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A New Multicomponent Synthesis of 1,2,3,4-Tetrahydroquinolines†

Rita Annunziata,* Mauro Cinquini, Franco Cozzi,* Valentina Molteni, and Olaf Schupp

Centro CNR and Dipartimento di Chimica Organica e Industriale - Universita' di Milano
via Golgi 19, I - 20133 Milano - Italy

Abstract: The synthesis of a variety of differently substituted 1,2,3,4- tetrahydroquinolines by a new three-component reaction involving an imine (Ar-N=CHR), an α-branched and enolizable aldehyde (R^1R^2CHCHO), and a nucleophile (ROH, ArSH, $ArNH_2$, H_2O) is described. The *in situ* generation of the imine (that allows a four-component process), and the reactions of an enantiomerically pure imine and/or aldehyde were also studied. A short discussion of the reaction mechanism is reported.

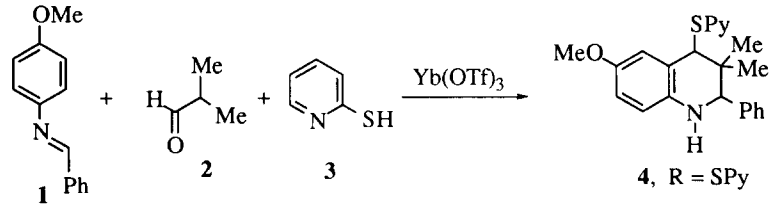
The Lewis acid promoted reaction of N-arylimines with alkenes,[1] dienes,[2] enamines,[3] enolethers,[2c-e,4] enolsilane,[4f] and vinylsulfides [2c,2d,5] represents a simple and mild procedure for the synthesis of 1,2,3,4-tetrahydroquinolines (THQ).[6] The powerful biological activity of THQ[7] recently prompted the development of a library[8] of these compounds, that is based on the reaction of *in situ* generated imines with variously substituted alkenes catalyzed by a polymer-supported scandium catalyst.[9]

We wish to report that a variety of chemically diverse THQ can be prepared in good yields by a new multicomponent synthesis in which an imine (pre-formed or generated *in situ*) is reacted with an α-branched and enolizable aldehyde, and a third reagent, likely acting as a nucleophile, under $Yb(OTf)_3$ ($OTf = OSO_2CF_3$) catalysis. The ready availability of the starting materials makes this new process a convenient entry to this class of compounds.

The synthesis of 2-phenyl-3,3-dimethyl-4-(2'-pyridylthio)-6-methoxy-1,2,3,4-tetrahydroquinoline **4** is illustrative of this new reaction (Scheme 1).[10] When 1.0 mol equiv each of imine **1**, aldehyde **2**, and thiol **3** were reacted for 15 h at room temperature in CH_2Cl_2 and in the presence of $Yb(OTf)_3$[11] (0.1 mol equiv) THQ **4** was obtained in 77% isolated yield as a 80 : 20 mixture of diastereoisomers, as determined by 300 MHz ^1H NMR analysis of the crude reaction product. The configuration of the major isomer was determined to be *trans* by n. O. e. experiments.[12]

The best conditions for the synthesis of THQ **4** were established by carrying out the reaction with different reagents/catalyst ratios and in various solvents. The data, collected in Table 1, show that as little as 0.01 mol equiv of $Yb(OTf)_3$ is enough to obtain the product in good yield (entry 3), whereas the reaction does not occur at an appreciable rate with 0.001 mol equiv of catalyst (entry 4). Remarkably, $Yb(OTf)_3$ can be recovered from the aqueous phase during the work-up,[2c,d] and the recycled catalyst is able to promote the reaction in comparable yield and stereoselectivity (entry 5). The synthesis of THQ **4** can be carried out in different solvents

Scheme 1.



(entry 6-9) in yields ranging from 50 to 60%. However, in methanol (entry 10) THQ **4** was obtained only in 29% yield, the major reaction product being the 4-methoxy substituted THQ **5** (see Table 2), isolated as a single isomer in 60% yield (Scheme 1).

Table 1. Synthesis of THQ **4** in Different Solvents and with Different Amounts of Catalyst.

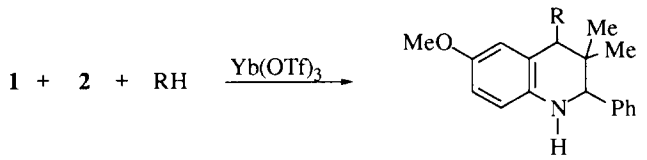
Entry	Mol Equiv of $Yb(OTf)_3$	Solvent	Yield%[a,b]
1	0.10	CH_2Cl_2	77
2	0.05	CH_2Cl_2	69
3	0.01	CH_2Cl_2	66
4	0.001	CH_2Cl_2	-
5	0.10[c]	CH_2Cl_2	67
6	0.10	CH_3NO_2	54
7	0.10	CH_3CN[d]	51
8	0.10	THF	61
9	0.10	AcOEt	62
10	0.10	CH_3OH	29[e]

[a] Isolated yield after flash chromatography. [b] Isomer ratio was 80 : 20 in all reactions. [c] This reaction was performed with a sample of catalyst that was recovered from a previous reaction and recycled [d] In this reaction, traces of the corresponding 3,4-dihydroquinoline were also detected. [e]THQ **5** was also obtained in 60% yield (see text).

In order to evaluate scope and limitations of this new THQ synthesis, the modification of the structure of the reagents was studied. The possibility of changing the substituent at C-4 suggested by the formation of THQ **5** was investigated with the experiments reported in Table 2. These indicate that several reagents, all nucleophilic in nature, such as methanol, benzyl alcohol, thiophenol, and 4-methoxyaniline can replace 2-pyridylthiol, their use leading to the formation of THQ **5** - **8** in good yields and in the indicated isomer ratios.[12] Not surprisingly, the yield of THQ **5** was higher when the reaction was carried out in methanol. It is also worth mentioning that in the absence of a nucleophile the reaction does not take place. When water was used instead of thiol **3**, its amount was crucial for the reaction outcome. Indeed, working with 1 mol equiv of H_2O in THF, the 4-OH substitued THQ **9** was obtained as a single isomer in 30% yield along with THQ **8** (27% yield, 59 : 41 mixture of isomers). However, the latter was the only product isolated (40% yield, same isomer ratio) when a large excess of water

(100 mol equiv) was employed. The formation of THQ **8** in these reactions can be accounted for by imine **1** hydrolysis followed by competitive incorporation of 4-methoxyaniline released from **1**.

