Supporting Information

Bifunctional Activation and Racemization in the Catalytic Asymmetric aza-Baylis-Hillman Reaction

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1. Abbreviations

Add	additive
BH	Baylis-Hillman
MVK	methylvinyl ketone
RT	room temperature
THF	tetrahydrofurane
Tos(yl)	*p*-toluenesulfonyl
TPP	triphenylphosphine

2. Experimental methods

All experiments were carried out under argon atmosphere using the Schlenk or dry box technique. THF was distilled from sodium benzophenone ketyl under argon atmosphere prior to use. All commercially obtained chemicals were degassed and stored under argon at room temperature. Methyl vinyl ketone was stored under argon at –30°C.
The tosylimines, used for the aza-BH reaction, were prepared from the corresponding aldehydes according to Love *et al*.[1] (*R*)-2'-Diphenylphosphanyl-[1,1']binaphthalenyl-2-ol was prepared according to Shi *et al*.[2]

1. Love, B. E.; Raje, P. S.; Williams, T. C., *Synlett* **1994**, 493-494.
2. Shi, M.; Chen, L.-H.; Li, C.-Q., *J. Am. Chem. Soc.* **2005**, *127*, 3790- 3800.

3. Analysis

NMR

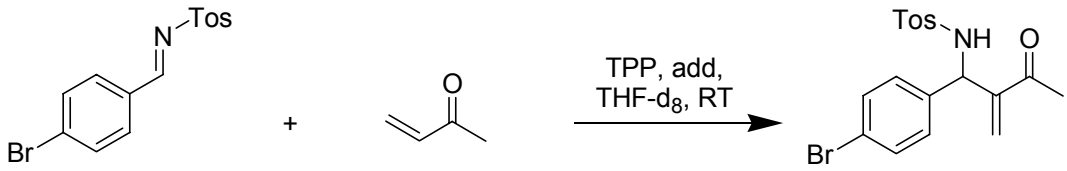
Routine measurements and kinetic experiments were carried out on a Bruker DPX300 and AV 600 spectrometer, respectively. The Bruker DPX 300 operates at frequencies of 299.6 MHz for ^{1}H, 75.3 MHz for ^{13}C, 121.29 MHz for ^{31}P and 282.4 MHz for ^{19}F. The Bruker AV600 operates at frequencies of 600.1 MHz for ^{1}H, 150.9 MHz for ^{13}C, 242.9 MHz for ^{31}P and 564.7 MHz for ^{19}F. Chemical shift values δ are given in ppm relative to tetramethylsilane (TMS) using solvent resonances as internal standard for ^{1}H and ^{13}C.

HPLC

HPLC analyses were performed on a Daicel Chiralcel OD-H column (223 nm, heptane/isopropanol = 50/50; Flow rate: 0.5 ml/min).

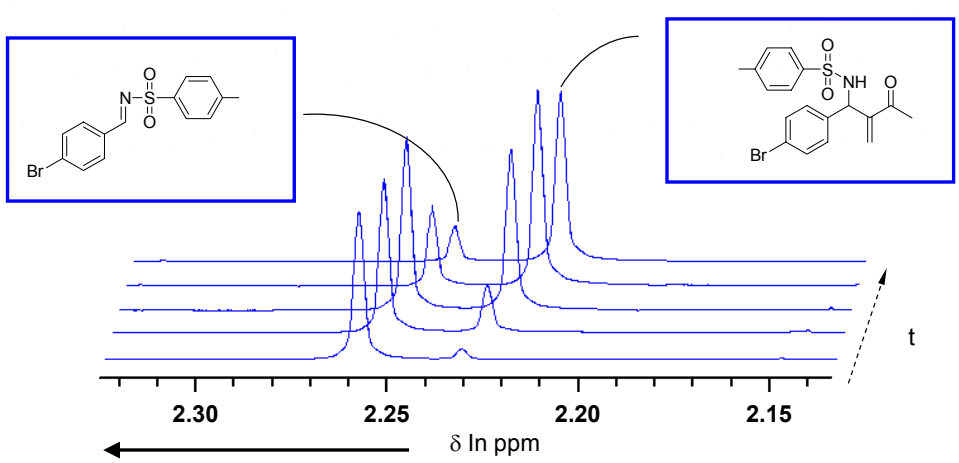
4. Acidic co-catalysts

For all kinetic experiments stock solutions were used to minimize the weighing error!



