Tetrahedron 64 (2008) 11335–11348

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

New pyridine *N*-oxides as chiral organocatalysts in the asymmetric allylation of aromatic aldehydes

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ARTICLE INFO

Article history:
Received 10 June 2008
Received in revised form 19 August 2008
Accepted 27 August 2008
Available online 4 September 2008

Dedicated to the memory of Dr. Andy Parkin

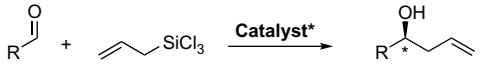
Keywords:
Enantioselective allylation
Allylsilane
Organocatalysis
Asymmetric catalysis
Pyridine *N*-oxides

ABSTRACT

Asymmetric allylation of aromatic aldehydes **1** with allyltrichlorosilane (**2**) can be catalyzed by new terpene-derived bipyridine *N*,*N*′-dioxides **12**–**15** and an axially chiral biisoquinoline dioxide **17b** with good enantioselectivities. Dioxides have been found to be more reactive catalysts than their monooxide counterparts.

1. Introduction

Asymmetric allylation of aldehydes **1** with allyl- and crotyl-trichlorosilanes,[1] catalyzed by chiral Lewis bases[1,2] (Scheme 1), has evolved into a robust methodology, allowing a simple and practical access to homoallylic alcohols.[3] Since the latter products are of interest to the pharmaceutical and fine-chemicals industries as basic building blocks for the construction of more complex molecules, further development, enhancing the catalyst efficiency, and broadening of the scope of the reaction is desirable.



1 2 3

Scheme 1. Asymmetric allylation of aromatic aldehydes. For R, see Table 1.

Chiral, pyridine-based *N*-oxides have emerged in the last few years as powerful Lewis-basic catalysts for this transformation with good to excellent enantioselectivities and with catalyst loading that is unusually low in the organocatalyst realm. Thus, various C_2-symmetrical bipyridine *N*,*N*′-dioxides, such as **4**–**7** (Chart 1), have been developed by several groups,[4–7] including our own,[8] and their enantioselectivities were demonstrated with the aid of a portfolio of aromatic aldehydes (with ≤90% ee for benzaldehyde; Table 1, entries 1–5). Simultaneously, we have shown that pyridine monooxides, such as **8**–**11** (entries 6–11), can more than successfully compete with the dioxides,[8–12] and METHOX (**10**)[11] can be regarded as the current champion catalyst in terms of enantioselectivity, reactivity,

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0040-4020/$ – see front matter
doi:10.1016/j.tet.2008.08.084

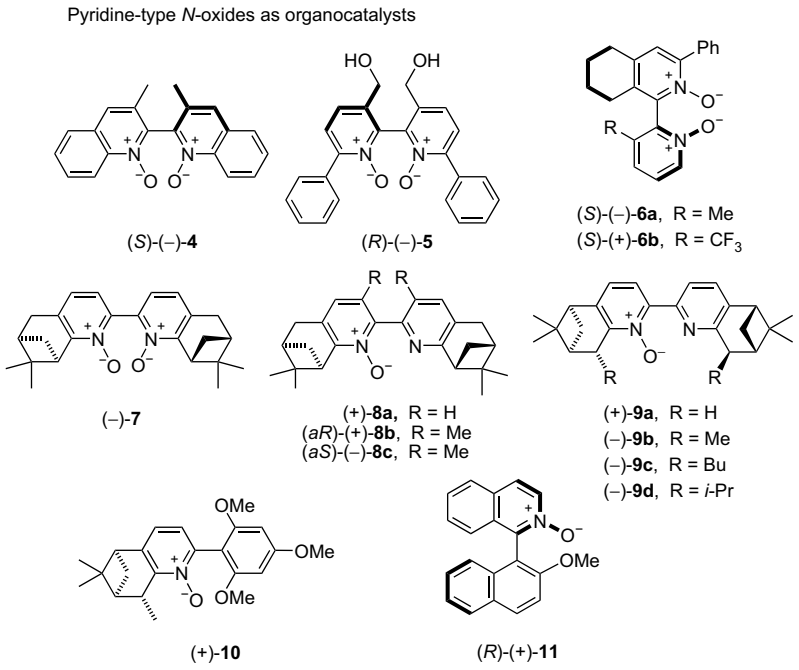


Chart 1. Pyridine-type *N*-oxides as organocatalysts.

Table 1
Allylation of aldehydes RCHO (**1**) with **2** catalyzed by Lewis bases **4**–**11** (Scheme 1 and Chart 1)[a]

Entry	Aldehyde **1** (R)	Catalyst (mol %)	Solvent	Temp (°C)	Time (h)	Yield (%)	ee (%)	Configuration of **3**	Ref
1	Ph	(*S*)-(−)-**4** (20)	CH_2Cl_2	−78	6	85	88	(*R*)-(+)	4
2	Ph	(*R*)-(−)-**5** (0.1)	MeCN	−45	2.5	95	84	(*S*)-(−)	5
3	Ph	(*S*)-(−)-**6a** (5)	CH_2Cl_2	−78	6	87	74	(*R*)-(+)	7
4	Ph	(*S*)-(+)-**6b** (5)	CH_2Cl_2	−78	6	53	72	(*R*)-(+)	7
5	Ph	(−)-**7** (10)	CH_2Cl_2	−90	48	18	41	(*R*)-(+)	8
6	Ph	(+)-**8a** (10)	CH_2Cl_2	−60	24	78	90	(*S*)-(−)	8
7	Ph	(−)-**9d** (10)	CH_2Cl_2	−20	18	23	93	(*S*)-(−)	8
8	Ph	(+)-**10** (5)	MeCN	−40	18	≥95	96	(*S*)-(−)	11
9	Ph	(*R*)-(+)-**11** (5)	CH_2Cl_2	−40	2	60	87	(*R*)-(+)	10
10	4-CF_3–C_6H_4	(*R*)-(+)-**11** (5)	CH_2Cl_2	−40	2	85	96	(*R*)-(+)	10
11	4-MeO–C_6H_4	(*R*)-(+)-**11** (5)	CH_2Cl_2	−40	12	70	16	(*R*)-(+)	10

synthetic availability, and scope (entry 8). QUINOX (**11**) proved to be rather more fastidious with respect to the aldehyde substrate, giving very high enantioselectivities with electron-poor aldehydes (entry 10) but low with their electron-rich congeners (entry 11).[10]

2. Results and discussion

2.1. Catalyst design

A comparison of the C_2-symmetrical dioxide **7** with its monooxide counterpart **8a** (PINDOX) clearly shows the superiority of the latter (41 vs 90% ee; Table 1, compare entries 5 and 6).[8] On the other hand, the non-terpene bipyridine dioxides **4** and **5** performed much better than **7** (entries 1 and 2),[4,5] exhibiting selectivities comparable with **8a** (entries 6 and 7). Since the relatively low level of asymmetric induction in the case of **7** may, a priori, be associated with its particular architecture, it was desirable to synthesize further terpene-derived dioxides for comparison. To this end, we set out to prepare the C_1-symmetrical dioxide **12** (Chart 2) as a quinoline analogue of the C_2-symmetrical catalyst **7**, the benzoquinoline

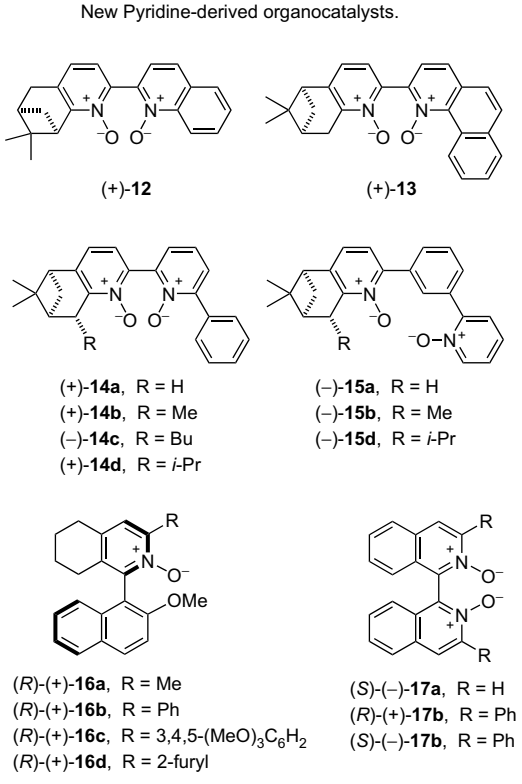
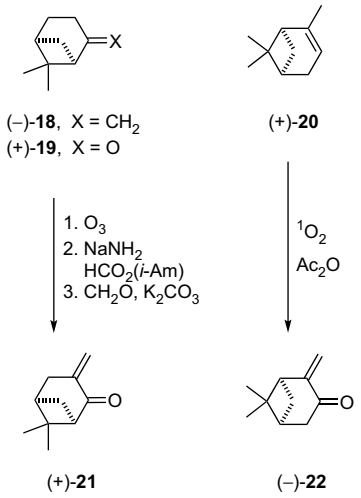


Chart 2. New pyridine-derived organocatalysts.

analogue **13** with an isomeric terpene unit, and a series of bipyridine analogues with a phenyl or (α-pyridyl)phenyl pendants **14a**–**d** and **15a**,**b**,**d**. This small library of catalyst candidates was extended by the axially chiral monooxides **16a**–**d** and dioxide **17b** (a derivative of the known dioxide **17a**[4] that can also be regarded as an analogue of **5**[5]) for additional comparison.



Scheme 2. Synthesis of terpene precursors.

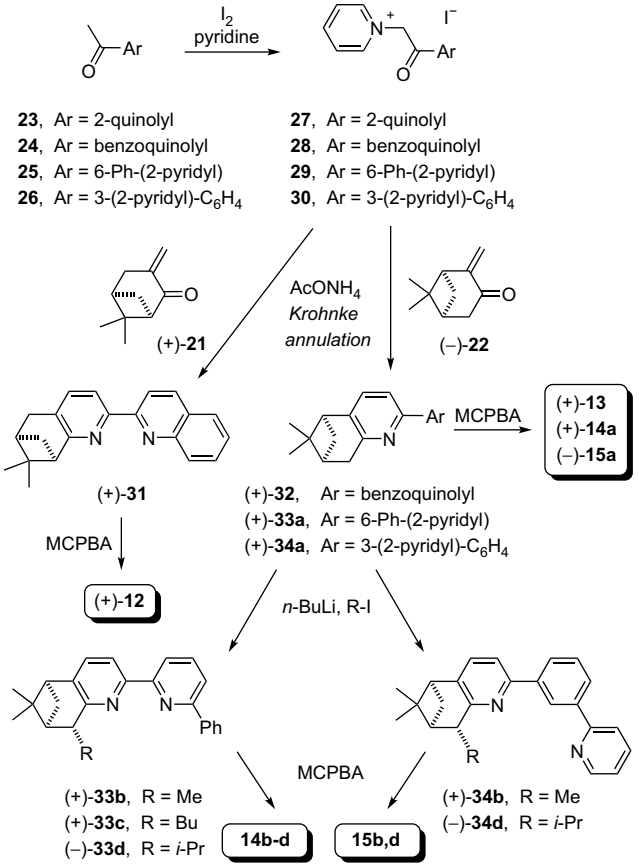
2.2. Catalyst synthesis

As in our previous work, enones (+)-**21** and (−)-**22** were utilized as the key building blocks for the terpene scaffold (Scheme 2).[8–11,13] The former enone was obtained from (−)-β-pinene (−)-**18** in a three-step procedure, including ozonolysis[13,14] and Claisen condensation of the resulting nopinone (+)-**19**, followed by a transaldolization reaction with formaldehyde.[13,15] Pinocarvone (−)-**22** was obtained via the ene-reaction of (+)-α-pinene (+)-**20** with singlet oxygen in the presence of acetic anhydride.[8,13,16]

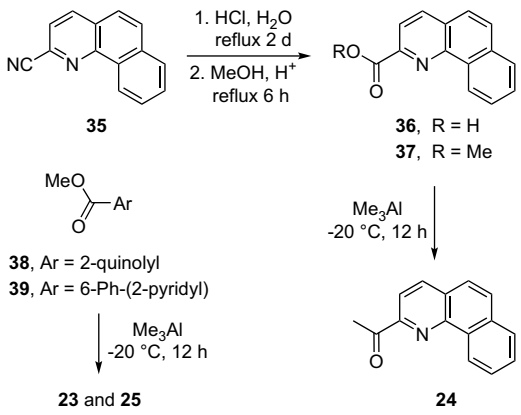
The enones (+)-**21** and (−)-**22** were employed as Michael acceptors in the Kröhnke annulation[17,18] with the easily enolizable α-pyridinio ketones **27**–**30**, which in turn were obtained from the corresponding methyl ketones **23**–**26** on iodination in pyridine at 110 °C for 3–24 h (Scheme 3). Unlike with acetophenone and its close congeners,[13] the heteroaromatic Kröhnke salts **27**–**30** proved to be more difficult to obtain in a pure state; nevertheless, the crude materials were used as obtained without further purification. These crude salts reacted with the terpenic enones **21**/**22** as expected under the standard annulation conditions ($AcONH_4$, piperidine, *n*-BuOH, AcOH, 110 °C, 1–2 days)[13,17,18] to produce the desired pyridine derivatives (+)-**31** (53%), (+)-**32** (53%), (+)-**33a** (47%),[19] and (+)-**34a** (36%), respectively. Under microwave conditions, the annulation proceeded much faster but with little effect on the yield. Thus, for instance, **33a** was obtained in 52% yield by microwave heating at 190 °C for 10 min, which differs marginally from the yield attained by traditional heating (47%).

The pyridinoterpene (+)-**33a** was deprotonated with *n*-BuLi (THF, −40 °C, 3 h) in the 'benzylic' position and the resulting anion was alkylated with alkyl iodides (THF, room temperature, overnight) to afford the alkylated products (+)-**33b** (39%), (+)-**33c** (45%), and (−)-**33d** (43%), respectively, in a highly diastereoselective fashion.[20] It is pertinent to note that the latter deprotonation with *n*-BuLi proved superior to that using LDA[8,19] in terms of efficiency. Similarly, deprotonation of **34a**, followed by alkylation, afforded the alkyl derivatives **34b** (31%) and **34d** (37%) with a similarly high stereoselectivity. Oxidation of all these bipyridines **31**, **32**, **33a**–**d**, and **34a**,**b**,**d** with *m*-chloroperoxybenzoic acid (2.2 equiv)[8] in CH_2Cl_2 at room temperature for two days gave rise to the desired dioxides (+)-**12** (86%), (+)-**13** (28%), (+)-**14a** (28%), (+)-**14b** (44%), (−)-**14c** (47%), (+)-**14d** (45%), (−)-**15a** (60%), (−)-**15b** (42%), and (−)-**15d** (45%), respectively.

