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Electrophilic Substitutions of Indoles and Pyrroles:

Kinetics and Synthetic Applications

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Erklärung

Diese Dissertation wurde im Sinne von § 13 Abs. 3 bzw. 4 der Promotionsordnung vom 29. Januar 1998 von Herrn Prof. Dr. Herbert Mayr betreut.

Ehrenwörtliche Versicherung

Diese Dissertation wurde selbständig und ohne unerlaubte Hilfe erarbeitet.

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Martin Westermaier

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Für meine Eltern

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Publikationen

„Electrophilic Allylations and Benzylations of Indoles in Neutral Aqueous or Alcoholic Solution“

M. Westermaier, H. Mayr, *Org. Lett.* **2006**, *8*, 4791–4794

„Nucleophilic Reactivities of Indoles“

S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial, H. Mayr, *J. Org. Chem.* **2006**, *71*, 9088–9095

“Regio- and Stereoselective Ring Opening Reactions of Epoxides with Indoles and Pyrroles in 2,2,2-Trifluoroethanol”

M. Westermaier, H. Mayr, *Chem. Eur. J.* **2007**, in print.

List of Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aryl
ATP	adenosine triphosphate
Bn	benzyl
b. p.	boiling point
Bu	butyl
CAN	cerium(IV) ammonium nitrate [$(NH_4)_2Ce(NO_3)_6$]
conv.	conversion
Cp	cyclopentadienyl
DAQ	demethylasterriquinone
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEA	diethylamine
dma	4-(dimethylamino)phenyl
DMAPP	dimethylallyl pyrophosphate
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
dpa	4-(diphenylamino)phenyl
DTBP	2,6-di-*tert*-butylpyridine
E	electrophilicity parameter
ee	enantiomeric excess
E_f	electrofugality parameter
e. g.	exempli gratia
eq	equivalent(s)
Et	ethyl
fur	2,3-dihydrobenzofuran-5-yl
HPLC	high pressure liquid chromatography
i. e.	id est
ind	*N*-methyl-2,3-dihydro-1*H*-indol-5-yl
k	rate constant
K	equilibrium constant

KIE	kinetic isotope effect
lil	lilolidin-8-yl (= 1,2,5,6-tetrahydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-8-yl)
M	mol/L
Me	methyl
mfa	4-[methyl-(2,2,2-trifluoroethyl)amino]phenyl
mor	4-(*N*-morpholino)phenyl
m. p.	melting point
mpa	4-(methylphenylamino)phenyl
MPLC	medium pressure liquid chromatography
MS	molecular sieves
N	nucleophilicity parameter
NADH	nicotinamide adenine dinucleotide (reduced form)
NBS	*N*-bromosuccinimide
N_f	nucleofugality parameter
pfa	4-[phenyl-(2,2,2-trifluoroethyl)amino]phenyl
Ph	phenyl
PP_i	pyrophosphate
Pr	propyl
pyr	4-(*N*-pyrrolidino)phenyl
rac	racemic
s	nucleophile-specific slope parameter
SCE	standard calomel electrode
s_E	electrophile-specific slope parameter
SPhos	2-(dicyclohexylphosphino)-2',6'-dimethoxy-1,1'-biphenyl
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBME	*tert*-butyl methyl ether
Tf	triflate
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl

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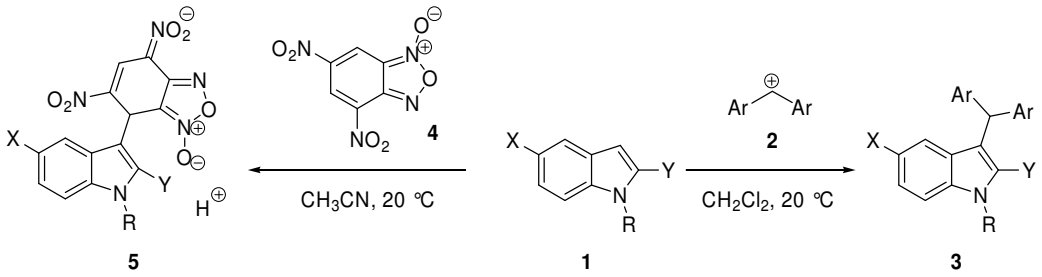
Chapter 1

Summary

1.1 Nucleophilic Reactivities of Indoles

The kinetics of the couplings of indole (**1a**), *N*-methylindole (**1b**), 5-methoxyindole (**1c**) and 5-cyanoindole (**1d**) with a set of reference benzhydryl cations **2** (for structures see Table 1.1) have been investigated in dichloromethane (Scheme 1.1).



5 4 1 2 3

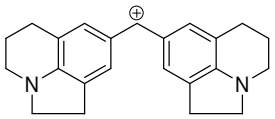
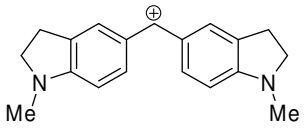
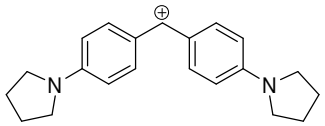
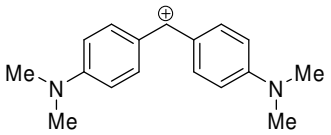
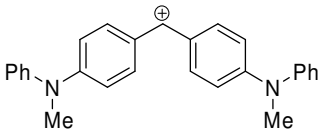
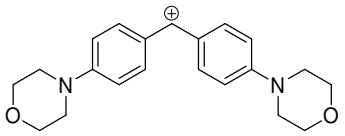
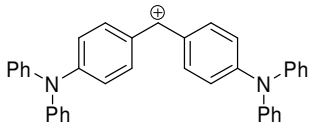
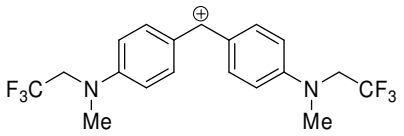
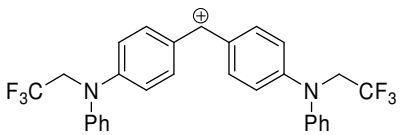
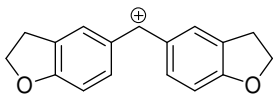
Scheme 1.1. Reactions of indoles **1** with benzhydrylium ions **2** (Ar_2CH^+) in CH_2Cl_2 and with 4,6-dinitrobenzofuroxan (**4**) in CH_3CN at 20 °C.

The second-order rate constants k_2 for these reactions correlate linearly with the electrophilicity parameters E of the benzhydryl cations **2** (Figure 1.1). This allows the determination of the reactivity parameters N and s, characterizing the nucleophilicity of indoles **1a**–**d** according to the linear free enthalpy relationship (1.1).

$$\lg k(20°C) = s(N + E) \tag{1.1}$$

The nucleophilicity parameters thus defined (Table 1.2) describe nicely the reactions of **1a**–**d** with 4,6-dinitrobenzofuroxan (**4**, Scheme 1.1), a neutral superelectrophilic heteroaromatic whose electrophilicity has been determined earlier. On this ground, the kinetics of the couplings of **4** with a large variety of indoles have been studied in acetonitrile in collaboration with Terrier and co-workers, leading to a ranking of this family of π-excessive carbon nucleophiles over a large domain of the nucleophilicity scale (Table 1.2 on page 4).

Table 1.1. List of carbocations **2** used as reference electrophiles.

reference electrophile[a]		E[b]
	**2a**	–10.04
	**2b**	–8.76
	**2c**	–7.69
	**2d**	–7.02
	**2e**	–5.89
	**2f**	–5.53
	**2g**	–4.72
	**2h**	–3.85
	**2i**	–3.14
	**2j**	–1.36

[a] All benzhydrylium ions were used as tetrafluoroborate salts, except $(fur)_2CH^+$ (**2j**) which was generated from the chloride **2j**-Cl with TMSOTf. [b] Electrophilicity parameters *E*.

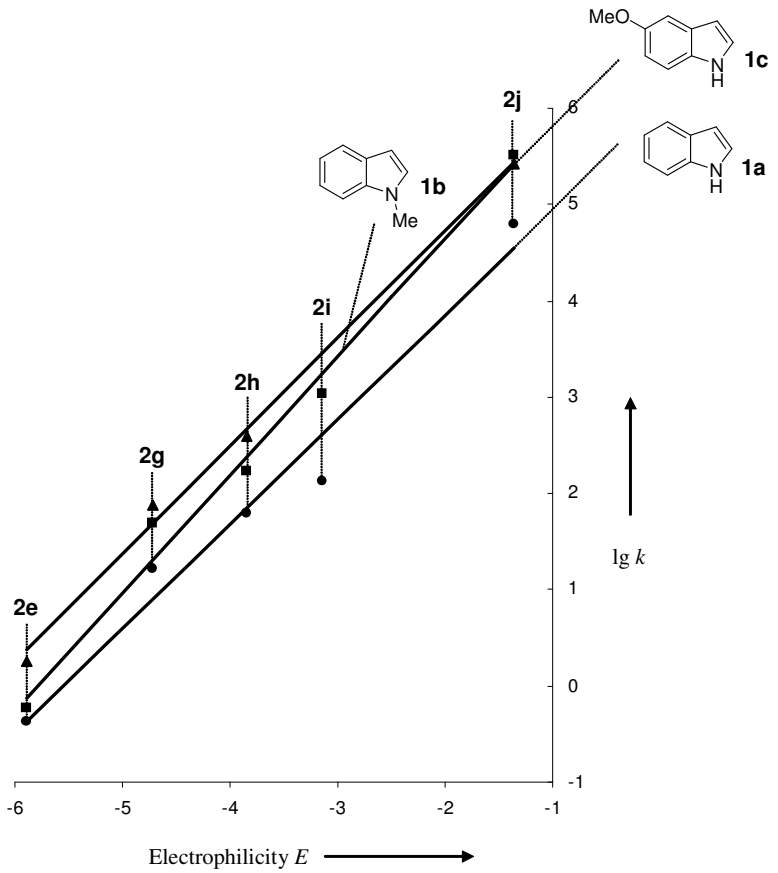
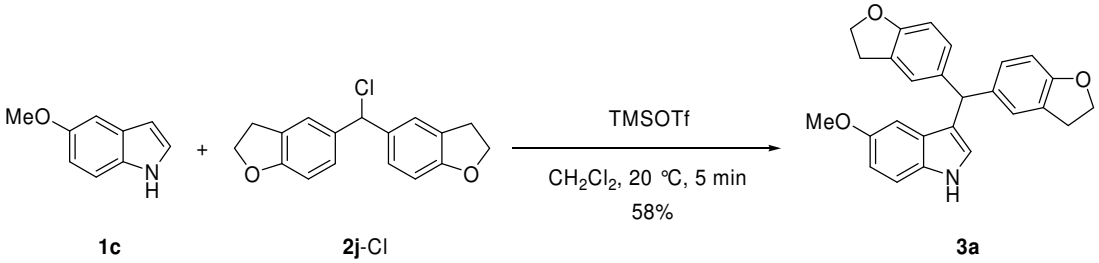


Figure 1.1. Plotting of the second-order rate constants k_2 of the reactions of indoles **1a–c** with benzhydrylium ions **2** in CH_2Cl_2 at 20 °C against their electrophilicity parameters *E* (since complex kinetics were obtained when **1d** was combined with the benzhydrylium ions **2**, no correlation was made).

Product analysis revealed that the reactions of the indoles **1** with the benzhydrylium ions **2** and with 4,6-dinitrobenzofuroxan (**4**) proceed with exclusive 3-substitution as demonstrated for the combination of 5-methoxyindole (**1c**) with **2j**-Cl (Scheme 1.2).



1c **2j**-Cl **3a**

Scheme 1.2. Reaction of 5-methoxyindole (**1c**) with benzhydrylium chloride **2j**-Cl in CH_2Cl_2.

Table 1.2. List of the indoles with their nucleophilicity parameters *N* and *s*, only indoles **1a**–**d** have been studied in this work.

nucleophile	*N*	*s*
5-cyanoindole (**1d**)	2.83	1.10[a]
7-azaindole (**1e**)	3.87	1.10[a]
5-carboxyindole (**1f**)	3.97	1.10[a]
5-bromoindole (**1g**)	4.38	1.10[a]
5-chloroindole (**1h**)	4.42	1.10[a]
4-methoxyindole (**1i**)	5.41	1.10[a]
indole (**1a**)	5.55	1.09
1-methylindole (**1b**)	5.75	1.23
5-methylindole (**1j**)	6.00	1.10[a]
5-chloro-2-methylindole (**1k**)	6.08	1.10[a]
5-methoxyindole (**1c**)	6.22	1.12
5-hydroxyindole (**1l**)	6.44	1.10[a]
2-methylindole (**1m**)	6.91	1.10[a]
5-aminoindole (**1n**)	7.22	1.10[a]
2,5-dimethylindole (**1o**)	7.22	1.10[a]
5-methoxy-2-methylindole (**1p**)	7.26	1.10[a]

[a] Assumed *s* parameters.

Different correlations between the *N* values and the pK_a(H_2O) values are obtained for 5-X-substituted indoles and 5-X-substituted 2-methylindoles (Figure 1.2). The *N* versus pK_a(H_2O) correlation for 5-X-substituted indoles is used for the determination of the C-3 basicity of indoles whose acidity constants cannot be measured through equilibrium studies in strongly acidic media.

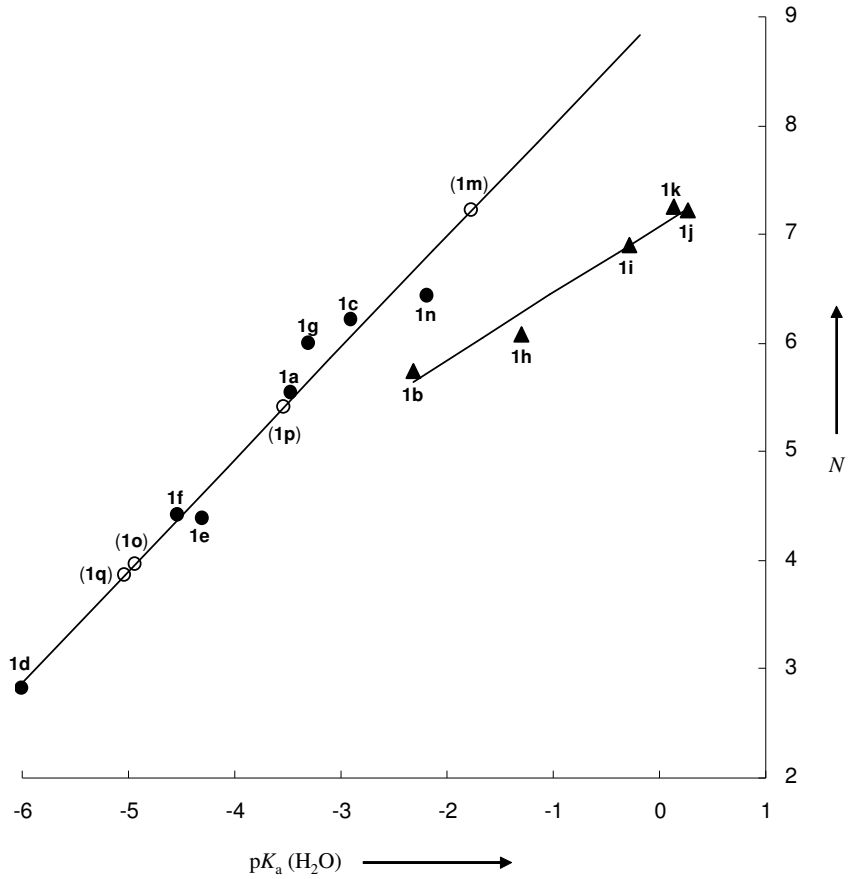


Figure 1.2. Correlation of the nucleophilicity parameters N of indoles **1a,c–g** (filled dots: $N = 1.025pK_a(H_2O) + 9.025$, $r^2 = 0.9669$, $n = 7$) and of 2-methyl-indoles **1h–k** (triangles: $N = 0.770pK_a(H_2O) + 7.097$, $r^2 = 0.9878$, $n = 4$) with the corresponding $pK_a(H_2O)$ values for C-3 protonation of these species in aqueous solution. Open circles: $pK_a(H_2O)$ values of indoles calculated from N on the basis of these correlations.

The kinetics of the reactions of 1,2-dimethylindole (**1q**) with the benzhydrylium salts **2c, 2d, 2e** and **2g** have been investigated in acetonitrile and the nucleophilicity parameters were defined according to Equation (1.1) as $N = 8.55$ and $s = 1.30$ (Figure 1.3). This value differs from the previously estimated value of $N = 6.54$, which has been derived from the rate constant $k_2 = 5.47 \times 10^3$ $M^{-1}s^{-1}$ for the reaction of **1q** with the bis[4-phenyl-(2,2,2-trifluoroethyl)amino]phenylmethylium ion (**2i**) assuming an s parameter of 1.10.

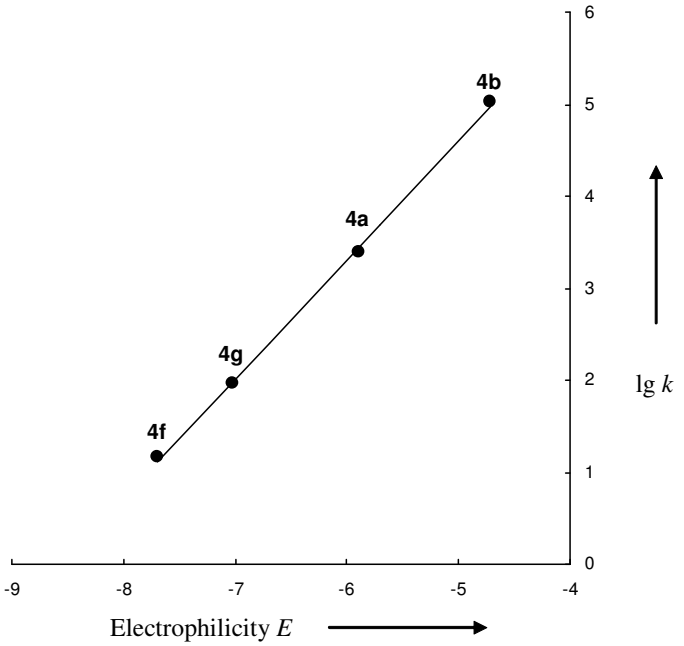
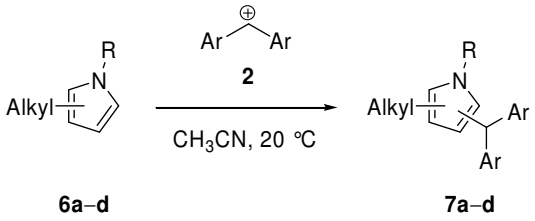


Figure 1.3. Correlation of the second-order rate constants k_2 of the reactions of 1,2-dimethylindole (**1q**) with benzhydrylium ions **2c, 2d, 2e** and **2g** in CH_3CN at 20 °C.

1.2 Nucleophilic Reactivities of Pyrroles

The kinetics of the couplings of 2,5-dimethylpyrrole (**6a**), 1,2,5-trimethylpyrrole (**6b**), 2,4-dimethylpyrrole (**6c**) and kryptopyrrole (**6d**) with a set of reference benzhydryl cations **2** have been investigated in acetonitrile (Scheme 1.3).



6a–d **7a–d**

Scheme 1.3. Reactions of pyrroles **6a–d** with benzhydrylium ions **2** (Ar_2CH^+) in CH_3CN at 20 °C.

The logarithms of the second-order rate constants k_2 of these reactions correlate linearly with the corresponding electrophilicity parameters E of the benzhydrylium ions **2** (Figure 1.4) and the nucleophilicity parameters N and s were derived by Equation (1.1) as listed in Table 1.3.

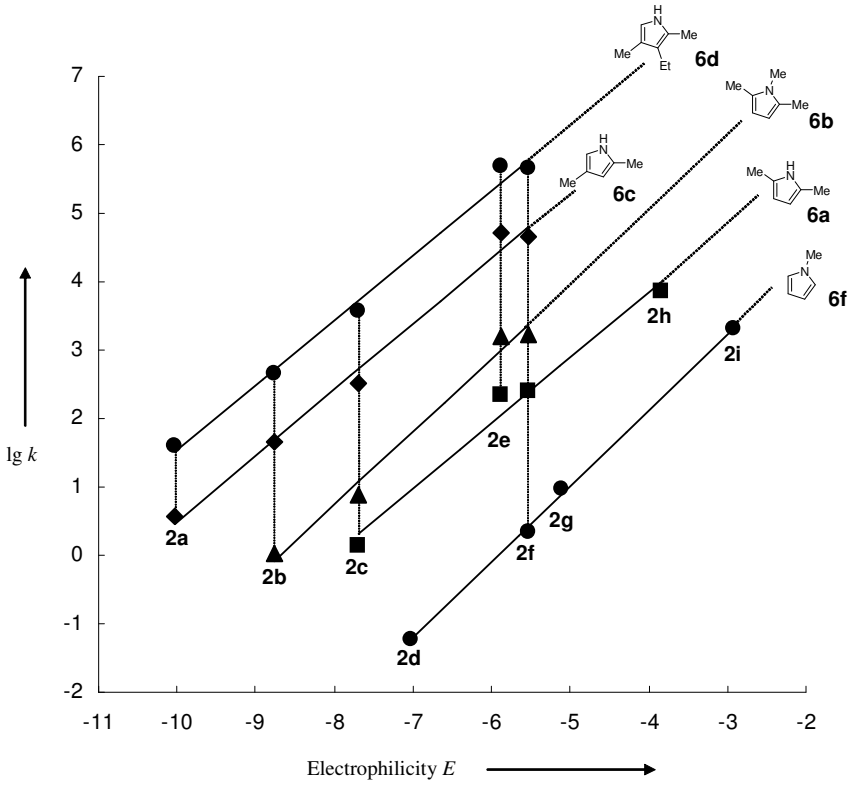
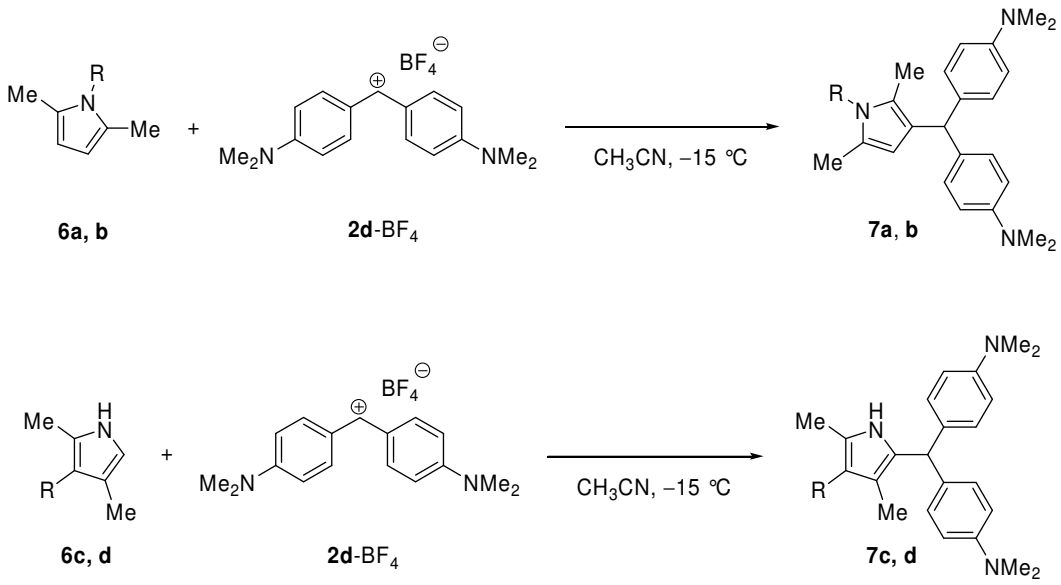


Figure 1.4. Correlation of the second-order rate constants k_2 of the reactions of the pyrroles **6a–f** with benzhydrylium ions **2** in CH_3CN at 20 °C.

Table 1.3. Resulting *N* and *s* parameters of pyrroles **6a**–**d** in acetonitrile.

pyrrole	*N*	*s*
2,5-dimethylpyrrole (**6a**)	8.01	0.96
1,2,5-trimethylpyrrole (**6b**)	8.69	1.07
2,4-dimethylpyrrole (**6c**)	10.49	0.96
3-ethyl-2,4-dimethylpyrrole (**6d**)	11.63	0.95

Pyrroles **6a**–**d** react with the benzhydrylium salt **2d**-BF_4 in acetonitrile at –15 °C to give the substituted pyrroles **7a** – **d,** respectively (Scheme 1.4).

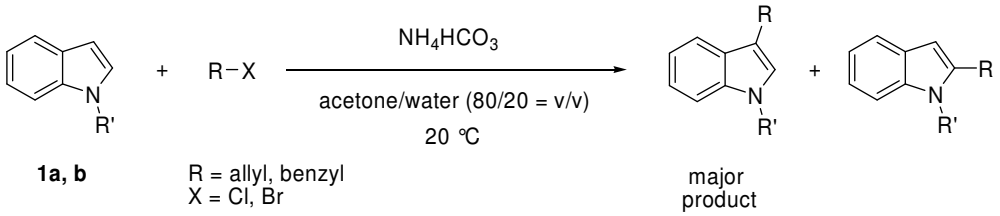


pyrrole	time	product	yield / %
6a (R = H)	30 min	**7a**	65
6b (R = Me)	10 min	**7b**	68
6c (R = H)	2 min	**7c**	93
6d (R = Et)	< 1 min	**7d**	78

Scheme 1.4. Reactions of pyrroles **6a**–**d** with benzhydrylium tetrafluoroborate **2d**-BF_4 in CH_3CN.

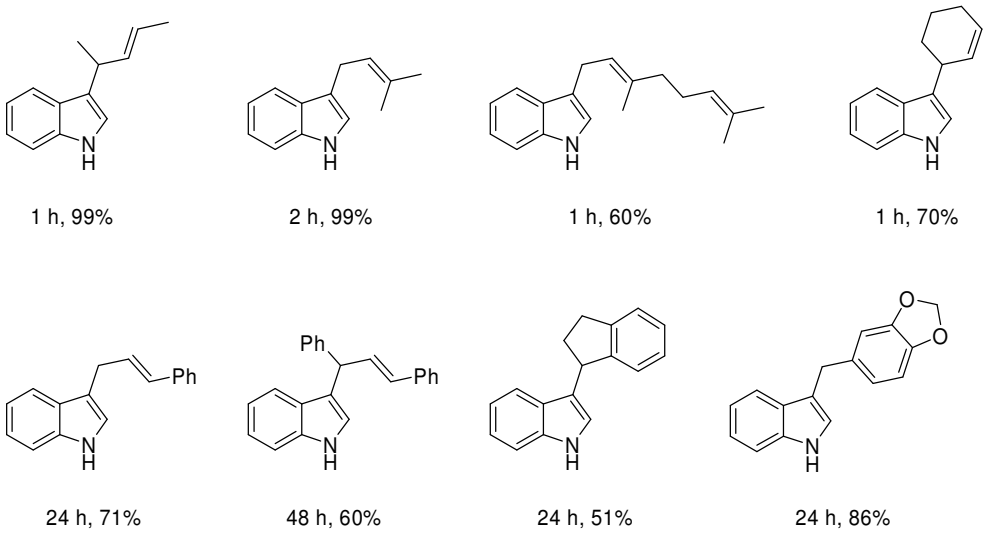
1.3 Allylations and Benzylations of Indoles in Aqueous Solution

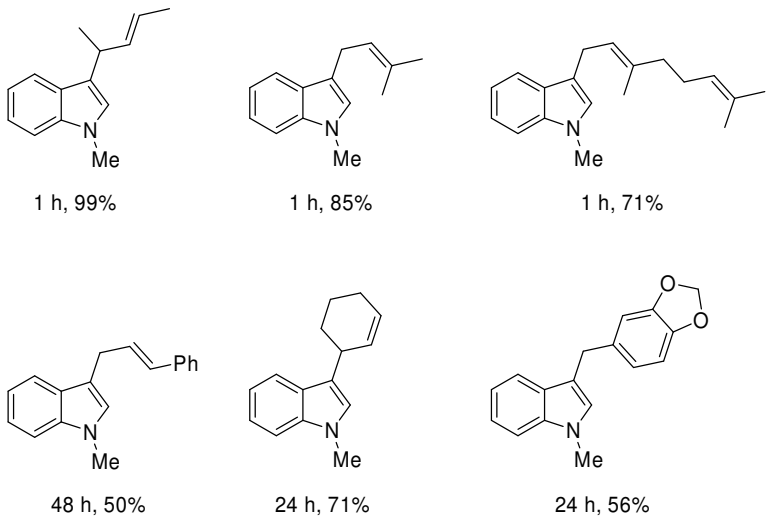
Indole (**1a**) and *N*-methylindole (**1b**) were allylated and benzylated in predominantely 3-position in good to quantitative yield when they were stirred with allyl and benzyl halides in 80% aqueous acetone in the presence of NH_4HCO_3 at room temperature (Scheme 1.5). The 3-substitution product was usually accompanied by approximately 10% of the 2-substitution product.



Scheme 1.5. Reactions of indoles **1a** and **1b** with allyl or benzyl halides (R–X) in 80% aq. acetone at room temperature.

This Friedel-Crafts protocol in neutral or slightly basic aqueous media was applied for the synthesis of several 3-allyl- and 3-benzylindoles as shown in Scheme 1.6.

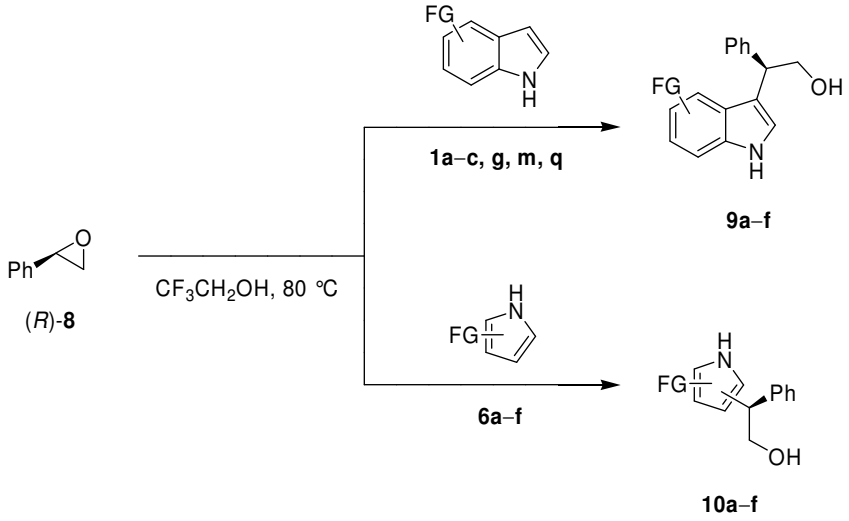




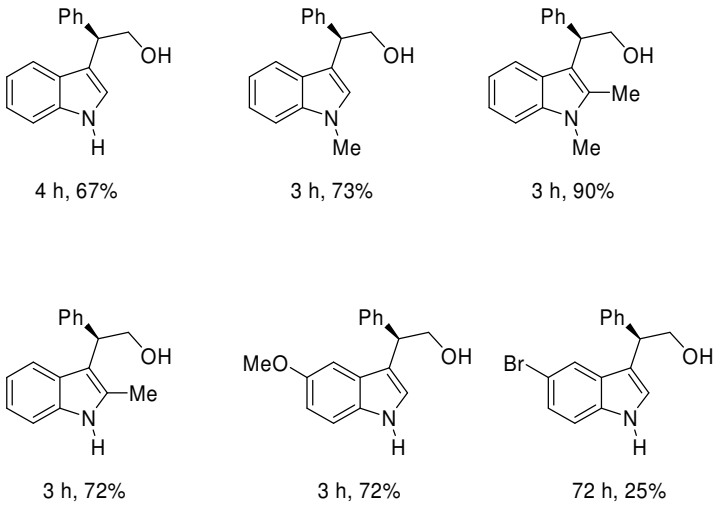
Scheme 1.6. Isolated 3-substituted indoles by treatment of the corresponding allyl or benzyl halide with an excess of indole (5 equiv.) in 80% aq. acetone in the presence of $(NH_4)HCO_3$ at room temperature.

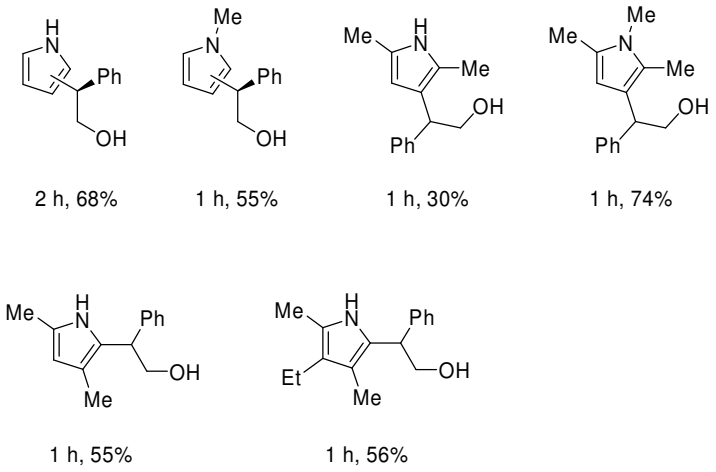
1.4 Ring Opening Reactions of Epoxides with Indoles and Pyrroles in 2,2,2-Trifluoroethanol

Indoles **1** and pyrroles **6** react with (*R*)-styrene oxide (**8**) in 2,2,2-trifluoroethanol at 80 °C without the use of any further additive to yield *β*-phenyl-*β*-heteroarylethanols **9** and **10** in good chemical and excellent optical yields (> 99% *ee*, Schemes 1.7 and 1.8).



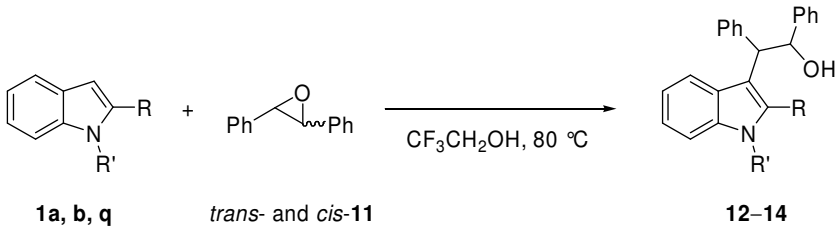
Scheme 1.7. Regio- and stereoselective ring opening reactions of (*R*)-styrene oxide (**8**) with indoles **1** and pyrroles **6** in CF_3CH_2OH at 80 °C.





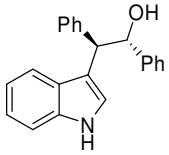
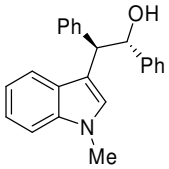
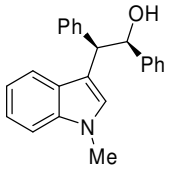
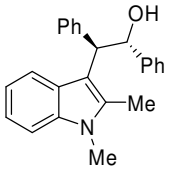
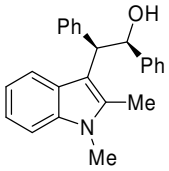
Scheme 1.8. Products of the reactions of styrene oxide (**8**) with indoles **1** and pyrroles **6** in CF_3CH_2OH (80 °C).

Indole (**1a**), *N*-methylindole (**1b**) and 1,2-dimethylindole (**1q**) react with *rac-trans*-stilbene oxide (*trans*-**11**) in CF_3CH_2OH at 80 °C stereospecifically to give 37–69% of *rac*-(**12–14**)**a** (Scheme 1.9, Table 1.4). The corresponding reactions with *cis*-**11** give *rac*-(**13–14**)**b** in 17–19% yield.

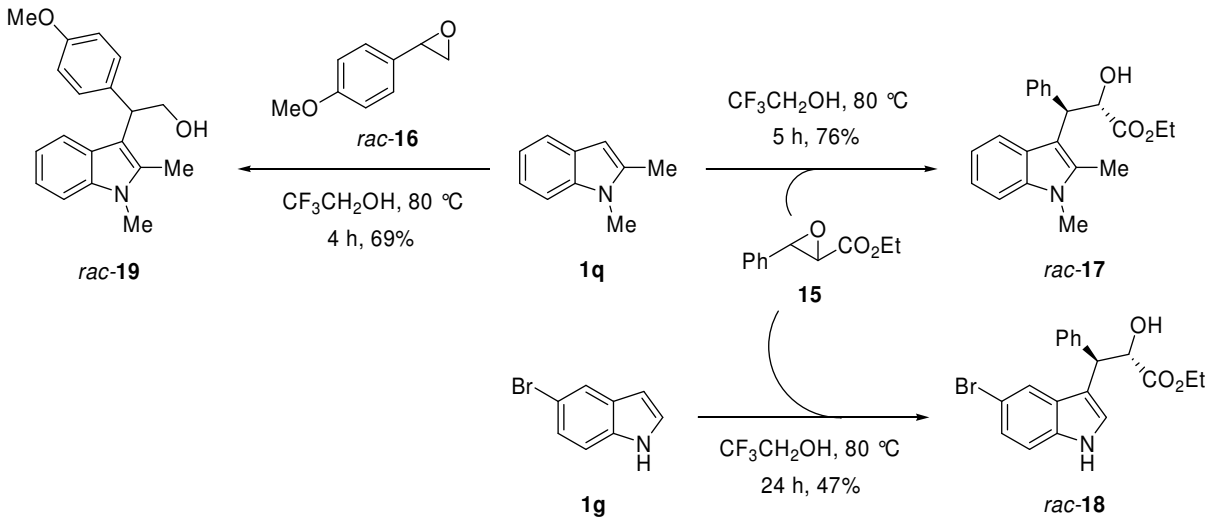


Scheme 1.9. Reactions of stilbene oxides (*trans*- and *cis*-**11**) with indoles **1a**, **1b** and **1q** in CF_3CH_2OH (80 °C).

Table 1.4. Products of the reactions of stilbene oxides (**11**) with indoles **1a**, **1b** and **1q** in CF_3CH_2OH at 80 °C.

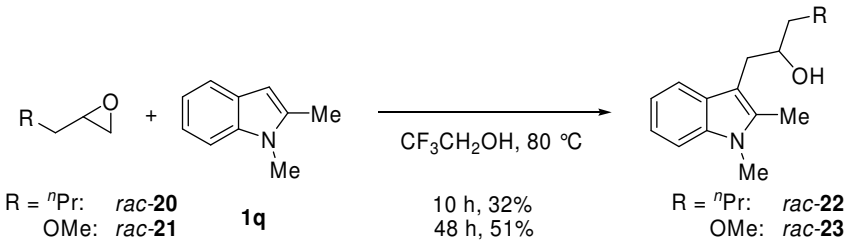
indole	epoxide	time / h	product		yield / %
1a	*rac-trans*-**11**	42		*rac*-**12a**	37
1a	*cis*-**11**	42	–	*rac*-**12b**	0
1b	*rac-trans*-**11**	29		*rac*-**13a**	69
1b	*cis*-**11**	29		*rac*-**13b**	19
1q	*rac-trans*-**11**	9		*rac*-**14a**	66
1q	*rac-cis*-**11**	24		*rac*-**14b**	17

Other aromatic epoxides, such as 3-phenyloxirane-2-carboxylic acid ethyl ester (**15**), which was used as a 8:1-mixture of *rac-trans*- and *cis*-isomers, or *rac-p*-methoxyphenyloxirane (*rac*-**16**), reacted smoothly in CF_3CH_2OH at 80 °C with indoles **1g** and **1q** to give 47–76% of the corresponding substitution products *rac*-**17**–**19** (Scheme 1.10).



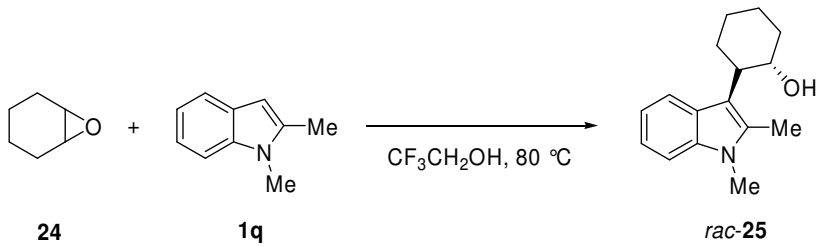
Scheme 1.10. Isolated products of the reactions of indoles **1g** and **1q** with **15** and *rac*-**16**.

The reactions of 1,2-dimethylindole (**1q**) with the aliphatic epoxides *rac*-**20** and *rac*-**21** proceed with exclusive attack at the sterically less hindered position of the epoxides to give tryptophol derivatives *rac*-**22** and *rac*-**23**, respectively (Scheme 1.11).



Scheme 1.11. Ring opening reactions of 1,2-dimethylindole (**1q**) with aliphatic epoxides *rac*-**20** and *rac*-**21**.

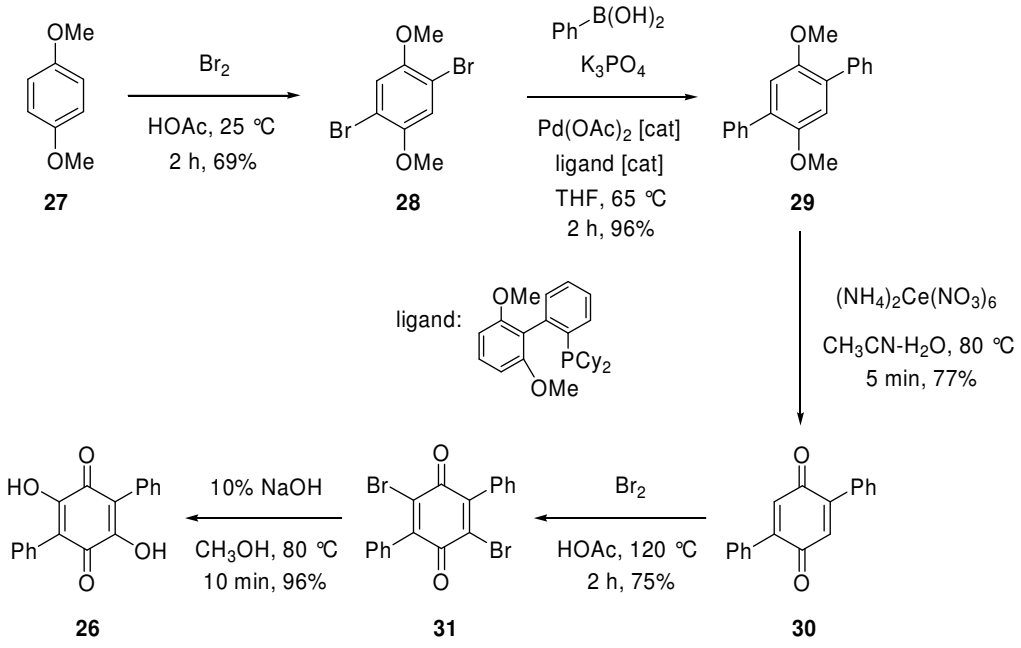
Cyclohexene oxide (**24**) was opened stereoselectively by 1,2-dimethylindole (**1q**) to give *rac*-**25** in 31% yield (Scheme 1.12). The *trans*-configuration was determined through coupling constants.



Scheme 1.12. Reaction of cyclohexene oxide (**24**) and 1,2-dimethylindole (**1q**).

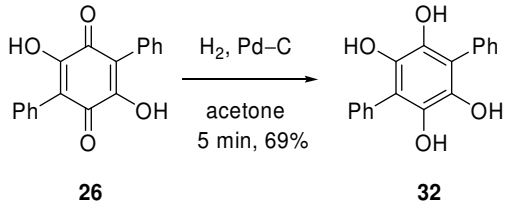
1.5 Synthesis of Naturally Occurring Quinones

The terphenylquinone polyporic acid (**26**) was synthesized *via* a 5-step sequence in 37% overall yield from 1,4-dimethoxybenzene (**27**, Scheme 1.13). The bromination of **27** with bromine in glacial acetic acid gave 2,5-dibromo-1,4-dimethoxybenzene (**28**) in 69% yield. Suzuki coupling of **28** with phenyl boronic acid furnished the terphenyl derivative **29** in 96% yield. Oxidative demethylation of **29** with $(NH_4)_2Ce(NO_3)_6$ in acetonitrile (77% yield of **30**) and bromination (75% yield) gave compound **31**, which furnished polyporic acid (**26**) in 96% yield by hydrolysis with 10% NaOH in refluxing methanol.



Scheme 1.13. Synthesis of polyporic acid (**26**).

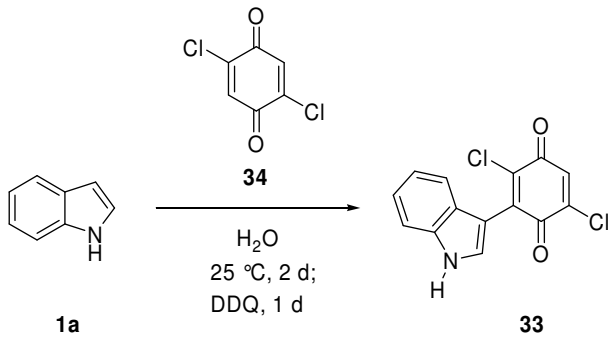
A smooth and easy reduction method was investigated for the model compound 2,3,5,6-tetrahydroxy-1,4-benzoquinone and then applied for the reduction of polyporic acid (**26**) to give in 69% yield the tetrahydroxyterphenyl **32** (Scheme 1.14).



Scheme 1.14. Reduction of polyporic acid (**26**).

Prenylations of **32** have been attempted under different conditions but did not give identified products.

2,5-Dichloro-3-(1*H*-indol-3-yl)-1,4-benzoquinone (**33**) has been synthesized with 75% yield according to a modified literature synthesis when indole (**1a**) and 2,5-dichloro-1,4-benzo-quinone (**34**) were stirred in water and treated with DDQ (Scheme 1.15).



Scheme 1.15. On water coupling of indole (**1a**) and 2,5-dichloro-1,4-benzo-quinone (**34**).

Chapter 2
Introduction

In 1994, Mayr and Patz introduced a new approach for a general reactivity scale based on two independent basis sets of nucleophiles and electrophiles.[1] The reactions of carbocations with nucleophiles can be described by Equation (2.1).

$$\lg k\ (20\ ^{\circ}\mathrm{C}) = s\ (N + E) \qquad (2.1)$$

Each electrophile is characterized by one parameter (electrophilicity parameter E) and nucleophiles are characterized by two parameters (nucleophilicity parameter N and nucleophile-specific slope parameter s).
With Equation (2.1) at hand, it is possible to determine the reactivity parameters of almost any nucleophile or electrophile. To date, 431 nucleophiles and 96 electrophiles have been characterized, including a variety of different classes of organic compounds, such as enamines,[2-4] diazo compounds,[5] organometallic compounds,[2, 6] hydride donors,[6-10] organo-phosphorous compounds,[11] amines and alkoxides[12, 13], carbanions,[14-18] electron-rich heteroarenes,[2, 4, 6, 19] cationic metal π-complexes[2, 6] or arylidene malononitriles.[20, 21]

The goal of this thesis was the determination of the nucleophilic reactivities of indoles and pyrroles and the incorporation of these π-excessive, electron-rich heteroarenes into the comprehensive scale of nucleophilicity. The data should be employed for developing new synthetic methods as it will be shown for allylations and benzylations of indoles and the regio- and stereoselective ring opening reactions of epoxides with indoles and pyrroles. Since prenylations of indoles were found to proceed in good yields in aqueous solutions, reactions of naturally occurring quinones with the prenyl cation should be investigated.
Since most of the chapters in this thesis have been published, more detailed introductions will be given at each chapter's beginning. For more detailed reviews on the linear free energy relationship (2.1) and its applications see refs. [1, 6, 22, 23] and our database on the WWW under http://cicum92.cup.uni-muenchen.de/mayr/reaktionsdatenbank.

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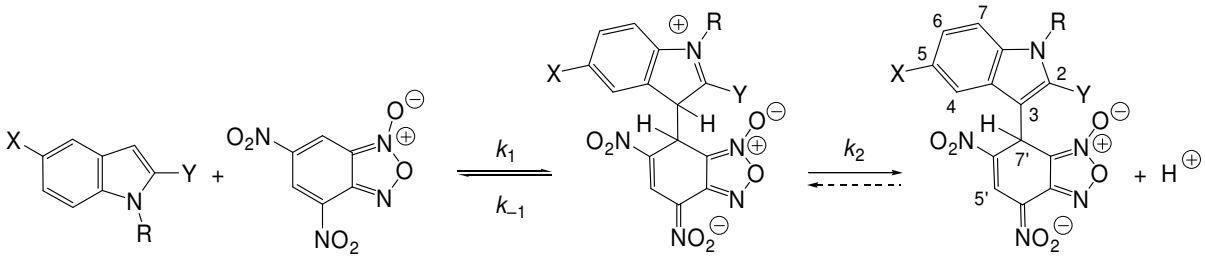
Chapter 3 Nucleophilic Reactivities of Indoles

This chapter has been published by S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial and H. Mayr in *J. Org. Chem.* **2006**, *71*, 9088–9095. The results in chapter 3.2.1 were obtained by Terrier *et al.* and are not listed in the Experimental Section.

3.1 Introduction

Like pyrroles, indoles are π-excessive heteroarenes which react much faster with electrophiles than most benzene derivatives. Terrier *et al*. have previously investigated the mechanism of the reactions of indoles **1** with electron deficient arenes and reported second-order rate constants for the C-C coupling of 4,6-dinitrobenzofuroxan (**2**) – a strongly electron-deficient heteroarene – with a number of differently substituted indoles **1a**–**k**, to give the corresponding anionic σ-adducts **3a**–**k** in different solvents (Scheme 3.1).[1] We have now extended this work and combined it with kinetic data on the reactions of indoles **1** with benzhydrylium ions **4** in order to include indoles into the comprehensive nucleophilicity scale based on benzhydrylium electrophiles,[2-7] which is useful for designing reactions of indoles in organocatalytic reactions.[8-12]



1a–q **2** **ZH ±** **3a–q**

	R	Y	X		R	Y	X
1a	H	H	H	**1j**	H	Me	Me
1b	Me	H	H	**1k**	H	Me	OMe
1c	H	H	OMe	**1l**	Me	Me	H
1d	H	H	CN	**1m**	H	H	NH_2
1e	H	H	Br	**1n**	H	H	OH
1f	H	H	Cl	**1o**	H	H	CO_2H
1g	H	H	Me	**1p**	4-methoxyindole		
1h	H	Me	Cl	**1q**	7-azaindole		
1i	H	Me	H				

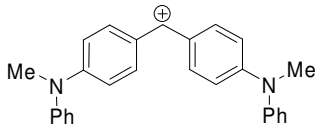
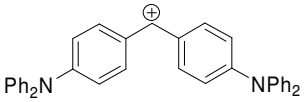
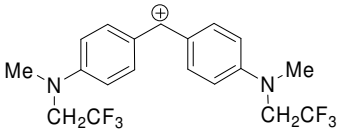
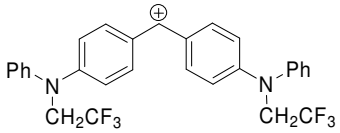
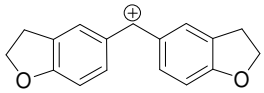
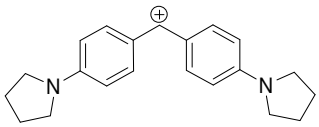
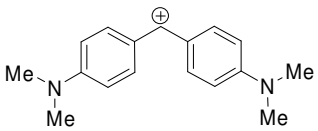
Scheme 3.1. Reactions of indoles **1** with 4,6-dinitrofuroxan (**2**) in CH_3CN.

Reactions of carbocations and of electron-deficient π_{CC} bonds with π-, *n*- and *σ*-nucleophiles have been reported to follow Equation (3.1),

$$\lg k(20\ ^\circ\mathrm{C}) = s(N + E) \tag{3.1}$$

where electrophiles are characterized by one parameter (electrophilicity *E*) and nucleophiles are characterized by the nucleophilicity parameter *N* and the slope parameter *s*. Benzhydrylium ions **4** (for structures see Table 3.1) and structurally related quinone methides have been recommended as reference electrophiles for determining the *N* and *s* parameters of almost any nucleophile.[2-7, 13, 14]

Table 3.1. Benzhydrylium ions **4** used as reference electrophiles in this work.

benzhydrylium ions		E [a]
	**4a**	–5.89
	**4b**	–4.72
	**4c**	–3.85
	**4d**	–3.14
	**4e**	–1.36
	**4f**	–7.69
	**4g**	–7.02

[a] Electrophilicity parameters from ref. [6].

Recently, it has been demonstrated that the *N* and *s* parameters defined by Equation (3.1) can also be employed for S_N2 type reactions, if an additional, electrophile-specific sensitivity parameter s_E is considered.[14]

Approximate *N* parameters of indole (**1a**), *N*-methylindole (**1b**) and 1,2-dimethylindole (**1l**) have previously been derived from the rate constants of the reactions of these compounds with the bis-[4-phenyl(2,2,2-trifluoroethyl)amino]phenylmethylium ion (**4d**) assuming the same slope parameter (s = 0.80) as for enamines.[15] We have now directly determined the *N* and *s* parameters of the indoles **1a**–**c** from the kinetics of their reactions with a series of benzhydrylium ions **4** and found that these parameters fit also very well the electrophilic behaviour of 4,6-dinitrobenzofuroxan (**2**).[1] Therefore, it was possible to link the two sets of data to derive the *N* parameters of an extended set of indoles.

3.2 Results

3.2.1 Reactions of Indoles with 4,6-Dinitrobenzofuroxan

Terrier *et al*. have shown that 4,6-dinitrobenzofuroxan (**2**) reacts readily with the indoles **1a**–**k** to give stable anionic C-adducts **3a**–**k** quantitatively which were structurally characterized either in their acid form **3a**–**k**,**H** or as the corresponding potassium or sodium salts by exchanging the H^+ counterion for a K^+ or Na^+ cation. No evidence for even a minor addition of **2** to C-2 of the indole moiety was found for indoles **1a**–**g** devoid of a 2-methyl group.[1] Because of solubility problems in dichloromethane we have now investigated the kinetics of the overall σ-complexation process of Scheme 3.1 at 20 °C in acetonitrile, extending the series of reactions studied to 5-aminoindole (**1m**), 5-hydroxyindole (**1n**), 5-carboxyindole (**1o**), 4-methoxyindole (**1p**) and 7-azaindole (**1q**). In general, the appearance of the resulting σ-adducts **3a-q** was followed by conventional or stopped-flow spectrophotometry at their absorption maxima (470–480 nm), where neither **2** nor the indoles **1a**–**q** have a notable absorption. All experiments were carried out under first-order conditions with a 3×10^{-5} mol L^{-1} concentration of **2** and a large excess of the indoles (1×10^{-3} to 2×10^{-2} mol L^{-1}). For the reactions of Scheme 3.1, the general Equation (3.2) of the observed first-order rate constant, k_{obs}, for the formation of the adducts **3a-q** can be derived under the assumption that the zwitterions $\mathbf{ZH^{\pm}}$ are low concentration intermediates.

$$k_{obs} = \frac{k_1 k_2}{k_{-1} + k_2} [\mathbf{1}] = k [\mathbf{1}] \qquad (3.2)$$

In accordance with Equation (3.2), excellent linear correlations with zero intercepts were obtained in all systems when the k_{obs} values were plotted versus the indole concentrations [**1a**–**q**]. Determination of the second-order rate constants k from the slopes of these lines was therefore straightforward. All measured k_H/k_D ratios were in the range 1.1–1.7, showing that proton removal from the zwitterionic intermediates $\mathbf{ZH^{\pm}}$ is rapid in acetonitrile, as previously observed in aqueous or methanolic solutions. Thus, electrophilic attack of **2** at C-3 of **1a**–**q** is the rate limiting step of the overall process in Scheme 3.1[16, 17] (As previously discussed for similar S_EAr processes, it is possible, using the observed KIE values and making different

assumptions, to derive the actual rate constant k_1 from the measured composite rate constant k.[16, 17] For the highest k_H/k_D ratio of 1.7 observed here, the correction is rather modest (k_1 = 2.46 instead of 2.29 $M^{-1}s^{-1}$ so that a direct identification of k to k_1 can be made without affecting the overall picture that emerges from our results). Accordingly, the rate constant k could be identified to the rate constant k_1 for the C-C coupling step. This situation is reminiscent of that prevailing in the majority of aromatic or heteroaromatic electrophilic substitution reactions in which the formation of the Wheland-Meisenheimer type intermediate (**ZH**$^{\pm}$) is rate-determining.[1, 18] In line with this interpretation, Jackson and Lynch have reported that the initial attack of the electrophile is rate-limiting in the coupling of indole (**1a**), *N*-methylindole (**1b**), and 2-methylindole (**1i**) with the *p*-nitrobenzenediazonium cation.[1, 19] Table 3.2 summarizes the k_1 values measured for the various 4,6-dinitrobenzofuroxan/indoles couplings carried out at 20 °C in acetonitrile.

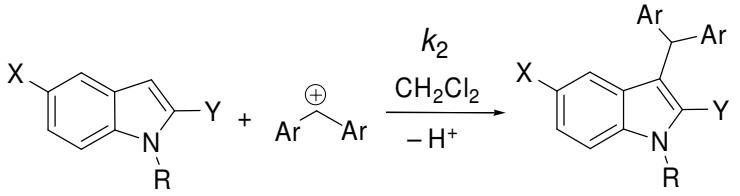
Table 3.2. Second-order rate constants k_1 for the addition of 4,6-dinitrobenzofuroxan (**2**) to indoles **1a–q** (CH_3CN, 20 °C).

indole	pK_a(H_2O)[a]	k_1 / M^{-1} s^{-1}	N [b]	s[c]
1a	–3.46	2.29 (1.4)[d]	5.55	1.09
1b	–2.32	13.40	5.75	1.23
1c	–2.90	20.84 (13.2)[d]	6.22	1.12
1d	–6.00	3.5×10^{-3} (2.38×10^{-3})[d]	2.83	(1.10)
1e	–4.30	0.18	4.38	(1.10)
1f	–4.53	0.20	4.42	(1.10)
1g	–3.30	10.71	6.00	(1.10)
1h	–1.30	13.40	6.08	(1.10)
1i	–0.28	108 (90)[d]	6.91	(1.10)
1j	+0.26	236	7.22	(1.10)
1k	+0.13	260 (245)[d]	7.26	(1.10)
1l	+0.30	–	6.54 [e]	(1.10)
1m	–1.76[f]	235	7.22	(1.10)
1n	–2.19	33.1 (28.2)[d]	6.44	(1.10)
1o	–4.93[f]	0.064 (0.058)[d]	3.97	(1.10)
1p	–3.53[f]	2.45	5.41	(1.10)
1q	–5.03[f]	0.049	3.87	(1.10)

[a] pK_a values for C-protonation at 25 °C from refs. [20, 21]; the slight temperature dependence can only have a minor effect on the derived N values. [b] For the determination of the N values see Chapter 3.3.1. [c] Estimated slope parameters are given in parentheses. [d] Second-order rate constants k_1 for 3-deuteriated indoles. [e] Recalculated from the rate constant for the reaction of **1l** with **4d** given in ref. [15] assuming s =1.10. [f] pK_a values estimated through the Brønsted correlation of log k_1 vs pK_a(H_2O) drawn for 5-X-substituted indoles **1a**, **c**–**g**, **n**; i. e., log k_1 = 1.125pK_a + 4.334.

3.2.2 Reactions of Indoles with Benzhydrylium Ions

The benzhydrylium ions **4a**–**e**,[13] which were used as reference electrophiles, were either employed as tetrafluoroborates, (**4a**–**d**)-BF_4, or generated in situ from the corresponding chloride **4e**-Cl and trimethylsilyl triflate[22, 23] (Table 3.1). The carbocations **4** reacted with the indoles **1** in dichloromethane to yield the 3-substituted indoles **5**, as demonstrated for the combinations listed in Scheme 3.2.



1 **4** **5**

1a	R = X = Y = H	**4d**	**5a** (70%)[a]
1b	R = Me, X =Y = H	**4d**	**5b** (22%)[a]
1c	R = Y = H, X = OMe	**4e**	**5c** (58%)
1l	R = Y = Me, X = H	**4d**	**5e** (34%)[a]
		4g	**5f** (61%)[b]

[a] Taken from ref. [15]. [b] Reaction performed in CH_3CN at –15 °C.

Scheme 3.2. Product analysis of the reactions of indoles **1a**–**c** with benzhydrylium ions **4** in CH_2Cl_2 at room temperature.

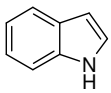
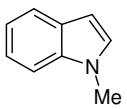
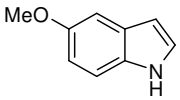
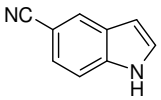
The kinetics of the reactions of the benzhydrylium ions **4** with the indoles **1a**–**d** in dichloromethane were monitored by UV/Vis spectroscopy at 20 °C with the instruments described previously.[2-7, 22-24] In some cases, one equivalent of the weakly nucleophilic base 2,6-di-*tert*-butylpyridine was added to the solutions of the benzhydrylium ions **4** in order to neutralize the liberated HBF_4. As described above for the reactions with 4,6-dinitrobenzofuroxan (**2**), the indoles **1a**–**d** were used in high excess (> 10 equivalents) to keep their concentration almost constant throughout the reactions. Exponential decays of the absorbances of the benzhydrylium ions were observed over more than two half-lives for all reactions with 5-methoxyindole (**1c**) and for most of the reactions with *N*-methylindole (**1b**) in dichloromethane. When the latter nucleophile was combined with **4a**, the weakest electrophile of this series, exponential decay of **4a** was only observed when a high excess of **1b** (70–80 equivalents) was employed. In this case, the second-order rate constant was

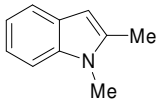
obtained by dividing the first-order rate constant k_{obs} by the concentration of **1b**. In all other cases, the second-order rate constants k_2 were derived as the slopes of plots of k_{obs} versus the concentrations of the nucleophiles.

The reactions of the benzhydrylium ions **4a–e** with the parent indole **1a** (> 10 equivalents) in dichloromethane followed first-order kinetics only during the first 50–80% of conversion. Plots of k_{obs} for the first half-life versus the concentrations of **1a** gave the second-order rate constants listed in Table 3.3. When the reactions of **1a** with **4a**, **4b** and **4d** were investigated in acetonitrile solution, however, first-order kinetics with exponential decay of the benzhydrylium absorbances were observed over more than three half-lives. The increase in reactivity from dichloromethane to acetonitrile solution (factor 3–5) is in the same order of magnitude as for additions of benzhydrylium ions to olefins.[2-7, 24] Because variation of the base (2,6-lutidine instead of 2,6-di-*tert*-butylpyridine) affects the reactivity of the least electrophilic benzhydrylium ion **4a** towards **1a** and **1c** by less than a factor of two, rate-determining C-C bond formation is assumed as in the reactions of the indoles **1** with 4,6-dinitrobenzofuroxan **2**.

Complex kinetics were observed for the reactions of the benzhydrylium tetrafluoroborates **4c**–BF_4 and **4d**–BF_4 and the benzhydrylium triflate **4e**–OTf with 5-cyanoindole (**1d**) in dichloromethane. Second-order rate laws were observed in acetonitrile solution, however, and the resulting rate constants are listed in Table 3.3.

