Literature Report

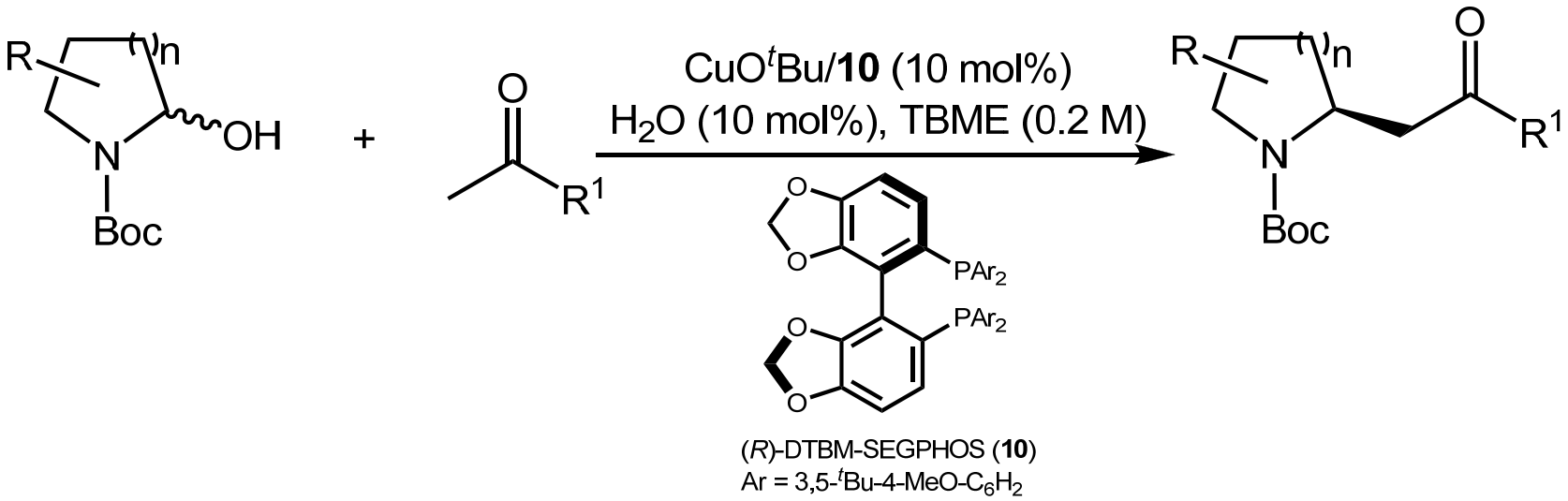
Copper(I)-Catalyzed Enantioselective Incorporation of Ketones to Cyclic Hemiaminals for the Synthesis of Versatile Alkaloid Precursors

Reporter: Mu-Wang Chen
Checker: Zhi-Shi Ye

University of Tokyo

Kanai, M. *et al.*

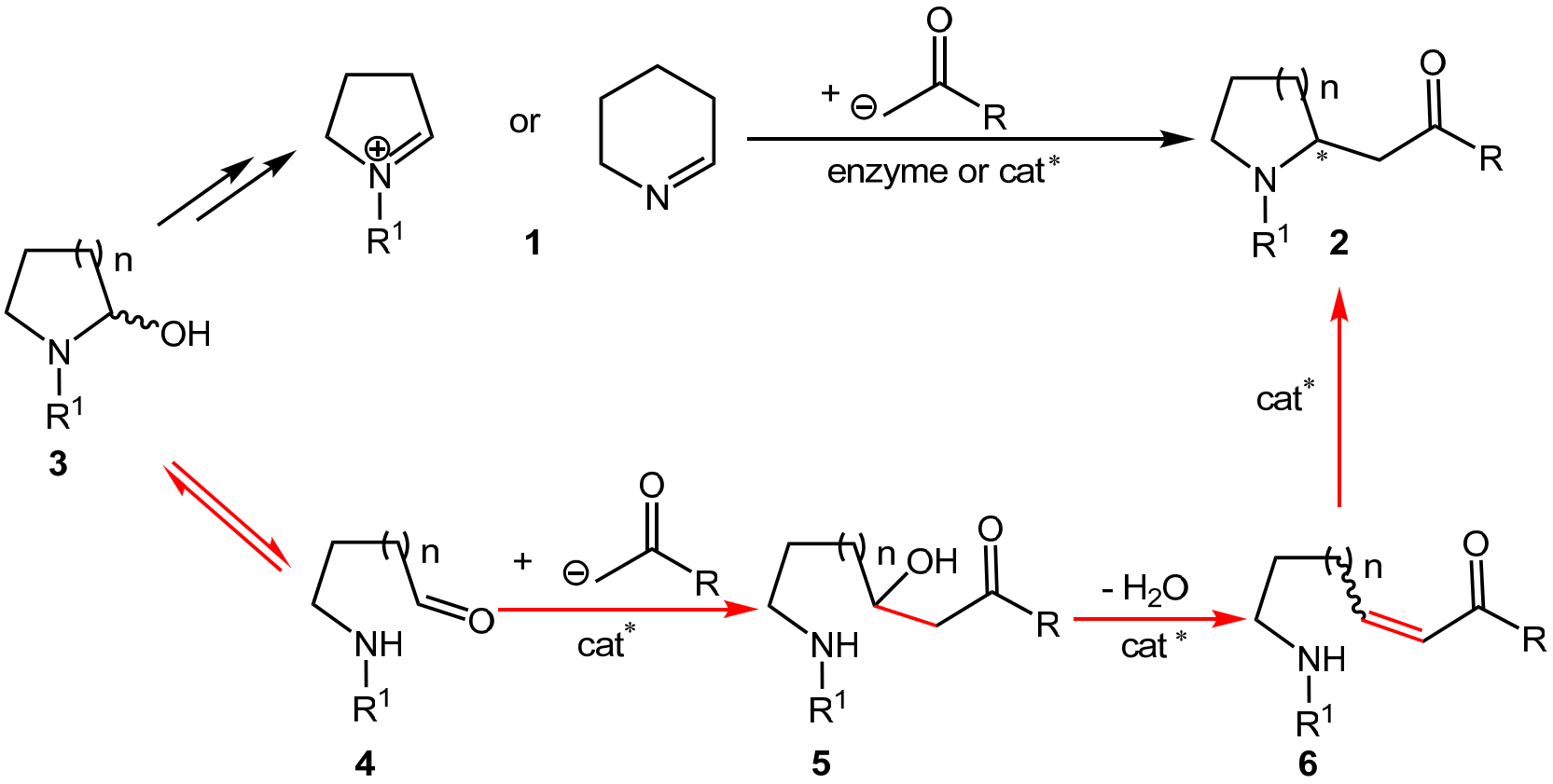
J. Am. Chem. Soc. **2012,** *134,* 17019-17022.



