Literature Report

An Isothiourea-Catalyzed Asymmetric [2,3]-Rearrangement of Allylic Ammonium Ylides

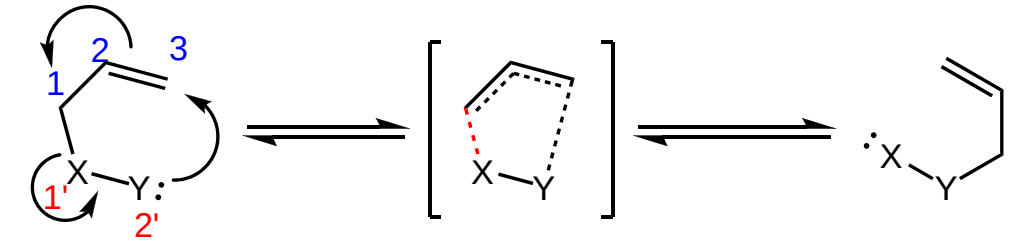
Reporter: Mu-Wang Chen
Checker: Zhang-Pei Chen
Date: 2014-04-22

Smith, A. D. *et al.*
J. Am. Chem. Soc. **2014,** *136,* 4476-4479.

University
of St Andrews

Contents

[2,3]-Sigmatropic Rearrangements:

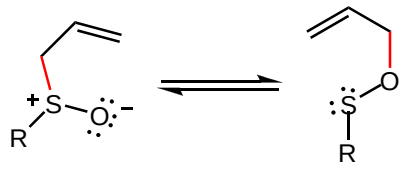


X and Y can be O, N, C, S, Se, P and others.

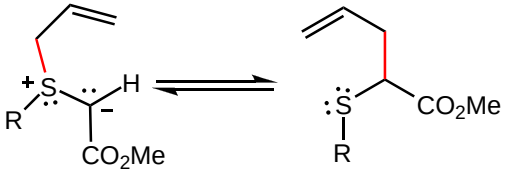
5-membered cyclic transition state

[2,3]-Sigmatropic Rearrangements

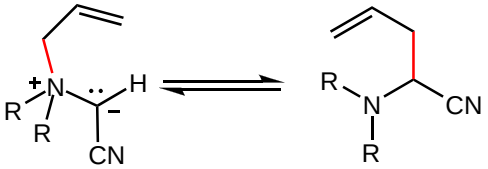
Ylidic (oxide, imide)



Sulfoxide-sulfenate

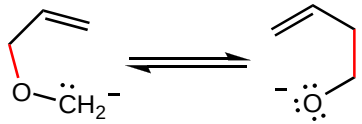


Sulfonium ylide

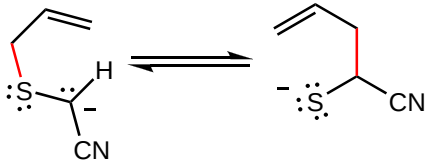


Ammonium ylide

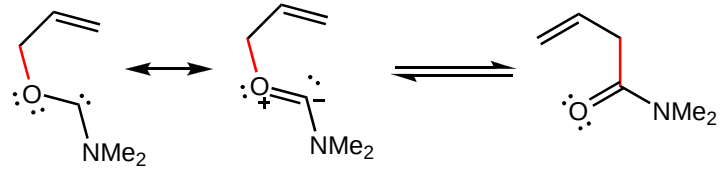
Anionic:



[2,3]-Wittig

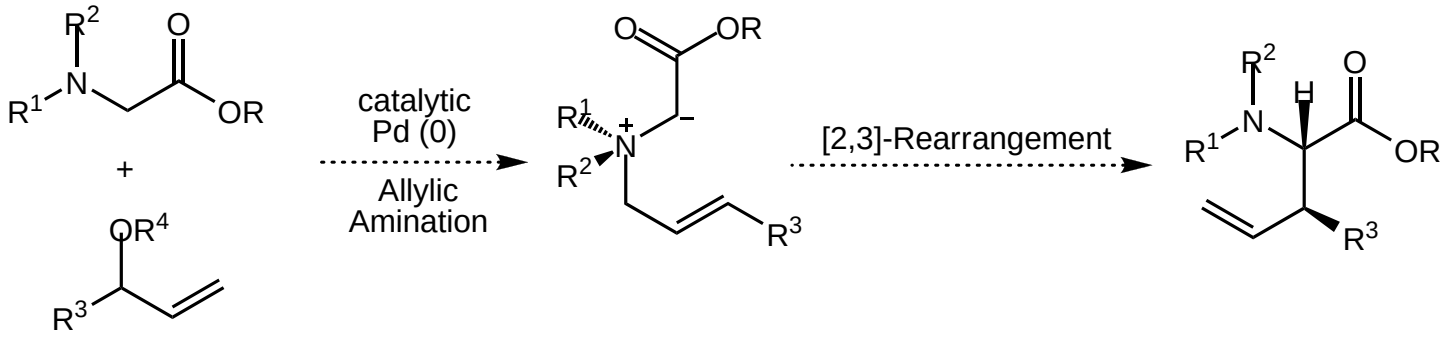


Carbenic:



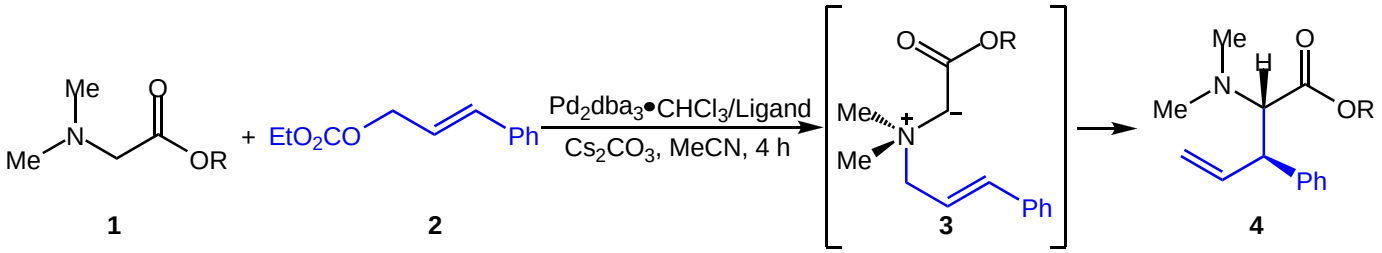
Stabilized carbene

Tandem Catalytic Allylic Amination and [2,3]-Stevens Rearrangement of Tertiary Amines



