Catalytic Asymmetric 6π-Electrocyclization: Accessing Highly Substituted Optically Active 2-Pyrazolines via Diastereoselective Alkylations

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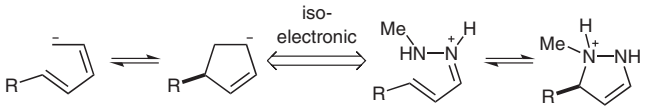
Dedicated to Professor R. Huisgen with admiration

Abstract: The chiral phosphoric acid catalyzed asymmetric electrocyclization of α,β-unsaturated hydrazones has been studied. This reaction is one of the first catalytic asymmetric 6π-electrocyclizations reported, and enables the synthesis of 2-pyrazolines in high yields and enantiomeric ratios. The obtained products are not only interesting because of their pharmaceutical properties, but can be manipulated in highly diastereoselective fashion, as shown for alkylation reactions. Thus, the combination of catalytic asymmetric 6π-electrocyclization followed by diastereoselective alkylation can provide interesting synthetic building blocks in optically active form.

Key words: electrocyclic reactions, enantioselective organocatalysis, heterocycles, diastereoselectivity, 2-pyrazolines

Electrocyclizations, cycloadditions, and sigmatropic rearrangements are the most prominent classes of pericyclic reactions. Due to their synthetic utility, these reactions have become very popular in synthetic organic chemistry and the development of catalytic asymmetric versions has been a logical consequence. Compared to cycloadditions[1] and sigmatropic rearrangements,[2] which are now well established in asymmetric catalysis, electrocyclizations remain largely unexplored in this respect. The first reports of catalytic asymmetric electrocyclization reactions date back to 2003, when the groups of Trauner and Aggarwal reported enantioselective Nazarov-4π-electrocyclizations catalyzed by chiral Lewis acids.[3] While other groups in the following years have also addressed the same problem,[4] corresponding catalytic asymmetric 6π-electrocyclizations have remained elusive.[5] Only recently, our group[6] and the group of Smith[7] independently reported the first catalytic asymmetric 6π-electrocyclizations. While Smith and co-workers employed asymmetric phase transfer catalysis to the cyclization of *ortho*-substituted benzaldimines, we were focusing on the 6π-electrocyclization of α,β-unsaturated hydrazones.[8]

Stimulated by a related project in our group, we became interested in the rearrangement of α,β-unsaturated hydrazones into the corresponding 2-pyrazolines. This reaction was originally discovered by E. Fischer[9] and is known to be acid catalyzed. Considering a protonated hydrazonium ion as the reactive species, we recognized the isoelectronic relationship between this process and the 6π-electrocyclization of the pentadienyl anion (Scheme 1). Interestingly, it turns out that our reasoning was not entirely new and that Huisgen had discussed this analogy 20 years earlier.[10]



Scheme 1 Isoelectronic 6π-electrocyclizations

In light of its cationic nature, we wondered whether or not it was possible to control the stereochemical outcome of this reaction with a chiral counteranion. Although examples of Fischer's pyrazoline synthesis employing substoichiometric amounts of acid are rare, we hypothesized that chiral phosphoric acids could possibly mediate the desired transformation.[11] Indeed, these catalysts turned out to smoothly promote the cycloisomerization of benzylideneacetone-derived phenylhydrazone **1a** to give pyrazoline **2a** in good yields and promising enantioselectivities. After intensive screenings, we identified the BINOL-derived phosphoric acid **3** (10 mol%), bearing 9-anthracenyl substituents in the 3,3′-positions, as the optimal catalyst. During further optimization of solvent, concentration, and temperature, we developed a fairly general method for the catalytic asymmetric 6π-electrocyclization of α,β-unsaturated hydrazones giving the desired products in high yields and optical purity (Table 1).

When carrying out the reaction in the presence of **3** (10 mol%) at 30 °C in chlorobenzene, 3-methyl-1,5-diphenyl-2-pyrazoline (**2a**) was obtained with 92% yield and 88:12 enantiomeric ratio (Table 1, entry 1). Different substituents on the aromatic ring in the 5-position, either of electron-withdrawing (entries 2–5) or electron-donating nature (entry 6), were well tolerated, giving the desired products with up to 98:2 enantiomeric ratio (entry 5). Furthermore, pyrazoline **2g**, the 3-methyl-analogue of the COX2-inhibitor (*S*)-(–)-E-6244,[12] was obtained with similarly good yield and enantiomeric excess.

We also developed a direct method for the synthesis of optically active 2-pyrazolines starting from α,β-unsaturated ketones **4** and phenylhydrazine (**5**; Scheme 2). When a mixture of **4** and **5** was stirred in chlorobenzene at 50 °C in the presence of 4 Å molecular sieves, the corresponding

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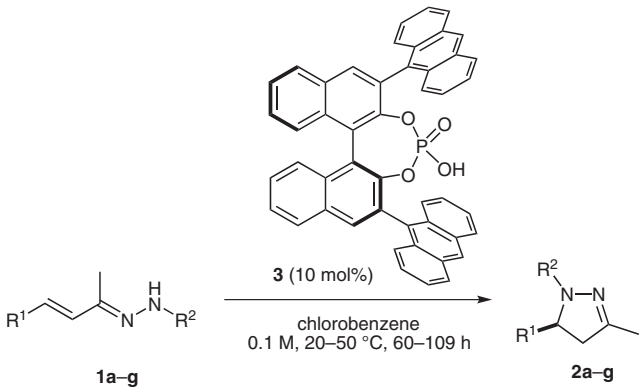
Table 1 Substrate Scope of the Catalytic Asymmetric 6π-Electrocyclization of α,β-Unsaturated Arylhydrazones[a]



