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Reversible Modulation of Thiourea Catalysts Activity with Anions. A Simple Approach to Switchable Asymmetric Catalysis

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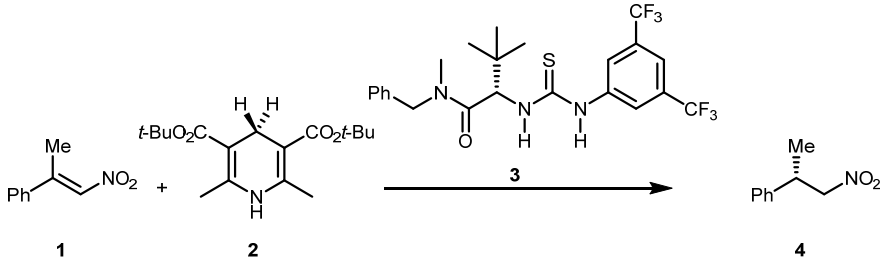
General methods and materials

^{1}H and ^{19}F spectra were recorded on a Varian AS 400 spectrometer. Chemical shifts (δ) are reported in ppm relative to residual solvent signals for ^{1}H NMR,[1] and to an external reference for ^{19}F NMR (C_6F_6, -164.9 ppm). Chromatographic purifications were performed using 70-230 mesh silica. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC. The absolute configuration of the compounds obtained from the catalytic reactions was determined by comparison with the literature.

Analytical grade solvents and commercially available reagents were used as received, unless otherwise stated. CH_2Cl_2 for the catalytic reactions was filtered on a plug of basic alumina before use. Compounds **1**,[2] ethyl *Z*-3-nitro-2-phenylacrylate,[3] **5**,[4] Hantzsch ester **2**,[5] catalysts **3**[6] and **7**,[7] the tris-(4-methoxyphenyl)phosphine derived ylide[8] used in the asymmetric Wittig reaction, the salt $NaBAr^F$,[9] were prepared following literature procedures. $TBABAr^F$ and $TPPBAr^F$ were prepared by anion exchange: equimolar amounts of TBACl or TPPCl and $NaBAr^F$ were mixed in CH_2Cl_2 (ca 0.1 M) and stirred for few minutes; aqueous work up (H_2O/CH_2Cl_2), followed by drying over $MgSO_4$, filtration and removal of the solvent, gave $TBABAr^F$ and $TPPBAr^F$ as white solids.

[1] H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512.
[2] H. Ohta, N. Kobayashi and K. Ozaki, *J. Org. Chem.*, 1989, **54**, 1803.
[3] N. J. A. Martin, X. Cheng and B. List, *J. Am Chem. Soc.*, 2008, **130**, 13862.
[4] X.-F. Xia, X.-Z. Shu, K.-G. Ji, Y.-F. Yang, A. Shaukat, X.-Y. Liu and Y.-M. Liang, *J. Org. Chem.*, 2010, **75**, 2893.
[5] M. W. Roomi, *J. Med. Chem.*, 1975, **18**, 457: care must be taken during the purification step. We found that reproducible results could be obtained by a fast crystallization of the crude with MeOH, under a N_2 atmosphere.
[6] (*a*) S. J. Zuend, M. P. Coughlin, M. P. Lalonde and E. N. Jacobsen, *Nature*, 2009, **451**, 968; (*b*) S. E. Reisman, A. G. Doyle and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2008, **130**, 7198.
[7] R. P. Herrera, V. Sgarzani, L. Bernardi and A. Ricci, *Angew. Chem., Int. Ed.*, 2005, **44**, 6576.
[8] L. Gramigna, S. Duce, G. Filippini, M. Fochi, M. Comes Franchini and L. Bernardi, *Synlett*, 2011, 2745.
[9] N. A. Yakelis and R. G. Bergman, *Organometallics*, 2005, **24**, 3579.

Catalytic enantioselective transfer hydrogenation reaction of nitroalkene 1 with Hantzsch ester 2 catalysed by 3



Experimental procedure: To a vial equipped with a magnetic stirring bar were sequentially added nitroalkene **1** (16.3 mg, 0.10 mmol), the additive salt (x mol%) dissolved in CH_2Cl_2 (200 μL), and catalyst **3** (5.1 mg, 0.010 mmol). The vial was placed in an ice bath (0 °C), then Hantzsch ester **2** (46.4 mg, 0.15 mmol) was added under stirring. The reaction evolution was monitored by sampling a Pasteur pipette tip from the reaction mixture at the given times, followed by immediate dilution in ca. 0.7 mL of $CDCl_3$ and ^{1}H NMR spectroscopy analysis. The reaction conversion was determined by comparing the integral value of the signal of the product **4**[10] at 4.54-4.51 ppm (2dd, C*H*$_2$NO$_2$, 2H), and the integral value of the signal of the nitroalkene **1** at 2.65 ppm (d, C*H*$_3$, 3H). When necessary, at the end of the reaction the product **4** was purified by a short plug of silica gel, and its enantiomeric excess determined by HPLC analysis (Chiralcel OJ-H, flow = 0.75 mL/min, eluent: *n*-hexane/*i*-PrOH 90:10, λ = 234 nm, t_{maj} = 20.2 min, t_{min} = 22.2 min).

[10] N. J. A. Martin, L. Ozores and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 8976.

Reproducibility tests: First of all, the reaction was performed thrice in the absence of additives (**standard reaction**), in order to check its reproducibility. The results reported in Table S1 and Figure S1 show that under these conditions, the reaction follow a regular and reproducible evolution over time, reaching almost complete conversion after 48 h. Inspection of the ^{1}H NMR spectra of the crude reaction mixtures showed very clean reaction profiles, with negligible amounts of byproducts. Furthermore, the amount of pyridine co-product formed reflects the conversion of the reaction, i.e. spontaneous oxidation of the Hantzsch ester **2** in the mixture does not occur. Enantioselectivity was found to be good and comparable in the three experiments.

Table S1. Evolution over time of the standard reaction (three independent runs).

Time (h)	Conversion (%)		
	Run 1	Run 2	Run 3
0	0	0	0
1.5	11.5	11.5	12.0
3.25	22.4	23.5	22.9
5.5	31.7	32.7	33.7
8	43.9	43.0	42.9
24	75.3	74.7	74.4
32	82.3	82.2	82.6
48	89.6 (88% ee)	90.1 (87% ee)	90.7 (88% ee)

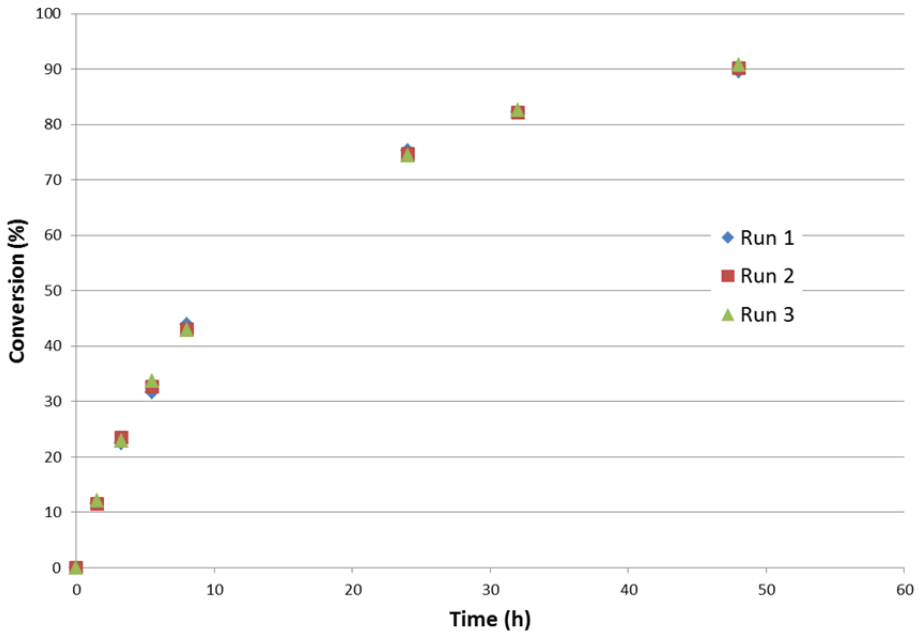


Figure S1. Evolution over time of the reaction performed in the absence of additives (standard reaction, three independent runs).

Evaluation of the effect of anionic additives in the reaction: The reaction was then performed using 15 mol% of different additives, 1.5 equivalents with respect to catalyst **3**. The results with the additives which gave a clean reaction profile are reported in Table S2, and plotted in Figures S2-S4 comparing their result with the reaction performed in their absence. TBAOAc and $TBANO_2$ caused the formation of substantial amounts of the deconjugated product,[11] while $TBABPh_4$ was found to be poorly soluble in the mixture. The results with these latter salts are thus not reported. Enantiomeric excesses were found to be comparable in all reactions; thus, these additives do not influence the stereoselectivity exerted by the catalyst. It proved not possible to obtain a reliable measure of the enantioselectivity in the reactions which gave low conversion (TBACl and TPPCl salts).

Table S2. Evolution over time of the reaction performed in the presence of additives (15 mol%).

	Additive	Time (h)								ee (%)
		0	1.5	3.25	5.5	8	24	32	48	
Conversion (%)	-	0	12.0	22.9	33.7	42.9	74.4	82.6	90.7	88
	TBACl	0	n.d.	n.d.	n.d.	11.4	24.8	29.1	34.9	n.d.
	TPPCl	0	n.d.	n.d.	n.d.	5.2	15.4	19.9	25.5	n.d.
	TBABr	0	n.d.	n.d.	n.d.	17.0	32.1	37.2	41.7	86
	TBAI	0	n.d.	n.d.	n.d.	25.1	56.6	65.9	75.1	88
	TBAOTf	0	11.2	18.5	28.2	34.6	62.9	70.5	81.0	86
	$TBABF_4$	0	10.4	18.7	29.2	38.4	67.1	76.8	83.5	86
	$TBAClO_4$	0	9.3	21.3	30.4	38.0	68.0	77.6	86.2	87
	$TBAPF_6$	0	12.5	22.0	30.9	41.0	73.9	81.2	89.0	88
	TBABArF	0	10.6	23.8	31.7	40.2	73.2	81.7	89.6	87
	$TPPBAr^F$	0	13.2	21.0	33.2	42.1	73.7	81.4	89.3	88

[11] L. Bernardi, F. Fini, M. Fochi and A. Ricci, *Synlett*, 2008, 1857.

