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Chemoselective Aromatic C−H Insertion of α-Diazo-β-ketoesters Catalyzed by Dirhodium(II) Carboxylates

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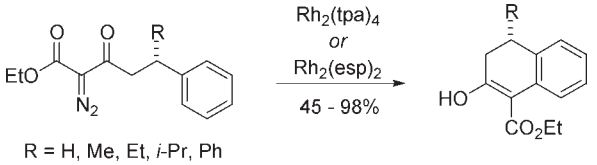
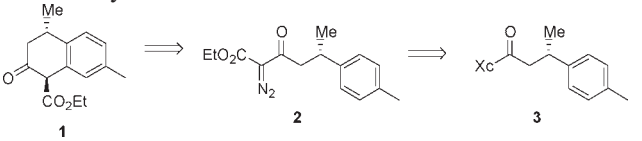
ABSTRACT



R = H, Me, Et, *i*-Pr, Ph

The ability of α-diazo-β-ketoesters bearing a substituent on the benzylic position to undergo aromatic C−H insertion is described. Good to excellent yields of the aromatic C−H insertion products were observed with $Rh_2(tpa)_4$ or $Rh_2(esp)_2$ catalysts. This is an attractive strategy to prepare tetralins carrying a methyl group on the benzylic position, a structural motif found in several types of natural products.

Several families of natural products possess a tetralin substructure bearing a methyl group on a chiral benzylic carbon. The aromatic sesquiterpenes (heritol,[1] laevigatin,[2] calamenenes),[3] diterpenes with a serrulatane (seco-pseudoterosins,[4] erogorgiaenes),[5] and those with an amphilectane skeleton (pseudopterosins,[6] helioporins,[7] pseudoteroxazoles)[8] contain this structural motif. We envisioned a very attractive strategy to build this tetralin framework by employing our conjugate addition products (Xc = oxazolidinethione chiral auxiliary)[9] and a Rh(II)-catalyzed aromatic C−H insertion of an acceptor/acceptor carbenoid species.[10] This strategy should be superior to an Ullman reaction because it avoids starting from an arylhalide.[11]



Rh(II)-carboxylate and carboxamide catalyzed intramolecular C—H insertion reactions of α-diazo carbonyl compounds have developed into powerful methods for the construction of carbocycles and heterocycles.[12] Remarkably high chemoselectivity can be achieved in a broad array of carbenoid transformations, such as X—H insertion, C═C addition, or ylide formation, by simply selecting the

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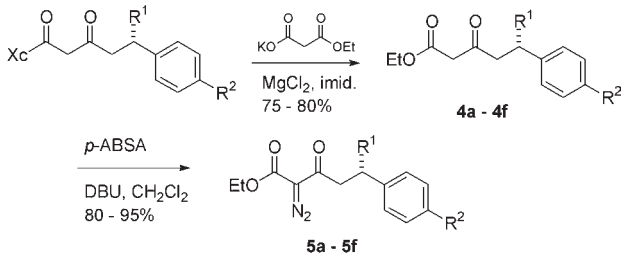
appropriate dirhodium(II) ligand.[13] Cyclization of aliphatic α-diazo-β-ketoesters provides highly functionalized cyclopentane derivatives.[14] The efficient intramolecular aromatic C—H insertion of α-diazo-β-ketoesters to form an indene skeleton was originally reported by Taber and Ruckle using $Rh_2(OAc)_4$ as the catalyst.[15] The selectivity between aliphatic and aromatic C—H insertion can also be tuned by the Rh(II) ligand. The Rh(II) catalyst exhibited an exceptionally high order of selectivity for aromatic C—H insertion over both aliphatic C—H insertion and cyclopropanation reactions when the bulky triphenylacetate ligand was used.[16] In the same manner, a perfluorocarboxamide ligand also favored aromatic over aliphatic C—H insertion.[17] Although five-membered ring cyclization of Rh(II) carbenoids has been widely explored, only a few isolated cases have been reported for the six-membered ring cyclization.[18]

