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Synthesis and Properties of Chiral Pyrazolidines Derived from (+)-Pulegone

Florian Jakob,[a] Eberhardt Herdtweck,[b] and Thorsten Bach*[a]

Abstract: Several enantiomerically pure N(2)-substituted octahydroindazoles were prepared as bicyclic pyrazolidine derivatives of (+)-pulegone. Condensation of pulegone with hydrazine delivered a hexahydroindazole intermediate, which underwent N(2)-substitution with various electrophiles (alkyl halides, acyl chlorides, phenyl isocyanate). The resulting N(2)-substituted hexahydroindazoles could be reduced with $LiBEt_3H$ in THF to the target compounds. In addition, a N(2)-thiobenzoyl and some N(2)-carbamoyl derivatives as well as a N(1)-substituted octahydroindazole were synthesized. The compounds showed medium activity as iminium ion catalysts promoting quantitatively the Michael addition of nitroethane to cinnamaldehyde in up to 82% *ee* for the resulting *syn*-diastereoisomer and 78% *ee* for the *anti*-diastereoisomer. Unexpectedly, the N(2)-acyloctahydroindazoles were readily oxidized under aerobic conditions. Moreover, it was shown that an oxidation of methyl phenyl sulfide to the corresponding sulfoxide is promoted by an N(2)-acyloctahydroindazole in deuterochloroform as solvent. It is proposed that the oxidation of N(2)-acyloctahydroindazoles proceeds by in situ generation of hydrogen peroxide, which in turn can act as an oxidant.

Keywords: heterocycles · Michael addition · organocatalysis · oxidation · terpenoids

Introduction

Iminium ion catalysis has emerged in recent years as one of the most useful activation modes in organocatalysis. Commonly used organocatalysts include a broad variety of cyclic secondary amines, which are capable of iminium ion formation with α,β-unsaturated aldehydes.[1] Due to the enhanced electrophilicity of the iminium ion—as compared to the aldehyde—catalytic cycles are possible, in which addition products at the double bond are formed. If an appropriate stereogenic element is present in the amine, an enantioselective reaction course is possible. Imidazolidinones derived from α-amino acids have been shown in a seminal contribution by MacMillan et al. to be useful catalysts for enantioselective cycloaddition reactions to α,β-unsaturated aldehydes.[2] Since this discovery various modified chiral amines have been synthesized and evaluated for iminium ion catalysis.[1] Mechanistic studies have been conducted in an attempt to elucidate all aspects pertinent to the activity and selectivity of the iminium ion forming catalysts.[3]

Pyrazolidines of the general structure **A** can be considered as azanalogues of pyrrolidine-based organocatalysts (Figure 1). They allow the evaluation of the so-called α-heteroatom effect or α-effect, according to which an enhanced nucleophilicity is to be expected from these secondary amines as compared to pyrrolidines.[4] In addition, the substituent R at the nitrogen atom, which is in close proximity to the iminium ion forming nitrogen atom N(1) can carry an additional stereogenic element.

Work by Ogilvie et al.[5] has been devoted to the synthesis of pyrazolidinones **B** as cyclic hydrazides, which are easily

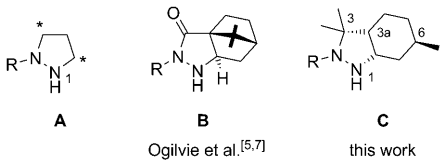

Figure 1. General structure of a chiral pyrazolidine **A**, of the chiral pyrazolidinones **B** earlier described by Ogilvie et al.,[5,7] and of the N(2)-substituted pyrazolidines **C** (octahydroindazoles), which are discussed in this report.

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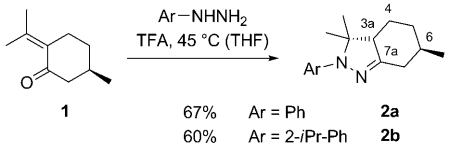
accessible from camphor sulfonic acid.[6] The catalysts have been successfully used in enantioselective Diels–Alder and nitrone cycloaddition reactions. The mechanism of the Diels–Alder reaction was studied in detail.[7] Enantioselectivities achieved with the catalysts vary but can reach up to 96% *ee*. For R being achiral the benzyl substituent showed the best performance. A further increase in selectivity can be achieved if the R substituent is chiral (R = 1-phenylethyl). Other groups have employed different cyclic hydrazides for related reactions.[8] A recent study by Tomkinson et al. has been concerned with a comparison of 2-alkyoxycarbonyl-substituted piperazines and pyrazolidines as iminium ion catalysts.[9]

Our interest in catalysts of type **A** was initially sparked by the idea to establish a chirality axis at the nitrogen substituent N(2) in general structure **C**, which would be perfectly located to induce enantioselectivity at the adjacent iminium ion. A similar concept has been previously employed in the construction of a chiral thiazolium-based organocatalyst from (+)-pulegone.[10] Rotational barriers around the respective N–C bond, however, seemed to be too low to guarantee the required configurational stability even if influenced by an adjacent stereogenic center at C(3). Intrigued by the restricted bicyclic structure of compounds **C** we decided to attempt their synthesis and evaluate their properties. It turned out that they do have catalytic potential in enantioselective iminium ion catalysis. In addition and much to our surprise the compounds proved to be capable of reducing atmospheric oxygen to hydrogen peroxide.

In this account we disclose our results regarding the preparation of compounds **C**. The structure of the resulting products is discussed based on X-ray crystallographic and NMR analysis. The Michael addition of nitroethane to cinnamaldehyde is presented as a test reaction to probe the potential of compounds **C** in enantioselective catalysis. Eventually, the above-mentioned reducing properties are disclosed in detail.

Results and Discussion

Synthesis of pyrazolidines from (+)-pulegone: Direct access to enantiomerically pure pyrazolidines has become possible in recent years by a variety of methods, which include the Zr-catalyzed [3+2]-cycloaddition of hydrazones to olefins,[11] the Pd-catalyzed cyclization of 3,4-allenylhydrazines,[12] and the [3+2]-cycloaddition of diazoalkanes to electron-deficient olefins.[13,14] The latter reactions proceed via pyrazolines, which are further reduced with $NaBH_3CN$ or $LiBEt_3H$. As a potential access to compounds of type **C** a direct condensation of (+)-pulegone (**1**) with hydrazines appeared feasible. Precedence for the formation of pyrazolines from hydrazines and α,β-unsaturated carbonyl compounds exists.[15] After trifluoroacetic acid (TFA) was identified as a suitable promoter for the condensation reaction the N(2)-aryl substituted hexahydroindazoles **2** were readily obtained (Scheme 1). The product **2a** of phenyl hydrazine was formed as a 85/15 mixture of diastereoisomers, while product **2b** formed from *ortho*-isopropylphenyl hydrazine was isolated as a single diastereoisomer.

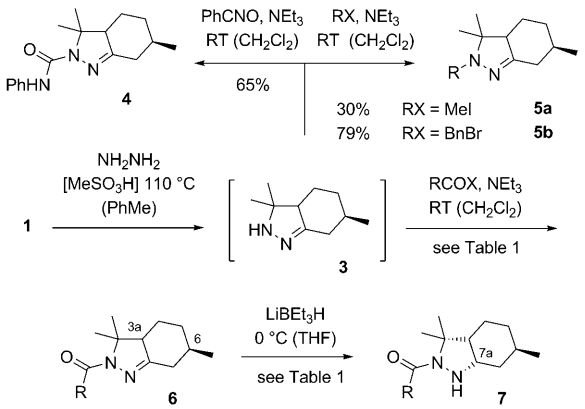


Scheme 1. Acid-promoted condensation of (+)-pulegone (**1**) and aromatic hydrazines to hexahydroindazoles **2**.

