

Iridium(III) Catalyzed Diastereo- and Enantioselective C–H Bond Functionalization

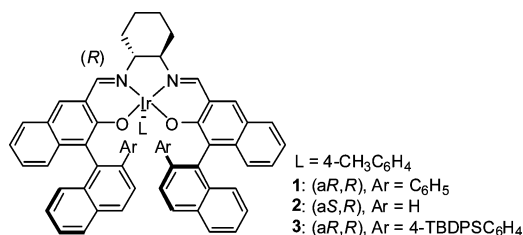
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Direct functionalization of C–H bond is one of the great contemporary challenges in organic synthesis.¹ In particular, the enantioselective metal–carbene insertion into the C–H bond provides a method for atom-efficient C–C bond formation, and high enantioselectivity has been achieved in various intramolecular C–H insertion reactions.² The seminal studies on intermolecular carbenoid C–H insertion using the combination of a rhodium catalyst and ethyl diazoacetate have been reported by Noels³ and Callot.⁴ Recently, Davies and co-workers reported a breakthrough in asymmetric carbene insertion reactions. The C–H insertion into alkanes and tetrahydrofuran (THF) using a Rh₂(S-DOSP)₄/RC(N₂)CO₂Me system (R = aryl or alkenyl) proceeded with high enantioselectivity and moderate diastereoselectivity (up to 98% ee, 44–60% de),^{2c,5} and the C–H bond insertion at the allylic^{2c,6} and benzylic positions^{2c} and at the α-position of N-Boc-protected amines occurred with high enantio- and diastereoselectivity.^{2c} On the other hand, many natural products have a subunit(s) arising from the propionate biosynthetic pathway, and carbenoid C–H insertion using α-diazopropionate should be an efficient method for the construction of the subunit. However, no insertion method using a simple α-alkyl-α-diazoacetate has been reported, probably due to competitive β-hydride elimination.^{2a,7}

We have discovered that iridium(III)-salen complexes bearing an aryl group at the apical position show potent and diverse cyclopropanation catalysis. Iridium-salen complex **1** catalyzes the highly *cis*- and enantioselective cyclopropanation of a variety of olefins including less reactive terminal alkenes and heterocyclic compounds such as benzofuran, using an α-diazoacetate,^{8a,b} while the reactions of conjugated olefins using a vinylidiazolactone show high *trans*- and enantioselectivity.^{8c} Hence, we expected that complex **1** might regulate the stereochemistry of a carbenoid intermediate derived from diazo ester so as not to cause the undesired β-hydride elimination and catalyze the desired C–H insertion. Herein, we communicate the first example of iridium-catalyzed asymmetric carbenoid insertion into the C–H bond at the α-position of THF and at the allylic carbon using not only α-aryl-α-diazoacetate but also α-diazopropionate.⁹



We initially examined the reaction of THF and methyl α-phenyl-α-diazoacetate in the presence of **1** at room temperature. However, the carbene dimer product was obtained as the major product. This

Table 1. Asymmetric C–H Insertion into THF Using Various α-Substituted α-Diazoacetates^a

entry		R ¹	R ²	5:6 ^b	% yield of 5 ^c	% ee of 5 ^d
1	a	C ₆ H ₅	Me	13:1	75	95 ^e
2	b	<i>p</i> -MeOC ₆ H ₄	Me	>20:1	64	97 ^e
3	c	<i>p</i> -MeC ₆ H ₄	Me	19:1	71	97 ^e
4	d	<i>p</i> -ClC ₆ H ₄	Me	19:1	82	94 ^e
5	e	<i>p</i> -BrC ₆ H ₄	Me	>20:1	76	93
6	f	<i>m</i> -MeOC ₆ H ₄	Me	9:1	75	97
7	g	<i>m</i> -ClC ₆ H ₄	Me	>20:1	82	95
8	h	2-naphthyl	Me	>20:1	80	98 ^e
9	i	<i>o</i> -MeOC ₆ H ₄	Me	>20:1	9	95
10 ^f	j	Me	<i>t</i> Bu	13:1	70	90

^a Reaction was carried out in THF (2 mL) on a 0.5 mmol scale with a molar ratio of **2**/diazo compound = 0.025/1. ^b Determined by ¹H NMR analysis. ^c Isolated yield. ^d Determined by HPLC analysis. ^e The absolute configuration was determined to be 2*S*,α*R* by comparison of the optical rotation with the literature value (ref 5b). ^f Run for 5 h at –60 °C.

Table 2. Asymmetric C–H Insertion into 1,4-Cyclohexadiene Using Various α-Substituted α-Diazoacetates^a

entry		R ¹	R ²	7:8	% yield ^b	% ee ^c
1	a	C ₆ H ₅	Me	>20:1	91	94 ^d
2 ^{e,f}	b	<i>p</i> -MeOC ₆ H ₄	Me	>20:1	39	90
3	c	<i>p</i> -ClC ₆ H ₄	Me	>20:1	79	95
4	d	<i>m</i> -MeOC ₆ H ₄	Me	>20:1	95	96
5	e	<i>m</i> -ClC ₆ H ₄	Me	>20:1	80	99
6	f	<i>o</i> -MeOC ₆ H ₄	Me	>20:1	54	97
7	g	<i>o</i> -ClC ₆ H ₄	Me	>20:1	53	99
8	h	3,4-Cl ₂ C ₆ H ₃	Me	>20:1	95	99
9	i	3-thienyl	C ₂ H ₄ Cl	>20:1	67	97
10	j	Me	Et	>20:1	68 ^g	83 ^{h,i,j}
11 ^j	k	Me	<i>t</i> Bu	>20:1	84 ^g	>99 ^h