(*R*)-DTBM-SEGPHOS (**10**)
Ar = 3,5-^{t}Bu-4-MeO-C_6H_2

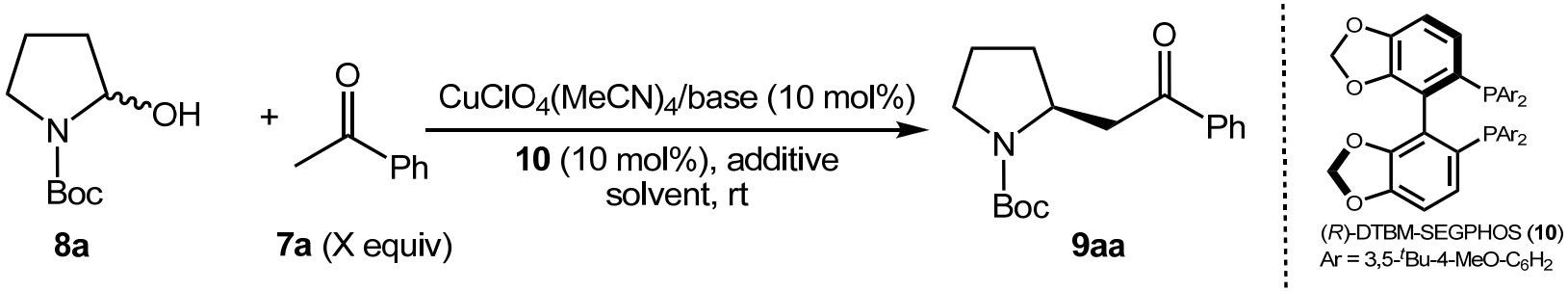
Two Catalytic Enantioselective Pathways for the Synthesis of Versatile Intermediate 2 in Alkaloid Synthesis

Biosynthetic pathway and previous works



This work: promoted in one-pot by an asymmetric catalyst

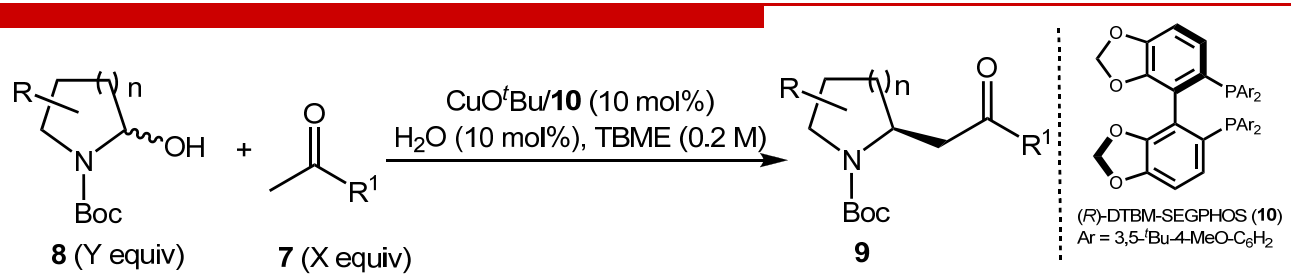
Optimization Study of the Catalytic Enantioselective Introduction of 7a to 8a

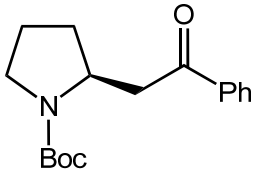


entry	X	solvent	base	time (h)	yield (%)[a]	ee (%)[b]
1	3	THF	LiO^{t}Bu	7	88	82
2[c]	3	THF	LiO^{t}Bu	13	40	91
3	3	TBME	LiO^{t}Bu	13	97	88
4[d]	3	TBME	LiO^{t}Bu	13	93	92
5[d]	2.5	TBME	KO^{t}Bu	13	99	94
6[d]	1.5	TBME	KO^{t}Bu	24	99	95
7[e]	1.5	TBME	KO^{t}Bu	72	60	94

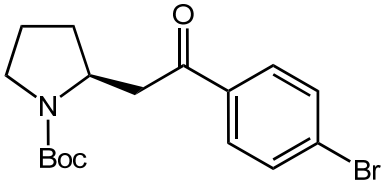
[a] Determined by ^{1}H NMR using an internal standard. [b] Determind by HPLC Using a Chiralpak AY-H column. [c] 4 A MS (250 g/mol) was added. [d] 10 mol% H_2O was added. [e] Catalyst loading and H_2O amount were 2.5 mol%, respectively.

Substrate Scope

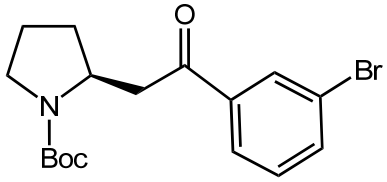




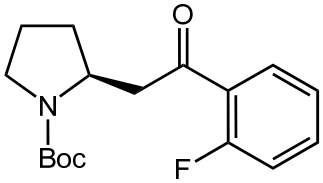
9aa X:Y = 1.5:1
95% ee (98%)



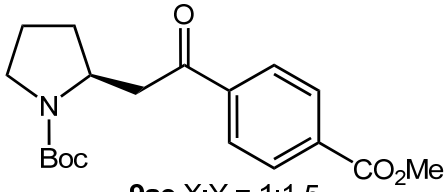
9ab X:Y = 1.5:1
95% ee (90%)



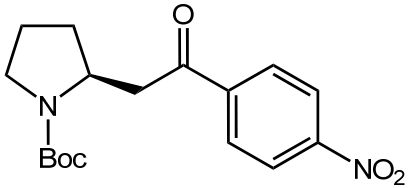
9ac X:Y = 1.5:1
91% ee (82%)



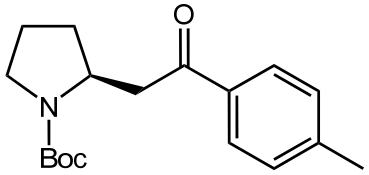
9ad X:Y = 1.5:1
94% ee (65%)



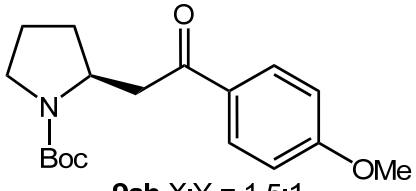
9ae X:Y = 1:1.5
97% ee (80%)



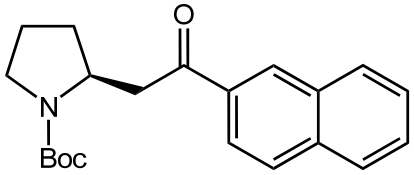
9af X:Y = 1:1.5
96% ee (98%)



9ag X:Y = 1.5:1
92% ee (85%)

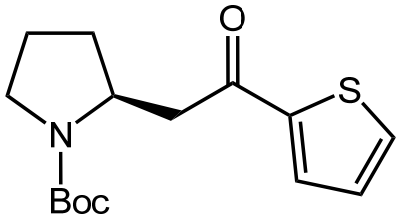


9ah X:Y = 1.5:1
90% ee (67%)

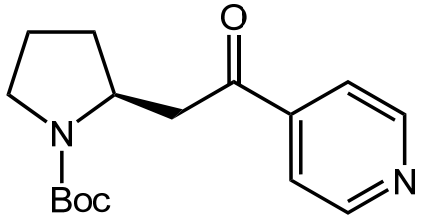


9ai X:Y = 1.5:1
93% ee (89%)

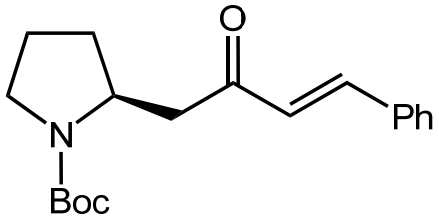
Substrate Scope



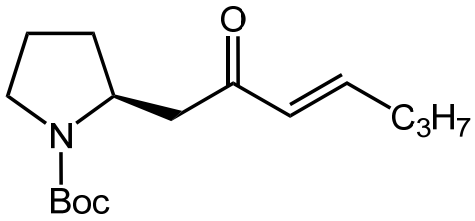
9aj X:Y = 1.5:1
92% ee (96%)



