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TETRAHEDRON: *ASYMMETRY*

Synthesis of dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*S*)-carboxylate], Rh_2(4*S*-MPPIM)$_4$

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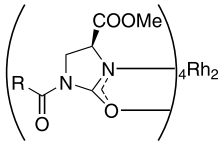
Abstract—The large-scale synthesis with greatly improved yields of methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*S*)-carboxylate and the chiral dirhodium(II) carboxamidate derived from it, Rh_2(4*S*-MPPIM)$_4$, is described. The key step in the overall synthesis is the Hofmann rearrangement of Boc-protected L-asparagine, the procedure for which has been modified to achieve near quantitative yield.

1. Introduction

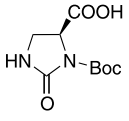
2-Oxaimidazolines, as cyclic ureas, have attracted considerable attention because of their applicability as HIV protease inhibitors,[1] $5HT_3$ receptor antagonists,[2] amongst others.[3] They are also useful chiral auxiliaries in a variety of highly diastereoselective reactions.[4] Various methods for their synthesis have been reported,[5] but those derived from amino acids remain important.[6]

Our interest in 2-oxaimidazolines stems from their use as chiral ligands for dirhodium(II)[7] with the resulting chiral imidazolidinone-ligated catalysts **1** proven to be exceptionally valuable for asymmetric catalytic cyclopropanation,[8] carbon–hydrogen insertion,[9] and hetero-Diels–Alder reactions.[10] The most convenient access to the ligands of these catalysts employs Boc-protected-L-asparagine whose conversion to **2** via the Hofmann rearrangement has until now remained problematic. Even with the 'improved procedure'[11] in which a 65% yield was reported, **2** could not be obtained in higher than the reported 81%[12] or 83% yield,[13] with often low yields of this product produced. To resolve this problem we have modified the Hofmann procedure so that we can routinely prepare **2** on a 60 g scale in nearly quantitative yield. This synthesis and its application to the preparation of **1b** is reported herein.



a: R = Me, Rh_2(4*S*-MACIM)$_4$
b: R = $PhCH_2CH_2$, Rh_2(4*S*-MPPIM)$_4$

1



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2. Results and discussion

Although the synthesis of Rh_2(4*S*-MPPIM)$_4$ on a 0.3 mmol scale has previously been reported,[14] several steps in its synthesis proved to be problematic when scaling up. The first step of the synthesis, the Hofmann cyclization of carbobenzyloxy-L-asparagines, **3** (Eq. (1)), was particularly troublesome, as impurities or incomplete conversion made crystallization of the desired product difficult. The most important discovery for this step was that excess bromine should not be used, as the resultant impurities made the product difficult to isolate. The optimal conditions to minimize the formation of impurities proved was the use of a slight molar excess of bromine (0.05 equiv.) to allow for evaporation that occurs during addition, along with a three-fold molar excess of sodium hydroxide, which was required to generate sodium hypobromite. If there was a stoichiometric match between the sodium hypobromite in

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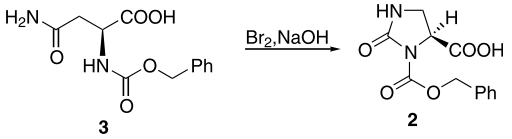
solution and carbobenzyloxy-L-asparagine, the solution became colorless upon completion of the addition. If the solution retained a yellow color after addition or became colorless before all of **3** was added, then **2** was generally difficult to isolate in high yield and/or purity. After optimization as described, the reaction was performed conveniently on 60 g-scale resulting in 99% isolated yields of **3** as a white powder.

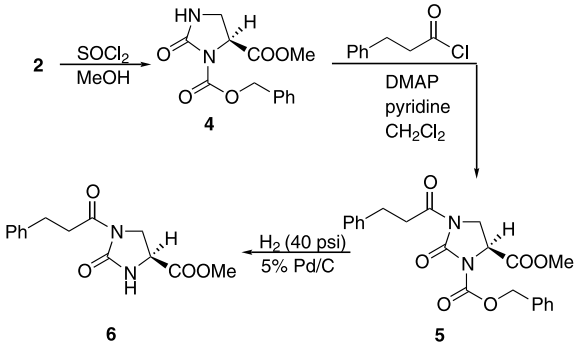


(1)

The Fischer esterification of **2** also proceeded smoothly on a large scale (Scheme 1). In this reaction, thionyl chloride was the source of anhydrous hydrogen chloride. However, when more than a slight molar excess of bicarbonate solution was used to quench the acid, a lower yield of **4** was obtained. Purification of **4** by column chromatography was not required. Yields were high (95%) and, while the desired product was a white powder, a slight yellow color was shown to be acceptable. A prior report of the same chemistry described the formation of **4** in 81% yield.[15]

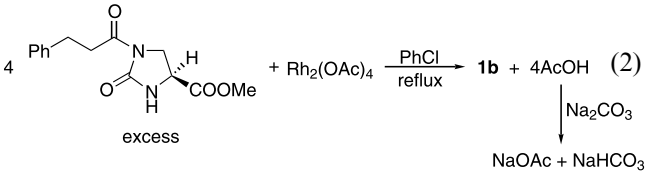
Attachment of the *N*-acyl group to **4** was accomplished in 98% isolated yield with 1.1 molar equiv. of hydrocinnamoyl chloride, rather than the 2.0 equiv. used in the prior report.[14] Purification of **5** by column chromatography on silica gel removed any impurities that would adversely affect the subsequent deprotection step.

