Asymmetric Catalysis

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A Novel Ligand for the Enantioselective Ruthenium-Catalyzed Olefin Metathesis**

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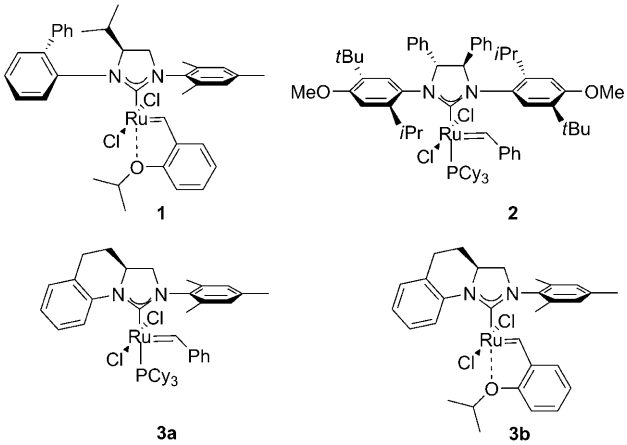
Recently the interest for chiral olefin metathesis catalysts with respect to the synthesis of enantioenriched molecules, as well as enhanced product selectivities, has increased significantly.[1] For these kind of transformations, a range of molybdenum-catalysts containing one stereogen metal center have been very successful.[2] However, in comparison to these catalysts, ruthenium metathesis catalysts offer improved handling and stability.[3]

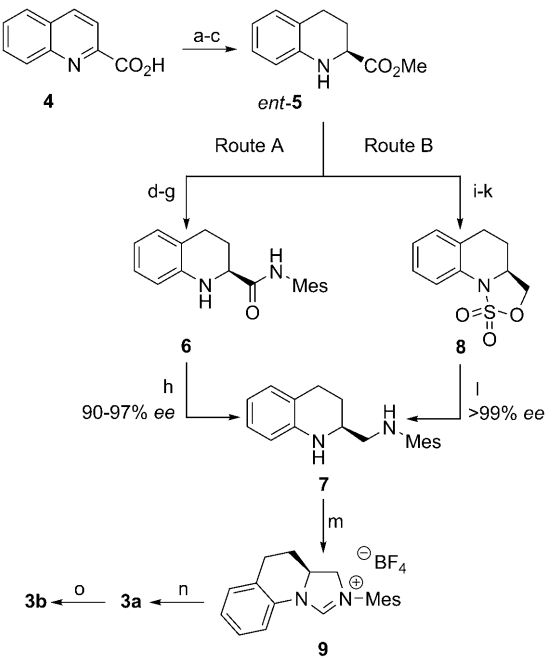
A challenge with such catalysts is an efficient transfer of chirality from the N-heterocyclic carbene (NHC) to the metal center without substitution of the chlorine ligands, which are important for the reactivity.[4] Recently, we introduced chiral ruthenium metathesis catalysts of type **1**,[5] which, compared to the catalysts of Grubbs et al. (e.g. **2**), have a different orientation of the stabilizing N-aryl groups (Scheme 1) which arises from the monosubstitution in the NHC-backbone.[6] The C3 substituent in the NHC twists the framework and hinders rotation of the N-aryl substituent, while at the same time the absence of the C4 substitution allows a planar orientation for the mesitylene moiety. The resulting highly active catalyst was used for asymmetric ring-opening cross-metathesis providing excellent results.[5]

Herein, we report a new type of chiral NHC-ligand in which rotation around the chirality transferring N-aryl bond is no longer possible, and the corresponding ruthenium metathesis catalysts. We decided to use a 2-substituted tetrahydroquinoline as the source of chirality, which is easy accessible via quinaldic acid **4**. After esterification of **4** and hydration to *rac*-**5**, a kinetic enzymatic resolution leads to the desired key structure *ent*-**5** in an overall yield of 41% (≥ 99% *ee*) (Scheme 2).[7]

Protection of amine *ent*-**5** (route A), ester saponification and subsequent amide coupling and deprotection, afforded amide **6**. A further reduction with $BH_3{\cdot}SMe_2$ led to the formation of diamine **7** in good yields. During this reaction a partial racemization and fluctuating *ee*-values were detected



Scheme 1. Chiral ruthenium metathesis (pre)catalysts.