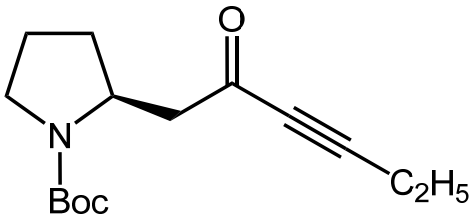
9ak X:Y = 1:1.5
97% ee (95%)



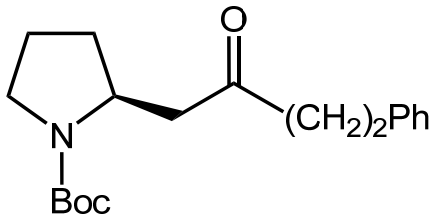
9al X:Y = 1.5:1
96% ee (99%)



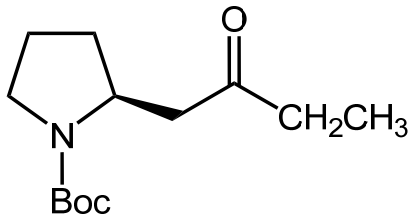
9am X:Y = 1.5:1
97% ee (73%)



9an X:Y = 1:1.5
97% ee (55%)

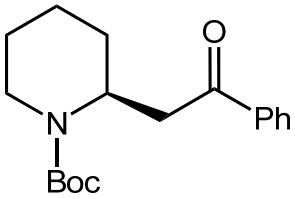


9ao X:Y = 1.5:1
84% ee (81%)

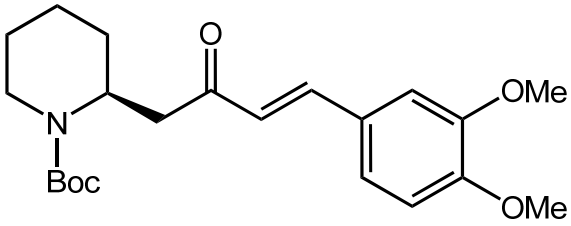


9ap X:Y = 3:1
89% ee (68%)

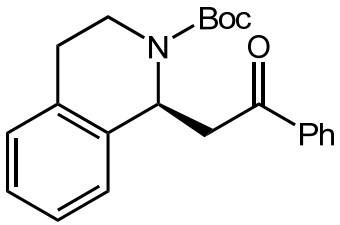
Substrate Scope



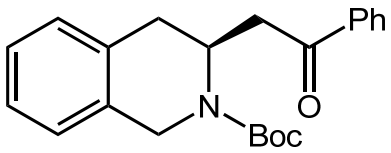
9ba X:Y = 1:1.5
98% ee (99%)



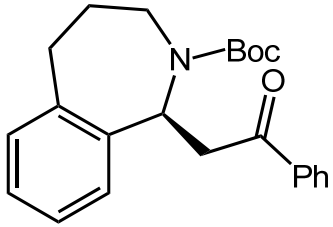
9bb X:Y = 1:1.5
97% ee (75%)



9ca X:Y = 1:3
94% ee (99%)

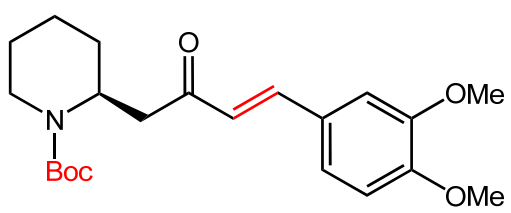


9da X:Y = 1:1.5
94% ee (95%)



9ea X:Y = 1:3
96% ee (53%)

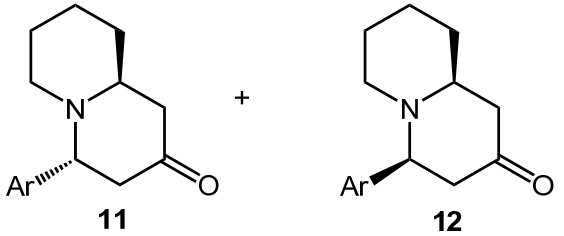
Representative Valuable Conversions of the Products



9bb 97% ee

1) TFA, CH_2Cl_2
2) base treatment

[Ar = 3,4-$(CH_3O)_2C_6H_3$]

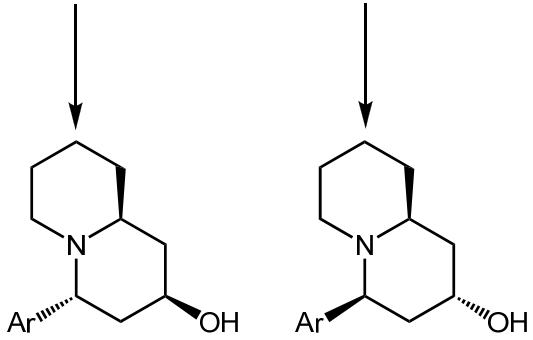


11 **12**

base treatment

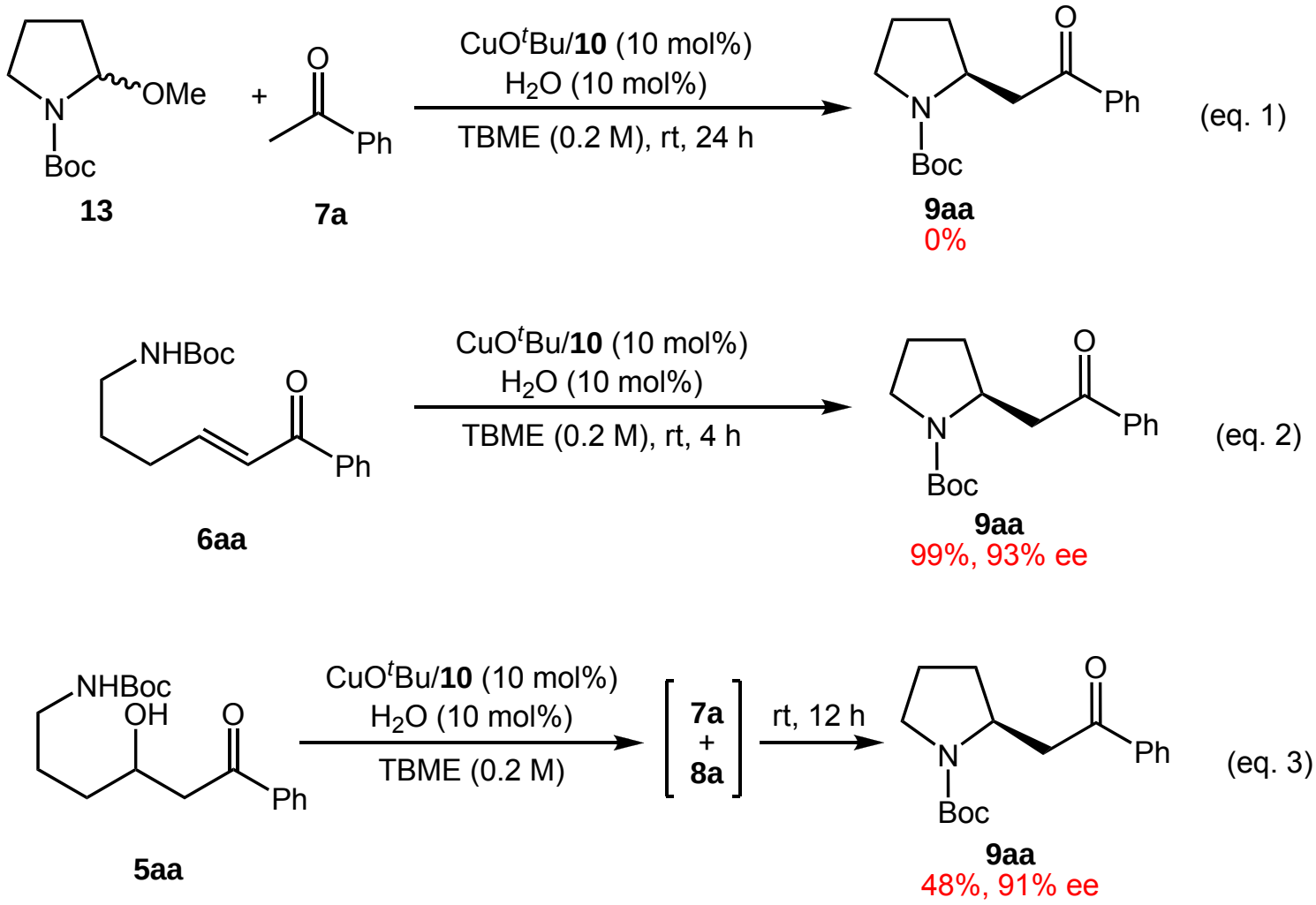
NH_4OH, MeOH, rt, 30 min: 73%, **11**:**12** = 6.7 (97% ee) : 1

