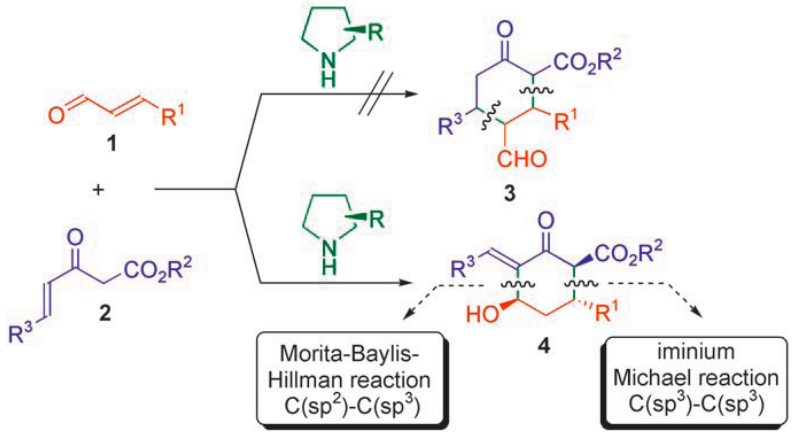
An Unexpected Organocatalytic Asymmetric Tandem Michael/Morita-Baylis-Hillman Reaction



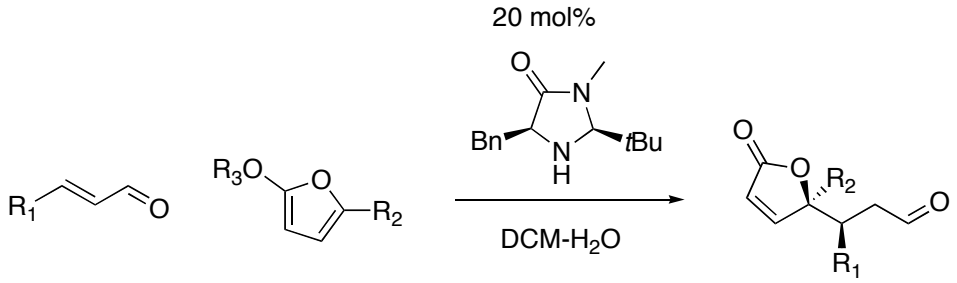
Silvia Cabrera, José Alemán, Patrick Bolze, Søren Bertelsen, and Karl Anker Jørgensen

Angew. Chem. Int. Ed. **2007** Early View

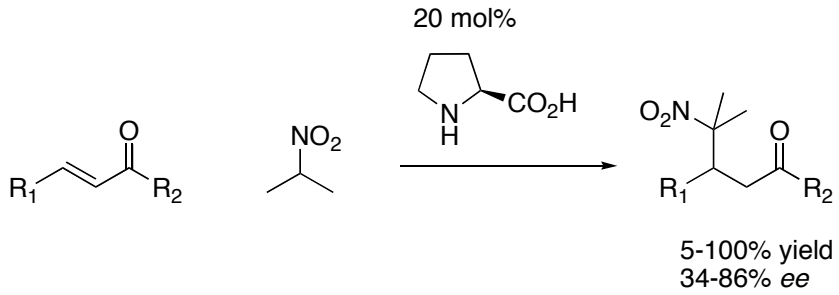
Bryan Wakefield

Current Lit. 11/23/07

Iminium Ion Activation of α,β Unsaturated Carbonyls with 2° Amines: 1,4 Additions