Scheme 2. Preparation of catalysts: a) $SOCl_2$/MeOH, 97%; b) PtO_2/H_2 (60–70 bar), MeOH, quant.; c) α-chymotrypsine, Sörensen-buffer (pH 7.4, 0.1 M), 41% (>99% *ee*); d) Na_2CO_3, ethyl chloroformate, H_2O/ CH_2Cl_2, quant.; e) NaOH, THF/H_2O, quant.; f) pyridine, NEt_3, CH_2Cl_2, PivCl, mesidine, 68%; g) $[Pd(PPh_3)_4]$, PPh_3, dimedone, THF, quant.; h) $BH_3{\cdot}SMe_2$, THF, 98%; i) $LiAlH_4$, THF, quant.; j) $SOCl_2$, pyridine, CH_2Cl_2, 85%; k) 2 mol% $RuCl_3{\cdot}H_2O$, $NaIO_4$, SiO_2, ethyl acetate, H_2O, 91%; l) NaH, Boc-mesidine, DMF, CH_2Cl_2, TFA (trifluoro acetic acid), 80% (99% *ee*); m) triethyl orthoformate, H_2CO_2H, NH_4BF_4, toluene, 92%; n) $KO(CH_3)_2CH_2CH_3$, hexane, $[(PCy_3)_2Cl_2Ru{=}CHPh]$, 82%; o) 1-isopropoxy-2-vinyl-benzene, **3a**, CH_2Cl_2, 56%.

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(90–97% *ee*). For this reason we developed synthetic route B. Reduction of *ent*-**5** with $LiAlH_4$ to the amino alcohol,[7] cyclization with $SOCl_2$ to the sulfamidite, and oxidation with $RuCl_3 \cdot H_2O/NaIO_4$ on wet silica afforded crystalline sulfamidate **8** in 80% overall yield.[8] The subsequent ring opening with Boc-protected mesidine led to formation of **7** without partial racemization (99.4% *ee*), which was easily transformed into the carbene precursor. The green microcrystalline complex **3a** was obtained by a phosphine–NHC exchange of the Grubbs I catalyst. A second phosphine exchange on **3a** afforded **3b** and recrystallization from *n*-hexane/CH_2Cl_2 resulted in single crystals.

The crystal structure of **3b** (Figure 1) provided an insight into the steric influence of the ligand on the metal centre. The C_2 bridge at the chirality center causes a large twist of 45° around the N-aryl bond and forces the carbon atom C13 into the coordination sphere of the ruthenium center. The short interatomic distance between Ru1–C13 of 3.131(6) Å results in an agostic Ru-H-C-interaction, that is reflected in a diminished ^1J (C13,H13) coupling constant of 154 Hz. Also notably herein is the downfield shifted H13 signal in the ^{1}H-spectra at $\delta = 9.23$ ppm. The metal coordination environment is no longer a square-pyramid, but rather a distorted octahedron.[9]

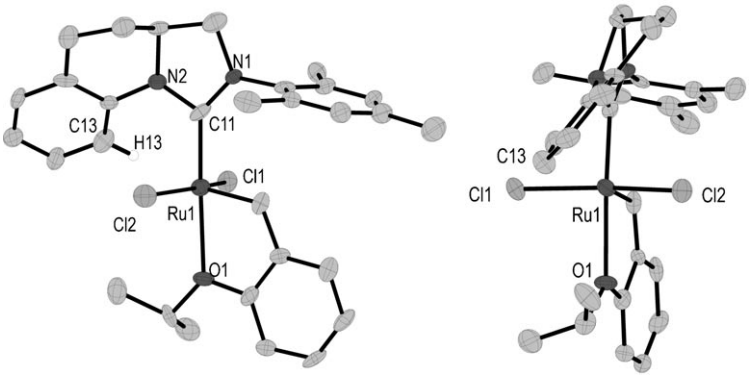
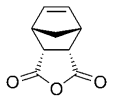
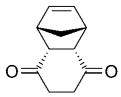
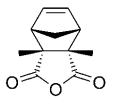
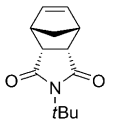


