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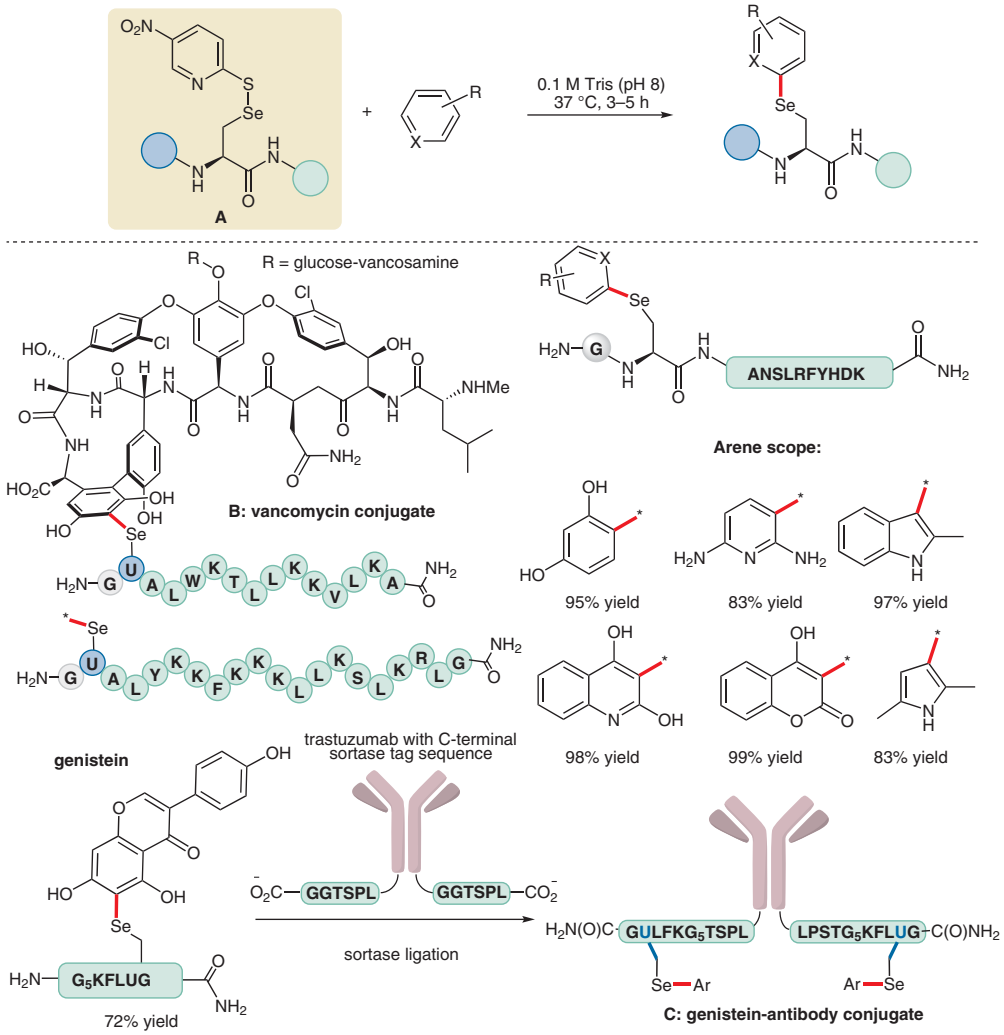
A Chemoselective Strategy for Late-Stage Functionalization of Complex Small Molecules with Polypeptides and Proteins
Nat. Chem. **2019**, *11*, 78–85.

A Chemoselective Conjugation of Peptides with Electron-Rich (Hetero)Arenes



Significance: The site-selective functionalization of peptides with small molecules is a formidable challenge in organic synthesis. Cohen, Pentelute, and co-workers have described a new high-yielding conjugation reaction between electron-rich aromatics and of 2-thiol-5-nitropyridine (TNP)-protected selenocysteine. This methodology is an important advance in the production of homogenously functionalized proteins such as antibody–drug conjugates.

Comment: A range of unprotected pharmaceutical agents and natural products are competent substrates, as demonstrated by the syntheses of vancomycin–peptide conjugates and a homogenous genistein–trastuzumab conjugate, generated by a two-step selenocysteine ligation–sortagging sequence. In general, electron-rich arenes with acidic N–H or O–H bonds are the most efficient substrates. $CuSO_4$ and a bipy ligand can be used to promote the reaction with less reactive arenes.

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Synfact of the Month