Organic LETTERS

Letter

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Ru(II)−Pheox-Catalyzed Asymmetric Intramolecular Cyclopropanation of Electron-Deficient Olefins

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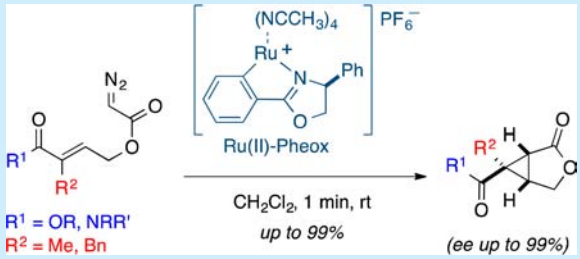
Supporting Information

ABSTRACT: The first highly enantioselective intramolecular cyclopropanation of electron-deficient olefins, in the presence of Ru(II)−Pheox catalyst, is reported. The corresponding cyclopropane-fused γ-lactones were obtained in high yields (up to 99%) with excellent enantioselectivities (ee up to 99%). Moreover, this method enables efficient access to enantioenriched dicarbonyl cyclopropane derivatives, which are important intermediates for the synthesis of various bioactive compounds.



The transition-metal-catalyzed cyclopropanation of olefins with diazo compounds, for the efficient construction of optically active cyclopropane compounds, has been continuously developed over the past two decades.[1] Since the pioneering efforts of Nozaki,[2] remarkable progress has been made on olefin cyclopropanation via electrophilic carbene transfer catalyzed by copper, rhodium, ruthenium, and cobalt.[3] Electron-rich olefins, such as styrene derivatives, are extensively studied because of their high reactivity with the electrophilic nature of the metal−carbene intermediates obtained by the reaction of metal complexes and diazoacetates. However, electron-deficient olefins such as α,β-unsaturated carbonyl compounds have not been widely used as substrates since their cyclopropanation reactions do not proceed with most of the currently used catalytic systems. Recently, the D_2-symmetric chiral porphyrin Co(II)-based and the chiral adamantylglycine-derived Rh(II)-based catalysts have been the most efficient catalytic systems for the asymmetric intermolecular cyclopropanation of electron-deficient olefins, as reported by the Zhang[4] and Davies[5] groups, respectively. The biocatalytic cyclopropanation of electron-deficient olefins was also developed by the Arnold[6] group. Although these significant catalysts have been developed, only one example of an asymmetric intramolecular cyclopropanation of an electron-deficient olefin has been reported, for which the yield and enantioselectivity were low (32% yield, 80% ee).[7]

Recently, our group reported that the Ru(II)−Pheox complex is an extremely efficient catalyst of asymmetric inter- and intramolecular cyclopropanation.[8] In our previous work, we successfully demonstrated the Ru(II)−Pheox-catalyzed intermolecular cyclopropanation of α,β-unsaturated carbonyl compounds with functionalized diazoacetates to afford dicarbonyl cyclopropane products in high yields with excellent stereoselectivities and enantioselectivities.[9] Our continuing interest in developing asymmetric cyclopropanation of electron-deficient olefins prompted us to explore the intramolecular cyclopropanation of α,β-unsaturated carbonyl diazoacetates.

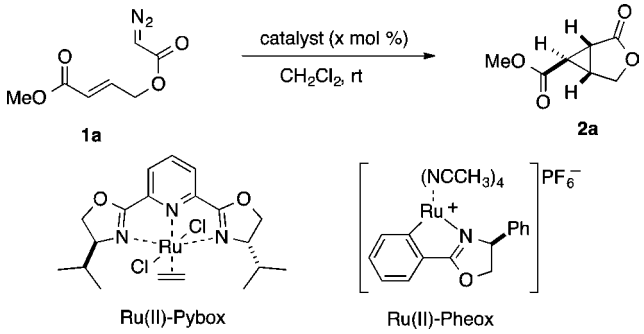
To test the efficiency of our Ru(II)−Pheox catalyst and other commonly used catalysts in cyclopropanation reactions, we began our investigation by treating the α,β-unsaturated carbonyl diazoacetate **1a** with each catalyst in dichloromethane (Table 1). We found only dimeric compounds when $Rh_2(OAc)_4$ was employed as the catalyst (Table 1, entry 1). Among the other catalyst systems that were also investigated, we found that no reactions occurred when $Pd(OAc)_2$, $Cu(OAc)_2$, and Ru(II)−Pybox[1d] were used as catalysts at room temperature. To improve their reaction efficiencies, we attempted the cyclopropanation reactions at 40 °C over 14 h; however, the dimerization of the diazo compound still proceeded preferentially (Table 1, entries 2−7). In contrast, the cyclization of the diazoacetate **1a** proceeded smoothly and remarkably quickly at room temperature in the presence of the Ru(II)−Pheox catalyst to give the cyclopropane-fused γ-lactone **2a** in high yield (90%) with excellent enantioselectivity (99% ee) (Table 1, entry 8). To the best of our knowledge, this is the first highly enantioselective intramolecular cyclopropanation of an electron-deficient olefin.

