

## Modular synthesis of cyclic *cis*- and *trans*-1,2-diamine derivatives†

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Structurally diverse carbocycles with two vicinal nitrogen-substituents were prepared in expedient three-component reactions from simple amines, aldehydes, and nitroalkenes. *trans,trans*-6-Nitrocyclohex-2-enyl amines were obtained in a one-pot domino reaction involving condensation, tautomerisation, conjugate addition, and nitro-Mannich cyclisation. Upon employment of less nucleophilic carboxamides, a concerted Diels–Alder cycloaddition mechanism operated to give the corresponding *cis,trans*-nitrocyclohexenyl amides. Both types of substituted carbocycles offer ample opportunities for chemical manipulations at the core and periphery. Ring oxidation with MnO<sub>2</sub> affords substituted nitroarenes. Reduction with Zn/HCl provides access to various *trans*- and *cis*-diaminocyclohexenes, respectively, in a straight-forward manner. With enantiopure secondary amines, a two-step synthesis of chiral nitrocyclohexadienes was developed (82–94% ee).

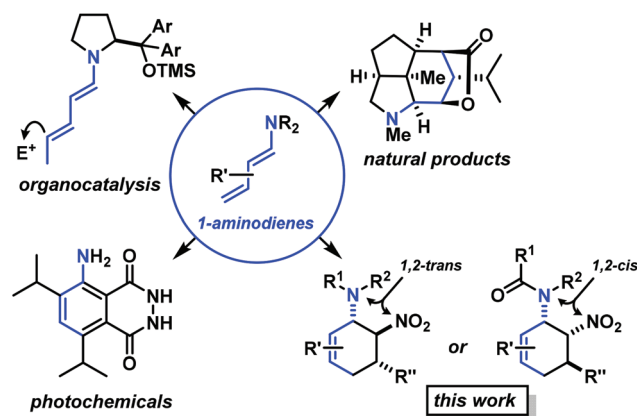
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## Introduction

Functionalised cyclohexanes are one of the most prevalent molecular architectures in nature and synthesis. Today, a plethora of synthetic procedures is available to provide access to various saturation states and peripheral substitution patterns. The majority of syntheses involve functionalisation of already cyclic precursors whereas *de-novo*-syntheses of functionalised cyclohexanes from two or more acyclic starting materials exhibit much higher modularity and provide access to a large chemical space.<sup>1</sup> The most prominent examples of such intermolecular cyclisation reactions include cyclo-additions<sup>2</sup> and many variants of sequential condensation-addition reactions with carbonyl compounds.<sup>3</sup> Heteroatom(X)-substituted cyclohexanes are arguably the most interesting structures for active pharmaceutical ingredients and fine chemical building blocks due to the distinct stereoelectronic properties and chemical reactivities of polar C–X bonds and the available lone pairs at X.<sup>4</sup> Aminodienes were widely used in method developments, syntheses of pharmaceutically active molecules, natural products and materials (Scheme 1).<sup>5</sup>



Scheme 1 1-Amino-1,3-butadienes in organic synthesis.

Aminodienes can be easily prepared from condensations of unsaturated carbonyl compounds and amines and exhibit high reactivity in normal-electron demand cycloadditions and nucleophilic additions due to their high-lying HOMO (highest occupied molecular orbital).<sup>6</sup> Further *N*-based substituents can be incorporated into the product structure by employment of  $\alpha$ -electrophilic nitrogen compounds. Nitroolefins are a readily available class of vinylogous nitrogenous electrophiles with widespread applications in Michael-type additions and cycloadditions.<sup>7</sup> We envisioned a domino process involving initial condensation of unsaturated aldehydes with amines followed by selective cyclisation of the resultant 1-amino-1,3-dienes with nitroolefins.<sup>8</sup> Such strategy would provide an expedient access to highly functionalised cyclohexenes

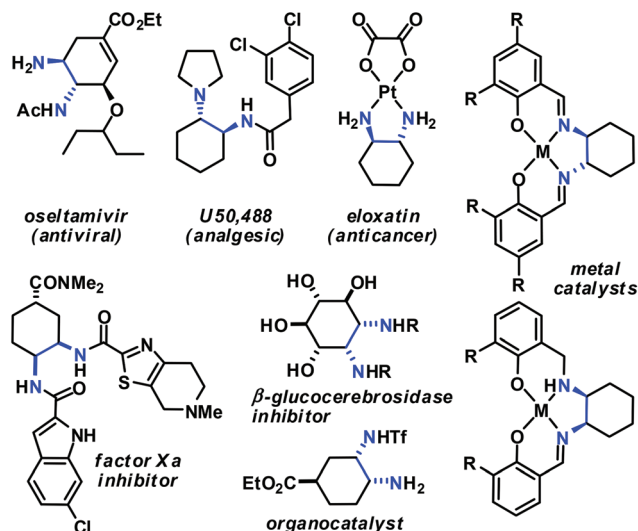
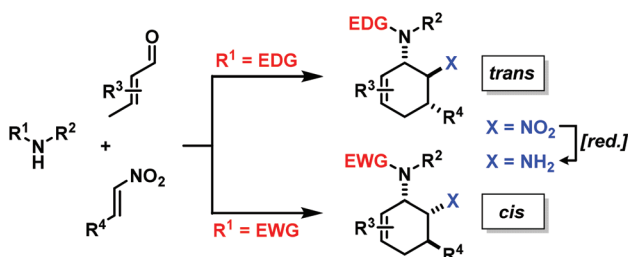
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Scheme 2 Applications of *trans*- (top) and *cis*-1,2-diaminocyclohexanes.Scheme 3 The stereoselectivity switch: amines vs. *N*-acyl amines.

containing two chemically orthogonal *N*-based substituents in vicinal positions ( $\text{NR}_2$ ,  $\text{NO}_2$ ). 1,2-Diaminocyclohexane motifs constitute important building blocks of pharmacologically active molecules, fine chemicals and catalysts (Scheme 2).<sup>9</sup>

The electronic nature of the intermediate aminodienes can be easily tuned by the introduction of various *N*-substituents. It has been demonstrated that highly nucleophilic aminodienes bearing electron-donating (EDG) alkyl substituents engage in rapid Michael-type additions to electrophiles.<sup>10</sup> However, a change of mechanism can be effected by electron-withdrawing (EWG) *N*-substituents. 1-*N*-Acyl-amino-1,3-butadienes undergo concerted [4 + 2]-cycloadditions with electron-deficient dienophiles.<sup>6</sup> Here, we report the viability of controlling the reaction mechanism and stereoselectivity by the employment of secondary amines ( $R^1 = \text{EDG}$ ) or less nucleophilic acylamines ( $R^1 = \text{EWG}$ ) in three-component cyclisations with  $\alpha,\beta$ -unsaturated aldehydes and nitroalkenes to give *trans*- or *cis*-1,2-diaminocyclohexenes (Scheme 3).

