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Catalytic Asymmetric Intermolecular Cyclopropanation of a Ketone Carbene Precursor by a Ruthenium(II)-Pheox Complex

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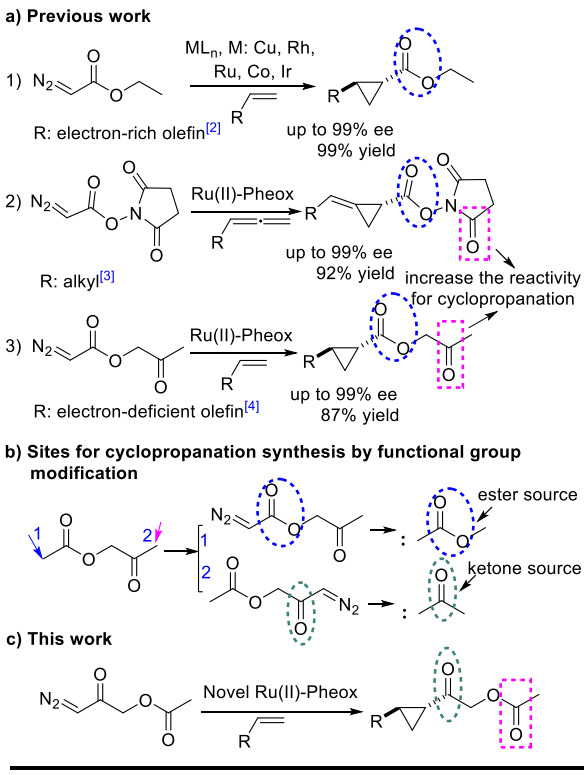
Abstract. The diazo derivative of acetonyl acetate is a useful basic skeleton for the synthesis of cyclopropyl ketones. The intermolecular cyclopropanations of diazo acetoxy acetone with olefins are accomplished by using a novel *p*-nitro-Ru(II)-diphenyl-Pheox catalyst to give the corresponding optically active cyclopropane derivatives in good yields (up to 95%) with excellent diastereoselectivities (up to 99:1) and enantioselectivities (up to 98% ee).

Keywords: Asymmetric synthesis; Cyclopropanation; Ruthenium catalyst; Diazo ketone

Optically active cyclopropane derivatives have received considerable attention in the fields of organic and pharmaceutical chemistry owing to the biological activities of cyclopropanes.[1] The transition metal-catalyzed asymmetric cyclopropanations of diazoacetates with olefins using chiral Cu,[2a-d] Rh,[2e-g], Ru,[2h-j] Co,[2k-l] and Ir[m] catalysts have been reported with excellent stereoselectivities. In most cases, steric hindrance plays an important role in obtaining high stereoselectivities (Scheme 1, reaction 1). For example, for a carbene transfer reaction of diazoacetate to olefins, sterically hindered ester substituents such as *i*-Pr and *t*-Bu gave generally higher stereoselectivities than that from the less hindered Et substituent. This prompted us to modify functionalized diazo compounds that promotes the catalytic asymmetric cyclopropanation in high yields with excellent enantioselectivity.

Recently, we reported on the modification of diazoacetates to improve catalytic asymmetric cyclopropanations not only for electron-rich olefins, but also for allenes and electron-deficient olefins. Thus, Ru(II)-pheox-catalyzed asymmetric cyclopropanation of succinimidyl diazoacetate with

Scheme 1. Cyclopropanation reactions of diazoacetates



Scheme 1. Cyclopropanation reactions of diazoacetates.

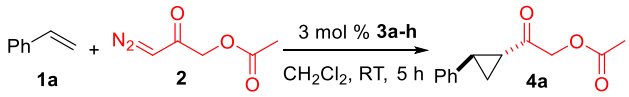
olefins and allenes resulted in cyclopropanes with high yields and excellent enantioselectivities (up to 99%) (Scheme 1, reaction 2).[3] Continuing this line of research, an asymmetric cyclopropanation of α,β-unsaturated carbonyl compounds with acetonyl diazoacetate by using Ru(II)-pheox was reported (Scheme 1, reaction 3).[4] Succinimidyl diazoacetate and acetonyl diazoacetate gave much higher stereoselectivities (diastereoselectivity >99:1 and enantioselectivity up to 99%) in the cyclopropanation

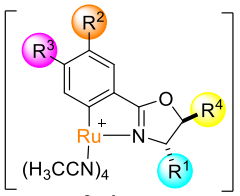
reactions compared with sterically hindered esters.[4] Consequently, we proposed that the carbonyl groups of succinimidyl diazoacetate and acetonyl diazoacetate played an important role in the improvement of stereoselectivity.