Figure S2 reports the evolution of the reaction performed in the presence of halide additives (chloride, bromide, iodide). A considerable inhibition of catalyst activity was observed with small anions, such as bromide and chloride, added as TBA salts, whereas iodide had a less relevant effect. Using tetraphenylphosphonium as chloride counteranion, an increase inhibitory effect was observed, highlighting the importance of the competition between the thiourea of catalyst **3** and the counteranion for halide coordination.[12]

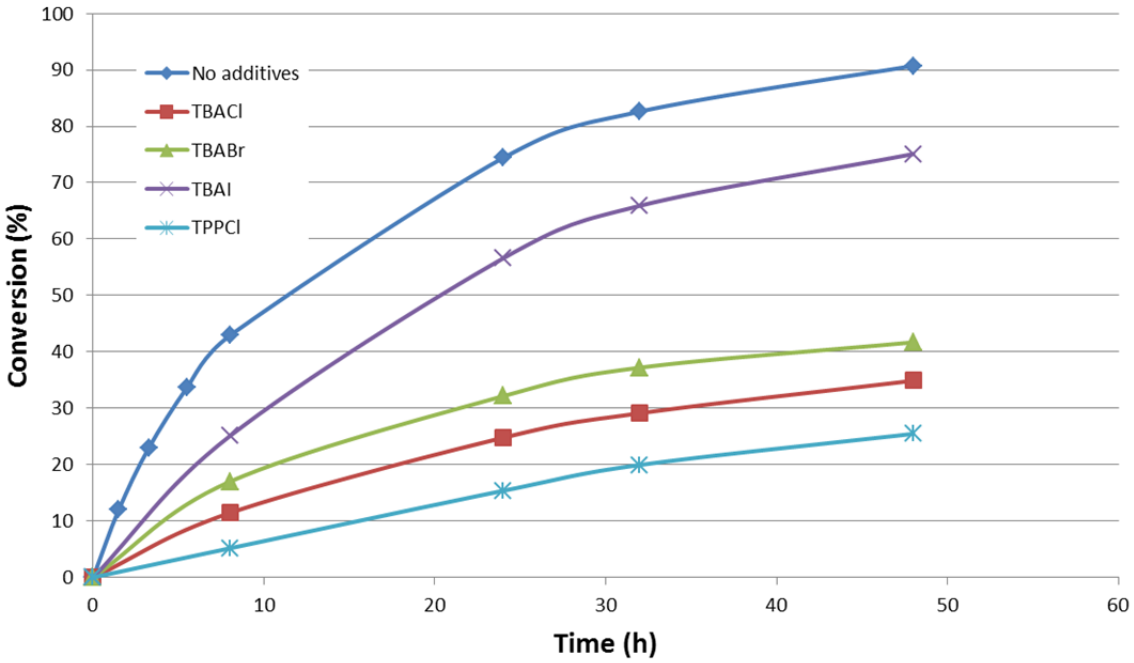


Figure S2. Evolution over time of the reaction performed in the presence of halide additives, and comparison with the standard reaction.

[12] R. Pajewki, R. Ferdani, J. Pajewska, R. Li and G. W. Gokel, *J. Am. Chem. Soc.*, 2005, **127**, 18281.

Figure S3 reports the evolution of the reaction performed in the presence of some weakly coordinating anions such as triflate, tetrafluoroborate and perchlorate, added as TBA salts. A small, yet observable, inhibitory effect was recorded in the reactions with these anions.

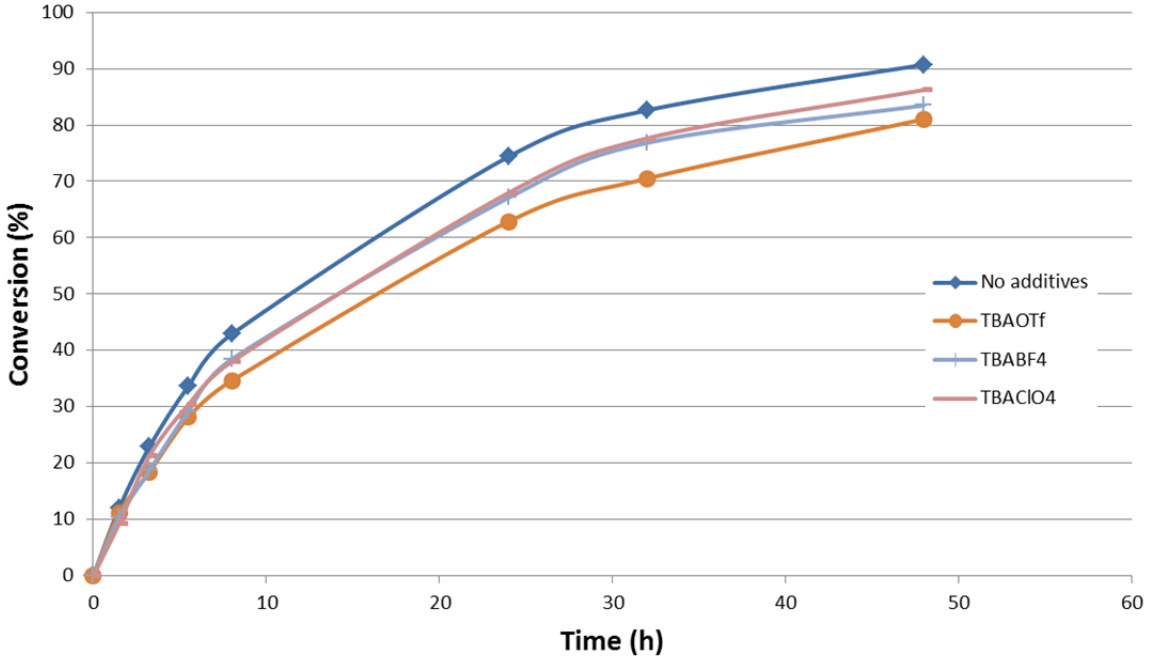


Figure S3. Evolution over time of the reaction performed in the presence of TBAOTf, $TBABF_4$, and $TBAClO_4$ as additives, and comparison with the standard reaction.

Figure S4 reports the evolution of the reaction performed in the presence of other weakly coordinating anions (BAr^{F-}, PF_6^-). These latter additives left the catalyst activity unaltered, as the kinetic curves are essentially superimposable with the one relative to the standard reaction.

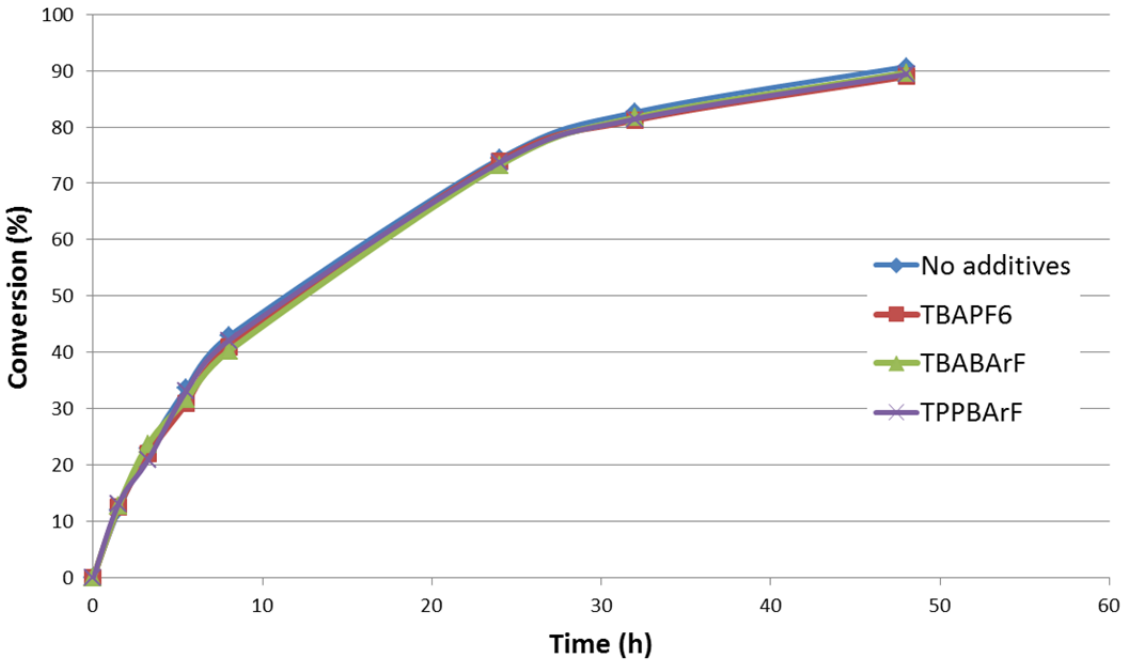


Figure S4. Evolution over time of the reaction performed in the presence of weakly coordinating anions ($TBABAr^F$, $TBAPF_6$, $TPPBAr^F$), and comparison with the standard reaction.

Evaluation of the effect of the amount of anionic additives in the reaction: Using the TPPCl salt, which had demonstrated to provide the highest inhibitory effect on catalyst activity, the variation of the reaction performance in dependence of its amount was evaluated. The results reported in Table S3 and plotted in Figure S5 show that at least 15 mol% of the salt (1.5 equiv. respect to catalyst) are necessary to achieve a satisfactory inhibition, while higher amounts do not bring additional inhibitory effect.

Table S3. Evolution over time of the reaction performed in the presence of different amounts of TPPCl salt.

	TPPCl mol%	Time (h)					ee (%)
		0	8	24	32	48	
Conversion (%)	-	0	42.9	74.4	82.6	90.7	88
	5	0	25.4	44.7	50.0	54.1	88
	10	0	12.0	23.5	28.0	33.5	n.d.
	15	0	5.2	15.4	19.9	25.5	n.d.
	20	0	5.4	13.7	17.7	23.0	n.d.
	30	0	2.3	10.7	14.3	20.5	n.d.

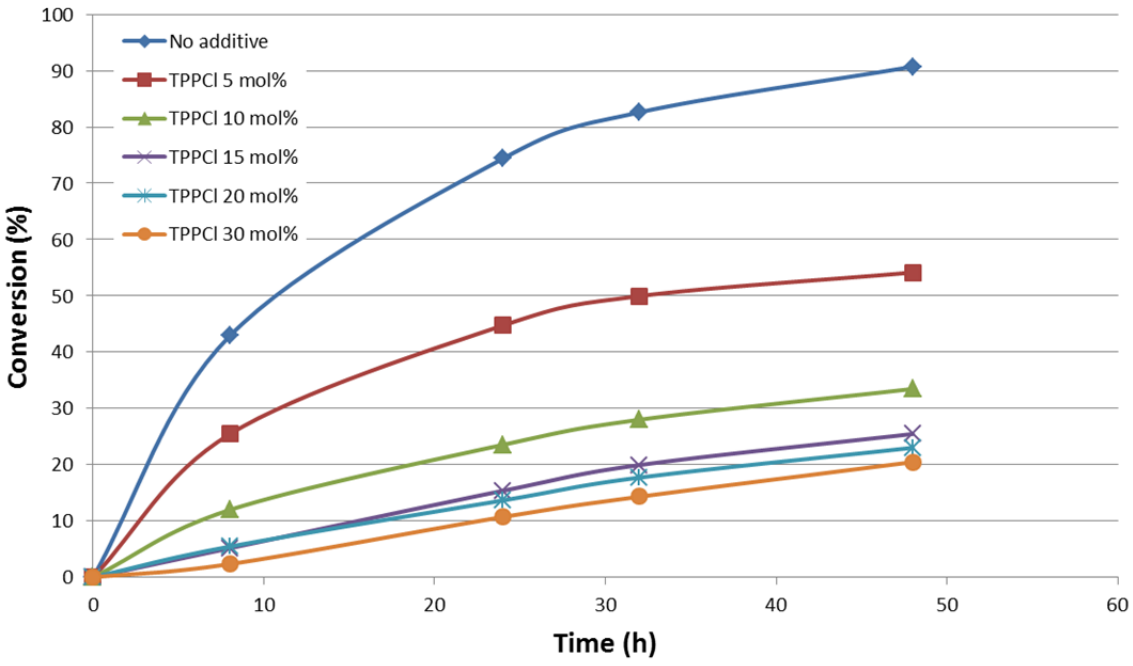


Figure S5. Evolution over time of the reaction performed in the presence of different amounts of TPPCl, and comparison with the standard reaction.

