Literature Seminar

M2 Horigome

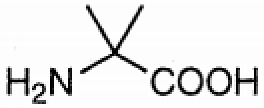
2018. 11. 15.

〈Topic〉

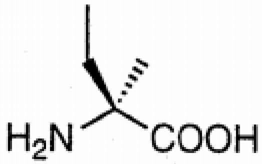
Stereoselective Synthesis of α,α-Disubstituted-α-amino Acids

Contents

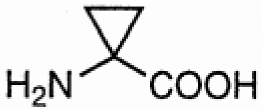
α,α-Disubstituted amino acids



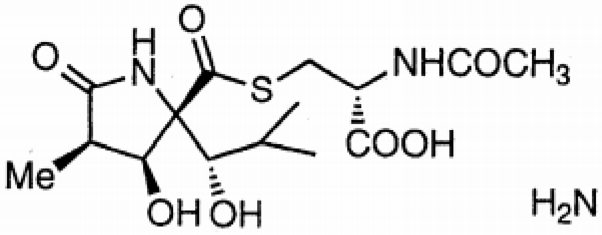
α-aminoisobutyric acid
(Aib)



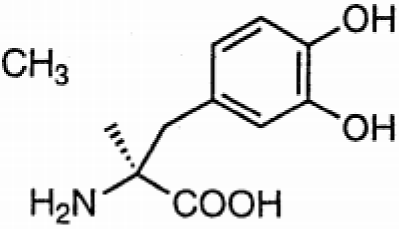
isovaline
(Iva)



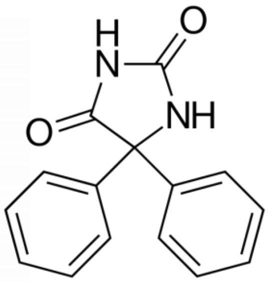
1-aminocyclopropane
carboxylic acid (Ac_3c)



Lactacystin



α-methyldopa



Phenytoin

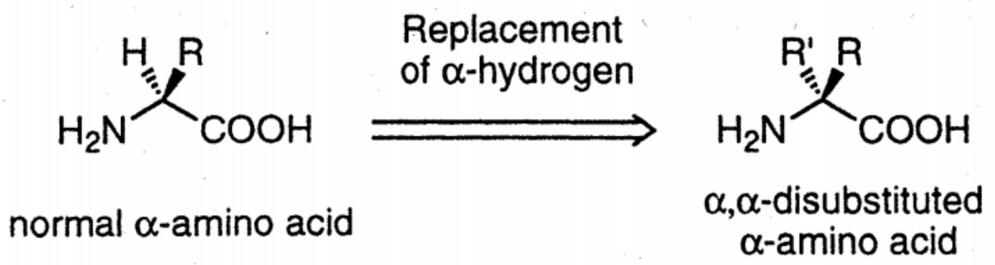
Alamethicin F-30:
Ac-Aib-Pro-Aib-Ala-Aib-Ala-Gln-Aib-Val-Aib-Gly-Leu-Aib-Pro-Val-Aib-Aib-Glu-Gln-Phl.

Antiamoebin I:
Ac-Phe-Aib-Aib-Aib-D-Iva-Gly-Leu-Aib-Aib-Hyp-Gln-D-Iva-Hyp-Aib-Pro-Phl.

(Hyp: hydroxyproline; Phl: L-phenylalaninol)

Characteristics of α, α-di-substituted amino acids

(1) Chemical stability.
(2) Increase in lipid solubility.
(3) Restriction on side chain conformation.
(4) Restriction of the conformation of the peptide containing it.
(5) Stabilization of the peptide containing it in vivo.



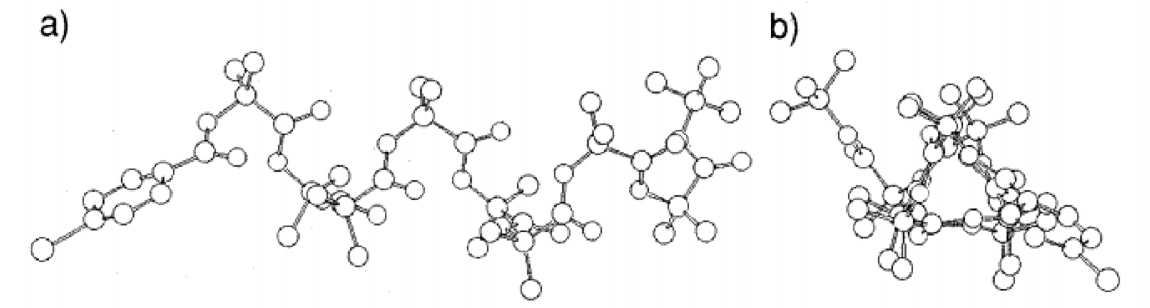


Fig. 6 3_{10}–Helical structure of Aib homopeptide: BrBz–(Aib)$_8$–O–*t*–Bu.
a) Perpendicularly to the helix axis; b) Along to the helix axis

Application of α,α-Disubstituted amino acids

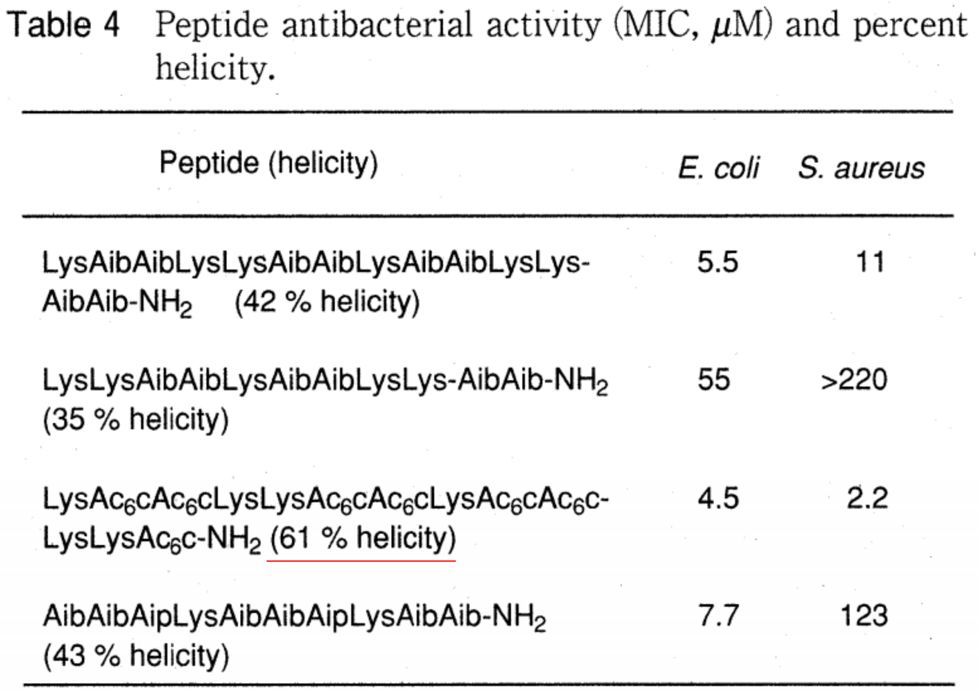
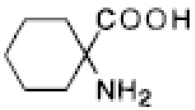


Table 4 Peptide antibacterial activity (MIC, μM) and percent helicity.

Peptide (helicity)	*E. coli*	*S. aureus*
LysAibAibLysLysAibAibLysAibAibLysLys-AibAib-NH_2 (42 % helicity)	5.5	11
LysLysAibAibLysAibAibLysLys-AibAib-NH_2 (35 % helicity)	55	>220
Lys$Ac_6c$$Ac_6c$LysLys$Ac_6c$$Ac_6cLysAc_6c$$Ac_6c$-LysLys$Ac_6c$-$NH_2$ (61 % helicity)	4.5	2.2
AibAibAipLysAibAibAipLysAibAib-NH_2 (43 % helicity)	7.7	123

Aib



Ac_6c

Aip

The higher the helicity is, the higher the antibacterial activity is.

M. L. McLaughlin et. al., *J. Med. Chem.*, 39, 3603

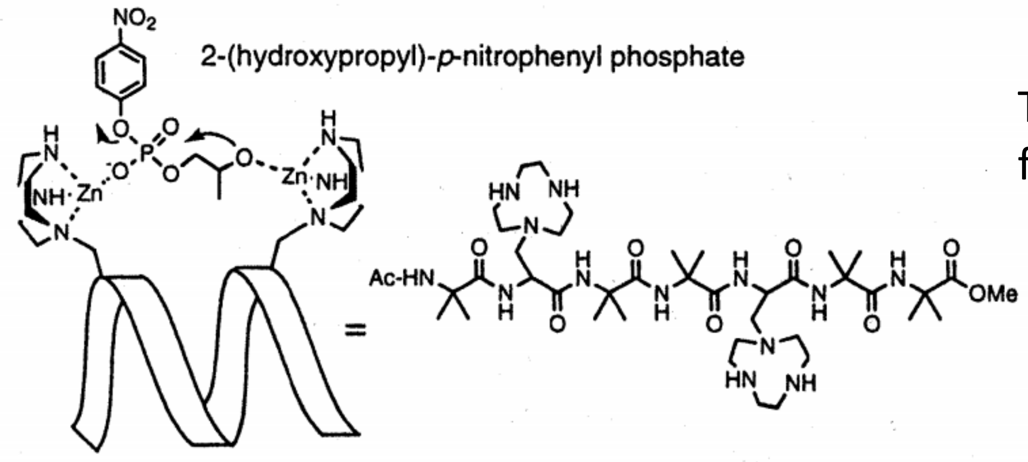
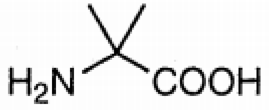


Fig. 16 Helical peptide as a transphosphorylation catalyst.

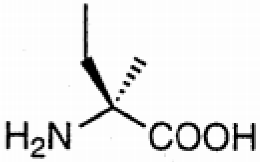
They use a helical structure to bring functional groups closer together.

P. Scrimin et. al., *J. Am. Chem. Soc.*, 121, 6948

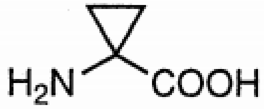
Chiral α,α-disubstituted amino acids



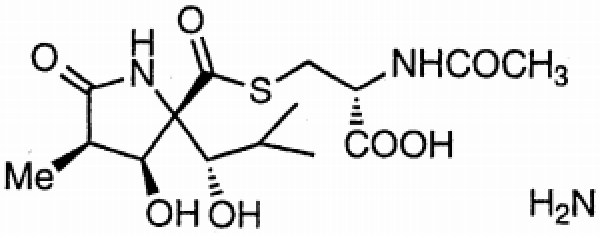
α-aminoisobutyric acid (Aib)



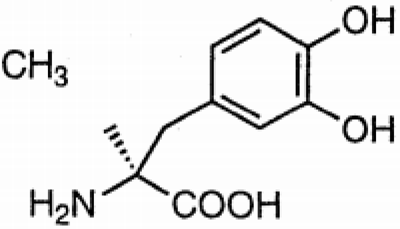
isovaline (Iva)



1-aminocyclopropane carboxylic acid (Ac_3c)

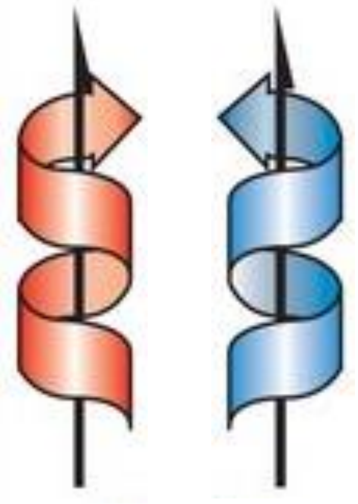


Lactacystin



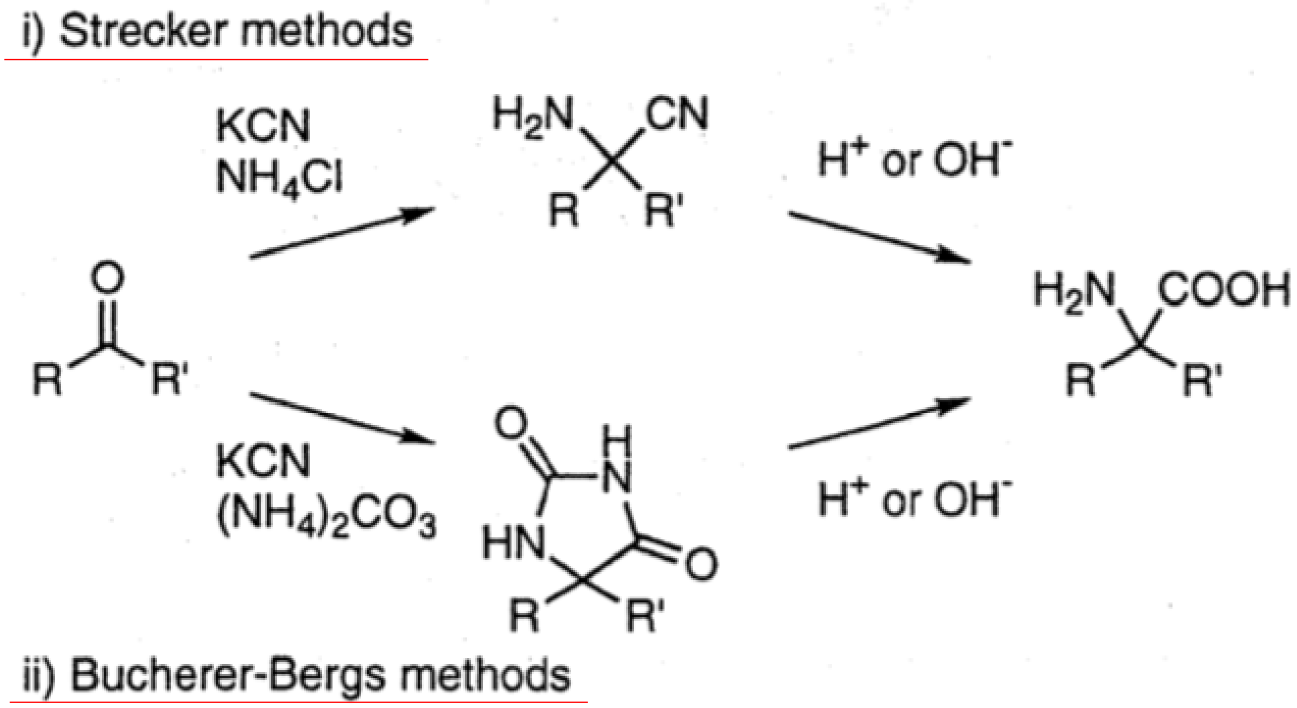
α-methyldopa

Chiral α,α-disubstituted α-amino acids are contained in various physiologically active natural products.



The direction of the helical structure of the peptide can be controlled by using Chiral α,α-disubstituted α-amino acids.