Tambar, U. K. *et al. J. Am. Chem. Soc.* **2011,** *133,* 12956-12959**.**

Optimization of Reaction Conditions



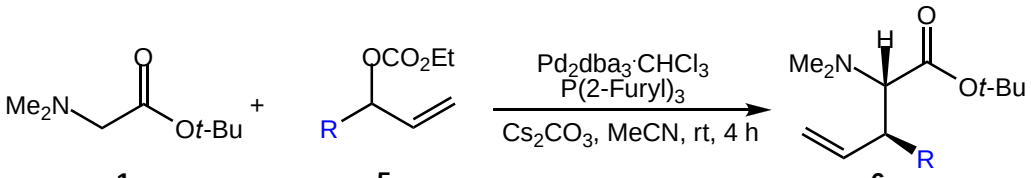
1 2 3 4

Entry	OR	Ligand	Yield [%][b]	Dr[c]
1	OEt	/	< 5	/
2	OEt	dppp	< 5	/
3	OEt	BINAP	< 5	/
4	OEt	PCy_3	< 5	/
5	OEt	$P(t\text{-Bu})_3$	< 5	/
6	OEt	PPh_3	90	2:1
7	O*t*-Bu	PPh_3	39	9:1
8	O*t*-Bu	$P(p\text{-Tol})_3$	< 5	/
9	O*t*-Bu	$P(p\text{-OMe-Ph})_3$	< 5	/

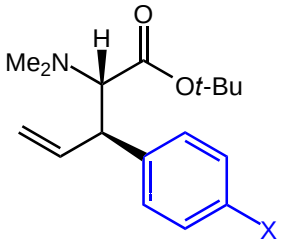
Entry	OR	Ligand	Yield [%][b]	Dr[c]
10	O*t*-Bu	P(*p*-Cl-Ph)$_3$	65	9:1
11	O*t*-Bu	P(2-Furyl)$_3$	95	9:1
12 [d]	O*t*-Bu	P(2-Furyl)$_3$	38	9:1

[a] Reaction conditions: 1.5 equiv. of aminoester **1**, 1 equiv of allylcarbonate **2**, 1 mol % Pd_2dba_3 . $CHCl_3$, 4 mol % ligand, 3 equiv of Cs_2CO_3, 0.2 M in MeCN. [b] GC yields. [c] Diastereomeric ratios as determined by GC. [d] No Cs_2CO_3 was used.

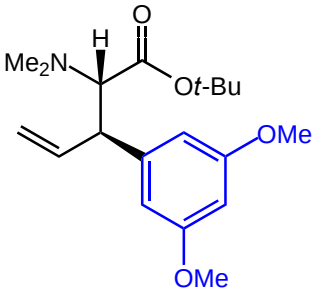
Substrate Scope of Allylcarbonates



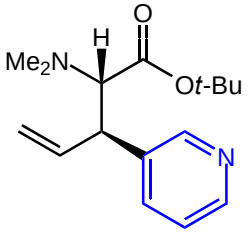
1 **5** **6**



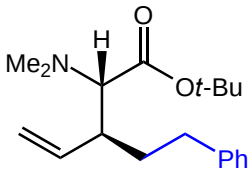
X = H, 87% (yield), 9:1 (dr)
X = Br, 89% (yield), 7:1 (dr)
X = Cl, 87% (yield), 7:1 (dr)
X = F, 87% (yield), 7:1 (dr)
X = OMe, 84% (yield), 9:1 (dr)



82% (yield), 12:1 (dr)

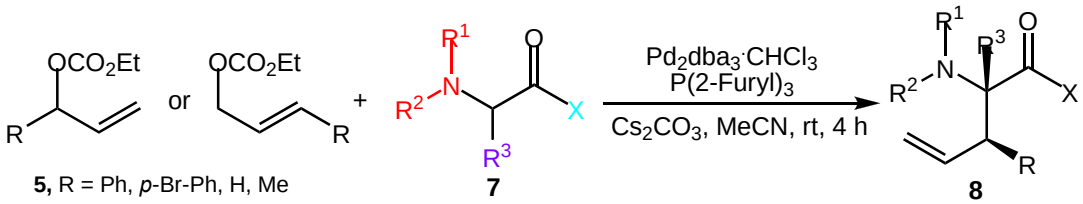


76% (yield), 5:1 (dr)



83% (yield), 9:1 (dr)

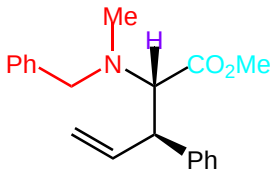
Substrate Scope of Tertiary Amine Nucleophiles



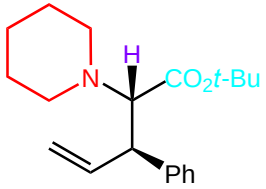
5, R = Ph, *p*-Br-Ph, H, Me

7

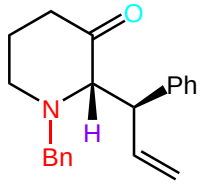
8



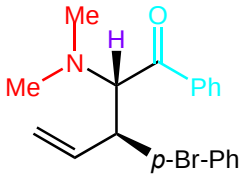
70% (yield), 3:1 (dr)



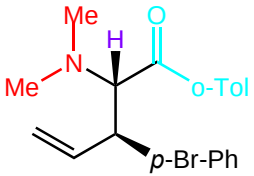
76% (yield), 6:1 (dr)



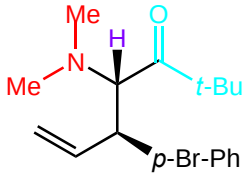
80% (yield), 4:1 (dr)



93% (yield), 2:1 (dr)

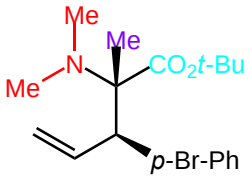


93% (yield), 4:1 (dr)

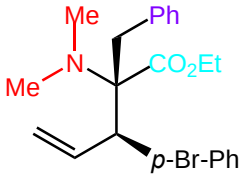


80% (yield), 7:1 (dr)

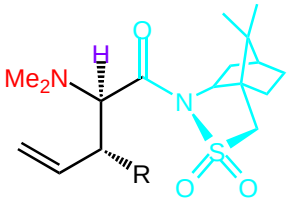
Substrate Scope of Tertiary Amine Nucleophiles



88% (yield), 6:1 (dr)

