Synthesis of enantioenriched azo compounds: organocatalytic Michael addition of formaldehyde $N$-tert-butyl hydrazone to nitroalkenes†

David Monge,*a Silvia Daza,a Pablo Bernal,b Rosario Fernández*a and José M. Lassaletta*b

The unprecedented diaza–ene reaction of formaldehyde $N$-tert-butyl hydrazone with nitroalkenes can be efficiently catalyzed by an axially chiral bis-thiourea to afford the corresponding diazenes in good to excellent yields (60–96%) and moderate enantioselectivities, up to 84 : 16 er; additional transformation of diazenes into their tautomeric hydrazones proved to be operationally simple and high-yielding, affording bifunctional compounds which represent useful intermediates for the synthesis of enantioenriched β-nitro-nitriles and derivatives thereof.

Introduction

Diazenes (azo compounds, R–N≡N–R′) constitute an important family of compounds with traditional uses in organic chemistry (Fig. 1).1 For example, the application of azodicarboxylates (RO$_2$C–N≡N–CO$_2$R) in organic synthesis as nitrogen electrophiles/dienophiles2 and the use of aromatic azo compounds (Ar–N≡N–Ar′) in the industrial field of dyes are well established.

Additionally, the importance of N≡N bonds in biologically active molecules and the need for the development of new antibiotics have stimulated the synthesis of new azo prodrugs of general structure Ar–N≡N–R (R = aryl or alkyll) which release therapeutically active amine drugs upon site-specific reduction by bacterial extracellular azoreductase enzymes and in the human colon.3

However, the synthesis of aliphatic azo compounds is less developed and still challenging, presumably due to their inherent instability.4 In fact, only a few examples on the enantioselective synthesis of azo compounds bearing a chiral alkyl chain (Ar–N≡N–alkyl* or alkyl-N≡N-alkyl*) are known. These include a radical carboamination/biocatalytic resolution procedure5 and a recent report on the use of aminocatalysis for the enantioselective conjugate addition of glyoxylate hydrazones6 (Scheme 1). On the other hand, we have recently reported on the use of H-bonding organocatalysts for the highly enantioselective addition of formaldehyde $N$-tert-butyl hydrazone to aromatic α-keto esters (formally heterocarbonyl–ene reactions) leading to functionalized diazenymethyl carbinals.7 Herein, we present a related organocatalytic conjugate addition of formaldehyde $N$-tert-butyl hydrazone to readily available nitroalkenes (formally diaza–ene reaction) leading to enantioenriched diazenes containing the synthetically versatile nitro group.8

†Electronic supplementary information (ESI) available: Experimental procedures, catalyst synthesis, characterization data, NMR spectra for new compounds, and HPLC traces. See DOI: 10.1039/c2ob26963e
In their pioneering work on the use of $N$-monosubstituted hydrazones as acyl anion equivalents, Baldwin et al. showed that the reactivity and the $C$- versus $N$-selectivity are strongly influenced by the substitution pattern at nitrogen and the azomethine carbon, the reaction conditions (basic or thermal) and the electrophilic partners. Reactions of $N$-monosubstituted hydrazones with nitroalkenes were reported to proceed affording mainly pyrazoles by the different reaction pathways depicted in Scheme 2. In these reactions, the regioselectivity is assumed to be controlled by the first nucleophilic attack. In general, the attack by the NH group on the electron-deficient $\beta$-carbon of the nitroalkene resulted in the regioselective formation of $1,3,5$-trisubstituted pyrazoles under either neutral (heating in MeOH or ethylene glycol) or acidic conditions (10 equiv. of TFA in CF$_3$CH$_2$OH), presumably through hydrazonium–nitronate intermediates A. Interestingly, strong bases such as t-BuOK promoted the obtention of regioisomeric 1,3,4-trisubstituted pyrazoles, presumably via type B intermediates. It was during early investigations in our group that we recognized the particular behaviour of formaldehyde phenylhydrazone giving the regioisomeric 1,4-disubstituted pyrazoles under neutral conditions. This result suggested that the initial attack takes place at the azomethine $C$-atom, assuming a stepwise reaction pathway which leads to the final product via intermediate C.

To the best of our knowledge, the reaction of monosubstituted formaldehyde hydrazones with nitroalkenes giving access to azo compounds has not been described to date. We envisioned that the presence of a phenyl group or a bulky tert-butyl group on the amino nitrogen would effectively inhibit the reactivity of the nitrogen center, while the low steric hindrance around the azomethine carbon in formaldehyde derivatives should allow performing $C$-selective conjugate additions under mild conditions, eventually enabling the isolation of the desired azo compounds. Additionally, the presence of an NH group offers opportunities to establish additional interactions with bifunctional H-bonding organocatalysts for the development of the enantioselective version of the reaction.

