Organic & Biomolecular Chemistry

RSC Publishing

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 326

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]

Received 9th October 2012,
Accepted 9th November 2012

DOI: 10.1039/c2ob26963e

www.rsc.org/obc

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_2C–N=N–CO_2R) in organic synthesis as nitrogen electrophiles/dienophiles[2] 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 procedure[5] and a recent report on the use of aminocatalysis for the enantioselective conjugate addition of glyoxylate hydrazones[6] (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]

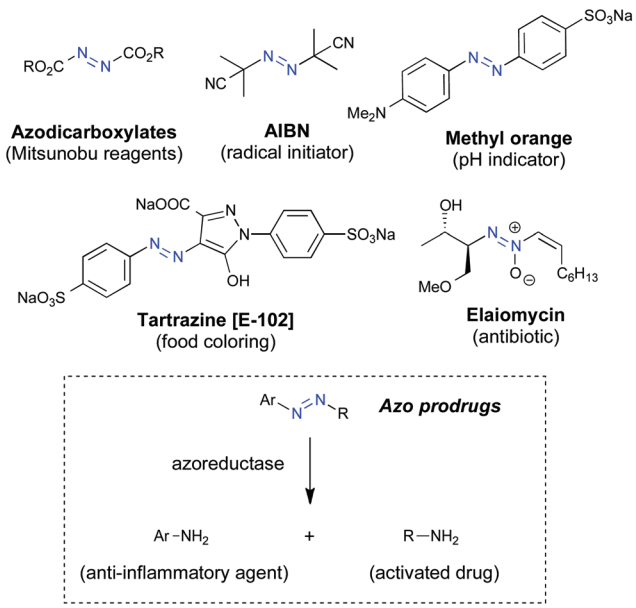
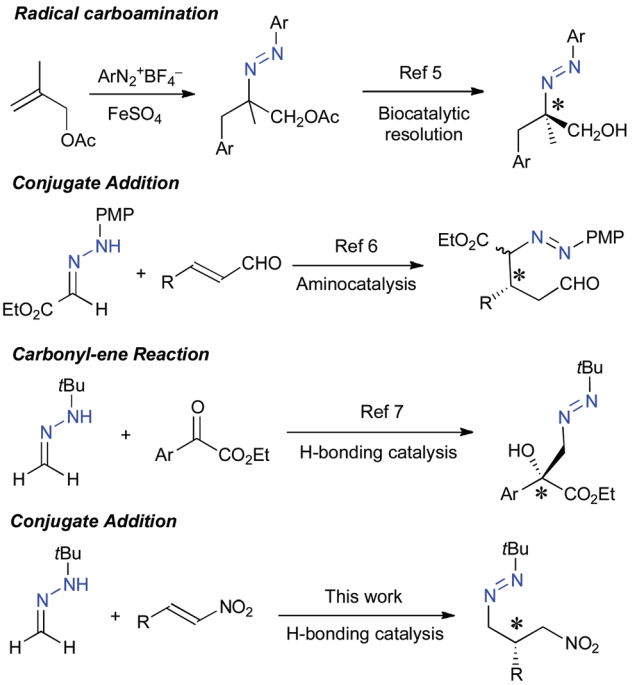


Fig. 1 Important azo compounds.

[a]*Departamento de Química Orgánica, Universidad de Sevilla, C/Prof. García González, 1, 41012 Sevilla, Spain. E-mail: dmonge@us.es, ffernan@us.es; Fax: +34 954624960; Tel: +34 954551518*
[b]*Instituto de Investigaciones Químicas CSIC-US, Américo Vespucio 49, E-41092 Sevilla, Spain. E-mail: jmlassa@iiq.csic.es; Fax: +34 954460565; Tel: +34 954489563*

