J|A|C|S COMMUNICATIONS

Published on Web 09/16/2009

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

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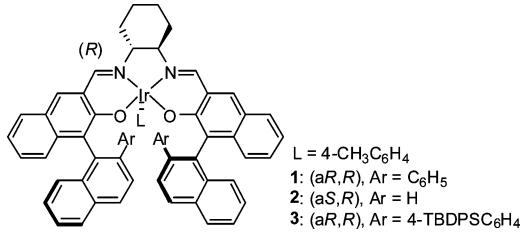
Direct functionalization of C−H bond is one of the great contemporary challenges in organic synthesis.[1] In particular, the enantioselective metal−carbene insertion into the C−H bond provides a method for atom-efficient C−C bond formation, and high enantioselectivity has been achieved in various intramolecular 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 Noels[3] 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 Rh_2(S-DOSP)$_4$ /RC(N$_2$)CO$_2$Me 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]

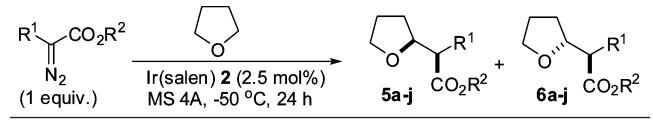
We have discovered that iridium(III)-salen complexes bearing an aryl group at the apical position show potent and diverse cyclopropanation catalysis. Iridium-salen complex **1** catalyzes the highly *cis*- and enantioselective cyclopropanation of a variety of olefins including less reactive terminal alkenes and heterocyclic compounds such as benzofuran, using an α-diazoacetate,[8a,b] while the reactions of conjugated olefins using a vinyldiazolactone 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]



L = 4-$CH_3C_6H_4$
1: (a*R*,*R*), Ar = C_6H_5
2: (a*S*,*R*), Ar = H
3: (a*R*,*R*), Ar = 4-TBDPSC_6H_4

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

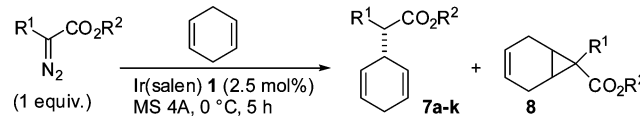
Table 1. Asymmetric C−H Insertion into THF Using Various α-Substituted α-Diazoacetates[a]



entry		R^1	R^2	5:6[b]	% yield of 5[c]	% ee of 5[d]
1	**a**	C_6H_5	Me	13:1	75	95[e]
2	**b**	*p*-MeOC_6H_4	Me	>20:1	64	97[e]
3	**c**	*p*-MeC_6H_4	Me	19:1	71	97[e]
4	**d**	*p*-ClC_6H_4	Me	19:1	82	94[e]
5	**e**	*p*-BrC_6H_4	Me	>20:1	76	93
6	**f**	*m*-MeOC_6H_4	Me	9:1	75	97
7	**g**	*m*-ClC_6H_4	Me	>20:1	82	95
8	**h**	2-naphthyl	Me	>20:1	80	98[e]
9	**i**	*o*-MeOC_6H_4	Me	>20:1	9	95
10[f]	**j**	Me	*t*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 ^{1}H 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_6H_5	Me	>20:1	91	94[d]
2[e,f]	**b**	*p*-MeOC_6H_4	Me	>20:1	39	90
3	**c**	*p*-ClC_6H_4	Me	>20:1	79	95
4	**d**	*m*-MeOC_6H_4	Me	>20:1	95	96
5	**e**	*m*-ClC_6H_4	Me	>20:1	80	99
6	**f**	*o*-MeOC_6H_4	Me	>20:1	54	97
7	**g**	*o*-ClC_6H_4	Me	>20:1	53	99
8	**h**	3,4-$Cl_2C_6H_3$	Me	>20:1	95	99
9	**i**	3-thienyl	C_2H_4Cl	>20:1	67	97
10	**j**	Me	Et	>20:1	68[g]	83[h,i,j]
11[j]	**k**	Me	*t*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 ^{1}H 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.

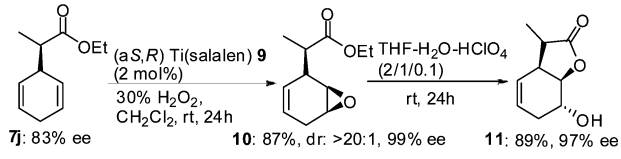
10.1021/ja9065267 CCC: $40.75

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 °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-diazoacetates and α-diazopropionates were examined (Table 1, entries 2−10). All the α-aryl-α-diazoacetates 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 °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-diazoacetate.

C−H insertion at the C3-methylene of 1,4-cyclohexadiene[2c,12] using methyl α-phenyl-α-diazoacetate was also examined in the presence of **2** (2.5 mol %) at 0 °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-diazoacetates 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-diazoacetate 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 °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 skeletone 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 differentiation[15] to give the corresponding epoxide **10** exclusively. Treatment of **10** with perchloric acid in water−THF[16] 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-diazoacetate and α-diazopropionate are available for these reactions.

Acknowledgment. Financial support from the Specially Promoted Research (Grant No. 18002011) and the Global COE Programs, "Science for Future Molecular Systems" from the MEXT (Japan) is gratefully acknowledged. H.S. is grateful for a JSPS Research Fellowship for Young Scientists. We thank Dr. Kenji Matsumoto (this laboratory) for the X-ray analysis of **12**.

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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(17) The absolute configuration of **11** was obtained by conversion of **11** to crystalline **12**, whose structure was confirmed by X-ray crystallography (see SI).

JA9065267