The relative configuration was assigned in all hexahydroindazoles based on the assumption that the methyl group at C(6) resides in an equatorial position and provides sufficient bias for the six-membered ring to adopt a chair-like conformation. In such an arrangement the hydrogen atom at C(3a) must be axially positioned if it displays a large $^3J_{HH}$ coupling constant to the axial proton at C(4). This was indeed the case for the major diastereoisomer with $^3J_{HH}$ varying between 11.9 and 12.8 Hz. The coupling constant to the equatorial proton at C(4) varied between 5.5 and 6.3 Hz. The same protons at C(3a) of the minor diastereoisomer led to incompletely resolved multiplets, from which coupling constants could not be obtained.

Unfortunately, the imine carbon atom C(7a) of products **2** turned out to be not sufficiently electrophilic to be attacked by conventional nucleophiles. A reduction of hexahydroindazoles **2** to the respective octahydroindazoles could not be achieved with a variety of reducing reagents ($NaBH_3CN$, $LiBEt_3H$, $NaBH_4$, $LiAlH_4$, Bu_3SnH, Et_3SiH, H_2) under different reaction conditions nor was it possible to conduct nucleophilic addition reactions again employing an array of different reagents (MeMgCl, MeLi, AllylMgCl, $AllylSiCl_3$, $NCSiMe_3$).

In order to vary the N-substituent of the pulegone-derived hexahydroindazoles, intermediate **3** was accessed by the known condensation reaction of (+)-pulegone (**1**) and hydrazine monohydrate (Scheme 2).[16] Carbamoylation (to **4**), alkylation (to **5**) and acylation (to **6**) were readily achieved via the crude condensation product **3**. Urea **4** was obtained as a diastereomeric mixture (d.r. 90:10) with phenylisocyanate as the electrophile while the reaction of intermediate **3** with alkylating reagents MeI and BnBr furnished pyrazolines **5a** (d.r. 87:13) and **5b** (d.r. 89:11). Studies related to the reactivity of hexahydroindazoles **5** towards nucleophiles mirrored the observations made with the N(2)-aryl-substituted hexahydroindazoles **2**. A reduction to the corresponding octahydroindazoles could not be achieved. The acylated products **6**, which were obtained by the reaction of intermediate **3** with acetic anhydride or acid chlorides, however, were suited for a reduction with $LiBEt_3H$ and delivered the octahydroindazoles **7**. The relative configuration of the product results from cyclic stereocontrol, with the major diastereoisomer of substrate **6** exhibiting a (3a*S*,6*R*)-configura-

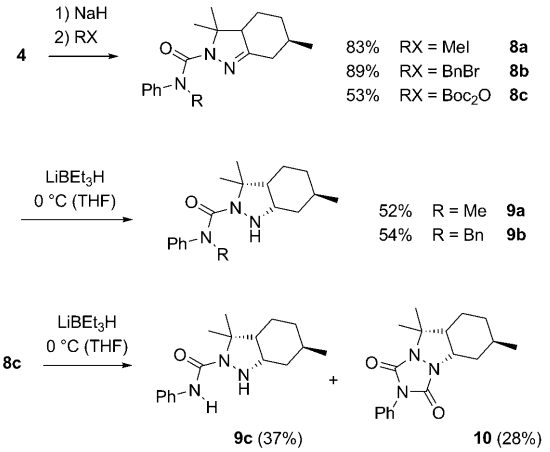


Scheme 2. Access to various N(2)-substituted hexahydroindazoles **4**–**6** from the known intermediate **3** and reduction of the N(2)-acyl derivatives **6** to octahydroindazoles **7**.

tion. The newly formed stereogenic center at C(7a) is also (*S*)-configurated (see below).

Octahydroindazoles **7** were isolated as single diastereoisomers after reduction, while the intermediate hexahydroindazole diastereoisomers were not separated. In Table 1 the yields for the individual steps of acylation and reduction are summarized. The diastereomeric ratio (d.r.) of the intermediately formed hexahydroindazoles **6** is given. The relatively low yield in the reduction step is partially due to the fact that it refers to the single diastereoisomer **7**, which was isolated, while no effort was made to isolate and characterize other diastereoisomers. Other reducing agents were tried but delivered less satisfactory results. Contrary to the observation made on unsubstituted pyrazolines,[17] reduction attempts with $NaCNBH_3$, $NaBH_4$, $LiAlH_4$ and BH_3 remained unsuccessful. The use of hydrogen in the presence of palladium (Pd/C) led to deacylation. Deacylation was also the major side reaction observed with $LiBEt_3H$ and the chosen reaction temperature of 0°C represents the best compromise between a sufficiently fast reaction rate and a chemoselective conversion.

The direct reduction of hexahydroindazole **4** was not possible. However, N-alkylation and N-*tert*-butyloxycarbonylation (Boc = *tert*-butoxycarbonyl) could be readily achieved delivering the N-substituted ureas **8** (d.r. 90:10). Reduction of these compounds with $LiBEt_3H$ was feasible and produced the octahydroindazoles **9a** and **9b** in moderate yields. Reduction of the Boc-protected substrate **8c** delivered the desired formal reduction product of hexahydroindazoles **4** via reduction and Boc cleavage. Significant amounts of triazoldione **10** were also obtained as a result of nucleophilic nitrogen attack at the carbonyl group of the carbamate (Scheme 3).



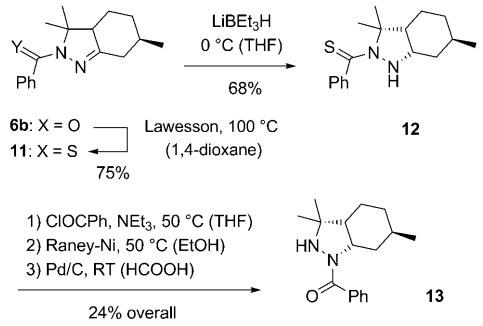
Scheme 3. N-Alkylation and N-acylation of the secondary carbamate **4** to hexahydroindazoles **8**, which were further reduced with lithium triethylborohydride.

Table 1. Preparation of diastereomerically pure N(2)-acyloctahydroindazoles **7** by acylation of intermediate **3** with RCOX and subsequent reduction of intermediate hexahydroindazoles **6** with $LiBEt_3H$ (Scheme 2).

Entry	R	X	**6**	Yield[a] [%]	d.r.	**7**	Yield[b] [%]
1	H_3C	OAc	**6a**	76	84:16	**7a**	41
2		Cl	**6b**	52	78:22	**7b**	61
3		Cl	**6c**	58	77:23	**7c**	66
4		Cl	**6d**	48	78:22	**7d**[c]	22
5		Cl	**6e**	39	78:22	**7e**	23
6		Cl	**6f**	28	78:22	**7f**	40
7		Cl	**6g**	21	78:22	**7g**	32

[a] Yield of isolated product **6** (diastereomeric mixture) after chromatographic purification. [b] Yield of diastereomerically pure product **7** after chromatographic purification. [c] The product is hydro-de-fluorinated in *para*-position.