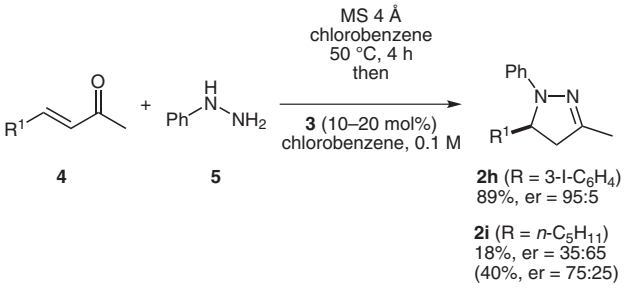
Entry	Product	R^1	R^2	Yield (%)[b]	er[c]
1	**2a**	Ph	Ph	92	88:12
2	**2b**	4-BrC_6H_4	Ph	95	95:5
3	**2c**	3-BrC_6H_4	Ph	95	96:4
4	**2d**	4-$F_3CC_6H_4$	Ph	88	96:4
5	**2e**	3-$O_2NC_6H_4$	Ph	99	98:2
6	**2f**	3,4-(OCH_2O)-C_6H_3	Ph	85	93:7
7	**2g**	4-$MeSO_2C_6H_4$	4-FC_6H_4	88	88:12

[a] Unless otherwise stated, the reactions were performed under an Ar atmosphere with hydrazones **1a–g** (0.10 mmol) and phosphoric acid **3** (10 mol%) in chlorobenzene (1.0 mL).
[b] Isolated yield.
[c] Determined by HPLC analysis on chiral stationary phase (the absolute configuration of **2c** was determined by X-ray structure analysis.[6]

phenylhydrazones were formed readily. After simple removal of the drying agent by filtration and addition of the catalyst, these intermediates underwent the cyclization well, as in the previous case. Thus, pyrazoline **2h** was obtained in 89% yield and 95:5 er. Furthermore, this protocol now also allowed the use of aliphatic enones. Previously, the corresponding aliphatic hydrazones had been more difficult to obtain in pure form compared to their aromatic counterparts. Although these substrates required higher catalyst loadings (20 mol%) and only low yields and enantioselectivities were obtained when phosphoric acid **3** was used as the catalyst, the corresponding *N*-triflyl-phosphoramide (20 mol%), albeit giving lower enantioselectivities in the case of aromatic substrates, turned out to improve both yields (40%) and optical purity (75:25 er). These results clearly demonstrate the potential of our new reaction to develop into a broadly applicable synthetic methodology.

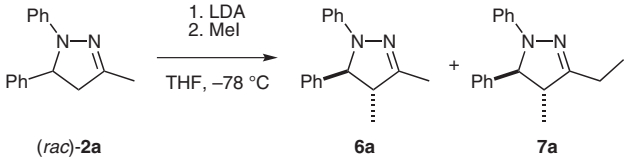
Besides a broad interest in pyrazolines due to their manifold biological activities,[13] the use of pyrazolines as synthetic building blocks is of high importance and interest due to the high diastereoselectivities usually observed in derivatization reactions.[14] To the best of our knowledge, no derivatizations of the 3-methyl-1,5-diarylpyrazolines obtained herein (except their oxidation to give the corresponding pyrazoles) have been reported so far. This fact, and the new opportunity to obtain pyrazolines **2** in optically active form, triggered our interest in possible further transformations. In particular, the substructure of a masked 1,3-diamine and the presence of five potentially acidic protons, which allows modifications of the pyrazoline core as well as the side chain in the 3-position, prompted us to investigate the follow-up chemistry of our products more closely.

When we treated a racemic sample of **2a** at –78 °C with lithium diisopropylamide followed by the addition of iodomethane, to our surprise, we found that rather than the 3-methyl group, the C-4-methylene unit inside the pyrazoline ring was alkylated under these conditions (Scheme 3). Remarkably, the methylated product **6a** was obtained as a single diastereoisomer (according to ^1H



Scheme 2 Phosphoric acid **3** catalyzed synthesis of optically active 2-pyrazolines from enones **4** and phenylhydrazine (**5**)

NMR analysis). Based on the ^{1}H NMR analysis and by comparison with literature data,[15] we were able to assign our new product as *trans*-3,4-dimethyl-1,5-diphenylpyrazoline (**6a**). We also obtained a byproduct that differed from **6a** by the presence of an additional methyl group and was identified as pyrazoline **7a**, resulting from the double methylation of **2a**. It is noteworthy, that heterocycle **7a** was also obtained as a single diastereoisomer (according to ^{1}H NMR analysis).

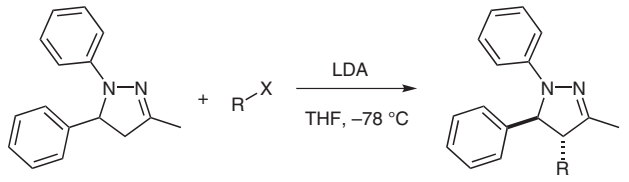


Scheme 3 Methylation of product **2a**

We found that **2a** is readily alkylated by a variety of alkylating agents and that products **6** were obtained in satisfactory yields with perfect diastereocontrol (Table 2).

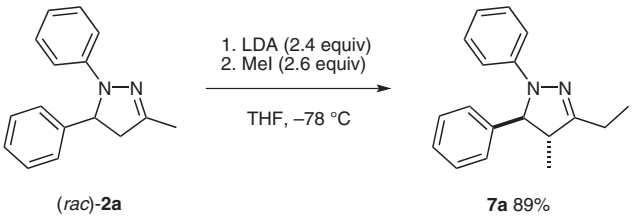
The scope of alkylating agents includes primary alkyl halides, allyl halides, benzyl halides, chloromethoxymethylether, and even secondary alkyl halides, although in the latter case **6e** was obtained in a slightly reduced yield.

