Cyclopropanation

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Efficient Construction of α-Spirocyclopropyl Lactones: Iridium–Salen-Catalyzed Asymmetric Cyclopropanation**

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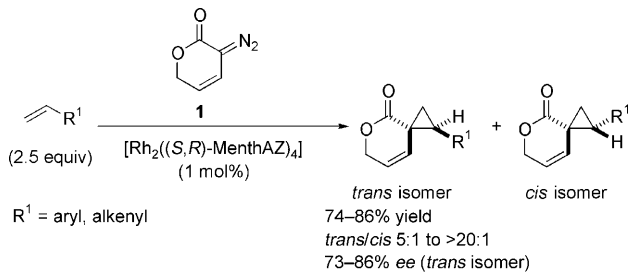
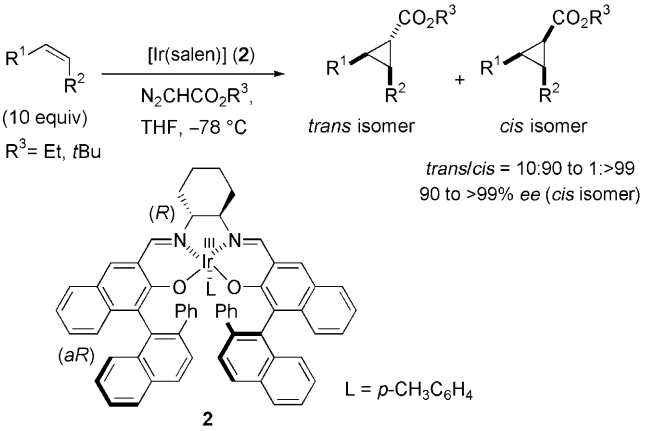
Chiral 1,4-cycloheptadiene structures are found in various natural products, and several useful methods for their construction have been reported.[1,2] Davies and co-workers developed a tandem asymmetric cyclopropanation[3]–Cope rearrangement with α-alkenyl α-diazoacetates as a carbene source in the presence of a rhodium catalyst as an efficient method for the synthesis of these structures.[4] Although the first cyclopropanation step was highly enantioselective, the yields of some reactions were unsatisfactory as a result of undesired side reactions.[5] Recently, Doyle and co-workers reported that cyclopropanation with the vinyl diazolactone **1** in the presence of the catalyst [Rh_2((*S*,*R*)-MenthAZ)$_4$] gave α-spirocyclopropyl lactones in good yields; *E* (*trans*) selectivity and enantioselectivity were moderate to good (Scheme 1).[6] Since unsaturated lactones can be converted



Scheme 1. Asymmetric cyclopropanation with the vinyl diazolactone **1**. MenthAZ = dirhodium(II) tetrakis[1*R*,2*S*,5*R*-menthyl 2-oxaazetidine-4*S*-carboxylate].

into various functional groups, these reaction products are intrinsically versatile and useful building blocks. These products were also converted into 1,4-cycloheptadiene derivatives by heating after reduction with $LiAlH_4$.[6]

We found recently that iridium–salen complexes with an aryl group at the apical position show unique asymmetric cyclopropanation catalysis: Complex **2** catalyzes the cyclopropanation of not only simple olefins but also heterocyclic compounds, such as benzofuran, with an α-diazoacetate at −78 °C with high *Z* (*cis*) selectivity and high enantioselectivity (Scheme 2).[7] Thus, we were intrigued by the possibility of



Scheme 2. Asymmetric cyclopropanation with the [Ir(salen)] complex **2**.

carrying out asymmetric cyclopropanation reactions with **1** in the presence of complex **2**.

We first examined the cyclopropanation of styrene (10 equiv) with **1** in the presence of **2** (1 mol%) at −78 °C (Table 1). The reaction in THF proceeded rapidly with good diastereo- and enantioselectivity, and to our delight[8] with *trans* rather than *cis* diastereoselectivity (Table 1, entry 1). The *trans* selectivity and enantioselectivity were improved when the reaction was carried out in acetone (Table 1, entry 2). Finally, the reaction in dichloromethane was found to proceed with almost complete *trans* selectivity and enantioselectivity (Table 1, entry 3). We observed previously that the dimerization of α-diazoacetates was accelerated by complex **2**;[7] however, the dimerization of **1** was found to be much slower. When the quantity of styrene was halved (5 equiv), the reaction also proceeded with high selectivity in good yield (Table 1, entry 4). However, the yield of the desired product was insufficient when the reaction was carried out with just one equivalent of styrene; ^{1}H NMR spectroscopic analysis of the reaction mixture showed the formation of a significant amount of 3,6-dihydro-3-hydroxy-2*H*-pyran-2-one, a product resulting from insertion into an O–H bond of water (Table 1, entry 5).[9] To suppress the formation of the undesired O–H-insertion product, we carried out the reaction in the presence of 4 Å molecular