## Results and discussion

### Synthesis of *trans*-nitrocyclohexenyl amines

As an extension of earlier work on functionalised aminocyclohexenes,<sup>8</sup> we optimised reaction conditions for the three-

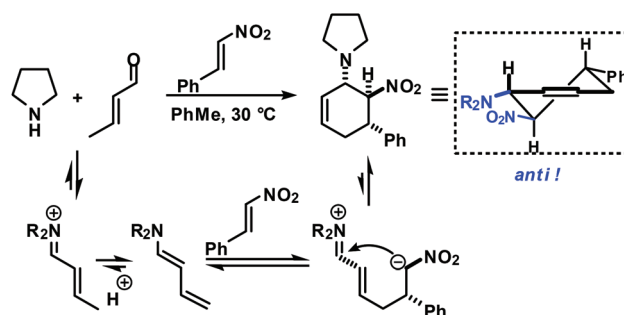
Table 1 Selected optimisation experiments<sup>a</sup>

Entry	Conditions	Yield <sup>b</sup> [%]
1	$\text{CH}_3\text{CN}$	27 (40) <sup>c</sup>
2	$\text{CH}_2\text{Cl}_2$	58
3	DMF	72
4	PhMe	76
5	PhMe, 2 equiv. aldehyde	68
6	PhMe, 2 equiv. amine	29
7	PhMe, slow addition (~2 h) of 1.2 equiv. aldehyde	90 (19/1) <sup>d,e</sup>
8	As entry 8, but with pyrrolidine/benzoic acid (1/1)	64 (18/1) <sup>d</sup>

<sup>a</sup> Optimised conditions: Pyrrolidine (2 mmol),  $\beta$ -nitrostyrene (2 mmol), PhMe (3 mL), slow addition of crotonaldehyde (2.4 mmol in 1 mL PhMe) over 2 h, 30 °C, 20 h. <sup>b</sup> GC yields vs. internal hexadecane. <sup>c</sup> 60 °C. <sup>d</sup> Diastereomeric ratio (dr). <sup>e</sup> 83% isolated yield.

component cyclisation of secondary amines,  $\alpha,\beta$ -unsaturated aldehydes and nitroalkenes. We chose pyrrolidine, crotonaldehyde and  $\beta$ -nitrostyrene as model substrates (Table 1). High selectivities were observed in toluene as solvent and upon slow addition of a slight excess of the aldehyde.<sup>10</sup>

Rapid aldehyde addition resulted in oligomer formation. The three-component cycloadduct 1-(6-nitro-5-phenylcyclohex-2-en-1-yl)pyrrolidine (**1**) was obtained with high thermodynamic stereocontrol (*trans,trans/cis,trans* = 19/1). The minor diastereomer exhibited a *cis*-relation of the amino and nitro groups. The preferential formation of the *all-trans* stereoisomer and the observation of an identical outcome from reactions with (*Z*)- $\beta$ -nitrostyrene suggest the operation of a stepwise mechanism (Scheme 4).<sup>10</sup> Initial condensation between the amine and aldehyde gives rise to the formation of an equilibrating mixture of imine, enamine and amination derivatives, of which the aminodiene undergoes reversible conjugate addition to the nitroolefin.<sup>11</sup> Subsequent nitro-Mannich ring-closure affords the thermodynamic product containing three vicinal equatorial substituents.<sup>12</sup>



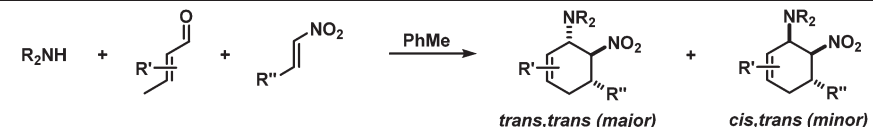
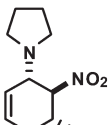
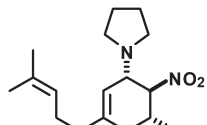
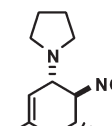
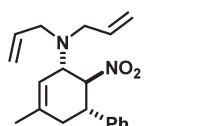
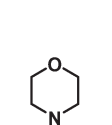
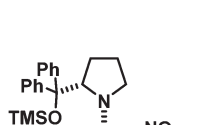
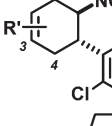
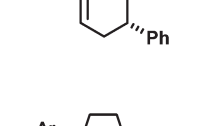
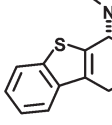
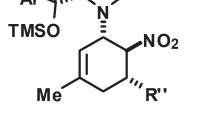
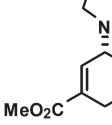
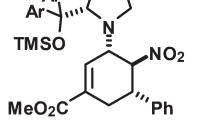
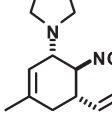
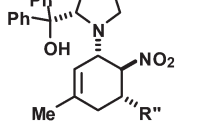
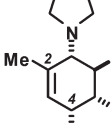
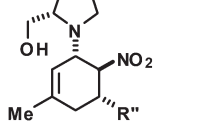
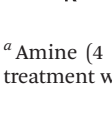
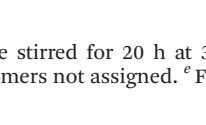


Scheme 4 Nitro-Mannich mechanism with secondary amines.



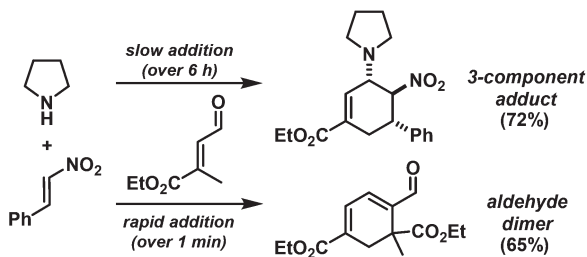
We extended the reaction conditions to various other amines, aldehydes and nitroolefins (Table 2).<sup>13</sup> The *trans,trans*-isomers were preferentially formed in diastereomeric ratios of >10/1.<sup>10</sup> Diastereomeric ratios (dr) were assigned based on high-resolution <sup>1</sup>H-NMR spectra. The *trans*-configurations of the vicinal amino/nitro and nitro/aryl groups, respectively, at the cyclohexene result in dihedral angles of 170–180° and <sup>3</sup>J<sub>HH</sub>

coupling constants of 10–12 Hz. Employment of morpholine gave lower dr values (**13**, **14**). Products with substituents in the 2-position formed rather slowly (**15**, **18**, **19**), possibly due to steric congestion with the amine substituent in the planar aminodiene species. Similarly, crotonaldehydes bearing γ-substituents reacted very slow due to steric inhibition of the Michael-type attack onto β-nitrostyrenes (**14**, **19**). The latter

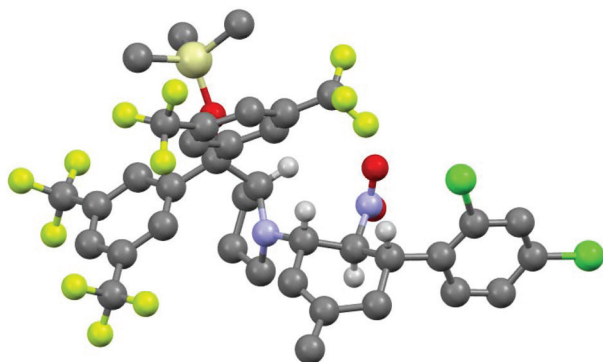
**Table 2** Three-component synthesis of *trans,trans*-nitrocyclohexenyl amines<sup>a</sup>