The preparation of the starting heteroaryl ketones **23**–**25** (Scheme 4) requires a brief comment. Several methods were attempted, including (a) the reaction of the corresponding nitrile ArCN (e.g., **35**) with MeMgI, followed by hydrolysis of the in situ-formed imine;[21] (b) addition of MeLi to the corresponding ester $ArCO_2Me$ at low temperature;[22] and (c) Claisen condensation of $ArCO_2Et$ with AcOEt, followed by decarboxylation of the resulting β-keto ester $ArCOCH_2CO_2Et$,[23] but the results were rather poor. Finally, we settled for the reaction of the corresponding methyl esters **37**–**39** with Me_3Al in CH_2Cl_2 at −20 °C,[24] which gave the respective methyl ketones **23** (88%), **24** (51%), and **25** (80%) consistently in good yields. The required starting methyl ester **37** was prepared by Fischer esterification[25] of acid **36** (MeOH, H_2SO_4, reflux; 88%), which in turn was obtained by hydrolysis of nitrile **35** (99%) under acidic conditions.[26] The remaining methyl esters **38** and **39** are known compounds.[27,28] The methyl ketone **26** was obtained by the Suzuki–Miyaura coupling of 2-bromopyridine with (3-acetyl)phenylboronic acid.[29]

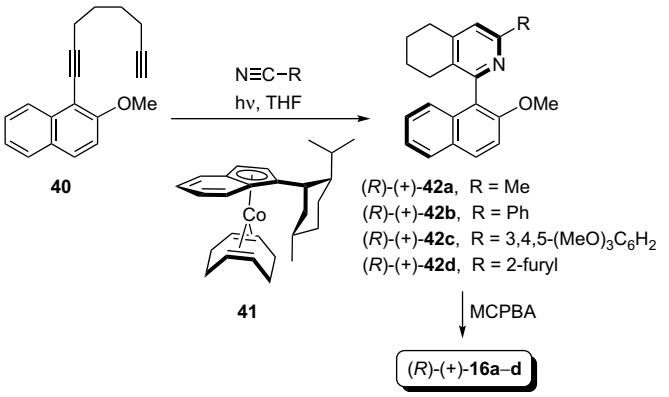


Scheme 3. Synthesis of new pyridine-derived organocatalysts.



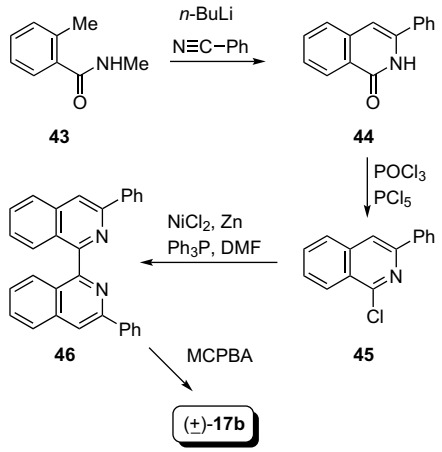
Scheme 4. Synthesis of ketones **23**–**25**.

The axially chiral tetrahydroisoquinoline-type catalyst candidates **16a–d** (Scheme 5) were synthesized by using the asymmetric [2+2+2] cyclotrimerization[30] of diyne **40** with a series of nitriles, catalyzed by the chiral cobalt complex (−)-(*pS*)-(η^4-cycloocta-1,5-diene)(η^5-1-neomenthylindenyl)cobalt (−)-**41** (1-2 mol %) under irradiation with a high intensity visible-light lamp (λ=350–500 nm) in THF at −20 °C for 24–72 h as the key step. The tetrahydroquinolines (+)-**42a** (86% yield, 93% ee),[30a] (+)-**42b** (88% yield, 88% ee),[30a] (+)-**42c** (64% yield, 91% ee),[30b] and (+)-**42d** (81% yield, 91% ee)[30b] thus obtained were purified to high enantiopurity (>99% ee) by recrystallization. Only (+)-**42c** resisted the purification and was used in its 91% enantiopurity. The absolute configuration of (+)-**42b** was established previously by X-ray crystallography to be (*R*)[30] and the configuration of the remaining members of this series (**42a**,**c**,**d**) is assumed to be the same by analogy (as all of them are dextrorotatory). The latter products were then oxidized with *m*-chloroperoxybenzoic acid to afford the corresponding *N*-oxides **16a** (40%), **16b** (35%), **16c** (57%), and **16d** (20%).



Scheme 5. Synthesis of axially chiral *N*-oxides **16**.

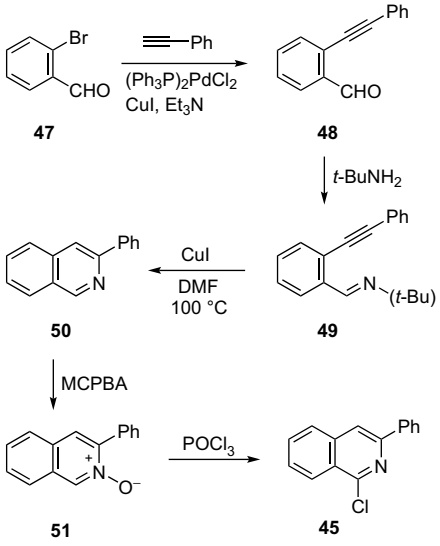
Finally, the synthesis of *N*,*N*′-dioxide **17b** (Scheme 6) commenced with the annulation of benzonitrile to *o*-methyl-benzamide **43**, mediated by an excess of *n*-butyllithium (5 equiv) in THF (−50 °C for 2 h, then at room temperature for 26 h), which afforded isoquinolinone **44** (36%).[31,32] Treatment of the latter product with a mixture of $POCl_3$ and PCl_5 (neat) at 120 °C for 2 h[33] furnished chloroisoquinoline **45**[32] (63%). Subsequent dimerization, mediated by the in situ-generated $(Ph_3P)_2NiCl_2$ and zinc in DMF at 50 °C for 3 h,[8,13,34] provided the biaryl derivative **46** (67%).[35] The final oxidation with *m*-chloroperoxybenzoic acid (10 equiv) in CH_2Cl_2 at room temperature for 48 h resulted in the formation of dioxide



Scheme 6. Synthesis of bisisoquinoline dioxide **17b**.

(±)-**17b** (57%), accompanied by the corresponding monooxide (20%). Racemic dioxide **17b** resisted a number of attempts at classical resolution (including our favorite co-crystallization with BINOL[4a,10]) and was eventually resolved by chiral HPLC. Attempted synthesis of enantiopure **17b** via a coupling of **17a** (which in turn can be prepared enantiomerically pure[4]) with PhBr, catalyzed by $(AcO)_2Pd$ in the presence of Bu_3P and HBF_4,[36] was unsuccessful.

An alternative synthesis of chloroisoquinoline **45** (Scheme 7), a precursor to **17b**, commenced with *o*-bromo-benzaldehyde (**47**) that was first coupled with phenylacetylene under the standard Sonogashira conditions, and the resulting aldehyde **48** (99%)[37] was converted into imine **49** on treatment with *t*-$BuNH_2$ (94%).[38] The latter imine was then cyclized on heating with CuI (20 mol %) in DMF to afford 3-phenylisoquinoline **50** (68%).[39] The N-oxidation of the latter product with *m*-CPBA gave rise to *N*-oxide **51** (75%),[40] whose treatment with $POCl_3$ provided the 1-chloro derivative **45** (50%).



Scheme 7. An alternative synthesis of **45**.

The absolute configuration of bisisoquinoline **17b** can be tentatively related to that of **17a**, whose absolute configuration was unequivocally established by X-ray analysis of the molecular crystal resulting from the co-crystallization of (±)-**17a** with (*R*)-(+)-BINOL.[4a] The levorotatory enantiomer (*S*)-(−)-**17a** thus obtained exhibited $[\alpha]_D$ −180 (*c* 1.0, $CHCl_3$). Chromatography of our (±)-**17b** on a chiral column afforded (−)-**17b**, exhibiting $[\alpha]_D$ −184 (*c* 0.45, $CHCl_3$), and (+)-**17b** with $[\alpha]_D$ +178 (*c* 0.32, $CHCl_3$), which correlates well with the optical rotation reported for (*S*)-**17a**. Moreover, the dextrorotatory enantiomers of BINOL[41] and its analogues, such as BINAM,[41] NOBIN,[41] 3,3′-diphenyl-BINOL,[42] 3-methoxycarbonyl-BINOL,[41] and 3,3′-(dimethoxycarbonyl)BINOL[41] are all (*R*)-configured. Therefore, it can be tentatively concluded that the molecular architecture of (*R*)-1,1′-binaphthyl and (*R*)-1,1′-bisisoquinolyl moieties with 2,2′-oxygen functions (i.e., diol or *N*,*N*′-dioxide) renders these derivatives dextrorotatory, unless other strongly contributing groups[42] interfere. Hence, the configuration of our bisisoquinoline can be assumed to be (*R*)-(+)-**17b** and (*S*)-(−)-**17a**. Further indirect evidence, stemming from the sense of asymmetric induction of the allylation reaction, catalyzed by **17b** and **4**–**6**, is discussed below.

2.3. Allylation of aromatic aldehydes

We have shown previously that chiral, terpene-derived *N*,*N*′-dioxides (e.g., **7**) and *N*-monooxides (e.g., **8**) with a flexible aryl–aryl axis adopt a suitable conformation on coordinating the silicon

Table 2
Allylation of aldehydes RCHO (**1**) with **2** catalyzed by Lewis bases **12**, **14**, **15**, **16**, and **17** (Scheme 1 and Chart 2)[a]

Entry	Aldehyde **1** (R)	Catalyst (mol %)	Solvent	Temp (°C)	Time (h)	Conversion (%)[b]	ee (%)[b]	Configuration of **3**[c]
1	Ph	(+)-**12a** (10)	CH_2Cl_2	−60	18	≥99	36	(*R*)-(+)
2	Ph	(+)-**12a** (10)	CH_2Cl_2	40	18	≥99	26	(*R*)-(+)
3	Ph	(+)-**12a** (10)	MeCN	−60	18	≥99	31	(*R*)-(+)
4	Ph	(+)-**12a** (10)	Toluene	−40	18	≥99	25	(*R*)-(+)
5	Ph	(+)-**13a** (10)	CH_2Cl_2	−40	18	19	42	(*R*)-(+)
6	Ph	(+)-**14a** (10)	CH_2Cl_2	−40	18	≥99	4	(*S*)-(−)
7	Ph	(+)-**14b** (10)	CH_2Cl_2	−40	18	≥99	40	(*S*)-(−)
8	Ph	(−)-**14c** (10)	CH_2Cl_2	−40	12	≥99	56	(*S*)-(−)
9	Ph	(−)-**14c** (10)	CH_2Cl_2	−90	18	18	34	(*S*)-(−)
10	Ph	(−)-**14c** (10)	CH_2Cl_2	−20	18	≥99	43	(*S*)-(−)
12	Ph	(−)-**14c** (10)	$CHCl_3$	−20	18	≥99	23	(*S*)-(−)
13	Ph	(−)-**14c** (10)	MeCN	−20	12	≥99	31	(*S*)-(−)
14	Ph	(−)-**14c** (10)	Toluene	−20	18	87	10	(*R*)-(+)
15	Ph	(−)-**14d** (10)	CH_2Cl_2	−40	18	≥99	23	(*S*)-(−)
16	Ph	(−)-**15a** (10)	CH_2Cl_2	−20	18	83	12	(*R*)-(+)
17	Ph	(−)-**15b** (10)	CH_2Cl_2	−20	18	87	2	(*R*)-(+)
18	Ph	(−)-**15d** (10)	CH_2Cl_2	−20	18	85	3	(*R*)-(+)
19	Ph	(*R*)-(+)-**16b** (5)	$CHCl_3$	−40	18	<5	4	(*S*)-(−)
20	Ph	(*R*)-(+)-**16c**[e] (5)	$CHCl_3$	−40	18	10	50[d]	(*S*)-(−)
21	Ph	(*R*)-(+)-**16c**[e] (10)	$CHCl_3$	−20	18	64	48[d]	(*S*)-(−)
22	4-CF_3–C_6H_4	(*R*)-(+)-**16c**[e] (10)	$CHCl_3$	−40	18	60	46[d]	(*S*)-(−)
23	4-MeO–C_6H_4	(*R*)-(+)-**16c**[e] (10)	$CHCl_3$	−40	18	16	8[d]	(*S*)-(−)
24	Ph	(*R*)-(+)-**16d**[e] (10)	$CHCl_3$	−40	18	60	7	(*S*)-(−)
25[f]	Ph	(*R*)-(+)-**17a**[e] (10)	CH_2Cl_2	23	2	85	52	—
26	Ph	(*R*)-(+)-**17b**[e] (1)	CH_2Cl_2	−40	18	≥99	77	(*S*)-(−)
27	Ph	(*R*)-(+)-**17b**[e] (1)	CH_2Cl_2	−80	18	≥99	81	(*S*)-(−)
28	4-MeC_6H_4	(*S*)-(−)-**17b**[e] (1)	CH_2Cl_2	−80	18	≥99	69[g]	(*R*)-(+)
29	3,5-$Me_2C_6H_3$	(*R*)-(+)-**17b**[e] (1)	CH_2Cl_2	−80	18	≥99	71	(*S*)-(−)
30	4-Cl–C_6H_4	(*S*)-(−)-**17b**[e] (1)	CH_2Cl_2	−80	30	≥99	76[g]	(*R*)-(+)
31	4-CF_3–C_6H_4	(*S*)-(−)-**17b**[e] (1)	CH_2Cl_2	−80	92	99	51[g]	(*R*)-(+)
32	4-MeO–C_6H_4	(*S*)-(−)-**17b**[e] (1)	CH_2Cl_2	−80	18	≥99	2	(*R*)-(+)
33	3,4-$(MeO)_2C_6H_3$	(*R*)-(+)-**17b**[e] (1)	CH_2Cl_2	−80	18	≥99	10	(*S*)-(−)

[a] The reaction was carried out at 0.2 mmol scale with 1.4 equiv of allyltrichlorosilane and 1.0 equiv of diisopropylethylamine.
[b] Determined by chiral HPLC or GC.
[c] The configuration of the products **3** was established by the comparison of their optical rotations (measured in $CHCl_3$) and their GC and HPLC retention times with the literature data and with the behavior of authentic samples (Ref. 8).
[d] Note that the enantiopurity of catalyst **16c** was only 91% ee (corresponding to the enantiopurity of **42c**; vide supra).
[e] The absolute configuration is assumed in analogy (see the text) but not rigorously proven.
[f] Ref. 4a.
[g] The (*S*)-catalyst was about 90% enantiopure, which is reflected in the ee of the product compared to the (*R*)-enantiomer.

of the allylsilane **2**;[8] here, the configuration at the axis is thus controlled by the chirality of the rest of the molecule in conjunction with the conformational effects introduced by coordination of the silicon. A similar scenario was expected to operate with the new *N*,*N*′-dioxides **12**–**15**. The latter derivatives, lacking the C_2 symmetry of **7** and having the chirality "concentrated" on one side of the molecule, proved to catalyze the allylation of benzaldehyde (**1**) with $AllylSiCl_3$ (**2**) efficiently with high isolated yields of the homoallylic alcohol **3**. However, the enantioselectivity (Table 2, entries 1–18) turned out to be rather low (≤56% ee; entry 8), reflecting the behavior of dioxide **7** (41% ee; Table 1, entry 5). Again, as shown previously,[8] dichloromethane proved to be the solvent of choice (Table 2; compare entry 10 with 12 and 13).

These experiments clearly demonstrated the superiority of *N*,*N*′-dioxides **4**–**6**, where the chiral axis is the only source of chirality in the molecule, over those *N*,*N*′-dioxides, where the chiral terpene moiety (**12**–**15**) is expected to exercise the enantiocontrol (compare entries 1–4 in Table 1 with entries 1–18 in Table 2).

