# Quinoline β-lactams by Rh(II)-catalyzed highly steroselective intramolecular carbene insertion into a carbon-hydrogen bond

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**Abstract**

A convenient synthesis of tricyclic β-lactams by chemo- and diastereoselective intramolecular C-H insertion of metal carbenes generated by dirhodium(II) tetraacetate catalyzed decomposition of α-diazoamides **1a-c** is reported. In the case of reagent **1b**, in the presence of the (+)-menthyl chiral auxiliary, the β-lactam is obtained with 76% e.e.

**Keywords:** Metal-carbene, diazoamide, C-H insertion, intramolecular cyclization, β-lactam, chemoselectivity, stereoselectivity

## Introduction

The intramolecular insertion of metal-coordinated carbenes, generated from α-diazocarbonyl compounds, into C-H bonds to form five- or six-membered heterocycles and carbocycles with a strong preference for the five-membered ring is a well-known process.[1] Instead, due to the minor stability, the four-membered β-lactam ring obtaining by carbenic photochemical or catalytic intramolecular cyclization of diazoamides is limited and often characterized by low yields. Rhodium(II) acetate has been demonstrated to be the catalyst of choice to perform the majority of transition metal carbene reactions from α-diazocarbonyl compounds.[2] Moreover, by changing the ligand, diversity in vast synthetic fields has been achieved,[3] including asymmetric synthesis.[4]

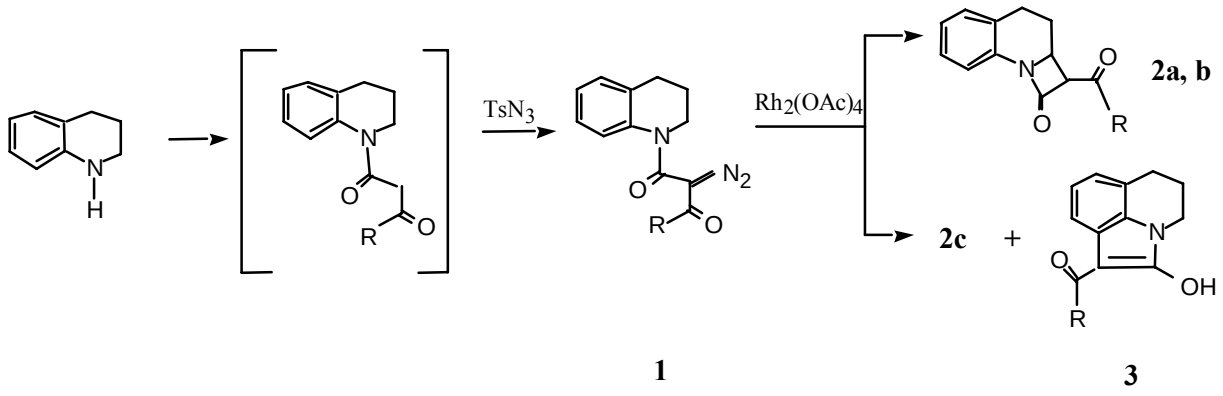
Following our interest in synthesis through stabilized metal-carbenes by its intramolecular cyclization reactions,[5] here we report the results of this process performed in a series of 1,2,3,4-tetrahydroquinolines **1a**, **1b**, and **1c** bearing a proper α-diazoester or α-diazocarbonyl chain tethered to the N atom. In principle, two different outcome of fused carbocyclic ring size formation would be expected: the carbenoid C-H insertion at the methylene near the N atom, with β-lactam ring formation, or the aromatic formal substitution at C8 quinoline carbon to obtain the five-membered ring closure, normally the preferred reaction course.[6] Metal carbene aromatic substitution in competition with C-H bond insertion was previous observed in catalytic

reactions of diazoamides and tentatively ascribed to the electronic character of the N-substituent or to steric factors.[7] Moreover, the (+)-menthyl diazoamidoester **1b** has been selected to control the stereochemical information transferred to the newly formed β-lactam carbon stereocenters by the chiral auxiliary.

## Results and Discussion

The diazoamides **1a**, **b**, **c** were prepared in convenient yields by diazo transfer reaction performed on the corresponding amides (tosyl azide, $Et_3N$, MeCN) which were in turn easy obtained (without isolation) by reaction of the 1,2,3,4-tetrahydroquinoline with ethyl malonyl chloride, (+)-menthyl malonyl chloride and 2,2,6-trimethyl-4*H*-1, 3-dioxin-4-one, respectively.
The $Rh_2(OAc)_4$-catalyzed decomposition of **1a**, **b**, performed in refluxing benzene, resulted in the regiospecific intramolecular carbene insertion at the C-H bond of the methylene near to nitrogen, affording the corresponding β-lactams **2a**, **b** respectively, in convenient yields. By using the same procedure, the diazoamide **1c** gave a 3:1 mixture of the β-lactam **2c**, and the pyrroloquinoline **3** (Scheme 1).