Using the TBAI salt, a preliminary quantitative evaluation of the influence of the amount of additive on reaction rate was carried out, using short reaction times to minimize undesired effects such as catalyst inhibition by the products. The recorded conversions at different times with various amounts of TBAI are reported in Table S3, and the kinetic curves in Figure S6.

Table S4. Evolution over time of the reaction performed in the presence of different amounts of TBAI salt.

	TBAI mol%	Time (h)						ee (%)
		0	1.5	3.25	5	7	10	
Conversion (%)	5	0	10.0	18.8	26.6	33.7	41.5	87
	10	0	8.0	15.3	22.7	29.3	37.9	88
	15	0	6.6	14.4	20.0	25.4	32.4	n.d.
	20	0	5.7	10.6	15.3	20.2	27.1	n.d.
	25	0	3.4	7.3	10.2	14.2	18.8	n.d.

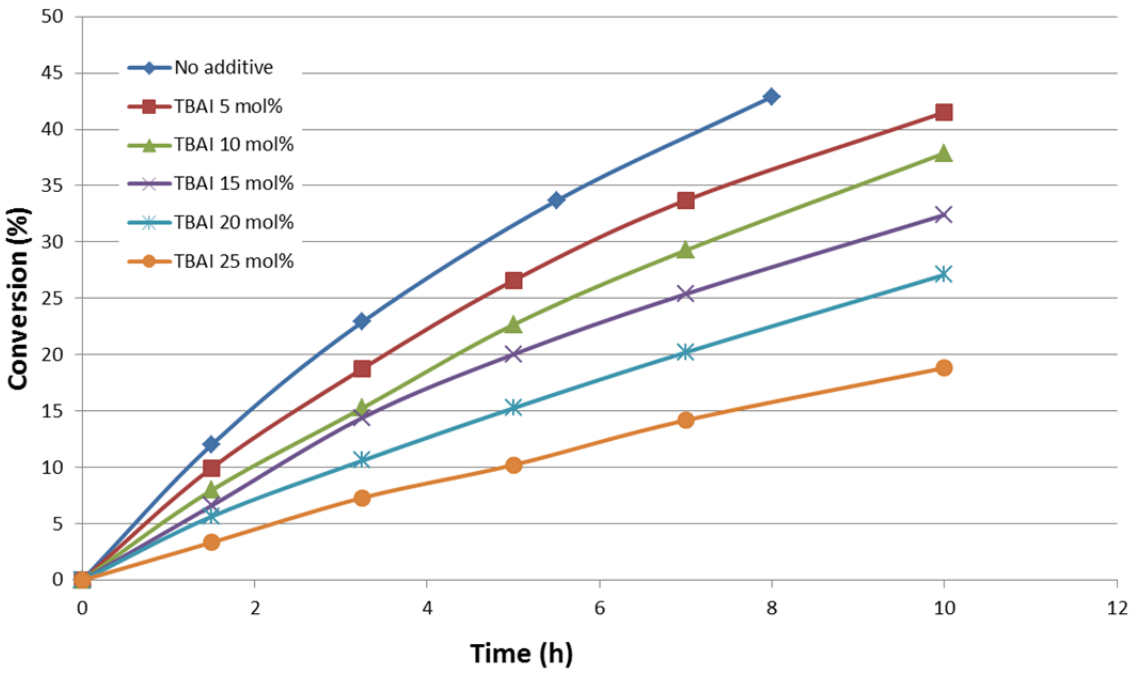


Figure S6. Evolution over time of the reaction performed in the presence of different amounts of TBAI, and comparison with the standard reaction.

These reactions were found to obey pseudo-second order reaction kinetics. The data reported in Table S4 (and the reaction performed in the absence of additives) were fitted with the equation:[13]

$$\ln\left(\frac{[1]_0 \times ([2]_0 - [6])}{[2]_0 \times ([1]_0 - [6])}\right) = ([2]_0 - [1]_0) \times k_{obs}t$$

where:

$[1]_0$ = 0.50 M; $[2]_0$ = 0.75 M; [6] = (0.50 x conversion) M

The straight lines reported in Figure S7 displayed very good correlation coefficients. Their slopes are k_{obs} (in $M^{-1}h^{-1}$) for the reactions.

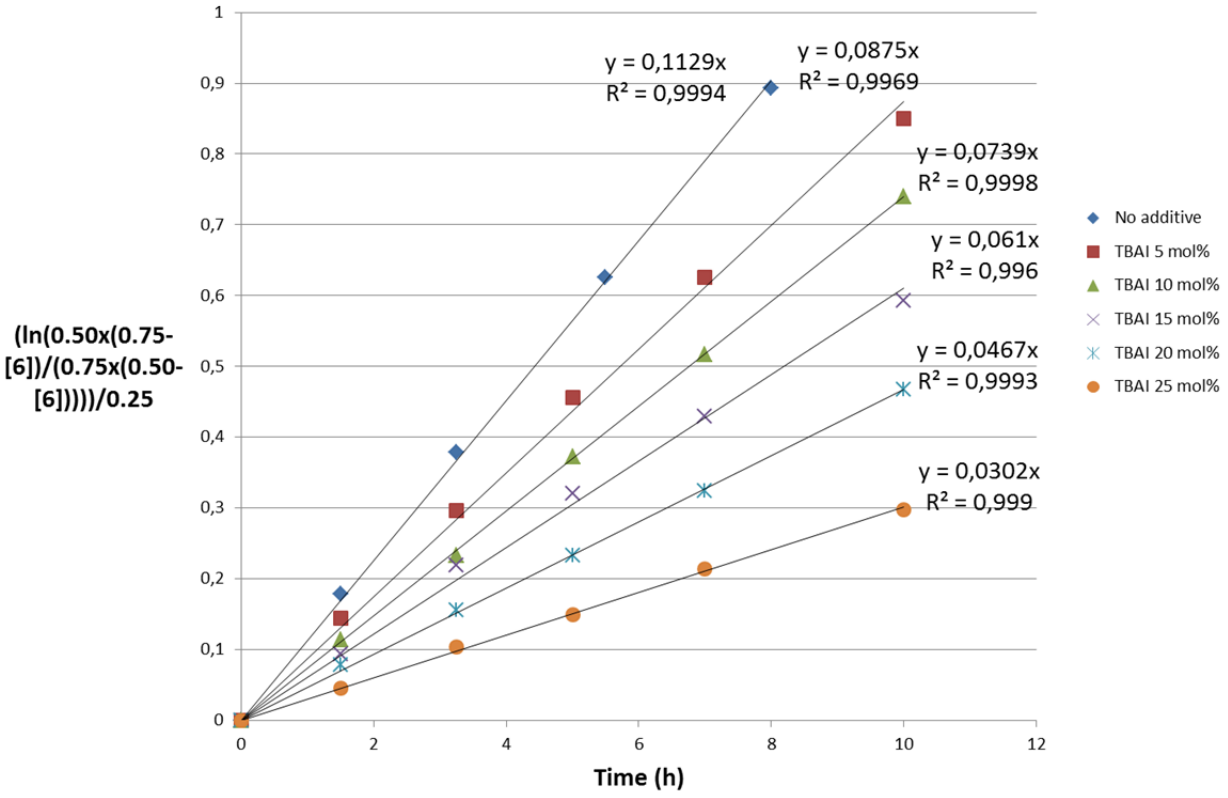


Figure S7. Pseudo-second order fit of the reactions performed with different amounts of TBAI as additive, and of the standard reaction.

[13] A. Cornish-Bowden, *Fundamentals of Enzyme Kinetics*, Portland Press, London, 1995.

Drawing the thus obtained k_{obs} vs the amount of TBAI additive, a relatively good linear correlation was found (Figure S8), demonstrating a linear response of the reaction rate to the amount of additive employed.

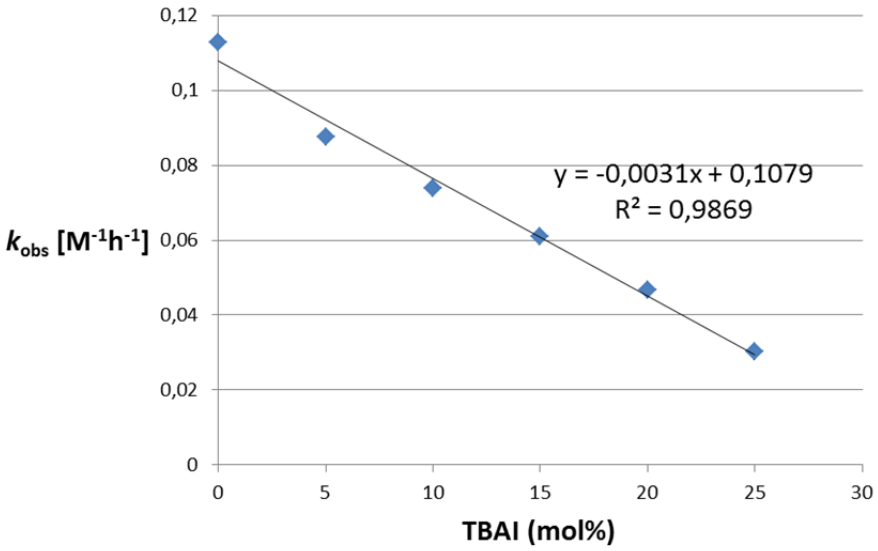


Figure S8. Correlation between k_{obs} and the amount of TBAI additive.

Reversibility of the modulation of catalyst activity with anions: experimental procedure

Reactions were performed in Schlenk tubes under inert atmosphere (N_2); we observed that for the prolonged reaction times required in these experiments, partial oxidation of the Hantzsch ester **2** by atmospheric oxygen occurred.

