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Regio- and stereo-selective aza-Diels–Alder reaction of ethyl glyoxylate 4-methoxyphenylimine with 1,3-dienes in the presence of $BF_3 \cdot Et_2O$. Evidence for a non-concerted mechanism

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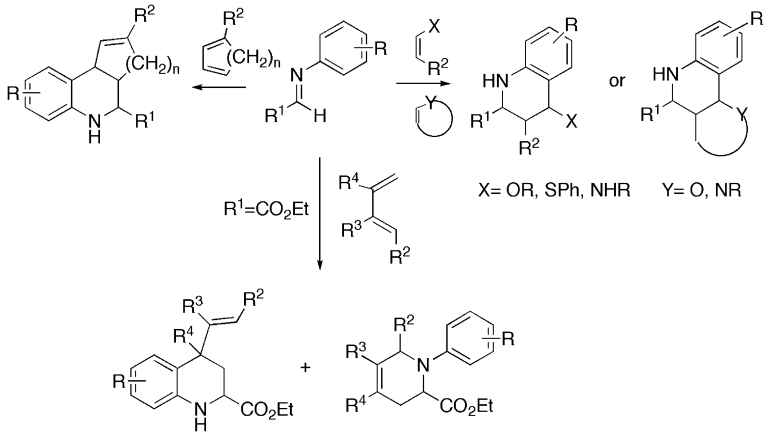
Abstract—Cycloadditions of the glyoxylate imine **1** with 1-substituted and 1,4-disubstituted 1,3-dienes furnished tetrahydroquinoline compounds **4** and **5/15** with total regio- and stereo-control, except for one case where a mixture of isomers was formed. A stepwise mechanism is proposed in view of the stereochemistry of the products.

1. Introduction

Various tetrahydroquinolines are biologically active compounds, several of them with pharmaceutical applications.[1] As an example they have been investigated for the treatment of severe pain as an alternative to opiates.[2]

There are several methods for the synthesis of tetrahydroquinolines, but the aza-Diels–Alder reaction of arylimines with dienophiles, usually in the presence of a Lewis acid catalyst, is one of the most powerful tools for obtaining 1,2,3,4-tetrahydro derivatives.[3] Cycloadditions of arylimines to dienophiles including enolates,[4–12] thioenolates,[4,11] enamines, [4,7,13,14] and cyclic dienes such as cyclopentadiene and cyclohexadiene[4,9,11,15,16] are well documented in the literature. However, cycloadditions of arylimines to open chain dienes acting as dienophiles are less abundant.[17] Scheme 1 gives a summary of the literature.

Tetrahydroquinolines are formed by an 'inverse electron demand' reaction. A competition with 'normal electron demand' reaction occurs in the case where the diene possesses



Scheme 1.

Keywords: 2-Azadienes; Glyoxylate arylimines; Diels–Alder cycloaddition.
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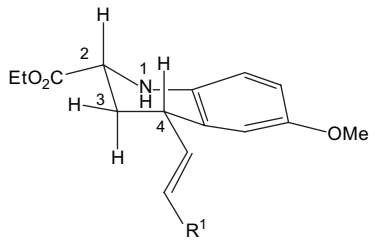
a bulky group at C-2 and/or C-3.[17] A substituent at position 1 of the diene, even a good electron releasing group, results in the formation of the tetrahydroquinoline compound.[17,18] This shows the major role played by the steric hindrance of the approaching reagents in the selection of reaction type.

In this work 1-monosubstituted and 1,4-disubstituted dienes were reacted with glyoxylate imine **1** with the aim of finding the relative configuration of the stereocentres in the products. The comparison of the product stereochemistry with the two types of diene, was expected to shed light on the mechanism of the reaction. We have found that in the case of reaction with 1,4-disubstituted dienes the stereochemistry of products is only possible on the basis of an ionic mechanism.



4a R^1=OMe

J 2-H_{ax}-3-H_{ax}= 11.1 Hz
J 3-H_{ax}-4-H_{ax}= 11.1 Hz
J 2-H_{ax}-3-H_{eq}= 3.3 Hz
J 3-H_{eq}-4-H_{ax}= 5.4 Hz

4b R^1=$OSiMe_2{}^tBu$

J 2-H_{ax}-3-H_{ax}= 11.4 Hz
J 3-H_{ax}-4-H_{ax}= 10.8 Hz
J 2-H_{ax}-3-H_{eq}= 3.3 Hz
J 3-H_{eq}-4-H_{ax}= 5.4 Hz

Figure 1.

2. Results and discussion

In a typical procedure the imine **1** was first combined with $BF_3\cdot$ether at −78 °C, in dry toluene, followed by addition of the diene **2** or **3** (1 equiv) after 5 min. $BF_3\cdot$ether 0.1 equiv was used in the cases of dienes **2** and 1 equiv with dienes **3a–c**, to accelerate the reaction. The reaction mixture was stirred at room temperature from 15 min to several hours. A longer period of time was needed with **3c** (3 h, rt) and **3d** (3 h, rt+19 h, 5 °C), to get the reaction to completion. Tetrahydroquinolines **4** (**4a**,**b**) (Scheme 2), **5** (**5a**,**d**) or an oxidation product of **5b** (**6b**) or **15** (**15c**) were obtained pure after work-up (Schemes 4 and 7).

In the reaction of the imine **1** with the 1-monosubstituted dienes **2a** and **2b** the regioselectivity shown in products **4** was expected due to primary electronic effects. The stereoselectivity of these reactions was determined by ^{1}H NMR spectroscopy. Adducts **4a** and **4b** show large axial–axial coupling constants (10.8–11.4 Hz) between 2-H and one of the 3-H (axial), and between 3-H and 4-H (Fig. 1). There are also small coupling constants for interactions between 2-H (axial) and 3-H (equatorial) (3.3 Hz), and between 3-H (equatorial) and 4-H (axial) (5.4 Hz). These values are consistent with the configuration shown in Figure 1.