							
Major isomer	Substituents	dr	Yield <sup>b</sup> [%]	Major isomer	Substituents	dr	Yield <sup>b</sup> [%]
	R'' = Ph	<b>1</b> 19 : 1	83			<b>20</b> 6 : 1	82 <sup>e</sup>
	2,3-(MeO) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	<b>2</b> 15 : 1	69			<b>21</b> 35 : 1	93
	3,4-(OCH <sub>2</sub> O)-C <sub>6</sub> H <sub>3</sub>	<b>3</b> 34 : 1	59			<b>22</b> 10 : 1	46
	2,6-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	<b>4</b> 30 : 1 <sup>c</sup>	66				
	R'' = Ph	<b>5</b> 28 : 1	94				
	2,3-(MeO) <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	<b>6</b> 14 : 1	62				
	3,4-(OCH <sub>2</sub> O)-C <sub>6</sub> H <sub>3</sub>	<b>7</b> 34 : 1	78				
	2-F-C <sub>6</sub> H <sub>4</sub>	<b>8</b> 18 : 1	91				
	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	<b>9</b> 15 : 1	90				
	2-NO <sub>2</sub> -C <sub>6</sub> H <sub>4</sub>	<b>10</b> 5 : 1	90				
	2,6-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	<b>11</b> 10 : 1 <sup>c</sup>	91				
	2-Furyl	<b>12</b> 12 : 1	90				
	R' = 3-Me	<b>13</b> 13 : 1	70				
	R' = 4-Me	<b>14</b> 7 : 2 : 1 <sup>d</sup>	53				
		<b>15</b> 2 : 1	38				
		<b>16</b> 6 : 1	72				
		<b>17</b> 50 : 1	90				
	R' = H	<b>18</b> 3 : 1 <sup>d</sup>	16				
	Me	<b>19</b> 28 : 6 : 1 <sup>d</sup>	39				

<sup>a</sup> Amine (4 mmol), aldehyde (1.2 equiv.) and nitroalkene in PhMe were stirred for 20 h at 30 °C. <sup>b</sup> Isolated yields of isomer mixtures. <sup>c</sup> After treatment with SiO<sub>2</sub> or wet CDCl<sub>3</sub>. <sup>d</sup> Major diastereomer shown, other isomers not assigned. <sup>e</sup> From citral. <sup>f</sup> Ar = 3,5-bis(trifluoromethyl)phenyl.



Scheme 5 Rate of aldehyde addition governs selectivity.

Fig. 1 Crystal structure of *trans,trans*-24.

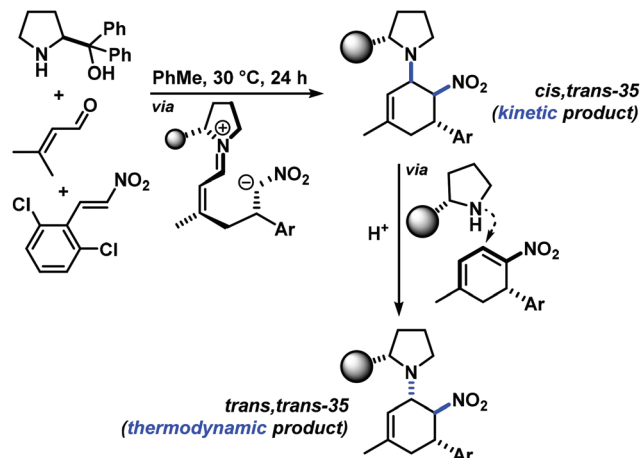
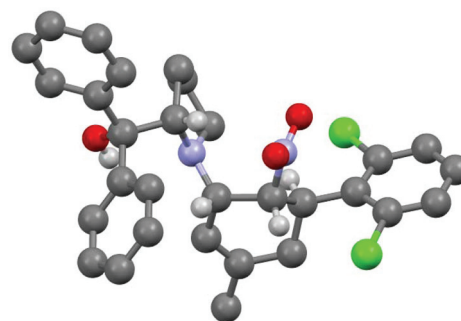
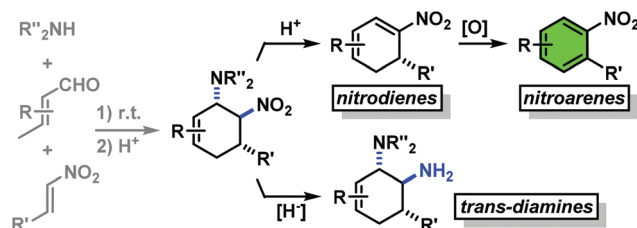
trend allowed selective conversion of citral to the 3-alkyl cycloadduct *via* the terminal aminodiene isomer (**20**, kinetic control). Cyclisation with diallylamine proceeded highly effective to give **21** which allows facile access to the free amine. Highly electrophilic methyl 2-methyl-4-oxobut-2-enoate dimerised upon rapid aldehyde addition (Scheme 5).<sup>14</sup>

The three contiguous stereocenters evolve under thermodynamic control. We have employed prolinol derivatives (**22–34**) among which bulky diarylprolinols exhibited the most effective facial discrimination of the intermediate iminium ion. Consistently, the *trans,trans*-isomers were formed preferentially. Crystal structure analysis confirmed the absolute and relative configuration of **24** (Fig. 1). However, bulky 1-nitro-2-(2',6'-dichlorophenyl)ethylene preferentially gave *cis,trans*-35 (*cis,trans* : *trans,trans* 5 : 1). Slow epimerisation at C-1 occurred during work-up (SiO<sub>2</sub>) or in the presence of acid (wet CDCl<sub>3</sub>, HCl) to give the thermodynamic *trans,trans*-35 (*cis,trans* : *trans,trans* ~1 : 1) possibly *via* elimination of the axial amine group (Scheme 6, Fig. 2).<sup>13</sup>

### Reactions of *trans*-nitrocyclohexenyl amines

We have studied various structural manipulations at the core and periphery of the synthesised cycloadducts. Eliminations, oxidations, and reductions were realised to give access to diene, arene and diamine derivatives (Scheme 7).

Oxidation of nitrocyclohexenyl amines with manganese dioxide (MnO<sub>2</sub>) resulted in unselective decomposition involving dehydrogenation and amine or nitrite elimination.<sup>15</sup> Similarly, various Nef conditions (base (NaH/*n*-BuLi), then acid (HCl); TiCl<sub>3</sub>; KMnO<sub>4</sub>)<sup>16</sup> afforded complex mixtures. In no case

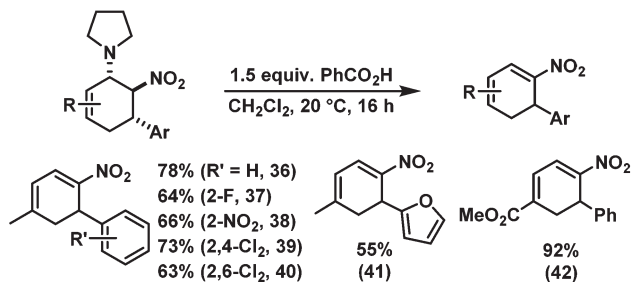
Scheme 6 Kinetic *cis,trans*-35 and thermodynamic *trans,trans*-35.Fig. 2 Crystal structure of the kinetic product *cis,trans*-35.