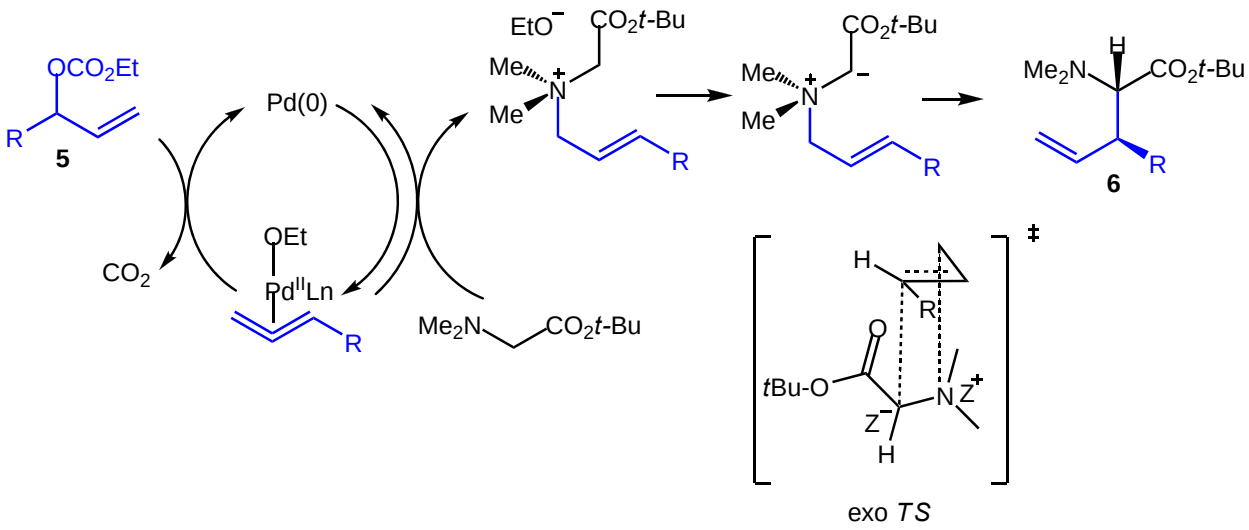


90% (yield), 7:3 (dr)

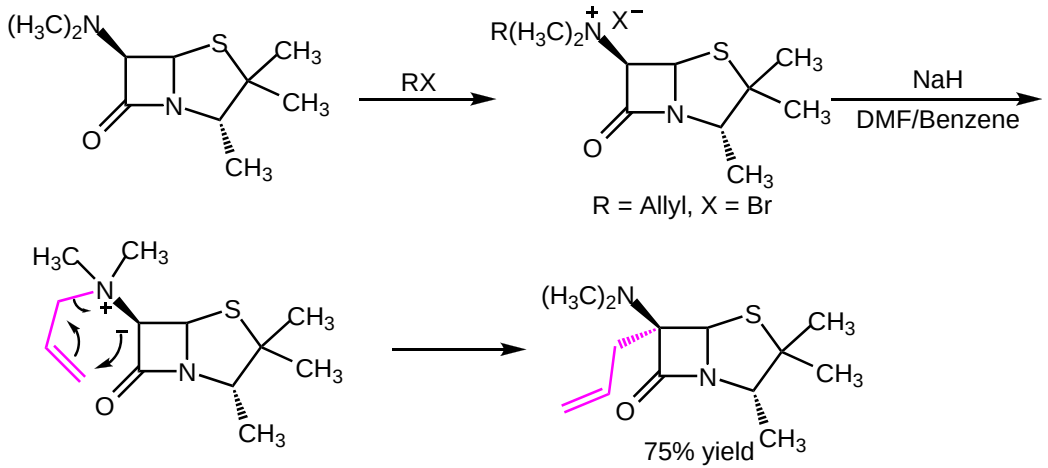


R = H, 89% (yield), 20:1 (dr)
R = Me, 97% (yield), 20:2:1:0 (dr),
R = Ph, 97% (yield), 22:2:1:0 (dr)

Proposed Mechanism

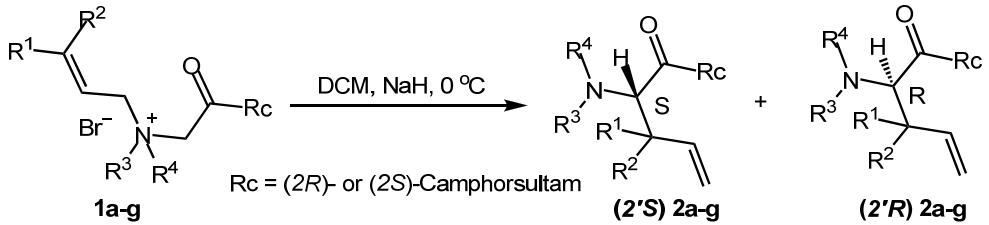


Stereospecific Alkylation of a Penicillin at C-6 Using a Nitrogen Ylide. Methyl 6-α-Allyl-6-β-*N*,*N*-dimethylaminopenicill



Kaiser, G. V. *et al. J. Am. Chem. Soc.* **1971,** *93,* 2342-2344.

Asymmetric [2,3]-Rearrangement of Glycine-Derived Allyl Ammonium Ylids

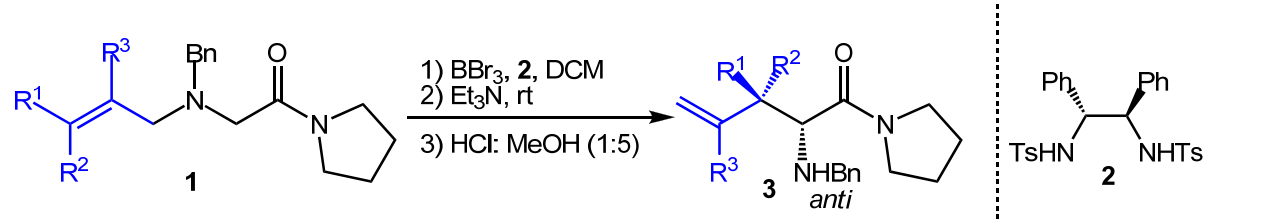


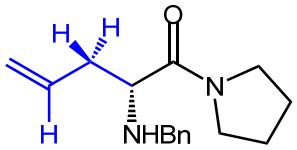
Entry	Salt	R^1	R^2	R^3	R^4	Yield [%][a]	anti:syn	2'S:2'R
1	**1a**[b]	H	H	Me	Me	99		2:98[a]
2	**1b**[c,d]	H	H	Me	allyl	99		97:3[e]
3	**1c**[c,d]	H	H	allyl	allyl	86		97:3[e]
4	**1d**[d]	H	H	Bn	allyl	80		>99:1[e]
5	**1e**[d]	Me	H	Me	Me	86	>99:1	96:4[a]
6	**1f**[d]	Me	Me	Me	Me	70		96:4[a]
7	**1g**[d]	MeO_2C	H	Me	Me	64[f]	>99:1	>99:1 [a]

[a] Absolute stereochemistry was assigned using X-ray crystallography. [b] Rc = (2*R*)-Camphorsultam. [c] Iodide salt used. [d] Rc = (*2S*)-Camphorsultam. [e] Stereochemistry assigned by analogy and/or chemical correlation. [f] Trace amount of [1,2]-product also observed.

