are correlated to the amount of **8a** in the isomeric mixture **8a/8b**.

tert-Butyl 1-(2-methylbut-3-en-2-yl)-2-octylidenehydrazine-1-carboxylate (9a). Mixture of allylhydrazines 8a/8b (250 mg, 1.75 mmol \triangleq 1.59 mmol of isomer 8a) and octanal (0.298 mL, 1.75 mmol) gave *N*-Boc-*N*-allylhydrazone 9a (178 mg, 0.576 mmol, 36% referred to isomer 8a) as colourless oil via GP1: R_f = 0.58 (hexanes/EtOAc 9:1); ¹H NMR (400 MHz, chloroform-*d*) δ/ppm = 7.71 (t, ³J_{H,H} = 5.6 Hz, 1H), 6.11 (dd, ³J_{H,H} = 17.5, 10.8 Hz, 1H), 5.07 - 4.86 (m, 2H), 2.35 (td, ³J_{H,H} = 5.6 Hz, 2H), 1.59 - 1.50 (m, 2H), 1.42 (s, 9H), 1.39 (s, 6H), 1.34 - 1.24 (m, 8H), 0.87 (m, 3H); ¹³C NMR (101 MHz, chloroform-*d*) δ/ppm = 169.5, 154.3, 146.3, 109.4, 80.9, 61.7, 33.0, 31.9, 29.5, 29.2, 28.6, 26.7, 26.2, 22.8, 14.3; IR (ATR) $\tilde{\nu}$ /cm⁻¹ = 3084, 3004, 2972, 2958, 2927, 2857, 1698, 1641, 1455, 1412, 1391, 1366, 1302, 1244, 1157, 1101, 1003, 991, 901, 855, 757, 724, 686; HRMS (ESI): *m/z* calcd for C₁₈H₃₅N₂O₂ [M+H]* 311.2693, found: 311.2694.

tert-Butyl 1-(2-methylbut-3-en-2-yl)-2-nonylidenehydrazine-1-carboxylate (9b). Mixture of allylhydrazines 8a/8b (404 mg, 2.02 mmol \triangleq 1.83 mmol of isomer 8a) and nonanal (0.346 mL, 2.02 mmol) gave *N*-Boc-*N*-allylhydrazone 9b (284 mg, 0.877 mmol, 48% referred to isomer 8a) as colourless oil via GP1: R_f = 0.58 (hexanes/EtOAc 9:1); ¹H NMR (500 MHz, chloroform-*d*) δ /ppm = 7.71 (t, ³J_{H,H} = 5.6 Hz, 1H), 6.11 (dd, ³J_{H,H} = 17.5, 10.8 Hz, 1H), 5.05 - 4.89 (m, 2H), 2.34 (td, ³J_{H,H} = 5.6 Hz, 2H), 1.55 (m, 2H), 1.42 (s, 9H), 1.39 (s, 6H), 1.36 - 1.21 (m, 10H), 0.89 - 0.85 (m, 3H); ¹³C NMR (101 MHz, chloroform-*d*) δ /ppm = 169.4, 154.3, 146.3, 109.4, 80.9, 61.7, 33.0, 31.9, 29.5, 29.4, 29.3, 28.5, 26.7, 26.2, 22.8, 14.2; IR (ATR) $\tilde{\nu}$ /cm⁻¹ = 3086, 2972, 2956, 2926, 2856, 1698, 1640, 1455, 1412, 1390, 1366, 1302, 1244, 1157, 1100, 1003, 992, 900, 874, 857, 783, 756, 723, 687, 599; HRMS (ESI): *m*/*z* calcd for C₁₉H₃₇N₂O₂ [M+H]⁺ 325.2849, found: 325.2849.

tert-Butyl 2-decylidene-1-(2-methylbut-3-en-2-yl)hydrazine-1carboxylate (9c). Mixture of allylhydrazines 8a/8b (115 mg, 0.574 mmol \triangleq 0.522 mmol of isomer 8a) and decanal (0.108 mL, 0.574 mmol) gave *N*-Boc-*N*-allylhydrazone 9c (56 mg, 0.17 mmol, 33% referred to isomer 8a) as colourless oil via GP1: R_f = 0.56 (hexanes/EtOAc 9:1). ¹H NMR (500 MHz, chloroform-*d*) δ/ppm = 7.71 (t, ³J_{H,H} = 5.6 Hz, 1H), 6.11 (dd, ³J_{H,H} = 17.5, 10.8 Hz, 1H), 5.01 (dd, ³J_{H,H} = 17.5, ²J_{H,H} = 0.7 Hz, 1H), 4.92 (dd, *J* ³J_{H,H} = 10.8, ²J_{H,H} = 0.7 Hz, 1H), 2.35 (td, ³J_{H,H} = 5.6 Hz, 2H), 1.57 − 1.54 (m, 2H), 1.42 (s, 9H), 1.39 (s, 6H), 1.26 (m, 12H), 0.89 − 0.86 (m, 3H). ¹³C NMR (126 MHz, chloroform-*d*) δ/ppm = 169.5, 154.3, 146.3, 109.4, 80.9, 61.7, 33.0, 32.0, 29.6, 29.5, 29.5, 29.4, 28.6, 26.7, 26.2, 22.8, 14.3. IR (ATR) $\tilde{\nu}$ /cm⁻¹ = 2924, 2853, 1696, 1458, 1407, 1368, 1310, 1245, 1158, 1101, 990, 903, 852, 754, 719, 665. HRMS (ESI): *m/z* calcd for C₂₀H₃₉N₂O₂ [M+H]⁺ 339.3006; found: 339.3011.