Table 2. Synthesis of THQ **5 - 9** from Imine **1**, Aldehyde **2**, and Different "Third Reagents" RH.[a]



5 - 9

Entry	RH	Product	Yield%[b]	Isomer Ratio[c]
1	MeOH	**5**	62	>98 : 2
2	MeOH[d]	**5**	93	>98 : 2
3	$PhCH_2OH$	**6**	55	80 : 20
4	PhSH	**7**	78	>98 : 2
5	4-$MeOPhNH_2$	**8**	61	40 : 60
6	H_2O	**9**[e,f]	30	>98 : 2

[a] All reaction carried out in CH_2Cl_2 unless otherwise stated. [b]Isolated yield after flash chromatography. [c]As determined by 300 MHz ^1H NMR analysis of the crude products.[d] In methanol as the solvent. [e]In THF as the solvent. [f] From this reaction compound **8** was also isolated in 27% yield (see text).

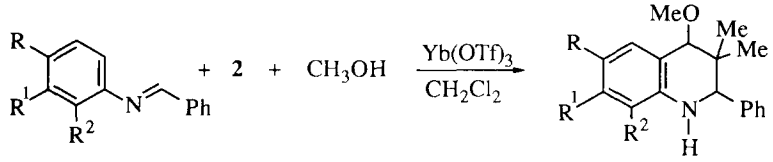
The variation of the imine component was then investigated by changing the substituent at both ends of the C=N double bond. As can be seen from the data collected in Table 3, the reaction can be extended to imines **10-15** derived from anilines featuring both electronwithdrawing and electrondonating substituents in different positions, affording THQ **16 - 21** as single isomers. The complete regioselectivity observed in the formation of THQ **18** and **20,** where the *meta* substituent of imines **12** and **14** ends up exclusively at C-7 of the THQ skeleton, is likely due to steric control.

The results obtained changing the C-substituent of the imine are reported in Table 4. They show that in addition to imines derived from aromatic aldehydes also those obtained from branched aliphatic aldehydes **22** and **23** can be used in this reaction, leading to the formation of THQ **26** and **27** in fair to good yields and with high level of stereoselectivity.[12] However, with the imines derived from 2-thienylcarbaldehyde **24** and allylglyoxylate **25**, the major products isolated were 3,4-dihydroquinolines **30** and **31**, respectively, obtained from the initially produced THQ **28** and **29**.[13] The imine derived from 4-methoxyaniline and acetone did not react in these conditions.

The replacement of aldehyde **2** in the reaction of Scheme 1 with a variety of different carbonyl derivatives was then attempted. From these experiments it was found that only enolizable *and* α-branched aldehydes can be used in this reaction, but not linear or β-branched aldehydes (butanal, 3-methylbutanal),[14] ketones (acetone, acetophenone, i-propyl phenyl ketone),[15] and β-ketoesters (methyl acetoacetate).[16] However, the structure of the reactive aldehyde greatly influenced the reaction outcome (Scheme 2). For instance, with the α-alkyl substituted aldehyde 2-methylbutanal *rac*-**32**, THQ **33** was obtained in 57% yield as a 50 : 50 mixture of diastereoisomers.

With the α-alkoxy substituted aldehyde 2-benzyloxypropanal (S)-**34** the expected THQ **35** was obtained only in

Table 3. Synthesis of THQ **16** - **21** from Imines **10** - **15**, Aldehyde **2**, and Methanol.



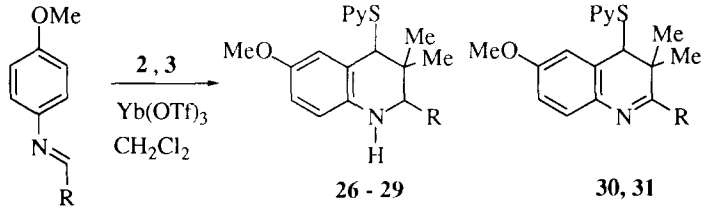
10 - 15 **16 - 21**

Imine	R	R^1	R^2	Product	Yield%[a,b]
10	H	H	H	**16**	80
11	H	H	MeO	**17**	34
12	H	Me	H	**18**	48
13	Cl	H	H	**19**	63
14	H	Cl	H	**20**	48
15	F	H	H	**21**	42

[a] Isolated yield after flash chromatography. [b] A single isomer was detected by 300 MHz ^{1}H NMR analysis of the crude products of all these reactions.

13% yield as an optically inactive 62 : 38 mixture of diastereoisomers. In this case the major reaction product was THQ **36**, that was isolated in 39% yield as an optically active 90 : 10 mixture of isomers {$[\alpha]_D^{23}$ = +176.1 (c 1, $CHCl_3$)}.[17]

Table 4. Synthesis of THQ **26** - **29** and 3,4-Dihydroquinolines **30**, **31** from Imines **22** - **25**, Aldehyde **2**, and 2-Pyridylthiol **3**.

