C—ON bond homolysis in Alkoxyamines. Part 12: Effect of the para-substituent in the 1-phenylethyl fragment.

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C—ON bond homolysis in Alkoxyamines. Part 12: Effect of the *para*-substituent in the 1-phenylethyl fragment.

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The application of alkoxyamines as initiators/controllers in Nitroxide Mediated Polymerization and as agents for Theranostics requires the development of switchable (from stable one to labile one) alkoxyamines. One way to achieve this is to tune the polarity of various groups carried by either the alkyl fragment or the nitroxyl fragment. Thus, the effect of protonation/deprotonation of the *para*-functionalized aryl moiety carried by the alkyl fragment in diethyl (2,2-dimethyl-1-((1,1-dimethylethyl)(1-*para*-subsitutedphenylethoxy) amino)propyl) phosphonate is investigated. An increase in k_d is observed with increasing localized electrical effect, i.e., with the presence of electron widthdrawing groups at the *para* position of the phenyl ring. A striking effect of the intimate ion pair on k_d is also observed. substituents on the aryl group in alkoxyamines **4** (Figure 2) on the homolysis rate constant k_d is investigated both in *tert*-butylbenzene (*t*-BuPh) as weakly polar organic solvent and in a water/methanol mixture. An increase in k_d is observed with the increasing polarity of the *para*-substituents, except for the ionic ones (NH_3^+ and COO^-) in an organic solvent for which, an effect due to the intimate ion pair is observed. These results are discussed using different Hammett constants.

Introduction

During the last 30 years,[1] alkoxyamines have mainly been developed as initiator/controller agents for NMP.[2-7] Recently, we proposed[8] and highlighted[9] the potential of alkoxyamines as agents for theranostics. Our concept (Figure 1) relies on a fast homolysis of the alkoxyamine C—ON bond which releases an alkyl radical (therapeutic agent) and a nitroxide (diagnostic agent). There are two key steps: release of an alkoxyamine, due to a specific biological activity followed by in situ chemical activation, *e.g.*, protonation.

Hence, the easy activation or pro-activation of the alkyl fragments carried by alkoxyamines is one of our goal in this field. The alkoxyamine potential for activation has been highlighted by protonation, oxidation or alkylation of a pyridyl moiety as alkyl fragment.[10] Interestingly, it was shown that alkoxyamine **1** (Figure 2) carrying a *para*-substituted aromatic ring was slightly sensitive to the polarity of the *para*-substituent.[11] This sensitivity to the polarity of the *para*-subtituent on the aryl group was also reported when C—ON bond was at a distance of 7 or 10 bonds for insulated systems (Figure 2) either by a carboxylic group in the case of alkoxyamines **2**[12] or by a methylene group, in the case of alkoxyamines **3**.[13] Taking into account that the nitroxyl fragment based on **1•** is prone to enhancing the effect of polar subtituents on the alkyl fragment, the effect of the *para*-

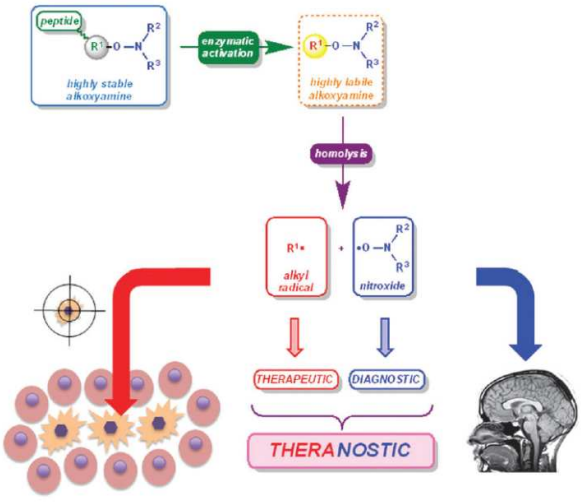

Figure 1. Concept for the application of alkoxyamines as theranostic agents (Audran, G.; Brémond, P.; Marque, S. R. A. *Chem. Commun.* 2014, *50*, 59, 7921-7928. Published by The Royal Society of Chemistry).

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Electronic Supplementary Information (ESI) available: Characterization data (^{1}H, ^{13}C NMR spectra) of compounds **4b,d,e,g-j**, procedure for kinetic and pKa measurements. X-ray crystallographic data for (*RS/SR*)-**4b**, (*RR/SS*)-**4d**. (CIF), and (*RS/SR*)-**4h**. (CIF). See DOI: 10.1039/x0xx00000x

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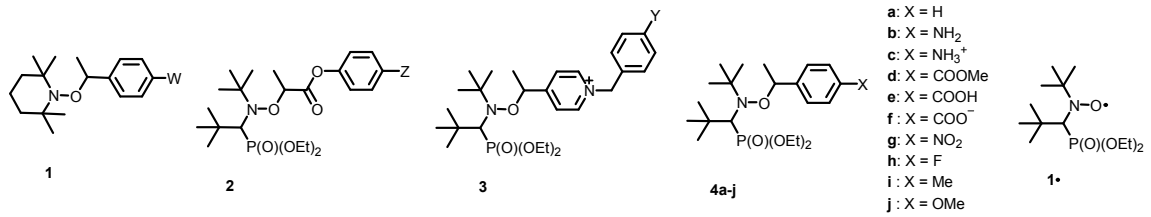


Figure 2. Alkoxyamines discussed in this article.

Results

Preparation of 4b,d,e,g,h-j.

Alkoxyamines **4b,h-j** were prepared by coupling of the alkyl radical generated from the corresponding *para*-substituted styrene using Mn(salen) salt[14] and **1•** (Scheme 1a). Oxidation of **4b** by *meta*-chloroperbenzoic acid afforded **4g** (Scheme 1b). Preparation of **4d** was performed using the procedure developed by Matyjazewski[15] using beforehand prepared methyl 4-(1-bromoethyl)benzoate (Scheme 1c).[16] Acid **4e** was obtained by basic hydrolysis of **4d**.

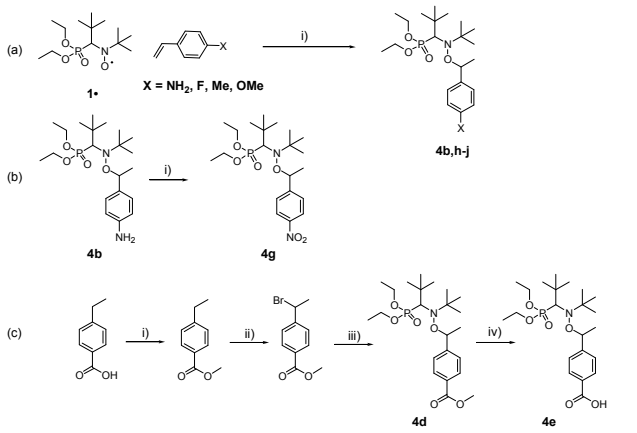
Based on the attribution of ^{31}P NMR shifts to the X-ray structures (**Figure 3**) of (*RS/SR*)-**4b**, of (*SS/RR*)-**4d**, and of (*RS/SR*)-**4h**‡ the lower and the higher value of δ were ascribed to the *RS/SR* and *RR/SS* diastereoisomers of **4i,j**, respectively. Preparation of **4e,g** was performed from the pure diastereoisomers of **4d** and **4b**, respectively (Scheme 1). Alkoxyamines **4c** and **4f** were generated *in situ* from the pure diastereoisomers of **4b** and **4e**, respectively. Protonation of **4b** was performed *in situ* either using trifluoroacetic acetic (TFA) in *t*-BuPh or by controlling the water/methanol solution pH. Deprotonation of **4e** was performed *in situ* either using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in *t*-BuPh or by controlling the water/methanol solution pH (Table 1). Formation of **4c** and **4f** was checked by ^{1}H NMR (vide infra).

Kinetic measurements.

For all alkoxyamines, very nice growths of **1•** were observed by EPR both in *tert*-butylbenzene (*t*-BuPh) and in a water/methanol mixture as solvents (not shown). Nice decays were observed by ^{31}P NMR (not shown).

$k'_{d,RS/SR}/k'_{d,RR/SS}$ ratii are never more than two-fold or less than half-fold, as already reported, and do not deserve further comments. For 1 eq. TFA and 1 eq. DBU, **4b** and **4e** were completely protonated and deprotonated, respectively, as shown by the absence of significant changes in k'_d or E_a when the amounts of acid and base were increased (Table 1).

A weak 2-3-fold increase in k'_d from *t*-BuPh to water/methanol was observed for **4a-e,g-j** as already reported.[17-19] More surprising is the 3-fold decrease in k'_d observed for **4f** (Table 1). Although very different alkyl fragments are carried by the alkoxyamines, most of them exhibit the same solvent effect, meaning that the main effect of the solvent is the stabilization of the released nitroxide, which is **1•**, for all alkoxyamines.



Scheme 1. Preparation of (a) 4b,h-j: i) 4-X-vinylbenzene, Mn(salen), $NaBH_4$, *i*-PrOH; of (b) 4g: i) *m*CPBA, CH_2Cl_2; and of (c) 4d,e: i) MeOH, DCC, DMAP, CH_2Cl_2; ii) NBS, CH_2Cl_2, hν; iii) Methyl 4-(1-bromoethyl)benzoate, CuBr, Cu, PMDETA, benzene; iv) LiOH•H_2O, THF-H_2O (1:1).