Table 3.3. Second-order rate constants (20 °C) for the reactions of the benzhydrylium ions **4** with the indoles **1a–d** and **1l** and resulting nucleophilicity (*N*) and slope (*s*) parameters for **1a–c** and **1l**.

indole	*N*	*s*	Ar_2CH^+	solvent	base	k_2 / M^{-1} s^{-1}
	5.55[a]	1.09[a]	**4a**	CH_2Cl_2	DTBP	4.17×10^{-1}
			4a	CH_2Cl_2	lutidine	9.96×10^{-1} [b]
1a			**4b**	CH_2Cl_2	DTBP	1.63×10^{1}
			4c	CH_2Cl_2	DTBP	6.14×10^{1}
			4d	CH_2Cl_2	–	1.34×10^{2} [c]
			4e	CH_2Cl_2	–	6.23×10^{4} [d]
			4a	CH_3CN	–	2.08×10^{0}
			4b	CH_3CN	–	1.53×10^{2}
			4d	CH_3CN	–	3.19×10^{2}
			4e	TFE[e]	–	2.31×10^{5}
	5.75	1.23	**4a**	CH_2Cl_2	DTBP	5.30×10^{-1}
			4b	CH_2Cl_2	DTBP	4.82×10^{1}
			4c	CH_2Cl_2	DTBP	1.32×10^{2}
1b			**4d**	CH_2Cl_2	–	1.09×10^{3} [c]
			4e	CH_2Cl_2	–	3.31×10^{5} [d]
	6.22	1.12	**4a**	CH_2Cl_2	DTBP	1.81×10^{0}
			4a	CH_2Cl_2	lutidine	1.51×10^{0} [b]
			4b	CH_2Cl_2	DTBP	7.67×10^{1}
1c			**4c**	CH_2Cl_2	DTBP	4.00×10^{2}
			4e	CH_2Cl_2	–	2.65×10^{5} [d]
	–	–	**4d**	CH_3CN	–	2.54×10^{0}
			4e	CH_3CN	–	5.06×10^{2}
1d						

	8.55	1.30	**4f**	CH_3CN	–	1.45×10^1
			4g	CH_3CN	–	9.08×10^1
			4b	CH_3CN	–	2.49×10^3
1l			**4a**	CH_3CN	–	1.04×10^5

[a] *N* and *s* values were calculated from rate constants in CH_2Cl_2. [b] Not used for the calculation of *N* and *s*. [c] From ref. [15]. [d] Because a large part of the reaction occurred during mixing in the stopped-flow instrument, only the final part of the exponential decay was evaluated. [e] TFE = 2,2,2-trifluoroethanol, here with 9 % CH_3CN.

3.3 Discussion

3.3.1 Nucleophilicities of Indoles

When the second-order rate constants obtained for the reactions of **1a–c** with a series of benzhydrylium ions **4** were plotted against the electrophilicity parameters *E* of the benzhydrylium ions, linear correlations were obtained (Figure 3.1 and Figure 3.8 on page 42 in the Experimental Section), which yield the nucleophilicity parameters *N* and *s*, as defined by Equation (3.1). Because only two rate constants were available for 5-cyanoindole (**1d**), which refer to different solvents, *N* and *s* parameters have not been calculated for this compound. Since the slopes of these correlations ($s \approx 1.10$) are larger than those of typical enamines, the previously published *N* values for indoles,[15] which were based on an estimated value of $s = 0.80$, have to be revised.

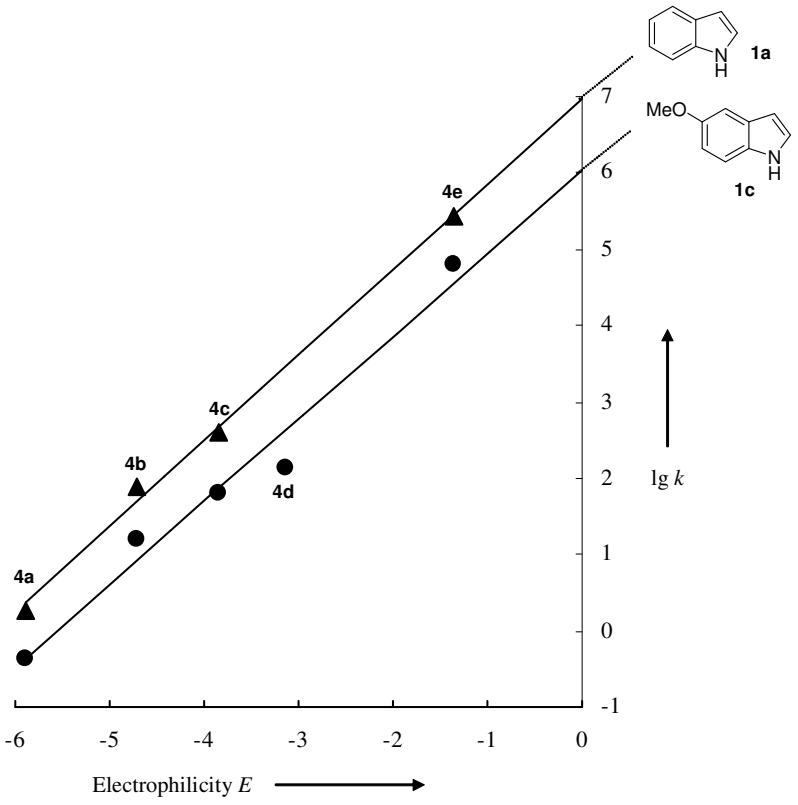


Figure 3.1. Correlation of the rate constants lg *k* (20 °C, CH_2Cl_2) for the reactions of **1a** and **1c** with the benzhydrylium ions **4a–e** with their electrophilicity parameters *E* (the corresponding correlation for the reactions of **1b** with **4a–e** is listed in the Experimental Section, Figure 3.8 on page 42).

We also determined the rate constants for the reactions of the parent indole (**1a**) with a set of benzhydrylium ions **4** in acetonitrile at 20 °C. The results (as listed in Table 3.3 and Table 3.5) indicate a slightly higher nucleophilicity parameter (N = 5.98) with a slightly lower slope parameter (s = 1.02, Figure 3.2).

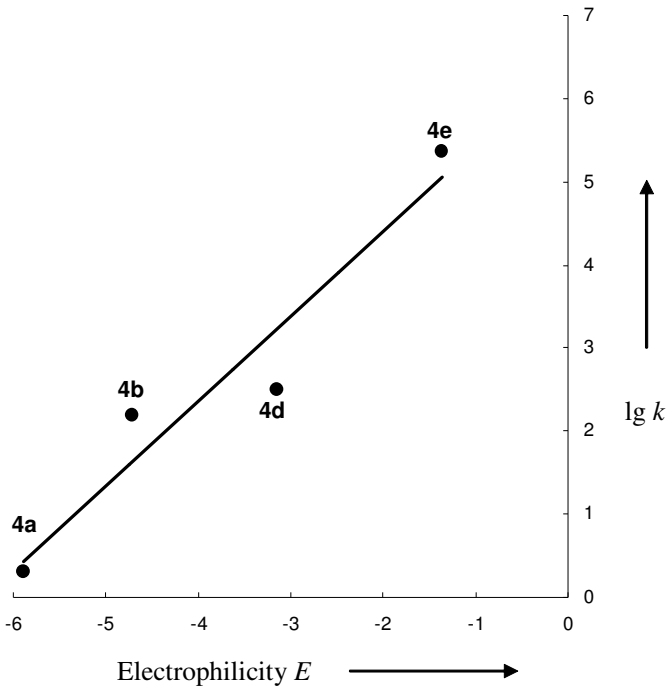


Figure 3.2. Correlation of the rate constants lg k_2 (20 °C, CH_3CN) for the reaction of **1a** with the benzhydrylium ions **4a–e** against their electrophilicity parameters E.

The correlation is moderate, but it indicates that the rates of the reactions of indole (**1a**) are not independent of the solvent. In acetonitrile solution the reactions proceed by a factor of 4 to 20 faster than in dichloromethane (Table 3.5). Possibly, the weak basic property of acetonitrile, in contrast to dichloromethane, stabilizes the σ-adduct and accelerates the reaction.

Table 3.5. Comparison of the rates of the reactions of indole (**1a**) with benzhydrylium ions **4** in different solvents.

benzhydrylium ion		k (CH_2Cl_2) / $M^{-1}s^{-1}$	k (CH_3CN) / $M^{-1}s^{-1}$	k (CH_3CN) / k (CH_2Cl_2)
$(mpa)_2CH^+$	**4a**	4.17×10^{-1}	2.08×10^{0}	5
$(dpa)_2CH^+$	**4b**	1.63×10^{1}	1.53×10^{2}	9
$(pfa)_2CH^+$	**4d**	1.34×10^{1}	3.19×10^{2}	20
$(fur)_2CH^+$	**4e**	6.23×10^{4}	2.31×10^{5}	4

When we determined the N and s value of 1,2-dimethylindole (**1l**) by plotting the second-order rate constants k_2 of its reactions with benzhydrylium ions **4** versus the electrophilicty parameters E of **4** a linear correlation was obtained (Figure 3.3).

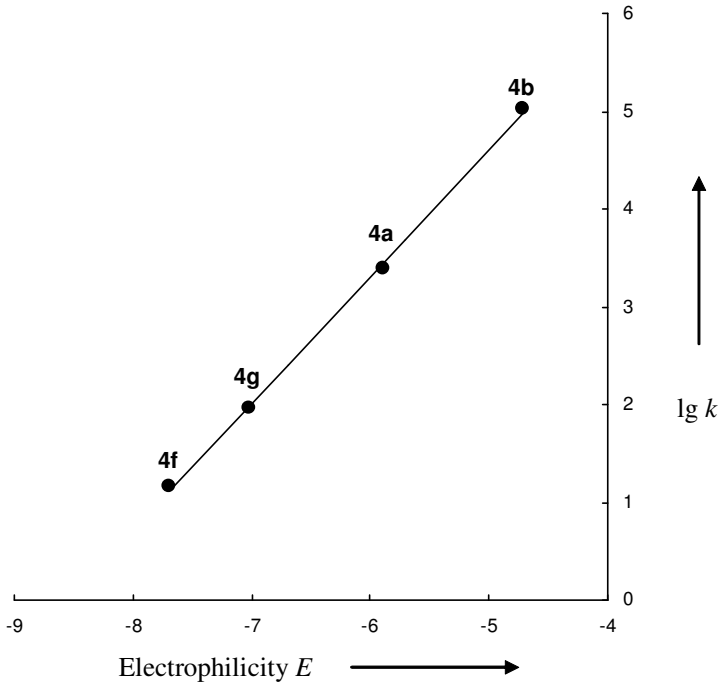


Figure 3.3. Plotting of the rate constants lg k_2 (20 °C, CH_3CN) for the reactions of **1l** with the benzhydrylium ions **4a**, **4b**, **4g** and **4f** against their electrophilicity parameters E.

Thus, N = 8.55 and s = 1.30 is derived by using Equation (3.1). When we recalculated the N value from the rate constant for the reaction of **1l** with **4d** in dichloromethane[15] assuming s = 1.10, a significantly different N parameter is obtained (N = 6.54, see Table 3.2 on page 24). This means that 1,2-dimethylindole (**2l**) reacts about 13000 times faster in acetonitrile as derived previously. The higher s value (1.30) is in line with the finding that N substituted indoles have larger slopes than N unsubstituted indoles.

3.3.2 Reactions of Indoles with 4,6-Dinitrobenzofuroxan

When the revised *N* and *s* values of the indoles **1a–c** are used for the evaluation of the electrophilicity of 4,6-dinitrobenzofuroxan (**2**)[25, 26] by minimizing $\Delta^2 = \Sigma[\log k_i - s_i(N_i + E)]^2$ the electrophilicity parameter $E = -5.06$ is obtained for 4,6-dinitrobenzofuroxan (**2**, Figure 3.4).

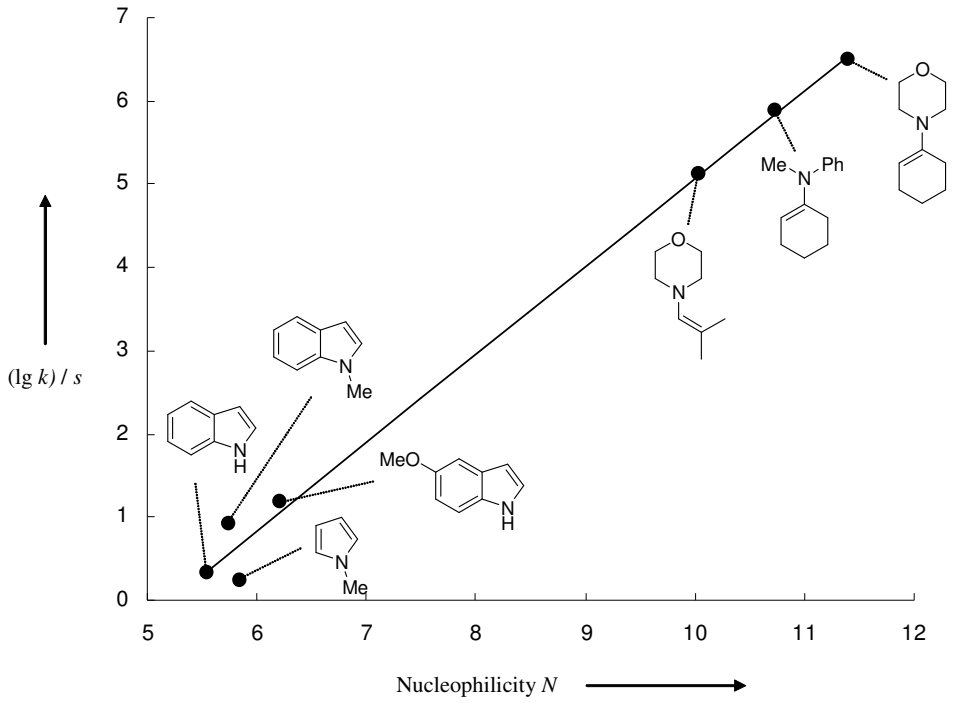


Figure 3.4. Determination of the electrophilicity of 4,6-dinitrobenzofuroxan (**2**).

With the assumption of $s = 1.10$ for *N*-unsubstituted indoles, we can now employ Equation (3.1) to calculate the *N* parameters for the indoles **1d–q** from the rate constants of their reactions with 4,6-dinitrobenzofuroxan (**2**, Table 3.2). From these data, significant information emerges on the ranking of this family of π-excessive heteroarenes on the nucleophilicity scale.

As can be seen in Table 3.2, the *N* parameters of indoles cover a domain of nucleophilic reactivity of 5 orders of magnitude from the weakest nucleophile, 5-cyanoindole (**1d**), to the strongest ones, *i. e.* 5-aminoindole (**1m**), 2,5-dimethylindole (**1j**) and 2-methyl-5-methoxyindole (**1k**). With *N* values of ~ 7.2, these three latter compounds have in fact an

enaminic reactivity which lies midway between the domains of stongly enaminic structures, *e.g.* N = 10.04 for morpholinoisobutylene, and weak enaminic structures, *e.g.* N = 3.84 for 4-(bis(trimethylsiloxy)amino)pent-4-enoic acid methyl ester.[15] So far, it is the C-3 basicity of indoles, as measured by the pK_a(H_2O) values of their conjugated acids in aqueous solution, which was the parameter employed to correlate the nucleophilic reactivity of these compounds in carbon-carbon coupling processes.[1, 18, 19, 27] In this regard, it is interesting that plotting the N values versus the pK_a(H_2O) values of indoles **1a**–**g** and **1h**–**k** gives rise to two separate linear correlations corresponding to a different behaviour of 5-X-substituted indoles and 5-X-substituted-2-methylindoles (Figure 3.5). This splitting corresponds to that previously observed in describing the reactivity of indoles through Brønsted relationships.[1]

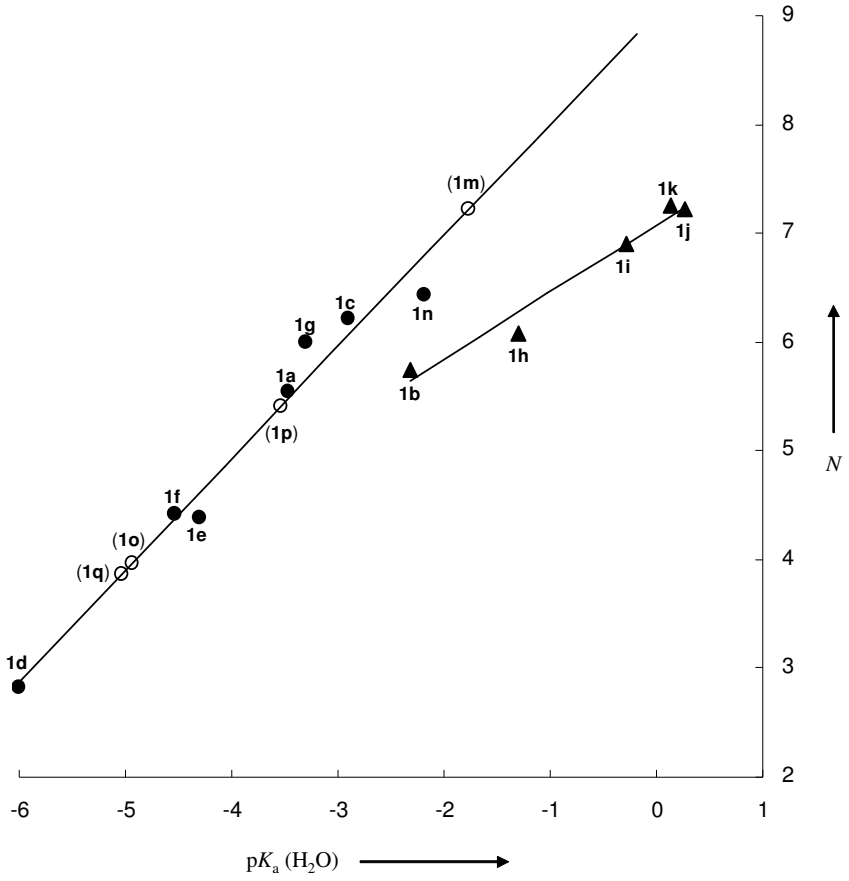


Figure 3.5. Correlation of the nucleophilicity parameters N of indoles **1a,c**–**g** and **n** (filled dots: $N = 1.025pK_a(H_2O) + 9.025$, $r^2 = 0.9669$, $n = 7$) and of 2-methyl-indoles **1h**–**k** (triangles: $N = 0.770pK_a(H_2O) + 7.097$, $r^2 = 0.9878$, $n = 4$) with the pK_a(H_2O) values for C-3 protonation of these species in H_2O. Open dots: pK_a(H_2O) values of indoles calculated from N on the basis of these correlations.

It thus appears that the 5-X-substituent exerts a similar electronic effect in the two series but that the presence of the methyl group in the position adjacent to the site of electrophilic attack reduces the rate of the 4,6-dinitrobenzofuroxan (**2**) addition to a notable extent (ca. 2 *N* units). This decrease can be reasonably attributed to steric hindrance of the approach of 4,6-dinitrobenzofuroxan (**2**) from the C-3 position of 2-methylindoles. Support for this idea is provided by a unique linear Brønsted relationship for the entire indole family in a reaction system where steric effects are minimized, for example, in the protiodetritiation at C-3 of indoles in aqueous solution.[1]

Figure 3.4 can be employed as a tool for estimating the basicities of the 3-positions of indoles for which the pK_a(H_2O) values cannot be derived from equilibrium studies in strongly acidic media. 7-Azaindole (**1q**) is such an example, because in aqueous solution the nitrogen in position 7 is much more basic [pK_a = 4.48] than C-3.[28] Coupling of **1q** with 4,6-dinitrobenzofuroxan (**2**) occurs, however, at a very convenient rate in acetonitrile (see Table 3.2), allowing a straightforward derivation of the *N* parameter through Equation (3.1). Therefore, the desired pK_a(H_2O) of the 3-position of **1q** can be derived from the upper line in Figure 3.4 [*N* = 3.87; pK_a(H_2O) = –5.03]. This large negative pK_a value reflects the strong decrease of C-3 proton basicity caused by the electron-withdrawing effect of the 7-aza group in **1q**. Another interesting system is 5-aminoindole **1m**. Despite a rather high basicity in aqueous solution [pK_a = 5.99],[29] the aniline-like 5-NH_2 group of this indole is less susceptible to 4,6-dinitrobenzofuroxan (**2**) addition than the 3-position so that, in contrast to the behavior of aniline,[30, 31] only the formation of the stable C-adduct **3m** is observed in acetonitrile. From the determined rate constant *k* for this reaction (see Table 3.2), *N* = 7.22 and pK_a(H_2O) = –1.76 can be obtained. Analogously, the previously unknown basicities at the 3-position of indole-5-carboxylic acid (**1o**) [pK_a(H_2O) = –4.93] and of 4-methoxyindole (**1p**) [pK_a(H_2O) = –3.53] could be derived from Figure 3.5.

The *N* parameters for 5-X-substituted indoles also correlate well with the oxidation peak potentials E_p^{ox} (Figure 3.6), as measured by electrochemical oxidation in acetonitrile by Mount and coworkers,[32] but it is found that the slope of this correlation is only one third of that observed for a large variety of different *C*-nucleophiles.[33]

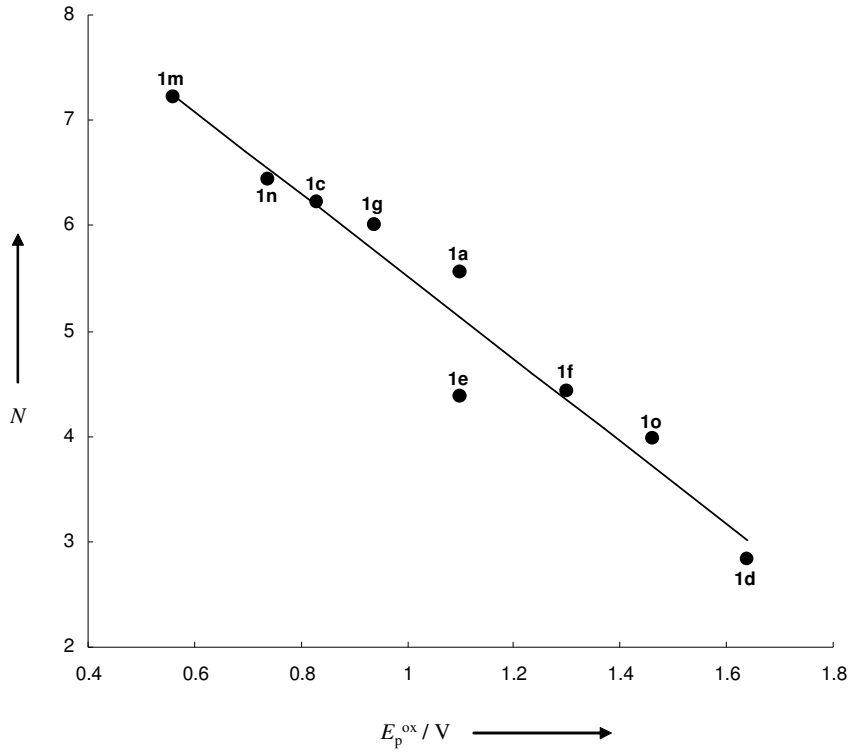
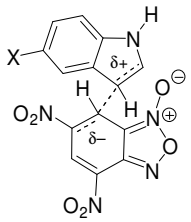


Figure 3.6. Correlation of the nucleophilicity parameters *N* of 5-X-substituted indoles **1** with the oxidation peak potentials E_p^{ox} of these species (from ref. [32]; the reported E_p^{ox} refer to a reference electrode (Ag/Ag^+ in MeCN) with a potential of +0.437 V *vs.* SCE).

Comparison of the rate data pertaining to the couplings of 5-X-substituted indoles with 4,6-dinitrobenzofuroxan (**2**) in acetonitrile with those obtained (at 25 °C) for these reactions in methanol, 50-50 (v/v) H_2O-Me_2SO and 70-30 (v/v) H_2O-Me_2SO reveals that the solvent has an appreciable effect on the rates of the reactions of Scheme 3.1. In accord with the rate-limiting formation of the zwitterionic Wheland-Meisenheimer intermediate $\mathbf{ZH^{\pm}}$ through a strongly dipolar transition state of type **6** (Scheme 3.4), the rates of the reactions decrease significantly with decreasing solvent polarity in the order 70-30 (v/v) H_2O-Me_2SO > 50-50 (v/v) H_2O-Me_2SO > methanol > acetonitrile.[1]



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Scheme 3.4. Transition state of the formation of the Wheland-Meisenheimer intermediate **ZH$^{\pm}$.**

Figure 3.7 shows the correlations obtained by plotting the logarithms of the rate constants k_1 determined in the four solvents versus the *N* values of the indoles **1a, c–g**.

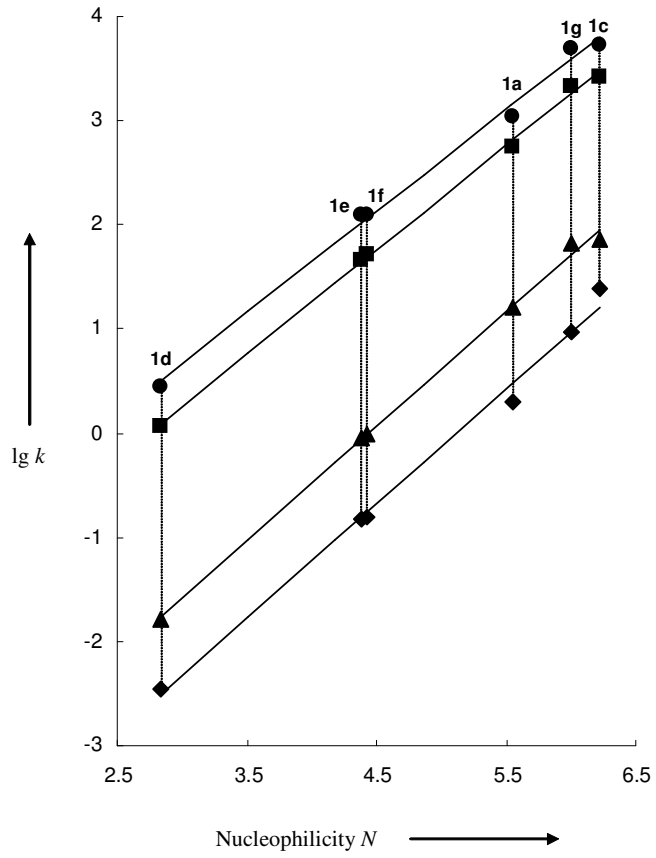


Figure 3.7. Effect of the solvent on the rates of the formation of σ-complexes of 4,6-dinitrobenzofuroxan (**2**) and the indoles **1a, c–g** (in CH_3CN at 20 °C from this work, for all other solvents at 25 °C from ref. [1]; the slight temperature difference between CH_3CN and the other solvents does not affect the comparison).

The four parallel correlation lines in Figure 3.7 indicate that the relative reactivities of the different indoles do not appreciably depend on the solvent. Because of the dipolar nature of the transition state, it is difficult at this stage to dissect the observed solvent effects in terms of individual contributions of the electrophilic and nucleophilic partners. Kinetic investigations of other C-C couplings involving two neutral reagents are needed for this purpose.

3.3.3 Reactions of Indoles with Other Electrophiles

As reported by Jackson and Lynch, the initial attack of the electrophile is rate-limiting in the coupling of indole (**1a**), *N*-methylindole (**1b**), and 2-methylindole (**1i**) with the *p*-nitrobenzenediazonium cation.[18, 19] The kinetics of the azo couplings between indoles **1a**, **1b**, and **1i** and a variety of aryl diazonium ions have extensively been studied by Shawali and co-workers.[34] Because the electrophilicity parameters of several diazonium ions have been determined previously,[35] we can use Equation (3.1) to calculate rate constants for the azo couplings of indoles. The comparison of experimental and calculated rate constants for azo couplings provides a test of the reliability of our approach, and Table 3.6 shows that Equation (3.1) predicts the rate constants of azo couplings within a factor of < 20 (for analogous comparison of calculated and experimental rate constants which was based on *N* parameters for indoles that were derived from σ^{+}_{arene} parameters, see ref. [22]).

With similar precision, the rate constants of the electrophilic alkylations of indoles **1a**, **1b**, and **1i** with the (2-methoxycyclohexadienylium)iron(tricarbonyl) ion, which were reported earlier by Kane-Maguire and Mansfield,[2, 36, 37] can be reproduced within a factor of < 40 by Equation (3.1).

Such deviations are typical for the predictive power of Equation (3.1), which covers a reactivity range of almost 30 orders of magnitude and usually predicts rate constants of polar organic reactions within a factor of 10–100.[2-7]

Table 3.6. Comparison between calculated [20 °C, Equation (3.1)] and experimentally determined second-order rate constants for the reactions of indole (**1a**), *N*-methylindole (**1b**), and 2-methylindole (**1i**) with different electrophiles.

	nucleophile (*N*/*s*)	electrophile	E[a]	k_{calcd} / M^{-1} s^{-1}	k_{exp} / M^{-1} s^{-1} [b]
1a	indole	4-OMe-C_6H_4-N_2^+	–8.4	2.4×10^{-3}	2.49×10^{-4}
	(5.55/1.09)	4-Me-C_6H_4-N_2^+	–7.7	1.1×10^{-2}	5.62×10^{-4}
		C_6H_5-N_2^+	–7.2	3.1×10^{-2}	2.24×10^{-3}
		4-Cl-C_6H_4-N_2^+	–6.7	8.8×10^{-2}	1.44×10^{-2}
		4-CN-C_6H_4-N_2^+	–5.5	1.11	4.69×10^{-1}
		4-NO_2-C_6H_4-N_2^+	–5.1	2.6	1.24×10^{0}
		(2-MeOC_6H_6)Fe$(CO)_3^+$	–8.94[c]	7.8×10^{-4}	1.60×10^{-2} [d]
1b	*N*-methylindole	4-OMe-C_6H_4-N_2^+	–8.4	7.0×10^{-3}	2.46×10^{-3}
	(5.75/1.23)	4-Me-C_6H_4-N_2^+	–7.7	2.6×10^{-2}	5.80×10^{-3}
		C_6H_5-N_2^+	–7.2	6.6×10^{-2}	2.57×10^{-2}
		4-Cl-C_6H_4-N_2^+	–6.7	1.7×10^{-1}	1.18×10^{-1}
		4-CN-C_6H_4-N_2^+	–5.5	1.6	3.72×10^{0}
		4-NO_2-C_6H_4-N_2^+	–5.1	3.4	6.61×10^{0}
		(2-MeOC_6H_6)Fe$(CO)_3^+$	–8.94[c]	2.5×10^{-3}	9.70×10^{-2} [d]
1i	2-methylindole	4-OMe-C_6H_4-N_2^+	–8.4	4.4×10^{-2}	2.50×10^{-1}
	(6.91/1.10)	4-Me-C_6H_4-N_2^+	–7.7	1.9×10^{-1}	6.20×10^{-1}
		C_6H_5-N_2^+	–7.2	5.4×10^{-1}	1.92×10^{0}
		4-Cl-C_6H_4-N_2^+	–6.7	1.6	1.51×10^{1}
		4-CN-C_6H_4-N_2^+	–5.5	1.9×10^{1}	1.78×10^{2}
		4-NO_2-C_6H_4-N_2^+	–5.1	4.4×10^{1}	4.27×10^{2}
		(2-MeOC_6H_6)Fe$(CO)_3^+$	–8.94[c]	1.4×10^{-2}	1.20×10^{-1} [d]

[a] From ref. [35]. [b] In CH_3CN at 25 °C, from ref. [34]. [c] From ref. [2]. [d] In CH_3NO_2 at 20 °C, from refs. [36, 37].

3.4 Experimental Section

3.4.1 General Comments

The benzhydrylium cations **4** used in this work were prepared according to literature procedure.[13] The various indoles **1a**–**q**, 2,6-di-*tert*-butylpyridine (DTBP) and trimethylsilyl triflate were commercially available products which were purified, as appropriate, by recrystallization, sublimation or distillation prior to use. Deuteriation of **1a**, **1c**, **1d**, **1i**, **1k**, **1n**, **1o** was effected by acid-catalyzed exchange, according to a procedure which was previously reported in detail.[18-21, 27, 38-43] Deuteriation at C-3 was in all cases found to be ≥98% on the basis of ^{1}H-NMR spectra recorded in d_6-DMSO. 4,6-Dinitrobenzofuroxan (**2**) was prepared according to the procedure by Drost[44] with m. p. 172°C (lit.[27, 45-52] m. p. 172–174°C).

Adducts **3a**–**l** have previously been isolated and fully characterized either in their acid form or as sodium salts.[1] Following the same methodology, the synthetic work has been extended to the adducts **3m**–**q**, which correspond to the σ-complexation of **2** by 5-aminoindole (**1m**), 5-hydroxyindole (**1n**), 5-indolecarboxylic acid (**1o**), 4-methoxyindole (**1p**) and 7-azaindole (**1q**), respectively. These have been prepared in their acid form upon mixing acetonitrile solutions of **2** (1 equivalent) and of the relevant indole (1 equivalent) at room temperature. Subsequent addition of diethyl ether resulted in the precipitation of **3m**–**q** as red-orange solids in 60–90% yields. As all σ-adducts of 4,6-dinitrobenzofuroxan (**2**) so far obtained, these solids did not melt prior to decomposition (explosion) and attempts to obtain satisfactory elemental analysis have been unsuccessful. However, dissolution of **3m**–**q** in d_6-DMSO gave NMR spectra identical to those recorded in the *in situ* generation of these adducts in this solvent. In accord with the proposed structures, the H-7' and C-7' resonances are typical for C-adducts of **2**, being in the ranges of 5.64–5.83 and 30.4–32.4 ppm, respectively.[1, 27, 47-53] Also noteworthy is that the σ-complexation process goes along with the loss of the resonance of the H-3 proton of the parent indoles **1m**–**q**. Concomitantly, there is a significant low-field shift of the C-3 resonance, in agreement with the fact that a negatively charged dinitrobenzofuroxanyl moiety exerts a strong –I effect.[48-51] Also the NMR data leave no doubt that the adducts **3m** and **3q** are characterized by the positioning of the proton at the 5-amino group or at the 7-aza nitrogen, respectively, i.e., **3m** and **3q** can be regarded as real zwitterions. Among other evidence for structure **3m** are the especially low-field resonances of the H-4 ($\delta_{H\text{-}4}$ = 6.69 for **1m**; $\delta_{H\text{-}4}$ = 7.48 for **3m**) and H-6 ($\delta_{H\text{-}6}$ = 6.49 for **1m**; $\delta_{H\text{-}6}$ = 7.42 for

3m) as well as of the related C-4 ($\delta_{C\text{-}4}$ = 103.2 for **1m**; $\delta_{C\text{-}4}$ = 111.9 for **3m**) and C-6 ($\delta_{C\text{-}6}$ = 111.8 for **1m**; $\delta_{C\text{-}6}$ = 115.9 for **3m**). Similarly, the H-4 ($\delta_{H\text{-}4}$ = 7.92 for **1q**; $\delta_{H\text{-}4}$ = 8.39 for **3q**) and C-4 ($\delta_{C\text{-}4}$ = 128.0 for **1q**; $\delta_{C\text{-}4}$ = 133.7 for **3q**) resonances of **3q** are typical for the adjacent protonated aza functionality. Definitive evidence that the adducts **3m**–**q** were isolated in their acid form comes from mass spectra experiments performed with the electrospray technique. Also, the UV-visible spectra of the adducts exhibit the strong absorption at λ = 470–480 nm typical of all σ-complexes of 4,6-dinitrobenzofuroxan (**2**) in acetonitrile.[1, 25-27, 47-53]

Representative NMR (^{1}H, ^{13}C) and mass spectroscopy data for the 4,6-dinitrobenzofuroxan adducts **3m**–**q** are available.

3.4.2 Kinetic Measurements

3.4.2.1 General

The kinetics of the reactions of indoles **1** with 4,6-dinitrobenzofuroxan (**2**) have been performed by Terrier *et al*. and are not listed here. The kinetic investigations of the reactions of benzhydrylium ions **4** with the indoles **1a–d** in dichloromethane and acetonitrile were carried out as previously described in detail for similar interactions.[2-7, 22-24]

3.4.2.2 Kinetics of the Reactions of Indoles with Benzhydrylium Ions

The rate constants for the reactions of indole (**1a**), *N*-methylindole (**1b**) and 1,2-dimethylindole (**1l**) with $(pfa)_2CH^+BF_4^-$ (**4d**) in dichloromethane have already been reported.[15]

Plotting of the logarithms of the second-order rate constants of the reactions of *N*-methylindole (**1b**) with the benzhydrylium ions **4a–e** against the electrophilicity parameters *E* of these electrophiles leads to a linear correlation (Figure 3.8). Using Equation (3.1) yields the *N* and *s* parameter of **1b** in dichloromethane as listed in Table 3.3 (on page 27).

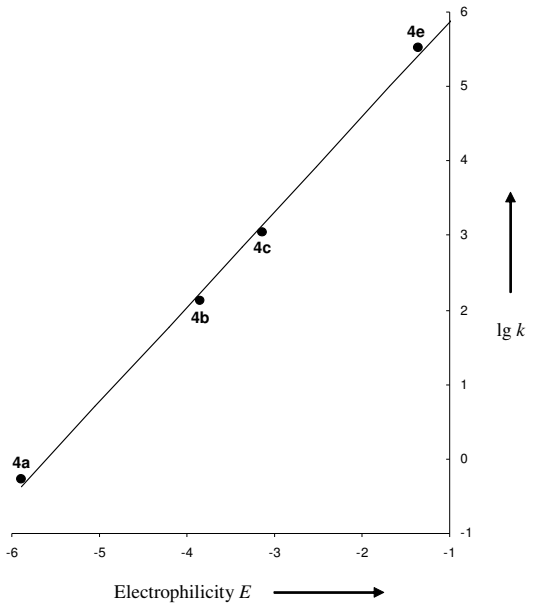
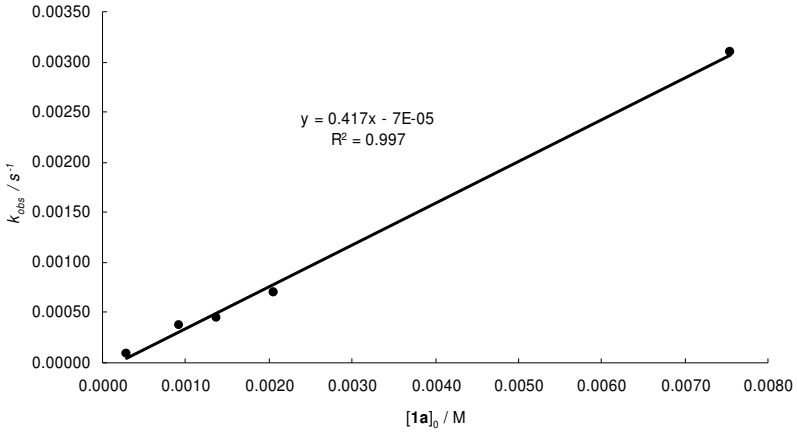


Figure 3.8. Correlation of the rate constants (lg *k* at 20 °C in CH_2Cl_2) for the reactions of **1b** with **4** in relation to *E* to yield *N* = 5.75 and *s* = 1.23 for **1b**.

Table 3.7. Rate constants for the reactions of indole (**1a**) with $(mpa)_2CH^+BF_4^-$ (**4a**-BF_4) in the presence of 2,6-di-*tert*-butylpyridine (DTBP).
(J&M technique, λ = 622 nm, 20 °C, in CH_2Cl_2).

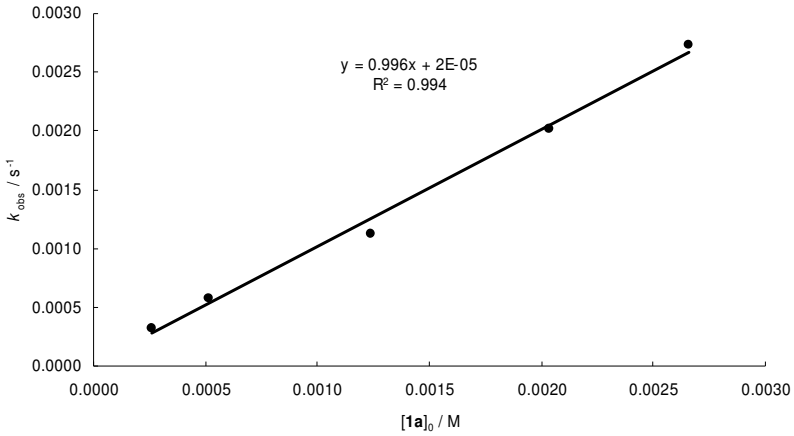
no.	$[\mathbf{1a}]_0$ / M	$[\mathbf{4a}]_0$ / M	$[DTBP]_0$ / M	$[\mathbf{1a}]_0$ / $[\mathbf{4a}]_0$	Conv. / %	k_{obs} / s^{-1}
1	4.98×10^{-4}	2.49×10^{-5}	2.49×10^{-5}	20	80	9.58×10^{-5}
2	9.15×10^{-4}	2.28×10^{-5}	2.28×10^{-5}	40	51	3.69×10^{-4}
3	1.37×10^{-3}	1.71×10^{-5}	1.71×10^{-5}	80	52	4.52×10^{-4}
4	2.07×10^{-3}	2.15×10^{-5}	2.15×10^{-5}	96	61	7.03×10^{-4}
5	7.55×10^{-3}	2.52×10^{-5}	2.52×10^{-5}	300	79	3.10×10^{-3}



$k_2 = 4.17 \times 10^{-1}$ M^{-1} s^{-1}.

Table 3.8. Rate constants for the reactions of indole (**1a**) with $(mpa)_2CH^+BF_4^-$ (**5a**-BF_4) in the presence of 2,6-lutidine.
(J&M technique, λ = 622 nm, 20 °C, in CH_2Cl_2).

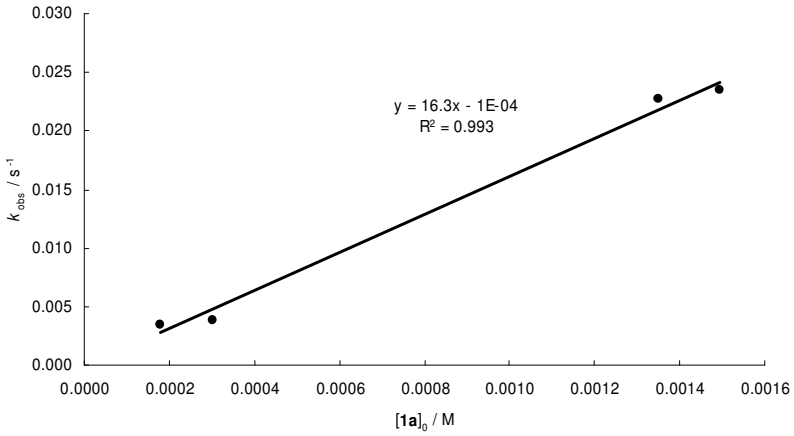
no.	$[\mathbf{1a}]_0$ / M	$[\mathbf{4a}]_0$ / M	$[DTBP]_0$ / M	$[\mathbf{1a}]_0$ / $[\mathbf{4a}]_0$	Conv. / %	k_{obs} / s^{-1}
1	2.64×10^{-4}	2.20×10^{-5}	2.20×10^{-5}	12	68	3.22×10^{-4}
2	5.17×10^{-4}	2.15×10^{-5}	2.15×10^{-5}	24	53	5.78×10^{-4}
3	1.24×10^{-3}	2.07×10^{-5}	2.07×10^{-5}	60	65	1.12×10^{-3}
4	2.04×10^{-3}	2.12×10^{-5}	2.12×10^{-5}	96	60	2.02×10^{-3}
5	2.66×10^{-3}	2.46×10^{-5}	2.46×10^{-5}	108	55	2.73×10^{-3}



$k_2 = 9.96 \times 10^{-1}$ M^{-1} s^{-1}.

Table 3.9. Rate constants for the reactions of indole (**1a**) with $(dpa)_2CH^+BF_4^-$ (**4b**-BF_4) in the presence of 2,6-di-*tert*-butylpyridine (DTBP). (J&M technique, λ = 672 nm, 20 °C, in CH_2Cl_2).

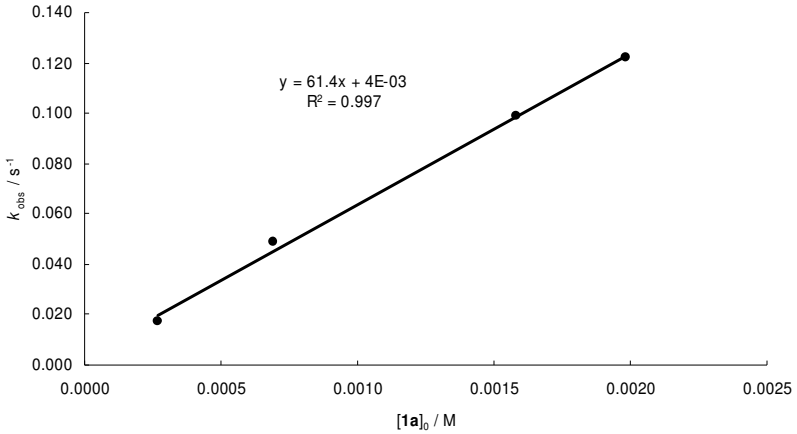
no.	[**1a**]$_0$ / M	[**5b**]$_0$ / M	[DTBP]$_0$ / M	[**1a**]$_0$ / [**5b**]$_0$	Conv. / %	k_{obs} / s^{-1}
1	1.79×10^{-4}	1.76×10^{-5}	1.76×10^{-5}	10	58	3.50×10^{-3}
2	3.03×10^{-4}	1.50×10^{-5}	1.50×10^{-5}	20	74	3.84×10^{-3}
3	1.35×10^{-3}	1.33×10^{-5}	1.33×10^{-5}	101	75	2.27×10^{-2}
4	1.50×10^{-3}	1.48×10^{-5}	1.48×10^{-5}	101	79	2.35×10^{-2}



$k_2 = 1.63 \times 10^{1}$ M^{-1} s^{-1}.

Table 3.10. Rate constants for the reactions of indole (**1a**) with $(mfa)_2CH^+BF_4^-$ (**4c**-BF_4) in the presence of 2,6-di-*tert*-butylpyridine (DTBP).
(J&M technique, λ = 593 nm, 20 °C, in CH_2Cl_2).

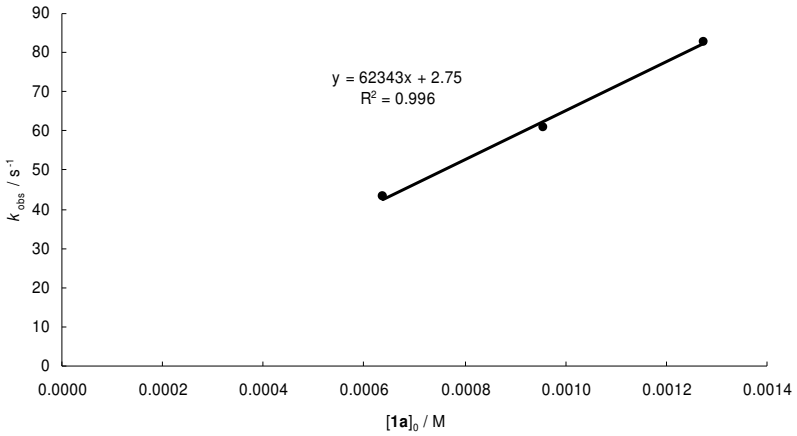
no.	$[\mathbf{1a}]_0$ / M	$[\mathbf{4c}]_0$ / M	$[DTBP]_0$ / M	$[\mathbf{1a}]_0$ / $[\mathbf{4c}]_0$	Conv. / %	k_{obs} / s^{-1}
1	2.72×10^{-4}	2.33×10^{-5}	2.33×10^{-5}	12	51	1.72×10^{-2}
2	6.91×10^{-4}	2.96×10^{-5}	2.96×10^{-5}	23	75	4.88×10^{-2}
3	1.58×10^{-3}	2.72×10^{-5}	2.72×10^{-5}	58	69	9.89×10^{-2}
4	1.98×10^{-3}	2.13×10^{-5}	2.13×10^{-5}	93	68	1.22×10^{-1}



$k_2 = 6.14 \times 10^1$ M^{-1} s^{-1}.

Table 3.11. Rate constants for the reactions of indole (**1a**) with $(fur)_2CHCl$ (**4e**-Cl) and trimethylsilyltriflate (TMSOTf).
(Stopped Flow technique, λ = 540 nm, 20 °C in CH_2Cl_2).

no.	$[\mathbf{1a}]_0$ / M	$[\mathbf{4e}\text{-Cl}]_0$ / M	$[TMSOTf]_0$ / M	$[\mathbf{1a}]_0$ / $[\mathbf{4e}]_0$	k_{obs} / s^{-1}
1	6.37×10^{-4}	1.62×10^{-5}	1.62×10^{-5}	39	4.32×10^1
2	9.55×10^{-4}	1.62×10^{-5}	1.62×10^{-5}	59	6.08×10^1
3	1.27×10^{-3}	1.62×10^{-5}	1.62×10^{-5}	79	8.29×10^1



$k_2 = 6.23 \times 10^4$ M^{-1} s^{-1}.

Table 3.12. Rate constants for the reactions of *N*-methylindole (**1b**) with $(mpa)_2CH^+BF_4^-$ (**4a**-BF_4) in the presence of 2,6-di-*tert*-butylpyridine (DTBP). (J&M technique, λ = 622 nm, 20 °C, in CH_2Cl_2).

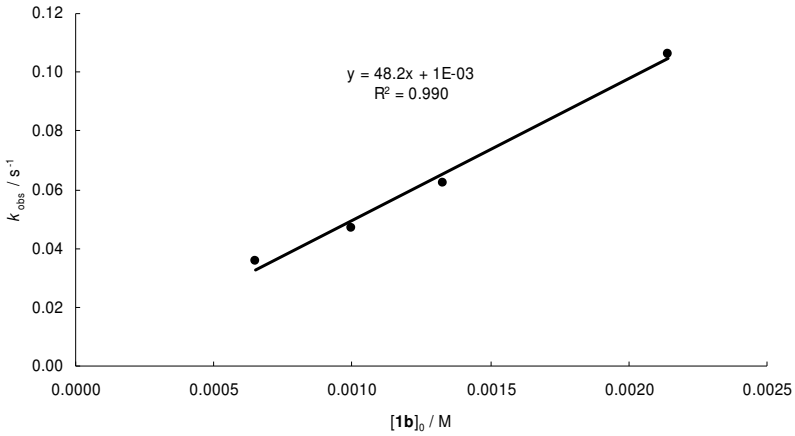
no.	[**1b**]$_0$ / M	[**4a**]$_0$ / M	[DTBP]$_0$ / M	[**1b**]$_0$ / [**4a**]$_0$	Conv. / %	k_{obs} / s^{-1}
1	2.71×10^{-3}	3.35×10^{-5}	3.35×10^{-5}	81	49	1.48×10^{-3}
2	3.14×10^{-3}	3.28×10^{-5}	3.28×10^{-5}	96	72	1.61×10^{-3}

no.	k_2 / M^{-1} s^{-1}
1	5.46×10^{-1}
2	5.13×10^{-1}

$\langle k_2 \rangle = 5.30 \times 10^{-1}$ M^{-1} s^{-1}.

Table 3.13. Rate constants for the reactions of *N*-methylindole (**1b**) with $(dpa)_2CH^+BF_4^-$ (**4b**-BF_4) in the presence of 2,6-di-*tert*-butylpyridine (DTBP). (J&M technique, λ = 672 nm, 20 °C, in CH_2Cl_2).

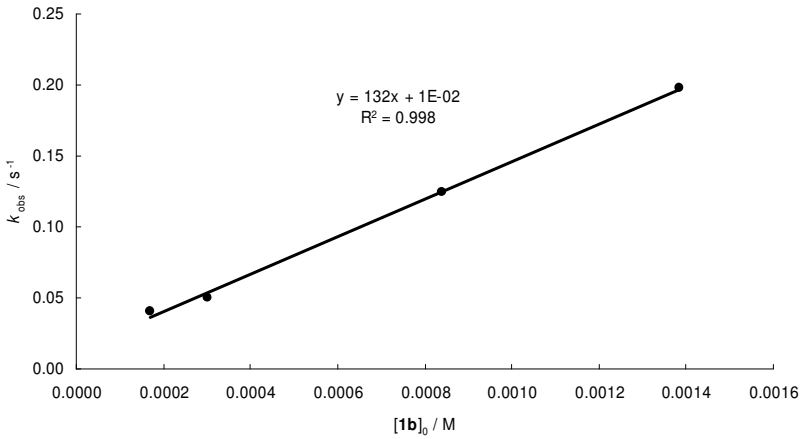
no.	[**1b**]$_0$ / M	[**4b**]$_0$ / M	[DTBP]$_0$ / M	[**1b**]$_0$ / [**4b**]$_0$	Conv. / %	k_{obs} / s^{-1}
1	6.52×10^{-4}	3.04×10^{-5}	3.04×10^{-5}	22	73	3.61×10^{-2}
2	1.00×10^{-3}	2.45×10^{-5}	2.45×10^{-5}	41	83	4.71×10^{-2}
3	1.33×10^{-3}	2.21×10^{-5}	2.21×10^{-5}	60	65	6.24×10^{-2}
4	2.14×10^{-4}	2.70×10^{-5}	2.70×10^{-5}	79	65	1.06×10^{-1}



$k_2 = 4.82 \times 10^1$ M^{-1} s^{-1}.

Table 3.14. Rate constants for the reactions of *N*-methylindole (**1b**) with $(mfa)_2CH^+BF_4^-$ (**4c**-BF_4) in the presence of 2,6-di-*tert*-butylpyridine (DTBP). (J&M technique, λ = 593 nm, 20 °C, in CH_2Cl_2).

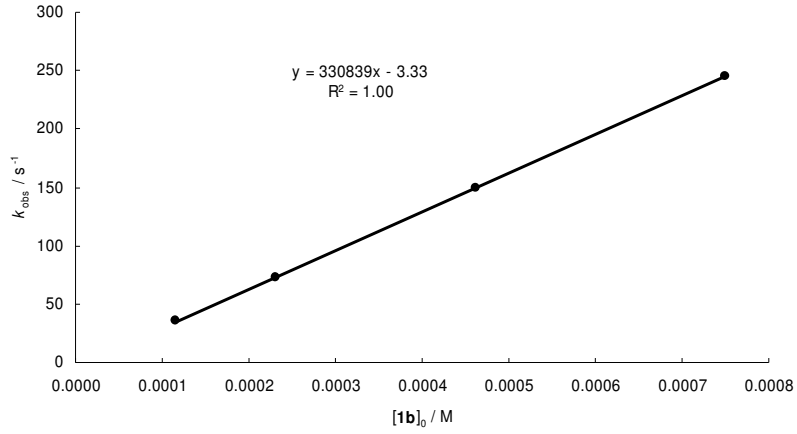
no.	[**1b**]$_0$ / M	[**4c**]$_0$ / M	[DTBP]$_0$ / M	[**1b**]$_0$ / [**4c**]$_0$	Conv. / %	k_{obs} / s^{-1}
1	1.70×10^{-4}	1.79×10^{-5}	1.79×10^{-5}	10	73	4.04×10^{-2}
2	3.03×10^{-4}	1.59×10^{-5}	1.59×10^{-5}	19	94	5.05×10^{-2}
3	8.39×10^{-4}	2.21×10^{-5}	2.21×10^{-5}	38	82	1.24×10^{-1}
4	1.38×10^{-3}	1.75×10^{-5}	1.75×10^{-5}	79	74	1.98×10^{-1}



$k_2 = 1.32 \times 10^2$ M^{-1} s^{-1}.

Table 3.15. Rate constants for the reactions of *N*-methylindole (**1b**) with $(fur)_2CHCl$ (**4e**-Cl) and trimethylsilyltriflate (TMSOTf).
(Stopped Flow technique, λ = 540 nm, 20 °C in CH_2Cl_2).

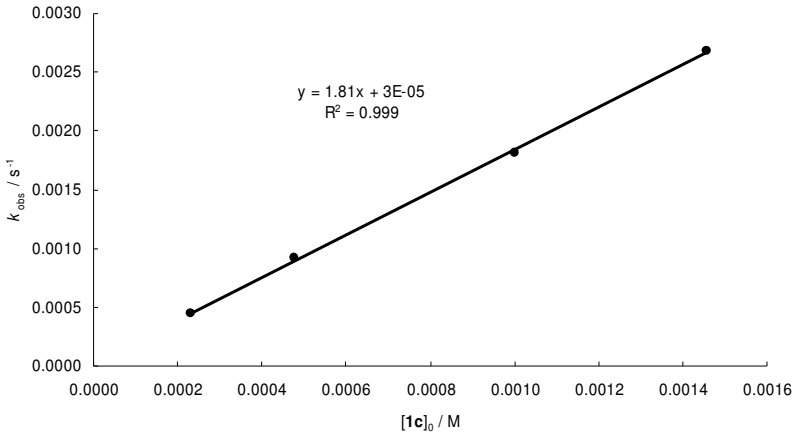
no.	$[\mathbf{1b}]_0$ / M	$[\mathbf{4e}\text{-Cl}]_0$ / M	$[TMSOTf]_0$ / M	$[\mathbf{1b}]_0$ / $[\mathbf{4e}]_0$	k_{obs} / s^{-1}
1	1.15×10^{-4}	1.20×10^{-5}	1.20×10^{-5}	10	3.56×10^{2}
2	2.31×10^{-4}	1.20×10^{-5}	1.20×10^{-5}	19	7.22×10^{2}
3	4.61×10^{-4}	1.20×10^{-5}	1.20×10^{-5}	38	1.49×10^{1}
4	7.50×10^{-4}	1.20×10^{-5}	1.20×10^{-5}	62	2.45×10^{1}



$k_2 = 3.31 \times 10^5$ M^{-1} s^{-1}.

Table 3.16. Rate constants for the reactions of 5-methoxyindole (**1c**) with $(mpa)_2CH^+BF_4^-$ (**4a**-BF_4) in the presence of 2,6-di-*tert*-butylpyridine (DTBP).
(J&M technique, λ = 622 nm, 20 °C, in CH_2Cl_2).

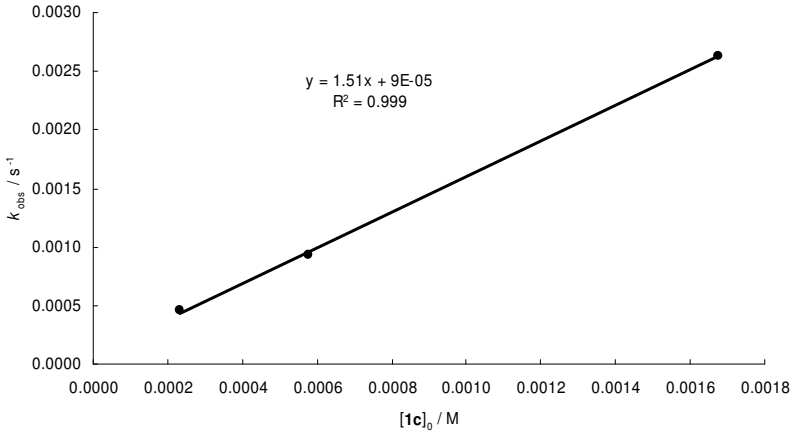
no.	$[\mathbf{1c}]_0$ / M	$[\mathbf{4a}]_0$ / M	$[DTBP]_0$ / M	$[\mathbf{1c}]_0$ / $[\mathbf{4a}]_0$	Conv. / %	k_{obs} / s^{-1}
1	2.30×10^{-4}	2.11×10^{-5}	2.11×10^{-5}	11	64	4.42×10^{-4}
2	4.76×10^{-4}	2.18×10^{-5}	2.18×10^{-5}	22	80	9.14×10^{-4}
3	1.00×10^{-3}	2.44×10^{-5}	2.44×10^{-5}	41	62	1.81×10^{-3}
4	1.46×10^{-3}	1.78×10^{-5}	1.78×10^{-5}	82	81	2.68×10^{-3}



$k_2 = 1.81 \times 10^0$ M^{-1} s^{-1}.

Table 3.17. Rate constants for the reactions of 5-methoxyindole (**1c**) with $(mpa)_2CH^+BF_4^-$ (**4a**-BF_4) in the presence of 2,6-lutidine. (J&M technique, λ = 622 nm, 20 °C, in CH_2Cl_2).

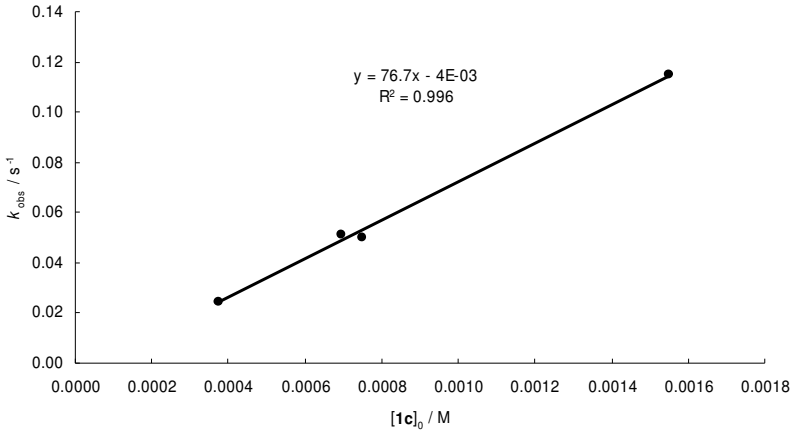
no.	$[\mathbf{1c}]_0$ / M	$[\mathbf{4a}]_0$ / M	$[DTBP]_0$ / M	$[\mathbf{1c}]_0$ / $[\mathbf{4a}]_0$	Conv. / %	k_{obs} / s^{-1}
1	2.31×10^{-4}	2.12×10^{-5}	2.12×10^{-5}	11	81	4.56×10^{-4}
2	5.76×10^{-4}	2.64×10^{-5}	2.64×10^{-5}	22	85	9.34×10^{-4}
3	1.68×10^{-3}	2.05×10^{-5}	2.05×10^{-5}	82	81	2.63×10^{-3}



$k_2 = 1.51 \times 10^0$ M^{-1} s^{-1}.

Table 3.18. Rate constants for the reactions of 5-methoxyindole (**1c**) with $(dpa)_2CH^+BF_4^-$ (**4b**-BF_4) in the presence of 2,6-di-*tert*-butylpyridine (DTBP). (J&M technique, λ = 672 nm, 20 °C, in CH_2Cl_2).

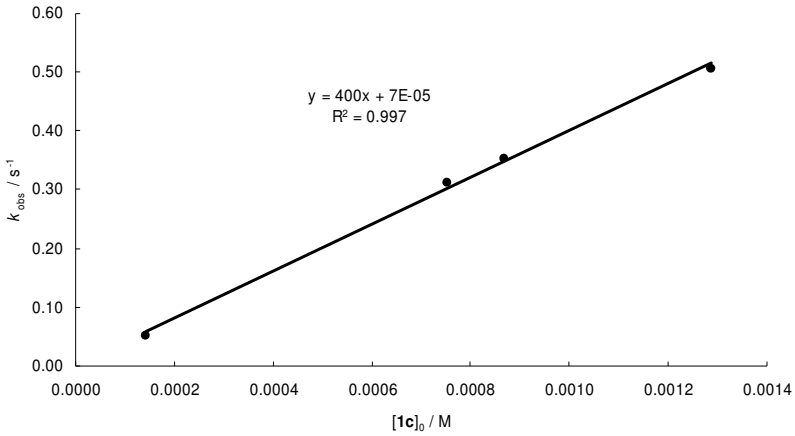
no.	$[\mathbf{1c}]_0$ / M	$[\mathbf{4b}]_0$ / M	$[DTBP]_0$ / M	$[\mathbf{1c}]_0$ / $[\mathbf{4b}]_0$	Conv. / %	k_{obs} / s^{-1}
1	3.73×10^{-4}	1.91×10^{-5}	1.91×10^{-5}	20	98	2.47×10^{-2}
2	6.94×10^{-4}	1.78×10^{-5}	1.78×10^{-5}	39	68	5.13×10^{-2}
3	7.49×10^{-4}	1.28×10^{-5}	1.28×10^{-5}	59	84	4.99×10^{-2}
4	1.55×10^{-3}	1.91×10^{-5}	1.91×10^{-5}	81	68	1.15×10^{-1}



$k_2 = 7.67 \times 10^1$ M $^{-1}$ s^{-1}.

Table 3.19. Rate constants for the reactions of 5-methoxyindole (**1c**) with $(mfa)_2CH^+BF_4^-$ (**4c**-BF_4) in the presence of 2,6-di-*tert*-butylpyridine (DTBP). (J&M technique, λ = 593 nm, 20 °C, in CH_2Cl_2).

