Chiral cyclopentadienyl Rh\textsuperscript{III}-catalyzed enantioselective cyclopropanation of electron-deficient olefins enable rapid access to UPF-648 and oxylipin natural products†

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Chiral cyclopentadienyl Rh\textsuperscript{III} complexes efficiently catalyze enantioselective cyclopropanations of electron-deficient olefins with N-enoxysuccinimides as the C1 unit. Excellent asymmetric inductions and high diastereoselectivities can be obtained for a wide range of substrate combinations. The reaction proceeds under mild conditions without precautions to exclude air and water. Moreover, the synthetic utility of the developed method is demonstrated by concise syntheses of members of the oxylipin natural products family and the KMO inhibitor UPF-648.

Introduction

Chiral cyclopropanes are important structural motifs frequently found in a diverse range of natural products and biologically active compounds.\textsuperscript{1} Cyclopropanes are attractive building blocks for drug discovery due to their rigid structure with defined three-dimensional vectors and their good metabolic stability.\textsuperscript{2} Moreover, they are versatile intermediates for synthesis as ring-opening reactions opens access to useful building blocks.\textsuperscript{3} Synthetically, the most practical strategy to build the cyclopropane motif consists of an enantioselective cycloaddition between an olefin and a suitable C1 unit.\textsuperscript{4} For instance, transition-metal catalyzed reactions\textsuperscript{5} – metal-carbenoid mediated transformations\textsuperscript{6} and the ring closure of \( \pi \)-allylpalladium species,\textsuperscript{7} Lewis-acid catalyzed Simmons–Smith reactions\textsuperscript{8} as well as radical processes\textsuperscript{9} have proven to be powerful methods for the asymmetric cyclopropanations of electron-rich olefins. Complementary, asymmetric Michael-initiated ring-closure (MIRC) reactions have been shown to be an attractive cyclopropanation method for electron-deficient olefins.\textsuperscript{10} Moreover, tailored transition-metal catalysts enable enantioselective cyclopropanations of electron-deficient olefins with diazo compounds.\textsuperscript{11} However, these transformations still have limitations in scope and frequently require potentially hazardous reactants. Therefore, the development of novel and efficient catalytic cyclopropanation strategies using complementary substrates remain an important and urgent task. In this respect, Rovis and co-workers recently reported a unique cyclopropanation using N-enophthalimides and Michael acceptors as substrates (Fig. 1).\textsuperscript{12} Tailored achiral cyclopentadienyl Rh\textsuperscript{III} catalysts enabled this transformation and moreover allowed to efficiently control its diastereoselectivity.\textsuperscript{12a} Given our longstanding focus on the development of chiral cyclopentadienyl (Cp\textsuperscript{3}) metal catalysts\textsuperscript{13} for challenging asymmetric transformations,\textsuperscript{14} we felt prompted to explore the feasibility of an enantioselective Rovis-cyclopropanation. This is
a formidable challenge to expand the current boundaries of asymmetric Cp*Rh*III catalysis beyond functionalizations of aryl Csp2–H bonds. Despite ample precedence with achiral Cp*Rh* complexes, the corresponding asymmetric functionalization of alkenyl Csp2–H bonds with Cp*Rh*III catalysts remained so far elusive.

Herein, we report a highly enantioselective alkenyl C–H bond functionalization providing access to chiral cyclopropanes under mild conditions.