tert-Butyl 1-(2-methylbut-3-en-2-yl)-2-(2-methylpropylidene)hydrazine-1-carboxylate (9d). Mixture of olefins 8a/8b (519 mg, 2.59 mmol \triangleq 2.36 mmol of isomer 8a) and isobutyraldehyde (0.237 mL, 2.59 mmol) gave *N*-Boc-*N*-allylhydrazone 9d (262 mg, 1.03 mmol, 44% referred to isomer 8a) as colourless oil via GP1: R_f = 0.55 (hexanes/EtOAc 9:1); ¹H NMR (400 MHz, chloroform-*d*) δ/ppm = 7.61 (d, ³J_{H,H} = 5.9 Hz, 1H), 6.11 (dd, ³J_{H,H} = 17.6, 10.8 Hz, 1H), 5.03 − 4.90 (m, 2H), 2.66 − 2.56 (m, 1H), 1.42 (s, 9H), 1.39 (s, 6H), 1.13 (s, 3H), 1.12 (s, 3H). ¹³C NMR (101 MHz, chloroform-*d*) δ/ppm = 173.2, 154.1, 146.3, 109.4, 80.9, 61.9, 32.2, 28.6, 26.6, 19.6. IR (ATR) $\tilde{\nu}$ (cm⁻¹ = 3086, 3008, 2973, 2930, 2872, 1698, 1641, 1456, 1412, 1390, 1366, 1304, 1289, 1244, 1156, 1092, 1058, 992, 970, 902, 879, 856, 756, 686, 599, 588. HRMS (ESI): *m*/*z* calcd for C₁₄H₂₇N₂O₂ [M+H]⁺ 255.2067; found: 255.2066.

tert-Butyl2-(2-ethoxy-2-oxoethylidene)-1-(2-methylbut-3-en-2-
yl)hydrazine-1-carboxylate (9e). Mixture of olefins 8a/8b (200 mg, 0.990
mmol, $\triangleq 0.901$ mmol of isomer 8a) and ethyl glyoxalate solution (~ 50% in
toluene, 0.198 mL, 0.990 mmol) gave N-Boc-N-allylhydrazone 9e (108 mg,
0.380 mmol, 42% referred to isomer 8a) as colourless oil via GP1: R_f =
0.44 (hexanes/EtOAc 9:1); ¹H NMR (400 MHz, chloroform-d) δ /ppm = 8.41

(s, 1H), 6.05 (dd, ${}^{3}J_{H,H}$ = 17.5, 10.8 Hz, 1H), 5.07 – 4.93 (m, 2H), 4.26 (q, ${}^{3}J_{H,H}$ = 7.1 Hz, 2H), 1.52 (s, 6H), 1.48 (s, 9H), 1.31 (t, ${}^{3}J_{H,H}$ = 7.1 Hz, 3H); ${}^{13}C$ NMR (101 MHz, chloroform-*d*) δ /ppm = 164.9, 151.9, 145.5, 135.7, 110.6, 83.6, 65.9, 60.9, 28.3, 27.7, 14.4; IR (ATR) $\tilde{\nu}$ /cm⁻¹ = 1742, 1708, 1585, 1477, 1456, 1369, 1339, 1288, 1242, 1206, 1181, 1148 , 1113, 1093, 1044, 911, 848, 798, 759, 744, 576; HRMS (EI): *m/z* calcd for C₉H₁₆N₂O₂ [M-Boc]⁻⁺ 184.1206, found: 184.1205.