Since the reaction of acetonyl diazoacetate with olefins gave the corresponding cyclopropyl esters in high yields and high stereoselectivities, we thought to introduce the diazo group onto the acetonyl group. This could give the corresponding cyclopropyl ketone moiety with high stereoselectivity, since the carbonyl group is the same distance from another carbonyl group of the acetyl group and therefore we would expect the same effect on the stereoselectivity.[5] Furthermore, cyclopropyl ketone moieties are found in natural products having important physiological properties,[6] but only α-diazoacetophenone has been developed as a ketone source, having been obtained in 67% yield with 86% ee.[7] Thus, we report herein the first catalytic asymmetric synthesis of a ketone carbene precursor based on an acetonyl acetate skeleton by using novel Ru(II)-Pheox complexes as chiral catalysts (Scheme 1).

Diazo acetoxy acetone[8] was prepared by modification of the diazo acetonyl acetate synthesis, and examined in the carbene transfer reaction by using a series of Ru(II)-Pheox complexes, which had been found to be efficient catalysts for the inter- and intramolecular cyclopropanation of various diazo compounds.[9]

Table 1. Initial catalyst screening.[a]





3a: R^1 = Ph, R^2 = R^3 = R^4 = H
3b: R^1 = *i*Pr, R^2 = R^3 = R^4 = H
3c: R^1 = *t*Bu, R^2 = R^3 = R^4 = H
3d: R^1 = Bn, R^2 = R^3 = R^4 = H
3e: R^1 = Ph, R^2 = NO_2, R^3 = R^4 = H
3f: R^1 = Ph, R^2 = OMe, R^3 = R^4 = H
3g: R^1 = Ph, R^2 = R^4 = H, R^3 = NO_2
3h: R^1 = Ph, R^2 = R^3 = H, R^4 = Ph

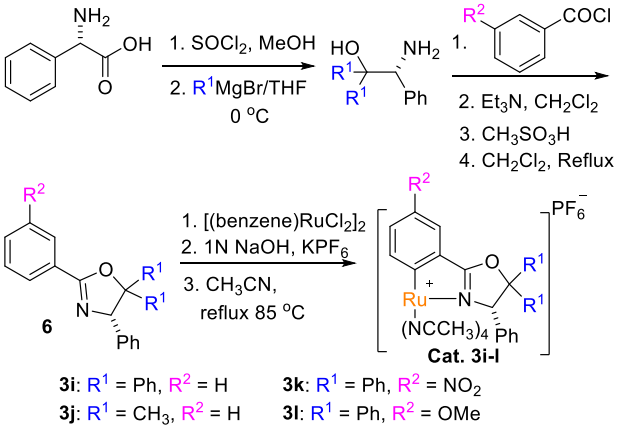
Entry	Catalyst	Yield [%][b]	dr [c]	-ee [%][d]
1	**3a**	70	92:8	68
2	**3b**	54	85:15	50
3	**3c**	60	90:10	65
4	**3d**	68	75:25	46
5	**3e**	50	95:5	74
6	**3f**	53	90:10	55
7	**3g**	60	90:10	43
8	**3h**	**73**	**95:5**	**75**

[a] Reaction conditions: A solution of diazo ketone **2a** (0.2 mmol) in CH_2Cl_2 (2.0 mL) was added to Ru(II)-Pheox **3** (3%) in CH_2Cl_2 (2.0 mL) under Ar. [b] Isolated yield. [c] Determined by ^1H NMR analysis. [d] Determined by chiral HPLC analysis.

As part of our ongoing interest in cyclopropanation reactions with alternative diazo esters, we first examined the reaction of styrene **1a** with diazo acetoxy acetone **2a** using $Rh_2(OAc)_4$ and the series of Ru(II)-Pheox derivatives **3a-g** as catalysts. The results are summarized in Table 1.