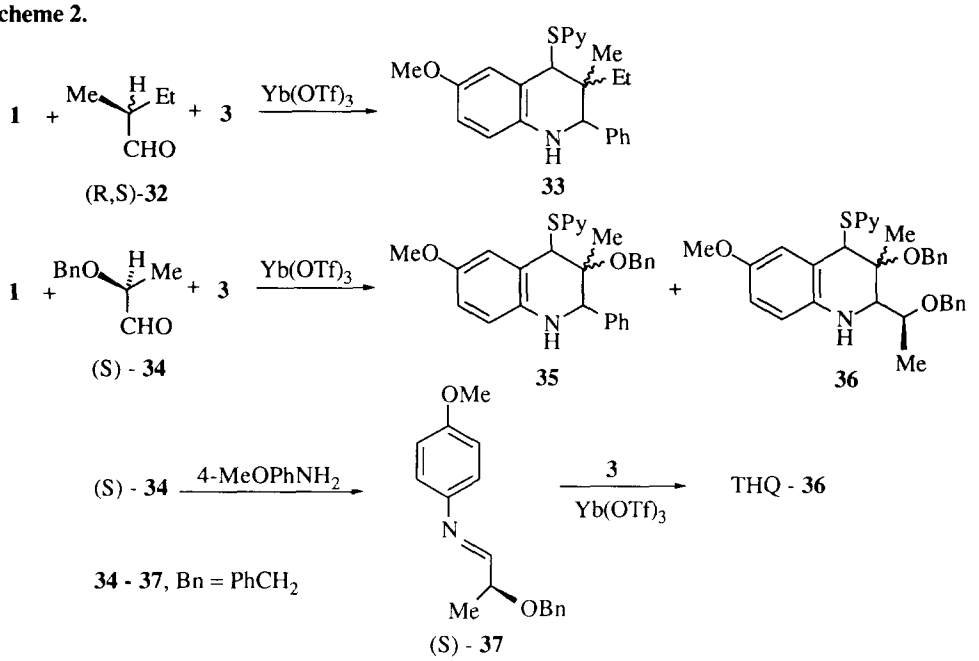


22 - 25 **26 - 29** **30, 31**

Imine	R	Product	Yield%[a]	Isomer Ratio[b]
22	c-C_6H_{11}	**26**	50	91 : 9
23	i-Pr	**27**	75	91 : 9
24	2-thienyl	**28+30**	48[c]	85 :15[d]
25	$COOC_3H_5$	**29+31**	97[c]	>98 : 2[e]

[a] Isolated yield after flash chromatography. [b]As determined by 300 MHz ^{1}H NMR analysis of the crude products. [c]Combined yield of THQ and dihydroquinoline. [d] Of THQ **28**. [e] Of THQ **29**.

Scheme 2.



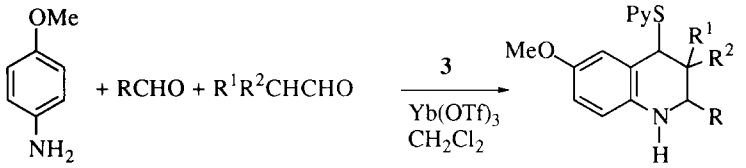
The generation of THQ **36** along with THQ **35** indicates that an exchange reaction has occurred, which converted imine **1** into imine **37** and competed with the formation of THQ **35**. By monitoring by 300 MHz ^1H NMR spectroscopy the reaction of aldehyde (S)-**34** (1 mol equiv) with imine **1** (1 mol equiv) in the presence of $Yb(OTf)_3$ (0.1 mol equiv) in CD_2Cl_2 at room temperature, it was shown that the exchange reaction was completed in about 5h.[18] The optical activity featured by **36** and the high level of stereoselection in which this compound was obtained strongly suggest that the exchange reaction of **1** with (S)-**34** to give **37** is not racemizing. To further elucidate this point, the synthesis of THQ **36** was studied starting from the pre-formed imine (S)-**37**. From this imine, compound **36** was obtained in 82% yield as a 89 : 11 mixture of the same two isomers isolated before.This mixture had $[\alpha]_D^{23} = +157.8$ (c 1, $CHCl_3$).

The THQ **33**, **35**, and **36** reported in Scheme 2 feature a stereocenter at C-3 in addition to those at C-2 and C-4. The configuration at C-3 of these compounds was not firmly determined. However, on the basis of the tendency of C-4 2-pyridylthio substituted THQ to be predominantly obtained in the *trans* configuration,[12] it seems reasonable to assume that they are mixtures of C-3 epimeric 2,4-*trans* configurated THQ. The remarkable level of stereocontrol observed in the synthesis of **36**, in which three new stereocenters are formed in up to 90 : 10 stereoselectivity independently of the method used (see above), is very promising in light of a possible application of this approach to the stereocontrolled synthesis of enantiomerically pure THQ.

Tryng to make this simple THQ synthesis even simpler, the *in situ* generation of the imine component was attempted (Table 5). When a mixture of 4-methoxyaniline (1 mol equiv), cyclohexane carboxyaldehyde (2 mol equiv), thiol **3** (1 mol equiv), and $Yb(OTf)_3$ (0.1 mol equiv) in CH_2Cl_2 was stirred at room temperature for 15h, THQ **38** was obtained in 35% yield as a 89 : 11 mixture of diastereoisomers. In similar conditions THQ **36** was obtained from aldehyde (S)-**34**, in yield and stereoselection identical to those observed starting from pre-formed imines (S)-**37**. Finally, the synthesis of THQ **4** was also achieved by the four-component reaction of 4-

methoxyaniline, benzaldehyde, 2-methylpropanal, and 2-pyridylthiol (1 mol equiv each) under $Yb(OTf)_3$ catalysis (57% yield, 86 : 14 *trans* : *cis* ratio).

Table 5. Synthesis of THQ **4**, **36**, and **38** from Imines Generated *in situ*.