tert-Butyl 2-(cyclopentylmethylene)-1-(2-methylbut-3-en-2yl)hydrazine-1-carboxylate (9f) Mixture of olefins 8a/8b. (430 mg, 2.15 mmol \triangleq 1.96 mmol of isomer 8a) and cyclopentane carboxaldehyde (0.229 mL, 2.15 mmol) gave *N*-Boc-*N*-allylhydrazone 9f (245 mg, 0.874 mmol, 45% referred to isomer 8a) as colourless oil via GP1: R_f = 0.57 (hexanes/EtOAc 9:1); ¹H NMR (400 MHz, chloroform-*d*) δ/ppm = 7.62 (d, ³J_{H,H} = 6.8 Hz, 1H), 6.11 (dd, ³J_{H,H} = 17.5, 10.8 Hz, 1H), 5.08 – 4.82 (m, 2H), 2.87 – 2.71 (m, 1H), 1.95 – 1.79 (m, 2H), 1.73 – 1.54 (m, 6H), 1.42 (s, 9H), 1.38 (s, 6H); ¹³C NMR (101 MHz, chloroform-*d*) δ/ppm = 172.6, 154.2, 146.2, 109.4, 80.8, 61.8, 42.9, 30.3, 28.6, 28.5, 26.6, 25.7; IR (ATR) $\hat{\nu}$ /cm⁻¹ = 3084, 2968, 2956, 2869, 1697, 1639, 1476, 1454, 1412, 1390, 1366, 1304, 1244, 1156, 1101, 1061, 1003, 992, 900, 877, 856, 783, 757, 687; HRMS (ESI): *m/z* calcd for C₁₆H₂₉N₂O₂ [M+H]⁺ 281.2224; found: 281.2225.

tert-Butyl 2-(cyclohexylmethylene)-1-(2-methylbut-3-en-2yl)hydrazine-1-carboxylate (9g). Mixture of olefins 8a/8b (91.6 mg, 0.686 mmol \triangleq 0.624 mmol of isomer 8a) and cyclohexanecarboxaldehyde (55.4 μL, 0.686 mmol) gave *N*-Boc-*N*-allylhydrazone 9f (63.3 mg, 0.215 mmol, 34% referred to isomer 8a) as colourless oil via GP1: R_f = 0.64 (hexanes/EtOAc 9:1); ¹H NMR (500 MHz, chloroform-*d*) δ/ppm = 7.58 (d, ³J_{H,H} = 6.0 Hz, 1H), 6.11 (dd, ³J_{H,H} = 17.5, 10.8 Hz, 1H), 5.01 (dd, ³J_{H,H} = 17.5, ²J_{H,H} = 0.9 Hz, 1H), 4.92 (dd, ³J_{H,H} = 10.8, ²J_{H,H} = 0.9 Hz, 1H), 2.42 – 2.25 (m, 1H), 1.89 – 1.80 (m, 2H), 1.80 – 1.73 (m, 2H), 1.70 – 1.64 (m, 1H), 1.41 (s, 9H), 1.39 (s, 6H), 1.35 – 1.28 (m, 4H), 1.27 – 1.18 (m, 1H). ¹³C NMR (101MHz, chloroform-*d*) δ/ppm = 172.6, 154.3, 146.3, 109.4, 80.8, 61.8, 41.5, 29.9, 28.6, 26.7, 26.1, 25.5; IR (ATR) $\tilde{\nu}$ /cm⁻¹ = 2929, 2854, 1709, 1366, 1308, 1244, 1160; HRMS (ESI): *m*/*z* calcd for C₁₇H₃₁N₂O₂: 295.2380 [M+H]⁺, found: 295.2385.

tert-Butyl 2-(cyclohex-1-en-1-ylmethylene)-1-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (9h). Mixture of olefins 8a/8b (200 mg, 0.999 mmol \triangleq 0.909 mmol of isomer 8a) and 1-cyclohexene-1-carboxaldehyde (0.114 mL, 0.990 mmol) gave *N*-Boc-*N*-allylhydrazone 9h (135 mg, 0.460 mmol, 51% referred to isomer 8a) as colourless oil via GP1: R₇ = 0.52 (hexanes/EtOAc 9:1); ¹H NMR (400 MHz, chloroform-*d*) δ/ppm = 7.99 (s, 1H), 6.18 – 6.05 (m, 2H), 5.05 – 4.85 (m, 2H), 2.37 – 2.12 (m, 4H), 1.70 – 1.61 (m, 4H), 1.43 (s, 9H), 1.41 (s, 6H); ¹³C NMR (101 MHz, chloroform-*d*) δ/ppm = 163.9, 153.9, 146.6, 138.2, 136.3, 109.1, 81.2, 62.7, 28.6, 26.9, 26.3, 23.4, 22.5, 22.1; IR (ATR) $\tilde{\nu}$ /cm⁻¹ =2976, 2931, 2859, 1697, 1639, 1596, 1366, 1291, 1243, 1152, 1107, 902, 881, 754, 699; HRMS (ESI): *m*/z calcd for C₁₇H₂₉N₂O₂ [M+H]* 293.2224; found: 293.2223.