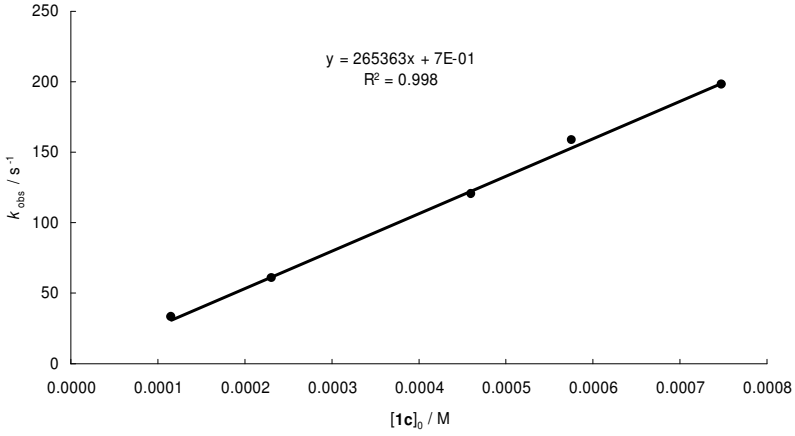
no.	$[\mathbf{1c}]_0$ / M	$[\mathbf{4c}]_0$ / M	$[DTBP]_0$ / M	$[\mathbf{1c}]_0$ / $[\mathbf{4c}]_0$	Conv. / %	k_{obs} / s^{-1}
1	1.44×10^{-4}	1.39×10^{-5}	1.39×10^{-5}	10	71	5.04×10^{-2}
2	7.52×10^{-4}	1.81×10^{-5}	1.81×10^{-5}	42	55	3.12×10^{-1}
3	8.68×10^{-4}	1.48×10^{-5}	1.48×10^{-5}	59	57	3.52×10^{-1}
4	1.29×10^{-3}	1.62×10^{-5}	1.62×10^{-5}	80	69	5.06×10^{-1}



$k_2 = 4.00 \times 10^2$ M^{-1} s^{-1}.

Table 3.20. Rate constants for the reactions of 5-methoxyindole (**1c**) with $(fur)_2CHCl$ (**4e**-Cl) and trimethylsilyltriflate (TMSOTf).
(Stopped Flow technique, λ = 593 nm, 20 °C, in CH_2Cl_2).

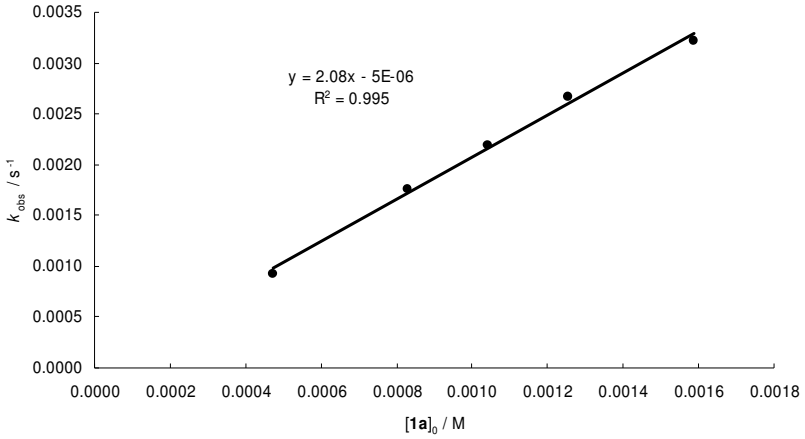
no.	[**1c**]$_0$ / M	[**4e**-Cl]$_0$ / M	[TMSOTf]$_0$ / M	[**1c**]$_0$ / [**4e**]$_0$	k_{obs} / s^{-1}
1	1.15×10^{-4}	1.20×10^{-5}	1.20×10^{-5}	10	3.26×10^1
2	2.30×10^{-4}	1.20×10^{-5}	1.20×10^{-5}	19	6.04×10^1
3	4.61×10^{-4}	1.20×10^{-5}	1.20×10^{-5}	38	1.20×10^2
4	5.76×10^{-4}	1.20×10^{-5}	1.20×10^{-5}	48	1.58×10^2
5	7.49×10^{-4}	1.20×10^{-5}	1.20×10^{-5}	62	1.98×10^2



$k_2 = 2.65 \times 10^5$ M^{-1} s^{-1}.

Table 3.21. Rate constants for the reaction of indole (**1a**) with $(mpa)_2CH^+BF_4^-$ (**4a**-BF_4). (J&M technique, λ = 622 nm, 20 °C, in CH_3CN).

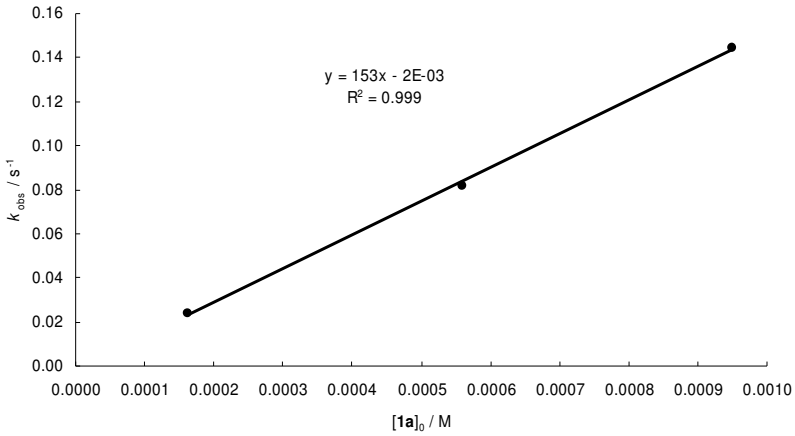
no.	$[\mathbf{1a}]_0$ / M	$[\mathbf{4a}]_0$ / M	$[\mathbf{1a}]_0$ / $[\mathbf{4a}]_0$	Conv. / %	k_{obs} / s^{-1}
1	4.75×10^{-4}	9.46×10^{-6}	50	99	9.19×10^{-4}
2	8.30×10^{-4}	9.92×10^{-6}	80	99	1.76×10^{-3}
3	1.04×10^{-3}	1.04×10^{-5}	100	41	2.19×10^{-3}
4	1.26×10^{-3}	9.79×10^{-6}	130	84	2.69×10^{-3}
5	1.59×10^{-3}	9.82×10^{-6}	160	96	3.22×10^{-3}



$k_2 = 2.08 \times 10^0$ M^{-1} s^{-1}.

Table 3.22. Rate constants for the reaction of indole (**1a**) with $(dpa)_2CH^+BF_4^-$ (**4b**-BF_4). (J&M technique, λ = 672 nm, 20 °C, in CH_3CN).

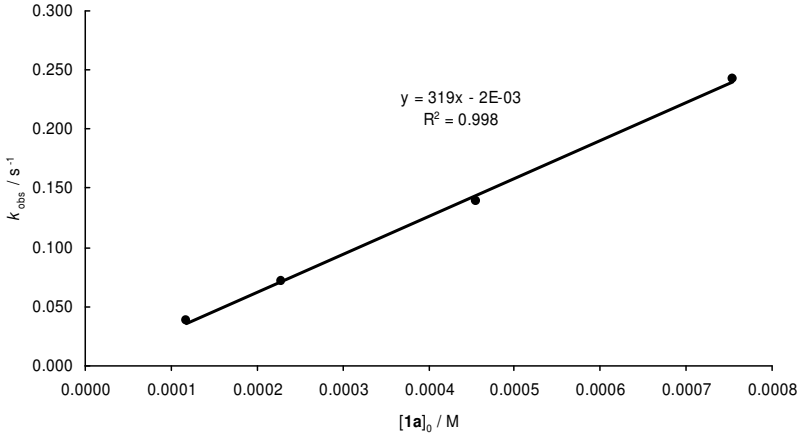
no.	$[\mathbf{1a}]_0$ / M	$[\mathbf{4b}]_0$ / M	$[\mathbf{1a}]_0$ / $[\mathbf{4b}]_0$	Conv. / %	k_{obs} / s^{-1}
1	1.63×10^{-4}	1.50×10^{-5}	11	62	2.36×10^{-2}
2	5.59×10^{-4}	1.40×10^{-5}	40	99	8.20×10^{-2}
3	9.49×10^{-3}	1.54×10^{-5}	62	99	1.44×10^{-2}



$k_2 = 1.53 \times 10^2$ M^{-1} s^{-1}.

Table 3.23. Rate constants for the reactions of indole (**1a**) with $(pfa)_2CH^+BF_4^-$ (**4d**-BF_4). (J&M technique, λ = 601 nm, 20 °C, in CH_3CN).

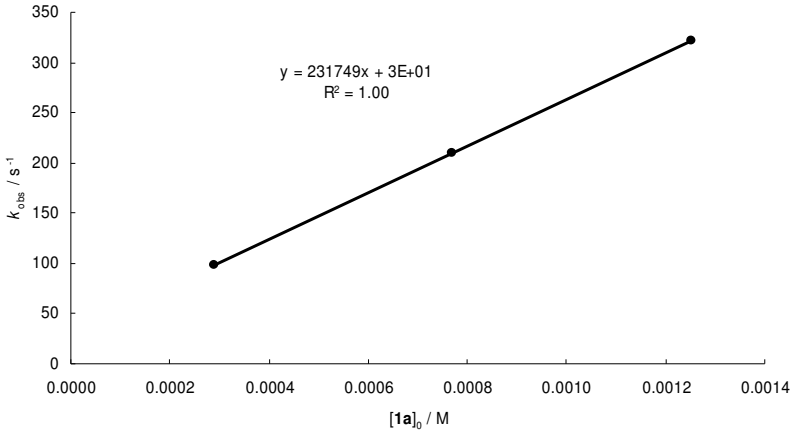
no.	$[\mathbf{1a}]_0$ / M	$[\mathbf{4d}]_0$ / M	$[\mathbf{1a}]_0$ / $[\mathbf{4d}]_0$	Conv. / %	k_{obs} / s^{-1}
1	1.17×10^{-4}	1.27×10^{-5}	9	98	3.82×10^{-2}
2	2.29×10^{-4}	1.25×10^{-5}	18	99	7.17×10^{-2}
3	4.56×10^{-4}	1.24×10^{-5}	37	60	1.39×10^{-1}
4	7.55×10^{-4}	1.26×10^{-5}	60	53	2.43×10^{-1}



$k_2 = 3.19 \times 10^2$ M^{-1} s^{-1}.

Table 3.24. Rate constants for the reaction of indole (**1a**) with $(fur)_2CHCl$ (**4e**-Cl). [Stopped Flow technique, λ = 535 nm, 20 °C, in CF_3CH_2OH/CH_3CN (v/v = 91/9)].

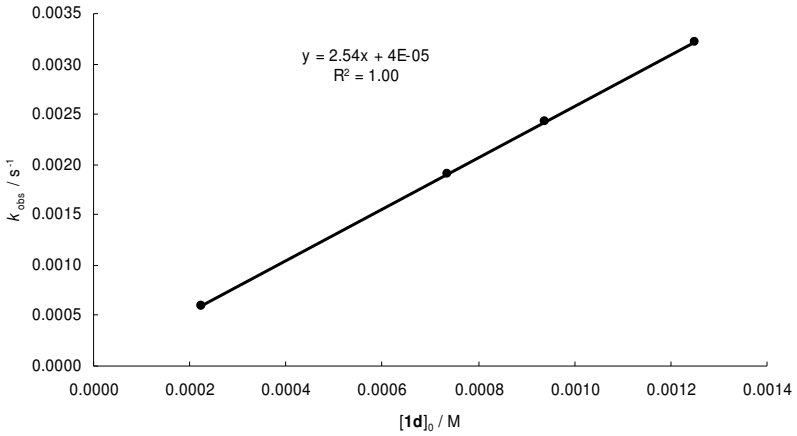
no.	$[\mathbf{1a}]_0$ / M	$[\mathbf{4e}\text{-Cl}]_0$ / M	$[\mathbf{1a}]_0$ / $[\mathbf{4e}]_0$	k_{obs} / s^{-1}
1	2.89×10^{-4}	2.15×10^{-5}	13	9.94×10^{1}
2	7.70×10^{-4}	2.15×10^{-5}	36	2.11×10^{2}
3	1.25×10^{-3}	2.15×10^{-5}	58	3.22×10^{2}



$k_2 = 2.31 \times 10^5$ M^{-1} s^{-1}.

Table 3.25. Rate constants for the reactions of 5-cyanoindole (**1d**) with $(pfa)_2CH^+BF_4^-$ (**4d**-BF_4). (J&M technique, λ = 601 nm, 20 °C, in CH_3CN).

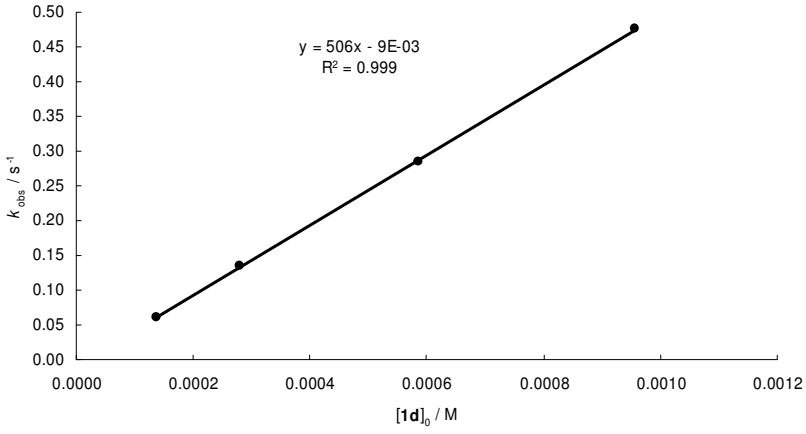
no.	$[\mathbf{1d}]_0$ / M	$[\mathbf{4d}]_0$ / M	$[\mathbf{1d}]_0$ / $[\mathbf{4d}]_0$	Conv. / %	k_{obs} / s^{-1}
1	2.23×10^{-4}	1.16×10^{-5}	19	72	6.01×10^{-2}
2	7.37×10^{-4}	1.18×10^{-5}	63	79	1.34×10^{-1}
3	9.39×10^{-4}	1.15×10^{-5}	82	99	2.84×10^{-1}
4	1.25×10^{-3}	1.24×10^{-5}	101	87	4.76×10^{-1}



$k_2 = 2.54 \times 10^0$ M^{-1} s^{-1}.

Table 3.26. Rate constants for the reaction of 5-cyanoindole (**1d**) with $(fur)_2CHCl$ (**4e**-Cl) and trimethylsilyltriflate (TMSOTf).
(J&M technique, λ = 535 nm, 20 °C, in CH_3CN).

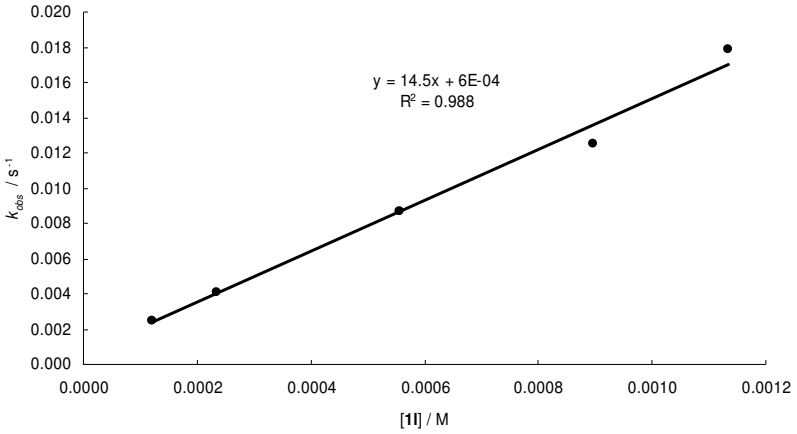
no.	[**1d**]$_0$ / M	[**4e**-Cl]$_0$ / M	[**1d**]$_0$ / [**4e**]$_0$	[TMSOTf]$_0$ / M	Conv./%	k_{obs} / s^{-1}
1	1.37×10^{-4}	2.81×10^{-5}	5	5.62×10^{-5}	91	6.01×10^{-2}
2	2.79×10^{-4}	2.85×10^{-5}	10	5.70×10^{-5}	68	1.34×10^{-1}
3	5.85×10^{-4}	2.76×10^{-5}	21	5.52×10^{-5}	90	2.84×10^{-1}
4	9.55×10^{-4}	3.26×10^{-5}	29	6.52×10^{-5}	78	4.76×10^{-1}



$k_2 = 5.06 \times 10^2$ M^{-1} s^{-1}.

Table 3.27. Rate constants for the reactions of 1,2-dimethylindole (**1l**) with $(pyr)_2CH^+BF_4^-$ (**4f**-BF_4).
(J&M technique, λ = 620 nm, 20 °C, in CH_3CN).

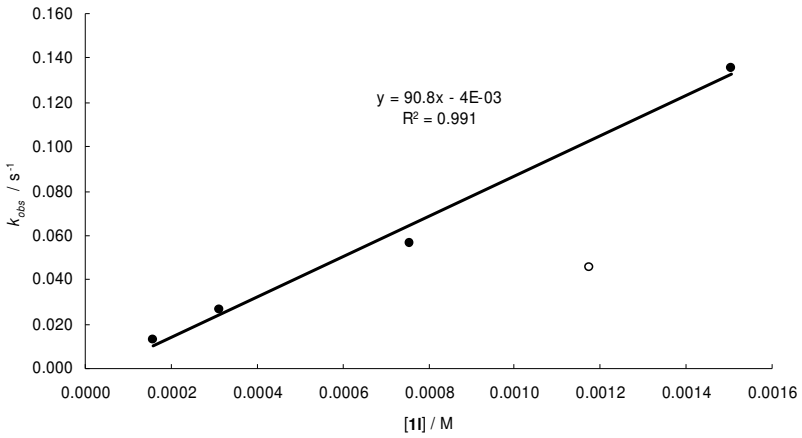
no.	$[\mathbf{1l}]_0$ / M	$[\mathbf{4f}]_0$ / M	$[\mathbf{1l}]_0$ / $[\mathbf{4f}]_0$	Conv. / %	k_{obs} / s^{-1}
1	1.20×10^{-4}	1.12×10^{-5}	11	92	2.49×10^{-3}
2	2.35×10^{-4}	1.09×10^{-5}	22	83	4.13×10^{-3}
3	5.56×10^{-4}	1.11×10^{-5}	50	82	8.70×10^{-3}
4	8.96×10^{-4}	1.09×10^{-5}	83	74	1.25×10^{-2}
5	1.13×10^{-3}	1.13×10^{-5}	101	71	1.79×10^{-2}



$k_2 = 1.45 \times 10^1$ $M^{-1}s^{-1}$.

Table 3.28. Rate constants for the reactions of 1,2-dimethylindole (**1l**) with $(dma)_2CH^+BF_4^-$ (**4g**-BF_4).
(J&M technique, λ = 613 nm, 20 °C, in CH_3CN).

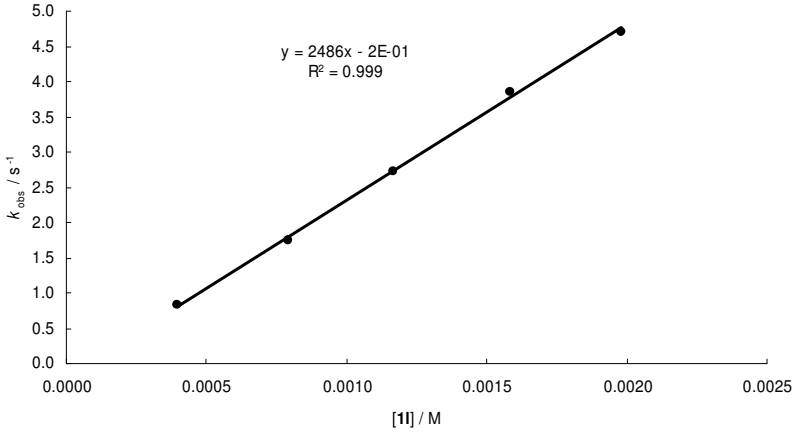
no.	$[\mathbf{1l}]_0$ / M	$[\mathbf{4g}]_0$ / M	$[\mathbf{1l}]_0$ / $[\mathbf{4g}]_0$	Conv. / %	k_{obs} / s^{-1}
1	1.59×10^{-4}	1.46×10^{-5}	11	98	1.30×10^{-2}
2	3.13×10^{-4}	1.44×10^{-5}	22	93	2.64×10^{-2}
3	7.55×10^{-4}	1.46×10^{-5}	52	88	5.64×10^{-2}
4	1.18×10^{-3}	1.44×10^{-5}	82	62	4.56×10^{-2}
5	1.50×10^{-3}	1.50×10^{-5}	101	95	1.36×10^{-1}



$k_2 = 9.08 \times 10^1$ M^{-1}s^{-1}.

Table 3.29. Rate constants for the reactions of 1,2-dimethylindole (**1l**) with $(mpa)_2CH^+BF_4^-$ (**4a**-BF_4).
(Stopped flow technique, λ = 622 nm, 20 °C, in CH_3CN).

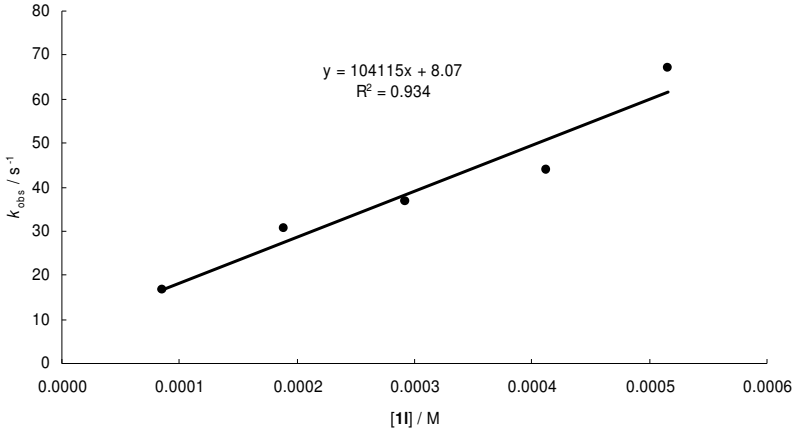
no.	$[\mathbf{1l}]_0$ / M	$[\mathbf{4a}]_0$ / M	$[\mathbf{1l}]_0$ / $[\mathbf{4a}]_0$	k_{obs} / s^{-1}
1	3.96×10^{-4}	2.51×10^{-5}	16	8.28×10^{-1}
2	7.93×10^{-4}	2.51×10^{-5}	32	1.75×10^{0}
3	1.17×10^{-3}	2.51×10^{-5}	47	2.73×10^{0}
4	1.59×10^{-3}	2.51×10^{-5}	63	3.86×10^{0}
5	1.98×10^{-3}	2.51×10^{-5}	79	4.70×10^{0}



$k_2 = 2.49 \times 10^3$ M^{-1}s^{-1}.

Table 3.30. Rate constants for the reactions of 1,2-dimethylindole (**1l**) with $(dpa)_2CH^+BF_4^-$ (**4b**-BF_4).
(Stopped flow technique, λ = 672 nm, 20 °C, in CH_3CN).

no.	$[\mathbf{1l}]_0$ / M	$[\mathbf{4b}]_0$ / M	$[\mathbf{1l}]_0$ / $[\mathbf{4b}]_0$	k_{obs} / s^{-1}
1	8.60×10^{-5}	4.95×10^{-6}	17	1.67×10^{1}
2	1.89×10^{-4}	4.95×10^{-6}	38	3.05×10^{1}
3	2.92×10^{-4}	4.95×10^{-6}	59	3.67×10^{1}
4	4.12×10^{-4}	4.95×10^{-6}	83	4.38×10^{1}
5	5.15×10^{-4}	4.95×10^{-6}	104	6.69×10^{1}

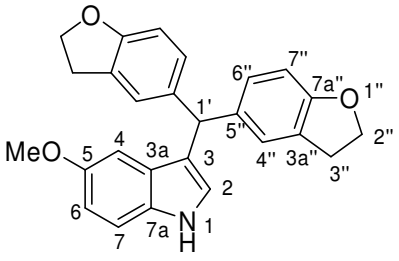


$k_2 = 1.04 \times 10^5$ $M^{-1}s^{-1}$.

3.4.3 Synthetic Experiments

3-[Bis(4-(phenyl(2,2,2-trifluoroethyl)amino)phenyl)methyl]-1*H*-indole (**5a**), 1-methyl-3-[bis(4-(phenyl(2,2,2-trifluoroethyl)amino)phenyl)methyl]-1*H*-indole (**5b**) and 1,2-dimethyl-3-[bis(4-(phenyl(2,2,2-trifluoroethyl)amino)phenyl)methyl]-1*H*-indole (**5d**) are known and characterized compounds.[15]

3-[Bis(2,3-dihydrobenzofuran-5-yl)methyl]-5-methoxy-1*H*-indole (**5c**)

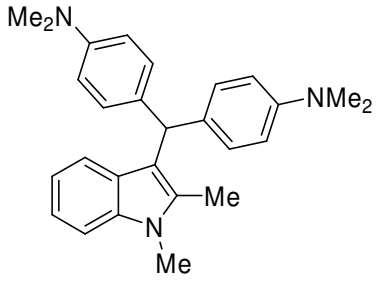


5c

A solution of $(fur)_2CHCl$ (**4e**–Cl, 85.3 mg, 0.297 mmol) and trimethylsilyl triflate (108 µL, 0.594 mmol) in dichloromethane (100 mL) was added dropwise to a stirred solution of 5-methoxyindole (**1c**, 437 mg, 2.97 mmol) in dichloromethane (200 mL). After the complete addition the solvent was removed *in vacuo* to give a yellow oil that was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 5:1) to yield **5c** as a colorless solid (69.1 mg, 0.174 mmol, 58 % yield).

R_f = 0.09. ^{1}H-NMR (400 MHz, CD_3CN): δ = 3.08 (t, J = 8.6 Hz, 4 H, H-3''), 3.64 (s, 3 H, OMe), 4.47 (t, J = 8.6 Hz, 4 H, H-2''), 5.48 (s, 1 H, H-1'), 6.63 (d, J = 8.0 Hz, 2 H, H-7''), 6.66 (m, 2 H, H-2, H-4), 6.76 (dd, J = 8.8 Hz, 2.4 Hz, 1 H, H-6), 6.95 (dd, J = 8.0 Hz, 2.0 Hz, 2 H, H-6''), 7.08 (s, 2 H, H-4''), 7.27 (d, J = 8.8 Hz, 1 H, H-7), 8.93 (br. s, 1 H, NH). ^{13}C-NMR (CD_3CN, 100 MHz): δ = 29.1 (2 t, C-3''), 47.2 (d, C-1'), 54.9 (q, OMe), 70.8 (2 t, C-2''), 101.4 (d, C-2), 108.0 (2 d, C-7''), 110.9 (d, C-6), 111.7 (d, C-7), 117.0 (s, C-3a), 120.0 (s, C-3), 124.4 (d, C-4), 124.9 (2 d, C-4''), 127.0 (2 s, C-3a''), 127.7 (2 d, C-6''), 131.8 (s, C-3a), 136.7 (2 s, C-5''), 153.2 (s, C-5), 158.1 (2 s, 2 C-7a''). Peak assignment is based on gHMBC, gHSQC, COSY and NOESY experiments.

3-[Bis-(4-dimethylaminophenyl)methyl]-1,2-dimethyl-1*H*-indole (**5e**)



5e

To a cooled solution of $(dma)_2CH^+BF_4^-$ (**4g**-BF_4, 70.0 mg, 0.276 mmol) in CH_3CN (20 mL, –15 °C) a solution of 1,2-dimethylindole (**1l**, 42.5 mg, 0.293 mmol) in CH_3CN (50 mL) is droped until the blue color of the solution faded completely. The clear reaction mixture is poured onto ice-water (50 mL) and saturated NaCl solution (1 mL) is added. The acetonitrile layer was separated at low temperature, dried ($MgSO_4$) and the solvent removed *in vacuo*. After purification by column chromatography (SiO_2, hexanes/ethyl acetate = 3:1) **5e** (66.9 mg, 0.168 mmol, 61 %) was obtained as a slight brown oil which decomposed within a few days to a pink residue.

R_f = 0.24. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 3 H, 2-Me), 2.92 (s, 12 H, 2 × NMe_2), 3.62 (s, 3 H, NMe), 5.62 (s, 1 H, H-8), 6.79 (d, J = 8.8 Hz, 4 H, Ph), 7.02–7.25 (m, 7 H, ArH), 7.50 (d, J = 7.6 Hz, 1 H, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 8.9 (q), 27.7 (q), 40.1 (q), 44.5 (d), 106.9 (d), 112.2 (d), 116.8 (d), 117.9 (d), 118.4 (d), 126.1 (s), 128.0 (d), 131.8 (s), 133.6 (s), 135.0 (s), 135.5 (s), 145.5 (s).

3.5 Literature

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Chapter 4

Nucleophilic Reactivities of Pyrroles

This chapter will be published as soon as possible by M. Westermaier, T. A. Nigst and H. Mayr in *Eur. J. Org. Chem.*

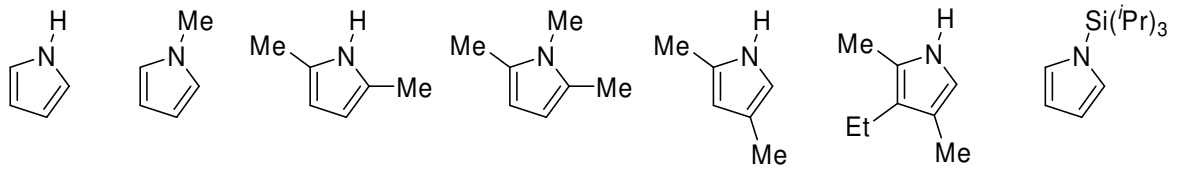
4.1 Introduction

Pyrrole and its derivatives are biochemically important compounds and can be found as substructures in many natural products, e. g. heme, chlorophyll and the pyrrole alkaloids.[1-4] Electrophilic substitutions of pyrroles, which incorporate electron-rich π-systems, have been investigated intensively.[5-12] In 1957, Treibs and Fritz derived a qualitative reactivity scale for alkyl substituted pyrroles from their reactions with diazonium salts of variable electrophilicity.[13] The most comprehensive quantitative comparison of the reactivities of arenes and heteroarenes has been based on the σ^+_{arene} constants, which are defined by the Hammett-Brown relationship (4.1)[14-20]

$$\lg k / k_0 = \rho \cdot \sigma^+_{arene} \tag{4.1}$$

The σ^+_{arene} constants (equivalent to σ^+_p or σ_m in the case of monosubstituted benzenes) are a measure for the relative reactivities of one position of an arene in relation to one position of benzene. They were typically derived by competition experiments, where an electrophile was allowed to select between a pair of arenes, or from the rates of S_N1 reactions of the side chain of the corresponding arenes.

However, σ^+_{arene} parameters have only been determined for few pyrroles, e. g. the parent compound and *N*-methylpyrrole. As knowledge of the nucleophilic reactivities of pyrroles is crucial for their well directed use in synthesis, particularly as nucleophiles in organocatalysis cycles (iminium catalysis),[21-30] we decided to obtain quantitative information on the nucleophilicities of alkyl substituted pyrroles (Scheme 4.1).



1 **2** **3** **4** **5** **6** **7**

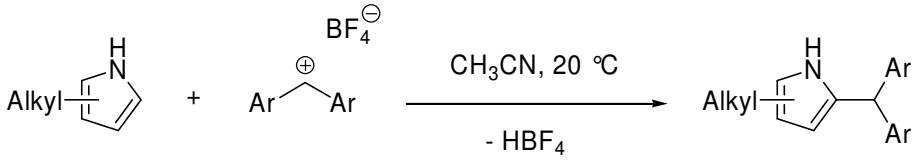
Scheme 4.1. Alkyl substituted pyrroles.

We have previously reported that the reactions of carbocations with π-systems follow Equation (4.2),

$$\lg k(20°C) = s(N + E) \tag{4.2}$$

where electrophiles are characterized by one parameter (electrophilicity E) and nucleophiles are characterized by two parameters (nucleophilicity N and slope s).[31-35] Recently, it has been demonstrated that Equation (4.2) can also be employed for S_N2 reactions, if an additional, electrophile-specific parameter s_E is considered.[36]

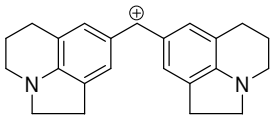
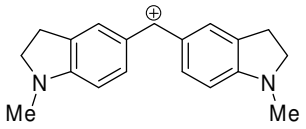
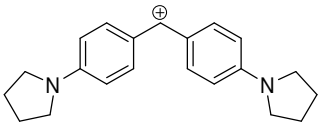
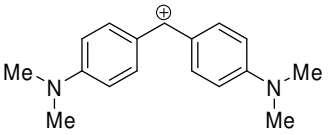
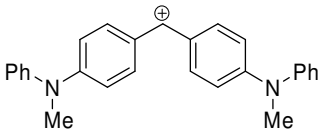
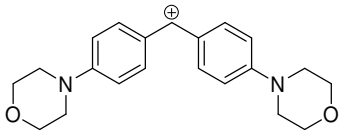
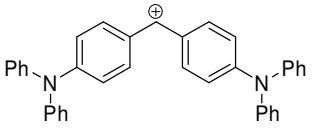
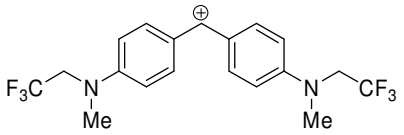
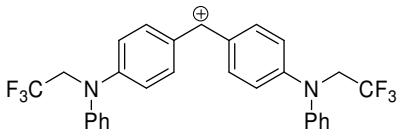
N and s parameters of N-methylpyrrole (**2**)[33] and N-(triisopropylsilyl)pyrrole (**7**)[37] have already been determined in dichloromethane and the N parameter of the parent compound (**1**) has been estimated.[37] We have now studied the reactions of four alkyl substituted pyrroles **3**–**6** with a series of benzhydrylium ions **8** (for structures see Table 4.1) in acetonitrile (Scheme 4.2) and used the kinetic data to determine the N and s parameters of these pyrroles.



3–6 **8** **9–12**

Scheme 4.2. Reactions of pyrroles **3**–**6** with benzhydrylium ions **8** in CH_3CN at 20 °C.

Table 4.1. List of carbocations **8** used in this study as reference electrophiles.

reference electrophile[a]		E[b]
	**8a**	–10.04
	**8b**	–8.76
	**8c**	–7.69
	**8d**	–7.02
	**8e**	–5.89
	**8f**	–5.53
	**8g**	–4.72
	**8h**	–3.85
	**8i**	–3.14

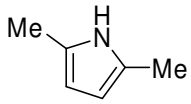
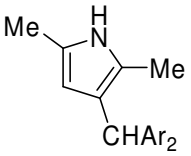
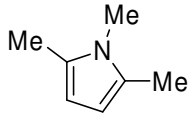
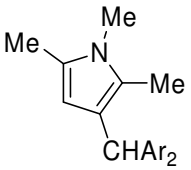
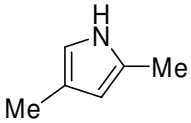
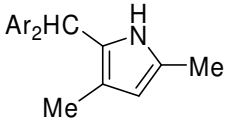
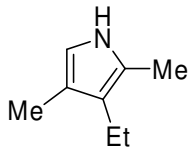
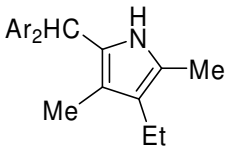
[a] All benzhydrylium ions were used as tetrafluoroborate salts.
[b] Electrophilicity parameters E taken from ref. [33].

4.2 Results and Discussion

4.2.1 Reaction Products

Product studies have been performed with the 4,4'-bis(dimethylamino)benzhydrylium ion [$(dma)_2CH^+$, **8d**, $E = -7.02$] because it is easy accessible and gives fast reactions with most of the pyrroles **3**–**6**. When the corresponding tetrafluoroborate, $(dma)_2CH^+BF_4^-$ (**8d**-BF_4), was combined with the pyrroles **3**–**6** in acetonitrile at room temperature, complex product mixtures were obtained as shown by their NMR spectra. The adducts **9**–**11** were synthesized by dropping a solution of benzhydrylium tetrafluoroborate **8d**-BF_4 in acetonitrile to a vigorously stirred solution of the corresponding pyrrole (two equivalents) in acetonitrile at –15 °C. **12** was synthesized by dropping a solution of kryptopyrrole (**6**) to a cooled solution of **8d**-BF_4 until the color faded (Table 4.2).

Table 4.2. Products **9**–**12** of the reactions of pyrroles **3**–**6** with the 4,4'-bis(dimethylamino)benzhydrylium tetrafluoroborate (**8d**-BF_4^-) in CH_3CN at –15 °C.

pyrrole		product[a]		yield / %
	**3**		**9**	65
	**4**		**10**	68
	**5**		**11**	93
	**6**		**12**	78

[a] Ar = *p*-Me_2N-C_6H_4.

The reaction products are highly sensitive against oxidation, light and heating and usually could not be stored for longer than several minutes before turning into pink oils. The NMR spectra of these oils, however, only show very little impurities and indicate convincingly the structures of **9**–**12** (Figure 4.1, for detailed information see also pages 79–82 in the Experimental Section). The products of the reactions of pyrroles **1**, **2**, and **7** with benzhydrylium ions **8** have been characterized previously.[33, 37, 38]

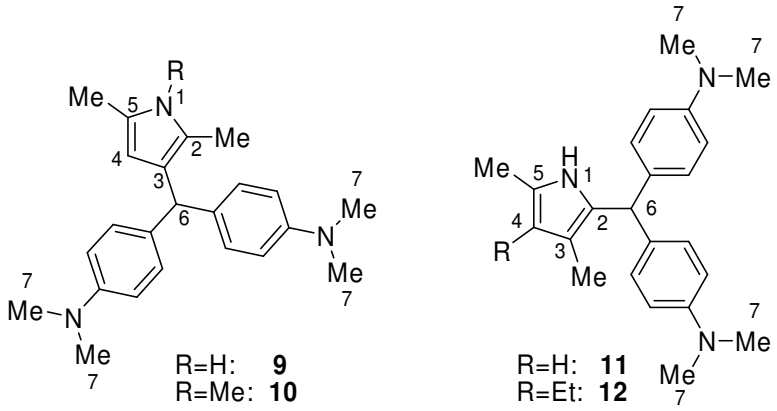


Figure 4.1. Products **9**–**12** of the reactions of pyrroles **3**–**6** with benzhydrylium ion **8d** in CH_3CN at –15 °C.

While pyrroles **3**, **4** and **6** have only one site for the attack, pyrrole **5** may in principle be attacked at C-3 and C-5. From the NMR spectra we can derive that regioselective substitution of 5-H took place.

Evidence for the formation of the adducts **9**–**12** is given by ^{1}H- and ^{13}C-NMR experiments. The proton H-6 absorbs as singlet at δ 5.13–5.16 ppm, if the pyrrole skeleton is substituted at the 3-position (in compounds **9** and **10**) and at δ 5.33–5.36 ppm, if the pyrrole ring is substituted at the 2-position (in compounds **11** and **12**). In the ^{13}C-NMR spectra of **9**, **10** and **12** C-6 absorbs at δ 45.1–45.2 ppm and in compound **11** at δ 46.5 ppm (Table 4.3).

Table 4.3. Chemical shifts δ (in ppm) of 6-H (singlet) and C-6 atom of **9**–**12** (in $CDCl_3$).

compound	$\delta_{6\text{-H}}$ / ppm	$\delta_{6\text{-C}}$ / ppm
9	5.13	45.1
10	5.16	45.3
11	5.33	46.5
12	5.36	45.2

4.2.2 Reactions of Pyrroles with Benzhydrylium Ions

The kinetics of the reactions of pyrroles **3**–**6** with benzhydrylium ions **8** were monitored by UV/Vis spectroscopy at 20 °C with the previously described instruments.[32-34] The pyrroles **3**–**6** were used in high excess (usually more than 10 equivalents) to keep their concentrations almost constant throughout the reactions. Exponential decay of the absorbances of the benzhydrylium ions **8** was observed for all reactions and linear correlations of the observed rate constants and the pyrrole concentrations have been obtained (as demonstrated in Figure 4.2 for the combination of **4** with **8b**).

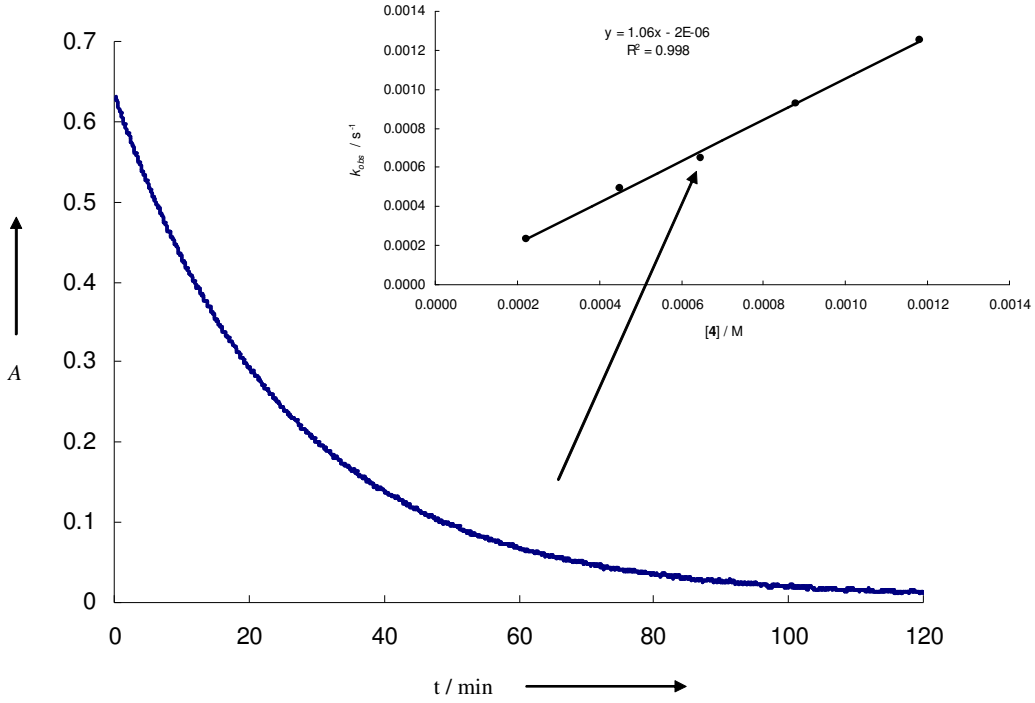
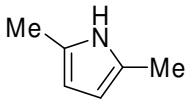
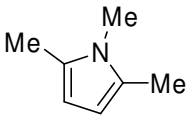
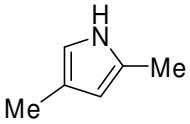
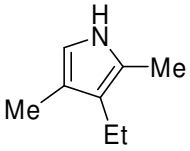


Figure 4.2. Exponential decay of the absorbance at 625 nm during the reaction of **4** with **8b**. Correlation of the first-order rate constants k_{obs} with the concentrations of **4** (in the insert) is linear with a slope corresponding to the second-order rate constant k_2.

The resulting second-order rate constants are listed in Table 4.4.

Table 4.4. Second-order rate constants k_2 for the reactions of the pyrroles **3**–**6** with the benzhydrylium ions **8** in CH_3CN at 20 °C and resulting *N*- and *s*-parameters.

pyrrole	*N* / *s*	benzhydrylium ion	k_2 / $M^{-1}s^{-1}$
 **3**	8.01 / 0.97	$(pyr)_2CH^+$ (**8c**)	1.39×10^0
		$(mpa)_2CH^+$ (**8e**)	2.19×10^2
		$(mor)_2CH^+$ (**8f**)	2.53×10^2
		$(dpa)_2CH^+$ (**8g**)	3.88×10^4 [a]
		$(mfa)_2CH^+$ (**8h**)	7.32×10^3
 **4**	8.69 / 1.07	$(ind)_2CH^+$ (**8b**)	1.06×10^0
		$(pyr)_2CH^+$ (**8c**)	7.72×10^0
		$(mpa)_2CH^+$ (**8e**)	1.59×10^3
		$(mor)_2CH^+$ (**8f**)	1.72×10^3
		$(dpa)_2CH^+$ (**8g**)	1.15×10^5 [a]
 **5**	10.49 / 0.96	$(lil)_2CH^+$ (**8a**)	3.78×10^0
		$(ind)_2CH^+$ (**8b**)	4.41×10^1
		$(pyr)_2CH^+$ (**8c**)	3.18×10^2
		$(mpa)_2CH^+$ (**8e**)	4.50×10^4
		$(mor)_2CH^+$ (**8f**)	4.66×10^4
		$(dpa)_2CH^+$ (**8g**)	2.28×10^6 [a]
 **6**	11.63 / 0.95	$(lil)_2CH^+$ (**8a**)	4.00×10^1
		$(ind)_2CH^+$ (**8b**)	4.53×10^2
		$(pyr)_2CH^+$ (**8c**)	3.83×10^3
		$(mpa)_2CH^+$ (**8e**)	6.53×10^5
		$(mor)_2CH^+$ (**8f**)	4.48×10^5

[a] The k_2 values for the reactions of **3**–**5** with $(dpa)_2CH^+$ (**8g**) deviate significantly from the linear correlation and have not been used for the determination of *N* and *s*.

For the reactions of 2,5-dimethylpyrrole (**3**) with $(dpa)_2CH^+$ (**8g**) pseudo-first order rate laws were only obeyed during the first three to four half-lives when the nucleophile was employed in higher excess ([**3**]/[**8g**] > 80). Possibly, the rate determining step is changing and deprotonation of the σ-complex becomes rate limiting in this case. Similar observations have been made when less than 20 equivalents of 1,2,5-trimethylpyrrole (**5**) were combined with $(mpa)_2CH^+$ (**8e**).

When 1,2,5-trimethylpyrrole (**4**) reacted with $(mpa)_2CH^+BF_4^-$ (**8e**) in dichloromethane we obtained complex kinetics and even addition of an equimolar amount of the non-nucleophilic base *N*-methylmorpholine[39, 40] resulted in complex kinetics that deviated from a first order behavior. The evaluation of the first three half-lives of these reactions resulted in $k_2 = 1.59 \times 10^3$ $M^{-1}s^{-1}$. When the same reactions were performed in acetonitrile solution, perfect first-order kinetics were obtained and the resulting k_2 value is the same than the one in dichloromethane. A reactivity increase from dichloromethane to acetonitrile, as observed for the reactions of benzhydrylium ions with indoles (factor 2 to 3),[41] therefore, does not occur in the analogoues reactions of pyrroles.

The kinetics of the reactions of **5** with benzhydrylium ions **8** should be handled with care and are considered preliminary, as problems occurred when we wanted to reproduce these data.

When we plotted the second-order rate constants k_2 (as listed in Table 4.4) and the previously reported rate constants for the analogous reactions of *N*-methylpyrrole (**2**) against the electrophilicity parameters *E* of the benzhydrylium ions **8**, linear correlations were obtained (Figure 4.3) that allowed the evaluation of the *N* and *s* parameters according to Equation (4.2). All correlation lines have slopes close to 1, i. e. the relative reactivities of the pyrroles are almost independent of the reaction partner. If a slope of 1.0 is also assumed for the parent pyrrole (**1**), one can calculate $N = 4.63$ for the unsubstituted pyrrole (**1**) from the previously published rate constant for its reaction with $(pfa)_2CH^+$ (**8i**), $k_2 = 31.2$ $M^{-1}s^1$ in dichloromethane. For a slope of 1.0, the range from $N = 4.63$ (**1**) to $N = 11.63$ (**6**) corresponds to an increase of reactivity by a factor of 10 million by the three alkyl groups in **6**.

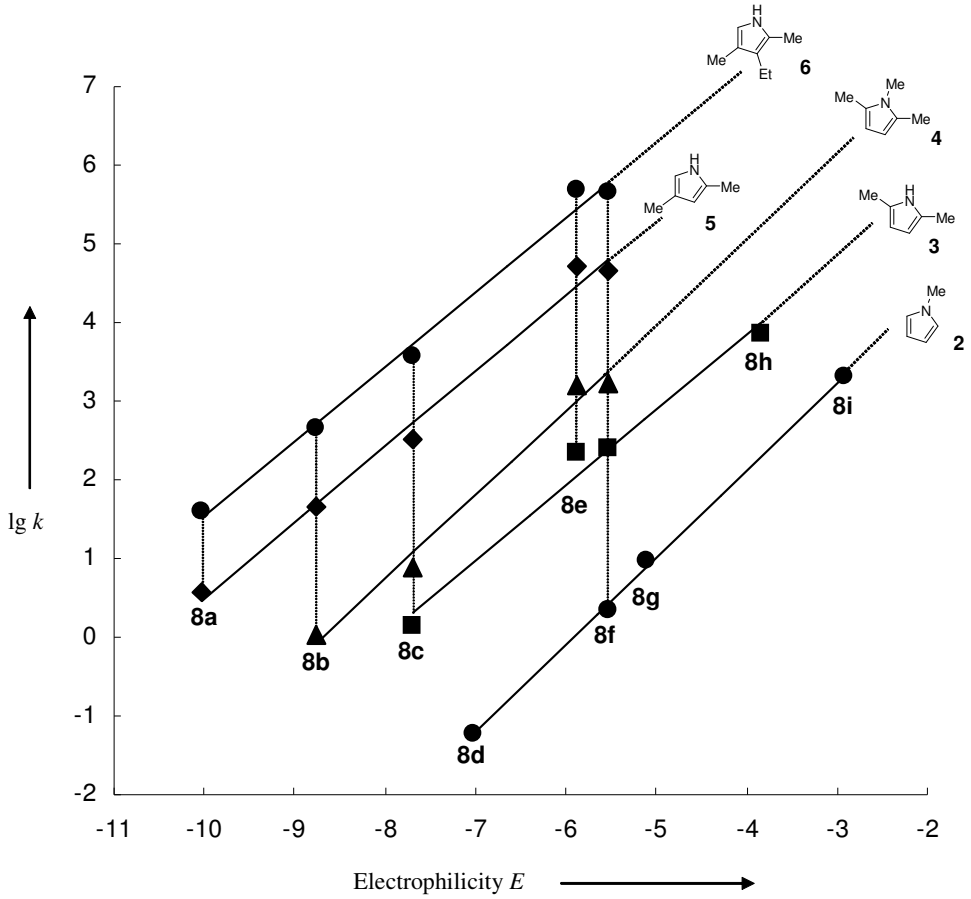


Figure 4.3. Correlation of the rate constants lg k_2 (20 °C, in CH_3CN) for the reactions of **2**–**6** with benzhydrylium ions **8** in relation to their electrophilicity parameters *E*; the values for *N*-methylpyrrole (**2**) are taken from ref. [33].

When we plotted the *N* values of the pyrroles **1**–**7** against the corresponding pK_{aH} values (Table 4.5), a linear correlation is observed ($N = 0.885pK_{aH} + 8.506$, $r^2 = 0.973$, Figure 4.4).

Table 4.5. pK_{aH}(H_2O) of the pyrroles **1**–**6** from refs. [42, 43].

	1	**2**	**3**	**4**	**5**	**6**
pK_{aH}	–3.80	–2.90	–1.07[a]	–0.49[a]	2.55	3.75

[a] pK_{aH} values for β protonation in acidic aqueous solution; the values differ from the values reported by Butler *et al*. (pK_{aH}(**3**) = –0.71 and pK_{aH}(**4**) = –0.10, taken from ref. [11, 12]).

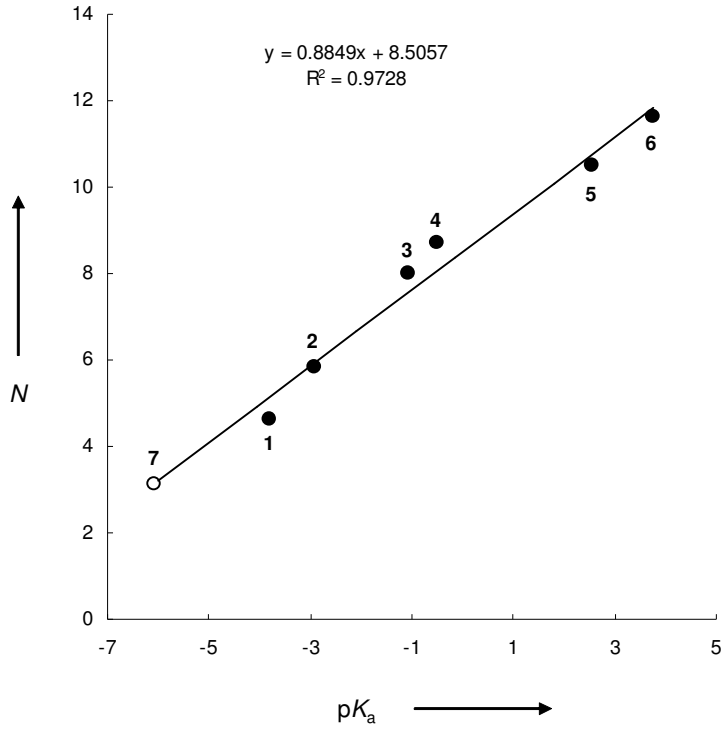


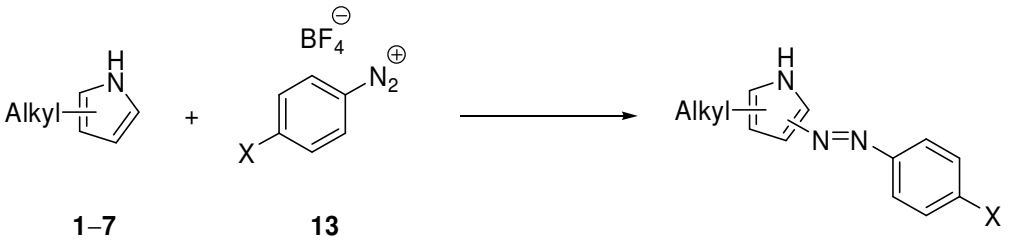
Figure 4.4. Correlation of the nucleophilicity parameters *N* of pyrroles **1**–**7** with the corresponding pK_{aH} values (taken from refs. [42, 43], for **7** the line was extrapolated).

The slope of the line in Figure 4.4 corresponds directly to the Brønsted parameter for pyrroles as the average *s* parameter of the pyrroles equals 1. We can thus conclude that 88% of the changes of basicities of pyrroles are found as changes of nucleophilicity.

Figure 4.4 can be used for indirect determination of the basicity of pyrroles whose pK_{aH} values cannot be determined from equilibrium studies in strong acidic media, where pyrroles tend to oligomerize rapidly. The pK_{aH} value of *N*-(triisopropylsilyl)pyrrole (**7**) derived from Figure 4.4 is –6.09. This value reflects the strong electron-withdrawing effect of the triisopropylsilyl group at the nitrogen atom.

4.2.3 Reactions of Pyrroles with Other Electrophiles

In 1977 Butler *et al*. reported on the rate constants of the reactions of pyrroles **1**–**6** with various *p*-substituted arenediazonium ions **13** in acidic solution (Scheme 4.3).[12]



1–7 **13**

Scheme 4.3. Reactions of pyrroles **1**–**6** with differently substituted aryldiazonium salts **13**.

Previously, we determined the rates of the reactions of various nucleophiles with arenediazonium salts in dichloromethane and determined the electrophilicity parameters *E* according to Equation (4.2).[44] From these data we can now calculate rate constants which are directly comparable to those reported by Butler (Table 4.6).

Table 4.6. Comparison of the rate constants for the reactions of pyrroles **1**–**6** with aryldiazonium salts **13** obtained by Butler[12] and calculated by Equation (4.2).

pyrrole	X = OMe (**13a**) (E = –8.4)[a]		X = H (**13b**) (E = –7.2)[a]		X = NO_2 (**13c**) (E = –5.1)[a]	
	k / $M^{-1}s^{-1}$ [b]	k_{calc} / $M^{-1}s^{-1}$ [c]	k / $M^{-1}s^{-1}$ [b]	k_{calc} / $M^{-1}s^{-1}$ [c]	k / $M^{-1}s^{-1}$ [b]	k_{calc} / $M^{-1}s^{-1}$ [c]
1	2.8	0.0002	6.8	0.003	220	0.33
2	10.9	0.003	25.2	0.05	1000	5.35
3	9.8	0.39	32.5	6.98	–[d]	622
4	11.8	1.87	24.4	24.7	1600	2265
5	6800	154	13400	2738	–[d]	152757
6	30500	2336	177000	42813	–[d]	1496236

[a] Electrophilicity parameters *E* taken from ref. [45]. [b] Rate constants taken from ref. [12].
[c] Calculated rate constants using Equation (4.2). [d] Not determined.

While calculated and experimental data for the azo-couplings with pyrroles **3**–**6** agree remarkably well within a factor of 2 to 20, the reported rate constants for the reactions with pyrrole (**1**) and *N*-methylpyrrole (**2**) are 190 to 14000 times larger than the calculated values. In view of the approximate nature of Equation (4.2) we do not want to claim that there is something wrong with the experimental data. However, it is at least surprising that the decrease of basicitiy from **3** and **4** to **1** and **2** is not accompanied by a reduced reactivity towards diazonium salts.

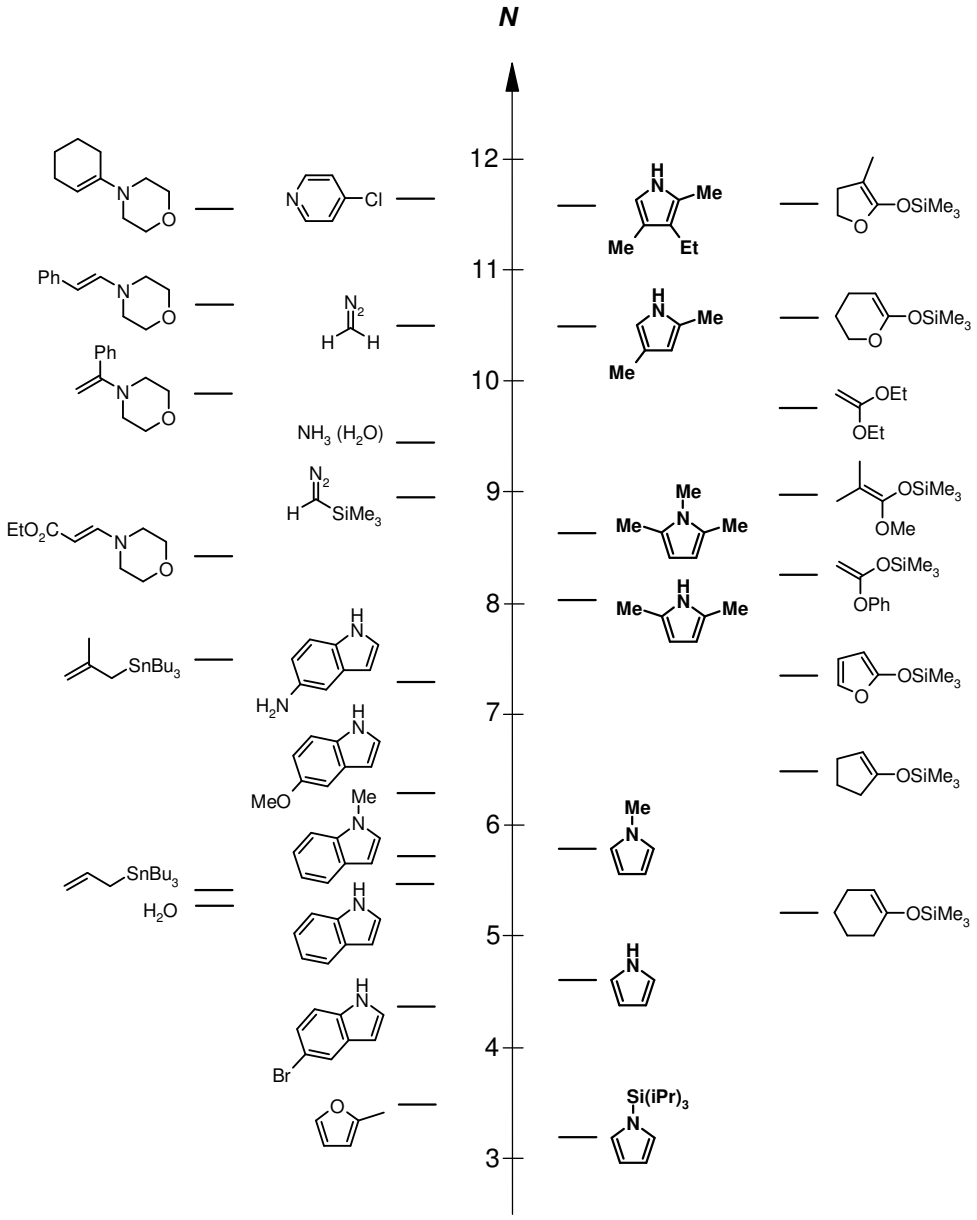
Mitsumura *et al*. reported on rate constants for the reactions of pyrrole (**1**) and *N*-methylpyrrole (**2**) in buffered aqueous solutions (pH = 6.3) at 20 °C[46] and obtained even higher values for the reactions with **13a** and **13b** than Butler. The reaction of **1** and **2** with **13a** is 5 times faster and the reaction with **13b** about 50 times faster. The rates of the reactions of pyrroles in aqueous solution with arenediazonium salts are therefore strongly depending on the pH value.

4.3 Conclusion

The second-order rate constants of the reactions of four alkyl substituted pyrroles **3**–**6** with a series of benzhydrylium ions **8** have been determined in acetonitrile solution. The linear correlation of the logarithms of these k_2 values with the electrophilicity parameters E allowed the determination of the N and s values of **3**–**6** according to Equation (4.2). With these findings a direct comparison of the nucleophilic reactivities of these π-excessive heterocycles with other nucleophiles became possible and the pyrroles were integrated into the comprehensive scale of nucleophilicity, covering a range of almost 9 orders of magnitude (Scheme 4.4).

Thus, highly reactive alkyl-substituted pyrroles, such as kryptopyrrole (**6**, N = 11.63), show similar nucleophilic reactivity as enamines or silylketenacetals. The less reactive pyrroles show reactivities as other heterocycles (indoles) or silyl enol ethers.

Since the nucleophilicity of the parent pyrrole (**1**) was only estimated and pyrroles bearing electron-withdrawing groups have not been investigated so far, future research in this field is desireable. Another interesting aspect for future research would be the examination of the reactions of pyrroles **3**–**5** with $(dpa)_2CH^+$ (**8g**) to find out why the rate constants of their combinations deviate from the linear correlation.



Scheme 4.4. *N* ranking of pyrroles (bold) in comparison to other nucleophiles.

4.4 Experimental Section

4.4.1 General

Acetonitrile was bought from Prolabo, kept dry over 3Å molecular sieve, packed under Argon and used as received. Pyrrole (**1**), *N*-methylpyrrole (**2**), 2,5-dimethylpyrrole (**3**), 1,2,5-trimethylpyrrole (**4**), 2,4-dimethylpyrrole (**5**), 3-ethyl-2,4-dimethylpyrrole (**6**), *N*-(triiso-propylsilyl)pyrrole (**7**) and 2,6-di-*tert*-butylpyridine were bought from Acros and distilled prior to use. The tetrafluoroborates of the benzhydrylium ions **8** have been synthesized by literature procedures.[33]

^{1}H-NMR spectra have been recorded on Varian Mercury 200 (200 MHz), Bruker ARX 300 (300 MHz) and Varian VXR 400 (400 MHz). Chemical shifts δ are reported in ppm in relation to the internal standard of the solvent (CD_3CN: 1.94 ppm, $CDCl_3$: 7.24 ppm) or TMS (0.00 ppm) as internal standard. Coupling constants are given in Hz, multiplicities are given as s (singulet), d (dublet), t (triplet), q (quartet) and m (multiplet). Broad signals are symbolized with "br". ^{13}C-NMR spectra were recorded on Bruker ARX 300 (75.5 MHz). Chemical shifts δ are reported in ppm in relation to the solvent signals as internal standard (CD_3CN: 1.3 and 118.4 ppm, $CDCl_3$: 77.0 ppm). Spin multiplicities were assigned according to DEPT135 spectra. Mass spectra have been recorded on MAT 95 Q by direct insertion of the samples. TLC was performed on silica gel 60 F_{254} alumina foils (neutral). The detection was done by UV light (254 or 366 nm).

Slow reactions ($\tau_{1/2}$ > 5 s) were monitored with a J&M TIDAS DAD 2062 diode array spectrophotometer that was controlled by Labcontrol Spectacle software. A Hellma 661.502-QX quartz Suprasil immersion probe (5 mm light path) via fiber optic cables and standard SMA connectors has been used. The kinetic experiments were carried out by dissolving the coloured electrophile and fast injection of the nucleophile solution via a Hamilton syringe.