Table 2 Highly Diastereoselective Alkylations of Pyrazoline **2a**



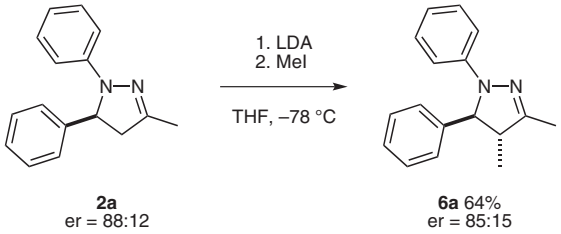
Entry	Product	R	X	Yield (%)
1	**6a**	Me	I	66
2	**6b**	allyl	Br	61
3	**6c**	Bn	Br	60
4	**6d**	CH_2OCH_3	Cl	60
5	**6e**	*i*-Pr	I	43

Since the only significant byproducts of the alkylation reactions were the doubly alkylated products **7**, this observation prompted us to modify the reaction conditions such that **7a** could be obtained as the major product. Indeed, when we used 2.4 equivalents of lithium diisopropylamide and an excess of iodomethane, the two carbon–carbon bond-forming reactions, namely the diastereoselective methylation of the pyrazoline core and the side chain homologization, could be performed in one step. Accordingly, **7a** was obtained in 89% yield, again as a single diastereoisomer (Scheme 4).



Scheme 4 Double alkylation of **2a**

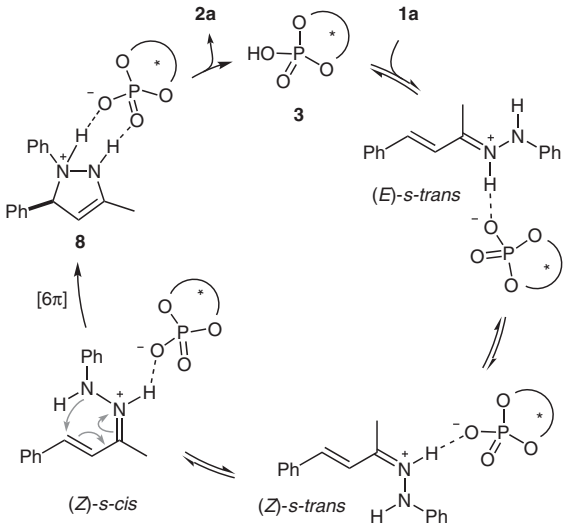
We also submitted an enantiomerically enriched sample of **2a** to the methylation conditions. Although deprotonation of the pyrazoline at C-4 could cause racemization by reversible intramolecular elimination, we were pleased to find that the enantiomeric ratio of **2a** dropped only slightly and the desired product **6a** was obtained with 64% yield (Scheme 5).



Scheme 5 Methylation of optically active 2-pyrazoline **2a**

The enantioselective cycloisomerization of α,β-unsaturated hydrazones thus turned out to be a powerful tool to access optically active 2-pyrazolines, which are not only interesting due to their pharmaceutical properties, but can undergo further highly diastereoselective transformations and as such serve as potentially useful synthetic building blocks.

Mechanistically, we assume the electrocyclization occurs as shown in Scheme 6. Hydrazone **1a** was obtained as a single isomer and X-ray structure analysis unambiguously proved that the compound had an *E*-configured carbon–nitrogen double bond.[6] To attain the reactive (*Z*)-*s*-*cis*-conformation, rotation around the carbon–carbon single bond, as well as isomerization of the carbon–nitrogen double bond has to occur. While the *s*-*trans*- to *s*-*cis*-isomerization should readily proceed at room temperature in solution, the carbon–nitrogen double bond isomerization requires acid catalysis or elevated temperatures. Indeed, we were able to show through HPLC analysis that a solution of **1a** in chlorobenzene contains exclusively the *E*-isomer, whereas after addition of the catalyst a second species, most likely the *Z*-isomer, is formed, which disappears again in the course of the reaction while the product is formed. After this isomerization process, the hydrazonium ion – the cation of the chiral hydrogen-bonding-assisted ion pair – can undergo the 6π-electrocyclization. 3-Pyrazoline **8** obtained after the cyclization subsequently isomerizes to give the thermodynamically favored 2-pyrazoline **2a** and releases the catalyst **3**.



Scheme 6 Plausible catalytic cycle

Although the need for the carbon–nitrogen double bond isomerization prior to the cyclization, as well as the formation of the thermodynamically favored 2-pyrazoline after the carbon–nitrogen bond-forming step are clear, one might argue about the key step of this mechanistic proposal: the 6π-electrocyclization. Can the ring-closure not also be described by a different mechanism? Huisgen already raised this question in 1980 and came up with a simple answer: '*Cannot the formation of pyrazolines also be classified as a nucleophilic addition of the NH_2 group* […] *to the electrophilic α,β-unsaturated imine? This is an alternative description of one and the same process, differing only in the choice of words and not in its meaning from that given above. Like the electrocyclization of* [the cyclopentadienyl anion]*, that of* [an α,β-unsaturated hydrazone] *requires the two 90° rotations about the axes of the terminal bonds*'.[10] But are these reaction modes really identical? In principle, we could imagine different transition states for both scenarios (Figure 1). In the case of a pericyclic 6π-electrocyclization, both ends of the conjugated π-electron system fulfill a rotation in disrotatory fashion, whereas in the case of the nucleophilic attack the nitrogen lone pair would interact with the LUMO of the conjugated carbon–carbon double bond in a Michael addition like mechanism.

