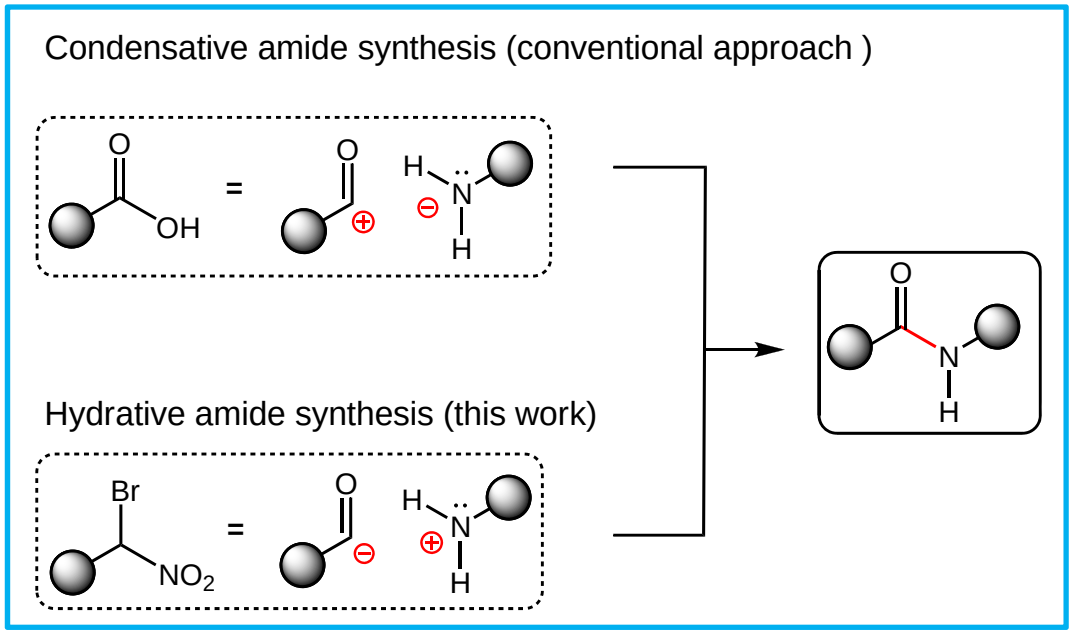
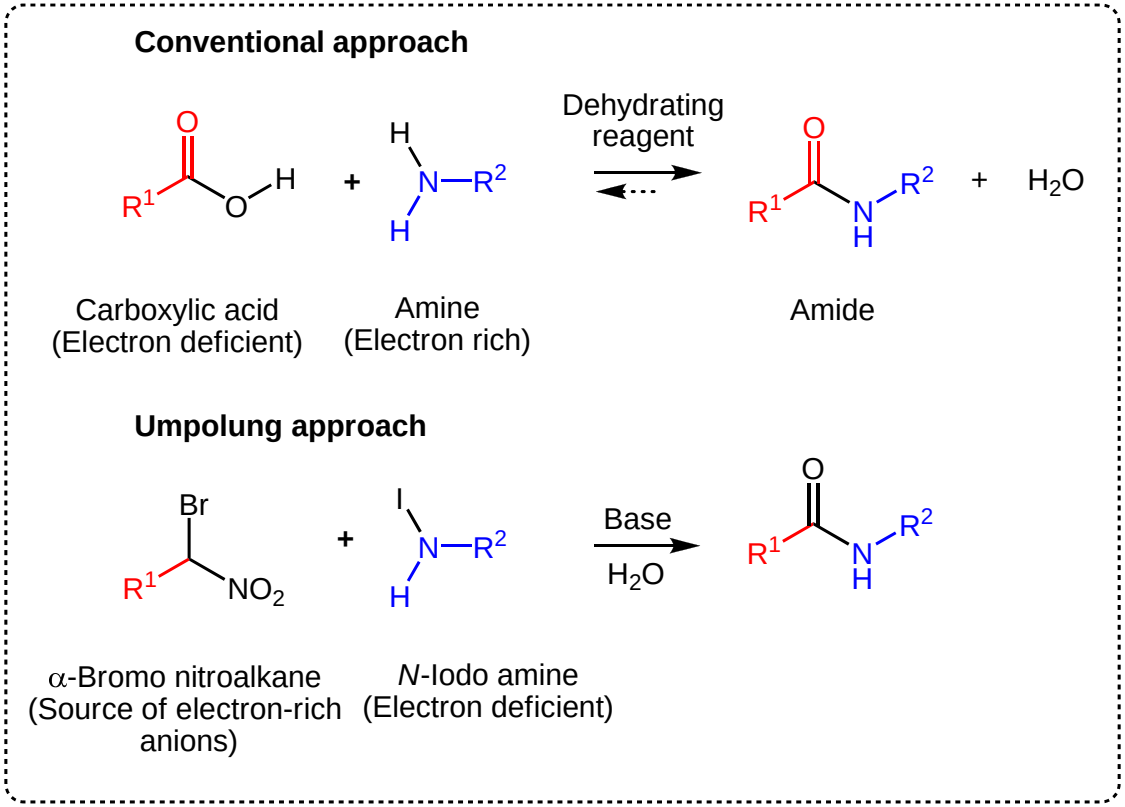
Umpolung reactivity in amide and peptide synthesis



Reporter: Ran-Ning Guo
Checker： Lei Shi
Date: 2012/12/18

Johnston, J. N. *Nature* **2010**, *465*, 1027; *J. Am. Chem. Soc.* **2012**, *134*, 15233.



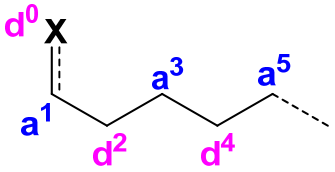
1. **Straightforward, versatile and exciting.**
2. **Given access to any basic collection of standard organic compounds, chemists will certainly be able to implement this method quickly.**
3. **The mechanistically unusual process also opens up possibilities. For example, it is valuable to be able to take safe, readily available sources of nitrogen and incorporate nitrogen atoms into organic compounds, and the authors' work highlights a useful strategy for doing this that has not been fully appreciated.**
4. **Finally, this *umpolung* reaction will undoubtedly aid medicinal chemists in making biologically active amide-containing compounds, some of which might one day help to treat disease.**

by Karl Scheidt

Contents

The Synthetic Problem in Retrosynthetic Analysis by Corey

Heteroatoms impose an alternating acceptor and donor reactivity pattern

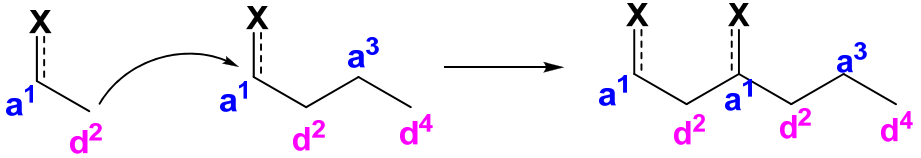


X = halogen, O, N

d = donor (-)

a = acceptor (+)