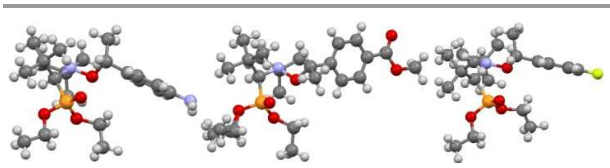


Figure 3. X-ray structures of (*RS/SR*)-4b (left), (*SS/RR*)-4d (middle), and (*RS/SR*)-4h (right).

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Table 1. Homolysis rate constant k_d of **4a-j** in various conditions (solvent, temperature, and pH) and the subsequent E_a values as well as re-estimated k'_d values at 120 °C.

alkoxyamine	solvent[a]	T (°C)	k_d (10^{-4} s^{-1})		E_a (kJ/mol)[b]		k'_d (10^{-3} s^{-1})[c]	
			RR/SS	*RS/SR*	*RR/SS*	*RS/SR*	*RR/SS*	*RS/SR*
a: X = H[d]	*t*-BuPh	100	4.8	7.6	126.4	125.0	3.8	5.9
b: X = NH_2	*t*-BuPh	100	7.9	4.9	124.9	126.3	6.1	3.9
c: X = NH_3^+[e]	*t*-BuPh + 1 eq. TFA	100	7.9	6.1	124.9	125.7	6.1	4.8
	t-BuPh + 2 eq. TFA	100	9.1	6.3	124.5	125.6	7.0	5.0
d: X = CO_2Me	*t*-BuPh	90	9.4	9.5	121.0	121.0	20.0	20.0
e: X = COOH	*t*-BuPh	90	12.3	11.4	120.2	120.4	25.7	23.9
f: X = COO^-[f]	*t*-BuPh + 1 eq. DBU	90	12.0	10.6	120.3	120.7	25.1	22.4
	t-BuPh + 2 eq. DBU	90	12.1	8.4	120.3	121.4	25.1	18.0
g: X = NO_2	*t*-BuPh	80	6.5	7.6	118.8	118.3	40.0	45.9
h: X = Me	*t*-BuPh	100	6.6	7.7	125.4	124.9	5.2	6.0
i: X = F	*t*-BuPh	100	5.2	20.4[g]	126.1	125.2	4.2	5.5
j: X = OMe	*t*-BuPh	100	6.8	4.8	125.3	126.4	5.3	3.8
a	H_2O/MeOH (1:1)	80	1.5	1.1	123.0	124.0	10.8	7.9
b	H_2O/MeOH (1:1, pH = 6.0)	80	1.9	0.9	122.4	124.6	13.0	6.7
c	H_2O/MeOH (1:4, pH = 2.2.)	80	2.1	1.3	122.1	123.4	14.1	9.6
d	H_2O/MeOH (1:1)	80	6.9	7.6	118.6	118.3	41.9	45.3
e	H_2O/MeOH (1:1, pH = 2.2.)	80	6.8	7.0	118.6	118.6	41.5	41.5
f	H_2O/MeOH (1:1, pH = 10.3)	80	1.2	2.0	123.7	122.2	8.8	13.8
g	H_2O/MeOH (1:1)	80	16.8	20.2	116.0	115.4	93.5	110.3
h	H_2O/MeOH (3:7)	80	1.0	1.4	124.2	123.2	7.4	10.1
i	H_2O/MeOH (3:7)	70	0.4	-	123.1	-	10.4	-
	H_2O/MeOH (3:7)	80	-	0.8	-	125.1	-	5.7
j	H_2O/MeOH (3:7)	80	1.0	0.8	124.2	125.1	7.4	5.7

[a] *t*-BuPh: *tert*-butylbenzene. TFA: trifluoroacetic acid. DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene. [b] Given by eq. 2 and using k_d values reported in the 4th and 5th columns. [c] Re-estimated k_d values at 120 °C using eq. 2 and E_a values reported in the 6th and 7th columns. [d] E_a = 124.5 kJ/mol for a mixture 1:1 of diastereoisomers. [e] trifluoroacetate as counter anion. [f] DBU—H^+ as counter-cation. [g] T = 110 °C.

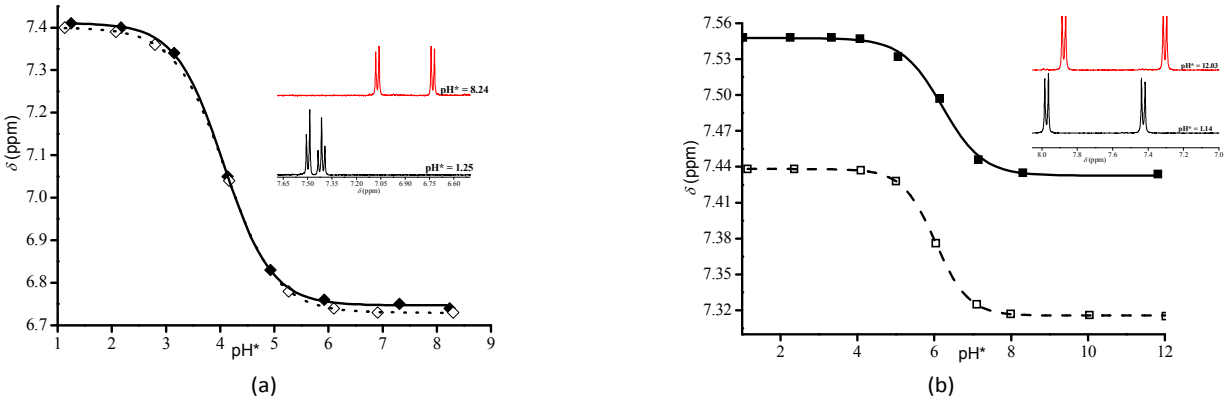
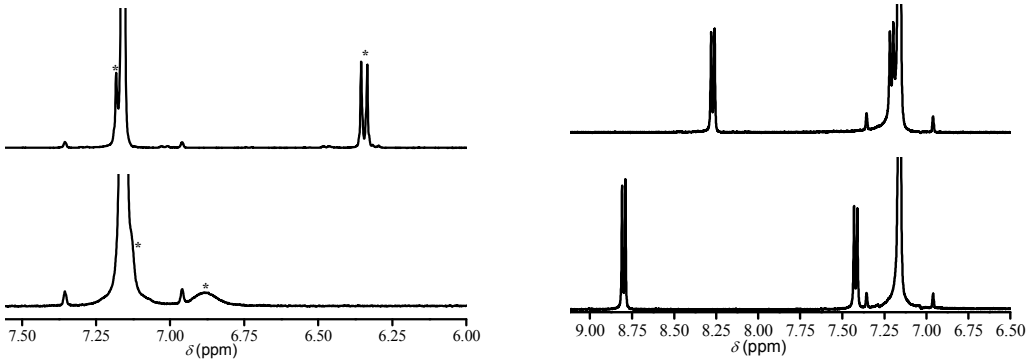


Figure 4. Titration curve of (a) *RR/SS*-4b (0.01 M, ♦, inset: signal zone of aromatic protons) and *RS/SR*-4b (0.01 M, ◊) diastereoisomers and of (b) *RR/SS*-4e (0.01 M, □) and *RS/SR*-4e (0.01 M, ■, inset: signal zone of aromatic protons) diastereoisomers. D_2O/MeOH-d_4 (1:1).



(a) (b)

Figure 5. ^{1}H NMR for the aromatic zone in C_6D_6 of (a) (*RR/SS*)-**4b** (top) and (*RR/SS*)-**4c** (bottom, 1 eq. TFA); and of (b) **4e** (top) and **4f** (bottom, 1 eq. DBU). Stars are for the shifting peaks

Protonation and deprotonation.

The values of pK_a (Figure 4) were determined for **4b** and **4e** as already reported (not dependent on the diastereoisomer).[20,§] The pK_a values of 4.20 and 4.23 for the *RR/SS* and the *RS/SR* diastereoisomer of **4b**, respectively, are slightly lower than those for their parent aniline (pK_a = 4.6). The pK_a values of 6.02 and 6.19 for the *RR/SS* and the *RS/SR* diastereoisomers of **4e**, respectively, are much larger than those for their parent benzoic acid (pK_a = 4.20). The low pK_a for **4b** is due to the electron widthdrawing effect of the nitroxyl fragment. However, at this time, the best rationale to account for the high pK_a of the benzoic acid derivative would be to assume an effect of the water/methanol mixture on the pK_a values.

As mentioned above, one equivalent of both the acid (TFA) and the base (DBU) was strong enough to protonate **4b** into **4c** and to deprotonate **4e** into **4f** in *t*-BuPh, respectively. The ^{1}H NMR signal of the aromatic protons was used to monitor protonation of **4b** (Figure 5a) and deprotonation of **4e** (Figure 5b).

Hammett constants for structure-reactivity relationships (SRR).

SRR have been developed for both the nitroxyl and the alkyl fragments. For the latter, k_d depends on the radical stabilization effect – described by the Hammett-type constant σ_{RS}[21] –, on the polar (electrical) effect – described by the Hammett constant σ_I[22-27,#] –, and on the steric effect – described by the Charton's constant υ.[28] To describe the stabilization effect of the released radical, the best would be to use σ_{RS}. However, knowledge of σ_{RS} relies on the determination of the Radical Stabilization Energy (RSE) as defined by Rüchardt,[29] which requires knowledge of the hydrogen hyperfine coupling constants $a_{H,\alpha}$ and $a_{H,\beta}$ at positions α and β in the considered radical. Unfortunately, only two a_H values have been reported for radicals in the series **a**• – **g**•, precluding the use of the σ_{RS} scale as well as of the σ_α• scale developed by Arnold.[30-32] Amongst the other scales available, such as σ_J•,[33] σ_{jj}•,[34] σ•,[35] σ_C•,[36,37] ΔD[38] which have been developed to describe the stabilization of benzylic type radicals, σ_{jj}• and ΔD – developed by Jiang[34] and Adam,[38] respectively – were selected since the values for 8 of the 10 investigated radicals were reported (Table 2).