$Rh(OAc)_2$ and other transition metals such as $FeSO_4.7H_2O$, Cu(OAc), and $Cu(OAc)_2$ are well-known carbene transfer catalysts, yet had almost no effect on the cyclopropanation reaction at room temperature. In contrast, using Ru(II)-Pheox derivatives **3a-g** as catalysts gave moderate to high reactivities and moderate to good stereoselectivities. Having a phenyl group on the oxazoline ring of the catalyst improved the enantioselectivity to 70% ee (Table 1, entries 1–4). The influence of the electron donating or withdrawing ability of the R^2 and R^3 groups on the Ru(II)-pheox complexes were then examined. Changing the R^2 or R^3 group improved the enantioselectivity to up to 74% ee (Table 1, entries 5–7). A Ru(II)-pheox skeleton bearing an R^4 substituent at the C5 position of the oxazoline ring was also examined (R^4=Ph, catalyst **3h**). This was the most efficient catalyst for both stereoselectivity and yield (73% yield and 75% ee) (Table 1, entry 8).

The enantioselectivity and yield were further improved when Ru(II)-Pheox **3h** was modified with bulky dialkyl substituents at the C5 position of the oxazoline ring (catalysts **3i–l**). Based on the previous method for synthesizing Ru(II)-Pheox derivatives,[9] catalysts **3i–l** were prepared as shown in Scheme 2. First we synthesized dialkylphenylglycinol[10] from the corresponding Grignard reagent, alkyl magnesium bromide, and (***S***)-2-amino-2-phenylacetic acid, and then treated it with benzoyl chloride and methanesulfonic acid[11] to give ligand **6**. Ru(II)-*diphenyl*-Pheox derivatives were synthesized from ligand **6** in high yields for each step, for an overall yield from the amino acid up to 60% in yield.

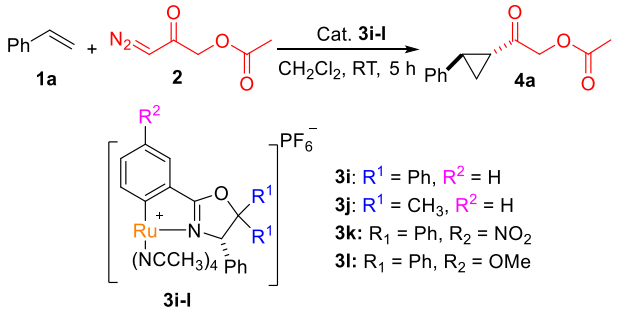


3i: R^1 = Ph, R^2 = H **3k**: R^1 = Ph, R^2 = NO_2
3j: R^1 = CH_3, R^2 = H **3l**: R^1 = Ph, R^2 = OMe

Scheme 2. Synthesis of Ru(II)-*dialkyl*-Pheox complexes.

The screening of Ru(II)-*diphenyl*-Pheox catalysts **3i–l** for the carbene transfer reaction is summarized in Table 2. We found that the bulky *p*-nitro-Ru(II)-*diphenyl*-Pheox complex **3k** had higher activity and enantioselectivity compared with Ru(II)-*phenyl*-Pheox **3h**, giving the corresponding product in high yield (78% yield) and good enantioselectivity (83% ee) (Table 2, entry 3). Ru(II)-*dimethyl*-Pheox catalyst **3j** was also tested for use in the cyclopropanation reaction, however, the enantioselectivity and yield decreased in comparison with **3k**.

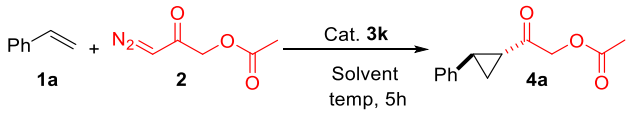
Table 2. Screening of various Ru(II)-pheox catalysts.



Entry	Catalyst	Yield [%][a]	dr[b]	-ee [%][c]
1	**3i**	75	95:15	79
2	**3j**	72	92:8	75
3	**3k**	**78**	**90:10**	**83**
4	**3l**	70	90:10	62

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis. [c] Determined by chiral HPLC analysis.

Table 3. Optimization of the reaction conditions.