**1a** R= OEt; **1b** R= O-(+)-Ment; **1c** R= Me

**Scheme 1**

In the case of diazoamides **1a** and **1b**, the exclusive β-lactam ring **2** formation is probably ascribed, according with previous results reported for similar diazoamides,[7c] to the reaction site activation due to the presence of a neighbour heteroatom,[2a,i] concomitant with a conformational preference in which the metal-carbene center is placed in close proximity to the less sterically hindered amide substituent, as shown in Figure. In the case of diazocompounds **1a**, **b** , this steric factor, probably due to destabilizing interaction between the rhodium carbenoid space and the H-8 quinoline moiety, even if attenuated by the conformational mobility of the piperidine ring,[8] should be able to control the chemoselectivity. Moreover, the electronic effect of the ester

substituent on the carbene electroaffinity[7c,9] would be in favour to this reaction course. Instead, in the catalytic decomposition of **1c**, the presence of the pyrroloquinoline **3**, deriving by the carbenoid attack to the aromatic ring, could be ascribed to the electronic influence of the carbonyl group which in this case may exert on the metal carbene center an effect able to partially contrast both the mentioned steric and site activation factors.

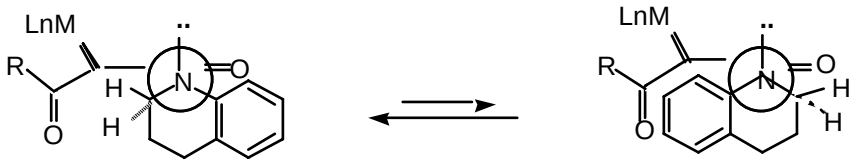



**Figure 1**

The previous observed diastereoselectivity of the carbenoid bond insertion into the pseudo-equatorially oriented C-H of the methylene group is confirmed in all the cases investigated, being controlled by the ring conformational rigidity of the quinoline system.[10]

The *trans* relationship assigned to the four-membered ring hydrogens of **2** was based upon their $^1$H NMR coupling constants.[7b,11] The amide **2b** was obtained as 88/12 mixture of enantiomers. This measure was performed by using the chiral reagent Eu(hfc)$_3$. Asymmetric induction by chiral auxiliaries was previous obtained in this type of intramolecular cyclizations.[12]

When the decomposition reactions were performed in the presence of Cu(acac)$_2$ as the catalyst, complex product mixtures were obtained. This is in agreement with the results obtained by Doyle and co-workers which have demonstrated rhodium(II) carboxylates to be the best catalysts for constructing the β-lactam ring, starting from diazoamides.[7b,11c,d]

Since Corey's methyl-6-aminopenicillinate[13] pioneering synthesis, the diazo-amide decomposition process for β-lactam ring construction has been employed, unfortunately with low yields.

In conclusion, the present work could be considered as a contribution in the effort to increase the chemoselectivity and the stereoselectivity in constructing β-lactam systems by the important strategy of the diazocarbonyl intramolecular cyclization process.

## Experimental Section

**General Procedures.** Reactions were monitored by TLC on commercially available precoated plates (silica gel 60, F 254); products were visualized with ammonium molybdate solution. Silica gel 60, 230-400 mesh, was used for column chromatography. Petrol refers for light petroleum, bp 30-40°C. Melting points were performed on a Büchi 510 capillary apparatus and are uncorrected.$^1$H and $^{13}$C NMR spectra were recorded on a Varian VXR-300 spectrometer at 300

and 75 MHz, respectively, in $CDCl_3$ solutions, with TMS as the internal standard. The IR spectra were performed on a Perkin-Elmer 983 spectrometer. Optical rotations were measured on a Perkin-Elmer 142 automatic polarimeter in a 1 dm tube for $CHCl_3$ solutions whose concentrations are expressed in g/100mL. Elemental analyses were performed on a Perkin-Elmer 240 B analyzer.

