



Stereoselective Synthesis of β -Alkylated α -Amino Acids via Palladium-Catalyzed Alkylation of Unactivated Methylene C(sp³)-H Bonds with Primary Alkyl Halides

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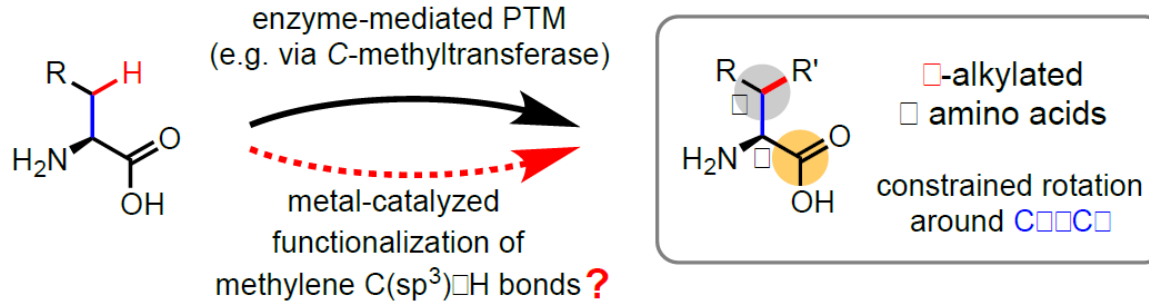
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Group: Prof. ZHAO

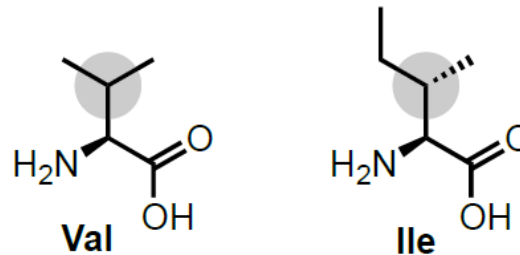
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Date: 2013-7-29

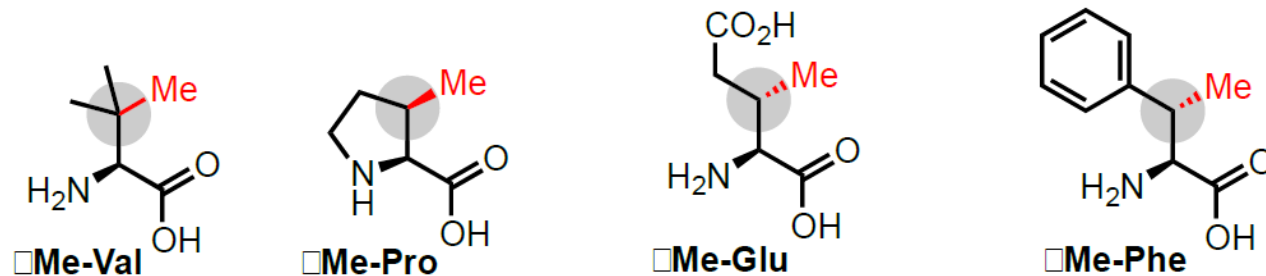
Occurrence of β -Alkylated α -Amino Acids