The regioisomer of compound **7b**, that is, the N(1)-benzoylated octahydroindazole **13** (Scheme 4), was accessible via thioamide **12**. Treatment of N(2)-benzoylhexahydroindazole **6b** (d.r. 78:22) with Lawesson reagent[18] delivered thioamide **11** (d.r. 78:22), which was reduced with $LiBEt_3H$ to octahydroindazole **12**. The diastereomerically pure compound was N(1)-benzoylated with benzoyl chloride. The thiobenzoyl group at N(2) was reduced to a benzyl group, which could be removed by hydrogen transfer hydrogenolysis.



Scheme 4. Synthesis of the N(1)-benzoylated octahydroindazole **13** from N(2)-benzoylated hexahydroindazole **6b** via thioamide **12**.

With octahydroindazoles **7a–g**, **9a–c**, **12**, and **13** a total of twelve compounds were prepared and could be tested for their catalytic properties. Prior to that, the three-dimensional structure of this new class of compounds was briefly investigated.

Configuration and conformation of octahydroindazoles: Suitable crystals for single crystal X-ray analysis could be obtained from a solution of N(2)-acetyloctahydroindazole **7a** in diethyl ether by diffusion with pentane. The structure confirmed the expected (3a*S*,6*R*,7a*S*)-configuration of the octahydroindazole skeleton and the previously mentioned chair-like conformation of the cyclohexane ring. In addition, it revealed a s-*trans*-conformation at the amide bond, with the carbonyl oxygen atom and the nitrogen atom N(1) being almost perfectly antiperiplanar to each other (Figure 2).

The conformational preference for a s-*trans*-amide bond in N(2)-acyloctahydroindazoles was further corroborated by ^{1}H NOESY spectra of N(2)-benzoylderivative **7b**, which revealed a strong contact between the hydrogen atom at N(1) and the *ortho*-protons of the phenyl ring (Figure 3). The remoteness of the anisotropic phenyl group from the geminal dimethyl substituents at C(3) was further undermined by the almost identical chemical shift of the methyl protons. The ^{1}H NMR properties of urea **9c** were similar to those of amides **7**. A ^{1}H-NOESY contact between the two NH protons suggests a s-*trans*-orientation in the predominantly populated conformer. Again, the methyl protons at C(3) are almost isochronous. In stark contrast, thioamide **12** exhibited completely different ^{1}H NMR shift values for these protons, one methyl group resonating at 0.90 ppm, the other at 1.45 ppm. In addition, ^{1}H-NOESY contacts between these methyl groups and the *ortho*-protons of the phenyl group were recorded strongly supporting an s-*cis*-thioamide conformation for this compound.

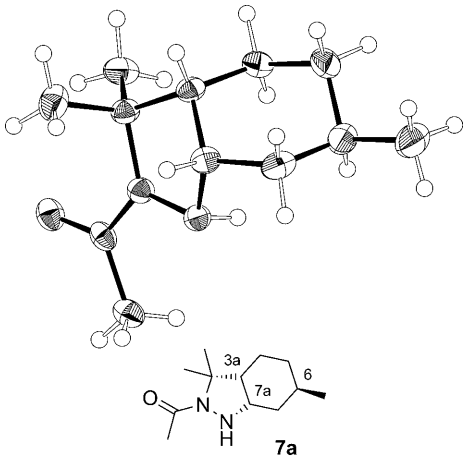


Figure 2. A molecule of compound **7a** in the crystal.

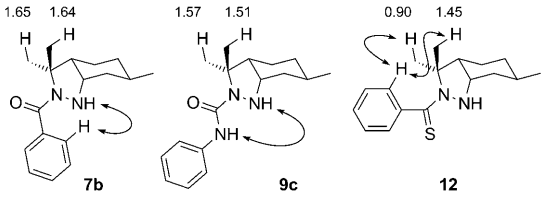
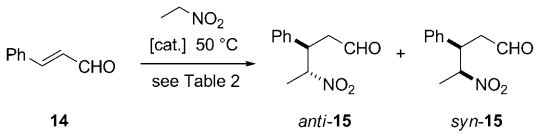


Figure 3. ^{1}H NMR chemical shift data of the *gem*-dimethyl substituents at C(3) and significant ^{1}H-NOESY contacts in octahydroindazoles **7b**, **9c**, and **12**.

Michael addition of nitroethane to cinnamaldehyde: The addition of nitroethane to cinnamaldehyde (**14**, Scheme 5) has been previously studied as a test reaction for proposed iminium ion catalysts. Pioneering studies were conducted by Arvidsson et al., who investigated in detail a possible iminium ion catalysis for the Michael addition of nitroalkanes to α,β-unsaturated aldehydes.[19] They developed an imidazole-containing imidazolidinone catalyst, which showed good activity and high enantioselectivity. The catalyst (20 mol%) delivered the respective addition products (*syn*/*anti* 50:50) in 91% yield if the addition to cinnamaldehyde was run in neat nitroethane (4 equiv) at ambient temperature for 47 h. The enantiomeric excess under these conditions was 82% *ee* for the *syn*-product and 80% *ee* for the *anti*-product. 2-Diphenyl(trimethylsilyloxy)methylpyrrolidine was found to be a very active catalyst under the same conditions giving 91% conversion in 15 h but with moderate enantioselectivity for the *syn*-diastereoisomer (45% *ee*) and poor enantioselectivity for the *anti*-diastereoisomer (5% *ee*). Later, it was claimed that the enantioselectivity with this catalyst can be signif-

icantly increased in the same reaction by changing the solvent and by addition of additives.[20]



Scheme 5. Michael addition of nitroethane to cinnamaldehyde (**14**) leading to the two diastereomeric addition products *anti*-**15** and *syn*-**15**.

The reactions we conducted were run in neat nitroethane as the solvent. It was found that the conversion at room temperature was slow, which made us increase the reaction temperature to 50 °C. Under these conditions the catalysts could be nicely compared to each other (Scheme 5, Table 2). There was a slight preference for the *anti*-product in all runs.

Table 2. Michael addition of nitroethane to cinnamaldehyde (**14**) to products **15** catalyzed by octahydroindazoles (20 mol %) **7**, **9**, **12**, and **13** (Scheme 5).

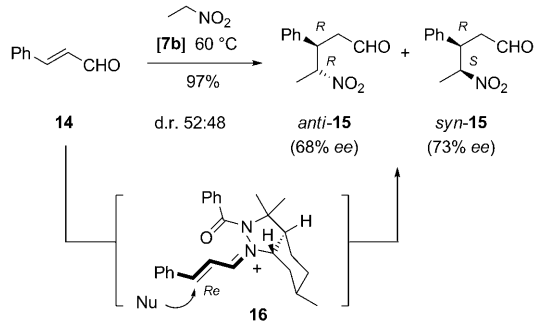
Entry	Cat.	Conv.[a] [%]	d.r. (*anti*/*syn*)	*ee* [%][b] (*anti*-**15**)	*ee* [%][b] (*syn*-**15**)
1	**7a**	10	52:48	n.d.[c]	28
2	**7b**	16	52:48	76	76
3	**7c**	32	52:48	72	65
4	**7d**	<3	n.d.	4	36
5	**7e**	4	52:48	19	26
6	**7f**	4	52:48	78	82
7	**7g**	27	57:43	67	51
8	**9a**	39	60:40	48	50
9	**9b**	22	60:40	51	50
10	**9c**	12	50:50	−11	0
11	**12**	10	50:50	8	9
12	**13**	51	63:37	−5	−12

[a] The conversion was determined by ^{1}H NMR after a reaction time of three days. [b] The *ee* was calculated from the enantiomeric ratio, which was determined by chiral GC analysis. [c] Not determined.