The deprotection of **5** proceeded well with 5% palladium on carbon in methanol with the catalyst loading at 0.1% in Pd; the rate can be greatly increased with the use of palladium black at atmospheric pressure. This reaction afforded a white solid in 93% yield, whereas a colorless oil has been reported in the past.[14] Recognizing that the formation of oil might be due to the presence of ethyl acetate trapped in **6** from column chromatography, addition of diethyl ether to the chromatographed sample and concentration under reduced pressure produced the white solid.



Scheme 1.

The procedure for imidazolidinone ligand exchange with rhodium(II) acetate (Eq. (2)) is well documented,[14] although a large-scale synthesis of an imidazolidinone-based dirhodium(II) carboxamidate catalyst has not been reported.[16] This reaction was performed on a 2.0 gram scale of rhodium(II) acetate. After chromatography and recrystallization, 4 g of (2,2-*cis*)-Rh_2(4*S*-MPPIM)$_4$ $(CH_3CN)_2$, **1b**, was obtained as red crystals (65% yield). Excess unreacted ligand was recovered in 90% yield through column chromatography without loss of enantiomeric excess. Large scale reactions performed using 4 g of the aforementioned catalyst **1b** could be expected to produce nearly one-third mole of product at 1.0 mol% catalyst loading.[9] If the amount of catalyst were dropped to 0.1 mol%, then up to three moles of product could be expected.[10]

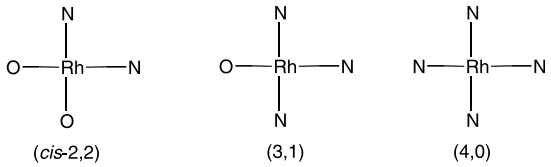


(2)

The imidazolidinone series of carboxamidate-ligated dirhodium compounds is unique in the formation of isomeric dirhodium(II) compounds (Scheme 2)—those in which three nitrogens and one oxygen (or three oxygens and one nitrogen) are bound to rhodium [the (3,1)-isomer][14] or four nitrogens (or four oxygens) are bound [the (4,0)-isomer].[17] As previously documented on smaller scale reactions, these isomers are in equilibrium with one another under the reaction conditions and, over time, the (4,0)-isomer will convert to a mixture of the (*cis*-2,2)- and (3,1)-isomers. However, the (3,1)-isomer and (*cis*-2,2)-isomer constitute a 1:5 equilibrium mixture. Fortunately, chromatographic separation is easily achieved, and further ligand exchange under equilibrium conditions will convert the (3,1)-isomer to the equilibrium mixture.

3. Conclusions

The process described here reports the four-step synthesis of imidazolidinone **6** on an initial 60 g scale in 87% overall yield, which represents a nearly 20% improvement over that previously reported.[14] An increase in the yield of the derivative chiral dirhodium(II) carboxamidate catalyst **16** from the earlier 0.23 g scale reaction[14] has also been achieved.



Scheme 2.

4. Experimental

4.1. General

All compounds have been previously synthesized, and references to physical and spectroscopic data refer to the original publications.[11–17] Compounds reported were analyzed for purity by comparison with published data. Solvents were dried by conventional methods. Carbobenzyloxy-L-asparagine and rhodium(II) acetate were obtained commercially.

4.2. 3-Benzyloxycarbonyl-2-oxaimidazolidinone-4(*S*)-carboxylic acid 3

A 1.0 L round bottom flask was charged with sodium hydroxide (29.8 g, 744 mmol) and 600 mL of distilled water and then cooled to 0°C. Bromine (11.7 mL, 243 mmol) was placed in an addition funnel, protected from evaporation with a layer of distilled water, and then added slowly over 30 min to the sodium hydroxide in water to yield a clear yellow solution. Dry carbobenzyloxy-L-asparagine (60.0 g, 225 mmol) was added as a solid through a funnel over a period of 2 min. The resulting clear, colorless solution was then heated at 55°C for 3 h. After cooling, the reaction mixture was washed with diethyl ether (2×50 mL), then acidified to pH 1 with 6 M HCl which precipitated a white solid. After cooling overnight in a refrigerator, the solution was filtered and the white solid dried under vacuum to afford 58.9 g of **3** (737 mmol, 99% yield). The physical and spectral data correspond to those previously published.[11–13]

4.3. Methyl 3-benzyloxycarbonyl-2-oxaimidazolidinone-4(*S*)-carboxylate 4

To a stirred solution of 3-benzyloxycarbonyl-2-oxaimidazolidine-4(*S*)-carboxylic acid **2** (30.0 g, 114 mmol) in methanol (400 mL), (6.75 g, 56.8 mmol) was added thionyl chloride (6.75 g, 56.8 mmol) dropwise at room temperature. The solution was allowed to stir for 24 h, at which time methanol was removed under reduced pressure to yield a white powder. This solid was dissolved in dichloromethane (300 mL), washed with 5% $NaHCO_3$ (100 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to afford 30.0 g of **4** (108 mmol, 95% yield).[12,15]