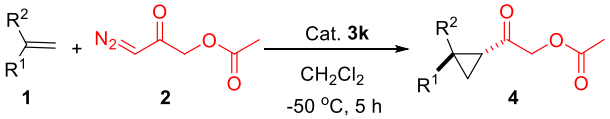


Entry	Solvent	Temp [°C]	Yield [%][a]	dr[b]	-ee [%][c]
1	Et_2O	RT	23	99:1	90
2	CH_2Cl_2/ Et_2O	RT	60	95:5	77
3	Acetone	RT	60	99:1	80
4	EDC[d]	RT	75	90:10	60
5	CH_2Cl_2	RT	78	90 : 10	83
6	CH_2Cl_2	0	80	95:1	84
7	CH_2Cl_2	-10	80	99:1	88
8	CH_2Cl_2	-30	82	99:1	90
9	**CH_2Cl_2**	**-50**	**85**	**99:1**	**95**
10	CH_2Cl_2	-70	85	99:1	92

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis, the enantioselectivity for trans product only. [c] Determined by chiral HPLC analysis. [d] 1,2-Dichloroethane

Next, we optimized the reaction using *p*-nitro-Ru(II)-*diphenyl*-Pheox **3k** as the catalyst in various solvents and temperatures as shown in Table 3. Dichloromethane was the best solvent among those examined, and the catalytic cyclopropanation proceeded at –50 °C to give the highest yield (85%) with excellent enantioselectivity (95% ee) (Table 3, entry 9). Although diethyl ether (Et_2O) was a more efficient solvent for diastereoselectivity, its use resulted in a very low yield (Table 3, entry 1).

Table 4. Asymmetric cyclopropanation of various olefins.



Entry	**1**: R^1, R^2	Yield [%][b]	dr[c]	-ee [%][d]
1	**1a**: R^1 = Ph, R^2 = H	85	99:1	95
2	**1b**: R^1 = p-CH_3-C_6H_4 R^2 = H	79	98:2	96
3	**1c**: R^1 = p-OMe-C_6H_4 R^2 = H	62	97:3	83
4	**1d**: R^1 = p-*t*Bu-C_6H_4 R^2 = H	72	98:2	91
5	**1e**: R^1 = p-Cl-C_6H_4 R^2 = H	95	97:3	98
6	**1f**: R^1 = m-CH_3-C_6H_4 R^2 = H	85	91:9	92
7	**1g**: R^1 = o-Cl-C_6H_4 R^2 = H	92	99:1	97
8	**1h**: 2-vinylnaphthalene	90	90:10	97
9	**1i**: R^1 = Ph, R^2 = CH_3	55	98:2	-85

[a] Isolated yield. [b] Determined by ^{1}H NMR analysis; the enantioselectivity is for the trans product only. [c] Determined by chiral HPLC analysis.

Encouraged by the above results, we investigated the cyclopropanation of diazo acetoxy acetone **2a** with olefins **1a–j** using *p*-nitro-Ru(II)-*diphenyl*-Pheox **3k** under the optimized conditions. The results are summarized in Table 4. Styrene derivatives having ortho, meta, or para substituents were all tolerated under the reaction conditions (Table 4, entries 2–7). It is noteworthy that styrenes bearing an electron-withdrawing group at the para position were more effective than those with an electron-rich substituent at that position, due to the strong electrophilic nature (Table 4, entries 2–5). The highest enantioselectivity (98% ee) and yield (95%) were obtained for the styrene bearing a para-Cl substituent (Table 4, entry 5). In contrast, the cyclopropanation of α-methyl substituted styrene afforded the desired product with good enantioselectivity (85% ee) but in only moderate yield (55%) (Table 4, entry 9).

In summary, we found that highly stereoselective catalytic asymmetric cyclopropanation reactions of diazo derivatives of acetonyl acetate with olefins using a novel *p*-nitro-Ru(II)-*diphenyl*-Pheox catalyst gave the corresponding optically active cyclopropyl ketone derivatives in good yields (up to 95%) with excellent diastereoselectivities (up to 99:1) and

enantioselectivities (up to 98% ee). Diazo acetonyl acetate can be used for a ketone carbene precursor.

Experimental Section

Typical Procedure for the intramolecular cyclopropanation reaction of various diazo ketone derivatives using Ru(II)-Pheox as a catalyst.

To a solution of Ru(II)-Pheox catalyst (0.003 mmol) and olefin (5.0 mmol) in CH_2Cl_2 (2.00 mL) was slowly added a solution of diazo ketone (1.0 mmol) in CH_2Cl_2 (2.00 mL) over 4 hours at −50 °C. The progress of the reaction was monitored by TLC. After the reaction was complete, the solvent was evaporated and the residue was purified using column chromatography on silica gel (10:1 Hex/EtOAc) to give the desired product. The enantiomeric excess of the product was determined by HPLC analysis.

Acknowledgements

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