The reaction was monitored by ^{1}H-NMR spectroscopy.

Typical sequence of time-resolved NMR spectra:



Reaction conditions: 25.4 mg (0.075 mmol, 1.00 eq) imine, 6.3 mg (0.090 mmol, 1.20 eq) MVK, 2.0 mg (0.0075 mmol, 0.10 eq) TPP, *n* mg additive (0.103 mmol, 1.375 eq), 0.6 ml THF-d_8.

The following compounds were tested as additives: aza-BH product (42.1 mg), methanol (3.3 mg), phenol (9.7 mg), *N*-methyl-tosylamide (19.1 mg), bis-3,5-(trifluormethyl)phenol (23.7 mg), benzoic acid (12.6 mg), water (1.9 mg), and malic acid (13.8 mg).

Conversion-time plots:

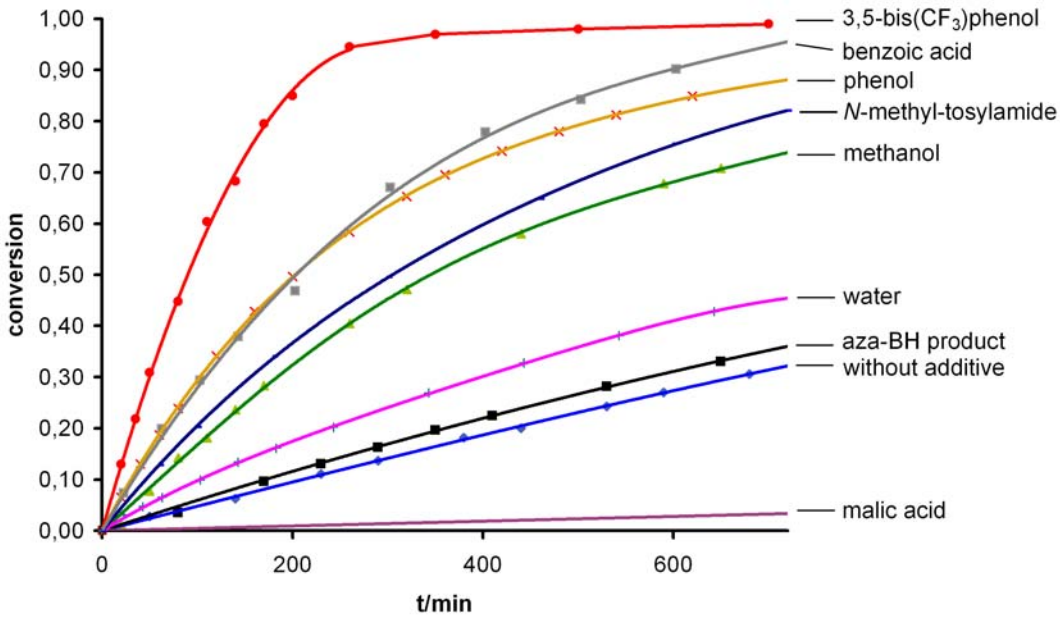
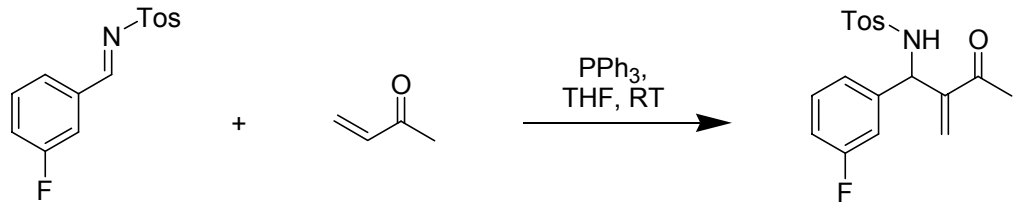