To a Schlenk tube equipped with a magnetic stirring bar and kept under an inert atmosphere (N_2) were sequentially added nitroalkene **1** (32.6 mg, 0.20 mmol), for run 2 the TPPCl salt (11.2 mg, 0.030 mmol, 15 mol%), CH_2Cl_2 (400 μL), and catalyst **3** (10.2 mg, 0.020 mmol, 10 mol%). The tube was placed in an ice bath (0 °C), then Hantzsch ester **2** (92.8 mg, 0.30 mmol) was added under stirring. At given times, $NaBAr^F$ (26.6 mg, 0.030 mmol, 15 mol%) to restore the catalyst activity, or TPPCl (11.2 mg, 0.030 mmol, 15 mol%) to reduce it were added. The reaction evolution was monitored by sampling a Pasteur pipette tip from the reaction mixture at the given times, followed by immediate dilution in ca. 0.7 mL of $CDCl_3$ and ^1H NMR spectroscopy analysis. The reaction conversion was determined by comparing the integral value of the signal of the product **4** at 4.54-4.51 ppm (2dd, C*H*$_2$NO$_2$, 2H), and the integral value of the signal of the nitroalkene **1** at 2.65 ppm (d, C*H*$_3$, 3H). At the end of the reaction the product **4** was purified by a short plug of silica gel, and its enantiomeric excess determined by CSP-HPLC analysis (Chiralcel OJ-H, flow = 0.75 mL/min, eluent: *n*-hexane/*i*-PrOH 90:10, λ = 234 nm, t_{maj} = 20.2 min, t_{min} = 22.2 min).

Reversibility of the modulation of catalyst activity with anions: results

Two experiments were performed, each involving two switches between the states.

In a first run (Table S5 and Figure S9), TPPCl (15 mol%) was added after 5 h, and $NaBAr^F$ (15 mol%) after 19 h. The same operations were performed after 26 and 43 h. "Effective time" (see Figure S11) indicates time with the catalyst in its most active state (in the absence of chloride).

Table S5. Evolution over time of the reaction performed starting without additives (Run 1).

Time (h)	Action	Effective time (h)	Conversion (%)
0	START	0	0
3	-	3	21.0
5	15 mol% TPPCl added	5	30.9
19	15 mol% $NaBAr^F$ added	5	36.0
22	-	8	45.7
26	15 mol% TPPCl added	12	57.2
43	15 mol% $NaBAr^F$ added	12	58.3
46	-	15	64.6
52	-	24	73.8
67	-	36	82.9
77	-	46	86.4
92	-	61	90.2 (84% ee)

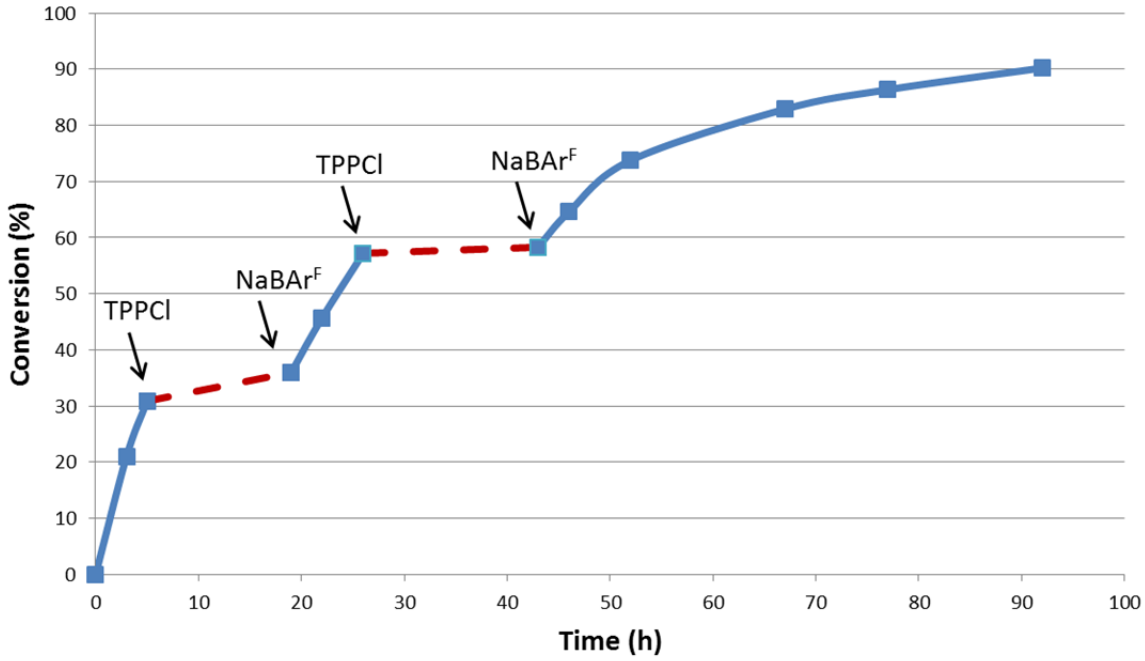


Figure S9. Evolution over time of the reaction performed starting without additives (Run 1).

In a second run (Table S6 and Figure S10), the reaction was set up in the presence of TPPCl. $NaBAr^F$ was added after 14 h, TPPCl after 24 h, $NaBAr^F$ after 38 h.

Table S6. Evolution over time of the reaction performed starting with TPPCl additive (Run 2).

Time (h)	Action	Effective time (h)	Conversion (%)
0	START 15 mol% TPPCl added	0	0
14	15 mol% $NaBAr^F$ added	0	9.0
17	-	3	25.4
20	-	6	38.0
24	15 mol% TPPCl added	10	50.3
38	15 mol% $NaBAr^F$ added	10	52.9
41	-	13	61.6
47	-	19	69.5
62	-	34	82.6
72	-	44	87.3
87	-	59	91.9 (83% ee)

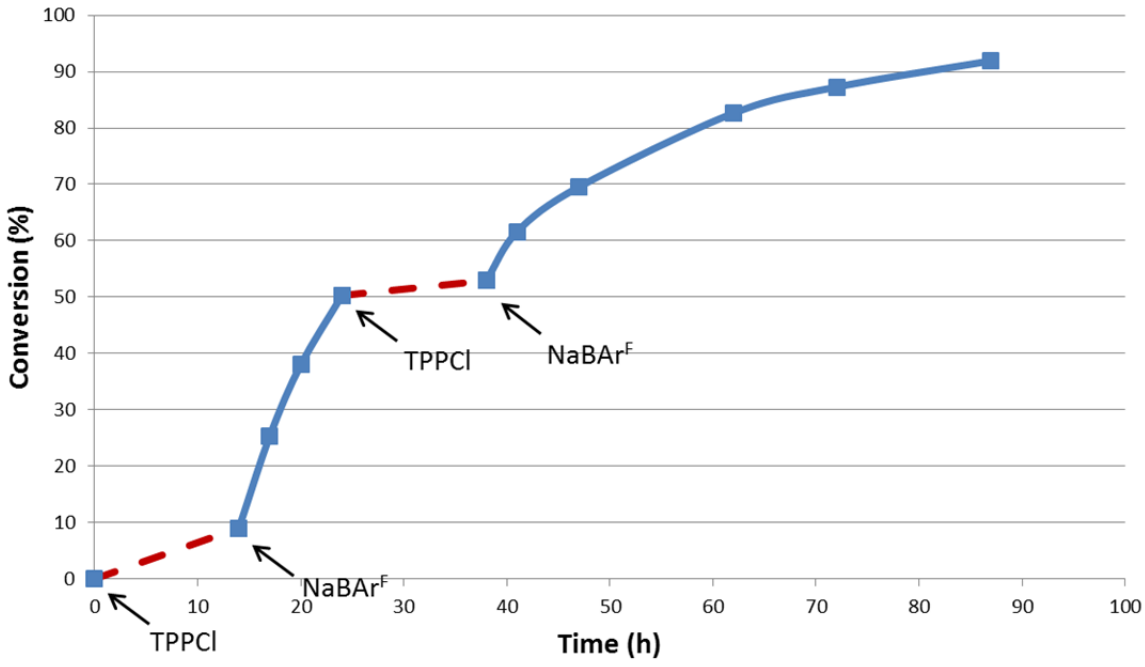


Figure S10. Evolution over time of the reaction performed starting with TPPCl additive (Run 2).

Tables S5-S6 and Figures S9-S10 show that upon the addition of TPPCl a decrease in reaction rate was observed due to catalyst inhibition, while upon adding $NaBAr^F$, the catalyst activity could be restored. Thus, the deactivation/activation processes are reversible. The enantiomeric excesses recorded at the end of the two runs are comparable, yet slightly lower, with the enantiomeric excesses displayed by the reaction performed in the absence of additives (83-84% vs 88% ee).

To gain a better insight on the reversibility of the processes (deactivation and activation), on the activity effectively exerted by the catalyst upon its reactivation, and on the fastness of the processes, the conversions recorded can be plotted vs the effective time, and compared with the standard reaction. To get a better comparison, additional points were collected in the kinetic curve of the standard reaction (Table S7).

Table S7. Evolution over time of the standard reaction, with additional points.

Time (h)	0	1.5	3.25	5.5	8	13	15	19	24	32	37	48	61
Conv. (%)	0	12.0	22.9	33.7	42.9	56.2	61.6	68.9	74.4	82.6	87.0	90.7	92.8

The conversions recorded vs effective time for the standard reaction, for Run 1 and Run 2, are plotted in Figure S11.

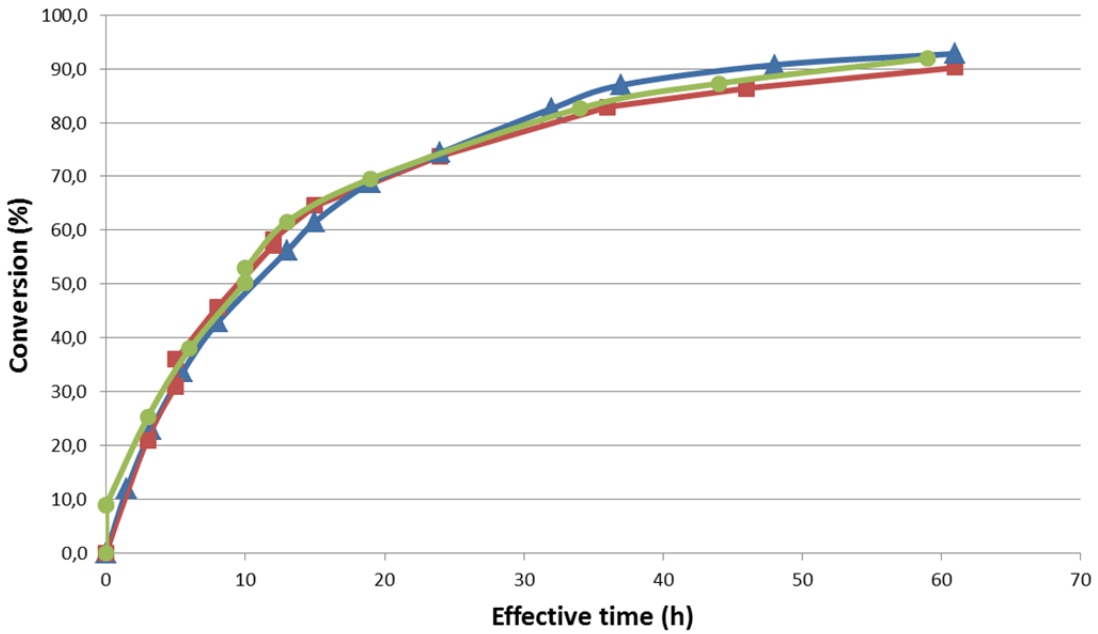
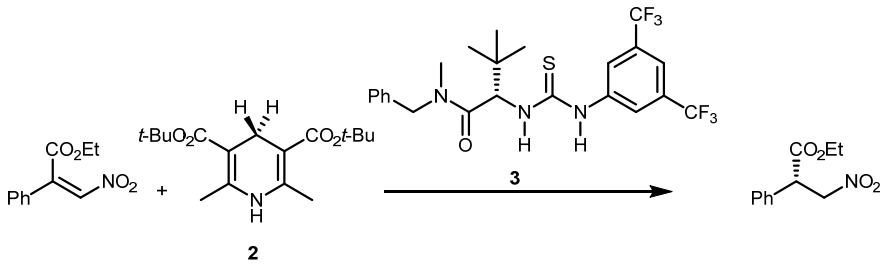


Figure S11. Conversion vs effective time for the standard reaction [▲], Run 1 [■] and Run 2 [●].