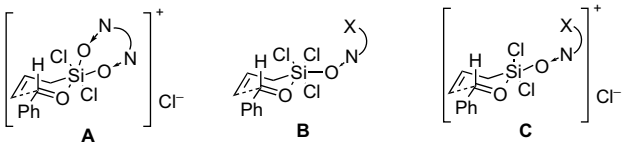
In view of the catalytic success of the axially chiral *N*-monooxide QUINOX **11** (Table 1, entries 9 and 10),[10] its analogues **16a**–**d** with an additional substituent R next to the *N*-oxide group, were investigated as the next step. However, these new derivatives proved rather inefficient (≤50% ee; Table 2, entries 19–24). Furthermore, the reactions catalyzed by these *N*-monooxides were considerably slower than those proceeding in the presence of *N*,*N*′-dioxides (compare the yields in entries 1–18 vs 19–24 in Table 2). This behavior indicates that chelation of the silicon atom of **2** between the two oxygens of the catalysts enhances the nucleophilicity of the allyl group considerably more than coordination to just one Lewis-basic oxygen of the *N*-monooxide,[43] unless other factors can contribute to the stabilization of the transition state and lowering of the activation energy.[10b] Furthermore, comparison of the efficiency of QUINOX **11** with that of its analogues **6a**,**b**[7] and **16a**–**d** indicates that the bulky substituent next to the N–O group interferes with the coordination of the silicon (vide infra).

Finally, the bis-isoquinoline *N*,*N*′-dioxide **17b** can be regarded as a hybrid between Nakajima's moderately successful unsubstituted analogue **17a** (Table 2, entry 24) and Hayashi's very efficient bipyridine *N*,*N*′-dioxide **5** (Table 1, entry 2). Indeed, our dioxide **17b** exhibited excellent reactivity even at −80 °C and 1 mol % loading. The enantioselectivity was in the range of that reported by Hayashi's for dioxide **5**, both for benzaldehyde (Table 2, entries 26 and 27), its methyl derivatives (entries 28 and 29), and electron-poor congeners (entries 30 and 31). Interestingly, the electron-rich derivatives of benzaldehyde turned out to give the products with poor selectivity (entries 32 and 33), which reflects the behavior of QUINOX **11**[10] (Table 1, entries 9–11).

The sense of asymmetric induction in the allylation catalyzed by the axially chiral *N*,*N*′-dioxides **4**–**6** correlates well with that observed for **17b**: here, the (*R*)-configured dioxides induce the formation of (*S*)-homoallylic alcohols (*S*)-(−)-**3** [and (*R*)-(+)-**3** results from the catalysis by (*S*)-dioxides] (Table 1, entries 1–4). Since (+)-**17b** promotes the formation of (*S*)-(−)-**3** (Table 2, entries 26, 27,

and 29) and (−)-**17b** gives (*R*)-(+)-**2** (entries 28, 30, and 31), this behavior can be used as another piece of evidence for the absolute configuration of dioxide **17b** as being (*R*)-(+)-**17b** and (*S*)-(−)-**17b**.[44]

The striking difference in the reactivity and selectivity of *N*,*N*′-dioxide and *N*-monooxide catalysts suggests that the two catalyst types may operate via different mechanisms. In the case of bidentate *N*,*N*′-dioxides, cationic transition state **A** (Scheme 8) can be envisioned, in analogy with the mechanism proposed by Denmark for his bis-phosphoramide activators.[2] It has been demonstrated[3–5,7,8] that the axial chirality of the catalyst plays a dominant role in controlling the enantioselectivity. The axially chiral *N*,*N*′-dioxides **17** follow the general trend, exhibiting good levels of ee. For the flexible dioxides **12**–**14**, the chiral twist about the 2,2′-bipyridine axis, which plays the key role in the enantiodiscrimination event, is created on chelation of the silicon and is influenced by the chirality of the annulated terpene unit. Low to moderate enantioselectivities obtained with catalysts **12**–**14** (Table 2, entries 1–15) suggest that the remote terpene fragment is not capable of promoting selective formation of only one of the possible atropoisomeric complexes. Our recent studies on the mechanism of allylation catalyzed by the *N*-monooxide QUINOX (**11**) revealed[10b] that the reaction proceeds via an associative, single catalyst pathway, involving the neutral octahedral silicon complex **B**. A highly crowded structure of the TS **B** provides an excellent enantiocontrol in the allylation of aromatic aldehydes, except for the electron-rich derivatives. However, the latter transition state is likely to be sensitive to any variation in the catalyst structure proximal to the coordinating center. To accommodate the increased steric demands created by the substituent next to the *N*-oxide group, as in the case of *N*-oxides **16**, one of the chlorides is likely to dissociate from the silicon, generating the cationic, trigonal bipyramidal complex **C**. Increased flexibility of **C** may account for the observed drop in enantioselectivity for **16** compared to the unsubstituted **11**. The low selectivity observed for the allylation of the electron-rich aromatic aldehydes appears to be a common feature of catalysis by **11**, **16**, and **17**, and may result from a change either in the rate liming step (RLS) or in the reaction mechanism. In the case of QUINOX (**11**), operating via TS **B**, the dramatic drop in enantioselectivity (from 96 to 16% ee, observed with 4–CF_3–C_6H_4CHO and 4–MeO–C_6H_4CHO, respectively) was attributed to the shift in the RLS from precoordination of the aldehyde to the C–C bond formation.[10b] Therefore, it might be tempting to speculate about similar effects in the case of catalysts **16** and **17**; however, we currently do not have sufficient kinetic and computational data to create a full mechanistic picture.



Scheme 8.

3. Conclusions

We have developed a set of monodentate and bidentate chiral Lewis bases featuring a pyridine *N*-oxide fragment as the key structural element. These compounds were employed as catalysts in the asymmetric allylation of aromatic aldehydes with allyl trichlorosilane (**1**+**2**→**3**). Dioxides **12**–**15**, whose chirality originates from the annulated terpene unit, reached up to 56% ee on this reaction (Table 2, entry 8). On the other hand, the C_2-symmetrical *N*,*N*′-dioxide **17b** exhibited good enantioselectivity and high reactivity even at −80 °C and with catalyst loading as low as 1 mol % (81% ee; Table 2, entry 27), which is in line with the earlier reports[4,5] on the axially chiral dioxides **4** and **5**. The axially chiral isoquinoline *N*-oxide **11** (QUINOX), known to be very efficient (except for the electron-rich aromatic aldehydes),[10] has been found to have a scaffold that is very sensitive to any substitution in the α-position to the *N*-oxide group, as the series of catalysts **16a**–**d** exhibited diminished selectivity and reaction rates. A study, which aims at shedding light on the mechanistic issues of these catalytic systems, is under way.

4. Experimental

4.1. General methods

All reactions were carried out under an inert atmosphere in an oven-dried glassware unless otherwise stated. Room temperature refers to ambient room temperature (18–20 °C); 0 °C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by thin layer chromatography (TLC) using aluminum backed silica gel 60 (F_{254}) plates, visualized using UV_{254nm} and potassium permanganate, PMA, Dragendorff and ninhydrin dips as appropriate. Flash chromatography was carried out routinely using 60 Å silica gel (Fischer) unless otherwise stated. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded for $CHCl_3$ solutions at 20 °C unless otherwise indicated with an error of $<\pm 0.1$. The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. The NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in δ units, parts per million (ppm) downfield from TMS. Coupling constants (J) are in hertz (Hz) and are unadjusted; therefore, due to limits in resolution, in some cases there are small differences (<1 Hz) in the measured J value of the same coupling constant determined from different signals. Splitting patterns are designed as follows: s, singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; td, triplet of doublets; ddd, doublet of doublet of doublets; tt, triplet of triplets; sp, septet; m, multiplet; br, broad. Various 2D techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for a thin film between NaCl plates, or as a KBr disc. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. Enantiomeric excess was determined by chiral GC analysis (using a Hewlett Packard 6890 Series GC system, Hewlett Packard 3395 integrator and Supelco α-DEX™ 120 fused capillary column 30 m×0.25 mm×0.25 μm film thickness) or by chiral HPLC analysis (using a Hewlett Packard Agilent 1100 Series quaternary pump, vacuum degasser, diode array detector, manual injector and Hewlett Packard ChemStation and a Chiralcel OJ-H or Chiralpak IB 0.46 cm×25 cm column) as stated. The chiral GC and HPLC methods were calibrated with the corresponding racemates.

4.2. General method for the preparation of acetyl derivatives 23–25[24]

The reaction was performed on a 5.0–26.7 mmol scale. A 2.0 M solution of Me_3Al in hexanes (2.0 equiv) was added dropwise to a stirred solution of the corresponding methyl esters **37**–**39** (1.0 equiv) in anhydrous CH_2Cl_2 (40 mL) at −78 °C (or −85 °C). The reaction mixture was then allowed to warm over a 30 min period, to −20 °C and then stirred at this temperature for 12 h. The reaction was quenched by addition of 10 M HCl (10–30 mL) at −20 °C and then left to stir at this temperature for 10 min before being warmed to 0 °C. It was further stirred for 30 min and then allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed in

vacuo to give the crude product, which was purified by chromatography on a column of silica gel (15–100 g) with a mixture of petroleum ether and ethyl acetate (5:1) to afford the pure ketones **23**–**25**.

*4.2.1. 2-Acetylquinoline (**23**)*

Prepared from methyl 2-quinolylcarboxylate **38** (5.00 g, 26.7 mmol) and 2.0 M Me_3Al (26.7 mL, 53.5 mmol), which was added at −78 °C. After work up, product **23** (3.658 g, 88%) was obtained as an off white solid, which was pure enough for the next step by ^{1}H NMR analysis. Mp 95–97 °C (lit.[23a] gives 80–97 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.79 (s, 3H), 7.58 (t, J=8.0 Hz, 1H), 7.72 (t, J=8.4 Hz, 1H), 7.79 (d, J=8.0 Hz, 1H), 8.05 (d, J=8.4 Hz, 1H), 8.13 (d, J=8.8 Hz, 1H), 8.18 (d, J=8.4 Hz, 1H), consistent with the literature data;[23] ^{13}C NMR δ 24.6 (CH_3), 116.9 (CH), 126.6 (CH), 127.5 (CH), 128.5 (C), 129.0 (CH), 129.5 (CH), 135.8 (CH), 146.2 (C), 152.1 (C), 199.7 (C); IR (KBr) ν 1695 (s) cm^{-1}.

*4.2.2. 2-Acetyl-1-benzo[h]quinoline (**24**)[24]*

Prepared from methyl benzo[*h*]quinoline-2-carboxylate **37** (2.000 g, 8.4 mmol) and 2.0 M Me_3Al (8.43 mL, 16.9 mmol), which was added at −85 °C. Purification of the crude product furnished ketone **24** (0.986 g, 51%) as a pale brown solid. Mp 116–118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.94 (s, 3H), 7.62 (d, J=8.8 Hz, 1H), 7.63–7.72 (m, 2H), 7.81 (d, J=8.8 Hz, 1H), 7.85 (d, J=8.4 Hz, 1H), 8.15 (s, 2H), 9.27 (d, J=8.0 Hz, 1H); ^{13}C NMR δ 25.84 (CH_3), 118.9 (CH), 124.5 (CH), 125.0 (CH), 127.5 (CH), 128.0 (CH), 128.39 (C), 128.7 (CH), 130.1 (CH), 131.6 (C), 133.7 (C), 136.6 (CH), 145.4 (C), 151.6 (C), 200.8 (C); IR (Golden Gate) ν 1687 (s) cm^{-1}; HRMS (EI) 221.0842 ($C_{15}H_{11}NO$ requires 221.0841).

*4.2.3. 1-Acetyl-6-phenylpyridine (**25**)[19,45]*

Prepared from methyl 6-phenylpyridine-2-carboxylate **39** (1.000 g, 5.0 mmol) and 2.0 M Me_3Al (5.0 mL, 10.0 mmol), which was added at −85 °C. Purification of the crude product was gave ketone **25** (784 mg, 80%) as a yellowish solid. Mp 59–61 °C (lit.[45] gives 75–76 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (s, 3H), 7.37–7.46 (m, 3H), 7.78–7.85 (m, 2H), 7.91 (dd, J=7.2, 1.6 Hz, 1H), 8.01–8.04 (m, 2H); ^{13}C NMR δ 25.9 (CH_3), 119.8 (CH), 123.5 (CH), 126.9 (2×CH), 128.9 (2×CH), 129.5 (CH), 137.7 (CH), 138.4 (C), 153.4 (C), 156.5 (C), 200.7 (C); IR (KBr) ν 1693 (s) cm^{-1}; HRMS (EI) 197.0842 ($C_{13}H_{11}NO$ requires 197.0841).

4.3. General procedure for the preparation of Kröhnke salts[17,19] 27–30

A solution of the respective substituted acetophenone **23**–**26** (10 mmol, 1.0 equiv) and iodine (2.53 g, 10 mmol, 1.0 equiv) in pyridine (6 mL) was refluxed overnight. The reaction mixture was then cooled to room temperature, inducing the precipitation of a dark solid, which was filtered off and washed with ether (3×20 mL). In some experiments, the mixture was concentrated by evaporation of the pyridine in vacuo to facilitate the precipitation prior to the washing with ether. The remaining solid was then stirred overnight in ether (20 mL) and the salts **27**–**30** were then isolated by filtration; this material was of sufficient purity for the subsequent Kröhnke annulation.

*4.3.1. 1-(2-Oxo-2-quinolin-2-yl-ethyl)-pyridinium iodide (**27**)*

Prepared from ketone **23** (1.200 g, 7.0 mmol), iodine (1.908 g, 7.5 mmol), and pyridine (15 mL) at reflux for 3 h. The dark brown solid product **27** was isolated in a mixture with pyridinium iodide (1:2), as determined by ^{1}H NMR analysis and was then used in the next step without separation. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 6.72 (s, 2H), 7.90–8.10 (m, 2H), 8.18 (d, J=8.4 Hz, 1H), 8.23 (d, J=8.0 Hz, 1H), 8.28 (d, J=8.4 Hz, 1H), 8.36 (t, J=8.0 Hz, 2H), 8.75 (d, J=8.8 Hz, 1H), 8.81 (t, J=8.0 Hz, 1H), 9.11 (d, J=5.6 Hz, 2H); ^{13}C NMR δ 66.5 (CH_2), 117.9 (CH), 127.0 (CH), 127.8 (CH), 128.4 (CH), 129.6 (CH), 129.8 (C), 131.3 (CH), 138.3 (CH), 142.7 (CH), 145.7 (CH), 146.3 (C), 146.4 (CH), 150.4 (C), 191.5 (C); IR (KBr) ν 1711 (s) cm^{-1}.

*4.3.2. 1-(2-Benzo[h]quinolin-2-yl-2-oxo-ethyl)-pyridinium iodide (**28**)*

Prepared from ketone **24** (0.850 g, 3.8 mmol), iodine (1.073 g, 4.2 mmol), and pyridine (10 mL) at reflux for 24 h. The dark brown solid product **28** was isolated in a mixture with pyridinium iodide (1:1.2), as determined by ^{1}H NMR analysis and was then used in the next step without separation. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 6.94 (s, 2H), 7.97–8.13 (m, 2H), 8.05–8.10 (m, 2H), 8.23 (t, J=8.8 Hz, 1H), 8.32–8.37 (m, 1H), 8.61 (t, J=7.6 Hz, 2H), 8.76–8.82 (m, 1H), 8.96 (t, J=6.4 Hz, 2H), 9.15 (d, J=5.2 Hz, 2H); ^{13}C NMR δ 66.8 (CH_2), 119.2 (CH), 124.0 (CH), 125.4 (CH), 126.8 (CH), 127.8 (CH), 127.9 (CH), 128.5 (CH), 129.0 (C), 129.4 (CH), 130.3 (C), 130.8 (CH), 133.6 (C), 138.0 (CH), 143.2 (CH), 144.5 (C), 145.0 (CH), 146.4 (CH), 148.8 (C), 191.5 (C); IR (KBr) ν 1703 (s) cm^{-1}.