A) Proteinogenic β -alkylated amino acids

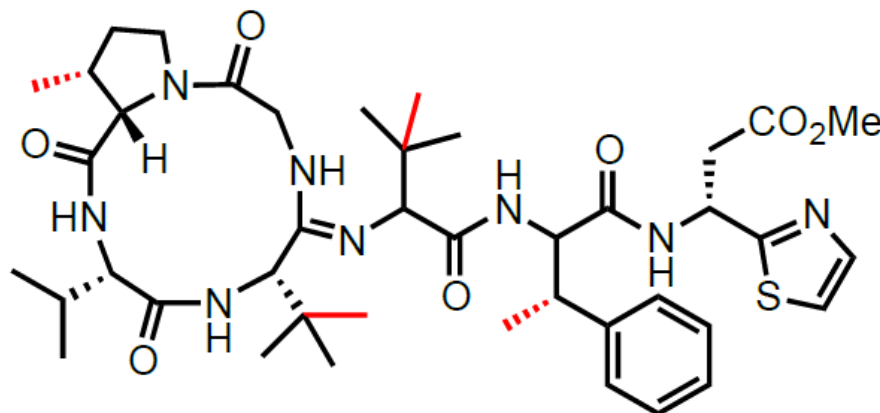


B) Selected naturally occurring β -methylated amino acids

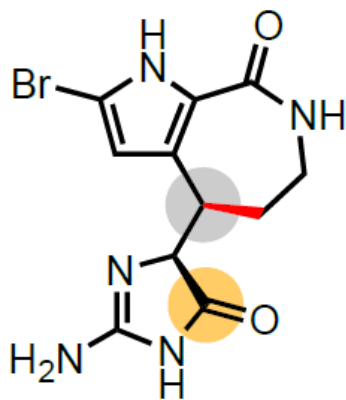


Occurrence of β -Alkylated α -Amino Acids

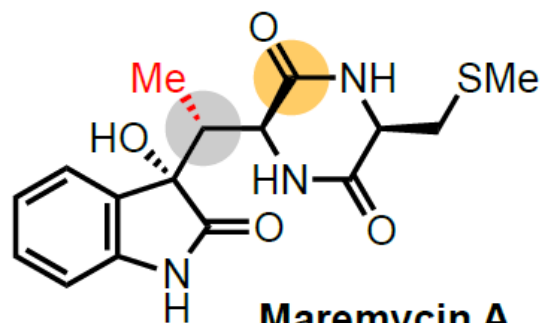
C) Selected natural products containing β -alkylated α amino acid motifs



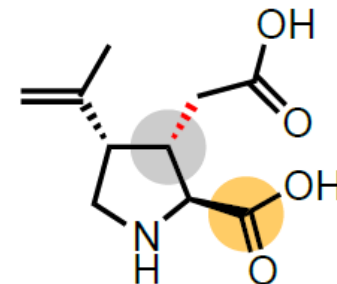
Bottromycin A₂



Dihydrohymenialdisine



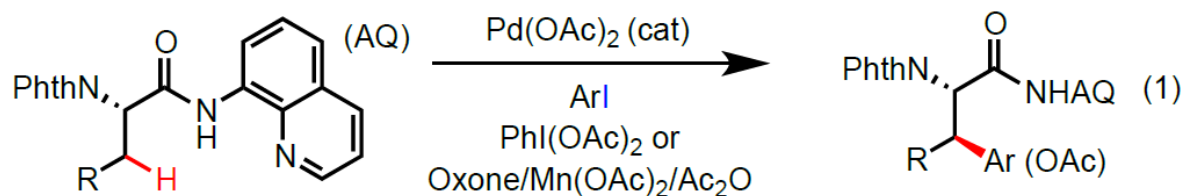
Maremycin A



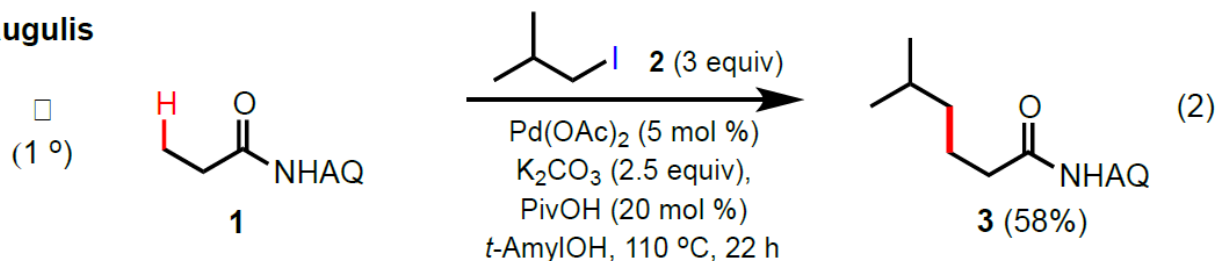
Kainic acid

DG-Mediated Pd-Catalyzed Alkylation of Unactivated C(sp³)-H Bonds with Primary Alkyl Halides

