Residue-Specific Peptide Modification: A Chemist's Guide

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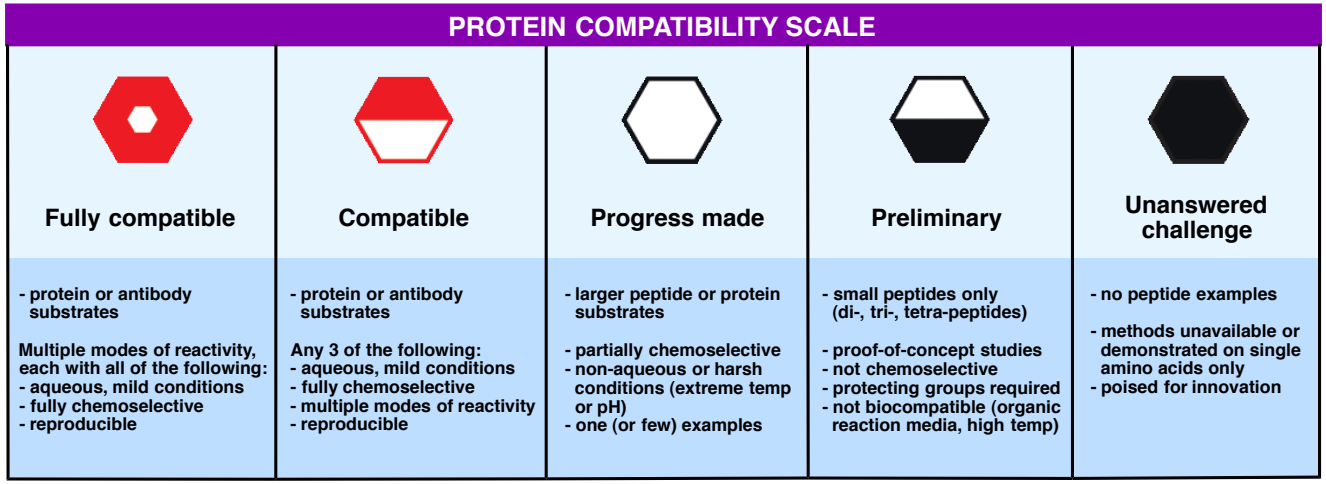
SUPPORTING INFORMATION

Amino acid side-chain modification report card



The amino acid side-chain modification report card provides a graphical overview of available residue-specific modification strategies. Organized by amino acid and subdivided into various reaction classifications (**A–L**), the report card aims to provide readers with an illustrative summary of available methods and the degree to which they have been evaluated on protein substrates. Historical methods for bioconjugation and recent developments for peptide and protein functionalization were categorized and evaluated on the basis of their suitability for the residue-specific modification of peptides, proteins, and antibodies. The specific parameters used for evaluation are outlined in the "Protein Compatibility Scale" above.

A few notes on the categorization and evaluation process:

- In some cases, a synthetic method falls into more than one reaction classification (**A–L**). We have generally categorized such methods into all relevant reaction classifications. For example, a Pd-catalyzed arylation might fall under the categories of arylation (**B**), cross-coupling (**H**), and transition-metal functionalization (**L**).

- The compatibility "score" is not meant to be a judgment of the quality of a particular strategy or specific body of work; rather, the score is intended to provide an objective assessment of the suitability of each reaction type, based on available literature, for residue-specific modifications. For example, a "preliminary" functionalization strategy has been demonstrated on small peptides, while a "fully compatible" approach has been successfully applied to the chemoselective modification of proteins and/or antibodies.

A number of comprehensive reviews and literature methods were consulted to assign appropriate compatibility scores. Relevant references are provided in the following lists and amino acid-specific charts. While we have aimed to thoroughly evaluate available methods (particularly those reported in the last decade), the following charts are intended to be representative rather than exhaustive in nature. We refer readers to relevant reviews, where applicable, and have highlighted in purple references that are discussed in more detail in the body of the manuscript.