tert-Butyl 2-benzylidene-1-(2-methylbut-3-en-2-yl)hydrazine-1carboxylate (9i). Mixture of olefins 8a/8b (580 mg, 2.90 mmol \triangleq 2.64 mmol of isomer 8a) and benzaldehyde (0.294 mL, 2.90 mmol) gave *N*-Boc-*N*-allylhydrazone 9i (312 mg, 1.08 mmol, 41% referred to isomer 8a) as colourless oil via GP1: R_f = 0.64 (hexanes/EtOAc 9:1); ¹H NMR (400 MHz, chloroform-*d*) δ/ppm = 8.65 (s, 1H), 7.74 − 7.68 (m, 2H), 7.43 − 7.34 (m, 3H), 6.17 (dd, ³/_{H,H} = 17.5, 10.8 Hz, 1H), 5.11 − 4.90 (m, 2H,), 1.52 (s, 6H), 1.47 (s, 9H); ¹³C NMR (101 MHz, chloroform-*d*) δ/ppm = 157.1, 153.6, 146.4, 135.4, 130.2, 128.7, 127.7, 109.4, 81.8, 63.6, 28.5, 27.2; IR (ATR) $\bar{\nu}$ /cm⁻¹ = 3083, 3062, 2976, 2932, 1697, 1642, 1574, 1476, 1449, 1412, 1391, 1366, 1289, 1243, 1149, 1109, 1071, 992, 947, 898, 856, 784, 753, 692, 659, 563; HRMS (ESI): *m*/*z* calcd for C₁₇H₂₅N₂O₂ [M+H]* 289.1910, found: 289.1909.

tert-Butyl2-(4-bromobenzylidene)-1-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (9j). Mixture of olefins 8a/8b (243 mg, 1.21mmol \triangleq 1.10 mmol of isomer 8a) and 4-bromobenzaldehyde (224 mg,1.21 mmol) gave N-Boc-N-allylhydrazone 9j (356 mg, 0.971 mmol, 88%)

referred to isomer **8a**) as colourless oil via GP1: R_f = 0.64 (hexanes/EtOAc 9:1); ¹H NMR (500 MHz, chloroform-*d*) δ /ppm = 8.68 (s, 1H), 7.56 (d, ³J_{H,H} = 8.4 Hz, 2H), 7.50 (d, ³J_{H,H} = 8.3 Hz, 2H), 6.14 (dd, ³J_{H,H} = 17.5, 10.8 Hz, 1H), 5.07 - 4.92 (m, 2H), 1.51 (s, 6H), 1.47 (s, 9H); ¹³C NMR (126 MHz, chloroform-*d*) δ /ppm = 153.9, 153.5, 146.3, 134.7, 131.9, 128.9, 124.1, 109.6, 82.1, 63.9, 28.5, 27.3; IR (ATR) $\tilde{\nu}$ /cm⁻¹ = 3086, 2979, 2932, 1696, 1643, 1591, 1564, 1487, 1455, 1412, 1392, 1367, 1289, 1244, 1148, 1115, 1098, 1069, 1044, 1009, 992, 953, 929, 901, 856, 819, 786, 752, 708, 691, 667; HRMS (ESI): *m*/*z* calcd for C₁₇H₂₄BrN₂O₂ [M+H]⁺ 367.1015; found: 367.1026.

tert-Butyl 2-(4-(dimethylamino)benzylidene)-1-(2-methylbut-3-en-2-yl)hydrazine-1-carboxylate (9k). Mixture of olefins 8a/8b (100 mg, 0.499 mmol \triangleq 0.454 mmol of isomer 8a) and 4-dimethylaminobenzaldehyde (74.5 mg, 0.499 mmol) gave *N*-Boc-*N*-allylhydrazone 9k (143 mg, 0.431 mmol, 95% referred to isomer 8a) as white crystalline solid via GP1: R_f = 0.35 (hexanes/EtOAc 9:1); m.p. = 73 - 75 °C; ¹H NMR (400 MHz, chloroform-*d*) δ /ppm = 8.30 (s, 1H), 7.61 (d, ${}^{3}J_{H,H} = 8.9$ Hz, 2H), 6.69 (d, ${}^{3}J_{H,H} = 8.9$ Hz, 2H), 6.19 (dd, ${}^{3}J_{H,H} = 17.5$, 10.8 Hz, 1H), 5.08 - 4.90 (m, 2H), 3.01 (s, 6H), 1.47 (s, 6H), 1.44 (s, 9H); ¹³C NMR (101 MHz, chloroform-*d*) δ /ppm = 162.4, 154.2, 152.2, 146.6, 129.4, 122.4, 111.8, 109.2, 80.9, 62.6, 40.4, 28.6, 26.9; IR (ATR) $\tilde{\nu}$ /cm⁻¹ = 2976, 2930, 1693, 1616, 1601, 1528, 1477, 1455, 1363, 1300, 1237, 1155, 1100, 1060, 894, 859, 816, 755, 731; HRMS (ESI): *m*/*z* calcd for C₁₉H₃₀N₃O₂ [M+H]⁺ 332.2333, found: 332.2333.

