

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.

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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 ($RO_2C-N=N-CO_2R$) 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 alkyl) 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

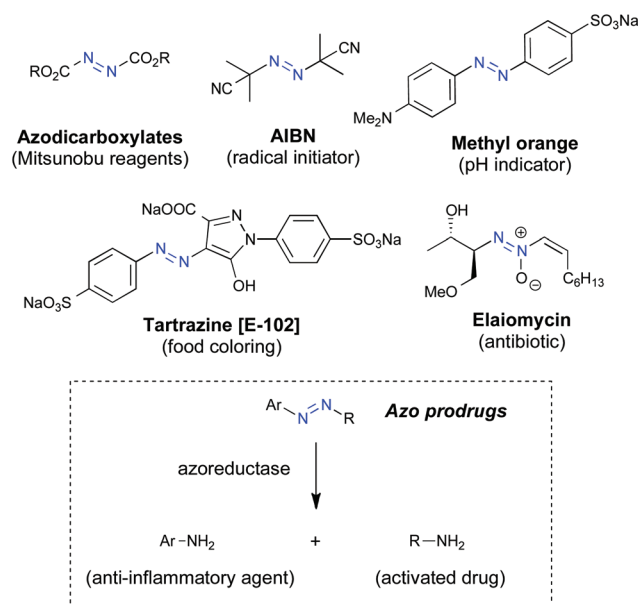


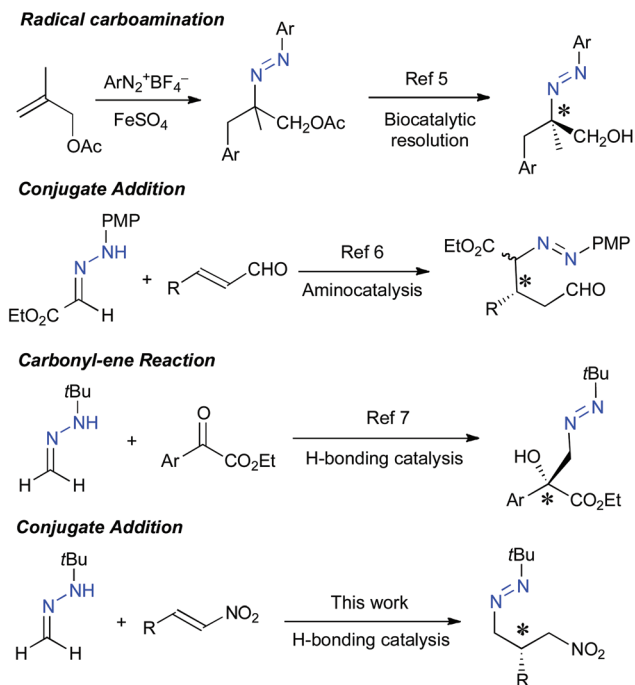
Fig. 1 Important azo compounds.

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 diazenylmethyl carbinols.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

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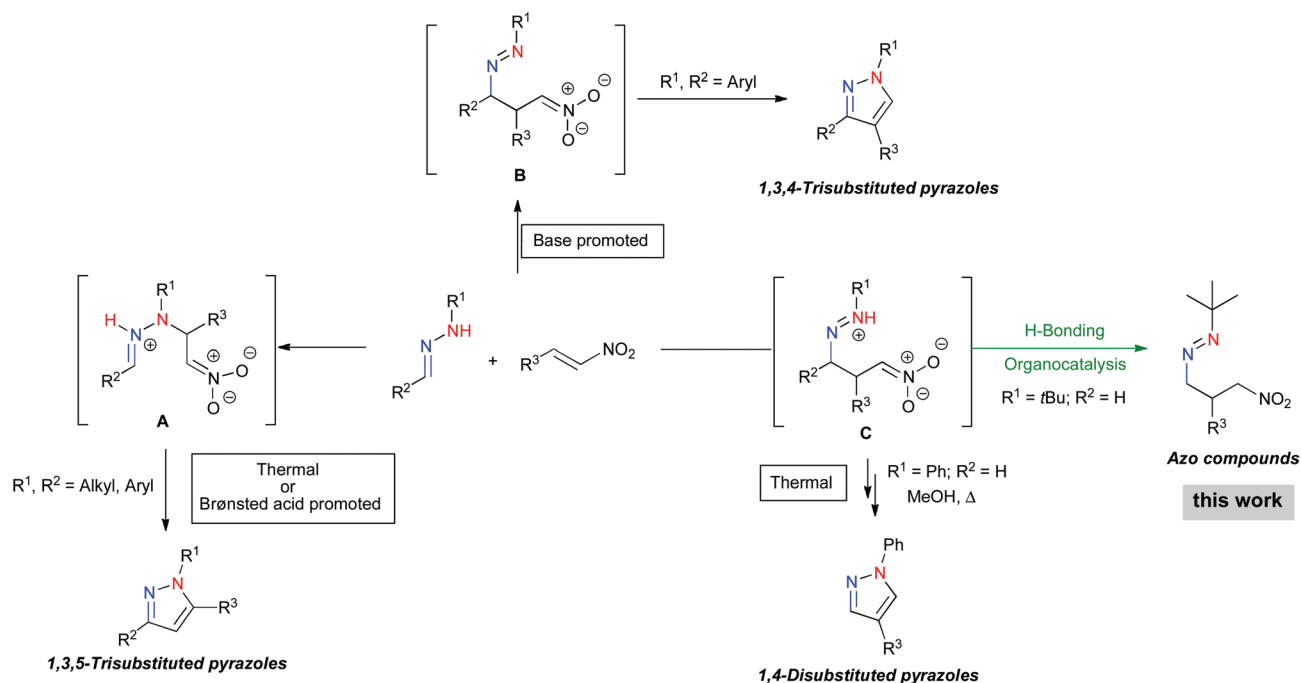