There is a significant reactivity difference for the various N-acyloctahydroindazoles **7**. Apparently, an electron-donating effect of the substituent R is beneficial for the reactivity (entries 3 and 8), while sterically encumbered substituents without a strong donor are unproductive (entries 4–6). The highest catalytic activity was recorded for the N(2)-carbamoyl substituted octahydroindazole **9a** (entry 8) and for the N(1)-benzoyl-substituted octahydroindazole **13** (entry 12).

With regard to enantioselectivity, the highest enantiomeric excesses were recorded for the N(2)-aroyl substituted octahydroindazoles **7b**, **7c**, **7f**, and **7g** (entries 2, 3, 6, and 7). It was hoped that catalyst **7g** would combine the very good enantioselectivity of the naphthoyl-substituted catalyst **7f** and the relatively high reactivity of the *para*-methoxybenzoyl substituted catalyst **7c**, but unfortunately it delivered a lower enantioselectivity than **7f** (entries 6 and 7). In general, enantioselectivities determined for both *syn*- and *anti*-diastereoisomer did not vary significantly. The low enantioselectivities recorded for octahydroindazoles **9c** (entry 10) and **13** (entry 12) were in favor of the enantiomer, which was disfavored with the other catalysts.

The assignment of the absolute configuration of the enantiomers was deduced from previous work. The (*S*,*S*)-enantiomer of *anti*-**15** was shown by Maruoka et al. in their studies on the enantioselective silyl nitronate addition to cinnamaldehyde[21] to be levorotatory in $CHCl_3$ as the solvent. The (*R*,*S*)-enantiomer of *syn*-**15** was shown by Wang et al. to be also levorotatory in $CHCl_3$.[20a] The major products *anti*-**15** and *syn*-**15** obtained in our study with N(2)-acyl substituted octahydroindazoles **7** were dextrorotatory in $CHCl_3$ indicating that they have the (*R*,*R*)- and (*S*,*R*)-configuration (Scheme 6). Under optimized conditions employing catalyst **7b**, products **15** were isolated from cinnamaldehyde (**14**) and four equivalents of nitroethane at 60 °C in 97 % yield.

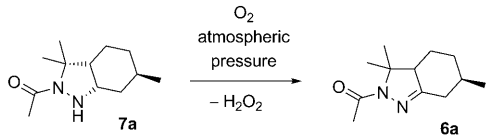


Scheme 6. Enantioselective preparation of Michael addition products *anti*-**15** and *syn*-**15** and presumed structure of the iminium ion intermediate **16** formed from aldehyde **14** and octahydroinazole **7b**.

In order to explain the absolute product configuration we invoke the iminium ion **16** as intermediate. The concave shape of this molecule favors an approach from the top face, which is the *Re* face if the iminium ion adopts the depicted (*Z*)-configuration around the C=N double bond. Condensation of aldehyde **14** requires a turn of the amide bond at N(2) from the preferred s-*trans*-conformation (see above) to the s-*cis* conformation. With bulky substituents (entries 4–6, Table 2), this rotation appears to be energetically so costly that iminium ion formation is retarded. Electron-donating substituents at the carbonyl group lower the rotational barrier around the amide bond and may therefore facilitate iminium ion formation. The yellow color of the intermediate iminium ion, which is observed immediately after addition of conventional secondary amines, such as pyrrolidine, to aldehyde **14**, does not occur with the octahydroindazoles listed in table 2. Only after an extended period of time a coloration of the reaction mixture was notable hinting at a slow formation of the iminium ion. The simple diastereoselectivity is low because the approaching nitronate nucleophile has no preferred orientation. In line with this assump-

tion, the absolute configuration in β-position to the carbonyl group is always identical (*R*) while the relative configuration at the γ-position is variable (*R* or *S*).

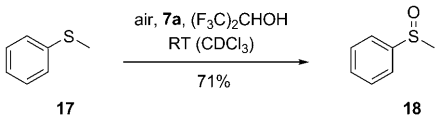
Reduction of oxygen to hydrogen peroxide: The crystal structure of compound **7a** revealed the presence of a molecule of hydrogen peroxide (H_2O_2) in the unit cell (see Experimental Section and Supporting Information). In addition, the oxidation product **6a** of octahydroindazole **7a** was obtained as an oily material from the recrystallization attempts. While the air sensitivity of pyrazolidines has been earlier mentioned by others,[13,14,22] we are not aware that this process was further studied. We assumed that pyrazolidine **7a** is capable of reducing oxygen under atmospheric pressure to hydrogen peroxide (Scheme 7) and would therefore be a source of water-free hydrogen peroxide in organic solvents. Commercially available hydrogen peroxide is normally delivered as an aqueous solution, which is obtained predominantly by the well-established anthraquinone process,[23] in which 2-alkyl-substituted anthrahydroquinones serve as reducing agents at 30–60 °C and at ambient oxygen pressure. Further methods for the generation of hydrogen peroxide have been described.[24]



Scheme 7. Oxidation of octahydroindazole **7a** to hexahydroindazole **6a** with concomitant formation of hydrogen peroxide.

Thioanisole (**17**) was chosen as a test substrate to substantiate the notion that in situ generated hydrogen peroxide was capable of oxidizing organic compounds in an organic solvent. It is known that thioanisole can be oxidized by hydrogen peroxide to the respective sulfoxide **18** at elevated temperature or upon addition of additives.[25] Indeed, following a known procedure,[25f] product **18** was obtained in 69% yield upon treatment of compound **17** with aqueous hydrogen peroxide at 60 °C. If run in an organic solvent ($CDCl_3$) the reaction slowed down significantly and remained incomplete even after four days delivering the respective product in 24% yield. A similar yield was obtained if one equivalent of thioanisole was stirred a 60 °C under air in the presence of one equivalent of octahydroindazole **7a**.

To further increase the activity of hydrogen peroxide hexafluoroisopropanol (HFIP) has been recommended as solvent. Rapid oxidation reactions of sulfides have been observed in this solvent in a short period of time.[26] We showed that oxygen is not capable of oxidizing sulfides in this solvent by appropriate test experiments. However, upon addition of one equivalent HFIP to $CDCl_3$ and upon stirring this solution with one equivalent of **7a** in air at ambient temperature, thioanisole oxidation was complete after nine days and 71% of racemic sulfoxide **18** were obtained (Scheme 8). In addition, reduction product **6a** was isolated in 96% yield. Based on these results it is likely that in situ generated hydrogen peroxide is responsible of the oxidation reaction.



Scheme 8. Aerobic oxidation of sulfide **17** to sulfoxide **18** mediated by octahydroindazole **7a**.