Results and discussion

The envisioned enantioselective cyclopropanation was investigated with N-enoxophthalimide 1 and ethyl acrylate (Table 1). Rh1 featuring our simplest first generation Cp* design† provided desired cyclopropane 4aa in 71% yield, >20 : 1 trans/cis ratio and 93.5 : 6.5 er (entry 1). Increasing of the size of the backwall using a diphenyl acetal (Rh2) or a silyl bridge (Rh3) reduced the enantioselectivity (entries 2 and 3). Complex Rh4 with a trisubstituted TMS-bearing Cp* ligand† was as well inferior (entry 4). Binaphthyl-derived ligands (Rh5–Rh8)† are not suited and gave a general poor performance concerning yield, diastereo- and enantioselectivity (entries 5–8). Moreover, usage of Rh9 with a cyclopentyl-backbone Cp* ligand† formed cyclopropane 4aa in negligible amounts (entry 9). The solvent has a large influence. Replacement of TFE by either ethanol or HFIP gave dramatically lower yields (entries 10 and 11). A lower reaction temperature (0 °C) caused a sluggish reaction with no discernible increase in enantioselectivity (entry 12), whereas heating to 50 °C triggered slight erosion in yield and selectivity (entry 13). A short premixing period between the rhodium catalyst and the oxidant increased the yield to 76% while maintaining an enantiomeric ratio of 93.5 : 6.5 (entry 14). The nature of the imide of the oxidizing directing group was important. A range of other oxidizing directing group Rα failed to provide the desired reactivity which was attributed to poor solubility. However, replacement of 1 by enoxysuccinimide 2a resulted in a cleaner and faster reaction, giving 4aa in 78% isolated yield with an improved excellent enantioselectivity of 97 : 3, although with a lower diastereoselectivity of 4 : 1 (entry 15).

With the optimized conditions, the scope of the reaction was investigated (Scheme 1). A variety of acrylic esters were tested. Commonly used methyl, ethyl, butyl and benzyl esters gave the cyclopropane products with good yields, >95 : 5 er and useful diastereomeric ratios between 4 : 1 and 6 : 1. Notably, tert-butyl acrylate provided in all aspects superior results, giving 4ac in 85% yield with >20 : 1 dr and 97 : 3 er. Moreover, acrylamide derivatives, exemplified with morpholine 3f reacted smoothly, giving 4af in excellent dr and suitable yields and enantioselectivity. In particular, Weinreb acrylamide proved to be well suited, giving cyclopropane 4ag in 75% yield with >20 : 1 dr and 97 : 3 er. Surprisingly, both acrolein and MVK acceptors gave high yields of the corresponding cyclopropanes 4ah and 4ai.
maintaining high levels of enantioselectivity. However, due to their small size, the diastereomeric ratio was with 1.6 : 1, respectively 2 : 1, lower. Interestingly, the cis-products were found in approximately the same enantioselectivity. Besides MVK, similar reactivity was observed for longer chain vinyl ketone giving 4aj. Considering the dearth of methods for enantiopure cis-cyclopropanes from electron-poor olefins, this observation could be a starting point in the development of an enantioselective cis-selective variant. Heteroatom-based Michael acceptor such as phenyl vinyl sulfone/selenone or ethenesulfonyl fluoride did not undergo cyclopropanation. Acrylates with α or β-substitution were not reactive acceptors with the current catalytic system.

The range of suitable enoxy-succinimides was investigated (Table 2). We first evaluated variations of the steric and electronic properties of the aryl-substituted enoxy-succinimides. Electron-donating and withdrawing groups in the para position were found to have very little influence on the reaction outcome, providing high yields and enantioselectivities of the corresponding cyclopropanes 4 (entries 1–4). Along the same lines, meta- (2f) and ortho- (2g) substitution as well as heteroaryl (2i) and condensed aromatic substituent (2h) were tolerated well. Due to limited solubility in TFE, substrates having a naphthyl (2h) or chloroarene substitutent (2e) required longer reaction times. Attractively, besides aryl-substituted enoxy-succinimides, the cyclopropanation worked very well with dienenoxy substrates such as 2j and 2k giving enone products 4je and 4ke in an excellent er of 96 : 4. Notably, no competing Diels–Alder cycloaddition between the electron-rich diene and the acrylate acceptor was observed under the reaction conditions. Moreover, the reactivity, diastereo- and enantioselectivity were excellent for alkyl substituents, leading to functionalized cyclopropanes 4le and 4me (entries 11 and 12).