Compounds **4a** and **4b** were obtained pure after flash chromatography, but the crude reaction mixtures showed no other isomer by ^{1}H NMR spectroscopy. The reaction of 1-acetoxy-1,3-butadiene reported by Whiting and co-workers showed a 5:1 mixture of cis (major) and trans (minor) isomers. When the reaction of the imine **1** with the diene **2b** was carried out using an old sample of the imine glyoxylate **1** a mixture of **4b** together with compound **7b** was formed (Scheme 2). Compound **7b** was obtained as a single compound in a separate experiment starting from **4b**, ethyl glyoxylate and the diene **2b** in the presence of $BF_3\cdot$etherate. A complete conversion of **4b** into the adduct **7b** was observed after 15 min. It is apparent that the hydrolysis of the imine **1** to form ethyl glyoxylate was the origin of compound **7b**. Cycloadducts of this type have been isolated before mixing together aromatic imines with cyclopentadiene and trifluoroacetic acid in the presence of formaldehyde.[19] ^{1}H and ^{13}C NMR spectra of compound **7b** showed a highly symmetrical structure and its HRMS showed the correct molecular ion. Compound **7b** would be formed from **4b** by approach of the diene **2b** by the less hindered face of the intermediate **8** (Fig. 2), probably by the same mechanism that led to the synthesis of **4b** from imine **1** and diene **2b**.

Reaction of the imine **1** with the 1-trimethylsilyloxy-1,3-butadiene was reported before by Whiting, forming an open chain aldehyde derivative **9** after hydrolysis.[17] A simple Mannich-process was proposed for the addition of the diene to the activated iminium chelate. If a cycloaddition had occurred as a primary process to obtain **4b** analog (R^1=TMS), the formation of the aldehyde **9** would include an extremely unlikely C–C cleavage. The isolated compound **4b** was hydrolyzed in HCl–THF. A single compound was detected and

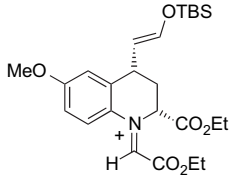


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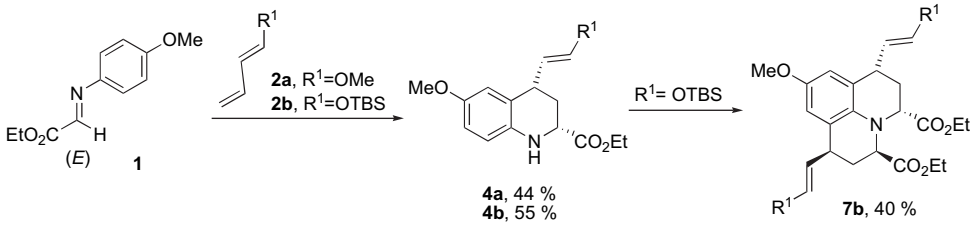
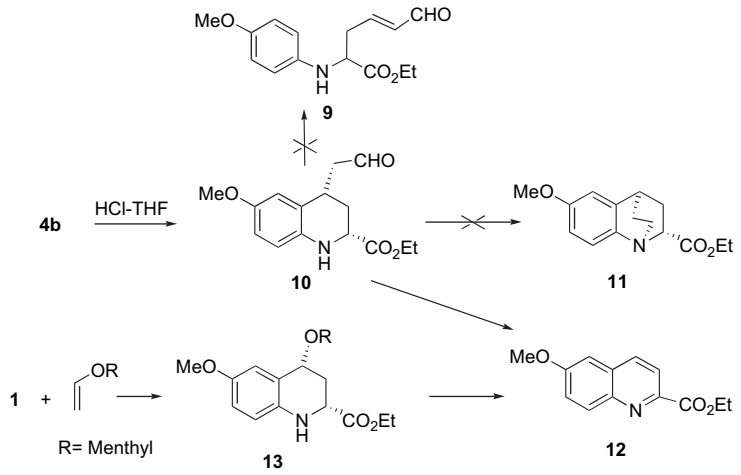
Figure 2.



Scheme 2.



Scheme 3.

isolated, the aldehyde **10**. Further exposition of **10** to acid (0.1 or 1 equiv of HCl) for 1 h at room temperature formed neither the open chain aldehyde **9** nor the expected quinuclidine **11**. The only product obtained was the quinoline **12** (Scheme 3). In the literature quinolines such as compounds **12** have been obtained in low yields from reactions of vinyl enol ethers and arylimines[10] or in good yields after acid treatment of crude products.[4] We therefore carried out the reaction of vinyl menthyl ether with the imine **1** with the aim of synthesizing compounds **13** and **12**. The quinoline **12** was observed during the course of the reaction and was isolated in 60% yield together with compound **13** in only 4% yield, contaminated with menthol. A $CDCl_3$ solution of compound **13** showed its complete conversion into quinoline **12** and menthol after 7 days at room temperature. A solid sample of compound **13** also showed conversion of half of the material into **12** after standing at room temperature for 7 days .

Reactions with symmetrical 1,4-disubstituted 1,3-dienes **3a**,**b** exhibited the same regioselectivity observed for dienes **2a**,**b** forming products with the vinyl group attached to the position 4 (**5a** and **6b**). The stereochemical outcome of the cycloadditions (Scheme 4) was found to be different from the mono-substituted dienes.[17]

Compound **5a** showed small coupling constants between H-2 and H-3 (3.0 Hz), and between H-3 and H-4 (4.8 Hz). Single X-ray crystallography showed the small dihedral angle between those protons and confirmed the stereochemistry of products to be cis (Figs. 3 and 5).[20]

Compound **5b** could not be isolated; an oxidation process producing **6b** occurs immediately as **5b** starts forming. Nevertheless, an aliquot of the reaction mixture run after 5 min from the start of the reaction showed together with reagents and incipient signals for **6b**, signals for compound **5b**. Protons H-2, H-3, and H-4 of **5b** showed vicinal coupling values comparable to those observed for H-2, H-3, and H-4 protons in compound **5a** (Fig. 4). Inspection of the NMR sample spectra over the time showed that consumption of the reagents and conversion of **5b** into **6b** was complete after 1 h.