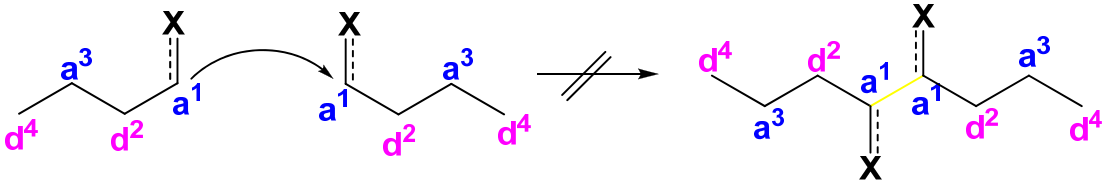
An odd number of carbons between functional groups



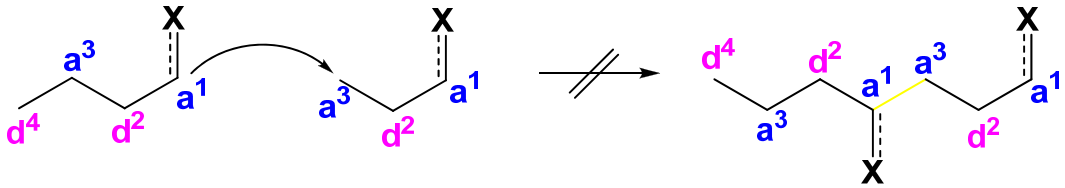
1,3-disubstitution

(e.g. Aldol reaction, Claisen condensation, Michael reaction, Claisen rearrangment, Diels-Alder reaction)

An even number of carbons between functional groups



1,2-disubstitution



1,4-disubstitution

Seebach, D. *Angew. Chem., Int. Ed. Engl.*, **1979**, *18*, 239.

Synthons & Umpolung

- **Synthons: structural units within a molecule which are related to possible synthetic operations.**

  Corey, E. J. *Pure Appl. Chem.*, **1967**, *14*, 19.

- **"*Symmetrization of reactivity*"**

  Corey, E. J. *Pure Appl. Chem.*, **1967**, *14*, 19.

- **"*Charge affinity inversion*"**

  Evans, D. A. *Acc. Chem. Res.* **1974**, *7*, 147.

- **Suggested the German word *umpolung* as a concise expression for the concept.**

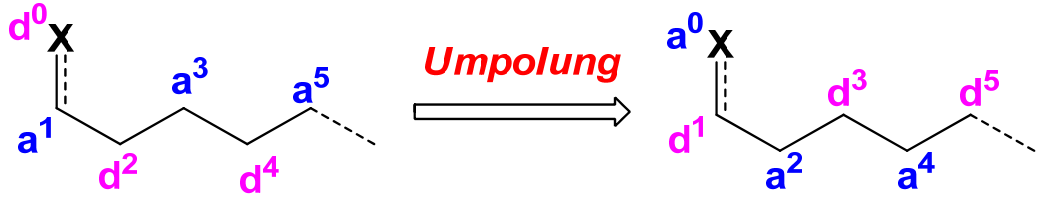
  Seebach, D. *Chem. Ind.* **1974**, 687.

***Umpolung* is any process by which donor and acceptor reactivity of an atom are interchanged (reversal in polarity).**

Normal reactivity:

C_{2n}= donor

C_{2n+1}= acceptor



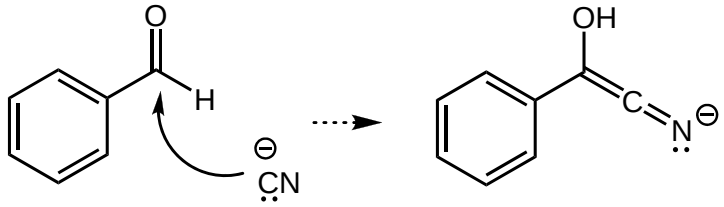
Umpolung reactivity:

C_{2n}= acceptor

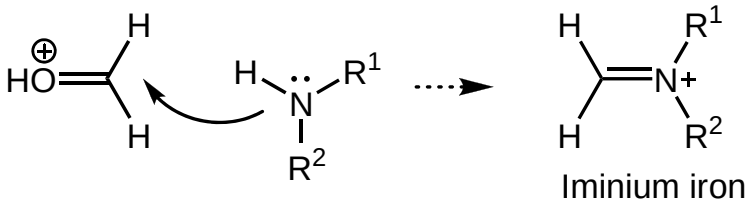
C_{2n+1}= donor

Umpolung: pole reversal; reversion of polarity; turn-over.
(http://en.wikipedia.org/wiki/Umpolung)

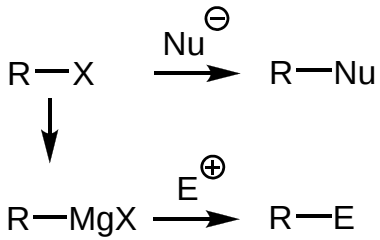
Umpolung reactivity



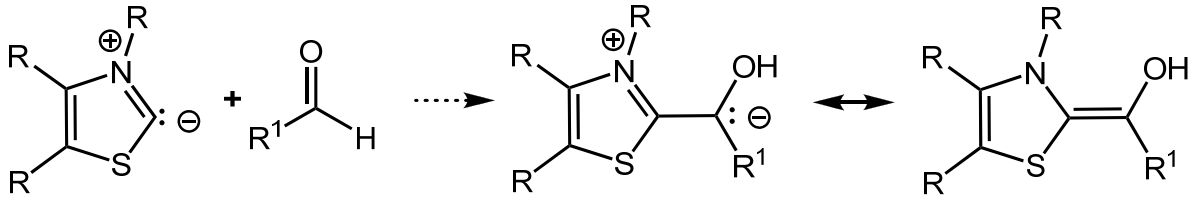
Bezoin condensation
1,2 addition



Mannich reaction

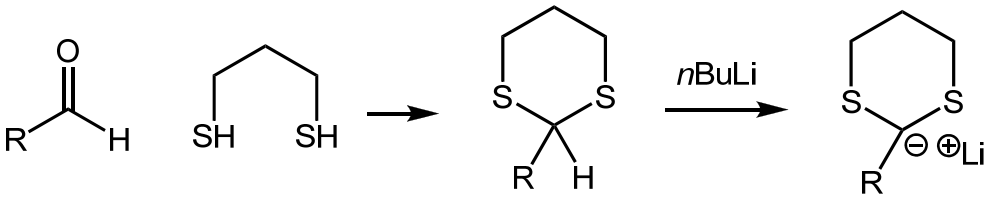


Grignard reagent



Stetter reaction
1,4 addition

Breslow intermediate



Corey-Seebach-Reaction

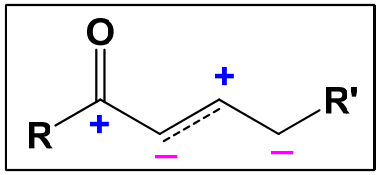
Beckmann rearrangement
Eschenmoser's salt
Duff reaction
Stephen reaction
Vilsmeier-Haack reaction
Pictet-Spengler reaction
……