Scheme 1 Synthesis of enantioenriched azo compounds.

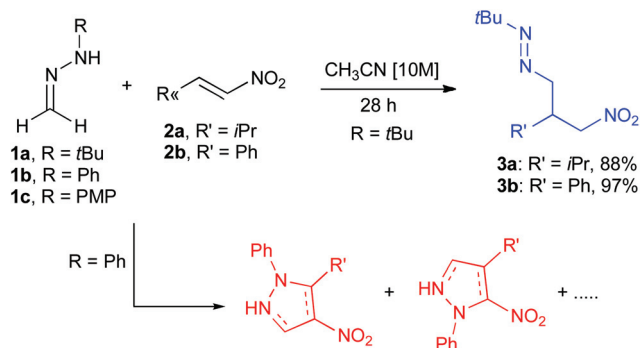
In their pioneering work on the use of *N*-monosubstituted hydrazones as acyl anion equivalents, Baldwin *et al.* showed that the reactivity and the *C*- versus *N*-selectivity are strongly influenced by the substitution pattern at nitrogen and the azomethine carbon, the reaction conditions (basic or thermal) and the electrophilic partners.⁹ Reactions of *N*-monosubstituted hydrazones with nitroalkenes were reported to proceed

affording mainly pyrazoles by the different reaction pathways depicted in Scheme 2.¹⁰ 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 β -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 CF₃CH₂OH), 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 step-wise 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.¹¹ We envisioned that the presence of a phenyl group or a bulky *tert*-butyl group on the amino nitrogen would efficiently 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 2 Different reaction pathways for the addition of monosubstituted hydrazones to nitroalkenes.

Scheme 3 Non-catalyzed addition of **1a–c** to **2a,b**.

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 nitropyrazolines,[†] 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_3CN [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_3CN 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 nucleophilic attack in a highly enantioselective manner.¹² Moreover, several H-bonding and Brønsted acid organocatalysts¹³ 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 (1*S*,2*R*)-1-aminoindan-2-ol-derived thiourea **4d**

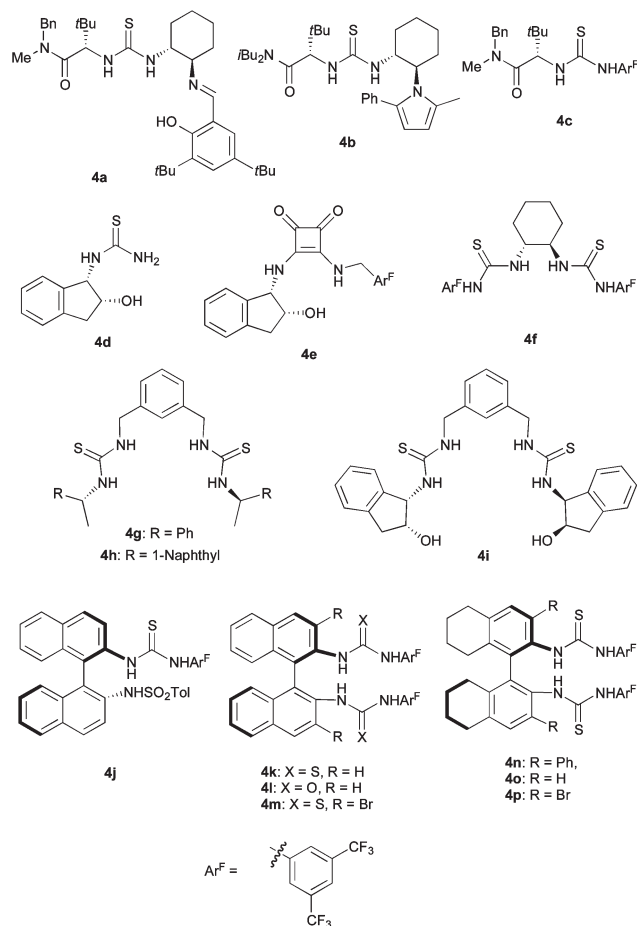
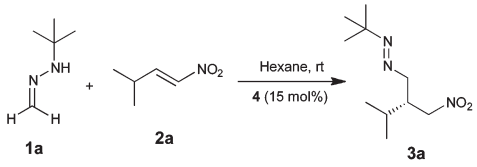


Fig. 2 H-bonding organocatalysts tested.