tert-Butyl 2-(4-methoxybenzylidene)-1-(2-methylbut-3-en-2yl)hydrazine-1-carboxylate (9I). Mixture of olefins 8a/8b (150 mg, 0.749 mmol \triangleq 0.682 mmol of isomer 8a) and 4-anisaldehyde (102 mg, 91.1 µL, 0.749 mmol) gave *N*-Boc-*N*-allylhydrazone 9I (151 mg, 0.475 mmol, 70% referred to isomer 8a) as colourless oil via GP1: R_f = 0.42 (hexanes/EtOAc 9:1); ¹H NMR (400 MHz, chloroform-*d*) δ/ppm = 8.48 (s, 1H), 7.66 (d, ³J_{H,H} = 8.8 Hz, 2H), 6.91 (d, ³J_{H,H} = 8.9 Hz, 2H), 6.17 (dd, ³J_{H,H} = 17.5, 10.8 Hz, 1H), 5.08 – 4.92 (m, 2H), 3.84 (s, 3H), 1.49 (s, 6H), 1.45 (s, 9H); ¹³C NMR (101 MHz, chloroform-*d*) δ/ppm = 161.5, 159.0, 153.9, 146.5, 129.3, 127.8, 114.1, 109.3, 81.4, 63.1, 55.5, 28.6, 27.0; IR (ATR) *V*/cm⁻¹ = 2975, 2932, 1693, 1606, 1512, 1456, 1366, 1293, 1245, 1150, 1104, 1031, 900, 859, 831, 75; HRMS (ESI): *m*/*z* calcd for C₁₈H₂₇N₂O₃ [M+H]⁺ 319.2016; found: 319.2015.

tert-Butyl 1-(2-methylbut-3-en-2-yl)-2-(4-nitrobenzylidene)hydrazine-1-carboxylate (9m). Mixture of olefins 8a/8b (250 mg, 1.25 mmol \triangleq 1.14 mmol of isomer 8a) and 4-nitrobenzaldehyde (0.126 mL, 1.25 mmol) gave *N*-Boc-*N*-allylhydrazone 9m (233 mg, 0.698 mmol, 61% referred to isomer 8a) as yellow solid via GP1: R_f = 0.51 (hexanes/EtOAc 9:1); m.p. = 67 – 69 °C; ¹H NMR (400 MHz, chloroform-*d*) δ/ppm = 9.02 (s, 1H), 8.24 – 8.19 (m, 2H), 7.82 – 7.75 (m, 2H), 6.12 (dd, *J* = 17.5, 10.8 Hz, 1H), 5.10 – 4.93 (m, 2H), 1.56 (s, 6H), 1.50 (s, 9H); ¹³C NMR (101 MHz, chloroform-*d*) δ/ppm = 152.9, 148.1, 147.7, 145.9, 142.7, 127.6, 124.0, 110.1, 82.9, 65.0, 28.5, 27.6; IR (ATR) $\tilde{\nu}$ /cm⁻¹ = 1699, 1598, 1572, 1518, 1368, 1343, 1286, 1246, 1146, 1107, 907, 849, 832, 729, 692, 647; HRMS (EI): *m/z* calcd for C₁₇H₂₃N₃O₄ [M]⁺ 333.1683; found: 333.1710.

1-(2-methylbut-3-en-2-yl)-2-(thiophen-2tert-Butvl ylmethylene)hydrazine-1-carboxylate (9n). Mixture of olefins 8a/8b (150 mg, 0.749 mmol ≙ 0.681 mmol of isomer 8a) and 2thiophenecarboxaldehyde (70 µL, 0.749 mmol) gave N-Boc-Nallylhydrazone 9n (104 mg, 0.352 mmol, 52% referred to isomer 8a) as light yellow oil via GP1: R_f = 0.60 (hexanes/EtOAc 9:1); ¹H NMR (400 MHz, chloroform-d) δ /ppm = 8.85 - 8.83 (m, 1H), 7.32 (dt, ${}^{3}J_{H,H}$ = 5.0, 1.0 Hz, 1H), 7.24 (dd, ${}^{3}J_{H,H}$ = 3.6, 1.2 Hz, 1H), 7.04 (dd, ${}^{3}J_{H,H}$ = 5.1, 3.6 Hz, 1H), 6.14 (dd, ³J_{H,H} = 17.5, 10.8 Hz, 1H), 5.08 – 4.91 (m, 2H), 1.49 (s, 6H), 1.47 (s, 9H); ¹³C NMR (101 MHz, chloroform-*d*) δ/ppm = 153.6, 150.2, 146.3, 140.9, 129.7, 127.9, 127.4, 109.5, 81.9, 63.7, 28.5, 27.2; IR (ATR) *v*/cm⁻¹ = 2985, 2938, 1742, 1708, 1585, 1369, 128, 1242, 1181, 1148, 1113, 1093, 1044, 911, 848, 759, 744, 576; HRMS (EI): m/z calcd for C15H22N2O2S [M]⁺ 294.1396; found: 294.1392.