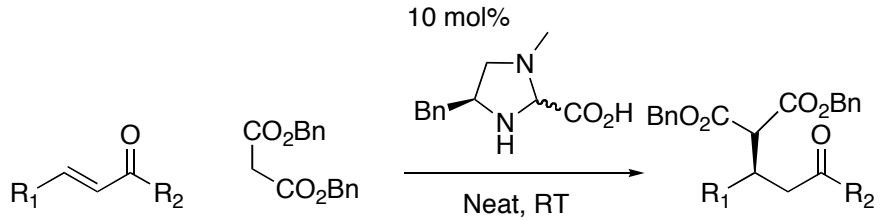


D. MacMillan and co-workers, *J. Am. Chem. Soc.* **2003**, 1192

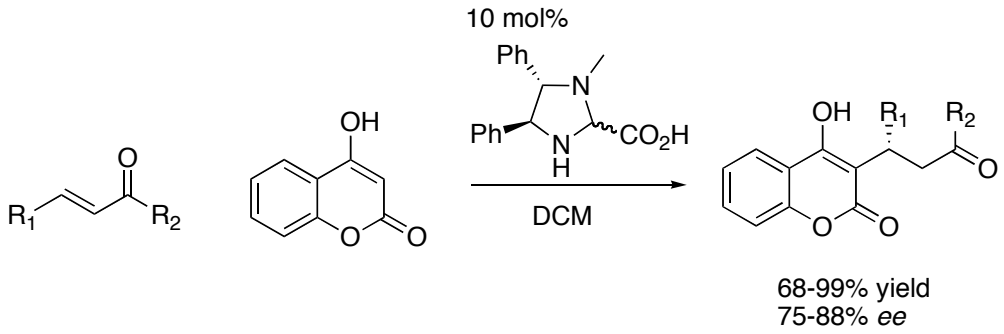


K. A. Jørgensen and coworkers *J. Am. Chem. Soc.* **2002**, 8831
also see
K. A. Jørgensen and coworkers *Org. Lett.* **2005**, 3897

Iminium Ion Activation of α,β Unsaturated Carbonyls with 2° Amines: 1,4 Additions

