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Three-component imino Diels–Alder reaction with essential oil and seeds of anise: generation of new tetrahydroquinolines

Vladimir V. Kouznetsov,* Arnold R. Romero Bohórquez and Elena E. Stashenko

Laboratorio de Química Orgánica y Biomolecular, Escuela de Química, Universidad Industrial de Santander, A.A. 678, Bucaramanga, Colombia

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Abstract—A simple and efficient one-pot method for the synthesis of 4-anisyl-2-phenyl-1,2,3,4-tetrahydroquinoline derivatives using a three-component imino Diels–Alder cycloaddition (Povarov reaction) between anilines, benzaldehyde, and *trans*-anethole in the presence of acidic catalysts is shown. New substituted tetrahydroquinolines are reported and their direct preparation from the anise essential oil is described. Also, a simple procedure of the same tetrahydroquinolines from the anise seeds under supercritical fluid (CO_2) conditions has been reported.

Tetrahydroquinoline derivatives are an important class of natural and synthetic compounds, which have shown a wide range of biological activities, including antagonist activity on the NMDA receptor glycine site,[1] antimalarial,[2] antitumoral,[3] antioxidant,[4] and antagonist activity on the FSH receptor,[5] hence a variety of approaches have been developed for synthesis of the tetrahydroquinoline skeleton.[6] The imino Diels–Alder reaction between aldimines and electron-rich alkenes is probably the most powerful synthetic tool for the construction of N-containing six-membered heterocyclic compounds, including tetrahydroquinolines. This imino Diels–Alder reaction (also called the Povarov reaction[7]) has been reported to be catalyzed by various Lewis or Brönsted acid catalysts.[8] This method allows the generation of quinoline derivatives with several degrees of structural diversity. Recently, multi-component imino Diels–Alder reactions have gained popularity.[9] Among the electron-rich alkenes, vinyl enol ethers,[10] and vinyl enamides[11] have been mainly used in this condensation. However, the utilization of styrene derivatives as a dienophile in this cycloaddition is poorly studied.[12] Moreover, the *trans*-anethole in the three-component imino Diels–Alder condensation has not been used in the preparation of polyfunctionalized tetrahydroquinolines. In addition, the *trans*-anethole is a main component of anise essential oil,[13] and presents several pharmacological properties as estrogenic action,[14] depressive action to the central nervous system,[15] potent antimicrobial properties,[16] insecticide,[17] anti-inflammatory,[18]and anesthetic activities.[19]

On the other hand, supercritical fluids are becoming increasingly important solvent systems for organic chemistry and engineering.[20] Among these so-called green solvents, supercritical carbon dioxide ($scCO_2$) is the most popular. The critical point of CO_2 is at 73 atm and 31.1 °C, which are conditions easily achieved in the laboratory. The advantages related to the use of $scCO_2$ are so numerous[21] that prompt an intense research to further develop its potential as an alternative solvent for green chemistry. However, the performance of multi-component imino Diels–Alder reactions under $scCO_2$ conditions has not been reported.[21b,22] We have published studies on the three-component imino Diels–Alder condensation at room temperature between diverse anilines, aldehydes, and *N*-vinylpyrrolidin-2-one using $BiCl_3$, a friendly ecological catalyst.[23] Bearing these results in mind, we investigated acid catalyzed three-component Povarov reaction between diverse anilines, benzaldehyde, and *trans*-anethole in traditional organic solvent (MeCN) to give diverse 2,4-diaryl substituted 1,2,3,4-tetrahydroquinolines. To explore an

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* Corresponding author. Tel./fax: +57 76 349069; e-mail: kouznet@uis.edu.co

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alternative environmentally benign condition for three-component Povarov reaction, we attempted to carry out this reaction, first using an anise essential oil as a dienophile component and then performing the same reaction from the anise seeds in $scCO_2$ in the presence of acid catalyst. Herein, we wish to describe our study on a three-component condensation between *trans*-anethole, anilines, and benzaldehyde, which resulted in a simple preparation of new 4-anisyl-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinolines, interesting rigid molecules in pharmacological studies.