Figure S11 show that there is a good overlap between the kinetic curves. Thus, catalyst activity can be reversibly reduced and restored, and the processes appear fast. However: qualitatively, for short reaction times (i.e. one deactivation-activation process) the reactivation process appears fully reversible (the curves show similar tangents, i.e. similar reaction rates); for longer times (after the second deactivation-activation process), there seems to be a moderate loss of catalyst activity.

Catalytic enantioselective transfer hydrogenation reaction of ethyl *Z*-3-nitro-2-phenylacrylate with Hantzsch ester 2 catalysed by 3



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Reactions were performed in Schlenk tubes under inert atmosphere (N_2) to avoid oxidation of the Hantzsch ester **2** by atmospheric oxygen due to the prolonged reaction times required in these experiments.

To a Schlenk tube equipped with a magnetic stirring bar and kept under an inert atmosphere (N_2) were sequentially added ethyl *Z*-3-nitro-2-phenylacrylate (44.2 mg, 0.20 mmol), for run 2 the TPPCl salt (11.2 mg, 0.030 mmol, 15 mol%), CH_2Cl_2 (400 μL), and catalyst **3** (10.2 mg, 0.020 mmol, 10 mol%). The tube was placed in a cooled bath (-42 °C), then Hantzsch ester **2** (123.7 mg, 0.40 mmol) was added under stirring. At given times, $NaBAr^F$ (26.6 mg, 0.030 mmol, 15 mol%) to restore the catalyst activity, or TPPCl (11.2 mg, 0.030 mmol, 15 mol%) to reduce it were added. The reaction evolution was monitored by sampling a Pasteur pipette tip from the reaction mixture at the given times, followed by immediate dilution in ca. 0.7 mL of $CDCl_3$ and ^1H NMR spectroscopy analysis. The reaction conversion was determined by comparing the integral value of the signal of the product[3] at 4.54 ppm (dd, J = 14.9, 5.6 Hz, C*H*HNO_2, 1H), and the integral value of the signal of the nitroalkene at 4.48 ppm (q, J = 7.2 Hz, C*H*$_2CH_3$, 2H). At the end of the reaction the product was purified by a short plug of silica gel, and its enantiomeric excess determined by HPLC analysis (Chiralcel OJ-H, flow = 0.75 mL/min, eluent: *n*-hexane/*i*-PrOH 90:10, λ = 234 nm, t_{maj} = 47.9 min, t_{min} = 36.5 min).

The conversions recorded at different times for the reaction performed in the absence of additives (standard reaction) are reported in Table S8 and plotted in Figure S12, showing a regular reaction evolution over time.

Table S8. Evolution over time of the standard reaction.

Time (h)	0	17	24	41	48	65	72	89	96	120
Conv. (%)	0	21.5	29.8	46.0	51.5	61.5	65.1	72.5	76.4	82.7 (90% ee)

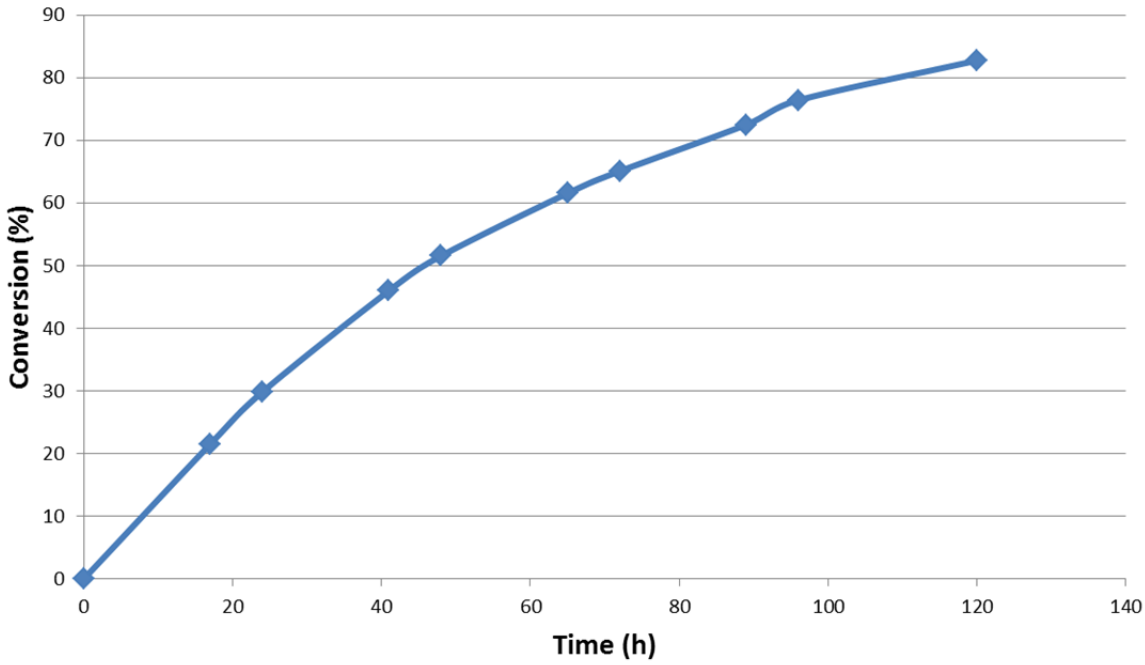


Figure S12. Evolution over time of the standard reaction.

Analogously to the approach previously used with nitroalkene **1**, two experiments were performed, each involving two conversions between the states.

In the first run (Table S9 and Figure S13), TPPCl (15 mol%) was added after 24 h, and $NaBAr^F$ (15 mol%) after 48 h. The same operations were performed after 72 and 96 h. "Effective time" (see Figure S15) indicates time with the catalyst in its most active state (in the absence of chloride).

Table S9. Evolution over time of the reaction performed starting without additives (Run 1).

Time (h)	Action	Effective time (h)	Conversion (%)
0	START	0	0
17	-	17	22.8
24	15 mol% TPPCl added	24	29.8
48	15 mol% $NaBAr^F$ added	24	34.2
65	-	41	48.2
72	15 mol% TPPCl added	48	54.1
96	15 mol% $NaBAr^F$ added	48	59.3
120	-	72	71.7
168	-	120	86.3 (82% ee)

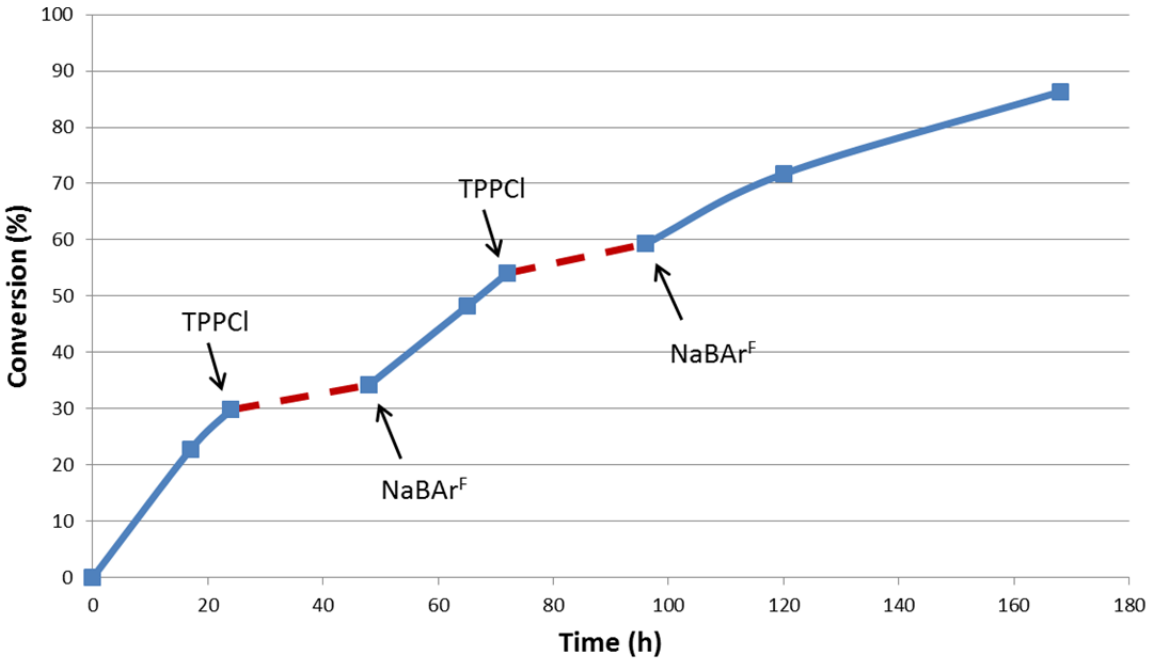


Figure S13. Evolution over time of the reaction performed starting without additives (Run 1).

In the second run (Table S10 and Figure S14), the reaction was set up in the presence of TPPCl. $NaBAr^F$ was added after 24 h, TPPCl after 48 h, $NaBAr^F$ after 72 h.

Table S10. Evolution over time of the reaction performed starting with TPPCl additive (Run 2).

