Synthèse Totale et
StéRéO
Réactivité Organique

Institut des Sciences Moléculaires de Marseille
UMR 6263

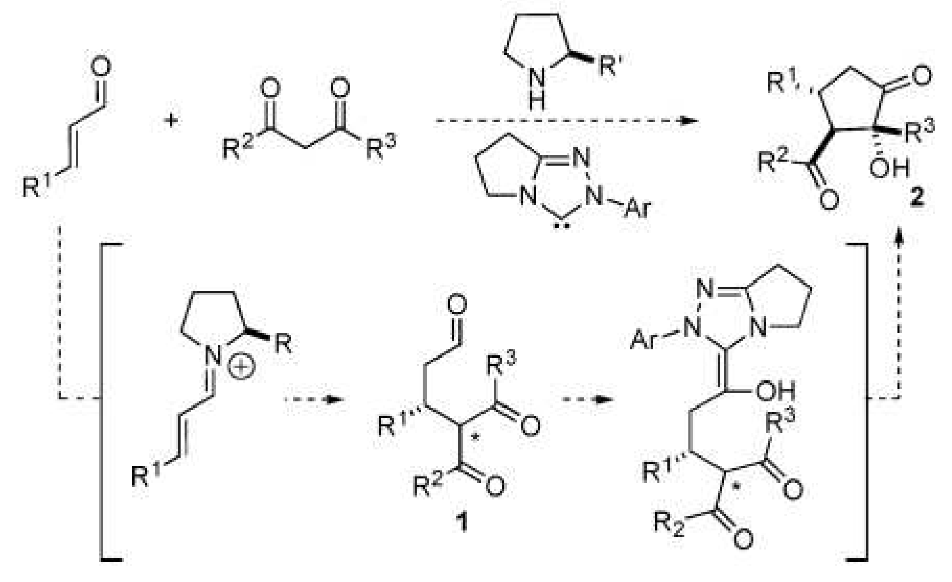
Asymmetric Organocatalytic Relay Cascades: Catalyst-Controlled StéRéOisomer Selection in the Synthesis of Functionalized Cyclohexanes

Wang, Y.; Han, R.-G.; Zhao, Y.-L.; Yang, S.; Xu, P.-F.; Dixon, D. J.
ACIE 2009 Early View

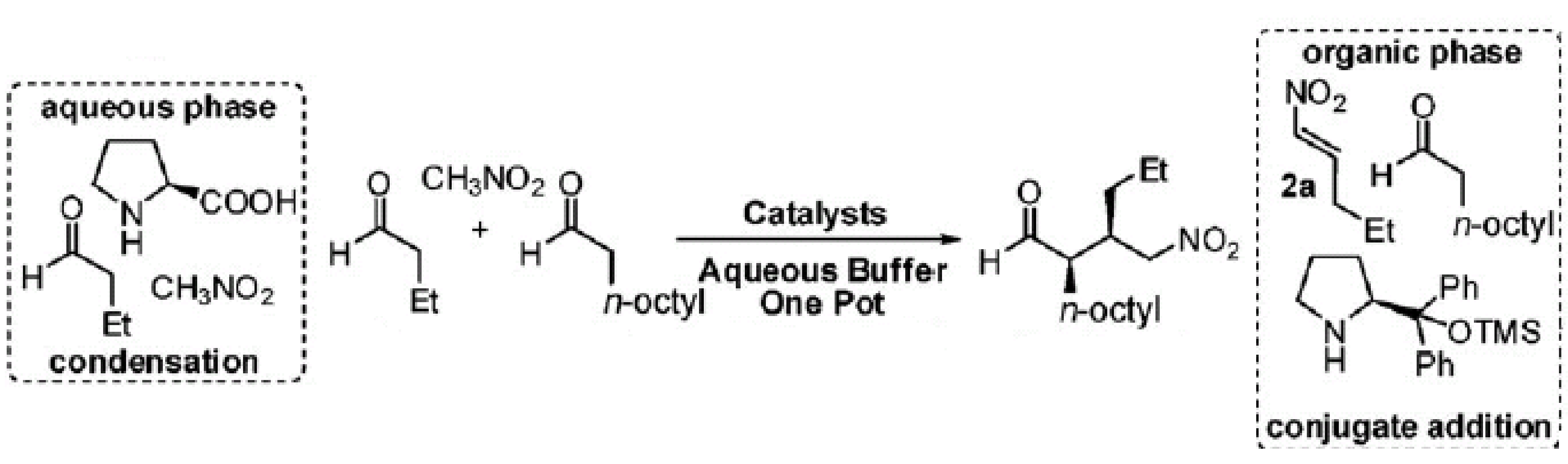
Marc PRESSET
StéRéO's famous RCC, 10/12/09

