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Enantioenriched Synthesis of Cyclopropenes with a Quaternary Stereocenter, Versatile Building Blocks

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Abstract: Ir(salen) complexes were found to catalyze enantioselective cyclopropenation efficiently. Cyclopropenation can be carried out using either a donor/acceptor- or an acceptor/acceptor-substituted diazo compound such as α-aryl-α-diazoacetates, α-phenyl-α-diazophosphonate, 2,2,2-trifluoro-1-phenyl-1-diazoethane, and α-cyano-α-diazoacetamide as carbenoid precursors. The reactions provide highly enantioenriched cyclopropenes (84−98% ee) with a functionalized quaternary carbon as versatile building blocks.

Cyclopropene, the smallest ring compound with a double bond, is highly strained and reactive, and it undergoes diverse reactions. Consequently, its optically active derivatives are useful chiral building blocks,[1] and a significant effort has been devoted to the development of enantioenriched synthesis of cyclopropenes. Of these methods, the most notable one is metal-catalyzed cyclopropenation of alkynes using diazo compounds as carbenoid precursors. In 1992, Doyle and Müller et al. reported a seminal study on enantioselective rhodium-catalyzed cyclopropenation using α-diazoacetates.[2a−e] Corey and co-workers recently reported significantly improved enantioselective cyclopropenation of 1-alkynes using a new rhodium complex, $Rh_2(OAc)(DPTI)_3$ (DPTI: diphenyltriflylimidazolidinone), as a catalyst.[2f,g] Moreover, the scope of the reaction was extended by providing access to products containing a quaternary stereocenter. Davies et al. reported asymmetric cyclopropenation using α-aryl-α-diazoacetates, a donor/acceptor-substituted diazo compound, and $Rh_2(S\text{-DOSP})_4$ [DOSP: (*N*-dodecylbenzenesulfonyl)prolinate] as a catalyst.[3] The reactions of arylacetylenes and α-phenyl-α-diazoacetate are highly enantioselective (86−96% ee), while only one example has been reported of the cyclopropenation of 1-alkyne (84% ee for the reaction of 1-hexyne).[4] In view of the high reactivity of cyclopropene and the limited availability of the all-carbon chiral quaternary center,[5] asymmetric cyclopropenation with disubstituted diazo compounds deserves further investigation.

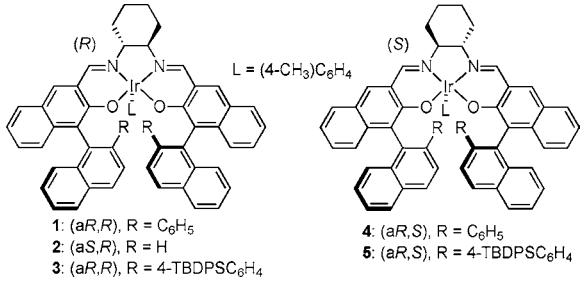
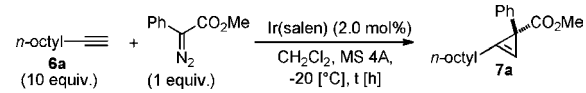


Figure 1. Structures of iridium(salen) complexes **1**−**5**.

We have demonstrated that Ir(salen) complexes **1**−**5** catalyze carbene π-bond addition[6] and σ-bond insertion[7] in a highly stereoselective manner. Since sigma and acetylenic bonds are both rotationally symmetric, we expected that an Ir(salen) complex would also catalyze cyclopropenation of terminal alkynes enantioselectively.

We first examined the reaction of 1-decyne using methyl α-phenyl-α-diazoacetate, a representative donor/acceptor-substituted diazo compound,[3] as the carbene precursor at −20 °C. The reaction was optimized using **1** with respect to solvent,[8] and dichloromethane (DCM) was chosen as the solvent in terms of yield, though better enantioselectivity was obtained in THF and hexane. We next examined the reaction with several complexes in DCM (Table 1). Of the complexes examined, complex **5** showed the highest enantioselectivity of 94% ee (entry 5).