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 stereoselection (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(isothiocyanatomethyl)benzene, 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.¹⁴ 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-arylthiourea-based organocatalysts¹⁵ **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 *t*-butyl-hydrazones were unreactive, even under forcing conditions.

Table 1 Screening of catalysts for the enantioselective addition of **1a** to **2a**^a


Entry	Cat.	Conv. ^b [%]	er ^d
1	4a	60	rac
2	4b	65 ^c	68 : 32
3	4c	70 ^c	67 : 33
4	4d	>95	59 : 41
5	4e	60 ^c	rac
6	4f	90	64 : 36
7	4g	70 ^c	rac
8	4h	60 ^c	rac
9	4i	60 ^c	rac
10	4j	90	64 : 36
11	4k	>95	74 : 26
12	4l	>95 ^c	74 : 26
13	4m	>95	rac
14	4n	>95	rac
15	4o	90	rac
16	4p	>95 ^c	rac

^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**^a

Entry	2	Solvent	T [°C]	t [h]	Conv. ^b [%]	er ^c
1	2a	Hexane	rt	24	>95	74 : 26
2	2a	Toluene	rt	24	85	60 : 40
3	2a	Pentane	rt	24	>95	68 : 32
4	2a	Heptane	rt	24	>95	63 : 37
5	2a	Cyclohexane	rt	24	>95	76 : 24
6	2a	Methylcyclohexane	rt	24	>95	74 : 26
7	2a	Methylcyclohexane	0	48	>95	82 : 18
8	2a	CyH-toluene (9 : 1)	0	48	>95	81 : 19
9 ^d	2a	CyH-toluene (9 : 1)	0	48	>95	63 : 37
10	2b	Hexane	rt	16	>95	72 : 28
11	2b	Cyclohexane	rt	16	>95	78 : 22
12	2b	Methylcyclohexane	0	48	>95	80 : 20
13	2b	CyH-toluene (9 : 1)	0	48	>95	84 : 16
14 ^d	2b	CyH-toluene (9 : 1)	0	48	>95	66 : 34

^a 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 methylcyclohexane 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).

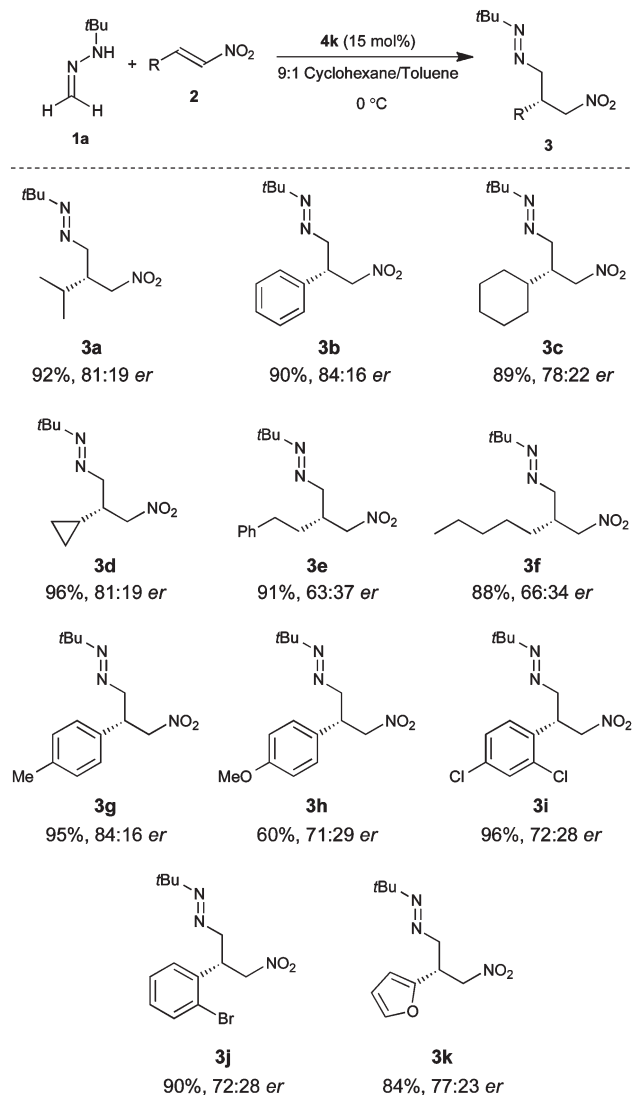
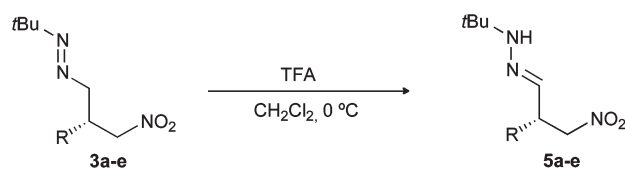
To explore the scope of this Michael reaction, a representative set of alkyl and aryl substituted nitroalkenes **2** was made to react with *N*-tert-butyl hydrazone **1a** under the optimal reaction conditions (Scheme 4). For γ,γ-dialkyl substituted nitroalkenes, the azo compounds **3a** and **3c,d** 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*-methoxyphenyl-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 **5**¹⁶ 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