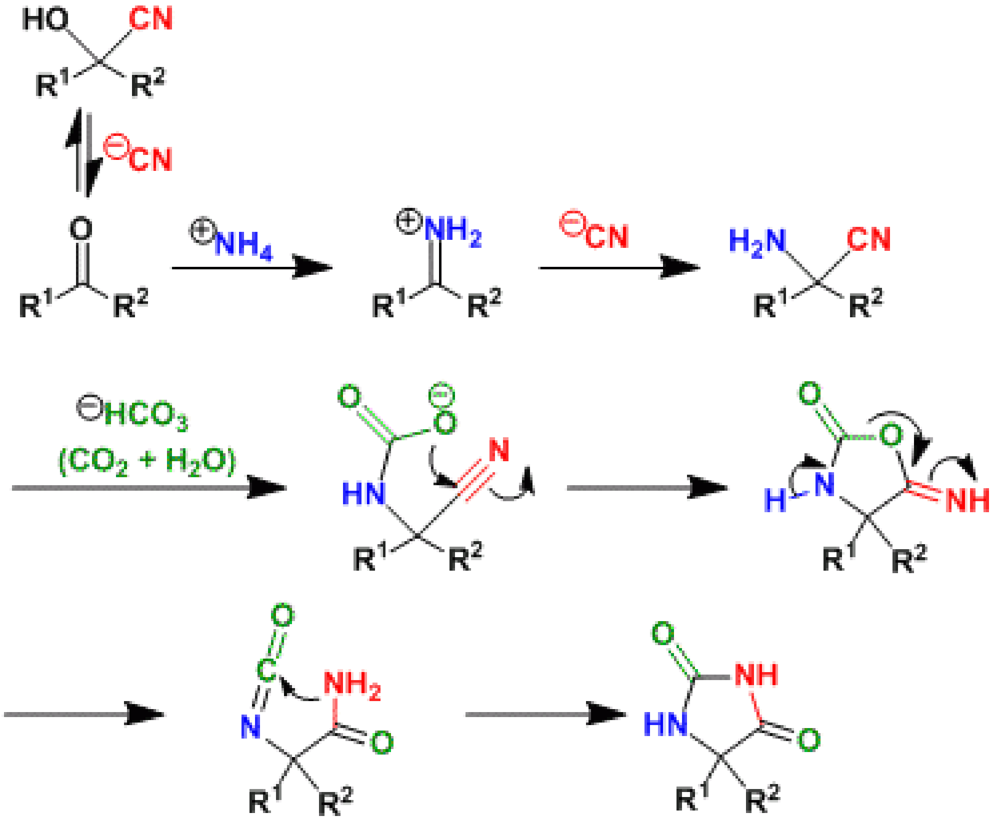
Synthesis of achiral α,α-disubstituted amino acids



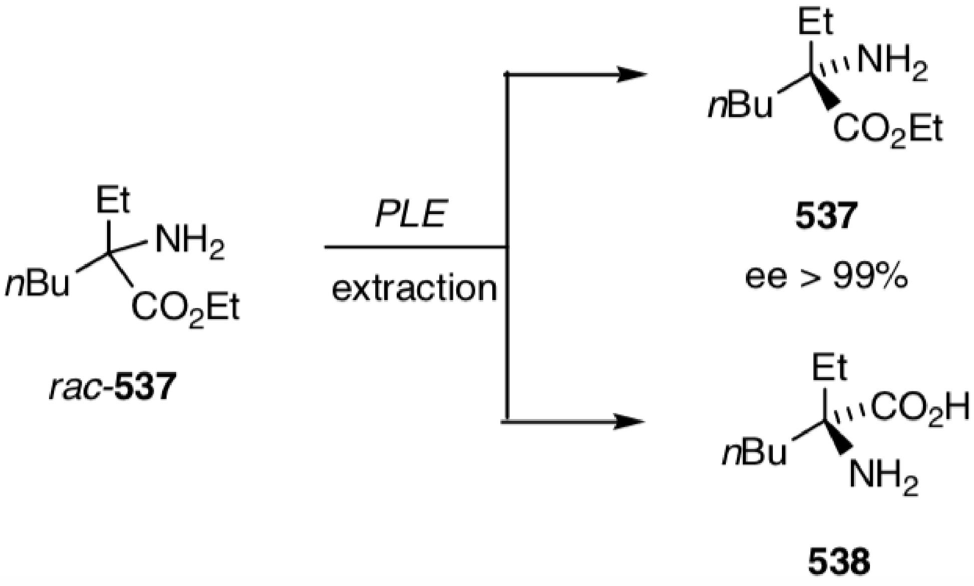
Strecker methods & Bucherer-Bergs methods

Strecker methods

Bucherer-Bergs methods



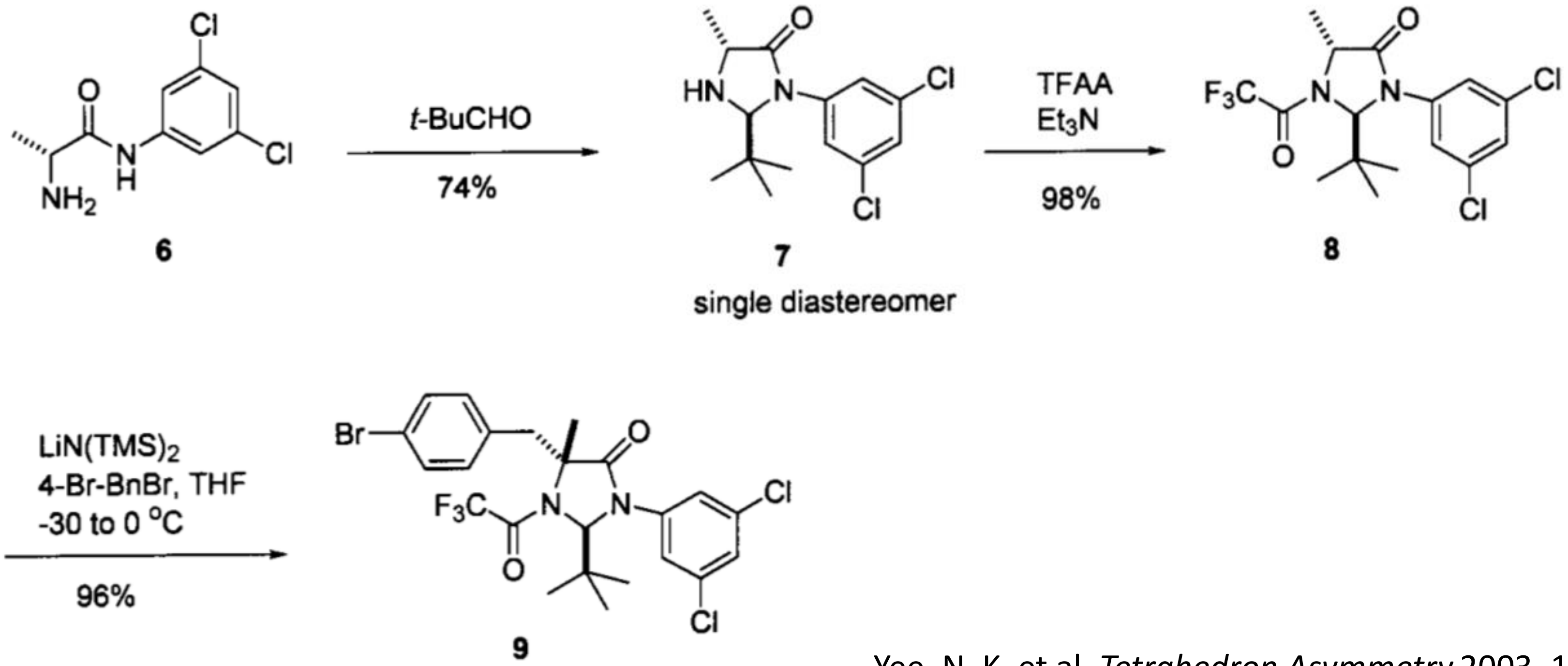
Synthesis of chiral α,α-disubstituted α-amino acids : Enzymatic procedures



The synthesis of racemic butylethylglycine (Beg) from butyl ethyl ketone by Strecker synthesis and subsequent resolution using pig liver estearase. The unreacted enantiomerically pure (S)-amino ester was recovered in 31% yield.

Imawaka, N. et. al. *Helv. Chim. Acta,* 2000, 83, 2823.

Self-regeneration of stereocentres

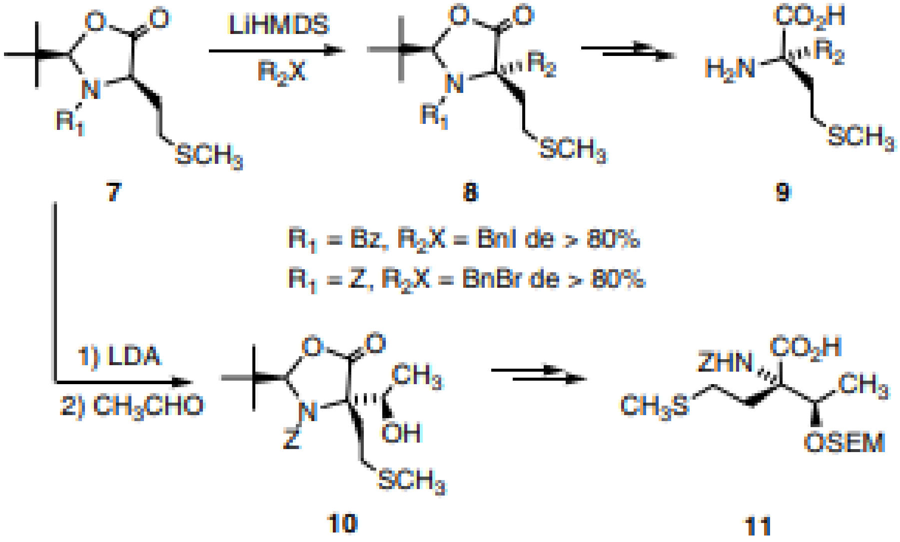


Yee, N. K. et al. *Tetrahedron Asymmetry* 2003, 14, 3495.

The principle of ‘**self-regeneration of stereocentres**’ 『in which the stereogenic centre of a chiral molecule generates a temporary centre of chirality, which in turn is used to introduce diastereoselectively a new ligand at the original stereogenic centre』 has been applied to the synthesis of various acyclic quaternary amino acids.

Self-regeneration of stereocentres

via oxazolidinones



de > 98%

Perciaccante, R. et.al. *Org. Biomol. Chem.* 2003, 1, 2853

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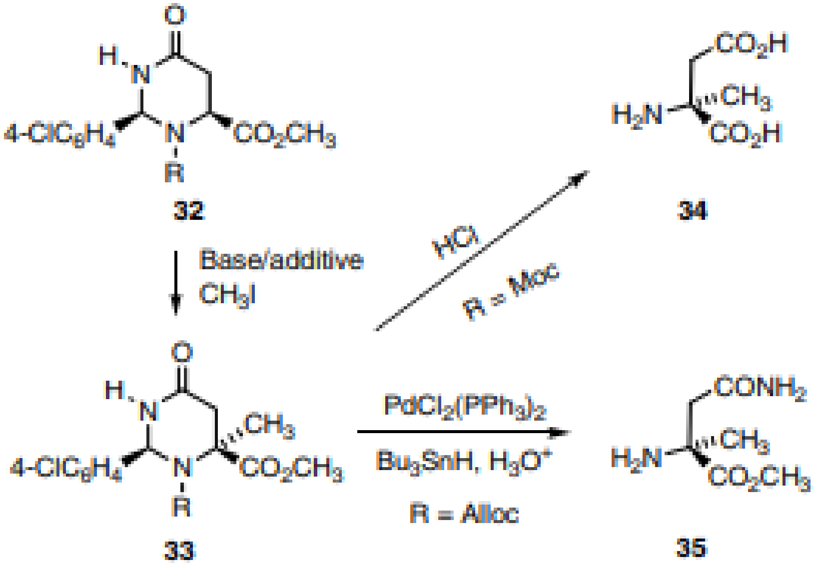
via tetrahydropyrimidinones
(Asparagine, Asparagic acid)

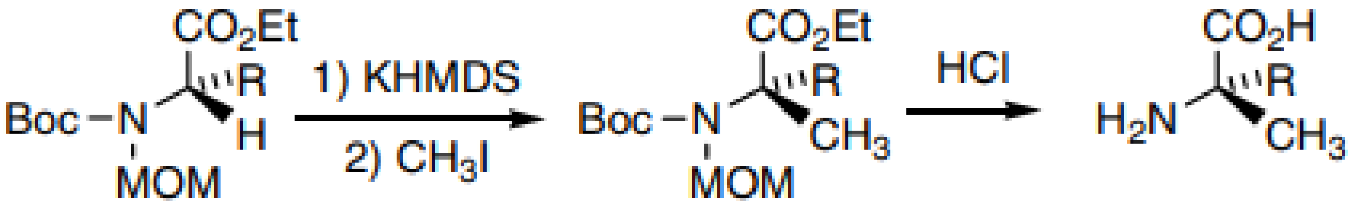


de > 95%

R = Moc, Alloc

Konopelski, J. P. et. al. *J. Org. Chem.* 1999, 64, 7885

Memory of chirality



74 **75** **76**

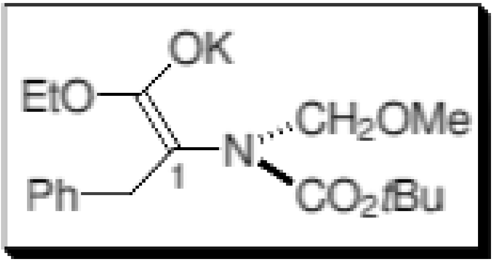
ee = 76-87%

R = Bn, 1-Boc-4-imidazolylmethyl, 4-MOMOC$_6$H$_4$CH$_2$, 3,4-(CH$_3$O)$_2$C$_6$H$_3$CH$_2$, 1-MOM-3-indolylmethyl, ^{i}Pr, ^{t}Bu

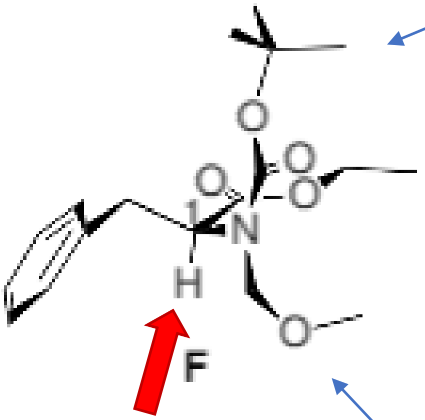
Memory of chirality is a phenomenon that occurs in processes where an initial stereogenic centre is destroyed during the generation of the corresponding reactive intermediate, but this intermediate is able to ‘remember’ the configuration of its precursor to transfer the chirality to the final compound without using any external chiral source.

Fuji, K. et. al. *Angew. Chem., Int. Ed.* 2000, 39, 2155.

Memory of chirality



E



F

Base & alkylation reagent

Steric hinderance

Base can approach H only when H and Boc are anti parallel.
And alkylation reagent approaches from opposite side.

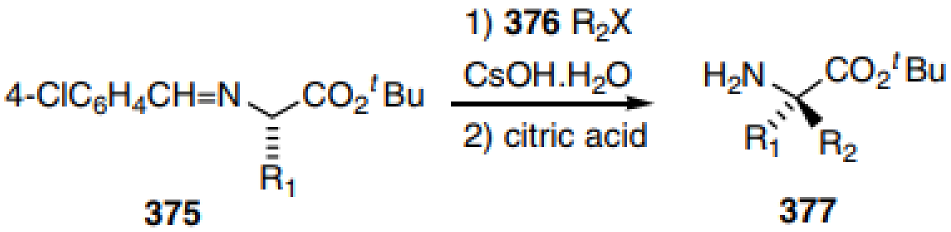
Chelate effect

The yield is low without MOM.
MOM is bringing the base close to H by chelating effect.
This promotes the base coming from the opposite side of Boc.

When the Bn part is small, the rotation barrier of C-N in E is small, and epimerization occurs.

Fuji, K. et. al. *Angew. Chem., Int. Ed.* 2000, 39, 2155.

Alkylation under phase-transfer conditions

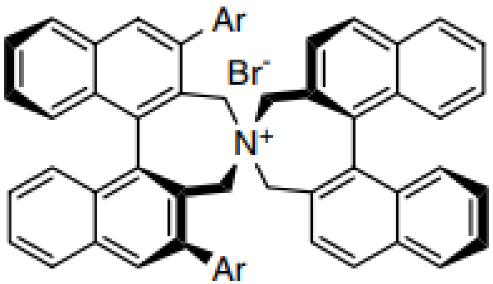


375 **377**

ee = 91-98%

$R_1 = CH_3$, Bn, ${}^tBu$

R_2 = BnBr, $CH_2{=}CHCH_2Br$, EtI, ${}^tBuO_2CCH_2Br$, 1-Boc-3-indolylmethylBr



Ar = 3,4,5-$F_3C_6H_2$

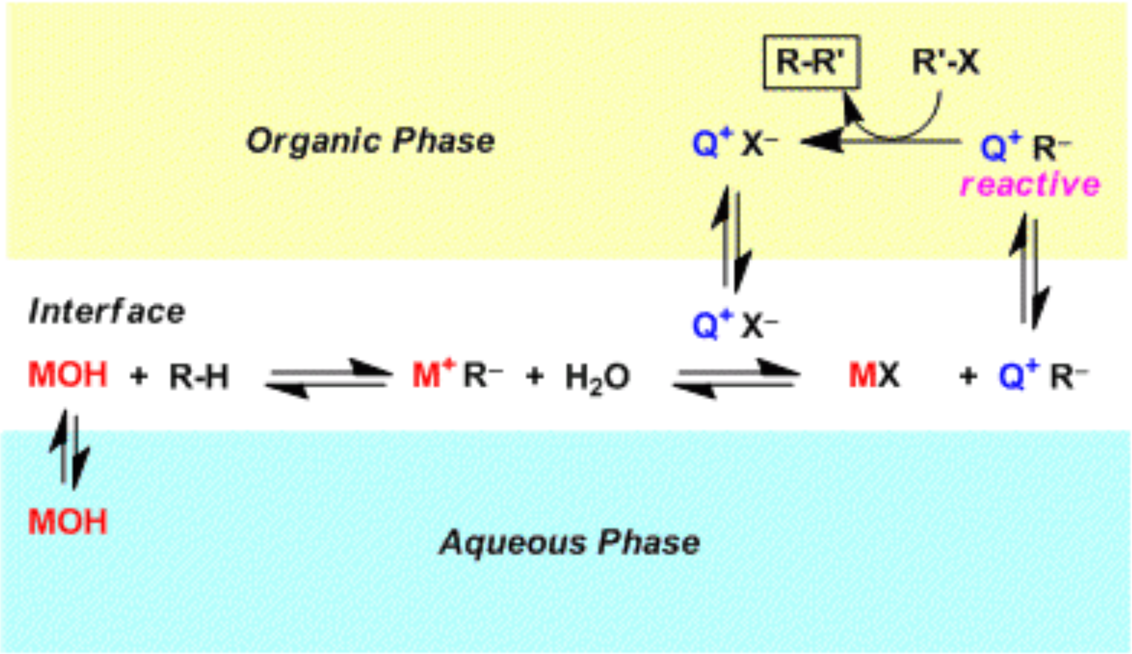
376

Maruoka, K. et. al. *Angew. Chem., Int. Ed*. 2005, 44, 1549.