Similar Concepts…

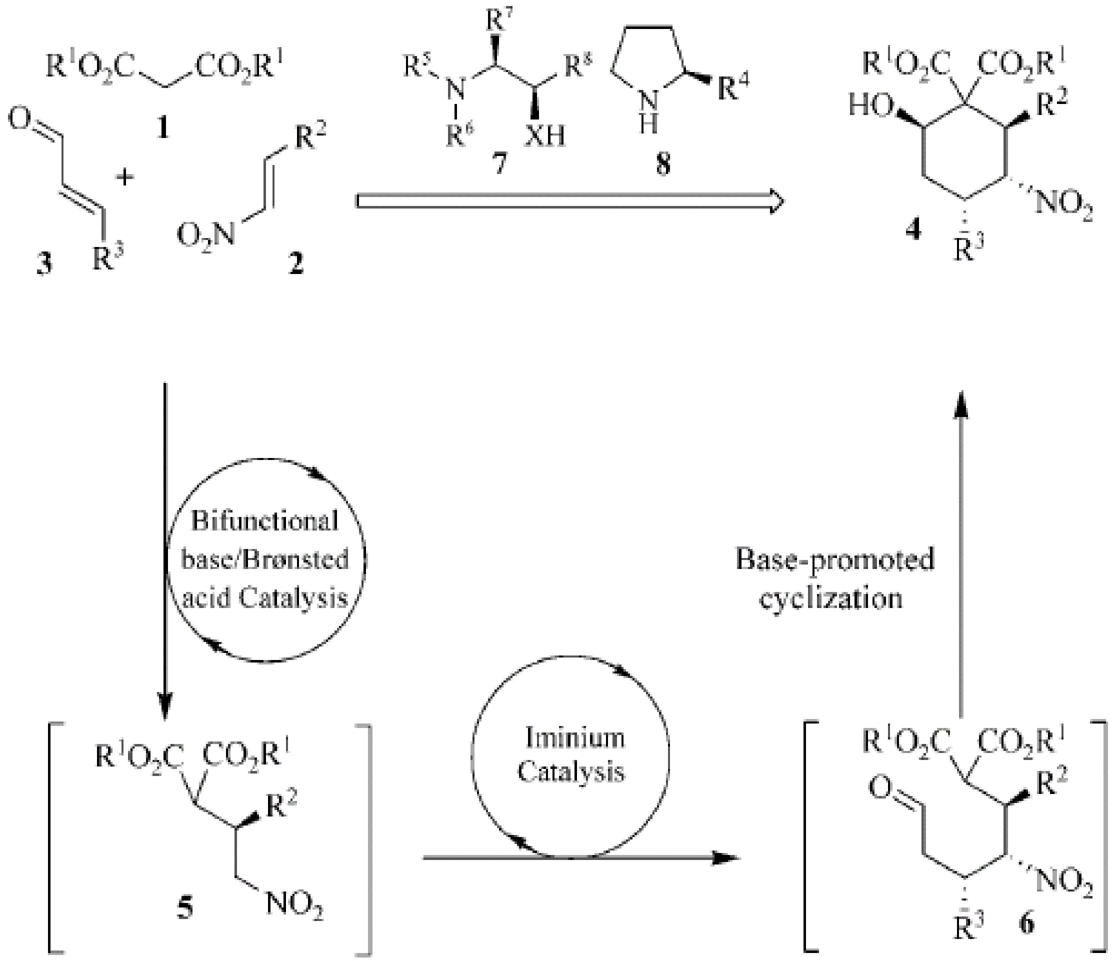
Rovis *et al. JACS* **2009**, 13628



Frechet *et al. ACIE* **2009**, Early View

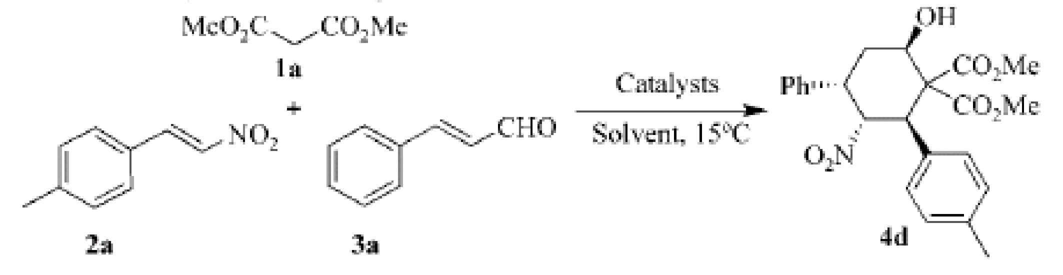