The localized electrical effect is due to the presence of electron widthdrawing (EWG) or electron donating (EDG) groups, which are either directly attached to the reactive centre (Figure 6a) or separated from it by a spacer (Figure 6b). The presence of a spacer can be disregarded, and the effect is described using σ_L, or the spacer is considered and, for **4a-g**, the effect is described by $\sigma_{L,4\text{-}XC6H4}$ given by eq. 4.[22,27]

$$\sigma_{L,4\text{-}XC6H4} = 0.138 \cdot \sigma_{L,X} + 0.137 \cdot \sigma^0_{R,X} + 0.120 \quad (4)$$

For the series **4a-g**, the occurrence of the delocalization of the radical or of some partial charges at TS cannot be disregarded. Then, the impact of this effect also depends on the presence of EWG and EDG. These groups can be either attached to the reactive centre (Figure 6a) or separated from it by a spacer (Figure 6b). The presence of a spacer can be disregarded, and the delocalization effect is described by $\sigma_{R,X}$, or the spacer is considered, and, for **4a-g**, the effect is described by $\sigma_{R,4\text{-}XC6H4}$ given by eq. 5.[22,27]

$$\sigma_{R,4\text{-}XC6H4} = 0.180 \cdot \sigma_{L,X} + 0.111 \cdot \sigma^0_{R,X} - 0.0988 \quad (5)$$

The Hammett constant $\sigma^0_{R,X}$ describes the normalized delocalized effect of an X group. Its values are in general similar to the values of $\sigma_{R,X}$, except for amino and some other groups.[22,Ω]

In general, the effect of a *para*-substituted aryl on the reactivity is investigated using the composite Hammett constant $\sigma_{p,X}$ given by eq. 6 which encompasses both the universal electrical effect ($\sigma_{L,X}$) and the resonance effect ($\sigma_{R,X}$).

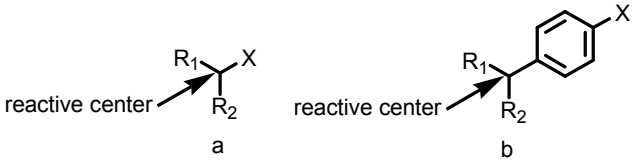


Figure 6. Position of X (EWG or EDG) to the reactive centre.

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Table 2. Values of Hammett-type constants $\sigma_{L,X}$, $\sigma_{R,X}$, $\sigma_{R,4\text{-}XC6H4}$, $\sigma_{L,4\text{-}XC6H4}$, $\sigma_{p,X}$, $\sigma_{jj}^{\bullet}$ and ΔD

alkoxyamine	$\sigma_{L,4\text{-}XC6H4}$ [a]	$\sigma_{L,X}$ [b]	$\sigma_{R,X}$ [b]	$\sigma_{R,4\text{-}XC6H4}$ [c]	$\sigma_{p,X}$ [b]	$\sigma_{jj,X}^{\bullet}$ [d]	ΔD_X [e]
a: X = H [e]	0.12 [b]	0	0	-0.11 [b]	0	0	0
b: X = NH_2	0.09 [f]	0.17	-0.80	-0.16 [f]	-0.63	1.0 [g]	0.30
c: X = NH_3^+	0.22 [f]	1.02 [h]	-0.31 [i]	0.05 [f]	0.71	- [j]	0.08
d: X = COOMe	0.18	0.32	0.11	-0.03	0.43	0.33	0.52
e: X = COOH	0.18	0.30	0.11	-0.03	0.41	0.38	- [j]
f: X = COO^-	0.13	-0.19	0.23	-0.11	0.04	- [j]	- [j]
g: X = NO_2	0.23	0.67	0.10	0.03	0.77	0.36	0.90
h: X = Me	0.10	-0.01	-0.16	-0.13	-0.17	0.15	0.02
i: X = F	0.13	0.45	-0.48	-0.07	0.06	-0.02	-0.17
j: X = OMe	0.11	0.29	-0.58	-0.19	-0.27	0.23	-0.04

[a] Given by eq. 4 unless otherwise mentioned. [b] See ref. 22 unless otherwise mentioned. [c] Given by eq. 5 unless otherwise mentioned. [d] Given in ref. 34 [e] See ref. 38. [f] For σ^0_R see ref. **Error! Bookmark not defined.**. [g] Assuming $\sigma_{jj,NH2}\bullet \approx \sigma_{jj,NMe}\bullet = 1$. See ref. 34. [h] Using $F = 0.92$ and eq. 9 in ref. 26. [h] Using eq. 6. [i] Given by eq. 6. [j] Not available.

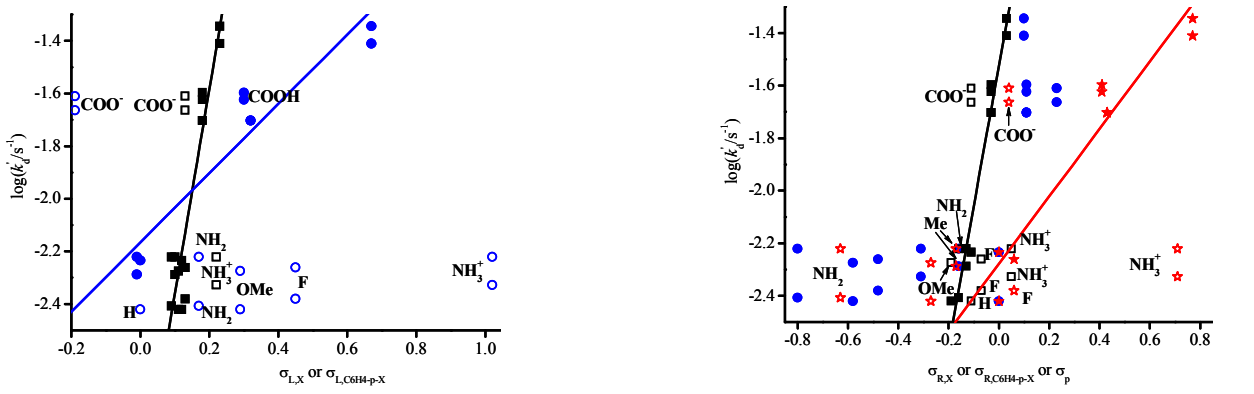

Figure 7. (a) Plots $\log(k'_d/s^{-1})$ vs $\sigma_{L,X}$ (blue line and ●) and $\log(k'_d/s^{-1})$ vs $\sigma_{L,4\text{-}XC6H4}$ (black line and ■) in *t*-BuPh . (b) Plots $\log(k'_d/s^{-1})$ vs $\sigma_{R,X}$ (●) and $\log(k'_d/s^{-1})$ vs $\sigma_{R,4\text{-}XC6H4}$ (black line and ■) and $\log(k'_d/s^{-1})$ vs σ_p (red line and ★) in *t*-BuPh. Empty symbols are for outliers.

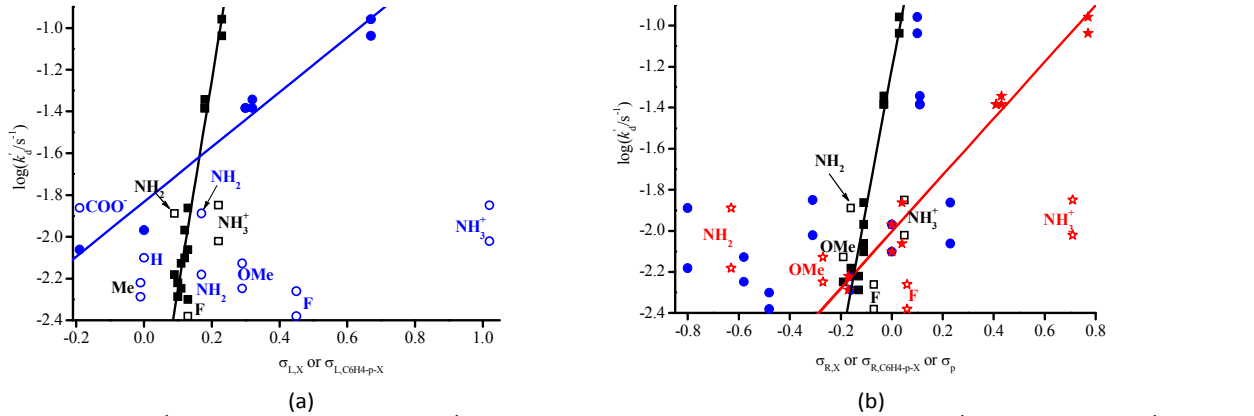

Figure 8. (a) Plots $\log(k'_d/s^{-1})$ vs $\sigma_{L,X}$ (blue line and ●) and $\log(k'_d/s^{-1})$ vs $\sigma_{L,4\text{-}XC6H4}$ (black line and ■) in water/methanol. (b) Plots $\log(k'_d/s^{-1})$ vs $\sigma_{R,X}$ (●) and $\log(k'_d/s^{-1})$ vs $\sigma_{R,4\text{-}XC6H4}$ (black line and ■) and $\log(k'_d/s^{-1})$ vs σ_p (red line and ★) in water/methanol. Empty symbols are for outliers.