Time (h)	Action	Effective time (h)	Conversion (%)
0	START 15 mol% TPPCl added	0	0
24	15 mol% $NaBAr^F$ added	0	5.9
41	-	17	27.4
48	15 mol% TPPCl added	24	34.8
72	15 mol% $NaBAr^F$ added	24	36.1
89	-	41	51.5
96	-	48	57.7
120	-	72	70.1
168	-	120	85.1 (80% ee)

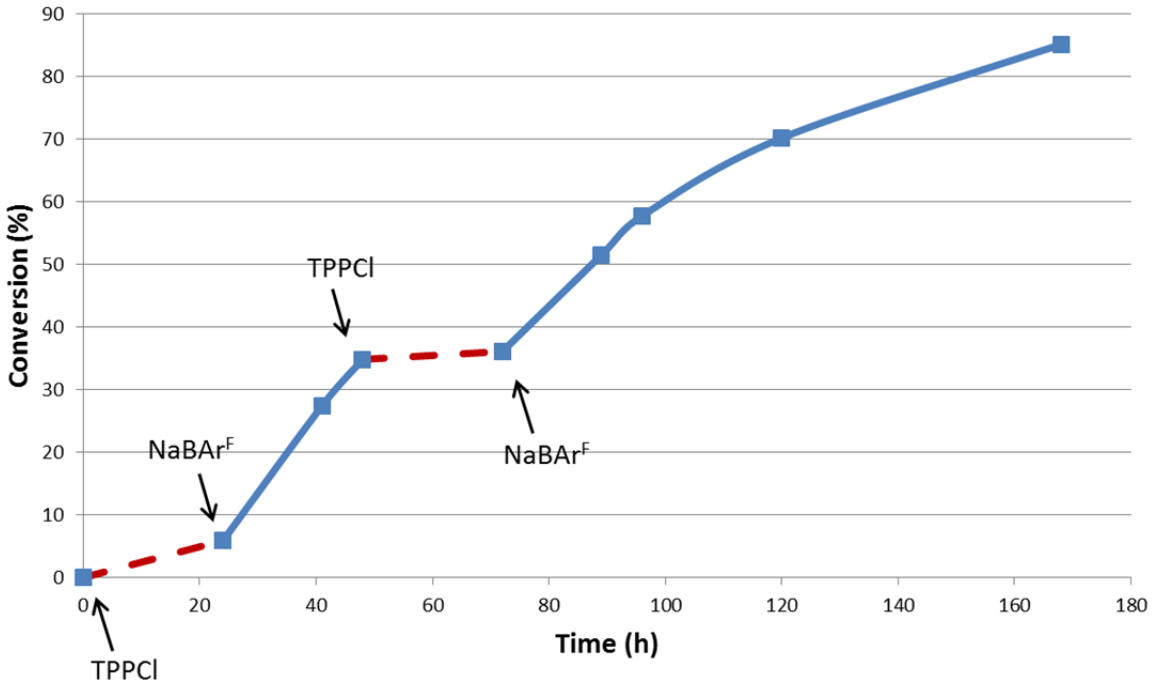


Figure S14. Evolution over time of the reaction performed starting with TPPCl additive (Run 2).

Tables S9-S10 and Figures S13-S14 show that upon the addition of TPPCl a decrease in reaction rate was observed due to catalyst inhibition, while upon adding $NaBAr^F$, the catalyst activity could be restored. Thus, the deactivation-activation process is reversible also for this reaction. In line with the previously studied reaction, the enantiomeric excesses recorded at the end of the two runs are

slightly lower than the enantiomeric excess of the product obtained in the reaction performed in the absence of additives (80-83% vs 90% ee).

Also in this case, to gain a better insight on the reversibility of the processes (deactivation and activation), on the activity effectively exerted by the catalyst upon its reactivation, and on the fastness of the processes, the conversions recorded were plotted vs the effective time, and compared with the standard reaction (Figure S15).

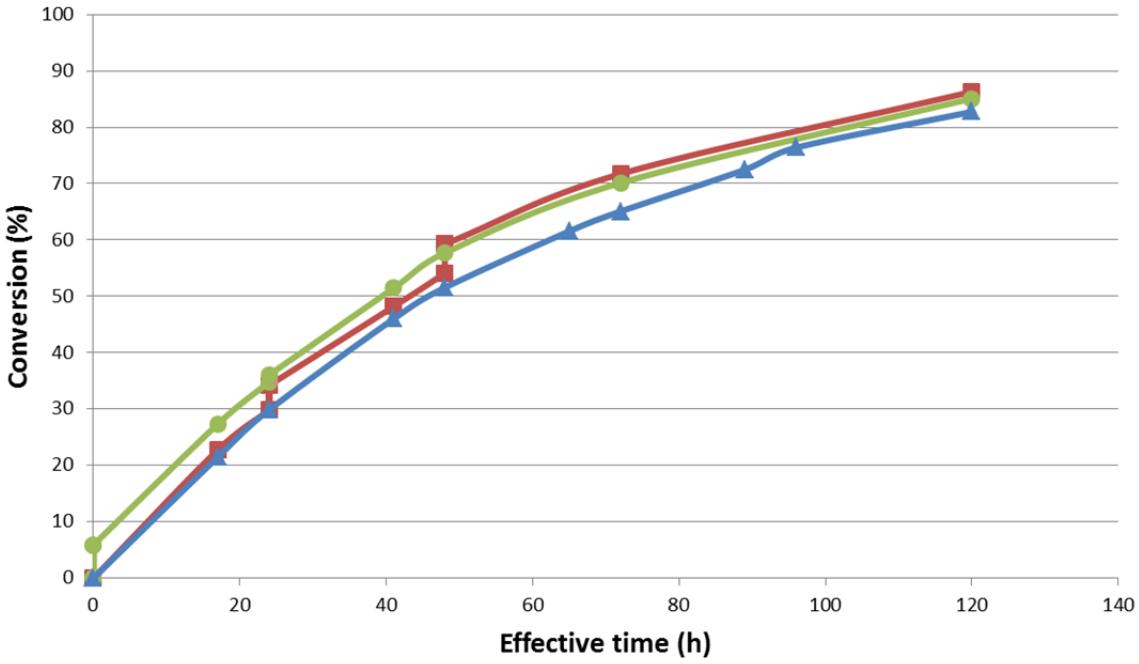
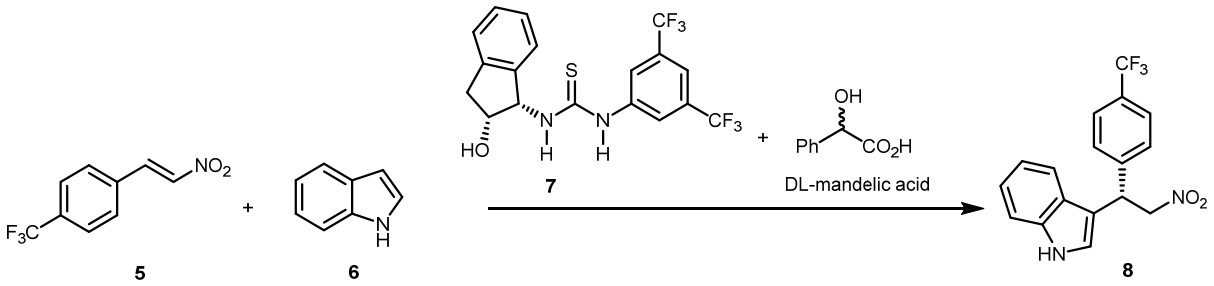


Figure S15. Conversion vs effective time for the reaction in the absence of additives [▲], Run 1 [■] and Run 2 [●].

Figure S15 shows a moderately good overlap between the curves. Besides, the tangents of the three curves (*viz* reaction rate) appears rather similar at any time; it can be concluded that catalyst activity is comparable in the three reactions during all their evolution.

Catalytic enantioselective Friedel-Crafts addition reaction of indole 6 to nitroalkene 5 catalysed by 7



To a test tube equipped with a magnetic stirring bar were sequentially added nitroalkene **5** (43.4 mg, 0.20 mmol), for run 2 the TPPCl salt (22.4 mg, 0.060 mmol, 30 mol%), DL-mandelic acid (6.2 mg, 0.040 mmol, 20 mol%), catalyst **7** (16.8 mg, 0.040 mmol, 20 mol%) and CH_2Cl_2 (200 μL). The tube was placed in a cooled bath (-20 °C), then indole **6** (35.1 mg, 0.30 mmol) was added under stirring. At given times, $NaBAr^F$ (53.2 mg, 0.060 mmol, 30 mol%) to restore the catalyst activity, or TPPCl (22.4 mg, 0.060 mmol, 30 mol%) to reduce it were added. The reaction evolution was monitored by sampling a Pasteur pipette tip from the reaction mixture at the given times, followed by immediate dilution in ca. 0.7 mL of $CDCl_3$ and ^{19}F NMR spectroscopy analysis. The reaction conversion was determined by comparing the integral value of the signal of the product **8**[14] at -62.63 ppm (3F), and the integral value of the signal of the nitroalkene **5** at -63.18 ppm (3F).[15] At the end of the reaction the product **8** was purified by a short plug of silica gel, and its enantiomeric excess determined by HPLC analysis (Chiralpak AD-H, flow = 0.75 mL/min, eluent: *n*-hexane/*i*-PrOH 90:10, λ = 254 nm, t_{maj} = 26.2 min, t_{min} = 21.4 min).

[14] F. Guo, G. Lai, S. Xiong, S. Wang and Z. Wang, *Chem. Eur. J.*, 2010, **16**, 6438.
[15] The trifluoromethyl groups of catalyst **7** resonates at -63.04 ppm (at -62.66 ppm in the presence of chloride), while the trifluoromethyl groups of BAr^F give a signal at -62.46 ppm.

The conversions recorded at different times for the reaction performed in the absence of anionic additives (standard reaction) are reported in Table S11 and plotted in Figure S16, showing a regular reaction evolution over time.

Table S11. Evolution over time of the standard reaction.

Time (h)	0	1	3	5	7	10	24	29	34	48
Conv. (%)	0	11.2	22.1	31.0	37.5	45.5	78.0	73.2	77.7	85.7 (84% ee)

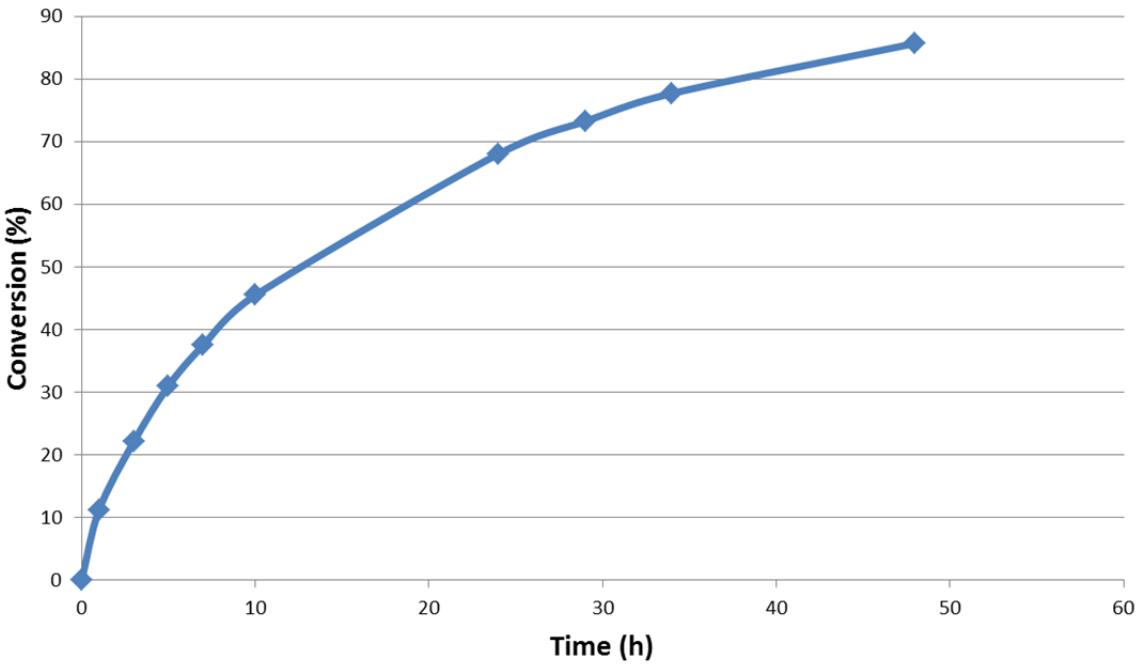


Figure S16 Evolution over time of the standard reaction.