Classifications

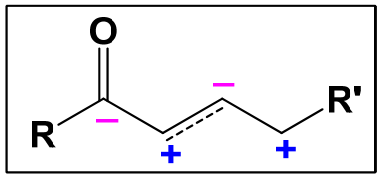
Products	Reversible & inreversible
Reaction type	1,2n-Oxidation, Exchange and Modification of the Heteroatom, Homologation and Its Reversal, Use of Cyclopropanes, Acetylenes.
Reagents	Cyanide-type umpolung, N-heterocyclic carbenes, 3-membered rings, Dithiane, oxidant such as iodine, halogen atom or an alkoxy group……
Substrates	Carbonyl, Amine, Alkanes.

Seebach, D. *Angew. Chem., Int. Ed. Engl*., **1979**, *18*, 239.

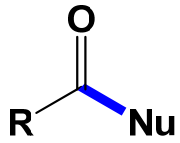
Carbonyl Umpolung



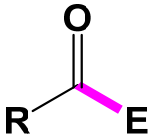
normal reaction polarity

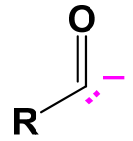


umpolung reaction polarity



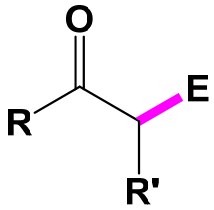
acyl transfer reaction
Friedel-Craft reactions



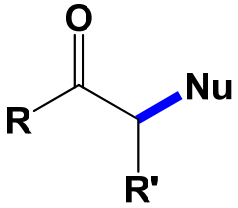


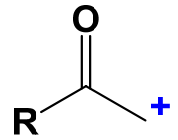
d^1 synthon

acyl anion



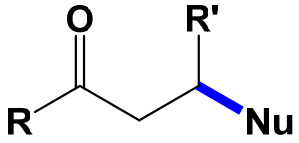
enolate anion alkylation
aldol and Claisen reactions



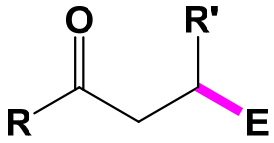


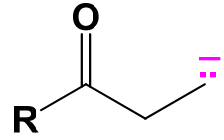
a^2 synthon

α-electrophile



conjugate additions
Michael reactions

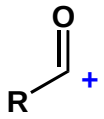
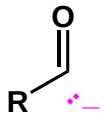
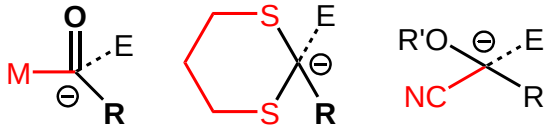
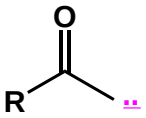
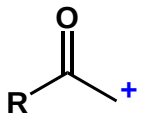
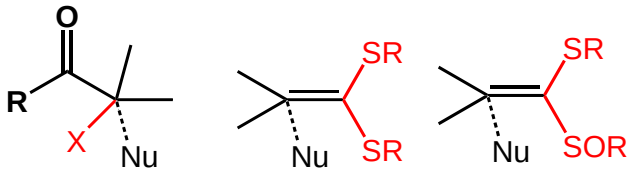
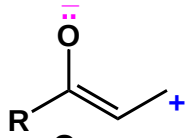
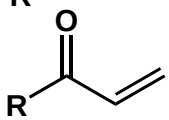
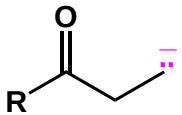
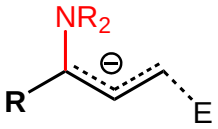
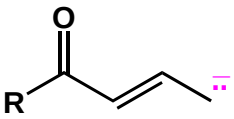
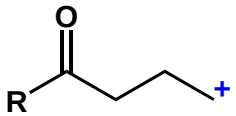
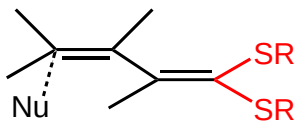




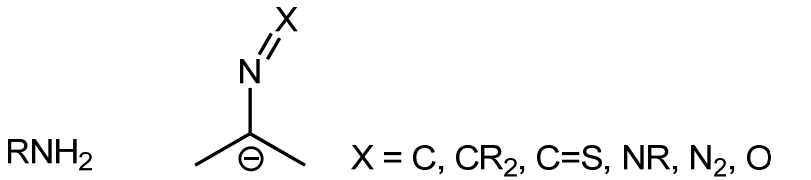
d^3 synthon

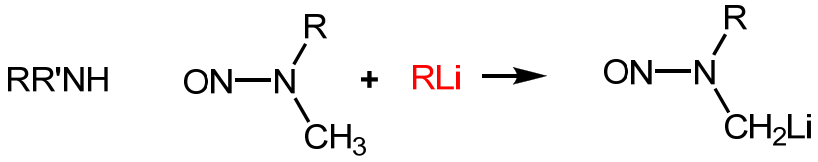
homoenolate

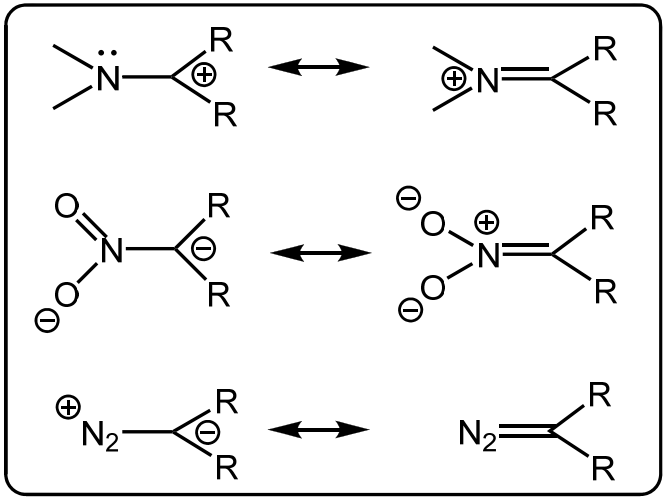
Carbonyl Umpolung

Normal Carbonyl reactivity	Umpolung Carbonyl reactivity	Umpolung reagents
 a^1 synthon	 d^1 synthon	
 d^2 synthon	 a^2 synthon	
  a^3 synthon	 d^3 synthon	
 d^4 synthon	 a^4 synthon	