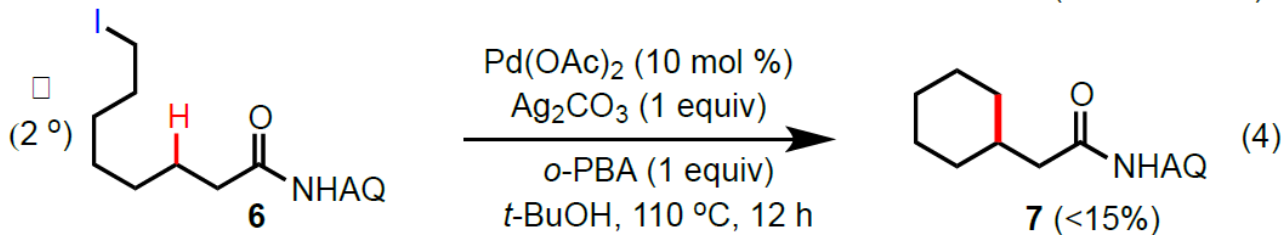
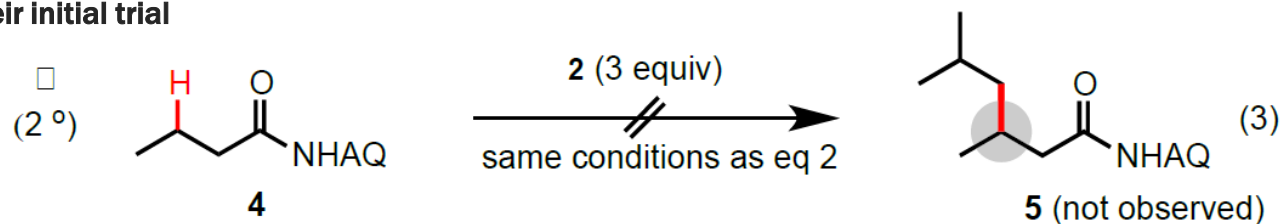
Daugulis, Corey



Daugulis

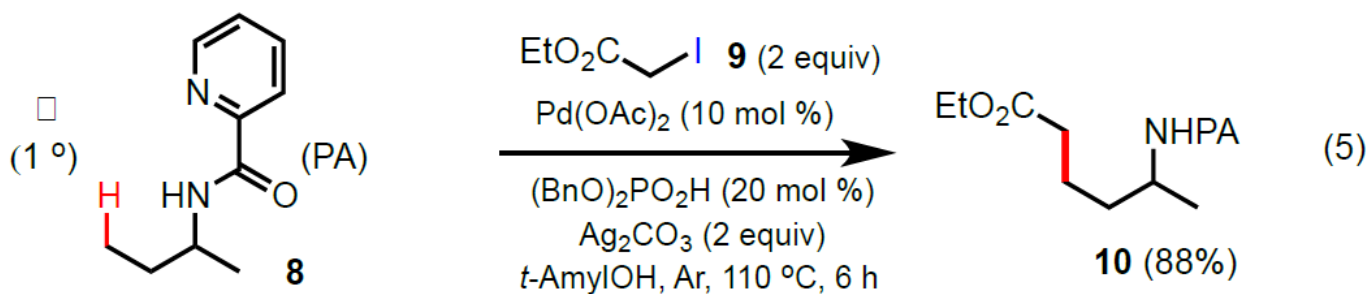


Their initial trial

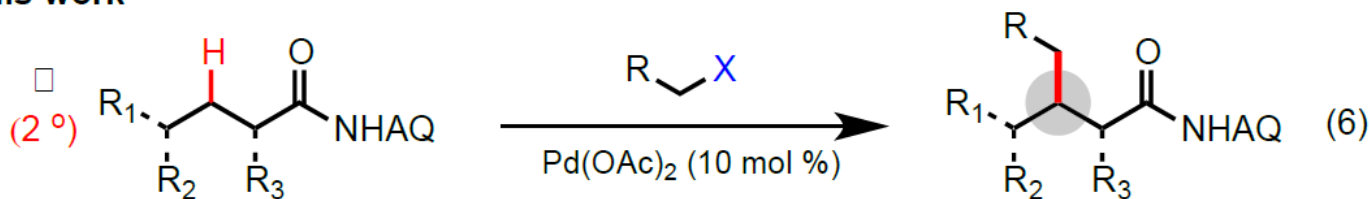


DG-Mediated Pd-Catalyzed Alkylation of Unactivated C(sp³)-H Bonds with Primary Alkyl Halides