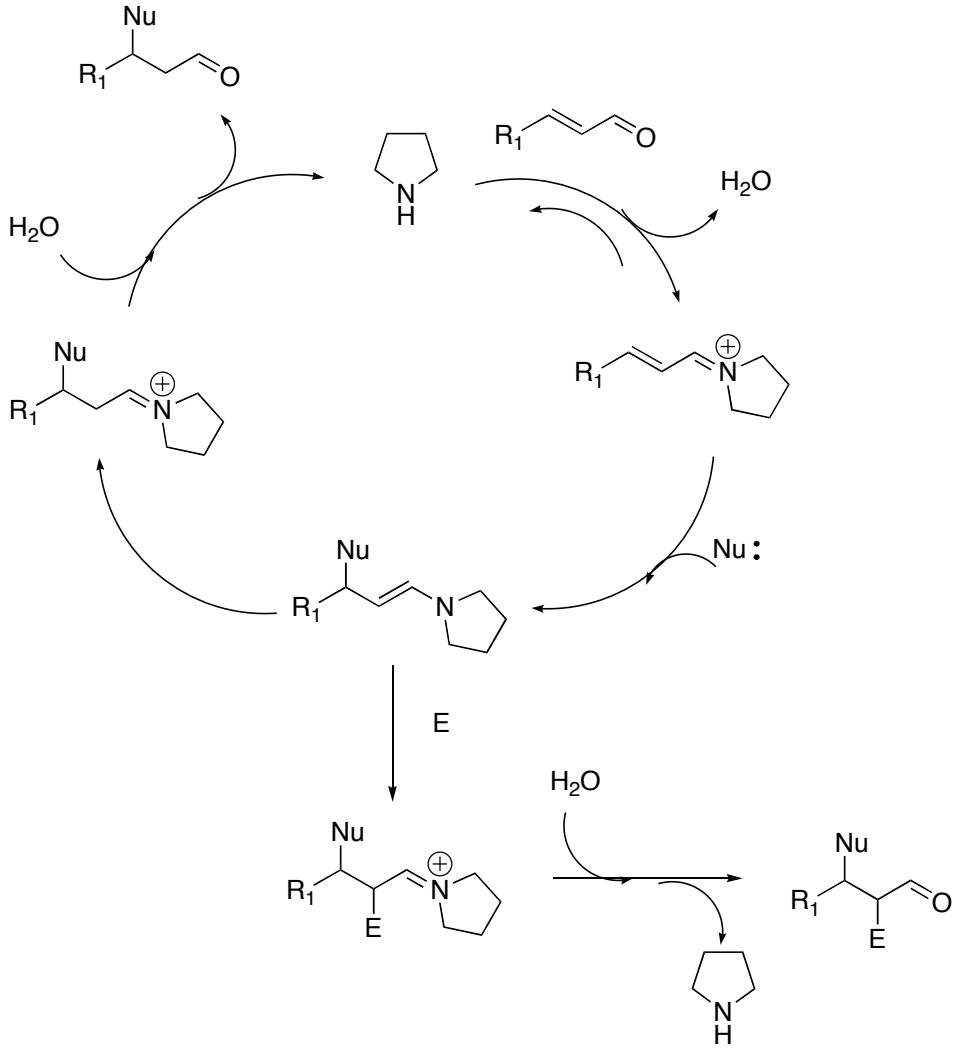


K. A. Jørgensen and coworkers *Angew. Chem. Int. Ed.* **2003**, 661

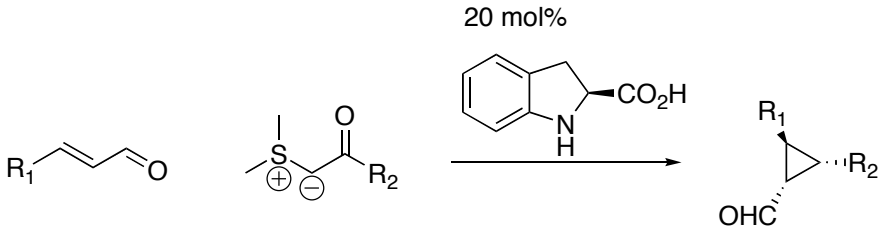


K. A. Jørgensen and coworkers *Angew. Chem. Int. Ed.* **2003**, 4955

Mechanistic Insights for the Design of Tandem Processes

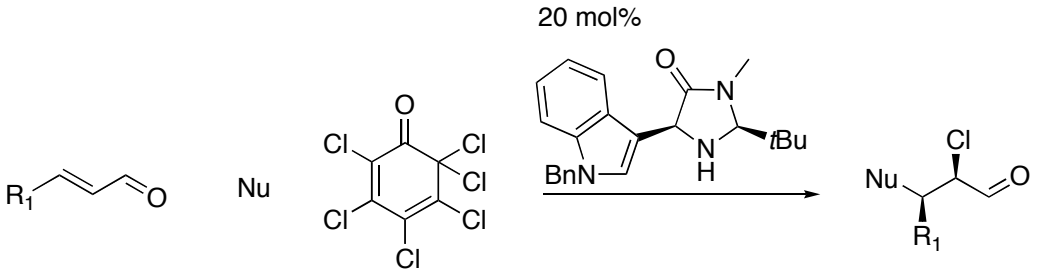


Examples of Iminium/Enamine Tandem Reactions



6:1 to 72:1 d.r.
63-85% yield
89-96% *ee*

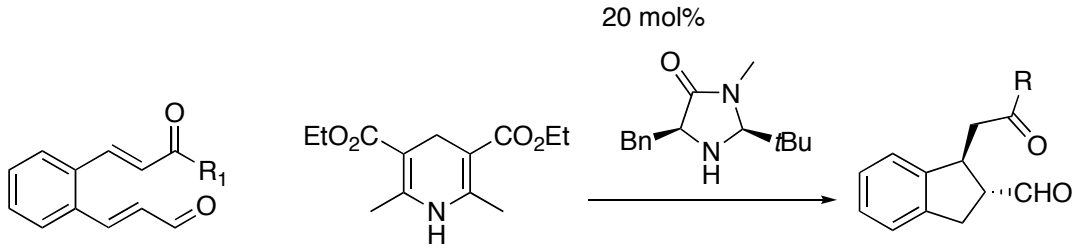
D. MacMillan and coworkers *J. Am. Chem. Soc.* **2005**, 3240