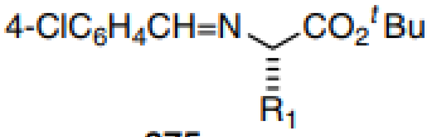
Suitable chiral catalysts to perform the synthesis of the asymmetric synthesis of α,α-disubstituted α-amino acids under phase-transfer conditions have been described.

Alkylation under phase-transfer conditions

<Makosza Interfacial Mechanism>



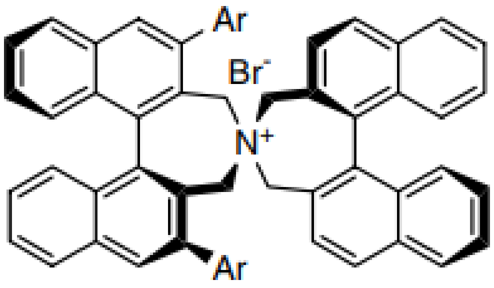
R-H =



375

,

Q+ =



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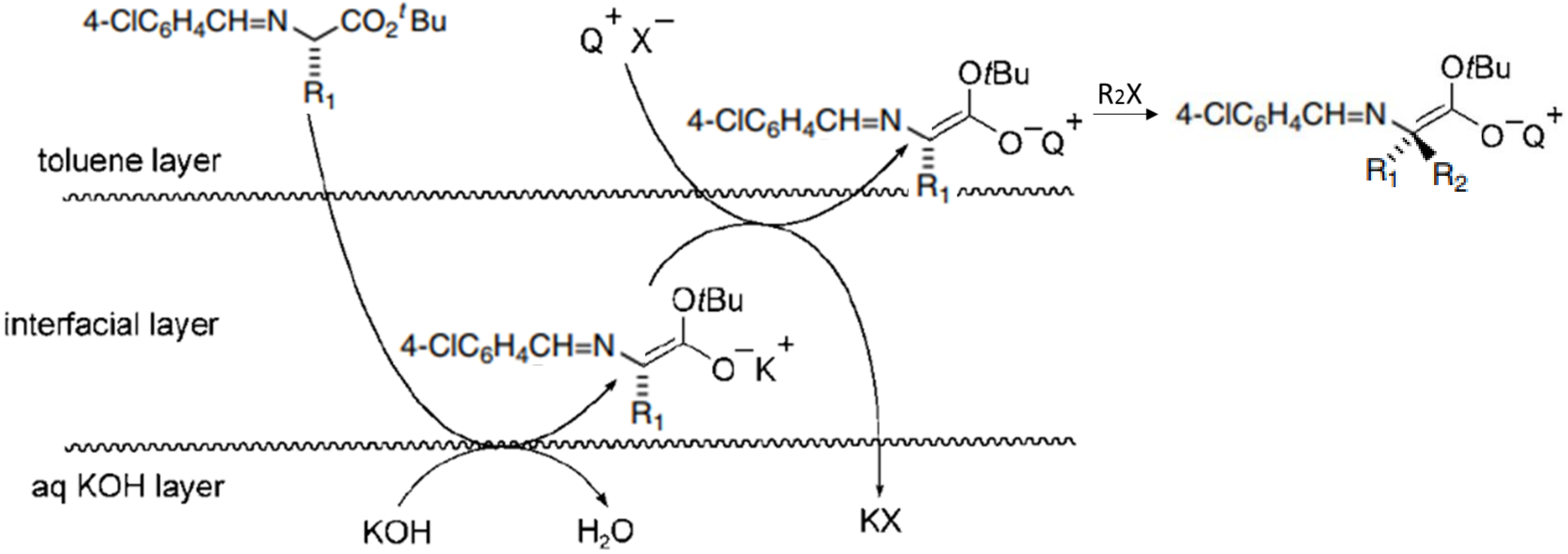
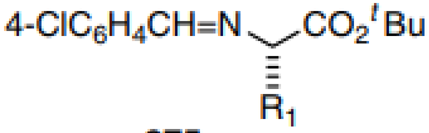
Alkylation under phase-transfer conditions



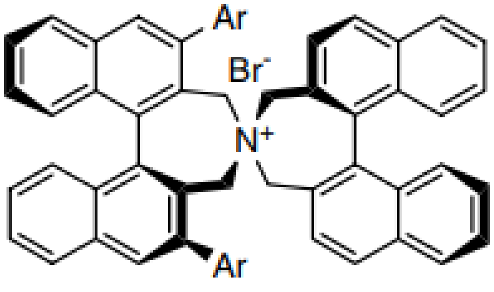
R-H =



375

,

Q⁺ =



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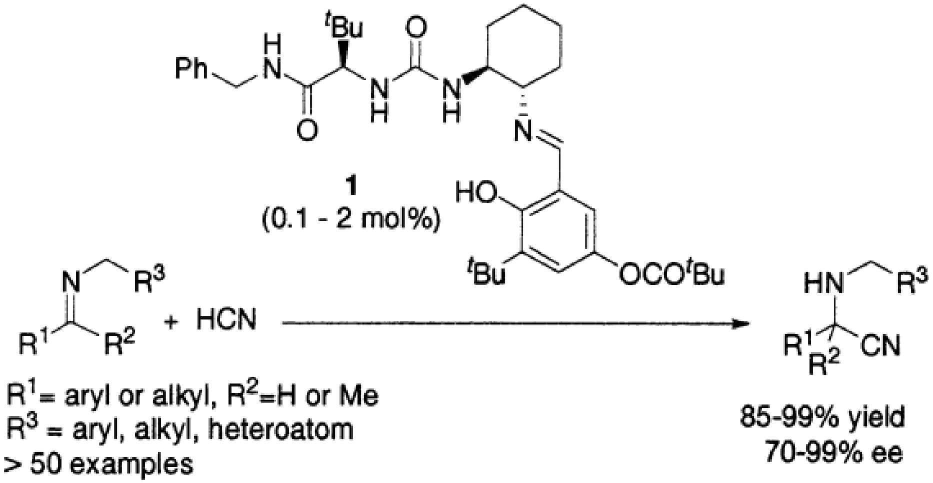
Addition of nucleophiles to the C≡N bond

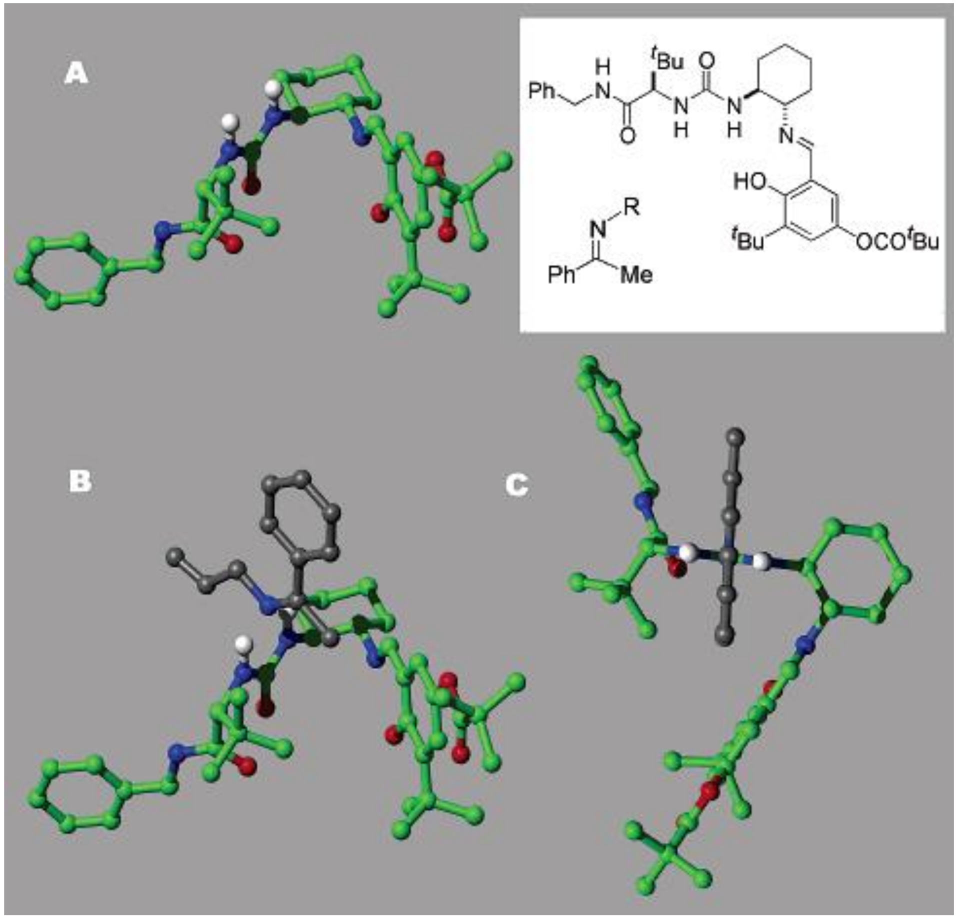
The catalytic enantioselective Strecker reaction is an attractive methodology for the synthesis of α,α-disubstituted α-amino acids.



1
(0.1 - 2 mol%)

R^1= aryl or alkyl, R^2=H or Me
R^3 = aryl, alkyl, heteroatom
> 50 examples

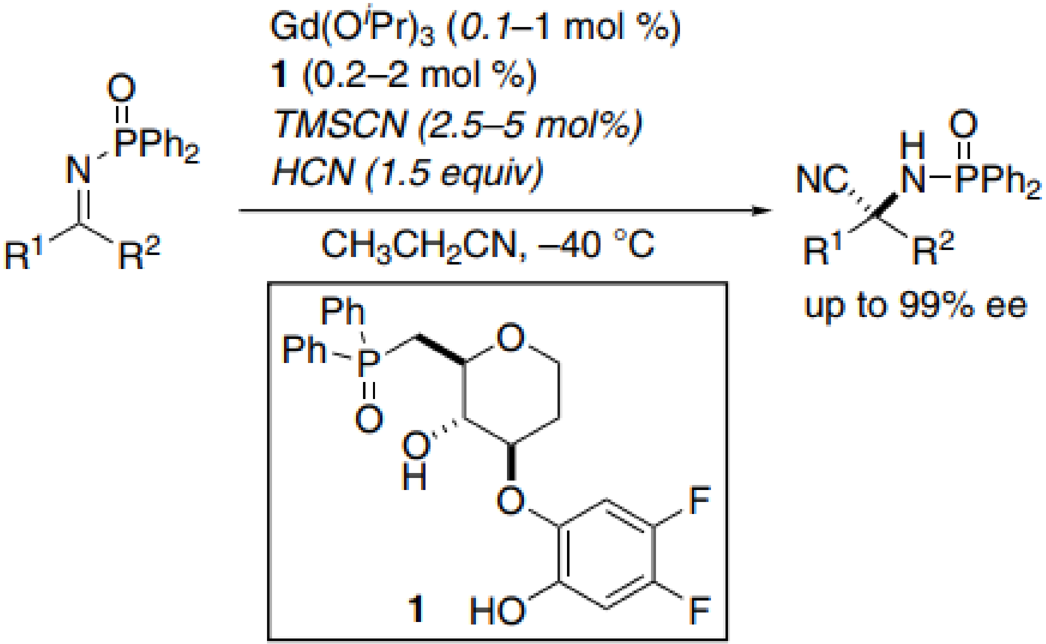
85-99% yield
70-99% ee



Jacobsen, E. N. J. Am. Chem. Soc. 2002, 124, 10012

Addition of nucleophiles to the C≡N bond

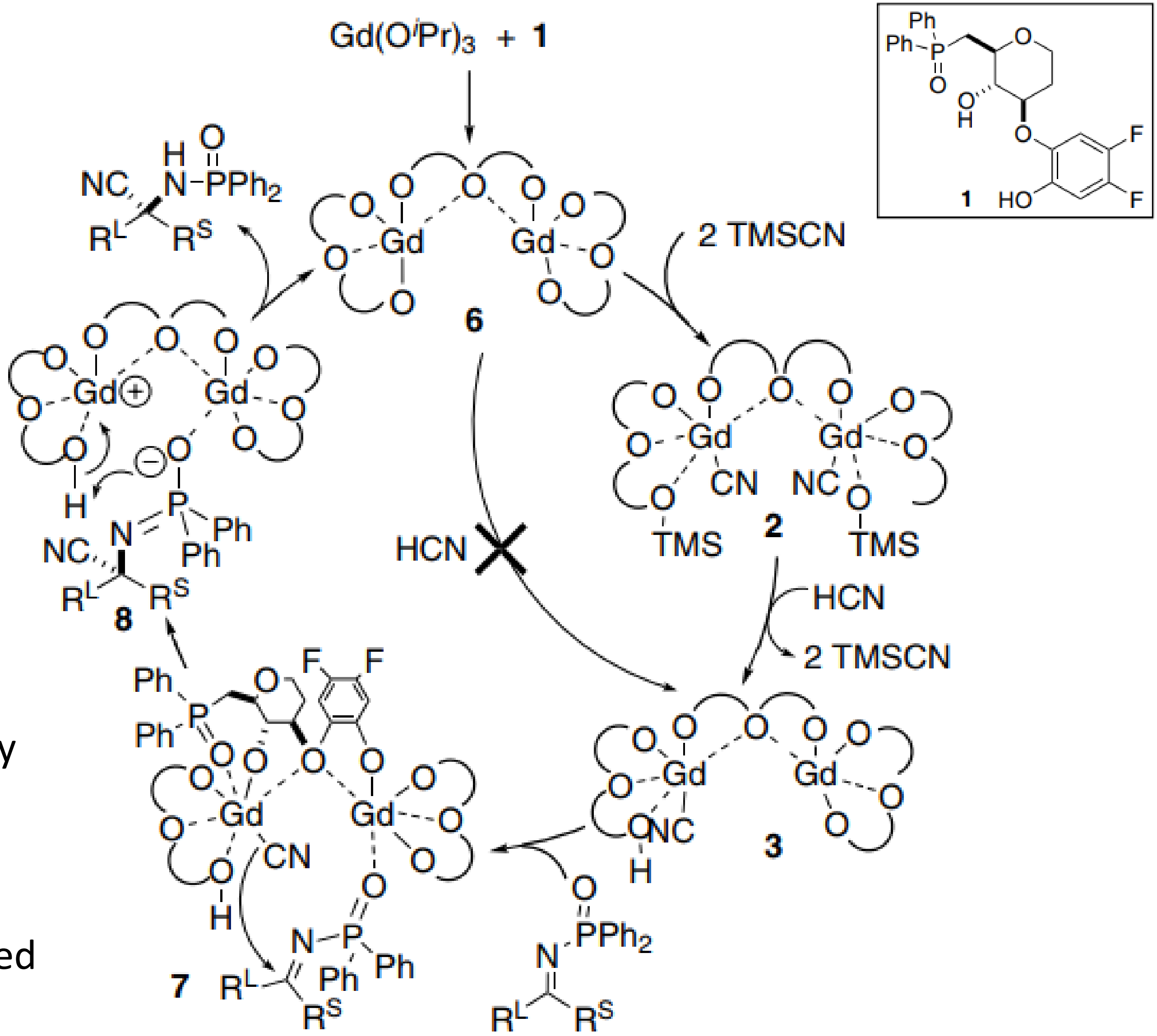
The catalytic enantioselective Strecker reaction is an attractive methodology for the synthesis of α,α-disubstituted α-amino acids.



N. Kato, M. Suzuki, M. Kanai, and M. Shibasaki, *Tetrahedron Lett.*, 45, 3153.

Addition of nucleophiles to the C≡N bond

Proposed catalytic cycle

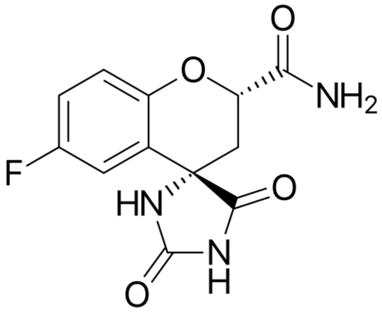


Lack of reactivity using only HCN is important from the mechanistic point of view, that is, the pre-catalyst **6** cannot be directly converted to the active catalyst **3**.

N. Kato, M. Suzuki, M. Kanai, and M. Shibasaki, *Tetrahedron Lett.*, 45, 3153.

Quaternary α-aryl amino acids

α-aryl amino acids and their derivatives are valuable precursors to bioactive molecules.



