Rhodium-Catalyzed Asymmetric C–H Functionalization of Methyl Ethers

General reaction:

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\text{CH}_2\text{O}_2\text{CH}_2\text{CCl}_3 + \text{CH}_2\text{O} \rightarrow \text{Rh}_2(\text{R}-\text{BPCP})_4 (0.5 \text{ mol\%}) \rightarrow \text{CH}_2\text{O}_2\text{CH}_2\text{CCl}_3 OR \rightarrow 34–83\% \text{ yield} 
\]

Selected examples:

- Cl\(_3\)CH\(_2\)CO\(_2\)H\(_2\)C\(\text{O}\)Br: 83% yield, 91% ee
- Cl\(_3\)CH\(_2\)CO\(_2\)H\(_2\)C\(\text{O}\)Br: 80% yield, 94% ee (gram scale: 95%, 90% ee)
- Cl\(_3\)CH\(_2\)CO\(_2\)H\(_2\)C\(\text{O}\)Br: 77% yield, 97% ee
- Cl\(_3\)CH\(_2\)CO\(_2\)H\(_2\)C\(\text{O}\)Br: 74% yield, 91% ee
- Cl\(_3\)CH\(_2\)CO\(_2\)H\(_2\)C\(\text{O}\)Br: 58% yield, 93% ee
- Cl\(_3\)CH\(_2\)CO\(_2\)H\(_2\)C\(\text{O}\)Br: 74% yield, 82% ee
- Cl\(_3\)CH\(_2\)CO\(_2\)H\(_2\)C\(\text{O}\)Br: 41% yield, 94% ee
- Cl\(_3\)CH\(_2\)CO\(_2\)H\(_2\)C\(\text{O}\)Br: 57% yield, 96% ee
- Cl\(_3\)CH\(_2\)CO\(_2\)H\(_2\)C\(\text{O}\)Br: 34% yield, 75% ee

Accessing different diastereomers utilizing a chiral menthol substrate:

Significance: The asymmetric site-selective functionalization of unactivated sp\(^3\) C–H bonds is one of the most challenging reactions to date. Davies and co-workers demonstrated in this article the utility of trichloroethyl aryldiazooacetates as excellent substrates in the Rh-catalyzed enantioselective functionalization of methyl ethers.

Comment: A wide spectrum of methyl ethers can be functionalized with trichloroethyl aryldiazooacetates with moderate and good yields and excellent enantioselectivities. In all cases, regioselectivity of the carbene insertion is on the less hindered methyl moiety. When a chiral ether was utilized, different diastereomeric products could be selectively accessed using opposite enantiomers of the chiral catalyst (matched and mismatched).