Synthesis of Pregabalin

Significance: Pregabalin (Lyrica®) is a lipophilic GABA analogue that is prescribed for the treatment of epilepsy. This short, small-scale synthesis of pregabalin features a highly enantioselective asymmetric conjugate addition of the alkenyl trifluoroborate to the α,β-unsaturated lactam catalyzed by a rhodium complex incorporating the chiral bicyclo[3.3.0]octa-2,5-diene ligand L.

Comment: A further 17 examples of this new variant of the Hayashi–Miyaura asymmetric conjugate addition reaction are reported using six α,β-unsaturated carbonyl substrates and ten alkenyl trifluoroborates. The asymmetric conjugate addition was also applied to the synthesis of the potent neuroexcitatory agent α-kainic acid (seven steps, 40% overall yield).

Further examples of adducts derived from the asymmetric conjugate addition reaction:

- 99% (91% ee)
- 74% (93% ee)
- 93% (78% ee)
- 93% (99% ee)
- 78% (99% ee)
- 97% (99% ee)