**Scheme 1** Synthesis of enantioenriched azo compounds.

**Scheme 2** Different reaction pathways for the addition of monosubstituted hydrazones to nitroalkenes.
Results and discussion

Initially, we examined the non-catalyzed reaction using formaldehyde N-monosubstituted hydrazones 1a–c and (E)-3-methyl-1-nitrobut-1-ene (2a) or β-nitrostyrene (2b) as model aliphatic and aromatic substrates, respectively (Scheme 3).

The first control experiments employing N-aryl-substituted hydrazones were disappointing as 1b afforded a complex mixture containing nitropyrazolidines,† and hydrazone 1c showed low solubility in most common solvents. However, experiments conducted with formaldehyde N-tert-butyl hydrazone 1a as a model reactant in CH$_3$CN [10 M] at room temperature showed full conversion of both nitroalkenes (aliphatic, 2a and aromatic, 2b) into the desired azo compounds 3a,b.§ Therefore, performing the reaction on a 2 mmol scale provides an easy access to rac-3a and rac-3b in 88 and 97% yields, respectively. Reaction rates were studied for the addition of 1a to 2a in different solvents (see ESI†). Interestingly, polar aprotic solvents such as CH$_3$CN showed a better efficiency (99% GC-yield in 24 h) whereas slower reactions [<50% GC-yield, 24 h] were observed in hydrocarbons (cyclohexane, toluene or hexane).

Previous studies had shown that chiral thiourea-based catalysts are effective promoters for conducting the activation of nitroalkenes towards nuclophilic attack in a highly enantioselective manner.‡ Moreover, several H-bonding and Brønsted acid organocatalysts§ were found to be compatible with N,N-dialkylhydrazones and such type of activation appears a priori to be particularly appropriate for this reaction. Hence, we performed an extensive screening using different chiral hydrogen-bond donor catalysts (Fig. 2). We first examined the reaction between N-tert-butyl hydrazone 1a and nitroalkene 2a, in hexane [0.1 M] at room temperature as the model system and the results are collected in Table 1. The Jacobsen-type thiourea catalysts 4a–c provided azo compound 3a in moderate conversions and enantiomeric ratios (entries 1–3). We were pleased to find that (1S,2R)-1-aminoindan-2-ol-derived thiourea 4d efficiently accelerated the reaction with respect to the non-catalyzed background reaction (>95% conversion, 24 h), unfortunately affording 3a in low enantioselectivity (59 : 41 er, entry 4). The related squaramide 4e afforded lower conversion and no stereoselectivity (entry 5). Interestingly, bis-thiourea 4f afforded moderate enantioselectivity (64 : 36 er, entry 6) whereas novel bis-thioureas 4g–i, readily available from 1,3-bis(isothiocyanato)methylenbenzene, promoted poor conversions to nearly racemic 3a (entries 7–9); the poor reactivity in this case is attributed to the reduced acidity associated with the aliphatic groups attached to both N atoms.‡‡ Axially chiral 1,1’-binaphthyl-derived 4j efficiently catalyzed the model reaction leading to 3a in good conversion (90%) and moderate enantioselectivity (64 : 36 er, entry 10). Finally, axially chiral bis-aryltiourea-based organocatalysts†† 4k–p were tested (entries 11–16) and the results revealed 4k as the best catalyst, providing 3a with full conversion and a moderate yet promising 74 : 26 er (entry 11). Analogue bis-urea 4l afforded 3a, also with full conversion and 74 : 26 er, albeit in a slower reaction (entry 12). Notably, any attempts to optimize the structure of catalyst 4k (installation of bromo substituents at C-3/C-3’ in 4m, or octahydro-analogues 4n–p) resulted in less selective activations (entries 13–16).

† The formation of 1,4-disubstituted pyrazoles (as described in Ref. 10d) was observed for a sugar-derived nitroalkene in boiling methanol.
§ Unfortunately, other aldehyde tert-butyl-hydrazones were unreactive, even under forcing conditions.
Table 1  Screening of catalysts for the enantioselective addition of 1a to 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Conv. [%]</th>
<th>er d</th>
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<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>60</td>
<td>rac</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>65 c</td>
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</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>76 c</td>
<td>67 : 33</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>&gt;95 d</td>
<td>59 : 41</td>
</tr>
<tr>
<td>5</td>
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<td>rac</td>
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<tr>
<td>6</td>
<td>4f</td>
<td>90</td>
<td>64 : 36</td>
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<tr>
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<td>4g</td>
<td>70 d</td>
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<td>8</td>
<td>4h</td>
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<td>63 : 36</td>
</tr>
<tr>
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<td>4k</td>
<td>&gt;95 d</td>
<td>rac</td>
</tr>
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<tr>
<td>16</td>
<td>4p</td>
<td>&gt;95 d</td>
<td>rac</td>
</tr>
</tbody>
</table>

a Unless otherwise stated, reactions were performed with 1a (0.15 mmol), 2a (0.1 mmol) and 4 (15 mol%) in hexane (1 mL) at rt for 24 h. b Determined by 1H NMR. c After 48 h. d Determined by HPLC on chiral stationary phases.