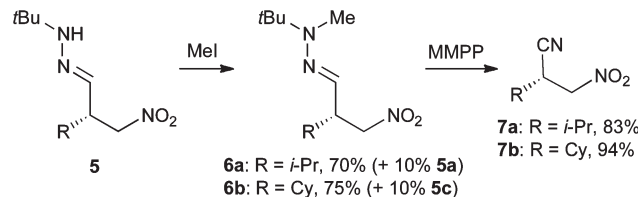
[†] Reactions were performed with **1a** (1.5 mmol), **2** (1 mmol) and **4k** (15 mol%) in dry cyclohexane–toluene (9 : 1) (10 mL) under argon at 0 °C for 72 h.

Scheme 4 Synthesis of enantioenriched azo compounds **3**.

5	R	Yield	er
5a	<i>i</i> Pr	90%	80:20
5a-TFA	<i>i</i> Pr	95%	80:20
5b	Ph	93%	79:21
5c	Cy	95%	80:20
5d	Cyclopropyl	90%	77:23
5e	<i>p</i> -Tolyl	90%	78:22

Scheme 5 Transformation of adducts **3** into *tert*-butyl hydrazones **5**.

moiety of **5** by the established oxidation/aza-Cope elimination using magnesium monoperoxyphthalate hexahydrate

Scheme 6 Synthesis of β -nitronitriles **7**.

(MMPP·6H₂O)¹⁸ leads to decomposition under standard conditions. Therefore, *N*-methylation was accomplished first to afford *N,N*-dialkyl hydrazones **6**,¹⁹ 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.²⁰

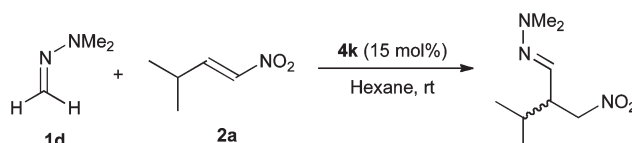
Mechanistic aspects

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.^{15c} Accordingly, the nitroalkene is presumably activated by double hydrogen bonding to a thiourea unit,²¹ 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.²²

¹H DOSY NMR (diffusion ordered spectroscopy) experiments were performed to explore the hydrazone (**1a**)-catalyst (**4k**) interactions in solution.²³ As shown in Fig. 4, the diffusion coefficients of the bis-thiourea **4k** and *tert*-butyl hydrazone **1a** significantly decreased ($\Delta D = 0.33$ 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

||^aReaction was performed with **1d** (0.15 mmol), **2a** (0.1 mmol) and **4k** (15 mol %) in hexane (1 mL) at room temperature for 72 h. ^b30% of conversion (determined by ¹H-NMR) into *rac*-adduct. ^c20% of conversion in the non-catalyzed reaction.



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,²⁴ 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 ($\Delta\delta = 0.03$ – 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

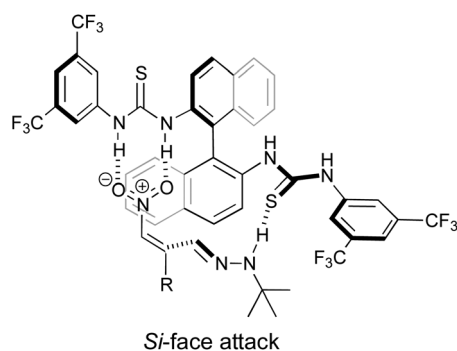


Fig. 3 Stereochemical model.

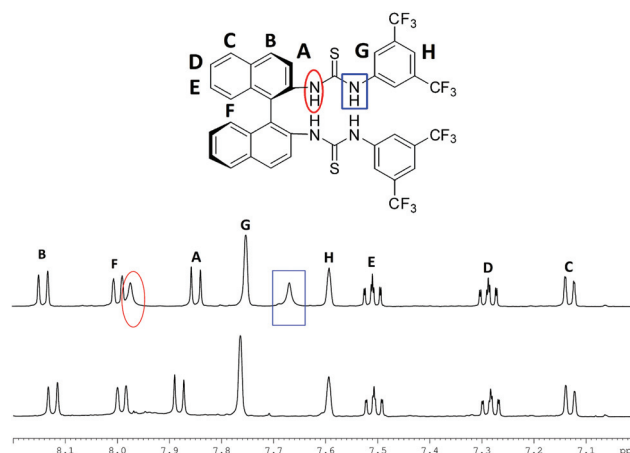


Fig. 5 ¹H NMR (500 MHz, 0.03 M, CD₂Cl₂) spectra for **4k** (up) and a 1 : 1 mixture of **4k** and **1a** (down).