FULL PAPER

tert-Butyl

1-(2-methylbut-3-en-2-yl)-2-(pyridin-4-

ylmethylene)hydrazine-1-carboxylate (9o). Mixture of olefins 8a/8b (350 mg, 1.75 mmol ≙ 1.59 mmol of isomer 8a) and 4-pyridinecarboxaldehyde (0.165 mL, 1.75 mmol) gave *N*-Boc-*N*-allylhydrazone 9o (342 mg, 1.18 mmol, 74% referred to isomer 8a) as light yellow oil via GP1: R_f = 0.12 (hexanes/EtOAc 9:1); ¹H NMR (400 MHz, chloroform-*d*) δ/ppm = 8.90 (s, 1H), 8.65 – 8.55 (m, 2H), 7.50 (dd, ³J_{H,H} = 6.1, 0.4 Hz, 2H), 6.11 (dd, ³J_{H,H} = 17.5, 10.8 Hz, 1H), 5.11 – 4.90 (m, 2H), 1.54 (s, 6H), 1.49 (s, 9H); ¹³C NMR (101 MHz, chloroform-*d*) δ/ppm = 152.9, 150.3, 147.7, 146.0, 143.8, 121.1, 109.9, 82.8, 64.9, 28.5, 27.6; IR (ATR) *i*/cm⁻¹ = 2977, 2933, 1698, 1590, 1367, 1287, 1246, 1147, 989, 903, 859, 814, 755, 732, 656; HRMS (ESI): *m/z* calcd for C₁₆H₂₄N₃O₂ [M+H]⁺ 290.1863; found: 290.1862.

tert-Butyl 1-(2-methylbut-3-en-2-yl)-2-(3phenylpropylidene)hydrazine-1-carboxylate (9p). Mixture of olefins 8a/8b (237 mg, 1.18 mmol \triangleq 1.07 mmol of isomer 8a) and 3phenylpropionaldehyde (0.157 mL, 1.18 mmol) gave N-Boc-Nallylhydrazone 9p (141 mg, 0.446 mmol, 42% referred to isomer 8a) as colourless oil via GP1: R_f = 0.46 (hexanes/EtOAc 9:1); ¹H NMR (400 MHz, DMSO- d_6) δ /ppm = 7.75 (t, ${}^{3}J_{H,H}$ = 5.3 Hz, 1H), 7.31 – 7.22 (m, 4H), 7.18 (m, 1H), 5.99 (dd, ${}^{3}J_{H,H}$ = 17.5, 10.8 Hz, 1H), 4.94 (dd, ${}^{3}J_{H,H}$ = 17.5, ${}^{2}J_{H,H}$ = 1.1 Hz, 1H), 4.86 (dd, ${}^{3}J_{H,H} = 10.8$, ${}^{2}J_{H,H} = 1.1$ Hz, 1H), 2.83 (t, ${}^{3}J_{H,H} = 7.3$ Hz, 2H), 2.59 (ddd, ³J_{H,H} = 7.3, 5.3 Hz, 2H),1.36 (s, 9H), 1.25 (s, 6H); ¹³C NMR (101 MHz, DMSO-d₆) δ/ppm = 166.7, 153.2, 145.7, 140.9, 128.3, 128.3, 125.9, 109.4, 80.1, 61.1, 33.9, 31.3, 27.9, 26.4; IR (ATR) *v*/cm⁻¹ = 2979, 2929, 1693, 1639, 1455, 1264, 1303, 1241, 1155, 1101, 903, 870, 856, 748; HRMS (ESI): m/z calcd for C19H29N2O2 [M+H]+ 317.2224; found: 317.2229.

tert-Butyl 1-(2-methylbut-3-en-2-yl)-2-((*E*)-3-phenylallylidene)hydrazine-1-carboxylate (9q). Mixture of olefins 8a/8b (250 mg, 1.25 mmol \triangleq 1.13 mmol of isomer 8a) and cinnamaldehyde (0.157 mL, 1.25 mmol) gave *N*-Boc-*N*-allylhydrazone 9q (228 mg, 0.725 mmol, 64% referred to isomer 8a) as yellow oil via GP1: R_f = 0.56 (hexanes/EtOAc 9:1); ¹H NMR (500 MHz, chloroform-*d*) δ/ppm = 8.33 (dd, ³J_{H,H} = 7.2, 1.5 Hz, 1H), 7.49 – 7.47 (m, 2H), 7.38 – 7.33 (m, 2H), 7.32 – 7.28 (m, 1H), 6.96 – 6.93 (m, 2H), 6.14 (dd, ³J_{H,H} = 17.5, 10.8 Hz, 1H), 5.07 – 4.92 (m, 2H), 1.47 (s, 6H), 1.46 (s, 9H); ¹³C NMR (101 MHz, chloroform-*d*) δ/ppm = 161.7, 153.7, 146.2, 140.5, 136.2, 128.9, 128.9, 127.2, 126.0, 109.5, 81.6, 62.9, 28.5, 26.9; IR (ATR) *V*/cm⁻¹ = 1694, 1449, 1366, 1289, 1243, 1148, 1109, 1051, 973, 906, 879, 850, 749, 689; HRMS (ESI): *m/z* calcd for C₁₉H₂₇N₂O₂ [M+H]⁺ 315.2067; found: 315.2066.