Table 1. Enantioselective Cyclopropenation of 1-Decyne with Methyl α-Phenyl-α-diazoacetate in the Presence of Complexes **1**−**5**[a]



entry	catalyst	Time (h)	% yield[b]	% ee[c]
1	**1**	24	57	−52
2	**2**	17	87	−85
3	**3**	>96	−[d]	−
4	**4**	24	96	91
5[e]	**5**	24	60	94

[a] Reaction was carried out on a 0.1 mmol scale with a molar ratio of 1-decyne/methyl α-phenyl-α-diazoacetate = 10:1 in the presence of MS 4 Å (30 mg) in DCM (0.25 mL) under N_2, unless otherwise mentioned. [b] Isolated yield. [c] Determined by HPLC analysis using chiral column (DAICEL CHIRALCEL OJ-H). [d] Reaction did not occur. [e] Reaction was carried out on a 0.3 mmol scale.

Based on these results, we examined the reactions of various substrates (Table 2). The reactions of 1-alkynes and arylacetylenes proceeded with high enantioselectivity (entries 1−7). The branching at the propargylic position did not affect enantioselectivity, though the yield was somewhat diminished (entry 3). The reaction is tolerant of functional groups such as ether, ester, amide, and halogeno substituents, and the presence of such a functional group scarcely affects the enantioselectivity (entries 1, 2, 5−7). Diazo compounds used as the carbenoid precursor for cyclopropenation in the previous studies have been mostly limited to ester[2,3] or sulfonyl derivatives.[1j] It is noteworthy that diazo compounds bearing a phosphonate or trifluoromethyl group as the acceptor group can also be applied to this iridium-mediated cyclopropenation. The reactions of α-phenyl-α-diazophosphonate with 1-decyne or phenylacetylene proceeded with high enantioselectivity of 85 and 86% ee, respectively (entries 8 and 9). *p*-Bromo substitution increased enantioselectivity (entry 10). Although *p*-substitution with the methoxy group lowered enantioselectivity down to 75% ee, the reaction in toluene had a better enantioselectivity of 84% ee (entry 11).[9] On the other hand, the reaction with 1-phenyl-2,2,2-trifluorom-

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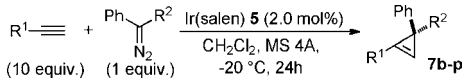
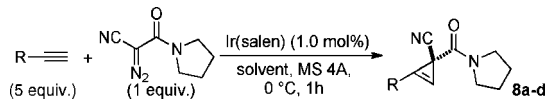
Table 2. Enantioselective Cyclopropenation of Various Acetylenes Using Complex **5** as the Catalyst[a]



entry	Product	R^1	R^2	% yield[b]	% ee[c]
1	**7b**	$BnOC_4H_8$	CO_2Me	61	96
2	**7c**	$BzOC_4H_8$	CO_2Me	67	94
3	**7d**	*c*-C_6H_{11}	CO_2Me	57	95
4	**7e**	Ph	CO_2Me	95	96
5[d]	**7f**	4-$MeOC_6H_4$	CO_2Me	88	96
6	**7g**	4-BrC_6H_4	CO_2Me	81	94
7[e]	**7h**	4-(NHBoc)C_6H_4	CO_2Me	80	93
8	**7i**	*n*-C_8H_{17}	$P(=O)(OMe)_2$	65	85
9	**7j**	Ph	$P(=O)(OMe)_2$	96	86
10[f]	**7k**	4-BrC_6H_4	$P(=O)(OMe)_2$	72	89
11[g]	**7l**	4-$MeOC_6H_4$	$P(=O)(OMe)_2$	96	84
12	**7m**	$BzOC_4H_8$	CF_3	91	96
13	**7n**	Ph	CF_3	94	96
14	**7o**	4-$MeOC_6H_4$	CF_3	96	94
15[h]	**7p**	4-$NO_2C_6H_4$	CF_3	91	98

[a] Reaction was carried out at −20 °C on a 0.3 mmol scale with the molar ratio of acetylene:diazo compound = 10:1 in the presence of MS 4 Å (90 mg) in CH_2Cl_2 (0.75 mL) under N_2, unless otherwise mentioned. [b] Isolated yield. [c] Determined as reported in the Supporting Information. [d] The reaction was carried out for 5 days. [e] 1.5 mL of solvent was used. [f] Reaction was run at 0 °C. [g] Reaction was run in toluene. [h] THF was used instead of CH_2Cl_2. 5 equiv of 4-nitrophenylacetylene were used.