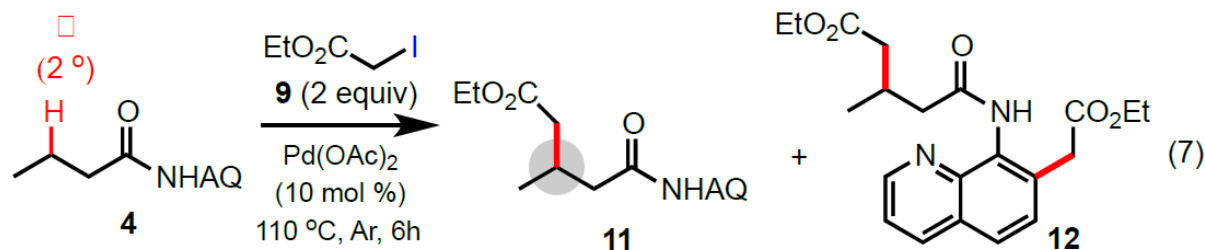
Their previous work



This work

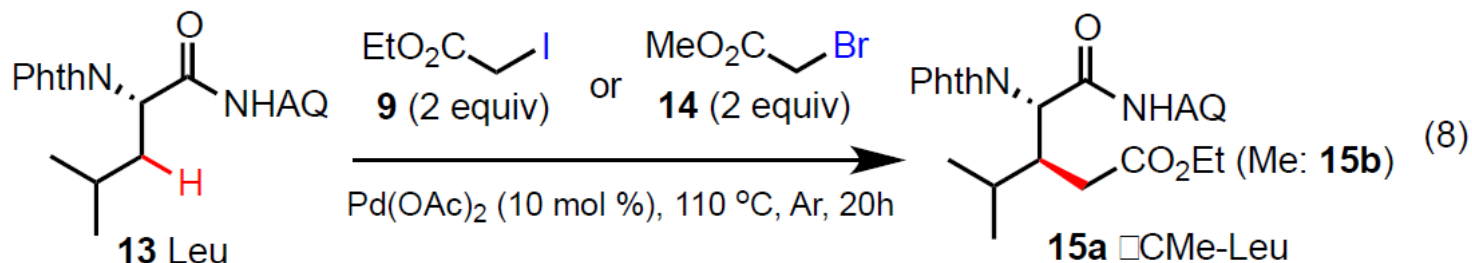


Optimization of AQ-Directed C(sp³)-H Alkylation of Simple Aliphatic Carboxamide 4



entry	reagents (equiv)	solvents ^a	Yields (%) ^b	
			11	12
1	K ₂ CO ₃ (2)	A	11	<2
2	K ₂ CO ₃ (2), PivOH (0.2)	A	18	<2
3	PivOH (0.2)	A	<2	<2
4	AgOAc (2)	A	85	3
5	AgOAc (2)	T	46	<2
6	Ag ₂ CO ₃ (2)	A	86	5
7	Ag ₂ CO ₃ (2), PivOH (0.2)	A	75	<3
8	Ag ₂ CO ₃ (2), (BnO) ₂ PO ₂ H (0.2)	A	91 (85) ^c	5
9	Ag ₂ CO ₃ (2), (BnO) ₂ PO ₂ H (0.2)	T	67	<2
10	Ag ₂ CO ₃ (2), TEMPO (1)	A	82	<2

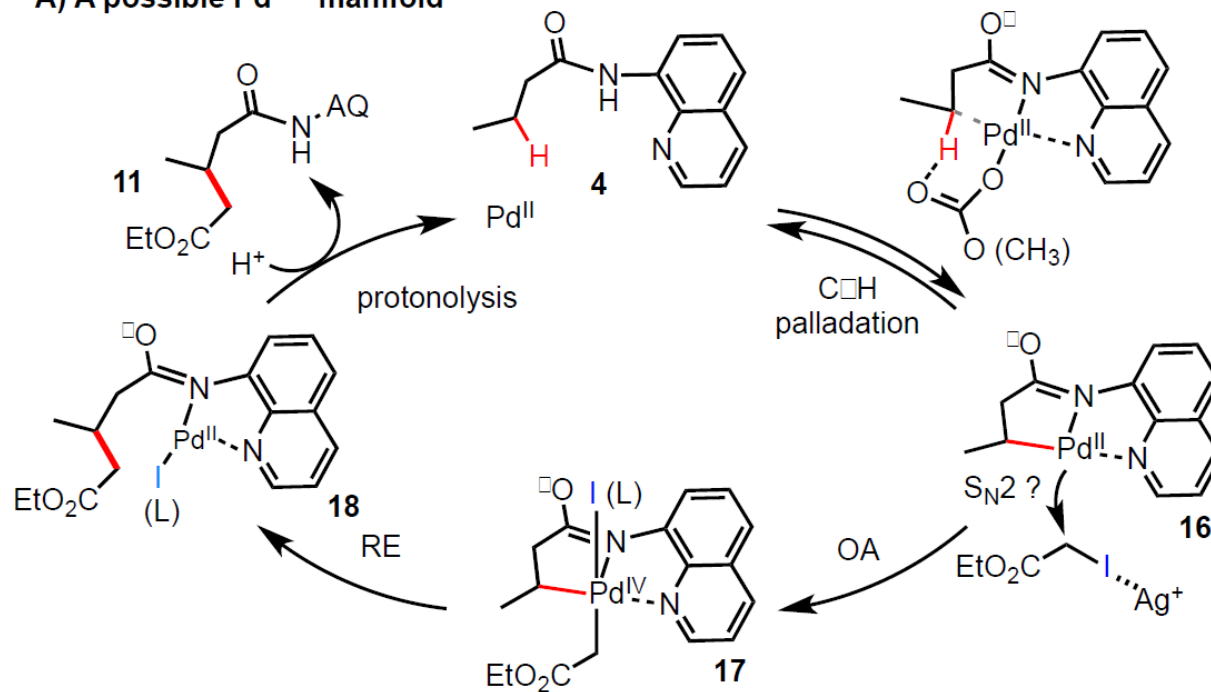
Optimization of AQ-Directed C(sp³)-H Alkylation of *N*-Phth Protected Leu 13