In analogy with the previous transformations, two experiments were performed involving two conversions between the states.

In the first run (Table S12 and Figure S17), TPPCl (30 mol%) was added after 5 h, and $NaBAr^F$ (30 mol%) after 24 h. The same operations were performed after 29 and 48 h. "Effective time" (see Figure S19) indicates time with the catalyst in its most active state (in the absence of chloride).

Table S12. Evolution over time of the reaction performed starting without additives (Run 1).

Time (h)	Action	Effective time (h)	Conversion (%)
0	START	0	0
1	-	1	9.4
3	-	3	18.8
5	30 mol% TPPCl added	5	29.5
24	30 mol% $NaBAr^F$ added	5	30.9
26		7	39.6
29	30 mol% TPPCl added	10	50.0
48	30 mol% $NaBAr^F$ added	10	52.0
51	-	13	59.0
58	-	20	71.2
72	-	34	81.3
83	-	45	86.2 (83% ee)

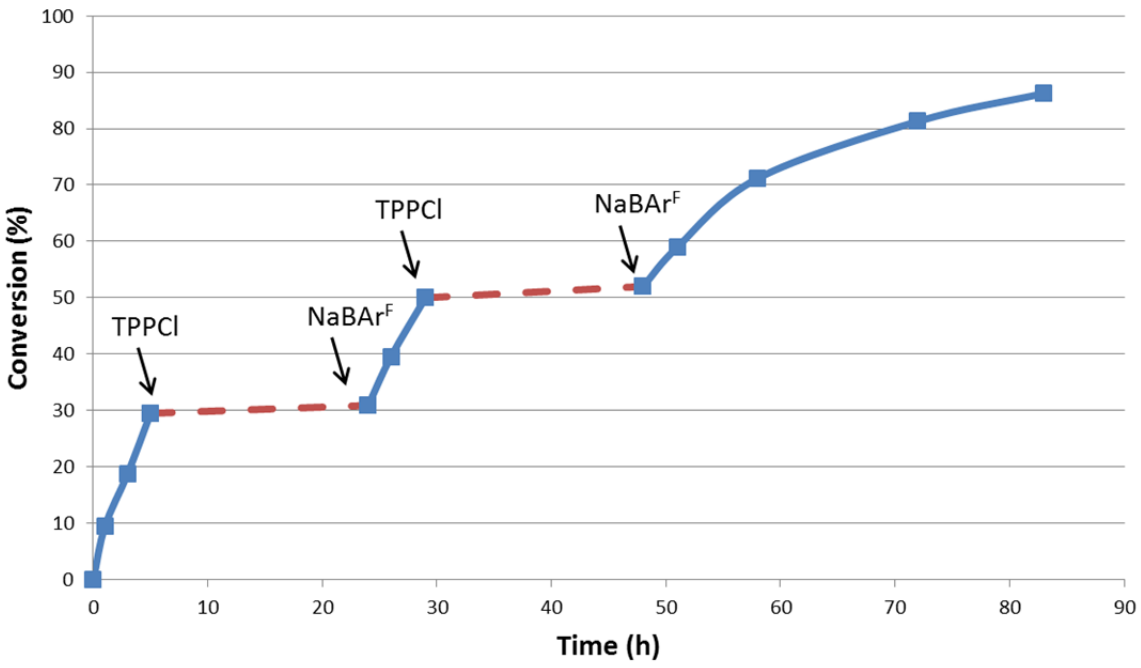


Figure S17. Evolution over time of the reaction performed starting without additives (Run 1).

In the second run (Table S13 and Figure S18), the reaction was set up in the presence of TPPCl. $NaBAr^F$ was added after 14 h, TPPCl after 19 h, $NaBAr^F$ after 38 h.

Table S13. Evolution over time of the reaction performed starting with TPPCl additive (Run 1).

Time (h)	Action	Effective time (h)	Conversion (%)
0	START 30 mol% TPPCl added	0	0
14	30 mol% $NaBAr^F$ added	0	2.5
15	-	1	9.1
17	-	3	21.5
19	30 mol% TPPCl added	5	30.8
38	30 mol% $NaBAr^F$ added	5	30.9
40	-	7	39.5
43	-	10	51.0
46	-	13	56.8
48	-	15	62.1
62	-	29	77.4
67	-	34	81.2
72	-	39	83.4 (82% ee)

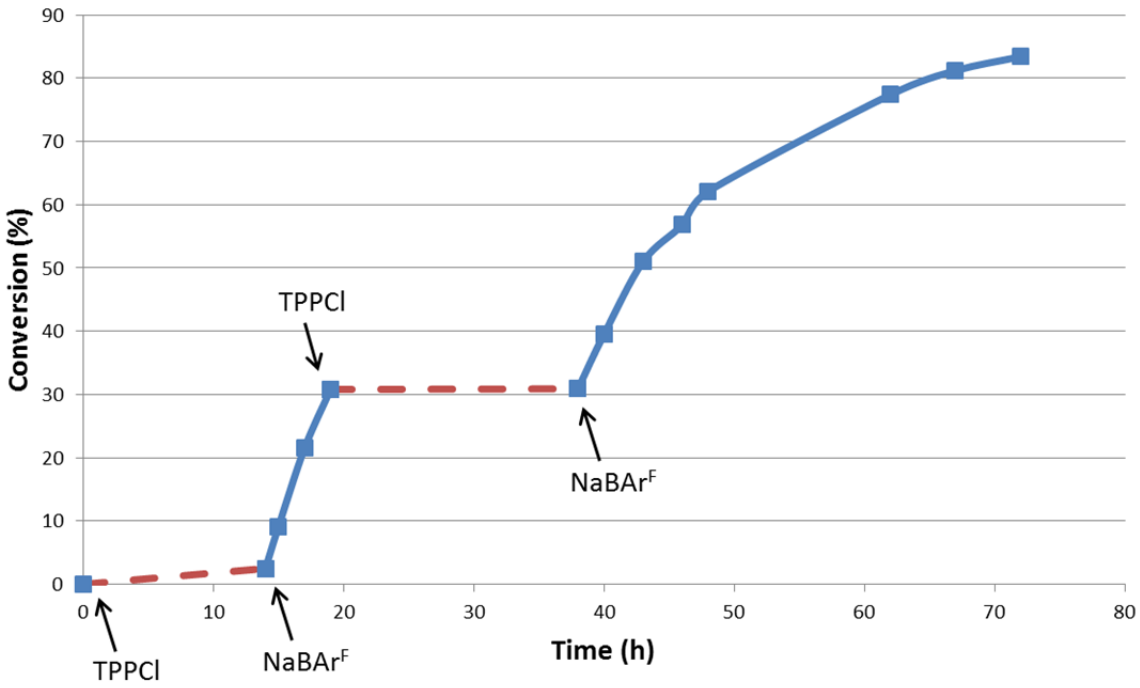


Figure S18. Evolution over time of the reaction performed starting with TPPCl additive (Run 2).

Tables S12-S13 and Figures S17-S18 show that upon the addition of TPPCl the reaction essentially stops, while upon adding $NaBAr^F$, the catalyst activity could be restored. Compared to the two previously studied transfer hydrogenation reactions, this reaction/catalyst can be more strongly inhibited by chloride, while maintaining a good reversibility of the deactivation-activation processes. Furthermore, in this reaction the enantiomeric excesses recorded at the end of the two runs are closer to the enantiomeric excess of product **8** obtained in the reaction performed in the absence of additives (82-83% vs 84% ee), compared to the transfer hydrogenation reactions.

Also for this transformation, a better comparison of catalytic activity during reaction evolution can be gained by plotting the recorded conversions for run 1 and run 2, and the reaction without anionic additives, vs the effective time (Figure S19).

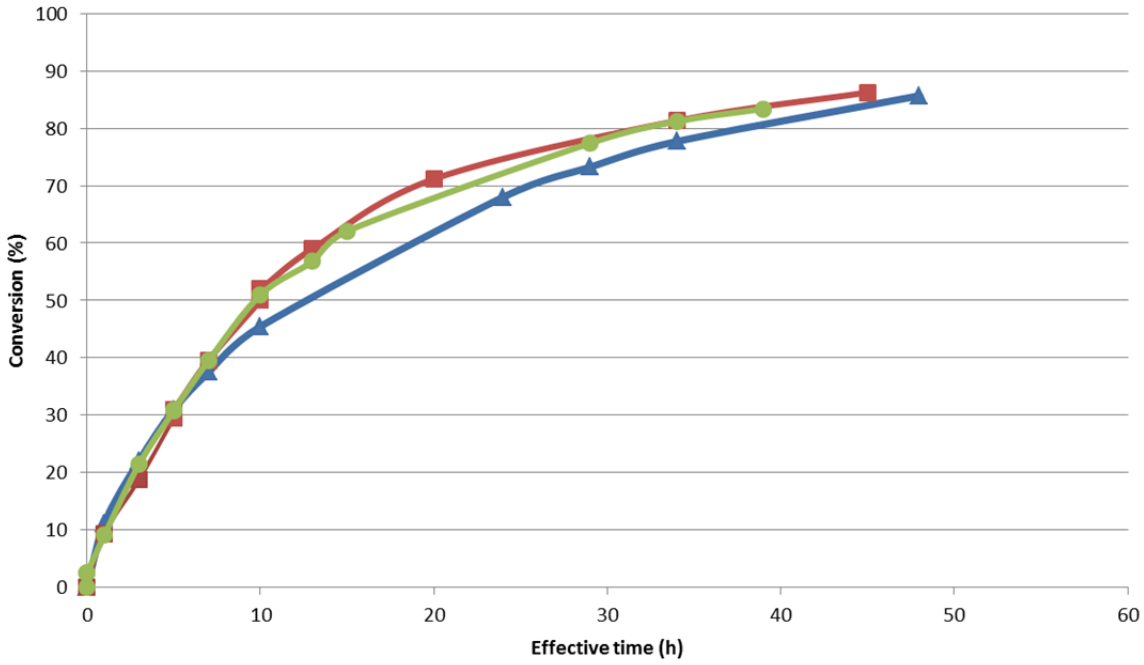
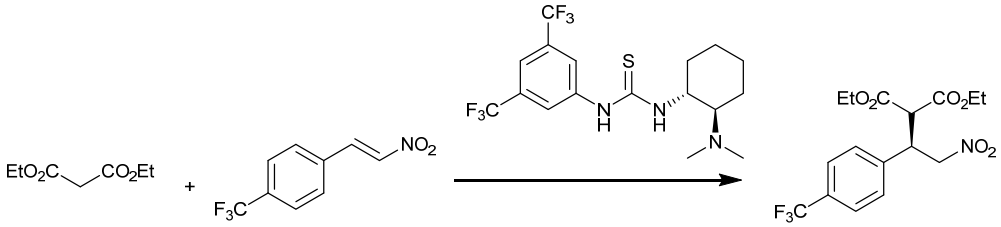


Figure S19. Conversion vs effective time for the reaction in the absence of additives [▲], Run 1 [■] and Run 2 [●].