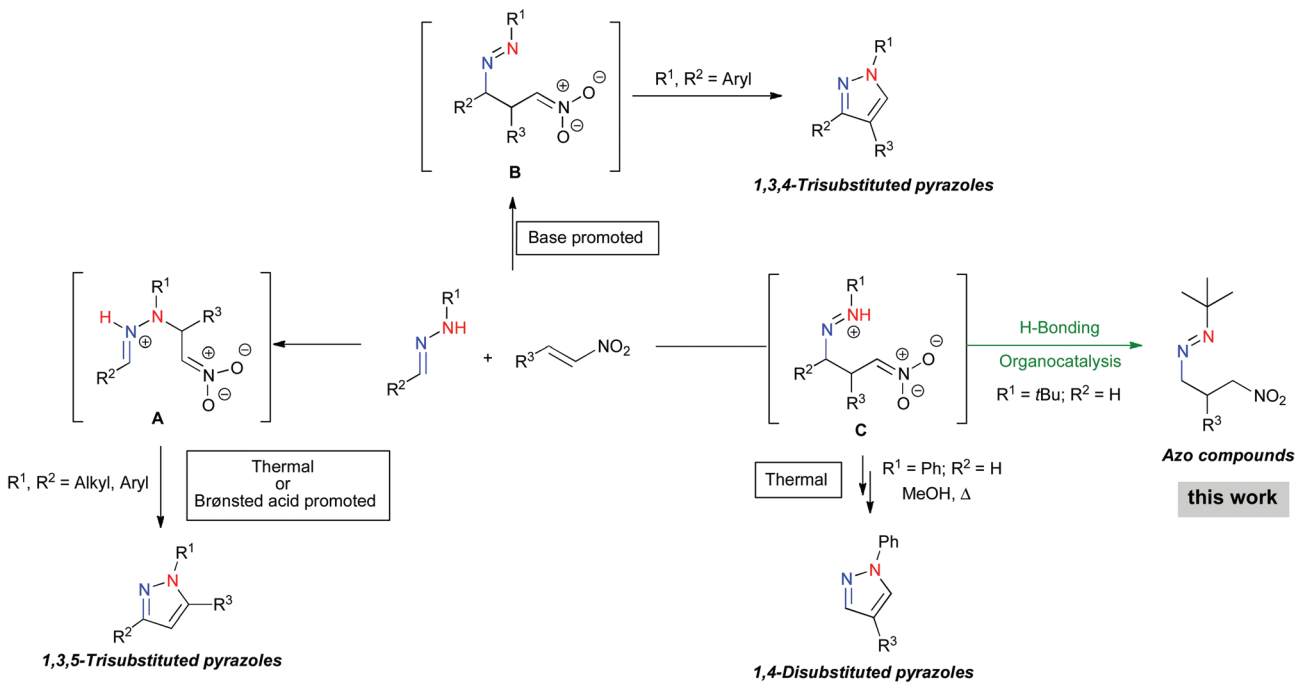
†Electronic supplementary information (ESI) available: Experimental procedures, catalyst synthesis, characterization data, NMR spectra for new compounds, and HPLC traces. See DOI: 10.1039/c2ob26963e



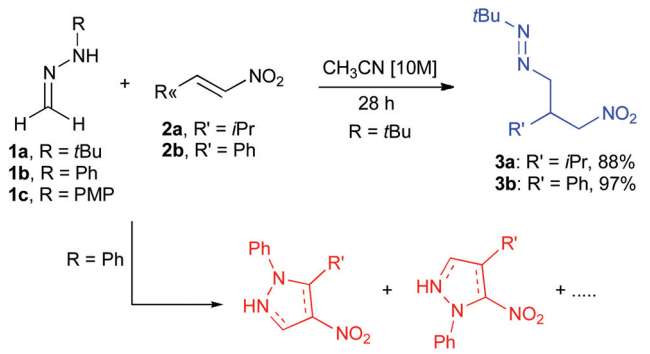
Scheme 1 Synthesis of enantioenriched azo compounds.

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 CF_3CH_2OH), 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.[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 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_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 organocatalysts[13] 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**

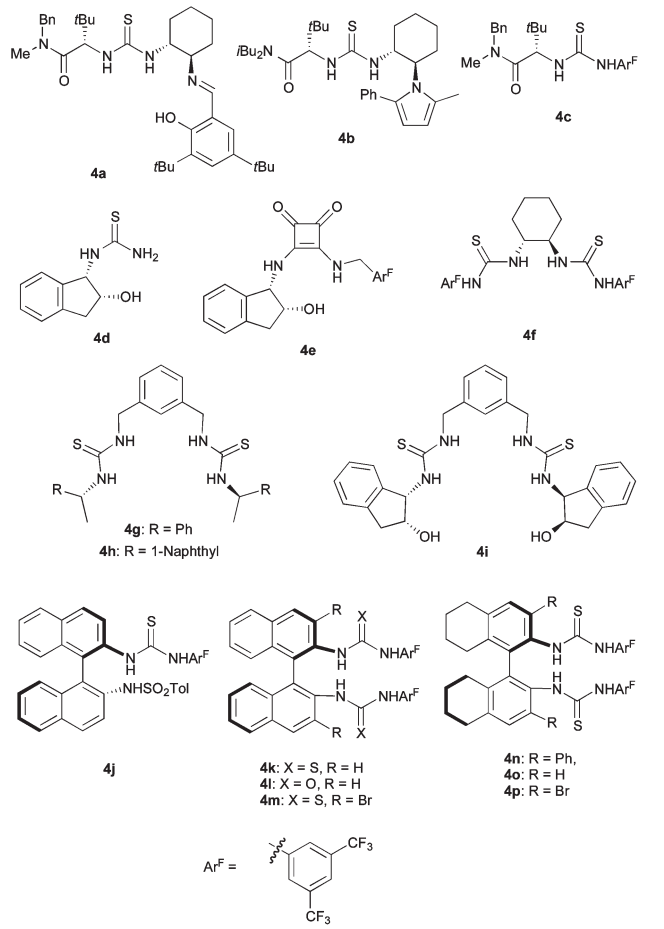


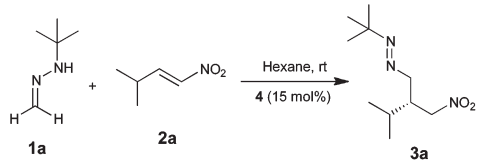
Fig. 2 H-bonding organocatalysts tested.