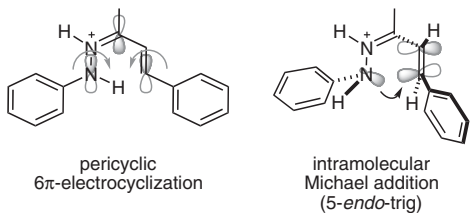


Figure 1 Two possible mechanistic scenarios

From the perspective of the synthetic chemist, the result is the same for both cases, because the structure of the substrates and products do not allow any conclusions concerning a possible torquoselectivity of the electrocyclization. In fact, depending on the mechanism, one could expect to obtain the 1,5-*cis*-configured product for the electrocyclization for steric reasons, whereas the nucleophilic addition should favor the corresponding *trans*-product. But, due to the configurational lability of the N-stereocenter, the outcome of the reaction is the same for both. However, the isoelectronicity mentioned above, and the fact that a nucleophilic addition would involve a 5-*endo*-trig cyclization, which is a disfavored process according to Baldwin's rules, point towards the electrocyclic mechanism. The true mechanism may well turn out to be something between these two descriptions and theoretical studies are clearly needed to gain clarity.

In summary, we have demonstrated that the catalytic asymmetric 6π-electrocyclization of α,β-unsaturated hydrazones is a powerful tool for the synthesis of 2-pyrazolines in high yields and enantioselectivites. Furthermore, it was shown that the 2-pyrazolines obtained undergo highly diastereoselective alkylation reactions with a broad variety of different alkylating reagents. These transformations allow both the modification of the pyrazoline core and the side chain in the 3-position and thus enable the creation of molecular diversity from readily available, optically active starting materials. The exploration of other types of diastereoselective transformations such as aldol- or Mannich-type reactions is the subject of future research.

Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. Phenylhydrazine was distilled prior to use. All solvents employed were distilled from appropriate drying agents prior to use. Column chromatography was performed on Merck silica gel 60 (particle size 0.040–0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AV-400 or AV-500 spectrometer at ambient temperature. Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (TMS), using the solvent resonance as internal standard. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad, coupling constants are given in hertz (Hz). Mass spectra were recorded using a Finnigan MAT 8200 at 70 eV in the EI mode. High-resolution mass spectra were determined using a Bruker APEX III FTMS (7 T magnet). Optical purity (er, ee) were measured by HPLC analysis on a chiral stationary phase, exact conditions are reported for each compound separately.

Preparation of Hydrazones 1a–g

Prepared from the corresponding enones and phenylhydrazines or their hydrochlorides following modified literature procedures.[16]

Cyclization of Hydrazones; General Procedure A

Hydrazone **1a–g** (0.10 mmol) and catalyst **3** (7.0 mg, 0.01 mmol) were placed in a reaction vial under Ar and dissolved in anhydrous chlorobenzene (1 mL). The mixture was stirred at 30 °C (unless otherwise stated) until the starting material was completely consumed (reaction monitored by TLC). After cooling to ambient temperature, the mixture was directly submitted to flash chromatography on silica gel to obtain pure **2a–g**.

(*S*)-3-Methyl-1,5-diphenyl-4,5-dihydro-1*H*-pyrazole (2a)

Following general procedure A, the product **2a** was obtained after column chromatography (hexane–EtOAc, 9:1).

Yield: 21.7 mg (92%); white solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.35–7.30 (m, 4 H), 7.27 (m, 1 H), 7.14 (dd, *J* = 7.9, 7.3 Hz, 2 H), 6.92 (d, *J* = 7.9 Hz, 2 H), 6.74 (t, *J* = 7.3 Hz, 1 H), 5.01 (dd, *J* = 11.9, 8.1 Hz, 1 H), 3.42 (dd, *J* = 17.5, 11.9 Hz, 1 H), 2.73 (dd, *J* = 17.5, 8.1 Hz, 1 H), 2.07 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.7, 146.2, 143.1, 129.2, 129.0, 127.5, 126.0, 118.8, 113.2, 64.9, 48.0, 16.1.

MS (EI, 70 eV): *m*/*z* (%) = 236 (100) $[M]^+$, 159 (67) $[M - C_6H_5]^+$.

HRMS (EI-MS): *m*/*z* calcd for $C_{16}H_{16}N_2$: 236.131348; found: 236.131539.

The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralcel OD-H column: *n*-heptane–*i*-PrOH, 90:10; flow rate: 0.5 mL/min; λ = 254 nm: major enantiomer t_R = 10.68 min, minor enantiomer t_R = 13.68 min.

(*S*)-5-(4-Bromophenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazole (2b)

Following general procedure A, the product **2b** was obtained after column chromatography (hexane–EtOAc, 6:1).

Yield: 30.0 mg (95%); yellowish solid.

^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 7.47 (d, *J* = 8.4 Hz, 2 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 7.11 (dd, *J* = 8.1, 7.3 Hz, 2 H), 6.86 (d, *J* = 8.1 Hz, 2 H), 6.72 (t, *J* = 7.3 Hz, 1 H), 4.99 (dd, *J* = 12.0, 7.9 Hz, 1 H), 3.43 (dd, *J* = 17.4, 12.0 Hz, 1 H), 2.67 (dd, *J* = 17.4, 7.9 Hz, 1 H), 2.05 (s, 3 H).

^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 149.0, 146.3, 142.7, 132.4, 129.2, 128.2, 121.3, 118.9, 113.3, 64.4, 47.9, 15.9.

MS (EI, 70 eV): *m*/*z* (%) = 316/314 (69/74) $[M]^+$, 159 (68) $[M - C_6H_4Br]^+$, 91 (100).

HRMS (EI-MS): *m*/*z* calcd for $C_{16}H_{15}N_2Br$: 314.041875; found: 314.041608.

The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralcel OD-H column: *n*-heptane–*i*-PrOH, 90:10; flow rate: 0.5 mL/min; λ = 254 nm: major enantiomer t_R = 10.83 min, minor enantiomer t_R = 13.31 min.