General procedure for the synthesis of olefins via [3,3]-sigmatropic rearrangement (GP2):

In an oven dried two-necked Schlenk flask HNTf₂ (10 mol %) was dissolved in dry diglyme (1 mL). A solution of the appropriate *N*-Boc-*N*allylhydrazone **9** (1.0 eq) in dry diglyme (2 mL + 1 mL rinse) was added at room temperature. The reaction mixture was fitted with a N₂ flashed reflux condenser and immediately heated to 125 °C in a pre-heated oil bath. After completion of the rearrangement detected by TLC (75 min), the reaction was immediately cooled to room temperature via water bath and then quenched with a sat. aq. NaHCO₃ solution (4 mL). Pentane (10 mL) was added and the organic layer was washed with at least 100 mL water. The solvent was removed *in vacuo* (30 °C, max. 700 mbar) and the crude product was purified by flash column chromatography.

2-Methyldodec-2-ene (10a). Allylhydrazone **9a** (155 mg, 0.500 mmol) and HNTf₂ (14 mg, 0.050 mmol) gave olefin **10a** (18 mg, 0.099 mmol, 20%) as colourless oil via GP2: R_{I} = 0.94 (pentane); ¹H NMR (400 MHz, chloroform-*d*) δ /ppm = 5.15 – 5.08 (m, 1H), 1.96 (q, ³J_{H,H} = 7.1 Hz, 2H), 1.69 (d, ³J_{H,H} = 1.4 Hz, 3H), 1.60 (d, ³J_{H,H} = 1.3 Hz, 3H), 1.26 (s, 14H), 0.88 (t, ³J_{H,H} = 2.9 Hz, 3H). ¹³C NMR (101 MHz, chloroform-*d*) δ /ppm = 131.3, 125.1, 32.1, 30.1, 29.8, 29.8, 29.5, 29.5, 28.2, 25.9, 22.9, 17.8, 14.3. IR (ATR) $\tilde{\nu}$ /cm⁻¹ = 2956, 2922, 2853, 1462, 1376, 1094, 985, 886, 833, 722; HRMS (EI): *m*/*z* calcd for C₁₃H₂₆ [M]⁺⁺ 182.2029, found: 182.2027.

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2-Methyltridec-2-ene (10b). Allylhydrazone **9b** (162 mg, 0.500 mmol) and HNTf₂ (14 mg, 0.050 mmol) gave olefin **10b** (19 mg, 0.10 mmol, 21%) as colourless oil via GP2: R_f = 0.88 (pentane/Et₂O 9:1); ¹H NMR (400 MHz, chloroform-*d*) δ /ppm = 5.12 (tdt, ³J_{H,H} = 7.2, 1.5 Hz, 1H), 1.96 (q, ³J_{H,H} = 6.8 Hz, 2H), 1.69 (d, ³J_{H,H} = 1.4 Hz, 3H), 1.60 (d, ³J_{H,H} = 1.3 Hz, 3H), 1.26 (s, 16H), 0.93 – 0.83 (m, 3H); ¹³C NMR (101 MHz, chloroform-*d*) δ /ppm = 131.3, 125.1, 32.1, 30.1, 29.8, 29.8, 29.8, 29.5, 29.5, 28.2, 25.9, 22.9, 17.8, 14.3; IR (ATR) $\tilde{\nu}$ /cm⁻¹ = 2955, 2922, 2853, 1456, 1376, 1094, 984, 886, 832, 721, 593, 556; HRMS (EI): *m*/z calcd for C₁₄H₂₈ [M]⁻⁺196.2185, found: 196.2183.

2-Methyltetradec-2-ene (10c). Allylhydrazone **9c** (169 mg, 0.500 mmol) and HNTf₂ (14 mg, 0.050 mmol) gave olefin **10c** (21 mg, 0.099 mmol, 20%) as colourless oil via GP2: $R_f = 0.98$ (pentane); ¹H NMR (400 MHz, chloroform-*d*) δ /ppm = 5.12 (ddt, ³J_{H,H} = 7.1 Hz, 1H), 1.96 (q, ³J_{H,H} = 6.9 Hz, 2H), 1.69 (s, 3H), 1.60 (s, 3H), 1.26 (br, 18H), 0.88 (t, ³J_{H,H} = 6.8 Hz, 3H); ¹³C NMR (101 MHz, chloroform-*d*) δ /ppm = 131.3, 125.1, 34.3, 32.1, 30.1, 29.9, 29.8, 29.8, 29.5, 28.2, 25.9, 22.9, 22.5, 17.8, 14.3; IR (ATR) $\tilde{\nu}$ /cm⁻¹ = 2958, 2921, 2850, 1461, 1372, 1260, 1090, 1022, 881, 806, 723; HRMS (EI): *m*/*z* calcd for C₁₅H₃₀ [M]⁻⁺ 210.2342; found: 210.2347.