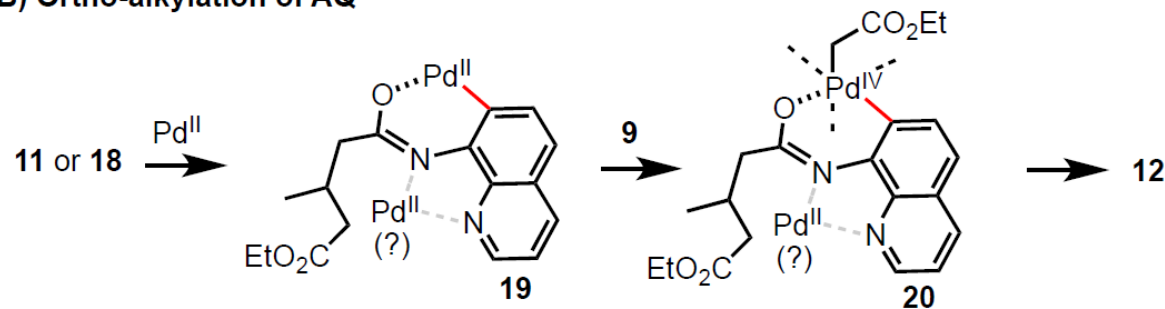
entry	reagents (equiv)	solvents ^a	Yields (%) ^b
			15
1	9 (2), AgOAc (2)	A	36
2	9 (2), Ag ₂ CO ₃ (1)	A	31
3	9 (2), Ag ₂ CO ₃ (1), (BnO) ₂ PO ₂ H (0.2)	A	59
4	9 (2), AgOAc (2), (BnO) ₂ PO ₂ H (0.2)	A	45
5	9 (2), Ag ₂ CO ₃ (2), (BnO) ₂ PO ₂ H (0.2)	A	74
6	9 (2), Ag ₂ CO ₃ (2), BINA-PO ₂ H ^c (0.2)	A	46
7	9 (2), Ag ₂ CO ₃ (2), (PhO) ₂ PO ₂ H (0.2)	A	59
8	14 (2), Ag ₂ CO ₃ (2), (BnO) ₂ PO ₂ H (0.2)	A	78 (70) ^d
9	14 (2), Ag ₂ CO ₃ (2), (BnO) ₂ PO ₂ H (1)	A	31