9:1 to 25:1 d.r.
67-97% yield
99% *ee*

D. MacMillan and coworkers *J. Am. Chem. Soc.* **2005**, 15051

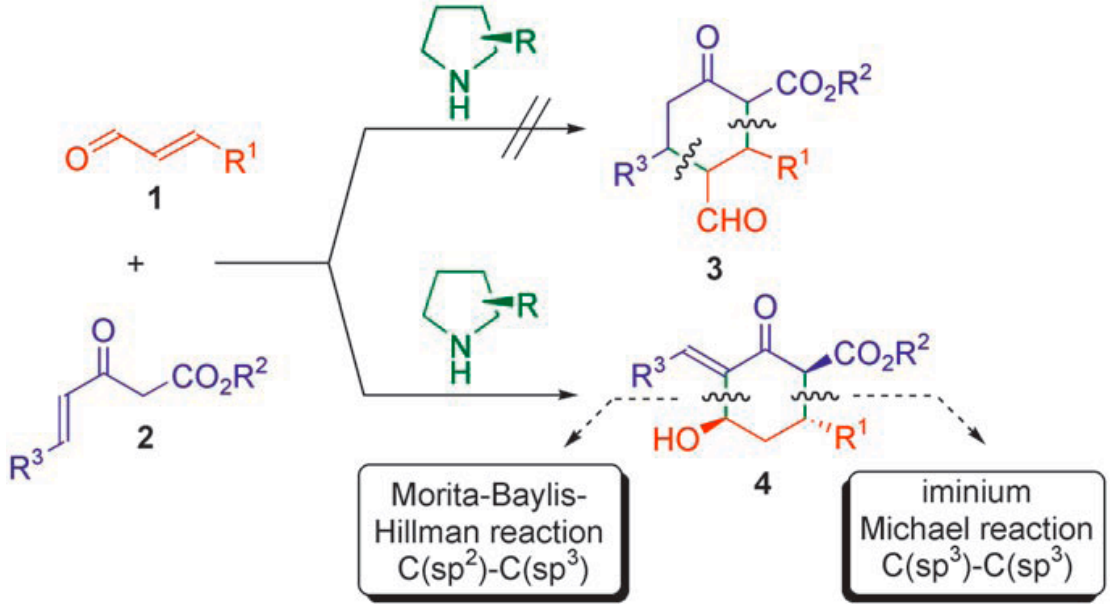
Examples of Iminium/Enamine Tandem Reactions

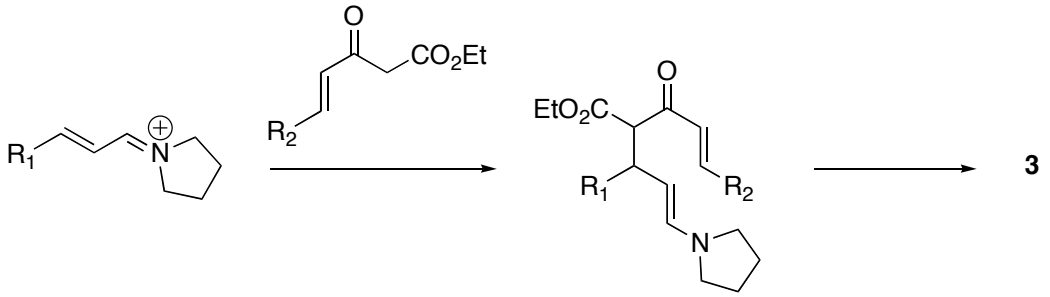


15:1 to 50:1 d.r.
86-98% yield
86-96% *ee*

B. List and coworkers *J. Am. Chem. Soc.* **2005**, 15036

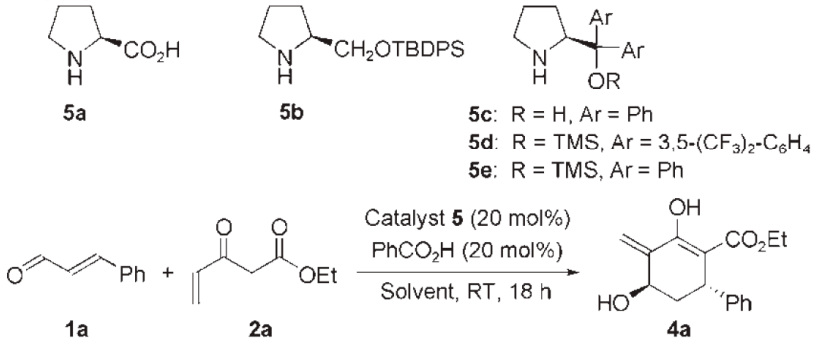
Reaction Design: Trapping of the Latent Enamine





Reaction Optimization

Table 1: Representative screening results for the reaction of cinnamaldehyde (**1a**) with β-ketoester **2a**.[a]

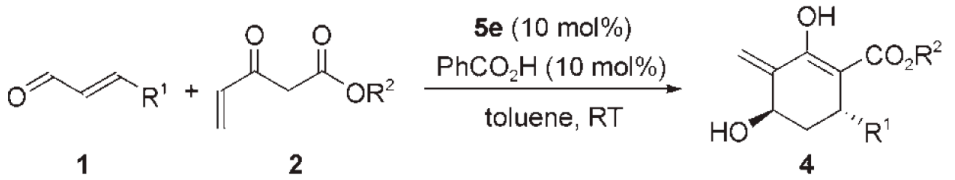


Entry	Cat.	Solvent	Conversion [%]	d.r.[b]	Yield [%][c]	*ee* [%][d]
1	**5a**	toluene	n.r.[e]	–	–	–
2	**5b**	toluene	>98	9:1	52	49
3	**5c**	toluene	>98	12:1	57	2
4	**5d**	toluene	80[f]	16:1	51	92
5	**5e**	toluene	>98	14:1	74	94
6	**5e**	toluene	>98	7:1	55	94[g]
7	**5e**	CH_2Cl_2	>98	9:1	63	94
8	**5e**	Et_2O	>98	3:1	71	92
9	**5e**	CH_3CN	>98	3:1	75	91
10	**5e**	neat	>98	4:1	55	90