Select comprehensive reviews:

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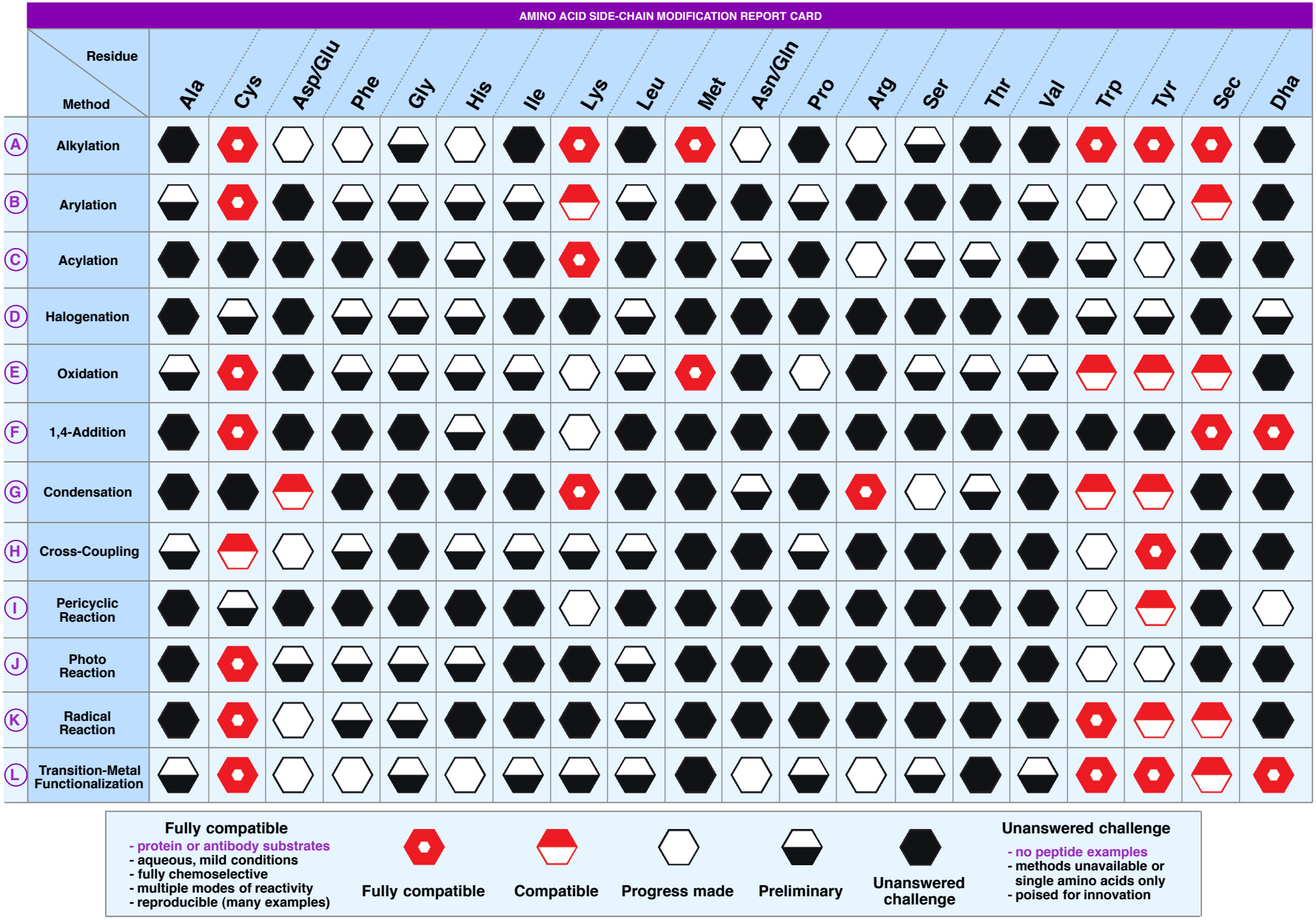
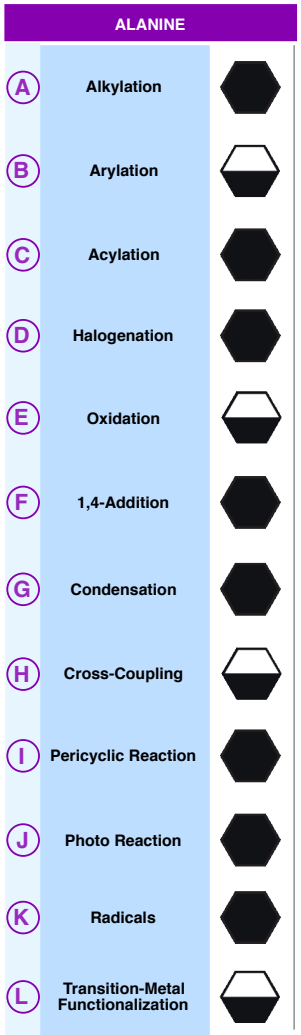