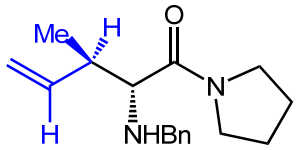
Sweeney, J. B. *et al. J. Am. Chem. Soc.* **2005,** *127,* 1066-1067.

Asymmetric [2,3]-Sigmatropic Rearrangement of Allylic Ammonium Ylides

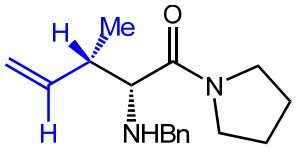




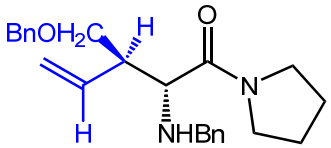
87% (yield), 97% (ee)



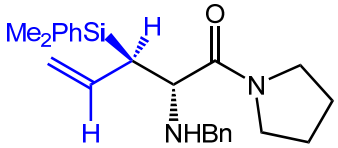
82% (yield), *anti* : *syn* = 79:21
96% (*2R,3R*): 75% (*2R,3S*) (ee)



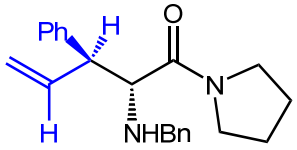
85% (yield), *anti* : *syn* = 20:80
82% (*2R,3R*): 90% (*2R,3S*) (ee)



70% (yield), *anti* : *syn* = 88:12
93% (*2R,3R*): n.d. (ee)



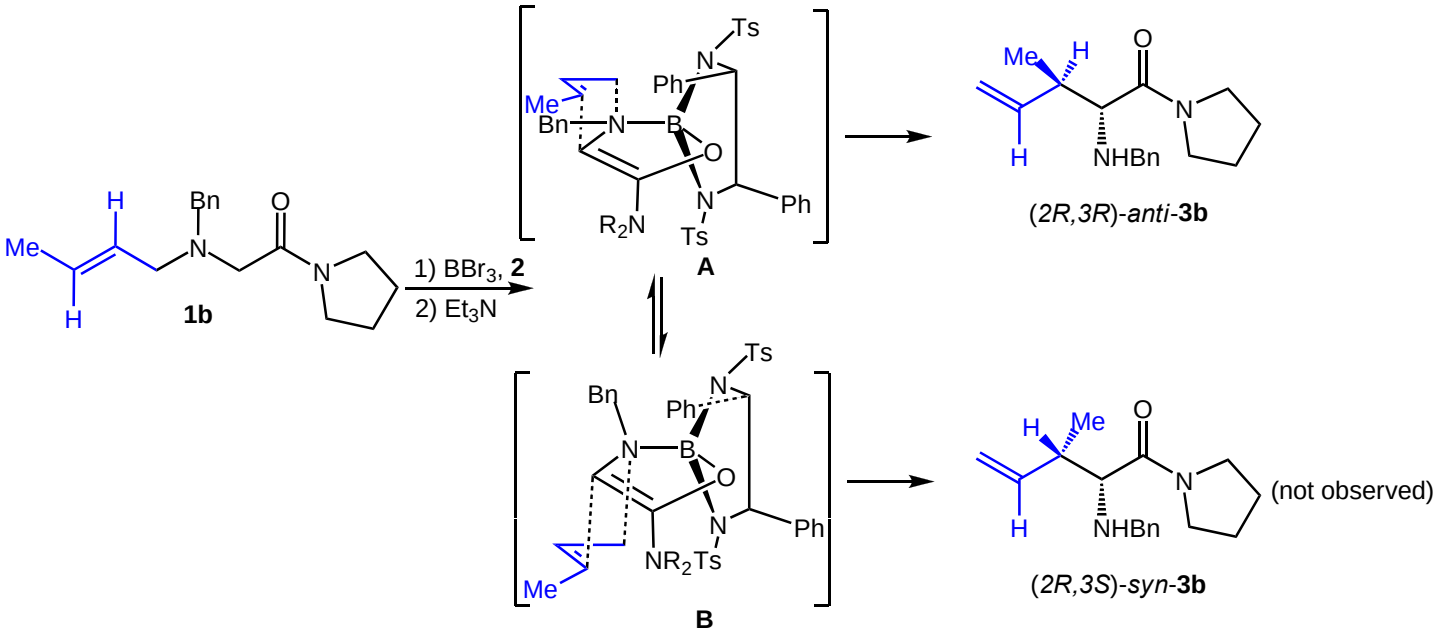
52% (yield), *anti* : *syn* = 95:5
99% (*2R,3R*): n.d. (ee)



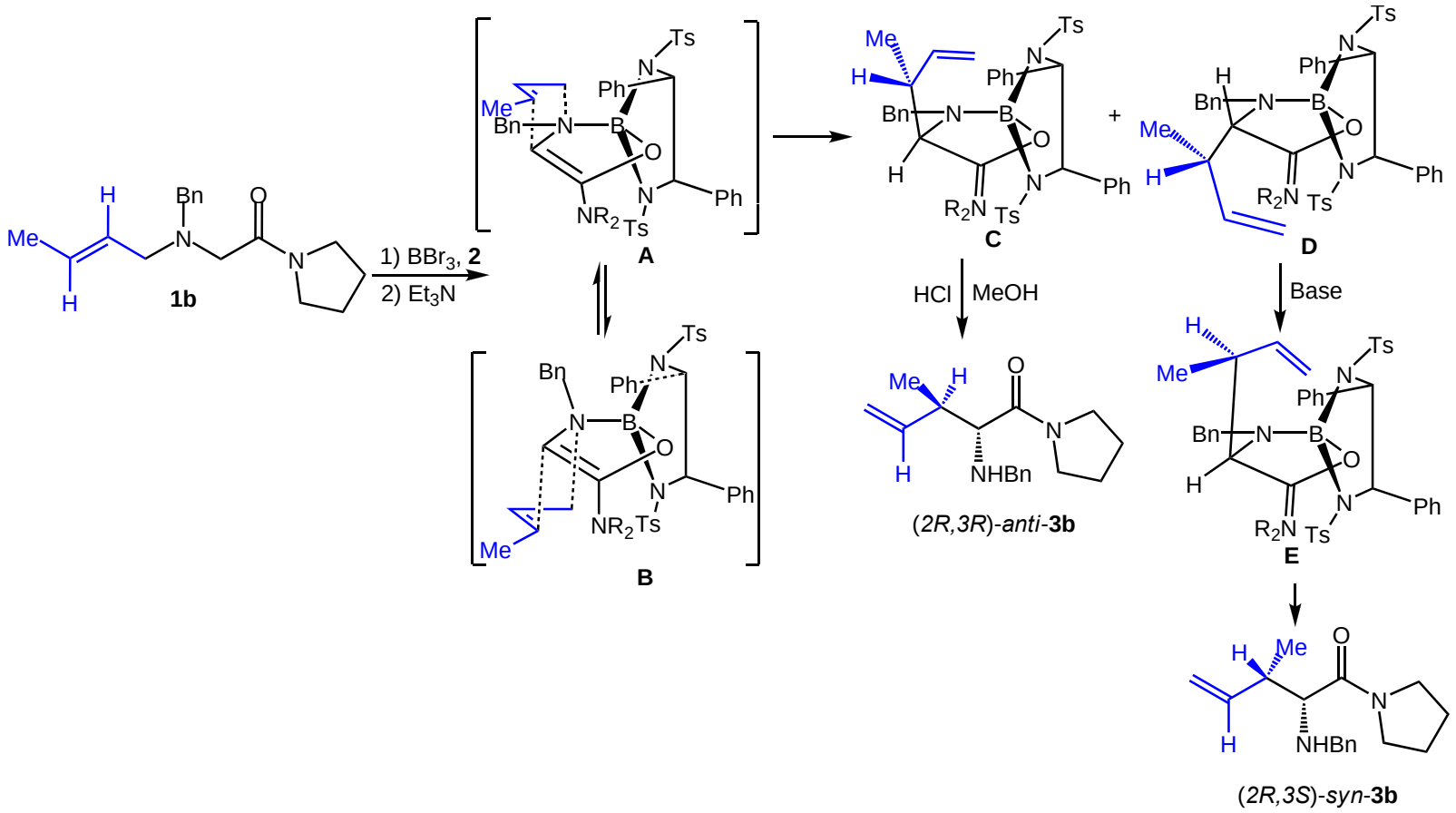
92% (yield), *anti* : *syn* = 67:33
97% (*2R,3R*): 77% (*2R,3S*) (ee)

