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Rational Design of an Organocatalyst for Peptide Bond Formation
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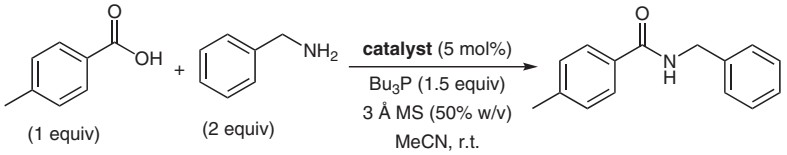
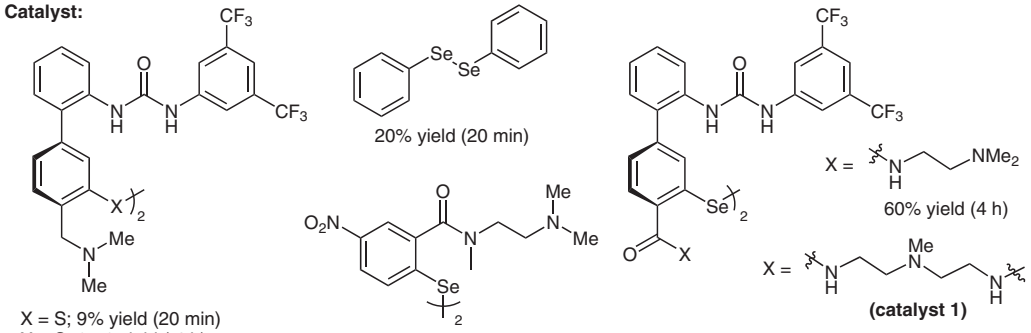
Design of an Organocatalyst for Peptide Synthesis

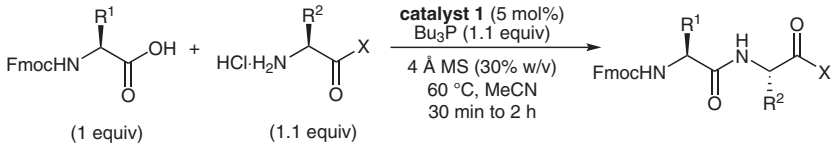
Development of an organocatalyst for amide bond formation:



Catalyst:



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



Fmoc-Ala-Ala-O*t*-Bu	Fmoc-Ala-Phe-O*t*-Bu	Fmoc-Ala-Lys(Z)-O*t*-Bu	Fmoc-Ala-Val-O*t*-Bu	Fmoc-Ala-Pro-O*t*-Bu
92% yield (1 h) 97% yield (1 h)[a]	99% yield (30 min) 95% yield (1 h)[a]	98% yield (1 h) 99% yield (1.5 h)[a]	96% yield (1 h) 99% yield (1 h)[a]	69% yield (1 h) 94% yield (2 h)[a]
Fmoc-Ala-Trp-NH_2	Fmoc-Phe-Ala-O*t*-Bu	Fmoc-Pro-Ala-O*t*-Bu	Fmoc-Val-Ala-O*t*-Bu	Fmoc-Aib-Ala-O*t*-Bu
73% yield (1 h) 99% yield (1 h)[a]	87% yield (30 min) 90% yield (1 h)[a]	82% yield (30 min) 90% yield (2 h)[a]	81% yield (30 min) 92% yield (2 h)[a]	53% yield (1.5 h) 91% yield (2 h)[a]

[a] Portionwise addition of Bu_3P (1.5 equiv)

Significance: Because to 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.

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Category
Peptide Chemistry

Key words
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urea-based catalysis
diselenides
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peptide coupling