AMINO ACID SIDE-CHAIN MODIFICATION REPORT CARD
Residue
Method
Ala
Cys
Asp/Glu
Phe
Gly
His
Ile
Lys
Leu
Met
Asn/Gln
Pro
Arg
Ser
Thr
Val
Trp
Tyr
Sec
Dha
A Alkylation
B Arylation
C Acylation
D Halogenation
E Oxidation
F 1,4-Addition
G Condensation
H Cross-Coupling
I Pericyclic Reaction
J Photo Reaction
K Radical Reaction
L Transition-Metal Functionalization
Fully compatible
- protein or antibody substrates
- aqueous, mild conditions
- fully chemoselective
- multiple modes of reactivity
- reproducible (many examples)
Fully compatible
Compatible
Progress made
Preliminary
Unanswered challenge
Unanswered challenge
- no peptide examples
- methods unavailable or single amino acids only
- poised for innovation

Amino acid-specific modification charts



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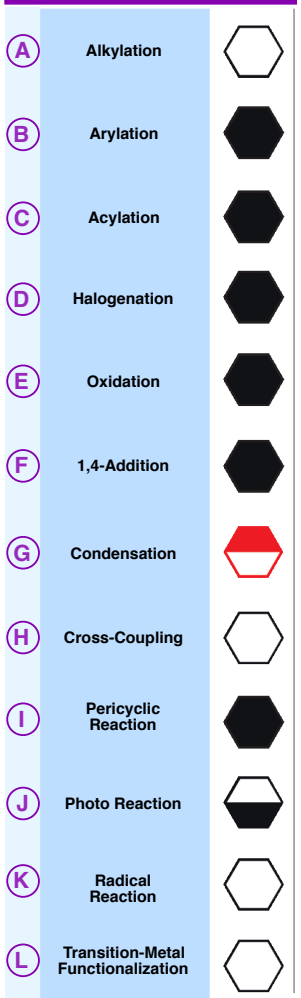

A

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L **Dirhodium metallopeptide functionalization:**

Popp, B. V. and Ball, Z. T. (2010) J. *Am. Chem. Soc. 132,* 6660–6662.
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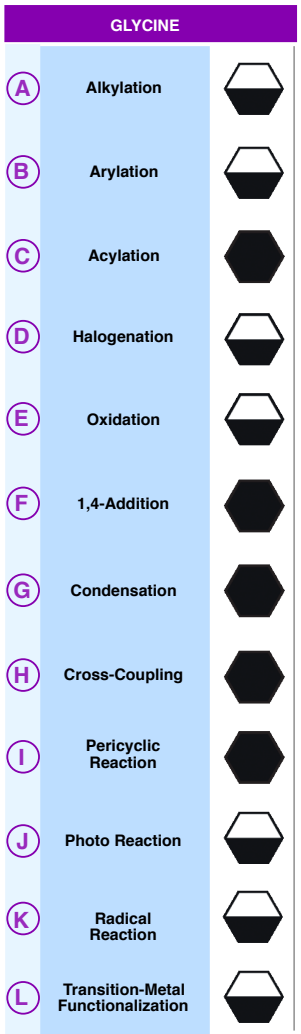

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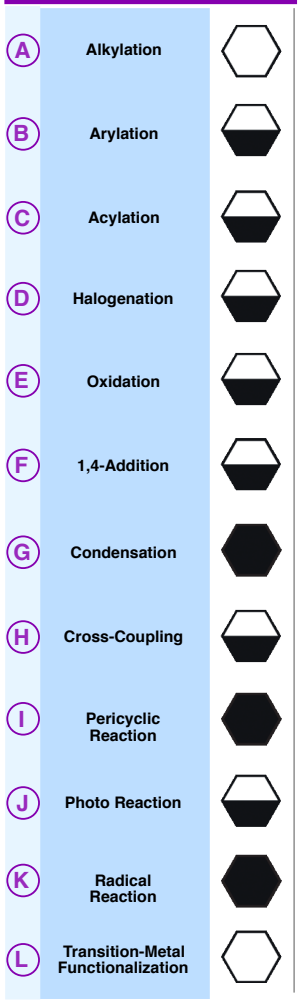
HISTIDINE