Fast reactions ($\tau_{1/2}$ < 5 s) were performed on a Hi-Tech SF-61DX2 stopped flow spectrophotometer. The kinetic experiments were initiated by rapidly mixing equal volumes of solutions of the nucleophiles and electrophiles. The observed rate constants k_{obs} have been obtained from at least five runs at each nucleophile concentration.

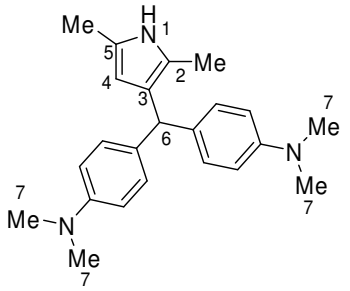
The temperature of all solutions was kept constant during all experiments (± 0.1 °C) by using a circulating bath thermostat and monitored by a thermocouple probe.

For the evaluation of the rate constants, absorption-time curves (which were taken up at wavelengths near to the absorption maxima of the electrophiles) were fitted to the single exponential function $A = A_0 \cdot \exp(-k_{obs}t) + C$.

4.4.2 Synthetic Experiments

The products of the reactions of pyrrole (**1**), *N*-methylpyrrole (**2**) and *N*-(triisopropylsilyl)-pyrrole (**7**) with benzhydrylium ions **8** have been characterized previously.[33,37,38]

2,5-Dimethyl-3-[bis-(4-dimethylaminophenyl)methyl]-1*H*-pyrrole (**9**)



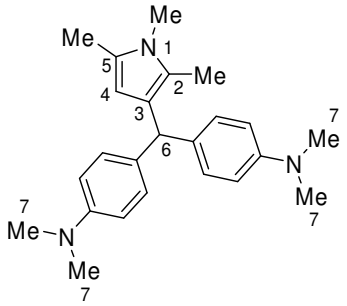
9

2,5-Dimethylpyrrole (**3**, 83 μL, 0.82 mmol) was dissolved in CH_3CN (20 mL) and cooled to –15 °C (ice water/NaCl bath). The benzhydrylium tetrafluoroborate **8d**-BF_4 (136 mg, 0.400 mmol) dissolved in CH_3CN (100 mL) was dropped to the vigorously stirred solution over a period of 3 h, allowing the reaction mixture to decolorize after each drop. The brownish solution was then washed with ice water containing saturated NaCl solution (1 mL) and the phases were separated at low temperature (homogenization upon warm-up). The acetonitril solution was dried over Na_2SO_4 and evaporated (60 °C bath temperature and 1 mbar for 1 h) to yield **9** as a light brown solid (90 mg, 0.26 mmol, 65%) which turned within minutes into a pink oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 2.02 (s, 3 H, 2-Me), 2.14 (s, 3 H, 5-Me), 2.93 (s, 12 H, 7-H), 5.13 (s, 1 H, 6-H), 5.45 (s, 1 H, 4-H), 6.84 (d,

	J = 8 Hz, 4 H, Ph), 7.09 (d, *J* = 8 Hz, 4 H, Ph), 7.58 (br. s, 1 H, NH).
^{13}C-NMR (75.5 MHz, $CDCl_3$)	δ = 9.5 (q), 11.2 (q), 40.2 (q), 45.1 (d), 105.2 (d), 112.4 (d), 120.0 (s), 120.1 (s), 122.8 (s), 127.9 (d), 135.3 (s), 145.2 (s).
EI-MS (70 eV)	*m/z* (%) = 348 (21), 347 (100) [M^+], 346 (39). 333 (17), 332 (52), 253 (17), 228 (16), 227 (71), 225 (43), 211 (15); HR-EI-MS: calcd. for $C_{23}H_{29}N_3$: 347.2361, found 347.2352.

1,2,5-Trimethyl-3-[bis-(4-dimethylaminophenyl)methyl]-1*H*-pyrrole (**10**)



10

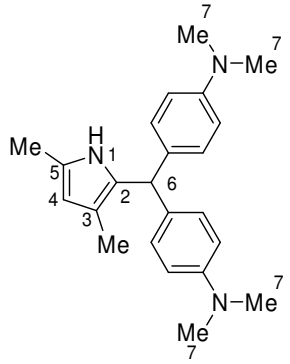
1,2,5-Trimethylpyrrole (**4**, 95 µL, 0.80 mmol) was dissolved in CH_3CN (20 mL) and cooled to –15 °C (ice water/NaCl bath). The benzhydrylium tetrafluoroborate **8d**-BF_4 (136 mg, 0.400 mmol) dissolved in CH_3CN (100 mL) was dropped to the vigorously stirred solution over a period of 1 h, allowing the reaction mixture to decolorize after each drop. The solution was then washed with ice-water (50 mL) containing saturated NaCl solution (1 mL) and the phases were separated at low temperature. The acetonitrile solution was dried over Na_2SO_4 and evaporated (60 °C bath temperature and 1 mbar for 1 h) to yield **10** as a light ochre solid (98 mg, 0.27 mmol, 68%) which turned within minutes into a pink oil.

^{1}H-NMR (300 MHz, $CDCl_3$)	δ = 2.03 (s, 3 H, 2-Me), 2.13 (s, 3 H, 5-Me), 2.95 (s, 12 H, 7-H), 3.34 (s, 3 H, 1-Me), 5.16 (s, 1 H, 6-H), 5.44 (s, 1 H, 4-H), 6.79 (d, *J* = 7 Hz, 4 H, Ph), 7.08 (d, *J* = 7 Hz, 4 H, Ph).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ = 8.5 (q), 10.7 (q), 28.3 (q), 40.2 (q), 45.3 (d), 104.3 (d), 112.1 (d), 119.2 (s), 121.9 (s), 124.4 (s), 127.9 (d), 135.2 (s), 145.3 (s).

EI-MS (70 eV) *m/z* (%) = 361 (42) [M^+], 360 (15), 346 (39), 255 (20), 254 (100), 253 (85), 241 (48), 240 (19), 239 (33), 237 (22), 210 (34), 134 (56), 127 (20), 126 (32), 118 (22), 109 (34), 108 (50); HR-EI-MS: calcd. for $C_{24}H_{31}N_3$: 361.2518, found 361.2516.

3,5-Dimethyl-2-[bis-(4-dimethylaminophenyl)methyl]-1*H*-pyrrole (**11**)



11

2,4-Dimethylpyrrole (**5**, 82 µL, 0.80 mmol) was dissolved in CH_3CN (20 mL) and cooled to –15 °C (ice water/NaCl bath). The benzhydrylium tetrafluoroborate **8d**-BF_4 (136 mg, 0.40 mmol) dissolved in CH_3CN (100 mL) was added in small portions to the vigorously stirred solution within 15 min, allowing the reaction mixture to decolorize after each addition. The solution was then washed with ice-water (50 mL) containing saturated NaCl solution (1 mL) and the phases were separated at low temperature. The acetonitrile solution was dried over Na_2SO_4 and evaporated (60 °C bath temperature and 1 mbar for 1 h) to yield **11** as an almost colorless residue (104 mg, 0.370 mmol, 93%) which turned within minutes into a pink oil.

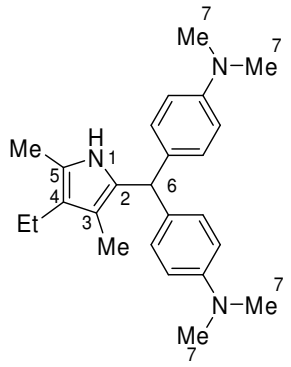
^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.85 (s, 3 H, 5-Me), 2.13 (s, 3 H, 3-Me), 2.94 (s, 12 H, 7-H), 5.33 (s, 1 H, 6-H), 5.70 (s, 1 H, 4-H), 6.73 (d,

J = 8 Hz, 4 H, Ph), 7.00 (d, J = 8 Hz, 4 H, Ph), 7.11 (br. s, 1 H, NH).

^{13}C-NMR (75.5 MHz, $CDCl_3$) δ = 11.1 (q), 13.0 (q), 41.2 (q), 46.5 (d), 108.2 (d), 113.2 (d), 114.5 (s), 124.9 (s), 128.1 (s), 129.5 (d), 132.9 (s), 148.4 (s).

EI-MS (70 eV) *m/z* (%) = 347 (9) [M^+], 255 (20), 254 (100), 253 (92), 240 (17), 239 (19), 237 (24), 211 (13), 210 (39), 134 (38), 126 (16), 120 (18), 118 (23); HR-EI-MS: calcd. for $C_{23}H_{29}N_3$: 347.2361, found 347.2347.

2,5-Dimethyl-3-[bis-(4-dimethylaminophenyl)methyl]-4-ethyl-1*H*-pyrrole (**12**)



12

The benzhydrylium tetrafluoroborate **8d**-BF_4 (136 mg, 0.400 mmol) was dissolved in CH_3CN (50 mL), cooled down to –15 °C and a solution of 3-ethyl-2,4-dimethylpyrrole (**6**, 100 µL, 0.740 mmol) in CH_3CN (20 mL) was allowed to drop to the blue reaction mixture. After the addition of 11.4 mL, the blue color faded and a slightly brown clear solution was obtained (0.42 mmol of **6** have been used). The solution was then washed with ice water (50 mL) containing saturated NaCl solution (1 mL) and the phases were separated at low temperature. The acetonitrile solution was dried over Na_2SO_4 and evaporated to yield **12** as a colorless oil (116 mg, 0.310 mmol, 78%) which turned within minutes into a pink oil.

^{1}H-NMR (300 MHz, $CDCl_3$) δ = 1.05 (t, J = 9 Hz, 3 H, CH_2CH_3), 1.79 (s, 3 H, 5-Me), 2.07 (s, 3 H, 3-Me), 2.36 (q, J = 9 Hz, 2 H, CH_2CH_3), 2.99 (s, 12 H, 7-H), 5.20 (br. s, 1 H, NH), 5.36 (s, 1 H,

	6-H), 6.93 (d, *J* = 8 Hz, 4 H, Ph), 7.04 (d, *J* = 8 Hz, 4 H, Ph).
^{13}C-NMR (75.5 MHz, $CDCl_3$)	δ = 7.5 (q), 9.3 (q), 13.9 (q), 15.9 (t), 40.5 (q), 45.2 (d), 111.8 (s), 113.1 (d), 119.0 (s), 119.2 (s), 124.1 (s), 128.0 (d), 133.8 (s), 144.9 (s).
EI-MS (70 eV)	*m/z* (%) = 375 (26) [M^+], 360 (20), 256 (16), 255 (42), 253 (100), 252 (93), 241 (27), 240 (21), 239 (30), 237 (21), 212 (18), 210 (34), 164 (25), 150 (17), 136 (17), 134 (33), 126 (17), 120 (17), 118 (16), 108 (27); HR-EI-MS: calcd. for $C_{25}H_{33}N_3$: 375.2674, found 375.2669.

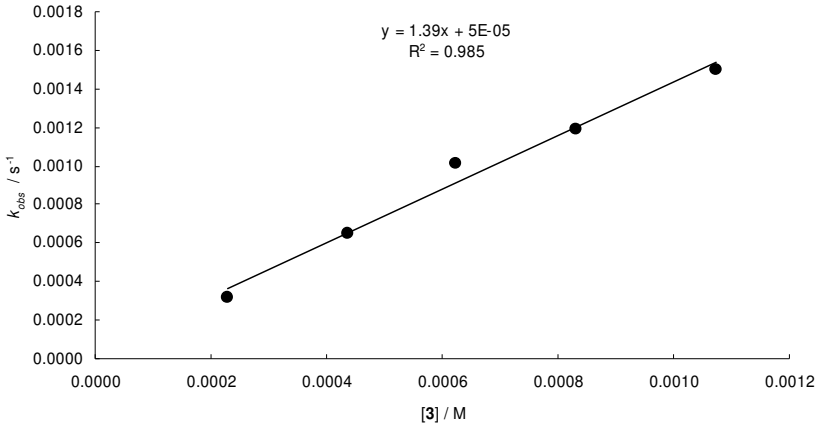
4.4.3 Kinetic Measurements

Rate constants for the reactions of pyrrole (**1**) with $(pfa)_2CH^+BF_4^-$ (**8i**-BF_4),[37] of *N*-methylpyrrole (**2**) with $(dma)_2CH^+BF_4^-$ (**8d**-BF_4),[38] $(mor)_2CH^+BF_4^-$ (**8f**-BF_4),[33] $Mn(CO)_3(\eta{\cdot}C_7H_8)^+$ [38] and fc(Ph)CHOAc[38] and of *N*-(triisopropylsilyl)pyrrole (**7**) with $(dpa)_2CH^+BF_4^-$ (**8h**-BF_4),[37] $(mfa)_2CH^+BF_4^-$ (**8h**-BF_4)[37] and $(pfa)_2CH^+BF_4^-$ (**8i**-BF_4) [37] have already been reported.

Unfilled dots in k_{obs} vs [nucleophile] plots were not used for the determination of k_2.

Table 4.7. Rate constants for the reactions of 2,5-dimethylpyrrole (**3**) with $(pyr)_2CH^+BF_4^-$ (**8c**-BF_4) in CH_3CN (J&M, 20 °C, λ = 622 nm).

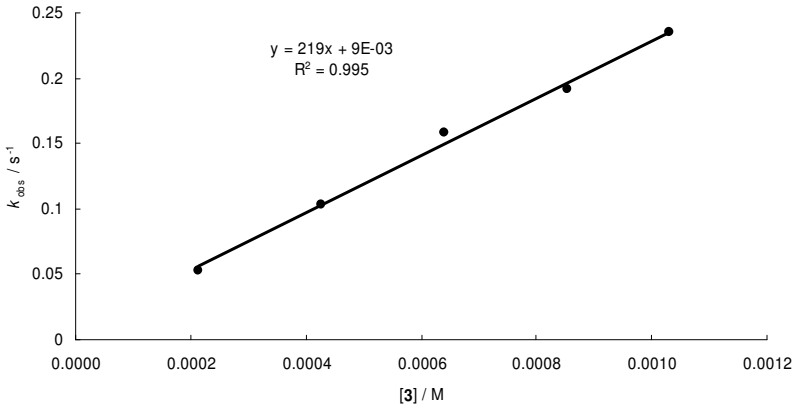
no.	$[\mathbf{8c}]_0$ / M	$[\mathbf{3}]_0$ / M	$[\mathbf{3}]_0$ / $[\mathbf{8c}]_0$	conv. / %	k_{obs} /s^{-1}
1	1.09×10^{-5}	2.28×10^{-4}	21	96	3.19×10^{-4}
2	1.04×10^{-5}	4.37×10^{-4}	42	99	6.46×10^{-4}
3	1.04×10^{-5}	6.23×10^{-4}	60	99	1.01×10^{-3}
4	1.06×10^{-5}	8.31×10^{-4}	78	99	1.19×10^{-3}
5	1.05×10^{-5}	1.07×10^{-3}	102	97	1.50×10^{-3}



$k_2 = 1.39 \times 10^0$ M^{-1} s^{-1}.

Table 4.8. Rate constants for the reactions of 2,5-dimethylpyrrole (**3**) with $(mpa)_2CH^+BF_4^-$ (**8e**-BF_4) in CH_3CN (Stopped-flow, 20 °C, λ = 622 nm).

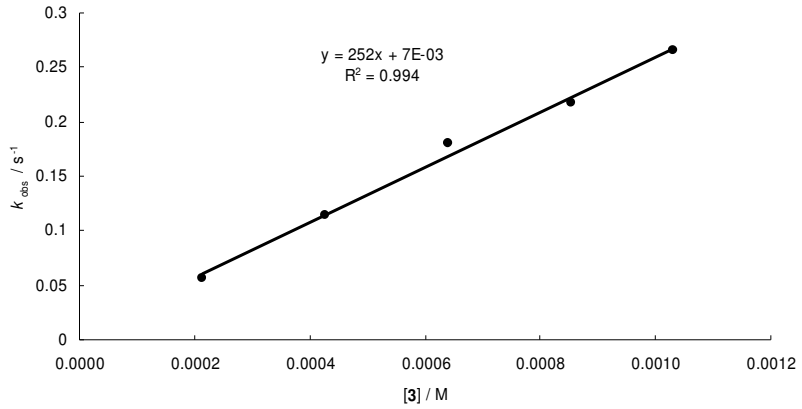
no.	$[\mathbf{8e}]_0$ / M	$[\mathbf{3}]_0$ / M	$[\mathbf{3}]_0$ / $[\mathbf{8e}]_0$	k_{obs} /s^{-1}
1	1.32×10^{-5}	2.13×10^{-4}	16	5.33×10^{-2}
2	1.32×10^{-5}	4.27×10^{-4}	32	1.03×10^{-1}
3	1.32×10^{-5}	6.40×10^{-4}	49	1.58×10^{-1}
4	1.32×10^{-5}	8.54×10^{-4}	65	1.92×10^{-1}
5	1.32×10^{-5}	1.03×10^{-3}	78	2.35×10^{-1}



$k_2 = 2.19 \times 10^2$ M^{-1} s^{-1}.

Table 4.9. Rate constants for the reactions of 2,5-dimethylpyrrole (**3**) with $(mor)_2CH^+BF_4^-$ (**8f**-BF_4) in CH_3CN (Stopped-flow, 20 °C, λ = 620 nm).

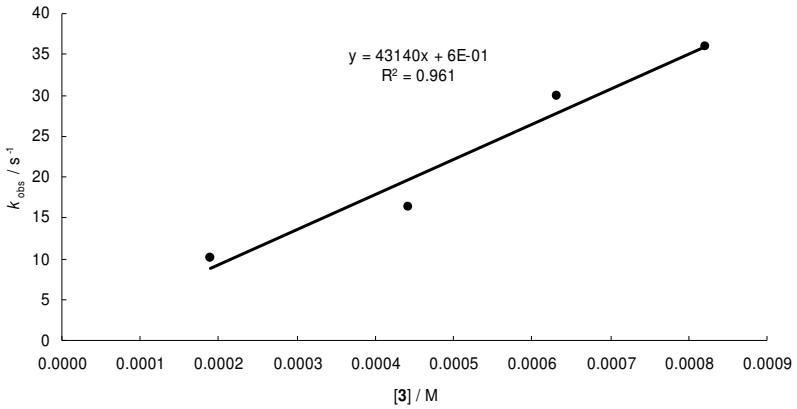
no.	$[\mathbf{8f}]_0$ / M	$[\mathbf{3}]_0$ / M	$[\mathbf{3}]_0$ / $[\mathbf{8f}]_0$	k_{obs} /s^{-1}
1	1.51×10^{-5}	2.13×10^{-4}	14	5.69×10^{-2}
2	1.51×10^{-5}	4.27×10^{-4}	28	1.14×10^{-1}
3	1.51×10^{-5}	6.40×10^{-4}	42	1.80×10^{-1}
4	1.51×10^{-5}	8.54×10^{-4}	56	2.18×10^{-1}
5	1.51×10^{-5}	1.03×10^{-3}	68	2.65×10^{-1}



$k_2 = 2.52 \times 10^2$ M^{-1} s^{-1}.

Table 4.10. Rate constants for the reactions of 2,5-dimethylpyrrole (**3**) with $(dpa)_2CH^+BF_4^-$ (**8g**-BF_4) in CH_3CN (Stopped-flow, 20 °C, λ = 672 nm).

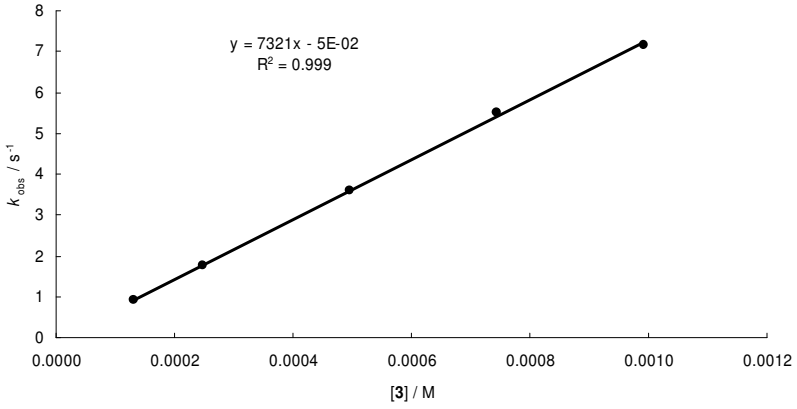
no.	$[\mathbf{8g}]_0$ / M	$[\mathbf{3}]_0$ / M	$[\mathbf{3}]_0$ / $[\mathbf{8g}]_0$	k_{obs} /s^{-1}
1	3.54×10^{-5}	7.12×10^{-4}	20	2.30×10^{1}
2	3.54×10^{-5}	1.43×10^{-3}	40	4.87×10^{1}
3	3.54×10^{-5}	2.14×10^{-3}	60	7.60×10^{1}
4	3.54×10^{-5}	2.85×10^{-3}	81	1.06×10^{2}
5	3.54×10^{-5}	3.56×10^{-3}	101	1.32×10^{2}



$k_2 = 4.31 \times 10^4$ M^{-1} s^{-1}.

Table 4.11. Rate constants for the reactions of 2,5-dimethylpyrrole (**3**) with $(mfa)_2CH^+BF_4^-$ (**8h**-BF_4) in CH_3CN (Stopped-flow, 20 °C, λ = 593 nm).

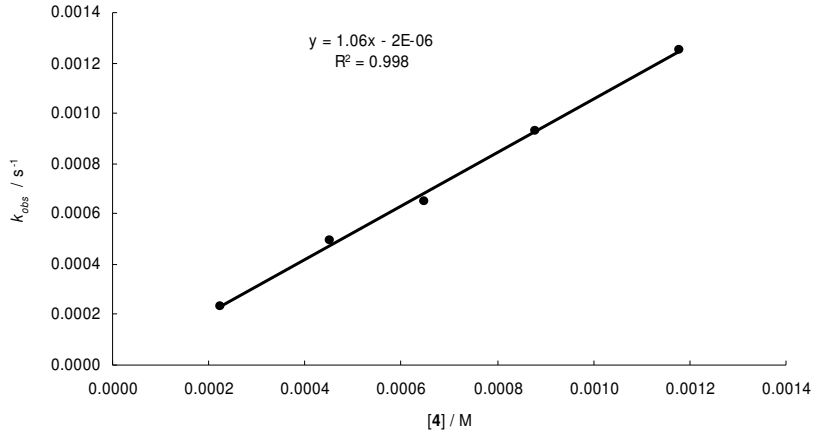
no.	$[\mathbf{8h}]_0$ / M	$[\mathbf{3}]_0$ / M	$[\mathbf{3}]_0$ / $[\mathbf{8h}]_0$	k_{obs} /s^{-1}
1	1.25×10^{-5}	1.32×10^{-4}	11	9.05×10^{-1}
2	1.25×10^{-5}	2.48×10^{-4}	20	1.76×10^{0}
3	1.25×10^{-5}	4.97×10^{-4}	40	3.59×10^{0}
4	1.25×10^{-5}	7.45×10^{-4}	60	5.50×10^{0}
5	1.25×10^{-5}	9.93×10^{-4}	80	7.16×10^{0}



$k_2 = 7.32 \times 10^3$ M^{-1} s^{-1}.

Table 4.12. Rate constants for the reactions of 1,2,5-trimethylpyrrole (**4**) with $(ind)_2CH^+BF_4^-$ (**8b**-BF_4) in CH_3CN (J&M, 20 °C, λ = 639 nm).

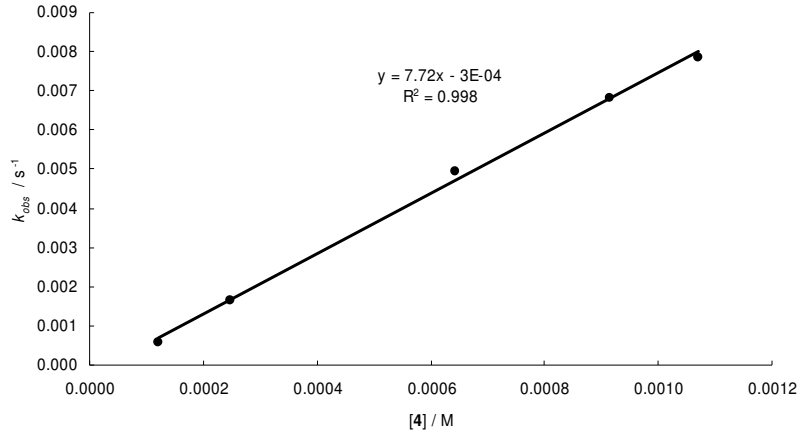
no.	$[\mathbf{8b}]_0$ / M	$[\mathbf{4}]_0$ / M	$[\mathbf{4}]_0$ / $[\mathbf{8b}]_0$	conv. / %	k_{obs} /s^{-1}
1	1.08×10^{-5}	2.23×10^{-4}	21	84	2.35×10^{-4}
2	1.10×10^{-5}	4.51×10^{-4}	41	99	4.92×10^{-4}
3	1.05×10^{-5}	6.48×10^{-4}	62	98	6.51×10^{-4}
4	1.11×10^{-5}	8.79×10^{-4}	79	99	9.29×10^{-4}
5	1.15×10^{-5}	1.18×10^{-3}	103	95	1.25×10^{-3}



$k_2 = 1.06 \times 10^0$ M^{-1} s^{-1}.

Table 4.13. Rate constants for the reactions of 1,2,5-trimethylpyrrole (**4**) with $(pyr)_2CH^+BF_4^-$ (**8c**-BF_4) in CH_3CN (J&M, 20 °C, λ = 639 nm).

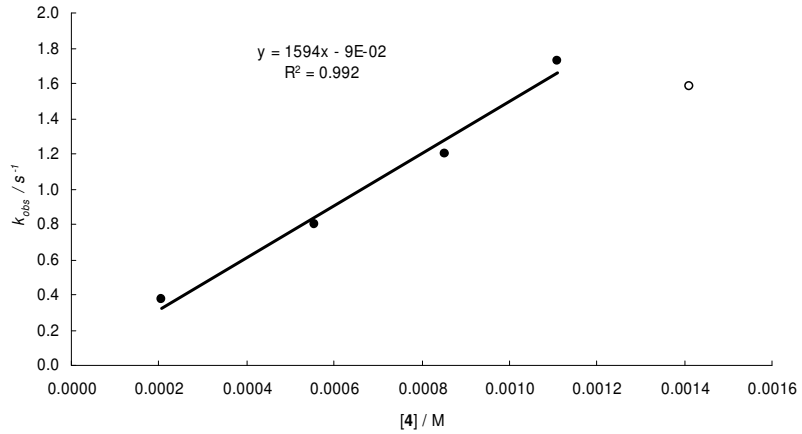
no.	$[\mathbf{8c}]_0$ / M	$[\mathbf{4}]_0$ / M	$[\mathbf{4}]_0$ / $[\mathbf{8c}]_0$	conv. / %	k_{obs} /s^{-1}
1	1.14×10^{-5}	1.22×10^{-4}	11	66	5.89×10^{-4}
2	1.17×10^{-5}	2.48×10^{-4}	21	81	1.65×10^{-3}
3	1.08×10^{-5}	6.44×10^{-4}	60	93	4.94×10^{-3}
4	1.13×10^{-5}	9.14×10^{-4}	81	92	6.82×10^{-3}
5	1.05×10^{-5}	1.07×10^{-3}	102	83	7.86×10^{-3}



$k_2 = 7.72 \times 10^0$ M^{-1} s^{-1}.

Table 4.14. Rate constants for the reactions of 1,2,5-trimethylpyrrole (**4**) with $(mpa)_2CH^+BF_4^-$ (**8e**-BF_4) in CH_3CN (Stopped-flow, 20 °C, λ = 622 nm).

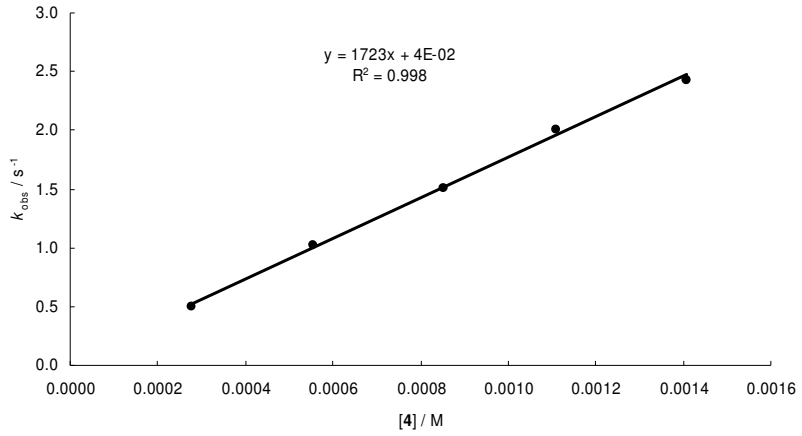
no.	[**8e**]$_0$ / M	[**4**]$_0$ / M	[**4**]$_0$ / [**8e**]$_0$	k_{obs} /s^{-1}
1	1.39×10^{-5}	2.78×10^{-4}	20	3.77×10^{-1}
2	1.39×10^{-5}	5.56×10^{-4}	40	7.98×10^{-1}
3	1.39×10^{-5}	8.52×10^{-4}	61	1.20×10^{0}
4	1.39×10^{-5}	1.11×10^{-3}	80	1.73×10^{0}
5	1.39×10^{-5}	1.41×10^{-3}	101	1.58×10^{0}



$k_2 = 1.59 \times 10^3$ M^{-1} s^{-1}.

Table 4.15. Rate constants for the reactions of 1,2,5-trimethylpyrrole (**4**) with $(mor)_2CH^+BF_4^-$ (**8f**-BF_4) in CH_3CN (Stopped-flow, 20 °C, λ = 620 nm).

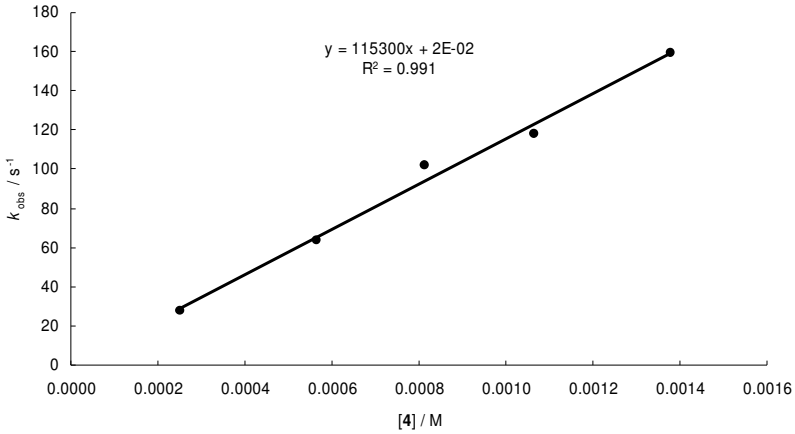
no.	$[\mathbf{8f}]_0$ / M	$[\mathbf{4}]_0$ / M	$[\mathbf{4}]_0$ / $[\mathbf{8f}]_0$	k_{obs} /s^{-1}
1	1.41×10^{-5}	2.78×10^{-4}	20	4.97×10^{-1}
2	1.41×10^{-5}	5.56×10^{-4}	39	1.02×10^{0}
3	1.41×10^{-5}	8.52×10^{-4}	60	1.51×10^{0}
4	1.41×10^{-5}	1.11×10^{-3}	79	2.01×10^{0}
5	1.41×10^{-5}	1.41×10^{-3}	100	2.43×10^{0}



$k_2 = 1.72 \times 10^3$ M^{-1} s^{-1}.

Table 4.16. Rate constants for the reactions of 1,2,5-trimethylpyrrole (**4**) with $(dpa)_2CH^+BF_4^-$ (**8g**-BF_4) in CH_3CN (Stopped-flow, 20 °C, λ = 672 nm).

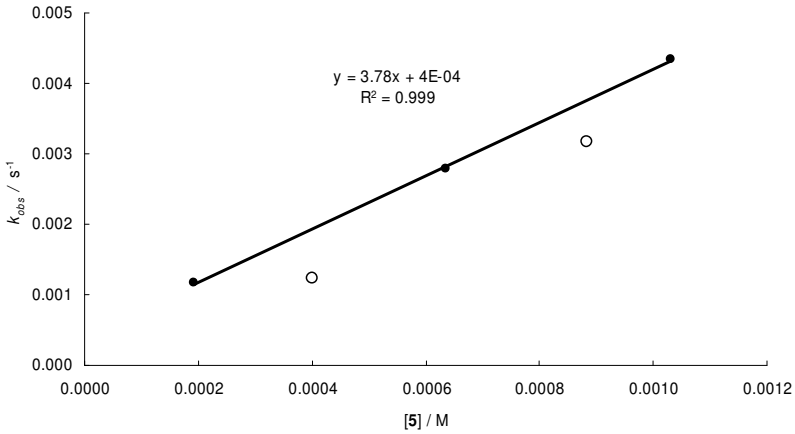
no.	$[\mathbf{8g}]_0$ / M	$[\mathbf{4}]_0$ / M	$[\mathbf{4}]_0$ / $[\mathbf{8g}]_0$	k_{obs} /s^{-1}
1	2.69×10^{-5}	2.55×10^{-4}	9	2.73×10^{1}
2	2.69×10^{-5}	5.64×10^{-4}	21	6.37×10^{1}
3	2.69×10^{-5}	8.15×10^{-4}	30	1.02×10^{2}
4	2.69×10^{-5}	1.07×10^{-3}	40	1.18×10^{2}
5	2.69×10^{-5}	1.38×10^{-3}	51	1.59×10^{2}



$k_2 = 1.15 \times 10^5$ M^{-1} s^{-1}.

Table 4.17. Rate constants for the reactions of 2,4-dimethylpyrrole (**5**) with $(lil)_2CH^+BF_4^-$ (**8a**-BF_4) in CH_3CN (J&M, 20 °C, λ = 639 nm).

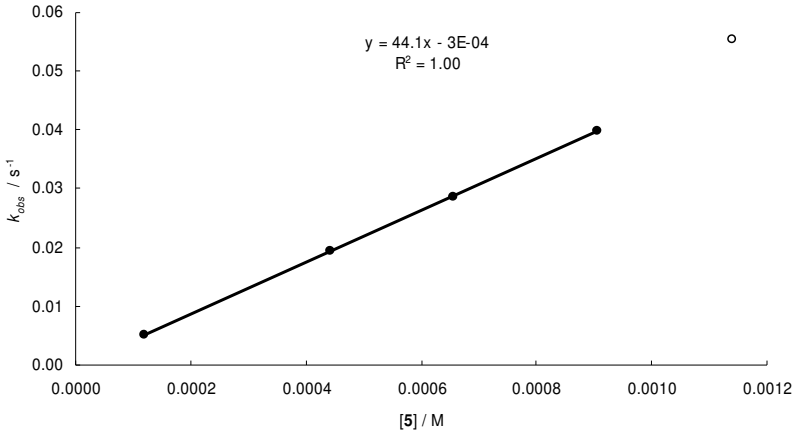
no.	$[\mathbf{8a}]_0$ / M	$[\mathbf{5}]_0$ / M	$[\mathbf{5}]_0$ / $[\mathbf{8a}]_0$	conv. / %	k_{obs} /s^{-1}
1	1.11×10^{-5}	1.93×10^{-4}	18	56	1.17×10^{-3}
2	9.82×10^{-4}	4.00×10^{-4}	41	68	1.24×10^{-3}
3	1.09×10^{-5}	6.35×10^{-4}	58	73	2.79×10^{-3}
4	1.06×10^{-5}	8.64×10^{-4}	82	85	3.16×10^{-3}
5	1.04×10^{-5}	1.03×10^{-3}	99	80	4.34×10^{-3}



$k_2 = 3.78 \times 10^0$ M^{-1} s^{-1}.

Table 4.18. Rate constants for the reactions of 2,4-dimethylpyrrole (**5**) with $(ind)_2CH^+BF_4^-$ (**8b**-BF_4) in CH_3CN (J&M, 20 °C, λ = 625 nm).

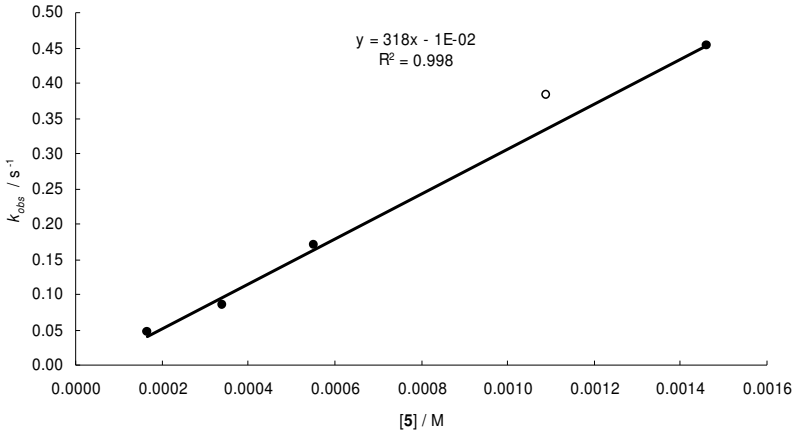
no.	$[\mathbf{8b}]_0$ / M	$[\mathbf{5}]_0$ / M	$[\mathbf{5}]_0$ / $[\mathbf{8b}]_0$	conv. / %	k_{obs} /s^{-1}
1	1.28×10^{-5}	1.20×10^{-4}	9	99	5.04×10^{-3}
2	1.36×10^{-5}	4.42×10^{-4}	33	98	1.93×10^{-2}
3	1.28×10^{-5}	6.55×10^{-4}	51	99	2.85×10^{-2}
4	1.30×10^{-5}	9.06×10^{-4}	70	99	3.98×10^{-2}
5	1.22×10^{-5}	1.14×10^{-3}	93	99	5.55×10^{-2}



$k_2 = 4.41 \times 10^1$ M^{-1} s^{-1}.

Table 4.19. Rate constants for the reactions of 2,4-dimethylpyrrole (**5**) with $(pyr)_2CH^+BF_4^-$ (**8c**-BF_4) in CH_3CN (J&M, 20 °C, λ = 620 nm).

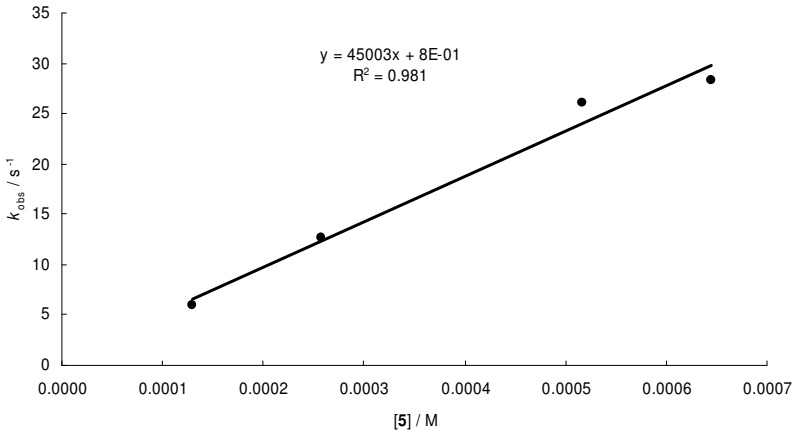
no.	$[\mathbf{8c}]_0$ / M	$[\mathbf{5}]_0$ / M	$[\mathbf{5}]_0$ / $[\mathbf{8c}]_0$	conv. / %	k_{obs} /s^{-1}
1	1.40×10^{-5}	1.65×10^{-4}	12	95	4.69×10^{-2}
2	1.44×10^{-5}	3.39×10^{-4}	24	82	8.43×10^{-2}
3	1.31×10^{-5}	5.53×10^{-4}	42	96	1.71×10^{-1}
4	1.37×10^{-5}	1.09×10^{-3}	80	97	3.82×10^{-1}
5	1.41×10^{-5}	1.46×10^{-3}	104	97	4.53×10^{-1}



$k_2 = 3.18 \times 10^2$ M^{-1} s^{-1}.

Table 4.20. Rate constants for the reactions of 2,4-dimethylpyrrole (**5**) with $(mpa)_2CH^+BF_4^-$ (**8e**-BF_4) in CH_3CN (Stopped-flow, 20 °C, λ = 622 nm).

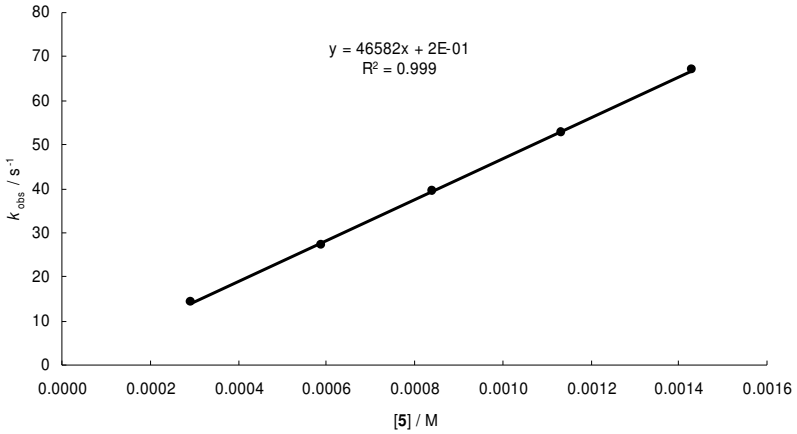
no.	[**8e**]$_0$ / M	[**5**]$_0$ / M	[**5**]$_0$ / [**8e**]$_0$	k_{obs} /s^{-1}
1	6.33×10^{-6}	1.29×10^{-4}	20	5.96×10^{0}
2	6.33×10^{-6}	2.58×10^{-4}	41	1.26×10^{1}
3	6.33×10^{-6}	3.87×10^{-4}	61	2.47×10^{1}
4	6.33×10^{-6}	5.16×10^{-4}	82	2.60×10^{1}
5	6.33×10^{-6}	6.45×10^{-4}	102	2.83×10^{1}



$k_2 = 4.50 \times 10^4$ M^{-1} s^{-1}.

Table 4.21. Rate constants for the reactions of 2,4-dimethylpyrrole (**5**) with $(mor)_2CH^+BF_4^-$ (**8f**-BF_4) in CH_3CN (Stopped-flow, 20 °C, λ = 620 nm).

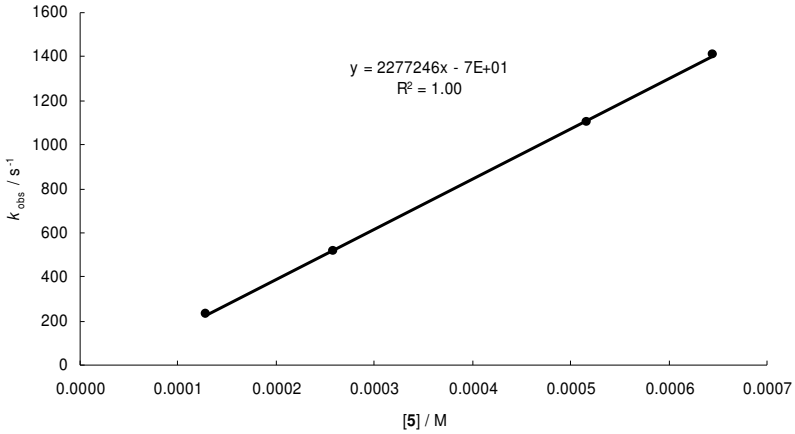
no.	$[\mathbf{8f}]_0$ / M	$[\mathbf{5}]_0$ / M	$[\mathbf{5}]_0$ / $[\mathbf{8f}]_0$	k_{obs} /s^{-1}
1	1.41×10^{-5}	2.94×10^{-4}	21	1.42×10^{1}
2	1.41×10^{-5}	5.89×10^{-4}	42	2.74×10^{1}
3	1.41×10^{-5}	8.41×10^{-4}	59	3.95×10^{1}
4	1.41×10^{-5}	1.14×10^{-3}	80	5.26×10^{1}
5	1.41×10^{-5}	1.43×10^{-3}	101	6.72×10^{1}



$k_2 = 4.66 \times 10^4$ M^{-1} s^{-1}.

Table 4.22. Rate constants for the reactions of 2,4-dimethylpyrrole (**5**) with $(dpa)_2CH^+BF_4^-$ (**8g**-BF_4) in CH_3CN (Stopped-flow, 20 °C, λ = 672 nm).

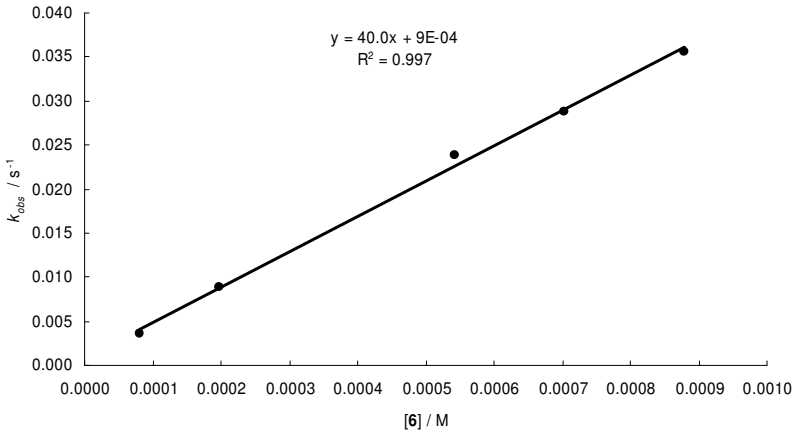
no.	$[\mathbf{8g}]_0$ / M	$[\mathbf{5}]_0$ / M	$[\mathbf{5}]_0$ / $[\mathbf{8g}]_0$	k_{obs} /s^{-1}
1	6.33×10^{-6}	1.29×10^{-4}	20	2.33×10^{2}
2	6.33×10^{-6}	2.58×10^{-4}	41	5.12×10^{2}
3	6.33×10^{-6}	3.87×10^{-4}	61	1.29×10^{3}
4	6.33×10^{-6}	5.16×10^{-4}	82	1.10×10^{3}
5	6.33×10^{-6}	6.45×10^{-4}	102	1.41×10^{3}



$k_2 = 2.28 \times 10^6$ M^{-1} s^{-1}.

Table 4.23. Rate constants for the reactions of 3-ethyl-2,4-dimethylpyrrole (**6**) with $(lil)_2CH^+BF_4^-$ (**8a**-BF_4) in CH_3CN (J&M, 20 °C, λ = 639 nm).

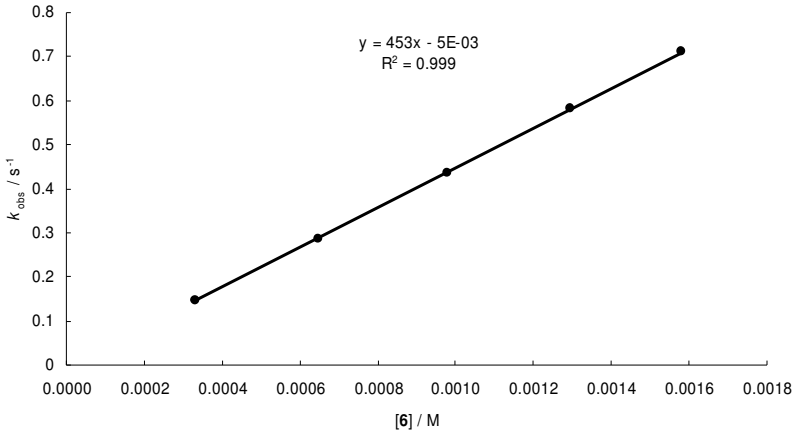
no.	[**8a**]$_0$ / M	[**6**]$_0$ / M	[**6**]$_0$ / [**8a**]$_0$	conv. / %	k_{obs} /s^{-1}
1	9.29×10^{-6}	8.03×10^{-5}	9	78	3.64×10^{-3}
2	9.18×10^{-6}	1.98×10^{-4}	22	88	8.90×10^{-3}
3	8.98×10^{-6}	5.42×10^{-4}	61	87	2.38×10^{-2}
4	9.04×10^{-6}	7.03×10^{-4}	78	92	2.88×10^{-2}
5	8.84×10^{-6}	8.79×10^{-4}	96	94	3.56×10^{-2}



$k_2 = 4.00 \times 10^1$ M^{-1} s^{-1}.

Table 4.24. Rate constants for the reactions of 3-ethyl-2,4-dimethylpyrrole (**6**) with $(ind)_2CH^+BF_4^-$ (**8b**-BF_4) in CH_3CN (Stopped-flow, 20 °C, λ = 625 nm).

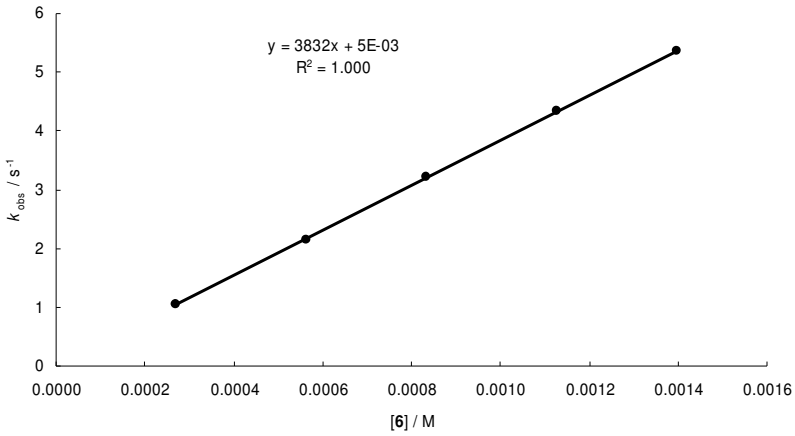
no.	$[\mathbf{8b}]_0$ / M	$[\mathbf{6}]_0$ / M	$[\mathbf{6}]_0$ / $[\mathbf{8b}]_0$	k_{obs} /s^{-1}
1	1.62×10^{-5}	3.32×10^{-4}	20	1.48×10^{-1}
2	1.62×10^{-5}	6.47×10^{-4}	40	2.85×10^{-1}
3	1.62×10^{-5}	9.79×10^{-4}	60	4.35×10^{-1}
4	1.62×10^{-5}	1.30×10^{-3}	80	5.81×10^{-1}
5	1.62×10^{-5}	1.58×10^{-3}	97	7.11×10^{-1}



$k_2 = 4.53 \times 10^2$ M^{-1} s^{-1}.

Table 4.25. Rate constants for the reactions of 3-ethyl-2,4-dimethylpyrrole (**6**) with $(pyr)_2CH^+BF_4^-$ (**8c**-BF_4) in CH_3CN (Stopped-flow, 20 °C, λ = 620 nm).

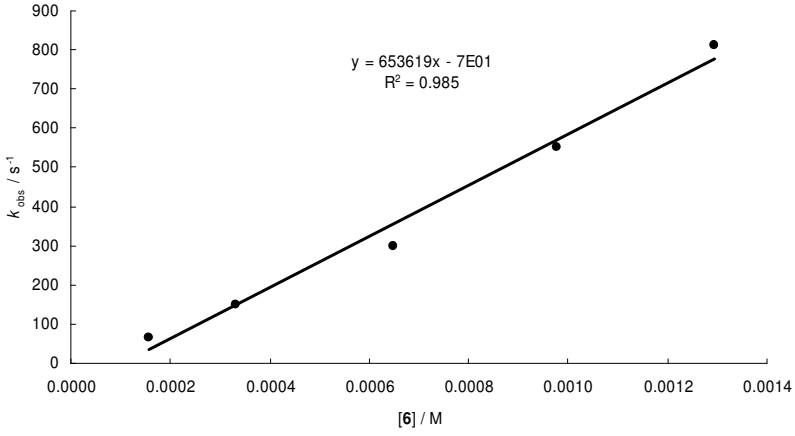
no.	$[\mathbf{8c}]_0$ / M	$[\mathbf{6}]_0$ / M	$[\mathbf{6}]_0$ / $[\mathbf{8c}]_0$	k_{obs} /s^{-1}
1	1.51×10^{-5}	2.71×10^{-4}	18	1.05×10^{0}
2	1.51×10^{-5}	5.64×10^{-4}	37	2.15×10^{0}
3	1.51×10^{-5}	8.32×10^{-4}	55	3.21×10^{0}
4	1.51×10^{-5}	1.13×10^{-3}	75	4.34×10^{0}
5	1.51×10^{-5}	1.40×10^{-3}	92	5.36×10^{0}



$k_2 = 3.83 \times 10^3$ M^{-1} s^{-1}.

Table 4.26. Rate constants for the reactions of 3-ethyl-2,4-dimethylpyrrole (**6**) with $(mpa)_2CH^+BF_4^-$ (**8e**-BF_4) in CH_3CN (Stopped-flow, 20 °C, λ = 622 nm).

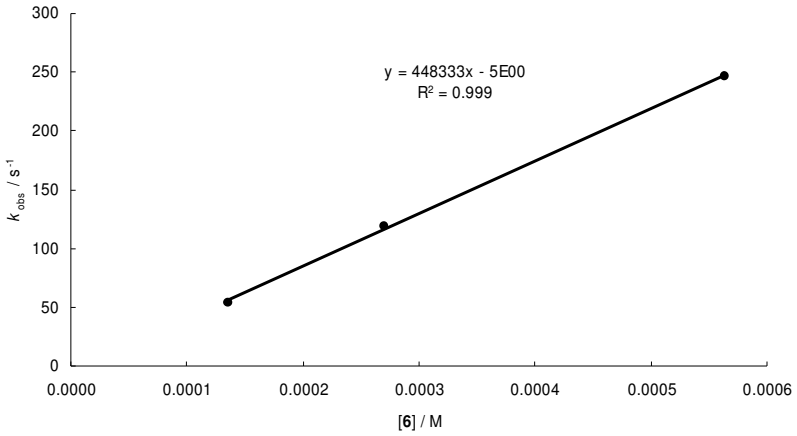
no.	$[\mathbf{8e}]_0$ / M	$[\mathbf{6}]_0$ / M	$[\mathbf{6}]_0$ / $[\mathbf{8e}]_0$	k_{obs} /s^{-1}
1	1.63×10^{-5}	1.58×10^{-4}	10	6.70×10^1
2	1.63×10^{-5}	3.32×10^{-4}	20	1.50×10^2
3	1.63×10^{-5}	6.47×10^{-4}	40	2.99×10^2
4	1.63×10^{-5}	9.79×10^{-4}	60	5.51×10^2
5	1.63×10^{-5}	1.30×10^{-3}	80	8.13×10^2



$k_2 = 6.53 \times 10^5$ M^{-1} s^{-1}.

Table 4.27. Rate constants for the reactions of 3-ethyl-2,4-dimethylpyrrole (**6**) with $(mor)_2CH^+BF_4^-$ (**8f**-BF_4) in CH_3CN (Stopped-flow, 20 °C, λ = 620 nm).

no.	$[\mathbf{8f}]_0$ / M	$[\mathbf{6}]_0$ / M	$[\mathbf{6}]_0$ / $[\mathbf{8f}]_0$	k_{obs} /s^{-1}
1	1.34×10^{-5}	1.35×10^{-4}	10	5.38×10^{1}
2	1.34×10^{-5}	2.71×10^{-4}	20	1.19×10^{2}
3	1.34×10^{-5}	5.64×10^{-4}	42	2.47×10^{2}



$k_2 = 4.48 \times 10^5$ M^{-1} s^{-1}.

Correlations of the second-order rate constants k_2 (20 °C) of the reactions of the pyrroles **3–6** with the benzhydrylium ions **8a**–**c**, **8e**, **8f**, **8h** and **8i** in CH_3CN at 20 °C versus the corresponding *E* parameters of these benzhydrylium ions and resulting *N*- and *s*-parameters for **3–6** (Figures 4.5 to 4.8).

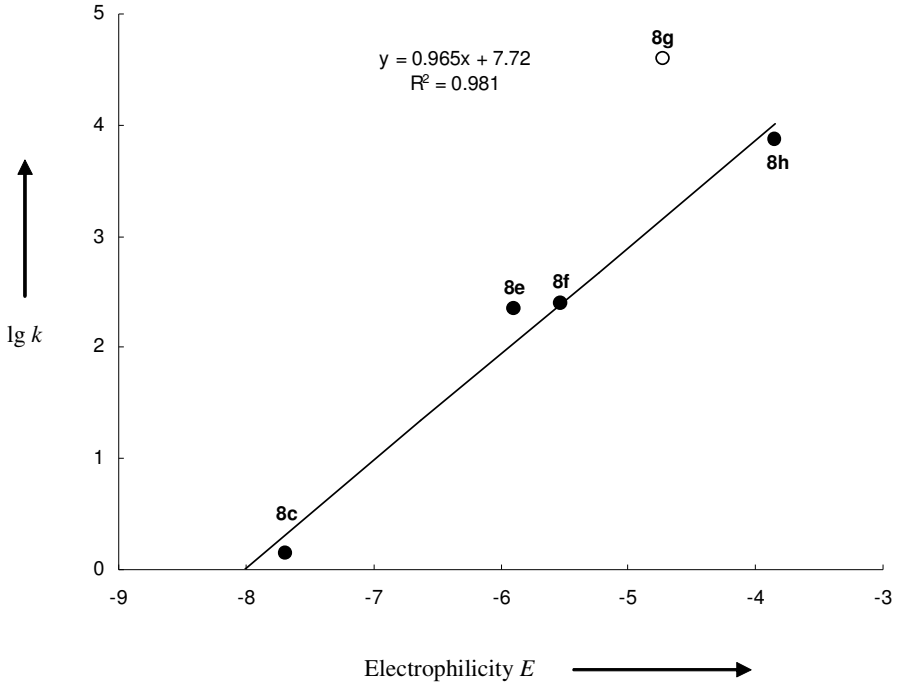


Figure 4.5. Plot of lg k_2 versus E for the reactions of 2,5-dimethylpyrrole (**3**) with **8c** and **8e–h** to yield $N = 8.01$ and $s = 0.97$.

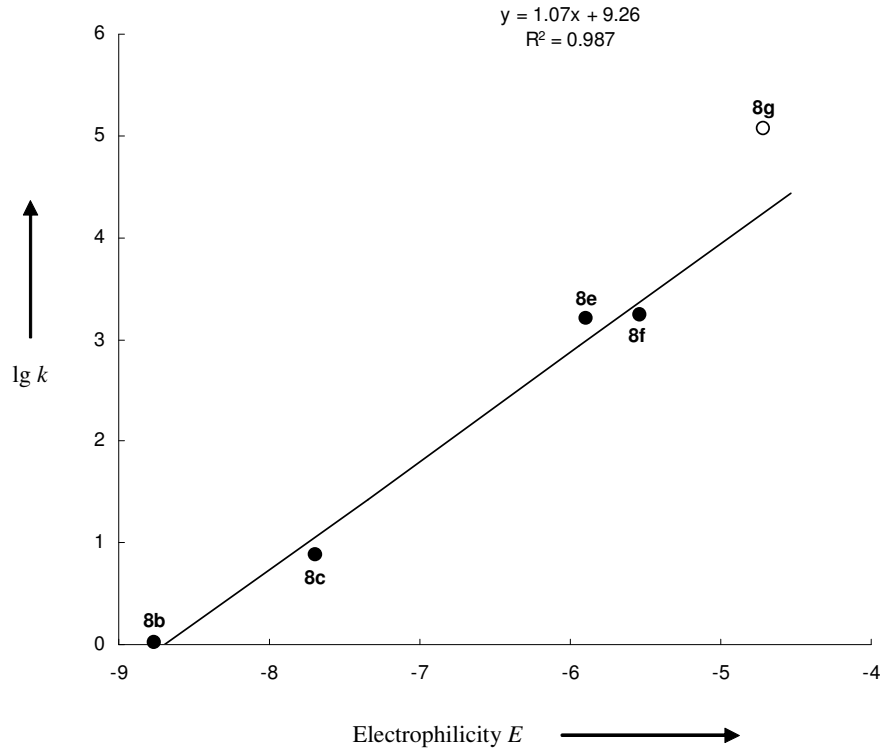


Figure 4.6. Plot of lg k_2 vs E for the reactions of 1,2,5-trimethylpyrrole (**4**) with **8b**, **8c**, **8e–g**, to yield $N = 8.69$ and $s = 1.07$.

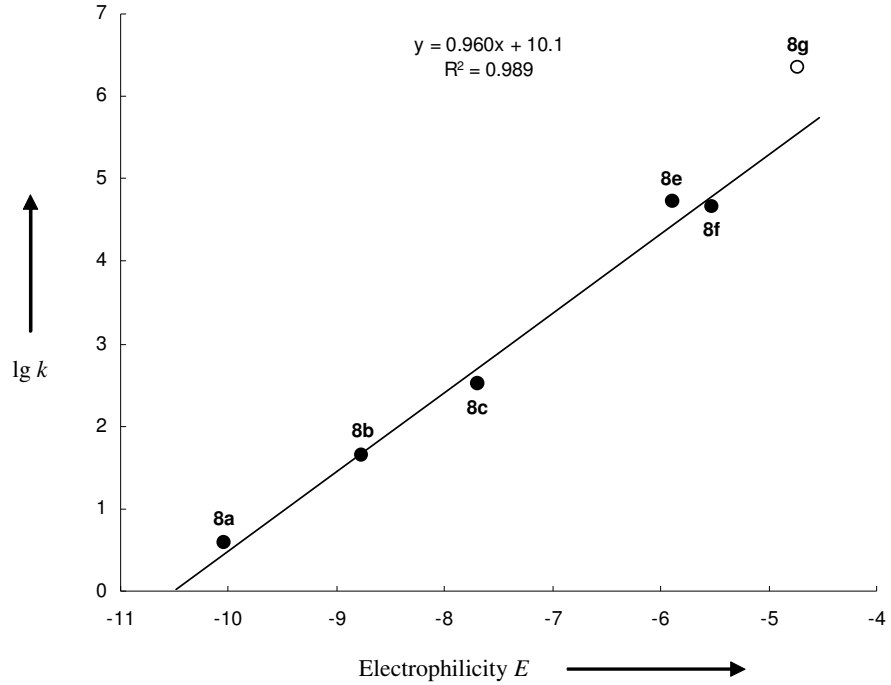


Figure 4.7. Plot of log k_2 versus E for the reactions of 2,4-dimethylpyrrole (**5**) with **8a**–**c**, **8e**, **8f** and **8g** to yield $N = 10.49$ and $s = 0.96$.