Compared to the two transfer hydrogenation reactions, there appears to be a more significant deviation of the curves derived from run 1 and run 2 from the curve relative to the reaction performed without anionic additives; these deviations are not dramatic; thus, catalyst activity is still comparable upon reactivation also in this reaction.

Preliminary studies on the catalytic enantioselective addition of diethylmalonate to 4-(trifluoromethyl)nitrostyrene catalyzed by Takemoto catalyst

In the presence of chloride, it was not possible to perform the reaction in CH_2Cl_2 as solvent, since we observed a very fast formation of a white precipitate due to decomposition of the nitroalkene, presumably through an oligomerization process promoted by the basic functionality of the catalyst. Moving to toluene as solvent, it was possible to collect some more meaningful data, even if oligomerization could not be fully avoided (i.e. measured conversion are not fully reliable as product yield), and it must be considered that chloride and bromide salts feature a limited solubility in toluene (i.e. perhaps the amount od anion is lower than the added salt). The results are presented here:



To a test tube equipped with a magnetic stirring bar were sequentially added Takemoto catalyst (4.1 mg, 0.01 mmol), the salt additive (0.015 mmol), toluene (200 μL), diethylmalonate (30.2 μL, 0.20 mmol) and 4-(trifluoromethyl)nitrostyrene (21.7 mg, 0.10 mmol). The tube was left at RT under stirring. The reaction evolution was monitored by sampling a Pasteur pipette tip from the reaction mixture at the given times, followed by immediate dilution in ca. 0.7 mL of $CDCl_3$ and ^{19}F NMR spectroscopy analysis. The reaction conversion was determined by comparing the integral value of the signal of the product at -63.18 ppm (s, 3F), with the signal at -62.82 (s, 3F). After the experiment the product was purified by a short plug of silica gel, and its enantiomeric excess determined by HPLC analysis (Chiralpak ADH, flow = 0.75 mL/min, eluent: *n*-hexane/*i*-PrOH 80:20, λ = 234 nm, t_{maj} = 16.5 min, t_{min} = 30.9 min).

Evaluation of the effect of anionic additives in the reaction: The reaction was performed using 15 mol% of different additives, 1.5 equivalents with respect to the Takemoto catalyst. The results with the additives are reported in Table S14, and plotted in Figure S20 comparing their result with the reaction performed in their absence. The graph show that the reaction kinetics were effected by the presence of coordinating anions. While bromide and chloride gave substantial rate reduction, iodide left the reaction profile nearly unaltered. Unfortunately, the reactions performed with bromide and chloride gave substantial amounts of insoluble oligomeric product. Besides, the enantioselectivities of these reaction was much lower than the standard catalytic reaction. It can be speculated that coordinating anions in this case block the thiourea functionality, while leaving the basic moiety of the catalyst still "active". This basic moiety can both promote a low enantioselective reaction and nitrostyrene decomposition through an oligomerization reaction (see Figure S21). The similar behavior of the chloride salt compared with bromide (which should be less coordinating), can be interpreted considering the lower solubility of the chloride salt in toluene.

Table S14. Evolution over time of the reaction performed in the presence of additives (15 mol%).

	Additive	Time (h)				ee (%)
		0	1	2	4	
Conversion (%)	-	0	64	82	97	91
	TPPCl	0	24	40	55	76
	TBABr	0	21	37	56	54
	TBAI	0	59	81	92	86

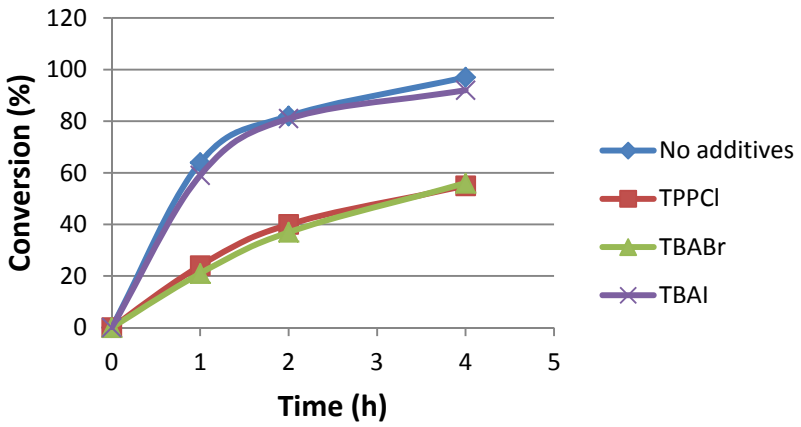


Figure S20. Evolution over time of the reaction performed in the presence of additives, and comparison with the standard reaction.

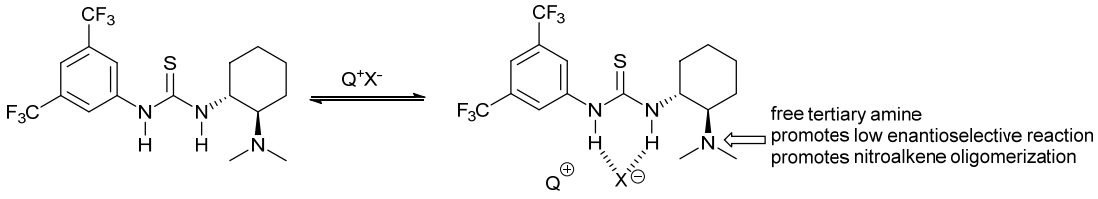
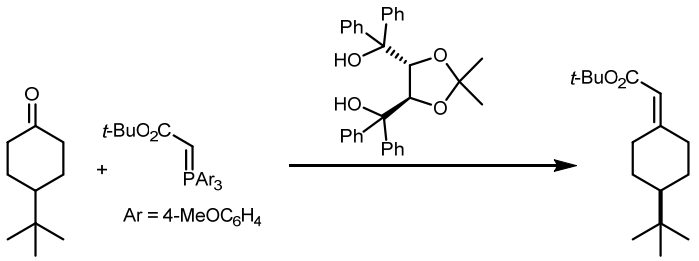


Figure S21.Rationalization of the effect of anions on Takemoto catalyst promoted reactions.

Preliminary studies on the catalytic enantioselective Wittig reaction of 4-*tert*-butylcyclohexanone catalysed by (*R*,*R*)-TADDOL



To a test tube equipped with a magnetic stirring bar were sequentially added *tert*-butylcyclohexanone (46.1 mg, 0.30 mmol), (*R*,*R*)-TADDOL (9.4 mg, 0.02 mmol), the salt additive (0.03 mmol), toluene (500 μL). The tube was placed in a cooled bath (0 °C), then the phosphorous ylide (26.6 mg, 0.10 mmol) was added under stirring. The reaction evolution was monitored by sampling a Pasteur pipette tip from the reaction mixture at the given times, followed by immediate dilution in ca. 0.7 mL of $CDCl_3$ and ^1H NMR spectroscopy analysis. The reaction conversion was determined by comparing the integral value of the signal of the product[8] at 5.52 ppm (br t, J= 1.7 Hz, 1H), with the signal at 4.62 ppm (br s, 2H) of the TADDOL catalyst used as internal standard. After the experiment the product was purified by a short plug of silica gel, and its enantiomeric excess determined by HPLC analysis (Chiralcel OD, flow = 1.0 mL/min, eluent: *n*-hexane/*i*-PrOH 99.9:0.1, λ = 254 nm, t_{maj} = 6.4 min, t_{min} = 4.9 min).

Evaluation of the effect of anionic additives in the reaction: The reaction was performed using 30 mol% of different additives, 1.5 equivalents with respect to the TADDOL catalyst. The results with the additives are reported in Table S15, and plotted in Figure S22 comparing their result with the reaction performed in their absence. The graph show that the reaction kinetics was only marginally effected by the presence of anionic additives, independently on their size and coordinating properties, although their moderate solubility in toluene might have slightly altered the results obtained with TBABr and TPPCl. Even if comparable, the enantioselectivities were slightly lower with some of the additives.

Table S15. Evolution over time of the reaction performed in the absence and in the presence of additives (30 mol%).

	Additive	Time (h)					ee (%)
		0	7	22.5	48	72	
Conversion (%)	-	0	7.1	14.9	23.2	30.4	68
	TPPCl	0	6.5	14.0	23.4	30.0	64
	TBABr	0	5.7	13.4	23.5	30.2	68
	TBAI	0	7.2	16.0	23.8	30.1	62
	$TBBAr^F$	0	6.8	14.4	23.1	29.7	61

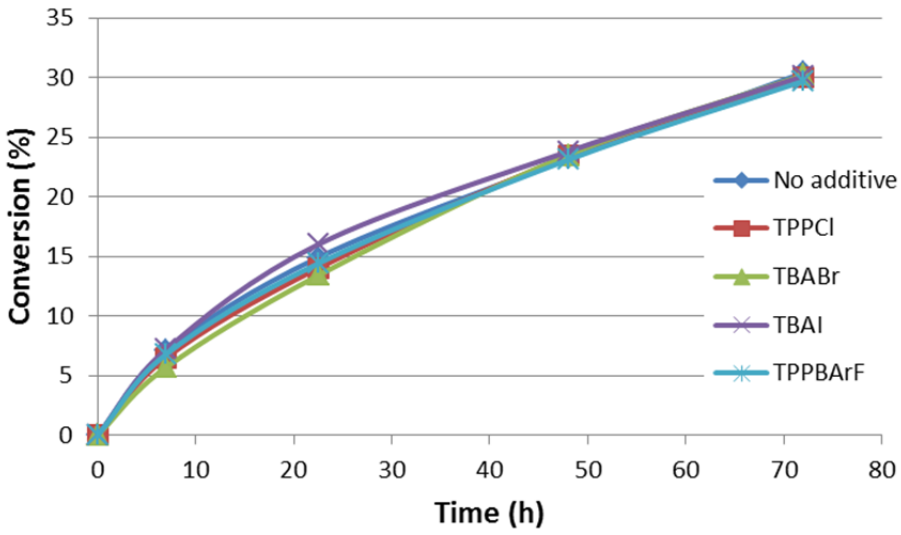


Figure S22. Evolution over time of the reaction performed in the presence of additives, and comparison with the standard reaction.