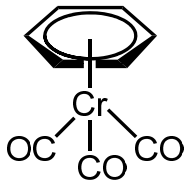
Amine and Alkanes Umpolung



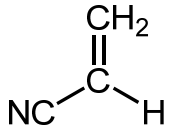




arene & heterocyclic arene ⇨ Transition metal complexes



alkene ⇨ -X, -CF_3, -CN, -CHO or Transition metal complexes

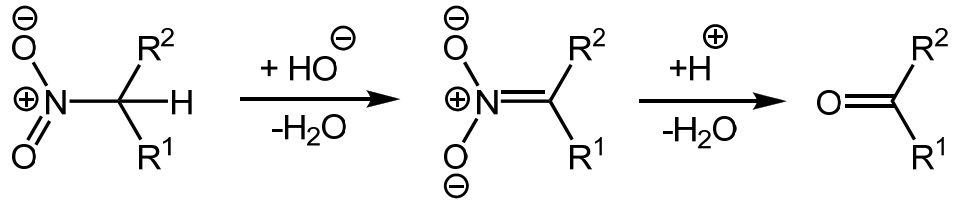


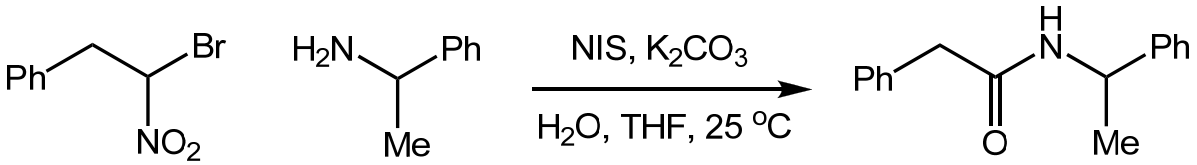
Halogenated alkane ⇨ Gringnard reagent etc.

RMgX

Development of an α-halo nitroalkane based amide synthesis

Nef Reaction:

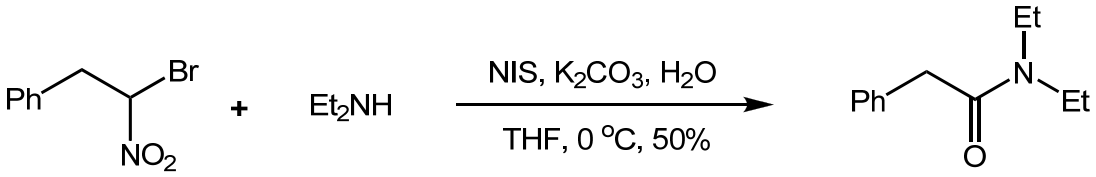




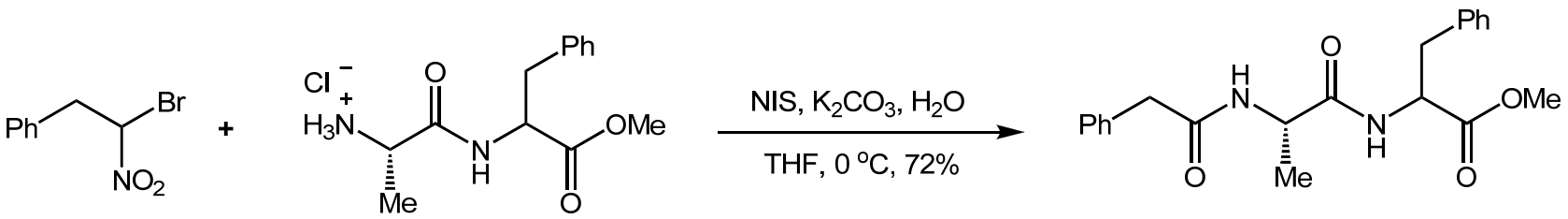
Entry	NIS(equiv.)	H_2O(equiv.)	K_2CO_3(equiv.)	Yield[a]
1[b]	0	93	0	<5
2[b]	0	93	2	<5
3[b]	1.2	93	0	61
4[c]	1.0	93	2	58
5[c]	1.0	5	2	70
6[c]	1.0	0	2	55
7[c/d]	1.0	5	2	75

Reactions used 1 equiv. of a-bromo nitroalkane (0.2M in THF) and rac-amine, with amine added as the final reagent at 25 °C. [a] Isolated yields. [b] 2 equiv. of amine used. [c] 1.2 equiv. of amine used. [d] Reaction temperature 0 °C .

