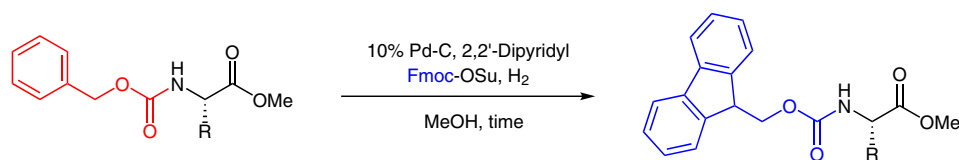


Synthesis of *N*^α-Fmoc-Protected Amino Acid Esters and Peptides



Substrate scope

Entry	Substrate	Product	Time (h)	Yield (%)	% ee ^a
1	<i>N</i> ^α -Cbz-Ala-OMe	<i>N</i> ^α -Fmoc-Ala-OMe	3.5	90	≥99
2	<i>N</i> ^α -Cbz-Phe-OMe	<i>N</i> ^α -Fmoc-Phe-OMe	15.0	88	≥99
3	<i>N</i> ^α -Cbz-Asp(<i>t</i> -Bu)-OMe	<i>N</i> ^α -Fmoc-Asp(<i>t</i> -Bu)-OMe	4.5	89	–
4	<i>N</i> ^α -Cbz-Leu-OMe	<i>N</i> ^α -Fmoc-Leu-OMe	15.0	89	≥99
5	<i>N</i> ^α -Cbz-Pro-OMe	<i>N</i> ^α -Fmoc-Pro-OMe	3.5	79	≥99
6	<i>N</i> ^α -Cbz-Lys(Boc)-OMe	<i>N</i> ^α -Fmoc-Lys(Boc)-OMe	7.0	88	–
7	<i>N</i> ^α -Cbz-Gly-Gly-OMe	<i>N</i> ^α -Fmoc-Gly-Gly-OMe	4.0	84	–
8	<i>N</i> ^α -Cbz-Thr(<i>t</i> -Bu)-Ala-OMe	<i>N</i> ^α -Fmoc-Thr(<i>t</i> -Bu)-Ala-OMe	4.0	83	≥99 ^b

^a% ee values were determined by chiral HPLC using either Chiralcel OD or Chiralpak AS columns (0.46×25 cm) using hexane and isopropanol as eluent at 20 °C and 1 mL/min flow-rate, at 280 nm. Fmoc-D-products were synthesized and used as standards to demonstrate that resolution of possible enantiomers was achieved with the HPLC conditions employed.

^b% ee value determined via RP-HPLC using a Vydac C4 peptide, protein column with water and 90% acetonitrile in water each containing 0.1% TFA as elution solvents.

Significance: Since the development of solid-phase peptide synthesis, the 9-fluorenylmethoxycarbonyl (Fmoc) group has been the protecting group of choice for obtaining peptides in high purities. Consequently, the peptide-chemistry industry has been searching for new methods to synthesize Fmoc-protected amino acids and peptides. In 2000, Schneider and Dzubeck developed a simple one-pot protocol for the conversion of *N*-benzyloxycarbonyl (Cbz)-protected amino acid esters or peptides into the corresponding *N*-Fmoc-protected compounds.

Comment: Conversion of *N*-Cbz-protected amino acid esters or peptides into the corresponding *N*-Fmoc-protected derivatives proceeds smoothly through hydrogenation in the presence of Pd/C and 2,2'-bipyridine as a catalyst system in the presence of Fmoc-*O*-succinimide (Fmoc-OSu). The reaction gives the desired compounds in high yields with excellent stereoselectivities, and it tolerates various other functional groups.