Due to the low reactive cyclopropanation of this type of diazo compound, we became interested in the influence of various solvents on the cyclization (Table 2). To our surprise, the yields of the cyclopropane product were highly dependent upon the organic solvent used, while the enantioselectivity was not. Higher yields could be obtained by a slow addition of the diazoacetate into the acetone and toluene solvents, but for dichloromethane, a slow addition had the opposite effect (Table 2, entries 3, 5, and 9). These results indicate that various

Received: April 23, 2015
Published: May 22, 2015

DOI: 10.1021/acs.orglett.5b01201
Org. Lett. 2015, 17, 2792−2795

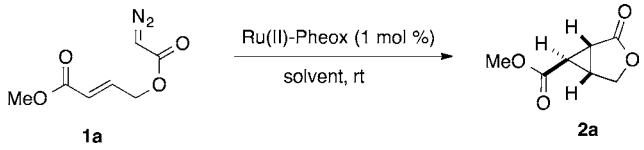
Table 1. Catalyst Screening[a]



entry	catalyst	x (mol %)	temp (°C)	time (h)	yield[b] (%)
1	$Rh_2(OAc)_4$	1	rt	2	0
2	$Pd(OAc)_2$	5	rt	1	0
3	$Pd(OAc)_2$	5	40	14	0
4	$Cu(OAc)_2$	5	rt	1	0
5	$Cu(OAc)_2$	5	40	14	0
6	Ru(II)−Pybox	1	rt	1	0
7	Ru(II)−Pybox	1	40	14	11
8[c]	Ru(II)−Pheox	1	rt	1 min	90

[a]Reaction conditions: to a solution of catalyst (1 or 5 mol %) in CH_2Cl_2 was added a solution of diazoacetate **1a** (0.2 mmol) under Ar. [b]Isolated yield. [c]The enantioselectivity was 99% ee.

Table 2. Optimization of Reaction Conditions[a]



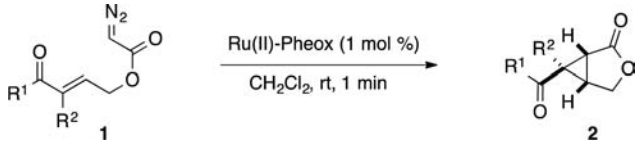
entry	solvent	time	yield[b] (%)	ee[c] (%)
1	THF	0.5 h	67	98
2	acetone	26 h	62	99
3[d]	acetone	5 h	89	99
4	toluene	1 h	41	99
5[d]	toluene	5 h	68	99
6	CH_3OH	5 min	11	
7	CH_3CN	24 h	75	99
8	CH_2Cl_2	1 min	90	99
9[d]	CH_2Cl_2	5 h	78	99

[a]Reaction conditions: to a solution of Ru(II)−Pheox (1 mol %) in CH_2Cl_2 was added a solution of diazoacetate **1a** (0.2 mmol) under Ar. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Diazoacetate **1a** diluted in CH_2Cl_2 was slowly added over 4 h by using syringe pump.

solvents decreased the activation of our catalytic system; the most dramatic influence was observed for methanol due to the side reaction of O−H insertion (Table 2, entry 6).

To further examine the generality of this reaction, other substrates were also tested for cyclopropanation under the optimized reaction conditions (Table 3). Diazoacetates bearing a variety of α,β-unsaturated ester-substituents (R^1 = MeO, EtO, and BnO) were easily cyclopropanated to give the corresponding cyclopropane-fused γ-lactones **2a**−**c** in high yields (90−99%) with excellent enantioselectivity (99% ee). The effect of the substituents at the α-position was examined using diazoacetates (R^2 = Me or Bn). High yields and enantioselectivities were obtained, regardless of whether the R^2 substituent was small or large (Table 3, entries 4−8). It is

Table 3. Ru(II)-Pheox Catalyzed Asymmetric Intramolecular Cyclopropanation of Electron-Deficient Olefins[a]



entry	substrate 1 R^1	R^2	2	yield[b] [%]	ee[c] [%]
1	MeO (1a)	H	2a	90	99
2	EtO (1b)	H	2b	99	99
3	BnO (1c)	H	2c	99	99
4	MeO (1d)	Me	2d	95	94
5	EtO (1e)	Me	2e	98	99
6	BnO (1f)	Me	2f	90	86
7[d]	BnO (1f)	Me	2f	90	98
8	EtO (1g)	Bn	2g	82	95
9	BnNH (1h)	H	2h	74	94
10	Bn(Me)N (1i)	H	2i	99	97
11	MeO(Me)N (1j)	H	2j	89	98