In our initial study, we have developed a three-component Povarov reaction between *trans*-anethole **1**, aniline **2a**, and benzaldehyde **3** to afford tetrahydroquinoline **4a** (Scheme 1) using different conditions. These condensations are carried out in different solvents (CH_2Cl_2, CH_3CN, toluene, etc.) at room temperature in the presence of various water tolerant acidic catalysts. First, we employed $BiCl_3$ that had seen successfully used in the synthesis of tetrahydroquinoline derivatives at room temperature.[23b] However, these conditions did not afford the desired tetrahydroquinoline **4a**. After several experiments we found that this condensation occurred only at high temperature in CH_3CN to give product **4a**, but in low yield (20–25%). To improve this condensation, several acidic catalysts were tested (Table 1).

Our study on the influence of selected catalysts demonstrated that (a) surprisingly, the powerful lanthanide catalyst ytterbium(III) triflate and its combination with zeolite NaY were inefficient (entries 2 and 3); (b) Brönsted acids, TFA and *p*-TSOH, catalysts of choice in this type of condensation were too inefficient (entries 4 and 5); (c) Lewis acid, $AlCl_3$ did not work at all (entries 6 and 7); (d) only the cheap $BF_3{\cdot}OEt_2$ offered better results (entry 8). It is noteworthy to mention that *p*-TSOH resulted in a complete diastereospecific process, while $BF_3{\cdot}OEt_2$ gave the best yield, but accompanied with a high account of the quinoline **5a** (24%)[24] (Scheme 1).

^1H NMR and ^{13}C NMR analysis of the tetrahydroquinoline product indicated that the structure of major diastereoisomer **4a** was cis-(2e,4e)-form. The large vicinal coupling constants $J_{2a,3a}$ and $J_{3a,4a} = 9.9–11.0$ Hz for this form indicate an axial–axial (trans) relationship and the aryl groups on C-2 and C-4 are both pseudo-equatorial and are located in cis-configuration (Fig. 1). The configuration of the minor diastereoisomer **4a** was judged to be trans-(2a,4e)-form.[25]

Table 1. Effect of catalyst on synthesis of tetrahydroquinoline **4a** in CH_3CN at 70 °C[a]

Entry	Catalyst	Yield (%)	Isomers ratio (cis:trans)[b]
1	$BiCl_3$	24	87:13
2	$Yb(OTf)_3$ (5 mol %)	19	83:17
3	$Yb(OTf)_3$-Zeolite Y	13	96:4
4	TFA	8	76:24
5	*p*-TSOH	11	100:0
6	$AlCl_3$	3	97:3
7	$AlCl_3$–Et_3N (1:3)	3	89:11
8	$BF_3{\cdot}OEt_2$	52	97:3

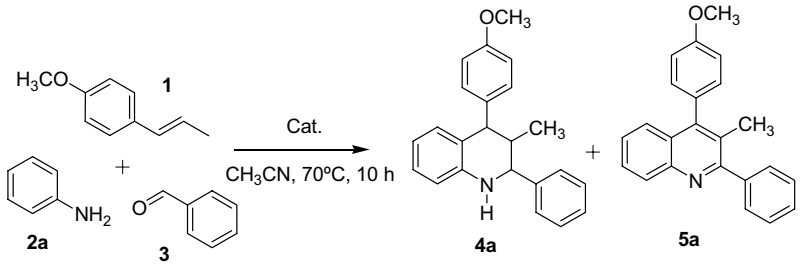
[a] All reactions were carried out under N_2.
[b] Determined by GC–MS method.

Next, the tetrahydroquinolines **4b–g** were obtained in good to excellent yield, by using the found condensation condition (Scheme 2, Table 2).

Analyzing the reaction crude, we noted that the diastereoisomeric ratio of tetrahydroquinolines and quinolines drastically depends on the nature of the substituents in the aniline ring. The efficiency of this condensation is easily related to the electron properties of the substituted anilines and, as expected, electron-withdrawing substituents, such as chlorine and nitro group, gave the best results (Table 2, entries 4–7), whereas the electron-donating ethyl and methoxy groups decreased the efficiency (Table 2, entries 2 and 3). Surprisingly, condensation of any substituted anilines **2b–g** produced only *cis*-(2e,4e)-tetrahydroquinoline isomers **4b–f**. Moreover, the electron-withdrawing substituents (NO_2 group) did not form quinoline by-products.