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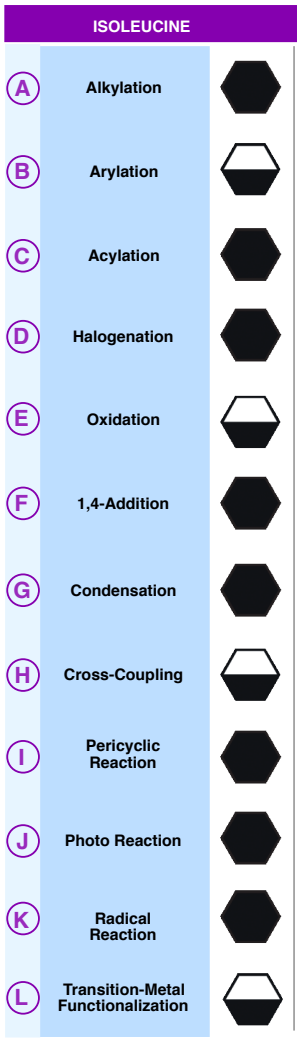

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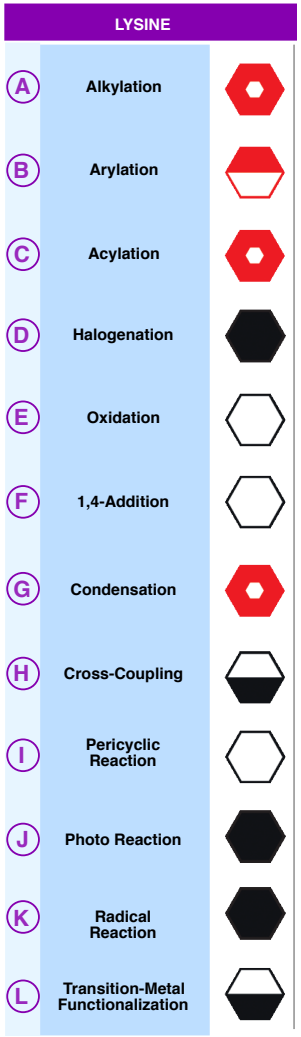

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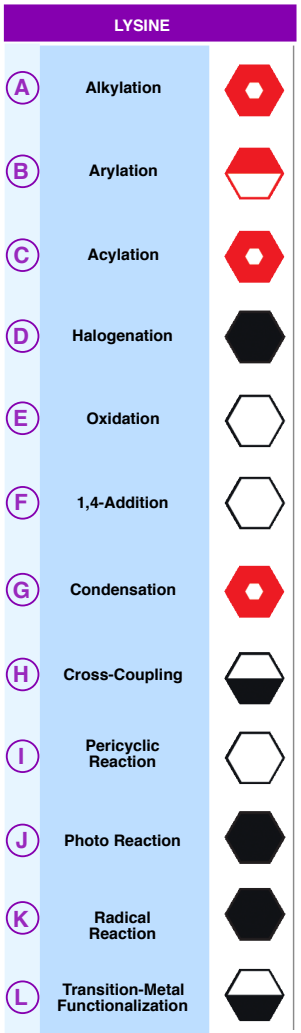

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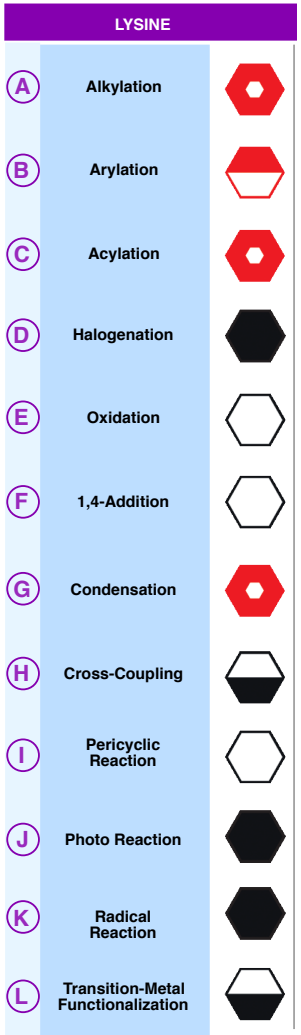