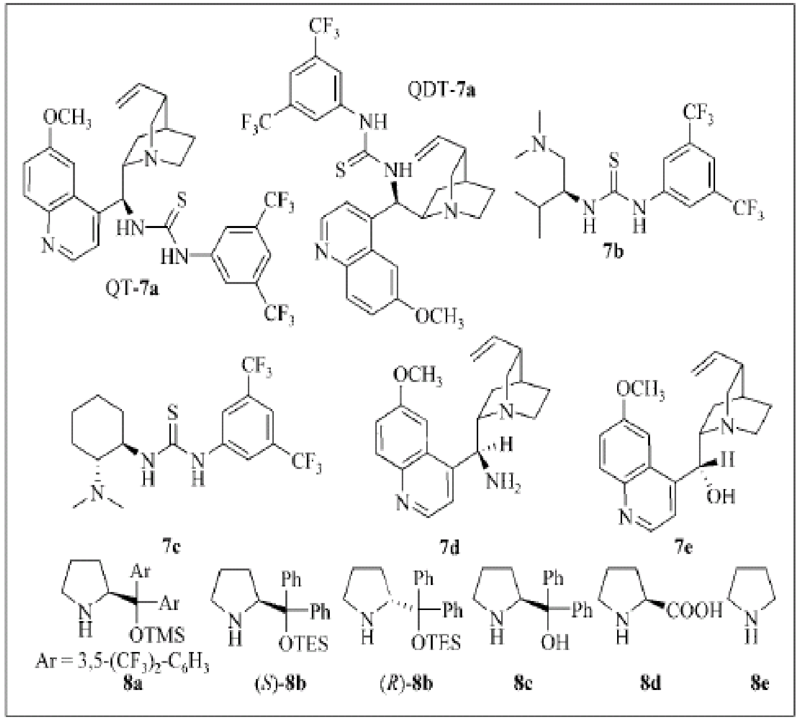
The idea…

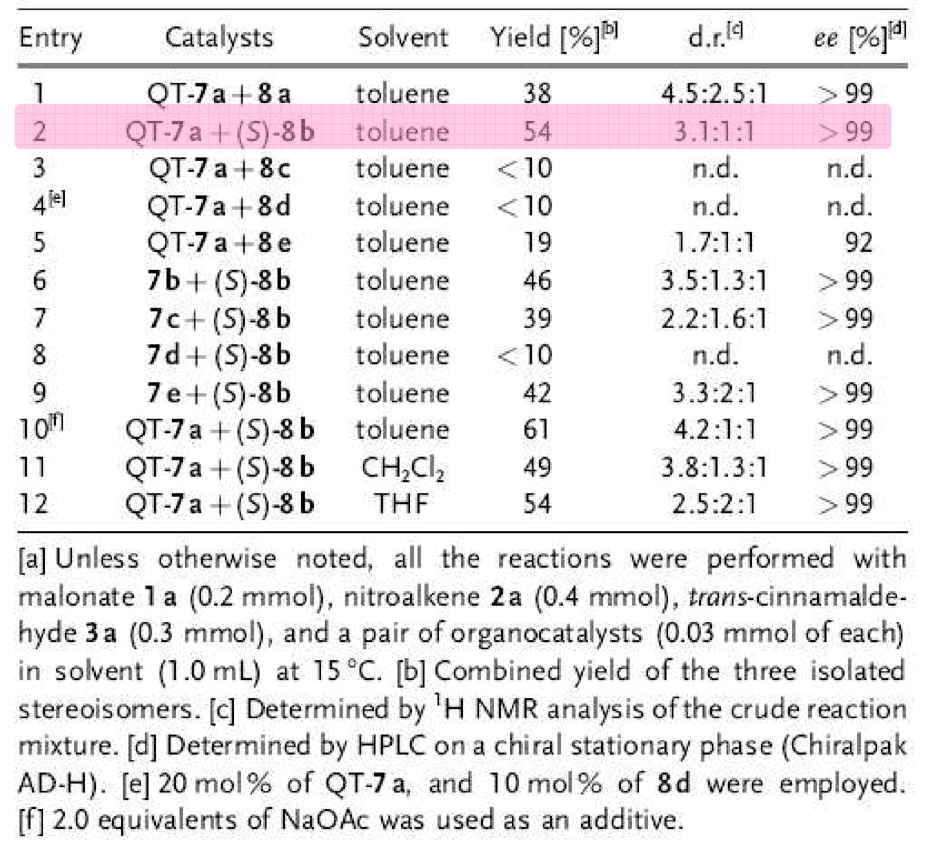


Scheme 1. AORC approach to polysubstituted cyclohexanes.