Table 1. Reaction rate dependence on pK_a of the additive

entry	additive (1 eq.)	pKa	$k`_{obs}/k_{obs}$
1	malic acid	3.6	0.1
2	–	-	1.0
3	aza-BH product	-	1.2
4	water	15.4	2.4
5	methanol	15.5	3.7
6	*N*-methyl-tosylamide	11.7	4.8
7	benzoic acid	4.2	6.5
8	phenol	9.9	7.3
9	3,5-bis(CF_3)-phenol	8.0	13.9

[a] Reactions were carried out with MVK (0.090 mmol), imine (0.075 mmol), PPh_3 (0.0075 mmol), additive (0.103 mmol), 0.6 ml THF-d_8

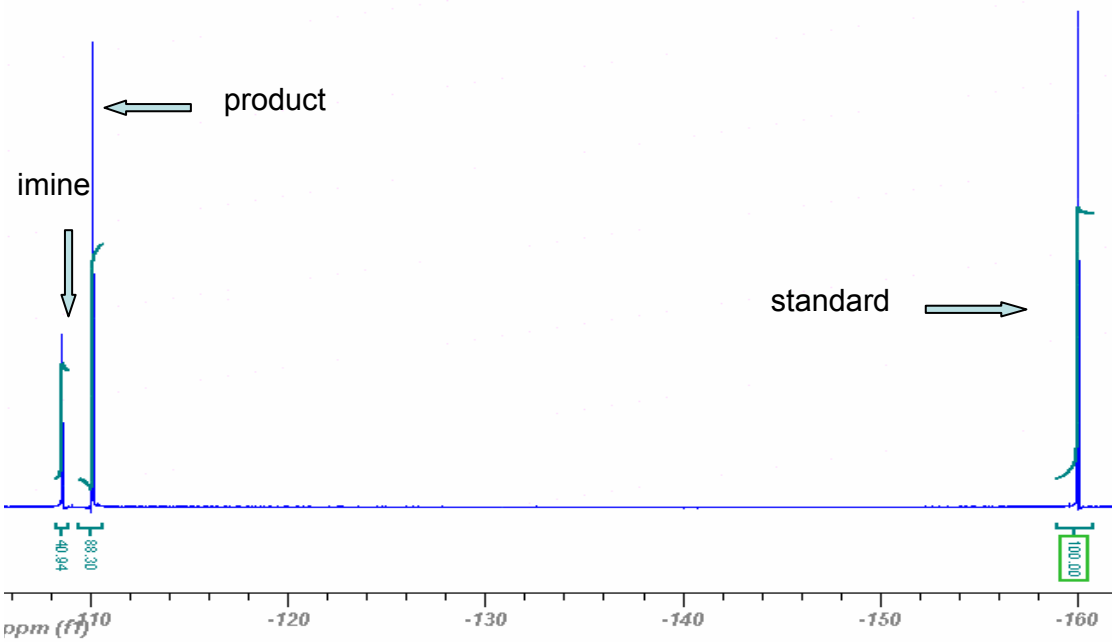
5. Order plots