Scheme 7 Core and peripheral reactions to dienes, arenes and diamines.

was the desired ketone detected (GC-MS, IR). The solid cycloadducts appeared to be stable toward air and water; their solutions in dichloromethane or toluene withstood exposure to weak acids and bases. The equatorial amino group inhibits base-mediated elimination (E1cb pathway). However, benzoic acid effected slow elimination of pyrrolidine to nitrocyclohexadienes (Scheme 8). Stronger acids (HCl, TFA) allowed elimination of prolinols to give the nitrocyclohexadienes **36**, **37**, **39** and **41** in good enantiomeric purity (82–94% ee, Table 3).<sup>13</sup> Amine/acid-co-catalyzed reactions of aldehydes and nitroalkenes gave low selectivities.<sup>13,17</sup>

The nitrocyclohexadienes were prone to oxidation under aerobic conditions but could be stored under nitrogen at 0 °C for days. However, selective dehydrogenation would render a





Scheme 8 Acid-mediated elimination of pyrrolidine.

Table 3 Acid-mediated elimination of chiral prolinols

Cyclohexenyl amine	Cyclohexadiene	ee <sup>a</sup> [%]	Yield <sup>b</sup> [%]
	R''' = Ph	36 <sup>c</sup>	94
	2-F-C <sub>6</sub> H <sub>4</sub>	37 <sup>c</sup>	85
	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	39 <sup>c</sup>	93
	2-Furyl	41 <sup>c</sup>	82
		39	92

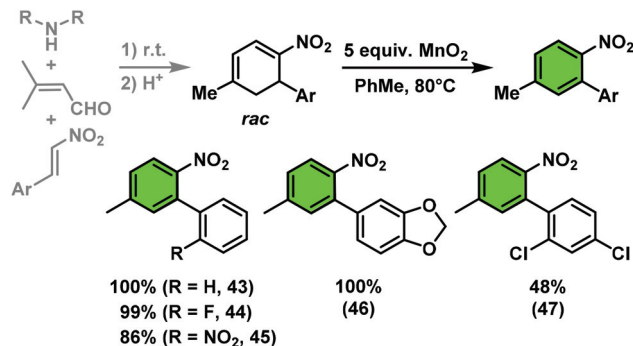
<sup>a</sup> Enantiomeric excess (ee) determined by chiral HPLC. <sup>b</sup> Isolated yields. <sup>c</sup> Ar = 3,5-bis(trifluoromethyl)phenyl.

straight-forward access to substituted nitroarenes. Several methods for the aromatisation of carbocycles were reported (Pt, Pd, Ni catalysts, elemental sulfur or selenium, quinones, oxygen, MnO<sub>2</sub>, SeO<sub>2</sub> etc.).<sup>18</sup> We obtained good yields of 2-aryl nitrobenzenes with 5 equiv. MnO<sub>2</sub> at 80 °C (Scheme 9). This strategy allows the three-step synthesis of 2-nitrobiaryls.

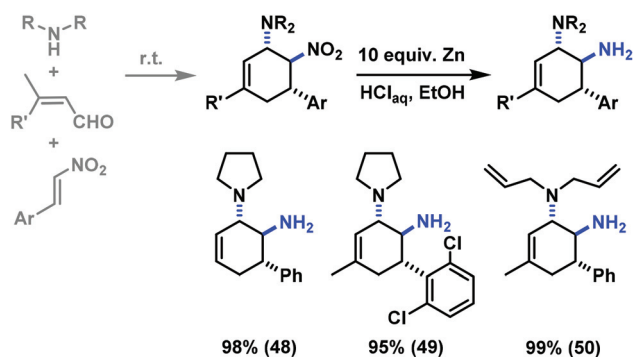
The reduction of a nitro function to a primary amine is an especially useful manipulation.<sup>19</sup> Application of such selective manipulation of one substituent of our three-component cycloadducts renders an expedient access to carbocyclic 1,2-*trans*-diamines (Scheme 10). The overall two-step sequence thus involves stereoselective three-component cyclisation with nitroolefins followed by reduction of the nitro substituents in with Zn/HCl in ethanol. The nitrocyclohexenyl amines **1**, **11** and **21** were cleanly converted to the corresponding diamine derivatives **48–50** in excellent yields with complete retention of stereochemistry.<sup>13</sup>

#### The stereoselectivity switch: synthesis of *cis*-nitrocyclohexenyl amides

The nature of the *N*-substituents controls all three elemental steps in the Michael/Mannich-type mechanism with amines.

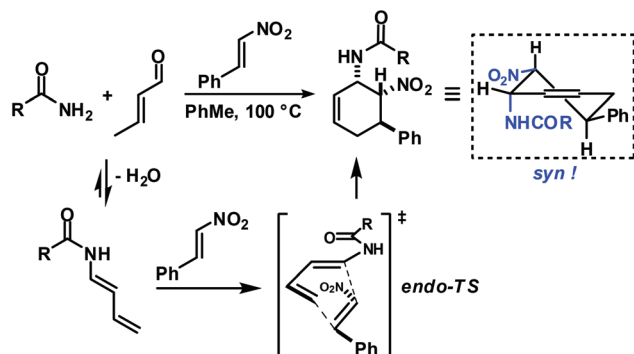


Scheme 9 Three-step synthesis of 2-nitrobiaryls.

Scheme 10 Two-step synthesis of *trans*-1,2-diaminocyclohexenes.

The nucleophilicity of the amine directly affects the rate of condensation with the  $\alpha,\beta$ -unsaturated aldehyde and the nucleophilic reactivity of the aminodiene intermediate at the terminal  $\delta$ -position (Scheme 4). Stereoelectronics also govern the formation of the 1-amino-2-nitroethylene moiety *via* a formal nitro-Mannich reaction. It is therefore obvious that fine-tuning of the *N*-substituents directly effects the cyclisation mechanism. Literature reports on Diels–Alder mechanisms of cyclisations of 1-*N*-acylaminodienes with electron-deficient olefins are in full accord with this notion.<sup>5,6</sup> The significantly lower nucleophilicity of carboxamides (*vs.* amines) favours an orbital-controlled, more or less concerted, cycloaddition pathway (over a stepwise charge-controlled Michael–Mannich pathway). In order to provide a stereo-chemical complement of the three-component synthesis of *trans*-nitrocyclohexenyl amines, we have replaced the secondary amines with simple carboxamides. Indeed, formation of the *cis*-nitrocyclohexenyl amides was observed in high diastereoselectivities (Scheme 11). The major product results from an *endo*-selective [4 + 2]-cycloaddition and bears the carboxamide in axial position. Despite the presence of an axial hydrogen atom at the CH–NO<sub>2</sub> moiety, the low propensity of carboxamide to act as leaving group under the reaction conditions prevents E2-type elimination (*cf.* Scheme 6). Table 4 shows a selection of cycloadducts prepared from three-component reactions of carboxamides, unsaturated aldehydes and nitrostyrenes.<sup>13</sup> The initial amide/aldehyde condensation required elevated





Scheme 11 Endo-selective Diels-Alder mechanism with carboxamides.