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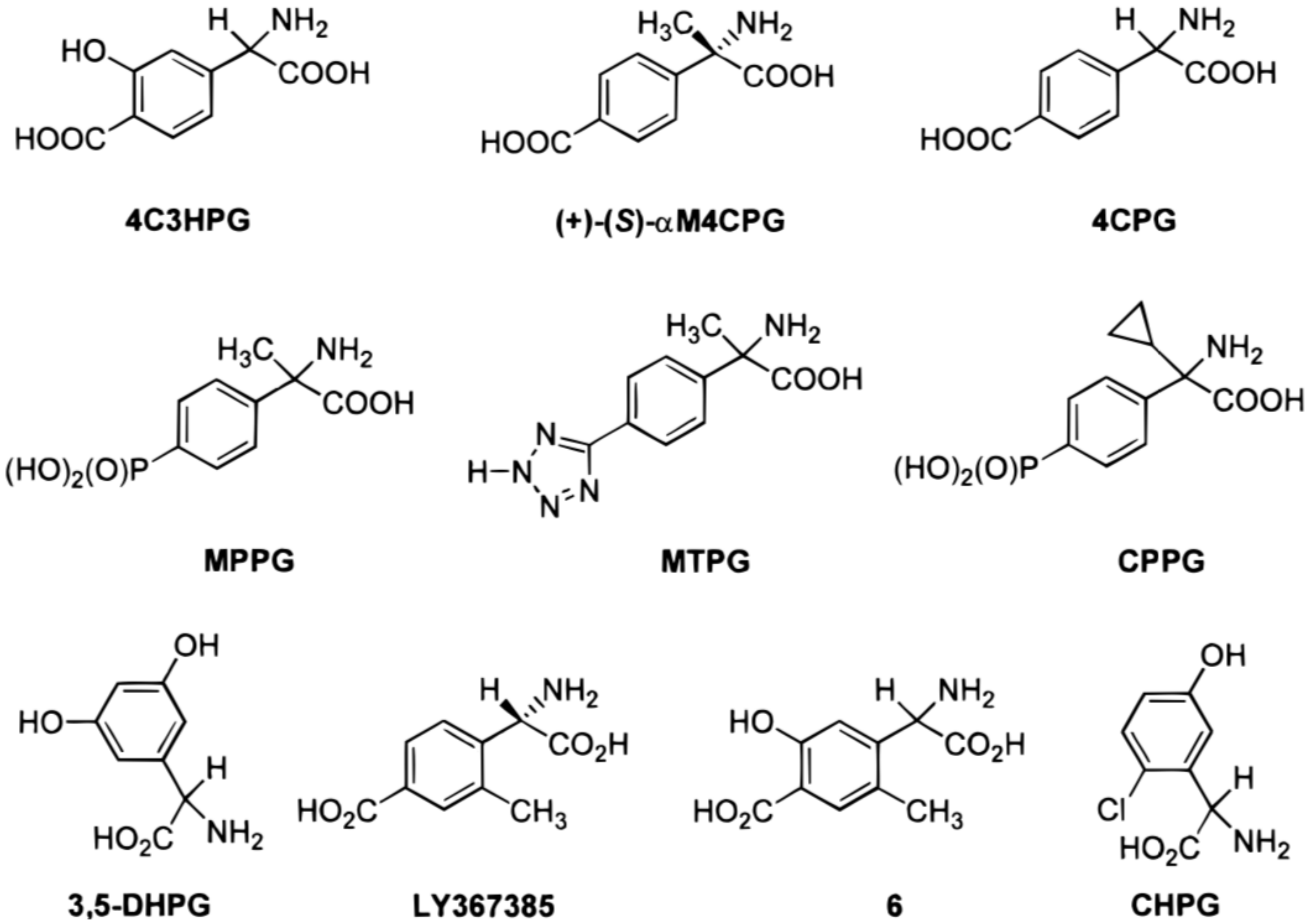
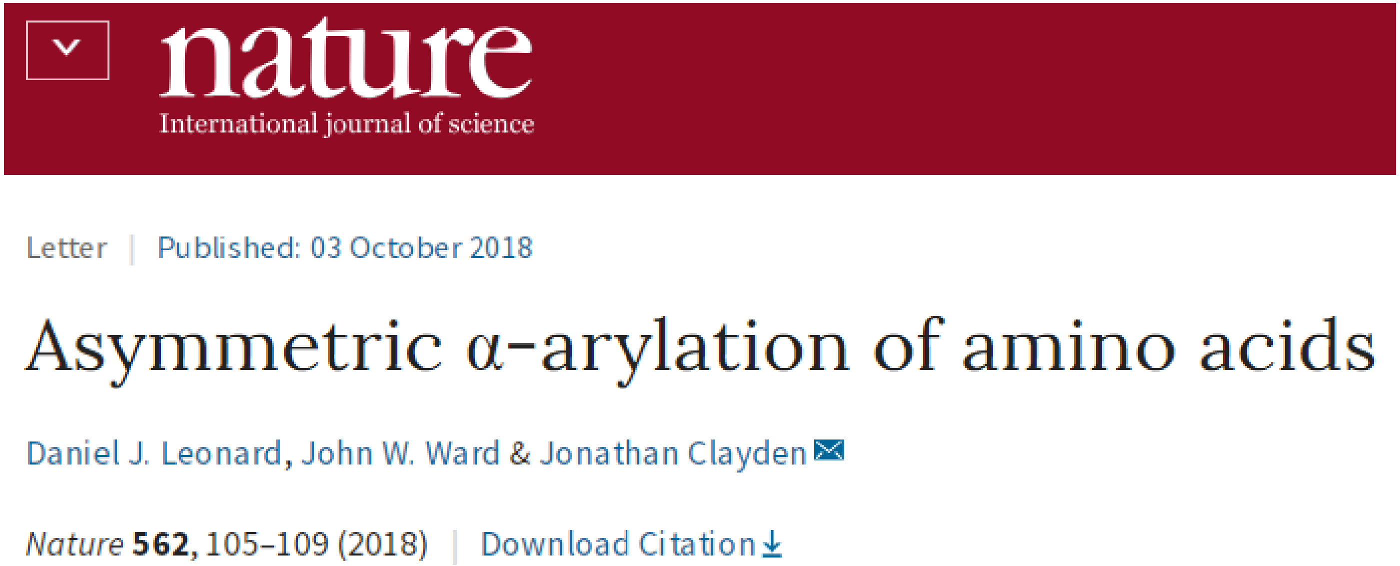


FIG. 7. Structures of phenylglycine analogues.

Enantioselective introduction of an aryl substituent at the α-carbon



nature
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Letter | Published: 03 October 2018

Asymmetric α-arylation of amino acids

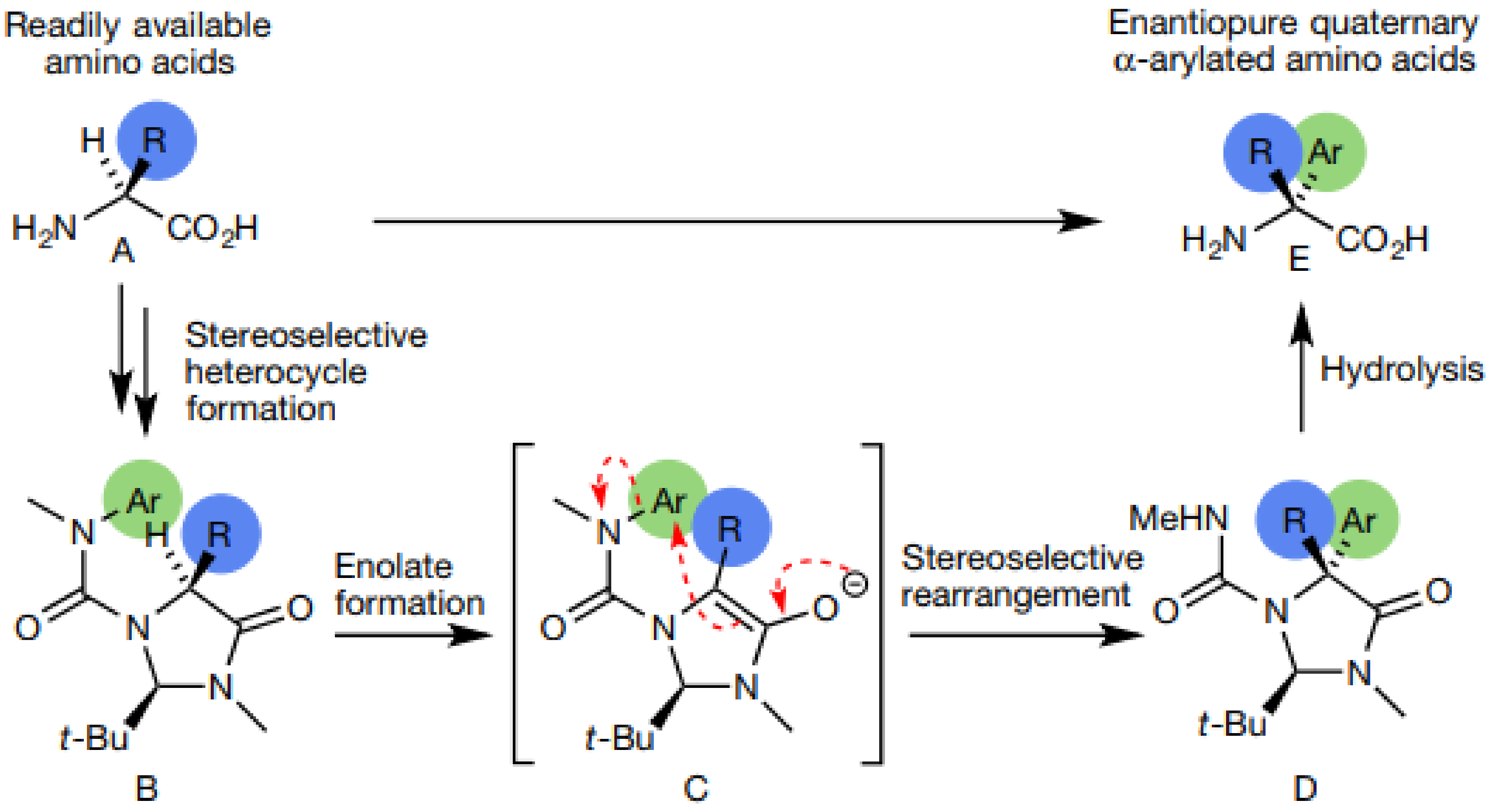
Daniel J. Leonard, John W. Ward & Jonathan Clayden

Nature **562**, 105–109 (2018) | Download Citation

Biography

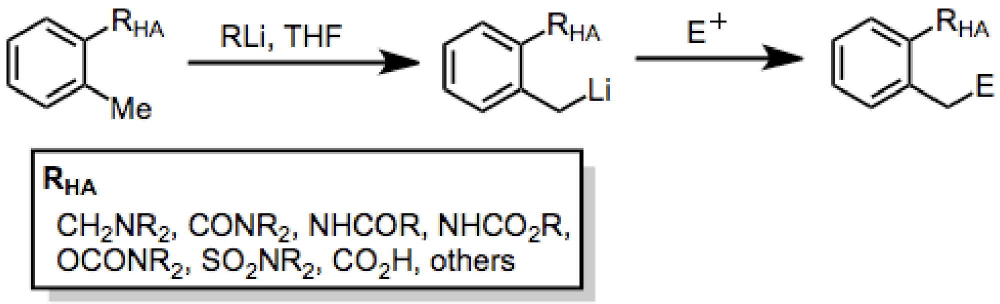
2015-present: Professor of Chemistry, University of Bristol
2001-2015: Professor of Organic Chemistry, University of Manchester
2000-2001: Reader in Chemistry, University of Manchester
1994-2000: Lecturer in Chemistry, University of Manchester
1992-1994: Royal Society Western European Research Fellow and Post-doc with Prof Marc Julia at the École Normale Supérieure, Paris on transition metal catalysed reactions of sulfones, and carbenoid chemistry
1989-1992: PhD at University of Cambridge with Dr Stuart Warren on asymmetric synthesis using phosphine oxide chemistry
1986-1989: BA (Natural Sciences) at Churchill College, University of Cambridge
1968: Born: Kampala, Uganda

Enantioselective introduction of an aryl substituent at the α-carbon

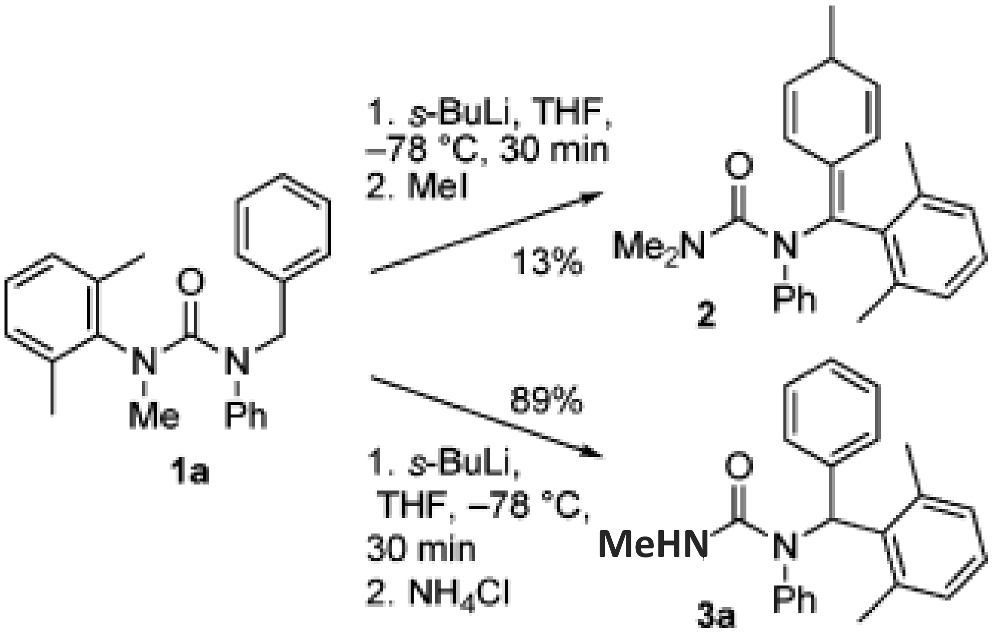


An amino acid (A) is converted diastereoselectively into an imidazolidinone (B) carrying a pendent urea function. Treatment with base forms an enolate (C) in which the aromatic substituent (Ar) of the urea migrates to the rear face of the imidazolidone, directed by the bulky tert-butyl group, as indicated by the red dotted arrows. Hydrolysis of the product (D) provides the quaternary α-aryl amino acid (E).

Clayden rearrangement



Heteroatom-promoted lateral lithiation is the site-selective replacement of a benzylic hydrogen atom for lithium for the purpose of further functionalization.



The origin of Clayden rearrangement

By replacing the final methylation with an aqueous quench, the rearranged product 3a was obtained in a satisfying 89% yield.

Clayden, J. et. al., *J. Am. Chem. Soc.* 129, 7488 (2007).

Substrate scope of clayden rearrangement

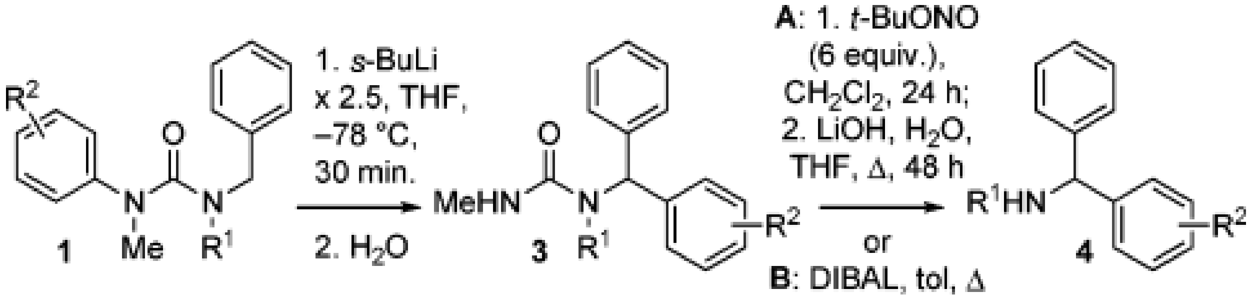
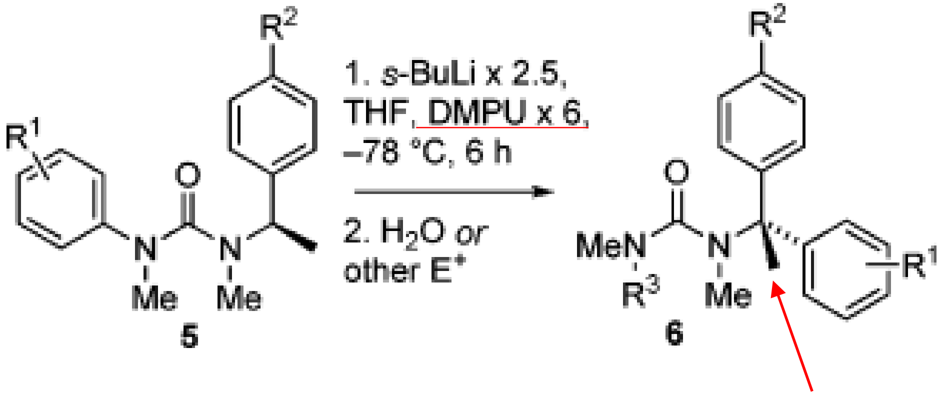


Table 1. Aryl Transfers in Lithiated *N*-Benzyl Ureas

entry	**1**	R^1	R^2	**3**, yield % (remaining **1**, %)	yield of **4**, % (method)
1	**1a**	Ph	2,6-diMe	**3a**, 89	
2	**1b**	Ph	4-Me	**3b**, 85	
3	**1c**	*p*-Tol	H	**3c**, 85	
4	**1d**	Me	H	**3d**, 78 (8)	84 (**B**)
5	**1e**	Me	2-Me	**3e**, 76 (15)	72 (**A**)
6	**1f**	Me	2-OMe	**3f**, 75 (21)	78 (**A**)
7	**1g**	Me	2,6-di-Me	**3g**, 82 (14)	84 (**A**)
8	**1h**	Me	4-Cl	**3h**, 69 (4)[a]	
9	**1i**	Me	4-OMe	**3i**, 76 (4)[a]	

This method could be applied to electron rich Ar.