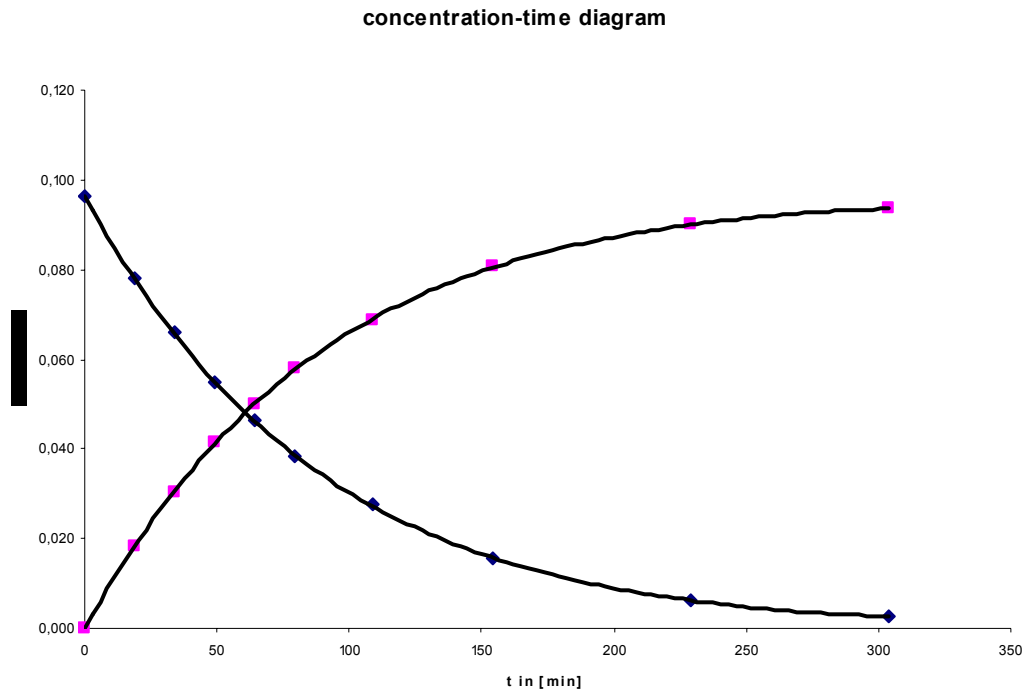
To determine the partial reaction order of imine, MVK, and TPP we applied the *initial rate method*.[3] The reactions were monitored by ^{19}F NMR spectroscopy using hexafluorobenzene as internal standard.

3. R. G. Wilkins, Kinetics and Mechanism of Reactions of Transition Metal Complexes, VCH, Weinheim, 1991.

Typical NMR spectrum (conversion = 68%):

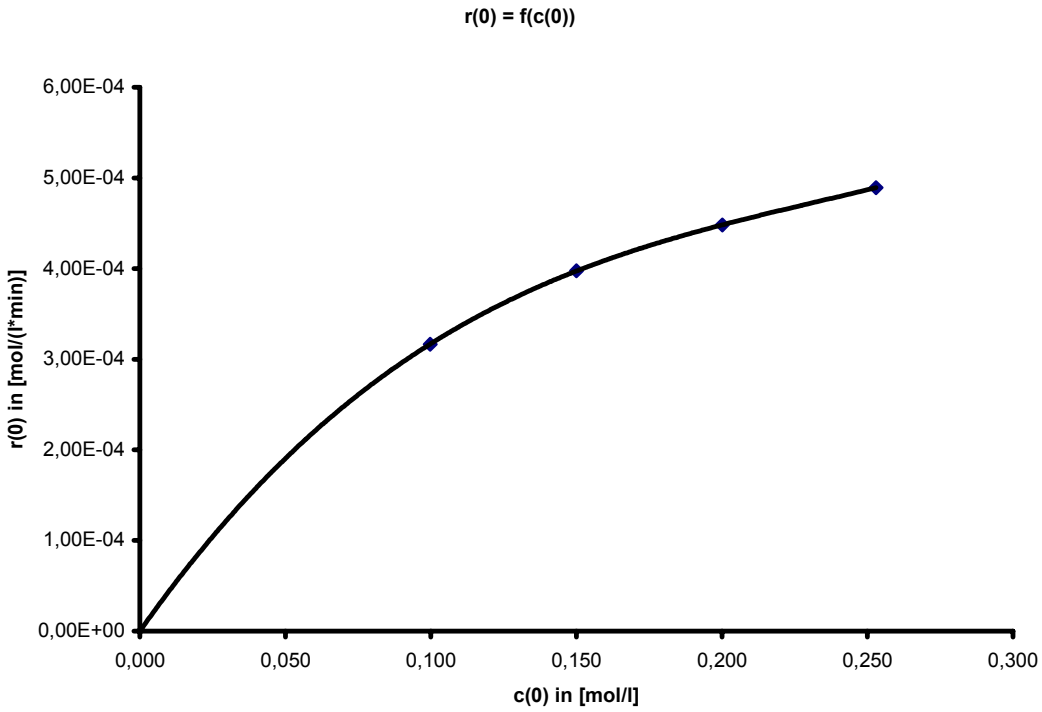


Typical concentration-time profile (imine and product):

