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Phthalides by Rhodium-Catalyzed Ketone Hydroacylation

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### Rhodium-Catalyzed Enantioselective Synthesis of Phthalides

**Significance:** The enantioselective synthesis of phthalides 2 via a rhodium-catalyzed intramolecular hydroacylation approach is reported. The appropriate choice of counterion was crucial to avoid decarbonylation and obtain high enantioselectivity. Substrates bearing EDGs and EWGs on the aromatic ring performed equally well in the reaction. However, introduction of a steric bulk ortho to the ketone (R1 = 3-Me) prohibited the reaction. Variation in the ketone moiety including primary and secondary alkyl groups and electron-rich or electron-deficient aromatics was also tolerated. Excellent enantioselectivities were observed in almost all cases.

**Comment:** Phthalides are known to exhibit broad bioactivities, such as lowering blood pressure, slowing memory loss, and anti-inflammatory properties (see Book below). Typical routes to enantioenriched phthalides rely on the use of chiral auxiliaries or chiral organometallic reagents, and as such are not catalytic. The present rhodium-catalyzed method is efficient, atom-economical, and proceeds with high levels of enantiocontrol, although somewhat long reaction times (up to three days) are often required.


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**Category**

Synthesis of Heterocycles

**Key words**

phthalides
hydroacylation
rhodium

![Chemical structure](image)

[Chemical structure of phthalides with reaction conditions and yields.

**[Equation](image) with reaction conditions and yields.**

R1 = H, 3-Me, 4-Me, 4-MeO, 5-Me, 5-t-Bu, 5-Cl, 5-O2N, 5-MeO2C, 6-MeO

R2 = Me, Et, i-Pr, n-Bu, Ph, 4-MeC6H4, 4-MeOC6H4, 4-O2NC6H4

67–97% yield
89–98% ee
16 examples