Figure 1. Two views of the crystal structure of **3b**.[13]

As a result of twist there is a strong steric interaction between the ligand and chlorine atom Cl1. The Ru–Cl bond lengths of 2.350(3) Å are significantly shortened and the Cl1-Ru1-Cl2 bond angle of 158.57(6)° is increased. Consistent with our expectations, the mesitylene group is orthogonally oriented to the styrene ether moiety. The ^{1}H-NMR spectrum for **3a** shows splitting for a multiplicity of proton signals at 0 °C, which disappear at room temperature, which suggests the presence of rotameres.[10] Since no splitting of the proton signals was observed for **3b** even at −50 °C, the rotameres in **3a** are presumably caused by different orientations of the benzylidene unit.

To compare the efficiency of **3a**/**b** with other chiral ruthenium catalysts, we chose the asymmetric ring-opening cross-metathesis (AROCM) of *meso*-norbornenes with styrene as the model reaction (Table 1). The new complexes furnish good *ee*-values with up to 92% *ee*, combined with pronounced *E*-selectivity. In contrast to the Grubbs catalyst, the reactivity is lower but the selectivities are however significantly higher (Table 1, entries 6 and 8).[6]

Table 1: Test of catalysts in AROCM with styrene as the cross-partner.[a]

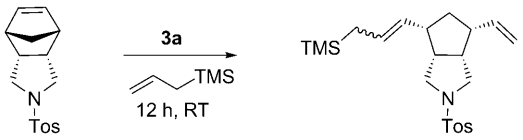
Entry	Substrate	Catalyst (mol%)	*t* [h]	Conv. [%][c] (*E*:*Z*)[d]	*ee* [%][b]
1		**3a** (7)	16[e]	78 (17:1)	86
2		**3b** (2.5)	16[f]	83 (13:1)	75
3		**3a** (6)	16[e]	36 (3:1)	85
4		**3a** (5)	24[e]	97 (8:1)	80
5		**3b** (5)	24[e]	96 (11:1)	71
6		**2** (1)	1[f]	>96 (1:1)[6]	57
7		**3b** (2.5)	72[f]	99 (11:1)	**91**
8		**3a** (2.5)	18[e]	98 (9:1)	**92**

[a] Conditions: 5 equiv styrene, CH_2Cl_2, 0.04 M with respect to substrate. [b] *E*-Isomer, determined by chiral HPLC. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by GC. [e] Reaction temperature 40 °C. [f] Reaction temperature 25 °C.

The most commonly used cross-partners in AROCM are styrenes. These are however limited in their usefulness for further reactions. Hence we focused on the AROCM of norbornenes with allyltrimethylsilane, which to our knowledge, has not been investigated to date. The substituted allyltrimethylsilanes obtained should offer diverse synthetic possibilities.

We investigated the solvent dependency of the enantioselectivity in the reaction of allyltrimethylsilane and **10** with **3a** (Table 2). In the process a clear solvent influence on the *ee*-values and surprisingly on the *E*/*Z*-ratios was observed. For instance, in MTBE or toluene the *E*-isomer was preferentially formed, whereas in CH_2Cl_2 the *Z*-isomer prevailed (Table 2, entries 1, 2, and 5).