Wide scope of a-bromo nitroalkane donor and the amine acceptor

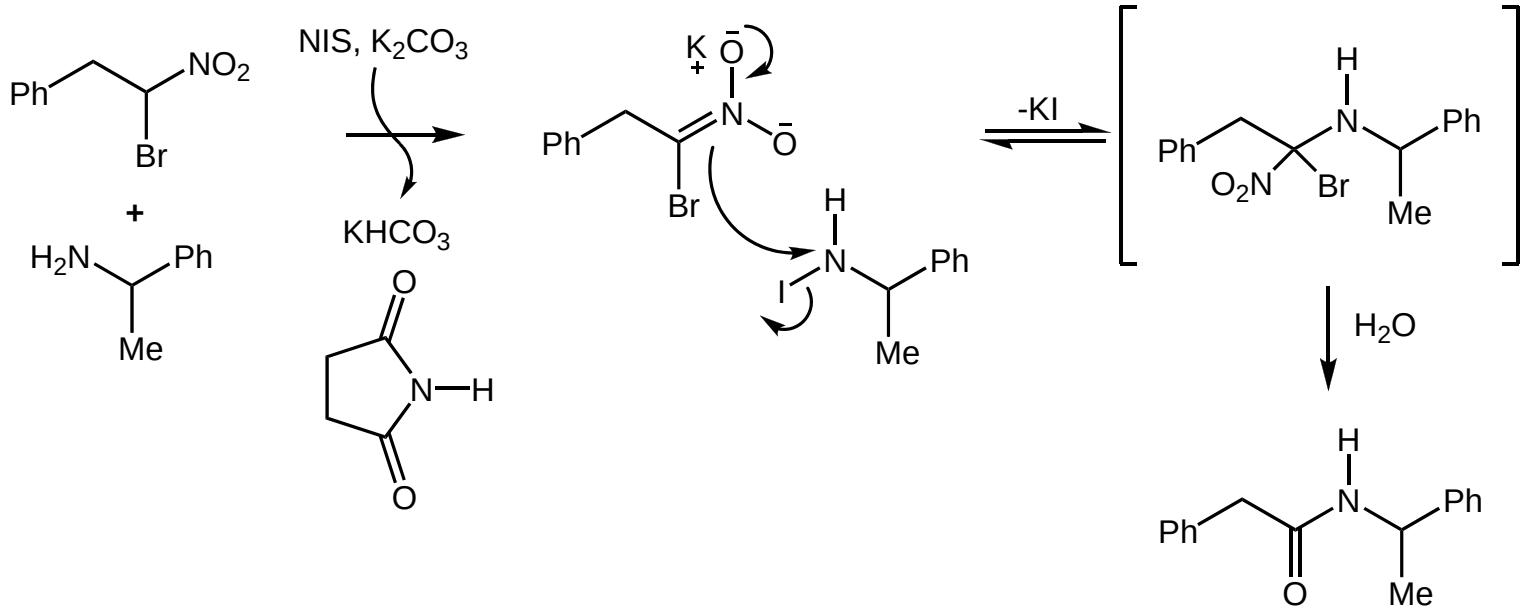


Disubstituted amine

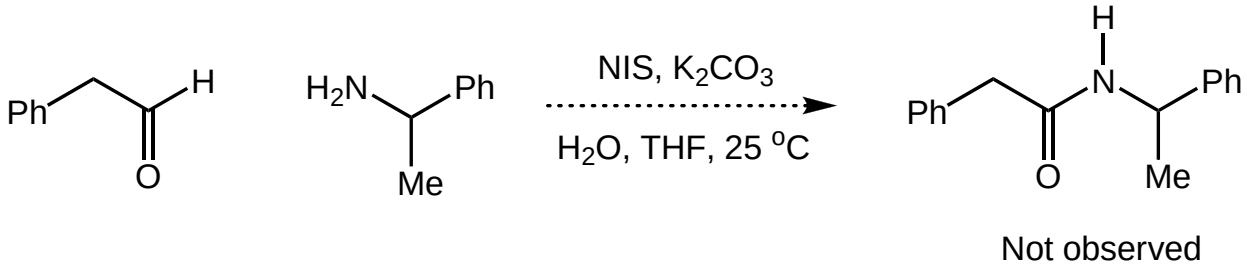


Dipeptide

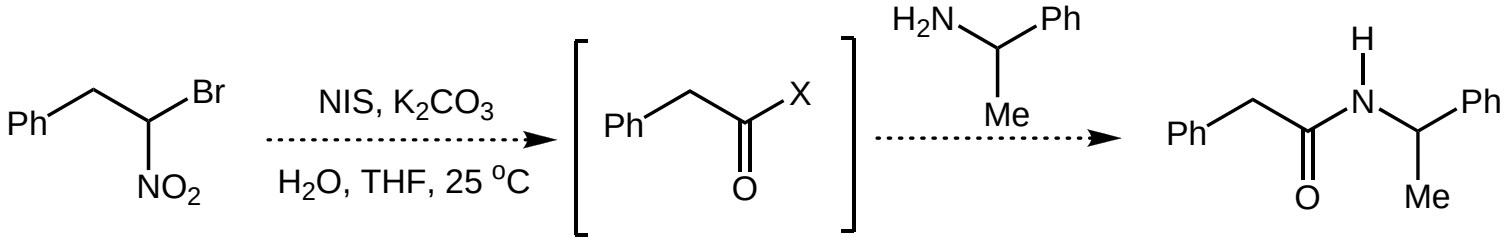
Mechanistic hypothesis for amide synthesis



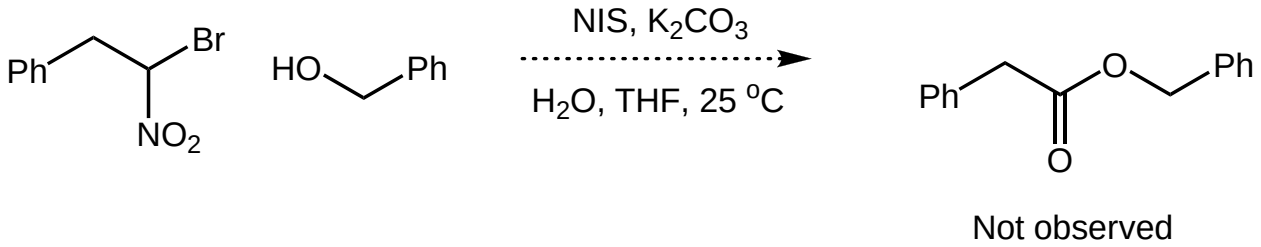
Experiments designed to probe intermediacy of possible carbonyl electrophiles



