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A new route to chiral imidazolidine salts and its application in organometallic synthesis

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ABSTRACT

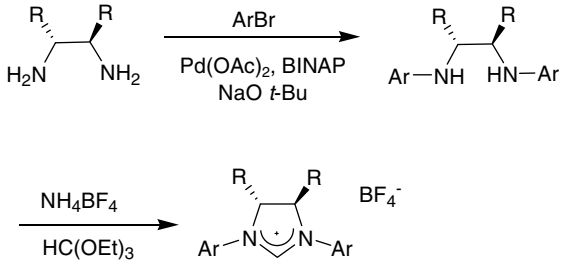
A cost-efficient and high-yielding synthesis of enantiomerically pure imidazolidine salts is presented in this work. Starting from non-chiral amines, chirality is introduced using a Grignard reagent. Separation by the formation of a diastereomeric salt and subsequent condensation of the separated material with $HC(OEt)_3$ and NH_4BF_4 leads to the desired chiral product. Transmetallation allows the attachment of the new imidazolidine ligand to organometallic metal precursors such as $[Rh(COD)Cl]_2$.

1. Introduction

Nearly 40 years have passed since the first successful incorporation of N-heterocyclic carbenes (NHCs) as ligands in transition metal complexes.[1] The strong σ-donor ability of NHCs to metals and their high temperature-, air- and moisture-stability in comparison to phosphines has led to a high interest in these compounds as ligands in organometallic chemistry and catalysis.[2] There are numerous applications of NHC ligated transition metal complexes, including reactions such as hydrosilylation, hydrogenation and metathesis.[3]

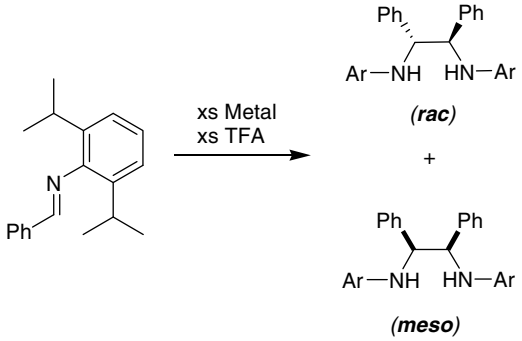
Asymmetric transition metal catalysis is an emerging area for the application of NHCs.[4] So far, the most successful example of a chiral monodentate non-chelating NHC–Ru complex applied in asymmetric metathesis was published by Grubbs et al.[5] The obtained high enantiomeric excess (ee = 90%) furthered the interest and belief in the potential of NHC complexes in enantioselective synthesis. Accordingly, special syntheses were developed for NHCs with stereogenic centres in their backbone. One widely applied synthesis consists of a two-step reaction first presented by Grubbs et al. (Scheme 1).[5] An enantiomerically pure diamine is substituted by a Pd-catalyzed cross coupling and subsequent condensation with triethyl orthoformate and ammonium tetrafluoroborate, resulting in the formation of a chiral imidazolidine salt.

For bulkier groups at the nitrogen, which are particularly interesting for chiral induction in asymmetric catalysis, unfortunately, the coupling takes place with low or non-measurable yields. Sigman et al. described an alternative synthesis using different metals



Scheme 1.

such as manganese, magnesium or zinc as both reduction agent and coupling agent for diimines (Scheme 2).[6] The major drawback of this method, however, is the high yield of the *meso* compound.



Scheme 2.

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An easy method of separation, especially for larger amounts, is not available and therefore makes this procedure unattractive.

Recently several chiral rhodium and iridium complexes with restricted ligand flexibility and their applications in catalysis have been reported.[7] In contrast to the usually advantageous application of chiral diamines as starting materials, we herein report a different approach towards asymmetric N-heterocyclic carbenes and the application of such carbenes as ligands in chiral rhodium complexes.