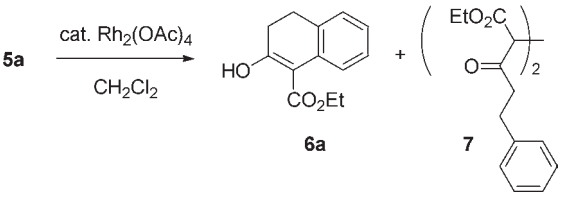
We decided to investigate the Rh(II) carbenoid aromatic C−H insertion of α-diazo-β-ketoesters **5a**−**f**, Scheme 1, Tables 1 and 2. Ethyl 3-oxo-5-phenylpentanoate (**4a**) was obtained from commercial sources. α-Diazo-β-ketoesters substituted at the benzylic position **5b**−**e** were prepared in two steps starting from the corresponding Michael addition products of chiral *N*-enoyl oxazolidinethiones (Scheme 1).[9] Displacement of the chiral auxiliary (Xc = oxazolidinethione) to yield the corresponding β-ketoesters **4b**−**e** was easily carried out employing known conditions.[19] The β-ketoester **4f** was prepared from 3,3-diphenylpropionyl chloride in two steps according to literature procedures.[20] Regitz diazotransfer reaction of β-ketoester **4a**−**4f**, with DBU and

Scheme 1



p-ABSA = *p*-acetamidobenzenesulfonyl azide

Table 1. Screening C−H Aromatic Insertion of α-Diazo-β-Ketoester **5a** with $Rh_2(OAc)_4$



entry[a]	CH_2Cl_2 (mL)	temp	time[b]	yield (%) **6a**	yield (%) **7**
1	4	0 °C	5 min	traces	–
2	4	rt	12 h	traces	–
3	6	reflux	5 min	traces	–
4	6	rt	1 h	20	24
5	12	rt	1 h	6	32
6	20	rt	1 h	20	42

[a] Reactions were carried out with 0.5 mmol of compound **5a** and catalytic amount of $Rh_2(OAc)_4$. [b] Time of addition of the α-diazo-β-ketoester **5a** utilizing a mechanical syringe.

p-acetamidobenzensulfonyl azide (*p*-ABSA),[21] afforded the α-diazo-β-ketoesters **5a**−**5f** in very good to excellent yields.

Initially, the Rh(II)-catalyzed cyclization of simple α-diazo-β-ketoester **5a** was investigated (Table 1). When diazoketoester **5a** was added either rapidly or very slowly to the catalyst suspended in CH_2Cl_2, only trace amounts of the desired product were isolated from the reaction mixture (entries 1 and 2). The poor yield did not improve when the reaction was subjected to higher temperatures (entry 3) or when toluene was used as solvent. A small amount of desired product **6a** together with dimer **7** was obtained when the substrate was added over 0.5 to 1 h (entries 4−6). Dimer **7** was isolated as an inseparable mixture of threo and erythro isomers. Increased dilution of the reaction resulted in larger yields of dimer **7** (entries 5 and 6). Other catalysts were then screened utilizing the best conditions found in these experiments (Table 2).[22]

Use of the bulky catalyst dirhodium(II) tetra(triphenylacetate), $Rh_2(tpa)_4$, gave a similar yield for the aromatic

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(22) **General procedure for the aromatic C-H insertion.** A suspension of α-diazo-β-ketoester (0.5 mmol) in CH_2Cl_2 (5 mL) is added via syringe pump at a rate of 5−10 mL/h to a stirred suspension of rhodium(II) catalyst (5 mg) in anhydrous CH_2Cl_2 (5 mL) at room temperature under a nitrogen atmosphere. After the addition is complete, the reaction mixture is stirred for 3 h. The solution is concentrated under reduced pressure. A sample is analyzed by NMR. Products are purified by silica gel chromatography eluting with petroleum ether−ethyl acetate, 98:2.