(*S*)-5-(3-Bromophenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazole (2c)

Following general procedure A, the product **2c** was obtained after column chromatography (hexane–EtOAc, 9:1).

Yield: 30.0 mg (95%); yellowish solid.

^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 7.48 (br s, 1 H), 7.42–7.40 (m, 1 H), 7.26–7.21 (m, 2 H), 7.13 (dd, *J* = 8.2, 7.3 Hz, 2 H), 6.88 (d, *J* = 8.2 Hz, 2 H), 6.73 (t, *J* = 7.3 Hz, 1 H), 4.98 (dd, *J* = 12.0, 7.9 Hz, 1 H), 3.43 (dd, *J* = 17.6, 12.0 Hz, 1 H), 2.69 (dd, *J* = 17.6, 7.9 Hz, 1 H), 2.05 (s, 3 H).

^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 149.0, 146.3, 146.1, 131.0, 130.8, 129.3, 129.2, 125.1, 123.3, 119.0, 113.3, 64.5, 48.0, 15.9.

MS (EI, 70 eV): *m*/*z* (%) = 316/314 (56/58) $[M]^+$, 159 (100) $[M - C_6H_4Br]^+$.

HRMS (ESI-MS): *m*/*z* calcd for $C_{16}H_{15}N_2NaBr^+$: 337.031089; found: 337.031150.

The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralcel OD-H column: *n*-heptane–*i*-PrOH, 90:10; flow rate: 0.5 mL/min; λ = 254 nm: major enantiomer t_R = 10.90 min, minor enantiomer t_R = 14.52 min.

(*S*)-3-Methyl-1-phenyl-5-[4-(trifluoromethyl)phenyl]-4,5-dihydro-1*H*-pyrazole (2d)

Following general procedure A (reaction time: 9 d), the product **2d** was obtained after column chromatography (hexane–EtOAc, 6:1).

Yield: 26.9 mg (88%); white solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.60 (d, *J* = 8.1 Hz, 2 H), 7.43 (d, *J* = 8.1 Hz, 2 H), 7.16 (dd, *J* = 8.4, 7.3 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 6.77 (t, *J* = 7.3 Hz, 1 H), 5.07 (dd, *J* = 12.0, 8.0 Hz, 1 H), 3.45 (dd, *J* = 17.5, 12.0 Hz, 1 H), 2.70 (dd, *J* = 17.5, 8.0 Hz, 1 H), 2.08 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 148.6, 147.1, 145.9, 130.0, 129.8, 129.1, 126.5, 126.2, 119.2, 113.2, 64.5, 47.7, 16.0.

MS (EI, 70 eV): *m*/*z* (%) = 304 (100) $[M]^+$, 159 (64) $[M - C_6H_4CF_3]^+$.

HRMS (ESI-MS): *m*/*z* calcd for $C_{17}H_{16}N_2F_3^+$: 305.126011; found: 305.126003.

The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralcel OD-H column: *n*-heptane–*i*-PrOH, 90:10; flow rate: 0.5 mL/min; λ = 254 nm: major enantiomer t_R = 9.62 min, minor enantiomer t_R = 13.18 min.

(*S*)-3-Methyl-5-(3-nitrophenyl)-1-phenyl-4,5-dihydro-1*H*-pyrazole (2e)

Following general procedure A (reaction temperature: 40 °C), the product **2e** was obtained after column chromatography (hexane–EtOAc, 4:1).

Yield: 28.0 mg (99%); orange oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.20 (dd, *J* = 1.7, 1.7 Hz, 1 H), 8.13 (dd, *J* = 8.1, 1.7 Hz, 1 H), 7.65 (d, *J* = 7.7 Hz, 1 H), 7.51 (dd, *J* = 8.1, 7.7 Hz, 1 H), 7.16 (dd, *J* = 7.9, 7.3 Hz, 2 H), 6.88 (d, *J* = 7.9 Hz, 2 H), 6.78 (t, *J* = 7.3 Hz, 1 H), 5.12 (dd, *J* = 12.0, 8.0 Hz, 1 H), 3.49 (dd, *J* = 17.5, 12.0 Hz, 1 H), 2.72 (dd, *J* = 17.5, 8.0 Hz, 1 H), 2.09 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 149.0, 148.6, 145.7, 145.4, 132.3, 130.4, 129.2, 122.8, 121.3, 119.5, 113.3, 64.3, 47.8, 16.0.

MS (EI, 70 eV): *m*/*z* (%) = 281 (100) $[M]^+$, 159 (67) $[M - C_6H_4NO_2]^+$.

HRMS (EI-MS): *m*/*z* calcd for $C_{16}H_{15}N_3O_2$: 281.116424; found: 281.116163.

The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralcel OD-H column: *n*-heptane–*i*-PrOH, 90:10; flow rate: 0.5 mL/min; λ = 254 nm: major enantiomer t_R = 27.20 min, minor enantiomer t_R = 31.92 min.

(*S*)-5-(Benzo[d][1,3]dioxol-5-yl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazole (2f)

Following general procedure A (reaction temperature: 20 °C), the product **2f** was obtained after column chromatography (hexane–EtOAc, 6:1).

Yield: 23.9 mg (85%); white solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.15 (dd, *J* = 8.5, 7.4 Hz, 2 H), 6.94 (d, *J* = 8.5 Hz, 2 H), 6.79–6.73 (m, 4 H), 5.94–5.92 (m, 2 H), 4.92 (dd, *J* = 11.9, 8.1 Hz, 1 H), 3.67 (dd, *J* = 17.5, 11.9 Hz, 1 H), 2.69 (dd, *J* = 17.5, 8.1 Hz, 1 H), 2.06 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 148.6, 148.4, 147.0, 146.1, 137.2, 129.0, 119.2, 118.8, 113.2, 108.7, 106.4, 101.2, 64.7, 48.0, 16.1.