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′-binaphtyl-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 organocatalysts[15] **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. 10*d*) 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]



1a **2a** **3a**

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 ^{1}H 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 ^{1}H 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), CH_3CN, Et_2O or CH_2Cl_2 (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).

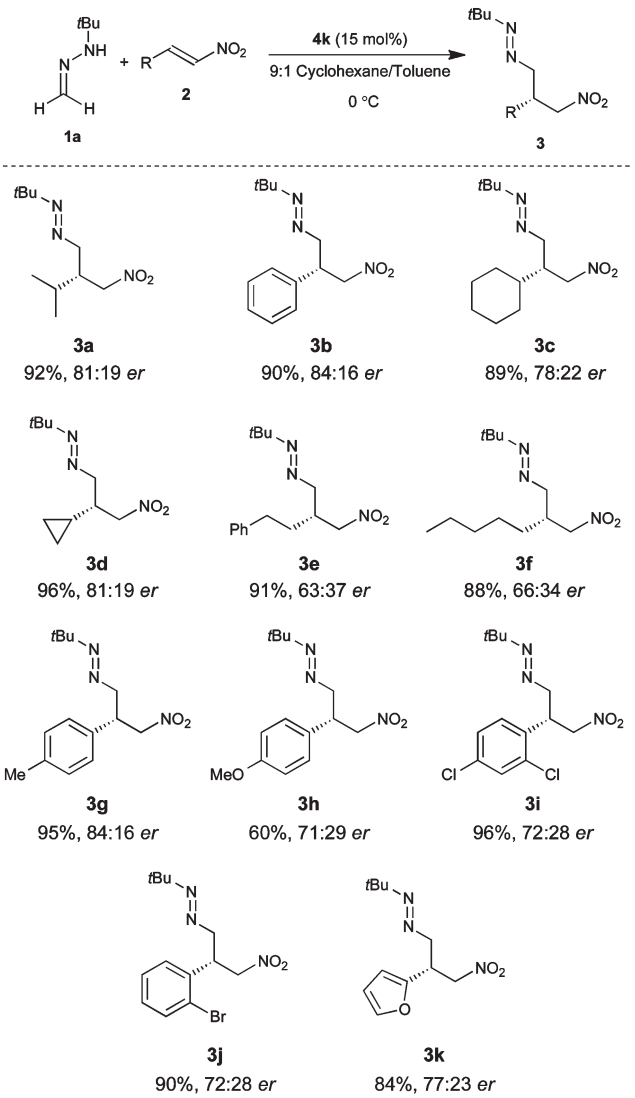
To explore the scope of this Michael reaction, a representative set of alkyl and aryl substituted nitroalkenes **2** was made to react with *N-tert*-butyl hydrazone **1a** under the optimal reaction conditions (Scheme 4). For γ,γ-dialkyl substituted nitroalkenes, the azo compounds **3a** and **3c,d**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

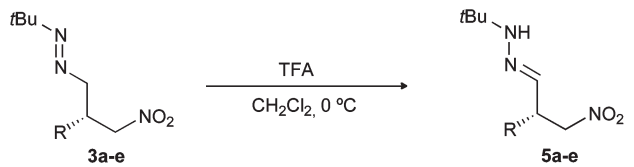
Diazenes **3** can be transformed into *N-tert*-butyl hydrazones **5**[16] by means of a simple acid-catalyzed isomerization (Scheme 5). Treating optically active azo compounds **3a–e** with TFA in CH_2Cl_2 at 0 °C afforded pure hydrazones **5a–e** in excellent yields (90–95%) without the need for chromatographic 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.



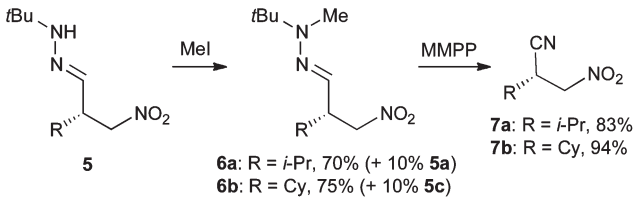
Scheme 4 Synthesis of enantioenriched azo compounds **3**.



5	R	Yield	er
5a	*i*Pr	90%	80:20
5a-TFA	*i*Pr	95%	80:20
5b	Ph	93%	79:21
5c	Cy	95%	80:20
5d	Cyclopropyl	90%	77:23
5e	*p*-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**.