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All Hammett constants are listed in Table 2. As the ratio $k'_{d(RR/SS)}/k'_{d(SR/RS)}$ is mainly in between 2 and 0.5 and often close to 1, k'_d values for the two diastereoisomers were indistinctly reported on the same plots (Figure 7 and Figure 8). The trends in k'_d are given using the averaged values of k'_d for the two diastereoisomers. Beside the conventional 2-3-fold solvent effect already reported, some clear differences are observed for **4b** and **4f**.

$$\sigma_{p,X} = \sigma_{L,X} + \sigma_{R,X} \qquad (6)$$

Discussion

A decade ago, SRR were developed to account for the various effects ruling k_d and due to both the nitroxyl[39] and the alkyl[21] fragments. It was shown that k_d values depend on the stabilization of the released alkyl radical (σ_{RS}), the bulkiness (υ) and the polarity (σ_L) of the alkyl fragment, as given by eq. 7.

$$\log(k_d/s^{-1}) = -14.33(\pm 0.54) + 15.06(\pm 1.17)\cdot\sigma_{RS} + 20.00(\pm 1.86)\cdot\sigma_L + 6.96(\pm 0.43)\cdot\upsilon \qquad (7)$$

It must be noted that all coefficients have a positive sign, meaning that k_d increases with increasing parameters. The polar effect is due to the difference in electronegativity χ between the oxygen and the carbon atoms in the C—ON bond, that is, an increase in χ of the C atom implies a destabilization of the alkoxyamine, leading to a smaller E_a, and, hence, to a higher k_d. The stabilization of the released alkyl radical stabilizes the late TS and, hence, decreases E_a, affording a higher k_d. Increasing the bulkiness of the alkyl fragment increases the internal strain in the alkoxyamine, destabilizing the starting material and leading to a smaller E_a and, hence, to a higher k_d. For the series **4b-j**, it was assumed that the substitution at the *para* position of the aromatic ring did not generate larger steric strain than in **4a** and, consequently, all changes observed in k_d were due to the polar and stabilization effects.

The trends (Figure 9) observed with $\sigma_{jj,X}$• and ΔD_X cannot account for the reactivity observed both in *t*-BuPh and water/methanol, that is, k'_d of **4b** should be larger than k'_d of **4a,d,e,g-j**, as given by $\sigma_{jj,X}$• in sharp contrast with the experimental trend, or k'_d of **4g** should be larger than k'_d of **4a-d,h-i** as given by ΔD_X. Moreover, the difference in $\sigma_{jj,X}$• or ΔD_X observed between **4a** and **4b**, which is in sharp contrast with their very similar k'_d, precludes any effect due to the stabilization of the released alkyl radical. There is a complete mismatch between the trend given by $\sigma_{R,X}$ in *t*-BuPh and the experimental trend in k'_d which leads to discard this parameter to describe the effects involved in k'_d. All other trends given by $\sigma_{L,4\text{-}XC6H4}$, $\sigma_{L,X}$, $\sigma_{p,X}$, and $\sigma_{R,4\text{-}XC6H4}$ in *t*-BuPh would agree with the experimental trend, provided the ionic species are removed. The likely occurrence of an intimate ion pair[40] is discussed later.

Consequently, plots of $\log(k'_d/s^{-1})$ vs Hammett constants are expected to provide linear correlations (Figure 7), as given by eq. (8). Good correlations are observed for $\sigma_{L,4\text{-}XC6H4}$, $\sigma_{R,4\text{-}XC6H4}$ in *t*-BuPh whereas $\sigma_{L,X}$ and $\sigma_{p,X}$ afford poor correlations (good R^2 values but 11-12 outliers for 20 data, see Table 3 and Figure 7), and the data were too scattered to plot a correlation with $\sigma_{R,X}$ (Figure 7). Hence, the absence of outliers$^{\surd}$ – except the ionic species **4c** and **4f** when $\sigma_{L,4\text{-}XC6H4}$ is used instead of $\sigma_{R,4\text{-}XC6H4}$ – supports strongly the need to take the spacer into account (Figure 6b) to describe the effect of EWG (localized electrical effect). Moreover, the trend in $\sigma_{L,4\text{-}XC6H4}$ predicts (Figure 9) very close values of k'_d ($\Delta E_a \approx 1$ kJ/mol observed in Table 1 for $\Delta\sigma_{L,4\text{-}XC6H4} = 0.03$ in Table 2 for Me, H, F, and OMe groups) for **4a,h-j** whereas the trend in $\sigma_{R,4\text{-}XC6H4}$ predicts a larger change in k'_d ($\Delta\sigma_{R,4\text{-}XC6H4}$, = 0.33 for Me, H, F and OMe), knowing that the larger difference in E_a ($\Delta E_a \approx 8$ kJ/mol) is observed between **4a** and **4g** with a $\Delta\sigma_{R,4\text{-}XC6H4}$, = 0.14.

For all alkoxyamines, the largest discrepancies are observed for the ionic species, pointing to an effect due to the presence of intimate ion pairs. Indeed, it is known that an intimate ion pair, which is likely to be observed in a weakly ion pair dissociative solvent such as *t*-BuPh, cancels or dampers the effect expected from a positive or a negative charge, that is, decrease in k_d with an anion[41] such as **COO$^-$** as EDG and increase in k'_d with a cation[40] such as **NH$_3^+$** as EWG.

$$\log(k_d/s^{-1}) = a + b\cdot\sigma \qquad (8)$$

k'_d in *t*-BuPh	$H \approx F \approx Me \approx NH_2 \approx NH_3^+ < CO_2Me \approx COOH \approx COO^- < NO_2$
k'_d in H_2O/MeOH	$F = OMe \approx NH_2 \leq H < Me \approx NH_3^+ < COO^- < CO_2H \approx COOMe < NO_2$
$\sigma_{L,4\text{-}XC6H4}$	$NH_2 < Me \leq OMe \leq H \leq F \approx COO^- < COOMe \approx COOH < NH_3^+ \leq NO_2$
$\sigma_{L,X}$	$COO^- < Me \leq H < NH_2 < OMe \leq COOH \approx COOMe < F < NO_2 < NH_3^+$
$\sigma_{R,X}$	$NH_2 < OMe < F < NH_3^+ < Me < H < NO_2 \approx COOH = COOMe < COO^-$
$\sigma_{R,4\text{-}XC6H4}$	$OMe < NH_2 < Me < H = COO^- < F < COOMe = COOH < NO_2 < NH_3^+$
$\sigma_{p,X}$	$NH_2 < OMe < Me < H < COO^- < F < COOMe \approx COOH < NH_3^+ < NO_2$
σ_{jj}•	$F < H < Me < OMe < COOMe < NO_2 < COOH < NH_2$
ΔD	$F < OMe < H < Me < NH_3^+ < NH_2 < COOMe < NO_2$

Figure 9. Trends for k'_d expected from the Hammett-type constants.

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Table 3. Coefficients for eq. 8 in *t*-BuPh and its statistical outputs

Eq.	*x*-abscissa	*y*-intercept[a]	slope[a]	N^b	R^{2c}	outliers
8a	$\sigma_{L,4\text{-}XC6H4}$	-3.1 (1)	7.8 (7)	16	0.89	NH_3^+,COO^-
8b	$\sigma_{L,X}$	-2.2 (1)	1.3 (2)	9	0.91	NH_3^+,COO^-,NH_2, COOH,F,OMe,H(*RS/SR*)
8c	$\sigma_{R,4\text{-}XC6H4}$	-1.5 (1)	5.3 (3)	11	0.97	NH_3^+,COO^-,F,H(*RR/SS*), NH_2(*RR/SS*),OMe(*RR/SS*)
8d	$\sigma_{p,X}$	-2.3 (1)	1.3 (1)	9	0.93	NH_3^+,COO^-,NH_2,Me, OMe,F(*RR/SS*)

[a] In parentheses, error given on the last digit. [b] Number of data. [c] Square of the linear regression coefficient

Table 4. Coefficients for eq. 8 in a water/methanol mixture and its statistical outputs

Eq.	*x*-abscissa	*y*-intercept[a]	slope[a]	N^b	R^{2c}	outliers
8e	$\sigma_{L,4\text{-}XC6H4}$	-3.3 (1)	10.0 (7)	16	0.93	NH_3^+,NH_2(*RS/SR*), F(*RR/SS*)
8f	$\sigma_{L,X}$	-1.9 (1)	1.3 (1)	8	0.96	NH_3^+,NH_2,F,Me,OMe, H(*RS/SR*),COO^- (*RS/SR*)
8g	$\sigma_{R,4\text{-}XC6H4}$	-1.2 (1)	6.7 (1)	14	0.97	NH_3^+,F,NH_2(*RR/SS*), OMe(*RR/SS*)
8h	$\sigma_{p,X}$	-2.0 (1)	1.4 (1)	12	0.98	NH_3^+,NH_2,F,OMe

[a] In parentheses, error given on the last digit. [b] Number of data. [c] Square of the linear regression coefficient.

Intimate ion pair effect.