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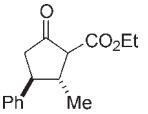

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Table 2. Catalyzed Rh(II) Aromatic C−H Insertion

entry	α-diazo-β-ketoester	Rh(II)	6	yield (%)[a]
1	**5a** R^1 = H, R^2 = H	$Rh_2(OAc)_4$	**6a**	20
2	**5a** R^1 = H, R^2 = H	$Rh_2(tpa)_4$	**6a**	20
3	**5a** R_1 = H, R^2 = H	$Rh_2(esp)_2$	**6a**	45
4	**5b** R_1 = CH_3, R^2 = H	$Rh_2(OAc)_4$	**6b**	10
5	**5b** R_1 = CH_3, R^2 = H	$Rh_2(tpa)_4$	**6b**	58
6	**5b** R^1 = CH_3, R^2 = H	$Rh_2(esp)_2$	**6b**	20
7	**5c** R^1 = CH_3, R^2 = CH_3	$Rh_2(tpa)_4$	**6c**	57
8	**5c** R^1 = CH_3, R^2 = CH_3	$Rh_2(esp)_2$	**6c**	80
9	**5d** R^1 = CH_2CH_3, R^2 = H	$Rh_2(tpa)_4$	**6d**, **8**	54, 39
10	**5d** R^1 = CH_2CH_3, R^2 = H	$Rh_2(esp)_2$	**6d**, **8**	60, 40
11	**5e** R^1 = *i*-Pr, R^2 = H	$Rh_2(tpa)_4$	**6e**	70
12	**5e** R^1 = *i*-Pr, R^2 = H	$Rh_2(esp)_2$	**6e**	47
13	**5f** R^1 = Ph, R^2 = H	$Rh_2(tpa)_4$	**6f**	98
14	**5f** R^1 = Ph, R^2 = H	$Rh_2(esp)_2$	**6f**	56

[a] Yield of purified product.

insertion product **6a**, Table 2 (entry 2).[23] An improved yield of cyclized product **6a** was achieved employing Du Bois' catalyst bis[rhodium (α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid)], $Rh_2(esp)_2$ (entry 3). This tetracarboxylate Rh dimer has proven exceptionally effective for nitrene insertion of tertiary C−H bonds.[24] Various substrates possessing a benzylic substituent were submitted to the catalyzed Rh(II) reaction (entries 4−14). These three catalysts were also screened to catalyze the reaction of the methyl substituted diazo compound **5b** (entries 4−6). The highest yield of the cyclized product **6b** was obtained with the $Rh_2(tpa)_4$ catalyst. When the 4-methyl aromatic diazo derivative **5c** was subjected to Rh(II) catalyzed cyclization (entries 7 and 8), we achieved the same yield as was observed with the $Rh_2(tpa)_4$ catalyst, but a higher yield was achieved with the Du Bois catalyst. The aliphatic C−H insertion product cyclopentanone **8** was also observed in slightly smaller amounts when the ethyl substituted substrate **5d** was reacted with the Rh(II) catalysts (entries 9 and 10).[25] A similar cyclopentanone (methyl ester) was reported by Taber as the only product when $Rh_2(OAc)_4$ was used as the catalyst.[26] Interestingly, we only observed and isolated the cyclized products **6c** and **6e** when the corresponding substrates carrying a methyl and an isopropyl group on the benzylic position were subjected to these two catalysts, and no aliphatic insertion product was isolated (entries 7, 8, 11, and 12). These results suggest that aromatic insertion is preferred over insertion to methyl or methine hydrogens when employing either $Rh_2(tpa)_4$ or $Rh_2(esp)_2$ catalysts. An excellent yield of tetralin **6f** was obtained when the diphenyl derivative **5f** was subjected to the $Rh_2(tpa)_4$ catalyst (entry 13).

In summary, we have shown a valuable chemoselective Rh(II)-catalyzed C−H aromatic insertion reaction. The reaction involves the insertion of a carbenoid moiety into a C−H aromatic bond, delivering a tetralin possessing a benzylic stereogenic center. Both $Rh_2(tpa)_4$ and $Rh_2(esp)_2$ were shown to be superior to a $Rh_2(OAc)_4$ catalyst for this chemoselective reaction. Further studies of this C−H insertion reaction and its applications to the syntheses of natural products containing this structural motif are currently underway in our laboratory.

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Supporting Information Available. General procedures and spectroscopy data for compounds **4a**−**f**, **6a**−**f**, **7**, and **8**, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.