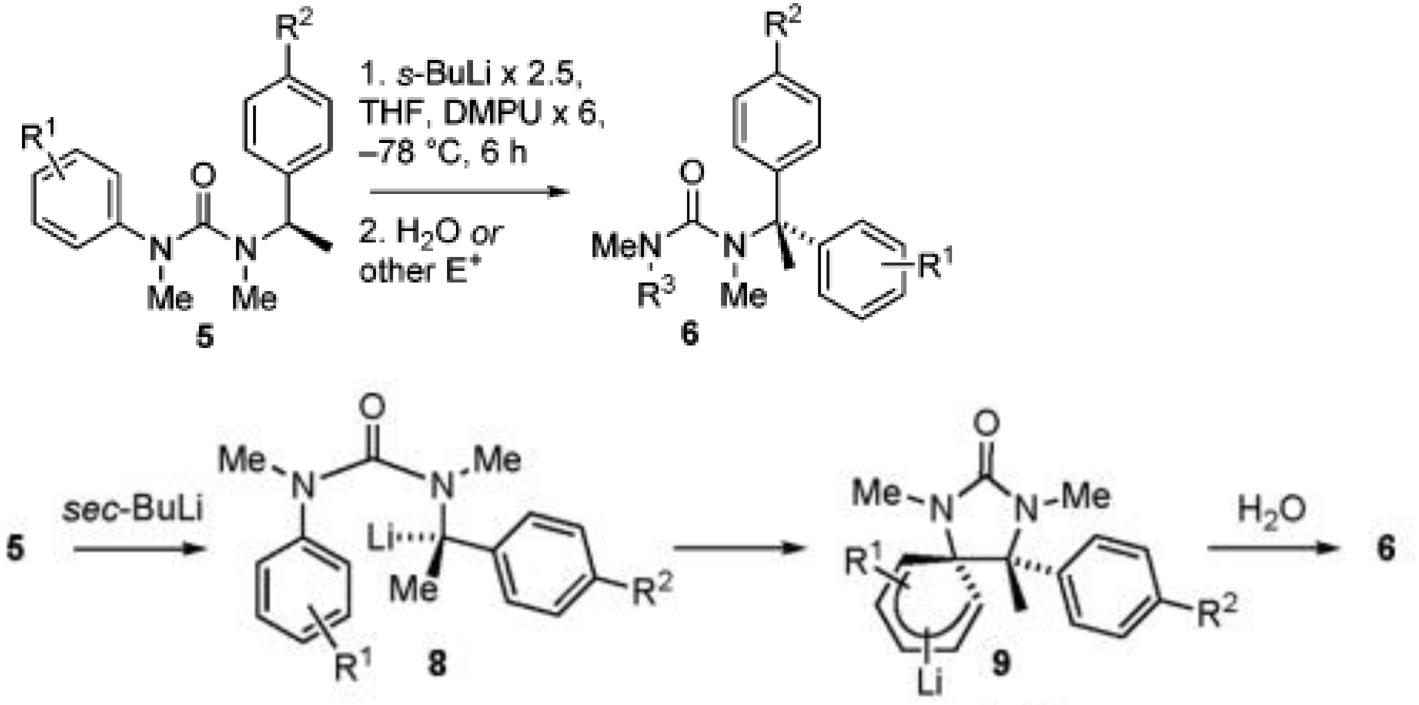
Asymmetric clayden rearrangement

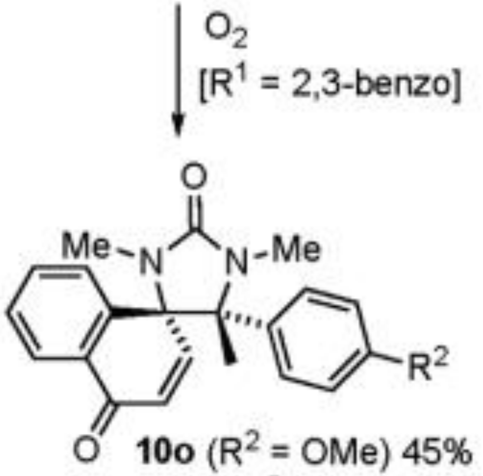


DMPU was added to increase the reactivity of the resulting organolithium.

Stereochemically retentive rearrangement.

Evidence that clayden rearrangement is occurring via intramolecular manner

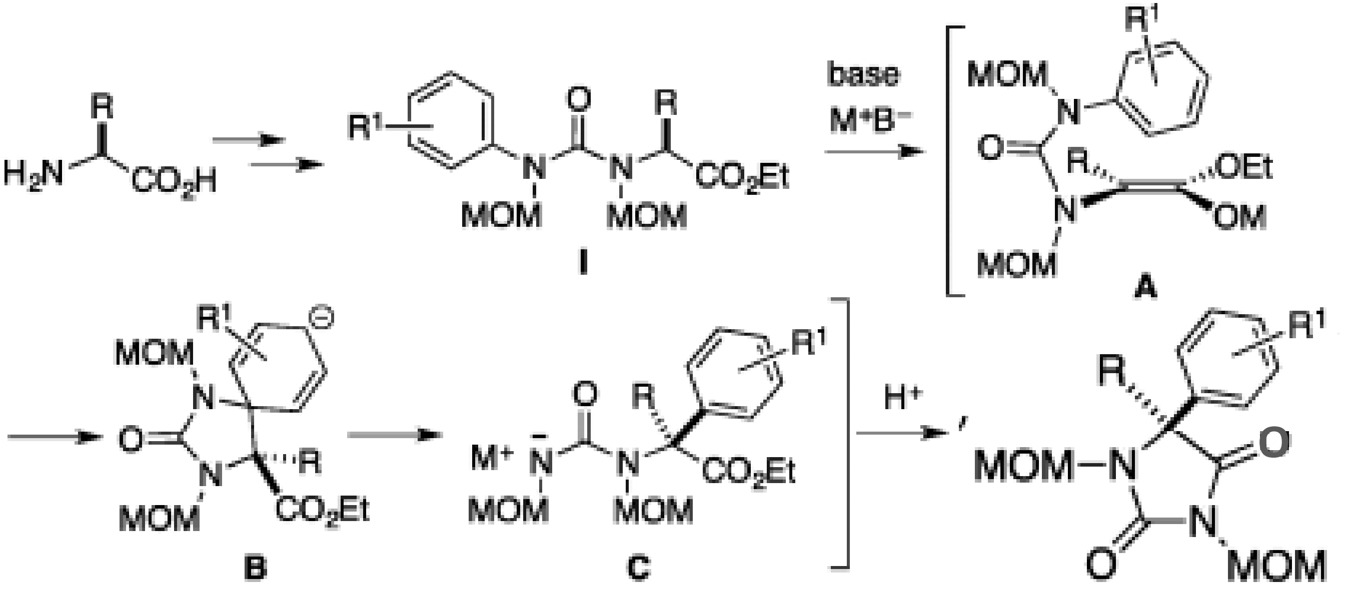




10o (R^2 = OMe) 45%
10p (R^2 = Cl) 56%

X-ray crystal structure of **10p**

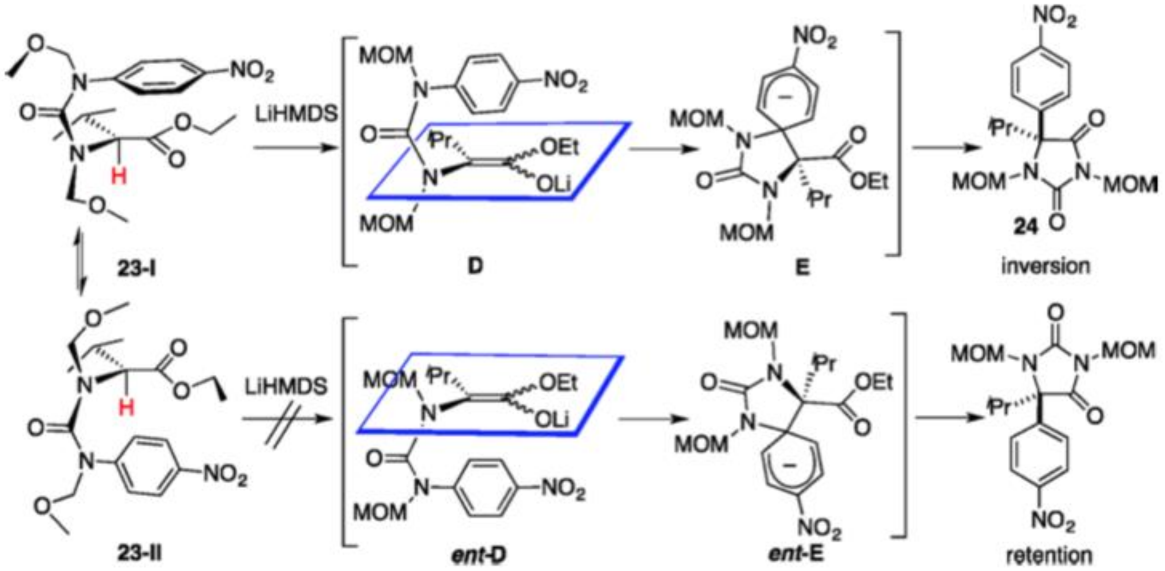
Application of clayden rearrangement to asymmetric α-arylation of amino acids



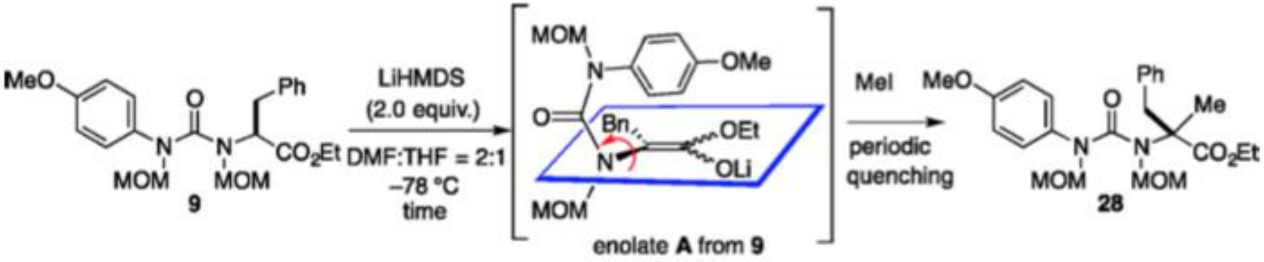
- **<u>Stereochemically invertive</u>** rearrangement.
- This method is applied to urea derivatives derived from L-phenylalanine, L-valine and L-methionine.

Kawabata, T. et. al. *J. Am. Chem. Soc.* 135, 13294 (2013).

Application of clayden rearrangement to asymmetric α-arylation of amino acids



It is deprotonated when the proton faces in a sterically empty direction.
Then, the anion reacts with the aromatic ring immediately and the stereochemistry reverses.

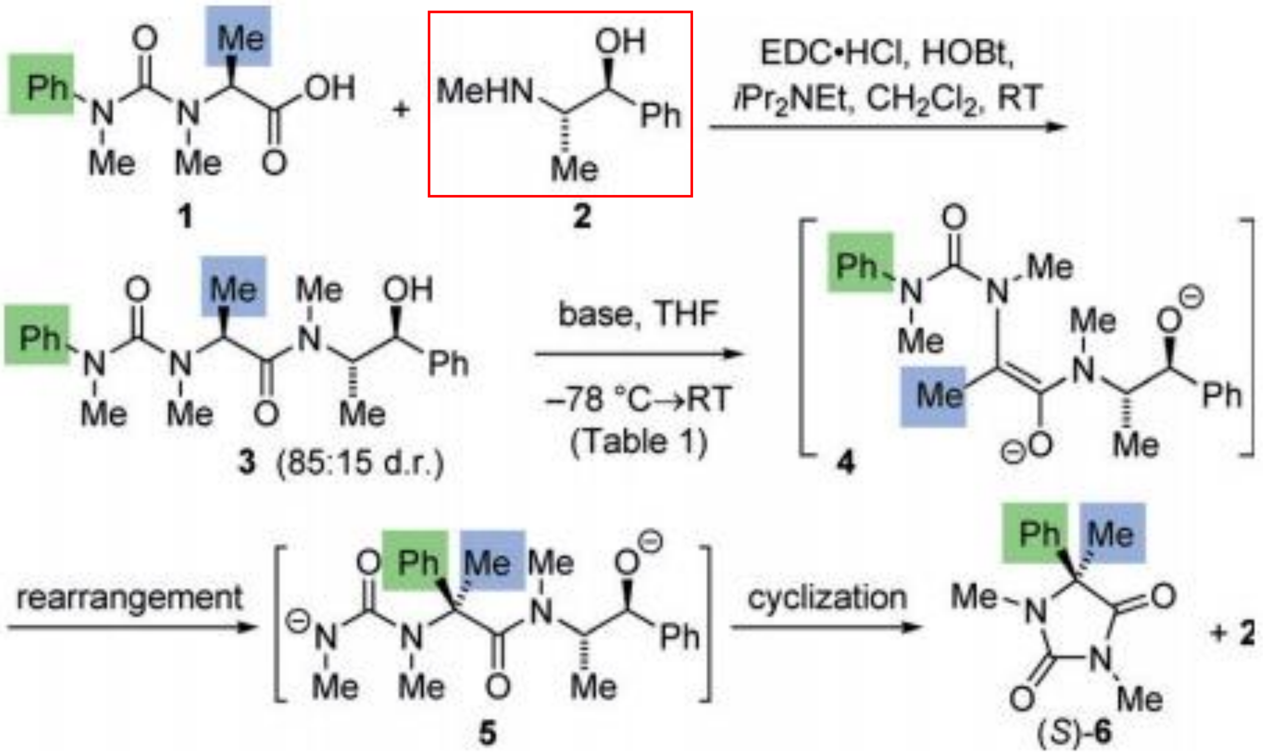


$t_{1/2}$ (racemization at –78 °C) = 2.6 h (experimentally measured)
ΔG^≠^ (racemization at –78 °C) =15.2 kcal/mol (calculated from $t_{1/2}$)
$t_{1/2}$ (racemization at –60 °C) = 5 min (roughly estimated from ΔG^≠^ at –78 °C)

When the Bn part is small, the rotation barrier is small, and epimerization occurs.