[a] All reactions were performed on a 0.2-mmol scale with $PhCO_2H$ (20 mol%) as additive in 0.2 mL of solvent and stopped after 18 h. [b] The diastereoisomeric ratio was determined by ^1H NMR analysis of the crude mixture, which consisted of epimers at the alcohol position. [c] Yield of the diastereoisomeric mixture after flash chromatography. [d] Determined by HPLC on a chiral stationary phase (see the Supporting Information). [e] No reaction. [f] The reaction was stopped after 40 h. [g] 10 mol% of catalyst **5e** and $PhCO_2H$ were used. TBDPS = *tert*-butyldiphenylsilyl, TMS = trimethylsilyl.

Substrate Scope

Table 2: Reaction of α,β-unsaturated aldehydes **1a–i** with β-ketoesters **2**.[a]

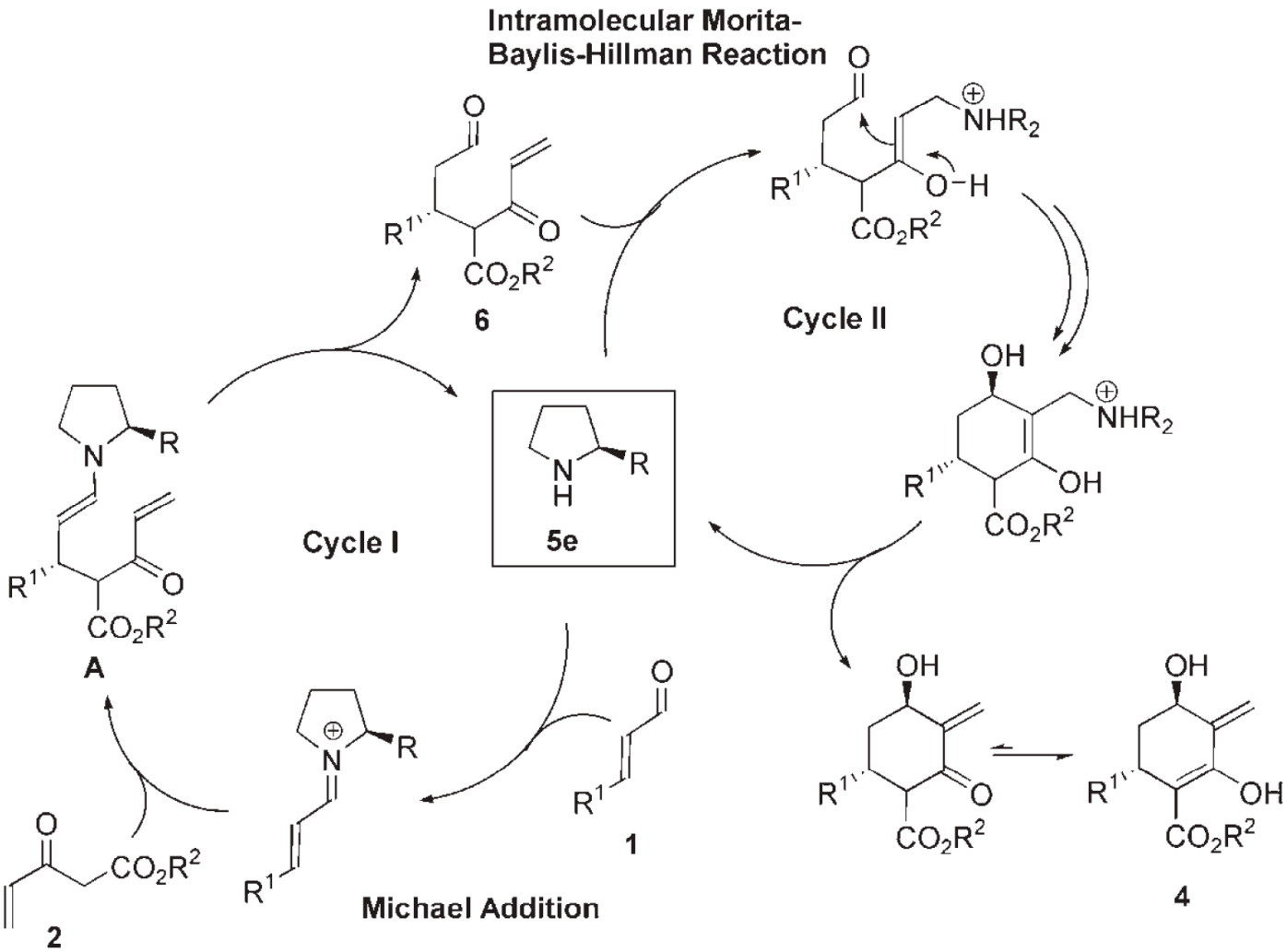


1 **2** **4**

Entry	R^1	R^2	d.r.[b]	Prod.	Yield [%][c]	*ee* [%][d]
1	Ph (**1a**)	Et (**2a**)	7:1	**4a**	55	94
2	Ph (**1a**)	Et (**2a**)	11:1	**4a**	53	−95[e,f]
3	Ph (**1a**)	*t*Bu (**2b**)	5:1	**4b**	68	94
4	Ph(**1a**)	allyl (**2c**)	6:1	**4c**	45	94
5	*p*-ClC_6H_4 (**1b**)	Et (**2a**)	7:1	**4d**	49 (76)[f]	93 (95)[f]
6	*p*-$MeOC_6H_4$ (**1c**)	Et (**2a**)	9:1	**4e**	69	93