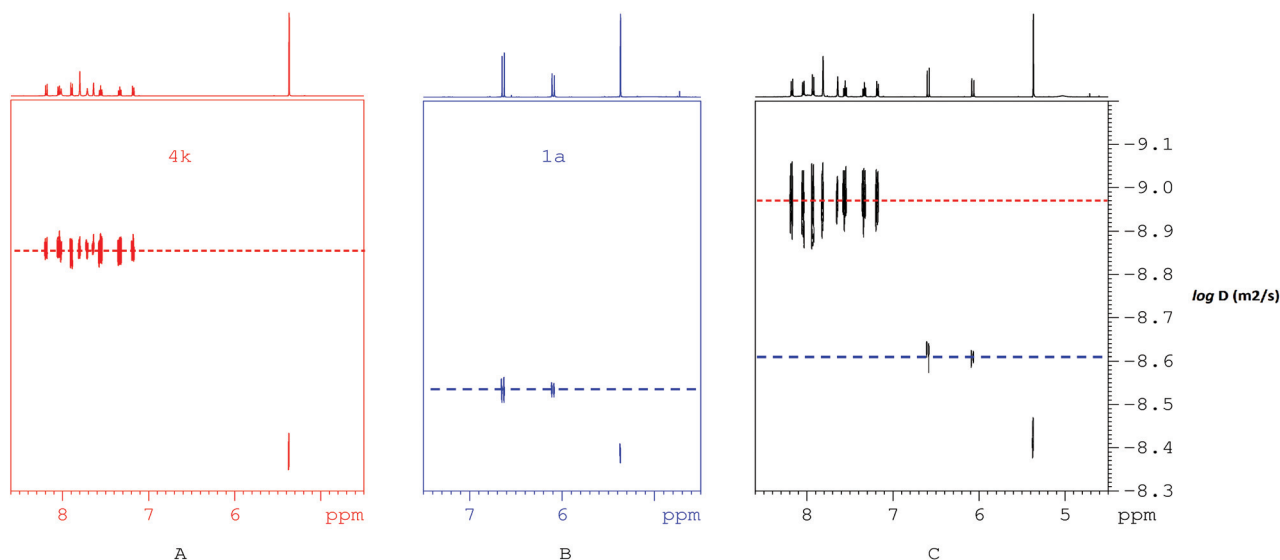


Fig. 4 ¹H DOSY NMR (500 MHz, 0.03 M, CD₂Cl₂) of A: **4k**; B: **1a**; C: **4k** + **1a**.

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 KMnO_4 , anisaldehyde or phosphomolybdic acid stains. Optical rotations were measured on a Perkin-Elmer 341 MC polarimeter. The enantiomeric ratios (er) of the products were determined by chiral stationary-phase HPLC (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 hydrazones **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 hydrazone **1a** to nitroalkenes **2**

Hydrazone **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/ CH_2Cl_2). Enantiomeric ratios were determined by HPLC analysis.

(*R,E*)-1-(*tert*-BUTYL)-2-[3-METHYL-2-(NITROMETHYL)BUTYL]DIAZENE (**3A**). Yellow oil (92% yield); $[\alpha]_{\text{D}}^{25} +6.8$ (c 1.2, CHCl_3). (81 : 19 er); ^1H NMR (300 MHz, CDCl_3) δ 4.49 (dd, $J = 12.7$, 7.1 Hz, 1H), 4.42 (dd, $J = 12.7$, 6.5 Hz, 1H), 3.75 (dd, $J = 13.1$, 4.9 Hz, 1H), 3.61 (dd, $J = 13.1$, 8.3 Hz, 1H), 2.75–2.62 (m, 1H), 1.90–1.70 (m, 1H), 1.11 (s, 9H), 0.94 (d, $J = 6.9$ Hz, 3H), 0.91 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 76.5, 67.8, 67.4, 42.3, 28.4, 26.7, 19.7, 18.8; HRMS (CI): calculated for $[\text{C}_{10}\text{H}_{22}\text{N}_3\text{O}_2]^+$ 216.1712; found: 216.1705. The enantiomeric ratio was determined by HPLC using a Chiralpak AD-H column [heptane–i-PrOH (99.5 : 0.5)]; flow rate 0.5 mL min^{-1} ; $\tau_{\text{minor}} = 9.9$ min, $\tau_{\text{major}} = 9.6$ min.

(*R,E*)-1-(*tert*-BUTYL)-2-(3-NITRO-2-PHENYLPROPYL)DIAZENE (**3B**). Yellow oil (90% yield); $[\alpha]_{\text{D}}^{25} -25.3$ (c 1.1, CHCl_3). (84 : 16 er); ^1H NMR (300 MHz, CDCl_3) δ 7.47–7.04 (m, 5H), 4.78 (dd, $J = 12.8$, 6.6 Hz, 1H), 4.67 (dd, $J = 12.8$, 8.2 Hz, 1H), 4.17–4.01 (m, 1H), 3.97 (dd, $J = 6.9$, 3.5 Hz, 2H), 1.07 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 137.8, 128.9, 127.8, 127.7, 78.3, 70.7, 67.9, 42.8, 26.6; HRMS (CI) calculated for $[\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}_2]^+$ 249.1477; found: 249.1469. The enantiomeric ratio was determined by HPLC using a Chiralpak OD column [hexane–i-PrOH (95 : 5)]; flow rate 1 mL min^{-1} ; $\tau_{\text{minor}} = 7.3$ min, $\tau_{\text{major}} = 9.1$ min.