($MMPP{\cdot}6H_2O$)[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]

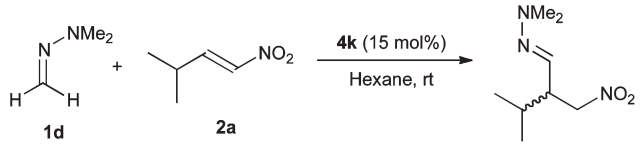
Mechanistic aspects

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]

^{1}H 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 (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 ^{1}H NMR titration studies, in which the addition of substoichiometric amounts of **4k** to **1a** resulted in

‖ [a]Reaction 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. [b]30% of conversion (determined by ^{1}H-NMR) into *rac*-adduct. [c]20% 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 downfield 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**.

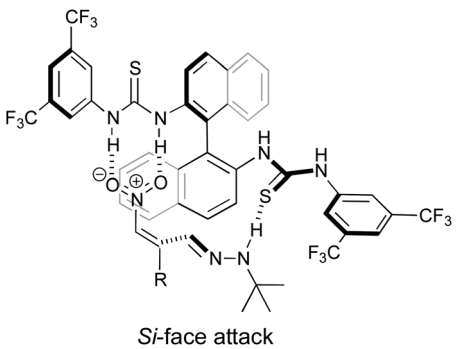


Fig. 3 Stereochemical model.

Experimental

General methods

^{1}H NMR spectra were recorded at 300 MHz, 400 MHz or 500 MHz; ^{13}C NMR spectra were recorded at 75 MHz, 100 MHz

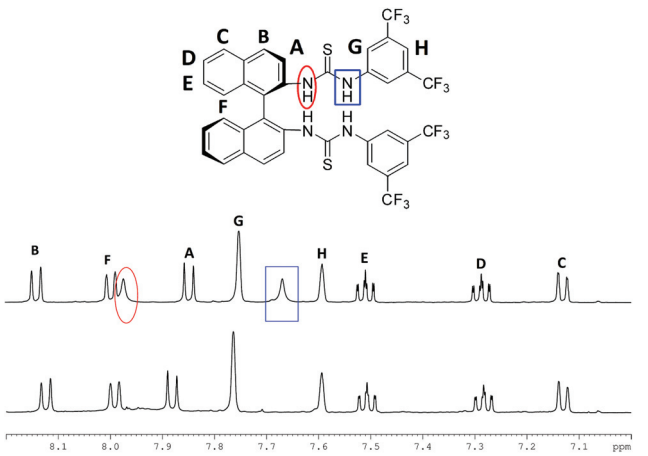


Fig. 5 ^{1}H NMR (500 MHz, 0.03 M, CD_2Cl_2) spectra for **4k** (up) and a 1 : 1 mixture of **4k** and **1a** (down).

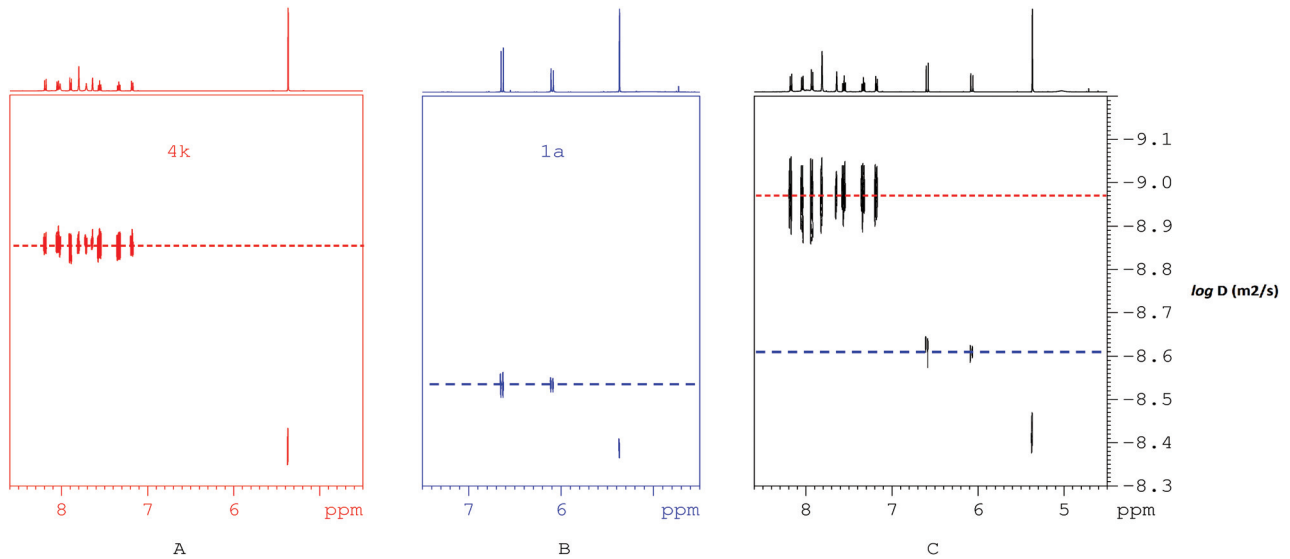


Fig. 4 ^{1}H DOSY NMR (500 MHz, 0.03 M, CD_2Cl_2) of A: **4k**; B: **1a**; C: **4k** + **1a**.