The same condensation condition of *m*-nitroaniline with *trans*-anethole and benzaldehyde yielded the 5-nitro derivative **4h** and 7-nitro-tetrahydroquinoline **4g** and in excellent regio- and diastereoselective manner (Table 2, entry 7).

Finally, due to our interest in the synthetic use of the anise essential oil and their constituents as renewable raw-material source, we tried to achieve the direct multi condensation with the anise oil.[26] The main component of the anise essential oil, extracted from the seeds of the star anise (*Illicium verum* Hook fillius), native to Southern China and Northern Vietnam, was found to be *trans*-anethole (90–93%). Thus, when a mixture of *p*-chloroaniline **2d**, *p*-nitroaniline **2e** or *o*-nitroaniline



Scheme 1.

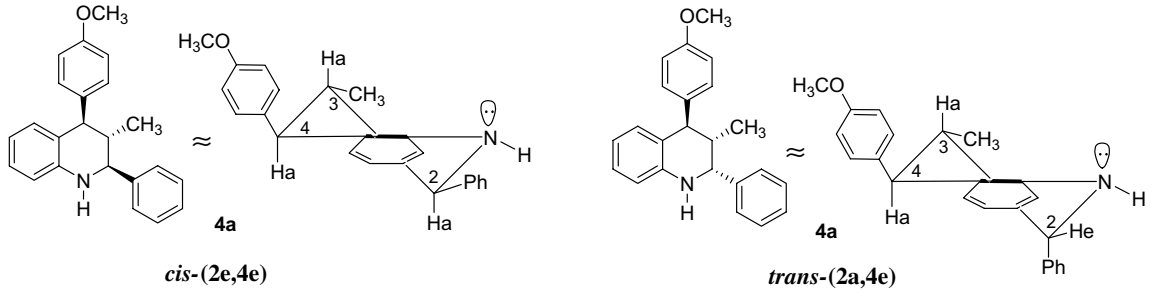
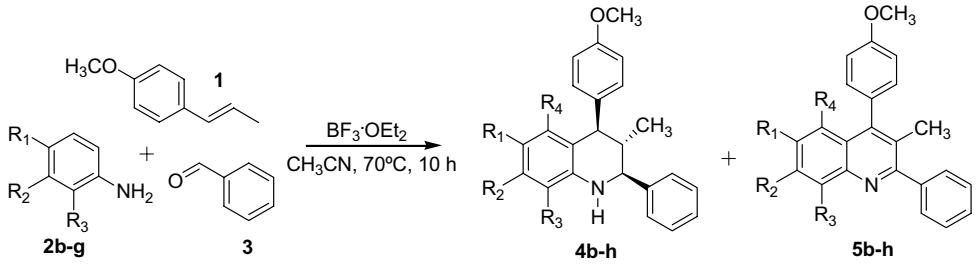


Figure 1. Configuration of the diastereoisomers **4a**.



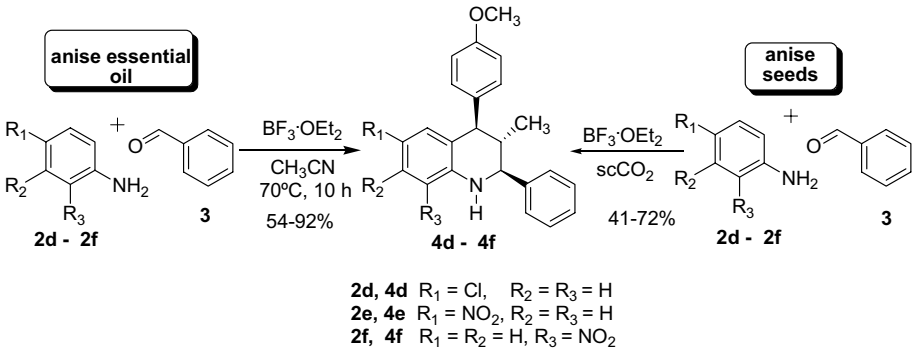
Scheme 2.