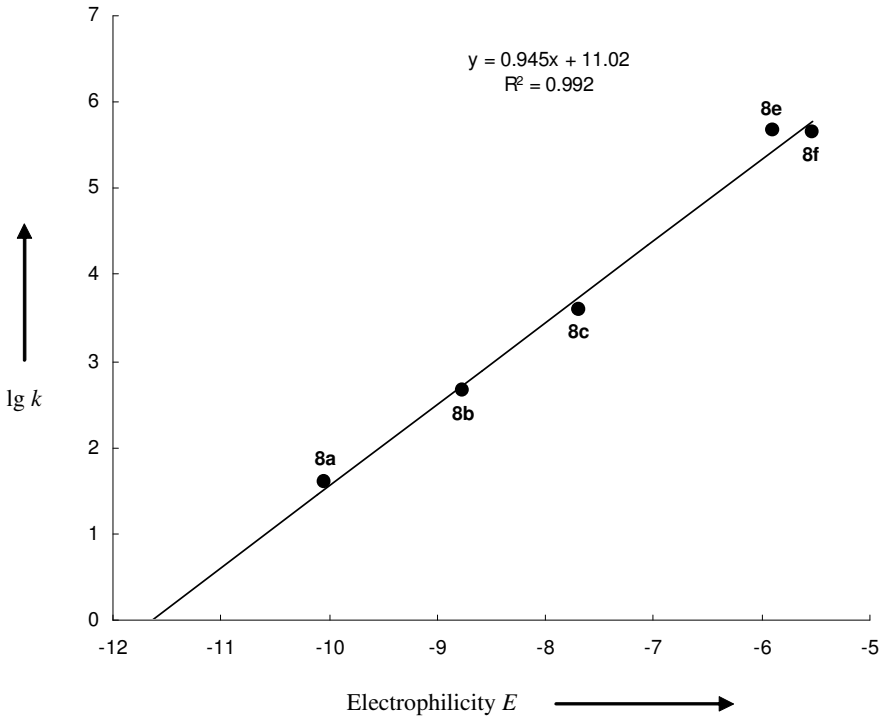
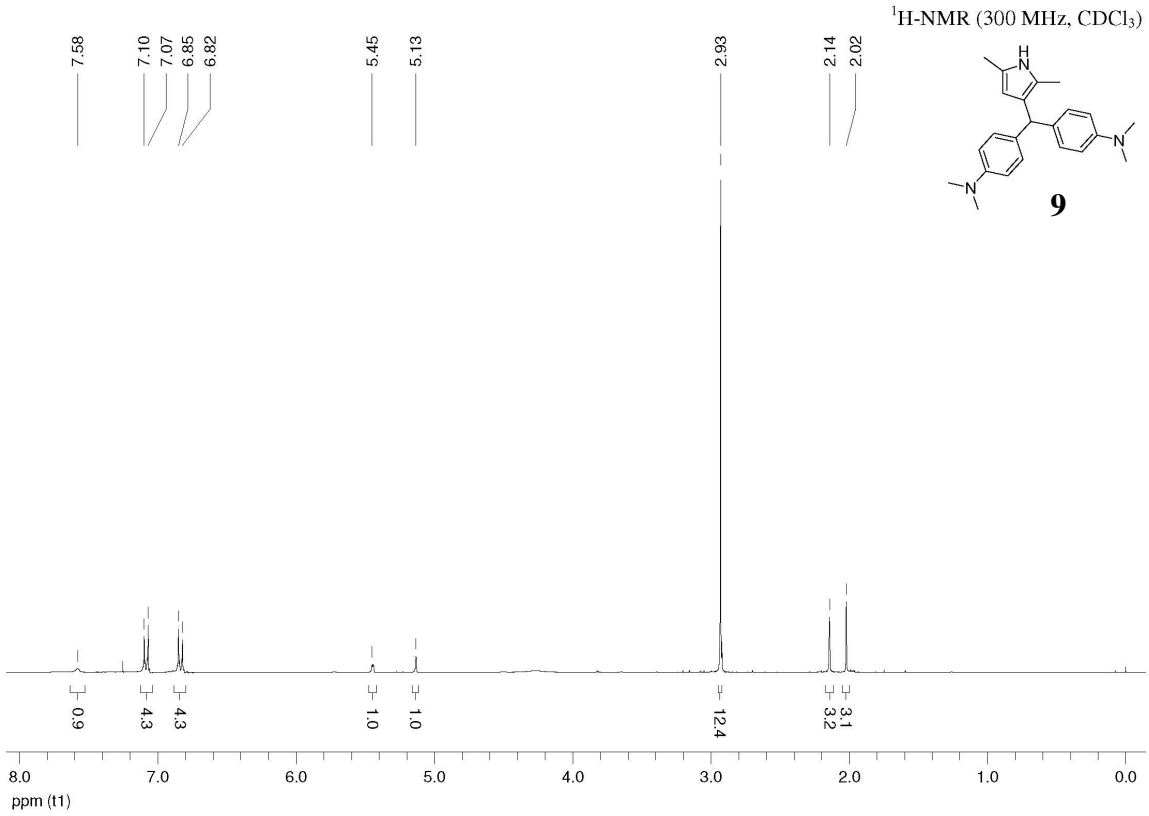
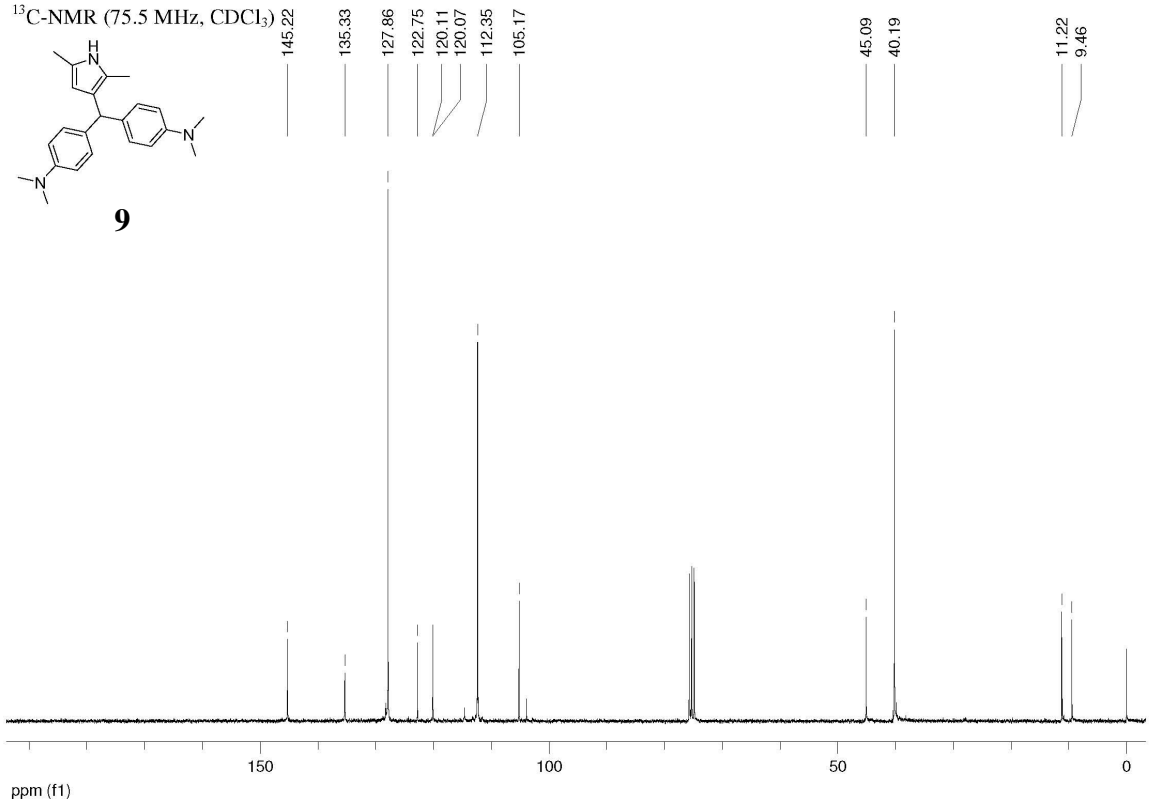


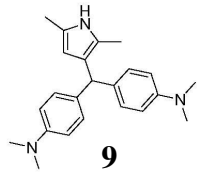
Figure 4.8. Plot of log k_2 versus E for the reactions of 3-ethyl-2,4-dimethylpyrrole (**6**) with **8a**–**c**, **8e** and **8f** to yield $N = 11.63$ and $s = 0.95$.

4.5 Appendix: NMR Spectra of Compounds 9–12



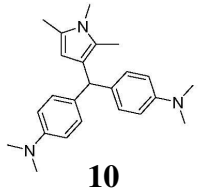


DEPT (75.5 MHz, $CDCl_3$)



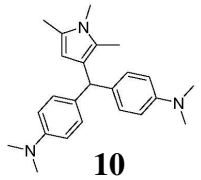
9

^{1}H-NMR (300 MHz, $CDCl_3$)



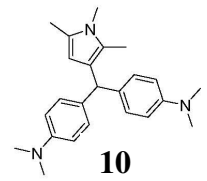
10

^{13}C-NMR (75.5 MHz, $CDCl_3$)



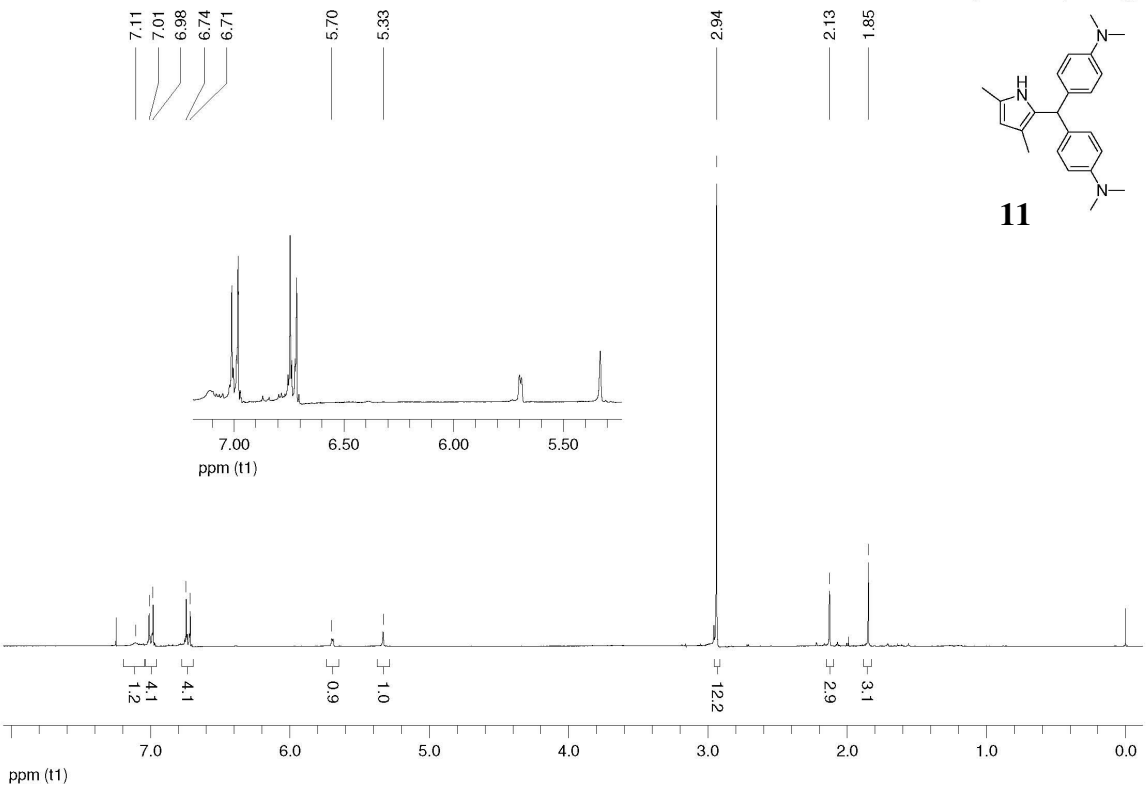
10

DEPT (75.5 MHz, $CDCl_3$)



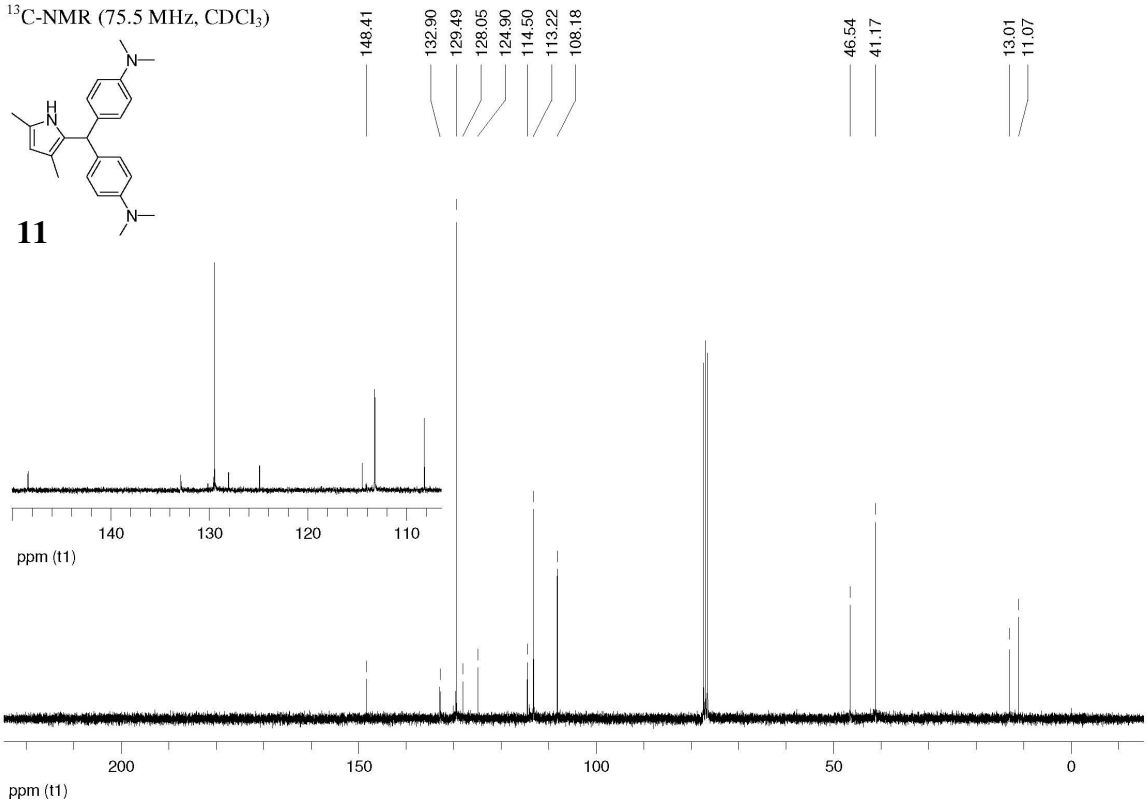
10

^{1}H-NMR (300 MHz, $CDCl_3$)



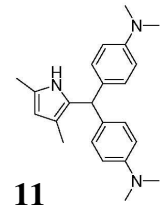
11

^{13}C-NMR (75.5 MHz, $CDCl_3$)



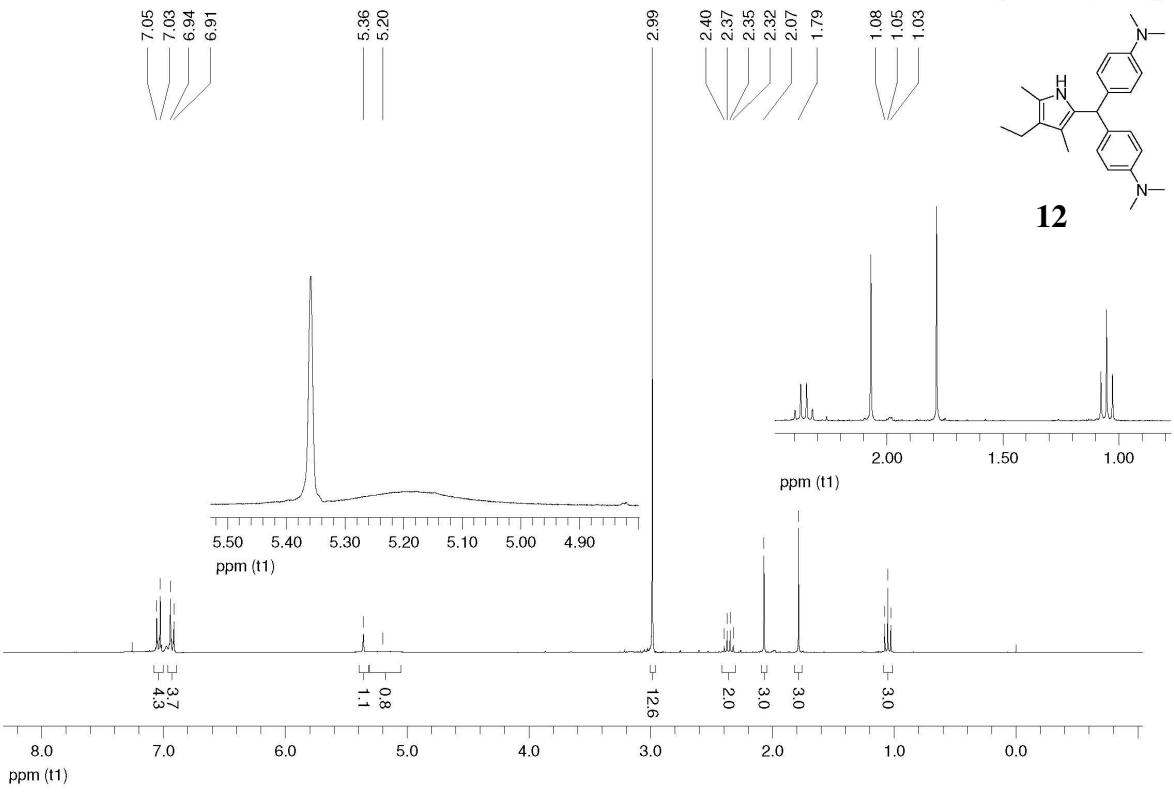
11

DEPT (75.5 MHz, $CDCl_3$)

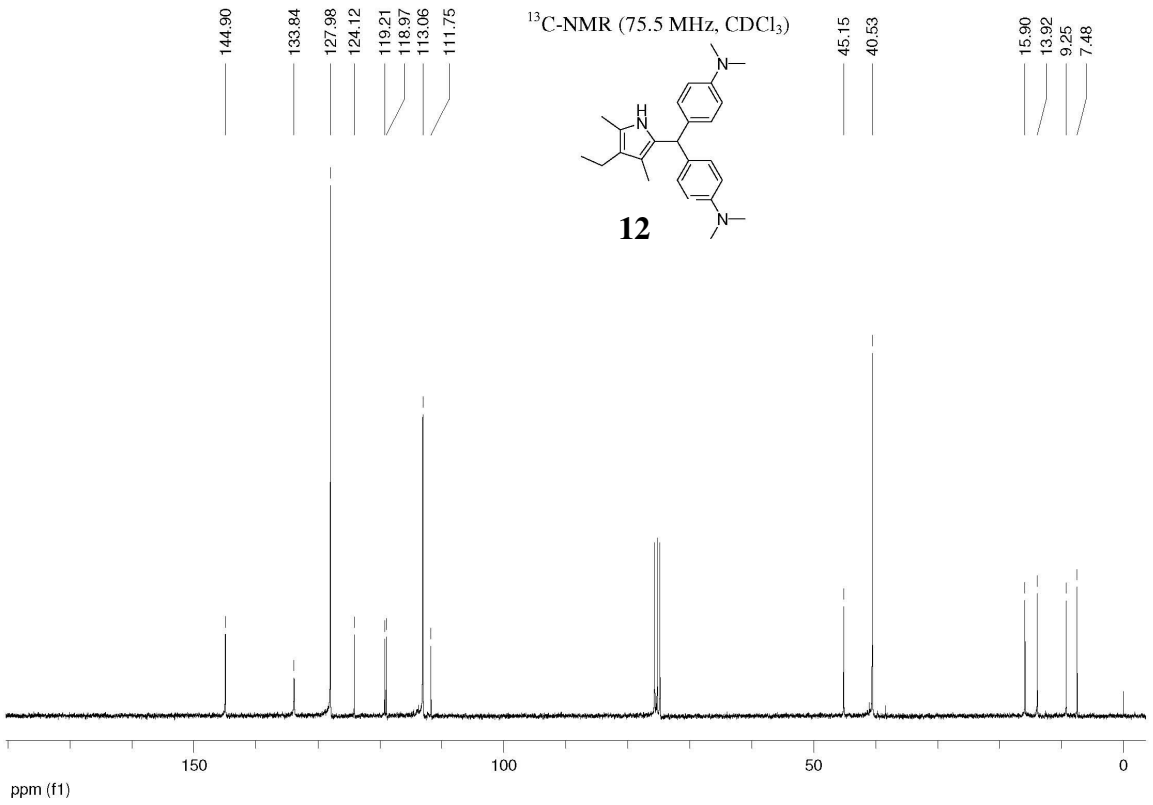


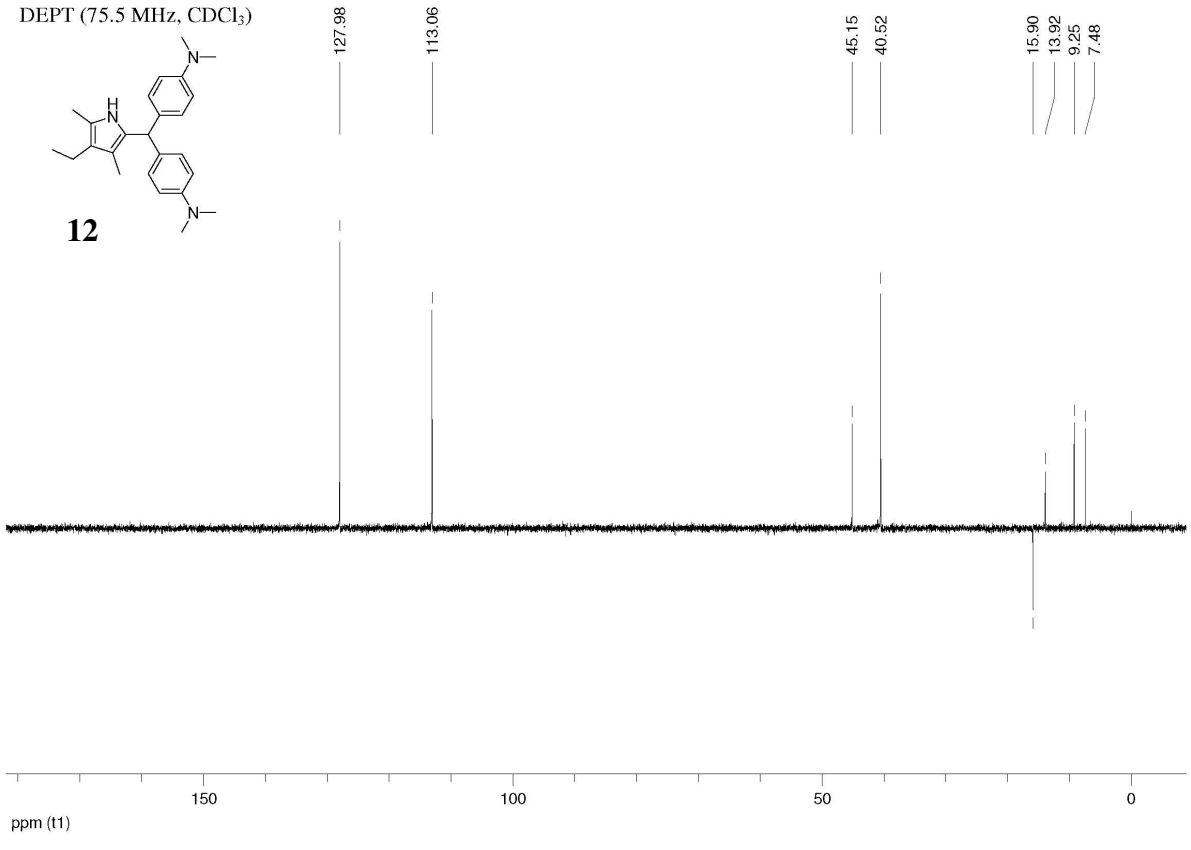
11

^{1}H-NMR (300 MHz, $CDCl_3$)



12


144.90
133.84
127.98
124.12
119.21
118.97
113.06
111.75
^{13}C-NMR (75.5 MHz, $CDCl_3$)
45.15
40.53
15.90
13.92
9.25
7.48
12
150
100
50
0
ppm (f1)


DEPT (75.5 MHz, $CDCl_3$)
127.98
113.06
45.15
40.52
15.90
13.92
9.25
7.48
12
150
100
50
0
ppm (t1)

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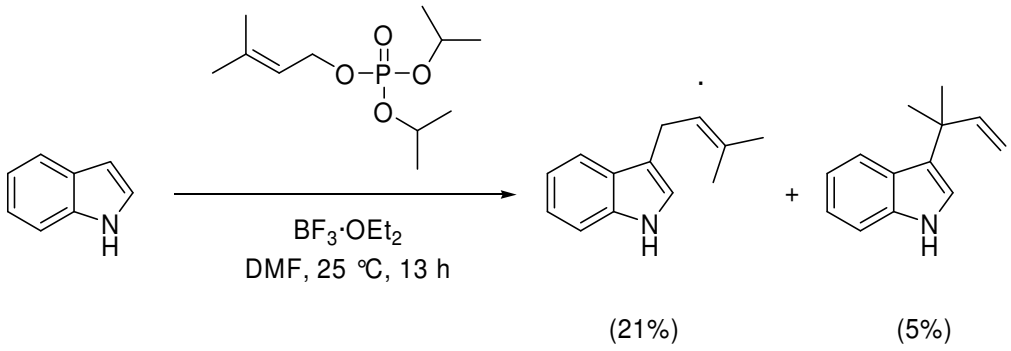
Chapter 5

Electrophilic Allylations and Benzylations in Neutral Aqueous and Alcoholic Solutions

This chapter was published by M. Westermaier and H. Mayr in *Org. Lett.* **2006**, *8*, 4791–4794.

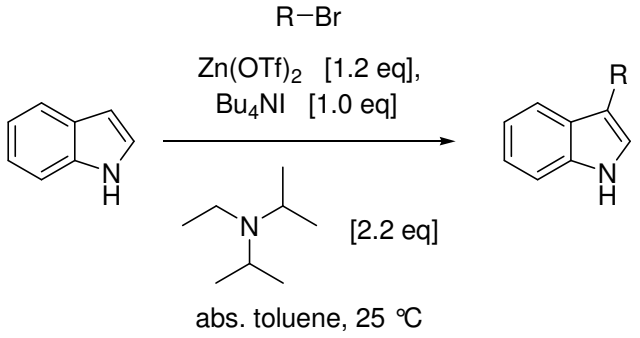
5.1 Introduction

Among the numerous methods to synthesize substituted indoles, substitution reactions play an important role, among which Friedel-Crafts type reactions are relatively rare. While the $BF_3{\cdot}OEt_2$ induced prenylation of indole with prenyl pyrophosphate gave only 26% of 3-prenylated indoles (Scheme 5.1),[1] electrophilic allylations of indoles with allyl bromides in the presence of 1.2 equivalents of zinc triflate, tetrabutylammonium iodide (1 equiv.) and Hünig's base (2.2 equiv.) in toluene have been reported to give 30–60% of 3-allylated products (Scheme 5.2).[2]



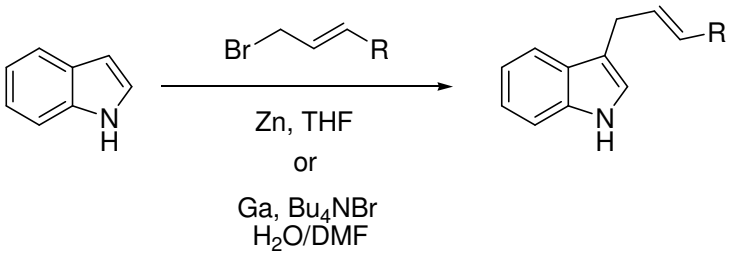
Scheme 5.1. $BF_3{\cdot}OEt_2$ catalyzed prenylation of indole with prenyl diisopropyl phosphate to yield a mixture of 3-prenylated product and the inverse prenylated product.[1]

Transition metal catalyzed allylations at the 3-position have been performed with Mo(II),[3] Ni(II),[4] and Pd(0) or Pd(II) complexes,[5, 6] and Pd-catalyzed allylations of 3-substituted indoles have also been used for the enantioselective synthesis of 3,3-disubstituted-3*H*-indoles.[7]



Scheme 5.2. Allylation of indole with allyl bromides in the presence of $Zn(OTf)_2$, Bu_4NI and Hünig's base to yield exclusively 3-substituted indoles.[2]

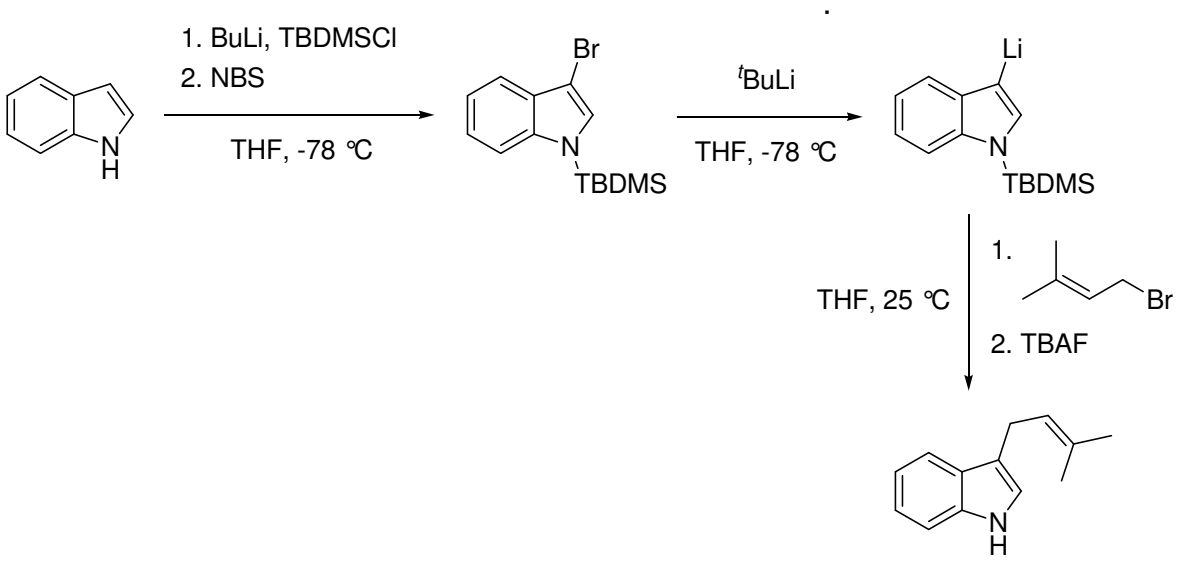
An alternative approach employs zinc- or gallium-mediated Barbier reactions,[8, 9] where the initially formed allylmetal compounds deprotonate indoles to yield *N*-metalated indoles, which act as nucleophiles in the succeeding S_N2 reactions to give good yields of the 3-allylated indoles (Scheme 5.3).[10]



Scheme 5.3. Barbier reactions of indoles with allyl halides in the presence of Zn or Ga.[8, 9]

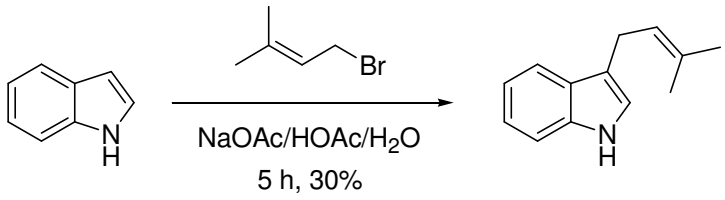
In contrast, Li and Na salts of indoles are predominantly alkylated and allylated at the nitrogen atom.[11, 12]

The 3-allylation of *N*-substituted indoles has also been achieved via 3-halogenation followed by halogen-metal exchange and consecutive treatment with allyl halides (Scheme 5.4).[13, 14]



Scheme 5.4. Indole prenylation by halogenation and halogen-metal exchange.[14]

The isolation of up to 30% 3-prenylindole from indole and prenyl bromide in buffered aqueous solutions by Casnati and co-workers[15] is of particular interest for this investigation because this observation indicates that indole can successively compete with the buffer system in the trapping of the intermediate prenyl cation (Scheme 5.5).



Scheme 5.5. Reaction of prenylbromide with indole in buffered aqueous solutions.[15]

5.2 Results and Discussion

We now report a novel approach to 3-substituted indoles which compares well with the best yields obtained previously but considerably exceeds previous methods with respect to its simplicity.

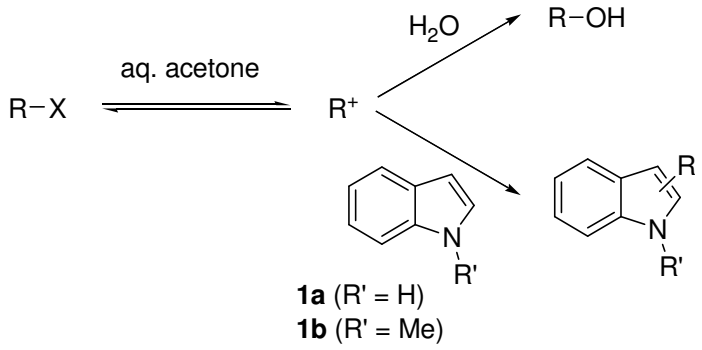
Previously, we have shown that the rates of the reactions of carbocations with n-, π- and σ-nucleophiles can be described by Equation (5.1).[16-18]

$$\lg k = s(N + E) \tag{5.1}$$

In Equation (5.1), k is a second order rate constant at 20 °C ($M^{-1}s^{-1}$), s is a nucleophile-specific slope parameter, N a nucleophile-specific parameter, and E is an electrophile-specific parameter.

Since Equation (5.1) also holds for the reactions of carbocations with solvents,[19] it can be employed to predict the relative reactivities of π-nucleophiles and solvents towards carbocations which are generated as intermediates of S_N1 processes. Stimulated by our reactivity scales which revealed many electron-rich π-systems being more nucleophilic than aqueous acetone or aqueous acetonitrile,[19, 20] we have recently introduced a novel protocol for Friedel-Crafts alkylations under neutral or slightly basic conditions by trapping the intermediates of S_N1 reactions in aqueous solutions with electron-rich π-systems.[21, 22]

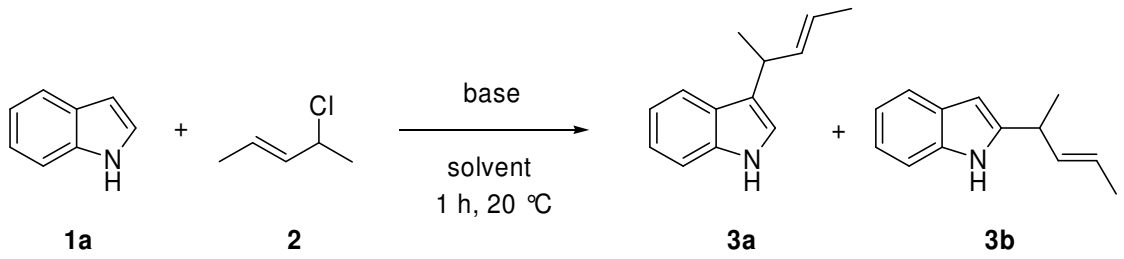
We now report that this method can be employed for the mild and efficient allylation and benzylation of indoles by dissolving indoles and S_N1 active allyl and benzyl halides in aqueous acetone or acetonitrile in the presence of a base (Scheme 5.6).



Scheme 5.6. Trapping of S_N1 intermediates by indoles **1**.

5.2.1 Optimization of the Reaction Conditions

In order to optimize the reaction conditions we examined the reaction of indole (**1a**) with (*E*)-4-chloropent-2-ene (**2**) under various conditions (Scheme 5.7). Acid catalysis by the liberated HCl was excluded by performing the reactions in the presence of a base; bisallylation was avoided by employing five equivalents of **1a**.



Scheme 5.7. Reactions of indole (**1a**) with (*E*)-4-chloro-pent-2-ene (**2**) under various conditions.

Table 5.1 shows that comparable yields of allylation products were obtained when the reactions were performed in 90% aqueous acetonitrile (N_1 = 4.56, s = 0.94)[19] or 80% aqueous acetone (N_1 = 5.77, s = 0.87)[20] using Na_2CO_3, $NaHCO_3$ or NH_4HCO_3 as base.

The yields were less satisfactory when 2,2,2-trifluoroethanol was used as solvent. Possibly, the acidity of this solvent (pK_a = 12.3)[23] is responsible for the formation of some oligomers of indole.[24]

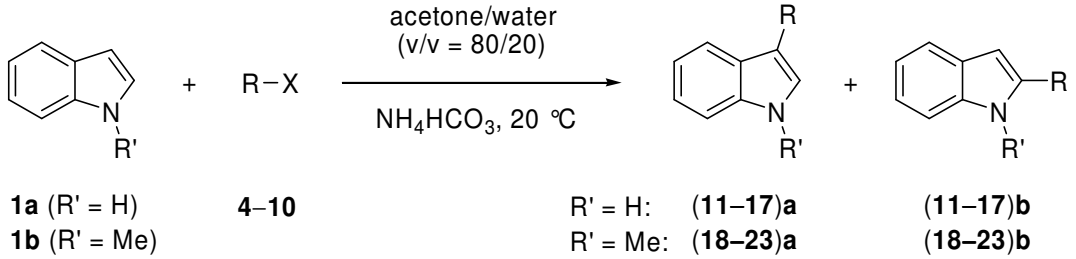
Table 5.1. Product ratios and yields of the reactions of indole (**1a**) with (*E*)-4-chloro-pent-2-ene (**2**) isolated after 1 h at ambient temperature.

no.	solvent	N[a]	base[b]		ratio **3a**:**3b**[c]	yield **3a** + **3b**[d]
1	90% aq. acetonitrile	4.56	Na_2CO_3	(2.0)	80:20	99
2			NH_4HCO_3	(2.0)	83:17	96
3			2,6-lutidine	(1.2)	67:33	97
4	80% aq. acetone	5.77	Na_2CO_3	(2.0)	78:22	96
5			$NaHCO_3$	(2.0)	80:20	95
6			NH_4HCO_3	(1.0)	81:19	95
7			NH_4HCO_3	(2.0)	80:20	99
8	2,2,2-trifluoroethanol	1.23	NH_4HCO_3	(2.0)	77:23	73

[a] Nucleophilicity parameters of the solvents used from refs. [19, 20]. [b] Equivalents of the auxiliary base relative to the electrophile are given in parentheses. [c] Peak areas (determined by GC-MS of the crude products). [d] Based on the isolated yield of pure **3a** which was obtained after column chromatography (in %).

5.2.2 Scope of the Method

The conditions of experiment no. 7 (Table 5.1), *i.e.* dissolving the reactants in 80% aqueous acetone in the presence of NH_4HCO_3, were then employed for the reactions of various S_N1-reactive allyl and benzyl halides **4**–**10** with the indoles **1a** and **1b** (Scheme 5.8). The reactions were monitored by GC-MS and interrupted after complete consumption of **4**–**10** or after three days.

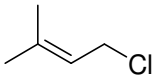
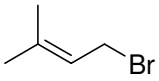
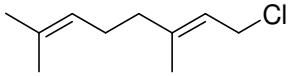
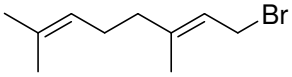
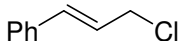
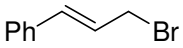
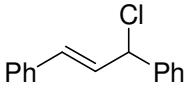
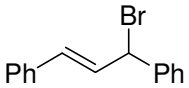
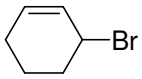
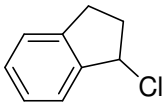
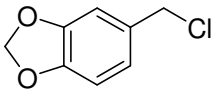


Scheme 5.8. Reactions of indoles **1** with allyl and benzyl halides **4**–**10**.

The reactions with indole (**1a**) gave mixtures of 3- and 2-allylated indoles in moderate to very good yields, when disubstitution was suppressed by employing 5 equivalents of **1a** (Table 5.2).

When indole (**1a**, 10 mmol), prenyl bromide (**4b**, 8.3 mmol), and NH_4HCO_3 (10 mmol) were stirred in 80% aqueous acetone (25 mL) for 1 h at room temperature, a significant amount of 2,3-diprenylindole [2,3-bis(2-methylpropenyl)-1*H*-indole, **11c**] was formed, and only 54% of **11a** could be isolated. Under the same conditions, disubstitution was favored when **4b** was used in excess, and compound **11c** was obtained as the major product (83% by GC-MS) from a 1:4-mixture of **1a** and **4b**. Because of the longer retention times of the 2-substituted isomers (**11**-**13**)**b**, the predominantly formed 3-substitution products (**11**-**13**)**a** could be obtained as pure isomers by chromatography on silica gel. Generally, the allyl bromides reacted faster and gave better yields than the corresponding chlorides. Exclusive 3-attack was observed when indole (**1a**) was treated with 3-bromocyclohexene (**8**) in 90% aqueous acetonitrile (Table 5.2, Entry 9). Surprisingly, the corresponding reaction in 80% aqueous acetone gave only 27% of **15a** along with cyclohex-2-enol as the major product. In the case of **14a/b**, **16a/b** and **17a/b**, the trace amounts of the 2-isomers were not removed by chromatography, and pure **17a** was obtained by crystallization. While the 1,1-dialkyl-substituted allyl cations derived from the allyl halides **4** and **5** were selectively attacked at the terminal position of the allyl cation,

Table 5.2. Reactions of indole (**1a**) with allyl and benzyl halides **4**–**10** in 80% aqueous acetone.

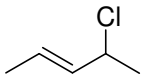
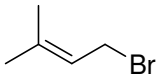
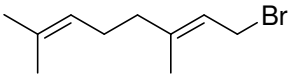
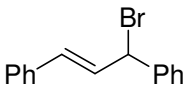
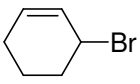
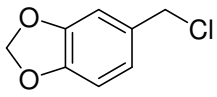
no.	electrophile		time / h	product ratio[a]	yield / %[b]
1		**4a**	8	**11a**:**11b** (91: 9)	87 (79)
2		**4b**	2	**11a**:**11b** (91: 9)	99 (91)
3		**5a**	24	**12a**:**12b** (92: 8)	34 (31)
4		**5b**	1	**12a**:**12b** (92: 8)	60 (56)
5		**6a**	72	**13a**:**13c** (62:10)[c]	22 [d]
6		**6b**	24	**13a**:**13c** (61:13)[e]	71 [d]
7		**7a**	72	–	–
8		**7b**	48	**14a**.**14b** (93: 7)	60 (56)
9		**8**	0.5	**15a**:**15b** (99: 1)	70 (70)[f]
10		**9**	24	**16a**:**16b** (94: 6)	51 [g]
11		**10**	24	**17a**:**17b** (92: 8)	86 (79)[h]

[a] Peak areas (determined by GC-MS of the crude products). [b] Isolated yields of the mixtures of the 3-substituted indoles (**a** isomers) and 2-substituted products (**b** isomers); the number in parentheses is the isolated yield of the pure **a** isomers. [c] Besides **13a** and 3-(1-phenylallyl)-1*H*-indole (**13c**), a third isomer was detected by GC-MS (28%, possibly **13b**). [d] 8:1-mixture of **13a** and **13c**. [e] A third isomer was detected by GC-MS (26%, possibly **13b**). [f] Reaction performed in 90% aqueous acetonitrile. [g] 10:1-mixture of **16a** and **16b**. [h] 15:1-mixture of **17a** and **17b**.

the 1-phenylallyl cation arising from **6a/b** was attacked at both allylic termini, with attack at the nonsubstituted allylic position predominating. As previously reported for Lewis acid catalyzed allylations of π-nucleophiles,[25, 26] the regioselectivity of attack is predominantly controlled by steric effects, and not by LUMO coefficients or charge distribution in the allyl cations.[27] Entries 10 and 11 of Table 5.2 show that this novel type of electrophilic substitutions of indoles is not restricted to allyl halides, but can also be employed for other types of S_N1 active substrates like benzyl halides.

Similar reactions were observed with *N*-methylindole (**1b**, Table 5.3). Preferential 3-attack is generally accompanied by some 2-attack, but 3-bromocyclohexene (**8**) again attacks the 3-position of **1b** selectively. As before, the reaction with **8** has to be carried out in 90% aqueous acetonitrile because cyclohex-2-enol is the major product in 80% aqueous acetone.

Table 5.3. Reactions of *N*-methylindole (**1b**) with allyl and benzyl halides **2**–**10** in 80% aqueous acetone at room temperature.

no.	electrophile		time / h	product ratio[a]	yield / %[b]
1		**2**	1	**18a**:**18b** (80:20)	99 [c]
2		**4b**	1	**19a**:**19b** (92: 8)	85
3		**5b**	1	**20a**:**20b** (95: 5)	71 (67)
4		**7b**	48	**21a**:**21b** (98: 2)	50
5		**8**	24	**22a**:**22b** (99: 1)	71
6		**10**	24	**23a**:**23b** (94: 6)	56 (53)

[a] Peak areas (determined by GC-MS of the crude product). [b] Isolated yields of the mixtures of the 3-substituted indoles (**18a**–**23a**) and the 2-substituted indoles (**18b**–**23b**); isolated yields of the **a** isomers are given in parentheses. [c] 10:1-mixture of **18a** and **18b**. [d] 10:1-mixture of **19a** and **19b**. [e] Product contains traces of **21b**. [f] Reaction performed in 90% aqueous acetonitrile.

5.3 Conclusion

Our previously published concept of Friedel-Crafts reactions under acid-free conditions has thus been demonstrated to be applicable for an important class of compounds. Since indoles are generally more nucleophilic than water in acetone,[19, 20] the competing trapping of the intermediate carbocation by water is usually not a problem. The method is rather limited by the rates of ionization of the corresponding allyl and benzyl halides.

Since nucleofugality parameters of $N_f = 2$ and 3 have been reported for chloride and bromide, respectively, in 80% aqueous acetone,[28] one can expect that ionization half-lives will exceed 1 d as the electrofugality of the carbocation gets smaller than –7 in the case of R-Cl and smaller than –8 in the case of R-Br. In line with the published electrofugality parameter of the cinnamyl cation ($E_f = -8$)[29] cinnamyl bromides but not chlorides have successfully been employed in this study. Reactions via less stabilized carbocations will require more harsh conditions.

5.4 Experimental Section

5.4.1 General

Acetone was distilled (b. p. 56 °C), acetonitrile was bought from Fischer Scientific and used as received, 2,2,2-trifluoroethanol was bought from Acros and distilled over drierite (b. p. 72 °C). Water was purified with Millipore MilliQplus. All starting materials were obtained from Aldrich, Acros, Lancaster and Merck and used without further purification. All allylic substrates were prepared by procedures following literature from the corresponding alcohols as follows: 4-chloropent-2-ene (**2**),[25] geranyl chloride (**5a**),[30] geranyl bromide (**5b**),[31] 3-chloro-1,3-diphenylpropene (**7a**),[32] 3-bromo-1,3-diphenylpropene (**7b**),[31] 1-chloroindane (**9**)[33] and 5-chloromethyl-benzo[1,3]-dioxole (**10**).[34] 1-methylindole (**1b**) was prepared according to literature.[12]

^{1}H-NMR spectra were recorded on Varian MERCURY 200 (200 MHz) or Bruker ARX 300 (300 MHz) spectrometers. Chemical shifts are reported from TMS with the solvent resonance as the internal standard ($CDCl_3$: δ = 7.26 ppm). Data are reported as follows: chemical shift (multiplicity, coupling constants, integration intensity) with s = singlet, d = doublet, t = triplet, q = quartet, br = broad and m = multiplet. ^{13}C-NMR spectra were recorded on a Bruker ARX 300 (75.5 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from TMS with the solvent as internal standard ($CDCl_3$: δ = 77.0 ppm). Spin multiplicities are derived from DEPT135 spectra. The assignment of the peak signals to the compounds is based on 2D-NMR experiments or made by alignment with simulated spectra by the program ACD. GC-mass spectra were recorded on Agilent 5973 MSD [HP-5MS-capillar column with length 30 m, diameter 0.25 mm, flow rate 1.0 mL/min, injector, split (23.9 mL/min), carrier gas helium, quadrupol mass spectrometer]. Data are reported as follows: retention time and heating programm [Method A: 70 °C (2 min) – 25 °C / min – 150 °C – 50 °C / min – 250 °C (12 min); method B: 70 °C (2 min) – 25 °C / min – 150 °C – 50 °C / min – 250 °C (18 min); method C: 110 °C (2 min) – 50 °C / min – 270 °C (5 min)]. Elemental analyses were carried out by using an Elementar Vario EL in the "Mikroanalytisches Labor" of the Department of Chemistry and Biochemistry of the Ludwig Maximilians University of Munich. Chromatographic purification was done with Merck silica gel 60 (mesh 40–63 μm). Detection was done with UV-light (λ = 254 or 366 nm). R_f-values are given for the major isomer.

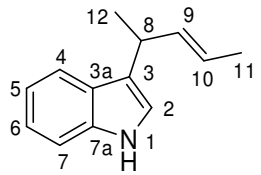
5.4.2 General Reaction Procedure

10 mmol (2.0 eq) of ammonium hydrogencarbonate was suspended in a 1 M solution of indole (**1a**, 25 mmol, 5.0 eq) in aqueous acetone or aqueous acetonitrile (25 mL), and 5.0 mmol (1.0 eq) of the allyl or benzyl halide was added. After the solution was stirred at room temperature for the time specified in tables 2 and 3, water was added (30 mL) and the organic phase was separated. The aqueous phase was extracted with diethyl ether (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and the solvents removed *in vacuo*. Indole (**1a**, b. p. 103–107 °C, 3 × 10^{-3} mbar) or *N*-methylindole (**1b**, b. p. 95–98 °C, 3 × 10^{-3} mbar) was removed from the crude product by Kugelrohr distillation. The residue was purified by flash column chromatography. The 2-substituted isomer was eluted earlier than the 3-substituted isomer.

5.4.3 Friedel-Crafts Reactions with Indole

3-[(*E*)-1-Methylbut-2-enyl]-1*H*-indole (3a)[5]

4-Chloropent-2-ene (**2**, 209 mg, 2.00 mmol) and indole (**1a**, 1.17 g, 10.0 mmol) were stirred in acetone/water (80/20 = v/v, 10 mL) with NH_4HCO_3 (316 mg, 4.00 mmol) for 1 h to give 365 mg (99 %) of a mixture of **3a** and **3b** as a brown oil, which was separated by column chromatography (*n*-hexane/EtOAc = 7:1) to give 297 mg (80 %) of **3a**.



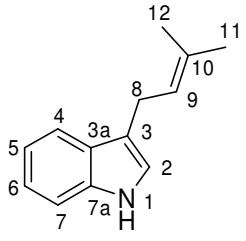
3a

R_f = 0.36. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.42 (d, *J* = 7.0 Hz, 3 H, 12-H), 1.66 (dd, *J* = 1.2 Hz, 6.0 Hz, 3 H, 11-H), 3.69 (dqd, *J* = 7.0 Hz, 6.6 Hz, 0.9 Hz, 1 H, 8-H), 5.54 (dqd, *J* = 15.0 Hz, 6.0 Hz, *J* = 0.9 Hz, 1 H, 10-H), 5.67 (ddq, *J* = 6.6 Hz, 15.0 Hz, 1.2 Hz, 1 H, 9-H), 6.88 (dd, *J* = 0.8 Hz, 2.4 Hz, 1 H, 2-H), 7.08 (ddd, *J* = 1.2 Hz, 7.0 Hz, 8.0 Hz, 1 H, 6-H), 7.16 (ddd, *J* = 8.0 Hz, 7.0 Hz, 1.2 Hz, 1 H, 5-H), 7.28 (dd, *J* = 1.2 Hz, 8.0 Hz, 1 H, 7-H), 7.64 (dd,

J = 1.2 Hz, 8.0 Hz, 1 H, 4-H), 7.78 (br. s, 1 H, NH). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ = 17.8 (q, C-11), 20.9 (q, C-12), 33.9 (d, C-8), 111.1 (d, C-7), 119.0 (d, C-4), 119.7 (d, C-5), 120.1 (d, C-6), 121.2 (s, C-3), 121.8 (d, C-2), 123.2 (d, C-10), 126.8 (s, C-3a), 136.2 (d, C-9), 136.6 (s, C-7a); peak assignment is based on gHMBC and gHSQC experiments. GC-MS (A): t = 8.2 min; *m/z* (%) = 185 (51) [M^+], 170 (100), 168 (13), 155 (23), 154 (20), 144 (18), 128 (11), 115 (12).

3-(3-Methylbut-2-enyl)-1*H*-indole (11a)[2]

Prenyl bromide (**4b**, 231 µL, 2.00 mmol) and indole (**1a**, 1.17 g, 10.0 mmol) were stirred in acetone/water (80/20 = v/v), 10 mL) with NH_4HCO_3 (316 mg, 4.00 mmol) for 2 h to give 370 mg (99 %) of a mixture of **11a** and other substituted indoles as a yellow oil, which was separated by column chromatography (*n*-hexane/EtOAc = 7:1) to give 338 mg (91 %) of **11a** as a pale yellow oil.

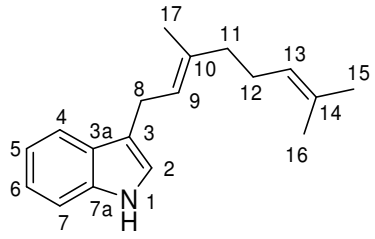


11a

R_f = 0.28. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.75, 1.76 (2 × d, J = 1.2 Hz, 2 × 3 H, 11-H, 12-H), 3.45 (d, J = 7.0 Hz, 2 H, 8-H), 5.43 (tsept, J = 7.0 Hz, 1.2 Hz, 1 H, 9-H), 6.90 (d, J = 2.1 Hz, 1 H, 2-H), 7.07–7.21 (m, 2 H, 5-H, 6-H), 7.30 (d, J = 7.8 Hz, 1 H, 7-H), 7.59 (d, J = 7.8 Hz, 1 H, 4-H), 7.79 (br. s, 1 H, NH). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ = 17.8, 25.7 (2 × q), 24.1 (t), 111.0 (d), 116.2 (s), 119.0 (d), 119.1 (d), 121.1 (d), 121.9 (d), 123.1 (d), 127.5 (s), 131.9 (s), 136.5 (s). GC-MS (A): t = 8.4 min; *m/z* (%) = 185 (97) [M^+], 170 (100), 155 (20), 143 (14), 130 (39), 117 (42), 77 (13).

3-[(2*E*)-3,7-Dimethylocta-2,6-dienyl]-1*H*-indole (12a)[2]

Geranyl bromide (**5b**, 726 µL, 5.00 mmol) and indole (**1a**, 2.93 g, 25.0 mmol) were stirred in acetone/water (80/20 = v/v, 25 mL) with NH_4HCO_3 (791 mg, 10.0 mmol) for 1 h to give 760 mg (60 %) of a mixture of **12a** and **12b** as a yellow oil, which was separated by column chromatography (*n*-hexane/EtOAc = 5:1) to give 713 mg (56 %) of **12a** as a yellow oil.

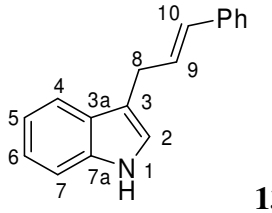


12a

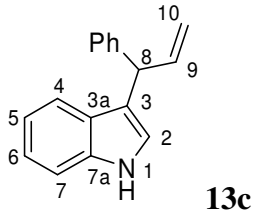
R_f = 0.53. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 1.60, 1.68 (2 × s, 2 × 3 H, 15-H, 16-H), 1.75 (s, 3 H, 17-H), 2.04–2.14 (m, 2 × 2 H, 11-H, 12-H), 3.46 (d, J = 6.8 Hz, 2 H, 8-H), 5.10–5.14 (m, 1 H, 13-H), 5.43–5.48 (m, 1 H, 9-H), 6.92 (d, J = 2.0 Hz, 1 H, 2-H), 7.07–7.23 (m, 2 × 1 H, 5-H, 6-H), 7.32 (dd, J = 7.9 Hz, 1.0 Hz, 1 H, 7-H), 7.59 (dd, J = 7.8 Hz, 1.0 Hz, 1 H, 4-H), 7.84 (br. s, 1 H, NH). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ = 16.1 (q), 17.7 (q), 24.0 (t), 25.7 (q), 26.7 (t), 39.7 (t), 111.0 (d), 116.2 (s), 119,0 (d), 119.1 (d), 121.2 (d), 121.9 (d), 122.9 (d), 124.4 (d), 127.5 (s), 131.4 (s), 135.6 (s), 136.5 (s). GC-MS (A): t = 11.1 min; *m/z* (%) = 253 (68) [M^+], 184 (100), 182 (48), 170 (54), 168 (47), 155 (15), 154 (15), 143 (18), 131 (22), 130 (77), 117 (35).

3-(3-Phenylallyl)-1*H*-indole (13a)[13] **und 3-(1-Phenylallyl)-1*H*-indole (13c)**

Cinnamyl bromide (**6b**, 763 mg, 5.00 mmol) and indole (**1a**, 2.93 g, 25.0 mmol) were stirred in acetone/water (80/20 = v/v, 25 mL) with NH_4HCO_3 (791 mg, 10.0 mmol) for 24 h to give 828 mg (71 %) of a mixture of **13a** and **13c** as a light brown oil.



13a



13c

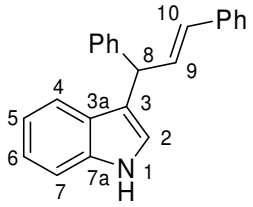
13a: ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.66 (d, J = 5.5 Hz, 2 H, 8-H), 6.58–6.42 (m, 2 × 1 H, 9-H, 10-H), 6.93 (s, 1 H, 2-H), 7.02–7.39 (m, 8 H, 5-H, 6-H, 7-H, Ar-H), 7.63 (d, J = 7.6 Hz, 1 H, 4-H), 7.83 (br. s, 1 H, NH). GC-MS (A): t = 12.7; *m/z* (%) = 233 (100) [M^+], 232 (56), 206 (17), 156 (24), 130 (42), 115 (24).

13c: ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.64 (d, J = 7.6 Hz, 1 H, 8-H), 4.88 (dd, J = 12 Hz, 7.6 Hz, 1 H, 9-H), 6.28–6.60 (m, 2 × 1 H, 2 × 10-H), 6.98 (s, 1 H, 2-H), 7.13–7.38 (m, 8 H,

5-H, 6-H, 7-H, Ar-H), 7.65 (d, J = 8.0 Hz, 1 H, 4-H), 7.82 (br. s, 1 H, NH). GC-MS (A): t = 10.5 min; m/z (%) = 233 (100) [M^+], 232 (67), 206 (39), 156 (29).

3-(1,3-Diphenylallyl)-1*H*-indole (14a)[5]

3-Bromo-1,3-diphenylpropene (**7b**, 1.37 g, 5.00 mmol) and indole (**1a**, 2.93 g, 25.0 mmol) were stirred in acetone/water (80/20 = v/v, 25 mL) with NH_4HCO_3 (791 mg, 10.0 mmol) for 48 h to give 928 mg (60 %) of a mixture of **14a** and **14b**, which was separated by column chromatography (*n*-hexane/EtOAc = 7:1) to give 866 mg (56 %) of **14a** as a colorless oil.

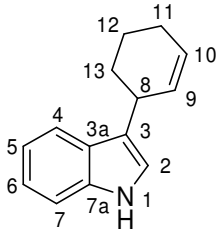


14a

R_f = 0.65. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.06 (d, J = 7.5 Hz, 1 H, 8-H), 6.34–6.42 (m, 1 H, 10-H), 6.63–6.67 (m, 1 H, 9-H), 6.80–7.01 (m, 3 H, Ar-H), 7.01–7.21 (m, 12 H, Ar-H), 7.91 (br. s, 1 H, NH). GC-MS (C): t = 9.5 min; m/z (%) = 232 (100) [M^+ – Ph], 219 (14), 117 (58), 90 (17).

3-Cyclohex-2-enyl-1*H*-indole (15a)[5]

3-Bromocyclohexene (**8**, 805 mg, 5.00 mmol) and indole (**1a**, 2.93 g, 25.0 mmol) were stirred in acetonitrile/water (90/10 = v/v, 25 mL) with NH_4HCO_3 (791 mg, 10.0 mmol) for 30 min to give 690 mg (70 %) of **15a** as a yellow oil.



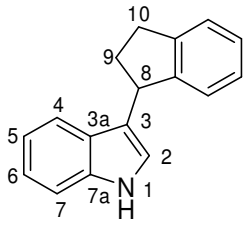
15a

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.56–2.12 (m, 3 × 2 H, 11-H, 12-H, 13-H), 3.70–3.75 (m, 1 H, 8-H), 5.84–5.86 (m, 2 × 1 H, 9-H, 10-H), 6.90 (d, J = 2.0 Hz, 2-H), 7.07 (dt, J = 7.5 Hz,

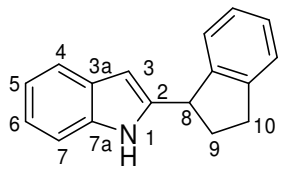
1.5 Hz, 1 H, 6-H), 7.18 (dt, *J* = 7.5 Hz, 1.5 Hz, 1 H, 5-H), 7.31 (dd, *J* = 8.0 Hz, 0.9 Hz, 1 H, 7-H), 7.65 (dd, *J* = 8.1 Hz, 1.0 Hz, 1 H, 4-H), 7.87 (br. s, 1 H, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 20.8, 25.3, 30.2 (3 × t), 32.7 (d), 111.2 (d), 119.1 (d), 119.2 (d), 120.9 (s), 121.4 (d), 121.8 (d), 126.7 (s), 127.6 (d), 130.4 (d), 136.6 (s). GC-MS (A): *t* = 9.3 min; *m/z* (%) = 197 (92) [M^+], 182 (11), 168 (100), 154 (11), 130 (12), 117 (28).

3-(Indan-1-yl)-1*H*-indole (16a) and 2-(Indan-1-yl)-1*H*-indole (16b)

1-Chloroindane (**9**, 763 mg, 5.00 mmol) and indole (**1a**, 2.93 g, 25.0 mmol) were stirred 24 h in acetone/water (80/20 = v/v, 25 mL) with NH_4HCO_3 (791 mg, 10.0 mmol) to give 595 mg (51 %) of a mixture of **16a** and **16b** as a colorless viscous oil.



16a

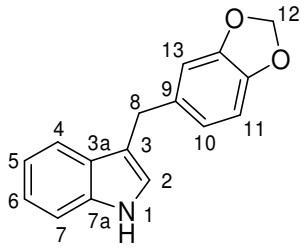


16b

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.15–2.28 (m, 1 H), 2.52–2.63 (m, 1 H), 2.91–3.06 (m, 2 H), 4.64 (t, *J* = 8.1 Hz, 1 H), 6.85 (d, *J* = 2.1 Hz, 1 H), 7.02–7.21 (m, 4 H), 7.31 (t, *J* = 8.1 Hz, 2 H), 7.46 (dd, *J* = 8.1 Hz, 0.9 Hz, 1 H), 7.83 (br. s, 1 H, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 31.7 (t), 34.8 (t), 42.4 (d), 111.2 (d), 119.2 (d), 119.5 (d), 119.7 (s), 121.4 (d), 121.9 (d), 124.4 (d) 124.7 (d), 126.2 (d), 126.4 (d), 126.9 (s), 136.7 (s), 144.0 (s), 146.6 (s). GC-MS (A): *t* = 11.8 min; *m/z* (%) = 233 (83) [M^+], 232 (100), 217 (25), 116 (26). HR-EI-MS: calcd. for $C_{17}H_{14}N$: 233.3158; found 233.1181.

3-Benzo[1,3]dioxol-5-ylmethyl-1*H*-indole (17a)

5-Chloromethyl-benzo[1,3]-dioxole (**10**, 676 mg, 5.00 mmol) and indole (**1a**, 2.93 g, 25.0 mmol) were stirred in acetone/water (80/20 = v/v, 25 mL) with NH_4HCO_3 (791 mg, 10.0 mmol) for 24 h to give 1.08 g (86 %) of a mixture of **17a** and **17b**, which was purified by recrystallization (*n*-hexane/Et_2O = 3:2) to give a white solid with m. p. = 197 °C.



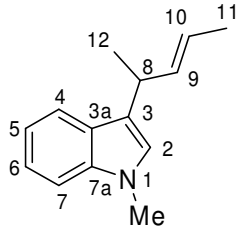
17a

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 4.03 (s, 2 H, 8-H), 5.89 (s, 2 H, 12-H), 6.69–6.76 (m, 3 × 1 H, 10-H, 11-H, 13-H), 6.93 (s, 1 H, 2-H), 7.07 (t, *J* = 7.5 Hz, 3.6 Hz, 1 H, 6-H), 7.18 (t, *J* = 7.2 Hz, 3.6 Hz, 1 H, 5-H), 7.35 (d, *J* = 3.9 Hz, 1 H, 7-H), 7.50 (d, *J* = 4.2 Hz, 1 H, 4-H), 7.94 (br. s, 1 H, NH). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ = 31.3 (t), 100.7 (t), 108.0 (d), 109.2 (d), 111.1 (d), 116.0 (s), 119.1 (d), 119.4 (d), 121.4 (d), 122.1 (d), 122.2 (d), 127.4 (s), 135.1 (s), 136.5 (s), 145.7 (s), 147.6 (s). GC-MS (A): *t* = 13.8 min; *m/z* (%) = 251 (100) [M^+], 250 (81), 220 (10), 191 (12), 130 (55). Anal. calcd. for ($C_{16}H_{13}NO_2$): C 76.47, H 5.23, N 5.58; found: C 76.20, H 5.42, N 5.52.

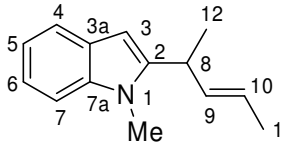
5.4.4 Friedel-Crafts Reactions with *N*-Methylindole

1-Methyl-3-(1-methylbut-2-enyl)-1*H*-indole (18a) and 1-Methyl-2-(1-methylbut-2-enyl)-1*H*-indol (18b)

4-Chloropent-2-ene (**2**, 580 µL, 5.00 mmol) and *N*-methylindole (**1b**, 3.20 mL, 25.0 mmol) were stirred in acetone/water (80/20 = v/v, 25 mL) with NH_4HCO_3 (791 mg, 10.0 mmol) for 1 h to give 986 mg (99 %) of a mixture of **18a** and **18b** as a yellow oil.