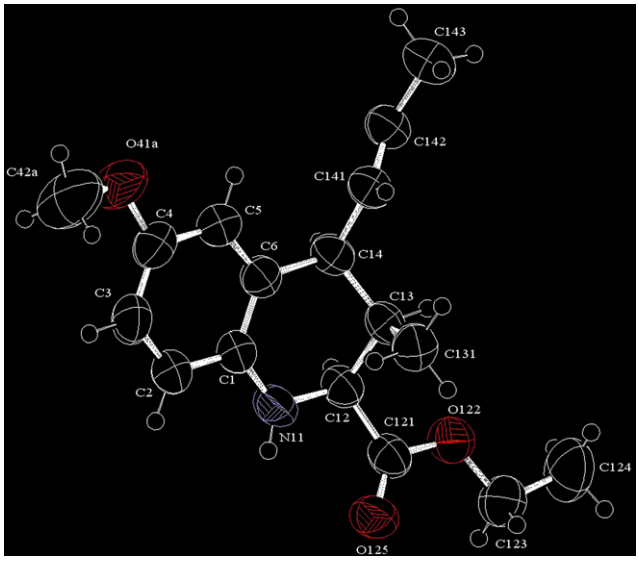
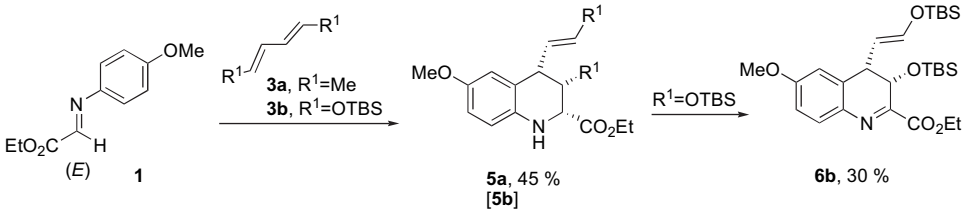
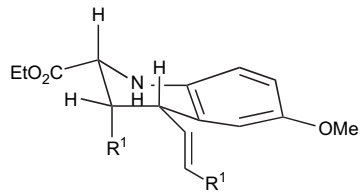


Figure 3. ORTEP view of the molecular structure of the 1,2,3,4-tetrahydroquinoline **5a**.



Scheme 4.



5a R^1=Me

J 2-H_{ax}-3-H_{eq}= 3.0 Hz
J 3-H_{eq}-4-H_{ax}= 4.8 Hz

5b R^1=$OSiMe_2{}^tBu$

J 2-H_{ax}-3-H_{eq}= 4.2 Hz
J 3-H_{eq}-4-H_{ax}= 3.9 Hz

Figure 4.

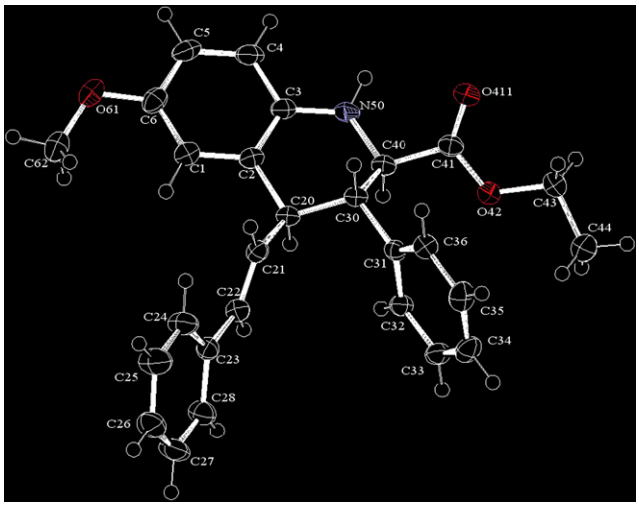


Figure 5. ORTEP view of the molecular structure of the 1,2,3,4-tetrahydroquinoline **15c**.

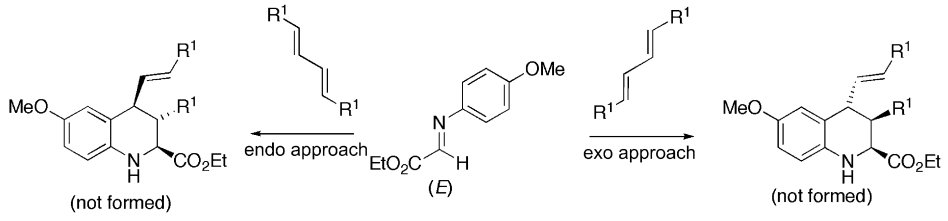
The presence of compound **6b** was confirmed by the absence of NH absorption band (IR spectrum), disappearance of the doublet at ca. δ_H 4 ppm expected for H-2, a doublet for H-3 due to coupling with H-4 (^{1}H NMR spectrum) and a signal at δ_C 156.1 ppm assigned to C-2 (^{13}C NMR spectrum). The coupling value for H-3/H-4 in **6b** is the same as the coupling of H-3/H-4 in the precursor structure **5b** (J=3.9 Hz).

Considering the stereochemistry of compounds **5** a concerted mechanism for their synthesis is not reasonable. Scheme 5 shows the two possible tetrahydroquinoline structures that would result from the *endo* and the *exo* approach in the imino Diels–Alder cycloaddition. None of the products were formed.