Somfai, P. *et al. J. Am. Chem. Soc.* **2005,** *127,* 9352-9353.

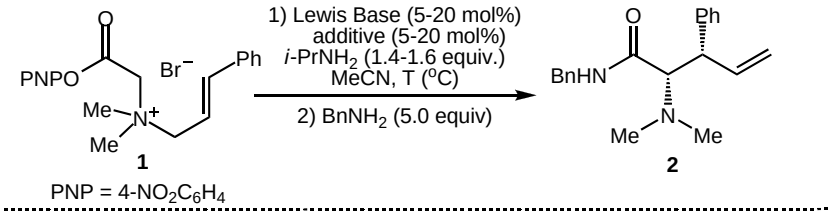
Kinetically Controlled Stereoselection in the Rearrangement of1b

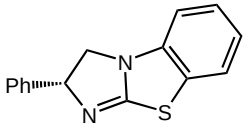


Thermodynamic Controlled Stereoselection in the Rearrangement of1b

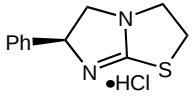


An Isothiourea-Catalyzed Asymmetric [2,3]-Rearrangement of Allylic Ammonium Ylides

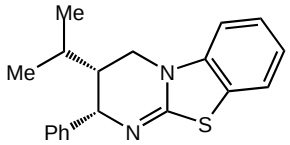




benzotetramisole **3**



tetramisole•HCl **4**



HBTM-2.1 **5**

Entry[a]	LB	Additive	T (°C)	Yield [%][b,c]	d.r.[d]	Ee (%)[e]
1	**4**	/	rt	83[c]	89:11	81 (*ent*)
2	**4**	HOBt	rt	68	93:7	84 (*ent*)
3	**4**	HOBt	0 to rt	88	92:8	89 (*ent*)
4	**4**	HOBt	-20	65	91:9	93 (*ent*)
5	**3**	/	-20	61	92:8	95

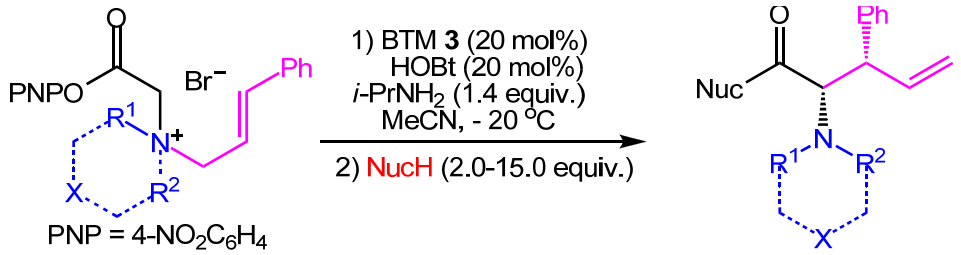
Smith, A. D. *et al. J. Am. Chem. Soc.* **2014,** *136,* 4476-4479.

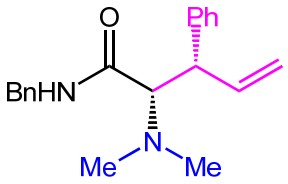
Optimization of Reaction Conditions

Entry[a]	LB	Additive	T (°C)	Yield [%][b,c]	d.r. [d]	Ee (%)[e]
6	**3**	HOBt	-20	76	>95:5	99
7	**5**	HOBt	-20	33[c]	62:38	ND[f]
8	**3**	HOAc	-20	49	90:10	98
9	**3**[g]	HOBt[g]	-20	62	88:12	96
10	**3**[h]	HOBt[h]	-20	41[i]	79:21	92

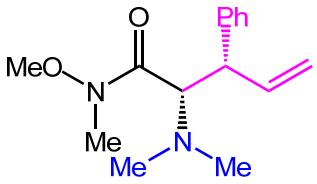
[a] Reactions performed on 0.24 mmol scale, 20 mol %, unless stated otherwise. [b] Isolated yield after chromatographic purification of >95:5 dr. [c] Yield in parentheses determined by ^{1}H NMR in comparison with internal standard (4-nitrotoluene). [d] Determined by ^{1}H NMR analysis of crude material. [e] Deter mined by chiral HPLC analysis. [f] ND = not determined. [g]10 mol %. [h] 5 mol %. [i] 84:16 mixture of diastereoisomers (isolated).