NaOH, MeOH, rt, 48 h: 70%, **11**:**12** = 1 : 7.0 (92% ee)

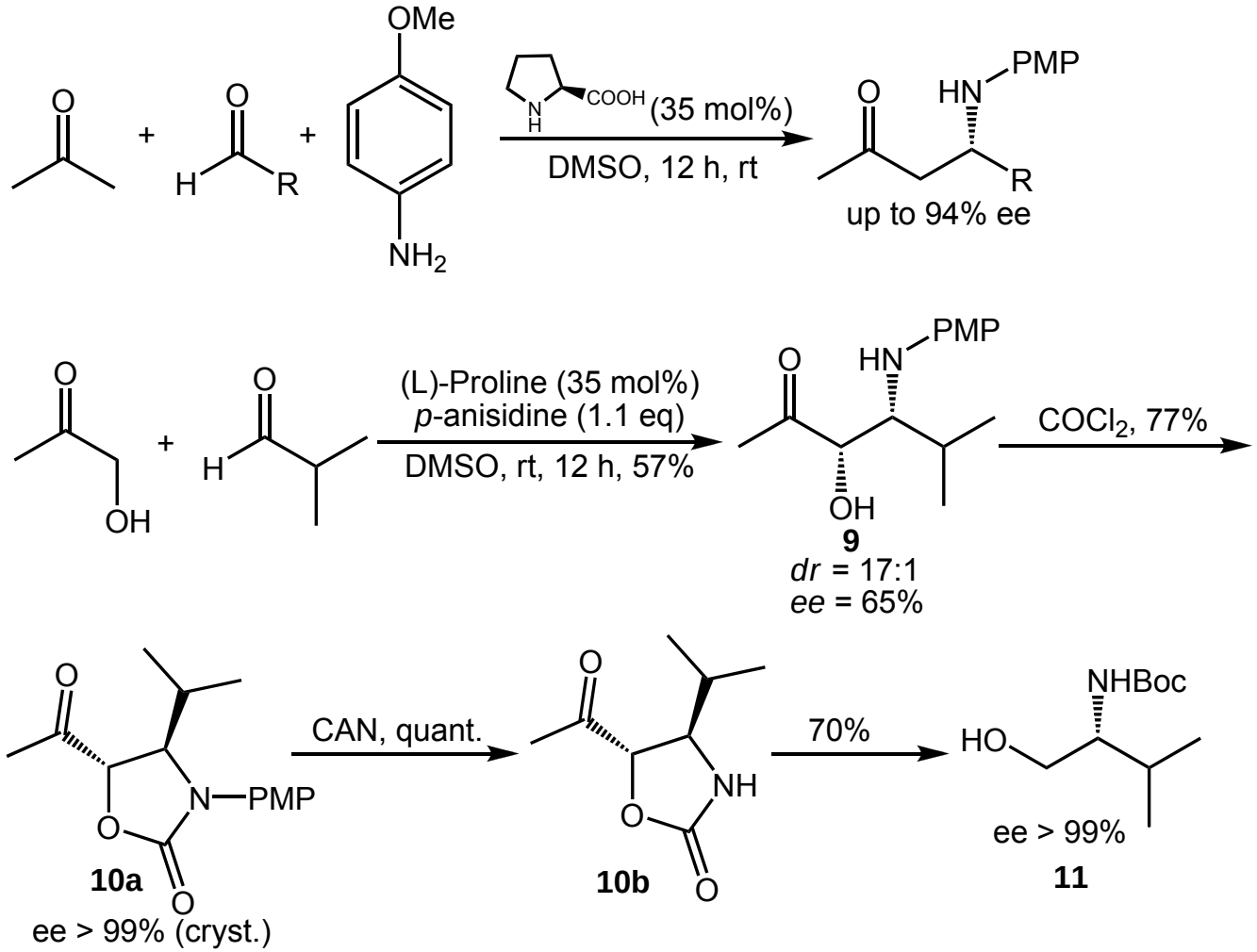


(+) lasunine **I** (-) lasubine **II**

Mechanistic Support

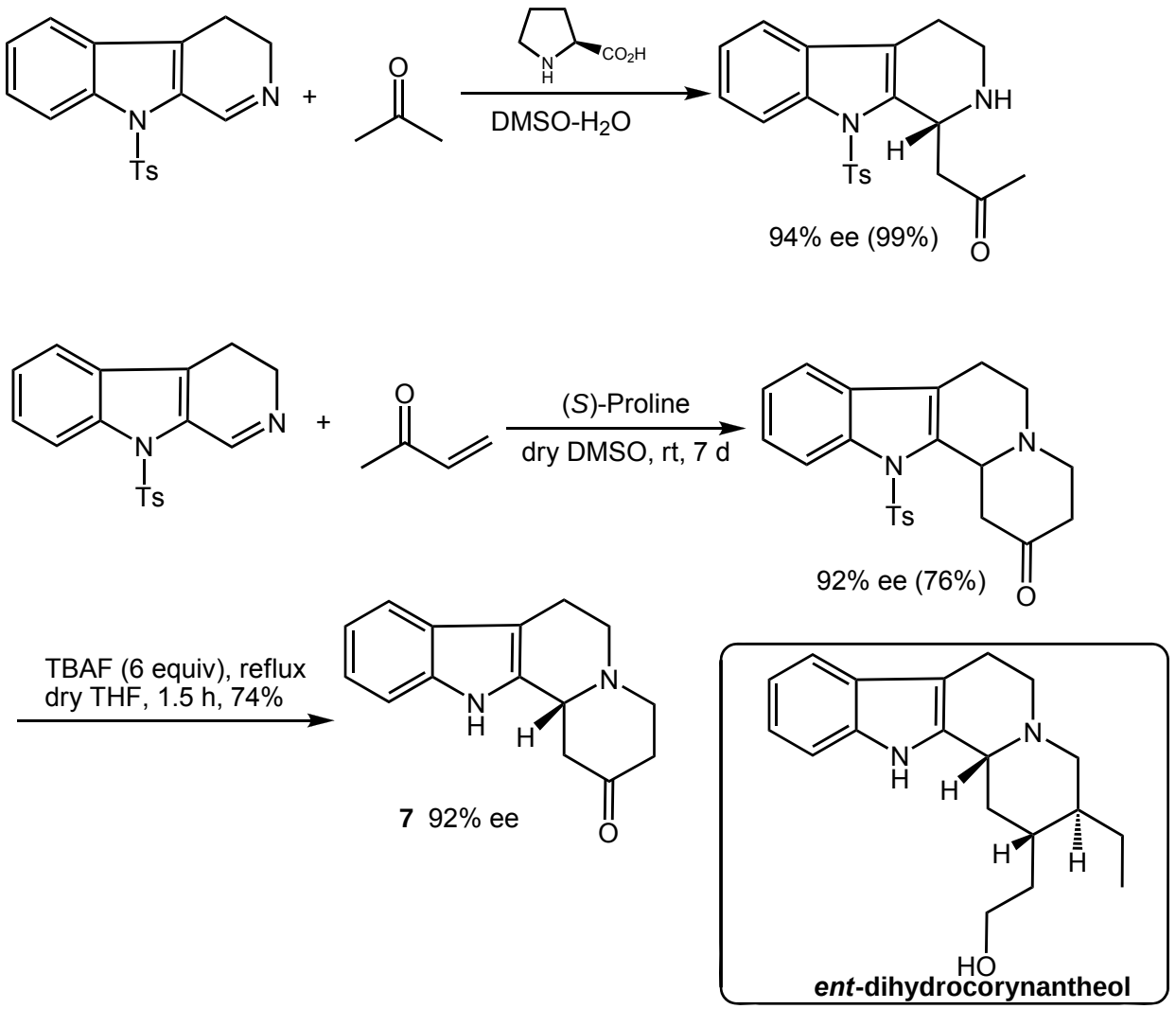


The Direct Catalytic Asymmetric Three-Component Mannich Reaction



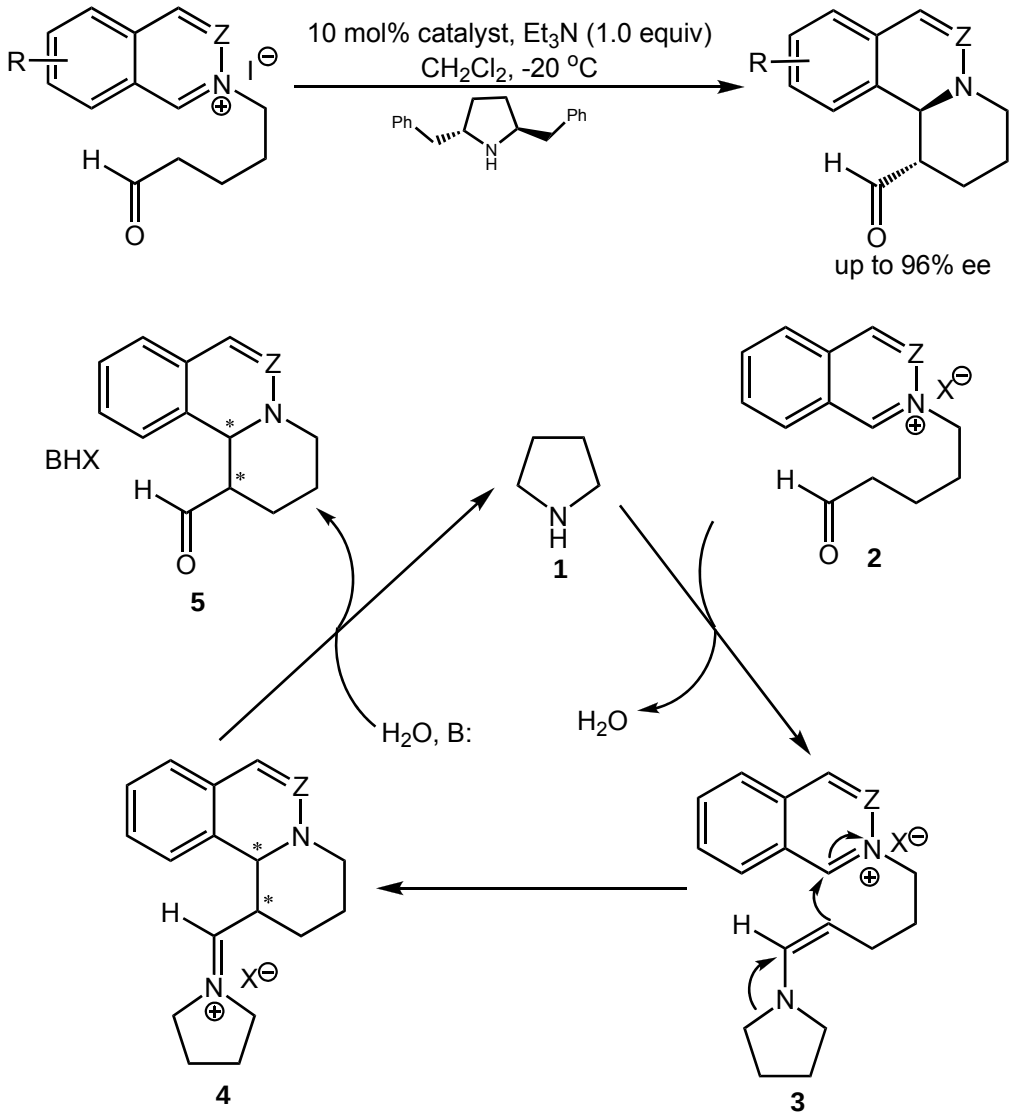