18a



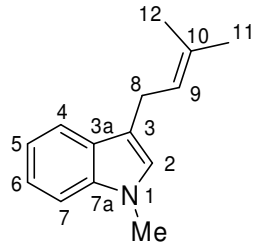
18b

18a: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.42 (d, J = 6.9 Hz, 3 H), 1.67 (dt, J = 6.0 Hz, J = 1.2 Hz, 3 H), 3.73 (s, 3 H), 5.48–5.73 (m, 2 H), 6.80 (s, 1 H), 7.05–7.28 (m, 3 H), 7.62 (d, J = 7.8 Hz, 1 H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 17.8 (q), 21.1 (q), 32.6 (d), 33.9 (q), 109.1 (d), 118.5 (d), 119.7 (d), 119.8 (s), 121.4 (d), 123.0 (d), 125.0 (d), 127.2 (s), 136.4 (d), 137.3 (s). GC-MS (A): t = 8.1 min; *m/z* (%) = 199 (47) [M^+], 184 (100), 168 (25).

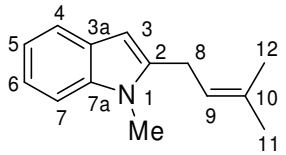
18b: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.37–1.42 (m, 3 H), 1.64–1.68 (m, 3 H), 3.65 (s, 3 H), 5.34–5.59 (m, 1 H), 6.28 (s, 1 H), 6.98–7.28 (m, 3 H), 7.55 (d, J = 7.5 Hz, 1 H). GC-MS (A): t = 8.2 min; *m/z* (%) = 199 (75) [M^+], 184 (100), 168 (29). Anal. calcd. for ($C_{14}H_{17}N$): C 84.13, H 8.58, N 7.05; found: C 84.37, H 8.60, N 7.03.

1-Methyl-3-(3-methylbut-2-enyl)-1*H*-indole (19a)[2] **und 1-Methyl-2-(3-methylbut-2-enyl)-1*H*-indole (19b)**[2]

Prenyl bromide (**4b**, 231 µL, 2.00 mmol) and *N*-methylindole (**1b**, 1.28 mL, 10.0 mmol) were stirred in acetone/water (80/20 = v/v, 10 mL) with NH_4HCO_3 (316 mg, 4.00 mmol) for 1 h to give 339 mg (85 %) of a mixture of **19a** and **19b** as a yellow liquid.



19a



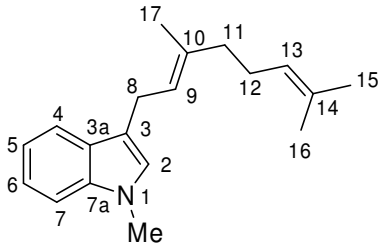
19b

19a: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.75, 1.76 (2 × s, 2 × 3 H, 11-H, 12-H), 3.43 (d, J = 6.9 Hz, 2 H, 8-H), 3.70 (s, 3 H, NMe), 5.42 (t*p*shept, J = 7.2 Hz, 1.2 Hz, 1 H, 9-H), 6.78 (s, 1 H, 2-H), 7.05–7.27 (m, 3 H, 5-H, 6-H, 7-H), 7.58 (dd, J = 8.1 Hz, 1.2 Hz, 1 H, 4-H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 17.8 (q), 24.0 (t), 25.7 (q), 32.5 (q), 109.1 (d), 114.6 (s), 118.5 (d), 119.1 (d), 121.5 (d), 123.3 (d), 126.0 (d), 127.8 (s), 131.7 (s), 137.2 (s). GC-MS (B): t = 8.3 min; *m/z* (%) = 199 (98) [M^+], 184 (100), 168 (25), 144 (44), 131 (55), 115 (12), 77 (9).

19b: ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.73, 1.75 (2 × s, 2 × 3 H, 11-H, 12-H), 3.43 (d, J = 6.9 Hz, 1 H, 8-H), 3.63 (s, 3 H, NMe), 5.31–5.37 (m, 1 H, 9-H), 6.23 (s, 1 H, 3-H), 7.02–7.27 (m, 3 H, 5-H, 6-H, 7-H), 7.51 (d, J = 8.1 Hz, 1 H, 4-H). GC-MS (B): t = 8.5 min; *m/z* (%) = 199 (100) [M^+], 184 (42), 168 (17), 158 (11), 144 (50), 131 (74), 115 (12), 77 (7).

1-Methyl-3-(3,7-dimethylocta-2,6-dienyl)-1*H*-indole (20a)

Geranyl bromide (**5b**, 434 mg, 2.00 mmol) and *N*-methylindole (**1b**, 1.28 mL, 10.0 mmol) were stirred in acetone/water (80/20 = v/v, 10 mL) with NH_4HCO_3 (316 mg, 4.00 mmol) for 1 h to give 365 mg (71 %) of a mixture of **20a** and **20b** as a yellow oil, which was separated by column chromatography (*n*-hexane/EtOAc = 7:1) to give 343 mg (67 %) of **20a**.



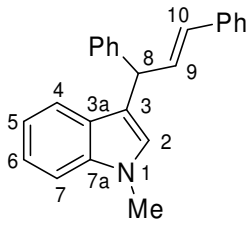
20a

R_f = 0.65^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.61, 1.68, 1.75 (3 × s, 3 × 3 H, 15-H, 16-H, 17-H), 1.97–2.17 (m, 2 × 2 H, 11-H, 12-H), 3.45 (d, J = 6.9 Hz, 8-H), 3.72 (s, 3 H, NMe), 5.10–5.15 (m, 1 H, 13-H), 5.42–5.47 (m, 1 H, 9-H), 6.78 (s, 1 H, 2-H), 7.08 (dt, J = 7.5 Hz,

1.5 Hz, 1 H, 6-H), 7.16–7.28 (m, 2 × 1 H, 5-H, 7-H), 7.57 (dd, *J* = 8.0 Hz, 1.2 Hz, 1 H, 4-H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 16.0 (q), 17.7 (q), 23.9 (t), 25.7 (q), 26.6 (t), 32.5 (q), 39.7 (t), 109.0 (d), 114.5 (s), 118.5 (d), 119.1 (d), 121.4 (d), 123.1 (d), 124.4 (d), 126.0 (d), 127.8 (s), 131.3 (s), 135.4 (s), 137.2 (s). GC-MS (A): *t* = 10.8 min; *m/z* (%) = 267 (100) [M^+], 198 (94), 184 (57), 168 (16), 144 (71), 131 (56). HR-EI-MS: calcd. for $C_{19}H_{25}N$: 267.4178; found 267.1997.

1-Methyl-3-(1,3-diphenylallyl)-1*H*-indole (21a)[5]

3-Bromo-1,3-diphenylpropene (**7b**, 1.37 g, 5.00 mmol) and *N*-methylindole (**1b**, 3.20 mL, 25.0 mmol) were stirred in acetone/water (80/20 = v/v, 25 mL) with NH_4HCO_3 (791 mg, 10.0 mmol) for 48 h to give 835 mg (50 %) of **21a** as a yellow oil containing traces of **21b**.

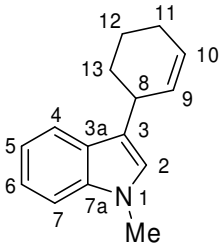


21a

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.73 (s, 3 H, NMe), 5.11 (d, *J* = 7.6 Hz, 1 H, 8-H), 6.41–6.47 (m, 1 H, 8-H), 6.69–6.77 (m, 1 H, 9-H), 6.99–7.18 (m, 1 H, Ar-H), 7.18–7.49 (m, 14 H, Ar-H). GC-MS (C): *t* = 10.1 min; *m/z* (%) = 246 (100) [M^+–Ph], 231 (51), 117 (64).

3-Cyclohex-2-enyl-1-methyl-1*H*-indole (22a)[13]

3-Bromocyclohexene (**8**, 585 µL, 5.00 mmol) and *N*-methylindole (**1b**, 3.20 mL, 25.0 mmol) were stirred in acetonitrile/water (90/10 = v/v, 25 mL) with NH_4HCO_3 (791 mg, 10.0 mmol) for 24 h to give 750 mg (71 %) of **22a** as a pale yellow oil.

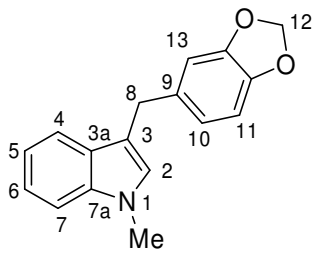


22a

^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.48–1.99 (m, 6 H, 11-H, 12-H, 13-H), 3.55 (s, 3 H, NMe), 3.56–3.64 (m, 1 H, 8-H), 5.71–5.82 (m, 2 × 1 H, 9-H, 10-H), 6.67 (s, 1 H, 2-H), 6.94–7.17 (m, 3 H, Ar-H), 7.53 (d, J = 7.8 Hz, 1 H, Ar-H). GC-MS (A): t = 9.09 min; *m/z* (%) = 211 (95) [M^+], 182 (100), 167 (29), 131 (29).

3-Benzo[1,3]dioxol-5-ylmethyl-1-methyl-1*H*-indole (23a)

5-Chloromethyl-benzo[1,3]-dioxole (**10**, 676 mg, 5.00 mmol) and *N*-methylindole (**1b**, 3.20 mL, 25.0 mmol) were stirred in acetone/water (80/20 = v/v, 25 mL) with NH_4HCO_3 (791 mg, 10.0 mmol) for 24 h to give 744 mg (56 %) of a mixture of **23a** and **23b**, which was separated by column chromatography (*n*-hexane/EtOAc = 7:1) to give 702 mg (53 %) of **23a**.

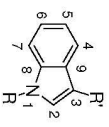


23a

R_f = 0.46. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.72 (s, 3 H, NMe), 4.00 (s, 2 H, 8-H), 5.88 (s, 2 H, 12-H), 6.69–6.76 (m, 4 H, Ar-H), 7.03–7.29 (m, 3 H, Ar-H), 7.49 (d, J = 7.8 Hz, 1 H, Ar-H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 31.6 (t), 32.9 (q), 101.1 (t), 108.3 (d), 109.4 (d), 109.6 (d), 114.7 (s), 119.1 (d), 119.5 (d), 121.6 (d), 121.9 (d), 127.3 (d), 128.1 (s), 135.7 (s), 137.5 (s), 146.0 (s), 147.9 (s). GC-MS (A): t = 13.1 min; *m/z* (%) = 265 (100) [M^+], 264 (74), 144 (83). HR-EI-MS: calcd. for $C_{19}H_{25}N$: 265.3146; found 265.1112.

5.4.5 Overview of ^{13}C-NMR Shifts of 3-Allylated Indoles

Table 5.4. Chemical shifts δ (ppm) in ^{13}C-NMR spectra (recorded at 75.5 MHz in $CDCl_3$) of 3-allylated indoles.



		3a	**11a**	**12a**	**15a**	**16a**	**17a**	**18a**	**19a**	**20a**	**23a**
Aliphatic and aromatic signals		17.8 (q)	17.8 (q)	16.1 (q)	20.8 (t)	31.7 (t)	31.3 (t)	17.8 (q)	17.8 (q)	16.0 (q)	31.6 (q)
		20.9 (q)	24.1 (t)	17.7 (q)	25.3 (t)	34.8 (t)	100.7 (t)	21.1 (q)	24.0 (t)	17.7 (q)	32.9 (t)
		33.9 (d)	25.7 (q)	24.0 (t)	30.2 (t)	42.4 (d)	108.0 (d)	32.6 (d)	25.7 (q)	23.9 (t)	101.1 (t)
		123.2 (d)	123.1 (d)	25.7 (q)	32.7 (d)	121.4 (d)	109.2 (d)	33.9 (q)	32.5 (q)	25.7 (q)	108.3 (d)
		136.2 (d)	131.9 (s)	26.7 (t)	127.6 (d)	124.7 (d)	122.1 (d)	123.0 (d)	123.3 (d)	26.6 (t)	109.4 (d)
				39.7 (t)	130.4 (d)	126.2 (d)	135.1 (s)	136.4 (d)	131.7 (s)	32.5 (q)	119.1 (d)
				121.2 (d)		126.4 (d)	145.7 (s)			39.7 (t)	135.7 (s)
				122.9 (d)		144.0 (s)	147.6 (s)			123.1 (d)	146.0 (s)
				131.4 (s)		146.6 (s)				124.4 (d)	147.9 (s)
				135.6 (s)						131.3 (s)	
										135.4 (s)	
Indole skeleton	C-7	111.1 (d)	111.0 (d)	111.0 (d)	111.2 (d)	111.2 (d)	111.1 (d)	109.1 (d)	109.1 (d)	109.0 (d)	109.6 (d)
	C-4	119.0 (d)	119.0 (d)	119.0 (d)	119.1 (d)	119.2 (d)	119.1 (d)	118.5 (d)	118.5 (d)	118.5 (d)	119.5 (d)
	C-5	119.7 (d)	119.1 (d)	119.1 (d)	119.2 (d)	119.5 (d)	119.4 (d)	119.7 (d)	119.1 (d)	119.1 (d)	121.6 (d)
	C-6	120.1 (d)	121.1 (d)	121.9 (d)	121.4 (d)	121.9 (d)	121.4 (d)	121.4 (d)	121.5 (d)	121.4 (d)	121.9 (d)
	C-3	121.2 (s)	116.2 (s)	116.2 (s)	120.9 (s)	119.7 (s)	116.0 (s)	119.8 (s)	114.6 (s)	114.5 (s)	114.7 (s)
	C-2	121.8 (d)	121.9 (d)	124.4 (d)	121.8 (d)	124.4 (d)	122.2 (d)	125.0 (d)	126.0 (d)	126.0 (d)	127.3 (d)
	C-9	126.8 (s)	127.5 (s)	127.5 (s)	126.7 (s)	126.9 (s)	127.4 (s)	127.2 (s)	127.8 (s)	127.8 (s)	128.1 (s)
	C-8	136.6 (s)	136.5 (s)	136.5 (s)	136.6 (s)	136.7 (s)	136.5 (s)	137.3 (s)	137.2 (s)	137.2 (s)	137.5 (s)

5.5 Literature

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Chapter 6

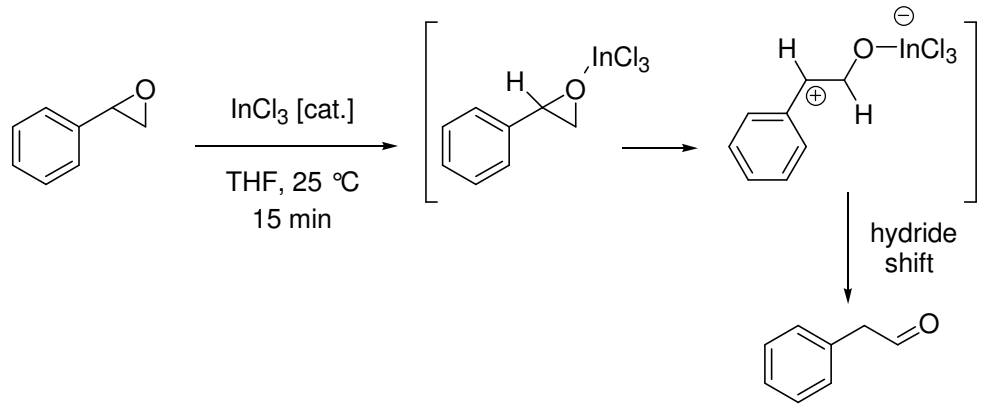
Regio- and Stereoselective Ring Opening Reactions of Epoxides with Indoles and Pyrroles in 2,2,2-Trifluoroethanol

This chapter is in print in *Chem. Eur. J.* by M. Westermaier and H. Mayr.

6.1 Introduction

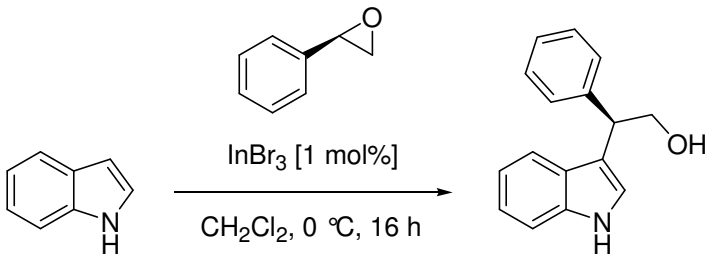
Epoxides are valuable building blocks in organic synthesis, as they are easily available in optically pure form[1-5] and give access to 1,2-difunctional ring opened products with two new stereocenters. Many methods for the stereoselective ring opening of epoxides with *N*-, *O*- and *S*-nucleophiles have been developed[6, 7], including enzymatic processes,[8-10] but regio- and stereoselective reactions with carbon nucleophiles have become the focus of recent research.[11-24] Apart from reactions with trimethylsilyl cyanide[11-15] and strong nucleophiles such as phenyllithium,[16] dialkyl zinc compounds,[17-20] or enolates,[21] reactions with electron-rich arenes, e. g. indoles and pyrroles, have been reported.[22-36]

As the nucleophilicities of indoles and pyrroles are not sufficient for a direct attack at ordinary epoxides, activation of the C-O bond is generally needed. The use of strong Lewis acids is problematic, because they may trigger isomerizations of the epoxides with formation of carbonyl compounds. Thus, Ranu and Jana reported a selective synthesis of benzylic aldehydes and ketones by treatment of the corresponding epoxides with 0.5 to 0.6 equivalents indium(III) chloride (Scheme 6.1).[25]



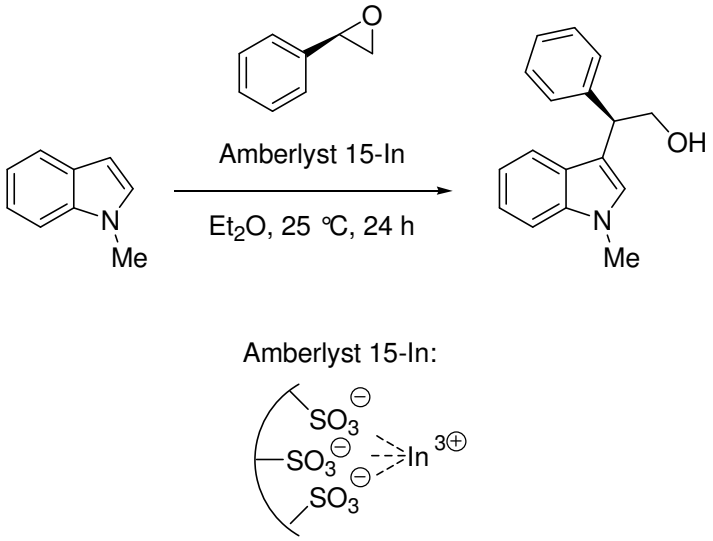
Scheme 6.1. Isomerization of styrene oxide in the presence of $InCl_3$ to form a carbonyl compound via cleavage of the C-O bond.[25]

On the other hand, the $InBr_3$-catalyzed reactions of indoles with optically pure styrene oxide gave 2-(1*H*-indol-3-yl)-2-phenylethanols in good yields with 99% *ee* (Scheme 6.2)[26] and $InCl_3$ has been successfully employed as catalyst for the reactions of indoles with racemic styrene oxide in dichloromethane. Under these conditions aliphatic epoxides gave mixtures of regioisomeric products with favored attack at the less substituted oxirane position.[27]



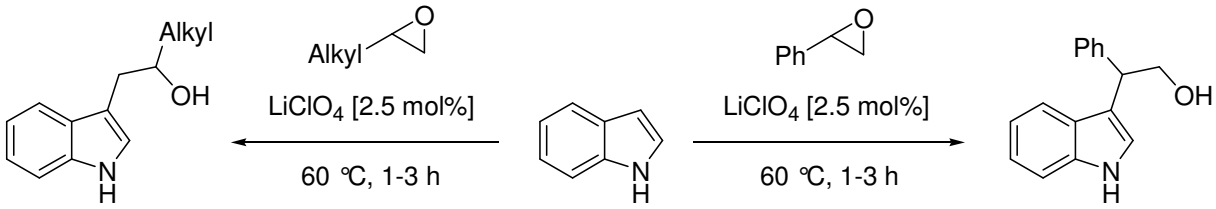
Scheme 6.2. Regio- and stereoselective ring opening reaction of indole with aromatic optically active epoxides in the presence of catalytic amounts of $InBr_3$.[26]

High enantioselectivities but lower yields (up to 64%) were obtained when the reaction of *N*-methylindole with enantiopure styrene oxide was catalyzed by a polymer-supported indium Lewis acid (Amberlyst-In, Scheme 6.3).[28]



Scheme 6.3. Regio- and stereoselective ring opening of optically pure (*R*)-styrene oxide with *N*-methylindole catalyzed by the heterogeneous Amberlyst 15-indium complex.[28]

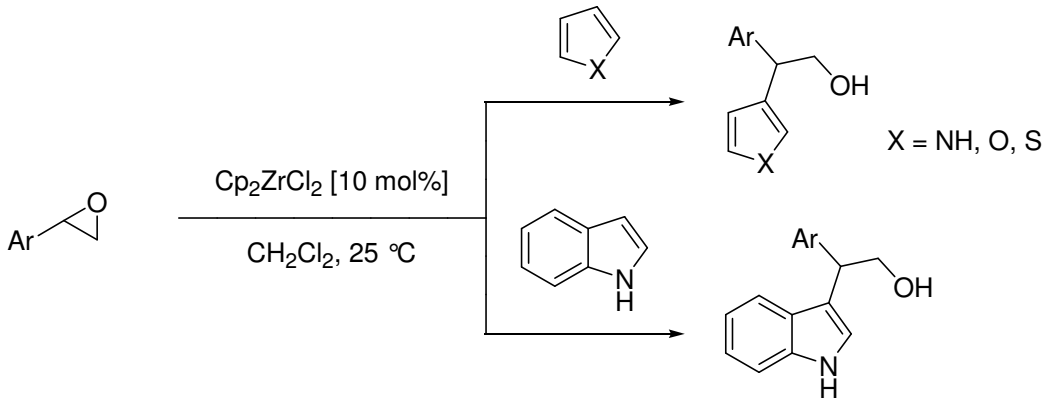
In order to avoid undesired isomerizations, most investigations of the reactions of indoles with epoxides employed mild Lewis acids. Thus, $LiClO_4$ has been reported to catalyze the reactions of aliphatic and aromatic epoxides with indoles to give high yields of 3-substituted indoles (Scheme 6.4); the stereochemistry of these reactions was not investigated.[29, 30]



Scheme 6.4. Reactions of indole with aliphatic and aromatic epoxides catalyzed by $LiClO_4$.[29]

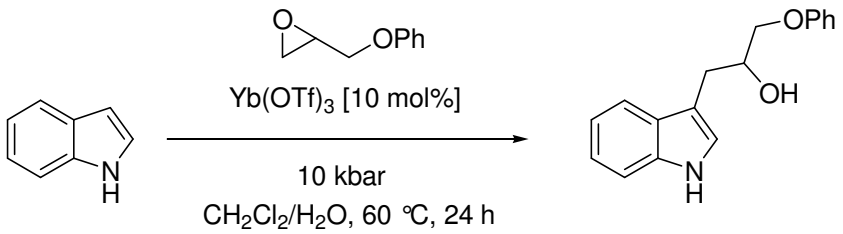
Somewhat lower yields of these substitution products were obtained when the reactions of indoles with styrene oxide were catalyzed by nanocrystalline titanium(IV) oxide.[31]

Aliphatic and aromatic epoxides were reported to react with indole, pyrrole, furan and thiophene in the presence of 10 mol% Cp_2ZrCl_2 to give good yields of substitution products (Scheme 6.5).[32] The NMR spectra which were claimed to indicate the regioselective 3-attack at these heteroarenes have not been published, however. Because enantiopure epoxides were not used in this study, the stereochemical course of these reactions could not be derived.



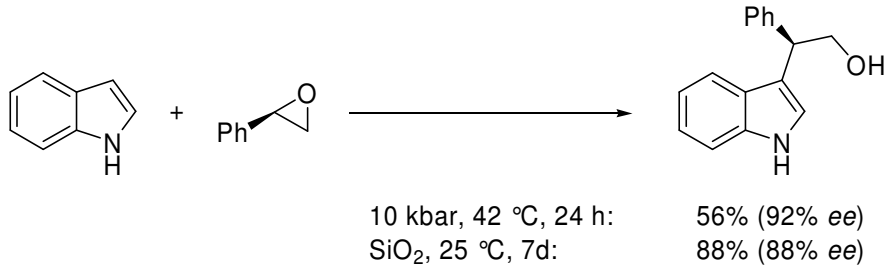
Scheme 6.5. Ring opening reactions of aromatic epoxides with heteraromatics catalyzed by bis(cyclopentadienyl)zirconium to yield regioselectively 3-substituted pyrroles, indoles, furans and thiophenes.[32]

Ytterbium(III) triflate was found to be the most efficient Lewis acid to catalyze the regio- and stereoselective reaction of indole with glycidyl phenyl ether at 10 kbar (Scheme 6.6).[33]



Scheme 6.6. $Yb(OTf_3)$-catalyzed ring opening reactions of glycidyl phenyl ether with indole under high pressure.[33]

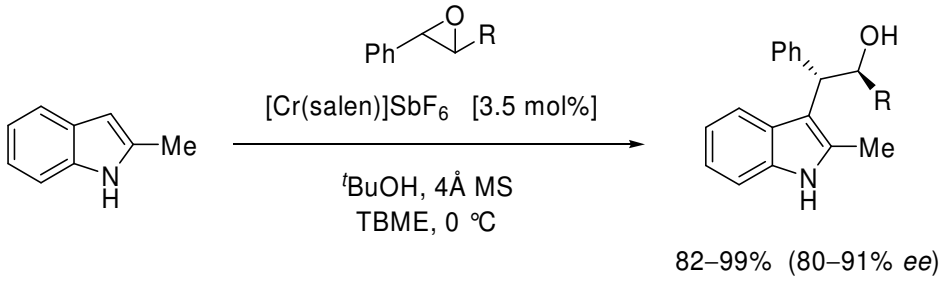
At elevated pressure (10 kbar) indole reacts with aromatic epoxides in acetonitrile even without a catalyst to give moderate yields of 2-(1*H*-indol-3-yl)-2-phenylethanols.[34] Later studies on the stereochemistry of the reaction of (*R*)-styrene oxide with indole in acetonitrile at 10 kbar and 42 °C showed that the substitution product was formed in 56% yield and 92% *ee* (Scheme 6.7). Addition of SiO_2 increased the yield but resulted in a slight drop of stereoselectivity.[35]



Scheme 6.7. High pressure and silica gel assisted ring opening reaction of indole with optically pure (*R*)-styrene oxide.[34, 35]

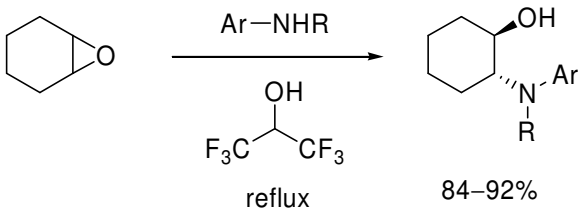
Also the HBF_4-silica gel supported reactions of styrene oxide with indoles and pyrroles in dichloromethane were reported to give substitution products in good yields but the stereochemistry was not investigated; aliphatic epoxides did not react.[36]

Enantioselective addition of 2-methylindole to aromatic epoxides catalyzed by [Cr(salen)] complexes resulted in kinetic resolution and formation of 3-substituted indoles in good yields with high enantioselectivities (Scheme 6.8).[37]



Scheme 6.8. Kinetic resolution of *trans*-epoxides with 2-methylindole.[37]

The well-known ionizing power of fluorinated alcohols[38] was previously employed by Bégué[39] to assist the ring opening of epoxides in their reactions with aromatic amines (Scheme 6.9).



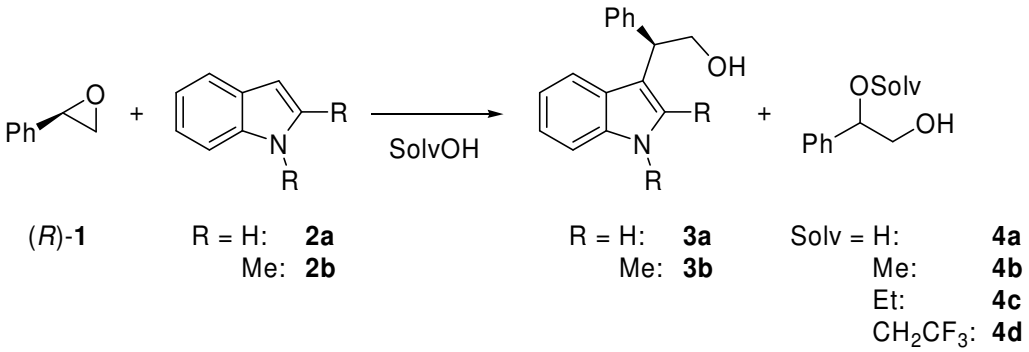
Scheme 6.9. Direct aminolysis of cyclohexene oxide with secondary amines in hexafluoro-isopropanol to yield racemates of β-aminoalcohols.[39]

We report now that 2,2,2-trifluoroethanol is also a suitable solvent for the non-catalyzed reaction of epoxides with indoles and pyrroles.

6.2 Results and Discussion

6.2.1 Screening of the Reaction Conditions

Winstein's investigations on the rates of nucleophilic substitutions have shown that the heterolyses of C-X bonds are assisted by protic solvents with high ionizing power *Y*.[40] In order to examine whether electrophilic assistance by protic solvents can also enable the attack of electron-rich arenes at epoxides, we studied the reactions of (*R*)-(+)-styrene oxide [(*R*)-**1**] with the parent indole (**2a**) and 1,2-dimethylindole (**2b**) in various solvents (Scheme 6.10).



Scheme 6.10. Optimization reactions of (*R*)-styrene oxide [(*R*)-**1**] with indole (**2a**) and 1,2-di-methylindole (**2b**) in different solvents.

Table 6.1 shows that indole (**2a**) did not react with racemic styrene oxide (*rac*-**1**) in methanol, ethanol, or 90% aqueous acetonitrile at 70–90 °C. In the latter case no conversion of **1** took place, while methanol and ethanol yielded small amounts of the corresponding 2-alkoxy-2-phenylethanols **4b** and **4c** (< 3% via GC-MS). Previously, we discovered that indoles are allylated and benzylated in 80% aqueous acetone in good yields when allyl and benzyl halides were stirred with indoles in this solvent.[41] Under these conditions no conversion of indole (**2a**) was observed at room temperature (Entry 4), but at 60 °C the reaction of **2a** with (*R*)-**1** gave 9% of (*R*)-**3a** in high optical yield (> 99% *ee*, Entry 5). Better yields of **3a** have been obtained in 40% aqueous ethanol (16% at room temperature and 45% at 80 °C, Entries 6 and 7). Best chemical yields (up to 79%, Entries 8 and 9) with high optical purity (> 99% *ee*) were observed when the reactions were performed in 2,2,2-trifluoroethanol.

Table 6.1. Reactions of (*R*)-styrene oxide [(*R*)-**1**] with indole (**2a**) and 1,2-dimethylindole (**2b**) in different solvents (1 M solutions) to yield compounds (*R*)-**3a** or (*R*)-**3b**.

no.	solvent[a]	Y[b]	N[c]	time / h	temp / °C	yield **3**[d] / %	*ee*[e] / %
Reactions with indole (**2a**)							
1	EtOH	–2.40	7.44	72	80	–[f]	–
2	MeOH	–1.12	7.54	72	70	–[g]	–
3	MeCN-H_2O (90/10)	–	4.56	72	90	–[h]	–
4	acetone-H_2O (80/20)	–0.70	5.77	72	25	–[h]	–
5	acetone-H_2O (80/20)	–0.70	5.77	72	60	9	> 99
6	EtOH-H_2O (40/60)	2.62	5.81	72	25	16	> 99
7	EtOH-H_2O (40/60)	2.62	5.81	72	80	45	> 99
8	CF_3CH_2OH	2.53	1.23	48	25	65[i]	> 99
9	CF_3CH_2OH	2.53	1.23	10	80	79	> 99
Reactions with 1,2-dimethylindole (**2b**)							
10	EtOH	–2.40	7.44	72	80	–[f]	–
11	MeOH	–1.12	7.54	72	70	–[g]	–
12	MeCN-H_2O (90/10)	–	4.56	72	90	–[h]	–
13	acetone-H_2O (80/20)	–0.70	5.77	72	25	7	> 99
14	acetone-H_2O (80/20)	–0.70	5.77	14	60	17	> 99
15	EtOH-H_2O (40/60)	2.62	5.81	72	25	29	> 99
16	EtOH-H_2O (40/60)	2.62	5.81	12	80	54	> 99
17	CF_3CH_2OH	2.53	1.23	24	25	77	> 99
18	CF_3CH_2OH	2.53	1.23	3	80	90	> 99

[a] Solvent mixtures are given as v/v. [b] Ionizing powers Y taken from ref.[38]. [c] Solvent nucleophilicities N taken from ref.[42]. [d] Isolated yields of **3a** (Entries 1–9) and **3b** (Entries 10–18) after column chromatography. [e] The enantiomeric excess was determined by chiral HPLC with probes taken from the crude reaction mixtures and from the isolated compounds, by comparing their retention times to those reported in literature (see also Experimental Section). [f] Trace amounts of **4c** have been detected in GC-MS. [g] Trace amounts of **4b** have been detected in GC-MS. [h] No conversion. [i] Trace amounts of **4d** have been detected in GC-MS.

1,2-Dimethylindole (**2b**) reacted similarly, but gave somewhat better yields. Again, nucleophilic attack of **2b** at *rac*-**1** was not observable in methanol, ethanol and acetonitrile/water (v/v = 90/10, Entries 10–12). When 80% aqueous acetone was used as the solvent 7% of (*R*)-**3b** have been isolated after 72 h at room temperature (Entry 13) and at 60 °C the yield increased to 17% after 14 h (> 99% *ee* in both cases, Entry 14).

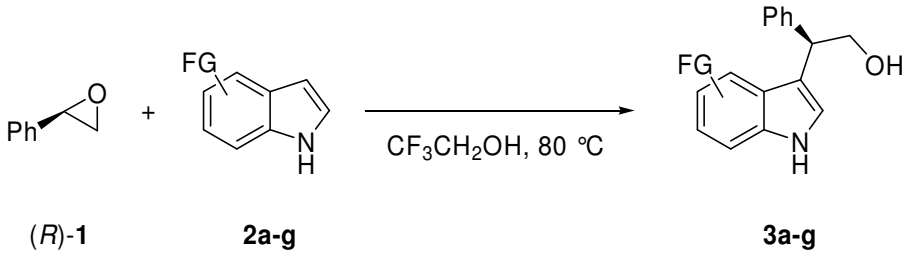
As with **2a**, higher yields of (*R*)-**3b** were obtained in ethanol/water (v/v = 40/60, Entries 15 and 16) and even 90% of optically pure (*R*)-**3b** have been obtained when 2,2,2-trifluoroethanol was used as the solvent (Entries 17 and 18).

These observations correlate with Winstein's ionizing power *Y* for the solvents used.[38] No reactions took place in poorly ionizing solvents such as ethanol (*Y* = –2.40) or methanol (*Y* = –1.12) while slow ring opening was observed in 80% aqueous acetone (*Y* = 0.70). The increased yields obtained in 40% aqueous ethanol reflect the higher ionizing power *Y* of this solvent (*Y* = 2.62). The excellent yields obtained in 2,2,2-trifluoroethanol are due to its high ionizing power (*Y* = 2.53) and low solvent nucleophilicity (*N* = 1.23), which explains the absence of side products which were observed in ethanol or methanol.

6.2.2 Variation of the Nucleophiles

6.2.2.1 Reactions of Styrene Oxide with Indoles

The conditions of experiments 9 and 18 (Table 6.1), *i. e.* heating equimolar amounts of heteroarenes and styrene oxide (**1**) in CF_3CH_2OH at 80 °C, were then employed for screening the scope of nucleophiles for this reaction (Scheme 6.11).

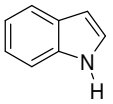
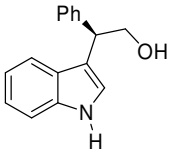
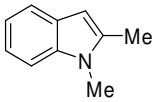
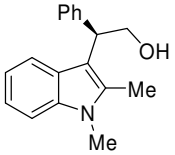
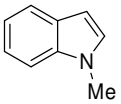
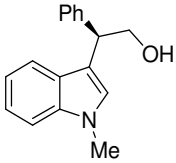
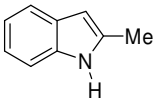
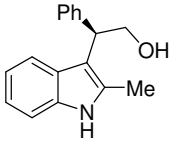
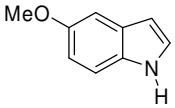
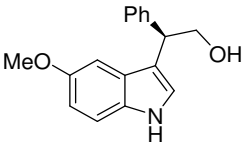
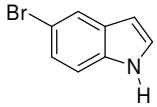
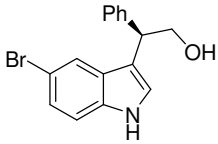
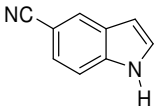


(*R*)-**1** **2a-g** **3a-g**

Scheme 6.11. Reactions of (*R*)-styrene oxide [(*R*)-**1**] with indoles **2a**–**g**.

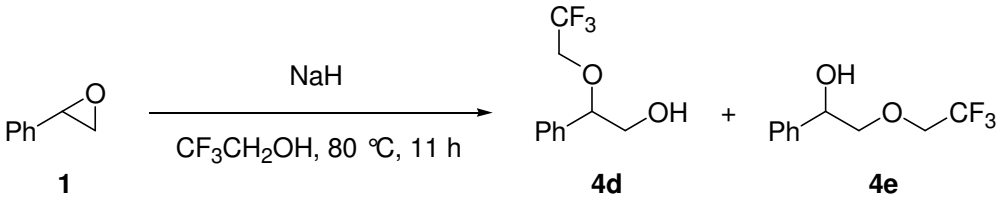
The reactions of the indoles **2a**–**e** with $N > 5$[43] gave exclusively the (*R*)-2-(1*H*-indol-3-yl)-2-phenylethanols **3a**–**e** in good chemical and excellent optical yields (Table 6.2). Exclusive substitution at the 3-position of the indole skeleton was observed. When indoles bearing electron-withdrawing groups have been used, the yields of the substitution products **3** decreased. 5-Bromoindole (**2f**) with $N = 4.38$[43] gave only 45% of **3f** accompanied by 19% of the trifluoroethyl ether **4d**, which is formed by nucleophilic attack of 2,2,2-trifluoroethanol at the benzylic position of **1**. The nucleophilicity of 5-cyanoindole (**2g**) is so low ($N = 2.83$)[43] that it does not act as a nucleophile at all and, again, the only reaction product detectable in GC-MS after 72 h at 80 °C was the ether **4d** in 17% yield. In line with these findings the even weaker nucleophile anisole ($N = -1.18$)[44, 45] did not react with styrene oxide (**1**) under these conditions.

Table 6.2. Reactions of optically pure (*R*)-styrene oxide [(*R*)-**1**] with indoles **2a**–**g** in CF_3CH_2OH (80 °C).

indole	N[a]	time / h	product		yield[b] / %	*ee*[c] / %
 **2a**	5.75	4		**3a**	79	> 99
 **2b**	8.55	3		**3b**	90	> 99
 **2c**	5.75	4		**3c**	73	> 99
 **2d**	6.91	3		**3d**	72	> 99
 **2e**	6.22	3		**3e**	72	> 99
 **2f**	4.38	72		**3f**	45[d]	> 99
 **2g**	2.83	72	–	**3g**	–[e]	–

[a] Nucleophilicity parameters *N* taken from ref. [43]. [b] Isolated yields of **3c**–**g** after column chromatography. [c] The enantiomeric excess was determined by chiral HPLC with probes taken from the crude reaction mixtures and from the isolated compounds, by comparing their retention times to those reported in literature (see also Experimental Section). [d] 19% of ether **4d** have been detected in GC-MS and conversion was not complete. [e] 17% of ether **4d** have been detected in GC-MS and no other conversion has been observed.

When CF_3CH_2OH acted as a nucleophile, styrene oxide (**1**) was also regioselectively attacked at the benzylic position to yield ether **4d**. Evidence for the constitution of **4d** comes from ^{13}C-NMR and GC-MS. A 2:1-mixture of **4d** and **4e** is formed by heating styrene oxide (**1**) in CF_3CH_2OH/CF_3CH_2ONa for 11 h at 80 °C (Scheme 6.12).



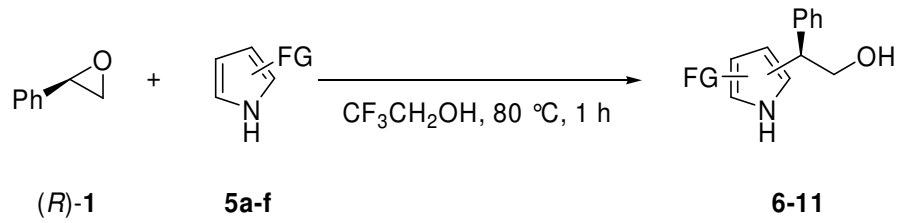
1 **4d** **4e**

Scheme 6.12. Synthesis of a 2:1-mixture of the trifluoroethyl ethers **4d** and **4e**.

Both ethers show only very small M^+-peaks, *m/z* = 220, but $PhCHOCH_2CF_3^{+\bullet}$ (*m/z* = 189) appears only in the spectrum of **4d**, whereas $PhCHOH^{+\bullet}$ (*m/z* = 107) was only found in the spectrum of **4e**. Both fragments are typical for each compound. According to the longer retention time of **4d** (*t* = 6.5 min) it is possible to differentiate both compounds in GC-MS. Another argument for the differentiation of **4d** and **4e** is given by the chemical shifts in the ^{13}C-NMR. While the benzylic carbon of **4d** absorbs at δ 84.6 ppm and the methylene group at δ 67.1 ppm, **4e** shows the corresponding peaks at δ 72.9 and δ 78.0 ppm. This is in line with the chemical shifts of the corresponding carbon atoms in 1-phenylethane-1,2-diol (**4a**) where the benzylic proton absorbs at δ 74.7 ppm and the CH_2 group at δ 67.9 ppm.[46] The ratio of 2:1 (**4d**:**4e**) was derived from the peak areas in GC-MS and ^{1}H-NMR integrals.

6.2.2.2 Reactions of Styrene Oxide with Pyrroles

As the pyrroles **5a**–**f** are somewhat more nucleophilic than the analogously substituted indoles, their reactions with styrene oxide (**1**) in CF_3CH_2OH at 80 °C were faster (Scheme 6.13, Table 6.3).



(*R*)-**1** **5a-f** **6-11**

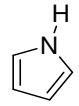
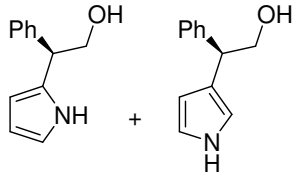
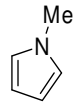
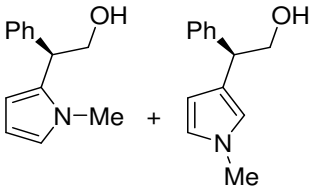
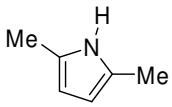
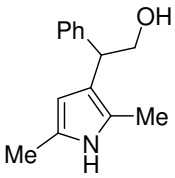
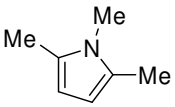
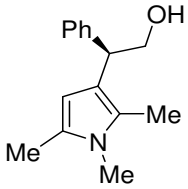
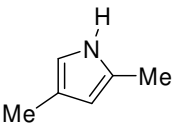
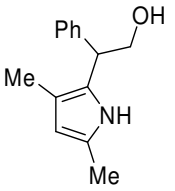
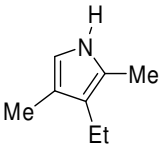
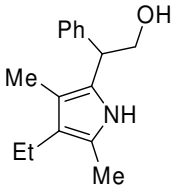
Scheme 6.13. Reactions of (*R*)-styrene oxide [(*R*)-**1**] with pyrroles **5a**–**f**.

The parent pyrrole (**5a**) gave a 2:1-mixture of the two regioisomers **6a** and **6b** in 68% yield within 1 h (Table 3, Entry 1). Monitoring the reaction via GC-MS revealed a change of the **6a/6b** ratio during the reaction. After 15 min only the 2-isomer **6a** was detectable in the GC. The ratio **6a/6b** decreased to 5.5 : 1 after 30 min, to 2.7 : 1 after 45 min and, finally, to 2.0 : 1 after 1 h. Attempts to elucidate the mechanism of the rearrangement of **6a** into **6b** have not been made. The bisalkylated pyrrole, 2-[5-(2-hydroxy-1-phenylethyl)-2-pyrrolyl]-2-phenyl-ethanol,[35] was obtained in 17% yield as a side product. Bisalkylation was suppressed when styrene oxide (**1**) was combined with 5 equivalents of pyrrole (**5a**).

N-Methylpyrrole (**5b**) reacted with (*R*)-**1** within 1 h to give a 1:1-mixture of **7a** and **7b**, which did not change during the reaction (Entry 2). Pyrroles **5c** and **5d**, where the 2- and 5-positions of the pyrrole ring are blocked by methyl groups, gave the 3-substitution products *rac*-**8** and (*R*)-**9** in 30% and 74% (> 99% *ee*) yield respectively. 2,4-Dimethylpyrrole (**5e**) and 3-ethyl-1,2-dimethylpyrrole (**5f**), the strongest nucleophiles in the series of alkyl substituted pyrroles, reacted with *rac*-**1** within 1 h to give *rac*-**10** and *rac*-**11** in 55% and 56% yield, respectively. The fact that in all reactions with pyrroles only moderate yields of substitution products are observed is probably due to their high tendency to oligomerize or polymerize leading to high boiling distillation residues.[47, 48] The isolated products showed high optical purity (> 99% *ee* in all examined cases).

All reactions in Tables 6.1 and 6.2, which were investigated stereochemically, were performed with racemic and optically pure styrene oxide (**1**). Because the two enantiomers obtained with racemic styrene oxide (*rac*-**1**) were separable by chiral HPLC, we can conclude that the substitution products obtained with enantiopure styrene oxide [(*R*)-**1**] had an optical purity of more than 99% *ee*.

Table 6.3. Reactions of (*R*)-styrene oxide [(*R*)-**1**] with pyrroles **5a–f** in CF_3CH_2OH (80 °C, 1 h).

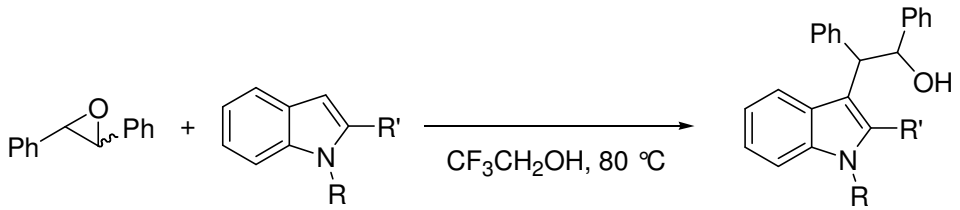
no.	pyrrole	product(s)		yield[a] / %	*ee*[b] / %
1	 **5a**		**6a/b**	68[c]	> 99
2	 **5b**		**7a/b**	55[d]	> 99
3	 **5c**		**8**	30	n. d.[e]
4	 **5d**		**9**	74	> 99
5	 **5e**		**10**	55	n. d.[e]
6	 **5f**		**11**	56	n. d.[e]

[a] Isolated yields of **6–11** after column chromatography. [b] The enantiomeric excess was determined by chiral HPLC with probes taken from the crude reaction mixtures and from the isolated compounds, by comparing their retention times to those reported in literature (see also Experimental Section). [c] 2:1-mixture of **6a/b**; 17% of 2,5-bis-(1-phenyl-2-hydroxyethyl)-1*H*-pyrrol have been obtained as a side product. [d] 1:1-mixture of **7a/b**, which was separated by column chromatography to yield 26% of (*R*)-**7a** and 21% of (*R*)-**7b**. [e] Not determined.

6.2.3 Variation of the Epoxides

6.2.3.1 Reactions of Indoles with Stilbene Oxides

Analogous reactions with *cis*- and *rac-trans*-stilbene oxide (**12**) were studied with the indoles **2a**–**c** (Scheme 6.14).

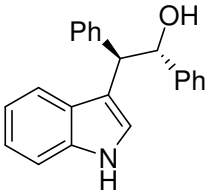
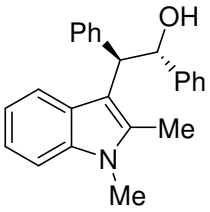
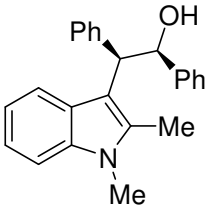
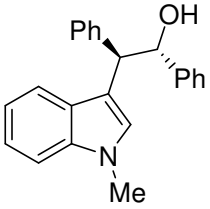
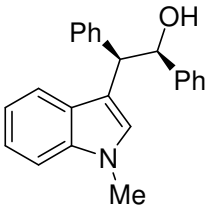


12 **2a-c** **13aa-13cb**

Scheme 6.14. Reactions of indoles **2a**–**c** with *rac-trans*- and *cis*-stilbene oxide (**12**).

In all cases the reactions with *rac-trans*-**12** gave considerably better yields than with *cis*-**12**; indole (**2a**) did not react with cis-**12** and the starting materials have been recovered (Table 4, Entry 2). Both diastereomers of stilbene oxide (**12**) reacted stereospecifically with **2b** and **2c**, and the NMR spectra of the resulting triarylethanols **13** showed that the diastereomers obtained from *trans*-**12** differed from those obtained from *cis*-**12**. In diastereomer **13ba**, obtained from *trans*-**12** and 1,2-dimethylindole (**2b**), the two benzylic protons absorb as doublets (J = 9.9 Hz) at δ 4.49 and δ 5.76 ppm while the corresponding resonances of the diastereomer **13bb** are at δ 4.55 (d, J = 8.9 Hz) and δ 5.76 ppm (dd, J = 8.9 and 3.6 Hz). The additional 3.6 Hz splitting of the δ 5.76 ppm resonance is due to coupling with the OH proton in CD_3CN (δ 3.05 ppm, d, J = 3.6 Hz). Analogous spectra were observed for the products **13ca** and **13cb** from the reactions of the stilbene oxides **12** with *N*-methylindole (**2c**).

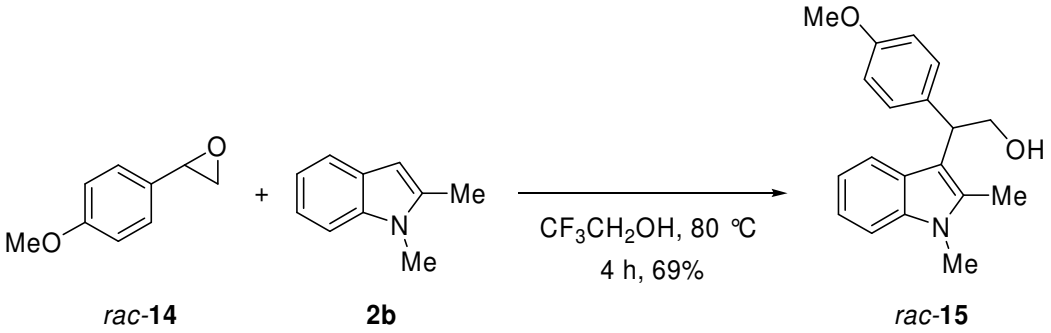
Table 6.4. Reactions of *rac-trans*- and *cis*-stilbene oxide (**12**) with indoles **2a**–**c** in CF_3CH_2OH (80 °C).

no.	indole	stilbene oxide	time / h	product		yield[a] / %
1	**2a**	*rac-trans*-**12**	42		*rac*-**13aa**	37
2	**2a**	*cis*-**12**	42	–	*rac*-**13ab**	–[b]
3	**2b**	*rac-trans*-**12**	9		***rac*-13ba**	66
4	**2b**	*cis*-**12**	24		*rac*-**13bb**	17
5	**2c**	*rac-trans*-**12**	29		*rac*-**13ca**	69
6	**2c**	*cis*-**12**	29		*rac*-**13cb**	19

[a] Isolated yields after column chromatography. [b] No conversion.

6.2.3.2 Reactions of Indoles with Other Aromatic Epoxides

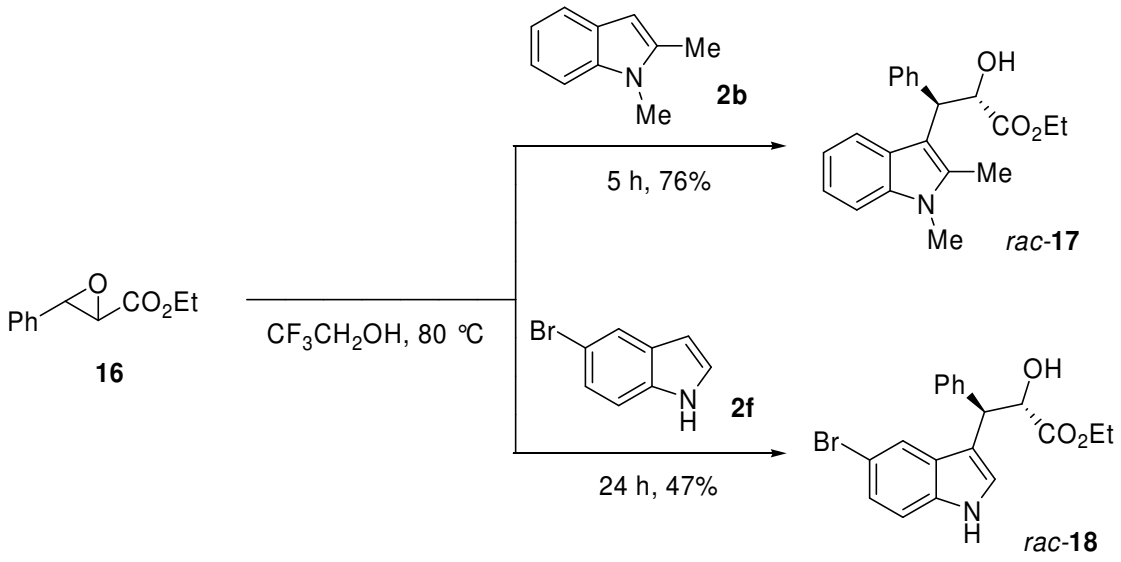
Racemic *p*-methoxyphenyloxirane (*rac*-**14**) reacted with 1,2-dimethylindole (**2b**) in 2,2,2-trifluoroethanol within 4 h to give alcohol *rac*-**15** in 69% yield (Scheme 6.15).



rac-**14** **2b** *rac*-**15**

Scheme 6.15. Reaction of 1,2-dimethylindole (**2b**) with *rac*-*p*-methoxyphenyloxirane (*rac*-**14**).

3-Phenyloxirane-2-carboxylic acid ethyl ester (**16**), which was used as a 8:1 mixture of *rac*-*trans*- and *cis*-isomers, turned out to be particularly reactive because this epoxide gave better yields with 5-bromoindole (**2f**) than styrene oxide (**1**, Scheme 6.16).

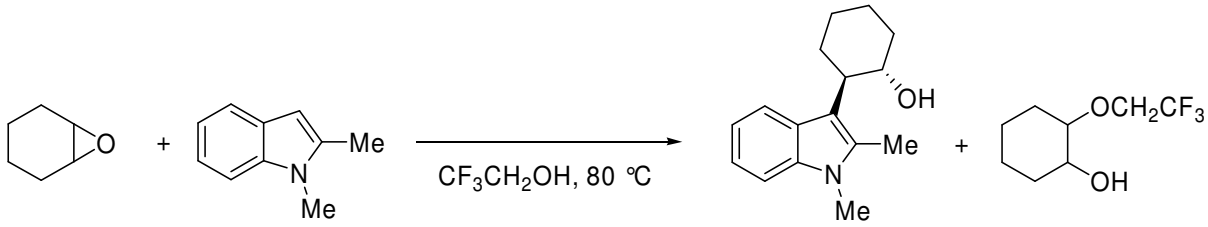


Scheme 6.16. Reactions of 1,2-dimethylindole (**2b**) and 5-bromoindole (**2f**) with 3-phenyloxirane-2-carboxylic acid ethyl ester (**16**) to yield α-hydroxy esters *rac*-**17** and *rac*-**18**.

NMR and GC-MS analysis of the products revealed that only one of the potential diastereomers (*rac*-**17**, *rac*-**18**) is formed. With the assumption that, again, back side attack of the nucleophile at the epoxide takes place, we can conclude that an exclusive reaction with *trans*-**16** took place while the *cis*-isomer was not attacked.

6.2.3.3 Reactions of 1,2-Dimethylindole with Aliphatic Epoxides

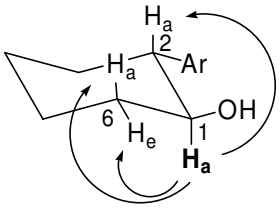
1,2-Dimethylindole (**2b**) was used as a probe to examine the reactions with aliphatic epoxides. Cyclohexene oxide (**19**) gave only 21% of **20** after 72 h whereas 2-(2,2,2-trifluoro-ethoxy)cyclohexanol (**21**) was obtained as the major product (Scheme 6.17). The yield of **20** increased to 31%, when the reaction mixture was heated for 1 week at 80 °C and additional 1.5 equivalents of **19** were added after 3 d and after 5d.



19 **2b** *rac*-**20** **21**

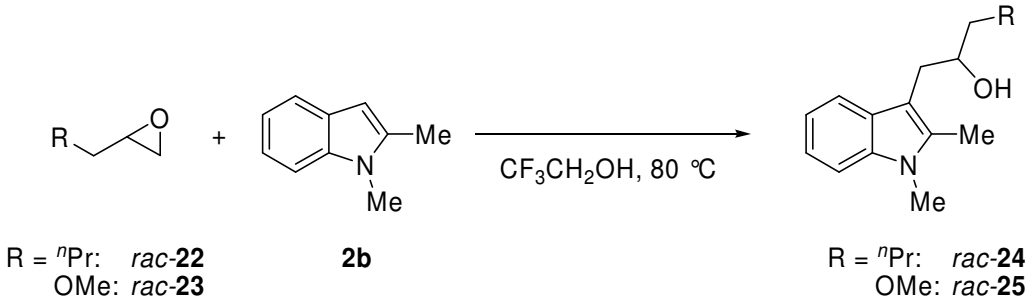
Scheme 6.17. Reaction of 1,2-dimethylindole (**2b**) with cyclohexene oxide (**19**) to yield secondary alcohol *rac*-**20**.

Again, back side attack at the epoxide is observed and **20** is formed as the only diastereomer. The *trans* configuration of **20** can be determined by analysis of the coupling constants of the C*H*OH group (H-1 in Scheme 6.18). It shows two axial-axial couplings of 10.4 Hz and one axial-equatorial coupling of 4.1 Hz, indicating that both OH group and indolyl group occupy equatorial positions of the cyclohexane ring.



Scheme 6.18. Chair conformation of **20** and vicinal coupling of 1-H (bold) with two axial protons (2-H, 6-H) and one equatorial proton (6-H).

The monosubstituted aliphatic epoxides *rac*-**22** and *rac*-**23** were selectively attacked at the less substituted oxirane position (Scheme 6.19).



Scheme 6.19. Reactions of 1,2-dimethylindole (**2b**) with 1,2-epoxyhexane (*rac*-**22**) and glycidyl methyl ether (*rac*-**23**).

1,2-Epoxyhexane (*rac*-**22**) gave 32% of alcohol *rac*-**24** after 10 h besides 28% of 1-(2,2,2-trifluoroethoxy)-2-hexanol (determined by GC-MS). The constitution of compound **24** is derived from its ^{1}H-NMR spectrum with a multiplet for C*H*OH at δ 3.84 ppm and two dd at δ 2.79 and 2.97 ppm for the diastereotopic protons at C-1 and from the ^{13}C-NMR spectrum where all CH_2 groups resonate at $\delta < 38$ ppm. The regioisomeric primary alcohol arising from nucleophilic attack at the higher substituted position of **22** should show the ^{1}H- and ^{13}C-NMR resonances of the CH_2OH group at lower field. Analogous NMR arguments allowed to identify *rac*-**25** as a secondary alcohol, which was formed in 51% yield when glycidyl methyl ether (*rac*-**23**) was heated with 1,2-dimethylindole (**2b**) for 48 h at 80 °C in 2,2,2-trifluoroethanol.

6.3 Conclusion

Aromatic and aliphatic epoxides can be attacked nucleophilically by electron-rich arenes when the ring opening reaction is electrophilically assisted by 2,2,2-trifluoroethanol. The high stereoselectivities of the reactions (> 99% *ee*) indicate the operation of S_N2 type processes also in case of styrene oxide, where nucleophilic attack occurs regioselectively at the benzylic position, i. e. at the position which is usually favored in S_N1 type reactions. The principle of electrophilic solvent assistance of S_N2 type reactions demonstrated in this work should systematically be explored also for other types of S_N2 reactions.

6.4 Experimental Section

6.4.1 General

All solvents were distilled prior to use. Water was purified with Millipore MilliQplus. All starting materials were commercially available and used as received, *N*-methylindole (**2c**), 2,5-dimethylpyrrole (**5c**), 2,4-dimethylpyrrole (**5e**) were distilled, 1,2-dimethylindole (**2b**) was recrystallized from methanol prior to use. 2-(4-Methoxyphenyl)oxirane (**14**) was synthesized according to the literature procedure.[49] ^{1}H-NMR spectra were recorded on Bruker ARX 300 and Varian Inova 400. Chemical shifts refer to TMS or the solvent resonance as the internal standard ($CDCl_3$: δ = 7.26 ppm, CD_3CN: δ = 1.94 ppm). Multiplicities are given as s = singlet, d = doublet, t = triplet, q = quartet, br = broad and m = multiplet. ^{13}C-NMR spectra were recorded on Bruker ARX 300 or Varian VXR 400 with broadband proton decoupling. Chemical shifts refer to TMS or the solvent as internal standard ($CDCl_3$: δ = 77.0 ppm, CD_3CN: δ = 1.32 and 118.3 ppm). Spin multiplicities are derived from DEPT135 spectra. GC-MS spectra were recorded on Agilent 5973 MSD (HP-5MS capillar column with 30 m length, 0.25 mm diameter, 1.0 mL/min flow rate, injector, split, He carrier gas, quadrupol mass spectrometer). The following temperature programs have been used: A: 40 °C (3 min) – 25 °C/min – 150 °C – 50 °C/min – 250 (8 min); B: 70 °C (2 min) – 25 °C/min – 150 °C – 50 °C/min – 250 °C (12 min); C: 70 °C (2 min) – 50 °C/min – 250 °C (8 min); D: 70 °C (2 min) – 25 °C/min – 150 °C – 50 °C/min – 250 °C (28 min). Chromatographic purification was done with Merck silica gel 60 (mesh 40-63 μm) by common or flash column chromatography. MPLC separation was done on a Büchi Sepacore System (pump manager C-615, C-605 pumps, C-660 fraction collector and C-635 photometer). HPLC analysis was performed on a Waters HPLC system (550 pumps, degasser, PDA, single injector). Chiralpak IB® was used as stationary phase (0.46 cm ID × 25 cm length) at 20 °C and calibrated with flavanone prior to use. Eluents, flow rate, detection and retention times are listed. In some cases Chiracel OD-H® (0.46 cm ID × 25 cm length) was used as chiral column. In some cases a basic additive (diethylamine = DEA) was added to the mobile phase. Kugelrohr distillations were performed on Büchi GKR-50 Kugelrohr oven. The boiling points refer to the oven temperature. Optical rotations were measured using a Perkin-Elmer polarimeter 343 over a path length of 10 cm with the sample temperature maintained at 20 °C in the solvent indicated. Melting points were measured on Büchi B-540 and are not corrected.

General reaction procedure:
To a solution of the nucleophile (3.0 mmol) in the corresponding solvent (3 mL), the epoxide (3.0 mmol) was added at once and stirred for the specified time at room temperature or under reflux.