or 125 MHz, with the solvent peak used as the internal standard. The following abbreviations are used to indicate the multiplicity in ^{1}H 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); $[\alpha]_D^{25}$ +6.8 (*c* 1.2, $CHCl_3$). (81 : 19 er); ^{1}H 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 $[C_{10}H_{22}N_3O_2]^+$ 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}; τ_{minor} = 9.9 min, τ_{major} = 9.6 min.

(*R*,*E*)-1-(*tert*-Butyl)-2-(3-nitro-2-phenylpropyl)diazene (3b). Yellow oil (90% yield); $[\alpha]_D^{25}$ −25.3 (*c* 1.1, $CHCl_3$). (84 : 16 er); ^{1}H 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 $[C_{13}H_{19}N_3O_2]^+$ 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}; τ_{minor} = 7.3 min, τ_{major} = 9.1 min.

(*R*,*E*)-1-(*tert*-Butyl)-2-(2-cyclohexyl-3-nitropropyl)diazene (3c). Yellow oil (89% yield); $[\alpha]_D^{25}$ +2.9 (*c* 1.1, $CHCl_3$). (78 : 22 er); ^{1}H 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 $[C_{13}H_{26}N_3O_2]^+$ 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}; τ_{minor} = 15.5 min, τ_{major} = 9.7 min.

(*R*,*E*)-1-(*tert*-Butyl)-2-(2-cyclopropyl-3-nitropropyl)diazene (3d). Yellow oil (96% yield); $[\alpha]_D^{25}$ −16.0 (*c* 1.0, $CHCl_3$). (81 : 19 er); ^{1}H 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 $[C_{10}H_{20}N_3O_2]^+$ 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}; τ_{minor} = 29.1 min, τ_{major} = 31.0 min.

(*R*,*E*)-1-(*tert*-Butyl)-2-[2-(nitromethyl)-4-phenylbutyl]diazene (3e). Yellow oil (91% yield); $[\alpha]_D^{25}$ −1.1 (*c* 1.3, $CHCl_3$). (63 : 37 er); ^{1}H 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 $[C_{15}H_{24}N_3O_2]^+$ 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}; τ_{minor} = 5.2 min, τ_{major} = 4.6 min.

(*R*,*E*)-1-(*tert*-Butyl)-2-[2-(nitromethyl)heptyl]diazene (3f). Yellow oil (88% yield); $[\alpha]_D^{25}$ −4.4 (*c* 1.1, $CHCl_3$). (66 : 34 er); ^{1}H 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 $[C_{12}H_{26}N_3O_2]^+$ 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}; τ_{minor} = 23.6 min, τ_{major} = 25.0 min.

(*R*,*E*)-1-(*tert*-Butyl)-2-[3-nitro-2-(*p*-tolyl)propyl]diazene (3g). Yellow oil (95% yield); $[\alpha]_D^{25}$ −36.5 (*c* 2.0, $CHCl_3$). (84 : 16 er); ^{1}H 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 $[C_{14}H_{22}N_3O_2]^+$ 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}; τ_{minor} = 6.0 min, τ_{major} = 9.0 min.

(*R*,*E*)-1-(*tert*-Butyl)-2-[2-(4-methoxyphenyl)-3-nitropropyl] diazene (3h). Yellow oil (60% yield); $[\alpha]_D^{25}$ −0.9 (*c* 0.8, $CHCl_3$). (71 : 29 er); ^{1}H 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}; τ_{minor} = 19.4 min, τ_{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, $CHCl_3$). (72 : 28 er); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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}; τ_{minor} = 7.1 min, τ_{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, $CHCl_3$). (72 : 28 er); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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}; τ_{minor} = 6.8 min, τ_{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, $CHCl_3$). (77 : 23 er); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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}; τ_{minor} = 13.9 min, τ_{major} = 19.5 min.