Table 2  Optimization for the enantioselective addition of 1a to 2a,b catalyzed by 4k

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Conv. [%]</th>
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<td>Hexane</td>
<td>rt</td>
<td>24</td>
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<td>2a</td>
<td>Heptane</td>
<td>rt</td>
<td>24</td>
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<tr>
<td>5</td>
<td>2a</td>
<td>Cyclohexane</td>
<td>rt</td>
<td>24</td>
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<tr>
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<td>2a</td>
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<td>rt</td>
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<td>&gt;95</td>
</tr>
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<td>7</td>
<td>2a</td>
<td>Methylcyclohexane</td>
<td>0</td>
<td>48</td>
<td>&gt;95</td>
</tr>
<tr>
<td>8</td>
<td>2a</td>
<td>CyH-toluene (9 : 1)</td>
<td>0</td>
<td>48</td>
<td>&gt;95</td>
</tr>
<tr>
<td>9 f</td>
<td>2a</td>
<td>CyH-toluene (9 : 1)</td>
<td>0</td>
<td>48</td>
<td>&gt;95</td>
</tr>
<tr>
<td>10</td>
<td>2b</td>
<td>Heptane</td>
<td>rt</td>
<td>16</td>
<td>&gt;95</td>
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<tr>
<td>11</td>
<td>2b</td>
<td>Cyclohexane</td>
<td>rt</td>
<td>16</td>
<td>&gt;95</td>
</tr>
<tr>
<td>12</td>
<td>2b</td>
<td>Methylcyclohexane</td>
<td>0</td>
<td>48</td>
<td>&gt;95</td>
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<td>13</td>
<td>2b</td>
<td>CyH-toluene (9 : 1)</td>
<td>0</td>
<td>48</td>
<td>&gt;95</td>
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<tr>
<td>14 f</td>
<td>2b</td>
<td>CyH-toluene (9 : 1)</td>
<td>0</td>
<td>48</td>
<td>&gt;95</td>
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</tbody>
</table>

da Reactions were performed with 1a (0.15 mmol), 2a,b (0.1 mmol) and 4k (15 mol%) in 1 mL of solvent. b Determined by 1H NMR. c Determined by HPLC on chiral stationary phases. d 10 mol% of 4k was used.

Having confirmed 4k as the most promising catalyst, an optimization of the reaction parameters was performed for nitroalkenes 2a,b, as outlined in Table 2. Generally, good conversions were obtained in all tested solvents; however, the enantiomeric ratio of 3a significantly dropped in toluene (60 : 40 er, entry 2), CH3CN, Et2O or CH2Cl2 (racemic mixture). In these cases the reaction rates are similar for the non-catalyzed background and the catalyzed reaction (see ESI†). Aromatic derivative 2b proved to be also a suitable substrate, providing 3b in full conversion and 72 : 28 er in hexane at room temperature (entry 10). Hydrocarbons proved to be convenient solvents (entries 1–6 for 2a and 10, 11 for 2b), cyclohexane being slightly superior (3a, 76 : 24 er; 3b, 78 : 22 er). A higher dilution proved to be inconsequential, while a higher concentration and/or higher (20 mol%) catalyst loading had a detrimental effect on enantioselectivity, suggesting that self-aggregation of the catalysts takes place under these conditions. We were pleased to observe that running reactions at 0 °C in methylecyclohexane or a 9 : 1 cyclohexane–toluene mixture led to the isolation of 3a,b in up to 82 : 18 and 84 : 16 er, respectively. These are better solvents than linear hydrocarbons and helped to keep homogeneous solutions (entries 7, 8, 12, and 13). Further cooling to −10 °C resulted in longer reaction times, while no enantioselectivity improvement was observed. Remarkably, reducing the catalyst loading from 15 mol% to 10 mol% also had a negative effect on enantioselectivity (entries 9 and 14).