2. Results and discussion

2.1. Synthesis of chiral imidazolidine salts

The starting material for the chiral imidazoline salt, compound **1**, was prepared according to literature procedures via the reaction of 2 equiv of 2,6-diisopropylphenylamine with 1 equiv of glyoxal.[8] Following the proposed mechanism by Simpkins et al., subsequent Grignard addition of the *t*Bu-moieties at the diimine proceeds in a two-step reaction (Fig. 1). In these additions, a rigid five-membered chelate is generated, including the two nitrogen atoms that lead to an activation of the imine double bonds. The stable conformation of this complex displays the C=N bonds in a coplanar fashion. The stereochemistry of the first *t*Bu group can be either (*S*) or (*R*), whilst the direction of entry of the second *t*Bu-moiety is determined by a 1,2-effect (from the newly established asymmetric centre) (Fig. 1).[9,10]

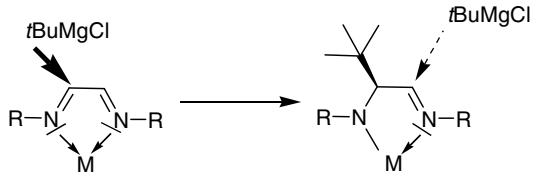
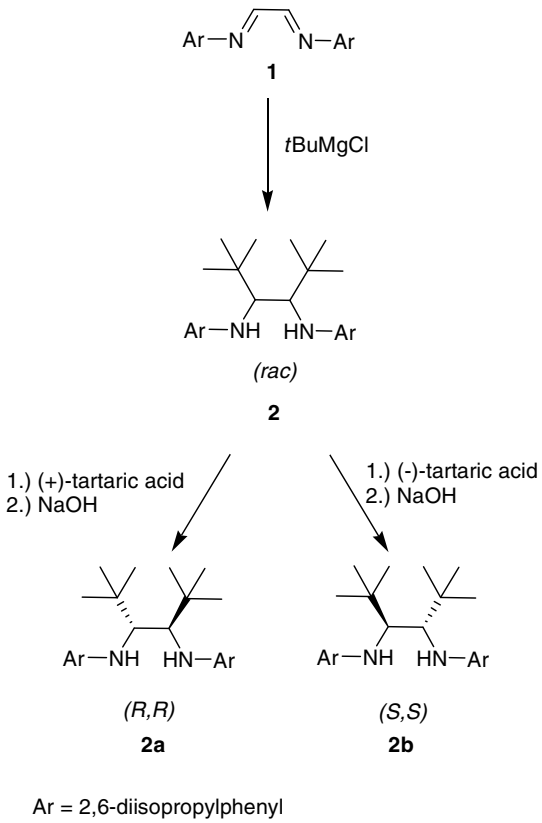


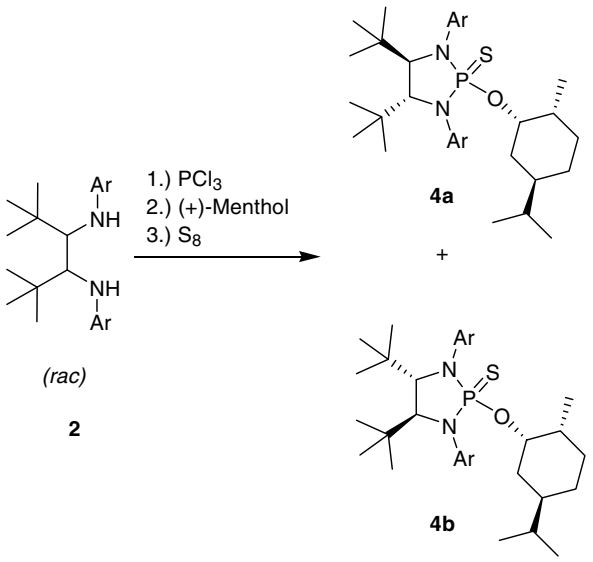
Figure 1. Chelation during Grignard addition.



Scheme 3.

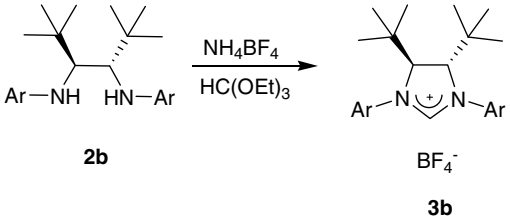
A racemic mixture of both enantiomers **2** can be isolated by extraction with diethyl ether in 91% yield. The enantiomers can be quantitatively separated by stereoselective crystallization with tartaric acid (Scheme 3).[11] Therefore, (+)-tartaric acid or (−)-tartaric acid is added to a solution of compound **2** in hot ethanol to yield a precipitate of the corresponding enantiomerically pure diamine tartrate.

Diamines **2a** and **2b** are liberated with NaOH, and the enantiomeric purity is verified with a CDA in NMR (Scheme 4).[12] The P-complexes **4a** and **4b** of both chiral diamines can be identified by their different shifts in ^{31}P NMR. The separation with tartaric acid is repeated until the compounds are enantiomerically pure.



Scheme 4.