List, B. *et al. J. Am. Chem. Soc.* **2000**, *122*, 9336-9337.

Proline-Catalyzed Asymmetric Addition Reaction of 9-Tosyl-3,4-dihydro-*β*-Carboline with Ketones



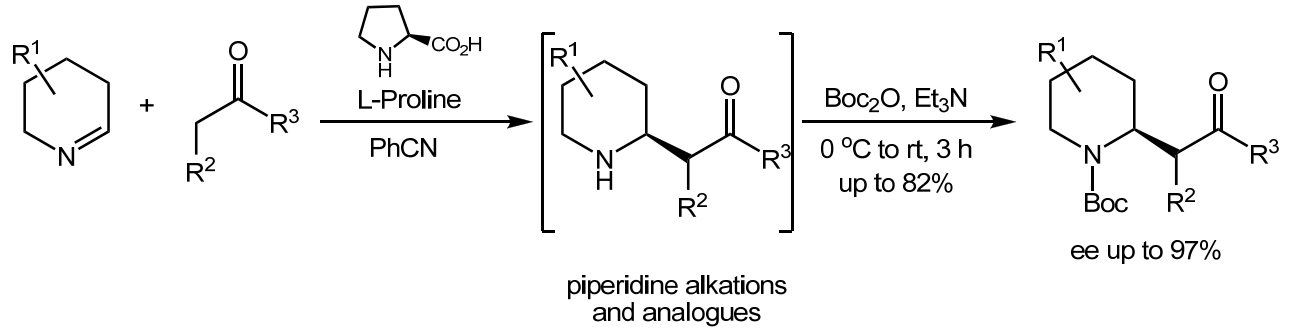
Itoh, T.; Ohsawa, A. *et al*. *Org. Lett.* **2003**, *5*, 4301-4304 and **2006**, *8*, 1533-1535.