4, 36, 38

R	R^1	R^2	Product	Yield%[a]	Isomer Ratio[b]
C_6H_{11}	$-(CH_2)_5-$		**38**	35	89 : 11
	Me	OCH_2Ph	**36**	87	90 : 10
Ph	Me	Me	**4**	57	86 : 14

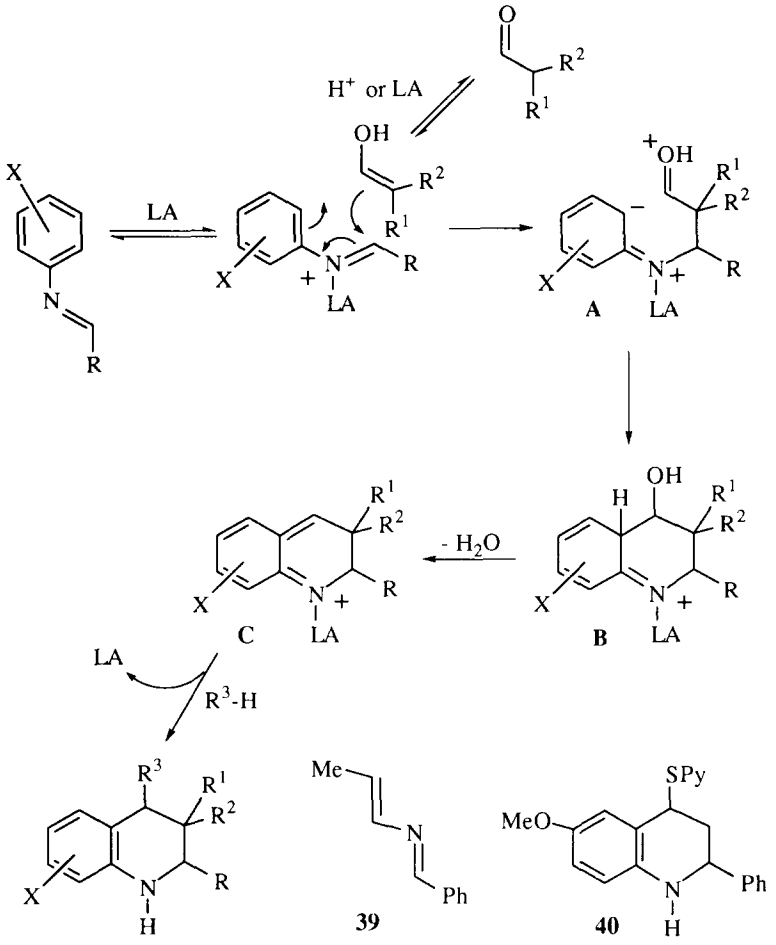
[a] Isolated yield after flash chromatography. [b]As determined by 300 MHz ^1H NMR analysis of the crude products.

The mechanism that is currently used as working hypothesis to explain this new THQ synthesis is reported in Scheme 3. The enol form of the aldehyde (obtained either by $Yb(OTf)_3$ or by TfOH[19] promoted enolization) should react with the imine activated by $Yb(OTf)_3$[20] (or TfOH) to afford adduct **B**, possibly *via* intermediate **A**. Upon water elimination **B** gives **C**. Addition of R^3-H, acting as a nucleophile, leads to rearomatization, formation of THQ, and catalyst release.

Experimental evidence supports this mechanism: i) both t-$BuMe_2SiOTf$ and TfOH catalyze the synthesis of THQ **4** in yield and stereoselectivity comparable to those observed in the $Yb(OTf)_3$ catalyzed reaction (same experimental procedure; 74% yield, 82 : 18 *trans* : *cis* ratio with t-$BuMe_2SiOTf$; 62% yield, 84 : 16 *trans* : *cis* ratio with TfOH). ii) the involvement of an achiral species derived from the aldehyde is consistent with the isolation of compound **35** in optically inactive form (see above). iii) the driving force provided by re-aromatization seems important, since when imine **1** was replaced by (1E,3E)-2-aza-1-phenyl-1,3-pentadiene **39**[21] (Scheme 3) the reaction did not take place. iv) when imine **1** was reacted with ethyl vinyl ether (1 mol equiv) in the presence of thiol **3** (1 mol equiv) and $Yb(OTf)_3$ (0.1 mol equiv), only THQ **40**[22] was obtained in 50% yield. This result can possibly be explained by formation of an adduct similar to **B** (OEt instead of OH at C-4; $R^1 = R^2 = H$), followed by elimination of EtOH to afford **C** ($R^1 = R^2 = H$) and by thiol **3** addition to give the product. v) as mentioned above, the reaction does not occur in the absence of the nucleophile.[23]

In conclusion, a new multicomponent synthesis of THQ by the $Yb(OTf)_3$ catalyzed reaction of an imine, an aldehyde, and a nucleophile has been realized. Work is underway to immobilize one of the reaction components on a polimeric matrix, to apply this method to the stereoselective synthesis of enantiomerically pure, biologically active THQ, and to fully elucidate the reaction mechanism.

Scheme 3.



Experimental

Imines **1**,[24] **10** and **13**,[25] **11** and **12**,[26] **14**,[27] **15**,[28] **22** and **24**,[10] **23**,[29] **25**,[30] were prepared according to literature procedures, as were aldehyde (S)-**34**[31] and imine (S)-**37**[32].

General Procedure for the Synthesis of THQ by the Three-Component Reaction. The reactions were carried out on 0.3 - 2.0 mmol scale; the preparation of **2-phenyl-3,3-dimethyl-4-(2'-pyridylthio)-6-methoxy-1,2,3,4-THQ 4** is illustrative of the procedure. To a stirred suspension of $Yb(OTf)_3$ (0.062g, 0.1 mmol) in dry CH_2Cl_2 (1 mL) stirred at room temperature under nitrogen, imine **1** (0.211g, 1 mmol) in CH_2Cl_2 (3 mL), freshly distilled 2-methylpropanal **2** (0.090 mL, 1 mmol), and 2-pyridylthiol **3** (0.111g, 1 mmol) in CH_2Cl_2 (3 mL) were added in this order. After 15h stirring, water (7 mL) was added and the organic phase was separated. The aqueous phase was extracted with 3x20 mL of CH_2Cl_2 and the combined organic phase was dried over sodium sulfate and evaporated *in vacuo* to give the crude product that was analyzed by 300 MHz ^1H NMR spectroscopy to evaluate the isomer ratio (to this end, the H-C4 singlet was generally exploited).

Purification by flash chromatography with a 80 : 20 hexanes : Et_2O mixture as eluant gave compound **4** (0.300g, 77% yield) as a 80 : 20 mixture of isomers. The mixture was a solid; the pure *trans* isomer had m.p. 144-145 °C. IR: 3375, 1577, 1504, 1254 cm^{-1}. Anal Calcd for $C_{23}H_{24}N_2OS$: C, 73.37; H, 6.42; N, 7.44. Found: C, 73.15; H, 6.40; N, 7.29. The reactions carried out with t-$BuMe_2SiOTf$ and TfOH as catalysts were similarly performed.