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

TFA (2 mL, 0.1 M in CH_2Cl_2) was added to a solution of azo compound **3** (0.2 mmol) in CH_2Cl_2 (0.1 mL) at 0 °C. The mixture was stirred for 12–15 h. Satd $NaHCO_3$ was added, and the mixture was extracted with Et_2O 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, $CHCl_3$). (80 : 20 er); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) 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}; τ_{minor} = 7.2 min, τ_{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, $CHCl_3$). (80 : 20 er); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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, $CHCl_3$). (79 : 21 er); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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}; τ_{minor} = 12.6 min, τ_{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, $CHCl_3$). (80 : 20 er); ^{1}H NMR (300 MHz, (C_6D_6)) 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); ^{13}C NMR (75 MHz, C_6D_6) 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}; τ_{minor} = 10.9 min, τ_{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, $CHCl_3$). (77 : 23 er); ^{1}H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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}; τ_{minor} = 11.7 min, τ_{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, $CHCl_3$). (78 : 22 er); ^{1}H NMR (500 MHz, $(CD_3)CO$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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

$NaHCO_3$ (solid, 0.5 mmol, 42 mg) and MeI (1.5 mmol, 93 μL) 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 $NaHCO_3$ was added, and the mixture was extracted with Et_2O and concentrated to dryness. Dialkylhydrazones **6** were isolated by FC (cyclohexane/Et_2O).

(*S*,*E*)-1-(*tert*-Butyl)-1-methyl-2-[3-methyl-2-(nitromethyl)butylidene]hydrazine (6A). Yellow oil (70%/10% recovered **5a**); $[\alpha]_D^{25}$ −6.5 (*c* 1.3, $CHCl_3$). (80 : 20 er); ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.3, 75.6, 58.5, 46.2, 31.7, 29.4, 26.9, 19.9, 18.8; HRMS: calculated for $[C_{11}H_{23}N_3O_2]^+$ 229.1790; found: 229.1786.

(*S*,*E*)-1-(*tert*-Butyl)-2-(2-cyclohexyl-3-nitropropylidene)-1-methylhydrazine (6B). Yellow oil (75%/10% recovered **5c**); $[\alpha]_D^{25}$ −5.6 (*c* 0.9, $CHCl_3$). (80 : 20 er); ^1H NMR (300 MHz, $CDCl_3$) 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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 $[C_{14}H_{27}N_3O_2]^+$ 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 CH_2Cl_2 and water. The organic layer was separated, washed with brine and water, and dried ($MgSO_4$). The solvent was removed and the residue purified by FC (cyclohexane/Et_2O) to afford pure β-nitronitrile **7**.

(*S*)-3-Methyl-2-(nitromethyl)butanenitrile (7A). Yellow oil (83%); $[\alpha]_D^{25}$ +2.0 (*c* 1.4, $CHCl_3$). (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%); $[\alpha]_D^{25}$ −5.6 (*c* 1.1, $CHCl_3$). (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]

Acknowledgements

We thank the Spanish 'Ministerio de Ciencia e Innovación' (grants CTQ2010-15297 and CTQ2010-14974), the European FEDER funds and the Junta de Andalucía (grants 2008/FQM-3833 and 2009/FQM-4537) for financial support. D.M. acknowledges a "Juan de la Cierva" contract.

Notes and references

1 *The Chemistry of the Hydrazo, Azo and Azoxy Groups*, ed. S. Patai, JohnWiley and Sons, Chichester, 1st edn, 1997.
2 J. Kosmrlj, M. Kocevar and S. Polanc, *Synlett*, 2009, 2217; D. L. Boger and S. N. Weinreb, *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press, San Diego, 1987.
3 D. A. Kennedy, N. Vembu, F. R. Fronczek and M. Devocelle, *J. Org. Chem.*, 2011, **76**, 9641, and references therein.
4 For studies on aliphatic azo compounds and their thermal and photochemical decomposition into radicals, see: (*a*) T. König, In *Free Radicals*, ed. J. K. Kochi, Wiley, New York, 1973, vol. I, p. 113; (*b*) P. S. Engel, *Chem. Rev.*, 1980, **80**, 99; (*c*) M. Schmittel and C. Rüchardt, *J. Am. Chem. Soc.*, 1987, **109**, 2750; (*d*) P. S. Engel, L. Pan, Y. Ying and L. B. Alemany, *J. Am. Chem. Soc.*, 2001, **123**, 3706; (*e*) P. S. Engel, C. Wang, Y. Chen, C. Rüchardt and H. Beckhaus, *J. Am. Chem. Soc.*, 1993, **115**, 65.
5 (*a*) F. R. Dietz, A. Prechter, H. Gröger and M. R. Heinrich, *Tetrahedron Lett.*, 2011, **52**, 655; (*b*) A. Prechter, H. Gröger and M. R. Heinrich, *Org. Biomol. Chem.*, 2012, **10**, 3384 and references therein.
6 M. Fernández, U. Uria, J. L. Vicario, E. Reyes and L. Carrillo, *J. Am. Chem. Soc.*, 2012, **134**, 11872.
7 A. Crespo-Peña, D. Monge, E. Martín-Zamora, E. Álvarez, R. Fernández and J. M. Lassaletta, *J. Am. Chem. Soc.*, 2012, **134**, 12912.
8 N. Ono, *The Nitro Group in Organic Synthesis*, Wiley-VCH, New York, 2001; A. G. M. Barrett, *Chem. Soc. Rev.*, 1991, **20**, 95 and reviews cited therein.
9 (*a*) R. M. Adlington, J. E. Baldwin, J. C. Bottaro and M. W. D. Perry, *J. Chem. Soc., Chem. Commun.*, 1983, 1040; (*b*) J. E. Baldwin, R. M. Adlington, J. C. Bottaro, A. U. Jain, J. N. Kolhe, M. W. D. Perry and I. M. Newington, *J. Chem. Soc., Chem. Commun.*, 1984, 1095; (*c*) J. E. Baldwin, R. M. Adlington and I. M. Newington, *J. Chem. Soc., Chem. Commun.*, 1986, 176; (*d*) J. E. Baldwin, R. M. Adlington, J. C. Bottaro, J. N. Kolhe, M. W. D. Perry and A. U. Jain, *Tetrahedron*, 1986, **42**, 4223; (*e*) J. E. Baldwin, R. M. Adlington, J. C. Bottaro, J. N. Kolhe, I. M. Newington and M. W. D. Perry, *Tetrahedron*, 1986, **42**, 4235; (*f*) J. E. Baldwin, R. M. Adlington, A. U. Jain, J. N. Kolhe and M. W. D. Perry, *Tetrahedron*, 1986, **42**, 4247; (*g*) B. B. Snider, R. S. E. Conn and S. Sealfon, *J. Org. Chem.*, 1979, **44**, 218.