*4.3.3. 1-[2-Oxo-2-(6-phenyl-pyridin-2-yl)-ethyl]-pyridinium iodide (**29**)*

Prepared from ketone **25** (0.750 g, 3.8 mmol), iodine (1.063 g, 4.2 mmol), and pyridine (10 mL) at reflux for 24 h. The dark brown solid product **29** was isolated in a mixture with pyridinium iodide (1:2), as determined by ^{1}H NMR analysis and it was then used in the next step without separation. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 6.72 (s, 2H), 8.05 (d, J=7.6 Hz, 1H), 8.11 (t, J=6.8 Hz, 2H), 8.26 (t, J=8.0 Hz, 1H), 8.30–8.33 (m, 3H), 8.45 (d, J=8.0 Hz, 1H), 8.64 (t, J=8.0 Hz, 2H), 8.79 (t, J=7.6 Hz, 1H), 9.07 (d, J=5.6 Hz, 2H); ^{13}C NMR δ 66.75 (CH_2), 120.5 (CH), 123.7 (CH), 125.2 (C), 126.9 (CH), 127.1 (CH), 127.8 (CH), 129.0 (CH), 130.1 (CH), 139.3 (CH), 142.6 (CH), 145.8 (CH), 146.3 (CH), 150.4 (C), 155.8 (C), 191.6 (C); IR (KBr) ν 1707 (s) cm^{-1}.

*4.3.4. 1-{2-Oxo-2-[3′-(2″-pyridinyl)phenyl]ethyl}pyridinium iodide (**30**)*

Prepared from ketone **26**[29] (3.58 g, 89%). ^{1}H NMR (400 MHz, d_6-DMSO) δ 6.63 (s, 2H, 1-H), 7.48 (dd, J=7.2, 5.1 Hz, 1H, 5″-H), 7.81 (t, J=7.8 Hz, 1H, 5′-H), 8.02 (t, J=7.2 Hz, 1H, 4″-H), 8.13 (s, 1H, 2′-H), 8.16 (d, J=7.8 Hz, 1H, 4′-H), 8.32 (t, J=7.0 Hz, 2H, 3‴-H, 5‴-H), 8.48 (d, J=7.8 Hz, 1H, 6′-H), 8.74–8.80 (m, 3H, 3″-H, 6″-H, 4‴-H), 9.05 (d, J=7.0 Hz, 2H, 2‴-H, 6‴-H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 66.3 (CH_2-1), 120.8 (CH-4′), 123.4 (CH-5″), 126.1 (CH-3″), 127.8 (2×CH-3‴,5‴), 128.7 (CH-2′), 129.7 (CH-5′), 132.3 (C-6′), 134.1 (C-1′), 138.0 (CH-4″), 138.9 (C-3′), 146.1 (2×CH-2‴,6‴), 146.3 (CH-4‴), 149.3 (CH-6″), 154.1 (C-2″), 190.5 (C=O-2); MS (FAB) *m*/*z* (%) 275 ($M^{\bullet+}$, 82), 241 (33), 136 (37), 122 (100), 101 (82), 82 (75); HRMS (FAB) 275.1181 ($C_{18}H_{15}N_2O$ requires 275.1184).

4.4. General method for the Kröhnke annulation[17,19]

A mixture of enone (+)-**21** or (−)-**22** (7.0 mmol, 1.00 equiv), the Kröhnke salts **27**–**30** (7.1 mmol, 1.1 equiv), $AcONH_4$ (9.0 g), and piperidine (7.1 mmol, 1.1 equiv) in *n*-butanol (30 mL) and acetic acid (10 mL), was heated at 110 °C for 6 h—two days. After this time, the reaction mixture was cooled to room temperature, diluted with water (25 mL), made neutral by addition of an aqueous solution of sodium hydroxide (2 M), and extracted with ethyl acetate (3×50 mL). The organic phase was successively washed with water (3×50 mL) and brine (50 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the crude product was purified by flash chromatography on silica gel (20 g) using a mixture of petroleum ether and ethyl acetate (3:1) to afford pure product.

*4.4.1. (1R,9R)-(+)-10,10-Dimethyl-4-(quinolin-2-yl)-3-aza-tricyclo[7.1.1.0^{2,7}]undeca-2,4,6-triene (+)-(**31**)*

Prepared by using 1-(2-oxo-2-quinolin-2-yl-ethyl)-pyridinium iodide **27** (330 mg, 0.88 mmol), enone (+)-**21** (106 mg, 0.704 mmol), piperidine (66 mg, 0.77 mmol), and ammonium acetate (3.000 g). Purification of the crude product afforded pure (+)-**31** (141 mg, 53%) as a yellow, amorphous solid. $[\alpha]_D$ +28.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.65 (s, 3H), 1.32 (d, *J*=9.7 Hz, 1H), 1.39 (s, 3H), 2.35–2.38 (m, 1H), 2.75–2.80 (m, 2H), 2.96 (s, 1H), 3.09 (t, *J*=5.6 Hz, 1H), 7.47 (t, *J*=7.1 Hz, 1H), 7.54 (d, *J*=7.8 Hz, 1H), 7.66 (t, *J*=7.0 Hz, 1H), 7.77 (d, *J*=8.1 Hz, 1H), 8.10 (d, *J*=8.5 Hz, 1H), 8.18 (d, *J*=8.7 Hz, 1H), 8.34 (d, *J*=7.8 Hz, 1H), 8.48 (d, *J*=8.6 Hz, 1H); ^{13}C NMR δ 21.3 (CH_3), 26.1 (CH_3), 30.9 (CH_2), 31.4 (CH_2), 39.2 (C), 40.2 (CH), 50.6 (CH), 119.2 (CH), 119.6 (CH), 126.4 (CH), 127.6 (CH), 128.1 (C), 129.4 (CH), 129.8 (CH), 131.1 (C), 136.1 (CH), 136.6 (CH), 148.0 (C), 152.3 (C), 156.9 (C), 165.9 (C); HRMS (EI) 300.1624 ($C_{21}H_{20}N_2$ requires 300.1626).

*4.4.2. (1S,9S)-(+)-10,10-Dimethyl-5-(2′-benzo[h]quinolinyl)-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene (+)-(**32**)*

Prepared by using 1-(2-benzo[*h*]quinolin-2-yl-2-oxo-ethyl)-pyridinium iodide **28** (900 mg, 2.11 mmol), enone (+)-**22** (253 mg, 1.7 mmol), piperidine (158 mg, 1.9 mmol), and ammonium acetate (4.0 g). Purification of the crude product furnished product (+)-**32** (392 mg, 53%) as a yellow solid. Mp 146–148 °C; $[\alpha]_D$ +26.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.64 (s, 3H), 1.29 (d, *J*=9.6 Hz, 1H), 1.36 (s, 3H), 2.33–2.37 (m, 1H), 2.63–2.68 (m, 1H), 2.79 (t, *J*=5.6 Hz, 1H), 3.18 (d, *J*=2.8 Hz, 2H), 7.36 (d, *J*=8.0 Hz, 1H), 7.59–7.72 (m, 4H), 7.83 (d, *J*=8.0 Hz, 1H), 8.19 (d, *J*=8.4 Hz, 1H), 8.50 (d, *J*=8.0 Hz, 1H), 8.62 (d, *J*=8.4 Hz, 1H), 9.41 (d, *J*=8.0 Hz, 1H); ^{13}C NMR δ 21.4 (CH_3), 26.1 (CH_3), 32.0 (CH_2), 36.8 (CH_2), 39.6 (C), 40.3 (CH), 46.6 (CH), 118.7 (CH), 119.3 (CH), 124.6 (CH), 125.4 (CH), 126.1 (C), 126.9 (CH), 127.6 (CH), 127.8 (CH), 128.1 (CH), 131.8 (C), 133.8 (C), 134.0 (CH), 136.5 (CH), 142.6 (C), 145.9 (C), 154.0 (C), 155.2 (C), 156.4 (C); HRMS (EI) 350.1785 ($C_{25}H_{22}N_2$ requires 350.1783).

*4.4.3. (1S,9S)-(+)-10,10-Dimethyl-5-(3′-phenyl-phenyl)-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene (+)-(**33a**)*

Prepared from 1-[2-oxo-2-(6-phenylpyridin-2-yl)-ethyl]-pyridinium iodide **29** (350 mg, 0.88 mmol), enone (−)-**22** (118 mg, 0.80 mmol), piperidine (74 mg, 0.88 mmol), and ammonium acetate (2.00 g). Purification of the crude product furnish the pure product (+)-**33a** as a whitish solid (136 mg, 47%). Mp 132–134 °C; $[\alpha]_D$ +38.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.61 (s, 3H), 1.26 (d, *J*=9.6 Hz, 1H), 1.35 (s, 3H), 2.31–2.35 (m, 1H), 2.61–2.66 (m, 1H), 2.76 (t, *J*=5.6 Hz, 1H), 3.13 (d, *J*=2.8 Hz, 2H), 7.29 (d, *J*=7.6 Hz, 1H), 7.33–7.36 (m, 1H), 7.44 (t, *J*=7.6 Hz, 2H), 7.66 (d, *J*=7.6 Hz, 1H), 7.79 (t, *J*=8.0 Hz, 1H), 8.09 (d, *J*=7.2 Hz, 2H), 8.24 (d, *J*=7.6 Hz, 1H), 8.28 (d, *J*=8.0 Hz, 1H); ^{13}C NMR δ 21.4 (CH_3), 26.1 (CH_3), 32.0 (CH_2), 36.8 (CH_2), 39.6 (C), 40.3 (CH), 46.5 (CH), 118.2 (CH), 119.1 (CH), 119.7 (CH), 127.0 (2×CH), 127.2 (C), 128.7 (2×CH), 128.9 (CH), 133.8 (CH), 137.6 (CH), 139.6 (C), 142.3 (C), 153.8 (C), 156.3 (C), 156.4 (C); HRMS (EI) 326.1784 ($C_{23}H_{22}N_2$ requires 326.1783) in accordance with the literature,[19] which however does not give the optical rotation, although presumably the same enantiomer was obtained.

*4.4.4. (1S,9S)-(+)-10,10-Dimethyl-5-[3′-(pyridin-2″-yl)phenyl]-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene (+)-(**34a**)*

Prepared from **30** and (−)-**22** (820 mg, 36%): foam. $[\alpha]_D^{18}$ +58.7 (*c* 1.0, $CHCl_3$); IR (NaCl) ν 2936 (m, C–H), 1587 (m, C=Car), 1466 (m, C=Car), 1437 (m, C=Car), 761 (s, *C*–Har) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.63 (s, 3H, C*H*$_3$C), 1.24 (d, *J*=9.5 Hz, 1H, 11-H), 1.33 (s, 3H, C*H*$_3$′C), 2.32 (tt, *J*=5.8, 2.8 Hz, 1H, 9-H), 2.61 (dt, *J*=9.5, 5.8 Hz, 1H, 11-H′), 2.70 (t, *J*=5.8 Hz, 1H, 1-H), 3.16 (d, *J*=2.8 Hz, 2H, 8-H), 7.11 (ddd, *J*=7.4, 4.8, 1.0 Hz, 1H, 5″-H), 7.18 (d, *J*=7.8 Hz, 1H, 4-H), 7.44 (d, *J*=7.8 Hz, 1H, 3-H), 7.49 (t, *J*=7.8 Hz, 1H, 5′-H), 7.62 (td, *J*=7.4, 1.8 Hz, 1H, 4″-H), 7.74 (dt, *J*=7.4, 1.0 Hz, 1H, 3″-H), 7.97 (ddd, *J*=7.8, 2.8, 1.6 Hz, 1H, 6′-H), 8.00 (ddd, *J*=7.8, 2.8, 1.6 Hz, 1H, 4′-H), 8.59 (t, *J*=1.6 Hz, 1H, 2′-H), 8.64 (ddd, *J*=4.8, 1.8, 1.0 Hz, 1H, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 (CH_3), 25.8 (CH_3), 31.7 (CH_2-11), 36.5 (CH_2-8), 39.2 (C-10), 39.9 (CH-9), 45.9 (CH-1), 117.0 (CH-3), 120.3 (CH-3″), 121.8 (CH-5″), 125.0 (CH-2′), 126.5 (CH-6′), 127.0 (CH-4′), 128.8 (CH-5′), 133.2 (CH-4), 136.3 (CH-4″), 139.4 (C-2), 140.2 (2×C-1′, 3′), 149.3 (CH-6″), 154.1 (C-2″), 156.5 (C-5), 157.0 (C-7); MS (EI) *m*/*z* (%) 326 (M$^{\bullet+}$, 100), 283 (66); HRMS (EI) 326.1780 ($C_{23}H_{22}N_2$ requires 326.1783).

4.5. General procedure for the alkylation of bipyridines 33a and 34a

The reaction was performed on a 1.6–3.3 mmol scale. A 2.5 M solution of *n*-BuLi in hexanes (1.7 equiv) was added dropwise to a solution of the pyridine derivative (+)-**33a**[19] or (+)-**34a** (1.0 equiv) in THF (5 mL) at −40 °C, turning the solution dark red. The stirring was continued for 3 h and then a solution of alkyl halide (1.7 equiv) in THF (2 mL) was added dropwise and the reaction mixture was stirred at room temperature overnight. Water (10 mL) was then added and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed in vacuo to give the crude product, which was purified by column chromatography on a column of silica gel (2 g) using a mixture of petroleum ether and ethyl acetate (24:1) to give the alkylated product. An alternative procedure employed LDA instead of *n*-BuLi.[19]

*4.5.1. (1S,8R,9S)-(+)-8,10,10-Trimethyl-5-(3′-phenyl-phenyl)-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene (+)-(**33b**)*

Prepared from bipyridine (+)-**33a**[19] (100 mg, 0.31 mmol), *n*-BuLi (2.5 M in hexanes) (0.20 mL, 0.53 mmol), and methyl iodide (75 mg, 0.53 mmol). Purification of the crude mixture afforded (+)-**33b** (41 mg, 39%) as a clear oil. $[\alpha]_D$ +24.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.65 (s, 3H), 1.29 (d, *J*=10.0 Hz, 1H), 1.43 (s, 3H), 1.42 (d, *J*=7.2 Hz, 3H), 2.13 (dt, *J*=6.0, 2.4 Hz, 1H), 2.48–2.54 (m, 1H), 2.82 (t, *J*=5.6 Hz, 1H), 3.17–3.22 (m, 1H), 7.27 (d, *J*=7.6 Hz, 1H), 7.35 (d, *J*=7.2 Hz, 1H), 7.41 (t, *J*=6.8 Hz, 2H), 7.66 (d, *J*=7.2 Hz, 1H), 7.79 (t, *J*=7.6 Hz, 1H), 8.09 (d, *J*=7.2 Hz, 2H), 8.24 (d, *J*=8.0 Hz, 1H), 8.30 (d, *J*=8.8 Hz, 1H); ^{13}C NMR δ 18.3 (CH_3), 21.0 (CH_3), 22.6 (CH_3), 26.4 (CH_2), 38.9 (CH), 41.5 (C), 46.8 (CH), 47.2 (CH), 118.0 (CH), 119.1 (CH), 119.6 (CH), 126.9 (2×CH), 128.7 (2×CH), 128.9 (CH), 133.5 (CH), 137.5 (CH), 139.6 (C), 142.2 (C), 153.5 (C), 156.2 (C), 156.5 (C), 160.1 (C); HRMS (EI) 340.1937 ($C_{24}H_{24}N_2$ requires 340.1939).