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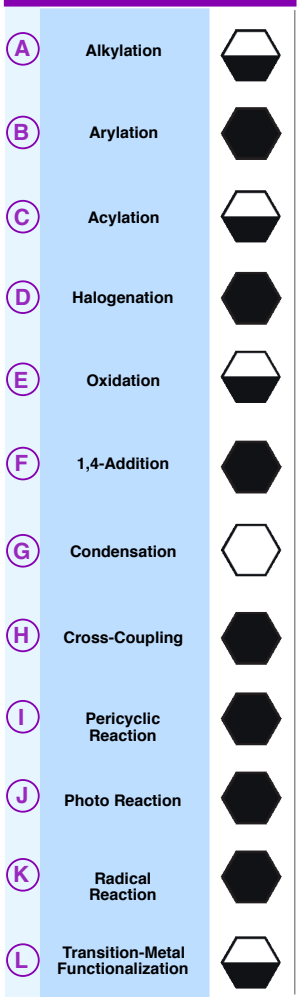
SERINE



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C **Acylation (e.g. depsipeptide synthesis):**

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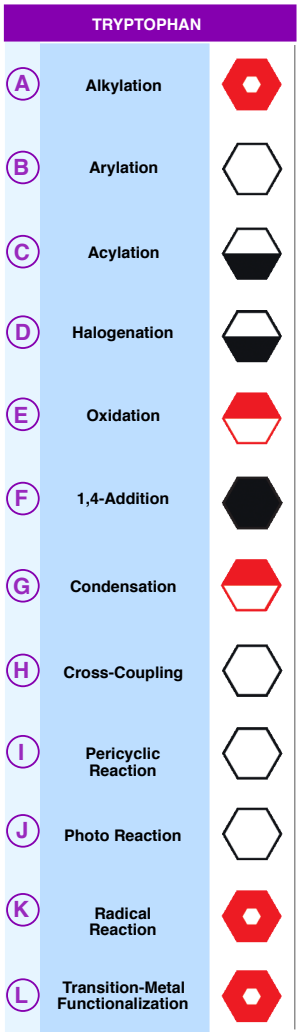

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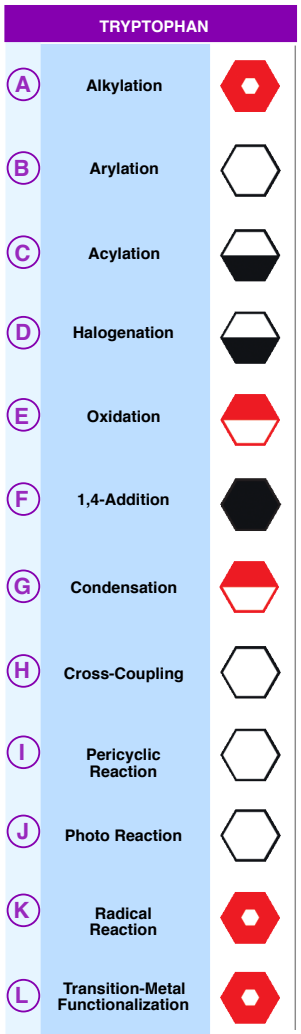

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Viswanatha, T., Lawson, W. B., and Witkop, B. (1960) *Biochim. Biophys. Acta 40*, 216–224.
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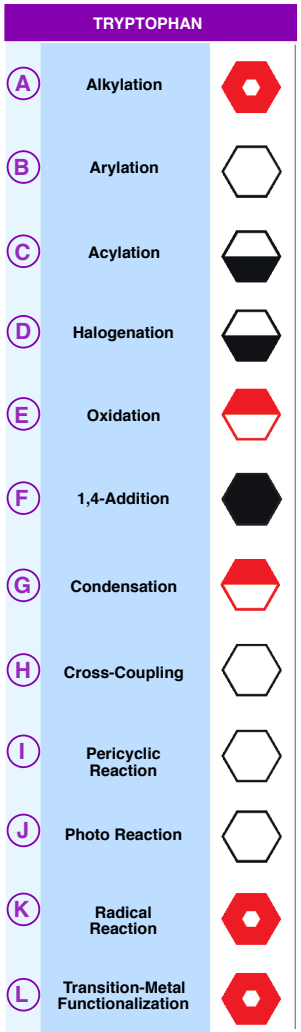