To explore the scope of this Michael reaction, a representative set of alkyl and aryl substituted nitroalkenes 2 was made to react with N-tert-butyl hydrazone 1a under the optimal reaction conditions (Scheme 4). For γ,δ-dialkyl substituted nitroalkenes, the azo compounds 3a and 3c,d were obtained in high to excellent yields (89–96%) and moderate enantioselectivities (78 : 22 to 81 : 19 er). Nitroalkenes 2e,f having linear alkyl substituents also afforded the products 3e,f in high yields (88–91%), albeit in lower enantioselectivities (63 : 37 : 66 : 34 er). In the aromatic series, the reaction tolerates a range of substitution patterns. Thus azo compounds 3b, 3g and 3i,k were formed in good yields (84–96%) and enantiomeric ratios up to 84 : 16 (3b and 3g). Only the p-methoxy-phenyl-substituted nitroalkene gave the desired product 3h in lower yield (60%), probably due to a combination of the poorer electrophilicity of the substrate 2h and its low solubility in the reaction medium.

To further explore the efficiency of the developed methodology, reactions were performed on a 1 mmol scale, as exemplified by the synthesis of 3a (75%, 80 : 20 er), 3b (95%, 80 : 20 er), and 3c (95%, 80 : 20 er).

Diazenes 3 can be transformed into N-tert-butyl hydrazones 516 by means of a simple acid-catalyzed isomerization (Scheme 5). Treating optically active azo compounds 3a–e with TFA in CH2Cl2 at 0 °C afforded pure hydrazones 5a–e in excellent yields (90–95%) without the need for chromatographic purifications and, importantly, without significant racemization. It should be mentioned that tert-butyl hydrazones 5 are relatively unstable compounds. However, the corresponding 5-TFA salt could be stored for several months at 0 °C.

The synthetic utility of products 5 was demonstrated through their transformation into β-nitronitriles 7 (Scheme 6), which represent useful intermediates for the synthesis of β-amino acids.17 The direct oxidative cleavage of the hydrazone...
moiety of 5 by the established oxidation/aza-Cope elimination using magnesium monoperoxyphthalate hexahydrate (MMPP·6H₂O) leads to decomposition under standard conditions. Therefore, N-methylation was accomplished first to afford N,N-dialkyl hydrazones 6, which were then used for subsequent racemization-free oxidative cleavage of the hydrazone moiety to afford the desired β-nitronitriles 7 in good overall yields (7a: 58%, 7b: 71%, 2 steps). The absolute configurations of (S)-7a,b were assigned by comparison of their HPLC retention times with those of ent-7a,b previously described in our group.

Mechanistic aspects

To gain some insight into the substrate(s)-catalyst interactions that lead to the observed stereoselectivity, we studied the reaction of N,N-dimethyl hydrazone 1d with 2a using catalyst 4k.

In contrast to the results obtained using 1a, the reaction with 1d afforded a racemic product in a much slower reaction, suggesting that interactions involving the NH functionality might play an important role. On the basis of the obtained results, catalyst 4k is believed to act in a bifunctional fashion, as previously proposed in the literature. Accordingly, the nitroalkene is presumably activated by double hydrogen bonding to a thiourea unit, while the hydrazone is directed for the nucleophilic attack on the Si-face of the C=C bond by a weak NH–S hydrogen bond with the second thiourea moiety (Fig. 3), in agreement with the observed absolute configuration.

1H DOSY NMR (diffusion ordered spectroscopy) experiments were performed to explore the hydrazone (1a)-catalyst (4k) interactions in solution. As shown in Fig. 4, the diffusion coefficients of the bis-thiourea 4k and tert-butyl hydrazone 1a significantly decreased (ΔD = 0.33 and 0.82 for 4k and 1a, respectively) in a 1:1 mixture at 0.03 M, indicating the existence of a significative association.

Further evidence for the interaction of 4k and 1a was provided by 1H NMR titration studies, in which the addition of substoichiometric amounts of 4k to 1a resulted in...
disappearance of thiourea NH protons. In contrast with low-field shifts of thiourea NH signals generally showing the presence of well-defined H-bonding complexation, these observations might indicate the existence of chemical exchange processes causing signal broadening. Moreover, aromatic CH signals (A and G) next to the thiourea moiety undergo down-field shifts, suggesting conformational changes in catalyst 4k to accommodate an interaction with hydrazone 1a (Fig. 5).

Interestingly, the azomethine protons shift progressively upfield when 1a and 4k are mixed (Δδ = 0.03–0.05, 1a : 4k 2 : 1, see ESI†). These shifts reflect an increasing local electronic density, as expected for the proposed weak (1a) NH–S (4k) hydrogen bond depicted in Fig. 3.