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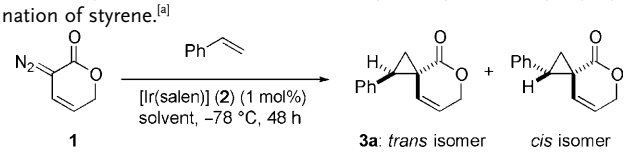
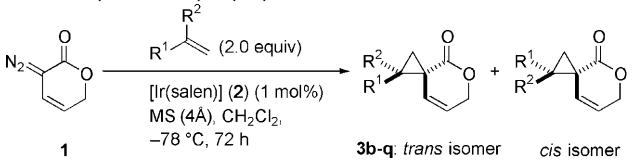
Table 1: Optimization of the iridium-catalyzed asymmetric cyclopropanation of styrene.[a]

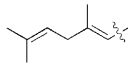


Entry	Styrene [equiv]	Solvent	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][d]
1	10	THF	82	88:12	84
2	10	Acetone	>99	92:8	86
3	10	CH_2Cl_2	>99	>99:1	99
4	5	CH_2Cl_2	92	>99:1	99
5	1	CH_2Cl_2	24[e]	>99:1	99
6[f]	2	CH_2Cl_2	94	>99:1	99
7[f,g]	2	CH_2Cl_2	85	>99:1	99

[a] The reaction of styrene and **1** (0.1 mmol) was carried out at −78 °C in a solvent (0.24 mL) in the presence of **2** (1.0 mol% with respect to **1**) under N_2, unless otherwise mentioned. [b] Yield of the isolated product. [c] The *trans*/*cis* ratio was determined by ^{1}H NMR spectroscopic analysis (400 MHz). [d] The *ee* value of the *trans* isomer was determined by HPLC analysis on a chiral phase (Daicel chiralcel OB-H). [e] The major product was 3,6-dihydro-3-hydroxy-2*H*-pyran-2-one. [f] Molecular sieves (4 Å) were added. [g] The reaction was carried out on a 1.0 mmol scale.

Table 2: Asymmetric cyclopropanation of various olefins.[a]



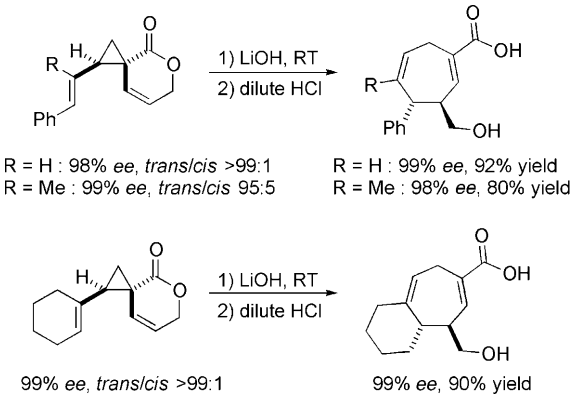
Entry	R^1	R^2	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][d]
1	4-MeO-C_6H_4	H	99 (>99)	>99:1	97
2[e]	4-Cl-C_6H_4	H	99 (>99)	>99:1	99
3[e]	4-Br-C_6H_4	H	92 (97)	>99:1	99
4	4-F-C_6H_4	H	94 (98)	>99:1	99
5	4-CH_3-C_6H_4	H	99 (>99)	>99:1	99
6	2-MeO-C_6H_4	H	96 (>99)	>99:1	99
7[e,f]	3-MeO-C_6H_4	H	93 (97)	>99:1	98
8[f,g]	2-Cl-C_6H_4	H	86 (88)	86:14	99
9[f,g]	3-Cl-C_6H_4	H	87 (90)	94:6	98
10[e,h]	2-naphthyl	H	67 (73)	>99:1	99
11	Ph	Me	99 (>99)	82:18	99
12		H	99 (>99)	>99:1	98
13		H	98 (>99)	>99:1	98
14[i]		H	79 (83)	95:5	99
15[i]		H	92 (98)	>99:1	99
16		H	97 (>99)	>99:1	98

[a] The reaction was carried out on a 0.1 mmol scale (with respect to **1**) at −78 °C in the presence of 4 Å molecular sieves (MS; 20 mg) in CH_2Cl_2 (0.20 mL) under N_2, unless otherwise mentioned. [b] Yield of the isolated product. The value in the parentheses is the yield determined by ^{1}H NMR spectroscopy with 1-bromonaphthalene as an internal standard. [c] The *trans*/*cis* ratio was determined by ^{1}H NMR spectroscopic analysis (400 MHz). [d] The *ee* value was determined as described in the Supporting Information. [e] The reaction was carried out with five equivalents of the olefin. [f] The reaction was carried out with 5 mol% of **2**. [g] The reaction was carried out with 10 equivalents of the olefin. [h] The reaction was carried out at −60 °C. [i] The reaction was carried out with 3 mol% of **2**.

sieves. Although the undesired O−H insertion was suppressed well under these conditions, the reaction with one equivalent of styrene was slow. With two equivalents of styrene, the product was obtained with excellent stereoselectivity (*trans*/*cis* > 99:1, 99% *ee* (*trans* isomer)) in good yield (Table 1, entry 6). The reaction was also efficient on a 1 mmol scale (Table 1, entry 7).