Table 4 Three-component synthesis of *cis*-nitrocyclohexenyl amides<sup>a</sup>

Major isomer	Substituents	dr	Yield [%]	
	R''' = Ph	51	18 : 1	66
	2,6-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	52	50 : 1	67
	2,4-Cl <sub>2</sub> -C <sub>6</sub> H <sub>3</sub>	53	28 : 1	57
	2-F-C <sub>6</sub> H <sub>4</sub>	54	15 : 1	44
	R'' = H	55	8 : 1	75
	4-Me	56	50 : 1	39
	2,4-Me <sub>2</sub>	57	40 : 1	74
	R''' = H	58	26 : 1	56
	3-Me	59	32 : 1	79
	2,4-Me <sub>2</sub>	60	13 : 1	18

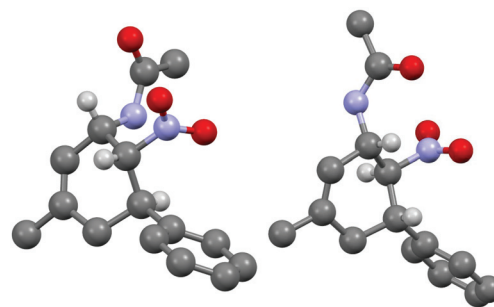
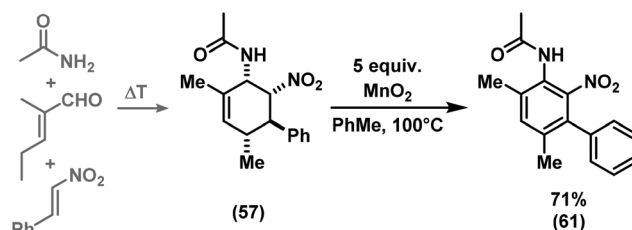
<sup>a</sup> Amide, aldehyde,  $\beta$ -nitrostyrene (each 3 mmol) in PhMe, 100 °C, 24 h.

temperature (100 °C). The *trans,trans*-*N*-acyl-6-nitrocyclohex-2-enyl amines were formed as minor stereoisomers.

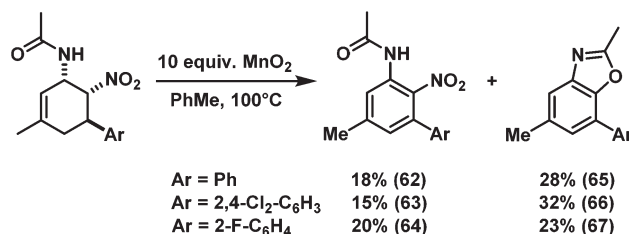
The relative configurations were assigned based on the  $^3J_{\text{HH}}$  coupling constants from  $^1\text{H}$ -NMR spectra. Crystal structure analyses of *cis,trans*-51 and *trans,trans*-51 confirmed the relative configurations of the substituents (Fig. 3).

### Reactions of *cis*-nitrocyclohexenyl amides

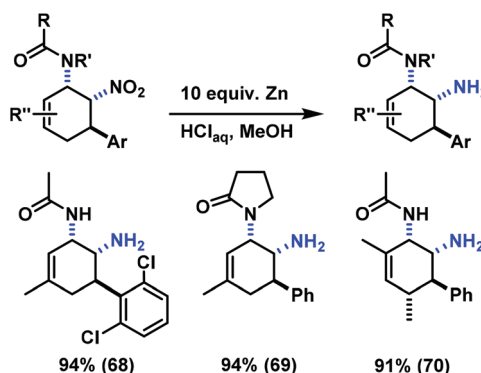
Similar post-synthesis modifications as for the amine series were evaluated with the synthesised *cis*-nitrocyclohexenyl amides. We were delighted to observe that direct oxidation of 57 with  $\text{MnO}_2$  proceeded with good selectivity (Scheme 12).<sup>15</sup> However, the related C3-substituted cyclohexenyl amines 51, 53 and 54 exhibited poor dehydrogenation selectivity. Competing

Fig. 3 Crystal structures of *cis,trans*-51 (left) and *trans,trans*-51 (right).

Scheme 12 Two-step synthesis of substituted 2-nitro acetanilide.



Scheme 13 Oxidative formation of acetanilides and benzoxazoles.

Scheme 14 Synthesis of *cis*-1,2-diaminocyclohexenes.

$\text{NO}_2$ -elimination was observed which resulted in mixtures of nitro-acetanilides (62–64) and benzoxazoles (65–67, Scheme 13).<sup>20</sup>

We have also applied the  $\text{Zn}/\text{HCl}$  reduction protocol to the cycloaddition products.<sup>19b</sup> Clean reduction of the nitro substituents gave the corresponding *cis*-diamines in excellent yields with retention of stereochemistry (Scheme 14). The overall



synthetic strategy allows the straight-forward preparation of carbocyclic 1,2-diamine derivatives with high *cis*-stereocontrol in a modular manner starting from simple amide, aldehyde, and nitroethylene precursors.

## Conclusions

We have applied an operationally simple one-pot protocol to the synthesis of multi-substituted carbocycles upon three-component reaction of amines, aldehydes, and nitroalkenes. The synthesis is highly modular, operates under practical reaction conditions with cheap starting materials (20–100 °C, toluene as solvent), and tolerates ester, ether, chloro, fluoro, thioether, and carbamate substituents. Upon wide variations of the starting materials, the synthesis allows the access to diverse cycloadducts in combinatorial fashion. The electronic properties of the employed amine component dictate the reaction mechanism and product stereochemistry. Reactions with secondary amines proceed *via* reversible Michael/nitro-Mannich reactions<sup>12</sup> to give *trans,trans*-6-nitrocyclohex-2-enyl amines. The less nucleophilic carboxamides trigger a Diels-Alder-type mechanism toward *N*-acyl *cis,trans*-6-nitrocyclohex-2-enyl amines.<sup>6</sup> Reduction with Zn/HCl afforded the corresponding 1,2-diamine derivatives. The tri-, tetra-, and penta-substituted carbocycles constitute derivatives of *cis*- and *trans*-1,2-diaminocyclohexanes which are key building blocks of various natural products, fine chemicals, drugs and catalysts.<sup>9</sup> In the presence of enantiopure prolinols, one enantiomerically pure set of diastereomers was formed.<sup>21</sup> Acid-mediated amine eliminations resulted in the formation of chiral cyclohexadienes. Oxidative aromatisations proceeded with MnO<sub>2</sub> to give 2-nitrobiaryls. It is important to note that the presence of two chemically orthogonal *N*-based substituents (NHR, NO<sub>2</sub>) allows various selective manipulations of the general structure. Likewise, the electronic polarisation (push-pull substitution) is of high relevance to photoactive materials.

## Experimental section

### General

Unless otherwise noted, all synthesised cycloadducts are racemic mixtures of one diastereomer. For reasons of clarity, only one enantiomer is depicted in the schemes. For atom numbering used in the spectroscopic data assignment, see chemical structures in schemes and tables above. All chemicals were purchased from commercial suppliers and used without further purification unless otherwise noted. Solvents were dried and distilled before use. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance II 600 (600.20 and 150.94 MHz), a Bruker DRX 500 (500.13 and 125.77 MHz) and a Bruker Avance 300 (300.13 and 75.48 MHz) at 298 K. Chemical shifts ( $\delta$  in ppm) are referenced to tetramethylsilane (TMS). Abbreviations for <sup>1</sup>H-NMR data: s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet), q\* (apparent quartet),