*4.5.2. (1S,8R,9S)-(+)-8-Butyl-10,10-dimethyl-5-(3′-phenyl-phenyl)-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene (+)-(**33c**)*

Prepared from bipyridine (+)-**33a**[19] (100 mg, 0.30 mmol), *n*-BuLi (2.5 M in hexanes) (0.20 mL, 0.53 mmol), and *n*-butyl iodide (98 mg, 0.53 mmol). Purification of the crude mixture furnished (+)-**33c** (52 mg, 45%) as a clear oil. $[\alpha]_D$ +8.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.58 (s, 3H), 0.92 (t, *J*=6.8 Hz, 3H), 1.27 (d, *J*=9.6 Hz, 1H), 1.36 (s, 3H), 1.43–1.47 (m, 5H), 2.25–2.34 (m, 2H), 2.45–2.51 (m, 1H), 2.74 (t, *J*=5.2 Hz, 1H), 2.97–3.00 (m, 1H), 7.25 (d, *J*=7.6 Hz, 1H), 7.36 (t, *J*=7.2 Hz, 1H), 7.43 (t, *J*=7.6 Hz, 2H), 7.65 (d, *J*=7.6 Hz, 1H), 7.79 (t, *J*=7.6 Hz, 1H), 8.08 (d, *J*=8.0 Hz, 2H), 8.23 (d, *J*=7.6 Hz, 1H), 8.34 (d, *J*=7.6 Hz, 1H); ^{13}C NMR δ 14.3 (CH_3), 21.0 (CH_3), 23.1 (CH_2), 26.5 (CH_3), 28.5 (CH_2), 30.2 (CH_2), 32.4 (CH_2), 41.2 (C), 43.4 (CH), 44.3 (CH), 47.0 (CH), 118.0 (CH), 119.1 (CH), 119.6 (CH), 127.0 (2×CH), 128.7 (2×CH), 128.9 (CH), 133.5 (CH), 137.6 (CH), 139.6 (C), 142.2 (C), 153.4 (C), 156.2 (C), 156.6 (C), 159.8 (C); HRMS (EI) 382.2406 ($C_{27}H_{30}N_2$ requires 382.2409).

*4.5.3. (1S,8R,9S)-(−)-10,10-Dimethyl-8-isopropyl-5-(3′-phenyl-phenyl)-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene (−)-(**33d**)*

Prepared from bipyridine (+)-**33a**[19] (50 mg, 0.16 mmol), *n*-BuLi (2.5 M in hexanes) (0.11 mL, 0.27 mmol), and isopropyl iodide

(43 mg, 0.27 mmol). Purification of the crude mixture gave (−)-**33d** (24 mg, 43%) as a clear oil. $[\alpha]_D$ −31.3 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.54 (s, 3H), 0.81 (d, *J*=6.8 Hz, 3H), 1.17 (d, *J*=6.8 Hz, 3H), 1.35 (s, 3H), 1.40 (d, *J*=9.6 Hz, 1H), 2.34 (dt, *J*=6.0, 2.0 Hz, 1H), 2.50–2.55 (m, 1H), 2.68 (t, *J*=5.8 Hz, 1H), 2.78–2.83 (m, 1H), 2.91 (dd, *J*=4.4, 2.0 Hz, 1H), 7.28 (d, *J*=7.6 Hz, 1H), 7.37 (d, *J*=8.8 Hz, 1H), 7.45 (t, *J*=7.6 Hz, 2H), 7.66 (d, *J*=7.6 Hz, 1H), 7.81 (t, *J*=7.6 Hz, 1H), 8.10 (d, *J*=8.0 Hz, 2H), 8.27 (d, *J*=8.0 Hz, 1H), 8.34 (d, *J*=7.6 Hz, 1H); ^{13}C NMR δ 20.3 (CH_3), 21.1 (CH_3), 22.4 (CH_3), 26.4 (CH_3), 29.4 (CH_2), 30.5 (CH), 41.5 (CH), 42.0 (C), 46.8 (CH), 49.2 (CH), 117.9 (CH), 119.1 (CH), 119.6 (CH), 126.9 (2×CH), 128.7 (2×CH), 128.9 (CH), 133.6 (CH), 137.5 (CH), 139.6 (C), 142.7 (C), 153.2 (C), 156.2 (C), 156.7 (C), 158.7 (C); HRMS (EI) 368.2255 ($C_{26}H_{28}N_2$ requires 368.2252).

4.5.4. (1S,8R,9S)-(+)-8,10,10-Trimethyl-8-isopropyl-5-[3′-(pyridin-2″-yl)phenyl]-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene (+)-(**34b**)

Prepared by alkylation of (+)-**34a**; purification afforded (+)-**34b** (64 mg, 31%). $[\alpha]_D^{23}$ +7.1 (*c* 1.0, CH_2Cl_2); IR (NaCl) ν 2926 (m, C–H), 1637 (m, C=Car), 1585 (m, C=Car), 1460 (m, C=Car), 773 (s, *C*–Har) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.61 (s, 3H, C*H*$_3$C), 1.27 (d, *J*=9.8 Hz, 1H, 11-H), 1.35 (s, 3H, C*H*$_3$′C), 1.41 (d, *J*=7.1 Hz, 3H, C*H*$_3$CH), 2.10 (td, *J*=5.7, 2.5 Hz, 1H, 9-H), 2.50 (dt, *J*=9.8, 5.7 Hz, 1H, 9-H′), 2.71 (t, *J*=5.7 Hz, 1H, 1-H), 3.20 (qd, *J*=7.1, 2.5 Hz, 1H, 8-H), 7.15 (ddd, *J*=7.6, 4.8, 1.1 Hz, 1H, 5″-H), 7.18 (d, *J*=7.8 Hz, 1H, 4-H), 7.44 (d, *J*=7.8 Hz, 1H, 3-H), 7.48 (t, *J*=7.7 Hz, 1H, 5′-H), 7.68 (td, *J*=7.6, 1.8 Hz, 1H, 4″-H), 7.75 (dt, *J*=7.6, 1.1 Hz, 1H, 3″-H), 7.93 (ddd, *J*=7.7, 1.7, 1.2 Hz, 1H, 6′-H), 8.02 (ddd, *J*=7.7, 1.7, 1.2 Hz, 1H, 4′-H), 8.53 (t, *J*=1.7 Hz, 1H, 2′-H), 8.64 (ddd, *J*=4.8, 1.8, 1.1 Hz, 1H, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3 (*C*H_3CH), 20.9 (*C*H_3C), 26.3 (*C*H_3-C), 28.7 (CH_2-11), 38.9 (CH-8), 41.4 (C-10), 46.8 (CH-9), 47.0 (CH-1), 117.2 (CH-3), 120.7 (CH-3″), 122.1 (CH-5″), 125.2 (CH-2′), 126.8 (CH-6′), 127.3 (CH-4′), 129.0 (CH-5′), 133.3 (CH-4), 136.7 (CH-4″), 139.7 (C-2), 140.4 (C-1′), 140.5 (C-3′), 149.6 (CH-6″), 154.1 (C-2″), 157.6 (C-5), 160.6 (C-7); MS (EI) *m*/*z* (%) 340 ($M^{\bullet+}$, 18), 325 (22, $M^{\bullet+}$, –CH_3), 82.9 (100); HRMS (EI) 340.1935 ($C_{24}H_{24}N_2$ requires 340.1939).

4.5.5. (1S,8R,9S)-(−)-10,10-Dimethyl-8-isopropyl-5-[3′-(pyridin-2″-yl)phenyl]-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene (−)-(**34d**)

Prepared by alkylation of (+)-**34a**; purification afforded (−)-**34d** (84 mg, 37%). $[\alpha]_D^{22}$ −1.9 (*c* 1.0, CH_2Cl_2); IR (NaCl) ν 2957 (m, C-H), 1585 (m, C=Car), 1565 (m, C=Car), 1434 (m, C=Car), 777 (s, *C*–Har) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.58 (s, 3H, C*H*$_3$C-10), 0.81 (d, *J*=7.0 Hz, 3H, CHC*H*$_3$), 1.18 (d, *J*=7.0 Hz, 3H, CHC*H*′$_3$), 1.35 (d, *J*=9.8 Hz, 1H, 11-H), 1.36 (s, 3H, C*H*$_3$′C-10), 2.32 (td, *J*=5.9, 1.8 Hz, 1H, 9-H), 2.52 (dt, *J*=9.8, 5.8 Hz, 1H, 11-H′), 2.68 (t, *J*=5.8 Hz, 1H, 1-H), 2.80–2.90 (m, 1H, C*H*(CH_3)$_2$), 2.93 (dd, *J*=4.2, 1.8 Hz, 1H, 8-H), 7.16 (ddd, *J*=7.5, 4.1, 1.1 Hz, 1H, 5″-H), 7.19 (d, *J*=7.8 Hz, 1H, 4-H), 7.48 (d, *J*=7.8 Hz, 1H, 3-H), 7.50 (t, *J*=7.7 Hz, 1H, 5′-H), 7.69 (td, *J*=7.5 ,1.7 Hz, 1H, 4″-H), 7.75 (dt, *J*=7.5, 1.1 Hz, 1H, 3″-H), 7.94 (d, *J*=7.8 Hz, 1H, 6′-H), 8.06 (d, *J*=7.8 Hz, 1H, 4′-H), 8.55 (s, 1H, 2′-H), 8.65 (ddd, *J*=4.1, 1.7, 1.1 Hz, 1H, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1 (*C*H_3CH), 21.0 (CH_3), 22.3 (*C*′H_3CH), 26.3 (CH_3), 29.4 (CH_2-11), 30.2 (*C*H(CH_3)$_2$), 41.2 (CH-9), 41.8 (C-10), 46.5 (CH-1), 49.1 (CH-8), 117.0 (CH-3), 120.6 (CH-3″), 122.0 (CH-5″), 125.0 (CH-2′), 126.7 (CH-6′), 127.2 (CH-4′), 129.0 (CH-5′), 133.3 (CH-4), 136.7 (CH-4″), 139.6 (C-2), 140.5 (C-1′), 140.9 (C-3′), 149.5 (CH-6″), 153.6 (C-2″), 157.5 (C-5), 159.1 (C-7); MS (EI) *m*/*z* (%) 368 ($M^{\bullet+}$, 22), 325 ($M^{\bullet+}$−*i*-Pr, 100), 283 (71); HRMS (EI) 368.2249 ($C_{26}H_{28}N_2$ requires 368.2252).

4.6. General procedure for the preparation of bipyridine *N,N′*-dioxides 12–15[8]

m-Chloroperoxybenzoic acid (70%, 106 mg, 0.60 mmol, 4.0 equiv) was added portion-wise to a respective cool (0 °C) solution of the bipyridine derivatives **31**, **32**, **33a–d**, or **34a**,**b**,**d** (0.15 mmol, 1.0 equiv) in CH_2Cl_2 (4 mL). The mixture was then allowed to warm up to room temperature and stirred overnight. The mixture was washed with an aqueous solution of $NaHCO_3$ (10%; 5 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by chromatography on silica gel (10 g) using a mixture of petroleum ether and ethyl acetate (5:1) to elute the unreacted starting material, followed by ethyl acetate, to give the pure product.

4.6.1. (1R,9R)-(+)-10,10-Dimethyl-4-(quinolin-2-yl)-3-aza-tricyclo[7.1.1.0^{2,7}]undeca-2,4,6-triene *N,N′*-dioxide (+)-(**12**)

Prepared from bipyridine (+)-**31** (150 mg, 0.5 mmol) and *m*-CPBA (190 mg, 1.1 mmol). Purification of the crude product afforded the dioxide (+)-**12** (142 g, 86%) as a pale yellow solid. Mp 202–204 °C; $[\alpha]_D$ +17.3 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.74 (s, 3H), 1.29 (d, *J*=10.0 Hz, 1H), 1.40 (s, 3H), 2.27–2.28 (m, 1H), 2.68–2.73 (m, 1H), 2.99 (s, 2H), 4.04 (t, *J*=6.0 Hz, 1H), 7.10 (d, *J*=8.0 Hz, 1H), 7.44 (d, *J*=8.0 Hz, 1H), 7.56 (d, *J*=8.8 Hz, 1H), 7.61 (t, *J*=7.6 Hz, 1H), 7.66–7.71 (m, 2H), 7.82 (d, *J*=8.0 Hz, 1H), 8.75 (d, *J*=8.8 Hz, 1H); ^{13}C NMR δ 21.8 (CH_3), 26.2 (CH_3), 30.7 (CH_2), 32.1 (CH_2), 39.6 (C), 40.3 (CH), 40.6 (CH), 120.7 (CH), 123.9 (CH), 124.5 (CH), 124.9 (CH), 125.1 (CH), 128.4 (CH), 129.3 (CH), 130.6 (CH), 130.8 (C), 135.0 (C), 139.7 (C), 140.6 (C), 142.6 (2×C); HRMS (EI) 332.1528 ($C_{21}H_{20}N_2O_2$ requires 332.1525).

4.6.2. (1S,9S)-(+)-10,10-Dimethyl-5-(2′-benzo[h]quinolinyl)-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene *N,N′*-dioxide (+)-(**13**)

Prepared from bipyridine (+)-**32** (50 mg, 0.14 mmol) and *m*-CPBA (49 mg, 0.29 mmol). Purification of the crude product furnished dioxide (+)-**13** (15 mg, 28%) as a pale yellow solid. Mp 82–84 °C; $[\alpha]_D$ +40.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.69 (s, 3H), 1.28 (d, *J*=10.0 Hz, 1H), 1.37 (s, 3H), 2.40–2.44 (m, 1H), 2.63–2.68 (m, 1H), 2.81 (t, *J*=5.6 Hz, 1H), 3.08–3.22 (m, 2H), 7.02 (d, *J*=8.0 Hz, 1H), 7.60–7.68 (m, 3H), 7.75 (d, *J*=8.8 Hz, 1H), 7.84 (d, *J*=8.0 Hz, 1H), 8.20 (dd, *J*=8.0, 5.6 Hz, 2H), 9.02 (d, *J*=8.4 Hz, 1H), 9.28 (d, *J*=8.0 Hz, 1H); ^{13}C NMR δ 21.2 (CH_3), 25.9 (CH_3), 31.2 (CH_2), 31.6 (CH_2), 39.4 (CH), 39.5 (C), 46.3 (CH), 123.5 (CH), 123.6 (CH), 124.5 (CH), 125.2 (CH), 125.5 (CH), 126.3 (C), 127.0 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 131.7 (C), 133.7 (C), 135.4 (CH), 145.6 (C), 145.9 (C), 146.0 (C), 146.9 (C), 149.5 (C); HRMS (EI) 382.1679 ($C_{25}H_{22}N_2O_2$ requires 382.1681).