Expansion of substrate scope of asymmetric α-arylation of amino acids

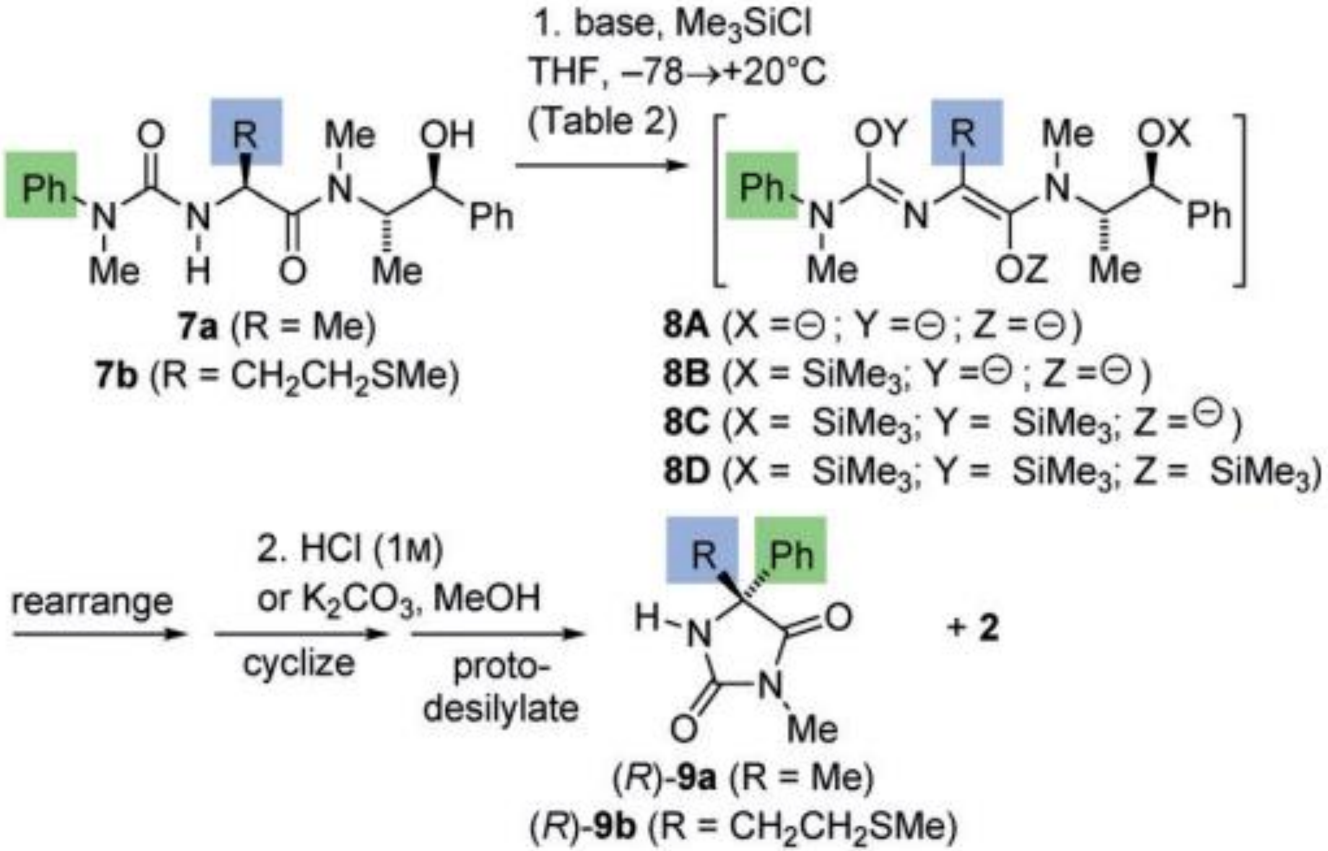
Pseudoephedrine auxiliary



- This method can be applied to urea derivatives derived from amino acids which **have small side chain.**
- **However**, The doubly N-methylated hydantoin product **6** proved extremely resistant to hydrolysis to the corresponding quaternary N-methylated amino acid.

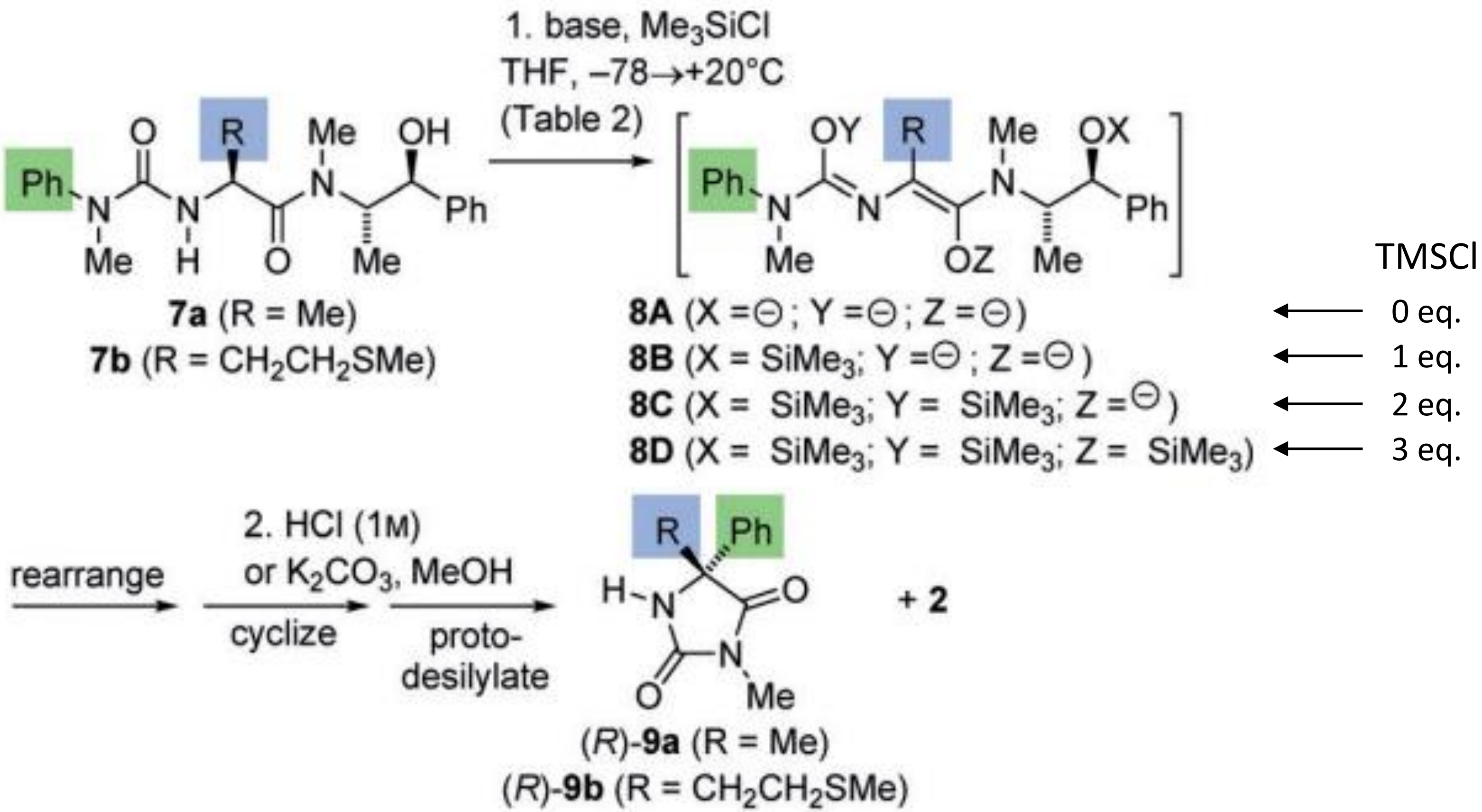
Clayden, J. et. al., *Angew.Chem.Int. Ed*. 54, 8961 (2015) .

Expansion of substrate scope of asymmetric α-arylation of amino acids



So they modified the substrates **3** with the aim of rearranging their N-unsubstituted analogues **7**.
Singly N-methylated hydantoin product **9** is easily hydrolyzed to the corresponding quaternary N-methylated amino acid.

Expansion of substrate scope of asymmetric α-arylation of amino acids



1. base, Me_3SiCl
THF, −78→+20°C
(Table 2)

rearrange

2. HCl (1 M)
or K_2CO_3, MeOH

cyclize

proto-desilylate

+ **2**

7a (R = Me)
7b (R = CH_2CH_2SMe)

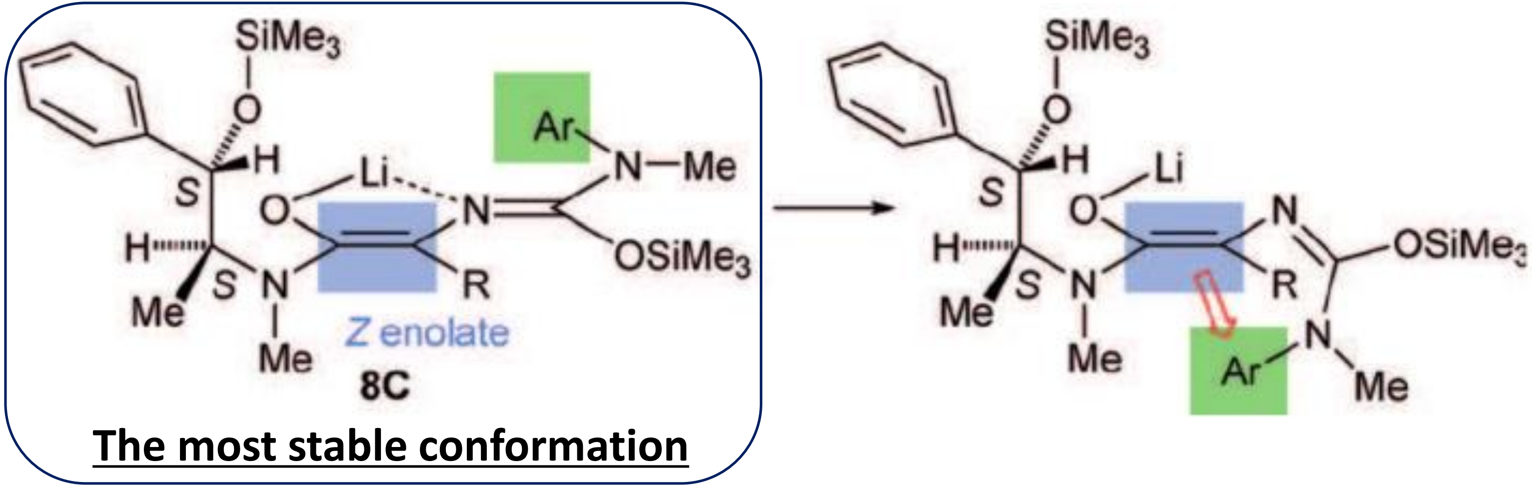
8A ($X = \ominus$; $Y = \ominus$; $Z = \ominus$)
8B ($X = SiMe_3$; $Y = \ominus$; $Z = \ominus$)
8C ($X = SiMe_3$; $Y = SiMe_3$; $Z = \ominus$)
8D ($X = SiMe_3$; $Y = SiMe_3$; $Z = SiMe_3$)

TMSCl
0 eq.
1 eq.
2 eq.
3 eq.

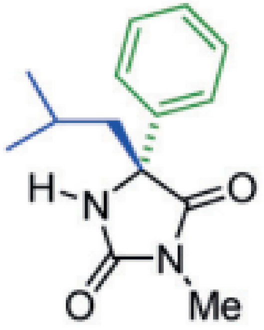
(*R*)-**9a** (R = Me)
(*R*)-**9b** (R = CH_2CH_2SMe)

Entry	SM	Base (equiv)	equiv of LiCl	equiv of Me_3SiCl	(*R*)-**9**, Yield[a] [%]	e.r. of **9** (*R*:*S*)
1	**7a**	LDA (4)	7	0	**9a**, 54	50:50
2	**7a**	LiTMP (4)	7	0	**9a**, 43	55:45
3	**7a**	LDA (4)	7	1	**9a**, 60	75:25
4	**7a**	LDA (4)	7	2[b]	**9a**, 65[b]	92:8
5	**7a**	LDA (4)	7	3 or 4	0	–[c]

Expansion of substrate scope of asymmetric α-arylation of amino acids

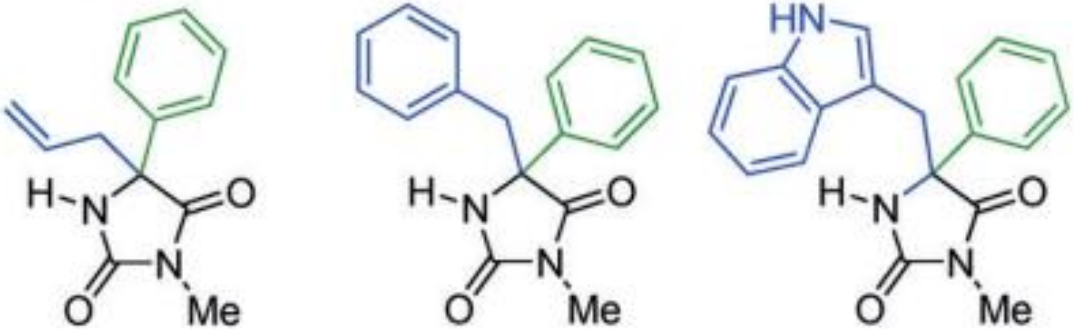


The most stable conformation



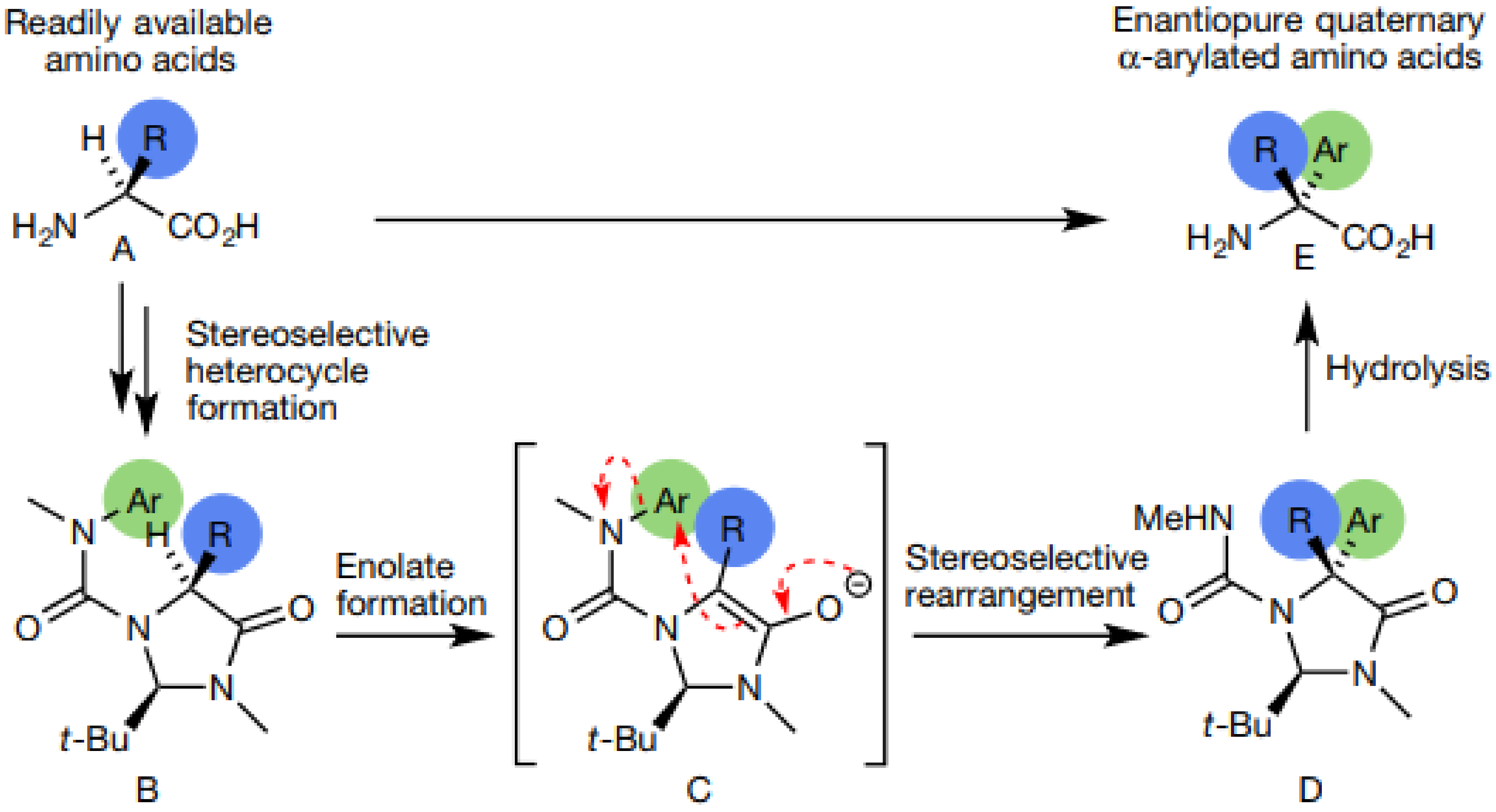
(*R*)-**9e** 46%; 80:20

Rearrangement of the more hindered leucine was less clean (and all attempted rearrangements of valine- or phenylglycine-derived ureas failed), suggesting that leucine lies at the limit of the methodÏs tolerance to steric hindrance.