4.4. Methyl 1-(3-phenylpropanoyl)-3-benzyloxycarbonyl-2-oxaimidazolidine-4(*S*)-carboxylate 5

To a 250 mL round bottom flask fitted with a reflux condenser was added **4** (15.0 g, 53.9 mmol), 4-dimethylaminopyridine (0.66 g, 5.39 mmol) and 150 mL of distilled dichloromethane, then pyridine (8.70 mL, 108 mmol). The flask was flushed with nitrogen, cooled to 0°C at which point hydrocinnamoyl chloride (8.30 mL, 59.3 mmol) was added dropwise over 30 min via syringe pump. After stirring at 0°C for an additional 30 min, the reaction mixture was heated at reflux overnight to afford a brown solution. After cooling to room temperature, 150 mL of dichloromethane was added, and the solution washed with cold 1 M HCl (2×75 mL), saturated $NaHCO_3$ (1×100 mL), and brine (1×100 mL). The organic solution was dried over anhydrous $MgSO_4$, filtered and concentrated to afford a yellow oil. Purification by column chromatography on silica gel (ethyl acetate:hexanes, 1:2) yielded 21.7 g of **6** (52.8 mmol, 98% yield) as a white solid.[14]

4.5. Methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*S*)-carboxylate 6

Hydrogenolysis of a solution containing **5** (15.0 g, 36.5), methanol (150 mL), and 5% Pd/C (75 mg, 0.1% Pd) with H_2 (40 psi) was performed with a Parr hydrogenator for 12 h. Dichloromethane (40 mL) was added and the mixture filtered through Celite. The resulting colorless solution was concentrated under reduced pressure to afford an oil which was subsequently purified via column chromatography on silica gel (ethyl acetate:hexanes 1:1). A small amount of **5** was isolated (0.59 g, 1.4 mmol, 3.9%). The title compound **7** was obtained as a colorless oil after evaporation of the solvent, at which time diethyl ether was added and removed under reduced pressure, giving **7** (9.34 g, 33.9 mmol) as a white solid in 93% yield, mp 82–83°C, $[\alpha]_D^{23} = +27.8$ (*c* 1.82 in $CHCl_3$); lit.[14] $[\alpha]_D^{23} = +26.0$ at the same concentration in $CHCl_3$.

4.6. Dirhodium(II) tetrakis[methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*S*)-carboxylate], Rh_2(4*S*-MPPIM)$_4$ 1b

A 100 mL two neck round bottom flask equipped with a Soxhlet extractor and reflux condenser was assembled while still warm (from being flame-dried) under a flow of argon. A drying thimble filled with an oven-dried mixture of sodium carbonate and sand (2:1) and capped with glass wool was placed in the Soxhlet extractor during assembly. Dirhodium(II) acetate (2.0 g, 4.52 mmol), methyl 1-(3-phenylpropanoyl)-2-oxaimidazolidine-4(*S*)-carboxylate **7** (10.0 g, 36.2 mmol) and chlorobenzene (65 mL) were added to the flask through the open neck. The neck was then closed with a septum, and the solution heated at a vigorous reflux for 16 hours. Progress of the exchange reaction was monitored by HPLC using a 3.9×150 mm reverse-phase-CN resin column. As the ligand band (2.6 min) became smaller, a major band appeared at 9.6 min (the 2,2-*cis* isomer), followed by two smaller bands at 15 and 19 min, respectively. When no further change was observed by HPLC, the reaction mixture was concentrated and purified via column chromatography on a reverse phase Bakerbond® CN resin (100% methanol to 99:1 methanol:acetonitrile). The first band, light brown in color, was excess ligand, while the following pink band was the desired (2,2-*cis*)-**1b** isomer. The (3,1) and (4,0) isomers remained at the top of the column and were eluted together using acetonitrile. After concentrating the (2,2-*cis*) fraction, a purple powder resulted. To this residue was added methanol (100 mL), and acetonitrile was added dropwise with gentle heating until the solid was completely dissolved (approx. 10 mL). The resulting red solution was placed in a refrigerator at 10°C

where red crystals slowly formed over the next 6 days. The crystals were removed by filtration, washed with a minimal amount of cold methanol, and dried under vacuum to give 4.08 g of (2,2-*cis*)-Rh_2(4*S*-MPPIM)$_4$(CH_3CN)$_2$ **1** (2.94 mmol, 65% yield). The purity of the crystals was determined to be greater than 99.5% by HPLC and $[\alpha]_D^{23}$ was the same (−310) as that previously reported.[14] The recovered ligand was purified via column chromatography (SiO_2; ethyl acetate) to afford 4.48 g of a white solid that was spectroscopically identical to **6**, mp 81–82°C, without loss of enantiomeric purity $[\alpha]_D^{23} = +27.7$ (*c* 1.82, $CHCl_3$).

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