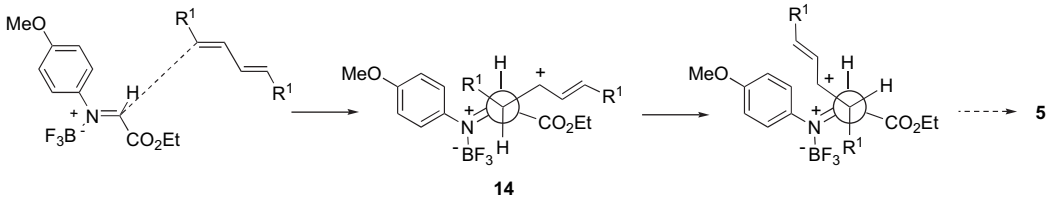
Whiting and co-workers recently found some evidence for a stepwise mechanism, rather than a Diels–Alder for the reactions of the arylimine **1** with dienes. We now have a stronger evidence for such ionic mechanism. Scheme 6 shows the less hindered approach of the diene to the activated imine following the Bürgi–Dunitz trajectory, with the major part of the diene oriented away from the ethoxy carbonyl group. This interaction would produce a cationic intermediate **14** that after rotation around C-3/C-4 would be attacked by the aromatic ring and will produce the tetrahydroquinoline **5** (Scheme 6). Presumably the cation bearing the propenyl moiety rotates to give the less hindered configuration of the product.

Reaction of 1,4-diphenyl-1,3-butadiene with the imine **1** gave a tetrahydroquinoline (**15c**) showing a different stereochemistry from compounds **5**. Configurations are 2,3-trans-2,4-cis. The different arrangements in turn of the tetrahedral carbons are evidenced by the coupling constants between H-2 and H-3 (8.7 Hz), and H-3 and H-4 (8.7 Hz). The structure of compound **15c** was definitely confirmed by X-ray analysis (Fig. 5).

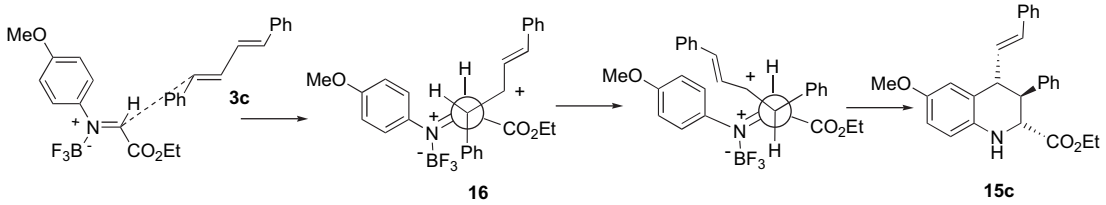
The different relative configurations of C-2/C-3 demand a different approach/mechanism from that observed for compounds **5**. Compound **15c** could either be accessed by an *endo* Diels–Alder or by the nucleophilic attack of the diene terminal to the imine, with formation of the carbocation **16**, as intermediate. In this case, the nucleophilic attack of the diene would occur with the phenyl group (R^1) approaching the iminium nitrogen ion on the same hand side of the



Scheme 5.



Scheme 6.



Scheme 7.

ethoxy carbonyl group, preferring the bulkier arrangement of reagents. Scheme 7 shows this approach.

Seeking for an explanation in literature for this bizarre result we systematically found that dienophiles bearing aliphatic groups, most frequently cyclic enes[21] but also acyclic[21,22] gave mainly the 2,3-*cis* tetrahydroquinolines. On the other side dienophiles attached to aromatic groups gave the 2,3-trans isomers[23] almost exclusively, unless a very strong bulky interaction occurs.[24] We believe that an electronically favored interaction of the iminium nitrogen with the approaching aromatic group explains the preference depicted in the formation of cation **16** (Scheme 7). Dihydropyrans and to a less extent also dihydrofurans behave differently from their carbodiene counterpart; they usually display a mixed stereochemistry around C-2/C-3.[6,8,10,25] A mixture of isomers is usually formed, being the 2,3-trans isomer favored most of the times, just like the case of the 1,4-diphenyl-1,3-butadiene. Resembling the approach of reagents to form the intermediate **16**, intermediate **17** would be stabilized by the oxygen atom in the proximity of the iminium ion, whereas the alternative intermediate **18** having the carbocation placed on the same side of the positive nitrogen atom would be less stable from the electronic point of view (Fig. 6).

The missing rotation of the carbocation in the intermediate **16**, around C3/C4 could be explained by the greater hindrance of the phenyl group compared to the groups occupying position 3 in compounds **5**.

The stereochemistry of the tetrahydroquinoline resulting from the reaction of the imine **1** with the diene **3b**, which has an oxygen directly attached to the terminal positions, shows that the approach of reagents would be like **18**, the oxygen atom preferring to drive away from the iminium ion. An explanation for this is that a strong steric interaction with the trimethylsilyl group would disfavor the approach like **17**. Another experiment was done with the diene **3d**, which combines a less bulky group at C-1 and C-4 with an oxygen (R^1=OAc). ^{1}H NMR of the crude product showed a mixture of two diastereomers (3:1). The major isomer (**5d**) was isolated in 22% yield, showing the stereochemistry to be 2,3-trans-2,4-cis. The minor isomer was observed in the crude, and in flash chromatography fractions, between unidentified sub-products. The vicinal couplings of H-2/H-3 and H-3/H-4 pairs are of the same magnitude (J=8.1 Hz), comparable to compound **15c**. The major isomer also showed the same coupling between H-2/H-3 and H-3/H-4 pairs, with a small coupling (J=2.4 Hz) similar to compound **5a**.

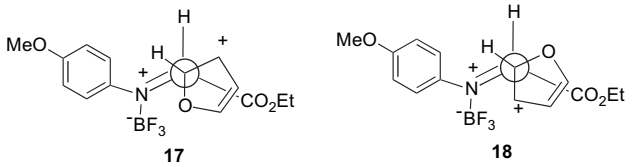


Figure 6.

