Chiral Ligands and Ni(II) Complexes for the Preparation of Tailor-Made Amino Acids

White Paper

Oakwood Chemical

Enabling Discovery

A valuable objective of peptide synthesis would be the ability to easily prepare amino acids with any imaginable side chain, as either enantiomer, on a practical scale.

At Oakwood Chemical, we are well on our way to this goal, using our chiral glycine equivalent, a nickel(II) complex[1] that can be alkylated with high efficiency and high stereoselectivity.

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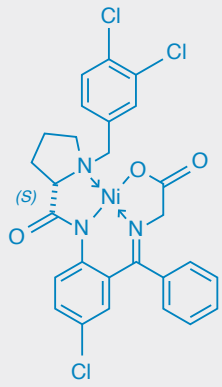

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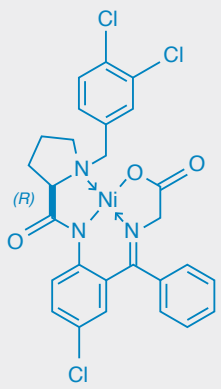
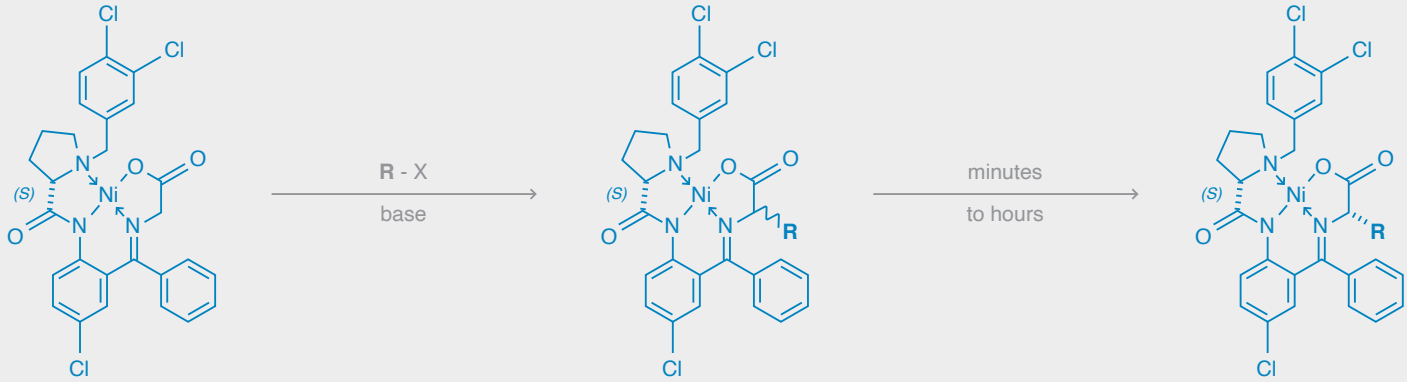
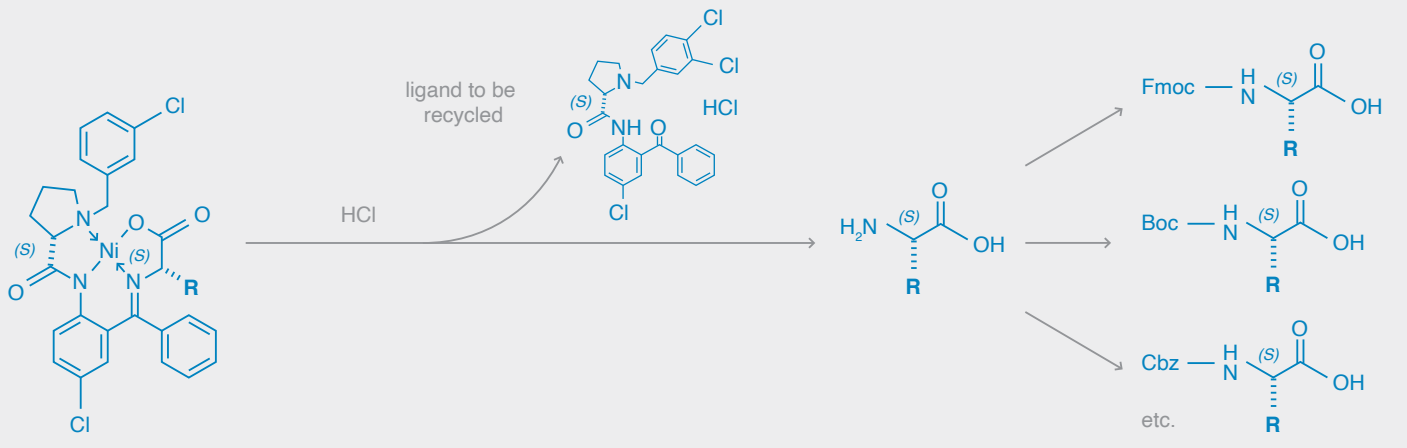


Upon alkylation under mild basic conditions with standard electrophiles, including halides, tosylates, and triflates, the stereochemistry at the glycine center will equilibrate during the reaction to match that of the proline center:



Disassembly of the complex under acidic conditions releases the free amino acid as well as the chirally pure ligands[2], the latter of which can be recycled to prepare new Ni(II) complexes.