Conclusions

In conclusion, formaldehyde tert-butyl hydrazone 1a appears as a convenient reagent for the synthesis of diazenes. As expected, the presence of a single bulky tert-butyl group on the amino nitrogen inhibits the reactivity of the nitrogen center while the low steric hindrance at the azomethine carbon allows C-selective conjugate addition of 1a to nitroalkenes. The reaction takes place spontaneously, but can be also accelerated by H-bonding organocatalysts. The interaction of the reagent’s NH group with axially chiral bis-thiourea 4k appears to be essential for the obtention of azo compounds 3 in good to excellent yields (60–90%) and moderate enantioselectivities, up to 84 : 16 er. The synthesis of β-nitro-nitriles 7, direct precursors of β-amino acids, can be accomplished using a two-step alkylation/oxidative cleavage protocol from tautomeric hydrazones 6.

Experimental

General methods

1H NMR spectra were recorded at 300 MHz, 400 MHz or 500 MHz; 13C NMR spectra were recorded at 75 MHz, 100 MHz...
or 125 MHz, with the solvent peak used as the internal standard. The following abbreviations are used to indicate the multiplicity in ¹H NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; m, multiplet; bs, broad signal. Analytical thin layer chromatography (TLC) was performed on 0.25 mm silica gel 60–F plates and visualized by ultraviolet irradiation and KMnO₄, anisaldehyde or phosphomolybdic acid stains. Optical rotations were measured on a Perkin-Elmer 341 MC polarimeter. The enantiomeric ratio was determined by HPLC analysis (Daicel Chiralpak AD-H, OD columns).

Materials

Unless otherwise noted, analytical grade solvents and commercially available reagents, or catalysts, were used without further purification. For flash chromatography (FC) silica gel (0.040–0.063 mm) was used. Formaldehyde hydrzones 1, 25 not commercially available nitroalkenes 2, 26 and catalysts 4d–f, k–p 27 were synthesized according to the literature.

General procedure for the enantioselective 1,4-addition of formaldehyde

N-tert-butyl hydrzone 1a to nitroalkenes 2

Hydrazine 1a (17.7 µL, 0.15 mmol) was added to a solution of nitroalkene 2 (0.1 mmol) and catalyst 4k (0.015 mmol) in 9:1 cyclohexane–toluene (1 mL) at 0 °C. The mixture was stirred for ~48 h. The enantiomerically enriched products 3 were purified by FC (pentane/CH₂Cl₂). Enantiomeric ratios were determined by chiral stationary-phase HPLC using a Chiralpak OD-H column [heptane

41.7, 38.5, 30.1, 29.3, 26.6, 26.4, 26.6, 26.3; HRMS (CI): calculated for [C₁₅H₂₄N₃O₂]⁺ 256.2025; found: 256.2105. The enantiomeric ratio was determined by HPLC using a Chiralpak AD-H column [hexane–i-ProH (98:2)]; flow rate 0.5 mL min⁻¹; τmin = 15.5 min, τmajor = 9.7 min.

(R,E)-1-(tert-Butyl)-2-[2-cyclopropyl-3-nitropropyl]diazene (3d). Yellow oil (96% yield); [α]D²⁵ −16.0 (c 1.0, CHCl₃); (81:19 er); ¹H NMR (300 MHz, CDCl₃) δ 4.63 (dd, J = 12.1, 6.8 Hz, 1H), 4.53 (dd, J = 12.1, 7.1 Hz, 1H), 3.89 (dd, J = 12.8, 5.2 Hz, 1H), 3.82 (dd, J = 12.8, 7.2 Hz, 1H), 2.13–1.95 (m, 1H), 1.18 (s, 9H), 0.82–0.67 (m, 1H), 0.62–0.49 (m, 2H), 0.32–0.18 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 78.6, 70.3, 67.8, 42.5, 26.7, 13.4, 4.1, 3.7; HRMS (CI): calculated for [C₁₃H₁₉N₃O₂]⁺ 214.1556; found: 214.1548. The enantiomeric ratio was determined by HPLC using a Chiralpak OD column [hexane–i-ProH (99:5:5)]; flow rate 0.25 mL min⁻¹; τmin = 29.1 min, τmajor = 31.0 min.

(R,E)-1-(tert-Butyl)-2-[2-nitromethyl-4-phenylbutyl]diazene (3e). Yellow oil (91% yield); [α]D²⁵ −1.1 (c 1.3, CHCl₃); (63:37 er); ¹H NMR (400 MHz, CDCl₃) δ 6.78–6.73 (m, 5H), 4.60 (dd, J = 12.5, 6.6 Hz, 1H), 4.44 (dd, J = 12.5, 6.7 Hz, 1H), 3.83 (dd, J = 13.1, 5.1 Hz, 1H), 3.76 (dd, J = 13.1, 6.7 Hz, 1H), 2.87–2.78 (m, 1H), 2.77–2.59 (m, 2H), 1.82–1.67 (m, 2H), 1.17 (s, 9H); ¹¹C NMR (100 MHz, CDCl₃) δ 140.8, 128.5, 128.2, 126.1, 77.9, 68.6, 36.3, 32.4, 31.7, 26.7; HRMS (CI): calculated for [C₁₀H₁₇N₃O₂]⁺ 278.1869; found: 278.1865. The enantiomeric ratio was determined by HPLC using a Chiralpak AD-H column [hexane–i-ProH (97:3)]; flow rate 1 mL min⁻¹; τmin = 5.2 min, τmajor = 4.6 min.