As mentioned above, an intimate ion pair may strikingly modify the reactivity expected in an organic solvent and, consequently, should be very sensitive to a dissociative solvent such as a binary mixture of water and methanol.[10,17,18] The comments concerning the trends (Figure 9) given by $\sigma_{L,X}$, $\sigma_{R,X}$, and $\sigma_{p,X}$ done in *t*-BuPh (vide supra) hold for the experiments performed in water/methanol as solvent. Interestingly, contrary to experiments performed in *t*-BuPh, **4f** is included in the trends given by $\sigma_{L,4\text{-}XC6H4}$ and $\sigma_{R,4\text{-}XC6H4}$ whereas NH_3^+ is again excluded. As in *t*-BuPh, correlations (eq. 8) between $\log(k'_d/s^{-1})$ and σ-values (Figure 8 and Table 4) were found in water/methanol. Except for $\sigma_{R,X}$, which shows a scattered plot, all other correlations are of very good quality, provided some outliers are removed (Table 4 and Figure 8). Interestingly, **4f** is included in the correlations based on $\sigma_{L,4\text{-}XC6H4}$ and $\sigma_{R,4\text{-}XC6H4}$ as expected, that is, the ratio $k'_{d,\mathbf{4e}}/k'_{d,\mathbf{4f}}$ increased from 1.02 in *t*-BuPh to 4.7 in water/methanol, highlighting nicely the effect of the intimate ion pair in *t*-BuPh and completely dissociated ion pair in water/methanol. That is, the counter-cation being in the vicinity of the carboxylate function balances the effect of the negative charge on the strength of the C—ON bond in **4f**, affording k_d values very close to those of **4e** in *t*-BuPh, whereas when the intimate ion pair is dissociated in the water/methanol mixture, a stronger effect of the negative charge is observed, affording a lower k_d for **4f** than for **4e**, as expected. Moreover, this intimate ion pair in **4f** leads to a reverted solvent effect, i.e., for all other alkoxyamines k_d increases from *t*-BuPh to water/methanol.

Surprisingly, the effect of the intimate ion pair is not observed with **4c**, as the ratio $k'_{d,\mathbf{4b}}/k'_{d,\mathbf{4c}}$ is very close to 1 in both solvents. In fact, the complete dissociation of the intimate ion pair – affording a strinking increase in k_d – is counterbalanced by the solvation , and hence the stabilization, of the alkoxyamine – affording a striking decrease in k_d. This is why the effect of the intimate ion pair is not apparent when the solvent is changed.

Conclusion

In this work, we confirm the efficiency of the polar effect to afford a 10-fold increase in k_d values from **4a** to **4g** whatever the solvent. The polar effect is nicely described by the universal electrical Hammett constant $\sigma_{L,4\text{-}XC6H4}$.

In the last few years, we have promoted the activation of the alkoxyamine C—ON bond homolysis by the protonation of the pyridine ring in the alkyl fragment, i.e., increasing the polarity. With this work, we highlight the de-activation of the alkoxyamine C—ON bond homolysis by de-protonation of the carboxylic fonction of the alkyl fragment, i.e., increasing the electron donating effect. However, we show that the impact of the polarity is dramatically related to the occurrence of solvent-dependent intimate ion pair and on the type of function, impeding any possibility to foresee the impact of this effect.

Experimental section.

Solvents and reactants for the preparation of alkoxyamines **4** were used as received. Alkoxyamine **4a**,[42] methyl 4-

ethylbenzoate,[43] and methyl 4-(1-bromoethyl)benzoate[44] were prepared according to the literature. Routine reaction monitoring was performed using silica gel 60 F_{254} TLC plates; spots were visualized upon exposure to UV light and a phosphomolybdic acid solution in EtOH, followed by heating. Purifications were performed on chromatography columns with silica gel grade 60 (230–400 mesh). ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ on a 300 or 400 MHz spectrometer. Chemical shifts (δ) in ppm were reported using residual nondeuterated solvents as internal reference for ^{1}H and ^{13}C-NMR spectra, and 85% H_3PO_4 for ^{31}P-NMR spectra.

General procedure for the preparation of 4b,h-j.

To a stirred solution of salen ligand (0.05 eq.) in *i*-PrOH was added $MnCl_2$ (0.05 eq.) in an open flask. After 30 minutes of stirring at room temperature, a solution of **1•** (1 eq.) and *para*-substitued-styrene (1.5 eq.) in *i*-PrOH was added first, then solid $NaBH_4$ (4 eq.) in small portions. The resulting suspension was stirred at room temperature for 1.5-4h. It was then diluted with EtOAc and 1 M aq. HCl was carefully added. Solid $NaHCO_3$ was then added until neutralization. The layers were separated, and the organic phase was washed with water, brine and dried over Na_2SO_4. After concentration under reduced pressure, the residue was purified by column chromatography to afford the corresponding alkoxyamines **4b**,**h** - **j.**

Diethyl (1-((1-(4-aminophenyl)ethoxy)(*tert*-butyl)amino)-2,2-dimethylpropyl)phosphonate (*RR/SS*-4b and *RS/SR*-4b)

Salen ligand (46 mg, 0.17 mmol, 0.05 eq.), $MnCl_2$ (21 mg, 0.17 mmol, 0.05 eq.), **1•** (1.0 g, 3.4 mmol, 1.0 eq.), 4-vinylaniline (0.61 g, 5.1 mmol, 1.5 eq.) and $NaBH_4$ (0.52 g, 13.6 mmol, 4.0 eq.). Solvent was evaporated to give the crude product as a 1:1 mixture of diastereoisomers (^{31}P-NMR ratio). The diastereomers were separated by automatic flash column chromatography (gradient of acetone in DCM) to afford (*RR/SS*)-**4b** (0.31 g, 23%) and *RS/SR*-**4b** (0.32 g, 24%). The sample for X-ray crystallography of (*RS/SR*)-**4b** was recrystallized from pentane/EtOAc. (*RR/SS*)-**4b**; Pale yellow solid; m.p.: 110 °C (decomp.); R_f = 0.46 (DCM/Acetone 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (d, J = 8.3 Hz, 2H), 6.64 (d, J = 8.3 Hz, 2H), 4.91 (q, J = 6.5 Hz, 1H), 3.92-4.40 (m, 4H), 3.34 (d, $J_{H\text{-}P}$ = 25.3 Hz, 1H), 1.57 (d, J = 6.8 Hz, 3H), 1.33 (t, J = 6.8 Hz, 3H), 1.32 (t, J = 7.0 Hz, 3 H), 1.24 (s, 9H), 0.85 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.2, 135.0, 128.3, 114.3, 84.0, 69.8 (d, $J_{C\text{-}P}$ = 138.6 Hz), 61.3 (d, $J_{C\text{-}P}$ = 6.6 Hz), 60.8, 58.5 (d, $J_{C\text{-}P}$ = 7.2 Hz), 35.3 (d, $J_{C\text{-}P}$ = 5.5 Hz), 30.0 (d, $J_{C\text{-}P}$ = 6.1 Hz), 28.3, 23.2, 16.5 (d, $J_{C\text{-}P}$ = 6.1 Hz),16.1 (d, $J_{C\text{-}P}$ = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 25.97; HRMS *m/z* (ESI) Calcd for $C_{21}H_{39}N_2O_4P$ $[M+H]^+$ 415.2720, Found: 415.2723; (*RS/SR*)-**4b**; pale yellow crystal; m.p.: 130 °C (decomp.); R_f = 0.31 (DCM/Acetone 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, J = 8.3 Hz, 2H), 6.62 (d, J = 8.3 Hz, 2H), 5.16 (q, J = 6.5 Hz, 1H), 3.21 - 4.07 (m, 4H), 3.39 (d, $J_{H\text{-}P}$ = 26.1 Hz, 1H), 1.52 (d, J = 6.5 Hz, 3H), 1.25 (t, J = 7.0 Hz, 3H), 1.20 (s, 9H), 1.19 (s, 9H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.7, 133.1, 129.0, 114.4, 77.8, 70.1 (d, $J_{C\text{-}P}$ = 139.7 Hz), 61.6 (d, $J_{C\text{-}P}$ = 6.1 Hz), 60.9, 58.4 (d, $J_{C\text{-}P}$ = 7.7 Hz), 35.2 (d, $J_{C\text{-}P}$ = 5.0 Hz), 30.5 (d, $J_{C\text{-}P}$ = 6.1 Hz), 28.1, 20.7, 16.3 (d, $J_{C\text{-}P}$ = 6.1 Hz), 16.1 (d, $J_{C\text{-}P}$ = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 24.63; HRMS *m/z* (ESI) Calcd for $C_{21}H_{39}N_2O_4P$ $[M+H]^+$ 415.2720, Found: 415.2722.

Methyl 4-(1-((*tert*-butyl(1-(diethoxyphosphoryl)-2,2-dimethylpropyl)amino)oxy)ethyl)benzoate (*RS/SR*-4d and *RR/SS*-4d).