We examined the transformation of a variety of olefin substrates under the optimized conditions (Table 2). The reactions of 4-substituted styrene derivatives proceeded with high enantio- (99% *ee*) and *trans* selectivity (>99:1), although the enantioselectivity was slightly lower when 4-methoxystyrene was used (97% *ee*; Table 2, entries 1–5). The reactions of 2- and 3-methoxystyrene also proceeded with high enantio- and *trans* selectivity (Table 2, entries 6 and 7); with 2- and 3-chlorostyrene, high enantioselectivity and good *trans* selectivity (86:14 and 94:6, respectively) were observed (Table 2, entries 8 and 9). Substitution at the 2- and/or 3-position reduced the reactivity of the substrate to some extent (Table 2, entries 7–10). The reaction of α-methylstyrene also proceeded with excellent enantioselectivity and in good yield, albeit with moderate *trans* selectivity (Table 2, entry 11). The reactions of various 1,3-butadiene derivatives occurred at the terminal double bond with excellent *trans* selectivity and enantioselectivity to furnish the desired dialkenyl cyclopropane products in good yields, irrespective of the substitution pattern of the internal 3-alkenyl moiety of the substrate (Table 2, entries 12–16). Although the presence of a substituent at C3 made the reaction slower, the products were obtained in acceptable yields when the catalyst loading was increased to 3 mol% under otherwise identical conditions (Table 2, entries 14 and 15).

Hydrolysis of the resulting 1-alkenyl 5-oxaspiro[2.5]oct-7-en-4-ones took place with a Cope rearrangement at room temperature to give 1,4-cycloheptadiene derivatives stereospecifically. Although the cyclopropane substrates included a small amount of the *cis* isomer, each product was a single isomer, because only the *trans* isomer underwent the rearrangement (Scheme 3).[10]



Scheme 3. Cope rearrangement of 1,2-divinyl cyclopropanes.

In summary, we have developed a powerful method for the synthesis of 5-oxaspiro[2.5]oct-7-en-4-ones, versatile chiral building blocks, in a highly enantio- and *trans*-selective manner with the iridium–salen catalyst **2**. The cyclopropanation of aryl- and alkenyl-substituted olefins proceeded with excellent enantioselectivity ($\geq 97\%$ *ee*) and high *trans* selectivity ($\geq 94{:}6$, with the exception of two examples). In particular, all the reactions of 1,3-dienes showed excellent enantio-, regio- and *trans* selectivity, irrespective of the substitution pattern of the internal conjugated alkenyl group. Upon hydrolysis, the 1-alkenyl spirocyclopropyl lactone products underwent stereospecific Cope rearrangement at room temperature to furnish 1,4-cycloheptadiene derivatives.

Experimental Section

Typical procedure (Table 1, entry 7): Styrene (0.23 mL, 2.0 mmol) was added with a syringe to a mixture of **1** (124.1 mg, 1.0 mmol) and 4 Å molecular sieves (200 mg) in dry dichloromethane (2.0 mL) in a Schlenk tube (10 mL) at room temperature under N_2. The resulting mixture was cooled to −78 °C and stirred for 10 min. Complex **2** (11.1 mg, 10.0 μmol) was then added, and the reaction mixture was stirred for 2 days. The mixture was then allowed to warm to room temperature, passed through a pad of silica gel to remove the catalyst, and concentrated on a rotary evaporator. The residue was submitted to ^{1}H NMR spectroscopic analysis to determine the *trans*/*cis* ratio (>99:1) and purified by chromatography on silica gel (hexane/diisopropyl ether 1:0–7:1) to give *trans*-**3a** (170.2 mg, 85 %) as a white solid. The *ee* value of the *trans* product was determined by HPLC analysis (Daicel chiralcel OB-H; 99 % *ee*).

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[8] The *cis*-dialkenyl cyclopropane is the starting material required for the subsequent Cope rearrangement.

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[10] Although the absolute configuration of the cyclopropanation and Cope rearrangement products was not determined, we could determine the relative configuration of the Cope rearrangement product derived from the cyclopropanation product in entry 12 of Table 2 by X-ray crystallographic analysis. CCDC 708640 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