m\* (apparent multiplet). Peaks were assigned based on H, H-COSY, H,C-HMQC, and H,C-HMBC. IR-ATR spectroscopy was performed on a Perkin-Elmer 100 Paragon FT-IR. ESI-MS were measured with a Finnigan MAT 900S and an Agilent LC/MSD VL G1956A, respectively. EI-MS were measured with a Finnigan Incos 50 Galaxy and a Finnigan MAT 95, respectively (ionisation 70 eV). Exact masses (HR-MS) were determined by peak matching method. GC-MS analyses were performed on a 6890N Agilent system with 5975 MS detector on an HP-5MS column (30 m  $\times$  0.25 mm i.d.  $\times$  0.25  $\mu$ m film thickness) with 5% phenylmethyl siloxane from Macherey-Nagel. H<sub>2</sub> was the mobile phase. Standard method 50–300 M: 50 °C (2 min hold), +25 °C min<sup>-1</sup>→300 °C (5 min hold). Determination of enantiomeric excesses (ee) were performed on a HP6890 GC-FID with chiral BGB 176 column (30 m, 0.25 mm i.d., 0.25  $\mu$ m film thickness). Helium was the mobile phase. Standard method: 50 °C (2 min hold), 3 °C min<sup>-1</sup>→150 °C, 1 °C min<sup>-1</sup>→180 °C. Chiral HPLC spectra were recorded on a Merck Hitachi HPLC with D-6000 interface, L-4000A UV-detector, L-6200A intelligent pump, and a Merck differential refractometer RI-71. Mixtures of *n*-hexane and 2-propanol were used as mobile phase. Crystal structure data were collected on a Nonius Kappa CCD diffractometer using monochromated Mo-K $\alpha$  radiation, structures refined by shelxs97 and shelxl97 (Table 5).<sup>22</sup>

### General procedures (selected examples)<sup>13</sup>

**Three-component cyclisation with secondary amines.** A 50 mL test tube was charged with the *sec*-amine (4 mmol), the nitroalkene (4 mmol) in toluene (10 mL). The mixture was stirred at 30 °C and the aldehyde (4.8 mmol) was slowly added over 2 h. After another 18 h, the solvent and other volatile compounds were removed in oil pump vacuum. The crude product was purified by SiO<sub>2</sub> flash column chromatography (ethyl acetate (ea)/cyclohexane (ch)) or crystallised from solution (for details see below).

*1-(5-(2,4-Dichlorophenyl)-3-methyl-6-nitrocyclohex-2-enyl) pyrrolidine (9).* TLC (ch–ea 5/1): *R*<sub>f</sub> 0.25. Yield: 90%; dr (*trans,trans/cis,trans*) 15/1. Mp. 137 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.39 (s, 1H), 7.21 (m, 2H), 5.50 (s, 1H), 4.95 (t, 10.7 Hz, 1H), 4.26 (d, 8.1 Hz, 1H), 4.21–4.11 (m, 1H), 3.14–2.90 (m, 1H), 2.81 (d, 6.5 Hz, 3H), 2.75–2.61 (m, 2H), 1.84–1.69 (m, 7H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  136.3 (2C), 135.6, 129.8, 129.0, 128.2, 127.7, 118.8, 89.2, 61.3, 47.6 (2C), 40.3, 38.0, 24.7 (2C), 24.1. FT-IR (ATR):  $\tilde{\nu}$  [cm<sup>-1</sup>] 2963 (m), 2912 (m), 2847 (m), 1668 (w), 1551 (s), 1474 (s), 1437 (w), 1368 (m), 1326 (w), 1277 (w), 1172 (w), 1125 (w), 1103 (m), 1046 (w), 910 (w), 865 (m), 823 (s), 764 (w), 744 (m), 732 (m). LR-MS (EI, 70 eV): *m/z* 354, 308, 272, 256, 152, 137, 122. HR-MS (ESI): calcd [M + H]<sup>+</sup> 355.0974, found 355.0977.

*N,N-Diallyl-3-methyl-6-nitro-5-phenylcyclohex-2-enyl-1-amine (21).* TLC (ch–ea 5/1): *R*<sub>f</sub> 0.3. Yield: 93%; dr (*trans,trans/cis,trans*) 35/1. Pale yellow solid. Mp. 128 °C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.43–6.97 (m, 5H), 5.83–5.74 (m, 1H), 5.74–5.66 (m, 1H), 5.43 (s, 1H), 5.19 (m, 1H), 5.13 (s, 2H), 5.10 (s, 1H), 4.86 (dd, 11.8, 9.8 Hz, 1H), 4.25–4.13 (m, 1H), 3.45 (ddd, 11.8, 9.4, 7.7 Hz, 1H), 3.33–3.28 (m, 1H), 3.28–3.22 (m, 1H),



Table 5 Crystal structure data for compounds **24**, **35**, *syn*-**51**, *trans*-**51**

Compound	<b>24</b>	<b>35</b>	<i>syn</i> - <b>51</b>	<i>trans</i> - <b>51</b>
CCDC number	973119	973120	973121	973122
Formula	C <sub>37</sub> H <sub>34</sub> Cl <sub>2</sub> F <sub>12</sub> N <sub>2</sub> O <sub>3</sub> Si	C <sub>30</sub> H <sub>30</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>3</sub>	C <sub>15</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>	C <sub>15</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub>
Formula mass	881.65	537.46	274.31	274.31
Crystal system	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic
<i>a</i> /Å	10.8393(5)	8.9169(13)	19.3984(10)	19.0719(12)
<i>b</i> /Å	16.7856(3)	17.351(3)	9.6352(5)	5.2738(3)
<i>c</i> /Å	42.689(2)	17.602(3)	16.2688(9)	27.2994(14)
$\alpha$ /°	90.00	90.00	90.00	90.00
$\beta$ /°	90.00	90.00	108.737(2)	90.632(4)°
$\gamma$ /°	90.00	90.00	90.00	90.00
Unit cell vol./Å <sup>3</sup>	7767.0(5)	2723.2(8)	2879.6(3)	2745.6(3)
Temperature/K	100(2)	100(2)	100(2)	100(2)
Space group	<i>C</i> 2 <sub>2</sub> 2 <sub>1</sub>	<i>P</i> 2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>	<i>P</i> 2 <sub>1</sub> / <i>c</i>	<i>C</i> 2/ <i>c</i>
Formula units/cell, <i>Z</i>	8	4	8	8
Reflections measured	13 598	12 769	13 657	7864
Independent refl.	6278	5633	5758	3000
<i>R</i> <sub>int</sub>	0.0651	0.0783	0.0667	0.0540
<i>R</i> <sub>1</sub> ( <i>I</i> > 2σ( <i>I</i> ))	0.0658	0.0630	0.1537	0.0540
w <i>R</i> ( <i>F</i> <sup>2</sup> ) ( <i>I</i> > 2σ( <i>I</i> ))	0.1413	0.1281	0.0713	0.1300
<i>R</i> <sub>1</sub> (all data)	0.1379	0.1520	0.1482	0.0948
w <i>R</i> ( <i>F</i> <sup>2</sup> ) (all data)	0.1657	0.1519	0.1851	0.1456

3.04 (d, 7.7 Hz, 1H), 2.99 (d, 7.7 Hz, 1H), 2.32 (d, 7.7 Hz, 2H), 1.74 (m, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 132.4, 131.3, 130.8, 94.9, 66.2, 64.4, 56.8, 48.8, 41.9, 26.2. FT-IR (ATR):  $\tilde{\nu}$  [cm<sup>-1</sup>] 2968, 2920, 2831, 2806, 1643, 1548, 1495, 1418, 1373, 1315, 1261, 1176, 1109, 1086, 996, 936, 913, 860, 816, 763, 698, 655, 621, 596, 541, 460, 438. HR-MS (EI): calcd [M]<sup>+</sup> 312.1838, found 312.1843.