To a degassed solution of CuBr (1.18 g, 8.3 mmol) and Cu (1.05 g, 16.5 mmol) in benzene, *N*,*N*,*N*',*N*'',*N*''-Pentamethyldiethylenetriamine (1.72 mL, 8.3 mmol) was added dropwise, and the solution was kept under argon bubbling for another 30 min. Then, a degassed benzene solution of **1•** (4.42 g, 16.5 mmol) and methyl 4-(1-bromoethyl)benzoate (4.01 g, 16.5 mmol) was added, and the mixture was stirred for 3 h at room temperature under argon. Then, Et_2O, water and NH_4OH was added and the mixture was washed with Et_2O. The organic layer was washed with H_2O and brine, dried with $MgSO_4$, and the solvent was evaporated to yield a crude product as a 2:1 mixture of diastereoisomers (^{31}P NMR ratio). The diastereoisomers were separated by flash column chromatography (petroleum ether/EtOAc, 9:1) to afford (*RS/SR*)-**4d** (2.81 g, 41%) and (*RR/SS*)-**4d** (0.87 g, 13%). The sample for X-ray crystallography of (*RR/SS*)-**4d** was recrystalized from pentane. (*RS/SR*)-**4d**; Colorless oil; R_f = 0.37 (Pentane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.3 Hz, 2H), 5.29 (q, J = 6.6 Hz, 1H), 3.91 (s, 3H), 3.42 (d, $J_{H\text{-}P}$=26.3 Hz, 1H), 3.18 - 3.53 and 3.79 - 4.04 (m, 4H), 1.55 (d, J = 6.6 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.22 (s, 9H), 1.21 (s, 9H), 0.91 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.8, 148.4, 129.1, 128.9, 127.4, 77.8, 69.6 (d, $J_{C\text{-}P}$ = 139.8 Hz), 61.3 (d, $J_{C\text{-}P}$ = 6.1 Hz), 61.1, 58.6 (d, $J_{C\text{-}P}$ = 7.7 Hz), 51.7, 35.1 (d, $J_{C\text{-}P}$ = 5.0 Hz), 30.5 (d, $J_{C\text{-}P}$ = 6.1 Hz), 28.0, 21.1, 16.1 (d, $J_{C\text{-}P}$ = 6.1 Hz), 16.0 (d, $J_{C\text{-}P}$ = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 24.53; HRMS *m/z* (ESI) Calcd for $C_{23}H_{41}NO_6P$ $[M+H]^+$ 458.2666, Found: 458.2665. (*RR/SS*)-**4d**; White solid; m.p.: 82-84 °C; R_f = 0.29 (Pentane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.2 Hz, 2H), 5.04 (q, J = 6.7 Hz, 1H), 3.92 - 4.43 (m, 4H), 3.89 (s, 3H), 3.34 (d, $J_{H\text{-}P}$ = 26.0 Hz, 1H), 1.59 (d, J = 6.8 Hz, 3H), 1.35 (d, J = 7.2 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.23 (s, 9H), 0.83 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.8, 150.4, 129.3, 128.7, 126.8, 84.8, 69.5 (d, $J_{C\text{-}P}$ = 138.6 Hz), 61.4 (d, $J_{C\text{-}P}$ = 6.6 Hz), 61.1, 58.8 (d, $J_{C\text{-}P}$ = 7.7 Hz), 51.8, 35.4 (d, $J_{C\text{-}P}$ = 5.5 Hz), 29.9 (d, $J_{C\text{-}P}$ = 6.1 Hz), 28.4, 23.9, 16.6 (d, $J_{C\text{-}P}$ = 5.5 Hz), 16.1 (d, $J_{C\text{-}P}$ = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 25.67; HRMS *m/z* (ESI) Calcd for $C_{23}H_{41}NO_6P$ $[M+H]^+$ 458.2666, Found: 458.2666.

4-(1-((tert-Butyl(1-(diethoxyphosphoryl)-2,2-dimethylpropyl)amino)oxy)ethyl)benzoic acid (RS/SR-4e).

To a solution of (*RS/SR*)-**4d** (0.92 g, 2.0 mmol) in THF-H_2O (1:1, 15 mL) was added $LiOH{\cdot}H_2O$ (0.42 g, 10.0 mmol) at room temperature. The mixture was stirred at rt for 5 h and then it acidified with 1M HCl. The mixture was diluted with water and extracted with DCM. The combined organic phase was dried with $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography (DCM: MeOH = 95: 5) to afford (*RS/SR*)-**4e** (0.82g, 87%). White solid; m.p.: 64-65 °C; R_f = 0.37 (DCM/MeOH 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J = 8.2 Hz, 2 H), 7.53 (d, J = 8.2 Hz, 2H), 5.30 (q, J = 6.7 Hz, 1H), 3.48 (d, $J_{H\text{-}P}$=26.7 Hz, 1 H), 3.32 - 4.17 (m, 4H), 1.58

(d, *J* = 6.5 Hz, 3H), 1.25 - 1.30 (m, 12H), 1.24 (s, 26H), 0.95 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (7,5 MHz $CDCl_3$) δ: 169.3, 148.3, 129.6, 129.4, 127.2, 78.0, 69.8 (d, J_{C-P} = 140.3 Hz), 61.9 (d, J_{C-P} = 6.6 Hz), 61.2, 59.3 (d, J_{C-P} = 7.7 Hz), 35.2 (d, J_{C-P} = 5.0 Hz), 30.5 (d, J_{C-P} = 6.1 Hz), 28.1, 21.3, 16.0 (d, J_{C-P} = 5.5 Hz), 15.9 (d, J_{C-P} = 6.6 Hz); ^{31}P-NMR (162 MHz, $CDCl_3$) δ: 24.80; HRMS *m/z* (ESI) Calcd for $C_{22}H_{39}NO_6P$ $[M+H]^+$ 444.2510, Found: 444.2507.

4-(1-((tert-Butyl(1-(diethoxyphosphoryl)-2,2-dimethylpropyl)amino)oxy)ethyl)benzoic acid (RR/SS-4e).

The same procedure as for (*RS/SR*)-**4e** was applied to (*RR/SS*)-**4d** (0.46 g, 1.0 mmol) with LiOH·H_2O (0.21 g, 5.0 mmol) to yield (*RR/SS*)-**4e** (0.35 g, 79%). White solid; m.p.: 65-66 °C; R_f = 0.41 (DCM/MeOH 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.2 Hz, 2H), 5.07 (q, *J* = 6.7 Hz, 1H), 3.93 - 4.49 (m, 4H), 3.38 (d, J_{H-P} = 26.3 Hz, 1H), 1.62 (d, *J* = 6.7 Hz, 3H), 1.38 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 1.25 (s, 9H), 0.86 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.7, 150.6, 129.9, 129.2, 126.9, 85.3, 69.8 (d, J_{C-P} = 139.2 Hz), 62.1 (d, J_{C-P} = 6.1 Hz), 61.3, 59.4 (d, J_{C-P} = 7.7 Hz), 35.7 (d, J_{C-P} = 6.1 Hz), 30.1 (d, J_{C-P} = 5.5 Hz), 28.6, 24.1, 16.7 (d, J_{C-P} = 5.5 Hz), 16.2 (d, J_{C-P} = 7.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 25.64; HRMS *m/z* (ESI) Calcd for $C_{22}H_{39}NO_6P$ $[M+H]^+$ 444.2510, Found: 444.2505.

Diethyl (1-((1-(4-nitrophenyl)ethoxy)(tert-butyl)amino)-2,2-dimethylpropyl)phosphonate (RR/SS-4g).

To a stirred solution of (*RR/SS*)-**4b** (1.97 g, 4.8 mmol) in DCM (40 mL), *m*-CPBA (3.19 g, 14.3 mmol, 77%) was added at 0°C. After stirring at 0°C for 1 h, the mixture was washed with $NaHCO_3$ and brine. Then it was dried over Na_2SO_4 and evaporated. The residue was purified on a chromatography column, eluted with DCM to afford (*RR/SS*)-**4g** 1.12 g (53%). Brown solid; m.p.: 68-70 °C; R_f = 0.42 (DCM/Acetone 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.19 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 5.11 (q, *J* = 6.6 Hz, 1H), 3.95 - 4.44 (m, 4H), 3.37 (d, J_{H-P} = 26.2 Hz, 1H), 1.62 (d, *J* = 6.7 Hz, 3H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.25 (s, 9H), 0.86 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.5, 146.8, 127.6, 123.3, 84.2, 69.4 (d, J_{C-P} = 139.2 Hz), 61.4 (d, J_{C-P} = 6.1 Hz), 61.2, 59.0 (d, J_{C-P} = 7.2 Hz), 35.4 (d, J_{C-P} = 5.0 Hz), 29.9 (d, J_{C-P} = 5.5 Hz), 28.3, 23.8, 16.6 (d, J_{C-P} = 5.5 Hz), 16.1 (d, J_{C-P} = 6.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 25.35; HRMS *m/z* (ESI) Calcd for $C_{21}H_{38}N_2O_6P$ $[M+H]^+$ 445.2462, Found: 445.2460.

Diethyl (1-((1-(4-nitrophenyl)ethoxy)(tert-butyl)amino)-2,2-dimethylpropyl)phosphonate (RS/SR-4g).

The same procedure as for (*RR/SS*)-**4g** was applied to (*RS/SR*)-**4b** (1.64 g, 4.0 mmol) with *m*CPBA (77%, 2.66 g, 11.9 mmol) to yield (*RS/SR*)-**4g** (1.12 g, 64%). Brown solid; m.p.: 72-74 °C; R_f = 0.54 (DCM/Acetone 9:1); ^{1}H NMR (400 MHz $CDCl_3$) δ: 8.17 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 5.33 (q, *J* = 7.0 Hz, 1H), 3.44 (d, J_{H-P} = 26.5 Hz, 1H), 3.28 - 4.07 (m, 4H), 1.57 (d, *J* = 6.5 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.23 (s, 9H), 1.21 (s, 9H), 0.96 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 150.7, 146.9, 128.1, 123.0, 77.4, 69.4 (d, J_{C-P} = 139.2 Hz), 61.2, 61.1 (d, J_{C-P} = 6.6 Hz), 58.8 (d, J_{C-P} = 7.7 Hz), 35.1 (d, J_{C-P} = 4.4 Hz), 30.5 (d, J_{C-P} = 6.1 Hz), 27.9, 21.2, 16.1 (d, J_{C-P} = 6.1 Hz), 15.9 (d, J_{C-P} = 7.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ: 24.43; HRMS *m/z* (ESI) Calcd for $C_{21}H_{38}N_2O_6P$ $[M+H]^+$ 445.2462, Found: 445.2460.