Table 2. Synthesis of new tetrahydroquinolines derivatives **4a**–**h**

Entry	Comp.	R_1	R_2	R_3	R_4	THQ **4**, yield (%)	Mp (°C)	Quinoline **5**[a], yield (%)
1	**a**	H	H	H	H	52	152–153	24
2	**b**	Et	H	H	H	55	157–158	17
3	**c**	MeO	H	H	H	59	182–183	17
4	**d**	Cl	H	H	H	58	214–214	7
5	**e**	NO_2	H	H	H	95	203–204	Nil
6	**f**	H	H	NO_2	H	68	160–161	Nil
	g	H	NO_2	H	H	8	141–142	Nil
7	**h**	H	H	H	NO_2	80	174–175	Nil

[a] Analyzed by GC–MS technique.

2f, benzaldehyde **3**, and the anise essential oil was heated for 10 h in the presence of $BF_3{\cdot}OEt_2$ in CH_3CN, the tetrahydroquinolines **4d**, **4e**, and **4f** were obtained in 54%, 92% and 64% yields, respectively, together with unreacted minor constituents of the starting oil (detected by GC–MS). The stereochemistry of **4d**–**f** was the same as that observed for the condensation with commercial *trans*-anethole, the cis-(2e,4e) isomer **4d**–**f** being the unique product (Scheme 3). In order to make these reactions 'greener', supercritical carbon dioxide replaced the conventional organic solvent, so that our multi-component imino Diels–Alder reaction was solventless. Thus, a mixture of the same nitroanilines (chloroanilines), benzaldehyde **3** and the anise seeds, in the presence of



Scheme 3.

$BF_3{\cdot}OEt_2$, was subjected to $scCO_2$ conditions.[27] After the system depressurization, tetrahydroquinolines **4d**, **4e**, and **4f** were obtained again in 41%, 72%, and 53% yields, respectively.

In conclusion, we have developed a simple and efficient one-pot method for the synthesis of new diversity-substituted 1,2,3,4-tetrahydroquinolines by applying three-component imino Diels–Alder reaction between *trans*-anethole, anilines, and benzaldehyde in presence of boron trifluoride diethyl etherate. In addition, we demonstrated that a multi-component condensation starting from anise oil or from the anise seeds under $scCO_2$ conditions, nitroanilines, and benzaldehyde in the presence of $BF_3{\cdot}OEt_2$ was very efficient to give tetrahydroquinolines **4**. The notable features of this procedure are mild and green reaction conditions, good yields and reaction rates, and cleaner reaction profiles. New heterocyclic compounds could serve as pharmaceutical models and precursors of more complex molecules of synthetic and biological interest. At present, further investigations are in progress to find additional synthetic applications of essential oil and seeds of anise under $scCO_2$ conditions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.063.