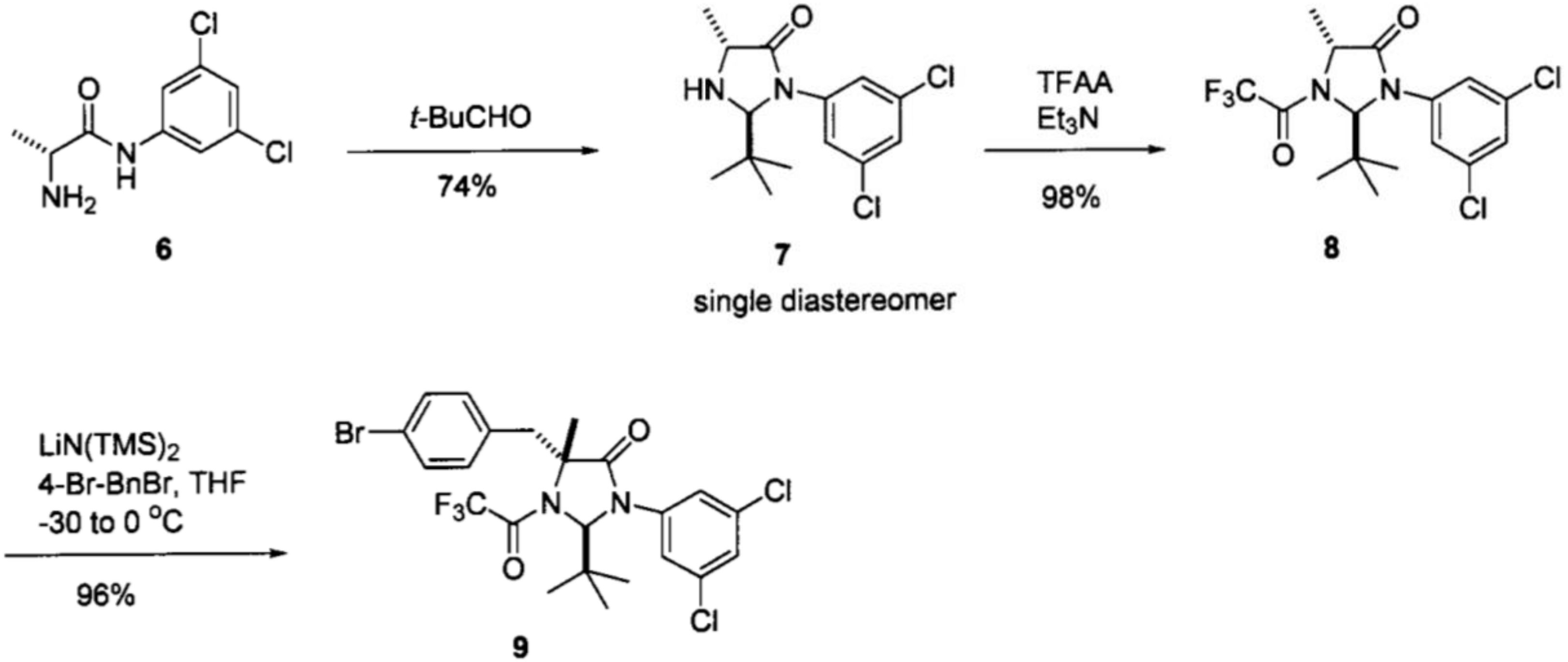
Some substrates (generally those with acidic protons in the β position) failed to rearrange cleanly.

Enantioselective introduction of an aryl substituent at the α-carbon



An amino acid (A) is converted diastereoselectively into an imidazolidinone (B) carrying a pendent urea function. Treatment with base forms an enolate (C) in which the aromatic substituent (Ar) of the urea migrates to the rear face of the imidazolidone, directed by the bulky tert-butyl group, as indicated by the red dotted arrows. Hydrolysis of the product (D) provides the quaternary α-aryl amino acid (E).

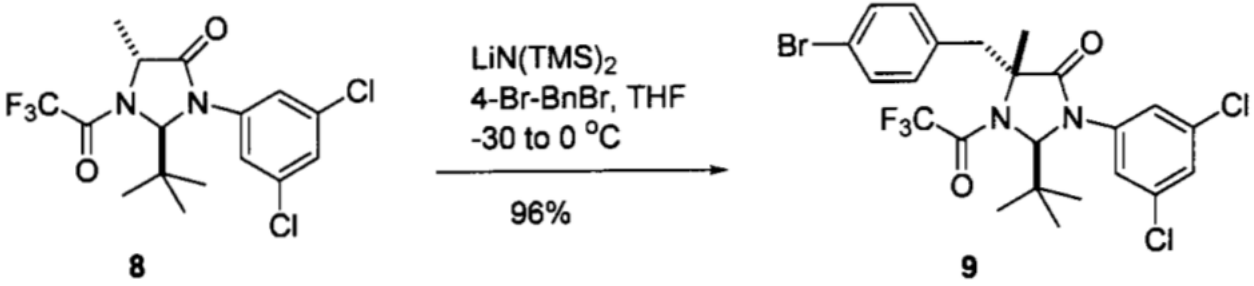
Self-regeneration of stereocentres



The principle of ‘**self-regeneration of stereocentres**’ 『in which the stereogenic centre of a chiral molecule generates a temporary centre of chirality, which in turn is used to introduce diastereoselectively a new ligand at the original stereogenic centre』 has been applied to the synthesis of various acyclic quaternary amino acids.

Self-regeneration of stereocentres & Clayden rearrangement

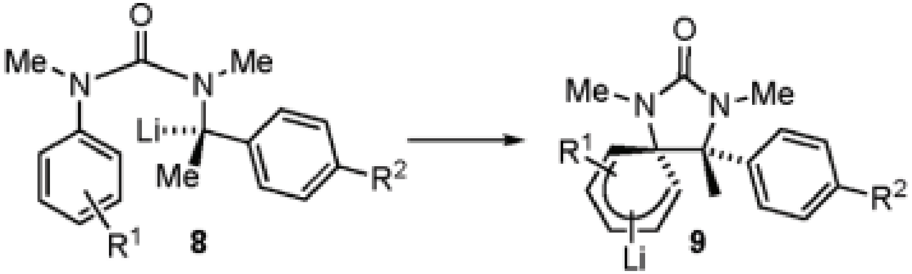
Self-regeneration of stereocentres



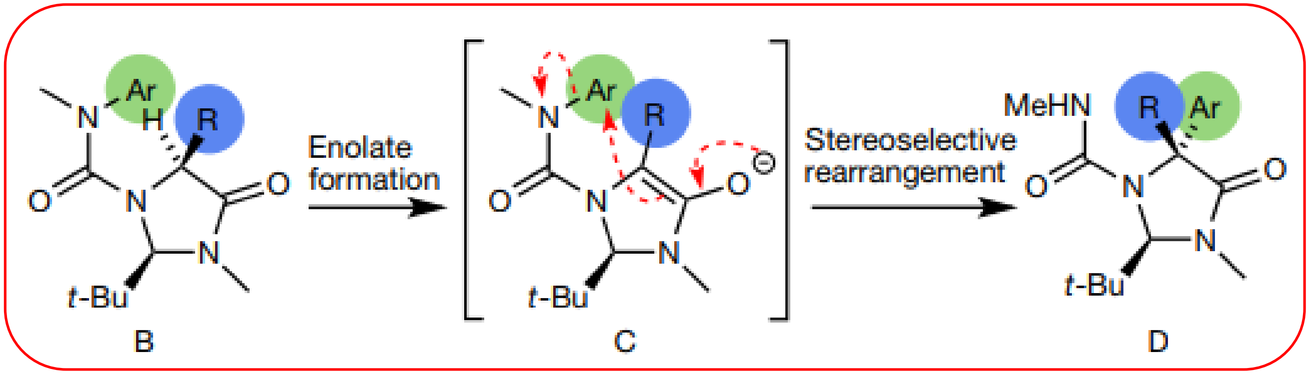
Stereoselective introduction of alkyl group to α-position of amino acid.

+

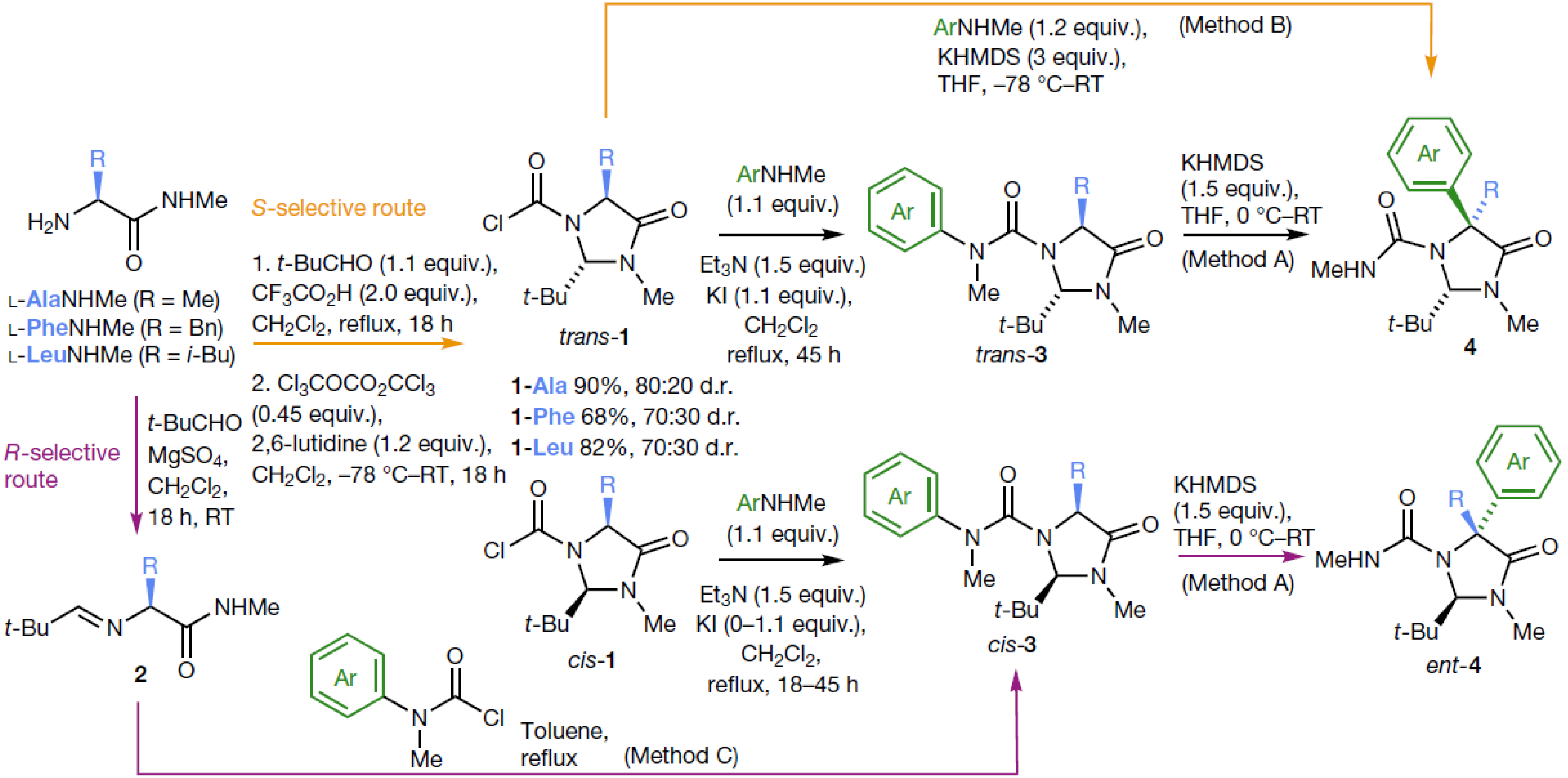
Clayden rearrangement



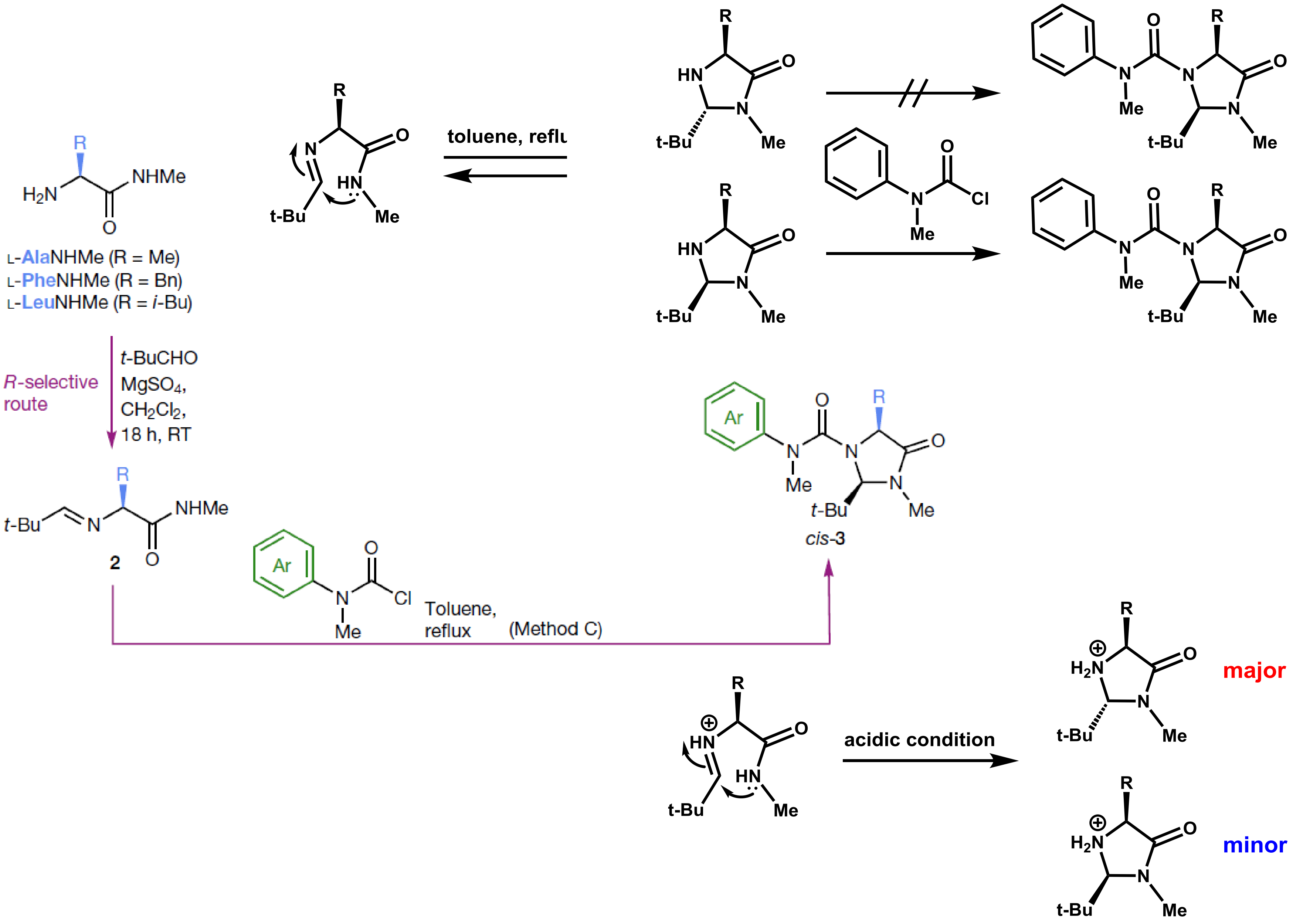
Intramolecular reaction using urea allows transposition of aryl.