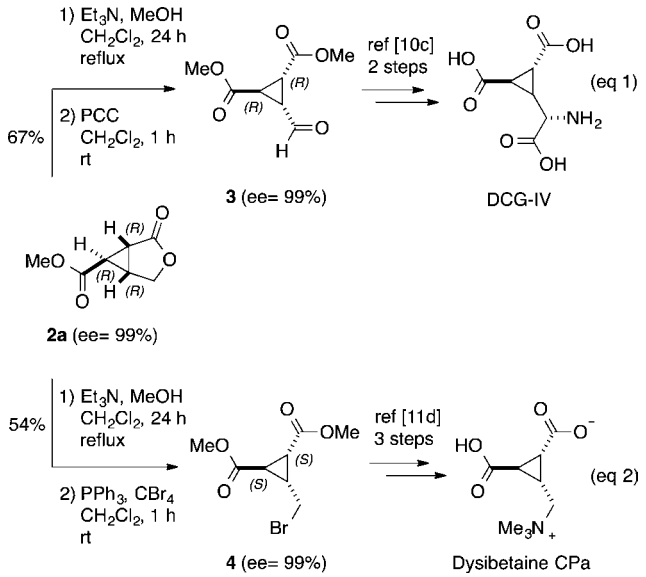
[a]Reaction conditions: to a solution of Ru(II)−Pheox (1 mol %) in CH_2Cl_2 was added a solution of diazoacetate (0.2 mmol) under Ar. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Reaction was carried out at 0 °C.

noteworthy that the enantioselectivity of this reaction was significantly improved by carrying out the reaction at 0 °C (Table 3, entries 6 and 7) (from 86% ee to 94% ee). To our delight, the reactions of diazoacetates bearing α,β-unsaturated amide substituents (R^1 = BnNH, Bn(Me)N, and MeO(Me)N) also proceeded in high yields with high enantioselectivities (Table 3, entries 9−11).

DOI: 10.1021/acs.orglett.5b01201
Org. Lett. 2015, 17, 2792−2795

To illustrate the utility of our enantioselective cyclization of α,β-unsaturated carbonyl diazoacetates, we prepared key intermediates in the reported synthesis of DCG-IV[10] and dysibetaine CPa[11] from the cyclopropane-fused γ-lactone **2a** (Scheme 1). DCG-IV is a (dicarboxycyclopropyl)glycine that is

Scheme 1. Preparation of Key Intermediates for the Synthesis of Bioactive Compounds



known to be an anticonvulsant agent, being a potent group II mGluR agonist with neuroprotective properties, and is also active as an agonist at the NMDA receptor. The shortest synthetic method is attributed to Wichmann and co-workers;[10c] however, chiral resolution was required to synthesize the enantiomerically pure starting substrate. Our synthetic method is a direct enantioselective intramolecular cyclopropanation of the α,β-unsaturated carbonyl diazoacetate **1a**, which gives the chiral cyclopropane-fused γ-lactone **2a**. A subsequent ring opening and oxidation reaction affords the desired product **3** efficiently and with complete enantioselectivity (99% ee) (Scheme 1, eq 1).

Dysibetaine CPa, a marine natural product consisting of a unique alkyltrimethylammonium carboxylate betaine on a cyclopropane core, is a potential pharmaceutical agent as a candidate GABA receptor ligand. Oikawa and co-workers previously reported an efficient synthesis of this natural product, which utilized the enantioselective solvolytic opening of a *meso*-cyclic anhydride as the key step for the construction of the chiral cyclopropyl intermediate, albeit with low yield and moderate enantioselectivity.[11d] Our synthetic method, a ring opening of the chiral cyclopropane-fused γ-lactone **2a** and subsequent bromination with PPh_3/CBr_4, afforded the desired product **4** in a 54% yield over two steps, with complete enantioselectivity (Scheme 1, eq 2). As the configuration of products **3** and **4** were confirmed by the comparison of their optical rotations,[10c,11d] the absolute configuration of the chiral cyclopropane-fused γ-lactone **2a** was determined to be (1*R*,5*R*,6*R*).

To summarize, we have established a highly enantioselective intramolecular cyclopropanation of electron-deficient olefins. The use of the Ru(II)−Pheox complex as a catalyst was found to be crucial to the reaction and gave the chiral cyclopropane-fused γ-lactones in high yield (up to 99%) with excellent enantioselectivity (ee up to 99%). This method enables efficient access to enantioenriched dicarbonyl cyclopropane derivatives, which are important building blocks for the synthesis of pharmaceuticals and natural products.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization of the products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01201.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research (B) (No. 26288087) from Japan Society for the Promotion of Science.

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DOI: 10.1021/acs.orglett.5b01201
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DOI: 10.1021/acs.orglett.5b01201
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