Conclusion

In summary, chiral N(2)-substituted octahydroindazoles can be easily prepared starting from (+)-pulegone. They represent chiral, cyclic hydrazides, which, however, show only limited effectivity in iminium ion catalysis. While enantioselectivities of up to 82% *ee* could be achieved in the Michael addition of nitroethane to cinnamaldehyde, a complete conversion was only possible at elevated temperature and after extended reaction times. This result is in line with similar observations made with simple achiral pyrazolidines, which proved to be ineffective catalysts for the Diels–Alder reaction of cinnamaldehyde.[9] A possible ring expansion to six-membered rings, that is, to piperazines, seems a possible way to achieve higher activity. The oxidation of octahydroindazoles occurs at room temperature under aerobic conditions. It was shown that the sulfoxidation of a sulfide is possible with air and octahydroindazole **7a** as a promoter under conditions conventionally used for a sulfoxidation by hydrogen peroxide. The reducing properties of octahydroindazoles might be useful for enantioselective reduction reactions.

Experimental Section

General: All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under argon. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium immediately prior to use. Dichloromethane and triethylamine were distilled from calcium hydride. All other chemicals were either commercially available or prepared according to the cited references. TLC: Merck glass sheets (0.25 mm silica gel 60, F_{254}), eluent given in brackets. Detection by UV or coloration with cerium ammonium molybdate [CAM]. ^1H and ^{13}C NMR spectra were recorded at ambient temperature. Chemical shifts are reported relative to tetramethylsilane as internal standard. Apparent multiplets which occur as a result of the accidental equality of coupling constants of magnetically nonequivalent protons are marked as virtual (virt.). Flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh) (ca. 50–100 g for 1 g of material to be separated) with the indicated eluent. Common solvents for chromatography [pentane, ethyl acetate (EtOAc), diethyl ether (Et_2O), dichloromethane] were distilled prior to use. The preparation and analytical data of compounds **2b**, **5b**, **6b–g**, **7b–g**, **8b** and **12** are reported in the Supporting Informa-

tion. ^{13}C NMR spectra of all new compounds are also presented in the Supporting Information.

(3a*S*,6*R*)-(2-Phenyl-3,3,6-trimethyl)-3,3a,4,5,6,7-hexahydroindazole (2a): (+)-Pulegone (538 μL, 502 mg, 3.30 mmol, 92%) was dissolved in THF (12 mL). Phenylhydrazine (331 μL, 364 mg, 3.37 mmol, 1.02 equiv) and trifluoroacetic acid (260 μL, 400 mg, 3.37 mmol, 1.02 equiv) were successively added and the mixture was stirred for 16 h at 45°C. Water (50 mL) and diethyl ether (50 mL) were added. The layers were separated and the aqueous layer was extracted with diethyl ether (3×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (pentane/Et_2O 15:1) to give **2a** (562 mg, 1.98 mmol, 67%) as a yellow solid. R_f=0.26 (pentane/Et_2O 8:1) [CAM]; m.p. 58°C; ^1H NMR (360 MHz, $CDCl_3$): δ = 1.05 (d, ^3J=6.5 Hz, 3H), 1.07 (s, 3H), 1.10–1.17 (m, 1H), 1.42 (s, 3H), 1.43–1.48 (m, 1H), 1.60–1.69 (m, 1H), 1.77–1.89 (m, 3H), 2.60 (dd, ^3J= 11.9, 5.5 Hz, 1H), 2.75 (ddd, ^2J=14.4, ^3J=4.3, ^4J=1.5 Hz, 1H), 6.92–6.98 (m, 1H), 7.21–7.29 ppm (m, 4H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ =20.1 (q), 22.4 (q), 25.6 (t), 27.8 (q), 33.5 (t), 33.6 (d), 36.2 (t), 57.3 (d), 67.6 (s), 119.1 (d), 121.4 (d), 128.5 (d), 146.0 (s), 155.2 ppm (s); IR (ATR): $\tilde{\nu}$ = 2946 (m), 2922 (m), 2863 (m), 1593 (s), 1492 (vs), 1385 (m), 1322 (m), 1275 (m), 1037 (w), 737 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 242 (18) [M^+], 227 (100), 171 (6), 77 (6); HRMS (EI): *m*/*z*: calcd for $C_{16}H_{22}N_2$: 242.1783 [M^+]; found: 242.1783.

(3a*S*,6*R*)-3,3,6-Trimethyl-3,3a,4,5,6,7-hexahydroindazole-2-carboxylic acid anilide (4): (+)-Pulegone (2.00 mL, 1.90 g, 11.5 mmol, 92%) was dissolved in toluene (20 mL). Hydrazine monohydrate (0.56 mL, 0.58 g, 11.5 mmol) and methanesulfonic acid (34.7 μL, 51.4 mg, 0.57 mmol, 0.05 equiv) were successively added at 80°C. The reaction mixture was heated under reflux for 20 h in an argon atmosphere, while water was continuously removed using a Dean–Stark apparatus. The solvent was removed under reduced pressure at ambient temperature and the residue was dissolved in CH_2Cl_2 (7 mL). The solution was cooled to 0°C, treated with NEt_3 (1.61 mL, 1.16 g, 11.5 mmol), and phenylisocyanate (1.25 mL, 1.37 g, 11.5 mmol) and stirred for 10 h while warming to room temperature. Saturated aqueous $NaHCO_3$ solution (30 mL) and CH_2Cl_2 (40 mL) were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (pentane/Et_2O 3:1) to give **4** (2.13 g, 7.48 mmol, 65%) as a pale red solid (d.r. 90:10). R_f=0.32 (pentane/Et_2O 3:1) [CAM]; m.p. 129°C; ^1H NMR (360 MHz, $CDCl_3$): δ = 1.06 (d, ^3J= 6.5 Hz, 3H), 1.14–1.20 (m, 1H), 1.41–1.47 (m, 1H), 1.43 (s, 3H), 1.58–1.66 (m, 1H), 1.60 (s, 3H), 1.82–1.90 (m, 3H), 2.59 (dd, ^3J=12.7 Hz, 5.8 Hz, 1H), 2.65 (ddd, ^2J=14.1 Hz, ^3J=4.5 Hz, ^4J=1.6 Hz, 1H), 6.97–7.02 (m, 1H), 7.24–7.28 (m, 2H), 7.45–7.50 (m, 2H), 7.99 ppm (br s, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 20.6 (q), 22.2 (q), 26.4 (t), 27.9 (q), 33.2 (t), 33.7 (d), 36.0 (t), 57.7 (d), 64.3 (s), 118.9 (d), 122.4 (d), 128.8 (d), 139.1 (s), 152.2 (s), 157.7 ppm (s); IR (ATR): $\tilde{\nu}$ = 3310 (m), 2961 (m), 2948 (m), 2931 (m), 1660 (s), 1590 (m), 1524 (s), 1550 (m), 1442 (s), 1396 (m), 1319 (m), 1230 (m), 1055 (m), 752 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 285 (23) [M^+], 166 (25), 151 (100), 109 (3), 95 (11), 69 (3), 41 (6); HRMS (EI): *m*/*z*: calcd for $C_{17}H_{23}N_3O$: 285.1841 [M^+]; found: 285.1842.