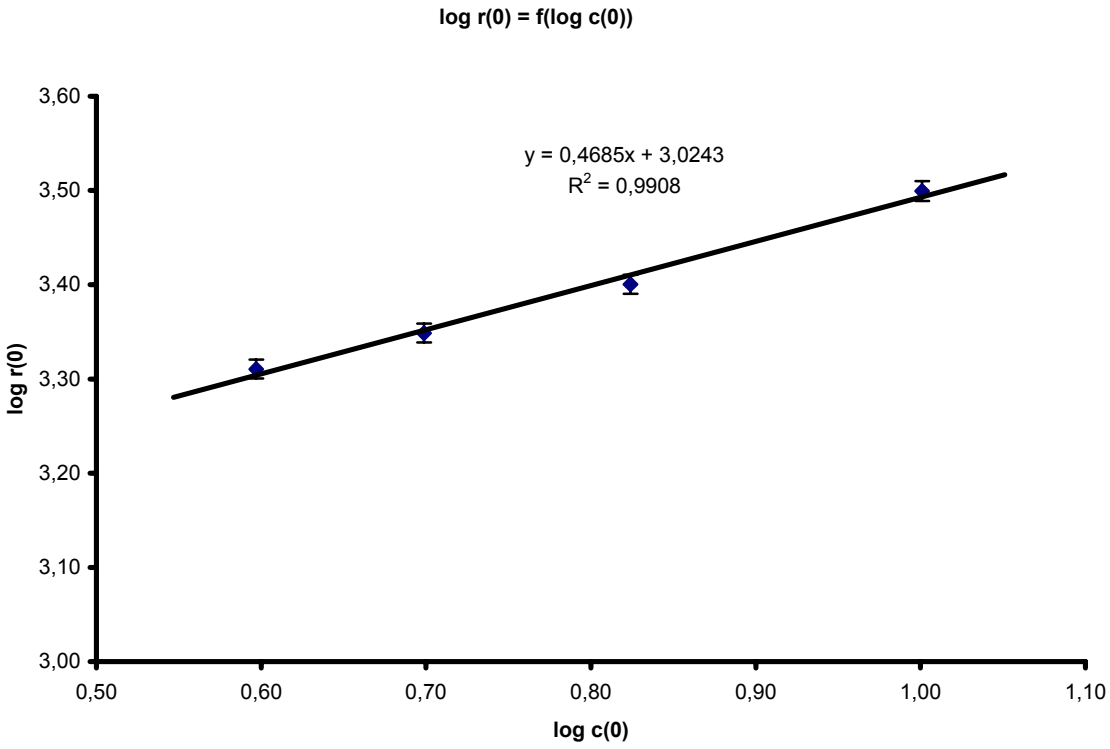


Partial order imine (normal, without additive):

Starting concentrations: c(TPP) = 0.0501 mol/l, c(MVK) = 0.1438 mol/l, c(standard) = 0.0243 mol/l, c(imine) = 0.0998-0.2530 mol/l.