Scope of Isolable Ammonium Salts

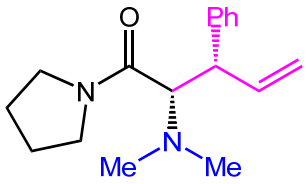




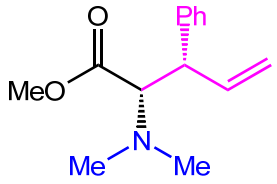
76% (yield), 99% (ee), >95:5 (dr)



65% (yield), >99% (ee), >95:5 (dr)

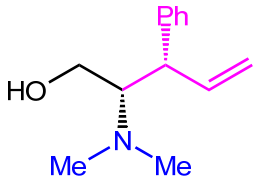


61% (yield), 99% (ee), >95:5 (dr)

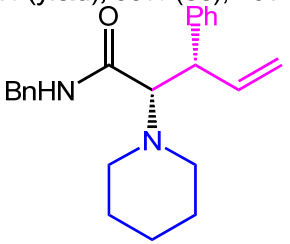


64% (yield), 98% (ee), 94:6 (dr)

87% (yield), 95% (ee), 95:5 (dr)
9.6 mmol scale

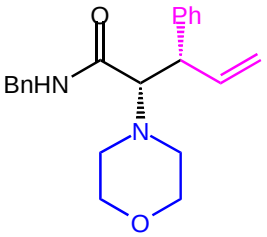


59% (yield), 96% (ee), >95:5 (dr)

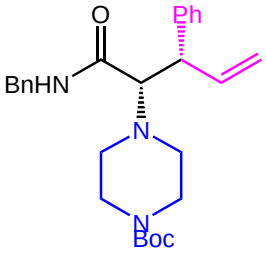


84% (yield), >99% (ee), >95:5 (dr)

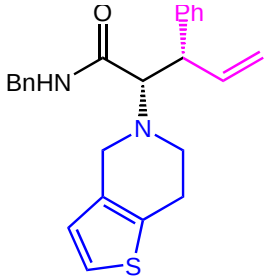
Scope of Isolable Ammonium Salts



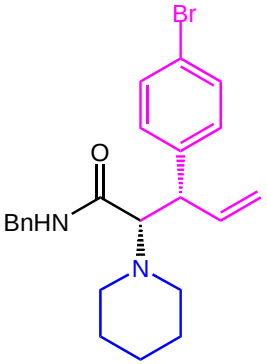
82% (yield), 86% (ee), 94:6 (dr)



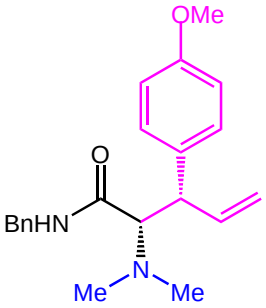
89% (yield), 96% (ee), 97:3 (dr)



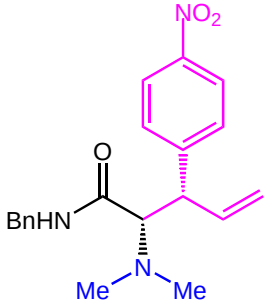
80% (yield), >99% (ee), >95:5 (dr)



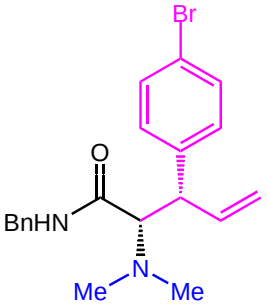
87% (yield), 98% (ee), >95:5 (dr)



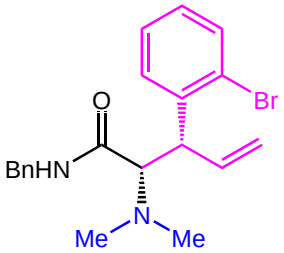
60% (yield), >99% (ee), 88:12 (dr)



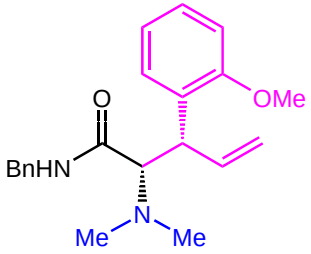
71% (yield), 96% (ee), >95:5 (dr)



76% (yield), >99% (ee), 95:5 (dr)

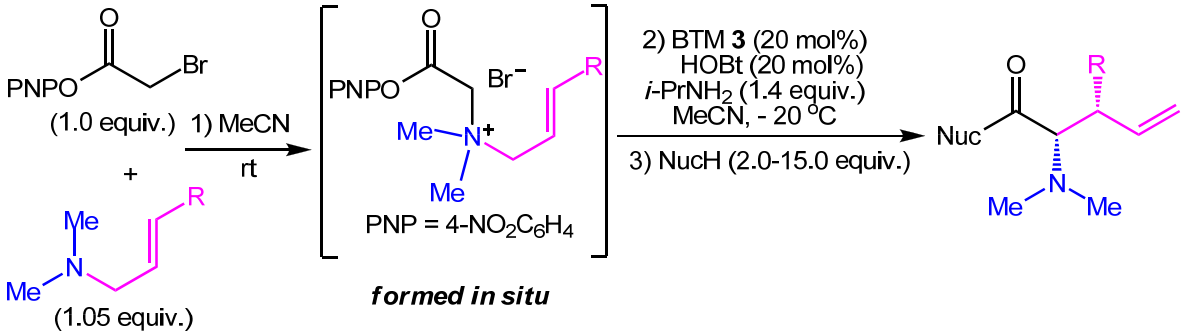


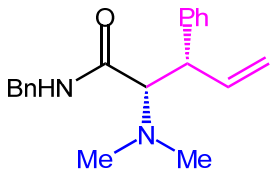
55% (yield), 86% (ee), >95:5 (dr)



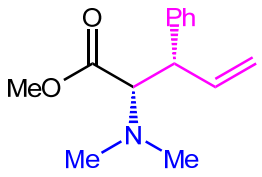
33% (yield), 95% (ee), 94:6 (dr)

In SituGenerated Ammonium Salts

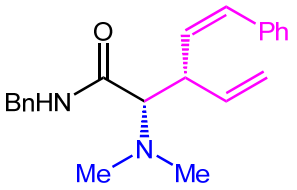




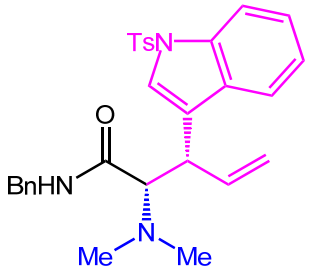
60% (yield), 92% (ee), >95:5 (dr)



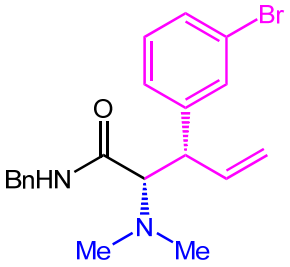
63% (yield), 94% (ee), 95:5 (dr)



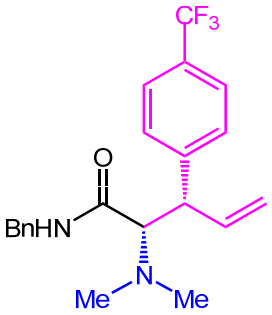
51% (yield), 96% (ee), 88:12 (dr)