**2-Diazo-3-(3,4-dihydro-*2H*-quinolin-1-yl)-3-oxo-propionic acid ethyl ester (1a).** To a stirred $CH_2Cl_2$ dry solution (10 mL) of ethyl malonyl chloride (1.36 g, 9.04 mmol) a solution of 1,2,3,4-tetrahydroquinoline (1.09 g, 8.2 mmol) in $CH_2Cl_2$ (10 mL) and $Et_3N$ (1.14 mL, 8.22 mmol) in $CH_2Cl_2$ (10 mL) were added dropwise and the mixture was stirred under argon for 2 h at 0° C. After washing with water (2X25 mL), the organic layer was dried ($MgSO_4$) and the solvent evaporated to furnish the 3-(3,4-dihydro-*2H*-quinolin-1-yl)-3-oxo-propionic acid ethyl ester (2.15 g, 81% yield). To a $CH_3CN$ solution (20 mL) of the crude ester (1.25 g, 5.07 mmol) tosyl azide[14] (1.49 g, 7.60 mmol) and triethylamine (0.78 mL, 5.57 mmol) were added. The mixture was stirred for 12 h under argon at room temperature and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel column (ethyl acetate/petrol 7:3) to give the diazo compound **1a** (1.14 g, 83 % yield). Yellow oil; IR (neat): 2947, 2125, 1713, 1687, 1624, 1579, 1489, 1380, 1289, 1106 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 7.25-7.06 (m, 4H), 3.94 (q, 2H, J=7.2 Hz), 3.80 (t , 2H, J=6.6 Hz), 2.76 (t, 2H, J=6.6 Hz), 2.04-1.98 (m, 2H), 1.07 (t, 3H, J=7.2 Hz); $^{13}C$ NMR ($CDCl_3$) δ: 161.7, 160.9, 139.2, 131.9, 128.4, 128.2, 126.2, 124.8, 121.7, 61.3, 44.9, 26.6, 23.7, 14.0. Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.40; H, 5.45; N, 15.16.

**2-Diazo-3-(3,4-dihydro-*2H*-quinolin-1-yl)-3-oxo-propionic acid (+)-menthyl ester (1b).** To a stirred $CH_2Cl_2$ dry solution (10 mL) of (+)-menthyl malonyl chloride (2.76 g, 10.6 mmol) a solution of 1,2,3,4-tetrahydroquinoline (1.30 mL, 10.3 mmol) in $CH_2Cl_2$ (10 mL) and $Et_3N$ (1.35 mL, 9.1 mmol) in $CH_2Cl_2$ (10 mL) were added dropwise and the mixture was stirred under argon for 2 h at 0° C. After washing with water (2X25 mL), the organic layer was dried ($MgSO_4$) and the solvent evaporated to furnish the 3-(3,4-dihydro-*2H*-quinolin-1-yl)-3-oxo-propionic acid (+)-menthyl ester (2.92 g, 79 % yield). To a $CH_3CN$ solution (20 mL) of the crude ester (1.25 g, 5.07 mmol) tosyl azide[14] (1.49 g, 7.60 mmol) and triethylamine (0.78 mL, 5.57 mmol) were added. The mixture was stirred under argon for 36 h at room temperature and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel column (ethyl acetate/petrol 7:3) to give the diazo compound **1b** (2.15 g, yield 93.4%). Yellow crystals; mp 68-70 °C; $[\alpha]^{25}_D$= 26.3 (c 0.1, $CHCl_3$); IR (nujol): 2121, 1697, 1632, 1491, 1287, 1266, 1105 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 7.23-7.02 (m, 4H), 4.50 (dt, 1H, J=4.5 and J=10.8 Hz), 3.96-3.86 (m, 1H), 3.73-3.65 (m, 1H), 2.77 (t, 2H, J=6.6 Hz), 2.08-1.92 (m, 2H), 1.74-1.58 (m, 4H), 1.39-1.71 (m, 2H), 1.01-0.58 (m, 12H); $^{13}C$ NMR ($CDCl_3$) δ: 161.3, 160.9, 139.5, 132.0, 128.5, 126.3, 124.9, 121.7, 75.3, 46.8, 44.8, 40.5, 34.0, 31.2, 26.7, 26.3, 23.8, 23.4, 21.9, 20.6, 16.4. Anal. Calcd. for $C_{22}H_{29}N_3O_3$: C, 68.90; H, 7.62; N, 10.96. Found: C, 68.78; H, 7.83; N, 10.79.

**2-Diazo-1-(3,4-dihydro-2*H*-quinolin-1-yl)-butane-1,3-dione (1c).** To a $CH_3CN$ solution (20 mL) of 1-(3,4-dihydro-2H-quinolin-1-yl)-butane-1,3-dione[15] (1.10 g, 5.07 mmol), tosyl azide (1.49 g, 7.60 mmol) and triethylamine (0.78 mL, 5.57 mmol) were added. The mixture was stirred for 12 h under argon at room temperature and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel column (ethyl acetate/petrol 7:3) to give the diazo compound **1c** (1.14 g, yield 92.6%). Yellow crystals; mp 63-64 °C; IR (nujol): 2126, 1625, 1579, 1488, 1361, 1275, 1252 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 7.20-7.12 (m, 4H), 3.80 (t, 2H, J=6.6 Hz), 2.71 (t, 2H, J=6.6 Hz), 2.40 (s, 3H), 2.04-1.98 (m, 2H); $^{13}C$ NMR ($CDCl_3$) δ: 188.0, 157.6, 135.1, 129.1, 125.9, 124.1, 122.5, 118.9, 41.2, 24.8, 23.5, 21.0. Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27 . Found: C, 64.35; H, 5.62; N, 17.01.