MS (EI, 70 eV): *m*/*z* (%) = 280 (100) $[M]^+$, 159 (38) $[M - C_7H_5O_2]^+$.

HRMS (EI-MS): *m*/*z* calcd for $C_{17}H_{16}N_2O_2$: 280.121178; found: 280.120995.

The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralcel OD-H column: *n*-heptane–*i*-PrOH, 95:05; flow rate: 0.5 mL/min; λ = 254 nm: major enantiomer t_R = 21.34 min, minor enantiomer t_R = 22.84 min.

(*S*)-1-(4-Fluorophenyl)-3-methyl-5-[4-(methylsulfonyl)phenyl]-4,5-dihydro-1*H*-pyrazole (2g)

Following general procedure A (reaction temperature: 50 °C), the product **2g** was obtained after column chromatography (hexane–EtOAc, 1:1).

Yield: 29.3 mg (88%); yellow solid.

^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 7.89 (d, *J* = 8.0 Hz, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 6.87–6.80 (m, 4 H), 5.03 (dd, *J* = 11.8, 8.7 Hz, 1 H), 3.47 (dd, *J* = 17.5, 11.8 Hz, 1 H), 3.03 (s, 3 H), 2.70 (dd, *J* = 17.5, 8.5 Hz, 1 H), 2.05 (s, 3 H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 158.0, 156.1, 149.5, 149.4, 143.1, 140.3, 128.5, 127.5, 115.7, 115.5, 114.6, 114.6, 65.3, 48.1, 44.7, 15.8.

MS (EI, 70 eV): *m*/*z* (%) = 332 (100) $[M]^+$, 177 (49) $[M - C_7H_7O_2S]^+$.

HRMS (ESI-MS): *m*/*z* calcd for $C_{17}H_{17}N_2O_2FSNa^+$: 355.088698; found: 355.088461.

The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralcel OD-3 column: *n*-heptane–*i*-PrOH, 70:30; flow rate: 0.5 mL/min; λ = 254 nm: minor enantiomer t_R = 15.67 min, major enantiomer t_R = 16.69 min.

Reaction of α,β-Unsaturated Ketones 4 and Phenylhydrazine (5); General Procedure B

The enones **4** (0.105 mmol in case of aromatic enones, 0.110 mmol in case of aliphatic enones) and molecular sieves 4 Å (30 mg) were placed in a reaction vial under argon and suspended in a stock solution of phenylhydrazine (**5**; 0.2 M in chlorobenzene, 0.5 mL). After stirring for 4 h at 50 °C, the cold mixture was filtered into a reaction vial containing **3** (10 mol% in case of aromatic enones, 20 mol% in case of aliphatic enones). The filtrate was washed with additional chlorobenzene (0.5 mL) and the resulting mixture was stirred at the given temperature until complete conversion (reaction monitored by TLC). After cooling to ambient temperature, the mixture was directly submitted to flash chromatography on silica gel to obtain the pure pyrazolines.

(*S*)-5-(3-Iodophenyl)-3-methyl-1-phenyl-4,5-dihydro-1*H*-pyrazole (2h)

Following general procedure B (reaction temperature: 40 °C), the product **2h** was obtained after column chromatography (hexane–EtOAc, 9:1).

Yield: 32.3 mg (89%); yellow solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.68 (s, 1 H), 7.60 (d, *J* = 7.8 Hz, 1 H), 7.27 (d, *J* = 7.8 Hz, 1 H), 7.16 (dd, *J* = 8.1, 7.6 Hz, 2 H), 7.06 (dd, *J* = 7.8, 7.8 Hz, 1 H), 6.90 (d, *J* = 8.1 Hz, 2 H), 6.77 (t, *J* = 7.3 Hz, 1 H), 4.92 (dd, *J* = 11.9, 8.2 Hz, 1 H), 3.41 (dd, *J* = 17.6, 11.9 Hz, 1 H), 2.70 (dd, *J* = 17.6, 8.2 Hz, 1 H), 2.07 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 148.6, 146.1, 145.7, 136.7, 135.0, 131.0, 129.1, 125.3, 119.1, 113.3, 95.1, 64.4, 47.9, 16.0.

MS (EI, 70 eV): *m*/*z* (%) = 362 (100) $[M]^+$, 159 (68) $[M - C_6H_4I]^+$.

HRMS (ESI-MS): *m*/*z* calcd for $C_{16}H_{15}N_2INa^+$: 385.017217; found: 385.017255.

The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralcel OD-H column: *n*-heptane–*i*-PrOH, 90:10; flow rate: 0.5 mL/min; λ = 254 nm: major enantiomer t_R = 11.23 min, minor enantiomer t_R = 14.39 min.

(*R*)-3-Methyl-5-pentyl-1-phenyl-4,5-dihydro-1*H*-pyrazole (2i)

Following general procedure B (reaction temperature: 50 °C, *N*-triflyl-phosphoramide of **3** was used as catalyst), the product **2i** was obtained after column chromatography (hexane–EtOAc, 30:1).

Yield: 9.1 mg (40%); colorless oil.

^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 7.20 (dd, *J* = 7.7, 7.6 Hz, 2 H), 6.96 (d, *J* = 8.3 Hz, 2 H), 6.73 (t, *J* = 7.2 Hz, 1 H), 4.10–4.06 (m, 1 H), 3.03 (dd, *J* = 17.3, 11.0 Hz, 1 H), 2.54 (dd, *J* = 17.3, 5.6 Hz, 1 H), 2.02 (s, 3 H), 1.81–1.74 (m, 1 H), 1.47–1.40 (m, 1 H), 1.31 (br m, 6 H), 0.89 (t, *J* = 6.1 Hz, 3 H).