Not observed

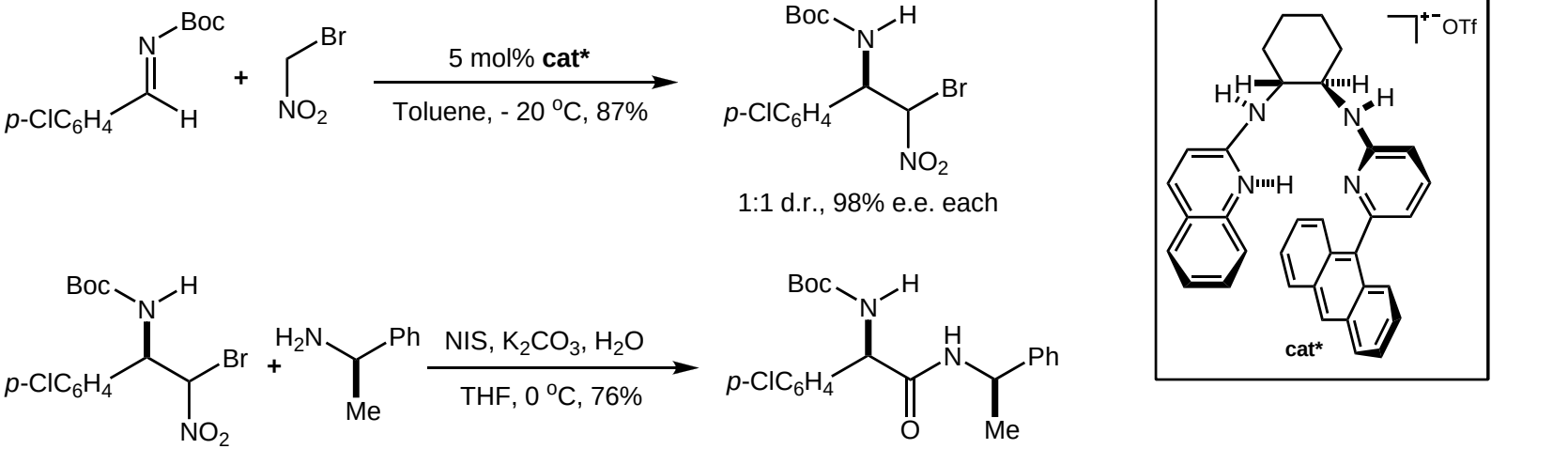


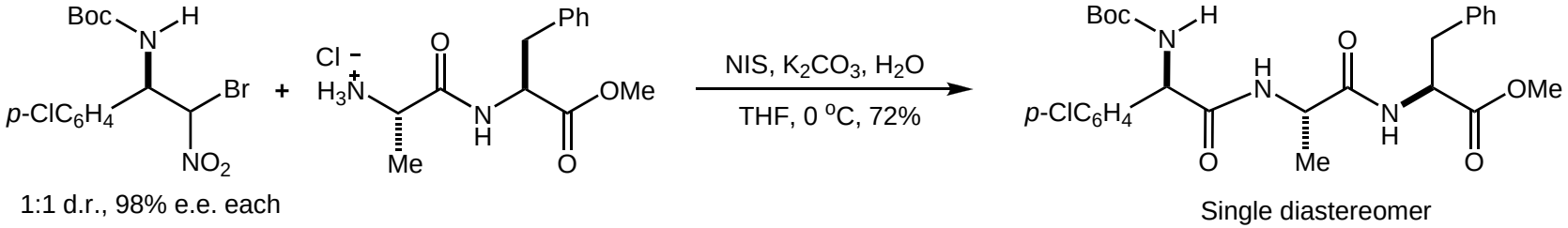
Not observed



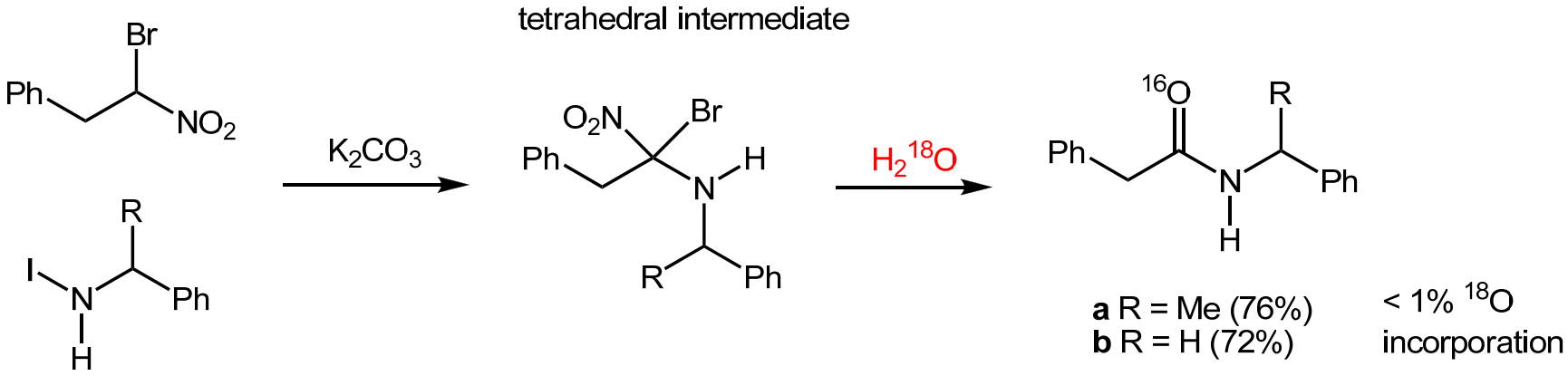
Not observed

Stereoselective peptide synthesis





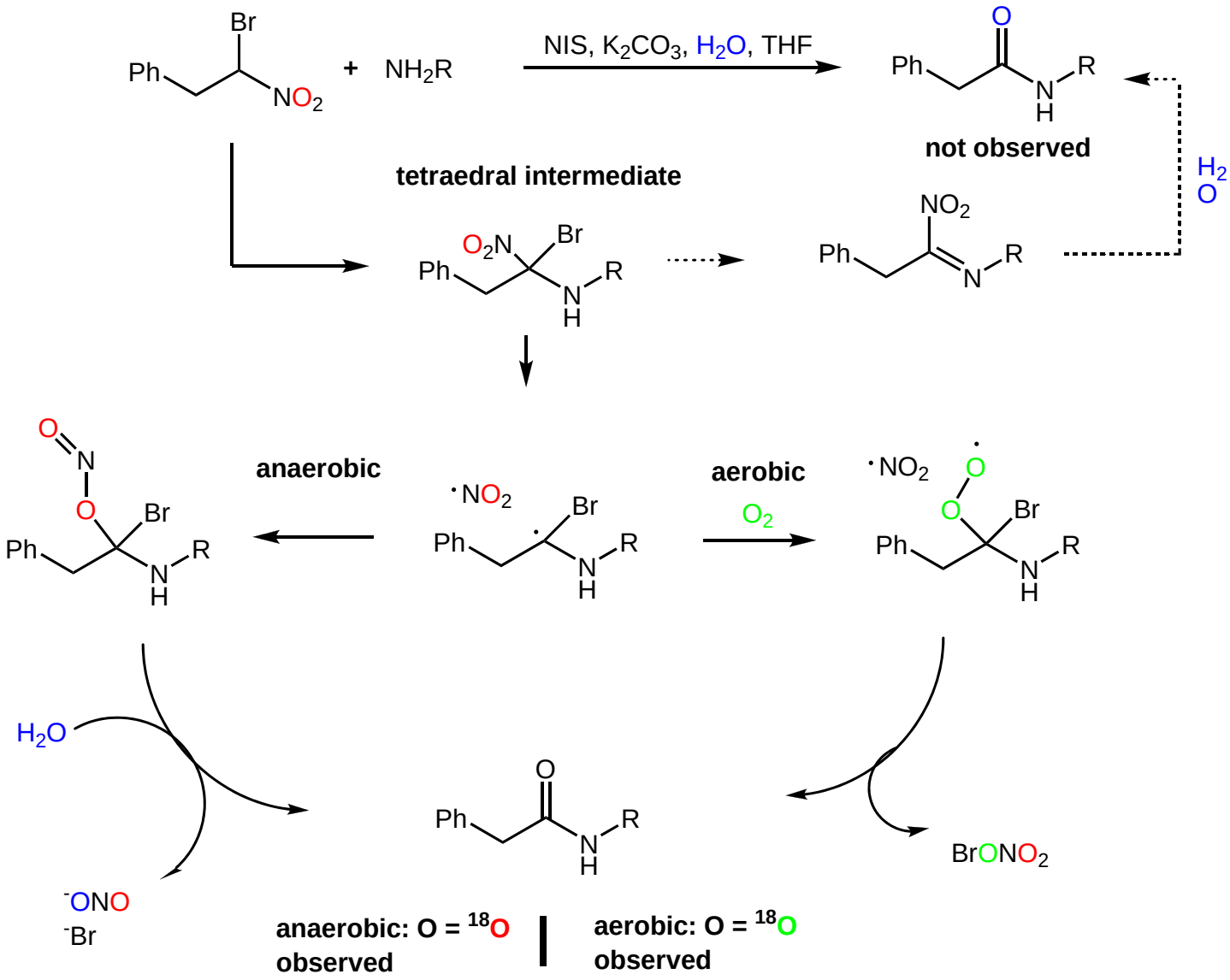
Potential sources for the oxygen of the product amide carbonyl