Three different work-up techniques were employed:
A: When the reaction was finished the solvent was removed in vacuo and the crude product was purified by Kugelrohr distillation and/or column chromatography;
B: When the product precipitated from the reaction mixture it was filtered off, washed with cold EtOH (3 × 5 mL) and recrystallized from EtOH;
C: When aqueous solvent mixtures were used, Et_2O (10 mL) and then H_2O (10 mL) were added and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), and after evaporation of the solvent in vacuo the crude product was purified by Kugelrohr distillation and/or column chromatography.

6.4.2 Screening Reactions of Indoles with Styrene Oxide

The reactions of *rac*-styrene oxide (*rac*-**1**) with indole (**2a**) and 1,2-dimethylindole (**2b**) in methanol, ethanol and 90% aqueous acetonitrile have been performed according to the general reaction procedure (*vide infra*). After 72 h the reaction mixture was allowed to come to room temperature and worked up according to method A and C respectively. After column chromatography or distillation the starting materials have been recovered.
The experiments of the reactions of *rac*-styrene oxide (*rac*-**1**) with indole (**2a**) and 1,2-dimethylindole (**2b**) in 80% aqueous acetone and 40% aqueous ethanol, which were repeated analogously with enantiopure (*R*)-styrene oxide [(*R*)-**1**], are summarized in Table 6.5 and have been performed according to the general reaction procedure (*vide infra*), followed by work-up C.

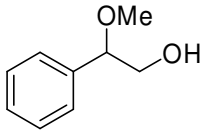
Table 6.5. Experiments for the reactions of styrene oxide (**1**) with indole (**2a**) and 1,2-dimethylindole (**2b**) in 80% aq. acetone and 40% aq. ethanol.

Solvent[a]	indole	**1**	time / h	temp / °C	product	yield / %[b]
acetone-H_2O (80/20)	**2a**: 5.0 mmol, 586 mg	5.0 mmol, 572 µL	72	25	**3a**	–[c]
	2a: 5.0 mmol, 586 mg	5.0 mmol, 572 µL	72	60	**3a**	107 mg (9%)
	2b: 2.5 mmol, 363 mg	2.5 mmol, 286 µL	72	25	**3b**	46.1 mg (7%)
	2b: 2.0 mmol, 291 mg	2.0 mmol, 229 µL	14	60	**3b**	90.3 mg (17%)
EtOH-H_2O (40/60)	**2a**: 5.0 mmol, 586 mg	5.0 mmol, 572 µL	72	25	**3a**	190 mg (16%)
	2a. 3.0 mmol, 351 mg	3.0 mmol, 343 µL	72	80	**3a**	171 mg (24%)
	2b: 5.0 mmol, 726 mg	5.0 mmol, 572 µL	72	25	**3b**	388 mg (29%)
	2b: 2.0 mmol, 291 mg	2.0 mmol, 229 µL	12	80	**3b**	287 mg (54%)

[a] Solvent mixtures given as v/v. [b] Isolated yields after column chromatography.
[c] Starting materials have been recovered.

2-Methoxy-2-phenylethanol (4b):[50]

Detected in GC-MS as a side product of the reaction of indole (**2a**) and 1,2-dimethylindole (**2b**) with styrene oxide (**1**) in methanol.

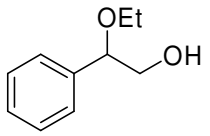


4b

GC-MS (B): t = 7.1 min; m/z (%) = 152 (5) [M^+], 135 (7) [M^+–H_2O], 121 (100) [M^+–CH_2OH], 91 (8).

2-Ethoxy-2-phenylethanol (4c):[51]

Detected in GC-MS as a side product of the reaction of indole (**2a**) and 1,2-dimethylindole (**2b**) with styrene oxide (**1**) in ethanol.

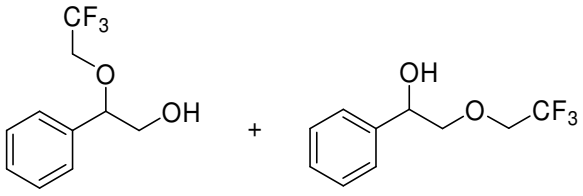


4c

GC-MS (B): t = 7.9 min; *m/z* (%) = 165 (5) [M^+], 135 (100) [M^+–CH_2OH], 91 (6).

2-Phenyl-2-(2,2,2-trifluoroethoxy)ethanol (4d) and 1-Phenyl-2-(2,2,2-trifluoroethoxy)-ethanol (4e):

A solution of *rac*-styrene oxide (*rac*-**1**, 571 µL, 5.00 mmol) in CF_3CH_2OH (5 mL) was cooled to 0 °C and sodium hydride (204 mg, 5.10 mmol) was added in portions. The reaction mixture was allowed to warm up to room temperature and then heated to 80 °C for 10 h. The mixture was poured onto saturated NaCl-solution (20 mL) and the aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with H_2O (30 mL) and dried ($MgSO_4$). After removal of the solvent *in vacuo* the crude product was purified by kugelrohr distillation (5×10^{-2} mbar, b. p. 131–140 °C) to yield a 2:1-mixture of **4d** and **4e** as a colorless liquid (561 mg, 51%).



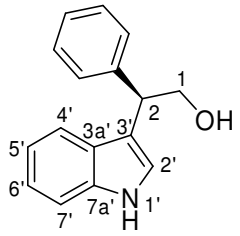
4e **4e**

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.55 (br. s, OH of **4d** and **4e**), 3.59–3.99 (m, 4 H, two CH_2 of **4d** and **4e**), 4.54 (dd, J = 3.6 Hz, 8.3 Hz, 0.66 H, CH of **4d**), 4.89 (dd, J = 3.2 Hz, 8.6 Hz, 0.34 H, CH of **4e**), 7.27–7.40 (m, 5 H, ArH of **4d** and **4e**); ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 66.2 (q, J_{CF} = 34 Hz), 67.1 (t), 68.8 (q, J_{CF} = 34 Hz), 72.9 (d), 78.0 (t), 84.6 (d), 123.9 (q, J_{CF} = 288 Hz), 126.2 (d), 126.9 (d), 128.1 (d), 128.2 (d), 128.6 (d), 128.9 (d), 136.7 (s), 139.7 (s); ^{19}F-NMR (282 MHz, $CDCl_3$): δ = –74.59 (t, J = 8.8 Hz, 3 F), –74.57 (t, J = 8.8 Hz, 3 F); GC-MS (B): **4e**: t = 6.2 min; m/z (%) = 189 (100); **4d**: t = 6.5 min; m/z (%) = 107 (100), 79 (59), 77 (37).

6.4.3 Reactions of Indoles with Styrene Oxide

(*R*)-2-(1*H*-Indol-3-yl)-2-phenylethanol (3a):[27, 30, 31, 34, 35]

Indole (**2a**, 351 mg, 3.00 mmol) and (*R*)-styrene oxide [(*R*)-1, 343 µL, 3.00 mmol] were stirred in CF_3CH_2OH (3 mL) at 80 °C (10 h) to yield (*R*)-**3a** after column chromatography (SiO_2, hexanes/ethyl acetate = 2:1) as a colorless solid (477 mg, 67%).

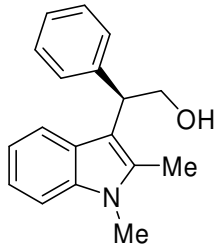


(*R*)-**3a**

R_f = 0.21. M. p. 121–122 °C (Lit: 120–122 °C).[27] $[\alpha^D_{20}]$ = + 12.8 ° (*c* 1.60, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.64 (br. s, 1 H, OH), 4.16 (dd, *J* = 7.1 Hz, 11 Hz, 1 H, 1-H), 4.23 (dd, *J* = 6.7 Hz, 11 Hz, 1 H, 1-H), 4.47 (t, *J* = 6.9 Hz, 1 H, 2-H), 7.04 (ddd, *J* = 0.9 Hz, 7.1 Hz, 7.9 Hz, 1 H, ArH), 7.07 (d, *J* = 2.2 Hz, 1 H, ArH), 7.15–7.24 (m, 2 H, ArH), 7.28–7.34 (m, 5 H, ArH), 7.44 (d, *J* = 7.9 Hz, 1 H, ArH), 8.09 (br. s, 1 H, NH). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 45.6 (d, 2-C), 66.4 (t, 1-C), 111.1 (d, 7'-C), 116.0 (s, 3'-C), 119.4 (d, 4'-C), 119.5 (d, 5'-C), 121.9 (d, 6'-C), 122.3 (d, Ph), 125.8 (d, 2'-C), 128.3 (s, 3a'-C), 128.6 (d, Ph), 128.7 (d, Ph), 136.5 (s, 7a'-C), 141.6 (s, Ph); peak assignment was done by 2D-NMR experiments. GC-MS (B): *t* = 12.6 min; *m/z* (%) = 237 (13) [M^+], 207 (18), 206 (100), 204 (17), 178 (13); Chiral HPLC: OD-H® (isocratic, *n*-heptane/*i*-propanol = 85:15, 0.5 mL/min, UV at 215 nm, $t_{(S)}$ = 28.7 min, $t_{(R)}$ = 37.8 min); IB® (isocratic, *n*-heptane/ *i*-propanol = 95:5 containing 0.01% DEA, 1.0 mL/min, UV at 275 nm, $t_{(S)}$ = 40.5 min, $t_{(R)}$ = 47.9 min), > 99% *ee*.

(*R*)-2-(1,2-Dimethyl-1*H*-indol-3-yl)-2-phenylethanol (3b):[28]

1,2-Dimethylindole (**2b**, 726 mg, 5.00 mmol) and (*R*)-styrene oxide [(*R*)-**1**, 572 µL, 5.00 mmol] were stirred in CF_3CH_2OH (5 mL) at 80 °C (3 h) to yield (*R*)-**3b** after column chromatography (SiO_2, hexanes/ethyl acetate = 1:1) as a yellow oil (1.19 g, 90%).

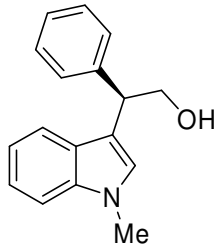


(*R*)-**3b**

R_f = 0.57. [α^D_{20}] = – 77.0 ° (*c* 1.45, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.53 (br. s, 1 H, OH), 2.29 (s, 3 H, 2'-Me), 3.59 (s, 3 H, NMe), 4.26 (d, *J* = 7.6 Hz, 2 H, 1-H), 4.43 (t, *J* = 7.6 Hz, 1 H, 2-H), 6.93 (ddd, *J* = 1.1 Hz, 7.0 Hz, 8.0 Hz, 1 H, ArH), 7.05–7.12 (m, 2 H, ArH), 7.15–7.27 (m, 5 H), 7.39 (d, *J* = 8.0 Hz, 1 H, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 10.7 (q), 29.6 (q), 45.4 (d), 65.1 (t), 108.9 (d), 109.3 (s), 119.1 (d), 119.2 (d), 120.7 (d), 126.2 (d), 127.9 (s), 128.4 (d), 135.2 (s), 136.9 (s), 141.9 (s). GC-MS (B): *t* = 13.5 min; *m/z* (%) = 265 (18) [M^+], 235 (20), 234 (100), 218 (10). Chiral HPLC: OD-H® (isocratic, *n*-heptane/*i*-propanol = 85:15, 0.5 mL/min, UV at 215 nm, $t_{(S)}$ = 24.3 min, $t_{(R)}$ = 29.0 min); IB® (isocratic, *n*-heptane/*i*-propanol = 95:5 containing 0.01% DEA, 1.0 mL/min, UV at 275 nm, $t_{(S)}$ = 11.7 min, $t_{(R)}$ = 26.3 min), > 99% *ee*.

(*R*)-2-(1-Methyl-1*H*-indol-3-yl)-2-phenylethanol (3c):[31, 34, 35]

N-Methylindole (**2c**, 384 µL, 3.00 mmol) and (*R*)-styrene oxide [(*R*)-**1**, 343 µL, 3.00 mmol] were stirred in CF_3CH_2OH (3 mL) at 80 °C (4 h) to yield (*R*)-**3c** after column chromatography (SiO_2, hexanes/ethyl acetate = 1:1) as a yellow oil (550 mg, 73%).



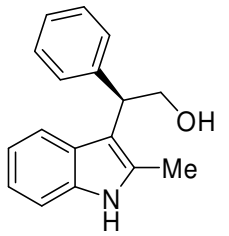
(*R*)-**3c**

R_f = 0.66. [α^D_{20}] = + 3.9 ° (*c* 1.66, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.82 (br. s, 1 H, OH), 3.73 (s, 3 H, NMe), 4.14 (dd, *J* = 7.1 Hz, 11 Hz, 1 H, 1-H), 4.21 (dd, *J* = 6.7 Hz, 11 Hz, 1 H, 1-H), 4.46 (t, *J* = 6.9 Hz, 1 H, 2-H), 6.93 (s, 1 H, ArH), 7.03 (ddd, *J* = 1.2 Hz, 6.9 Hz, 8.0 Hz, 1 H, ArH), 7.17–7.35 (m, 7 H, ArH), 7.45 (td, *J* = 0.9 Hz, 8.0 Hz, 1 H, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 32.7 (q), 45.6 (d), 66.4 (t), 109.2 (d), 114.4 (s), 119.0 (d),

119.4 (d), 121.8 (d), 126.6 (d), 126.7 (d), 127.4 (d), 128.2 (s), 128.6 (d), 137.2 (s), 141.8 (s); GC-MS (B): t = 12.0 min; *m/z* (%) = 251 (13), [M^+], 221 (18), 220 (100), 204 (11); Chiral HPLC: OD-H® (isocratic, *n*-heptane/*i*-propanol = 85:15, 0.5 mL/min, UV at 215 nm, $t_{(S)}$ = 22.7 min, $t_{(R)}$ = 45.3 min), IB® (isocratic, *n*-heptane/*i*-propanol = 90:10 containing 0.01% DEA, 1.0 mL/min, UV at 275 nm, $t_{(S)}$ = 13.6 min, $t_{(R)}$ = 23.3 min), > 99% *ee*.

(*R*)-2-(2-Methyl-1*H*-indol-3-yl)-2-phenylethanol (3d):[27, 30, 31, 34, 35]

2-Methylindole (**2d**, 394 mg, 3.00 mmol) and (*R*)-styrene oxide [(*R*)-**1**, 343 µL, 3.00 mmol] were stirred in CF_3CH_2OH (3 mL) at 80 °C (4 h) to yield (*R*)-**3d** after column chromatography (SiO_2, hexanes/ethyl acetate = 1:1) as a yellow oil (536 mg, 72%).

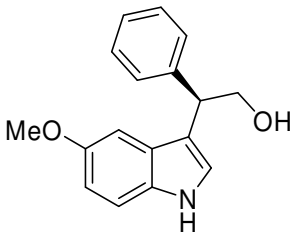


(*R*)-**3d**

R_f = 0.48. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.03 (s, 3 H, Me), 2.56 (s, 1 H, OH), 4.16 (d, J = 7.6 Hz, 2 H, 1-H), 4.31 (t, J = 7.6 Hz, 1 H, 2-H), 6.90–7.14 (m, 7 H, ArH), 7.20–7.22 (m, 2 H, ArH), 7.37 (d, J = 7.8 Hz, 1 H, ArH), 7.99 (s, 1 H, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 11.6 (q), 30.4 (d), 64.6 (t), 109.6 (d), 110.4 (d), 117.2 (d), 119.0 (d), 120.5 (d), 125.9 (d), 127.7 (d), 128.1 (d), 128.9 (s), 133.0 (s), 135.2 (s), 141.6 (s). GC-MS (B): t = 13.3 min; *m/z* (%) = 251 (15) [M^+], 221 (19), 220 (100), 204 (8), 178 (7). Chiral HPLC: IB® (isocratic, *n*-heptane/*i*-propanol = 90:10 containing 0.01% DEA, 1.0 mL/min, UV at 275 nm, $t_{(S)}$ = 18.4 min, $t_{(R)}$ = 21.1 min), > 99% *ee*.

(*R*)-2-(5-Methoxy-1*H*-indol-3-yl)-2-phenylethanol (3e):[31, 35]

5-Methoxyindole (**2e**, 442 mg, 3.00 mmol) and (*R*)-styrene oxide [(*R*)-**1**, 343 µL, 3.00 mmol] were stirred in CF_3CH_2OH (3 mL) at 80 °C (3 h) to yield (*R*)-**3e** after column chromatography (hexanes/ethyl acetate = 1:1) as a beige solid (577 mg, 72%).



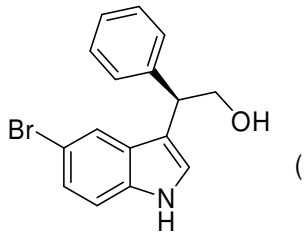
(*R*)-**3e**

R_f = 0.42. M. p. 89–90 °C (Lit: 89–90 °C).[35] ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.51 (br. s, 1 H, OH), 3.61 (s, 3 H, OMe), 4.00 (dd, *J* = 7.2 Hz, 11 Hz, 1 H, 1-H), 4.07 (dd, *J* = 6.8 Hz, 11 H,

1 H, 1-H), 4.30 (t, *J* = 6.9 Hz, 1 H, 2-H), 6.73–6.82 (m, 3 H, ArH), 7.00–7.24 (m, 6 H, ArH), 8.37 (br. s, 1 H, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 45.3 (d), 55.5 (q), 66.0 (t), 101.0 (d), 111.7 (d), 111.8 (d), 115.0 (s), 122.7 (d), 126.3 (d), 127.2 (s), 128.1 (d), 128.2 (d), 131.5 (s), 141.7 (s), 153.4 (s). GC-MS (B): *t* = 17.2 min; *m/z* (%) = 267 (16) [M^+], 237 (18), 236 (100), 204 (13); Chiral HPLC: IB® (isocratic, *n*-heptane/*i*-propanol = 90:10 containing 0.01% DEA, 1.0 mL/min, UV at 275 nm, $t_{(S)}$ = 31.5 min, $t_{(R)}$ = 33.4 min), > 99% *ee*.

(*R*)-2-(5-Bromo-1*H*-indol-3-yl)-2-phenylethanol (3f):

5-Bromoindole (**2f**, 588 mg, 3.00 mmol) and (*R*)-styrene oxide [(*R*)-**1**, 343 µL, 3.00 mmol] were stirred in CF_3CH_2OH (3 mL) at 80 °C (72 h) to yield **3f** as a colorless solid (427 mg, 45%).



(*R*)-**3f**

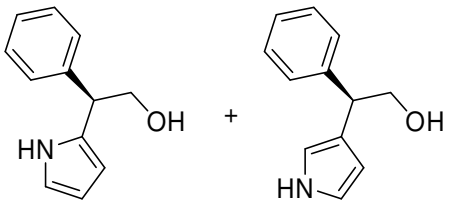
M. p. 127–128 °C (Lit: 129–130 °C). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.80 (br. s, 1 H, OH), 4.09 (dd, *J* = 7.1 Hz, 11 Hz, 1 H, 1-H), 4.16 (dd, *J* = 6.6 Hz, 11 Hz, 1 H, 1-H), 4.41 (t, *J* = 6.7 Hz, 1 H, 2-H), 7.11 (s, 1 H, ArH), 7.20–7.43 (m, 7 H, ArH), 7.58 (s, 1 H, ArH), 8.28 (br. s, 1 H, NH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 45.4 (d), 66.4 (t), 112.6 (d), 112.8 (s), 115.8 (s), 121.8 (d), 123.1 (d), 125.1 (d), 126.9 (d), 128.2 (d), 128.7 (d), 128.8 (s), 135.0 (s), 141.2 (s). GC-MS (B): *t* = 21.1 min; *m/z* (%) = 317 (12), 315 (12), 287 (15), 286 (99), 285 (17), 284 (100), 204 (39), 176 (10). Chiral HPLC: IB® (isocratic, *n*-heptane/*i*-propanol = 98:2

containing 0.01% DEA, 1.0 mL/min, UV at 275 nm, $t_{(S)}$ = 45.3 min, $t_{(R)}$ = 53.8 min), > 99% *ee*.

6.4.4 Reactions of Pyrroles with Styrene Oxide

(*R*)-2-Phenyl-2-(1*H*-pyrrol-2-yl)ethanol (6a) and (*R*)-2-phenyl-2-(1*H*-pyrrol-3-yl)-ethanol (6b):[35]

Pyrrole (**5a**, 119 µL, 1.00 mmol) and (*R*)-styrene oxide [(*R*)-**1**, 114 µL, 1.00 mmol] were stirred in CF_3CH_2OH (1 mL) at 80 °C (1 h) to yield a 2:1-mixture of **6a** and **6b** after column chromatography (SiO_2, hexanes/ethyl acetate = 1:2) as a yellow oil (127 mg, 68%).



(*R*)-**6a** (*R*)-**6b**

6a: R_f = 0.31. GC-MS (A): *t* = 10.8 min; *m/z* (%) = 187 (100) [M^+], 156 (100), 128 (12). Chiral HPLC: OD-H® (isocratic, *n*-heptane/*i*-propanol = 85:15, 0.5 mL/min, UV at 215 nm, $t_{(S)}$ = 38.7 min, $t_{(R)}$ = 41.1 min), > 99% *ee*.

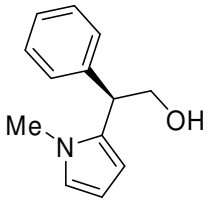
6b: R_f = . 0.37. GC-MS (A): *t* = 10.4 min; m/z (%) = 187 (8) [M^+], 156 (100), 128 (17). Chiral HPLC: OD-H® (isocratic, *n*-heptane/*i*-propanol = 85:15, 0.5 mL/min, UV at 215 nm, $t_{(S)}$ = 25.9 min, $t_{(R)}$ = 31.0 min), > 99% *ee*.

6a + **6b**: ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 2.73 (br. s, 1 H, OH of **6b**), 3.02 (br. s, 2 H, OH of **6a**), 3.87–4.17 (m, 3 H, 1-H and 2-H of **6b** and 6 H, 1-H and 2-H of **6a**), 5.90–5.93 (m, 2 H of **6a**), 6.02–6.09 (m, 2 H of **6a** d 1 H of **6b**), 6.57–6.61 (m, 1 H of **6b**), 6.62–6.71 (m, 2 H of **6a** and 1 H of **6b**), 7.18–7.40 (m, 10 H of **6a** and 5 H of **6b**), 9.08 (br. s, 1 H of **6b** and 2 H of **6a**).

(*R*)-2-Phenyl-2-(1-methyl-1*H*-pyrrol-2-yl)ethanol (7a) and (*R*)-2-phenyl-2-(1-methyl-1*H*-pyrrol-3-yl)ethanol (7b):[35]

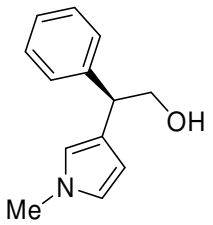
1-Methylpyrrole (**5b**, 119 µL, 1.00 mmol) and (*R*)-styrene oxide [(*R*)-**1**, 114 µL, 1.00 mmol] were stirred in CF_3CH_2OH (1 mL) at 80 °C (1 h) to yield a 1:1-mixture of **7a** and **7b** after

column chromatography (SiO_2, hexanes/ethyl acetate = 1:1) as a yellow oil (111 mg, 55%) which was separated again by column chromatography.



(*R*)-**7a**

7a: R_f = 0.42. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.78 (br. s, 1 H, OH), 3.33 (s, 3 H, NMe), 3.89–4.20 (m, 3 H, 1-H, 2-H), 6.14–6.18 (m, 2 H, ArH), 6.59 (t, J = 2.4 Hz, 1 H, ArH), 7.14–7.32 (m, 5 H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 33.7 (q), 46.5 (d), 66.4 (t), 105.5 (d), 106.8 (d), 122.4 (d), 126.9 (d), 128.2 (d), 128.7 (d), 131.6 (s), 140.2 (s). GC-MS (A): t = 10.7 min; *m/z* (%) = 201 (9) [M^+], 170 (100). Chiral HPLC: OD-H® (isocratic, *n*-heptane/*i*-propanol = 85:15, 0.5 mL/min, UV at 215 nm, $t_{(S)}$ = 17.2 min, $t_{(R)}$ = 10.5 min, > 99% *ee*.

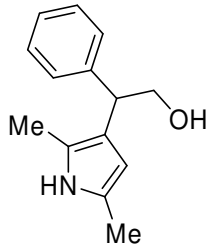


(*R*)-**7b**

7b: R_f = 0.39. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.78 (br. s, 1 H, OH), 3.60 (s, 3 H; NMe), 3.94–4.10 (m, 3 H, 1-H, 2-H), 6.03 (t, J = 2.1 Hz, 1 H, ArH), 6.43 (s, 1 H, ArH), 6.56 (t, J = 2.1 Hz, 1 H, ArH), 7.20–7.31 (m, 5 H, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 41.8 (q), 47.2 (d), 67.3 (t), 107.8 (d), 120.1 (s), 122.3 (d), 123.8 (d), 126.7 (d), 128.3 (d), 128.7 (d), 142.8 (s). GC-MS (A): t = 10.4 min; m/z (%) = 201 (11) [M^+], 170 (100). Chiral HPLC: OD-H® (isocratic, *n*-heptane/*i*-propanol = 85:15, 0.5 mL/min, UV at 215 nm, $t_{(S)}$ = 9.2 min, $t_{(R)}$ = 12.6 min), > 99% *ee*.

***rac*-2-(2,5-Dimethyl-1*H*-pyrrol-3-yl)-2-phenylethanol (*rac*-8):**[35]

2,5-Dimethylpyrrole (**5c**, 119 µL, 1.00 mmol) and *rac*-styrene oxide (*rac*-**1**, 114 µL, 1.00 mmol) were stirred in CF_3CH_2OH (1 mL) at 80 °C (1 h) to yield *rac*-**8** after column chromatography (SiO_2, hexanes/ethyl acetate = 1:1) as orange oil (65 mg, 30%).

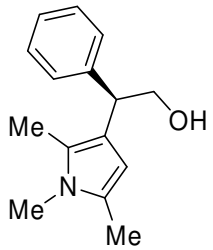


rac-**8**

R_f = 0.31. ^{1}H-NMR (400 MHz, CD_3CN): δ = 2.07 (s, 3 H, 2'-Me), 2.12 (s, 3 H, 5'-Me), 2.44 (br. s, 1 H, OH), 3.88–3.97 (m, 3 H, 1-H, 2-H), 5.64 (s, 1 H, 4'-H), 7.12–7.27 (m, 5 H, ArH), 8.43 (br. s, 1 H, NH). ^{13}C-NMR (100 MHz, CD_3CN): δ = 11.0 (q), 12.7 (q), 46.6 (d), 66.9 (t), 105.2 (d), 127.4 (d), 128.5 (d), 128.9 (d), 129.2 (s), 130.6 (s), 138.3 (s), 145.4 (s). GC-MS (B): t = 9.0 min; *m/z* (%) = 215 (12) [M^+], 185 (15), 184 (100).

(*R*)-2-Phenyl-2-(1,2,5-trimethyl-1*H*-pyrrol-3-yl)ethanol (9):

1,2,5-Trimethylpyrrole (**5d**, 238 µL, 2.00 mmol) and (*R*)-styrene oxide [(*R*)-1, 228 µL, 2.00 mmol] were stirred in CF_3CH_2OH (2 mL) at 80 °C (1 h) to yield **9** after column chromatography (SiO_2, hexanes/ethyl acetate = 3:1) as a yellow oil (339 mg, 74%).

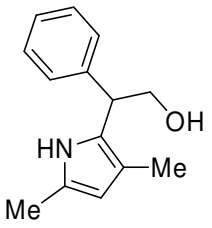


(*R*)-**9**

R_f = 0.31. ^{1}H-NMR (400 MHz, CD_3CN): δ = 2.09 (s, 3 H), 2.14 (s, 3 H), 2.49 (br. s, 1 H, OH), 3.31 (s, 3 H, NMe), 3.82–3.97 (m, 3 H, 1-H, 2-H), 5.71 (s, 1 H, 4'-H), 7.13–7.17 (m, 1 H, ArH), 7.22–7.29 (m, 4 H, ArH). ^{13}C-NMR (100 MHz, CD_3CN): δ = 10.1 (q), 12.4 (q), 30.4 (q), 46.8 (d), 66.9 (t), 104.6 (d), 119.3 (s), 124.9 (s), 126.6 (d), 127.7 (s), 128.9 (d), 129.0 (d), 145.5 (s); GC-MS (B): t = 9.4 min; *m/z* (%) = 229 (14) [M^+], 198 (100), 196 (7), 182 (7), 181 (6). Chiral HPLC: IB® (isocratic, *n*-heptane/*i*-propanol = 90:10 containing 0.01% DEA, 1.0 mL/min, UV at 275 nm, $t_{(S)}$ = 31.5 min, $t_{(R)}$ =36.6 min), > 99% *ee*. HR-EI-MS: $C_{15}H_{19}NO$ calcd. 229.1467, found 229.1473.

***rac*-2-(3,5-Dimethyl-1*H*-pyrrol-2-yl)-2-phenylethanol (10):**

2,4-Dimethylpyrrole (**5e**, 119 µL, 1.00 mmol) and *rac*-styrene oxide (*rac*-**1**, 114 µL, 1.00 mmol) were stirred in CF_3CH_2OH (1 mL) at 80 °C (1 h) to yield *rac*-**10** after column chromatography (SiO_2, hexanes/ethyl acetate = 1:1) as a yellow oil (118 mg, 55%).

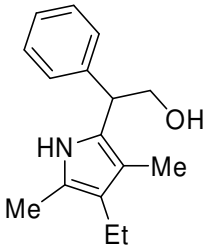


rac-**10**

R_f = 0.30. ^{1}H-NMR (400 MHz, CD_3CN): δ = 1.90 (s, 3 H, 3'-Me), 2.13 (s, 3 H, 5'-Me), 2.80 (br. s, 1 H, OH), 3.93–4.01 (m, 2 H, 1-H), 4.11–4.14 (m, 1 H, 2-H), 5.52 (s, 1 H, 4'-H), 7.16–7.31 (m, 5 H, ArH), 8.59 (br. s, 1 H, NH). ^{13}C-NMR (100 MHz, CD_3CN): δ = 11.2 (q), 12.8 (q), 45.9 (d), 65.7 (t), 108.5 (d), 115.2 (s), 126.4 (s), 127.0 (d), 127.1 (s), 128.9 (d), 129.3 (d), 143.6 (s). GC-MS (B): *t* = 8.5 min; *m/z* (%) = 215 (12) [M^+], 185 (15), 184 (100).

***rac*-2-(4-Ethyl-3,5-dimethyl-1*H*-pyrrol-2-yl)-2-phenylethanol (11):**

3-Ethyl-2,4-dimethylpyrrole (**5f**, 246 mg, 2.00 mmol) and *rac*-styrene oxide (*rac*-**1**, 229 µL, 2.00 mmol) were stirred in CF_3CH_2OH (2 mL) at 80 °C (1 h) to yield *rac*-**11** after column chromatography (SiO_2, hexanes/ethyl acetate = 2:1) as a yellow oil (272 mg, 56%).



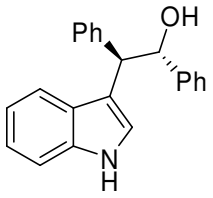
rac-**11**

R_f = 0.33. ^{1}H-NMR (400 MHz, CD_3CN): δ = 0.98–1.03 (m, 3 H, CH_2CH_3), 1.88 (s, 3 H, 3'-Me), 2.09 (s, 3 H, 5'-Me), 2.29–2.35 (m, 2 H, CH_2CH_3), 3.79 (s, 1 H, OH), 3.94 (dd, *J* = 6.8 Hz, 11 Hz, 1 H, 1-H), 3.99 (dd, *J* = 6.6 Hz, 11 Hz, 1 H, 1-H), 4.13 (dd, *J* = 6.7 Hz, 6.7 Hz, 1 H, 2-H), 7.24–7.32 (m, 5 H, ArH), 8.40 (br. s, 1 H, NH). ^{13}C-NMR (100 MHz, CD_3CN): δ = 9.26 (q), 10.8 (q), 16.1 (q), 18.1 (t), 45.9 (d), 65.6 (t), 113.9 (s), 126.7 (s), 127.0 (d), 128.9 (d), 129.2 (s), 129.3 (d), 143.7 (s). GC-MS (B): *t* = 9.2 min; *m/z* (%) = 243 (15) [M^+], 213 (21), 212 (100), 196 (8), 181 (9).

6.4.5 Reactions of Indoles with Stilbene Oxides

***rac*-2-(1*H*-Indol-3-yl)-1,2-diphenylethanol (13aa)**:[27, 31, 34]

Indole (**2a**, 234 mg, 2.00 mmol) and *rac-trans*-stilbene oxide (*rac-trans*-**12**, 397 mg, 2.00 mmol) were stirred in CF_3CH_2OH (2 mL) at 80 °C (42 h) to yield *rac*-**13aa** after column chromatography (SiO_2, hexanes/ethyl acetate = 2:1) as a pale yellow oil (231 mg, 37%).

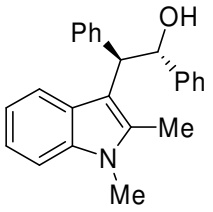


rac-**13aa**

R_f = 0.52. ^{1}H-NMR (400 MHz, CD_3CN): δ = 3.24 (d, J = 4.3 Hz, 1 H, OH), 4.63 (d, J = 8.7 Hz, 1 H, 2-H), 5.46 (dd, J = 4.3 Hz, 8.7 Hz, 1 H, 1-H), 6.94–7.50 (m, 15 H, ArH), 9.06 (br. s, 1 H, NH). ^{13}C-NMR (100 MHz, CD_3CN): δ = 50.9 (d), 76.6 (d), 110.9 (d), 116.8 (s), 119.2 (d), 119.3 (d), 122.0 (d), 122.5 (d), 126.6 (d), 126.8 (d), 127.0 (s), 127.4 (d), 128.0 (d), 128.3 (d), 129.4 (d), 135.9 (s), 140.2 (s), 142.8 (s). GC-MS (D): t = 26.0 min; m/z (%) = 313 (1) [M^+], 207 (28), 206 (100), 204 (13), 178 (10), 77 (4).

***rac*-2-(1,2-Dimethyl-1H-indol-3-yl)-1,2-diphenylethanol (13ba):**

1,2-Dimethylindole (**2b**, 291 mg, 2.00 mmol) and *rac-trans*-stilbene oxide (*rac-trans*-**12**, 397 mg, 2.00 mmol) were stirred in CF_3CH_2OH (2 mL) at 80 °C (9 h) to yield *rac*-**13ba** as colorless crystals (450 mg, 66%).



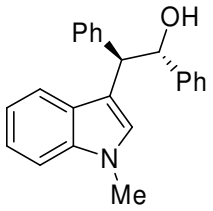
rac-**13ba**

M. p. 158–159 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.02 (s, 3 H, 2'-Me), 2.26 (s, 1 H, OH), 3.42 (s, 3 H, NMe), 4.49 (d, J = 9.9 Hz, 1 H, 2-H), 5.76 (d, J = 9.9 Hz, 1 H, 1-H), 6.99–7.33 (m, 11 H, ArH), 7.58–7.60 (m, 2 H, ArH), 7.69–7.71 (m, 1 H, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 10.2 (q), 29.4 (q), 52.1 (d), 74.9 (d), 108.6 (d), 111.2 (s), 118.7 (d), 119.6 (d),

120.1 (d), 126.3 (d), 126.4 (d), 126.6 (s), 127.2 (d), 127.7 (d), 128.5 (d), 128.8 (d), 133.6 (s), 136.7 (s), 142.0 (s), 143.1 (s). GC-MS (D): t = 25.2 min; *m/z* (%) = 341 (1) [M^+], 235 (20), 234 (100), 218 (8).

***rac*-2-(1-Methyl-1*H*-indol-3-yl)-1,2-diphenylethanol (13ca):**

N-Methylindole (**2c**, 260 µL, 2.00 mmol) and *rac-trans*-stilbene oxide (*rac-trans*-**12**, 397 mg, 2.00 mmol) were stirred in CF_3CH_2OH (2 mL) at 80 °C (29 h) to yield *rac*-**13ca** after column chromatography (SiO_2, hexanes/ethyl acetate = 3:1) as an orange oil (452 mg, 69%).

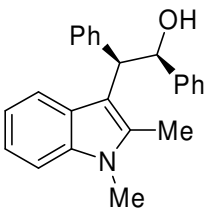


rac-**13ca**

R_f = 0.44. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.33 (br. s, 1 H, OH), 3.36 (s, 3 H, NMe), 4.52 (d, J = 6.3 Hz, 1 H, 2-H), 5.33 (d, J = 6.3 Hz, 1 H, 1-H), 6.87–6.92 (m, 2 H, ArH), 7.03–7.15 (m, 10 H, ArH), 7.18–7.22 (m, 2 H, ArH), 7.27 (ddd, J = 0.7 Hz, 1.8 Hz, 7.8 Hz, 1 H, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 32.3 (q), 50.8 (d), 76.3 (d), 108.9 (d), 115.2 (s), 118.6 (d), 119.1 (d), 121.3 (d), 126.4 (d), 126.5 (d), 127.1 (d), 127.2 (d), 127.3 (s), 127.8 (d), 128.0 (d), 129.3 (d), 136.6 (s), 140.4 (s), 142.9 (s). GC-MS (D): t = 22.6 min; *m/z* (%) = 327 (1) [M^+], 221 (20), 220 (100), 204 (8), 178 (5).

***rac*-2-(1,2-Dimethyl-1*H*-indol-3-yl)-1,2-diphenylethanol (13bb):**[28]

1,2-Dimethylindole (**2b**, 294 mg, 2.00 mmol) and *cis*-stilbene oxide (*cis*-**12**, 397 mg, 2.00 mmol) were stirred in CF_3CH_2OH (2 mL) at 80 °C (24 h) to yield *rac*-**13bb** after column chromatography (SiO_2, hexanes/ethyl acetate = 2:1) as colorless crystals (116 mg, 17%).

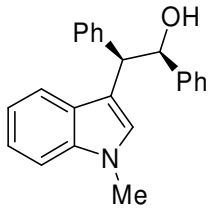


rac-**13bb**

R_f = 0.48. M. p. 147–148 °C (Lit: 147–150 °C). ^{1}H-NMR (400 MHz, CD_3CN): δ = 2.34 (s, 3 H, 2'-Me), 3.05 (d, J = 3.6 Hz, 1 H, OH), 3.63 (s, 3 H, NMe), 4.55 (d, J = 8.9 Hz, 1 H, 2-H), 5.76 (dd, J = 3.6 Hz, 8.9 Hz, 1 H, 1-H), 6.98–7.05 (m, 2 H, ArH), 7.09–7.14 (m, 3 H, ArH), 7.17–7.26 (m, 3 H, ArH), 7.30–7.36 (m, 5 H, ArH), 7.81 (d, J = 8.0 Hz, 1 H, ArH). ^{13}C-NMR (100 MHz, CD_3CN): δ = 10.8 (q), 30.0 (q), 52.7 (d), 75.8 (d), 109.8 (d), 111.3 (s), 119.5 (d), 120.6 (d), 121.1 (d), 126.6 (d), 127.8 (s), 128.0 (d), 128.2 (d), 128.7 (d), 128.8 (d), 129.5 (d), 136.3 (s), 137.9 (s), 144.2 (s), 145.2 (s). GC-MS (D): t = 26.8 min; *m/z* (%) = 341 (1) [M^+], 235 (20), 234 (100), 218 (8).

***rac*-2-(1-Methyl-1*H*-indol-3-yl)-1,2-diphenylethanol (13cb)**:[37]

N-Methylindole (**2c**, 260 µL, 2.00 mmol) and *cis*-stilbene oxide (*cis*-**12**, 397 mg, 2.00 mmol) were stirred in CF_3CH_2OH (2 mL) at 80 °C (29 h) to yield *rac*-**13cb** after column chromatography (SiO_2, hexanes/ethyl acetate = 2:1) as colorless crystals (124 mg, 19%).



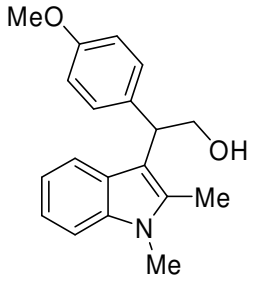
rac-**13cb**

R_f = 0.54. M. p. 36–38 °C (Lit: 36–39 °C). ^{1}H-NMR (300 MHz, CD_3CN): δ = 2.53 (br. s, 1 H, OH), 3.77 (s, 3 H, NMe), 4.56 (d, J = 8.1 Hz, 1 H, 2-H), 5.31 (d, J = 8.1 Hz, 1 H, 1-H), 7.00–7.28 (m, 14 H, ArH), 7.44 (br. d, J = 7.8 Hz, 1 H, ArH). ^{13}C-NMR (75.5 MHz, CD_3CN): δ = 32.8 (q), 52.2 (d), 77.7 (d), 109.2 (d), 113.7 (s), 119.1 (d), 119.5 (d), 121.9 (d), 126.2 (d), 126.8 (d), 127.2 (d), 127.3 (d), 127.9 (d), 128.0 (s), 128.1 (d), 128.6 (d), 137.1 (s), 141.9 (s), 142.5 (s). GC-MS (D): t = 22.6 min; *m/z* (%) = 327 (1) [M^+], 221 (20), 220 (100), 204 (8), 178 (5).

6.4.6 Reactions of Indoles with Other Aromatic Epoxides

***rac*-2-(1,2-Dimethyl-1*H*-indol-3-yl)-2-(4-methoxyphenyl)ethanol (15):**

1,2-Dimethylindole (**2b**, 436 mg, 3.00 mmol) and 2-(4-methoxyphenyl)oxirane (*rac*-**14**, 451 mg, 3.00 mmol) were stirred in CF_3CH_2OH (3 mL) at 80 °C (4 h) to yield *rac*-**15** after column chromatography (SiO_2, hexanes/ethyl acetate = 2:1) as a yellow oil (611 mg, 69%).

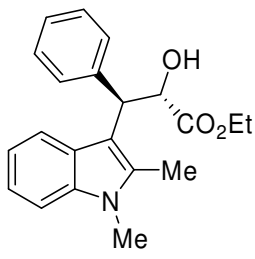


rac-**15**

R_f = 0.42. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.61 (br. s, 1 H, OH), 2.36 (s, 3 H, 2'-Me), 3.66 (s, 3 H, NMe), 3.75 (s, 3 H, OMe), 4.29 (d, J = 8.4 Hz, 2 H, 1-H), 4.45 (t, J = 7.8 Hz, 1 H, 2-H), 6.80 (d, J = 6.3 Hz, 2 H, ArH), 7.00 (dd, J = 8.1 Hz, 8.1 Hz, 1 H, ArH), 7.14 (dd, J = 8.1 Hz, 8.1 Hz, 1 H, ArH), 7.22–7.28 (m, 3 H, ArH), 7.46 (d, J = 8.1 Hz, 1 H, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 10.6 (q), 29.6 (q), 44.6 (d), 55.2 (q), 65.3 (t), 108.8 (d), 109.5 (s), 113.8 (d), 119.1 (d), 119.3 (d), 120.6 (d), 126.6 (s), 128.8 (d), 133.9 (s), 135.0 (s), 136.9 (s), 157.9 (s). GC-MS (B): t = 19.7 min; *m/z* (%) = 295 (11) [M^+], 277 (11), 265 (21), 264 (100), 262 (8), 220 (9).

***rac*-Ethyl 3-(1,2-dimethyl-1*H*-indol-3-yl)-2-hydroxy-3-phenylpropanoate (17):**

1,2-Dimethylindole (**2b**, 290 mg, 2.00 mmol) and 3-phenyloxirane-2-carboxylic acid ethyl ester (**16**, 343 µL, 2.00 mmol) were stirred in CF_3CH_2OH (2 mL) at 80 °C (5 h) to yield *rac*-**17** after column chromatography (SiO_2, hexanes/ethyl acetate = 2:1) as colorless crystals (513 mg, 76%).

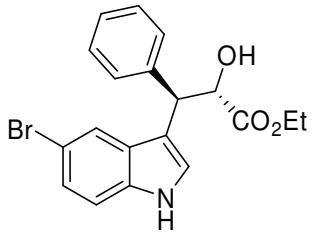


rac-**17**

R_f = 0.35. M. p. 113–114 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.32 (s, 3 H, 2'-Me), 2.78 (d, J = 7.3 Hz, 1 H, OH), 3.62 (s, 3 H, NMe), 3.93, 3.95 (2 × q, J = 7.1 Hz, 2 H, diastereotopic OCH_2CH_3), 4.70 (d, J = 6.6 Hz, 1 H, 3-H), 5.01 (dd, J = 6.6 Hz, 7.3 Hz, 1 H, 2-H), 6.98–7.04 (m, 1 H, ArH), 7.09–7.27 (m, 5 H, ArH), 7.42 (d, J = 7.7 Hz, 2 H, ArH), 7.59 (d, J = 7.7 Hz, 1 H, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 10.8 (q), 13.6 (q), 29.5 (q), 47.1 (d), 61.2 (t), 73.5 (d), 108.5 (d), 110.5 (s), 119.0 (d), 119.5 (d), 120.6 (d), 126.3 (d), 127.0 (s), 128.2 (d), 128.6 (d), 134.1 (s), 136.6 (s), 140.6 (s), 174.1 (s). GC-MS (B): t = 17.4 min; m/z (%) = 337 (3) [M^+], 235 (19), 234 (100), 218 (7).

***rac*-Ethyl 3-(5-bromo-1*H*-indol-3-yl)-2-hydroxy-3-phenylpropanoate (18):**

5-Bromoindole (**2f**, 980 my, 5.00 mmol) and 3-phenyloxirane-2-carboxylic acid ethyl ester (**16**, 858 µL, 5.00 mmol) were stirred in CF_3CH_2OH (5 mL) at 80 °C (24 h) to yield *rac*-**18** after column chromatography (SiO_2, hexanes/ethyl acetate = 1:1) as a yellow oil (912 mg, 47%).



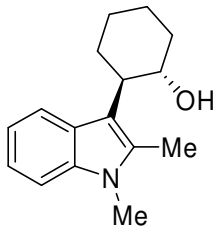
rac-**18**

R_f = 0.61. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.27 (t, J = 7.2 Hz, 3 H, OCH_2CH_3), 2.90 (d, J = 6.6 Hz, 1 H, OH), 4.20 (q, J = 7.2 Hz, 2 H, OCH_2CH_3), 4.69–4.71 (m, 1 H, 3-H), 4.86–4.89 (m, 1 H, 2-H), 7.17–7.29 (m, 7 H, ArH), 7.47 (s, 1 H, ArH), 7.49 (s, 1 H, ArH), 8.20 (br. s, 1 H, NH). ^{13}C-NMR (150 MHz, $CDCl_3$): δ = 14.2 (q), 46.0 (d), 61.9 (t), 73.8 (d), 112.5 (d), 112.7 (s), 115.9 (s), 121.5 (d), 124.2 (d), 124.9 (d), 127.3 (d), 128.3 (d), 128.7 (s), 129.1 (d), 134.6 (s), 138.1 (s), 173.4 (s). GC-MS (C): t = 7.8 min; m/z (%) = 212 (34), 211 (12), 210 (100), 175 (51), 165 (49), 147 (80), 137 (31), 129 (29), 102 (90), 77 (15), 75 (17), 51 (17). HR-EI-MS: $C_{19}H_{18}{}^{35}BrNO_3$, calcd 388.0538, found 388.0531.

6.4.7 Reactions of 1,2-Dimethylindole with Aliphatic Epoxides

***rac*-2-(1,2-Dimethyl-1*H*-indol-3-yl)cyclohexanol (20)**:[52]

1,2-Dimethylindole (**2b**, 436 mg, 3.00 mmol) and cyclohexene oxide (**19**, 303 µL, 3.00 mmol) were stirred in CF_3CH_2OH (3 mL) at 80 °C (72 h) to yield *rac*-**20** after column chromatography (SiO_2, hexanes/ethyl acetate = 4:1) as white crystals (153 mg, 21%). When this reaction was repeated, and another 3.00 mmol (304 µL) of **19** were added after 72 h and 1.50 mmol (152 µL) of **19** after 160 h **20** was obtained in 31% yield.

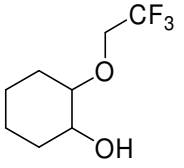


rac-**20**

R_f = 0.29. M. p. 187–188 °C (Lit: 190–193 °C).[52] ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.15–2.21 (m, 9 H), 2.40 (s, 3 H, 2'-Me), 2.61–2.75 (m, 1 H, 2-H), 3.66 (s, 3 H, NMe), 4.06 (td, J = 4.1 Hz, 10 Hz, 1 H, 1-H), 7.00–7.28 (m, 3 H, ArH), 7.68 (d, J = 8.0 Hz, 1 H, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 11.0 (q), 24.6 (t), 27.2 (t), 29.2 (q), 31.7 (t), 32.1 (d), 37.3 (t), 75.3 (d), 108.5 (d), 109.2 (s), 119.2 (d), 119.4 (d), 120.1 (d), 132.9 (s), 136.6 (s), 136.7 (s). GC-MS (B): t = 10.9 min; *m/z* (%) = 243 (86) [M^+], 184 (78), 171 (19), 158 (100), 144 (12), 115 (7).

2-(2,2,2-Trifluoroethoxy)cyclohexanol (21):

Detected in GC-MS as a side product of the reaction of 1,2-dimethylindole (**2b**) with cyclohexene oxide (**19**).

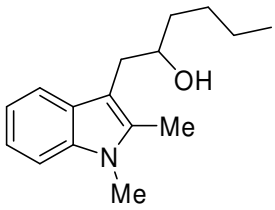


21

GC-MS (B): t = 7.9 min; *m/z* (%) = 198 (5) [M^+], 180 (17), 152 (32), 139 (10), 98 (68), 81 (100), 70 (17), 55 (12), 41 (20).

***rac*-1-(1,2-Dimethyl-1*H*-indol-3-yl)hexan-2-ol (24):**

1,2-Dimethylindole (**2b**, 436 mg, 3.00 mmol) and 1,2-epoxyhexane (*rac*-**22**, 361 µL, 3.00 mmol) were stirred in CF_3CH_2OH (3 mL) at 80 °C (48 h) to yield *rac*-**24** after column chromatography (SiO_2, hexanes/ethyl acetate = 3:1) as a pale yellow oil (236 mg, 32%).

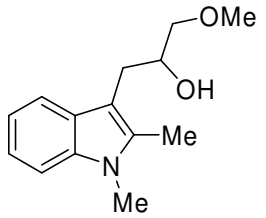


rac-**24**

R_f = 0.61. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, J = 6.9 Hz, 3 H, 6-H), 1.32–1.62 (m, 6 H, 3-H, 4-H, 5-H), 2.37 (s, 3 H, 2'-Me), 2.74 (dd, *J* = 8.7 Hz, 14 Hz, 1 H, 1-H), 2.94 (dd, *J* = 4.2 Hz, 14 Hz, 1 H, 1-H), 3.65 (s, 3 H, NMe), 3.79–3.89 (m, 1 H, 2-H), 7.04–7.26 (m, 3 H, ArH), 7.51 (d, J = 7.8 Hz, 1 H, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 10.5 (q), 14.1 (q), 22.8 (t), 28.2 (t), 29.5 (q), 32.9 (t), 36.6 (t), 71.1 (d), 107.1 (s), 108.5 (d), 118.1 (d), 118.9 (d), 120.7 (d), 127.9 (s), 134.4 (s), 136.7 (s); GC-MS (B): *t* = 10.2 min; *m/z* (%) = 245 (15) [M^+], 159 (13), 158 (100), 143 (5).

***rac*-1-(1,2-Dimethyl-1*H*-indol-3-yl)-3-methoxypropan-2-ol (25):**

1,2-Dimethylindole (**2b**, 436 mg, 3.00 mmol) and glycidylmethyl ether (*rac*-**23**, 265 mg, 3.00 mmol) were stirred in CF_3CH_2OH (3 mL) at 80 °C (48 h) to yield *rac*-**25** after column chromatography (SiO_2, hexanes/ethyl acetate = 1:1) as a colorless oil (357 mg, 51%).



rac-**25**

R_f = 0.40. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3 H, 2'-Me), 2.62 (br. s, 1 H, OH), 2.88 (d, *J* = 6.9 Hz, 2 H, 1-H), 3.23–3.36 (m, 5 H, 3-H, NMe), 3.52 (s, 3 H, OMe), 3.95–4.03 (m, 1 H, 2-H), 7.01–7.18 (m, 3 H, ArH), 7.49 (d, *J* = 7.8 Hz, 1 H, ArH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 10.2 (q), 28.6 (t), 29.4 (q), 58.9 (q), 70.8 (d), 75.9 (t), 106.4 (s), 108.5 (d), 117.9 (d), 118.8 (d), 120.6 (d), 127.9 (s), 134.2 (s), 136.5 (s). GC-MS (B): *t* = 9.6 min; *m/z* (%) = 233 (21) [M^+], 159 (11), 158 (100).

6.5 Literature

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Chapter 7

Synthesis of Naturally Occurring Quinones

7.1 Introduction

Filamentous fungi have many characteristics that make them highly interesting for research. Mainly, the biosynthesis of natural products (*i. e.* secondary metabolites) displays new compounds that show useful activities for pharmaceutical and agricultural purposes ranging from antibiotic to antifungal properties.[1-4] On the other hand, also not desired attributes, such as phyto- and mycotoxic activities, arise from the studies of the secondary metabolites of these fungi.[5,6]

The quinone skeleton is a widespread structure in nature and thousands of quinones have been discovered, most of which show biological activity of some kind. Usually, this large class of natural products is differentiated by the substituents on the quinone core; besides naphtho-quinones, anthraquinones, phenanthraquinones and polycyclic quinones, simple 1,4-benzo-quinones exhibit a large class of natural products, mainly found in fungi.

In order to synthesize the secondary metabolites produced by fungi, biomimetic pathways have been favored. The investigation of the genes of these fungi is inevitable to gain knowledge about these pathways. The main characteristic of the genes of secondary metabolites – in contrast to the genes of primary metabolites – is that they are clustered in fungal genomes and knowledge about the biosynthetic loci opens the door for the biosynthesis of these compounds.

7.1.1 Biochemical Background

Terrequinone A (**1**) is a member of a family of bisindolylbenzoquinones commonly known as asterriquinones (Figure 7.1). They all consist of a benzoquinone core with a different number of hydroxy or methoxy groups and vary in the pattern of prenylation on the indole or quinone structure. They show cytotoxic activities that intercalate genomic DNA, thus predisposing tumor cells to apoptosis.[7]

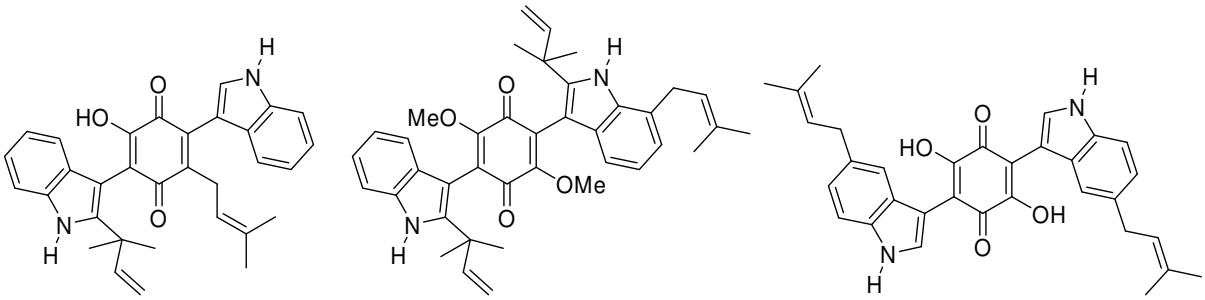
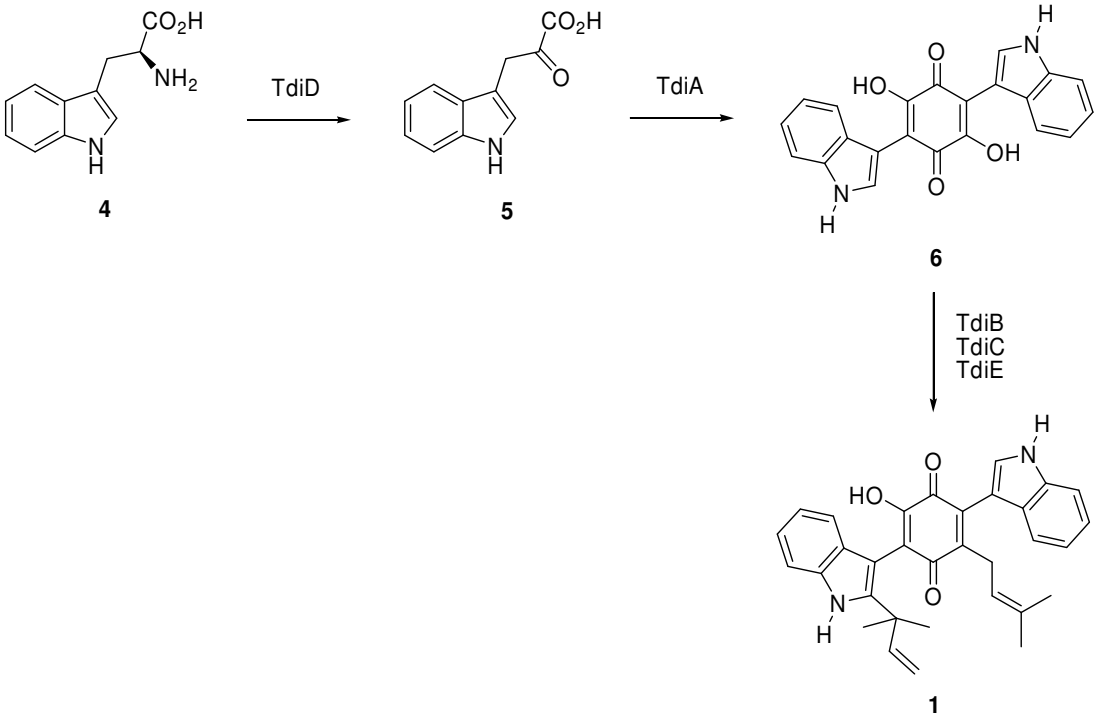


Figure 7.1. Structures of representative members of the asterriquinone family: terrequinone A (**1**), asterriquinone A4 (**2**) and cochliodinol (**3**).

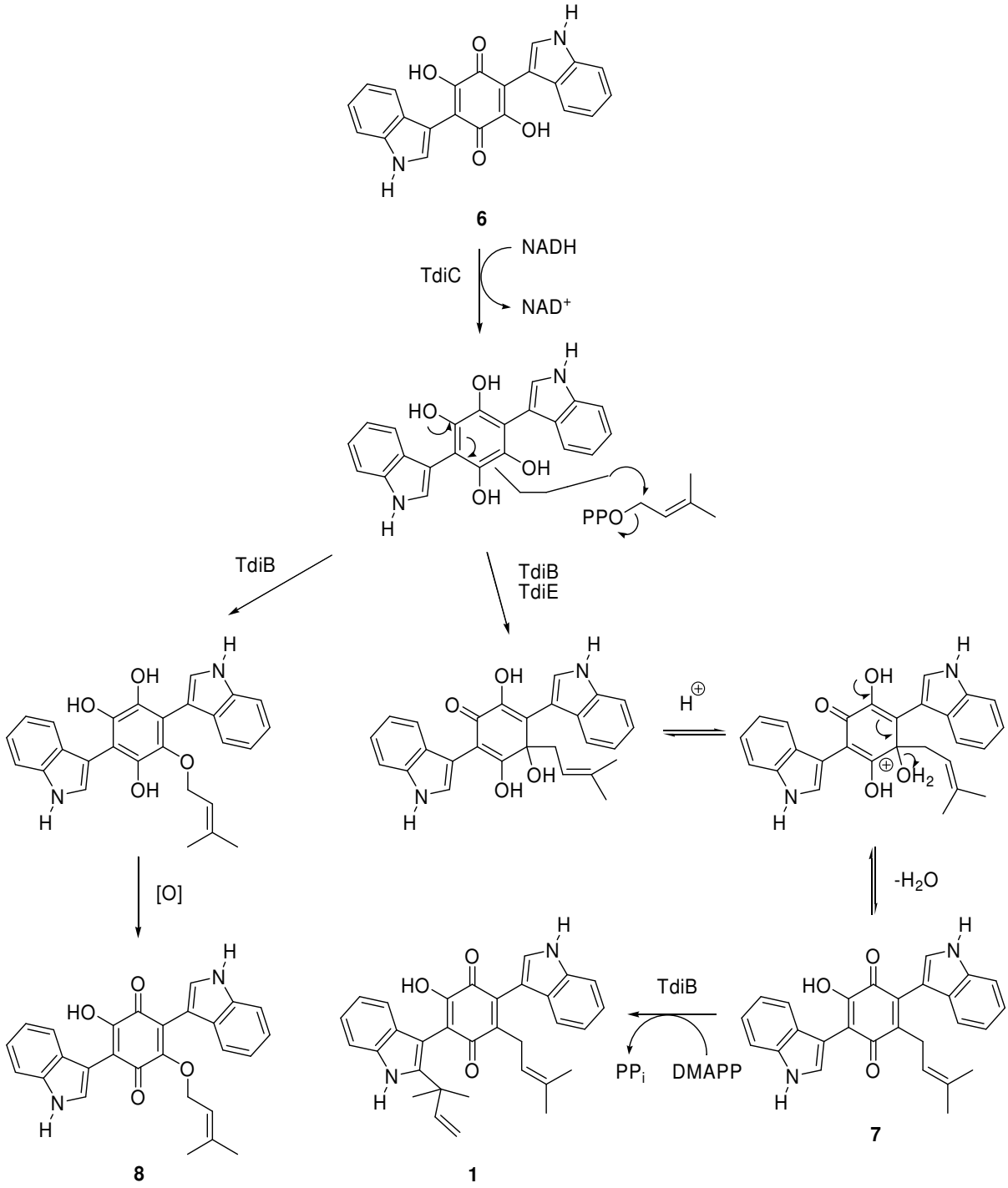
Terrequinone A (**1**) was isolated besides many other asterriquinonenes from *Aspergillus terreus* (*Ascomycota*) and exhibits moderate activity in cancer cell lines.[8] Bok and co-workers discovered that *A. nidulans* exhibits a gene cluster that is regulated by LaeA, a nuclear methyltransferase that acts as a global regulator of natural product gene expression in *Aspergillus* species, which turned out to be the terrequinone A (**1**) biosynthetic locus.[9] *A. nidulans* is one of many species of filamentous fungi in the phylum Ascomycota and has been studied intensively in the past years.[10-12] The genome with its 30 million base pairs in size contains about 9500 protein-coding genes on 8 chromosomes and was sequenced by Galagan and co-workers in 2005.[13] Since terrequinone A (**1**) is unknown to be produced by *Aspergillus nidulans*, almost all genes that express the enzymes of the terrequinone A (**1**) biosynthesis pathway have been decrypted by Walsh and co-workers and a biosynthetic pathway has been proposed.[14]

The involved genes code a peptide synthetase (*tdiA*), an indole prenyltransferase (*tdiB*), an oxidoreductase (*tdiC*), a pyridoxal-5'-phosphate-dependent aminotransferase (*tdiD*) and a gene of unknown function (*tdiE*), and the overall biosynthetic pathway to terrequinone A (**1**) was proposed as shown in Scheme 7.1.



Scheme 7.1. Biosynthetic pathway to terrequinone A (**1**).[14]

The first step in the biosynthesis of terrequinone A (**1**) is the conversion of L-tryptophan (**4**) into indolyl pyruvic acid (**5**) catalyzed by the aminotransferase TdiD containing a covalent PLP cofactor. Transformation of **5** with ATP-PP_i exchange catalyzed by TdiA, a three-domain apoprotein, gives demethylasterriquinone D (DAQ-D, **6**). The final step is likely to be catalyzed by the TdiB/TdiC/TdiE enzyme system in the presence of DMAPP and NADH (Scheme 7.2).

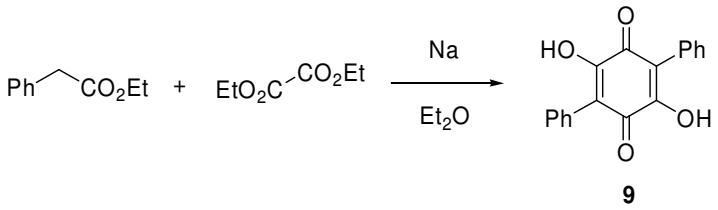


Scheme 7.2. Proposed formation of terrequinone A (**1**) from DAQ-D (**6**).