^{13}C NMR (CD_2Cl_2, 100 MHz): δ = 149.8, 146.2, 129.3, 118.2, 113.1, 60.3, 42.9, 33.1, 32.1, 25.2, 23.0, 16.1, 14.1.

MS (EI, 70 eV): *m*/*z* (%) = 230 (23) $[M]^+$, 159 (100) $[M - C_5H_{11}]^+$.

HRMS (ESI-MS): *m*/*z* calcd for $C_{15}H_{22}N_2Na^+$: 253.167519; found: 253.167351.

The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralcel OD-H column: *n*-heptane–*i*-PrOH, 95:5; flow rate: 0.5 mL/min; λ = 254 nm: major enantiomer t_R = 10.69 min, minor enantiomer t_R = 12.82 min.

(4*R*,5*S*)-3,4-Dimethyl-1,5-diphenyl-4,5-dihydro-1*H*-pyrazole (6a)

A solution of (*S*)-**2a** (100 mg, 0.423 mmol, er = 88:12) in THF (1 mL) was added dropwise to a solution of LDA [freshly prepared from *n*-BuLi (300 μL, 0.75 mmol, 2.5 M in hexanes) and diisopropylamine (100 μL, 0.712 mmol) in THF (4 mL)] at –78 °C. The resulting red solution was stirred at –78 °C for 1 h before MeI (40 μL, 0.635 mmol) was added. After stirring at –78 °C for 3 h, the mixture was quenched by addition of brine (2 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and, after evaporation of the solvent, the residue was purified by column chromatography on silica gel (hexane–EtOAc, 50:1) to give **6a**.

Yield: 67.7 mg (64%); white solid.

^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 7.39–7.34 (m, 4 H), 7.31–7.28 (m, 1 H), 7.13–7.09 (m, 2 H), 6.91 (dd, *J* = 8.7, 0.9 Hz, 2 H), 6.72 (t, *J* = 7.3 Hz, 1 H), 4.43 (d, *J* = 8.9 Hz, 1 H), 2.91 (m, 1 H), 2.03 (d, *J* = 1.0 Hz, 3 H), 1.32 (d, *J* = 7.2 Hz, 3 H).

^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 153.0, 146.9, 143.1, 129.4, 129.0, 127.8, 126.2, 119.0, 113.7, 73.3, 55.2, 16.6, 13.9.

MS (EI, 70 eV): *m*/*z* (%) = 250 (100) $[M]^+$, 235 (13) $[M - CH_3]^+$, 173 (53).

HRMS (ESI-MS): *m*/*z* calcd for $C_{17}H_{18}N_2Na^+$: 273.136220; found: 273.136182.

The enantiomeric ratio was determined by HPLC analysis using a Daicel Chiralcel OD-H column: *n*-heptane–*i*-PrOH, 90:10; flow rate: 0.5 mL/min; λ = 254 nm: major enantiomer t_R = 9.31 min, minor enantiomer t_R = 10.02 min.

***trans*-4-Allyl-3-methyl-1,5-diphenyl-4,5-dihydro-1*H*-pyrazole (6b)**

Following the procedure described for the synthesis of **6a** with allylbromide as the alkylating agent, the title compound was obtained after column chromatography on silica gel (hexane–EtOAc, 50:1).

Yield: 70.9 mg (61%); white solid.

^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 7.36–7.33 (m, 2 H), 7.28–7.27 (m, 3 H), 7.12 (dd, *J* = 8.1, 7.2 Hz, 2 H), 6.89 (d, *J* = 8.1 Hz, 2 H), 6.70 (t, *J* = 7.2 Hz, 1 H), 5.79–5.74 (m, 1 H), 5.25–5.19 (m, 2 H), 4.72 (d, *J* = 6.6 Hz, 1 H), 3.02–2.99 (m, 1 H), 2.57–2.52 (m, 1 H), 2.42–2.36 (m, 1 H), 2.06 (s, 3 H).

^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 150.5, 145.9, 143.0, 134.9, 129.3, 129.1, 127.7, 126.3, 118.5, 118.4, 113.0, 68.9, 59.7, 35.8, 14.5.

MS (EI, 70 eV): *m*/*z* (%) = 276 (40) $[M]^+$, 235 (100) $[M - CH_2CHCH_2]^+$.

HRMS (ESI-MS): *m*/*z* calcd for $C_{19}H_{20}N_2Na^+$: 299.151865; found: 299.151789.

trans-4-Benzyl-3-methyl-1,5-diphenyl-4,5-dihydro-1*H*-pyrazole (6c)

A solution of **2a** (100 mg, 0.423 mmol) in THF (1 mL) was added dropwise to a solution of LDA [freshly prepared from *n*-BuLi (200 μL, 0.50 mmol, 2.5 M in hexanes) and diisopropylamine (72 μL, 0.50 mmol) in THF (1 mL)] at –78 °C. The resulting red solution was stirred at –78 °C for 1 h before a solution of benzylbromide (100 μL, 0.846 mmol) in THF (1 mL) was added over a period of 30 min. After stirring at –78 °C for 8 h, the mixture was quenched by addition of brine (2 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and, after evaporation of the solvent, the residue was purified by column chromatography on silica gel (hexane–EtOAc, 50:1) to give **6c**.

Yield: 83.4 mg (60%); yellow oil.

^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 7.38–7.35 (m, 2 H), 7.32–7.29 (m, 1 H), 7.23 (d, *J* = 7.1 Hz, 2 H), 7.20–7.17 (m, 3 H), 7.13–7.09 (m, 2 H), 6.85 (d, *J* = 8.0 Hz, 2 H), 6.82–6.80 (m, 2 H), 6.69 (t, *J* = 7.3 Hz, 1 H), 4.75 (d, *J* = 5.2 Hz, 1 H), 3.23–3.19 (m, 2 H), 2.74 (dd, *J* = 14.9, 11.4 Hz, 1 H), 2.08 (s, 3 H).