(R,E)-1-(tert-Butyl)-2-[2-nitrophenyl]heptadiazene (3f). Yellow oil (88% yield); [α]D²⁵ −4.4 (c 1.1, CHCl₃); (66:34 er); ¹H NMR (300 MHz, CDCl₃) δ 4.57 (dd, J = 12.5, 6.7 Hz, 1H), 4.41 (dd, J = 12.5, 6.8 Hz, 1H), 3.78 (dd, J = 13.0, 5.0 Hz, 1H), 3.68 (dd, J = 13.0, 7.1 Hz, 1H), 2.84–2.72 (m, 1H), 1.57–1.19 (m, 8H), 1.17 (s, 9H), 0.92–0.79 (m, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 78.2, 69.0, 67.8, 36.8, 31.6, 30.0, 26.7, 25.8, 22.4, 13.9; HRMS (CI): calculated for [C₁₅H₂₆N₃O₃]⁺ 244.2025; found: 244.2028. The enantiomeric ratio was determined by HPLC using a Chiralpak OD column [hexane–i-ProH (99.5:0.5)]; flow rate 0.25 mL min⁻¹; τmin = 23.6 min, τmajor = 25.0 min.

(R,E)-1-(tert-Butyl)-2-[3-nitro-2-(p-tolyl)propyl]diazene (3g). Yellow oil (95% yield); [α]D²⁵ −36.5 (c 2.0, CHCl₃); (84:16 er); ¹H NMR (400 MHz, CDCl₃) δ 7.20–6.98 (m, 4H), 4.81 (dd, J = 12.7, 6.4 Hz, 1H), 4.69 (dd, J = 12.7, 8.2 Hz, 1H), 4.16–4.02 (m, 1H), 3.99 (dd, J = 6.9, 1.7 Hz, 2H), 2.30 (s, 3H), 1.14 (s, 9H); ¹¹C NMR (125 MHz, CDCl₃) δ 137.5, 134.7, 129.6, 127.6, 78.5, 70.8, 67.9, 42.5, 26.6, 21.0; HRMS (CI): calculated for [C₁₅H₂₃N₃O₂]⁺ 264.1712; found: 264.1706. The enantiomeric ratio was determined by HPLC using a Chiralpak OD column [hexane–i-ProH (95:5)]; flow rate 1 mL min⁻¹; τmin = 6.0 min, τmajor = 9.0 min.

(R,E)-1-(tert-Butyl)-2-[2-cyclohexyl-3-nitropropyl]diazene (3h). Yellow oil (60% yield); [α]D²⁵ −0.9 (c 0.8, CHCl₃); (71:29 er); ¹H NMR (300 MHz, CDCl₃) δ 7.15 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 4.81 (dd, J = 12.7, 6.3 Hz, 1H), 4.68 (dd, J = 12.7, 8.1 Hz, 1H), 4.17–4.05 (m, 1H), 4.05–3.95 (m, 2H), 3.78 (s, 3H), 1.15 (s, 9H); ¹¹C NMR (75 MHz, CDCl₃) δ 159.1, 129.7,
Organic & Biomolecular Chemistry Paper

128.8, 114.3, 78.6, 70.8, 67.9, 55.2, 42.2, 26.6; HRMS (CI) calculated for [C14H14N2O3]2+ 280.1661; found: 280.1657. The enantiomeric ratio was determined by HPLC using a Chiralpak AD-H column [hexane-i-PrOH (98:2)]; flow rate 0.5 mL min−1; tminor = 19.4 min, tmajor = 20.6 min.