Diethyl (1-(tert-butyl(1-(4-fluorophenyl)ethoxy)amino)-2,2-dimethylpropyl)phosphonate (4h).

Salen ligand (0.65 mmol), $MnCl_2$ (0,65 mmol), **1•** (17 mmol), 4-fluorostyrene (25.5 mmol) and $NaBH_4$ (17 mmol) to give after concentration under reduced pressure a crude product as a 1:3 mixture of diastereoisomers (^{31}P-NMR ratio). The diastereomers were separated by automatic flash column chromatography (gradient of ethyl acetate in petroleum ether) to afford (*RR/SS*)-**4h** and (*RS/SR*)-**4h** (4.1 g, 58%). (*RS/SR*)-**4h**; Colourless solid; m.p.: 56 °C; R_f = 0.61 (petroleum ether/AcOEt = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (dd, *J* = 8.5, 5.7 Hz, 2H), 6.93 (t, *J* = 8.7 Hz, 2H), 5.21 (q, *J* = 6.6 Hz, 1H), 4.51 – 3.64 (m, 2H), 3.48 – 3.18 (m, 2H), 3.38 (d, J_{H-P} = 26.2 Hz, 1H), 1.51 (d, *J* = 6.6 Hz, 3H), 1.34 – 1.08 (m, 21H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.3 (d, J_{C-P} = 245.1 Hz), 139.2 (d, J_{C-P} = 3.2 Hz), 129.7, 129.6, 114.9, 114.6, 77.8, 70.2 (d, J_{C-P} = 139.3 Hz), 61.6 (d, J_{C-P} = 6.5 Hz), 61.3, 58.8 (d, J_{C-P} = 7.5 Hz), 35.4 (d, J_{C-P} = 5.0 Hz), 30.8 (d, J_{C-P} = 6.0 Hz), 28.3, 21.2, 16.4 (d, J_{C-P} = 5.8 Hz), 16.3 (d, J_{C-P} = 6.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ: -115.3; ^{31}P NMR (121 MHz, $CDCl_3$) δ: 24.7; HRMS *m/z* (ESI) calcd for $C_{21}H_{37}FNO_4P$ $[M + H]^+$ 418.2522, found: 418.2520. (*RR/SS*)-**4h**; Colorless oil; R_f = 0.50 (EP/AcOEt = 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26 (dd, *J* = 8.5, 5.5 Hz, 2H), 6.97 (t, *J* = 8.6 Hz, 2H), 4.98 (q, *J* = 6.6 Hz, 1H), 4.31 (m, 1H), 4.17 – 3.79 (m, 3H), 3.35 (d, J_{H-P} = 26.3 Hz, 1H), 1.57 (d, *J* = 6.7 Hz, 3H), 1.31 (q, *J* = 6.9 Hz, 6H), 1.23 (s, 9H), 0.84 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 161.9 (d, J_{C-P} = 245.0 Hz), 140.9 (d, J_{C-P} = 3.2 Hz), 128.8 (d, J_{C-P} = 7.8 Hz), 127.0 (d, J_{C-P} = 8.0 Hz), 114.7 (d, J_{C-P} = 21.2 Hz), 83.9, 69.8 (d, J_{C-P} = 138.6 Hz), 61.6 (d, J_{C-P} = 6.3 Hz), 61.2, 59.0 (d, J_{C-P} = 7.4 Hz), 35.5 (d, J_{C-P} = 5.5 Hz), 30.2 (d, J_{C-P} = 6.0 Hz), 28.5, 23.6, 16.6 (d, J_{C-P} = 5.7 Hz), 16.2 (d, J_{C-P} = 6.7 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ: -115.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ: 25.7; HRMS *m/z* (ESI) calcd for $C_{21}H_{37}FNO_4P$ $[M + H]^+$ 418.2522, found : 418.2520.

Diethyl (1-(tert-butyl(1-(p-tolyl)ethoxy)amino)-2,2-dimethylpropyl)phosphonate (4i).

Salen ligand (0.65 mmol), $MnCl_2$ (0,65 mmol), **1•** (17 mmol), 4-methylstyrene (25.5 mmol) and $NaBH_4$ (17 mmol) to give after concentration under reduced pressure a crude product as a 1:4 mixture of diastereoisomers (^{31}P-NMR ratio). The diastereomers were separated by automatic flash column chromatography (gradient of ethyl acetate in petroleum ether) to afford (*RR/SS*)-**4i** and (*RS/SR*)-**4i** (4.4 g, 63%). (*RS/SR*)-***4i***. Colourless solid; m.p.: 63 °C; R_f = 0.42 (petroleum ether/AcOEt 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34 (d, *J* = 7.9 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 2H), 5.21 (q, *J* = 6.5 Hz, 1H), 4.17 – 3.65 (m, 2H), 3.49-3.27 (m, 2H), 3.40 (d, J_{H-P} = 26.1 Hz, 1H), 2.30 (s, 3H), 1.54 (d, *J* = 6.5 Hz, 3H), 1.28 – 1.17 (m, 21H), 0.90 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.5, 137.0, 128.7, 127.9, 78.3, 70.3 (d, J_{C-P} = 139.2 Hz), 61.7 (d, J_{C-P} = 6.4 Hz), 61.3, 58.7 (d, J_{C-P} = 7.4 Hz), 35.5 (d, J_{C-P} = 5.1 Hz), 30.8 (d, J_{C-P} = 6.0 Hz), 28.4, 21.2, 16.5 (d, J_{C-P} = 5.8 Hz), 16.3 (d, J_{C-P} = 6.8 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ: 24.8; HRMS *m/z* (ESI) calcd for $C_{22}H_{40}NO_4P$ $[M + H]^+$ 414.2773, found: 414.2767. (*RR/SS*)-**4i**; Colorless solid; m.p.: 79 °C; R_f = 0.52 (EP/AcOEt 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29 (d, *J* = 7.9 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 2H), 5.07 (q, *J* = 6.8 Hz, 1H), 4.47 (m, 1H), 4.34 – 3.95 (m, 3H), 3.46 (d, J_{H-P} =

26.2 Hz, 1H), 2.43 (s, 3H), 1.70 (d, *J* = 6.7 Hz, 3H), 1.43 (m, 6H), 1.36 (s, 9H), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 142.5, 136.6, 128.7, 127.2, 85.1, 70.0 (d, $J_{C\text{-}P}$ = 138.5 Hz), 61.7 (d, $J_{C\text{-}P}$ = 6.3 Hz), 61.2, 59.0 (d, $J_{C\text{-}P}$ = 7.5 Hz), 35.7 (d, $J_{C\text{-}P}$ = 5.7 Hz), 30.3 (d, $J_{C\text{-}P}$ = 5.9 Hz), 28.7, 24.1, 21.2, 16.8 (d, $J_{C\text{-}P}$ = 5.6 Hz), 16.4 (d, $J_{C\text{-}P}$ = 6.6 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) *δ*: 26.0; HRMS *m/z* (ESI) calcd for $C_{22}H_{40}NO_4P$ $[M + H]^+$ 414.2773, found: 414.2767.

Diethyl (1-(tert-butyl(1-(4-methoxyphenyl)ethoxy)amino)-2,2-dimethylpropyl)phosphonate (4j).

Salen ligand (0.65 mmol), $MnCl_2$ (0,65 mmol), **1•** (17 mmol), 4-methoxystyrene (25.5 mmol) and $NaBH_4$ (17 mmol) to give after concentration under reduced pressure a crude product as a 1:4 mixture of diastereoisomers (^{31}P-NMR ratio). The residue was purified by automatic flash column chromatography (gradient of ethyl acetate in petroleum ether) to afford (*RR/SS*)-**4j** and (*RS/SR*)-**4j** (4.6 g, 66%). Colourless oil; R_f = 0.56 (petroleum ether/AcOEt 4:1); ^{1}H NMR (300 MHz, $CDCl_3$) *δ*: 7.40 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.3 Hz, 2H), 6.83 (dd, *J* = 8.6, 3.6 Hz, 4H), 5.21 (q, *J* = 6.6 Hz, 1H), 4.96 (q, *J* = 6.8 Hz, 1H), 4.42 – 4.28 (m, 1H), 4.23 – 3.82 (m, 5H), 3.79 (s, 3H), 3.78 (s, 3H), 3.61 – 3.06 (m, 4H), 1.59 (d, *J* = 6.7 Hz, 3H), 1.54 (d, *J* = 6.6 Hz, 3H), 1.32 (td, *J* = 7.0, 4.9 Hz, 6H), 1.25 (s, 12H), 1.21 (s, 9H), 1.20 (s, 9H), 0.92 (t, *J* = 7.1 Hz, 3H), 0.85 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 159.0, 158.8, 137.6, 135.6, 129.2, 128.6, 126.7, 113.9, 113.3 (d, $J_{C\text{-}P}$ = 1.5 Hz), 84.2, 77.9, 70.29 (d, $J_{C\text{-}P}$ = 139.3 Hz), 70.06 (d, $J_{C\text{-}P}$ = 138.6 Hz), 62.5 – 61.5 (m), 61.2, 58.9 (d, $J_{C\text{-}P}$ = 7.9 Hz), 58.7 (d, $J_{C\text{-}P}$ = 7.4 Hz), 55.3, 55.2, 35.7 (d, $J_{C\text{-}P}$ = 5.7 Hz), 35.4 (d, $J_{C\text{-}P}$ = 5.2 Hz), 30.8 (d, $J_{C\text{-}P}$ = 6.0 Hz), 30.3 (d, $J_{C\text{-}P}$ = 5.8 Hz), 28.6, 28.3, 23.6, 21.1, 16.8 (d, $J_{C\text{-}P}$ = 5.7 Hz), 16.6 – 16.1 (m); ^{31}P NMR (121 MHz, $CDCl_3$) *δ*: 25.9, 24.8; HRMS *m/z* (ESI) calcd for $C_{22}H_{40}NO_5P$ $[M + H]^+$ 430.2722, found: 430.2713.