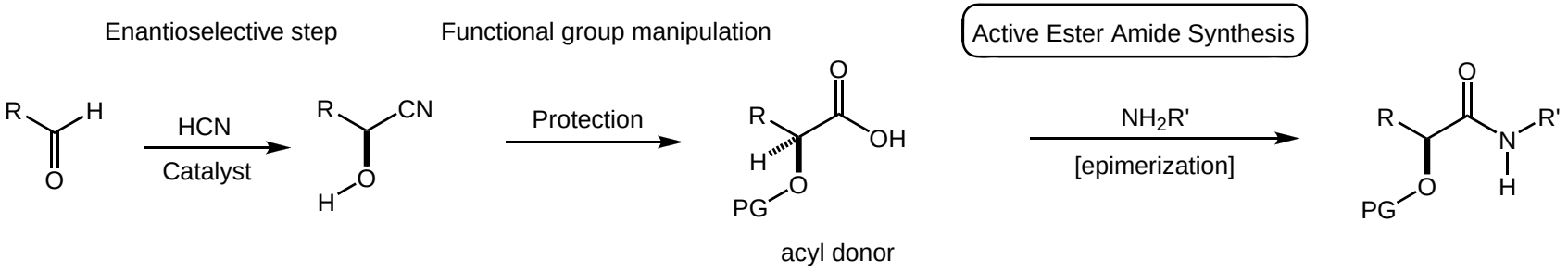
Water is not the source of amide oxygen in umpolung amide synthesis

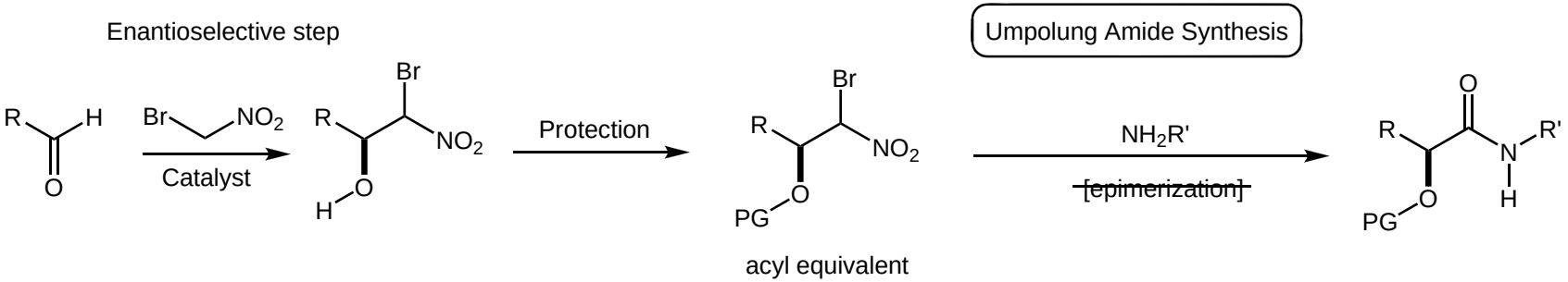
Johnston, J. N. *PNAS*. **2012**, *109*, 44.