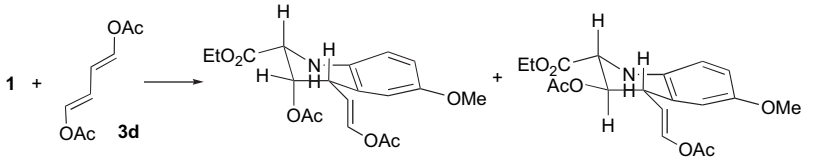
A steric/electronic balance seems to operate in the reaction of the imine **1** with **3d**, which led to the simultaneous formation of diastereomers **5d** (major) and **15d** (minor) (Scheme 8).

In conclusion adducts are formed with total regio- and stereo-control with 1-substituted and 1,4-disubstituted dienes. Based on the stereochemistry of the products an ionic stepwise mechanism is proposed for the reaction of 1,4-disubstituted dienes with the imine **1**.

3. Experimental section

3.1. General

^{1}H NMR spectra were recorded on a Varian Unity Plus 300 (300 MHz) spectrometer. Multiplicities are recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), doublets of doublets (dd), doublets of doublets of doublets (ddd), doublets of triplets (dt), triplets (t), quartets (q), and multiplets (m). J values are in Hertz and δ in parts per million. Infrared spectra were recorded on a Bomem MB 104 or



5d (major) J 2-H_{ax}-3-H_{eq}= 2.4 Hz
J 3-H_{eq}-4-H_{ax}= 2.4 Hz

15d (minor) J 2-H_{ax}-3-H_{eq}= 8.1 Hz
J 3-H_{eq}-4-H_{ax}= 8.1 Hz

Scheme 8.

on a Perkin–Elmer 1600 FT-IR spectrophotometer. Samples were run as Nujol mulls, and oils as thin films. MS spectra were recorded on a VG Autospec M. spectrometer. Microanalyses were performed in a LECO-CHNS-932 analyser. Melting points (mp) were determined on a Gallenkamp block and are uncorrected. Dry column flash chromatography was carried out using Kieselgel 60 and water pump vacuum. Toluene was dried over sodium followed by distillation. Dichloromethane (DCM) was dried over CaH_2. Dry flash chromatography was performed on silica gel 60 <0.063 mm for column chromatography. Petroleum ether 40–60 °C was distilled before use. The imine **1** was obtained from the reaction of ethyl glyoxylate (freshly distilled) and *p*-anisidine in dry toluene, in the presence of 4 Å molecular sieves. Evaporation of the solvent gave an oil that was used without further purification. 1,3-Dienes were used as purchased with the exception of cyclopentadiene, which was pyrolyzed and distilled prior to use.

3.1.1. General procedure for the synthesis of compounds 4 and 5. The imine **1** was dissolved in dry toluene (25 mL) and the solution refrigerated in an acetone/CO_2 bath. $BF_3 \cdot Et_2O$ (0.1–1 equiv) was added dropwise and the diene (0.7–1.2 equiv) added within 5 min. The cold bath was removed after addition was complete and the solution was kept under magnetic stirring for 15 min to several hours. The mixture was then quenched with saturated aq $NaHCO_3$ (100 mL) and extracted with DCM (2×50 mL). The combined organic solutions were dried over $MgSO_4$ and evaporated.

3.1.1.1. Ethyl 6-methoxy-4-(2-methoxyvinyl)-1,2,3,4-tetrahydroquinoline-2-carboxylate 4a. Compound **4a** was obtained using the general procedure: Imine **1** (1.05 g, 5.00 mmol); $BF_3 \cdot Et_2O$ (0.50 mmol); 1-methoxy-1,3-butadiene (0.52 g, 6.38 mmol). Reaction time: 45 min. Dry flash chromatography [silica; ether–light petroleum, polarity gradient] gave compound **4a**; yield: (0.64 g, 2.20 mmol, 44%); a white solid; mp 88–90 °C (ether–light petroleum). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.32 (t, *J*=7.2 Hz, 3H), 1.79 (dt, *J*=11.1, 12.9 Hz, 1H), 2.35 (ddd, *J*=3.3, 5.4, 12.9 Hz, 1H), 3.44 (dt, *J*=5.4, 11.1 Hz, 1H), 3.57 (s, 3H), 3.73 (s, 3H), 4.05 (dd, *J*=3.3, 11.1 Hz, 1H), 4.24 (dq, *J*=1.5, 7.2 Hz, 2H), 4.68 (dd, *J*=9.3, 12.6 Hz, 1H), 6.50 (d, *J*=12.6 Hz, 1H), 6.57 (d, *J*=8.4 Hz, 1H), 6.65 (dd, *J*=2.7, 8.4 Hz, 1H), 6.75 (d, *J*=2.7 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (Me), 34.1 (CH_2), 36.8 (CH), 54.1 (CH), 55.7 (OMe), 55.9 (OMe), 61.2 (OCH_2), 105.4 (CH), 113.2 (CH), 114.2 (CH), 115.7 (CH), 125.4 (C), 137.0 (C), 149.0 (CH), 152.1 (C), 172.8 (CO). IR (Nujol) 3392, 1733, 1648 cm^{-1}. MS (FAB): *m*/*z* (%)=292 (28) $[M+1]^+$, 291 (100) $[M]^+$, 218 (25), 186 (6), 160 (19). HRMS calcd for $C_{16}H_{22}NO_4$ $[M+H]^+$: 292.154883; found: 292.154513.