(*R,E*)-1-(*tert*-BUTYL)-2-(2-CYCLOHEXYL-3-NITROPROPYL)DIAZENE (**3C**). Yellow oil (89% yield); $[\alpha]_{\text{D}}^{25} +2.9$ (c 1.1, CHCl_3). (78 : 22 er); ^1H NMR (300 MHz, CDCl_3) δ 4.55 (dd, $J = 11.2$, 5.4 Hz, 1H), 4.49 (dd, $J = 11.2$, 4.9 Hz, 1H), 3.82 (dd, $J = 13.0$, 4.9 Hz, 1H), 3.68 (dd, $J = 13.0$, 8.3 Hz, 1H), 2.81–2.66 (m, 1H), 1.87–1.21 (m, 11H), 1.17 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 76.4, 67.7, 67.6,

41.7, 38.5, 30.1, 29.3, 26.6, 26.4, 26.4, 26.3; HRMS (CI): calculated for $[\text{C}_{13}\text{H}_{26}\text{N}_3\text{O}_2]^+$ 256.2025; found: 256.2021. 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} ; $\tau_{\text{minor}} = 15.5$ min, $\tau_{\text{major}} = 9.7$ min.

(*R,E*)-1-(*tert*-BUTYL)-2-(2-CYCLOPROPYL-3-NITROPROPYL)DIAZENE (**3D**). Yellow oil (96% yield); $[\alpha]_{\text{D}}^{25} -16.0$ (c 1.0, CHCl_3). (81 : 19 er); ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) δ 78.6, 70.3, 67.8, 42.5, 26.7, 13.4, 4.1, 3.7; HRMS (CI): calculated for $[\text{C}_{10}\text{H}_{20}\text{N}_3\text{O}_2]^+$ 214.1556; found: 214.1548. 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} ; $\tau_{\text{minor}} = 29.1$ min, $\tau_{\text{major}} = 31.0$ min.

(*R,E*)-1-(*tert*-BUTYL)-2-[2-(NITROMETHYL)-4-PHENYLBUTYL]DIAZENE (**3E**). Yellow oil (91% yield); $[\alpha]_{\text{D}}^{25} -1.1$ (c 1.3, CHCl_3). (63 : 37 er); ^1H NMR (400 MHz, CDCl_3) δ 7.68–6.73 (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); ^{13}C NMR (100 MHz, CDCl_3) 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 $[\text{C}_{15}\text{H}_{24}\text{N}_3\text{O}_2]^+$ 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} ; $\tau_{\text{minor}} = 5.2$ min, $\tau_{\text{major}} = 4.6$ min.

(*R,E*)-1-(*tert*-BUTYL)-2-[2-(NITROMETHYL)HEPTYL]DIAZENE (**3F**). Yellow oil (88% yield); $[\alpha]_{\text{D}}^{25} -4.4$ (c 1.1, CHCl_3). (66 : 34 er); ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) 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 $[\text{C}_{12}\text{H}_{26}\text{N}_3\text{O}_2]^+$ 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} ; $\tau_{\text{minor}} = 23.6$ min, $\tau_{\text{major}} = 25.0$ min.

(*R,E*)-1-(*tert*-BUTYL)-2-[3-NITRO-2-(*p*-TOLYL)PROPYL]DIAZENE (**3G**). Yellow oil (95% yield); $[\alpha]_{\text{D}}^{25} -36.5$ (c 2.0, CHCl_3). (84 : 16 er); ^1H NMR (400 MHz, CDCl_3) 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); ^{13}C NMR (125 MHz, CDCl_3) 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 $[\text{C}_{14}\text{H}_{22}\text{N}_3\text{O}_2]^+$ 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} ; $\tau_{\text{minor}} = 6.0$ min, $\tau_{\text{major}} = 9.0$ min.

(*R,E*)-1-(*tert*-BUTYL)-2-[2-(4-METHOXYPHENYL)-3-NITROPROPYL] DIAZENE (**3H**). Yellow oil (60% yield); $[\alpha]_{\text{D}}^{25} -0.9$ (c 0.8, CHCl_3). (71 : 29 er); ^1H NMR (300 MHz, CDCl_3) 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); ^{13}C NMR (75 MHz, CDCl_3) δ 159.1, 129.7,

128.8, 114.3, 78.6, 70.8, 67.9, 55.2, 42.2, 26.6; HRMS (CI) calculated for $[C_{14}H_{22}N_3O_3]^+$ 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; $\tau_{\text{minor}} = 19.4$ min, $\tau_{\text{major}} = 20.6$ min.