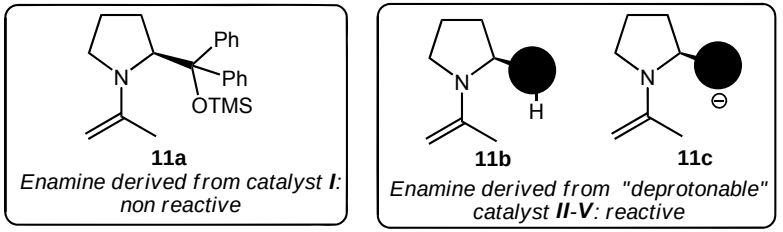
Organocatalytic Diastereo- and Enantioselective Annulation Reactions-Construction of Optically Active 1,2-Dihydroisoquinoline and1,2-Dihydrophthalazine Derivatives

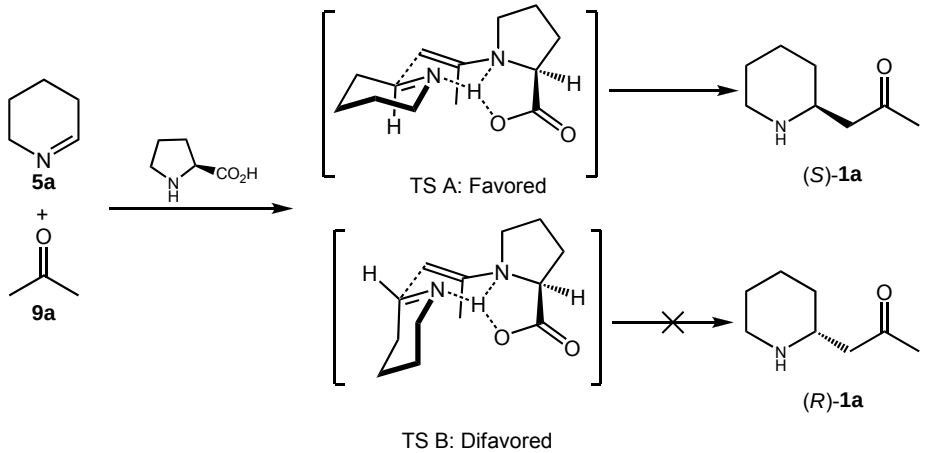


Jørgensen, K. A. *et al. Angew. Chem. Int. Ed.* **2005**, *50*, 6058-6063.

Biomimetic Organocatalytic Asymmetric Synthesis of 2-Substituted Piperidine-Type Alkaloids and Their Analogues

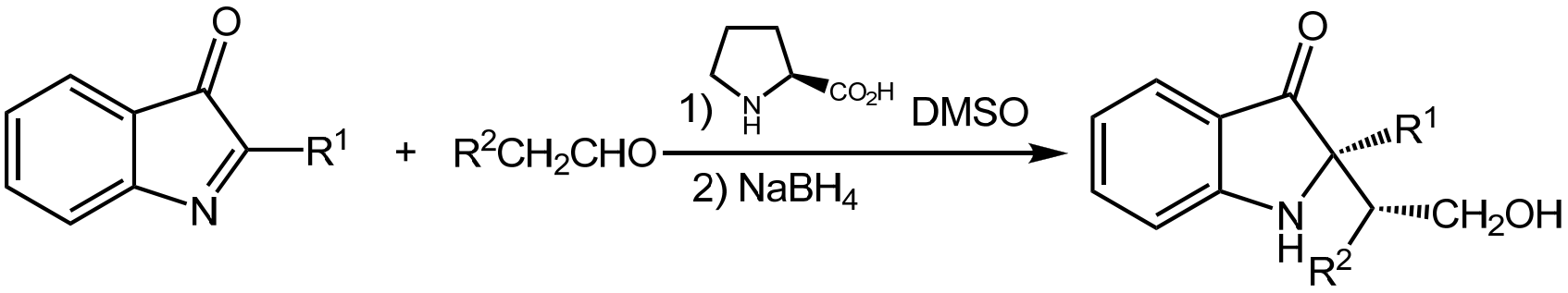






Bella, M. *et al. Org. Lett.* **2011**, *13*, 4546-4549.

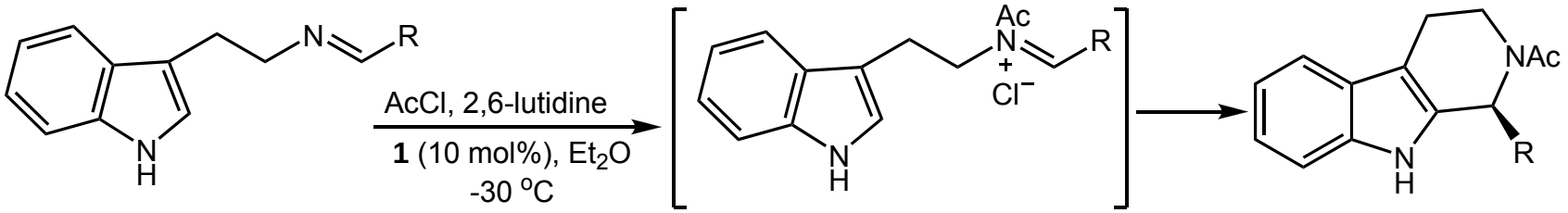
Proline-Catalyzed Enantioselective Synthesis of Aza-Quaternary Carbon Derivatives

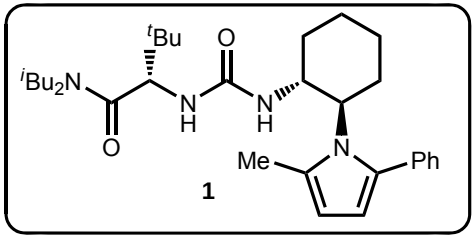


Xie, Z. *et al. Synlett.* **2011**, 1727-1730.