The synthetic utility of the method was demonstrated as key step in the synthesis of natural products and inhibitor UPC-648. Constanlactones and ent-eicosanoid 8 are marine oxylipins containing a trans-cyclopropane. Previous syntheses used lactone 7 as common intermediate which could be accessed in 6 22 or 13 steps. 23 In a streamlined access to required N-enoxysuccinimide 2n, we developed a gold(I)-catalyzed addition of N-hydroxyxuccinimide to terminal alkyne which directly provided substrate 2n in 68% yield (Scheme 2). 24 Subjecting 2n to the developed optimized enantioselective cyclopropanation conditions in the presence of Weinreb acryl amide gave cyclopropane 4ng in 89% yield, 97 : 3 enantiomeric ratio and >20 : 1 dr. The transformation was efficient for gram-scale preparation giving 1.10 g of 4ng. Diastereoselective reduction of 4ng with Noyori’s catalyst gave secondary alcohol 6 in 89% yield and 85 : 15 dr. Reduction of the Weinreb amide over the isopropyl ester of 6 and subsequent lactonization under acidic conditions yielded intermediate 7 in 50% yield over 2 steps. This intermediate can be elaborated either in a single step operation into constanolactone A and B, or by a two-step sequence into ent-eicosanoid 8. 22

Table 2 Variations of the N-enoxysuccinimide partner

<table>
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<tr>
<th>Entry</th>
<th>4 (R)</th>
<th>% yield</th>
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<sup>a</sup> 0.10 mmol 2, 5.0 μmol Rh1, 5.0 μmol (BzO)2, 0.12 mmol 3e, 0.20 mmol CsOAc, 0.2 M in TFE at 23 °C for 16 h. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by 1H-NMR of the crude product. <sup>d</sup> Determined by HPLC analysis with a chiral stationary phase. <sup>e</sup> For 40 h. <sup>f</sup> For 56 h.

Scheme 2 Synthetic application of the enantioselective cyclopropanation in the formal synthesis of members of oxylipin natural products family.
UPF-648, a potent inhibitor (IC_{50} = 40 nM) for kynurenine 3-monooxygenase (KMO),\textsuperscript{1,25,26} was identified as another attractive target. Inhibition of KMO has therapeutic potential for several neurodegenerative disorders, including Huntington’s disease.\textsuperscript{27} The two reported syntheses of UPF-648 are long and use a stoichiometric chiral auxiliary\textsuperscript{28} or involve a resolution.\textsuperscript{29} Therefore, a short catalytic enantioselective route represents significant synthetic value. Our synthesis starts with a gold-catalyzed cyclopropanation without any precaution to exclude moisture or oxygen, giving \( \text{3) The enantioselective cyclopropanation was conducted using enoxysuccinimides as the one-carbon component. The synthetic value. Our synthesis starts with a gold-catalyzed addition of N-hydroxy succinimide to 3,4-dichloro phenyl acetylene (9) affording N-enoxysuccinimide 20 in 53% yield (Scheme 3). The enantioselective cyclopropanation was conducted without any precaution to exclude moisture or oxygen, giving cyclopropane 4oe in 80% yield and 95 : 5 er. Alternatively, application of our recently developed \textit{in situ} Cp\textsuperscript{+}Rh catalyst preparation\textsuperscript{14} provided 4oe in 76% yield and 94.5 : 4.5 er. Cleavage of the tert-butyl ester gave UPF-648 ester. A subsequent recrystallization increased its optical purity to 99 : 1 er. Overall, UPF-648 could be synthesized in 3 steps in a catalytic enantioselective fashion with an overall yield of 39%.

\textbf{Conclusions}
In summary, we have developed a highly enantioselective and diastereoselective cyclopropanation of electron-deficient olefins using enoxysuccinimides as the one-carbon component. The transformation is catalyzed by chiral Cp\textsuperscript{+}Rh\textsuperscript{31} complexes and operates under mild and open-flask reaction conditions. We applied the transformation as a key step in the synthesis of the oxylipin family of natural products and the kynurenine 3-monoxygenase inhibitor UPF-648, showcasing its synthetic utility.

\textbf{Conflicts of interest}
There are no conflicts to declare.

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\textbf{Notes and references}