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24. *General procedure for synthesis of tetrahydroquinoline with commercial anethole*: $BF_3{\cdot}OEt_2$ (0.61 g, 4.30 mmol) was added to a mixture of aniline (0.40 g, 4.30 mmol) and benzaldehyde (0.50 g, 4.73 mmol) in anhydrous CH_3CN (15 mL), stirred at room temperature for 30 min. Over a period of 20 min, a solution of commercial *trans*-anethole (0.84 g, 5.68 mmol) in CH_3CN (10 mL) was added dropwise. The resulting mixture was stirred at 70 °C for 10 h. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 × 15 mL). The organic layer was separated and dried (Na_2SO_4), concentrated in vacuo and the crude product was purified by column chromatography using silica gel (60–120 mesh) and eluted with petroleum ether–ethyl acetate to afford pure tetrahydroquinoline **4a–h**. *cis-4-(4-Methoxyphenyl)-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline* (**4a**): White solid, mp 152–153 °C, yield 52%. IR (KBr): 3368, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ): 0.58 (3H, d, $J = 6.5$ Hz, 3-CH_3), 2.20 (1H, m, 3-H), 3.76 (1H, d, $J = 11.0$ Hz, 2-H), 3.82 (3H, s, –OCH_3), 4.08 (1H, s, N–H), 4.14 (1H, d, $J = 9.9$ Hz, 4-H), 6.53–6.60 (2H, m, 5-H, 6-H and 8-H), 6.88 (1H, dt, $J = 8.7$, 2.9 Hz, 2′-H_{Ar}), 6.99 (1H, tq, $J = 8.0$, 2.0, 0.6 Hz, 7-H), 7.15 (2H, dt, $J = 8.7$, 2.9 Hz, 3′-H_{Ar}), 7.46–7.31 (5H, m, all-H_{Ar}); ^{13}C NMR (100 Hz, $CDCl_3$, δ): 158.4, 145.1, 143.0, 136.8, 130.4, 130.1, 128.6, 127.9, 127.8, 126.9, 125.8, 117.5, 114.0, 113.6, 64.1, 55.2, 51.7, 41.8, 16.4; GC–MS (EI) ($t_R = 44.86$ min), *m*/*z*: 329 (52, M^+), 300 (20), 283 (29), 206 (100). Anal. Calcd for $C_{23}H_{23}NO$: C, 83.85; H, 7.04; N, 4.25. Found: C, 83.66; H, 6.98; N, 4.15. *cis-6-Ethyl-4-(4-methoxyphenyl)-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline* (**4b**): White solid, mp 157–158 °C, yield 55%. IR (KBr): 3369, 1611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ): 0.57 (3H, d, $J = 6.5$ Hz, 3-CH_3), 1.07 (3H, t, $J = 7.6$ Hz, CH_3–), 2.18 (1H, m, 3-H), 2.39 (2H, q, $J = 7.6$ Hz, –CH_2–), 3.73 (1H, d, $J = 10.9$ Hz, 2-H), 3.83 (3H, s, Ar-OCH_3), 3.98 (1H, s, NH), 4.10 (1H, d, $J = 9.9$ Hz, 4-H), 6.42 (1H, br s, 5-H), 6.49 (1H, d, $J = 8.0$, Hz, 8-H), 6.84 (1H, dd, $J = 8.6$, 2.1 Hz, 7-H), 6.88 (2H, dt, $J = 8.7$, 2.9 Hz, 2′-H_{Ar}), 7.14 (2H, dt, $J = 8.7$, 2.9 Hz, 3′-H_{Ar}), 7.29–7.45 (5H, m, all-H_{Ar}); ^{13}C NMR (100 Hz, $CDCl_3$, δ): 158.1, 143.0, 142.9, 136.8, 133.4, 130.4, 129.4, 128.5, 127.9, 127.8, 126.2, 125.7, 113.7, 113.7, 64.1, 55.2, 51.7, 42.0, 28.0, 16.5, 16.1; GC–MS (EI) ($t_R = 31.25$ min), *m*/*z*: 357 (71, M^+), 328 (23), 266 (24), 234 (100). Anal. Calcd for $C_{25}H_{27}NO$: C, 83.99; H, 7.61; N, 3.92. Found: C, 84.06; H, 7.58; N, 3.99. *cis-6-Methoxy-4-(4-methoxyphenyl)-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline* (**4c**): White solid, mp 182–183 °C, yield 52%. IR (KBr): 3369, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ): 0.57 (3H, d, $J = 6.5$ Hz, 3-CH_3), 2.18 (1H, m, 3-H), 3.59 (3H, s, 6-OCH_3), 3.72 (1H, d, $J = 10.8$ Hz, 2-H), 3.81 (3H, s, Ar-OCH_3), 3.86 (1H, s, NH), 4.06 (1H, d, $J = 9.9$ Hz, 4-H), 6.19 (1H, dd, $J = 2.2$, 0.7 Hz, 5-H), 6.49 (1H, d, $J = 8.6$, Hz, 8-H), 6.61 (1H, dd, $J = 8.6$, 2.8 Hz, 7-H), 6.86 (2H, dt, $J = 8.7$, 2.8 Hz, 2′-H_{Ar}), 7.13 (2H, dt, $J = 8.7$, 2.7 Hz, 3′-H_{Ar}), 7.46–7.31 (5H, m, all-H_{Ar}); ^{13}C NMR (100 Hz, $CDCl_3$, δ): 147.3, 141.1, 132.1, 128.6, 125.8, 119.5, 117.6, 117.1, 117.0, 116.3, 105.0, 103.7, 102.9, 101.9, 53.4, 44.9, 44.4, 41.2, 31.2, 5.7; GC–MS (EI) ($t_R = 33.20$ min), *m*/*z*: 359 (100, M^+), 330 (36), 268 (21), 236 (81). Anal. Calcd for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.06; H, 6.98; N, 3.79. *cis-6-Chloro-4-(4-methoxyphenyl)-3-methyl-2-phenyl-1,2,3,4-tetrahydroquinoline* (**4d**): White solid, mp 214–214 °C, yield 58%. IR (KBr): 3368, 1599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, δ): 0.56 (3H, d, $J = 6.5$ Hz, 3-CH_3), 2.15 (1H, m, 3-H), 3.68 (1H, d, $J = 11.0$ Hz, 2-H), 3.83 (3H, s, Ar-OCH_3), 4.07 (1H, s, NH), 4.09 (1H, d, $J = 10.0$ Hz, 4-H), 6.44 (1H, d, $J = 8.5$, Hz, 8-H), 6.53 (1H, dd, $J = 2.2$, 0.9 Hz, 5-H), 6.88 (2H, dt, $J = 8.6$, 2.9 Hz, 2′-H_{Ar}), 6.92 (1H, dd, $J = 8.5$, 2.0 Hz, 7-H), 6.88 (2H, dt, $J = 8.6$, 2.8 Hz, 3′-H_{Ar}), 7.46–7.31 (5H, m, all-H_{Ar}); ^{13}C NMR (100 Hz, $CDCl_3$, δ): 158.4, 143.6, 142.4, 135.6, 130.2, 129.6, 128.6, 128.0, 127.8, 127.3, 126.8, 121.8, 114.6, 114.0, 63.8, 55.2, 51.4, 41.2, 16.4; GC–MS (EI) ($t_R = 53.39$ min), *m*/*z*: 363 (39, M^+), 334 (10), 299 (12), 272 (18), 240 (100). Anal. Calcd for $C_{23}H_{22}ClNO$: C, 75.92; H, 6.09; N, 3.85. Found: C, 75.86; H, 6.18; N, 3.54. *cis-4-(4-Methoxyphenyl)-3-methyl-6-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline* (**4e**): Yellow solid, mp 203–204 °C, yield 95%. IR (KBr): 3448, 3339, 1610, 1495, 1305 cm^{-1}; UV max (CH_2Cl_2) = 456 nm; ^1H NMR (400 MHz, $CDCl_3$, δ): 0.58 (3H, d, $J = 6.5$ Hz, –CH_3), 2.15 (1H, m, 3-H), 3.70 (1H, d, $J = 11.2$ Hz, 2-H), 3.83 (3H, s, Ar-OCH_3), 4.23 (1H, d, $J = 10.0$ Hz, 4-H), 4.87 (1H, s, NH), 6.44 (1H, d, $J = 8.9$ Hz, 8-H), 6.90 (2H, d, $J = 8.6$ Hz, 2′-H_{Ar}), 7.11 (2H, d, $J = 8.6$ Hz, 3′-H_{Ar}), 7.35–7.40 (5H, m, all-H_{Ar}), 7.48 (1H, br s, 5-H), 7.90 (1H, dd, $J = 8.9$, 2.4 Hz, 7-H); ^{13}C NMR (100 Hz, $CDCl_3$, δ): 158.7, 150.2, 141.2, 138.0, 133.8, 130.1, 128.9, 128.5, 127.7, 126.6, 124.8, 124.2, 114.4, 112.2, 63.6, 55.2, 50.6, 40.1, 16.2; GC–MS (EI) ($t_R = 34.36$ min), *m*/*z*: 374 (15, M^+), 344 (11), 283 (11), 251 (100), 135 (23), 121 (53). Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.96; H, 6.01; N, 7.22. *cis-4-(4-Methoxyphenyl)-3-methyl-8-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline* (**4f**): Yellow solid, mp 160–161 °C, yield 68%. IR (KBr): 3349, 1606, 1509, 1305 cm^{-1}; UV max (CH_2Cl_2) = 403 nm; ^1H NMR (400 MHz, $CDCl_3$, δ): 0.60 (3H, d, $J = 6.5$ Hz, –CH_3), 2.15 (1H, m, 3-H), 3.73 (1H, d, $J = 11.4$ Hz, 2-H), 3.83 (3H, s, Ar-OCH_3), 4.33 (1H, d, $J = 10.1$ Hz, 4-H), 6.44 (1H, dd, $J = 8.6$, 7.4 Hz, 6-H), 6.74 (1H, br d, $J = 7.6$ Hz, 5-H), 6.90 (2H, d, $J = 8.7$ Hz, 2′-H_{Ar}), 7.10 (2H, d, $J = 8.7$ Hz, 3′-H_{Ar}), 7.35–7.42 (5H, m, all-H_{Ar}), 8.01 (1H, dt, $J = 8.7$, 1.2 Hz, 7-H), 8.48 (1H, s, N–H); ^{13}C NMR (100 Hz, $CDCl_3$, δ): 158.5, 143.1, 141.2, 136.5, 134.3, 130.8, 130.4, 129.6, 128.9, 128.4, 127.6, 124.7, 115.2, 114.2, 62.8, 54.5, 50.6, 39.6, 16.4; GC–MS (EI) ($t_R = 40.31$ min): 374 (20, M^+), 251 (100), 105(17), 77 (19). Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.65; H, 6.08; N, 7.23. *cis-4-(4-Methoxyphenyl)-3-methyl-7-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline* (**4g**): Yellow solid, mp 141–142 °C, yield 8%. IR(KBr) 3376, 1610, 1521, 1317 cm^{-1}; UV max (CH_2Cl_2) = 410 nm; ^1H NMR (400 MHz, $CDCl_3$, δ): 0.59 (3H, d, $J = 6.5$ Hz, –CH_3), 2.17 (1H, m, 3-H), 3.73 (1H, d, $J = 11.0$ Hz, 2-H), 3.82 (3H, s, Ar-OCH_3), 4.17 (1H, d, $J = 10.0$ Hz, 4-H), 4.38 (1H, s, N–H), 6.66 (1H, d, $J = 8.8$ Hz, 8-H), 6.89 (2H, d, $J = 8.6$ Hz, 2′-H_{Ar}), 7.10 (2H, d, $J = 8.6$ Hz, 3′-H_{Ar}), 7.35–7.40 (7H, m, all-H_{Ar} and 6-H, 7-H); ^{13}C NMR (100 Hz, $CDCl_3$, δ): 158.5, 147.1, 145.4, 141.7, 134.8, 132.5, 131.2, 130.5, 128.8, 128.6, 127.7, 114.0, 111.7, 107.5, 64.8, 54.5, 50.8, 40.3, 16.3; GC–MS (EI) ($t_R = 36.41$ min): 374 (67, M^+), 357 (53), 340 (100), 251 (45), 180 (60), 77 (56). Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.65; H, 6.13; N, 7.32. *cis-4-(4-Methoxyphenyl)-3-methyl-5-nitro-2-phenyl-1,2,3,4-tetrahydroquinoline* (**4h**): Yellow solid, mp 174–175 °C, yield 80%. IR (KBr): 3395, 1609, 1527, 1323 cm^{-1}; UV max (CH_2Cl_2) = 375 nm; ^1H NMR (400 MHz, $CDCl_3$, δ): 0.68 (3H, d, $J = 6.6$ Hz, –CH_3), 2.03 (1H, m, 3-H), 3.75 (3H, s, Ar-OCH_3), 4.01 (1H, d, $J = 10.2$ Hz, 2-H), 4.21 (1H, d, $J = 10.2$ Hz, 4-H), 4.36 (1H, s, N–H), 6.75 (1H, dd, $J = 8.1$, 1.2 Hz, 8-H), 6.76 (2H, d, $J = 8.7$ Hz, 2′-H_{Ar}), 6.89 (1H, dd, $J = 7.8$, 1.2 Hz, 6-H), 6.98 (2H, d, $J = 8.7$ Hz, 3′-H_{Ar}), 7.08 (1H, td, $J = 8.1$,