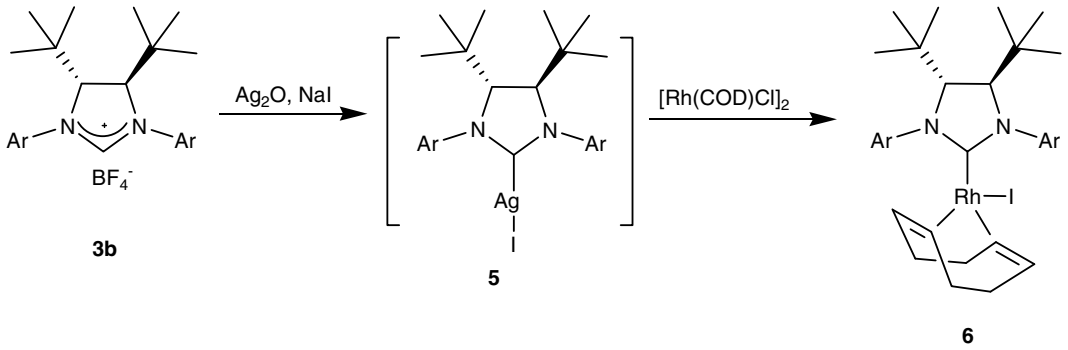
The reaction of the chiral diamine **2b** to form the imidazolidine salt **3b** is carried out by condensation with triethyl orthoformate and ammonium tetrafluoroborate.[13] After extraction, evaporation of the solvent and recrystallization in ethanol, the salt is obtained as an off-white solid in 83% yield (Scheme 5). An equivalent reaction of the (*R*,*R*)-enantiomer **2a** yields the corresponding chiral salt **3a**.



Scheme 5.

2.2. Synthesis of [(4*R*,5*R*)-1,3-bis[2,6-diisopropylphenyl]-4,5-di-*tert*-butylimidazolin-2-ylidene][(1,2,5,6-η)-1,5-cyclooctadiene]-iodorhodium(I)

Amongst the various synthetic pathways for obtaining transition metal carbene complexes,[3a] a mild carbene transfer method



Scheme 6.

was developed by Wang and Lin.[14] For the transmetallation, a silver carbene complex (compound **5**) was prepared and subsequently reacted with $[Rh(COD)Cl]_2$ as a metal precursor (Scheme 6).

The suspension was stirred for 16 h, after which the precipitate was filtered over Celite and the complex recovered using gradient column chromatography. In a first fraction using CH_2Cl_2 as an eluent, small amounts of unreacted starting material were obtained. Additional elutions with acetone were used to retrieve complex **6**. Subsequent re-crystallization in a mixture of acetone and Et_2O led to air-stable, pale-yellow crystals.

The successful carbene transfer was confirmed by analytical methods. The most indicative result is the carbene–carbon signal at 224 ppm, observed by ^{13}C NMR spectroscopy. The ^{103}Rh–^{13}C coupling constant is $^1J_{Rh,C} = 47$ Hz. Both findings are in good accordance with results previously reported for saturated NHC-complexes.[7a] Due to the high nucleophilicity of these types of complexes compared to unsaturated NHC-complexes, a shift of the carbene–carbon signal to lower field is usual. The preservation of chirality was determined by polarimetry, which showed a specific rotation of −60.6°.

3. Conclusions

An inexpensive and high-yielding synthesis of chiral imidazolidine salts is reported in this work. With this procedure new substitution patterns on the backbone of the complex should be possible, leading to a broadening of the range of chiral imidazolidine salts. The use of the synthesized compound as a chiral ligand in an asymmetric rhodium–NHC complex is also discussed. Their potential application in asymmetric transition metal catalysis is currently under investigation in our laboratories.

4. Experimental

4.1. General

All reactions were carried out in an air atmosphere unless stated otherwise. *N*,*N*′-Bis(2,6-diisopropylphenyl)imine **1** was synthesized in accordance with previously reported methods.[8] All other materials were obtained commercially and used without further purification. All solvents, except for those used in extraction procedures, were dried on an alumina-based solvent purification system. NMR spectra were recorded on a JEOL JMX-GX 400 spectrometer operating at 400 MHz (^1H NMR), 100 MHz (^{13}C NMR) and on a Bruker AMX 400 operating at 400 MHz (^1H NMR), 100 MHz (^{13}C NMR). The spectra were calibrated to the residual proton of the solvents. Coupling constants *J* are given in Hertz. NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. MS spectra were measured at the TU München Mass Spectrometry Laboratory on a Finnigan MAT 90 mass spectrometer using FAB and CI techniques. Optical rotations were measured on a Perkin–Elmer 341. Elemental analyses were carried out by the Microanalytic Laboratory at the TU München.