(3a*S*,6*R*)-(2,3,3,6-Tetramethyl)-3,3a,4,5,6,7-hexahydroindazole (5a): (+)-Pulegone (2.00 mL, 1.90 g, 11.5 mmol, 92%) was dissolved in toluene (20 mL). Hydrazine monohydrate (0.56 mL, 0.58 g, 11.5 mmol) and methanesulfonic acid (34.7 μL, 51.4 mg, 0.57 mmol, 0.05 equiv) were successively added at 80°C. The reaction mixture was heated under reflux for 20 h in an argon atmosphere, while water was continuously removed using a Dean–Stark apparatus. The solvent was removed under reduced pressure at ambient temperature and the residue dissolved in CH_2Cl_2 (4 mL). The solution was cooled to 0°C, treated with NEt_3 (1.61 mL, 1.16 g, 11.5 mmol), methyl iodide (0.72 mL, 1.63 g, 11.5 mmol) and stirred for 10 h while warming to room temperature. Aqueous 6 M NH_3 solution (30 mL) and CH_2Cl_2 (20 mL) were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (pentane/Et_2O 9:1) to give hexahydroindazole **5a** (0.62 g, 3.45 mmol, 30%) as a red oil (d.r. 87:13). R_f=0.35 (pentane/Et_2O=7:3) [CAM]; ^1H NMR (360 MHz, $CDCl_3$): δ = 0.93 (s, 3H), 0.98 (d, ^3J=6.5 Hz, 3H), 1.03–1.09 (m, 1H), 1.17 (s, 3H), 1.35 (virt. qd, $^2J \cong {}^3J$=12.4, ^3J=3.2 Hz, 1H), 1.46–1.61 (m, 1H), 1.65–1.80 (m, 3H), 2.34 (dd, ^3J=12.4, 5.7 Hz, 1H), 2.56 (ddd, ^2J= 14.4, ^3J=4.3, ^4J=1.8 Hz, 1H), 2.68 ppm (s, 3H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 17.1 (q), 22.2 (q), 24.8 (t), 25.1 (q), 33.5 (d), 33.5 (t), 34.6 (q), 36.3 (t), 56.0 (d), 66.0 (s), 155.2 ppm (s); IR (ATR): $\tilde{\nu}$ = 2950 (s), 2928 (s), 2867 (m), 1676 (s), 1455 (m), 1414 (m), 1379 (m), 1363 (m), 941 (w), 782 (w), 749 cm^{-1} (w); MS (EI, 70 eV): *m*/*z* (%): 180 (20) [M^+], 165 (100), 123 (4), 109 (24), 56 (3); HRMS (EI): *m*/*z*: calcd for $C_{11}H_{20}N_2$: 180.1626 [M^+]; found: 180.1629.

(3a*S*,6*R*)-(2-Acetyl-3,3,6-trimethyl)-3,3a,4,5,6,7-hexahydroindazole (6a): (+)-Pulegone (2.00 mL, 1.90 g, 11.5 mmol, 92%) was dissolved in toluene (20 mL). Hydrazine monohydrate (0.56 mL, 0.58 g, 11.5 mmol) and methanesulfonic acid (34.7 μL, 51.4 mg, 0.57 mmol, 0.05 equiv) were successively added at 80°C. The reaction mixture was heated under reflux for 20 h in an argon atmosphere, while water was continuously removed using a Dean–Stark apparatus. The solvent was removed under reduced pressure at ambient temperature. The residue was cooled to 0°C, treated with acetic anhydride (5.94 mL, 6.40 g, 46.0 mmol, 4.00 equiv) and the resulting mixture stirred for 10 h while allow to warm up to ambient temperature. Sat. aqueous $NaHCO_3$ (50 mL) was added and the aqueous layer extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography (pentane/Et_2O=2:1) to give **6a** (1.82 g, 8.74 mmol, 76%) as a pale yellow oil (d.r. 84:16). R_f=0.34 (pentane/Et_2O 2:1) [CAM]; ^1H NMR (360 MHz, $CDCl_3$): δ = 1.05 (d, ^3J= 6.5 Hz, 3H), 1.12–1.18 (m, 1H), 1.36–1.40 (m, 1H), 1.42 (s, 3H), 1.57 (s, 3H), 1.59–1.69 (m, 1H), 1.79–1.91 (m, 3H), 2.25 (s, 3H), 2.56 (dd, ^3J= 12.8, 5.8 Hz, 1H), 2.64 ppm (dd, ^2J=14.0, ^3J=4.1 Hz, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 20.3 (q), 22.1 (q), 23.0 (q), 26.6 (t), 27.5 (q), 33.1 (t), 33.6 (d), 36.1 (t), 57.6 (d), 64.6 (s), 160.9 (s), 169.7 pm (s); IR (ATR): $\tilde{\nu}$ = 2950 (m), 2939 (m), 1655 (s), 1637 (m), 1573 (m), 1440 (m), 1413 (s), 1361 (m), 1326 (m), 932 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 208 (20) [M^+], 193 (7), 166 (13), 151 (100), 109 (6), 95 (12), 43 (11); HRMS (EI): *m*/*z*: calcd for $C_{12}H_{20}N_2O$: 208.15756 [M^+]; found: 208.15759.

(3a*S*,6*R*,7a*S*)-(2-Acetyl-3,3,6-trimethyl)-octahydroindazole (7a): Hexahydroindazole **6a** (208 mg, 1.00 mmol) was dissolved in dry THF (20 mL) and cooled to 0°C. 1 M $LiEt_3BH$ (2.25 mL, 2.25 mmol, 2.25 equiv) was added slowly and the solution was stirred for 100 min at 0°C. The reaction was then hydrolyzed with 2 M aqueous NaOH (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3× 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (pentane/EtOAc 1:1) yielding the corresponding diastereomerically pure **7a** (86.1 mg, 0.41 mmol, 41%) as a colorless solid. Although **7a** can be manipulated in the air, it is unstable and slowly oxidizes to the corresponding **6a**. In order to prevent its oxidation, it has to be stored under argon. R_f=0.54 (pentane/Et_2O 1:2) [CAM]; m.p. 109°C; $[\alpha]_D^{20}$ = −57.4 (*c*=0.59 in $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$): δ = 0.83–0.88 (m, 1H), 0.89 (d, ^3J=6.3 Hz, 3H), 1.27–1.33 (m, 2H), 1.38–1.42 (m, 1H), 1.45 (s, 3H), 1.48 (s, 3H), 1.69–1.73 (m, 2H), 1.75–1.82 (m, 1H), 1.95–2.02 (m, 1H), 2.10 (s, 3H), 3.40–3.48 (m, 1H), 4.35 ppm (br s, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 21.9 (q), 22.3 (q), 23.0 (t), 23.8 (q), 25.9 (q), 27.0 (d), 33.1 (t), 33.3 (d), 50.6 (d), 55.6 (d), 66.1 (s), 169.6 ppm (s); IR (ATR): $\tilde{\nu}$ = 3223 (s), 2922 (s), 1628 (s), 1617 (s), 1481 (m), 1414 (s), 1377 (m), 1362 (m), 1128 (m), 972 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 210 (21) [M^+], 167 (100), 153 (12), 95 (22), 43 (12); HRMS (EI): *m*/*z*: calcd for $C_{12}H_{22}N_2O$: 210.1732 [M^+]; found: 210.1731.