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; 1,3,4-trisubstituted 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.

11 Addition of formaldehyde *N,N*-dimethylhydrazone to nitroalkenes: (*a*) J. M. Lassaletta and R. Fernández, *Tetrahedron Lett.*, 1992, **33**, 3691; (*b*) J. M. Lassaletta, R. Fernández, C. Gash and J. Vázquez, *Tetrahedron*, 1996, **52**, 9143.

12 Selected examples on thiourea catalyzed asymmetric 1,4-additions to nitroalkenes. For H-bonding activation only: (*a*) C. Rabalakos and W. D. Wulff, *J. Am. Chem. Soc.*, 2008, **130**, 13524; (*b*) N. J. A. Martin, L. Ozores and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 8976; (*c*) L. Lykke, D. Monge, M. Nielsen and K. A. Jørgensen, *Chem.–Eur. J.*, 2010, **16**, 13330. For dual activation by bifunctional catalysts: (*d*) S. H. McCooey and S. J. Connon, *Angew. Chem., Int. Ed.*, 2005, **44**, 6367; (*e*) J. Ye, D. J. Dixon and P. S. Hynes, *Chem. Commun.*, 2005, 4481; (*f*) M. P. Lalonde, Y. Chen and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2006, **45**, 6366; (*g*) H. Li, J. Wang, L. Zu and W. Wang, *Tetrahedron Lett.*, 2006, **47**, 2585; (*h*) R. P. Herrera, V. Sgarzani, L. Bernardi and A. Ricci, *Angew. Chem., Int. Ed.*, 2005, **44**, 6576.

13 Examples on H-bonding/Brønsted acid organocatalysis involving *N,N*-dialkylhydrazones: (*a*) D. J. Dixon and A. L. Tillman, *Synlett*, 2005, 2635; (*b*) D. Pettersen, R. P. Herrera, L. Bernardi, F. Fini, V. Sgarzani, R. Fernández, J. M. Lassaletta and A. Ricci, *Synlett*, 2006, 239; (*c*) M. Rueping, E. Sugiono, T. Theissmann, A. Kuenkel, A. Ko1ckritz, A. Pews-Davtyan, N. Nemati and M. Beller, *Org. Lett.*, 2007, **9**, 1065; (*d*) R. P. Herrera, D. Monge, E. Martín-Zamora, R. Fernández and J. M. Lassaletta, *Org. Lett.*, 2007, **9**, 3303; (*e*) T. Hashimoto, M. Hirose and K. Maruoka, *J. Am. Chem. Soc.*, 2008, **130**, 7556; (*f*) T. Hashimoto, H. Kimura and K. Maruoka, *Tetrahedron: Asymmetry*, 2010, **21**, 1187.

14 For discussions on hydrogen-bond donating ability, see: (*a*) A. Wittkopp and P. R. Schreiner, *Chem.–Eur. J.*, 2003, **9**, 407; (*b*) S. J. Connon, *Synlett*, 2009, 354; (*c*) G. Jakab, C. Tancon, Z. Zhang, K. M. Lippert and P. R. Schreiner, *Org. Lett.*, 2012, **14**, 1724.

15 For first synthesis, see: (*a*) E. M. Fleming, T. McCabe and S. J. Connon, *Tetrahedron Lett.*, 2006, **47**, 7037. For selected examples, see: (*b*) X.-G. Liu, J.-J. Jiang and M. Shi, *Tetrahedron: Asymmetry*, 2007, **18**, 2773; (*c*) C. Rampalakos and W. D. Wulff, *Adv. Synth. Catal.*, 2008, **350**, 1785; (*d*) M. Shi and X.-G. Liu, *Org. Lett.*, 2008, **10**, 1043.