The released amino acid can be recovered in free form or with N-protection; the usual forms being Fmoc and Boc, but any protecting group is available in principle:



We offer the purified ligands in both S- and R-configurations:

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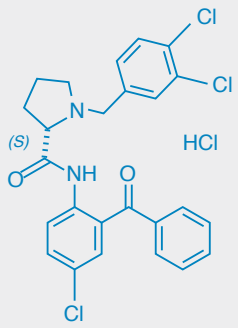

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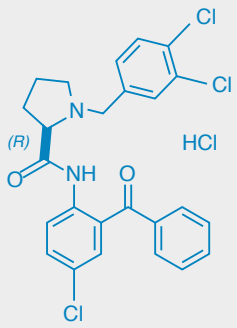
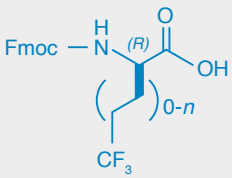
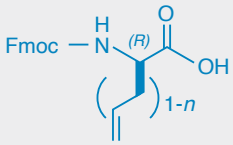


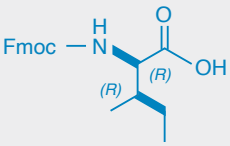
Among our initial offerings will be ω-CF3 and terminal alkene amino acids (both enantiomers), as well as the difficult-to-obtain D-isoleucine:



for increased uptake



for stapled peptides



rare amino acid

There are numerous examples (mostly on small scale) of this technology reported in the literature.3 We are able to provide chirally pure amino acids on a scale from tens to hundreds of grams and even larger on request.

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1 Romoff, Todd T.; Ignacio, Bernardo G.; Mansour, Noel; Palmer, Andrew B.; Creighton, Christopher J.; Abe, Hidenori; Moriwaki, Hiroki; Han, Jianlin; Konno, Hiroyuki; Soloshonok, Vadim A. "Large-Scale Synthesis of the Glycine Schiff Base Ni(II) Complex Derived from (S)- and (R)-N-(2-Benzoyl-4-chlorophenyl)-1-[(3,4-dichlorophenyl)methyl]-2-pyrrolidinecarboxamide." *Organic Process Research & Development* **2020**, *24*(2), 294-300

2 Romoff, Todd T.; Palmer, Andrew B.; Mansour, Noel; Creighton, Christopher J.; Miwa, Toshio; Ejima, Yuki; Moriwaki, Hiroki; Soloshonok, Vadim A. "Scale-up synthesis of (R)- and (S)-N-(2-benzoyl-4-chlorophenyl)-1-(3,4-dichlorobenzyl)pyrrolidine-2-carboxamide hydrochloride, a versatile reagent for the preparation of tailor-made α-and β-amino acids in an enantiomerically pure form." *Organic Process Research & Development* **2017**, *21*(5), 732-739

3 (a) Sorochinsky, A. E.; Aceña, J. L.; Moriwaki, H.; Sato, T.; Soloshonok, V. A. "Asymmetric synthesis of α-amino acids via homologation of Ni(II) complexes of glycine Schiff bases; Part 1: Alkyl halide alkylations." *Amino Acids* **2013**, *45,* 691–718. (b) Sorochinsky, A. E.; Aceña, J. L.; Moriwaki, H.; Sato, T.; Soloshonok, V. A. "Asymmetric synthesis of α-amino acids via homologation of Ni(II) complexes of glycine Schiff bases. Part 2: Aldol, Mannich addition reactions, deracemization and (S) to (R) interconversion of α-amino acids." Amino Acids **2013**, *45,* 1017–1033. (c) Aceña, J. L.; Sorochinsky, A. E.; Solosh nok, V. A. "Asymmetric synthesis of α-amino acids via homologation of Ni(II) complexes of glycine Schiff bases. Part 3: Michael addition reactions and miscellaneous transformations." *Amino Acids* **2014**, *46,* 2047–2073. (d) Aceña, J. L.; Sorochinsky, A. E.; Moriwaki, H.; Sato, T.; Soloshonok, V. A. "Synthesis of fluorine-containing α-amino acids in enantiomerically pure form via homologation of Ni(II) complexes of glycine and alanine Schiff bases." *J. Fluor. Chem.* **2013**, *155,* 21-38. (e) Wang, Y.; Song, X; Wang, J.; Moriwaki, H.; Soloshonok, V. A.; Liu, H. "Recent approaches for asymmetric synthesis of α-amino acids via homologation of Ni(II) complexes." *Amino Acids,* **2017**, *49,* 1487–1520.

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