Mechanistic Hypothesis

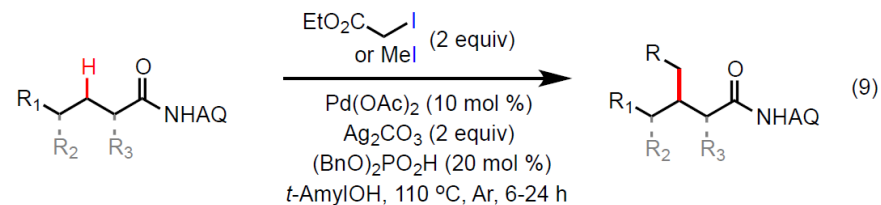
A) A possible Pd^{II/IV} manifold



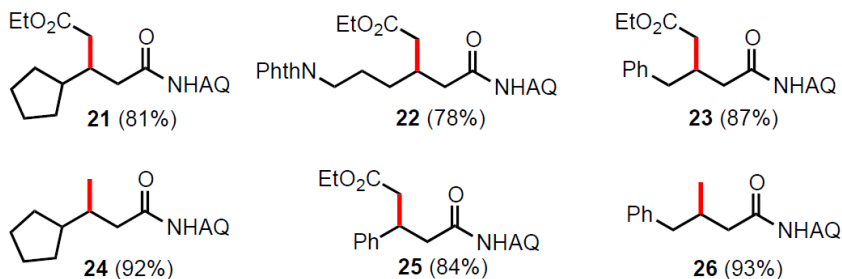
B) Ortho-alkylation of AQ



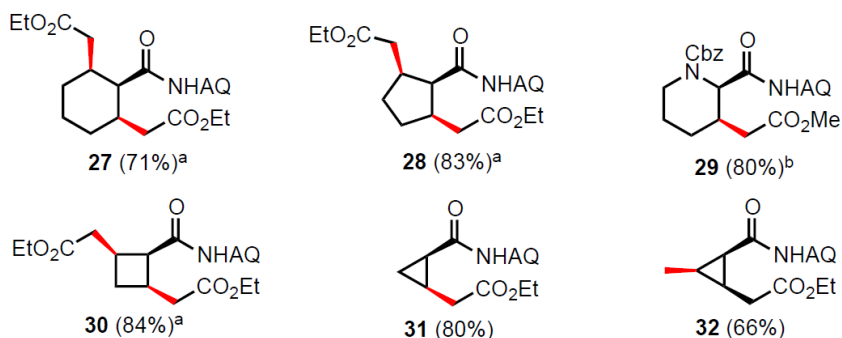
AQ-Directed C(sp³)-H Alkylation of Simple Aliphatic Carboxamide Substrates



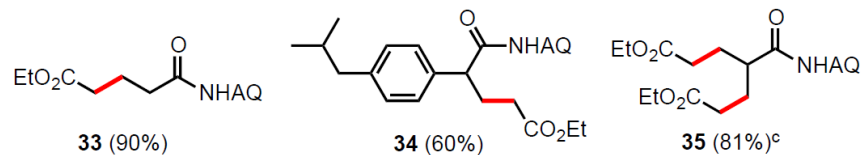
A) Alkylation of 2° C(sp³)-H bonds of substrates without α -substituents



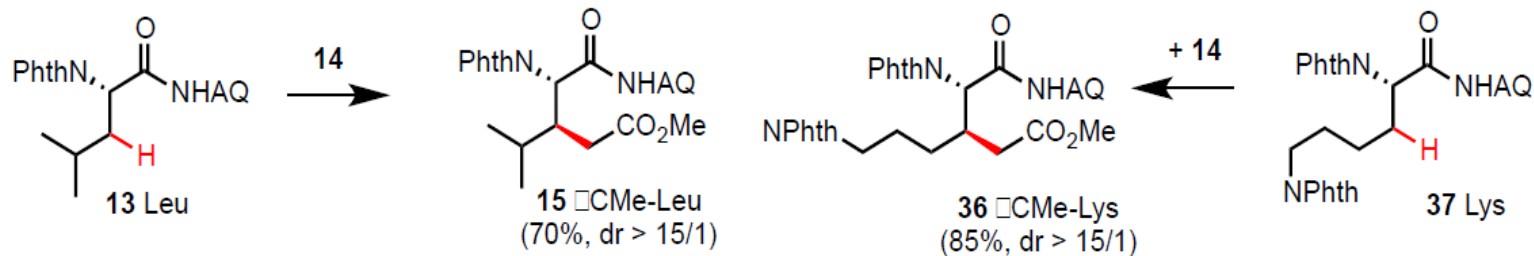
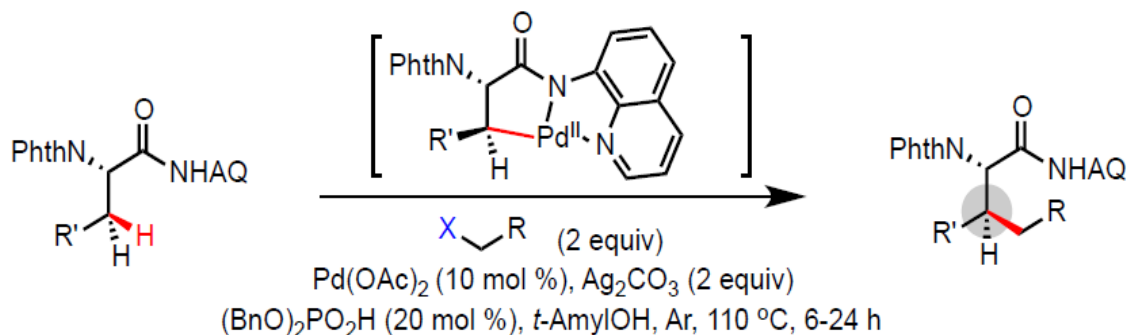
B) Alkylation of 2° C(sp³)-H bonds of cyclic substrates