4.2. Synthesis of *N*,*N*′-bis-(2,6-diisopropyl-phenyl)-rac-1,2-diamino-1,2-di-*tert*-butylethane 2

At first, 30 mL of *tert*-butylmagnesiumchloride (1.7 M in Et_2O) was suspended in 300 mL of *n*-hexane and heated to 50 °C. A solution of 8 g (21 mmol) of diimine **1** in 80 mL of *n*-hexane was then added dropwise to the Grignard mixture, after which the suspension is stirred for 1 h under argon atmosphere.

After cooling to room temperature, 120 mL of a saturated NH_4Cl solution and 100 mL of Et_2O were added. The obtained reaction mixture is stirred for another 30 min. The phases were subsequently separated and the water phase was extracted with Et_2O (2×100 mL). The combined organic phases were dried over K_2CO_3. After evaporation of the solvent and recrystallization in ethanol, compound **2** (9.45 g, 90%) was isolated as a colourless solid. δ_H (400 MHz, $CDCl_3$): 0.89–0.93 (dd, J 6, 12H, $CH(CH_3)_2$), 1.17–1.28 (dd + s, 30H, $CH(CH_3)_2 + C(CH_3)_3$), 2.25–3.31 (m, 2H, $CH(CH_3)_2$), 3.29–3.36 (m, 2H, $CH(CH_3)_2$), 3.76 (br s, 2H, NH), 3.98 (d, *J* 6.2, 2H, NCH), 6.95–7.05 (m, 6H, CH_{phenyl}); δ_C (100 MHz, $CDCl_3$) 22.9, 24.1, 27.1, 28.1, 35.5, 71.4, 122.6, 123.7, 137.2, 140.3, 140.9, 148.8. *m*/*z* (CI): 491.3 ([M^+], 39%), 435.3 (100), 377.3 (3). Anal. Calcd for $C_{104}H_{174}N_6O$: C, 81.93; H, 11.50; N, 5.51. Found: C, 82.03; H, 11.09; N, 5.76.

4.3. Enantiomer separation of *N*,*N*′-bis-(2,6-diisopropyl-phenyl)-rac-1,2-diamino-1,2-di-*tert*-butylethane 2

At first, 9.45 g of diamine **2** (19.2 mmol) was dissolved in 110 mL of hot ethanol. A solution of 1.44 g L-(+)-tartaric acid (9.6 mmol) in the minimum volume of water was added. After 16 h the precipitate was filtered off and washed with cold ethanol. For liberating the enantiomer, 40 mL of NaOH (4 M) and 40 mL of Et_2O were added and the suspension stirred for 30 min. The phases were separated, and the water phase is extracted again with Et_2O (2×40 mL). The combined organic phases were dried over $MgSO_4$. After removing the solvent, **2a** was obtained as a colourless solid. 4.70 g (99%). The enantiomeric purity was verified by a CDA according to literature procedures.[12] $[\alpha]_D^{20} = -16$ (*c* 0.0063, Et_2O).

For obtaining the (*S*,*S*)-enantiomer **2b**, the mother liquor and the washing fractions of the separation mentioned above were collected, and the solvent was evaporated. The obtained solid was stirred in NaOH (4 M) and extracted with Et_2O as described for

the (*R*,*R*)-enantiomer. For chiral purification, the solid was dissolved in 110 mL of hot ethanol and 1.44 g (9.6 mmol) of D-(−)-tartaric acid, which is dissolved in a minimum volume of water, then added. After 16 h, the crystallized diamine tartrate was filtered off, washed in cold ethanol and stirred in 40 mL of NaOH (4 M) and 40 mL of Et_2O for 30 min. The phases were then separated, and the water phase is extracted again with Et_2O (2 × 40 mL). The solvent was removed and 4.72 g (100%) of the product as a colourless solid was obtained. The enantiomeric purity was verified by a CDA according to literature procedures.[12] $[\alpha]_D^{20} = +16$ (*c* 0.006, Et_2O).