7	*p*-$NO_2C_6H_4$ (**1d**)	Et (**2a**)	4:1	**4f**	58	96
8	*p*-$NO_2C_6H_4$ (**1d**)	*t*Bu (**2b**)	4:1	**4g**	51	95
9	2-thienyl (**1e**)	Et (**2a**)	6:1	**4h**	57	95
10	2-furyl (**1f**)	Et (**2a**)	4:1	**4i**	66	92
11	CO_2Et (**1g**)	Et (**2a**)	5:1	**4j**	51	98[f]
12	Et (**1h**)	Et (**2a**)	6:1	**4k**	64	86[f,g]
13	(*Z*)-hex-3-enyl (**1i**)	Et (**2a**)	3:2	**4l**	51	92[f,g]

[a] All reactions were performed on a 0.2-mmol scale with $PhCO_2H$ (10 mol%) as additive in 0.2 mL of toluene. [b] The diastereoisomeric ratio was determined by ^1H NMR spectroscopic analysis of the crude mixture, which consisted of epimers at the alcohol. [c] Yield of the diastereoisomeric mixture after flash chromatography. [d] Determined by HPLC on a chiral stationary phase (see the Supporting Information). [e] The *R* enantiomer of the catalyst **5e** was used. [f] 20 mol% of catalyst **5e** and $PhCO_2H$ were used. [g] The *ee* value was determined after derivatization (see the Supporting Information).

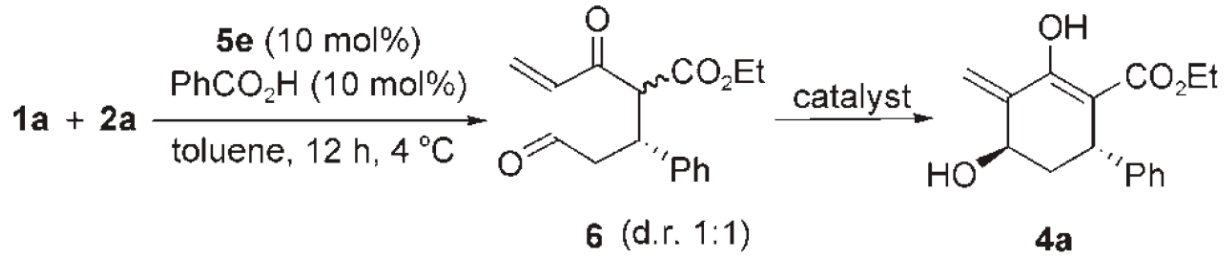
Mechanism



Scheme 2. Proposed mechanism for the Michael/Morita–Baylis–Hillman tandem reaction.