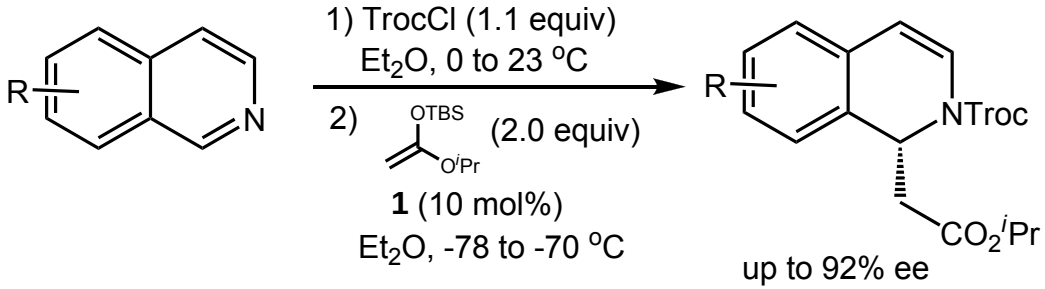
Enantioselective Thiourea-Catalyzed Acyl-Mannich Reactions of Isoquinolines

Enantioselective acyl-Pictet–Spengler reaction catalyzed by **1**





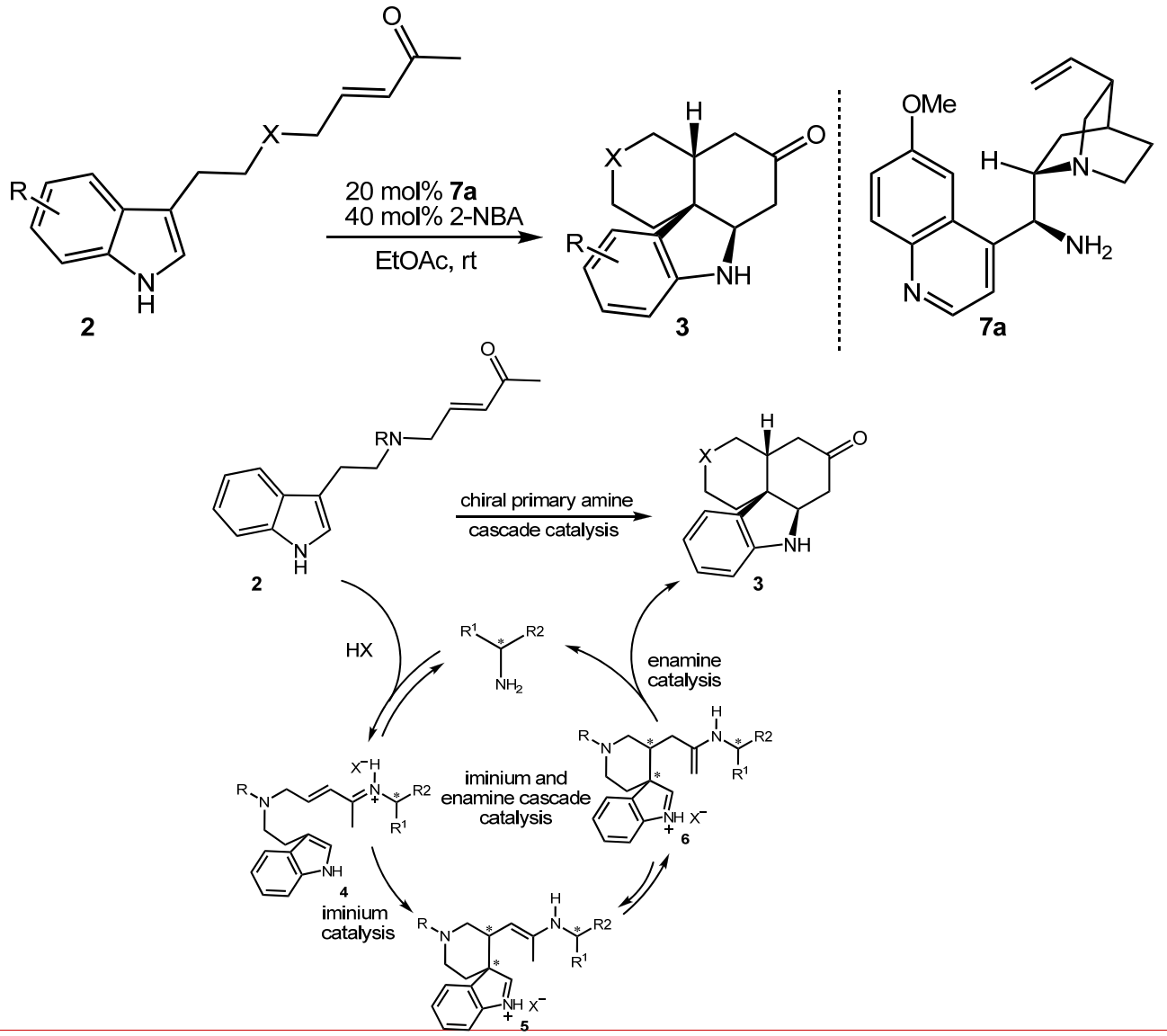
Acyl-Mannich reaction ofsubstituted isoquinolines



up to 92% ee

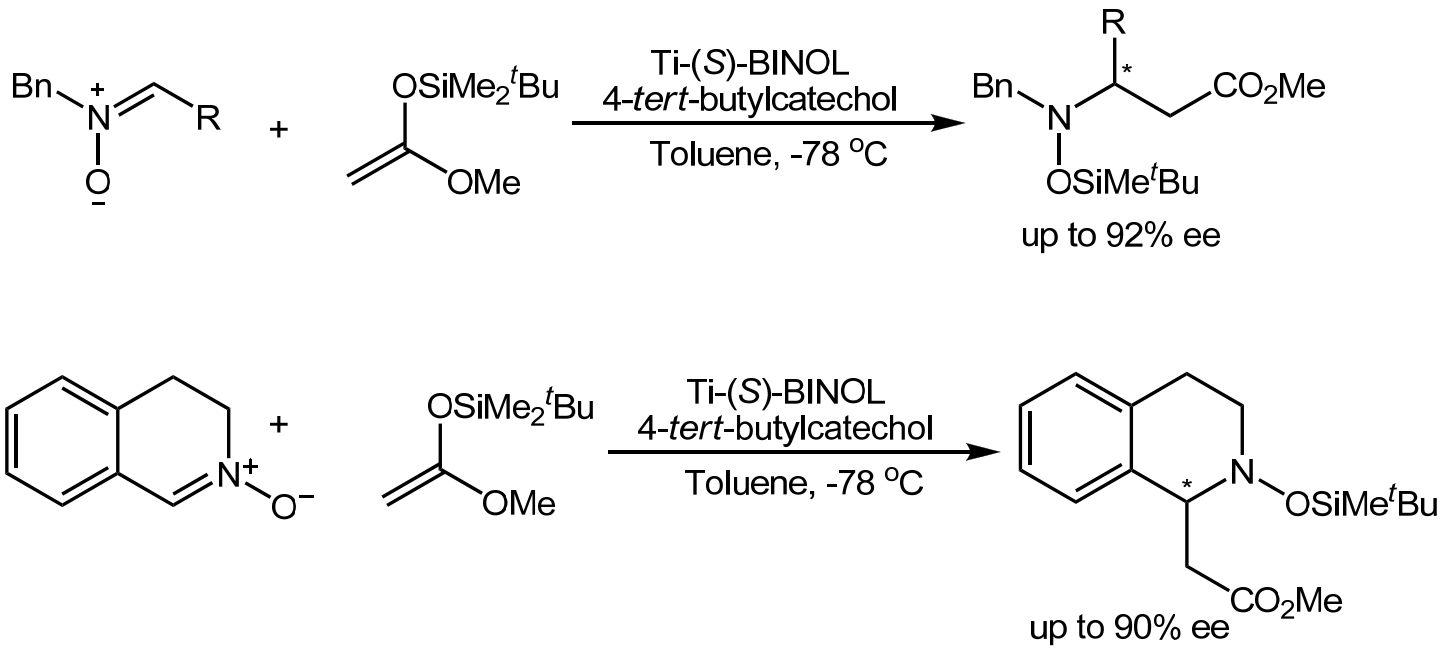
Jacobsen, E. N. *et al. Angew. Chem. Int. Ed.* **2005**, *44*, 6700-6704.