3.1.1.2. Ethyl [2-(*tert*-butyldimethylsilyloxy)vinyl]-6-methoxy-1,2,3,4-tetrahydroquinoline-2-carboxylate 4b. Compound **4b** was obtained using the general procedure: Imine **1** (1.00 g, 4.83 mmol); $BF_3 \cdot Et_2O$ (0.48 mmol); 1-*tert*-butyldimethylsilyloxy 1,3-butadiene (0.64 g, 3.49 mmol). Reaction time: 15 min. Dry flash column chromatography [silica; ether–light petroleum, polarity gradient] gave compound **4b**; yield: (0.75 g, 1.93 mmol, 55%); a white solid; mp 59–60 °C (light petroleum). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.19 (s, 6H), 0.97 (s, 9H), 1.32 (t, *J*=7.2 Hz, 3H), 1.76 (dt, *J*=11.4, 12.9 Hz, 1H), 2.33 (ddd, *J*=3.3, 5.4, 12.9 Hz, 1H), 3.42 (dt, *J*=5.4, 10.8 Hz, 1H), 3.73 (s, 3H), 4.05 (dd, *J*=3.3, 11.4 Hz, 1H), 4.15 (br s, 1H, NH)*, 4.25 (dq, *J*=2.7, 7.2 Hz, 2H), 4.95 (dd, *J*=9.9, 12.0 Hz, 1H), 6.44 (d, *J*=12.0 Hz, 1H), 6.65 (dd, *J*=2.7, 8.7 Hz, 1H), 6.73 (d, *J*=2.7 Hz, 1H). * Disappears with D_2O shake. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=−5.3 (Me), −5.2 (Me), 14.1 (Me), 18.3 (C), 25.7 (Bu^t), 33.8 (CH_2), 36.5 (CH), 54.1 (CH), 55.7 (OMe), 61.3 (OCH_2), 113.6 (CH), 113.7 (CH), 115.9 (CH), 125.3 (C), 136.9 (C), 142.4 (CH), 152.2 (C), 172.9 (CO). IR (Nujol) 3392, 1738, 1661, 1504 cm^{-1}. Anal. Calcd for $C_{21}H_{33}NO_4Si$: C, 64.41; H, 8.49; N, 3.58. Found: C, 63.96; H, 8.30; N, 3.68.

3.1.1.3. Ethyl 6-methoxy-3-methyl-4-(prop-1-enyl)-1,2,3,4-tetrahydroquinoline-2-carboxylate 5a. Compound **5a** was obtained using the general procedure: Imine **1** (0.65 g, 3.14 mmol); $BF_3 \cdot Et_2O$ (3.14 mmol); 2,4-hexadiene (0.28 g, 3.45 mmol). Reaction time: 1 h. Dry flash column chromatography [silica; ether–light petroleum, polarity gradient] gave compound **5a**; yield: (0.40 g, 1.40 mmol, 45%); a white solid; mp 88–90 °C (ether–light petroleum). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.77 (d, *J*=6.9 Hz, 3H), 1.32 (t, *J*=7.2 Hz, 3H), 1.81 (dd, *J*=1.5, 6.6 Hz, 3H), 2.42 (m, 1H), 3.68 (dd, *J*=4.8, 9.0 Hz, 1H), 3.74 (s, 3H), 4.18 (d, *J*=3.0 Hz, 1H), 4.27 (m, 2H), 5.50 (ddd, *J*=1.8, 9.0, 15.0 Hz, 1H), 5.72 (dq, *J*=6.6, 15.0 Hz, 1H), 6.57 (m, 1H), 6.65 (m, 2H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=8.6 (Me), 14.2 (Me), 18.0 (Me), 34.0 (CH), 46.0 (CH), 55.7 (OMe), 58.8 (CH), 61.2 (OCH_2), 112.7 (CH), 114.9 (CH), 114.9 (CH), 123.4 (C), 129.0 (CH), 131.2 (CH), 136.3 (C), 152.0 (C), 172.4 (CO). IR (Nujol) 3387, 1741, 1725 cm^{-1}. MS (FAB): *m*/*z* (%)=290 (17) $[M+1]^+$, 289 (55) $[M]^+$, 288 (10), 287 (23), 286 (100), 216 (25), 212 (27). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.13; H, 7.99; N, 4.91.

3.1.1.4. Ethyl 3-(*tert*-butyldimethylsilyloxy)-4-(2-(*tert*-butyldimethylsilyloxy)vinyl)-6-methoxy-3,4-dihydroquinoline-2-carboxylate 6b. Compound **6b** was obtained using the general procedure: Imine **1** (0.14 g, 0.67 mmol); $BF_3 \cdot Et_2O$ (0.67 mmol); 1,4-di-*tert*-butyldimethylsilyloxy1,3-butadiene (0.21 g, 0.67 mmol. Reaction time: 1 h. Dry flash column chromatography [silica; ether–light petroleum, polarity gradient] gave compound **6b** as an oil; yield: (0.10 g, 2.0 mmol, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=−0.02 (s, 3H), 0.10 (s, 3H), 0.21 (s, 6H), 0.72 (s, 9H), 0.97 (s, 9H), 1.43 (t, *J*=7.2 Hz, 3H), 3.20 (dd, *J*=3.9, 9.6 Hz, 1H), 3.84 (s, 3H), 4.43 (m, 2H), 4.65 (d, *J*=3.9 Hz, 1H), 5.23 (dd, *J*=9.6, 12.3 Hz, 1H), 6.45 (d, *J*=12.3 Hz, 1H), 6.82 (dd, *J*=8.7 Hz, 1H), 6.87 (d, *J*=3.0 Hz, 1H), 7.56 (d, *J*=8.7 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=−5.3 (Me), −5.1 (Me), −4.9 (Me), −4.6 (Me), 14.2 (Me), 18.1 (C), 18.3 (C), 25.6 (Me), 25.7 (Me), 41.4 (CH), 55.3 (OMe), 62.0 (OCH_2), 64.0 (CH), 106.6 (CH), 111.7 (CH), 113.4 (CH), 130.5 (CH), 133.1 (C), 136.4 (C), 144.1 (CH), 156.1 (C), 160.7 (C), 165.0 (C). IR (Nujol) 1732, 1710, 1661, 1620, 1568 cm^{-1}. HRMS calcd for $C_{27}H_{46}NO_5Si_2$ $[M+H]^+$: 520.291456; found: 520.291232.