56% (yield), 92% (ee), >95:5 (dr)



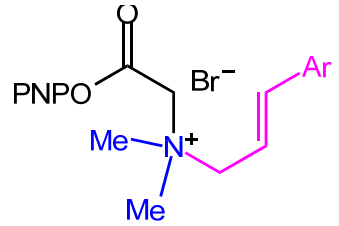
70% (yield), 91% (ee), >95:5 (dr)



52% (yield), 85% (ee), >95:5 (dr)

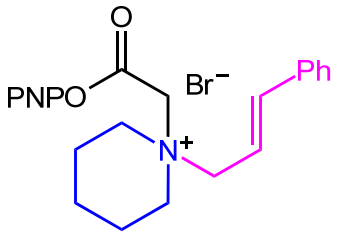
Mechanistically Significant Examples

1)



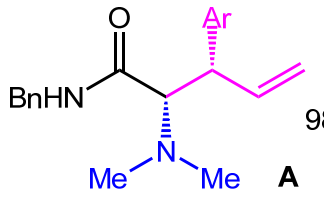
Ar = 4-BrC_6H_4 (0.5 equiv.)

+



1) BTM **4** (20 mol%)
HOBt (20 mol%)
i-PrNH_2 (1.4 equiv.)
MeCN, - 20 °C

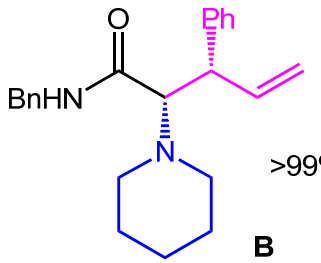
2) $BnNH_2$ (5.0 equiv.)



98% ee

A

+

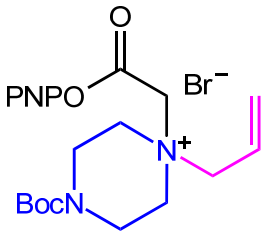


>99% ee

B

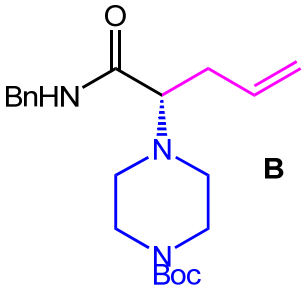
A and **B** only products
1:1 ratio

2)



1) BTM **4** (20 mol%)
HOBt (20 mol%)
i-PrNH_2 (1.4 equiv.)
MeCN, - 20 °C

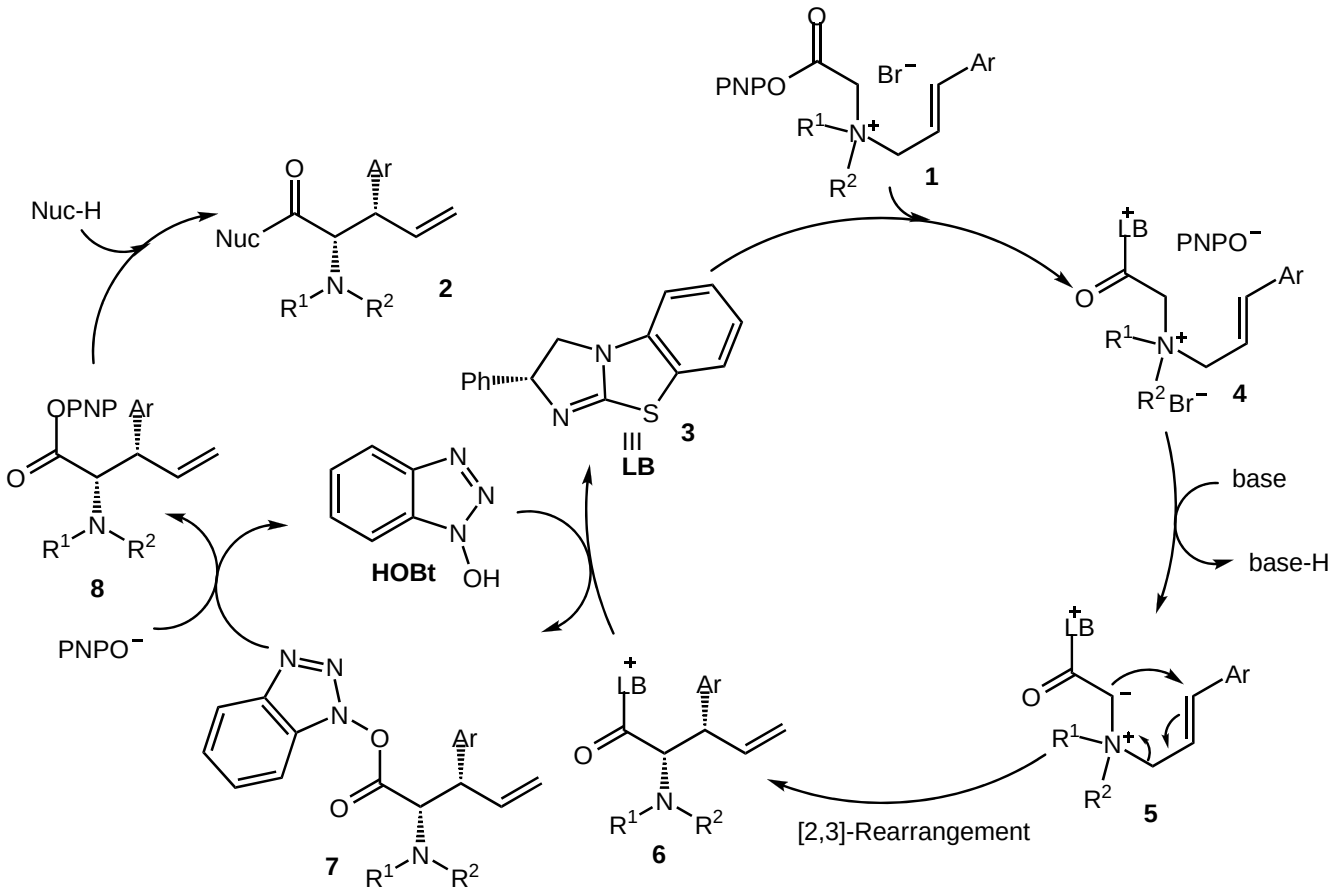
2) $BnNH_2$ (5.0 equiv.)