Investigation of Morita-Baylis-Hillman Reaction

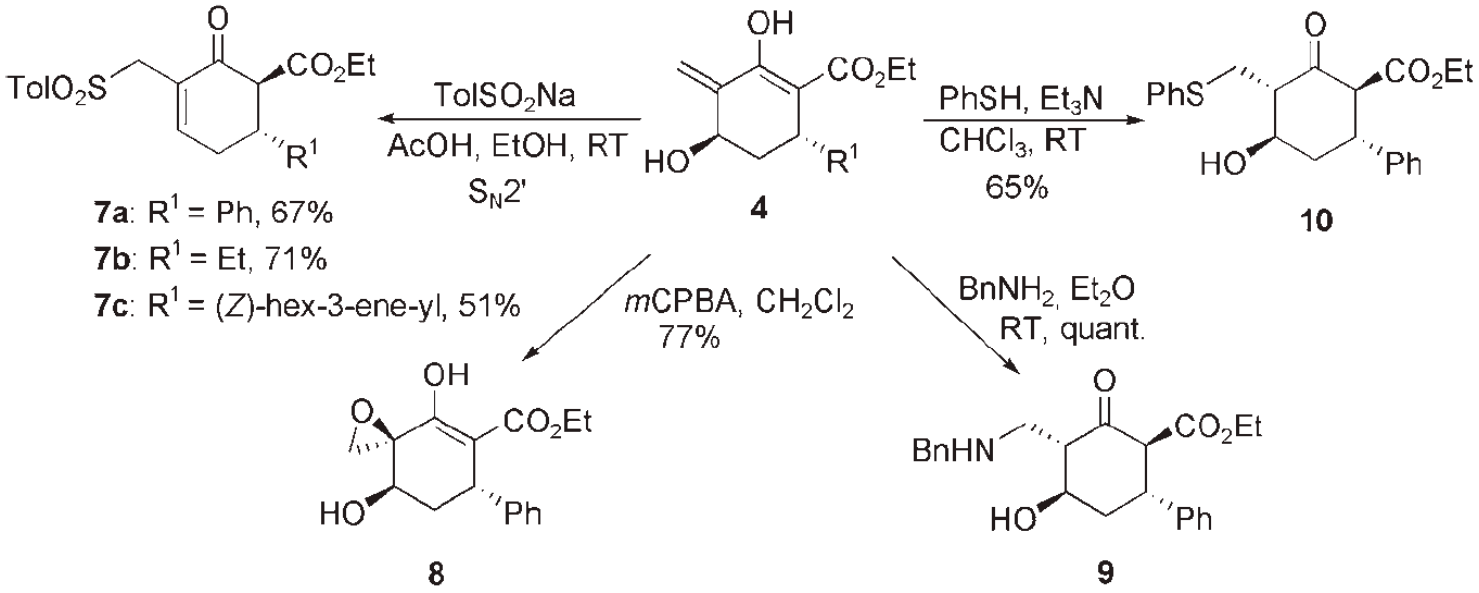
Table 3: Catalyst investigations for the Morita–Baylis–Hillman step.[a]



Entry	Catalyst	mol %	d.r.[b]	*ee* [%][c]
1	–	–	n.r.	–
2	H_2O	100	n.r.	–
3	$PhCO_2H$	20	n.r.	–
4	(*S*)-**5e**	20	5:1	89
5	(*R*)-**5e**	20	5:1	94
6	pyrrolidine	20	6:1	92
7	DABCO	50	11:1	93
8	PPh_3	20	>20:1	94

[a] All reactions were performed in toluene with the diastereoisomeric mixture of intermediate **6** and the corresponding catalyst. [b] Diastereoisomeric ratio determined by ^{1}H NMR spectroscopic analysis of the crude mixture. n.r.: no reaction. [c] Determined by HPLC (see the Supporting Information). DABCO = 1,4-diazabicyclo[2.2.2]octane.

Functionalization of the Products



Scheme 3. Stereoselective synthesis of diverse products. Tol = tolyl, *m*CPBA = *meta*-chloroperoxybenzoic acid, Bn = benzyl.

Conclusion

- A new tandem organocatalytic reaction has been reported.
- This is an unusual sequence involving the use of a secondary amine in a Morita-Baylis-Hillman reaction.
- This reaction generates highly functionalized cyclohexanones that could be used as library building blocks or in natural products total synthesis.