As an intermediate of this reaction ochrindole A (**7**, Schem 7.2) was indentified, which was turned into terrequinone A (**1**) by the action of TdiB. Ochrindole A (**7**) naturally occurs in *A.* ochraceus. Further side reactions have been reported to yield irreversibly *O*-iso-pentenyldemethylasterriquinone (**8**) which is a dead end of the biosynthetic pathway.
In order to gain knowledge about the final steps in the biosynthesis we wanted to perform the reduction and prenylation reactions of DAQ-D (**6**) by chemical methods. Several methods for the preparation of members of the asterriquinone family have been reported to date, but no data have been found for the synthesis of DAQ-D (**6**). For that purpose and due to the fact that the decisive step in the biosynthesis should be independent from the aryl substituents at the quinone core, we decided to use polyporic acid (**9**) as a model compound and find an easy and convenient method for the synthesis of DAQ-D (**6**).

7.1.2 Synthesis of Polyporic Acid

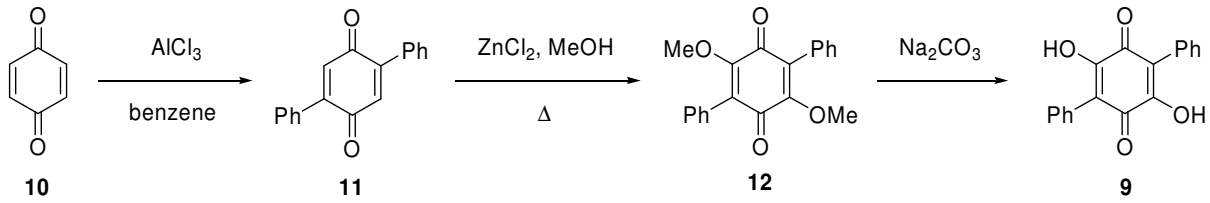
Polyporic acid (**9**), which can be found in nature in wood rotting fungi and lichens, was mentioned and isolated from *Hapalopilus rutilans* in 1877 by Stahlschmidt[15] and shows antileukaemic activities.[16] Polyporic acid (**9**) bears phenyl groups in the 3- and 6-positions on the quinone core instead of indole units and, therefore, should not be sensitive towards basic reactions conditions or oxidations. Numerous methods for the synthesis of polyporic acid (**9**) have been developed.
Fichter described the formation of **9** as a side product of the condensation of ethyl phenylacetate with ethyl oxalate in the presence of sodium in dry ether (Scheme 7.3).[17] The revised mechanism[18] for this reaction states that two units of ethyl phenylacetate react to an enediolate which is converted to a 1,2-diketone through autoxidation. This intermediate condenses with ethyl oxalate to yield polyporic acid (**9**) in very small yield (~ 1%).



9

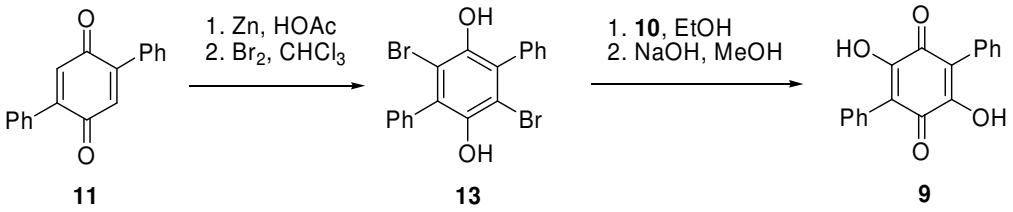
Scheme 7.3. Fichter's condensation of ethyl phenylacetate with ethyl oxalate to give polyporic acid (**10**) with very low yield.[17]

Kögl prepared 2,5-diaryl-1,4-benzoquinones by a variation of the method of Pummerer (Scheme 7.4).[18] Reaction of 1,4-benzoquinone (**10**) with benzene in the presence of $AlCl_3$ yielded 2,5-diphenyl-1,4-benzoquinone (**11**).[19] Further treatment of **11** with $ZnCl_2$ in refluxing methanol and demethylation of **12** with soda yielded polyporic acid (**9**) in moderate yields, but intricate oxidation and reduction steps diminish the synthetic relevance of this method.



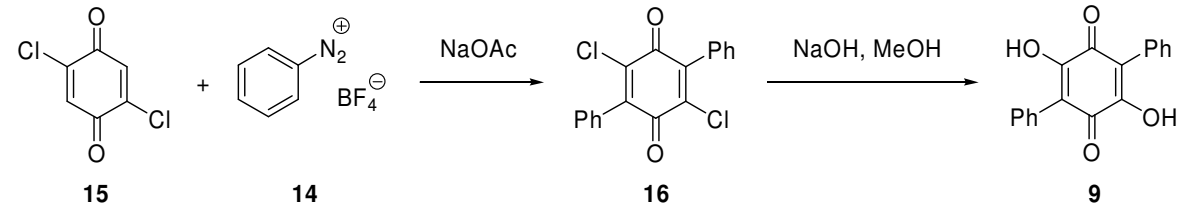
Scheme 7.4. Formation of 2,5-diphenyl-1,4-benzoquinone (**11**) by Pummerer[19] and conversion to polyporic acid (**9**).[18]

Shildneck and Adams reported on a synthesis for polyporic acid (**9**) starting from 2,5-diphenyl-1,4-benzoquinone (**11**, Scheme 7.5).[20] Treatment of **11** with Zn in glacial acetic acid followed by bromination in chloroform yielded 3,6-dibromo-2,5-diphenyl-1,4-dihydroxybenzene (**13**) which hydrolyses after oxidation by 1,4-benzoquinone (**10**) to give polyporic acid (**9**) in moderate yield.



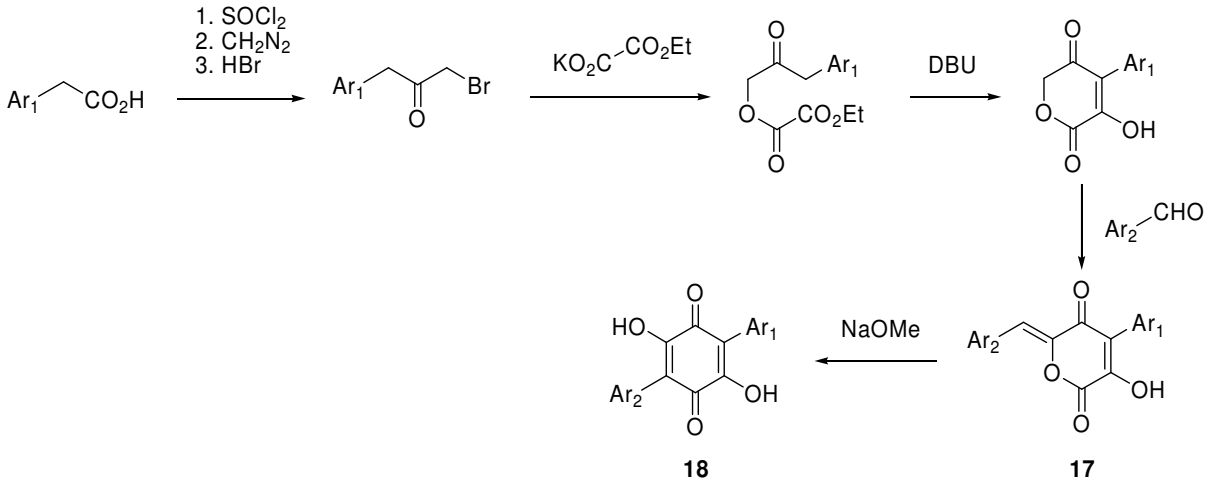
Scheme 7.5. Preparation of polyporic acid (**9**) from 2,5-diphenyl-1,4-benzoquinone (**11**).[20]

The reaction of two equivalents of benzenediazonium salt (**14**)[21] – or *N*-nitrosoacetanilide[22] – with 2,5-dichloro-1,4-benzoquinone (**15**) in the presence of NaOAc was reported to give 3,6-dichloro-2,5-diphenyl-1,4-benzoquinone (**16**). Polyporic acid (**9**) was formed upon hydrolysis with NaOH in refluxing methanol (Scheme 7.6).

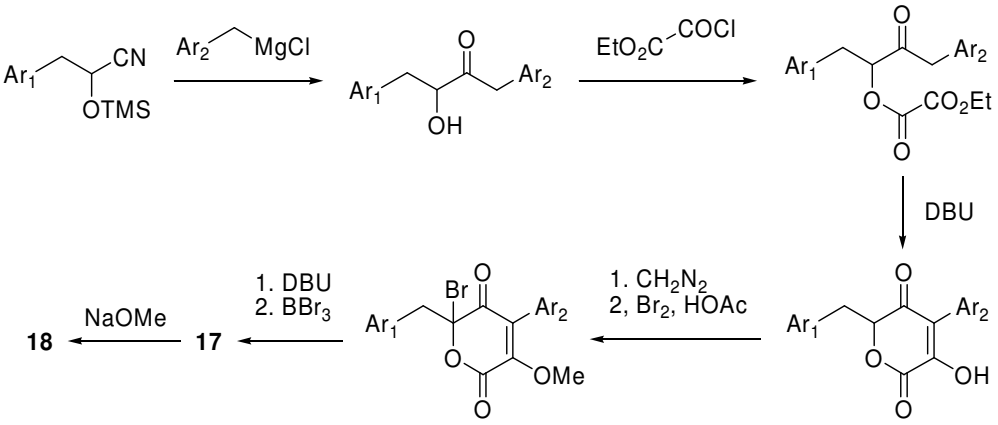


Scheme 7.6. Free radical arylation of 2,5-dichloro-1,4-benzoquinone (**15**).[21]

A convenient approach to polyporic acid (**9**) was described by Steglich[23,24] and, later, by Pattenden[25] using grevillines **17** as intermediates, which are also fungal pigments and sometimes co-occur with terphenylquinones in fungi (Schemes 7.7 and 7.8). Key step in the preparation is the methoxide-catalyzed rearrangement of grevillins **17** to give 2,5-diaryl-3,6-dihydroxy-1,4-benzoquinones **18** in good yields. Both approaches permit the formation of unsymmetrically substituted terphenylquinones as the substituents at the quinone ring originate from different reactants in the synthesis and are not attached to the quinone ring in one single step.

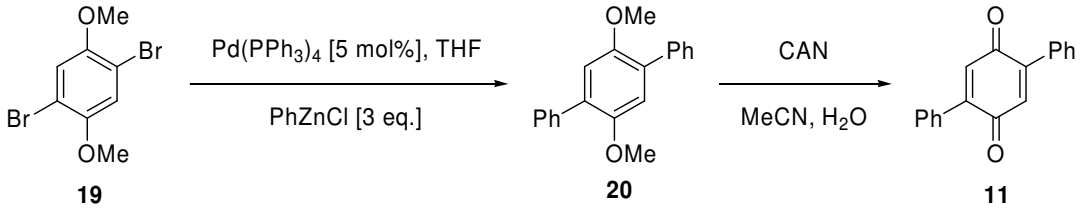


Scheme 7.7. Steglich's approach to 2,5-diarylsubstituted quinones **18** *via* grevillines **17** (for $Ar_1 = Ar_2 = Ph$, polyporic acid (**9**) is accessible).[23,24]



Scheme 7.8. Pattenden's synthesis of grevillines **17**.[25]

Organometallic routes to polyporic acid (**9**) have become very popular in recent times. Besides the work of Dallacker[26] and Moore,[27] who used lithiation reactions, Pd-catalyzed reactions (Negishi coupling) of **19** and consecutive oxidative demethylation of **20** with $(NH_4)_2Ce(NO_3)_6$ provided 2,5-diphenyl-1,4-benzoquinone (**11**) in good yields from commercially available precursors (Scheme 7.9).[28] Halogenation and hydrolysis of **11** was reported to give easy access to polyporic acid (**9**).[29]

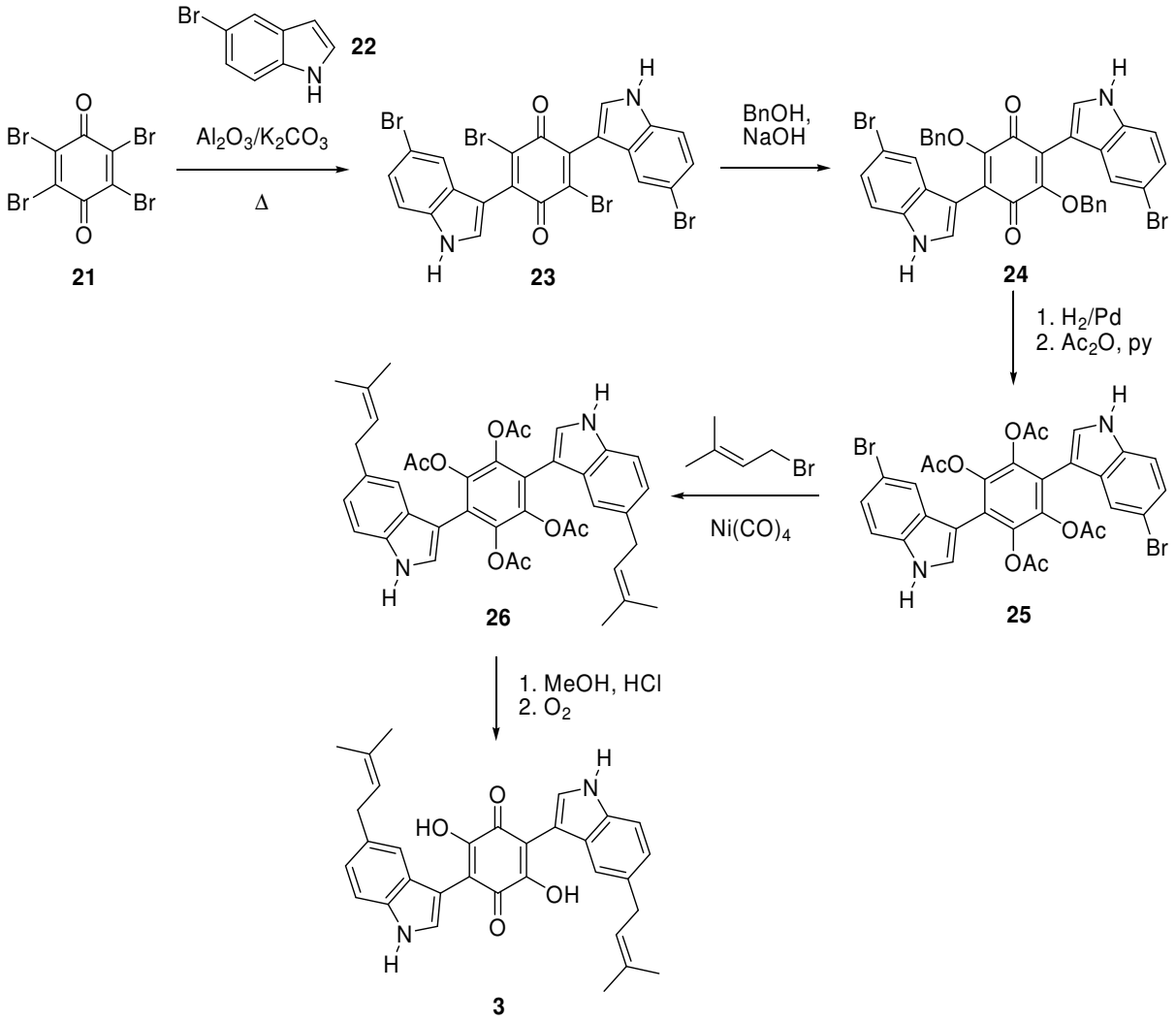


Scheme 7.9. Negishi cross coupling of **19** with a transmetallated zinc species and oxidative demethylation of **20**.[28]

7.1.3 Synthesis of Bisindolylquinones

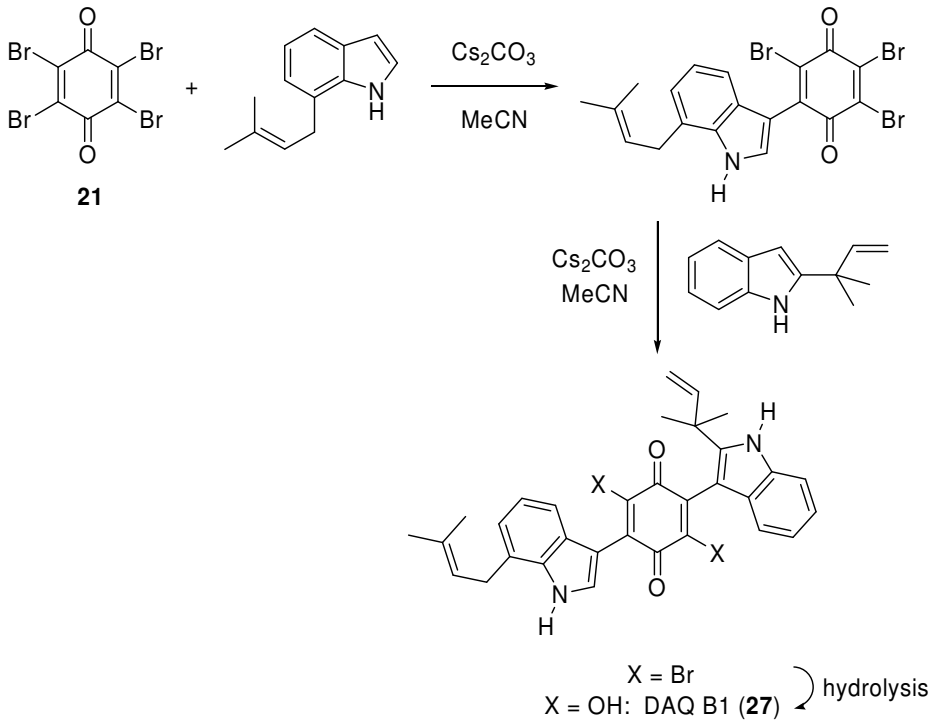
Several methods have been developed for the synthesis of members of the asterriquinone family. Mainly, these compounds and their derivatives have been isolated from the natural product.

Cochliodinol (**3**), which was isolated from *Chaetomium globosum* and *Chaetomium cochliodes*,[30] is one of few symmetrically substituted bisindolylquinones. The total synthesis was performed by Hörcher and co-workers (Scheme 7.10).[31] *p*-Bromanil (**21**) reacted with 5-bromoindole (**22**) in a solid phase Michael addition to yield the bisindolylquinone **23**. Reaction of **23** with NaOH and benzyl alcohol furnished **24** which was transformed by reduction with H_2, Pd/C and acetylation with Ac_2O in pyridine into leuco acetate **25**. Introduction of the prenyl groups with a complex of isopentenyl bromide and $Ni(CO)_4$ gave access to **26**. Consecutive deprotection and oxidation gave cochliodinol (**3**) in 0.001% overall yield.

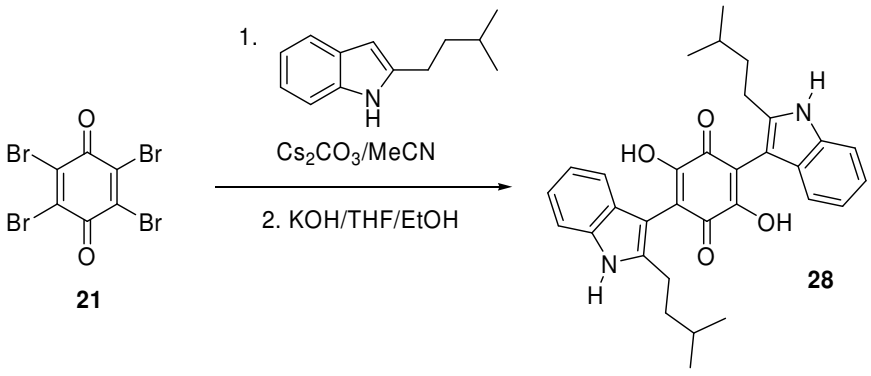


Scheme 7.10. Total synthesis of cochliodinol (**3**).[31]

An approach to bisindolylquinones by reaction of indoles to *p*-bromanil (**21**) using catalytic amounts of Cs_2CO_3 was reported by Pirrung and co-workers (Scheme 7.11) as demonstrated for the synthesis demethylasterriquinone B1 (**27**).[32] This method was also applied by Harris Jr. *et al.* when they prepared tetrahydroasterriquinone E (**28**) in a one pot synthesis (Scheme 7.12).[33]

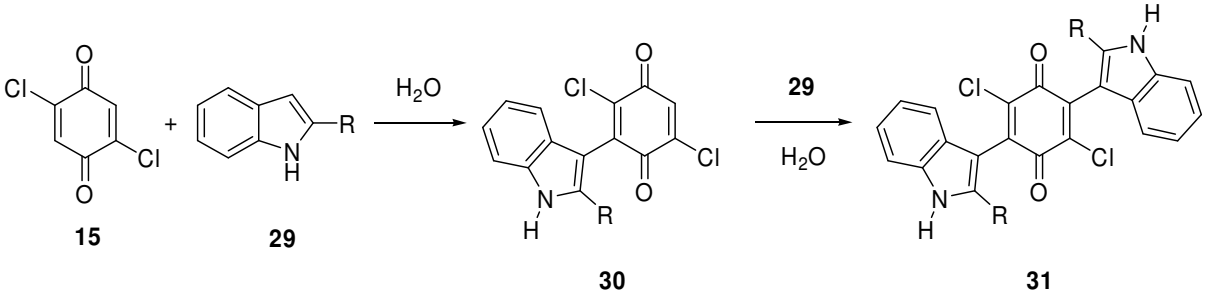


Scheme 7.11. Pirrung's total synthesis of demethylasterriquinone B1 (**27**).[32]



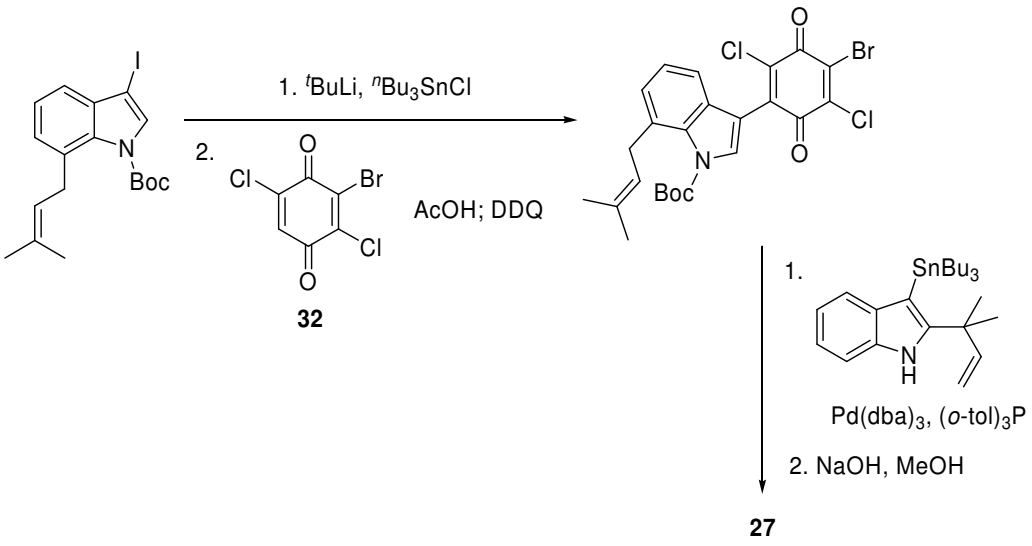
Scheme 7.12. Total synthesis of tetrahydroasterriquinone E (**28**).[33]

Simple oxidative coupling of 2-substituted indoles **29** to 2,5-dichloro-1,4-benzoquinone (**15**) in water was reported to give good yields of monoindolylquinones **30** and addition of another indole unit resulted in bisindolylquinones **31** (Scheme 7.13).[34] The reaction of **30** with the parent indole was not examined.



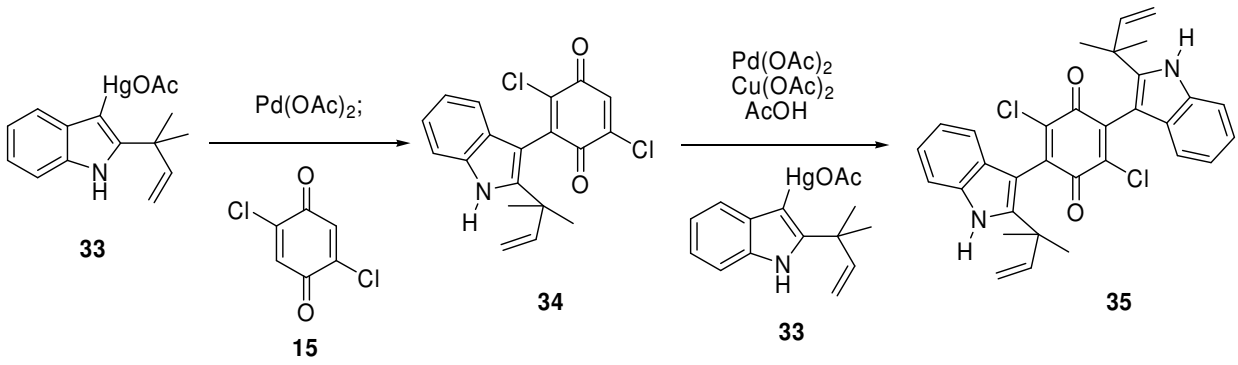
Scheme 7.13. "On water"-promoted direct coupling of indoles with 1,4-benzoquinone **15**.[34]

Pirrung and co-workers described an alternative route to bisindolylquinones by lithiation of the indoles in 3-position and nucleophilic addition to 2-bromo-3,6-dichloro-1,4-benzoquinone (**32**).[32] After oxidation with DDQ the Stille coupling with another indole unit and consecutive hydrolysis furnished asterriquinones as demonstrated for DAQ-B1 (**27**, Scheme 7.14).



Scheme 7.14. Total synthesis of demethylasterriquinone B1 (**27**) with Stille coupling as key step.[32]

The Pd-catalyzed reaction of the mercurated indole **33** with 2,5-dichloro-1,4-benzoquinone (**15**) was reported to yield the monoindolylquinone **34**, which formed the bisindolylquinone **35** upon treatment with a second equivalent of **33** in the presence of a stoichiometric amount of $CuCl_2$ catalyzed by $Pd(OAc)_2$ in acetonitrile.[35] This method was applied for the synthesis of demethylasterriquinone B4 (**35**) as shown in Scheme 7.15.



Scheme 7.15. Total synthesis of demethylasterriquinone B4 (**29**) from mercurated indole species **33**.[35]

Acid-catalyzed condensation of indoles with 2,5-dichlorobenzoquinone (**15**) followed by DDQ oxidation was reported by Pirrung to give good yields of 3-indolylquinones.[36] Moderate yields of bisindolylquinones were obtained when these monoindolylquinones reacted with indoles in the presence of $Zn(OTf)_2$ under various conditions.[37]

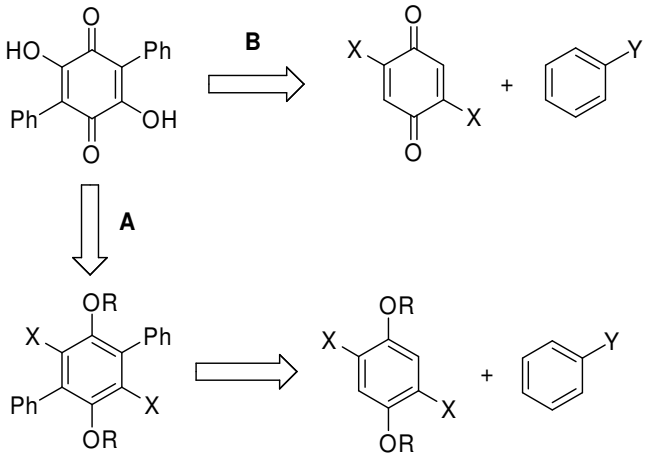
In summary, there are several methods that give access to bisarylquinones. Total syntheses for polyporic acid (**9**) have been described, but no route to demethylasterriquinone D (**6**) has been reported. In order to gain knowledge about the final steps in the biosynthesis of terrequinone A (**1**) we used polyporic acid (**9**) as a model compound to find a way for the reduction and prenylation of the quinone core. Synthesis of **9** and DAQ-D (**6**), the precursor of **1** in its biosynthesis, should be developed.

7.2 Results and Discussion

7.2.1 Synthesis of Polyporic Acid

7.2.1.1 Retrosynthetic Approach

Since the published complex, low-yielding syntheses for polyporic acid (**9**) were inadequate for our purposes, we put effort on the development of a new and more efficient access for synthesizing polyporic acid (**9**) and its derivatives. Besides the route via grevillines **17** (see pages 179-180), coupling of two phenyl units with a dibromoaryl unit and consecutive oxidation (way A in Scheme 7.16) or Michael addition of arenes to quinones (way B) are considered as best routes to **9**.

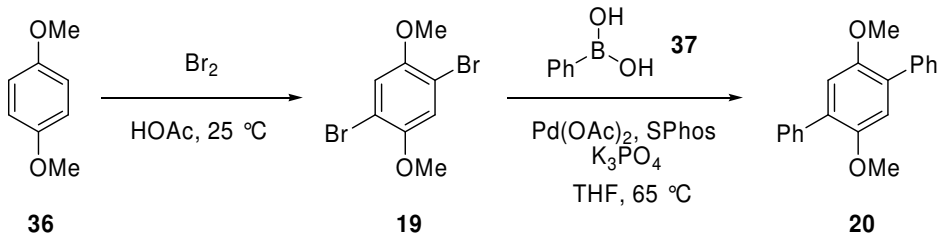


Scheme 7.16. Retrosynthetic analysis of polyporic acid (**9**).

7.2.1.2 Total Synthesis of Polyporic Acid

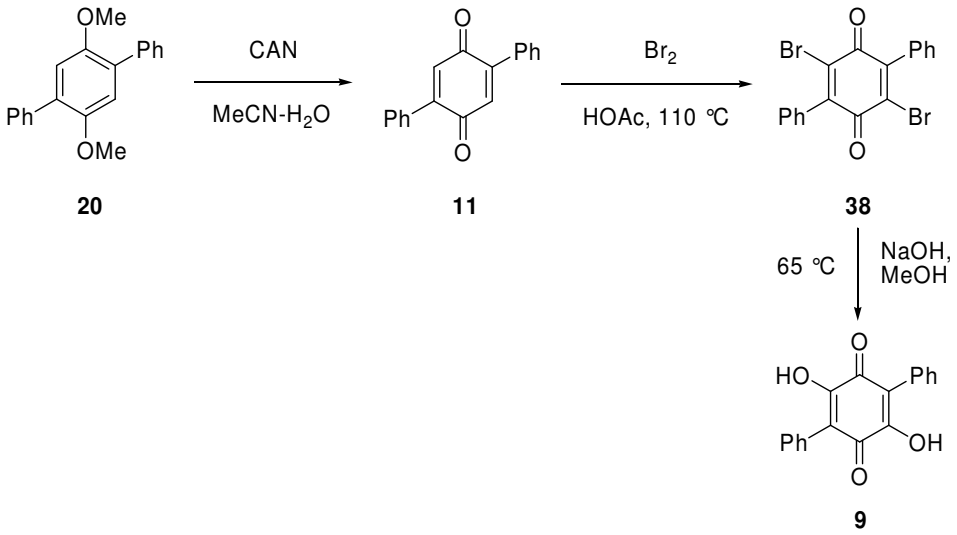
As pointed out before, most literature procedures used the retrosynthetic approach B. When we carried out the synthesis of **9** as reported by Kögl[18] and Shildneck,[20] we didn't obtain satisfying results. We therefore decided to develop a new approach to **9** using retrosynthetic way A with a cross-coupling reaction as key step for the formation of the terphenyl structure. When we carried out the Pd-catalyzed Negishi coupling of 2,5-dibromo-1,4-dimethoxybenzene (**19**) with phenylzinc chloride (generated *in situ* from phenyllithium and $ZnCl_2$ in dry THF) as reported for the synthesis of bisindolylquinones[28] we did not obtain the coupling product **20**.

We then examined the Suzuki cross coupling reaction of **19** with phenyl boronic acid (**37**) catalyzed by Pd(II) and SPhos (Buchwald ligand)[38] in the presence of K_3PO_4 in dry THF (Scheme 7.18). After column chromatography the desired product **20** was isolated in 96% yield as a colorless solid. The dibromoaryl compound **19** is readily accessible by bromination of 1,4-dimethoxybenzene (**36**) in glacial acetic acid.



Scheme 7.18. Suzuki coupling of **19** with phenyl boronic acid (**37**).

Polyporic acid (**9**) is furnished in 3 steps by commonly known transformations (Scheme 7.19). Oxidative demethylation of **20** with $(NH_4)_2Ce(NO_3)_6$ in acetonitrile-water solution yielded 2,5-diphenyl-1,4-benzoquinone (**11**) in 77% yield. Bromination in refluxing glacial acetic acid (to give 75% of **38**) and hydrolyis with NaOH in refluxing methanol (96%) gave **9** in 37% overall yield.

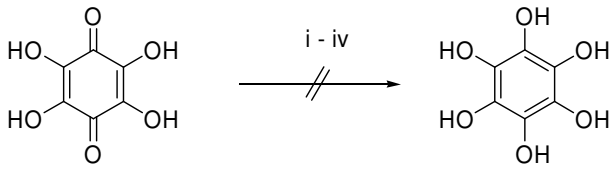


20 **11** **38** **9**

Scheme 7.19. Final steps in the total synthesis of polyporic acid (**9**).

7.2.2 Reduction of Polyporic Acid

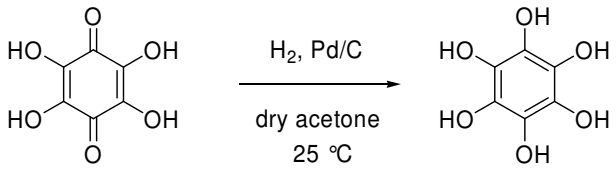
As a model compound for the reductions of quinoid structures we chose commercially available 2,3,5,6-tetrahydroxy-1,4-benzoquinone (**39**). When we performed the reduction with $SnCl_2$ in half-concentrated HCl[39,40] we obtained a brown residue, whose color intensified during the work-up and the resulting mixture was not purified any further. Reduction of **39** was also not achieved when **39** was treated with three equivalents of zinc in triflic acid, by treatment with $LiAlH_4$ in dry THF at 0°C[41] or with $Na_2S_2O_4$ in water[42] (Scheme 7.20).



39 (purple) **40** (colorless)

Scheme 7.20. Reduction attempts of **39** with not satisfying results (i: $SnCl_2$, HCl, Δ; ii: Zn, TFA, 25 °C; iii: $LiAlH_4$, THF, 0 °C; iv: $Na_2S_2O_4$, H_2O).

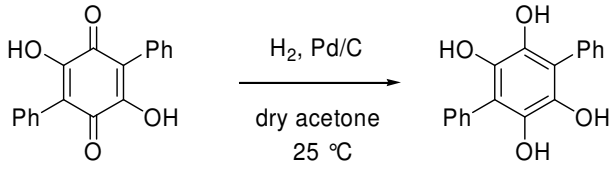
Hörcher described the reduction of a quinone structure, which was substituted in the 3- and 6-positions by two indolyl groups, with H_2 over palladium on charcoal in dry acetone.[31] This method was found to be convenient for **39** (Scheme 7.21). The purple color of **39** vanished after stirring the reactants for 5 min at room temperature, and a colorless solid was obtained upon evaporation of the solvent which was characterized by NMR and mass spectroscopy as hexahydroxybenzene (**40**).



39 **40**

Scheme 7.21. Reduction of the model compound **34** with H_2, Pd/C at room temperature.

Analogous treatment of polyporic acid (**9**) with H_2/Pd-C, filtration of the colorless precipitate under argon and evaporation of the solvent gave tetrahydroxyterphenyl **41** in 69% yield, which was characterized by NMR and mass spectroscopy (Scheme 7.22).

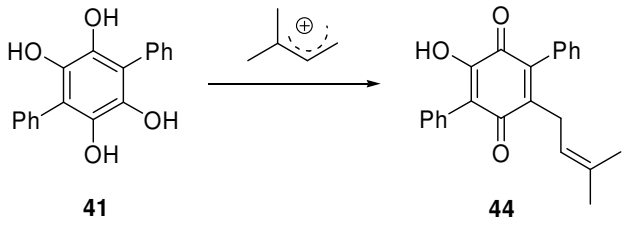


9 **41**

Scheme 7.22. Reduction of polyporic acid (**9**) with H_2, Pd/C at room temperature.

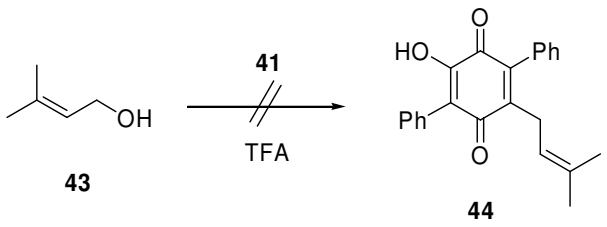
7.2.3 Prenylation Attempts of the Leuco Form of Polyporic Acid

With the reduced form of polyporic acid **41** at hand and based on the biosynthesis proposal for terrequinone A (**1**)[14] we screened the reaction conditions for the prenylation of the 1,2,4,5-tetrahydroxy-3,6-diphenylbenzene (**41**, Scheme 7.23).



Scheme 7.23. Prenylation attempts on 3,6-diphenyl-1,2,4,5-benzenetetrol (**41**).

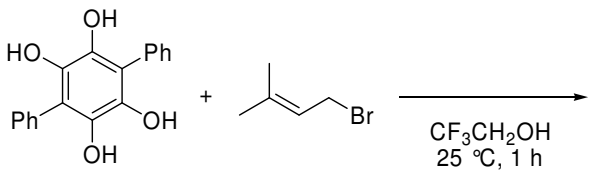
Successful prenylation should lead to a coloration of the former colorless hydroquinone **41** solution as rearrangement to the quinone structure should follow the electrophilic attack of the prenyl cation. The reaction of **41** with prenyl alcohol **43** in TFA (Scheme 7.24) was not successful as no change in color was observed. We assumed that **43** ionizes readily under these conditions. Possibly, due to the poor solubility of the reactants in TFA, no conversion was observed as indicated by TLC control of the reaction.



Scheme 7.24. Prenylation attempt using **43** in TFA as electrophile.

Previous results in our group have shown that various aqueous solvent mixtures and 2,2,2-trifluoroethanol are reaction media with high ionizing power and low solvent nucleophilicity which can be used for Friedel-Crafts alkylations under neutral conditions.[43,44] Formation of the 1,1-dimethylallyl cation has been achieved by dissolving the corresponding halide in these solvents. We combined 1,2,4,5-tetrahydroxy-3,6-diphenylbenzene (**41**) with 1-bromo-3-methylbut-2-ene (**45**) in 80% aq. acetone at room temperature but no conversion was

observed when the reaction mixture was stirred in this solvent for 24 h. When we treated **41** with **45** in 2,2,2-trifluoroethanol at room temperature (Scheme 7.25), the color of the reaction mixture changed after 5 min. We continued stirring for 1 h and TLC showed two new spots besides the spot for **41**. One spot was identified to be polyporic acid (**9**) which was formed by reoxidation of **41**. The second spot eluting earlier than **9** turned yellow when the TLC plate was held over ammonia fumes and turned green-blue when the TLC plate was held over fuming HCl. The mass spectrum of this new spot, however, indicated that **44** was not formed. Further attempts to elucidate the structure of this unknown compound have not been made.



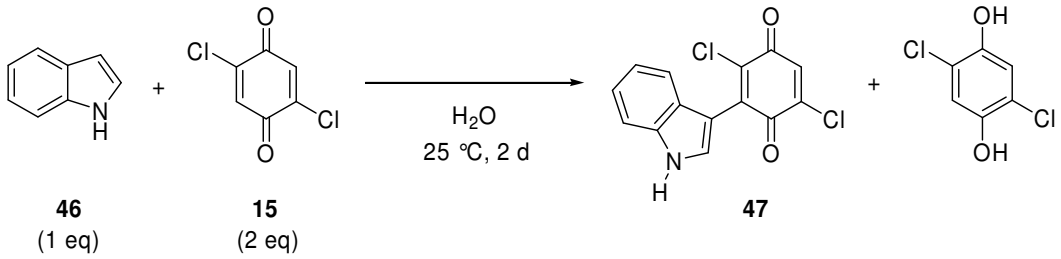
41 **45**

Scheme 7.25. Attempted reaction of **41** with **45** in CF_3CH_2OH.

7.2.4 Synthetic Approach to Demethylasterriquinone D

In order to find a straightforward access to DAQ-D (**6**) some literature methods described for the synthesis of other members of the asterriquinone family were examined.

Since organic reactions in water have caught more and more interest, we followed the procedure reported by Wang and Li,[34] stirring a heterogenous mixture of indole (**46**) and readily accessible 2,5-dichloro-1,4-benzoquinone (**15**) in water (Scheme 7.26). After purification of the crude reaction mixture we obtained 45% of the monoarylated quinone **47**. Since one major side product of the reaction is the reduced form **47**, treatment of the reaction mixture with one equivalent of DDQ after 7 d almost doubled the yield of **47**.

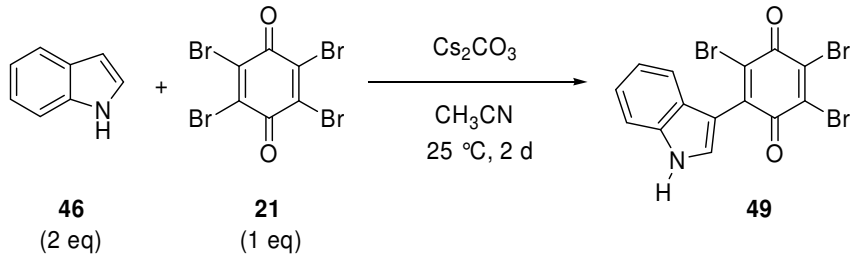


Scheme 7.26. "On water" coupling of indole (**46**) with quinone **15**.

Treatment of indole (**46**) with two equivalents of **47** for 7 d resulted in the formation a new, red compound, presumably the bisindolylquinone **48**. Several side products, as indicated by TLC, and the very slow conversion rate diminish the value of this method. This method – and the later described methods too – bear the disadvantage that quinone **15** has to be employed in excess as one equivalent is needed for the oxidation of the intermediate 2,5-dichloro-3-(1*H*-indol-3-yl)-1,4-hydroquinone to **47**. An excess (two equivalents) of quinone **47** is also needed when it is coupled with another indole unit to give bisindolylquinone **48**. This addition is – depending on the electronic nature of the indole – usually very slow for the parent indole (**46**) and the formation of some side products is observed. The low yields of the reaction of indole (**46**) might also be caused by an alternative non-covalent mechanism *via* indole radical cations.[45-48]

$Bi(OTf)_3$ or $Zn(OTf)_2$ catalyzed reactions of indole (**46**) with **15** in dichloromethane gave low yields (15–21%).

The reaction of indole (**46**) with *p*-bromanil (**21**) in acetonitrile and an excess of Cs_2CO_3 gave a complex product mixture, from which only 17% of **49** was isolated (Scheme 7.27).



46 (2 eq) **21** (1 eq) **49**

Scheme 7.27. Reaction of *p*-bromanil (**21**) with indole (**46**) in the presence of Cs_2CO_3 in CH_3CN.

In summary, an easy and convenient synthesis of DAQ-D (**6**) was not achieved, but valuable precursors have been synthesized.

7.3 Conclusion and Outlook

A convenient and efficient synthesis of polyporic acid (**9**) with a Suzuki cross-coupling reaction as key building step for the terphenyl structure was achieved. The reduction of **9** with H_2, Pd/C gives access to the corresponding hydroquinone derivative **41** which can be used as a model compound for the studies of the possible biomimetic prenylation. The easy approach to the starting materials at hand and the significance of the prenylation for the biosynthetic pathway show that future research on this project is worthwile.

2,5-Dichloro-3-(1*H*-indol-3-yl)-1,4-benzoquinone (**47**) was synthesized from indole (**46**) and readily available 2,5-dichloro-1,4-benzoquinone (**15**) by a modified method of Wang and Li. The synthesis of DAQ-D (**6**) might thus be achieved when a suitable protocol for the addition of another indole unit to the quinone core is found. Hydrolysis of this product should give access to demethylasterriquinone D (**6**).

7.4 Experimental Section

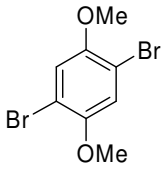
7.4.1 General

All reactions were carried out with magnetic stirring and, if moisture or air sensitive, in flame-dried glassware under argon or nitrogen atmosphere. Syringes which were used to transfer reagents or solvents were purged with argon prior use. Solvents were dried according to standard methods by distillation. All reagents were purchased from Acros, Fluka or Lancaster and used without further purification. ^{1}H-NMR spectra were recorded on Bruker ARX 300 and Varian Inova 400. Chemical shifts refer to trimethylsilane or the solvent resonance as the internal standard ($CDCl_3$: δ = 7.26 ppm, d_6-DMSO: δ = 2.50 ppm, d_6-acetone: δ = 2.05 ppm). Multiplicities are given as s = singlet, d = doublet, t = triplet, q = quartet, br = broad and m = multiplet. ^{13}C-NMR spectra were recorded on Bruker ARX 300 or Varian VXR 400 with broadband proton decoupling. Chemical shifts refer to TMS or the solvent as internal standard ($CDCl_3$: δ = 77.0 ppm, d_6-DMSO: δ = 39.4, d_6-acetone: δ = 29.8, 206.3 ppm). Spin multiplicities are derived from DEPT135 spectra. GC-MS spectra were recorded on Agilent 5973 MSD (HP-5MS capillar column with 30 m length, 0.25 mm diameter, 1.0 mL/min flow rate, injector, split, He carrier gas, quadrupol mass spectrometer). Chromatographic purification was done with Merck silica gel 60 (mesh 40-63 μm) by common or flash column chromatography. MPLC separation was done on a Büchi Sepacore System (pump manager C-615, C-605 pumps, C-660 fraction collector and C-635 photometer). Melting points were measured on Büchi B-540 and are not corrected. High resolution (HR-MS) and MS spectra were recorded on a Finnigan Mat 95 instrument. Electron impact ionization was conducted with an energy of 70 eV.

7.4.2 Total Synthesis of Polyporic Acid

1,4-Dibromo-2,5-dimethoxybenzene (19)[28]

To a solution of 1,4-dimethoxybenzene (**36**, 13.82 g, 100.0 mmol) in glacial acetic acid (28 mL) a solution of Br_2 (10.25 mL, 200.0 mmol) in glacial acetic acid (10 mL) was added dropwise at room temperature. After stirring the reaction mixture for 2 h, the solution was cooled to 0 °C, saturated $Na_2S_2O_3$ solution (200 mL) was added and extracted with EtOAc (300 mL). The combined organic layers were washed with saturated NaCl solution (100 mL) and dried ($MgSO_4$). After evaporation of the solvent, the crude reaction product was recrystallized (acetone) to yield (**19**) as a colorless solid (19.93 g, 69%).



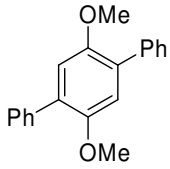
19

M. p. 149–150 °C (Lit: 144–149 °C).[28] ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.85 (s, 6 H), 7.10 (s, 2 H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 57.0 (q), 110.5 (s), 117.2 (d), 150.6 (s). MS (EI, 70 eV): *m/z* (%) = 297.9 (44) [M^+, ^{81}Br], 295.9 (100) [M^+, ^{79}Br, ^{81}Br], 293.9 (46) [M^+, ^{79}Br], 286.1 (49), 283.9 (23), 282.9 (22). HR-MS: $C_8H_8Br_2O_2$, calcd. 293.8891, found 293.8900.

1,4-Dimethoxy-2,5-diphenylbenzene (20)[28]

To a suspension of phenyl boronic acid (**37**, 366 mg, 3.00 mmol), $Pd(OAc)_2$ (3.3 mg, 0.50 mol%), SPhos (12.3 mg, 1.00 mol%) and K_3PO_4 (1.59 g, 7.50 mmol) in dry THF (15 mL) 1,4-dibromo-2,5-dimethoxybenzene (**19**, 296 mg, 1.00 mmol) was added under argon atmosphere and the reaction mixture was stirred for 1.5 h (65 °C). Completion of the reaction was checked by GC-MS of reaction aliquots which were poured on saturated NH_4Cl solution and extracted with EtOAc. When conversion was complete, saturated NH_4Cl solution (5 mL) was added to the reaction mixture and after extraction with EtOAc (3 × 50 mL) the combined organic layers were washed with saturated NaCl solution (50 mL), dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. After purification by column chromatography (SiO_2, *n*-pentane/EtOAc = 9:1) **20** was obtained as a colorless solid (278 mg, 96%).

When the reaction was carried out using 1.48 g (5.00 mmol) of **19**, 1.83 g (15.0 mmol) of **37**, 16.5 mg (1.50 mol%) $Pd(OAc)_2$ and 7.59 g (37.5 mmol) K_3PO_4 the yield of **20** decreased dramatically (682 mg, 47%).

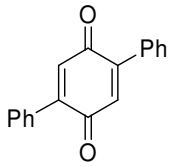


20

M. p. 145–146 °C (Lit: 149 °C).[28] ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 3.82 (s, 6 H), 7.02 (s, 2 H), 7.36–7.65 (m, 10 H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 56.5 (q), 114.8 (d), 127.1 (d), 128.1 (d), 129.5 (d), 130.4 (s), 138.3 (s), 150.7 (s). MS (EI, 70 eV): *m/z* (%) = 291.1 (18) [M^++H], 290.1 (100) [M^+], 275.1 (13), 260 (20). HR-MS: $C_{20}H_{18}O_2$, calcd. 290.1307, found 290.1287.

2,5-Diphenyl-1,4-benzoquinone (11)[49]

To a hot solution of 1,4-dimethoxy-2,5-diphenylbenzene (**20**, 870 mg, 3.00 mmol) in CH_3CN (2 mL) a solution of $(NH_4)_2Ce(NO_3)_6$ (4.40 g, 8.10 mmol) in water (6 mL) was added slowly. The reaction mixture was stirred for 5 min, water (5 mL) was added and the yellow precipitate was collected and dried *in vacuo* to yield **11** as yellow crystals (600 mg, 77%).

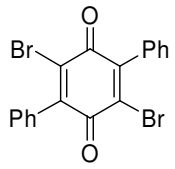


11

M. p. 218–220 °C (Lit: 218 °C).[49] ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 6.97 (s, 2 H), 7.45–7.49 (m, 6 H), 7.54–7.56 (m, 4 H). ^{13}C-NMR (150 MHz, $CDCl_3$): δ = 128.6 (d), 129.3 (d), 130.1 (d), 132.5 (s), 133.2 (s), 145.6 (s), 187.0 (s). MS (EI, 70 eV): *m/z* (%) = 262.1 (56) [M^++2H], 261.1 (24) [M^++H], 260.1 (100) [M^+], 259.1 (25), 232.0 (10), 231.0 (14), 202.0 (10), 130.0 (11), 102.1 (15). HR-MS: $C_{18}H_{12}O_2$, calcd. 260.0837, found 260.0833.

2,5-Dibromo-3,6-diphenyl-1,4-benzoquinone (38)[50]

To a stirred solution of 2,5-diphenyl-1,4-benzoquinone (**11**, 195 mg, 0.750 mmol) in glacial acetic acid (5 mL) Br_2 (0.12 mL, 2.25 mmol) was added dropwise. The mixture was stirred for 2 h (110 °C). Water (15 mL) was added, the yellow precipitate was collected and washed with cold water (3 × 5 mL). The filtrate was extracted with EtOAc (50 mL), washed with saturated NaCl solution (20 mL) and dried ($MgSO_4$). The crude product was recrystallized (toluene) to yield **38** as a yellow solid (234 mg, 75%).

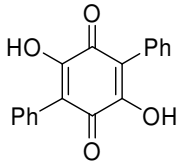


38

M. p. 227–229 °C (Lit: 227–229 °C).[50] ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.31–7.35 (m, 4 H), 7.47–7.51 (m, 6 H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 128.2 (d), 1292.2 (d), 129.7 (d), 133.2 (s), 136.2 (s), 147.1 (s), 176.9 (s). MS (EI, 70 eV): *m/z* (%) = 419.9 (26) [M^+, ^{81}Br], 417.9 (42) [M^+, ^{81}Br, ^{79}Br], 415.9 [M^+, ^{79}Br], 338.0 (25), 336.0 (23), 259.1 (15), 258.1 (81), 202.1 (28), 200.1 (10), 129.0 (100), 101.0 (19), 75.0 (14). HR-MS: $C_{18}H_{10}Br_2O_2$, calcd. 415.9048, found 415.9050.

2,5-Dihydroxy-3,6-diphenyl-1,4-benzoquinone (polyporic acid, 9)[20]

To a refluxing solution of 2,5-dibromo-3,6-diphenyl-1,4-benzoquinone (**38**, 109 mg, 0.260 mmol) in CH_3OH (10 mL) a solution of NaOH (500 mg, 12.5 mmol) in water (5 mL) was added dropwise. The solution was refluxed for further 30 min, poured onto cold water (20 mL) and acidified with conc. HCl (5 drops). The precipitate was collected, washed with cold water (2 × 5 mL) and recrystallized (acetone) to yield **9** as a brown solid (74 mg, 96%).



9

M. p. 300–303 °C (Lit: 305 °C).[20] ^{1}H-NMR (400 MHz, d_6-DMSO): δ = 3.37 (br. s, OH), 7.31–7.43 (m, 10 H). ^{13}C-NMR (100 MHz, d_6-DMSO): δ = 115.5 (s), 127.3 (d), 127.5 (d), 130.3 (d), 130.7 (s). MS (EI, 70 eV): *m/z* (%) = 294.1 (15) [M^+ + 2H], 292.1 (41) [M^+], 278.1 (10). HR-MS: $C_{18}H_{12}O_4$, calcd. 292.0736, found 292.0730.

7.4.3 Reductions and Prenylations

7.4.3.1 Synthesis of Hexahydroxybenzene (40)

Attempted Reduction of 39 with $SnCl_2 \cdot H_2O$

To a solution of 2,3,5,6-tetrahydroxy-1,4-benzoquinone (**39**, 416 mg, 2.00 mmol) in 2N HCl (10 mL) $SnCl_2 \cdot H_2O$ (4.15 g, 15.2 mmol) was added and the reaction mixture was stirred for 8 h at 100 °C. When we carried out the work-up as described[40] we didn't obtain the desired colorless solid.

Attempted Reduction of 39 with $LiAlH_4$

$LiAlH_4$ (152 mg, 4.00 mmol) was suspended in dry THF (10 mL). 2,3,5,6-tetrahydroxy-1,4-benzoquinone (**39**, 416 mg, 2.00 mmol) in dry THF (5 mL) was added to the solution dropwise maintaining a temperature of 0 °C. The solution was allowed to warm up to room temperature and was stirred for 12 h. Since the color of the solution did not change during the reaction and TLC indicated no conversion of **39** the mixture was not worked up.

Attempted Reduction of 39 with $Na_2S_2O_4$

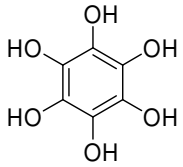
2,3,5,6-tetrahydroxy-1,4-benzoquinone (**39**, 104 mg, 0.500 mmol) and $Na_2S_2O_4$ (174 mg, 1.00 mmol) were exhibited in a flask and hot water (10 mL) was added. The reaction mixture was stirred for 12 h. As indicated by TLC, no conversion was of **39** observed.

Attempted Reduction of 39 with Zn/TFA

2,3,5,6-tetrahydroxy-1,4-benzoquinone (**39**, 21 mg, 0.100 mmol) was dissolved in TFA (3 mL). Zn powder (195 mg, 0.3 mmol) was added and the reaction mixture was stirred for 24 h. As indicated by TLC, no conversion was of **39** observed.

Reduction of 39 with H_2, Pd/C

In a dry and argon flushed flask 2,3,5,6-tetrahydroxy-1,4-benzoquinone (**39**, 25 mg, 0.15 mmol) was dissolved in dry and degassed acetone (5 mL). Palladium (10% on charcoal, 16 mg, 10 mol%) was added and hydrogen was conducted through the suspension. After 5 min decolorization was observed. The catalyst was removed by filtration under argon and the solvent was evaporated *in vacuo* to yield **40** as a colorless solid (20 mg, 80%).

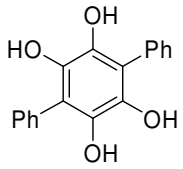


40

^{1}H-NMR (400 MHz, d_6-acetone): δ = 2.84 (br. s, OH). ^{13}C-NMR (100 MHz, d_6-acetone): δ = no signal was detected. MS (EI, 70 eV): *m/z* (%) = 174.1 (100) [M^+], 172.0 (80), 156.0 (32), 144.0 (83), 128.0 (36), 114.0 (22), 100.0 (27), 97.1 (22), 87.0 (24), 83.1 (27), 71.1 (22), 71.0 (22), 70.0 (78), 69.1 (41), 58.1 (35), 57.2 (36), 55.2 (32), 54.1 (33), 42.3 (79), 40.9 (32), 40.8 (39), 39.1 (26). HR-MS: $C_6H_6O_6$, calcd. 174.0164, found 174.0152.

7.4.3.2 Synthesis of 1,2,4,6-Tetrahydroxy-3,6-diphenylbenzene (41)

In a dry and argon flushed flask polyporic acid (**9**, 100 mg, 0.340 mmol) was dissolved in dry and degassed acetone (5 mL). Palladium (10% on charcoal, 55 mg, 10 mol%) was added and hydrogen was conducted through the suspension. After 5 min decolorization was observed. The catalyst was removed by filtration under argon and the solvent evaporated *in vacuo* to yield **41** as a colorless solid (67 mg, 68%).



41

^{1}H-NMR (400 MHz, d_6-acetone): δ = 6.73 (br. s, 4 H, OH), 7.28–7.32 (m, 2 H), 7.28–7.40 (m, 4 H), 7.42–7.5.0 (m, 4 H). ^{13}C-NMR (100 MHz, d_6-acetone): δ = 128.7 (d), 129.8 (d), 130.2 (s), 132.0 (s), 132.9 (d), 136.2 (s), 137.6 (s). MS (EI, 70 eV): *m/z* (%) = 294.1 (71) [M^+], 293.1 (23), 292.1 (100), 191.1 (13), 189.1 (12), 129.0 (18), 118.0 (18), 105.0 (15), 91.1 (13), 89.0 (19), 77.0 (11), 69.1 (12), 57.1 (11), 43.5 (12), 42.4 (23). HR-MS: $C_{18}H_{14}O_4$, calcd. 294.0892, found 294.0893.

7.4.3.3 Attempted Prenylations of 41

1,2,4,5-Tetrahydroxy-3,6-diphenylbenzene (**41**, 9 mg, 0.03 mmol) was dissolved in TFA (3 mL) and 3-methylbut-2-en-1-ol (**43**, 17 mg, 0.20 mmol) was added. The reaction mixture was stirred for 24 h. No conversion was detectable by TLC.

1,2,4,5-Tetrahydroxy-3,6-diphenylbenzene (**41**, 88 mg, 0.30 mmol) was dissolved in 80% aq. acetone (5 mL) and 1-bromo-3-methylbut-2-ene (**45**, 49 mg, 0.33 mmol) was added. The reaction mixture was stirred for 24 h. No conversion was detectable by TLC.

1,2,4,5-Tetrahydroxy-3,6-diphenylbenzene (**41**, 135 mg, 0.466 mmol) was dissolved in CF_3CH_2OH (3 mL) and 1-bromo-3-methylbut-2-ene (**45**, 76.5 mg, 0.513 mmol) was added. After 5 min the color of the reaction mixture became dark brown. After stirring for additional 60 min the TLC showed two new spots. One was identified as polyporic acid (**9**) as it turned purple upon placing the TLC plate over ammonia fumes. The earlier eluting spot turned yellow. When the TLC plate was placed over fuming HCl, the spot of **9** turned brown and the new spot turned into greenish-blue indicating that this compound is not the corresponding ether which results from *O*-prenylation. When we tried to separate the compounds *via* preparative TLC and MPLC we obtained a compound that caused a blue acetone solution. HR-MS of this compound, however, showed that it is not the *C*-prenylated polyporic acid. Further attempts to elucidate the constitution of this product have not been made.

7.4.4 Synthesis of 2,5-Dichloro-3-(1*H*-indol-3-yl)-1,4-benzoquinone

2,5-Dichloro-1,4-benzoquinone (**15**) was synthesized from 1,4-dimethoxybenzene (**36**) in two steps according to literature procedure.[51] *p*-Bromanil (**21**) was synthesized according to Datta and Chatterjee.[52]

Reaction of Indole (46) with 2,5-Dichloro-1,4-benzoquinone (15) in Water

Indole (**46**, 682 mg, 5.82 mmol) and 2,5-dichloro-1,4-benzoquinone (**15**, 2.06 g, 11.6 mmol) were stirred in water (10 mL) for 7 d. The color of the suspension changed from yellow to purple and a dark precipitate formed, which was filtrated off and washed with cold water (3 × 30 mL). After column chromatography (SiO_2, hexanes/EtOAc = 1:1) **47** was obtained as a purple solid (765 mg, 45%).

The reaction was repeated analogously, DDQ (1.32 g, 5.82 mmol) was added after 7 d and stirred for 2 d. Water (20 mL) was added and the phases separated and dried ($MgSO_4$). After evaporation of the solvent *in vacuo* and purification by column chromatography (SiO_2, hexanes/EtOAc = 1:1) **47** was obtained as purple solid (1.28 g, 75%).

Reaction of Indole (46) with *p*-Bromanil (21) and Cs_2CO_3 in Acetonitrile

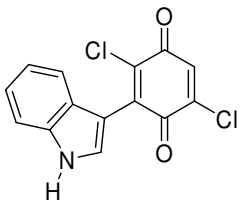
Indole (**46**, 223 mg, 1.90 mmol) and bromanil (**21**, 815 mg, 1.90 mmol) were dissolved in CH_3CN and Cs_2CO_3 (1.25 g, 3.85 mmol) was added. The reaction mixture was stirred for 12 h, bromanil (**21**, 815 mg, 1.90 mmol) and Cs_2CO_3 (1.25 g, 3.85 mmol) were added and the mixture was stirred for another 8 h. The red-purple solution containing 8 different compounds as indicated by TLC was evaporated and after column chromatography (SiO_2, hexanes/EtOAc = 1:1) **47** was obtained as purple solid (94.3 mg, 17%).

Reaction of Indole (46) with 2,5-Dichloro-1,4-benzoquinone (15) in Dichloromethane Catalyzed by $Bi(OTf)_3$

Indole (**46**, 586 mg, 5.00 mmol) and 2,5-dichloro-1,4-benzoquinone (**15**, 1.77 g, 10.0 mmol) were dissolved in CH_2Cl_2 (20 mL) and $Bi(OTf)_3$ (164 mg, 0.250 mmol) was added. The reaction mixture was stirred for 24 h under argon. DDQ (1.14 g, 5.00 mmol) was added and the mixture was stirred for another 8 h. Water (50 mL) was added and the organic layer was

washed with 2N HCl (20 mL), saturated NaCl solution (2 × 20 mL) and water (20 mL). The combined organic phases were dried ($MgSO_4$) and the solvent evaporated *in vacuo*. After purification by column chromatography (SiO_2, hexanes/EtOAc = 1:1) **47** was obtained as a purple solid (219 mg, 15%).

When the reaction was carried out analogously with $Zn(OTf)_2$ instead of $Bi(OTf)_3$ 21% of **47** was obtained.



47

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.53 (s, 1 H), 7.17–7.32 (m, 5 H), 8.60 (br. s, 1 H, OH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 111.8 (d), 116.1 (d), 119.8 (s), 120.7 (s), 121.1 (d), 121.8 (d), 123.1 (d), 129.5 (s), 133.0 (d), 133.2 (s), 144.7 (s), 145.5 (s), 177.2 (s), 177.9 (s). MS (EI, 70 eV): *m/z* (%) = 293.1 (76), 292.1 (14), 291.1 (75), 277.1 (20), 256.1 (22), 180.0 (50), 178.0 (100), 176.0 (60), 114.0 (25), 113.0 (38), 87.9 (47), 60.0 (31), 53.0 (32).

7.5 Literature

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