Optimization



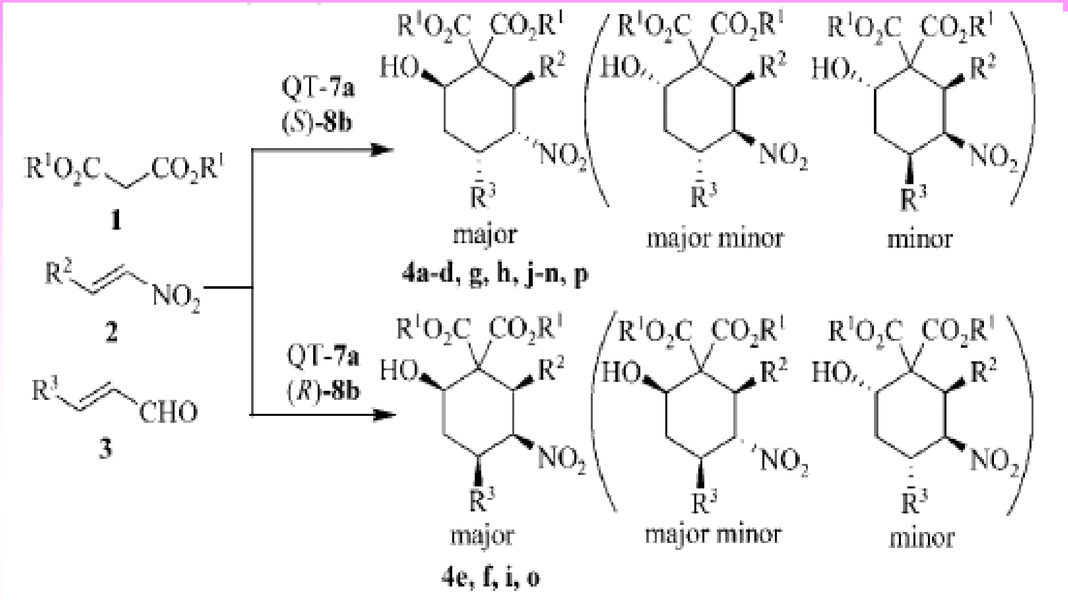


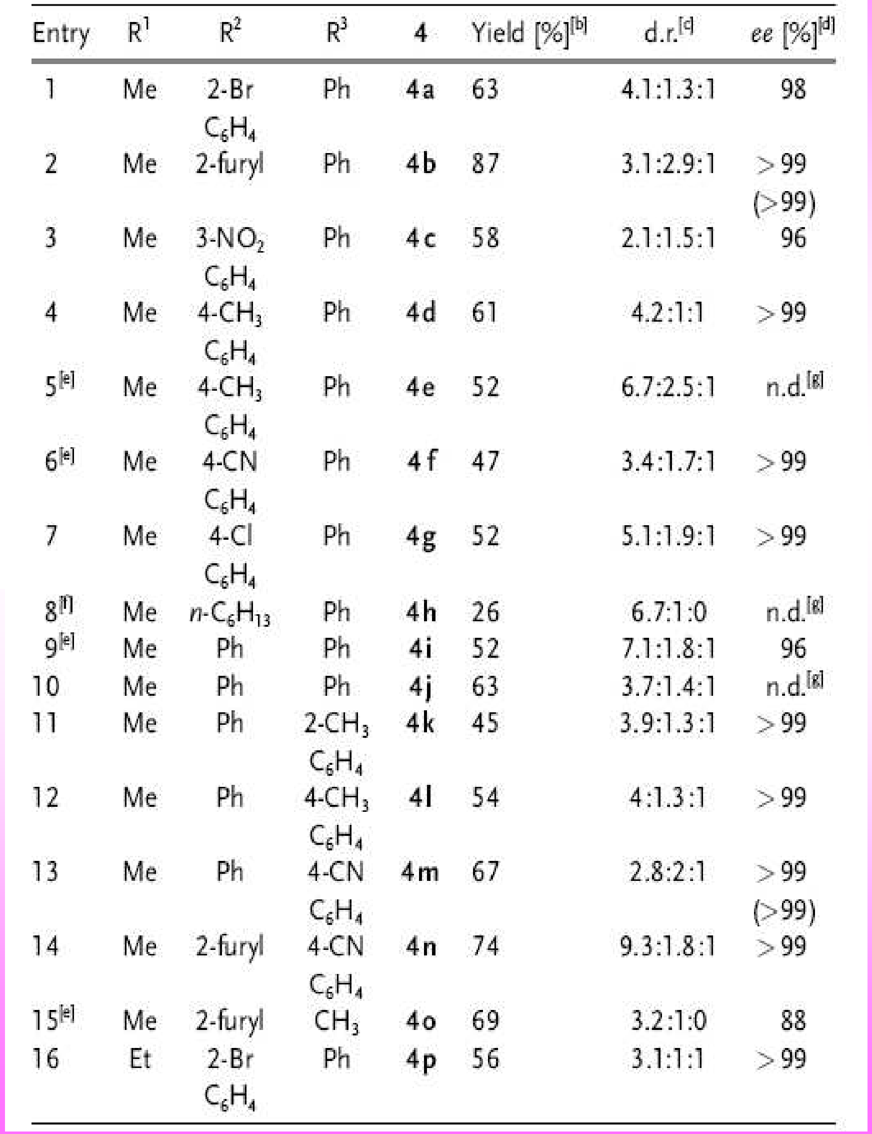


Entry	Catalysts	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	QT-**7a** + **8a**	toluene	38	4.5:2.5:1	> 99
2	QT-**7a** + (*S*)-**8b**	toluene	54	3.1:1:1	> 99
3	QT-**7a** + **8c**	toluene	< 10	n.d.	n.d.
4[e]	QT-**7a** + **8d**	toluene	< 10	n.d.	n.d.
5	QT-**7a** + **8e**	toluene	19	1.7:1:1	92
6	**7b** + (*S*)-**8b**	toluene	46	3.5:1.3:1	> 99
7	**7c** + (*S*)-**8b**	toluene	39	2.2:1.6:1	> 99
8	**7d** + (*S*)-**8b**	toluene	< 10	n.d.	n.d.
9	**7e** + (*S*)-**8b**	toluene	42	3.3:2:1	> 99
10[f]	QT-**7a** + (*S*)-**8b**	toluene	61	4.2:1:1	> 99
11	QT-**7a** + (*S*)-**8b**	CH_2Cl_2	49	3.8:1.3:1	> 99
12	QT-**7a** + (*S*)-**8b**	THF	54	2.5:2:1	> 99