Single-crystal X-ray structure determination of compound 7a: Crystal data and details of the structure determination (see also Supporting Information): formula: $C_{12}H_{22}N_2O\cdot(H_2O_2)$; M_r=244.33; crystal color and shape: colorless plate, crystal dimensions=0.14×0.46×0.51 mm; crystal system: orthorhombic; space group $P2_12_12_1$ (no.: 19); a=6.3417(2), b= 11.1846(3), c=19.1812(5) Å; V=1360.51(7) Å^3 ; Z=4; $\mu(Cu_{K\alpha})$= 0.692 mm^{-1}; ρ_{calcd}=1.193 g cm^{-3}; Θ range=4.58–66.59°; data collected:

17033; independent data [$I_o > 2\sigma(I_o)$/all data/R_{int}]: 2318/2356/0.022; data/restraints/parameters: 2356/0/250; R^1 [$I_o > 2\sigma(I_o)$/all data]: 0.0246/0.0250; wR^2 [$I_o > 2\sigma(I_o)$/all data]: 0.0648/0.0652; GOF = 1.060; $\Delta\rho_{max/min}$ = 0.12/−0.12 e Å^{-3}.

CCDC 759340 (**7a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

(3a*S*,6*R*)-3,3,6-Trimethyl-3,3a,4,5,6,7-hexahydroindazole-2-carboxylic acid *N*-methyl-anilide (8a): Hexahydroindazole **4** (285 mg, 1.00 mmol) was dissolved in dry CH_3CN (10 mL) and treated with NaH (41.7 mg, 1.05 mmol, 60%, 1.05 equiv) at 0°C for 30 min. Methyl iodide (68.5 μL, 156 mg, 1.10 mmol, 1.10 equiv) was added dropwise and the mixture was stirred for 20 h at ambient temperature. The reaction was then hydrolyzed with saturated aqueous NH_4Cl solution (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (pentane/Et_2O 2:1) yielding hexahydroindazole **8a** (247 mg, 0.83 mmol, 83%) as a yellow oil. R_f = 0.29 (pentane/Et_2O 1:1) [CAM]; ^{1}H NMR (360 MHz, $CDCl_3$): δ [ppm] = 0.90 (d, ^3J = 6.5 Hz, 3H), 0.98–1.04 (m, 1H), 1.22–1.32 (m, 2H), 1.44 (s, 3H), 1.47–1.53 (m, 1H), 1.55 (s, 3H), 1.71–1.81 (m, 2H), 2.19 (ddd, ^2J = 14.0, ^3J = 4.5, ^4J = 1.7 Hz, 1H), 2.59 (dd, ^3J = 12.5, 5.6 Hz, 1H), 3.28 (s, 3H), 7.01–7.07 (m, 3H), 7.20–7.27 ppm (m, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 20.1 (q), 22.1 (q), 26.5 (t), 27.0 (q), 33.2 (t), 33.9 (d), 35.9 (t), 38.9 (q), 56.7 (d), 65.0 (s), 123.8 (d), 124.1 (d), 128.8 (d), 147.7 (s), 156.1 (s), 157.0 ppm (s); IR (ATR): $\tilde{\nu}$ = 2951 (m), 2925 (m), 2865 (m), 1647 (s), 1596 (m), 1428 (s), 1397 (s), 1327 (m), 1101 (m), 740 (m), 695 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 299 (53) [M^+], 284 (40), 134 (100), 106 (29), 77 (18), 69 (13), 41 (7); HRMS (EI): *m*/*z*: calcd for $C_{18}H_{25}N_3O$: 299.1998 [M^+]; found: 299.1995.

(3a*S*,6*R*)-3,3,6-Trimethyl-3,3a,4,5,6,7-hexahydroindazole-2-carboxylic acid *N*-(*tert*-butyloxycarbonyl)anilide (8c): Hexahydroindazole **4** (285 mg, 1.00 mmol) was dissolved in dry THF (10 mL) and treated with NaH (41.7 mg, 1.05 mmol, 60%, 1.05 equiv) at 0°C for 30 min. Boc_2O (1.09 g, 5.00 mmol, 5.00 equiv) was added, the mixture was heated under reflux for 20 h. Upon cooling to room temperature the reaction was quenched by the addition of water (40 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (pentane/Et_2O 3:1) to give **8c** (204 mg, 0.53 mmol, 53%) as a pale yellow solid. R_f = 0.21 (pentane/Et_2O 3:1) [CAM]; m.p. 109°C; ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.05 (d, ^3J = 6.5 Hz, 3H), 1.12–1.18 (m, 1H), 1.46 (s, 12H), 1.54–1.64 (m, 2H), 1.60 (s, 3H), 1.78–1.94 (m, 3H), 2.62–2.69 (m, 2H), 7.17–7.22 (m, 1H), 7.30–7.35 ppm (m, 4H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 20.0 (q), 22.2 (q), 26.9 (t), 27.0 (q), 28.2 (q), 33.1 (t), 33.6 (d), 36.0 (t), 57.7 (d), 64.6 (s), 81.4 (s), 126.0 (d), 126.2 (d), 128.8 (d), 138.9 (s), 151.4 (s), 152.3 (s), 160.4 ppm (s); IR (ATR): $\tilde{\nu}$ = 2976 (w), 2927 (w), 1722 (s), 1671 (s), 1418 (s), 1333 (m), 1310 (m), 1232 (m), 1156 (s), 1015 (w), 740 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 385 (26) [M^+], 285 (20), 166 (45), 151 (100), 105 (8), 57 (39), 41 (12); HRMS (EI): *m*/*z*: calcd for $C_{22}H_{31}N_3O_3$: 385.2365 [M^+]; found: 385.2363.

(3a*S*,6*R*)-(2-Benzthioyl-3,3,6-trimethyl)-3,3a,4,5,6,7-hexahydroindazole (11): Hexahydroindazole **6b** (405 mg, 1.50 mmol) was dissolved in 1,4-dioxane (4 mL). Lawesson's reagent (424 mg, 1.05 mmol, 0.70 equiv) was added and the mixture was stirred for 16 h at 100°C. Water (50 mL) and Et_2O (75 mL) were added at ambient temperature. The layers were separated and the aqueous layer was extracted with Et_2O (2×75 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. After purification by flash chromatography (pentane/Et_2O 4:1) **11** (322 mg, 1.13 mmol, 75%) was obtained as a yellow solid. R_f = 0.35 (pentane/Et_2O 7:3) [CAM]; m.p. 127°C; ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.02 (d, ^3J = 6.5 Hz, 3H), 1.12–1.18 (m, 1H), 1.46–1.64 (m, 2H), 1.74–1.80 (m, 1H), 1.82 (s, 3H), 1.86–1.95 (m, 2H), 1.98 (s, 3H), 2.48 (ddd, ^2J = 14.2, ^3J = 4.2, ^4J = 1.9 Hz, 1H), 2.75 (dd, ^3J = 12.7, 6.1 Hz, 1H), 7.26–7.29 (m, 3H), 7.34–7.37 ppm (m, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 19.5 (q), 22.1 (q), 26.7 (t), 26.9 (q), 32.9 (t), 33.6 (d), 35.8 (t), 58.6 (d), 70.0 (s), 127.0 (d), 127.2 (d), 128.2 (d), 145.6 (s), 164.1 (s), 194.6 ppm (s); IR (ATR): $\tilde{\nu}$ = 2951 (m), 2926 (m), 1644 (m), 1454 (m), 1438 (s), 1269 (m), 1090 (m), 749 (m), 693 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 286 (100) [M^+], 271 (10), 215 (24), 203 (25), 176 (20), 150 (16), 121 (96), 105 (30), 77 (27), 41 (19); HRMS (EI): *m*/*z*: calcd for $C_{17}H_{22}N_2S$: 286.1504 [M^+]; found: 286.1511.