Table 3. Iridium-Catalyzed Enantioselective Cyclopropenation with Terminal Acetylene Using α-Cyano-α-diazoacetamide[a]



entry	product	cat.	solvent	R	% yield[b]	% ee[c]
1[d]	**8a**	5	CH_2Cl_2	Ph	—[e]	—
2	**8a**	1	toluene	Ph	91	94
3	**8b**	1	toluene	4-$MeOC_6H_4$	97	87
4[f]	**8c**	1	THF	4-$NO_2C_6H_4$	83	93
5	**8d**	1	toluene	*n*-C_8H_{17}	92	93

[a] Reaction was carried out at 0 °C on a 0.3 mmol scale with the molar ratio of acetylene/diazo compound = 5:1 in the presence of MS 4 Å (90 mg) in solvent (0.75 mL) under N_2, unless otherwise mentioned. [b] Isolated yield. [c] Determined as reported in the Supporting Information. [d] Reaction was carried out on a 0.1 mmol scale and reaction time was 96 h. [e] Reaction did not occur. [f] 5 mol % catalyst was used, and reaction time was 12 h.

ethyldiazoethane proceeded with an excellent enantioselectivity of ≥94% ee, irrespective of the electronic nature of the *p*-substituents (entries 12−15).

In general, acceptor/acceptor-substituted diazo compounds are less reactive toward metal-catalyzed decomposition, while the resulting carbenoids are highly electrophilic and their reactions are less selective.[3] To explore the scope of the present cyclopropenation, we also examined the reaction of phenylacetylene and α-cyano-α-diazoacetamide,[10] an acceptor/acceptor-substituted diazo compound, using catalyst **5** under the conditions described in Table 2. As indicated from its low reactivity, the reaction did not occur even under extended conditions (96 h) (Table 3, entry 1). Thus, we surveyed the reaction with catalysts **1**−**4** in various solvents[11] and found that complex **1** showed the highest enantioselectivity in toluene (entry 2). The reaction of 4-methoxyphenylacetylene also proceeded with high enantioselectivity of 87% ee (entry 3). As 4-nitrophenylacetylene is poorly soluble in toluene, its reaction was carried out in tetrahydrofuran, the second best solvent, with 5 mol % of **1**, and high enantioselectivity and good yield were obtained (entry 4). To our delight, the reaction of 1-decyne also proceeded with a high enantioselectivity of 93% in good yield (entry 5).

In conclusion, we were able to achieve highly enantioselective cyclopropenation by using Ir(salen) complexes as catalysts. Both 1-alkynes and arylacetylenes can be used as substrates, and both acceptor/acceptor- and acceptor/donor-substituted diazo compounds are available as the carbenoid precursors. Moreover, the reaction is tolerant of a variety of functional groups and exhibits a remarkably broad substrate scope.[12] To the best of our knowledge, this is the first highly enantioselective pathway to chiral cyclopropenes that include a chiral quaternary carbon carrying cyano, phosphonate, and trifluoromethyl groups,[13c] which have wide pharmaceutical and synthetic applications.[10,13]

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Supporting Information Available: Experimental procedures, spectra data for cyclopropenation, and HPLC condition. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) See the Supporting Information (Table S-1).

(9) Most reactions in Tables 1 and 2 had a similar level of enantioselectivity either in DCM or in toluene. For example, 85% ee and 96% ee were obtained in the reactions of phenylacetylene with α-phenyl-α-diazophosphonate and 1-phenyl-2,2,2-trifluoromethyldiazoethane, respectively (cf. Table 2, entries 9 and 13).

(10) Asymmetric cyclopropanation with α-cyano-α-diazoacetamides has been reported: (a) Marcoux, D.; Azzi, S.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 6970. (b) Zhu, S.; Xu, X.; Perman, J. A.; Zhang, X. P. *J. Am. Chem. Soc.* **2010**, *132*, 12796, and references cited therein.

(11) See the Supporting Information (Table S-2).

(12) The cyclopropenation of 1-decyne with benzyl diazoacetate using **5** as a catalyst proceeds with 80% ee.

(13) For the cyclopropanation reactions using diazo compounds bearing a phosphonate or trifluoromethyl group, see:(a) Reddy, R. P.; Lee, G. H.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 3437. (b) Denton, J. R.; Sukumaran, D.; Davies, H. M. L. *Org. Lett.* **2007**, *9*, 2625. (c) Müller, P.; Grass, S.; Shahi, S. P.; Bernardinelli, G. *Tetrahedron* **2004**, *60*, 4755.

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