3.1.1.5. Ethyl 6-methoxy-3-phenyl-4-styryl-1,2,3,4-tetrahydroquinoline-2-carboxylate 15c. Compound **15c** was obtained using the general procedure: Imine **1** (0.73 g,

3.50 mmol); $BF_3 \cdot Et_2O$ (3.50 mmol); 1,4-diphenyl-1,3-butadiene (0.72 g, 3.50 mmol). Reaction time: 3 h. Dry flash column chromatography [silica; ether–light petroleum, polarity gradient] gave compound **15c**; yield: (0.59 g, 1.43 mmol, 41%), mp 57–60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.89 (t, J=7.2 Hz, 3H), 3.22 (t, J=8.7 Hz, 1H), 3.73 (s, 3H), 3.82–3.94 (m, 3H), 4.13, (d, J=8.7 Hz, 1H), 4.20 (br s, 1H, NH)*, 6.01 (dd, J=8.7, 15.9 Hz, 1H), 6.18 (d, J=15.9 Hz, 1H), 6.75 (m, 3H), 7.25 (m, 10H). * Disappear with D_2O shake. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=13.6 (Me), 42.2 (OCH_2 or CH), 48.1 (CH), 55.7 (OMe), 60.1 (CH), 60.9 (CH or OCH_2), 113.8 (CH), 114.7 (CH), 116.9 (CH), 124.5 (C), 126.1 (CH), 126.8 (C), 127.1 (C), 128.2 (CH), 128.3 (CH), 128.4 (CH), 131.3 (CH), 132.9 (CH), 136.4 (C), 137.1 (C), 140.9 (C), 152.6 (C), 172.7 (CO). IR (Nujol) 3376, 1731, 1599, 1505 cm^{-1}. HRMS calcd for $C_{27}H_{28}NO_3$ $[MH]^+$: 414.206919; found: 414.207913.

3.1.1.6. Syntheses of ethyl 3-acetoxy-4-[(2-acetoxy)-vinyl]-6-methoxy-1,2,3,4-tetrahydroquinoline-2-carboxylate 5d and 15d. Compounds **5d** and **15d** were obtained using the general procedure: Imine **1** (0.31 g, 1.47 mmol); $BF_3 \cdot Et_2O$ (1.69 mmol); 1,4-diacetoxy1,3-butadiene (0.13 g; 0.74 mmol). Reaction time: 3 h (rt)+19 h (5 °C). Dry flash column chromatography [silica; ether–light petroleum, polarity gradient] gave compound **5d**; yield: (0.06 g, 0.16 mmol, 22%); a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.29 (t, J=7.5 Hz, 3H), 1.96 (s, 3H), 2.11 (s, 3H), 3.62 (br d, J=6.6 Hz, H-4), 3.73 (s, 3H), 4.13 (d, J=2.4 Hz, H-2), 4.18–4.34 (m, 2H), 5.34 (t, J=2.4 Hz, 1H, H-3), 5.55 (dd, J=6.9, 12.0 Hz, 1H), 6.55 (d, J=2.4 Hz, 1H), 6.64–6.78 (m, 2H), 7.01 (dd, J=1.5, 12.0 Hz). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (Me), 20.6 (Me), 20.9 (Me), 40.6 (C-4), 53.2 (C-2), 55.6 (OMe), 61.8 (OCH_2), 69.2 (C-3), 114.8 (CH), 115.0 (CH), 115.3 (C-1), 116.8 (CH), 119.0 (C), 135.4 (C), 139.3 (C-2′), 152.6 (C), 167.7 (CO), 170.2 (CO), 170.5 (CO). IR (neat) 3395, 3083, 2979, 2935, 2855, 1742, 1672 cm^{-1}. HRMS calcd for $C_{19}H_{24}NO_7$ $[MH]^+$: 378.1547; found: 378.1540.

A minor isomer, compound **15d**, was observed in the crude and in fractions of the flash chromatography. Some significant ^{1}H NMR peaks are registered: ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.26 (t=7.8 Hz, 3H), 1.99 (s, 3H), 2.08 (s, 3H), 3.54 (t, J=8.1 Hz, 1H, H-4), 4.00 (d, J=8.1 Hz, 1H, H-2), 4.19 (dq, J=1.2, 7.5 Hz, 1H, OCH_2), 5.21 (t, J=8.1 Hz, 1H, H-3), 7.06 (dd, J=1.2, 12.6 Hz, 1H, H-2′).

3.1.1.7. Synthesis of diethyl 1,7-bis((*E*)-2-(*tert*-butyldimethylsilyloxy)vinyl)-9-methoxy-1,2,3,5,6,7-hexahydropyrido[3,2,1-*ij*]quinoline-3,5-dicarboxylate 7b. The adduct **4b** (0.12 g, 0.30 mmol) was dissolved in dry toluene (10 mL) and ethyl glyoxylate (0.03 g, 0.30 mmol) was added. After cooling to −78 °C, $BF_3 \cdot Et_3O$ (4.3 mg, 0.03 mmol) was added with a syringe and the diene **2b** (55 mg, 0.30 mmol) followed after 5 min. Stirring was continued for 15 min at −78 °C and 30 min after removal of the refrigerating bath, then DCM (50 mL) was added. The solution was washed with saturated $NaHCO_3$ (50 mL) and water (50 mL). The organic phase was dried over $MgSO_4$ and evaporated to give an oil, pure by ^{1}H NMR (0.17 g, 0.26 mmol, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93 (s, 18H), 1.15 (s, 12H), 1.25 (t, J=7.2 Hz, 6H), 1.97 (dt, J=9.0, 12.6 Hz, 2H), 2.38 (dt, J=5.7, 12.6 Hz, 2H), 3.35 (dt, J=4.8, 9.0 Hz, 2H), 3.70 (s, 3H), 4.04 (dd, J=6.0, 8.1 Hz, 2H), 4.09–4.22 (m, 4H), 4.98 (dd, J=9.0, 11.7 Hz, 2H), 6.31 (d, J=11.7 Hz, 2H), 6.57 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=−5.24 (Me), 14.2 (Me), 18.3 (C), 25.7 (Me), 34.5 (CH_2), 34.9 (CH), 55.6 (OMe), 58.6 (CH), 60.8 (OCH_2), 111.9 (CH), 113.3 (CH), 127.4 (C), 133.9 (C), 142.2 (CH), 151.2 (C), 173.2 (CO). IR (Nujol) 1740, 1661, 1472 cm^{-1}. HRMS calcd for $C_{35}H_{58}NO_7Si_2$ $[M+H]^+$: 660.375186; found: 660.374173.