^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 150.5, 145.6, 142.6, 138.6, 129.7, 129.1, 129.1, 129.0, 127.5, 127.1, 126.0, 118.3, 112.7, 68.7, 61.9, 38.2, 14.7.

MS (EI, 70 eV): *m*/*z* (%) = 326 (35) $[M]^+$, 235 (100) $[M - Bn]^+$.

HRMS (ESI-MS): *m*/*z* calcd for $C_{23}H_{22}N_2Na^+$: 349.167520; found: 349.167337.

trans-4-(Methoxymethyl)-3-methyl-1,5-diphenyl-4,5-dihydro-1*H*-pyrazole (6d)

The procedure for the synthesis of **6c** was followed. After complete addition of the chloromethyl methyl ether solution, the mixture was stirred for 2 h at –78 °C and then worked up as described to give **6d** after column chromatography on silica gel (hexane–EtOAc, 20:1).

Yield: 71.4 mg (60%); white solid.

^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 7.37–7.31 (m, 4 H), 7.29–7.26 (m, 1 H), 7.11 (dd, *J* = 8.0, 7.3 Hz, 2 H), 6.88 (d, *J* = 8.0 Hz, 2 H), 6.70 (t, *J* = 7.3 Hz, 1 H), 4.82 (d, *J* = 8.0 Hz, 1 H), 3.58 (d, *J* = 5.1 Hz, 2 H), 3.38 (s, 3 H), 3.08–3.06 (m, 1 H), 2.04 (s, 3 H).

^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 149.1, 146.3, 143.2, 129.3, 129.1, 127.8, 126.3, 118.8, 113.3, 71.3, 67.9, 61.0, 59.3, 14.5.

MS (EI, 70 eV): *m*/*z* (%) = 280 (59) $[M]^+$, 235 (100) $[M - CH_2OCH_3]^+$.

HRMS (ESI-MS): *m*/*z* calcd for $C_{18}H_{20}N_2ONa^+$: 303.146778; found: 303.146534.

trans-4-Isopropyl-3-methyl-1,5-diphenyl-4,5-dihydro-1*H*-pyrazole (6e)

The procedure for the synthesis of **6c** was followed. After complete addition of the isopropyl iodide solution, the mixture was stirred for 8 h at –78 °C, then warmed up to –35 °C within 12 h and worked up as described to give **6e** after column chromatography on silica gel (hexane–EtOAc, 50:1).

Yield: 51.7 mg (43%); yellowish oil.

^{1}H NMR (CD_2Cl_2, 400 MHz): δ = 7.35–7.32 (m, 2 H), 7.27–7.24 (m, 3 H), 7.15–7.10 (m, 2 H), 6.90–6.87 (m, 2 H), 6.70–6.66 (m, 1 H), 4.78 (d, *J* = 5.2 Hz, 1 H), 2.91–2.89 (m, 1 H), 2.16–2.10 (m, 1 H), 2.06 (d, *J* = 0.8 Hz, 3 H), 1.11 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (CD_2Cl_2, 100 MHz): δ = 150.3, 145.3, 144.1, 129.3, 129.2, 127.5, 126.2, 118.1, 112.5, 66.8, 64.9, 28.6, 20.3, 17.2, 14.9.

MS (EI, 70 eV): *m*/*z* (%) = 278 (47) $[M]^+$, 235 (100) $[M - i\text{-Pr}]^+$.

HRMS (ESI-MS): *m*/*z* calcd for $C_{19}H_{22}N_2Na^+$: 301.167514; found: 301.167422.

trans-3-Ethyl-4-methyl-1,5-diphenyl-4,5-dihydro-1*H*-pyrazole (7a)

A solution of **2a** (100 mg, 0.423 mmol) in THF (1 mL) was added dropwise to solution of LDA [freshly prepared from *n*-BuLi (415 μL, 1.04 mmol, 2.5 M in hexanes) and diisopropylamine (143 μL, 1.02 mmol) in THF (4 mL)] at –78 °C. The resulting red solution was stirred at –78 °C for 1 h before MeI (35 μL, 0.55 mmol) was added. After stirring at –78 °C for 2 h, a second portion of MeI (35 μL, 0.55 mmol) was added. After stirring for an additional 5 h at –78 °C, the mixture was quenched by addition of brine (2 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over $MgSO_4$ and, after evaporation of the solvent, the residue was purified by column chromatography on silica gel (hexane–EtOAc, 50:1) to give **7a**.

Yield: 99.4 mg (89%); colorless oil.

^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 7.37–7.33 (m, 4 H), 7.30–7.27 (m, 1 H), 7.10 (dd, *J* = 8.0, 7.3 Hz, 2 H), 6.91 (d, *J* = 8.0 Hz, 2 H), 6.71 (t, *J* = 7.3 Hz, 1 H), 4.42 (d, *J* = 8.7 Hz, 1 H), 2.98–2.92 (m, 1 H), 2.49–2.40 (m, 1 H), 2.34–2.26 (m, 1 H), 1.30 (d, *J* = 7.2 Hz, 3 H), 1.21 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 157.3, 147.0, 143.1, 129.3, 129.0, 127.8, 126.2, 118.9, 113.7, 73.3, 54.0, 21.8, 16.7, 11.1.

MS (EI, 70 eV): *m*/*z* (%) = 264 (100) $[M]^+$, 249 (17) $[M - CH_3]^+$, 187 (45).

HRMS (ESI-MS): *m*/*z* calcd for $C_{18}H_{20}N_2Na^+$: 287.151864; found: 287.151826.

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