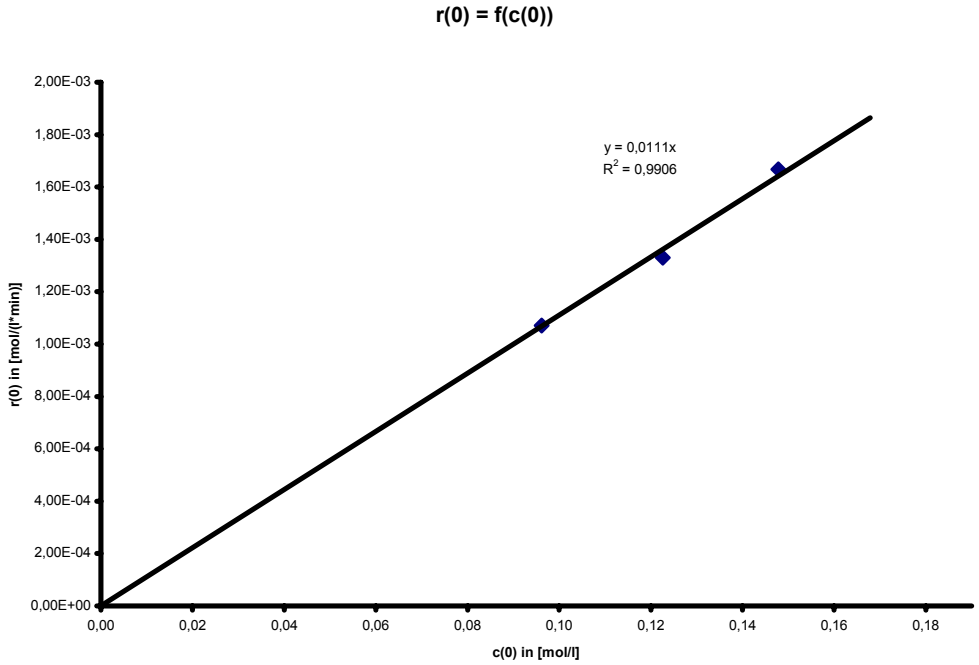


Partial order imine (logarithmic, without additive):



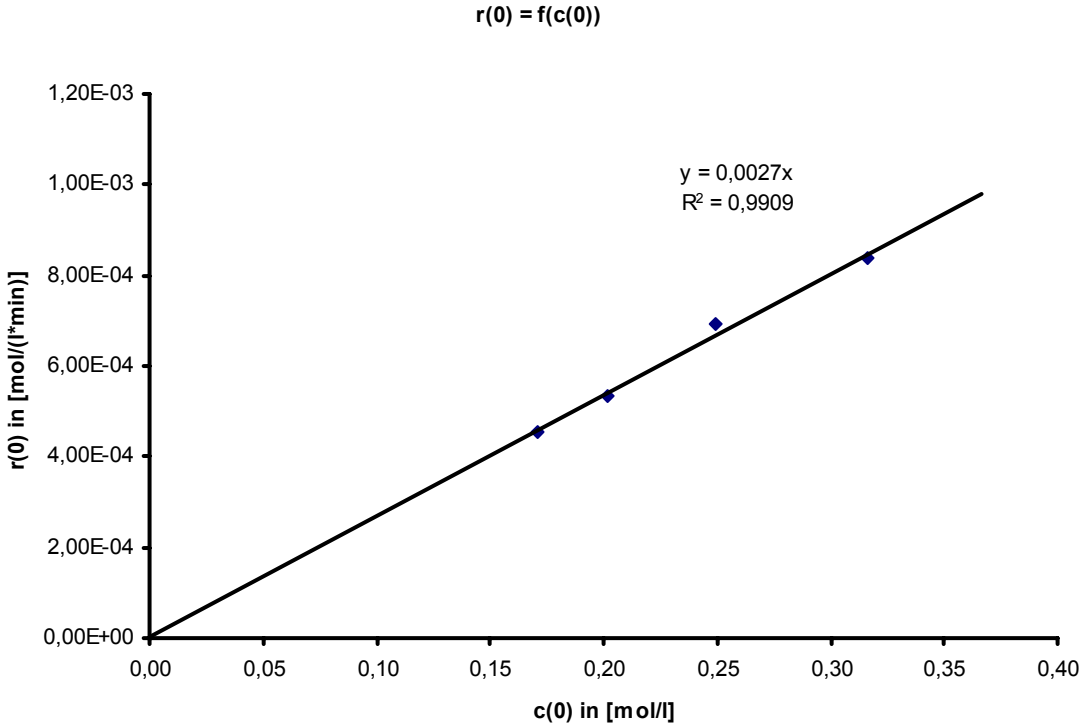
Partial order imine (normal, with additive):

Starting concentrations: c(TPP) = 0.0294 mol/l, c(MVK) = 0.1502 mol/l, c(add) = 0.1584 mol/l, c(standard) = 0.0341 mol/l, c(imine) = 0.0962 – 0.1479 mol/l