(R,E)-1-(3-BUTYL)-2-[2,4-DICHLOROPHENYL]-3-NITROPROPYLIDIAZINE (3i). Yellow oil (96% yield); [α]25D −10.4 (c 1.5, CHCl3). (72:28 er); 1H NMR (400 MHz, CDCl3) δ 7.42 (d, J = 2.1 Hz, 1H), 7.21–7.17 (m, 2H), 4.82 (dd, J = 7.2, 2.4 Hz, 2H), 4.71–4.61 (m, 1H), 4.05 (dd, J = 6.6, 2.4 Hz, 1H), 1.13 (s, 9H); 13C NMR (100 MHz, CDCl3) δ 134.8, 134.3, 133.0, 130.0, 129.4, 127.3, 77.1, 68.7, 68.1, 38.6, 26.5; HRMS (CI) calculated for [C16H17Cl2N3O2]2+ 318.0412; found: 318.0401. The enantiomeric ratio was determined by HPLC using a Chiralpak AD-H column [hexane-i-PrOH (98:2)]; flow rate 1 mL min−1; tminor = 7.1 min, tmajor = 9.1 min.

(R,E)-1-(3-BUTYL)-2-[2-FURANYL]-3-NITROPROPYLIDIAZINE (3k). Brown oil (90% yield); [α]25D −16.6 (c 1.5, CHCl3). (72:28 er); 1H NMR (300 MHz, CDCl3) δ 6.760 (dd, J = 8.0, 1.2 Hz, 1H), 7.33–7.18 (m, 2H), 7.17–7.10 (m, 1H), 4.88–4.82 (m, 2H), 4.80–4.68 (m, 1H), 4.08 (d, J = 6.5 Hz, 2H), 1.13 (s, 9H); 13C NMR (75 MHz, CDCl3) δ 137.3, 134.2, 129.8, 129.0, 128.3, 125.4, 77.5, 69.8, 68.6, 41.9, 27.2; HRMS (CI) calculated for [C15H19BrN3O2]2+ 328.0661; found: 328.065. The enantiomeric ratio was determined by HPLC using a Chiralpak OD column [hexane-i-PrOH (95:5)]; flow rate 1 mL min−1; tminor = 6.8 min, tmajor = 9.1 min.

General procedure for the transformation of azo compounds 3 into hydrazones 5

TFA (2 mL, 0.1 M in CH2Cl2) was added to a solution of azo compound 3 (0.2 mmol) in CH2Cl2 (0.1 mL) at 0 °C. The mixture was stirred for 12–15 h. Satd NaHCO3 was added, and the mixture was extracted with Et2O and concentrated to dryness to yield the pure hydrazones 5. Alternatively, excess of TFA could be evaporated as an azetrop with toluene (3 × 1 mL) to obtain 5-TFA salts in high purity. Enantiomeric ratios were determined by HPLC analysis of the corresponding hydrazones 5.

(S,E)-1-(3-BUTYL)-2-[3-METHYL-2-(NITROMETHYL)BUTYLIDENE] HYDRAZINE (5a). Yellow oil (90%); [α]25D −13.3 (c 1.0, CHCl3). (80:20 er); 1H NMR (300 MHz, CDCl3) δ 7.00 (d, J = 4.1 Hz, 1H), 4.75 (dd, J = 13.1, 9.0 Hz, 1H), 4.37 (dd, J = 13.1, 5.4 Hz, 1H), 3.13–2.99 (m, 1H), 1.96–1.81 (m, 1H), 1.12 (s, 9H), 0.97 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H); HRMS: calculated for [C15H24N4O2]+ 256.1548; found: 256.1542. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane-i-PrOH (98:2)]; flow rate 1 mL min−1; tminor = 11.9 min, tmajor = 11.5 min.

(S,E)-1-(3-BUTYL)-2-[3-CYCLOHEXYL-3-NITROPROPYLIDENE] HYDRAZINE (5c). Yellow oil (95%); [α]25D −1.8 (c 0.9, CHCl3). (80:20 er); 1H NMR (300 MHz, CDCl3) δ 6.40 (d, J = 4.5 Hz, 1H), 4.38 (dd, J = 13.0, 9.6 Hz, 1H), 3.83 (dd, J = 13.0, 5.0 Hz, 1H), 2.84–2.70 (m, 1H), 1.64–1.23 (m, 6H), 1.07 (s, 9H), 1.03–0.56 (m, 5H); 13C NMR (75 MHz, CDCl3) δ 137.56, 75.3, 53.4, 45.8, 39.3, 30.4, 29.8, 28.4, 26.6, 26.4, 26.3; HRMS: calculated for [C15H26N4O2]+ 256.1548; found: 256.1552. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane-i-PrOH (98:2)]; flow rate 1 mL min−1; tminor = 12.6 min, tmajor = 11.5 min.