Enantioselective Michael/Mannich Polycyclization Cascade of Indolyl Enones Catalyzed by Quinine-Derived Primary Amines



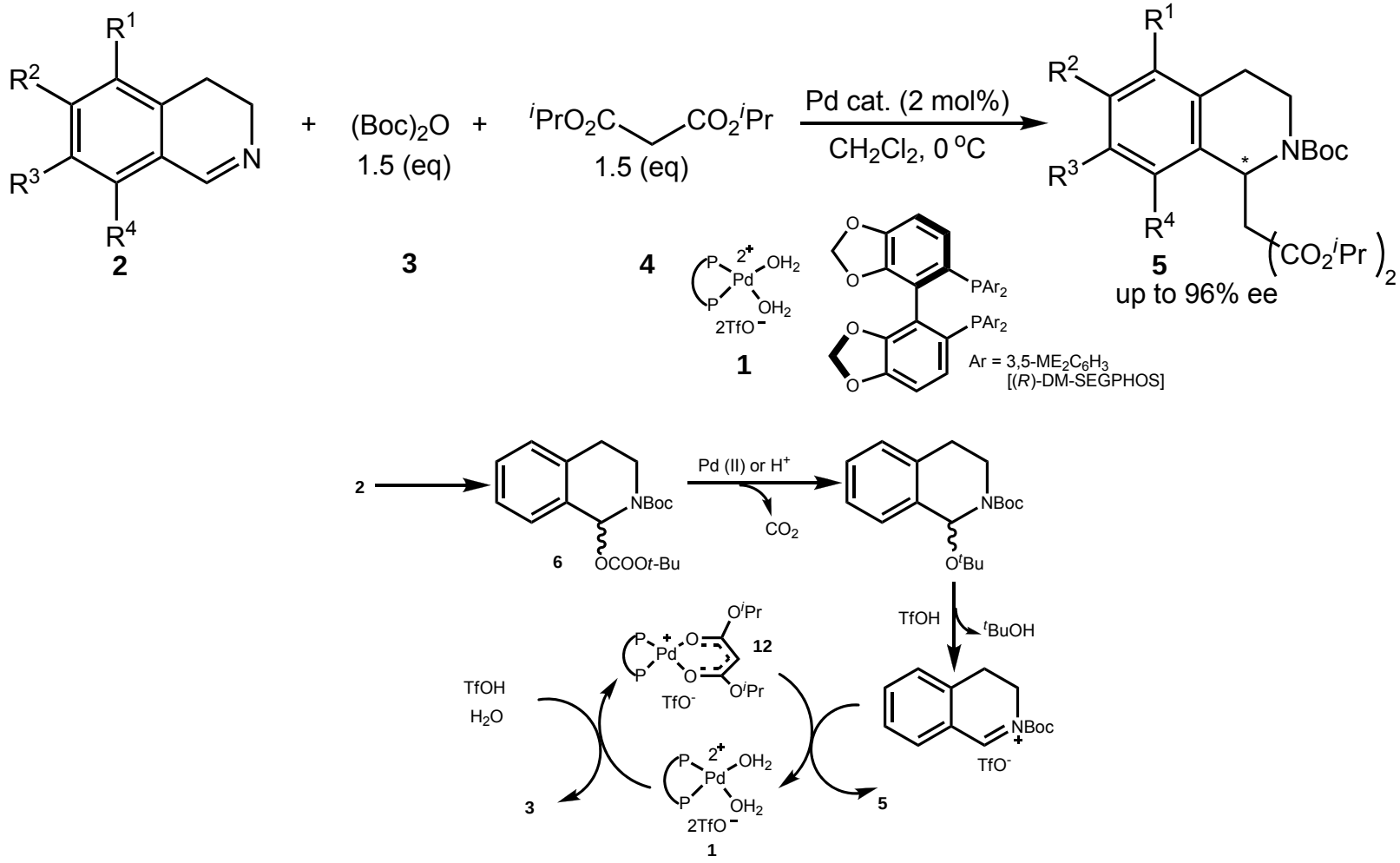
You, S.-L. *et al. Angew. Chem. Int. Ed.* **2011**, *50*, 8665-8669.

Enantioselective addition of Ketene Silyl Acetal Catalyzed by Chiral Titanium Complexes. Synthesis of Optically Active *β*-Amino Acids



Murahashi, S.-I. *et al*. *J. Am. Chem. Soc*. **2002**, *124*, 2888-2889.

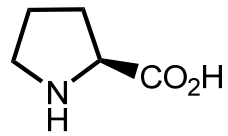
Pd(II)-Catalyzed Asymmetric Addition of Malonates to Dihydroisoquinolines

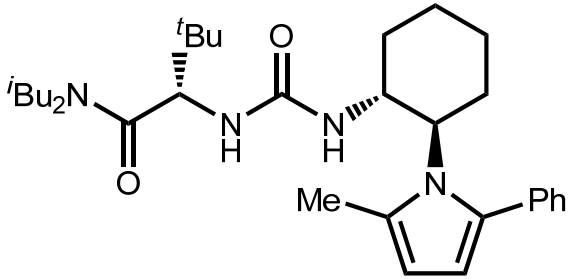


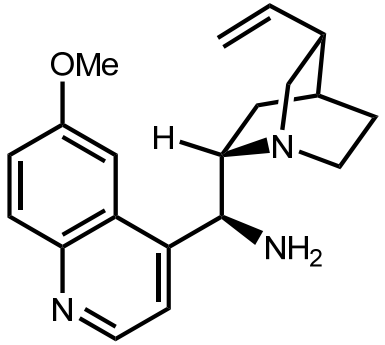
Sodeoka, M. *et al*. *J. Am. Chem. Soc*. **2006**, *128*, 14010-14011.

Summary

1. Organocatalytic Mannich Reaction







2. Metal-Catalytic Mannich Reaction

   Ti, Cu, Pd

Chiral nitrogen-containing heterocycles (*N*-heterocycles) are ubiquitous structural motifs in natural products, synthetic pharmaceuticals, and chiral catalysts. Specifically, functionalized pyrrolidines and piperidines are fundamental components of naturally occurring pyrrolidine and piperidine alkaloids, which are further assembled to construct more complex structures such as indolizidine and quinolizidine alkaloids. In nature, chiral pyrrolidine and piperidine alkaloids are synthesized through enzyme-catalyzed Mannich-type reactions between enolates derived from acetyl-CoA or acetoacetyl-CoA and cyclic imine/iminium intermediates **1** as a key enantioselective carbon−carbon bond-forming step. Subsequent structural modifications of **2** (e.g.,decarboxylation and ring formation) afford various alkaloid structures. Thus, **2** is a general chiral intermediate for the synthesis of various alkaloids.

In conclusion, we have developed a catalytic enantioselective method for the introduction of ketones to hemiaminals. This is the first catalytic enantioselective method for introducing various ketones to *N*-heterocycles with differing ring sizes (five-, six-, and seven-membered rings). The process comprises three distinct steps in one pot, all of which are promoted by the chiral copper(I)-conjugated Brønsted base catalyst. This method offers general and straightforward access to versatile enantiomerically enriched precursors for alkaloid and drug syntheses, including pyrrolidines, piperidines, indolizidines, quinolizidines, tetrahydroisoquinolines, and tetrahydrobenzazepines, starting from stable and easily available substrates.