4.4. Synthesis of 1,3-bis-(2,6-diisopropylphenyl)-(*4R*,*5R*)-di-*tert*-butyl-4,5-dihydro-imidazolin tetrafluoroborate 3a and 1,3-bis-(2,6-diisopropylphenyl)-(4*S*,5*S*)-di-*tert*-butyl-4,5-dihydro-imidazolin tetrafluoroborate 3b

At first, 2 g of diamine **2a** or **2b** (4.1 mmol) was dissolved in 5 mL of $HC(OEt)_3$, after which 0.51 g of NH_4BF_4 (4.9 mmol) is added and the suspension is refluxed for 5 h. After cooling to room temperature, 5 mL of Et_2O was added, and the phases were separated. The water phase was extracted two more times with Et_2O (2 × 5 mL). The organic phases were combined, and the solvent is evaporated. The residue is extracted with DCM, filtered, dried over Na_2SO_4, and the solvent is evaporated. Then 1.99 g (83%) of a beige solid was finally obtained $[\alpha]_D^{20} = -83.3$ (*c* 0.0012, CH_2Cl_2). δ_H (400 MHz, $CDCl_3$): 1.08–1.33 (qd, 24H, $CH(CH_3)_2$), 1.23 (s, 18 H, $C(CH_3)_3$), 2.31 (m, 4H, $CH(CH_3)_2$), 3.42 (m, 2H, NC*H*), 7.26–7.34 (m, 4H, CH_{phenyl}), 7.50 (t, *J* 7.83, 1H, CH_{phenyl}), 7.59 (t, *J* 7.84, 1H, CH_{phenyl}), 8.83 (s, 1H, NC*H*); δ_C (100 MHz, $CDCl_3$): 21.5, 23.9, 24.2, 26.1, 29.0, 29.5, 32.7, 77.0, 121.7, 124.5, 124.8, 129.6, 129.8, 132.6, 138.9, 145.4, 145.6. *m*/z (FAB): 445.2 ([M^+−*t*Bu], 100%). Anal. Calcd for $C_{35}H_{55}N_2BF_4$: C, 71.17; H, 9.39; N, 4.74. Found: C, 71.01; H, 9.06; N, 4.59.

4.5. Synthesis of [(4*R*,5*R*)-1,3-bis[2,6-diisopropylphenyl]-4,5-di-*tert*-butylimidazolin-2-ylidene][(1,2,5,6-η)-1,5-cyclooctadiene]-iodorhodium(I) 6

To a solution of **3a** (590 mg, 1.2 mmol) 15 mL of dry CH_3CN, Ag_2O (301 mg, 1.3 mmol) and NaI (225 mg, 1.5 mmol) was added in the dark. The mixture was refluxed for 1 h at 60 °C under argon. The silver precipitate was removed by filtration over Celite. The solvent was removed under vacuum and the complex used without further purification. The solid was dissolved in 15 mL of CH_2Cl_2, after which 301 mg of $[Rh(COD)Cl]_2$ (0.6 mmol) was added. The suspension was stirred for 16 h in the dark. Purification of the complex was carried out by filtration over a pad of Celite and gradient column chromatography over silica gel. Elution with CH_2Cl_2 led to a $[Rh(COD)Cl]_2$ fraction and subsequent elution with acetone yielded compound **6**. After evaporation of the solvent, the yellow solid was recrystallized in a mixture of acetone and Et_2O (1:1). Yield: 737 mg, 0.8 mmol, 73% $[\alpha]_D^{20} = -60.6$ (*c* 0.025, CH_2Cl_2). δ_H (400 MHz, $CDCl_3$): 1.11–1.25 (m, 30H, $CH(CH_3)_2$ + $C(CH_3)_3$), 1.76–1.80 (m, 4H, COD–CH_2), 2.36–2.53 (m, 4H, COD–CH_2, 4H, $CH(CH_3)_2$), 3.66 (m, 4H, COD–C*H*), 6,82 (d, 2H, NC*H*), 7.19–7.23 (d, 4H, CH_{phenyl}), 7.38–7.46 (dd, 2H, CH_{phenyl}); δ_C (100 MHz,$CDCl_3$): 22.2, 24.3, 24.7, 27.2, 28.6, 29.1, 30.5, 68.0, 78.6, 120.0, 124.3, 124.5, 130.5, 130.9, 145.5, 146.3, 224.3. *m*/*z* (CI): 550.5 ([M^+−(COD+I+*t*Bu)], 70%), 506.7 (46), 444.9 (100). Anal. Calcd for $C_{43}H_{65}N_2RhI{\cdot}CH_3CN$: C, 61.26; H, 8.00; N, 4.30. Found: C, 61.78; H, 7.75; N, 4.65.

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