(*R,E*)-1-(*tert*-butyl)-2-[2-(2,4-dichlorophenyl)-3-nitropropyl] diazene (3i). Yellow oil (96% yield); $[\alpha]_D^{25} -10.4$ (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, 2H), 1.13 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 134.8, 134.1, 133.7, 130.0, 129.4, 127.3, 77.1, 68.7, 68.1, 38.6, 26.5; HRMS (CI) calculated for $[C_{13}H_{17}Cl_2N_3O_2]^+$ 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; $\tau_{\text{minor}} = 7.1$ min, $\tau_{\text{major}} = 6.4$ min.

(*R,E*)-1-[2-(2-bromophenyl)-3-nitropropyl]-2-(*tert*-butyl) diazene (3j). Brown oil (90% yield); $[\alpha]_D^{25} -16.6$ (c 1.5, CHCl₃). (72 : 28 er); ¹H NMR (300 MHz, CDCl₃) δ 7.60 (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 $[C_{13}H_{19}BrN_3O_2]^+$ 328.0661; found: 328.0665. The enantiomeric ratio was determined by HPLC using a Chiralpak OD column [hexane-*i*-PrOH (95 : 5)]; flow rate 1 mL min⁻¹; $\tau_{\text{minor}} = 6.8$ min, $\tau_{\text{major}} = 9.1$ min.

(*R,E*)-1-(*tert*-butyl)-2-[2-(furan-2-yl)-3-nitropropyl] diazene (3k). Yellow oil (84% yield); $[\alpha]_D^{25} -10.2$ (c 0.5, CHCl₃). (77 : 23 er); ¹H NMR (400 MHz, CDCl₃) δ 7.34 (s, 1H), 6.29 (s, 1H), 6.14 (d, *J* = 3.0 Hz, 1H), 4.80 (d, *J* = 7.1 Hz, 2H), 4.34–4.19 (m, 1H), 4.05 (d, *J* = 7.3 Hz, 2H), 1.16 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 150.9, 142.3, 110.3, 107.5, 76.2, 68.1, 68.0, 36.7, 26.6; HRMS (CI) calculated for $[C_{11}H_{17}N_3O_3]^+$ 239.1270; found: 239.1276. 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; $\tau_{\text{minor}} = 13.9$ min, $\tau_{\text{major}} = 19.5$ 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 azeotrope 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-(*tert*-butyl)-2-[3-methyl-2-(nitromethyl)butylidene] hydrazine (5a). Yellow oil (90%); $[\alpha]_D^{25} -13.3$ (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); ¹³C NMR (75 MHz, (CD₃)₂CO) δ 138.9, 77.1, 54.5, 47.7, 30.2, 29.5, 21.2, 20.2;

HRMS: calculated for $[C_{10}H_{22}N_3O_2]^+$ 216.1712; found: 216.1707. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane-*i*-PrOH (98 : 2)]; flow rate 1 mL min⁻¹; $\tau_{\text{minor}} = 7.2$ min, $\tau_{\text{major}} = 6.8$ min.

(*S,E*)-1-(*tert*-butyl)-2-[3-methyl-2-(nitromethyl)butylidene] hydrazine 2,2,2-trifluoroacetate (5a-TFA). Yellow solid (95%); MP: 90–92 °C; $[\alpha]_D^{25} -3.5$ (c 0.8, CHCl₃). (80 : 20 er); ¹H NMR (300 MHz, CDCl₃) δ 9.95 (s, 1H), 8.24 (d, *J* = 3.9 Hz, 1H), 4.77 (dd, *J* = 13.9, 9.2 Hz, 1H), 4.43 (dd, *J* = 13.9, 4.8 Hz, 1H), 3.35–3.21 (m, 1H), 2.09–1.94 (m, 1H), 1.34 (s, 9H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 169.2, 162.6 (q, *J*_{C-F} = 35.9 Hz), 116.2 (q, *J*_{C-F} = 291.7 Hz), 73.2, 59.3, 46.5, 28.8, 24.9, 19.7, 18.9; HRMS: calculated for $[C_{10}H_{22}N_3O_2]^+$ 216.1712; found: 216.1711. The enantiomeric excess was determined by HPLC in the corresponding hydrazone 5a.

(*S,E*)-1-(*tert*-butyl)-2-(3-nitro-2-phenylpropylidene)hydrazine (5b). Orange oil (93%); $[\alpha]_D^{25} -71.7$ (c 0.6, CHCl₃). (79 : 21 er); ¹H NMR (300 MHz, CDCl₃) δ 7.55–7.04 (m, 5H), 6.96 (d, *J* = 3.2 Hz, 1H), 4.97 (dd, *J* = 13.3, 8.4 Hz, 1H), 4.43 (dd, *J* = 13.3, 6.7 Hz, 1H), 4.36–4.26 (m, 1H), 1.08 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 137.2, 136.6, 129.1, 128.3, 128.1, 77.3, 53.7, 46.0, 28.3; HRMS: calculated for $[C_{13}H_{20}N_3O_2]^+$ 250.1556; found: 250.1557. 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; $\tau_{\text{minor}} = 12.6$ min, $\tau_{\text{major}} = 11.5$ min.