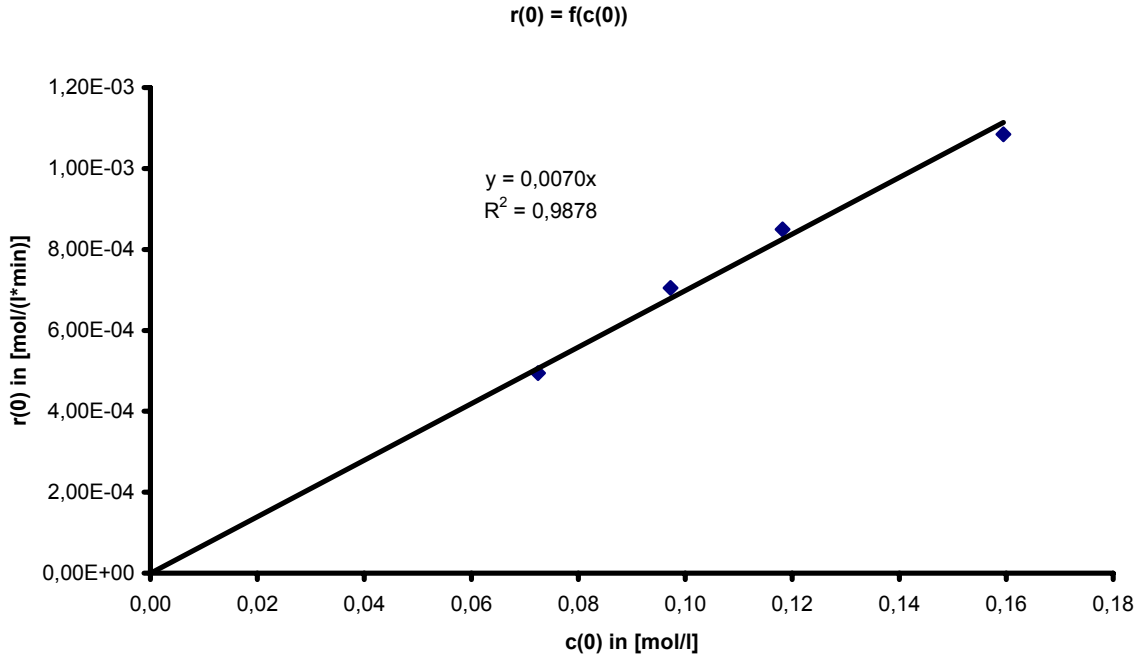
Partial order MVK:

Starting concentrations: c(TPP) = 0.0500 mol/l, c(imine) = 0.1506 mol/l, c(standard) = 0.0214 mol/l, c(MVK) = 0.1712 – 0.3163 mol/l.



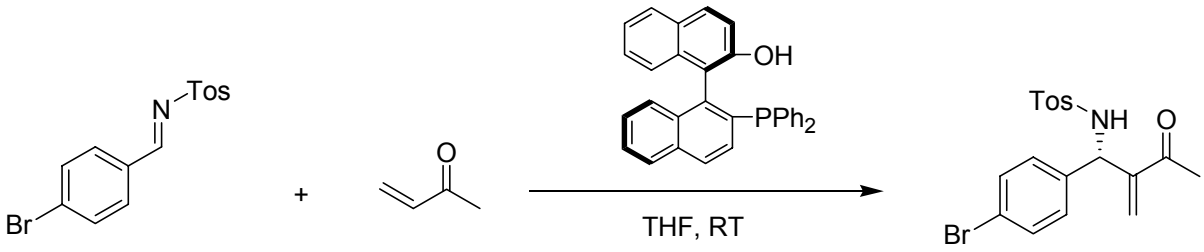
Partial order TPP:

Starting concentrations: c(MVK) = 0.1531 mol/l, c(imine) = 0.1514 mol/l, c(standard) = 0.0285 mol/l, c(TPP) = 0.0724 – 0.1595 mol/l