**1-[5-(2,4-Dichlorophenyl)-3-methyl-6-nitrocyclohex-2-enyl]-2-(*S*)-[di-(3,5-bis(trifluoromethyl)phenyl) (trimethylsilyloxy)-methyl]pyrrolidine (**24**).** TLC (ch-*ea* 20/1): *R*<sub>f</sub> 0.4. Yield: 82%; dr (*trans,trans*/*cis,trans*) 19/1. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.94 (s, 4H), 7.87 (s, 2H), 7.40 (s, 1H), 7.19 (d, 13.9 Hz, 2H), 5.17 (s, 1H), 5.09 (s, 1H), 4.60 (s, 1H), 4.10 (d, 8.9 Hz, 1H), 3.49 (s, 1H), 2.83 (dd, 16.2, 8.5 Hz, 1H), 2.45–2.25 (m, 2H), 2.08–1.82 (m, 3H), 1.69 (s, 3H), 1.65–1.55 (m, 1H), 0.25–0.10 (m, 1H), –0.15 (d, 3.1 Hz, 9H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 145.1, 143.7, 135.7, 135.2, 135.0, 133.8, 131.4, 131.2, 131.0, 130.8, 130.1, 129.5, 128.7, 127.7, 127.2, 125.0, 123.8, 122.0, 121.4, 117.8, 84.8, 83.7, 67.5, 62.3, 40.0, 37.4, 29.1, 23.3, 22.3, 1.5. FT-IR (ATR):  $\tilde{\nu}$  [cm<sup>-1</sup>] 3094 (w), 2956 (m), 2917 (m), 2855 (w), 1676 (w), 1620 (w), 1588 (w), 1547 (s), 1474 (s), 1446 (w), 1368 (s), 1337 (m), 1316 (m), 1275 (s), 1170 (s), 1125 (s), 1047 (m), 1014 (w), 983 (w), 934 (m), 905 (s), 870 (s), 840 (s), 761 (m), 753 (m), 709 (s), 681 (s). LR-MS (EI, 70 eV): *m/z* 881, 875, 873, 871. HR-MS (ESI): [M + H]<sup>+</sup> calcd 881.1596, found 881.1592.

**Acid-mediated elimination to give nitrocyclohexadienes.** A 10 mL flask was charged with the aminocyclohexene (1 mmol) in dichloromethane (4 mL). Then, trifluoroacetic acid (3 mmol) was added (or 2 mmol benzoic acid in case of small amine substituents). After 10–16 h at room temperature, all volatiles were removed in vacuum and the crude product subjected to SiO<sub>2</sub> flash chromatography (ethyl acetate/cyclohexane).

**2,4-Dichloro-1-(5-methyl-2-nitrocyclohexa-2,4-dienyl)-benzene (**39**).** From **24** (with TFA): TLC (ch-*ea* 12/1): *R*<sub>f</sub> = 0.25. Yield: 60%; 93% ee (HPLC). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 7.72

(d, 6.3 Hz, 1H), 7.44 (d, 2.3 Hz, 1H), 7.11 (d, 8.4 Hz, 1H), 6.99 (d, 8.4 Hz, 1H), 5.97 (d, 7.2 Hz, 1H), 4.81 (d, 11.1 Hz, 1H), 3.05 (dd, 18.5, 11.3 Hz, 1H), 2.46 (d, 18.0 Hz, 1H), 1.83 (s, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 147.4, 145.0, 135.8, 133.5, 133.5, 131.9, 130.1, 128.0, 127.3, 117.3, 37.2, 33.4, 23.9. FT-IR (ATR):  $\tilde{\nu}$  [cm<sup>-1</sup>] 3067 (w), 2870 (w), 2666 (w), 2544 (w), 1688 (s), 1602 (m), 1583 (s), 1558 (w), 1503 (s), 1466 (m), 1450 (w), 1426 (m), 1316 (s), 1289 (m), 1269 (w), 1103 (w), 1085 (w), 1050 (w), 1025 (w), 938 (w), 866 (w), 841 (m), 812 (m), 711 (s), 663 (m). LR-MS (EI, 70 eV): *m/z* 283, 266, 148, 236, 216, 202, 183, 165. HR-MS (EI, 70 eV): calcd 283.0167, found 283.018.

**MnO<sub>2</sub>-mediated oxidation to nitrobiaryls.** The nitrocyclohexadiene (1 mmol, 1 equiv.), MnO<sub>2</sub> (85%, 5 equiv.) and toluene (5 mL) were combined in a reaction tube. The tube was sealed with a septum and the reaction stirred at 80 °C. After 6 h, the solvent and other volatile compounds were removed by oil pump vacuum. Silica gel flash chromatography (ethyl acetate/cyclohexane) gave the aromatic product in analytically pure form.

**2,4-Dichloro-5'-methyl-2'-nitrobiphenyl (**47**).** TLC (ch-*ea* 10/1): *R*<sub>f</sub> 0.2. Yield: 48%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 8.05 (d, 8.4 Hz, 1H), 7.46 (s, 1H), 7.40–7.30 (m, 2H), 7.19 (d, 8.0 Hz, 1H), 7.11 (s, 1H), 2.48 (s, 3H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 146.1, 144.6, 136.2, 134.5, 133.6, 133.4, 132.7, 131.0, 130.5, 130.0, 129.8, 129.2, 128.2, 127.5, 127.3, 124.8, 115.8, 21.4. FT-IR (ATR):  $\tilde{\nu}$  [cm<sup>-1</sup>] 2922 (w), 1609 (w), 1586 (m), 1519 (s), 1466 (m), 1377 (w), 1342 (s), 1100 (m), 1066 (w), 1025 (w), 888 (w), 866 (w), 837 (s), 790 (s), 759 (m), 688 (w). LR-MS (EI, 70 eV): *m/z* 248, 246 [M – Cl]<sup>+</sup>, 216, 165, 154, 127, 97, 81, 69, 57, 55.

**Zn/HCl-mediated reduction of cyclohexenyl amines.<sup>19b</sup>** The 6-nitrocyclohexenyl amine (0.4 mmol, 1.0 equiv.) was dissolved in ethanol (3.0 mL) and aqueous HCl (6 N, 2.2 mL) was added. Zinc powder (262 mg, 4.0 mmol, 10 equiv.) was added in small portions and the reaction mixture was stirred for 2 h at room



temperature. After addition of saturated aqueous  $\text{NaHCO}_3$  (20 mL), the solution was extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 20$  mL), the combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure to give the diamine in >95% purity and yield.

***N*<sup>2</sup>,*N*<sup>2</sup>-Diallyl-3-methyl-5-phenylcyclohex-2-ene-1,2-diamine (50).** Yield: 99%. Mp. 100 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.39–7.24 (m, 5H), 6.27–6.07 (m, 2H), 5.64–5.40 (m, 1H), 5.32–5.20 (m, 4H), 3.73 (d, 10.5 Hz, 1H), 3.58–3.51 (m, 2H), 3.47–3.24 (m, 3H), 3.13–2.98 (m, 2H), 2.46–2.14 (m, 2H), 1.77 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  139.8, 139.6, 129.7, 128.1, 121.9, 116.1, 77.4, 54.5, 38.6, 23.3. FT-IR (ATR):  $\tilde{\nu}$  [ $\text{cm}^{-1}$ ] 2912, 1600, 1454, 1150, 1098, 1065, 998, 965, 814, 760, 701, 645, 604, 574, 526, 461. HR-MS (EI): calcd  $[\text{M}]^+$  282.2096; found 282.20976.