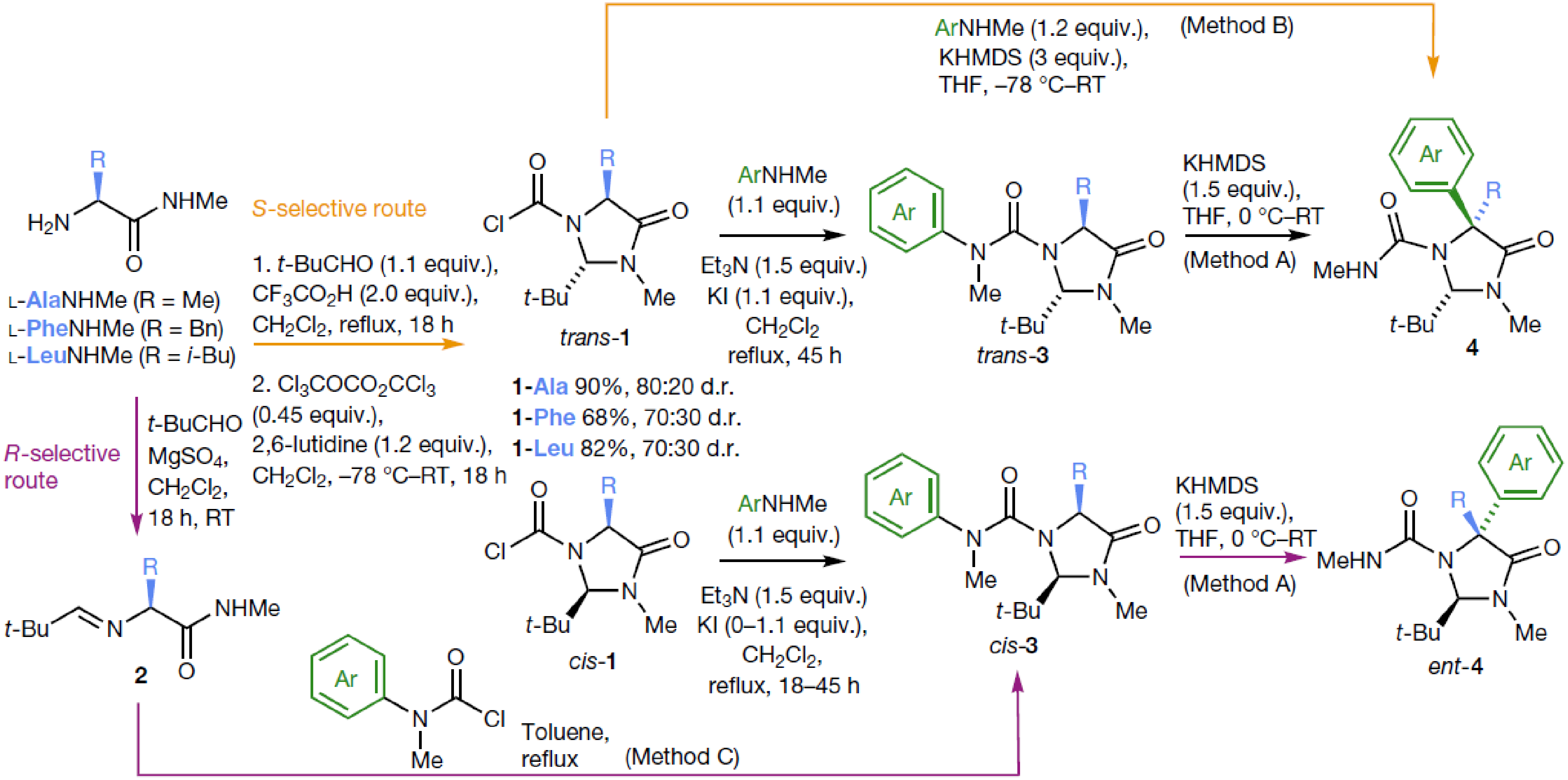
Synthesis imidazolidinone intermediate



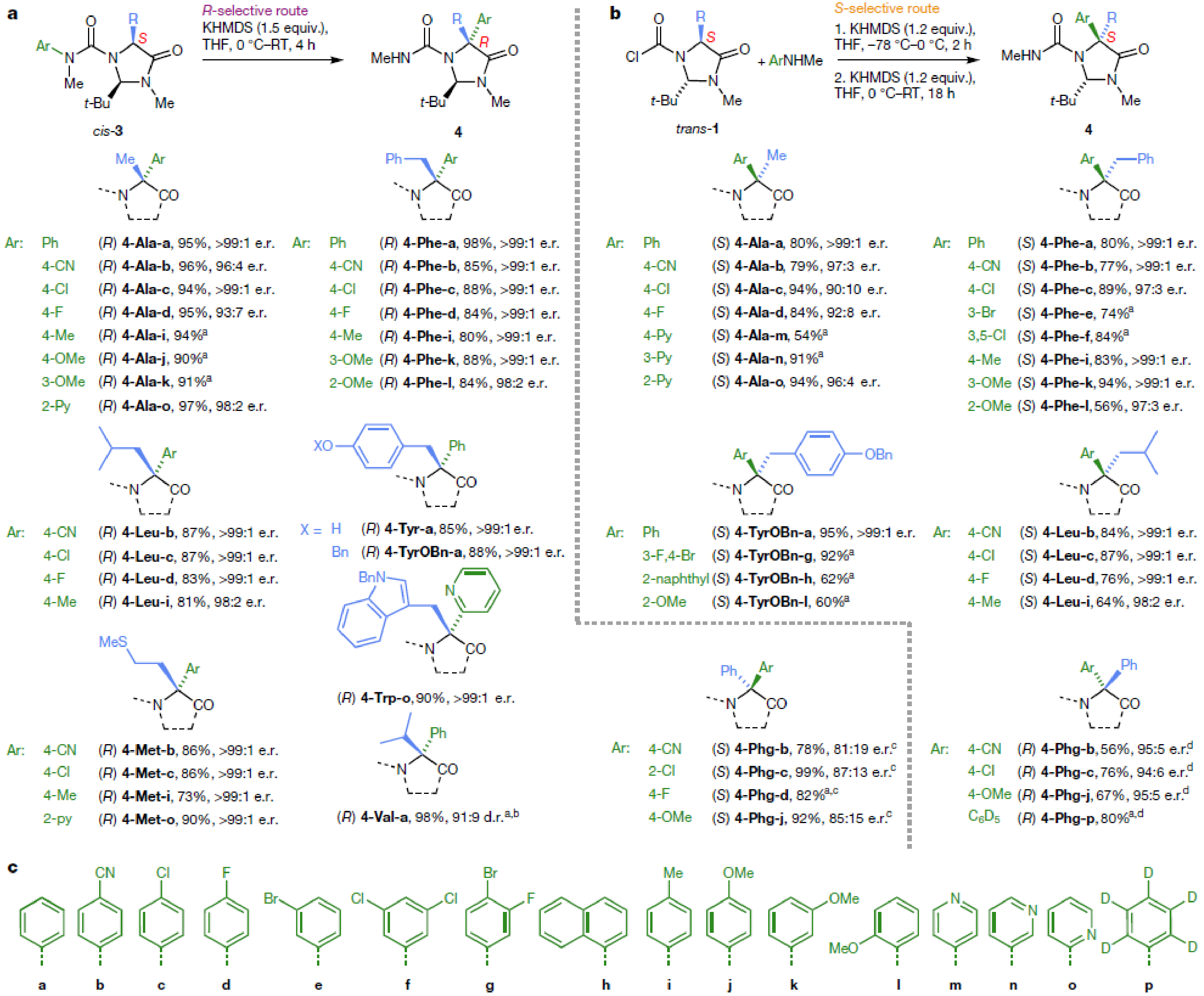
Synthesis imidazolidinone intermediate cis-3



Synthesis imidazolidinone intermediate cis-3



Scope of the imidazolidinone arylation: amino acids and migrating groups



a *R*-selective route: KHMDS (1.5 equiv.), THF, 0 °C–RT, 4 h

Ar:	Ph	(*R*) **4-Ala-a**, 95%, >99:1 e.r.
	4-CN	(*R*) **4-Ala-b**, 96%, 96:4 e.r.
	4-Cl	(*R*) **4-Ala-c**, 94%, >99:1 e.r.
	4-F	(*R*) **4-Ala-d**, 95%, 93:7 e.r.
	4-Me	(*R*) **4-Ala-i**, 94%^{a}
	4-OMe	(*R*) **4-Ala-j**, 90%^{a}
	3-OMe	(*R*) **4-Ala-k**, 91%^{a}
	2-Py	(*R*) **4-Ala-o**, 97%, 98:2 e.r.

Ar:	Ph	(*R*) **4-Phe-a**, 98%, >99:1 e.r.
	4-CN	(*R*) **4-Phe-b**, 85%, >99:1 e.r.
	4-Cl	(*R*) **4-Phe-c**, 88%, >99:1 e.r.
	4-F	(*R*) **4-Phe-d**, 84%, >99:1 e.r.
	4-Me	(*R*) **4-Phe-i**, 80%, >99:1 e.r.
	3-OMe	(*R*) **4-Phe-k**, 88%, >99:1 e.r.
	2-OMe	(*R*) **4-Phe-l**, 84%, 98:2 e.r.

Ar:	4-CN	(*R*) **4-Leu-b**, 87%, >99:1 e.r.
	4-Cl	(*R*) **4-Leu-c**, 87%, >99:1 e.r.
	4-F	(*R*) **4-Leu-d**, 83%, >99:1 e.r.
	4-Me	(*R*) **4-Leu-i**, 81%, 98:2 e.r.

X =	H	(*R*) **4-Tyr-a**, 85%, >99:1 e.r.
	Bn	(*R*) **4-TyrOBn-a**, 88%, >99:1 e.r.

(*R*) **4-Trp-o**, 90%, >99:1 e.r.

Ar:	4-CN	(*R*) **4-Met-b**, 86%, >99:1 e.r.
	4-Cl	(*R*) **4-Met-c**, 86%, >99:1 e.r.
	4-Me	(*R*) **4-Met-i**, 73%, >99:1 e.r.
	2-py	(*R*) **4-Met-o**, 90%, >99:1 e.r.

(*R*) **4-Val-a**, 98%, 91:9 d.r.^{a,b}

b *S*-selective route: 1. KHMDS (1.2 equiv.), THF, −78 °C–0 °C, 2 h; 2. KHMDS (1.2 equiv.), THF, 0 °C–RT, 18 h

Ar:	Ph	(*S*) **4-Ala-a**, 80%, >99:1 e.r.
	4-CN	(*S*) **4-Ala-b**, 79%, 97:3 e.r.
	4-Cl	(*S*) **4-Ala-c**, 94%, 90:10 e.r.
	4-F	(*S*) **4-Ala-d**, 84%, 92:8 e.r.
	4-Py	(*S*) **4-Ala-m**, 54%^{a}
	3-Py	(*S*) **4-Ala-n**, 91%^{a}
	2-Py	(*S*) **4-Ala-o**, 94%, 96:4 e.r.

Ar:	Ph	(*S*) **4-Phe-a**, 80%, >99:1 e.r.
	4-CN	(*S*) **4-Phe-b**, 77%, >99:1 e.r.
	4-Cl	(*S*) **4-Phe-c**, 89%, 97:3 e.r.
	3-Br	(*S*) **4-Phe-e**, 74%^{a}
	3,5-Cl	(*S*) **4-Phe-f**, 84%^{a}
	4-Me	(*S*) **4-Phe-i**, 83%, >99:1 e.r.
	3-OMe	(*S*) **4-Phe-k**, 94%, >99:1 e.r.
	2-OMe	(*S*) **4-Phe-l**, 56%, 97:3 e.r.

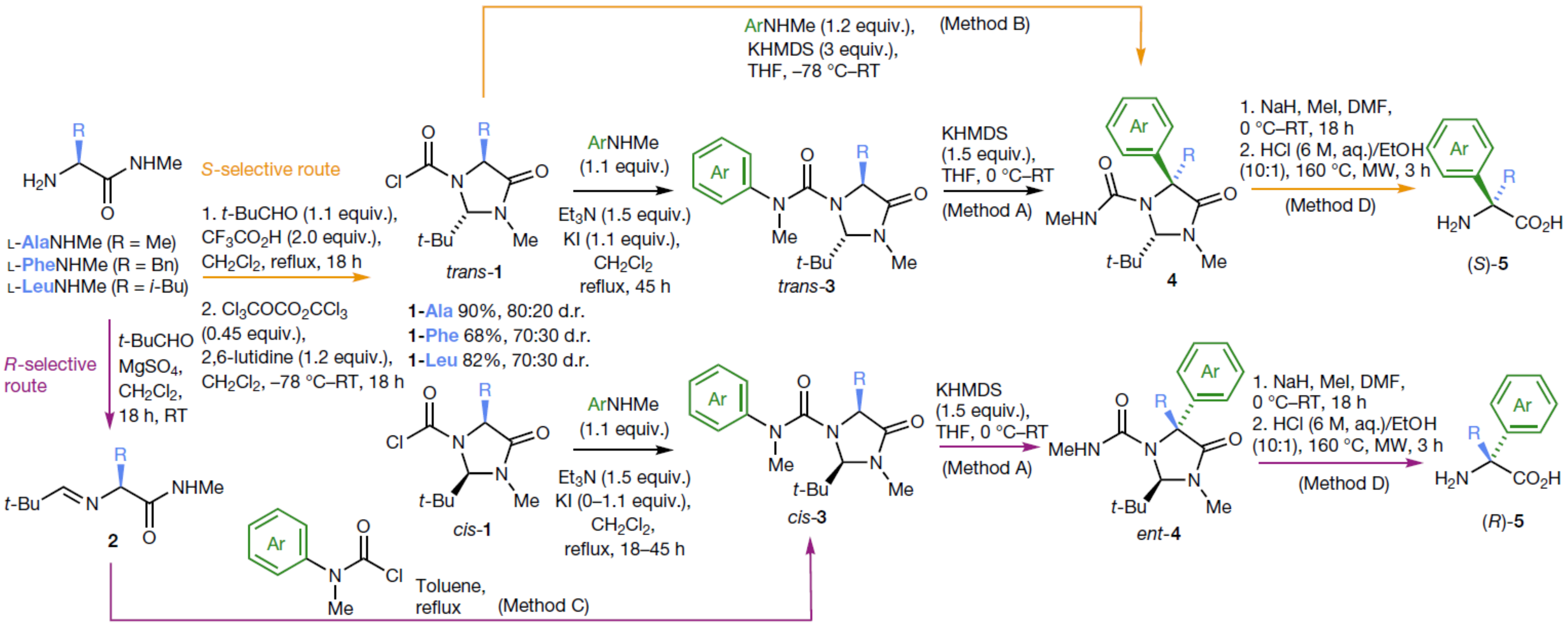
Ar:	Ph	(*S*) **4-TyrOBn-a**, 95%, >99:1 e.r.
	3-F,4-Br	(*S*) **4-TyrOBn-g**, 92%^{a}
	2-naphthyl	(*S*) **4-TyrOBn-h**, 62%^{a}
	2-OMe	(*S*) **4-TyrOBn-l**, 60%^{a}

Ar:	4-CN	(*S*) **4-Leu-b**, 84%, >99:1 e.r.
	4-Cl	(*S*) **4-Leu-c**, 87%, >99:1 e.r.
	4-F	(*S*) **4-Leu-d**, 76%, >99:1 e.r.
	4-Me	(*S*) **4-Leu-i**, 64%, 98:2 e.r.

Ar:	4-CN	(*S*) **4-Phg-b**, 78%, 81:19 e.r.^{c}
	2-Cl	(*S*) **4-Phg-c**, 99%, 87:13 e.r.^{c}
	4-F	(*S*) **4-Phg-d**, 82%^{a,c}
	4-OMe	(*S*) **4-Phg-j**, 92%, 85:15 e.r.^{c}

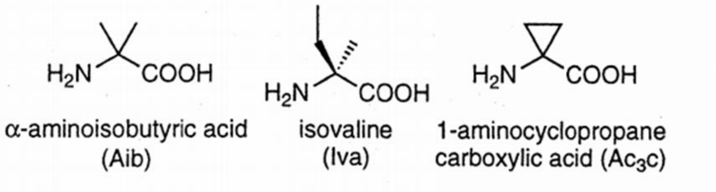
Ar:	4-CN	(*R*) **4-Phg-b**, 56%, 95:5 e.r.^{d}
	4-Cl	(*R*) **4-Phg-c**, 76%, 94:6 e.r.^{d}
	4-OMe	(*R*) **4-Phg-j**, 67%, 95:5 e.r.^{d}
	C_6D_5	(*R*) **4-Phg-p**, 80%^{a,d}

Clayden’s Quaternary amino acid synthesis



- It avoids the use of **valuable transition metals**.
- It enables arylation with electron-rich, electron-poor and heterocyclic substituents.
- **Either enantiomer** of the product can be formed from a **single** amino acid precursor.
- The method is practical and scalable, and provides the opportunity to produce α-arylated quaternary amino acids in multi-gram quantities.

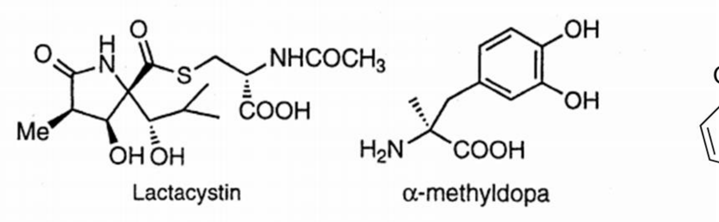
Summary



α-aminoisobutyric acid (Aib)

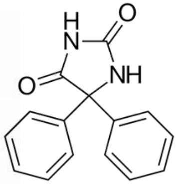
isovaline (Iva)

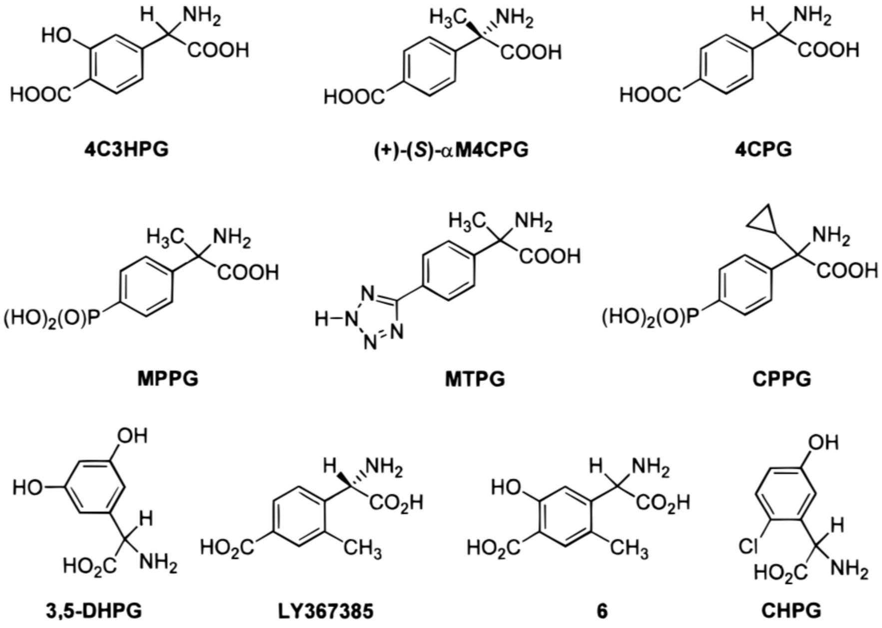
1-aminocyclopropane carboxylic acid (Ac_3c)



Lactacystin

α-methyldopa





4C3HPG

(+)-(*S*)-αM4CPG

4CPG

MPPG

MTPG

CPPG

3,5-DHPG

LY367385

6

CHPG

Medicine

phytosulfokine peptide