4.6.3. (1S,9S)-(+)-10,10-Dimethyl-5-(3′-phenyl-phenyl)-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene *N,N′*-dioxide (+)-(**14a**)

Prepared from bipyridine (+)-**33a** (50 mg, 0.15 mmol) and *m*-CPBA (54 mg, 0.32 mmol). Purification of the crude product gave dioxide (+)-**14a** as a yellowish amorphous solid (15 mg, 28%). $[\alpha]_D$ +67.8 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.67 (s, 3H), 1.27 (d, *J*=9.6 Hz, 1H), 1.38 (s, 3H), 2.40–2.43 (m, 1H), 2.63–2.68 (m, 1H), 2.81 (t, *J*=5.6 Hz, 1H), 3.07–3.20 (m, 2H), 7.00 (d, *J*=7.6 Hz, 1H), 7.34–7.45 (m, 3H), 7.72 (d *J*=8.0 Hz, 1H), 7.85 (t, *J*=8.0 Hz, 1H), 8.02 (d, *J*=8.4 Hz, 2H), 8.13 (d, *J*=8.0 Hz, 1H), 8.85 (d, *J*=8.0 Hz, 1H); ^{13}C NMR δ 15.9 (CH_3), 20.5 (CH_3), 25.5 (CH_2), 26.0 (CH_2), 33.9 (CH), 34.2 (C), 41.0 (CH), 117.5 (CH), 119.4 (CH), 119.6 (CH), 121.9 (CH), 122.3 (CH), 122.8 (2×CH), 124.2 (CH), 124.4 (2×CH), 127.3 (C), 127.4 (C), 135.5 (C), 138.8 (C), 141.1 (C), 144.6 (C); HRMS (EI) 358.1682 ($C_{23}H_{22}N_2O_2$ requires 358.1681).

4.6.4. (1S,8R,9S)-(+)-8,10,10-Trimethyl-5-(3′-phenyl-phenyl)-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene *N,N′*-dioxide (+)-(**14b**)

Prepared from bipyridine (+)-**33b** (40 mg, 0.12 mmol) and *m*-CPBA (45 mg, 0.26 mmol). Purification of the crude product afforded dioxide (+)-**14b** (20 mg, 44%) as an amorphous solid. $[\alpha]_D$ +16.6 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.61 (s, 3H), 1.36 (s, 3H), 1.41 (d, *J*=10.0 Hz, 1H), 1.44 (d, *J*=6.8 Hz, 3H), 2.08–2.11 (m,

1H), 2.48–2.53 (m, *J*=6.0 Hz, 1H), 2.76 (t, *J*=5.6 Hz, 1H), 3.34–3.38 (m, 1H), 6.88 (d, *J*=7.6 Hz, 1H), 7.27–7.47 (m, 6H), 7.54 (d, *J*=7.6 Hz, 1H), 7.77 (d, *J*=6.0 Hz, 2H); ^{13}C NMR δ 15.2 (CH_3), 18.6 (CH_3), 20.1 (CH_3), 24.9 (CH_2), 37.2 (CH), 39.6 (C), 45.7 (CH), 46.1 (CH), 121.5 (CH), 123.6 (CH), 124.1 (CH), 126.3 (CH), 126.5 (CH), 127.0 (2×CH), 128.4 (CH), 128.6 (2×CH), 131.8 (C), 140.2 (C), 143.0 (C), 145.8 (C), 148.8 (C), 173.1 (C); HRMS (EI) 372.1838 ($C_{24}H_{24}N_2O_2$ requires 372.1838).

4.6.5. (1S,8R,9S)-(−)-8-Butyl-10,10-dimethyl-5-(3′-phenyl-phenyl)-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene N,N′-dioxide (−)-(**14c**)

Prepared from bipyridine (+)-**33c** (50 mg, 0.13 mmol) and *m*-CPBA (50 mg, 0.29 mmol). Purification of the crude product furnished dioxide (−)-**14c** (25 mg, 47%) as an amorphous solid. $[\alpha]_D$ −27.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.58 (s, 3H), 0.83 (t, *J*=7.2 Hz, 3H), 1.30 (d, *J*=10.0 Hz, 1H), 1.37–1.42 (m, 8H), 2.28–2.32 (m, 1H), 2.46–2.52 (m, 1H), 2.51–2.57 (m, 1H), 2.76 (t, *J*=5.6 Hz, 1H), 3.12–3.14 (m, 1H), 6.86 (d, *J*=8.0 Hz, 1H), 7.31 (dd, *J*=8.0, 2.0 Hz, 2H), 7.34–7.40 (m, 3H), 7.44 (dd, *J*=8.0, 2.0 Hz, 1H), 7.53 (dd, *J*=8.0, 2.0 Hz, 1H), 7.77 (dd, *J*=8.0, 2.0 Hz, 2H); ^{13}C NMR δ 13.3 (CH_3), 19.8 (CH_3), 21.8 (CH_2), 25.0 (CH_3), 26.5 (CH_2), 27.3 (CH_2), 29.4 (CH_2), 39.4 (CH), 40.2 (C), 42.7 (CH), 45.9 (CH), 121.4 (CH), 123.6 (CH), 124.1 (CH), 126.3 (CH), 126.5 (CH), 127.0 (2×CH), 128.4 (CH), 128.6 (2×CH), 131.7 (C), 140.2 (C), 142.9 (C), 145.3 (C), 148.9 (C), 172.8 (C); HRMS (EI) 414.2306 ($C_{27}H_{30}N_2O_2$ requires 414.2307).

4.6.6. (1S,8R,9S)-(+)-10,10-Dimethyl-8-isopropyl-5-(3′-phenyl-phenyl)-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene N,N′-dioxide (+)-(**14d**)

Prepared from bipyridine (−)-**33d** (20 mg, 0.05 mmol) and *m*-CPBA (21 mg, 0.11 mmol). Purification of the crude product gave dioxide (+)-**14d** (9 mg, 45%) as an amorphous solid. $[\alpha]_D$ +7.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.56 (s, 3H), 0.91 (d, *J*=7.2 Hz, 3H), 0.97 (d, *J*=7.2 Hz, 3H), 1.35 (s, 3H), 1.58 (d, *J*=10.0 Hz, 1H), 2.26–2.34 (m, 1H), 2.41–2.52 (m, 1H), 2.76 (t, *J*=5.2 Hz, 1H), 3.12–3.19 (m, 1H), 3.17–3.22 (m, 1H), 6.88 (d, *J*=8.0 Hz, 1H), 7.19–7.31 (m, 3H), 7.33–7.38 (m, 3H), 7.44 (d, *J*=8.0 Hz, 1H), 7.77 (d, *J*=8.0 Hz, 2H); ^{13}C NMR δ 14.0 (CH_3), 19.6 (CH_3), 22.1 (CH_3), 24.9 (CH_3), 25.7 (CH_2), 29.4 (CH), 31.4 (CH), 40.3 (C), 42.1 (CH), 45.3 (CH), 121.4 (CH), 123.6 (CH), 124.0 (CH), 126.3 (CH), 126.4 (CH), 127.0 (2×CH), 128.5 (CH), 128.6 (2×CH), 131.8 (C), 140.7 (C), 142.7 (C), 145.3 (C), 148.9 (C), 171.7 (C); HRMS (EI) 400.2152 ($C_{26}H_{28}N_2O_2$ requires 400.2151).

4.6.7. (1S,9S)-(−)-10,10-Dimethyl-5-[3′-(pyridin-2′-yl)phenyl]-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene N,N-dioxide (−)-(**15a**)

Prepared from (+)-**34a**; purification afforded (−)-**15a** (32 mg, 60%). $[\alpha]_D^{21}$ −22.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.72 (s, 3H, C*H*$_3$C), 1.31 (d, *J*=9.8 Hz, 1H, 11-H), 1.42 (s, 3H, C*H*$_3$′C), 2.44 (tt, *J*=5.9, 2.9 Hz, 1H, 9-H), 2.69 (dt, *J*=9.8, 5.9 Hz, 1H, 9-H′), 2.81 (t, *J*=5.9 Hz, 1H, 1-H), 3.10 (dd, *J*=19.2, 5.9 Hz, 1H, 8-H), 3.18 (dd, *J*=19.2, 5.9 Hz, 1H, 7-H′), 6.93 (d, *J*=7.8 Hz, 1H, 3-H), 7.22 (ddd, *J*=7.6, 6.5, 2.0 Hz, 1H, 5″-H), 7.27 (d, *J*=7.8 Hz, 1H, 4-H), 7.30 (td, *J*=7.6, 1.3 Hz, 1H, 4″-H), 7.52 (dd, *J*=7.6, 2.0 Hz, 1H, 3″-H), 7.56 (t, *J*=7.9 Hz, 1H, 5′-H), 7.87 (ddd, *J*=7.9, 1.7, 1.2 Hz, 1H, 6′-H), 7.90 (ddd, *J*=7.9, 1.7, 1.2 Hz, 1H, 4′-H), 8.25 (t, *J*=1.7 Hz, 1H, 2′-H), 8.31 (dd, *J*=6.5, 1.3 Hz, 1H, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 25.8 (CH_3), 31.1 (CH_2-8), 31.5 (CH_2-11), 39.3 (CH-9, C-10), 46.1 (CH-1), 123.1 (CH-3), 124.0 (CH-4), 124.6 (CH-5″), 125.8 (CH-4″), 127.7 (CH-3″), 128.0 (CH-5′), 129.8 (CH-4′), 130.5 (CH-6′), 130.7 (CH-2′), 132.3 (C-2), 133.3 (C-1′), 140.3 (CH-6″), 144.6 (C-3′), 146.4 (C-2″), 146.8 (C-5), 149.0 (C-7); MS (FAB) *m*/*z* (%) 359 ((M+H)$^+$, 100); HRMS (FAB) 359.1829 ($C_{23}H_{23}N_2O_2$ (M+H)$^+$ requires 359.1827).

4.6.8. (1S,8R,9S)-(−)-8,10,10-Trimethyl-8-isopropyl-5-[3′-(pyridin-2″-yl)phenyl]-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene N,N′-dioxide (−)-(**15b**)

Prepared from (+)-**34b**; purification afforded (−)-**15b** (23 mg, 42%). $[\alpha]_D^{14}$ −31.0 (*c* 1.0, $CHCl_3$); IR (NaCl) ν 2933 (m, C–H), 1585 (m, C=Car), 1462 (m, C=Car), 1431 (m, C=Car), 1216 (m, N$^+$–O$^-$), 761 (s, *C*–Har) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (s, 3H, C*H*$_3$C), 1.33 (s, 3H, C*H*$_3$′C), 1.36 (d, *J*=9.9 Hz, 1H, 11-H), 1.41 (d, *J*=6.6 Hz, 3H, C*H*$_3$CH), 2.08 (td, *J*=6.0, 2.8 Hz, 1H, 9-H), 2.48 (dt, *J*=9.9, 6.0 Hz, 1H, 11-H′), 2.71 (t, *J*=6.0 Hz, 1H, 1-H), 3.33 (qd, *J*=6.6, 2.8 Hz, 1H, 8-H), 6.82 (d, *J*=7.8 Hz, 1H, 4-H), 7.12–7.18 (m, 2H, 3-H, 5″-H), 7.22 (td, *J*=7.7, 1.1 Hz, 1H, 4″-H), 7.42 (dd, *J*=7.7, 2.0 Hz, 1H, 3″-H), 7.48 (t, *J*=7.8 Hz, 1H, 5′-H), 7.77 (dd, *J*=7.8, 1.7 Hz, 2H, 6′-H, 4′-H), 8.13 (t, *J*=1.7 Hz, 1H, 2′-H), 8.24 (dd, *J*=6.4, 1.1 Hz, 1H, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.7 (*C*H$_3$CH), 20.5 (CH_3), 25.8 (CH_3), 28.2 (CH_2-11), 35.0 (CH-8), 41.5 (C-10), 46.8 (CH-1), 47.3 (CH-9), 123.1 (CH-3), 124.3 (CH-4), 124.6 (CH-5″), 125.9 (CH-4″), 127.7 (CH-3″), 128.0 (CH-5′), 129.7 (CH-6′), 130.6 (CH-4′), 130.8 (CH-2′), 132.3 (C-2), 133.5 (C-1′), 140.3 (CH-6″), 144.6 (C-3′), 147.0 (C-2″), 149.0 (C-5), 150.1 (C-7); MS (FAB) *m*/*z* (%) 373 ((M+H)$^+$, 31), 338 (100), 215 (10), 75 (96); HRMS (FAB) 373.1919 ($C_{24}H_{25}N_2O_2$ (M+H)$^+$ requires 373.1916).

4.6.9. (1S,8R,9S)-(−)-10,10-Dimethyl-8-isopropyl-5-[3′-(pyridin-2″-yl)phenyl]-6-aza-tricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene N,N′-dioxide (−)-(**15d**)

Prepared from (−)-**34d**; purification afforded (−)-**15d** (27 mg, 45%). $[\alpha]_D^{14}$ −64.0 (*c* 1.0, $CHCl_3$); IR (NaCl) ν 2935 (m, C–H), 1587 (m, C=Car), 1465 (m, C=Car), 1436 (m, C=Car), 1216 (m, N$^+$–O$^-$), 762 (s, *C*–Har) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H, C*H*$_3$C), 0.88 (d, *J*=7.0 Hz, 3H, CHC*H*$_3$), 0.95 (d, *J*=7.0 Hz, 3H, CHC*H*′$_3$), 1.33 (s, 3H, C*H*$_3$C), 1.54 (d, *J*=9.9 Hz, 1H, 11-H), 2.31 (td, *J*=5.8, 2.4 Hz, 1H, 9-H), 2.46 (dt, *J*=9.9, 5.8 Hz, 1H, 11-H′), 2.67 (t, *J*=5.8 Hz, 1H, 1-H), 3.10–3.20 (m, 2H, 8-H, C*H*(CH$_3$)$_2$), 6.81 (d, *J*=7.8 Hz, 1H, 3-H), 7.11–7.17 (m, 2H, 3-H, 5″-H), 7.21 (td, *J*=7.7, 1.2 Hz, 1H, 4″-H), 7.42 (dd, *J*=7.7, 2.0 Hz, 1H, 3″-H), 7.48 (t, *J*=7.8 Hz, 1H, 5′-H), 7.74–7.78 (m, 2H, 6′-H, 4′-H), 8.09 (t, *J*=1.5 Hz, 1H, 2′-H), 8.24 (dd, *J*=6.4, 1.2 Hz, 1H, 6″-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6 (*C*H$_3$C), 20.9 (*C*H$_3$CH), 21.5 (*C*′H$_3$CH), 25.8 (C′H$_3$C), 27.8 (*C*H(CH$_3$)$_2$), 28.2 (CH_2-11), 42.3 (CH-9), 42.9 (C-10), 45.5 (CH-8), 46.6 (CH-1), 123.0 (CH-3), 124.3 (CH-4), 124.6 (CH-5″), 125.8 (CH-4″), 127.7 (CH-3″), 128.1 (CH-5′), 129.6 (CH-6′), 130.5 (CH-4′), 130.8 (CH-2′), 132.4 (C-2), 133.8 (C-1′), 140.3 (CH-6″), 145.2 (C-3′), 147.2 (C-2″), 149.0 (C-5), 149.2 (C-7); MS (FAB) *m*/*z* (%) 401 ((M+H)$^+$, 100), 385 ((M+H)$^+$−O, 26), 338 (23), 71 (20); HRMS (FAB) 401.2232 ($C_{26}H_{29}N_2O_2$ (M+H)$^+$ requires 401.2229).