General Procedure for the Synthesis of THQ by the Four-Component Reaction. The preparation of THQ **4** is illustrative of the procedure. To a stirred suspension of $Yb(OTf)_3$ (0.062g, 0.1 mmol) in dry CH_2Cl_2 (1 mL) stirred at room temperature under nitrogen, 4-methoxyaniline (0.123g, 1 mmol) in CH_2Cl_2 (3 mL), freshly distilled benzaldehyde (0.101 mL, 1 mmol) were added in sequence. After 1h stirring at room temperature freshly distilled 2-methylpropanal **2** (0.090 mL, 1 mmol), and 2-pyridylthiol **3** (0.111g, 1 mmol) in CH_2Cl_2 (3 mL) were added in this order. After 15h stirring at room temperature the reaction was worked up as described above to give THQ **4** (0.214g, 57% yield) as a 86 : 14 mixture of isomer.

When THQ **36** and **38** were prepared by this procedure 2.0 mol equiv of aldehyde were added in one portion after 4-methoxyaniline, and were immediately followed by thiol **3**.

For each THQ the flash chromatographic hexanes : Et_2O eluting mixture is indicated in parenthesis after the compound name. Yields and isomer ratios of THQ are reported in Tables 1-5 and in the text. Selected NMR data of major (**M**) and minor (**m**, if detected) isomers of 3,3 -dimethylsubstituted compounds **4 - 9**, **16 - 21**, and **26 - 31** are collected in Tables 6 and 7; those of compounds **33**, **35**, **36**, and **38** are reported in this section; the resonances are listed in the following order: H-C2, H-C4, H-C5, H-C7, H-C8, Me-C3 (if present); C-2, C-3, C-4, C-5, C-7, C-8, C of Me -C3 (if present).

2-Phenyl-3,3-dimethyl-4,6-dimethoxy-1,2,3,4-THQ 5 (80 : 20). M.p.110-112 °C. IR: 3377, 1504, 1256 cm^{-1}. Anal Calcd for $C_{19}H_{25}NO_2$: C, 76.73; H, 7.79; N, 4.71 Found: C, 76.48; H, 7.69; N, 4.60.

2-Phenyl-3,3-dimethyl-4-phenylmethoxy-6-methoxy-1,2,3,4-THQ 6 (80 : 20). M.p. 110-112°C. IR: 3377, 1504, 1258 cm^{-1}. Anal Calcd for $C_{25}H_{27}NO_2$: C, 80.39; H, 7.29; N, 3.75 Found: C, 80.21; H, 7.37; N, 3.84.

2-Phenyl-3,3-dimethyl-4-phenylthio-6-methoxy-1,2,3,4-THQ 7 (90 : 10). M.p. 144-145 °C. IR: 3354, 1506, 1251 cm^{-1}. Anal Calcd for $C_{24}H_{25}NOS$: C, 76.76; H, 6.71; N, 3.73 Found: C, 76.58; H, 6.80; N, 3.81.

2-Phenyl-3,3-dimethyl-4-[N-(4'-methoxyphenyl)amino]-6-methoxy-1,2,3,4-THQ 8 (80 : 20). M.p. 58-62 °C. IR: 3379, 1509, 1232 cm^{-1}. Anal Calcd for $C_{25}H_{28}N_2O_2$: C, 77.29; H, 7.26; N, 7.21. Found: C, 77.44; H, 7.37; N, 7.12.

2-Phenyl-3,3-dimethyl-4-hydroxy-6-methoxy-1,2,3,4-THQ 9 (80 : 20). M.p. 145- 146 °C. IR: 3370, 1505, 1258 cm^{-1}. Anal Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94 Found: C, 76.11; H, 7.58; N, 4.90.

2-Phenyl-3,3-dimethyl-4-methoxy-1,2,3,4-THQ 16 (80 : 20), was a waxeous solid.
IR: 3377, 1494, 1301 cm^{-1}. Anal Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24 Found: C, 81.00; H, 8.00; N, 5.19.

2-Phenyl-3,3-dimethyl-4,8-dimethoxy-1,2,3,4-THQ 17 (80 : 20), was a thick oil. IR: 3377, 1500, 1301 cm^{-1}. Anal Calcd for $C_{19}H_{23}NO_2$: C, 76.73; H, 7.79; N, 4.71 Found: C, 76.66; H, 7.88; N, 4.61.

2-Phenyl-3,3,7-trimethyl-4-methoxy-1,2,3,4-THQ 18 (90 : 10). M.p. 65°C. IR: 3387, 1619, 1484, 1305 cm^{-1}. Anal Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98 Found: C, 80.96; H, 8.09; N, 5.05.

2-Phenyl-3,3-dimethyl-4-methoxy-6-chloro-1,2,3,4-THQ 19 (90 : 10), was a waxeous solid. IR: 3403, 1607, 1494, 1304 cm^{-1}. Anal Calcd for $C_{18}H_{20}ClNO$: C, 71.63; H, 6.68; N, 4.64 Found: C, 71.50; H,

6.79; N, 4.55.

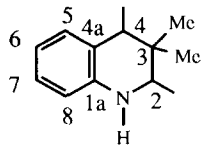
2-Phenyl-3,3-dimethyl-4-methoxy-6-chloro-1,2,3,4-THQ 19 (90 : 10), was a waxy solid. IR: 3403, 1607, 1494, 1304 cm^{-1}. Anal Calcd for $C_{18}H_{20}ClNO$: C, 71.63; H, 6.68; N, 4.64 Found: C, 71.50; H, 6.79; N, 4.55.

2-Phenyl-3,3-dimethyl-4-methoxy-7-chloro-1,2,3,4-THQ 20 (90 : 10) M.p. 76-77°C. IR: 3421, 1605, 1492, 1303 cm^{-1}. Anal Calcd for $C_{18}H_{20}ClNO$: C, 71.63; H, 6.68; N, 4.64 Found: C, 71.53; H, 6.59; N, 4.51.