(*S,E*)-1-(*tert*-butyl)-2-(2-cyclohexyl-3-nitropropylidene) hydrazine (5c). Yellow oil (95%); $[\alpha]_D^{25} -1.8$ (c 0.9, CHCl₃). (80 : 20 er); ¹H NMR (300 MHz, (C₆D₆)) 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, C₆D₆) δ 137.56, 75.3, 53.4, 45.4, 39.3, 30.4, 29.8, 28.4, 26.6, 26.4, 26.3; HRMS: calculated for $[C_{13}H_{26}N_3O_2]^+$ 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; $\tau_{\text{minor}} = 10.9$ min, $\tau_{\text{major}} = 8.4$ min.

(*S,E*)-1-(*tert*-butyl)-2-(2-cyclopropyl-3-nitropropylidene) hydrazine (5d). Yellow oil (90%); $[\alpha]_D^{25} -63.8$ (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 $[C_{10}H_{20}N_3O_2]^+$ 214.0965; found: 214.0970. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H column [hexane-*i*-PrOH (98 : 2)]; flow rate 1 mL min⁻¹; $\tau_{\text{minor}} = 11.7$ min, $\tau_{\text{major}} = 10.7$ min.

(*S,E*)-1-(*tert*-butyl)-2-[3-nitro-2-(*p*-tolyl)propylidene] hydrazine (5e). Orange oil (90%); $[\alpha]_D^{25} -54.1$ (c 0.8, CHCl₃). (78 : 22 er); ¹H NMR (500 MHz, (CD₃)₂CO) δ 7.18 (s, 4H), 7.09 (d, *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 137.9, 137.6, 133.5, 129.8, 128.2, 77.4, 53.7, 45.7, 28.3, 21.0; HRMS: calculated for $[C_{14}H_{22}N_3O_2]^+$ 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; τ_{minor} = 12.0 min, τ_{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 μ 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]HYDRAZINE (6A). Yellow oil (70%/10% recovered 5a); [α]_D²⁵ -6.5 (*c* 1.3, CHCl₃). (80 : 20 er); ¹H NMR (300 MHz, CDCl₃) δ 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), 3.21–3.05 (m, 1H), 2.57 (s, 3H), 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); ¹³C NMR (75 MHz, CDCl₃) δ 130.3, 75.6, 58.5, 46.2, 31.7, 29.4, 26.9, 19.9, 18.8; HRMS: calculated for [C₁₁H₂₃N₃O₂]⁺ 229.1790; found: 229.1786.

(*S,E*)-1-(*TERT*-BUTYL)-2-(2-CYCLOHEXYL-3-NITROPROPYLIDENE)-1-METHYLHYDRAZINE (6B). Yellow oil (75%/10% recovered 5c); [α]_D²⁵ -5.6 (*c* 0.9, CHCl₃). (80 : 20 er); ¹H NMR (300 MHz, CDCl₃) δ 6.53 (d, *J* = 3.9 Hz, 1H), 4.77 (dd, *J* = 12.9, 9.2 Hz, 1H), 4.40 (dd, *J* = 12.9, 5.4 Hz, 1H), 3.19–3.02 (m, 1H), 2.57 (s, 3H), 1.87–1.46 (m, 6H), 1.44–1.16 (m, 5H), 1.14 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 130.9, 75.6, 58.5, 45.9, 39.7, 31.7, 30.4, 29.7, 26.9, 26.5, 26.3 (2C); HRMS: calculated for [C₁₄H₂₇N₃O₂]⁺ 269.2103; found: 269.2096.

General procedure for the transformation of dialkylhydrazones 6 into β -nitronitriles 7

To a cooled (0 °C) suspension of MMPP (1.5 mmol) in MeOH (1 mL) was added dropwise a solution of the dialkylhydrazone 6 (0.3 mmol) in MeOH (2 mL). The mixture was stirred overnight at room temperature and then poured into a mixture of CH₂Cl₂ and water. The organic layer was separated, washed with brine and water, and dried (MgSO₄). The solvent was removed and the residue purified by FC (cyclohexane/Et₂O) to afford pure β -nitronitrile 7.

(*S*)-3-METHYL-2-(NITROMETHYL)BUTANENITRILE (7A). Yellow oil (83%); [α]_D²⁵ +2.0 (*c* 1.4, CHCl₃). (78 : 22 er). 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; τ_{minor} = 20.4 min, τ_{major} = 23.9 min. Spectroscopic and analytical data as previously reported.²⁰

(*S*)-2-CYCLOHEXYL-3-NITROPROPANENITRILE (7B). Yellow oil (94%); [α]_D²⁵ -5.6 (*c* 1.1, CHCl₃). (80 : 20 er). 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; τ_{minor} = 64.7 min, τ_{major} = 36.1 min. Spectroscopic and analytical data as previously reported.²⁰

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