Carbene catalyzed enantioselective synthesis of optically enriched 3-substituted phthalides was demonstrated, which could be used for structural modification on heteroatoms as prodrug within the medicinally significant molecules. The generality of this approach was demonstrated, and marketed drugs were synthesized. The methodology shall expand the synthetic toolbox and bring significant values for the discovery and manufacturing of better chiral prodrugs in enantiomerically enriched forms.