4.7. General method for the preparation of isoquinoline *N*-oxides (*R*)-16a–d[8]

The oxidation was carried out on a 0.22–0.28 mmol scale. A solution of *m*-CPBA (1.5 equiv) in CH_2Cl_2 (5 mL) was added to a cooled stirred solution of the respective isoquinoline derivative (*R*)-**42a–d** (1.0 equiv) in CH_2Cl_2 (2 mL) at 0 °C and the resulting mixture was stirred at room temperature for 2 d. After this period the mixture was treated with aqueous saturated Na_2CO_3 (10 mL) and then extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed in vacuo to give the crude product, which was purified by column chromatography on silica gel (2 g) using a mixture of petroleum ether and ethyl acetate (5:1) to elute the unreacted starting material, followed by ethyl acetate, to give the pure product.

4.7.1. (R)-(+)-1–(2-Methoxy-naphthalen-1-yl)-3-methyl-5,6,7,8-tetrahyroisoquinoline 2-oxide (R)-(+)-(**16a**)

Prepared from (*R*)-(+)-**42a**[30a] (90 mg, 0.30 mmol) and *m*-CPBA (86 mg, 0.50 mmol). Purification of the crude product gave *N*-oxide

(*R*)-(+)-**16a** as a pale yellow solid (38 mg, 40%). Mp 138–140 °C; $[\alpha]_D$ +206.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.58–1.72 (m, 2H), 1.82 (quin, *J*=6.8 Hz, 2H), 2.05–2.12 (m, 1H), 2.24–2.31 (m, 1H), 2.59 (s, 3H), 2.84 (t, *J*=6.4 Hz, 2H), 3.91 (s, 3H), 7.12–7.15 (m, 2H), 7.33–7.45 (m, 3H), 7.84–7.86 (m, 1H), 7.99 (d, *J*=9.2 Hz, 1H); ^{13}C NMR δ 17.9 (CH_3), 22.1 (CH_2), 22.2 (CH_2), 25.8 (CH_2), 28.6 (CH_2), 56.5 (CH_3), 113.2 (CH), 115.8 (C), 123.2 (CH), 123.7 (CH), 125.6 (CH), 127.4 (CH), 128.3 (CH), 129.1 (C), 130.7 (CH), 132.0 (C), 133.8 (C), 135.7 (C), 145.8 (C), 145.8 (C), 154.3 (C); HRMS (EI) 319.1574 ($C_{21}H_{21}NO_2$ requires 319.1572).

4.7.2. (*R*)-(+)-1-(2-Methoxy-naphthalen-1-yl)-3-phenyl-5,6,7,8-tetrahydroisoquinoline 2-oxide (*R*)-(+)-(**16b**)

Prepared from (*R*)-(+)-**42b**[30a] (100 mg, 0.28 mmol) and *m*-CPBA (74 mg, 0.42 mmol). Purification of the crude product gave *N*-oxide (*R*)-(+)-**16b** as a pale yellow solid (37 mg, 35%). Mp 95–97 °C; $[\alpha]_D$ +220.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.56–1.68 (m, 2H), 1.77 (quin, *J*=5.1 Hz, 2H), 2.02–2.09 (m, 1H), 2.21–2.29 (m, 1H), 2.81 (t, *J*=6.2 Hz, 2H), 3.83 (s, 3H), 7.16–7.21 (m, 2H), 7.24–7.35 (m, 6H), 7.67 (d, *J*=7.4 Hz, 1H), 7.83 (d, *J*=8.4 Hz, 2H), 7.89 (d, *J*=9.1 Hz, 1H); ^{13}C NMR δ 21.0 (CH_2), 21.1 (CH_2), 25.0 (CH_2), 28.7 (CH_2), 55.7 (CH_3), 113.3 (CH), 114.6 (C), 123.8 (CH), 126.5 (CH), 127.1 (2×CH), 127.5 (CH), 127.9 (CH), 128.1 (C), 128.3 (C), 128.3 (2×CH), 128.9 (CH), 129.7 (CH), 130.8 (CH), 132.2 (C), 132.4 (C), 134.3 (C), 135.5 (C), 145.4 (C), 153.3 (C); HRMS (EI) 381.1727 ($C_{26}H_{23}NO_2$ requires 381.1729).

4.7.3. (*R*)-(+)-1-(2-Methoxy-naphthalen-1-yl)-3-(3,4,5-trimethoxyphenyl)-5,6,7,8-tetrahydroisoquinoline 2-oxide (*R*)-(+)-(**16c**)

Prepared from (*R*)-(+)-**42c**[30b] (100 mg, 0.2 mmol) and *m*-CPBA (57 mg, 0.3 mmol). Purification of the crude product gave *N*-oxide (*R*)-(+)-**16c** as a white solid (59 mg, 57%). Mp 88–90 °C; $[\alpha]_D$ +38.0 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.53–1.65 (m, 2H), 1.77 (quin, *J*=6.2 Hz, 2H), 1.98–2.07 (m, 1H), 2.19–2.27 (m, 1H), 2.81 (t, *J*=6.3 Hz, 2H), 3.78 (s, 3H), 3.80 (s, 6H), 3.83 (s, 3H), 7.07 (s, 2H), 7.16–7.20 (m, 2H), 7.24–7.32 (m, 3H), 7.77 (d, *J*=8.8 Hz, 1H), 7.89 (d, *J*=9.0 Hz, 1H); ^{13}C NMR δ 22.03 (CH_2), 22.17 (CH_2), 26.00 (CH_2), 28.79 (CH_2), 56.41 (2×CH_3), 56.50 (CH_3), 60.85 (CH_3), 107.62 (2×CH), 113.30 (CH), 115.97 (C), 123.31 (CH), 123.82 (CH), 126.46 (CH), 127.44 (CH), 128.35 (CH), 129.18 (C), 129.55 (C), 130.92 (CH), 131.92 (C), 135.29 (C), 136.49 (C), 138.81 (C), 146.37 (C), 152.80 (2×C), 154.34 (C); HRMS (EI) 471.2047 ($C_{29}H_{29}NO_5$ requires 471.2046).

4.7.4. (*R*)-(+)-3-Fur-2-yl-1-(2-methoxy-naphthalen-1-yl)-5,6,7,8-tetrahydroisoquinoline 2-oxide (*R*)-(+)-(**16d**)

Prepared from (*R*)-(+)-**42d**[30b] (100 mg, 0.28 mmol) and *m*-CPBA (74 mg, 0.42 mmol). Purification of the crude product gave *N*-oxide (*R*)-(+)-**16d** as a pale yellow solid (21 mg, 20%). Mp 144–146 °C; $[\alpha]_D$ +175.3 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.50–1.66 (br m, 2H), 1.76 (quin, *J*=6.0 Hz, 2H), 1.97–2.04 (m, 1H), 2.16–2.24 (m, 1H), 2.78–2.87 (m, 2H), 3.80 (s, 3H), 6.46 (dd, *J*=3.6, 2.0 Hz, 1H), 7.10 (d, *J*=9.2 Hz, 1H), 7.23–7.35 (m, 4H), 7.48 (s, 1H), 7.76 (d, *J*=9.1 Hz, 1H), 7.91 (t, *J*=8.8 Hz, 2H); ^{13}C NMR δ 22.1 (CH_2), 22.2 (CH_2), 25.9 (CH_2), 28.9 (CH_2), 56.5 (CH_3), 112.4 (CH), 113.3 (CH), 115.5 (C), 115.8 (CH), 121.4 (CH), 123.1 (CH), 123.9 (CH), 127.6 (CH), 128.3 (C), 128.4 (CH), 129.2 (C), 130.9 (CH), 132.0 (C), 133.7 (C), 137.8 (C), 142.9 (CH), 145.9 (C), 154.4 (C); HRMS (EI) 371.1521 ($C_{24}H_{21}NO_3$ requires 371.1521).

4.7.5. 3,3′-Diphenyl-[1,1′]-biisoquinolinyl-N,N′-dioxide (**17b**)

m-CPBA (2.6 g, 12 mmol, 10 equiv) was added to a pre-cooled (0 °C) solution of biisoquinoline **46** (500 mg, 1.2 mmol, 1.0 equiv) in CH_2Cl_2 (22 mL), the reaction mixture was allowed to reach room temperature and then stirred for 48 h. The resulting mixture was diluted with water (30 mL) and the aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were washed with 10% aqueous Na_2CO_3 (2×10 mL), dried over $MgSO_4$ and evaporated. The residue was chromatographed on a column of on silica gel (12 g) with a mixture of petroleum ether and ethyl acetate (1:1) to afford the corresponding monooxide (100 mg, 20%), followed by dioxide **17b** (531 mg, 57%), both as white solids that decomposed on heating before melting. Monooxide: amorphous solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.20–8.10 (m); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 117.9 (CH), 124.8 (CH), 125.1 (CH), 126.1 (CH), 126.2 (C), 126.8 (C), 126.9 (CH), 127.2 (CH), 127.3 (CH), 127.6 (CH), 128.1 (2CH), 128.4 (CH), 128.5 (CH), 128.66 (CH), 128.75 (CH), 128.83 (CH), 129.0 (CH), 129.37 (CH), 129.40 (CH), 129.44 (C), 130.0 (CH), 130.7 (CH), 132.9 (C), 137.3 (C), 139.5 (C), 144.2 (C), 147.2 (C), 151.4 (C), 152.5 (C); IR (KBr) ν 3054, 1620, 1496, 1314, 1233, 885, 770, 746, 700 cm^{-1}; FABMS *m*/*z* (%) 425 ($[M+H]^+$, 50), 359 (12), 331 (20), 282 (100), 280 (18), 256 (12), 240 (4), 150 (2), 99 (30), 71 (60), 57 (78). Dioxide **17b**: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.20 (d, *J*=8.6 Hz, 2H), 7.41–7.49 (m, 8H), 7.54–7.58 (m, 2H), 7.89–7.93 (m, 6H), 7.81 (s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 123.4 (CH), 125.4 (CH), 127.2 (CH), 127.9 (CH), 128.5 (CH), 128.7 (C), 128.9 (C), 129.3 (CH), 129.6 (CH), 130.0 (CH), 132.5 (C), 138.8 (C), 147.4 (C); IR (KBr) ν 3424, 3054, 1595, 1487, 1357, 1312, 1213, 1129, 949, 896, 771, 689 cm^{-1}; EIMS *m*/*z* (%) 440 ($M^{\bullet+}$, 9), 424 (13), 407 (100), 239 (66), 204 (64), 105 (29), 77 (32); HRMS (EI) 440.1520 ($C_{30}H_{20}N_2O_2$ requires 440.1525). The resolution of racemic dioxide **17b** was carried out by HPLC in batches of 1.5 mg each on Chiralpak OP(+), (250×46 mm) MeOH, 0.5 mL/min, which afforded (+)-**17b** as the faster eluting enantiomer: $[\alpha]_D$ +178 (*c* 0.32, $CHCl_3$). The slower component was (−)-**17b**, $[\alpha]_D$ −184 (*c* 0.45, $CHCl_3$). Each enantiomer was obtained in >99% ee ($t_{(+)}$=24.55 min, $t_{(-)}$=57.00 min).

4.7.6. Benzo[h]quinoline-2-carboxylic acid (**36**)[26]

A mixture of 10 M HCl (75 mL) and benzo[*h*]quinoline-2-carbonitrile **35**[26] (5.00 g, 24.5 mmol) was refluxed for two days. The reaction mixture was then cooled to room temperature and water (60 mL) was added. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL) and the organic layer was washed with aqueous saturated aqueous $NaHCO_3$ (50 mL). The organic extracts were dried over $MgSO_4$ and the solvent was removed in vacuo to afford pure acid **36** (5.895 g, 99%) as a yellow crystalline solid. Mp 180–181 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.69–7.75 (m, 3H), 7.88–7.91 (m, 2H), 8.34 (t, *J*=8.4 Hz, 2H), 9.11 (d, *J*=9.2 Hz, 1H), 12.80 (s, 1H); ^{13}C NMR δ 120.5 (CH), 124.0 (CH), 124.7 (CH), 128.0 (CH), 128.4 (CH), 129.2 (C), 129.4 (CH), 130.2 (C), 130.8 (CH), 134.0 (C), 138.5 (CH), 144.1 (C), 144.5 (C), 164.4 (C); IR (KBr) ν 2580–3050, 1685 cm^{-1}; HRMS (EI) 223.0632 ($C_{14}H_9NO_2$ requires 223.0633).

4.7.7. Methyl benzo[h]quinoline-2-carboxylate (**37**)

Concd. H_2SO_4 (7.910 g, 80.7 mmol) was added slowly to a solution of benzo[*h*]quinoline-2-carboxylic acid **36** (6.000 g, 26.9 mmol) in methanol (100 mL) and the reaction mixture was then stirred under reflux for 6 h. The reaction mixture was cooled to room temperature, the methanol was removed by evaporation and the residue was poured onto ice. Aqueous concd. NH_3 (20 mL) was added slowly and the product was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over $MgSO_4$ and the solvent was removed in vacuo to furnish the crude product, which was recrystallized from hexane to give the pure ester **37** (5.650 g, 88%) as an orange solid. Mp 64–66 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.01, (s, 3H), 7.62 (d, *J*=8.8 Hz, 1H), 7.63–7.72 (m, 2H), 7.79–7.83 (m, 2H), 8.23 (q, *J*=8.4 Hz, 2H), 9.34 (d, *J*=8.0 Hz, 1H); ^{13}C NMR δ 53.0 (CH_3), 122.2 (CH), 124.7 (CH), 125.0 (CH), 127.6 (CH), 127.9 (CH), 128.2 (C), 128.8 (CH), 130.2 (CH), 131.5 (C), 133.7 (C), 136.7 (CH), 146.2 (C), 146.3 (C), 166.3 (C); IR (KBr) ν 1733 (s) cm^{-1}; HRMS (EI) 237.0791 ($C_{15}H_{11}NO_2$ requires 237.0790). For the method, see Ref. 25.

*4.7.8. (R)-(+)-1-(2-Methoxy-1-naphthyl)-3-methyl-5,6,7,8-tetrahydroisoquinoline (R)-(+)-(**42a**)*[30a]

Mp 160–161 °C (pentane); $[\alpha]_D^{25}$ +138.9 (*c* 0.1, toluene); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, 1H, *J*=9.1 Hz), 7.73–7.71 (m, 1H), 7.28–7.21 (m, 3H), 7.05–7.03 (m, 1H), 6.87 (s, 1H), 3.78 (s, 3H), 2.76–2.73 (m, 2H), 2.47 (s, 3H), 2.33–2.26 (m, 1H), 2.07–2.0 (m, 1H), 1.71–1.5 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 22.8, 23.4, 24.5, 25.7, 29.8, 57.0, 114.0, 123.1, 123.9, 124.0, 125.0, 126.9, 128.3, 129.7, 130.0, 130.4, 133.6, 147.0, 154.2, 154.8, 155.5; MS (70 eV), *m*/*z* 303 (74) [M^+], 302 (100), 284 (57), 272 (38), 259 (24). Enantiomeric purity by HPLC analysis was >99% ee; HPLC conditions: Chiralcel OD-H, hexane/ethanol 99.95:0.05, 1.5 mL/min, t_1=4.72 min, t_2=5.94 min.