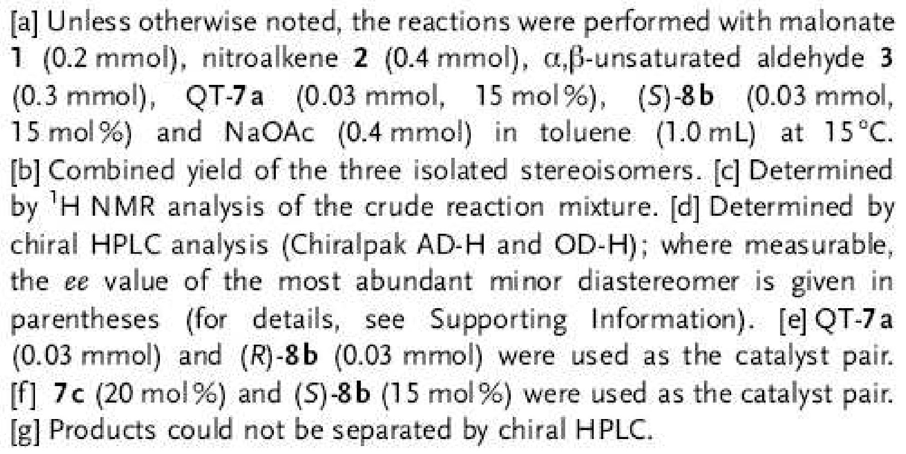
[a] Unless otherwise noted, all the reactions were performed with malonate **1a** (0.2 mmol), nitroalkene **2a** (0.4 mmol), *trans*-cinnamaldehyde **3a** (0.3 mmol), and a pair of organocatalysts (0.03 mmol of each) in solvent (1.0 mL) at 15 °C. [b] Combined yield of the three isolated stereoisomers. [c] Determined by ^1H NMR analysis of the crude reaction mixture. [d] Determined by HPLC on a chiral stationary phase (Chiralpak AD-H). [e] 20 mol% of QT-**7a**, and 10 mol% of **8d** were employed. [f] 2.0 equivalents of NaOAc was used as an additive.