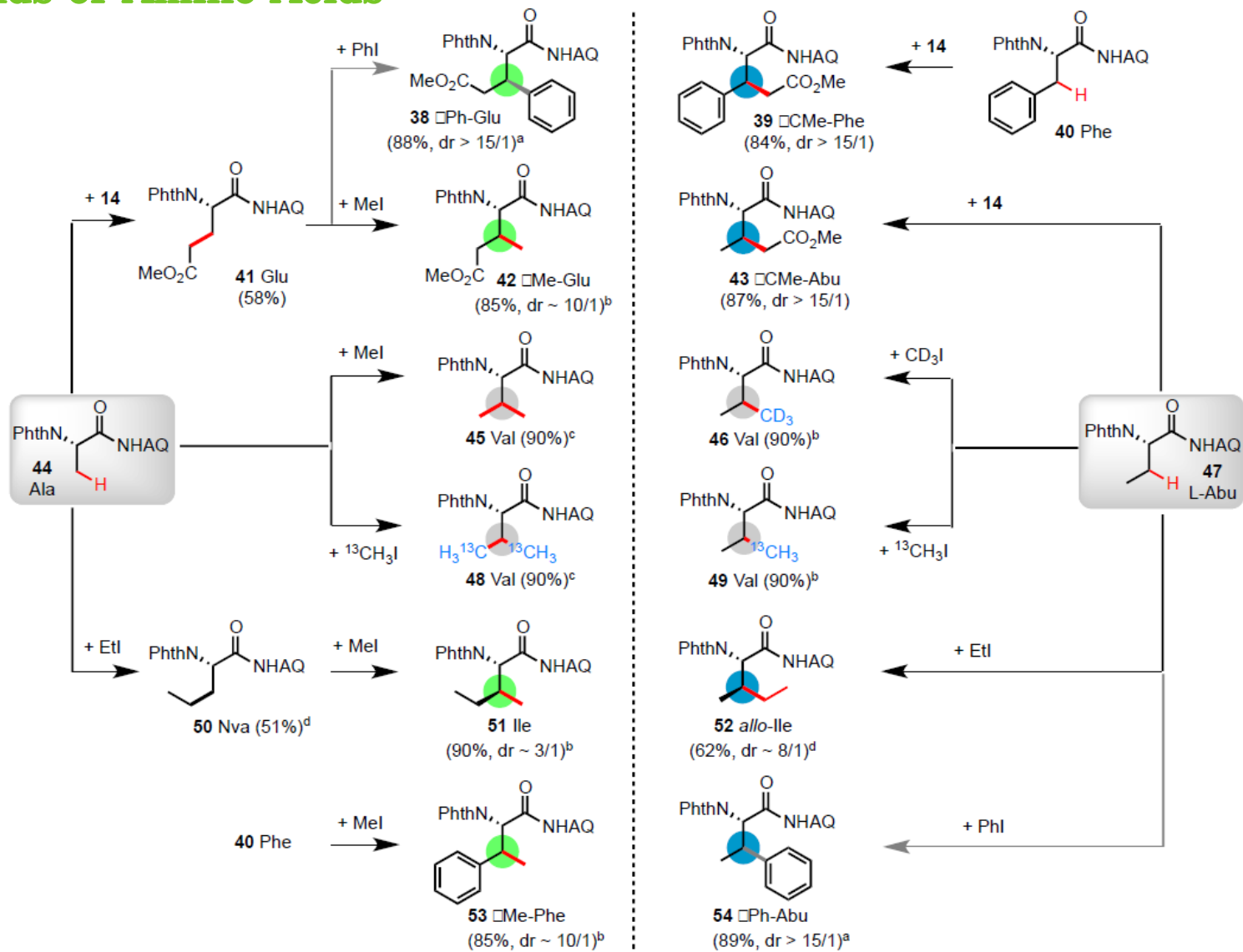
C) Alkylation of 1° C(sp³)-H bonds



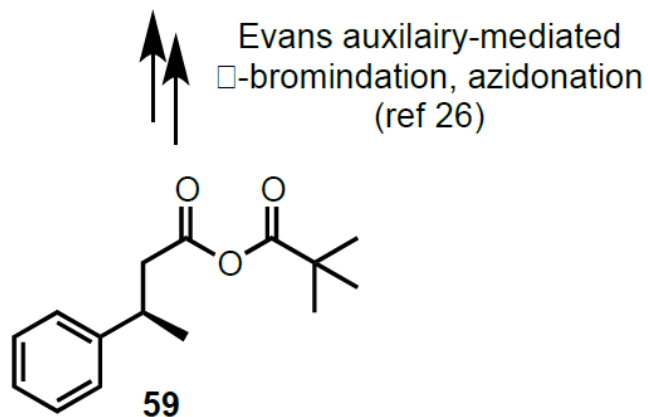
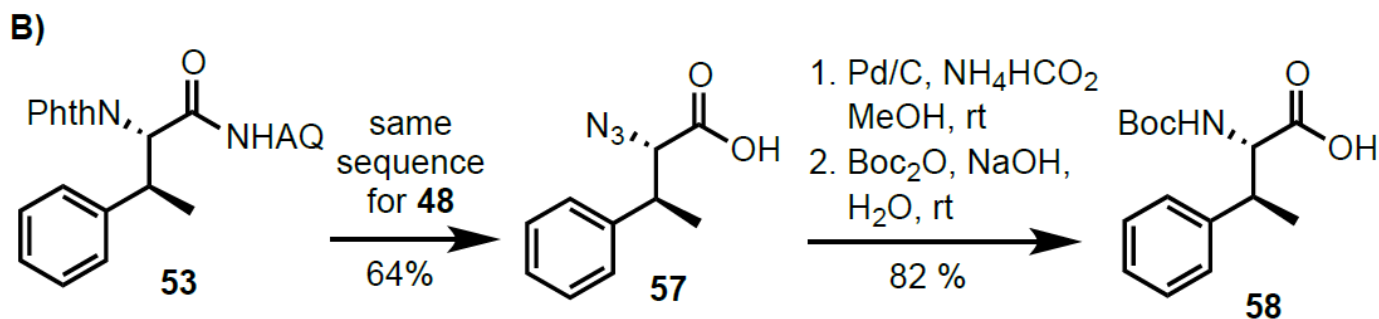
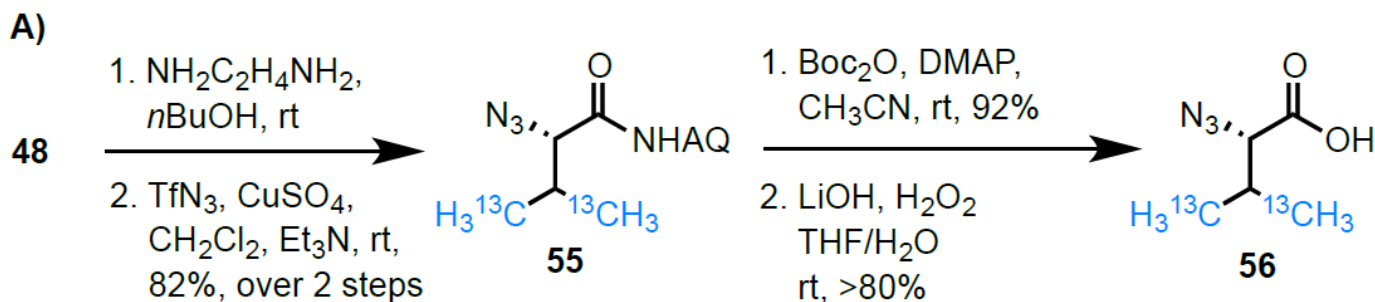
Pd-Catalyzed AQ-Directed Alkylation of β -C(sp³)-H Bonds of Amino Acids



Pd-Catalyzed AQ-Directed Alkylation of β -C(sp³)-H Bonds of Amino Acids



Removal of AQ Group Under Mild Conditions





THANK YOU !