2-Phenyl-3,3-dimethyl-4-methoxy-6-fluoro-1,2,3,4-THQ 21 (90 : 10). M.p. 115-116 °C. IR: 3387, 1503, 1247 cm^{-1}. Anal Calcd for $C_{18}H_{20}FNO$: C, 75.76; H, 7.06; N, 4.91 Found: C, 75.61; H, 6.98; N, 4.83.

2-Cyclohexyl-3,3-dimethyl-4-(2'-pyridylthio)-6-methoxy-1,2,3,4-THQ 26 (80 : 20) was a waxy solid. IR: 3410, 1575, 1504, 1256 cm^{-1}. Anal Calcd for $C_{23}H_{30}N_2OS$: C, 72.21; H, 7.90; N, 7.32 Found: C, 72.06; H, 8.01; N, 7.18.

Table 6. Selected ^1H NMR Data of Compounds **4,5-9,16-21,26-31**[a]



	H-2	H-4	H-5	H-6	H-7	H-8	Me-3	Other signals[b]
4M	4.43	5.33	6.87	-	6.67	6.49	1.00 ; 0.88	7.47; 7.47; 7.00; 8.48[c]
4m	4.45	5.67	6.80	-	6.65	6.49	1.03 ; 1.00	7.47; 7.47; 7.00; 8.45[c]
5M	4.51	3.52	6.73	-	6.78	6.53	0.93 ; 0.72	3.43[d]
6M	4.67	3.79	6.73	-	6.76	6.57	0.98 ; 0.84	4.67[e]
6m	4.67	3.85	6.83	-	6.76	6.53	0.92 ; 0.75	4.77[e]
7M	4.68	4.04	6.43	-	6.70	6.50	1.05 ; 0.96	6.67[f]
8M	4.60	4.43	6.89	-	6.67	6.48	0.88	6.70; 6.80[g]
8m	4.20	3.96	6.67	-	6.67	6.53	0.95 ; 0.90	6.70; 6.82[g]
9M	4.40	4.12	6.83	-	6.77	6.53	0.92 ; 0.75	
16M	4.46	3.60	7.16	6.70	7.18	6.60	1.00 ; 0.75	3.60[d]
17M	4.53	3.58	6.80	6.60	6.77	-	0.97 ; 0.70	3.58[d]
18M	4.57	3.55	7.03	6.51	-	6.44	0.96 ; 0.72	3.55[d]
19M	4.51	3.48	7.07	-	7.07	6.50	0.92 ; 0.66	3.38[d]
20M	4.53	3.52	7.00	6.63	-	6.60	0.94 ; 0.66	3.35[d]
21M	4.50	3.50	6.80	-	6.80	6.50	0.92 ; 0.69	3.41[d]
26M	3.03	5.19	6.87	-	6.60	6.41	1.14 ; 1.08	7.13; 7.43; 6.98; 8.50[c]
26m	2.90	5.43	6.87	-	6.60	6.41	1.10 ; 1.00	7.13; 7.43; 6.98; 8.40[c]
27M	3.10	5.20	6.80	-	6.66	6.47	1.14 ; 1.08	7.13; 7.47; 6.98; 8.50[c,h]
27m	3.13	5.40	6.78	-	6.68	6.48	1.12 ; 1.00	7.30; 7.50; 7.00; 8.37[c,j]
28M	4.73	5.38	6.84	-	6.66	6.50	1.10 ; 0.95	7.17; 7.47; 7.00; 8.48[c,k]
28m	4.73	5.60	6.84	-	6.66	6.50	1.10 ; 1.07	7.17; 7.47; 7.00; 8.40[c,l]
29M	4.07	5.24	6.77	-	6.66	6.55	1.31 ; 0.99	7.13; 7.43; 7.00; 8.47[c,m]
30	-	5.26	6.83	-	6.79	7.36	1.65 ; 1.33	7.06; 7.43; 7.00; 8.49[c,n]
31	-	5.31	6.87	-	6.78	7.41	1.42 ; 1.33	7.10; 7.43; 7.00; 8.47[c,o]

[a] **M** = major isomer; **m** = minor isomer.[b] The C-2 Ph protons are in the range 7.30 - 7.50 ppm.[c] HC-3'; HC-4'; HC-5'; HC-6' of the pyridine nucleus.[d] Of MeO at C-4.[e] Of $PhCH_2O$ at C-4.[f] Of PhS at C-4.[g] Of C_6H_4 at C-4.[h] 2.12 ($CHMe_2$); 1.01, 1.09 ($CHMe_2$).[j] 2.23 ($CHMe_2$).[k] Thienyl protons: 7.00, 7.07, 7.27.[l] Thienyl protons: 7.00, 7.07, 7.27.[m] Allyl protons: 4.67, 5.30, 5.37, 5.90.[n] Thienyl protons: 7.06, 7.39, 7.49.[o] Allyl protons: 4.80, 5.30, 5.37, 6.03.

2-(1-Methylethyl)-3,3-dimethyl-4-(2'-pyridylthio)-6-methoxy-1,2,3,4-THQ **27** (80 : 20) was a waxeous solid. IR: 3408, 1577, 1504, 1256 cm^{-1}. Anal Calcd for $C_{20}H_{26}N_2OS$: C, 70.14; H, 7.65; N, 8.18. Found: C, 70.06; H, 7.53; N, 8.27.

2-(2'-Thienyl)-3,3-dimethyl-4-(2"-pyridylthio)-6-methoxy-1,2,3,4-THQ **28** (90 : 10). This compound melted between 45 and 65°C, likely because of its conversion into compound **30**. The infrared spectrum and the elemental analysis were not obtained.

2-Carboallyloxy-3,3-dimethyl-4-(2'-pyridylthio)-6-methoxy-1,2,3,4-THQ **29** (80 : 20). This compound could not be obtained free from its dehydro derivative **31**.