6. Racemization experiment

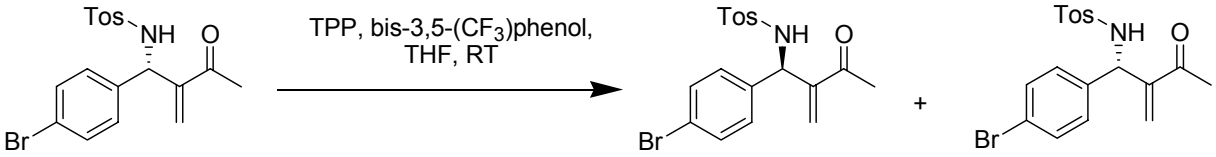
a) Preparation of enantio-enriched aza-Baylis-Hillman product[4]



338.2 mg (1.00 mmol, 1.00 eq) *p*-bromobenzaldehyde-*N*-tosylimine and 45.4 mg (0.10 mmol, 0.10 eq) (*R*)-2'-diphenylphosphanyl-[1,1']binaphthalenyl-2-ol were dissolved in 8.0 ml (8.0 ml/mmol imine) THF. After addition of 84.1 mg (1.20 mmol, 1.20 eq) MVK the reaction mixture was stirred at RT. After 24 h, THF and MVK were removed *in vacuo*.

y = 60%, ee = 88%

b) Racemization with TPP/bis-3,5-(CF_3)phenol

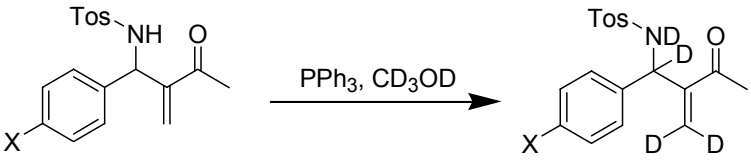


The mixture (imine, product, chiral catalyst) resulting from **a** was dissolved in 8.0 ml THF (8.0 ml/mmol imine). After addition of 262.29 mg (1.00 mmol, 1.00 eq) TPP and 759.4 mg (3.30 mmol, 3.30 eq) bis-3,5-(CF_3)phenol the reaction mixture was stirred at RT for *n* h.

n = 12: ee = 20%
n = 120: ee = 0%

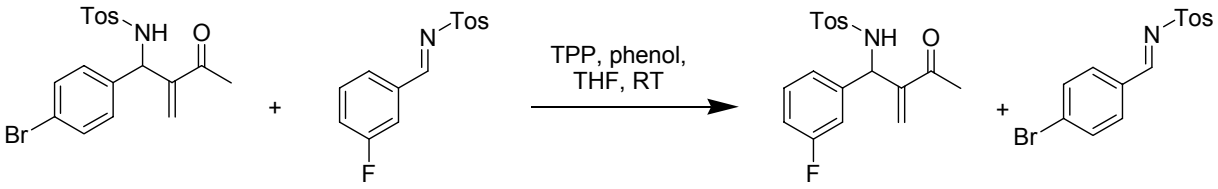
4. Shi, M.; Chen, L.-H. *Chem. Commun*. **2003**, 1310-1311.

7. Deuteration experiment



20.4 mg (0.050 mmol, 1.00 eq) aza-BH product (X=Br) and 13.1 mg (0.050 mmol, 1.00 eq) TPP were dissolved in 1.0 ml methanol-d_4 and stirred at RT. After 24 h the solvent was removed *in vacuo*. The resulting residue was dissolved in $CDCl_3$ and characterized by NMR spectroscopy.

8. Cross-aldolization experiment



30.0 mg (0.0735 mmol, 1.00 eq) *N*-[1-(4-Bromo-phenyl)-2-methylene-3-oxo-butyl]-4-methyl-benzenesulfonamide and 203.7 mg (0.735 mmol, 10.0 eq) *m*-fluorobenzaldehyde-*N*-tosylimine were dissolved in 2 ml (2.7 ml/mmol imine) THF. After addition of 19.3 mg (0.0735 mmol, 1.00 eq) TPP and 34.6 mg (0.367 mmol, 5.00 eq) phenol the mixture was stirred at RT for *n* h.

n = 24 h: no cross-mannich products
n = 72 h: no cross-mannich products