(4-Methylpent-3-en-1-yl)cyclopentane (10f). Allylhydrazone **9f** (140 mg, 0.500 mmol) and HNTf₂ (14 mg, 0.050 mmol) gave olefin **10f** (15 mg, 0.099 mmol, 20%) as colourless oil via GP2: $R_f = 0.95$ (pentane); ¹H NMR (500 MHz, chloroform-*d*) δ /ppm = 5.15 – 5.10 (m, 1H), 2.01 – 1.95 (m, 2H), 1.77 – 1.73 (m, 2H), 1.69 (d, ³J_{H,H} = 1.4 Hz, 3H), 1.60 (d, ³J_{H,H} = 1.2 Hz, 3H), 1.52 – 1.46 (m, 2H), 1.34 – 1.30 (m, 2H), 1.11 – 1.05 (m, 2H), 0.91 – 0.86 (m, 3H); ¹³C NMR (126 MHz, chloroform-*d*) δ /ppm = 131.1, 125.2, 39.9, 36.6, 32.8, 27.4, 25.9, 25.4, 17.8; IR (ATR) $\tilde{\nu}$ /cm⁻¹ = 2983, 2950, 2922, 2857, 1452, 1376, 1105, 985, 907, 830, 735, 650, 574, 560; HRMS (EI): *m/z* calcd for C₁₁H₂₀ [M]⁻⁺ 152.1559, found: 152.1558.

(4-Methylpent-3-en-1-yl)cyclohexane (10g). Allylhydrazone 9g (147 mg, 0.500 mmol) and HNTf₂ (14 mg, 0.050 mmol) gave olefin 10g (17 mg, 0.10 mmol, 20%) as colourless oil via GP2. (4-Methylpent-3-en-1-yl)cyclohexane (10g, 30 mol% HNTf₂). Allylhydrazone 9g (127 mg, 0.433 mmol) and HNTf₂ (37 mg, 0.13 mmol) gave olefin 10g (18 mg, 0.11 mmol, 22%) as colourless oil via GP2. (4-Methylpent-3-en-1-yl)cyclohexane (10g, 3.00 mmol scale). Allylhydrazone 9g (822 mg, 3.00 mmol) and HNTf₂ (84 mg, 0.30 mmol) gave olefin 10g (129 mg, 0.759 mmol, 25%) as colourless oil via GP2: R_f = 0.91 (pentane); ¹H NMR (500 MHz, chloroform-*d*) δ /ppm = 5.15 - 5.00 (m, 1H), 2.03 - 1.91 (m, 2H), 1.75 - 1.57 (m, 11H), 1.25 - 1.15 (m, 6H), 0.92 - 0.83 (m, 2H); ¹³C NMR (126 MHz, chloroform-*d*) δ /ppm = 131.1, 125.3, 37.8, 37.5, 33.5, 26.9, 26.6, 25.9, 25.5, 17.8; IR (ATR) \hat{v} /cm⁻¹ = 2923, 2852, 1694, 1448, 1376; HRMS (EI): *m/z* calcd for C₁₂H₂₂ [M]⁺⁺166.1722, found: 166.1720.

(6-Methylhept-5-en-1-yl)benzene (10p). Allylhydrazone 9p (217 mg, 0.686 mmol) and HNTf₂ (14 mg, 0.068 mmol) gave olefin 10p (25 mg, 0.13 mmol, 19%) as colourless oil via GP2: $R_f = 0.48$ (pentane); ¹H NMR (400 MHz, methylene chloride- d_2) δ /ppm = 7.29 – 7.23 (m, 2H), 7.20 – 7.13 (m, 3H), 5.12 (tdt, ³J_{H,H} = 7.2, 1.5 Hz, 1H), 2.60 (t, ³J_{H,H} = 7.7 Hz, 2H), 2.01 (q, ³J_{H,H} = 7.3 Hz, 2H), 1.68 (d, ³J_{H,H} = 1.4 Hz, 3H), 1.64 – 1.58 (m, 5H), 1.41 – 1.33 (m, 2H); ¹³C NMR (101 MHz, methylene chloride- d_2) δ /ppm = 143.6, 131.8, 128.9, 128.7, 126.1, 125.2, 36.4, 31.8, 30.1, 28.4, 25.9, 17.9; IR (ATR) \tilde{v} /cm⁻¹ = 3026, 2922, 2853, 1602, 1494, 1451, 1378, 1108, 1079, 1029, 741, 698, 571; HRMS (EI): *m/z* calcd for C₁₄H₂₀ [M]⁻⁺ 188.1565; found: 188.1565.

Keywords: hydrazones • isoprenylation • sigmatropic rearrangement • traceless bond construction • triflimide

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Entry for the Table of Contents



Key Topic: traceless isoprenylation

A traceless isoprenylation method of non-conjugated aldehydes is reported. Synthesis of the required *N*-Boc-*N*-(1,1dimethylallyl)hydrazine precursor, as well as the *N*-Boc-*N*-allylhydrazones are described. Optimisation reactions for the rearrangement were performed and the scope of the rearrangement was studied.