**Dirhodium tetraacetate catalysed reaction of the diazoamides (1a-c).** The diazoamides (2.36 mmol) were dissolved in dry benzene under argon. $Rh_2(OAc)_4$ (5 mol %) was added to the solution and the mixture was stirred at 85 °C until the disappearance of the IR absorption of the diazo function. After filtration and evaporation, the residue was flash chromatographed on silica gel column (ethyl acetate/petrol 7:3).

**1-Oxo-2,2a,3,4-tetrahydro-1*H*-azeto[1,2-*a*]quinoline-2-carboxylic acid ethyl ester (2a).** Yield 75 %. Oil; IR (neat): 1758, 1721, 1487, 1357, 1318, 1251, 1194 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 7.48-7.01 (m, 4H), 4.27 (q, 2H, J=7.2 Hz), 4.10 (dt, 1H, J=2.7 and J=11.7 Hz), 3.90 (d, 1H, J=2.7 Hz), 2.88-2.85 (m, 2H), 2.41-2.36 (m, 1H), 1.70-1.56 (m, 1H), 1.33 (t, 3H, J=7.2 Hz); $^{13}C$ NMR ($CDCl_3$) δ: 166.7, 159.3, 133.6, 129.1, 127.2, 124.4, 123.9, 118.5, 61.8, 60.9, 51.3, 25.9, 25.0, 14.1. Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.37; H, 5.90; N, 5.44.

**1-Oxo-2,2a,3,4-tetrahydro-1*H*-azeto[1,2-*a*]quinoline-2-carboxylic acid (+)-menthyl ester (2b).** Yield 79 %. White crystals; mp 104-106 °C (petrol); IR (nujol): 1770, 1726, 1488, 1314, 1253, 1206, 1195, 1157 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 7.49-6.98 (m, 4H), 4.84-4.75 (m, 1H), 4.10-4.04 (m, 1H), 3.88 (d, 1H, J=2.5), 2.91-2.86 (m, 2H), 2.42-2.37 (m, 1H), 2.05-1.42 (m, 7H), 1.11-0.76 (m, 12H); $^{13}C$ NMR ($CDCl_3$) δ: 166.3, 159.2, 133.7, 129.1, 127.3, 124.3, 123.8, 118.6, 76.0, 61.2, 51.2, 46.8, 40.7, 34.1, 31.4, 26.3, 26.0, 25.1, 23.3, .21.9, 20.8, 16.2. Anal. Calcd. for $C_{22}H_{29}NO_3$: C, 74.33; H, 8.22; N, 3.94 . Found: C, 74.55; H, 7.97; N, 4.08.

**2-Acetyl-2,2a,3,4-tetrahydro-1*H*-azeto[1,2-*a*]quinolin-1-one (2c).** Yield 65%. White crystals; mp 120-122 °C (petrol-methylene chloride); IR (nujol): 1753, 1713, 1487, 1354, 1319, 1190, 1130 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 7.44-6.98 (m, 4H), 4.16 (dt, 1H, J=2.7 and J=11.7 Hz), 4.05 (d, 1H, J=2.7 Hz), 2.89-2.84 (m, 2H), 2.39 (s, 3H), 2.38-2.29 (m, 1H), 1.67-1.53 (m, 1H); $^{13}C$ NMR ($CDCl_3$) δ: 199.6, 160.4, 133.5, 129.0, 127.1, 124.5, 123.7, 118.3, 69.2, 49.4, 29.4, 25.9, 24.7. Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.22; H, 5.82; N, 6.33.

**1-(2-Hydroxy-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1-yl)ethanone (3).** Yield 23%. Colourless crystals; mp 157-159 °C (petrol-methylene chloride); IR (nujol): 1655, 1607, 1359, 1303, 1242 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ: 13.03 (s, 1H), 7.14-6.92 (m, 3H), 3.80 (t, 2H, J=5.86 Hz), 2.80 (t, 2H, J=5.86 Hz), 2.38 (s, 3H), 2.07-1.99 (m, 2H); $^{13}C$ NMR ($CDCl_3$) δ: 172.6, 169.7, 134.8, 123.7, 121.5, 120.5, 120.3, 117.4, 102.5, 38.3, 24.5, 21.2, 20.0. Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.35; H, 6.31; N, 6.69.

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## References and Notes

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