2-(2'-Thienyl)-3,3-dimethyl-4-(2"-pyridylthio)-6-methoxy-3,4-dihydroquino- line **30** (90 : 10). M. p. 65-68°C. IR: 1610, 1578, 1413, 1254 cm^{-1}. Anal Calcd for $C_{21}H_{20}N_2OS_2$: C, 66.28; H, 5.28; N, 7.36. Found: C, 66.41; H, 5.41; N, 7.38.

2-Carboallyloxy-3,3-dimethyl-4-(2'-pyridylthio)-6-methoxy-3,4-dihydroquinoline **31** (80 : 20) was a thick red oil. IR: 1728, 1615, 1576, 1416, 1249 cm^{-1}. Anal Calcd for $C_{21}H_{22}N_2O_3S$: C, 65.94; H, 5.80; N, 7.32. Found: C, 66.11; H, 5.70; N, 7.19.

Table 7. Selected ^{13}C NMR data of compounds **4,5-9,16-21,26-31**[a,b]

	C-2	C-3	C-4	C-4a	C-1a	Me-3	C-5	C-6	C-7	C-8
4M	61.8	37.1	53.1	122.3	137.7	24.5 ; 21.0	115.2	151.8	114.7	114.9
4m	66.9	37.0	54.5	122.2	138.5	25.5 ; 16.0	116.0	152.0	113.8	114.6
5M	59.9	36.1	85.4	119.6	138.2	19.2 ; 23.3	116.5	150.7	114.6	115.3
6M	60.0	36.2	82.5	119.5	138.5	23.7 ; 19.2	116.5	150.5	114.7	115.4
6m	55.4	36.7	81.3	122.0	c	23.1 ; 22.4	116.0	151.9	114.9	113.3
7M	61.3	37.4	60.8	121.6	137.7	25.9 ; 21.9	115.4	151.8	114.8	114.8
8M	62.0	37.0	66.6	124.0	137.1	24.7 ; 13.9	115.2	152.0	113.3	114.7
8m	61.3	37.8	62.0	125.5	138.6	23.6 ; 20.8	115.1	152.2	113.5	114.9
9M	59.6	36.8	76.1	122.6	136.0	22.9 ; 18.9	116.3	151.6	115.1	115.3
16M	59.3	36.5	75.8	121.9	143.9	22.8 ; 18.9	131.1	115.7	129.0	113.7
17M	59.4	35.8	85.0	118.5	133.9	23.3 ; 19.3	123.2	109.8	114.4	145.9
18M	59.7	36.0	84.9	115.9	142.0	24.5 ; 19.3	131.0	117.0	138.9	114.2
19M	59.7	35.6	84.7	119.9	142.0	23.1 ; 19.2	130.3	120.0	129.1	114.8
20M	59.5	35.6	84.4	116.9	144.9	23.2 ; 19.2	132.0	115.6	134.6	113.1
21M	59.8	35.8	84.9	119.3	140.3	23.1 ; 19.1	116.8	153.5	115.8	114.3
26M	61.7	36.8	54.5	122.7	138.1	24.3 ; 23.0	114.8	151.4	114.9	114.9
26m	66.2	36.8	55.3	122.7	138.1	24.2 ; 23.0	114.8	151.5	114.9	114.9
27M	61.2	36.8	54.6	122.6	138.0	24.3 ; 23.5	114.7	151.5	115.0	114.9
28M	58.3	37.2	52.8	122.6	137.1	24.4 ; 21.2	114.8	152.2	115.3	115.1
28m	63.3	37.2	54.1	122.6	137.0	25.3 ; 16.8	113.7	155.0	116.0	115.0
30	165.0	39.6	52.7	130.6	130.6	25.0 ; 25.0	112.2	158.6	113.4	121.4
31	163.5	38.5	51.0	131.5	135.0	23.7 ; 21.4	113.0	160.0	113.2	129.2

[a] See Table 6 for numbering. [b] **M** = major isomer; **m** = minor isomer. [c] Undetected.

2-Phenyl-3-ethyl-3-methyl-4-(2'-pyridylthio)-6-methoxy-1,2,3,4-THQ **33** (90 : 10). M.p. 42 - 45 °C. IR: 3369, 1577, 1504, 1413, 1250 cm^{-1}. ^1H NMR of one of the two isomers: 6.90(d), 6.67(dd), 6.48(d), 5.68(s), 4.56(s), 1.77(q), 1.01(s), 0.77(t); of the other isomer: 6.87(d), 6.70(dd), 6.48(d), 5.38(s), 4.42(s), 1.77(q), 1.01(t), 0.92(s). ^{13}C NMR of one of the two isomers: 151.8, 137.8, 127.9, 129.6, 124.3, 114.5, 115.0, 114.7, 63.2, 49.8, 39.0, 30.0, 21.0, 7.6; of the other isomer: 151.5, 136.6, 129.2, 127.9, 122.4,

114.8, 114.7, 113.7, 62.8, 49.1, 39.3, 24.7, 17.0, 7.3. Anal Calcd for $C_{24}H_{26}N_2OS$: C, 73.81; H, 6.71; N, 7.17 Found: C, 74.21; H, 6.88; N, 7.43.

2-Phenyl-3-methyl-3-phenylmethoxy-4-(2'-pyridylthio)-6-methoxy-1,2,3,4-THQ 35 (80 : 20) was an oil. IR: 3391, 1577, 1504, 1414, 1255 cm^{-1}. ^1H NMR of the major isomer: 7.67(d), 7.33(m), 6.82(d), 6.68(dd), 6.53(d), 6.00(s), 4.70-4.57 (AB system), 4.47(s), 1.20(s); of the minor isomer: 7.60(d), 7.33(m), 6.87(d), 6.67(dd), 6.53(d), 5.87(s), 4.73, 4.45-4.30 (AB system), 1.27(s). ^{13}C NMR of the major isomer: 152.0, 138.1, 127.9, 114.9, 115.1, 115.1, 76.4, 63.8, 62.6, 45.6, 19.2; of the minor isomer: 151.9, 136.6, 127.9, 114.3, 115.2, 115.7, 77.4, 63.7, 61.5, 50.5, 17.25. Anal Calcd for $C_{29}H_{28}N_2O_2S$: C, 74.33; H, 6.02; N, 5.98. Found: C, 74.51; H, 6.08; N, 6.10.

