

Design of an Organocatalyst for Peptide Synthesis

Category

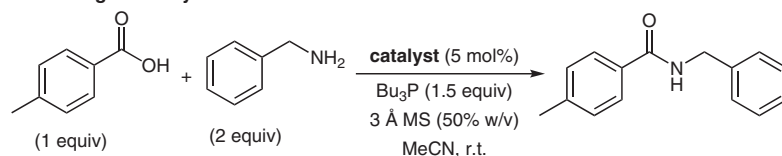
Peptide Chemistry

Key words

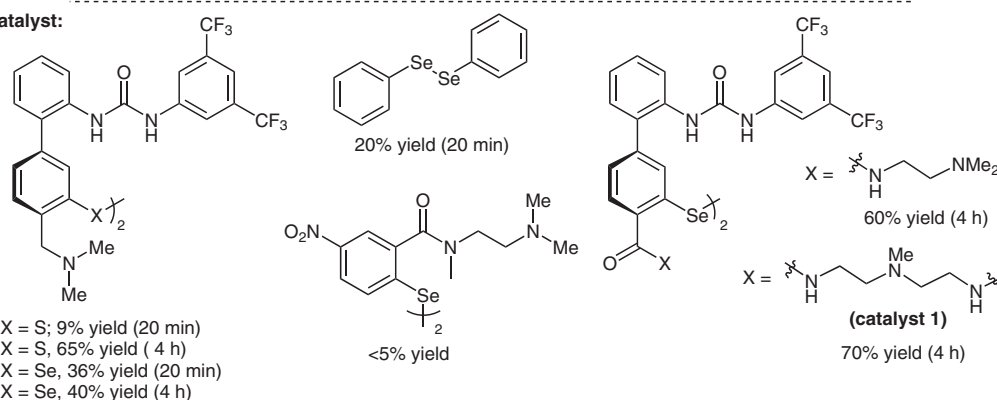
organocatalysis
urea-based catalysis
diselenides
selenoesters
peptide coupling

Synfact
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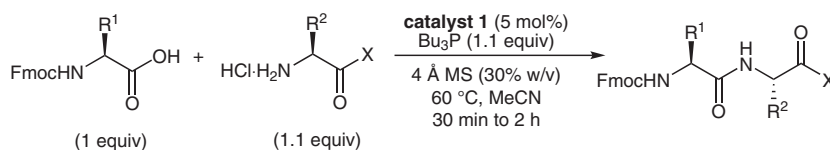
Development of an organocatalyst for amide bond formation:



Catalyst:



Diselenide 1a catalyzed coupling of Fmoc-protected amino acids into dipeptides:



Fmoc-Ala-Ala-Ot-Bu	Fmoc-Ala-Phe-Ot-Bu	Fmoc-Ala-Lys(Z)-Ot-Bu	Fmoc-Ala-Val-Ot-Bu	Fmoc-Ala-Pro-Ot-Bu
92% yield (1 h)	99% yield (30 min)	98% yield (1 h)	96% yield (1 h)	69% yield (1 h)
97% yield (1 h) ^a	95% yield (1 h) ^a	99% yield (1.5 h) ^a	99% yield (1 h) ^a	94% yield (2 h) ^a
Fmoc-Ala-Trp-NH ₂	Fmoc-Phe-Ala-Ot-Bu	Fmoc-Pro-Ala-Ot-Bu	Fmoc-Val-Ala-Ot-Bu	Fmoc-Aib-Ala-Ot-Bu
73% yield (1 h)	87% yield (30 min)	82% yield (30 min)	81% yield (30 min)	53% yield (1.5 h)
99% yield (1 h) ^a	90% yield (1 h) ^a	90% yield (2 h) ^a	92% yield (2 h) ^a	91% yield (2 h) ^a

^a Portionwise addition of Bu₃P (1.5 equiv)

Significance: Because of the growing impact of peptides as biological reagents and therapeutics, the development of efficient methods for the construction of amide bonds is an important research area for organic chemists. The authors have designed an organocatalyst based on the concept of urea-based hydrogen bonding and covalent catalysis for amide bond formation.

Comment: The designed diselenide catalyst activates the carboxylic acid as a selenoester by a reduction–oxidation condensation procedure. The developed macrocyclic diselenide catalyst showed near-quantitative conversion, was active for a diverse range of amino acids without significant racemization, and was reactive in solid-phase peptide synthesis.

Further insights can also be found in this issue: *Synfacts* **2019**, *15*, 1424.