3.1.1.8. Synthesis of ethyl 6-methoxy-4-(2-oxoethyl)-1,2,3,4-tetrahydroquinoline-2-carboxylate 10. The tetrahydroquinoline **4b** (1.0 g, 2.57 mmol) was dissolved in THF (50 mL) and aq HCl 10% (10 mL) was added in an ice-water bath. The solution was then stirred at room temperature for 1 h. After addition of saturated aq $NaHCO_3$ (100 mL) the mixture was concentrated on the rotary evaporator and extracted with DCM (3×50 mL). The extracts were combined, dried over $MgSO_4$ and concentrated to give a light yellow oil identified as compound **10**; yield (0.56 g, 2.0 mmol, 78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.31 (t, J=7.2 Hz, 3H), 1.75 (dt, J=10.5, 12.6 Hz, 1H), 2.49 (ddd, J=3.9, 5.4, 12.6 Hz, 1H), 2.69 (ddd, J=2.1, 8.4, 17.7 Hz, 1H), 2.97 (ddd, J=1.2, 4.5, 17.7 Hz, 1H), 3.53 (m, 1H), 3.73 (s, 3H), 4.03 (dd, J=3.9, 10.5 Hz, 1H), 4.24 (q, J=7.2 Hz, 2H), 6.59 (d, J=8.7 Hz, 1H), 6.60 (d, J=2.7 Hz, 1H), 6.67 (dd, J=2.7, 8.7 Hz, 1H), 9.88 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.1 (Me), 30.4 (CH), 31.5 (CH_2), 48.9 (CH_2), 53.7 (CH), 55.7 (OMe), 61.3 (OCH_2), 112.5 (CH), 113.2 (CH), 116.1 (CH), 123.9 (C), 137.3 (C), 152.3 (C), 172.7 (CO), 201.3 (CHO). IR (Nujol) 3387, 1726, 1650, 1620 cm^{-1}. HRMS calcd for $C_{15}H_{19}NO_4$ $[M]^+$: 277.131408; found: 277.131619.

3.1.1.9. Synthesis of ethyl 6-methoxyquinoline-2-carboxylate 12. *Method 1*. To a solution of the aldehyde **10** (0.26 g, 0.94 mmol) dissolved in dry acetonitrile (20 mL) was added anilinium chloride (12.2 mg, 0.094 mmol). The mixture was kept stirring at room temperature for 60 h. Evaporation of the solvent gave an oil that was purified by dry flash chromatography [silica; ether–pet ether, polarity gradient]. Compound **12** was obtained as a solid (133 mg, 0.58 mmol, 62%), mp (ether–pet ether) 128–129 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.47 (t, J=7.2 Hz, 3H), 3.93 (s, 3H), 4.53 (q, J=7.2 Hz, 2H), 7.07 (d, J=2.7 Hz, 1H), 7.40 (dd, J=2.7, 9.6 Hz, 1H), 8.13 (s, 2H), 8.18 (d, J=9.6 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.3 (Me), 55.6 (OMe), 62.0 (OCH_2), 104.5, 121.4, 123.3, 130.7 (C), 132.2, 135.5, 143.7 (C), 145.7 (C), 159.3 (C), 165.5 (CO). IR (Nujol) 1729, 1621 cm^{-1}. HRMS calcd for $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.09728; found: 232.09748.

Method 2. The imine **1** (0.61 g, 2.96 mmol) was dissolved in dry toluene (10 mL) and the solution was refrigerated in an acetone/CO_2 bath. $BF_3 \cdot Et_2O$ (0.1 equiv, 0.30 mmol, 37 μl) was added dropwise followed by (1*S*,2*R*,4*R*)-1-isopropyl-4-methyl-(2-vinyloxy)cyclohexane (0.54 g, 2.96 mmol) in toluene (10 mL). The cold bath was removed after addition was complete and the solution was kept under magnetic stirring for 30 min at room temperature. The mixture was quenched with saturated aq $NaHCO_3$ (20 mL) and extracted with DCM (2×50 mL). The combined organic solutions

were dried over $MgSO_4$ and evaporated to give a yellow oil. Flash chromatography (silica; pet ether–ether, 5.5:1) gave a white solid (107 mg) that was a mixture of ethyl 4-[(1*S*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyloxy)methoxy]-1,2,3,4-tetrahydroquinoline-2-carboxylate[†] and menthol, and a second fraction (ether) a white solid for which the ^{1}H NMR compared with the one described for compound **12** is obtained in method 1.

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[†] Some peaks of ^{1}H NMR (300 MHz, $CDCl_3$) for compound **13**: δ=2.53 (ddd, *J*=3.6, 5.1, 12.3 Hz, 1H, H-3), 3.76 (s, 3H), 4.07 (dd, *J*=3.6, 10.8 Hz, 1H, H-2), 4.12 (br s, 1H, NH), 4.66 (dd, *J*=5.4, 9.6 Hz, 1H, H-4), 6.56 (d, *J*=8.4 Hz, 1H), 6.69 (dd, *J*=3.0, 8.4 Hz, 1H), 6.95 (1H, d, *J*=3.0 Hz, 1H).