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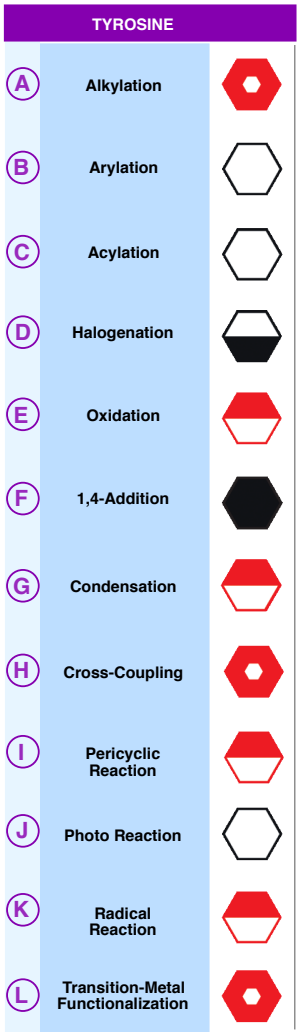

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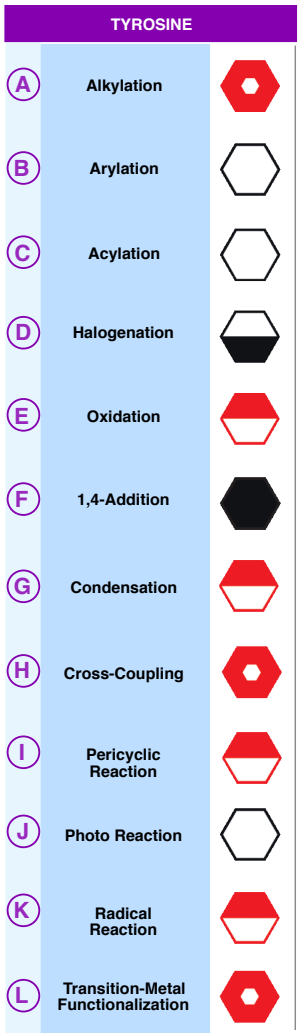

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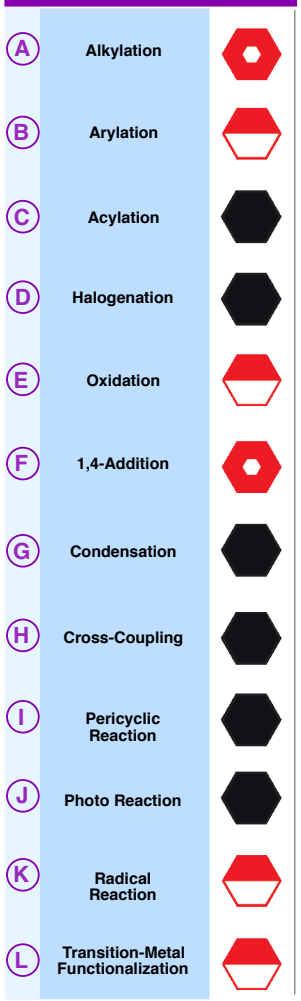
SELENOCYSTEINE



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B

Cu-catalyzed umpolung-based arylation: Cohen, D. T., Zhang, C., Pentelute, B. L., and Buchwald, S. L. (2015) *J. Am. Chem. Soc. 137*, 9784–9787.

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- For additional examples, see the supporting information section on Dha

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Oxidation of Sec to the corresponding diselenide dimer is a common mode of reactivity:
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DEHYDROALANINE

- A Alkylation
- B Arylation
- C Acylation
- D Halogenation
- E Oxidation
- F 1,4-Addition
- G Condensation
- H Cross-Coupling
- I Pericyclic Reaction
- J Photo Reaction
- K Radical Reaction
- L Transition-Metal Functionalization

Review: Schmidt, U., Hausler, J., Ohler, E., and Poisel, H. (1979) F*ortschr. Chem. Org. Naturst.* 37, 251.

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From Cys:

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Strumeyer, D. H., White, W. N., and Koshland, D. E., Jr. (1963) *Proc. Natl. Acad. Sci. U. S. A. 50*, 931–935.
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Ferreira, P. M. T., Monteiro, L. S., Pereira, G., Ribeiro, L., Sacramento, J., and Silva, L. (2007) *Eur. J. Org. Chem.* 5934–5949.

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Okeley, N. M., Zhu, Y., and van der Donk, W. A. (2000) *Org. Lett. 2*, 3603–3606.
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