Screening



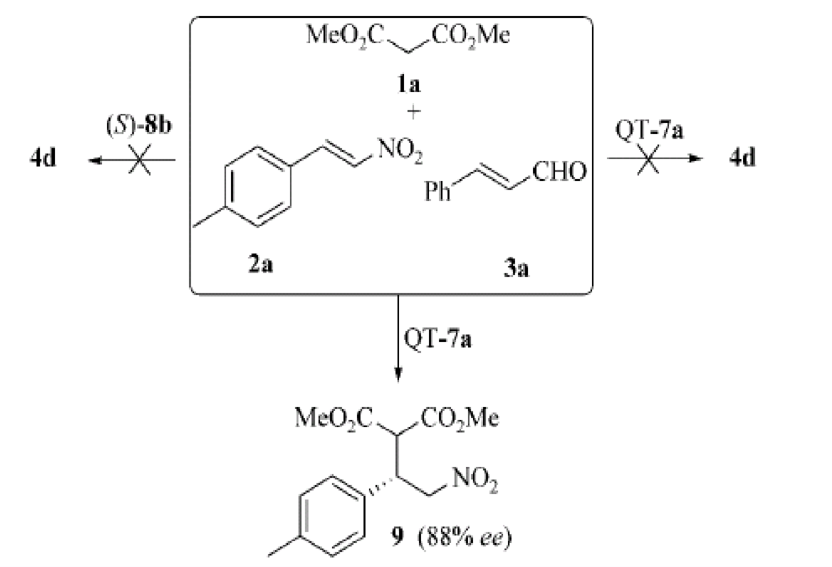


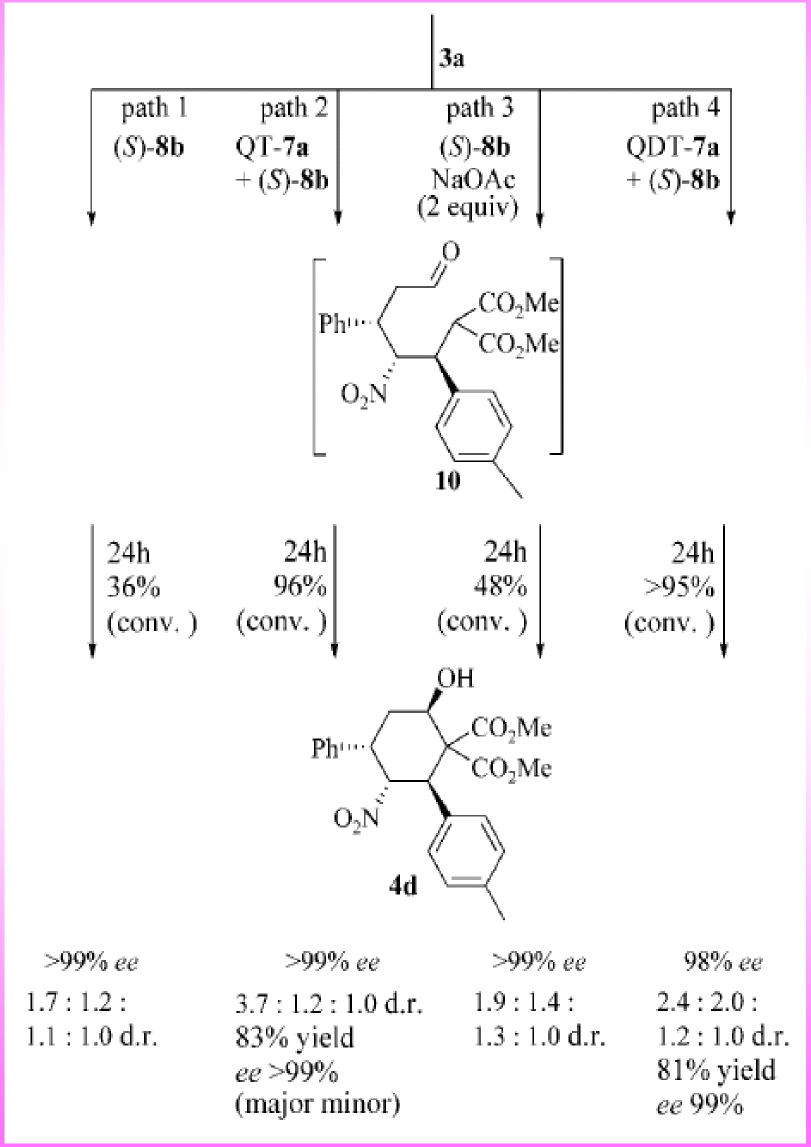
Entry	R^1	R^2	R^3	4	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Me	2-BrC_6H_4	Ph	**4a**	63	4.1:1.3:1	98
2	Me	2-furyl	Ph	**4b**	87	3.1:2.9:1	> 99 (>99)
3	Me	3-$NO_2C_6H_4$	Ph	**4c**	58	2.1:1.5:1	96
4	Me	4-$CH_3C_6H_4$	Ph	**4d**	61	4.2:1:1	> 99
5[e]	Me	4-$CH_3C_6H_4$	Ph	**4e**	52	6.7:2.5:1	n.d.[g]
6[e]	Me	4-CNC_6H_4	Ph	**4f**	47	3.4:1.7:1	> 99
7	Me	4-ClC_6H_4	Ph	**4g**	52	5.1:1.9:1	> 99
8[f]	Me	*n*-C_6H_{13}	Ph	**4h**	26	6.7:1:0	n.d.[g]
9[e]	Me	Ph	Ph	**4i**	52	7.1:1.8:1	96
10	Me	Ph	Ph	**4j**	63	3.7:1.4:1	n.d.[g]
11	Me	Ph	2-$CH_3C_6H_4$	**4k**	45	3.9:1.3:1	> 99
12	Me	Ph	4-$CH_3C_6H_4$	**4l**	54	4:1.3:1	> 99
13	Me	Ph	4-CNC_6H_4	**4m**	67	2.8:2:1	> 99 (>99)
14	Me	2-furyl	4-CNC_6H_4	**4n**	74	9.3:1.8:1	> 99
15[e]	Me	2-furyl	CH_3	**4o**	69	3.2:1:0	88
16	Et	2-BrC_6H_4	Ph	**4p**	56	3.1:1:1	> 99



[a] Unless otherwise noted, the reactions were performed with malonate **1** (0.2 mmol), nitroalkene **2** (0.4 mmol), α,β-unsaturated aldehyde **3** (0.3 mmol), QT-**7a** (0.03 mmol, 15 mol%), (*S*)-**8b** (0.03 mmol, 15 mol%) and NaOAc (0.4 mmol) in toluene (1.0 mL) at 15°C. [b] Combined yield of the three isolated stereoisomers. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by chiral HPLC analysis (Chiralpak AD-H and OD-H); where measurable, the *ee* value of the most abundant minor diastereomer is given in parentheses (for details, see Supporting Information). [e] QT-**7a** (0.03 mmol) and (*R*)-**8b** (0.03 mmol) were used as the catalyst pair. [f] **7c** (20 mol%) and (*S*)-**8b** (15 mol%) were used as the catalyst pair. [g] Products could not be separated by chiral HPLC.

Study of the mechanism





- Only the bifunctionnal catalyst catalyses the Michael addition
- Cooperation of the catalysts
- NaOAc improves the conversion


Joyeux Noël !
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