B

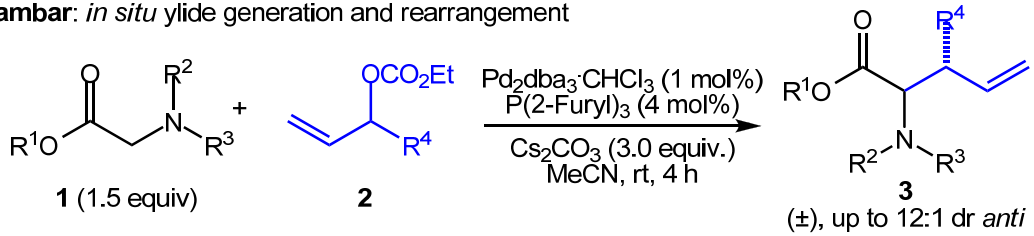
76%, 56% ee

Mechanistic and Stereochemical Proposal

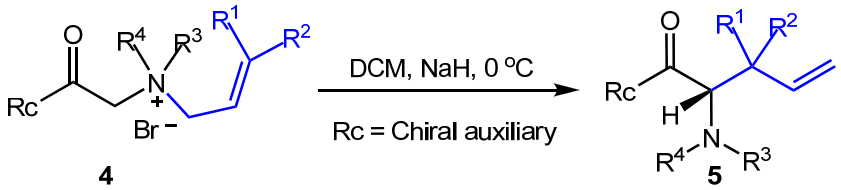


Summary:

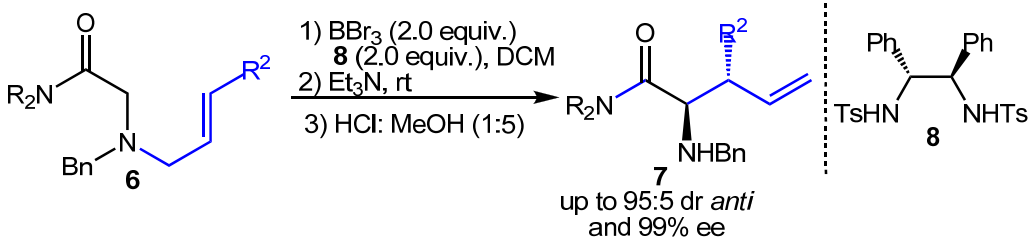
Tambar: *in situ* ylide generation and rearrangement



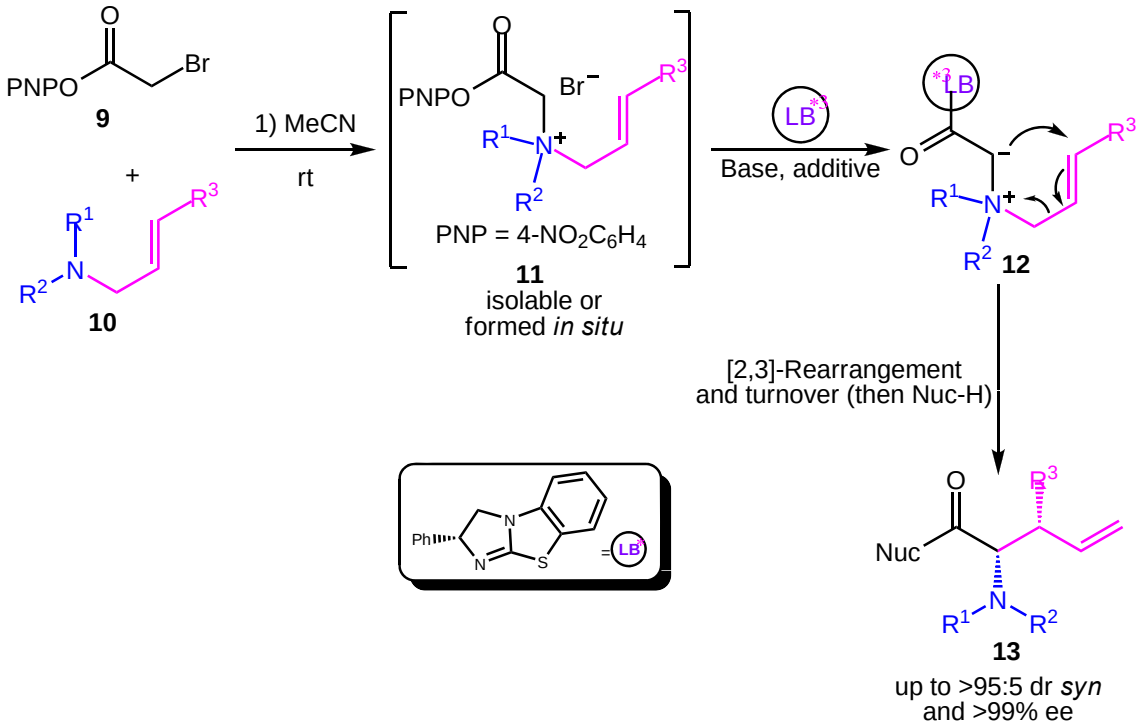
Kaiser and **Sweeney**: rearrangement relied on intramolecular chirality transfer



Somfai: stoichiometric asymmetric rearrangement



Simth: catalytic asymmetric rearrangement



The [2,3]-rearrangement of glycine-derived allylic ammonium ylides is widely recognized as a versatile process for the synthesis of stereodefined unnatural *α*-amino acid derivatives containing multiple stereocenters. Current limitations of this process include the difficulty associated with the generation and isolation of the reactive ammonium salts, alongside the paucity of catalytic asymmetric methods for inducing enantiocontrol. Recent work by Tambar and Sohelie has elegantly utilized Pd-catalyzed allylic substitution to facilitate tandem ammonium ylide generation and [2,3] rearrangement, generating racemic *anti*-configured products with high diastereoselectivity. While asymmetric [2,3]-rearrangements of allylic ammonium ylides can be induced by chiral auxiliary control as demonstrated by Sweeney and co-workers, Somfai *et al*. have applied stoichiometric asymmetric Lewis acids to promote the enantioselective rearrangement of allylic. Within the past 15 years, advances in asymmetric organocatalysis have been applied to asymmetric [3,3]-sigmatropic rearrangements. However, organocatalytic [2,3]- sigmatropic rearrangements are an underexplored concept, with the secondary amine-catalyzed [2,3]-Wittig rearrangement developed by Gaunt *et al*. representing the current

state-of the-art within this area. Given our interest in Lewis base promoted organocatalytic processes, in this manuscript we show that sub-stoichiometric isothioureas promote the asymmetric [2,3]-rearrangement of ylides derived from isolable *or in situ* generated allylic ammonium salts, forming stereodefined *α*-amino acid derivatives with excellent *syn*-diastereo- and enantiocontrol (up to >95:5 dr and 99% ee).

In summary, we have developed the first catalytic asymmetric [2,3]-rearrangement of allylic ammonium ylides. Isothiourea BTM12 promotes the rearrangement of *p*-nitrophenyl ester ammonium salts, producing *syn*-configured α-amino acid derivatives with excellent stereocontrol (up to >95:5 dr and >99% ee). Further investigations into this process are currently being pursued in our laboratory.