0.6 Hz, 7-H), 7.33–7.42 (5H, m, all-H_{Ar}); ^{13}C NMR (100 Hz, $CDCl_3$, δ): 158.0, 152.3, 147.8, 141.2, 135.1, 130.4, 128.6, 128.2, 127.7, 127.1, 119.4, 118.0, 114.1, 113.4, 62.6, 55.1, 48.0, 45.0, 16.1; GC–MS (EI) ($t_R = 47.71$ min): 374 (30, M^+), 251 (100), 179 (19), 152 (20), 121 (20). Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.97; H, 5.98; N, 7.33.

25. From ^1H NMR analysis we were unable to find the small constants of $J_{2e,3a}$ and the large constants of $J_{3a,4a}$ Hz for the minor diastereoisomer **4a**. However, all the chemical literature fonts for minor component of imino Diels–Alder reactions indicate at an equatorial–axial (cis) relationship for the protons H_2 and H_3 and an axial–axial (trans) relationship for the protons H_3 and H_4, see: (a) Fadel, F.; Titouni, S. L.; Soufioui, M.; Ajamay, H.; Mazzah, A. *Tetrahedron Lett.* **2004**, *45*, 5905; (b) Zhang, W.; Guo, Y.; Liu, Z.; Jin, X.; Yang, L.; Liu, Z.-L. *Tetrahedron* **2005**, *61*, 1325.
26. *General procedure for synthesis of tetrahydroquinoline with anise essential oil*: The anise essential oil was extracted by microwave-assisted hydrodistillation technique affording 3% yield from the star anise dry seeds. The obtained oil was characterized by GC–MS, which showed that *trans*-anethole content was 93% (by weight). It was used without further purification in the imino Diels–Alder reaction according to the following general procedure: A mixture of *p*-nitroaniline (0.40 g, 3.13 mmol) and benzaldehyde (0.37 g, 3.44 mmol) in anhydrous CH_3CN (15 mL) was stirred at room temperature for 30 min, then $BF_3{\cdot}OEt_2$ (0.44 g, 3.13 mmol) was added. Over a 20 min period, a solution of anise oil (0.50 g) in CH_3CN (10 mL) was added dropwise. The resulting mixture was stirred and heated at 70 °C for 10 h. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3×15 mL). The organic layer was separated and dried (Na_2SO_4), concentrated in vacuo and the resulting product was purified by column chromatography (silica gel, petroleum ether/EtOAc) to afford the pure tetrahydroquinolines **4d–f**.
27. *General procedure for synthesis of tetrahydroquinoline from the anise seeds*: A mixture of *p*-nitroaniline (0.20 g, 1.45 mmol), benzaldehyde (0.17 g, 1.60 mmol) and $BF_3{\cdot}OEt_2$ (0.21 g, 1.45 mmol) was placed in the mini Soxhler extractor flask,[13b] while in the extractor body 15 g of previously crushed star anise seeds was added. (Extract yield from dry seeds was 6% and 75% by weight was represented by *trans*-anethole, which therefore was in excess during the reaction). The temperature and the pressure of the system were adjusted to guarantee that the CO_2 was inside the range of the supercritical conditions (ca. 1100 psi and 50 °C) for 5 h. After the very slow system depressurization, the reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3×15 mL). The organic layer was separated and dried (Na_2SO_4), concentrated in vacuo and the resulting product was purified by column chromatography (silica gel, petroleum ether/EtOAc) to afford the pure tetrahydroquinolines **4d–f**.