(3a*S*,6*R*,7a*S*)-(1-Benzoyl-3,3,6-trimethyl)-octahydroindazole (13): Octahydroindazole **12** (0.45 g, 1.6 mmol) was dissolved in dry THF (50 mL), Et_3N (0.39 mL, 0.47 g, 4.7 mmol, 3.0 equiv) and benzoyl chloride (0.54 mL, 0.66 g, 4.7 mmol, 3.0 equiv) were successively added at 0°C. The mixture was then heated to 50°C and stirred at this temperature for 20 h. Upon cooling to room temperature water (15 mL) was added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography (pentane/Et_2O/CH_2Cl_2 70:27:3) to give a yellow solid (0.59 g, R_f = 0.20 [pentane/Et_2O 7:3]), which was directly reduced with activated Raney-Ni (0.20 g, 2.3 mmol) in dry EtOH (10 mL) at 50°C for 2 h. The suspension was then filtered through a pad of Celite under argon and the Celite was rinsed with CH_2Cl_2 (30 mL). After evaporation of the solvents, the oily residue was purified by flash chromatography (pentane/Et_2O/CH_2Cl_2 66:30:4) to give a yellow solid (0.21 g, R_f = 0.27 [pentane/Et_2O 2:1]), which was then dissolved in formic acid (5 mL). Pd/C (40 mg, 0.36 μmol, 10%) was added and the mixture was stirred for 2 h at ambient temperature. The suspension was filtered and the filtrate was concentrated under reduced pressure. After purification by flash chromatography (pentane/Et_2O/CH_2Cl_2 50:47:3) **13** was obtained as a colorless solid (114 mg, 27%). R_f = 0.34 (pentane/Et_2O 1:1) [CAM]; m.p. 180°C; $[\alpha]_D^{20}$ = 187.3 (*c* = 0.45 in $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 0.87–0.93 (m, 1H), 0.91 (d, ^3J = 6.0 Hz, 3H), 0.99 (s, 3H), 1.04 (s, 3H), 1.08.1.15 (m, 1H), 1.25–1.36 (m, 2H), 1.62–1.81 (m, 2H), 1.90–1.96 (m, 1H), 2.45–2.53 (m, 1H), 4.37 (br s, 1H), 4.40–4.48 (m, 1H), 7.35–7.42 (m, 3H), 7.59–7.65 ppm (m, 2H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 20.0 (q), 22.1 (q), 24.9 (q), 25.4 (t), 27.9 (d), 32.7 (t), 35.6 (t), 46.5 (d), 58.1 (d), 61.8 (s), 127.6 (d), 128.5 (d), 130.0 (d), 136.8 (s), 174.0 ppm (s); IR (ATR): $\tilde{\nu}$ = 3261 (w), 2958 (w), 1614 (s), 1576 (m), 1449 (m), 1392 (m), 1375 (m), 1368 (m), 1354 (m), 1338 (m), 711 (s), 690 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 272 (30) [M^+], 257 (10), 167 (100), 105 (60), 77 (20), 58 (30); HRMS (EI): *m*/*z*: calcd for $C_{17}H_{24}N_2O$: 272.1889 [M^+]; found: 272.1890.

4-Nitro-3-phenylpentanal (15): *Iminium ion catalysis:* Cinnamaldehyde (63 mL, 66 mg, 0.50 mmol) was dissolved in nitroethane (0.14 mL, 0.15 g, 2.0 mmol, 4.0 equiv) followed by the addition of catalyst **7**. The mixture was stirred at the indicated temperature and for the indicated period of time in an argon atmosphere. After evaporation of residual nitroethane under reduced pressure and purification of the residue by flash chromatography (pentane/Et_2O 3:2) diastereomers *anti*-**15** and *syn*-**15** were obtained as colorless oils. *anti*-**15**: R_f = 0.47 (pentane/Et_2O 1:1) [CAM]; $[\alpha]_D^{20}$ = 8.9 (*c* = 0.69 in $CHCl_3$, 68% *ee*); *ee* values were determined by GC (HP, 2,3-dimethyl-6-TBDMS-β-cyclodextrin), 33.6 and 34.1 min (60 → 140°C [5°C min^{-1}]); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.53 (d, ^3J = 6.8 Hz, 3H), 2.95–3.03 (m, 2H), 3.82 (td, ^3J = 8.2, ^3J = 6.8 Hz, 1H), 4.87 (quin, ^3J = 6.8 Hz, 1H), 7.16–7.19 (m, 2H), 7.27–7.35 (m, 3H), 9.68 ppm (t, ^3J = 1.1 Hz, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 16.7 (q), 43.5 (d), 44.8 (t), 86.3 (d), 127.9 (d), 128.0 (d), 128.8 (d), 137.3 (s), 198.9 ppm (s). *syn*-**15**: R_f = 0.42 (pentane/Et_2O 1:1) [CAM]; *ee* values were determined by GC (HP, 2,3-dimethyl-6-TBDMS-β-cyclodextrin), 30.9 and 31.2 min (60 → 140°C [5°C min^{-1}]); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 1.34 (d, ^3J = 6.7 Hz, 3H), 2.75 (ddd, ^2J = 17.4, ^3J = 4.3 Hz, ^3J = 0.9 Hz, 1H), 2.97 (ddd, ^2J = 17.4, ^3J = 9.8, ^3J = 1.9 Hz, 1H), 3.75 (td, ^3J = 9.8, ^3J = 4.3 Hz, 1H), 4.78 (dq, ^3J = 9.8, ^3J = 6.7 Hz, 1H), 7.18–7.22 (m, 2H), 7.29–7.38 (m, 3H), 9.56 ppm (dd, ^3J = 1.9, ^3J = 0.9 Hz, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$): δ = 17.7 (q), 44.2 (d), 46.4 (t), 87.1 (d), 128.1 (d), 128.2 (d), 129.2 (d), 137.5 (s), 198.6 ppm (s).

Methyl phenyl sulfoxide (18): *Aerobic oxidation of sulfide* **17** *to* **18** *mediated by* **7a**: Sulfide **17** (62 μL, 59 mg, 0.5 mmol) was dissolved in $CDCl_3$ (0.5 mL) and treated with octahydroindazole **7a** (104 mg, 0.5 mmol, 1.0 equiv) and hexafluoroisopropanol (53 μL, 84 mg, 0.5 mmol,

1.0 equiv). The mixture was stirred under an atmosphere of oxygen for 14 d at ambient temperature. The solvent was removed under reduced pressure and the oily residue purified by flash chromatography (EtOAc) yielding **18** (50 mg, 0.36 mmol, 71 %) as a colorless oil, which was in analytical data identical to the previously described compound.[28] Chiral HPLC analysis (Daicel Chiralcel AS-H, isopropanol/hexane = 7:3) revealed the product to be completely racemic.

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