16 For an example of C-coupling of aryl bromides with *N*-*tert*-butylhydrazones, see: A. Takemiya and J. F. Hartwig, *J. Am. Chem. Soc.*, 2006, **128**, 14800.

17 N. Sewald, *Angew. Chem., Int. Ed.*, 2003, **42**, 5794.

18 R. Fernández, C. Gasch, J. M. Lassaletta, J. M. Llera and J. Vázquez, *Tetrahedron Lett.*, 1993, **34**, 141.

19 For general reviews on reactivity of *N,N*-dialkylhydrazones, see: (*a*) D. Enders, L. Wortmann and R. Peters, *Acc. Chem. Res.*, 2000, **33**, 157; (*b*) R. Brehme, D. Enders, R. Fernández and J. M. Lassaletta, *Eur. J. Org. Chem.*, 2007, 5629; (*c*) R. Lazny and A. Nodzewska, *Chem. Rev.*, 2010, **110**, 1386.

20 P. Bernal, R. Fernández and J. M. Lassaletta, *Chem.–Eur. J.*, 2010, **16**, 7714.

21 For the recognition of the nitro group by (thio)urea moieties, see: (*a*) M. C. Etter and T. W. Panunto, *J. Am. Chem. Soc.*, 1988, **110**, 5896; (*b*) T. R. Kelly and M. H. Kim, *J. Am. Chem. Soc.*, 1994, **116**, 7072 For discussions on different possibilities of hydrogen bonding between the nitro group and the thiourea moiety, see: (*c*) A. Hamza, G. Schubert, T. Soós and I. Pápai, *J. Am. Chem. Soc.*, 2006, **128**, 13151; (*d*) D. A. Yalalov, S. B. Tsogoeva and S. Schmatz, *Adv. Synth. Catal.*, 2006, **348**, 826; (*e*) B.-L. Li, Y.-F. Wang, S.-P. Luo, A.-G. Zhong, Z.-B. Li, X.-H. Du and D.-Q. Xu, *Eur. J. Org. Chem.*, 2010, 656.

22 For a similar multi-hydrogen-bond cooperative substrate activation using a C_2-symmetric bis-urea, see: Y. Cheng, J. An, L.-Q. Lu, L. Luo, Z.-Y. Wang, J.-R. Chen and W.-J. Xiao, *J. Org. Chem.*, 2011, **76**, 281.

23 (*a*) H. B. Jang, H. S. Rho, J. S. Oh, E. H. Nam, S. E. Park, H. Y. Bae and C. E. Song, *Org. Biomol. Chem.*, 2010, **8**, 3918; (*b*) C. S. Johnson, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1999, **34**, 203; (*c*) G. Morris, *Magn. Reson. Chem.*, 2002, **20**, S2; (*d*) Y. Cohen, L. Avramand and L. Frish, *Angew. Chem., Int. Ed.*, 2005, **44**, 520; (*e*) J. W. Lee, T. H. Ryu, J. S. Oh, H. Y. Bae, H. B. Jang and C. E. Song, *Chem. Commun.*, 2009, 7224.

24 See for example: Z. Zhang, K. M. Lippert, H. Hausmann, M. Kotke and P. R. Schreiner, *J. Org. Chem.*, 2011, **76**, 9764.

25 **1a,b**: (*a*) J.-S. M. Lehn, S. Javed and D. M. Hoffman, *Inorg. Chem.*, 2007, **46**, 993; (*b*) Ref. 9*d*; (*c*) Y. Kamitori, M. Hojo, R. Masuda, T. Yoshida, S. Ohara, K. Yamada and N. Yoshikawa, *J. Org. Chem.*, 1988, **53**, 129**1c**: (*d*) M. Barbero, S. Cadamuro, S. Dughera and G. Ghigo, *Eur. J. Org. Chem.*, 2008, 862**1d**: (*e*) Ref. 25*c*.

26 (*a*) R. A. Kunetsky and A. D. Dilman, *Tetrahedron Lett.*, 2005, **46**, 5203; (*b*) D. Lucet and S. Sabelle, *Eur. J. Org. Chem.*, 1999, 2583; (*c*) E. Hata, T. Yamada and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1995, **68**, 3629.

27 For catalyst **4d**: (*a*) Ref. 12*e*; For Catalyst **4e**: (*b*) H. Jiang, M. W. Paixão, D. Monge and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2010, **132**, 2775 For catalyst **4f**: (*c*) Y. Sohtome, A. Tanatani, Y. Hashimoto and K. Nagasawa, *Tetrahedron Lett.*, 2004, **45**, 5589 For catalyst **4k–p**: (*d*) X. G. Liu, J. J. Jiang and M. Shi, *Tetrahedron Lett.*, 2007, **18**, 2773.