*4.7.9. (R)-(+)-1-(2-Methoxy-1-naphthyl)-3-phenyl-5,6,7,8-tetrahydroisoquinoline (R)-(+)-(**42b**)*[30a]

Mp 200–201 °C (ethyl acetate); $[\alpha]_D^{25}$ +202.5 (*c* 0.1, toluene); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.28–8.26 (m, 2H), 8.17 (d, 1H, *J*=9.1 Hz), 8.12–8.08 (m, 1H), 7.78 (s, 1H), 7.69–7.55 (m, 7H), 4.11 (s, 3H), 3.18 (m, 2H), 2.81–2.73 (m, 1H), 2.51–2.44 (m, 1H), 2.11–1.86 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 156.3, 154.6, 154.4, 147.4, 140.6, 133.8, 132.5, 130.2, 129.8, 129.0 (2×), 128.7, 128.4, 127.6 (2), 127.0, 125.2, 124.3, 124.0, 120.7, 114.3, 57.2, 30.2, 26.0, 23.5, 22.9; MS (70 eV), *m*/*z* 365 (72) [M^+], 364 (100), 346 (40), 334 (27), 321 (18), 306 (6). Enantiomeric purity by HPLC analysis >99% ee; HPLC conditions: Chiralpak AD-H, hexane/ethanol 99:1, 1.0 mL/min, t_1=6.67 min, t_2=8.31 min.

*4.7.10. (R)-(+)-1-(2-Methoxy-1-naphthyl)-3-(3,4,5-trimethoxyphenyl)-5,6,7,8-tetrahydroisoquinoline (R)-(+)-(**42c**)*[30b]

Mp 140–141 °C (benzene/hexane); $[\alpha]_D^{25}$ +173.2 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, *J*=8.9 Hz, 1H), 7.77–7.72 (m, 1H), 7.34 (s, 1H), 7.29–7.16 (m, 4H), 7.10 (s, 2H), 3.80 (s, 6H), 3.78 (s, 3H), 3.77 (s, 3H), 2.89–2.78 (m, 2H), 2.43–2.35 (m, 1H), 2.14–2.06 (m, 1H), 1.77–1.69 (m, 2H), 1.67–1.61 (m, 1H), 1.6–1.51 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 156.1, 154.3, 153.7, 147.3, 138.8, 136.5, 133.7, 132.4, 130.0, 129.6, 128.8, 128.3, 126.8, 125.2, 124.2, 123.9, 120.5, 114.2, 104.8, 61.3, 57.1, 56.6, 30.1, 25.9, 23.4, 22.8; MS (70 eV), *m*/*z* 455 (100) [M^+], 440 (20), 436 (25), 424 (19), 227 (12). Enantiomeric purity by HPLC analysis 91% ee; HPLC conditions: Chiralpak AD-126, hexane/ethanol 95:5, 1.0 mL/min, t_1=13.8 min, t_2=19.8 min.

*4.7.11. (R)-(+)-1-(2-Methoxy-1-naphthyl)-3-(2-furyl)-5,6,7,8-tetrahydroisoquinoline (R)-(+)-(**42d**)*[30b]

Mp 198–199 °C (acetone); $[\alpha]_D^{25}$ +172.5 (*c* 0.31, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (d, *J*=8.9 Hz, 1H), 8.12–8.10 (m, 1H), 7.78 (br s, 2H), 7.64–7.59 (m, 3H), 7.54–7.5 (m, 1H), 7.23 (d, *J*=3.2 Hz, 1H), 6.74–6.76 (m, 1H), 3.14 (s, 3H), 3.17–3.20 (m, 2H), 2.75–2.67 (m, 1H), 2.46–2.38 (m, 1H), 2.1–1.88 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 156.2, 154.7, 154.3, 147.2, 146.7, 143.0, 133.6, 132.4, 130.1, 129.7, 128.8, 128.3, 127.0, 125.1, 124.0, 118.6, 114.3, 112.1, 108.2, 57.2, 30.0, 26.0, 23.3, 22.8; MS (70 eV), *m*/*z* 355 (70) [M^+], 354 (100), 336 (43), 326 (25), 324 (27), 311 (20). Enantiomeric purity by HPLC analysis >98% ee; HPLC conditions: Chiracel OD-H, hexane/ethanol 99:1, 1.0 mL/min, t_1=5.76 min, t_2=7.94 min.

*4.7.12. 3-Phenyl-2H-isoquinoline (**44**)*

n-Butyllithium (2.5 M in hexane, 84 mL, 197 mmol) was added to a solution of *N*-methyl-*o*-toluamide **43** (10.0 g, 67 mmol) in THF (250 mL) at −20 °C. The reaction mixture was stirred at the same temperature for 2 h, then a solution of benzonitrile (11.7 mL, 109 mmol) in THF (20 mL) was added at −50 °C and the mixture was left stirred at room temperature for 18 h. The reaction was quenched with water (40 mL) and the product was extracted into CH_2Cl_2 (3×40 mL). The organic layers were combined, dried over $MgSO_4$ and evaporated. Crystallization of the residue from AcOEt afforded **44** (5.3 g, 36%). Mp 203–205 °C [lit.[32] gives 205 °C]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.80 (s, 1H), 7.49–7.78 (m, 8H), 8.40 (d, *J*=7.5 Hz, 1H), 10.54 (s, 1H) in agreement with the literature data.[32]

*4.7.13. 1-Chloro-3-phenylisoquinoline (**45**)*

4.7.13.1. Method A. A mixture of $POCl_3$ (5 mL, 54 mmol) and PCl_5 (100 mg, 0.48 mmol) was added to 3-phenyl-2*H*-isoquinoline **44** (564 mg, 2.3 mmol) and the mixture was stirred at 120 °C for 2 h. The mixture was then cooled and poured onto ice, the precipitate was collected and washed successively with 40% aqueous ammonia and water. The precipitate was dissolved in ethyl acetate (50 mL) and the solution was washed with water dried over $MgSO_4$, and evaporated. The residue was crystallized from hexane to afford **45** (350 mg, 63%). Mp 68–69 °C (ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (tt, *J*=7.4, 1.3 Hz, 1H), 7.40–7.46 (m, 2H), 7.58 (ddd, *J*=8.3, 6.9, 1.2 Hz, 1H), 7.67 (ddd, *J*=8.1, 6.9, 1.2 Hz, 1H), 7.82 (d, *J*=8.2 Hz, 1H), 7.94 (s, 1H), 8.03–8.07 (m, 2H), 8.26 (d, *J*=8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 116.3 (CH), 126.0 (C), 126.5 (CH), 126.9 (CH), 127.4 (CH), 128.3 (2×CH), 128.9 (2×CH), 129.0 (CH), 131.3 (CH), 138.0 (C), 138.7 (C), 150.3 (C), 151.4 (C); IR (KBr) ν 1950, 1562, 1312, 1258, 979, 850, 764, 688 cm^{-1}; EIMS *m*/*z* (%) 239 ($M^{\cdot+}$, 100), 204 (54), 176 (13), 151 (5), 119 (5), 102 (9), 88 (9), 75 (6); HRMS (EI) 239.0506 ($C_{15}H_{10}^{35}ClN$ requires 239.0502).

4.7.13.2. Method B. Phosphoryl chloride (2.56 g, 16.70 mmol, 3.3 equiv) was added to a solution of **51** (1.2 g, 5.06 mmol, 1.0 equiv) in chloroform (20 mL) and the mixture was refluxed for 3 h, then cooled to room temperature and poured onto ice. Concentrated aqueous ammonia was added dropwise until the solution was basic. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×20 mL). Combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on a column of silica gel (40 g) with a mixture of petroleum ether and ethyl acetate (10:1) to furnish **45** (0.61 g, 50%) as a white solid: mp 68–69 °C (ethyl acetate/hexane), identical with the product prepared by Method A.

*4.7.14. 3,3′-Diphenyl-[1,1′]-biisoquinolinyl (**46**)*

Activated zinc powder (570 mg, 8.7 mmol) was added to a stirred blue solution of $NiCl_2 \cdot 6H_2O$ (2.07 g, 8.7 mmol) and Ph_3P (9.10 g, 34.8 mmol) in DMF (45 mL) at 50 °C and the mixture was stirred at that temperature for 1 h under argon, during which time the color of the mixture had changed to red-brown. A solution of 1-chloro-3-phenylisoquinoline **45** (2.10 g, 8.7 mmol) in DMF (15 mL) was then added and the mixture was stirred at the same temperature for another 3 h. The mixture was then cooled to room temperature, diluted with 40% aqueous ammonia, and the product was extracted into CH_2Cl_2 (3×50 mL), the combined organic extracts were washed with water (3×50 mL), dried over $MgSO_4$, and evaporated. The residue was chromatographed on a column of silica gel (10 g) with a mixture of petroleum ether and ethyl acetate (15:1) to afford **46** (1.20 g, 67%) as a white solid. Mp 181–183 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.42 (*m*, 2H), 7.45–7.50 (m, 6H), 7.69–7.73 (m, 2H), 7.97–8.01 (m, 4H), 8.18–8.21 (*m*, 4H), 8.24 (*s*, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.9 (CH), 127.1 (CH), 127.2 (CH), 127.3 (CH), 127.5 (CH), 128.5 (CH), 128.7 (CH), 130.3 (CH), 138.0 (C), 139.5 (C), 149.8 (C), 157.9 (C); IR (KBr) ν 3047, (aryl C–H), 1619, 1590, 1558, 1496 (aromatic rings) cm^{-1}; CIMS *m*/*z* (%) 409 ([M+H]$^+$, 100), 206 (3), 113 (2), 85 (6), 69 (9); HRMS (CI) 409.1707 ($C_{30}H_{21}N_2$ requires 409.1705).

*4.7.15. 2-(Phenylacetylene)benzaldehyde (**48**)*

$(Ph_3P)_2PdCl_2$ (152 mg, 0.22 mmol) and CuI (21 mg, 0.11 mmol) were added to a solution of 2-bromobenzaldehyde **47** (2.00 g, 10.81 mmol) and phenylacetylene (1.32 g, 12.97 mmol) in dry triethylamine (45 mL). The resulting mixture was heated under an argon atmosphere at 50 °C for 2 h and then allowed to cool to room temperature. The ammonium salt formed was removed by filtration and the filtrate was concentrated under reduced pressure and

purified by flash chromatography on a column of silica gel (125 g) with a mixture of petroleum ether and ethyl acetate (24:1) to give **48** (2.20 g, 99%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.45 (m, 3H), 7.49 (t, J=7.5 Hz, 1H), 7.59–7.65 (m, 3H), 7.69 (dd, J=7.7, 1.2 Hz, 1H), 7.99 (dd, J=7.8, 1.3 Hz, 1H), 10.69 (s, 1H); ^{13}C NMR δ 85.0 (C*sp*), 96.4 (C*sp*), 122.4 (C), 126.9 (C), 127.3 (CH), 128.5 (CH), 128.7 (CH), 129.1 (CH), 131.7 (CH), 133.3 (CH), 133.8 (CH), 135.8 (C), 191.6 (CH) in agreement with the reported data.[37]

*4.7.16. t-Butyl-(2-phenylethynyl-benzylidine)-amine (**49**)*

A solution of **48** (1.96 g, 9.50 mmol, 1.0 equiv) in *tert*-butylamine (6.0 mL, 57.02 mmol, 6.0 equiv) was stirred under an Ar atmosphere at room temperature for 24 h. The resultant mixture was extracted with ether (3×30 mL) and the combined organic extracts were dried over $MgSO_4$, and concentrated under reduced pressure to give **49** (2.32 g, 94%) as a crystalline yellow solid. Mp 54–56 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (s, 9H), 7.27–7.34 (m, 5H), 7.44–7.50 (m, 3H), 7.99 (dd, J=5.7, 3.6 Hz, 1H), 8.86 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.7 (CH_3), 56.8 (CMe_3), 85.7 (C*sp*), 93.8 (C*sp*), 122.0 (C), 122.8 (C), 124.9 (CH), 127.5 (CH), 127.5 (CH), 127.6 (CH), 128.7 (CH), 130.4 (CH), 131.2 (CH), 136.8 (C), 153.2 (CH) in agreement with the published data.[38]

*4.7.17. 3-Phenylisoquinoline (**50**)*

Copper(I) iodide (185 mg, 0.97 mmol, 0.1 equiv) was added to a solution of imine **49** (2.54 g, 9.72 mmol, 1.0 equiv) in DMF (20 mL) and the mixture was heated to 100 °C for 4 h. The mixture was then allowed to reach room temperature, diluted with ether, and washed with saturated ammonium chloride solution (2×35 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash chromatography on a column of silica gel (100 g) with a mixture of petroleum ether and ethyl acetate (20:1) to afford **50** (1.72 g, 86%) as a beige solid. Mp 102–103 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (tt, J=7.4, 1.2 Hz, 1H), 7.41–7.47 (m, 2H), 7.51 (ddd, J=8.0, 6.9, 1.0 Hz, 1H), 7.62 (ddd, J=8.1, 6.9, 1.2 Hz, 1H), 7.80 (d, J=8.1 Hz, 1H), 7.92 (d, J=8.1 Hz, 1H), 8.00 (s, 1H), 8.04–8.08 (m, 2H), 9.27 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 116.5 (CH), 126.9 (CH), 127.0 (CH), 127.1 (CH), 127.6 (CH), 127.8 (C), 128.5 (2×CH), 128.8 (2×CH), 130.5 (CH), 136.7 (C), 139.6 (C), 151.3 (C), 152.4 (CH), in agreement with the published data.[39]

*4.7.18. 3-Phenylisoquinoline N-oxide (**51**)*

m-CPBA (2.42 g, 14.04 mmol, 2.0 equiv) was added to a precooled (0 °C) solution of **50** (1.44 g, 7.02 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) and the reaction was then allowed to reach room temperature and stirred for 4 h. The resulting mixture was diluted with CH_2Cl_2 (25 mL) and water (25 mL), the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2×25 mL). Combined organic extracts were washed with 10% aqueous sodium carbonate (2×25 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on a column of silica gel (100 g), first with ethyl acetate to elute impurities, followed by a mixture of ethyl acetate and methanol (10:1) to furnish **51** (1.16 g, 75%) as a white solid. Mp 159–160 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49–7.56 (m, 3H), 7.61–7.66 (m, 2H), 7.78 (d, J=9.2 Hz, 1H), 7.83–7.86 (m, 4H), 9.00 (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 124.5 (CH), 124.8 (CH), 126.6 (CH), 128.3 (CH), 128.9 (CH), 129.0 (C), 129.1 (CH), 129.3 (C), 129.4 (CH), 129.8 (CH), 132.9 (C), 137.1 (CH), 147.1 (C) in agreement with the literature data.[40]

4.8. General procedure for the allylation reaction

Allyltrichlorosilane **2** (40 μL, 0.28 mmol) was added to a solution of the catalyst (1–10 mol %), diisopropylethylamine (34 μL, 0.2 mmol), and aldehyde **1** (0.2 mmol) in solvent (2 mL) under nitrogen at the required temperature (Table 2). The mixture was then stirred at this temperature until completion (by TLC monitoring) and then quenched with aqueous satd $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3×5 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. Products **3** were either identical with the authentic sample[8–11] or their NMR data corresponded to those published; for their full characterization, see our earlier papers.[8–11]

Acknowledgements

We thank Schering-Plough (formerly Organon) for a fully-funded studentship to MMW, the Ministry of Education and Science of Spain for a fellowship to PR-L, the Socrates-Erasmus exchange program for a fellowship to A.K., the Czech Science Foundation for Grant No. 203/08/0350, the Ministry of Education of the Czech Republic (Project No. LC06070, MSM0021620857 and MSM-6046137301), and the University of Glasgow and Dr. Alfred Bader for additional support.

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