(S,E)-1-(3-BUTYL)-2-[3-CYCLOHEXYL-3-NITROPROPYLIDENE] HYDRAZINE (5d). Yellow oil (90%); [α]25D −63.8 (c 0.9, CHCl3). (77:23 er); 1H NMR (300 MHz, CDCl3) δ 7.05 (d, J = 3.6 Hz, 1H), 4.80 (dd, J = 12.9, 8.2 Hz, 1H), 4.47 (dd, J = 12.9, 6.2 Hz, 1H), 2.47–2.26 (m, 1H), 1.11 (s, 9H), 0.66 (m, 1H), 0.61–0.50 (m, 2H), 0.35–0.19 (m, 2H); 13C NMR (75 MHz, CDCl3) δ 138.7, 77.0, 53.6, 44.9, 28.2, 11.9, 3.7, 3.0; HRMS: calculated for [C15H24N4O2]+ 256.1406; found: 256.1407. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane-i-PrOH (98:2)]; flow rate 1 mL min−1; tminor = 10.9 min, tmajor = 8.4 min.

(S,E)-1-(3-BUTYL)-2-[3-METHYL-2-(NITROMETHYL)BUTYLIDENE] HYDRAZINE (5e). Orange oil (90%); [α]25D −54.1 (c 0.8, CHCl3). (78:22 er); 1H NMR (500 MHz, CD3CO2H) δ 7.18 (s, 4H), 7.09 (dd, J = 3.7 Hz, 1H), 5.05 (dd, J = 13.4, 8.7 Hz, 1H), 4.68 (dd, J = 13.4, 6.7 Hz, 1H), 4.37–4.32 (m, 1H), 2.30 (s, 3H), 1.14 (s, 9H); 13C NMR (75 MHz, CDCl3) δ 137.99, 137.66, 133.5, 123.8, 128.2, 77.4, 53.7, 45.7, 28.3, 21.0; HRMS: calculated for [C15H22N4O2]+ 264.1712; found: 264.1708. The enantiomeric excess was determined by
HPLC using a Chiralpak AD-H column [hexane-i-PrOH (98:2)]; flow rate 1.0 mL min⁻¹; \( \tau_{\text{minor}} = 12.0 \) min, \( \tau_{\text{major}} = 10.4 \) min.

**General procedure for the transformation of hydrazones 5 into dialkylhydrazones 6**

NaHCO₃ (solid, 0.5 mmol, 42 mg) and MeI (1.5 mmol, 93 \( \mu \)L) were added to a solution of hydrazone 5 (0.5 mmol) in MeOH (1 mL) at room temperature and the mixture was stirred overnight. Satd NaHCO₃ was added, and the mixture was extracted with Et₂O and concentrated to dryness. Dialkylhydrazones 6 were isolated by FC (cyclohexane/Et₂O).

\( (S,E)-1-(tert-Butyl)-1-methyl-2-[3-methyl-2-(nitromethyl)butylidene]hydrazone \) (6a). Yellow oil (70%/10% recovered 5a); [\( \alpha \]⁺]D²⁵ = −6.5 (c 1.3, CHCl₃). (80 : 20 er); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 6.59–6.46 (m, 1H), 4.77 (dd, \( J = 12.9, 9.1 \) Hz, 1H), 4.38 (dd, \( J = 12.9, 5.5 \) Hz, 1H), 3.21 (m, 1H), 2.00–1.81 (m, 1H), 1.15 (s, 9H), 0.99 (d, \( J = 7.0 \) Hz, 3H), 0.95 (d, \( J = 7.0 \) Hz, 3H); \(^1\)^13C NMR (75 MHz, CDCl₃) \( \delta \) 130.9, 75.6, 58.5, 46.2, 36.1, 31.7, 26.9, 19.9, 19.8; HRMS: calculated for [C₁₃H₂₃N₃O₂]⁺ 229.1790; found: 229.1786.

**Notes and references**


10 1,3,5-Trisubstituted pyrazoles: (a) X. Deng and N. S. Mani, Org. Lett., 2006, 8, 3505; (b) X. Deng and N. S. Mani, J. Org. Chem., 2008, 73, 2412; (d) 1,4-disubstituted pyrazoles: (c) X. Deng and N. S. Mani, Org. Lett., 2008, 10, 1307; (d) 1,4-disubstituted pyrazoles: M. Gómez-Guillén and J. M. Lassaletta, Carbohydr. Res., 1991, 210, 175.


17 For catalyst $9$ in Par. 21, see: Ref. 25.

18 For catalyst $9$ in Par. 21, see: Ref. 25.

19 For catalyst $9$ in Par. 21, see: Ref. 25.

20 For catalyst $9$ in Par. 21, see: Ref. 25.

21 For catalyst $9$ in Par. 21, see: Ref. 25.

22 For catalyst $9$ in Par. 21, see: Ref. 25.

23 For catalyst $9$ in Par. 21, see: Ref. 25.

24 For catalyst $9$ in Par. 21, see: Ref. 25.

25 For catalyst $9$ in Par. 21, see: Ref. 25.