**Three-component cyclisation with carboxamides.** A 50 mL pressure tube was charged with the carboxamide, unsaturated aldehyde, and nitroalkene (each 3 mmol) and toluene (20 mL) and heated to 100 °C in an oil bath. After 16 h, the volatile components were removed by vacuum distillation. The viscous residue was treated with cold diethylether (15 mL) upon which a white precipitate formed. The solids were collected and dried in vacuum.

***N*-3-Methyl-(6-nitro-5-phenylcyclohex-2-enyl) acetamide (51).** TLC (ch-ea 1/3):  $R_f$  0.3. Yield: 66%; dr (*cis,trans/trans,trans*) 18/1. Mp. 205 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.41–7.09 (m, 5H), 5.93 (d, 9.0 Hz, 1H), 5.47 (d, 3.3 Hz, 1H), 5.34–5.21 (m, 1H), 5.13 (dd, 11.1, 4.9 Hz, 1H), 3.53 (td, 10.3, 6.1 Hz, 1H), 2.45 (dd, 18.4, 6.0 Hz, 1H), 2.24 (dd, 18.5, 10.0 Hz, 1H), 1.98 (s, 3H), 1.77 (s, 3H).  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  169.7, 140.0, 138.1, 129.0 (2C), 127.6, 127.1 (2C), 118.8, 88.0, 45.6, 39.9, 37.6, 23.1, 22.8. FT-IR (ATR):  $\tilde{\nu}$  [ $\text{cm}^{-1}$ ] 3271 (w), 3030 (w), 2970 (w), 2912 (w), 1732 (w), 1654 (s), 1549 (s), 1455 (w), 1438 (w), 1369 (m), 1281 (w), 1246 (w), 1055 (w), 1029 (w), 975 (w), 832 (w), 802 (w), 785 (w), 758 (m), 699 (m). LR-MS (EI, 70 eV):  $m/z$  274  $[\text{M}]^+$ , 227  $[\text{M} - \text{NO}_2]^+$ . HR-MS (ESI): calcd  $[\text{M} + \text{Na}]^+$  297.1215, found 297.121.

***N*-(2,4-Dimethyl-6-nitro-5-phenylcyclohex-2-enyl) acetamide (57).** TLC (ch-ea 1/1):  $R_f$  0.2. Yield: 74%; dr (*cis,trans/trans,trans*) 40/1. Mp 203 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.26–7.19 (m, 5H), 5.64 (d, 1H, 9.6 Hz), 5.52 (s, 1H), 5.26 (m, 1H), 5.22 (dd, 1H, 12.3/4.9 Hz), 2.81 (dd, 1H, 12.3/10.3 Hz), 2.36 (m, 1H), 2.02 (s, 3H), 1.80 (s, 3H), 0.91 (d, 3H, 6.9 Hz).  $^{13}\text{C}$  NMR (75 MHz, APT,  $\text{CDCl}_3$ ):  $\delta$  170.3, 138.9, 131.5, 130.3, 128.9, 128.0, 127.7 (5C), 89.0, 49.3, 46.7, 38.1, 23.2, 20.6, 19.5. IR (ATR):  $\tilde{\nu}$  [ $\text{cm}^{-1}$ ] 3271 (w), 2970 (w), 1733 (m), 1653 (s), 1550 (s), 1454 (m), 1371 (s), 1241 (s), 1042 (m), 913 (w), 725 (m). LR-MS (ESI,  $\text{MeOH}/\text{CH}_2\text{Cl}_2$ ):  $m/z$  289  $[\text{M} + \text{H}]^+$ , 242  $[\text{M} - \text{NO}_2]^+$ , 200, 183, 157. HR-MS (ESI): calcd  $[\text{M} + \text{H}]^+$  289.1552, found 289.154.

**$\text{MnO}_2$ -mediated oxidation to nitroanilides.** As above, but 10 equiv.  $\text{MnO}_2$  were used and reactions heated to 100 °C for 12 h.

***N*-(4,6-Dimethyl-2-nitrobiphen-3-yl) acetamide (61).** TLC (ch-ea 1/1):  $R_f$  0.6. Yield: 71%.  $^1\text{H}$  NMR (500 MHz,  $\text{MeOH}-d_4$ ):  $\delta$  7.46–7.35 (m, 5H), 7.08 (s, 1H), 2.54 (s, 3H), 2.52 and 2.27 (2s, 6H), NH resonance obscured.  $^{13}\text{C}$  NMR (125 MHz, APT,  $\text{MeOH}-d_4$ ):  $\delta$  165.1, 150.5, 138.9, 136.4, 133.5, 131.0, 129.4,

128.7, 128.6, 128.5, 123.7, 19.8, 16.3, 14.1. IR (ATR):  $\tilde{\nu}$  [ $\text{cm}^{-1}$ ] 2920 (m), 2860 (w), 1720 (w), 1607 (m), 1486 (m), 1441 (m), 1383 (m), 1250 (m), 1223 (s), 1061 (s), 926 (m), 759 (s), 700 (s). LR-MS (ESI,  $\text{MeOH}$ ):  $m/z$  238  $[\text{M} - \text{NO}_2]^+$ , 223  $[\text{M} - \text{NO}_2 - \text{Me}]^+$ , 213, 186, 137, 129, 105.

**Zn/HCl-mediated reduction of cyclohexenyl amides.<sup>19b</sup>** As above, but methanol was used instead of ethanol. ***N*-(6-Amino-2,4-dimethyl-5-phenylcyclohex-2-enyl) acetamide (70):** Yield: 72%. Mp. 67 °C.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.33–7.21 (m, 5H), 5.59 (s, 1H, 9.4 Hz, NH), 5.48 (s, 1H), 4.60 (q\*, 1H, 4.69 Hz), 3.36 (dd, 1H, 11.5/4.7 Hz), 2.34 (m, 1H), 2.15 (br m, 3H), 2.10 (s, 3H), 1.76 (s, 3H), 0.81 (d, 3H, 6.8 Hz).  $^{13}\text{C}$  NMR (75 MHz, APT,  $\text{CDCl}_3$ ):  $\delta$  171.4 (CO), 141.4, 131.7, 131.5, 128.8, 128.7, 127.0, 54.2, 51.4 (2C), 38.2, 23.7, 21.0, 19.8. IR (ATR):  $\tilde{\nu}$  [ $\text{cm}^{-1}$ ] 3256 (w), 3027, (w), 2963 (w), 1643 (s), 1536 (s), 1493 (m), 1452 (m), 1370 (m), 1285 (w), 1092 (w), 1092 (w), 1036 (w), 907 (m), 755 (s), 727 (s), 700 (s). LR-MS (EI, 70 eV):  $m/z$  258  $[\text{M}]^+$ , 199  $[\text{M} - \text{AcNH}]^+$ , 184, 167, 139, 119, 108. HR-MS (ESI): calcd  $[\text{M} + \text{Na}]^+$  281.1624, found 281.162.

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