^{18}O-labeling experiments

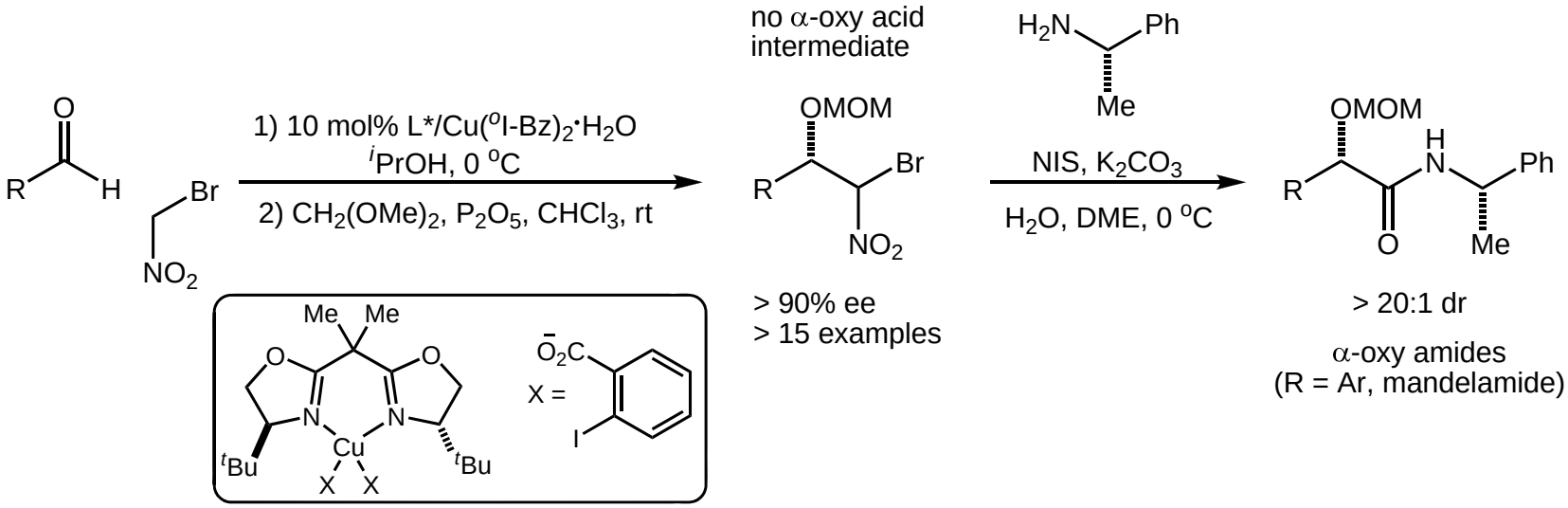


α-Oxy Amide Synthesis by UmAS

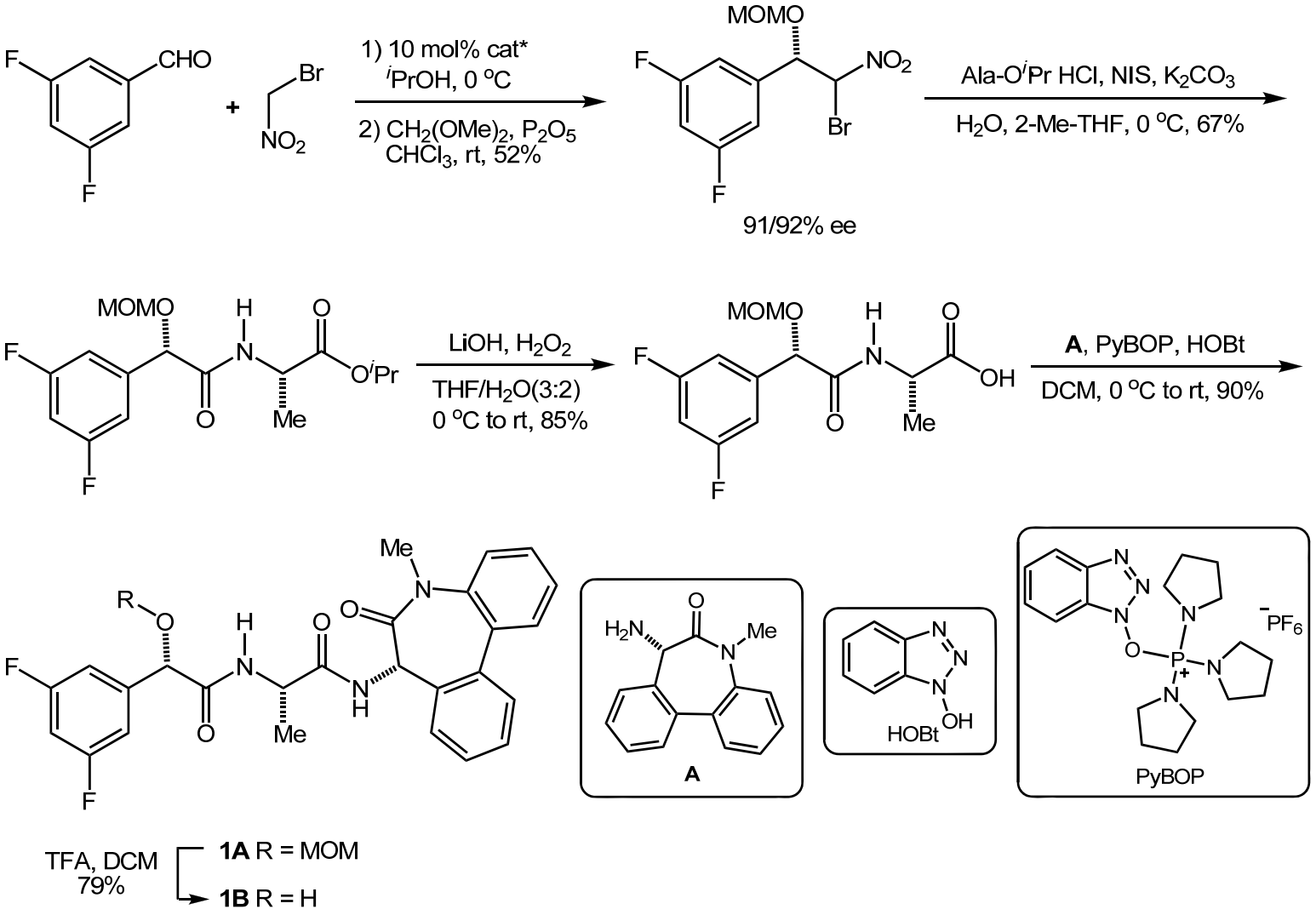




α-Oxy Amide Synthesis by UmAS



Preparation of LY411575 Using the Enantioselective Mandelamide Synthesis



Great structural diversity in protein synthesis is achieved in nature through the rather straightforward condensation of amino acids (dehydrative amide synthesis). Large and complex, yet functionally precise, proteins are formed in this manner from a remarkably small number of naturally occurring amino acids. The formation of the amide bond is the strategic lynchpin, one that is often mirrored in the laboratory through condensative methods for the preparation of amides and peptides. The reliance on condensative amide synthesis further benefits from the widespread availability of simple carboxylic acids and amines. This otherwise solid foundation often weakens as the size of the target increases, or when the steric, functional and stereochemical complexity places a greater demand on the condensative acyl carbon–nitrogen bond-forming reaction. For example, the use of disubstituted amines, aryl glycines or peptidic amine/carboxylic acid combinations are often met with low conversion and/or epimerization of the carboxylic acid before coupling. In addition to solid phase peptide synthesis, which often uses reagent excess to drive the condensation to completion, alternatives to conventional amide synthesis have emerged recently to address these practical challenges, including highly innovative approaches. Among these, Staudinger ligation, native chemical ligation, hydrative amide synthesis through alkyne–azide coupling, oxidative amidation of alcohols, aldehydes or alkynes, and ketoacid-hydroxylamine ligation are of contemporary importance.

We have discovered a non-conventional amide synthesis via iodonium-promoted nitroalkane–amine coupling. The conditions are only mildly basic and have been shown to accommodate a range of nitroalkanes and amines. At the levels of strategy and mechanism, this amide synthesis appears to reverse the reactive polarity of acyl and amine subunits relative to traditional condensative approaches, providing a nucleophilic acyl donor and an electrophilic amine acceptor. This approach led to the development of an aryl glycine amide synthesis without epimerization or extensive protection/deprotection schemes. In addition, the first use of commercially available bromo nitromethane in stereoselective peptide synthesis establishes a practical alternative in peptide synthesis to the longstanding reliance on the carboxylic acid feedstock. This strategic shift may ultimately enable the efficient fully chemical synthesis of chiral, non-racemic peptides using a combination of entirely enantioselective methods and nitroalkane–amine couplings, as demonstrated in equation (8).

Thanks!