^a Reaction was carried out in diene (1 mL) on a 0.5 mmol scale with a molar ratio of **1**/diazo compound = 0.025/1. ^b Isolated yield. ^c Determined by HPLC analysis. ^d The absolute configuration was determined to be *R* by comparison of the optical rotation with the literature value (ref 5b). ^e 10 equiv of diene were used. ^f The reaction was carried out in acetone as the solvent with 2.5 mol % of **3** at rt for 24 h. ^g Determined by ¹H NMR analysis with 1-bromonaphthalene as an internal standard. ^h Determined by GLC analysis. ⁱ The absolute configuration was determined to be *R* (see Scheme 1 and SI). ^j Run with 1.0 mol % of **2** at –50 °C for 5 h.

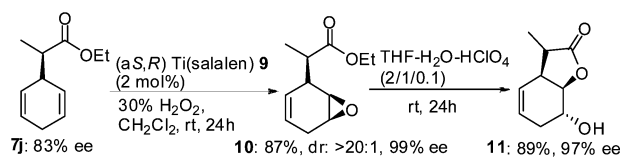
result indicated that the formation of the carbenoid intermediate occurred but the ensuing C–H insertion was hampered by a

hindrance around the carbenoid. Thus, we examined the catalysis of a sterically less congested iridium-salen complex **2**. Optimization of the reaction conditions (see, Table S1, Supporting Information (SI)) revealed that the insertion proceeded well at $-50\text{ }^{\circ}\text{C}$ with high diastereo- and enantioselectivity in an acceptable yield (Table 1, entry 1).¹⁰

Under the optimized conditions, the reactions with a variety of α -aryl- α -diazooacetates and α -diazopropionates were examined (Table 1, entries 2–10). All the α -aryl- α -diazooacetates reacted to produce the corresponding α -aryl(tetrahydrofuran-2-yl)acetates with good to high diastereoselectivity and high enantioselectivity. The electronic nature of the aromatic *p*- or *m*-substituents did not affect largely on the stereoselectivity of the reaction (entries 2–9). Yet, the presence of the *o*-methoxy group slowed the reaction, probably due to steric hindrance (entry 9). What is noteworthy for this reaction, however, is that high diastereo- and enantioselectivity as well as an acceptable yield was obtained at $-60\text{ }^{\circ}\text{C}$ with *tert*-butyl α -diazopropionate (entry 10).¹¹ To the best of our knowledge, this is the first example of asymmetric intermolecular C–H carbene insertion using an α -alkyl-substituted α -diazooacetate.

C–H insertion at the C3-methylene of 1,4-cyclohexadiene^{2c,12} using methyl α -phenyl- α -diazooacetate was also examined in the presence of **2** (2.5 mol %) at $0\text{ }^{\circ}\text{C}$, but the enantioselectivity was moderate (61% ee, 51%). To our delight, however, the desired reaction using complex **1** as the catalyst proceeded with high enantioselectivity in a high yield (Table 2, entry 1), and the undesired cyclopropanation was not observed (**7**:**8** = >20:1). The reactions using other α -aryl-substituted α -diazooacetates also proceeded with high enantioselectivity greater than 94% and moderate to good yields (entries 3–9), except that the reaction with methyl α -(*p*-methoxyphenyl)- α -diazooacetate gave moderate ee (79%) and modest yield (34%). The enantioselectivity of this reaction was significantly improved by using a bulky complex **3** in acetone, though the yield was still modest (entry 2). The reaction with ethyl α -diazopropionate using complex **1** as the catalyst did not proceed. To our surprise and delight, the reaction proceeded with good enantioselectivity at $-50\text{ }^{\circ}\text{C}$, when complex **2** was used as the catalyst (entry 10). Moreover, the reaction with *tert*-butyl α -diazopropionate proceeded with significantly improved enantioselectivity and yield (entry 11).

Scheme 1. Stereoselective Approach to a 7-Methyl-9-oxabicyclo[4.3.0]nonane Skeleton



To explore the utility of this reaction, we examined the conversion of **7j** to **11**. 7-Methyl-9-oxabicyclo[4.3.0]nonane skeleton is the subunit found in several *Stemona* alkaloids (e.g., stenine and neostenine); however, their previous construction methods need a rather long step.¹³ A combination of asymmetric C–H insertion with an α -diazopropionate and enantioselective epoxidation was expected to provide a short step approach toward it. Thus, we examined the epoxidation of the cyclohexadiene **7j** using titanium(salalen) complex **9** (for structure, see SI) as the catalyst.¹⁴ The epoxidation proceeded with high exoselectivity and enantiomer differentiation¹⁵ to give the corresponding epoxide **10** exclusively. Treatment of **10** with perchloric acid in water–THF¹⁶ provided

(1*R*,2*R*,6*S*,7*R*)-2-hydroxy-7-methyl-9-oxabi-cyclo[4.3.0]non-4-en-8-one **11** that has a common skeleton with neostenine,¹⁷ in three steps from commercial cyclohexadiene.

In conclusion, this study revealed the excellent but undeveloped asymmetric catalysis of intermolecular carbene C–H insertion by iridium(III)-salen complexes. The C–H insertion reactions examined were highly enantio- and diastereoselective, and both α -aryl- α -diazooacetate and α -diazopropionate are available for these reactions.

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Supporting Information Available: Full experimental data of all compounds and the X-ray data of **12**. These materials are available free of charge via the Internet at <http://pubs.acs.org>.

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