2-[(S)-1-Phenylmethoxyethyl]-3-methyl-3-phenylmethoxy-4-(2'-pyridylthio)-6-methoxy-1,2,3,4-THQ 36 (80 : 20) was an oil. IR: 3419, 1577, 1504, 1414, 1256 cm^{-1}. ^1H NMR of the major isomer: 7.67(m), 7.33(m), 6.80(d), 6.67(dd), 6.49(d), 5.79(s), 4.70-4.57 (AB system), 4.53 (AB system), 4.03(dq), 3.43(d), 1.44(s), 1.43(d); of the minor isomer: 7.60(m), 7.33(m), 6.80(d), 6.65(dd), 6.52(d), 5.93(s), 4.70-4.47 (AB system), 4.51(AB system), 4.00(dq), 3.33(d), Me undetermined. ^{13}C NMR of the major isomer: 151.5, 138.4, 127.8, 113.8, 115.5, 115.1, 75.1, 73.5, 70.5, 63.8, 60.9, 50.5, 18.4, 18.0; of the minor isomer: 151.6, 138.5, 127.9, 114.1, 115.5, 115.1, 77.1, 73.0, 70.4, 63.5, 58.9, 52.0, 19.0, 16.0. Anal Calcd for $C_{32}H_{34}N_2O_3S$: C, 72.97; H, 6.51; N, 5.32. Found: C, 73.31; H, 6.37; N, 5.50.

Spiro[[2-cyclohexyl-4-(2'-pyridylthio)-6-methoxy-1,2,3,4-tetrahydroquinoline]-3,1'-cyclohexane] 38 (90 : 10). M.p. 58 - 62 °C. IR: 3410, 1577, 1504, 1413, 1252 cm^{-1}. ^1H NMR of the major isomer: 6.87(d), 6.60(dd), 6.42(d), 5.80(s), 3.07(d), 1.99-1.00(bm); of the minor isomer: 6.87(d), 6.62(dd), 6.40(d), 5.82(s), 3.17(d), 1.99-1.00(bm). ^{13}C NMR of the major isomer: 151.2, 137.5, 121.1, 114.3, 114.3, 114.3, 61.4, 55.7, 54.4, 47.9, 37.9, 34.6, 28.2, 27.1, 26.7, 26.4. The ^{13}C spectrum of the minor isomer was not determined. Anal Calcd for $C_{26}H_{34}N_2OS$: C, 73.89; H, 8.11; N, 6.63. Found: C, 73.62; H, 8.29; N, 6.47.

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References and Notes

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10 This new THQ synthesis was serendipitously discovered while studying a three-component synthesis of β-lactams by $Yb(OTf)_3$ catalyzed addition of silyl ketene thioacetals derived from 2-pyridylthioesters to imines: Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *J. Org. Chem.* **1996**, *61*, 8293.

11 Two different samples of commercially available (Aldrich) $Yb(OTf)_3$ were employed and used without the need of any further purification. When purchased, the first sample contained ca. 1.5 and the second one ca. 2.3 moles of water/mole of $Yb(OTf)_3$. However, they behave identically.

12 The *trans* isomer did not show n. O. e. between HC-2 and HC-4, whereas n. O. e. was observed in the *cis* compound. The HC-2/HC-4 interproton distance calculated from the 2D NOESY map for *cis* - **4** was 3.2 Å. The configuration of THQ **6** (see below) was also established by similar NMR experiments. In this case, the major isomer has the *cis* configuration. Comparison of the chemical shift values of diagnostic proton and carbon signals (HC-2 and C-2; HC-4 and C-4) within homogeneous pairs of diastereoisomeric THQ (see Table 6 and 7) suggests the *trans* configuration for the major isomers of THQ **26-28**, and the *cis* one for the major isomer of **8**. The *cis* configuration of THQ **5**, **9**, and **16-21**, obtained as single isomers, is a likely hypothesis that requires demonstration. The isomeric composition of THQ **4** and **5** did not change after 24 h exposure to 1.0 mol equiv of pyridine (RT, CH_2Cl_2).

13 Since the two isomers of **28** and **29** can be converted into **30** and **31**, respectively, at different rates, the isomer ratios reported in Table 4 may not reflect the original composition of the diastereoisomeric mixture.

14 From these reactions complex mixtures of products were obtained. Apparently, these aldehydes react with two molecules of imine **1**.

15 Unreacted imine **1** was recovered in high yield from these reactions.

16 From the reaction with methyl acetacetate in nitromethane a product was obtained in 26% yield as a mixture of isomers, likely deriving from reaction of C-2 and C-4 of methyl acetacetate with two molecules of **1**.

17 (R)-*O,O*-Cyclohexylidene glyceraldehyde behaved similarly to **34** affording products analogous to **35** and **36**, in 23 and 39% yield, respectively. Both were mixtures of diastereoisomers; the former was optically inactive and the latter optically active.

18 This exchange reaction is currently under active investigation in our laboratories.

19 TfOH can be present in the reaction medium because of $Yb(OTf)_3$ hydrolysis promoted either by the water molecules associated with the catalyst (see ref. 11), or by traces of water present in the solvents.

20 $Yb(OTf)_3$ is a powerful imine activator (see ref. 2c, 2d, and 10) We recently collected NMR evidence that $Yb(OTf)_3$ co-ordinates the nitrogen of imine **1** (see ref. 10).

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22 This product was a 86 : 14 mixture of *trans* and *cis* isomers both featuring an equatorial C-2 Ph substituent.

23 However,we failed both to isolate any product by reacting the benzaldehyde imine of 2,6-dimethylaniline with aldehyde **2** in the presence of $Yb(OTf)_3$, and to trap adduct C with dienophiles. In addition, replacement of 2-methylpropanal **2** with its N-morpholinoenamine did not afford any THQ.

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