Homolysis rate constants k_d were measured by EPR,[45] as previously reported, and given by eq. 1. For **4b**, ^{31}P NMR[46] was used at pH = 2.2, as previously reported, with k_d given by eq. 2. Air and TEMPO were used as alkyl radical scavengers for EPR and ^{31}P NMR experiments, respectively. Activation energies E_a were estimated using eq. 3 and the averaged frequency factor $A = 2.4\ 10^{14}\ s^{-1}$. Values of k_d and E_a are listed in Table 1.

$$\ln\frac{[\text{nitroxide}]_\infty - [\text{nitroxide}]_t}{[\text{nitroxide}]_\infty} = -k_d \cdot t \quad (1)$$

$$\ln\frac{[\text{alkoxyamine}]_t}{[\text{alkoxyamine}]_0} = -k_d \cdot t \quad (2)$$

$$E_a = 8.314 \cdot T \cdot \ln\frac{2.4 \cdot 10^{14}}{k_d} \quad (3)$$

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Notes and references

‡ CCDC: 1441553 for (*RS/SR*)-**4b**; CCDC:1441554 for (*RR/SS*)-**4d** and CCDC: 1452314 for (*SR/RS*)-**4h**.

§ All pH measured in D_2O–MeOH-d_4 were re-estimated using pH = 0.929·pH* + 0.42. pH* is the pH measured in D_2O–MeOH-d_4 solutions using a pH-meter calibrated with non-deuterated water. See ref. 20.

The electrical effect is considered as an universal effect which is described by the same "universal" constant σ_I, σ_U, *F*, σ_L, σ_F and so on, depending on the authors. See refs. 22-24.

Ω $\sigma^0_{R,NH2}$ = -0.42 and assuming $\sigma^0_{R,NH3+} \approx \sigma^0_{R,NMe3+}$ = -0.32. See refs. 25 and 26.

√ R^2 = 0.94 is observed for $\sigma_{L,4\text{-}XC6H4}$ with 13 data when **H(***RR/SS***)**, **F(***RR/SS***)** and **OMe(***RS/SR***)** are also considered as outliers.

1 G. Audran, P. Brémond, S. R. A. Marque, *Chem. Commun.*, 2014, **50**, 59, 7921-7928.
2 D. H. Solomon, E. Rizzardo, P. Cacioli, 1985, Eur. Pat. Appl. 135280; 1986, US Patent 4,581,429; 1985, Chem. Abstr., 102, 221335q.
3 A. Goto, T. Fukuda, *Prog. Polym. Sci.*, **2004**, 29, 329–385.
4 P. Nesvadba, *Chimia* 2006, **60**, 832-840 and references cited therein.
5 R. B. Grubbs, *Polym. Rev.* 2011, **51**, 104-137.
6 J. Nicolas, Y. Guillaneuf, C. Lefay, D. Bertin, D. Gigmes, B. Charleux, *Progr. Polym. Sci.*, 2013, **38**, 1, 63.
7 Nitroxide Mediated Polymerization: From Fundamentals to Applications in Materials Science Series: RSC Polymer Chemistry Series Ed. D. Gigmes, 2015.
8 G. Audran, P. Brémond, J.-M. Franconi, S. R. A. Marque, P. Massot, P. Mellet, E. Parzy, E. Thiaudière, Org. Biomol. Chem. 2014, 12, 719-723.
9 9 D. Moncelet, P. Voisin, V. Bouchaud, P. Massot, E. Parzy, G. Audran, J.-M. Franconi, S. R. A. Marque, P. Brémond, P. Mellet, *Mol. Pharmaceutics* 2014, **11**, 2412-2419.
10 10 P. Brémond, A. Koïta, S. R. A. Marque, V. Pesce, V. Roubaud, D. Siri Org. Lett., 2012, 14, 1, 358-361.
11 S. Marque, H. Fischer, E. Baier, A. Studer, *J. Org. Chem.* 2001, **66**, 4, 1146-1156.
12 D. Bertin, D. Gigmes, S. R. A. Marque, S. Milardo, J. Peri, P. Tordo, *Collect. Czech. Chem. Commun.*, 2004, **69**, 12, 2223-2238
13 G. Audran, M. Bim Batsiandzy Ibanou, P. Brémond, S. R. A. Marque, G. Obame, V. Roubaud, D. Siri *J. Phys. Org. Chem.* 2014, **27**,387-391.

14 R. Braslau, N. Naik, H. Zipse, *J. Am. Chem. Soc.*, 2000, **122**, 8421-8434.
15 K. Matyjaszewski, B. E. Woodworth, X. Zhang, S. G. Gaynor, Z. Metzner, *Macromolecules* 1998, **31**, 5955-5957
16 A. C. Greene, R. B. Grubbs, *J. Polym. Sci.: Part. A. Polym. Chem.*, 2009, **47**, 6342-6352.
17 G. Audran, P. Brémond, S. Marque, G. Obame, *Polym. Chem.*, 2012, **3**, 2901-2908.
18 G. Audran, P. Brémond, S. R. A. Marque, G. Obame, *J. Org. Chem.* 2012, **77**, 21, 9634-9640.
19 E. G. Bagryanskaya, P. Brémond, T. Butscher, S. R. A. Marque, D. Parkhomenko, V. Roubaud, D. Siri, S. Viel, *Macromol. Chem. Phys.*, 2015, **216**, 5, 475-488.
20 A. Krężel, W. J. Bal, *Inorg. Biochem.*, 2004, **98**, 161–166.
21 D. Bertin, D. Gigmes, S. R. A. Marque, P. Tordo, *Macromolecules* 2005, **38**, 7, 2638-2650.
22 O. Exner *J. Phys. Org. Chem.* 1999, **12**, 265.
23 M. Charton *J. Phys. Org. Chem.* 1999, **12**, 275.
24 O. Exner, M. Charton, V. Galkin *J. Phys. Org. Chem.* 1999, **12**, 289.
25 M. Charton, *Prog. Phys. Org. Chem.* 1981, **13**, 119.
26 M. Charton, *Prog. Phys. Org. Chem.* 1987, **16**, 287.
27 C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* 1991, **91**, 165–195.
28 M. Charton, *Top. Curr. Chem.* 1983, 58–91.
29 J. J. Brocks, H. D. Beckhaus, A. Beckwith, C. Rüchardt, *J. Org. Chem.* 1998, **63**, 1935–1943.
30 J. M. Dust, D. R. Arnold, *J. Am. Chem. Soc.* 1983, **105**, 1221-1227.
31 D. R. Arnold, A. M. D. P. Nicholas, M. S. Snow, *Can. J. Chem.* 1985, **63**, 1150-1155.
32 D. R. Arnold, In Substituent Effects in Radical Chemistry; Viehe, H. G., Janousek, Z., Merényi, R., Eds.; Kluiwert Academy Press: Dordrecht, The Netherlands, 1986; Vol. 189, pp 171-188.
33 R. A. Jackson, M. Sharifi, *J. Chem. Soc., Perkin Trans. 2* 1996, 775-778.
34 X.-K. Jiang, *Acc. Chem. Res.* 1997, **30**, 283-289.
35 I. B. Afanas'ev, *Int. J. Chem. Kinet*. 1975, **7**, 857-877.
36 X. Creary, M. E. Mehrsheikh-Mohammadi, S. McDonald, *J. Org. Chem.* 1987, **52**, 3254-3263.
37 X. Creary, P. S. Engel, N. Kavaluskas, L. Pan, A. Wolf, *J. Org. Chem.* 1999, **64**, 5634-5643.
38 W. Adam, H. M. Harrer, F. Kita, H.-G. Korth, W. M. Nau, *J. Org. Chem.* 1997, **62**, 1419-1426.
39 S. Marque, *J. Org. Chem.* 2003, **68**, 20, 7582-7590.
40 D. Bertin, D. Gigmes, S. R. A. Marque, P. Tordo, *Macromolecules* 2005, **38**, 7, 7754-7757.
41 D. Bertin, D. Gigmes, S. R. A. Marque, D. Siri, P. Tordo, G. Trappo, *ChemPhysChem*, 2008, **9**, 272-281.
42 D. Bertin, D. Gigmes, C. Le Mercier, S. Marque, P. Tordo *J. Org. Chem.* 2004, **69**, 15, 4925-4930
43 B. Schmalzbauer, D. Menche, *Org. Lett.* 2015, **17**, 12, 2956.
44 A. C. Greene, R. B. Grubbs, *J. Polym. Sci. Part A Polym. Chem.* 2009, **47**, 23, 6342.
45 S. Marque, C. Le Mercier, P. Tordo, H. Fischer, *Macromolecules*, 2000, **33**, 12, 4403-4410.
46 D. Bertin, D. Gigmes, S. Marque, P. Tordo, *e-Polymers*, 2003, **2**,