Table 2: Solvent effects on AROCM of **10** with catalyst **3a**.[a]



10 **11**

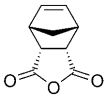
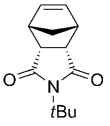
Entry	Solvent	Conv. [%][b]	*E*:*Z*[c]	*ee* [%] *E* (*Z*)[c]
1	CH_2Cl_2	>99	1:1.5	75 (78)
2	MTBE[d]	>99	2:1	58 (39)
3	THF	>99	1:1	63 (66)
4	benzene	>99	2:1	53 (36)
5	toluene	>99	2:1	57 (36)
6	trifluorotoluene	92	1.5:1	69 (50)

[a] Conditions: 2 equiv allyltrimethylsilane, CH_2Cl_2, 0.05 M with respect to substrate, 12 h, room temperature, 3 mol% **3a**. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral HPLC. [d] methyl-*tert*-butylether.

Solvent-dependent changes in the *ee*-values for the *E*/*Z*-isomers are also remarkable, for example in toluene 57% *ee* for the *E*- and 36% *ee* for the *Z*-product, whereas in CH_2Cl_2 the difference is relatively low, 75% *ee* and 78% *ee*, respectively (Table 2, entries 1 and 5).

Once CH_2Cl_2 was recognized as the solvent of choice, we investigated the influence of temperature. As expected the enantiomeric excess increased at low temperature (Table 3, entries 1–4) as did the amount of *Z*-product. Ruthenium-catalyzed *Z*-selective cross-metathesis is rare and to our knowledge only described with acrylonitrile as the cross partner.[11] In our case the preferred *Z*-product formation is caused by the catalyst, because the same reaction catalyzed with the chiral Grubbs-complex **2** led to the preferred formation of *E*-product (Table 3, entry 6).

Table 3: Test of the catalyst in AROCM with allyltrimethylsilane as the cross partner.[a]

Entry	Substr.	Catalyst (mol%)	*t* [h]	Conv.[c] (*E*:*Z*)[b]	*ee* [%] *E* (*Z*)[b]
1		**3a** (2.5)	1	>99 (1:1.5)	75 (75) (40 °C)
2		**3a** (2.5)	2	>99 (1:1.5)	75 (78)
3		**3a** (2.5)	2	>99 (1:2)	79 (85) (0 °C)
4		**3a** (2.5)	48	>99 (1:2)	79 (87) (−10 °C)
5		**3b** (2.5)	18	>99 (1:1)	73 (71)
6		**2** (2.5)	2	>99 (3:1)	34 (8)
7		**3a** (2.5)	2	>99 (2:1)	80 (75)[d]
8		**3a** (2.5)	6	>99 (2:1)	82 (82)[d] (0 °C)
9		**3a** (2.6)	72	87 (2:1)	72 (n.d.)
10		**3a** (3.0)	96[e]	96 (2:1)	**98 (92)**
11		**3b** (3.0)	96	>99 (2:1)	**95 (91)**
12		**2** (2.0)	18	>99 (2:1)	35 (15)

[a] Conditions: 2 equiv allyltrimethylsilane, CH_2Cl_2, 0.04 M with respect to substrate, room temperature. [b] Determined by chiral HPLC. Highest values are highlighted in bold, n.d. = not determined. [c] Determined by ^{1}H NMR spectroscopy. [d] After conversion into the N-Tos protected product. [e] After 18 h 51% conversion.

A particularly notable feature of these reactions is the significant difference in the enantioselectivity. The C_2-symmetric carbene ligand with partially rotatable N-aryl groups in ruthenium complex **2** led to very low *ee* values in the AROCM with the allylsilane and as already observed with other reaction partners, the enantioselectivity for the *Z*-product was again significantly lower (Table 3, entries 6 and 12). The fixed, non-rotatable N-aryl unit in our ligand causes a considerably higher enantioselectivity that is of similar magnitude for both stereoisomers of the olefins. These results are in accordance with the calculations of Cavallo et al.[12] who found that the steric demand of the NHC-ligand in the ruthenium coordination sphere is an important factor. Our ligand forms a well-defined rigid reaction pocket, which provides high enantioselectivities. In **2** however there is the possibility of a partial N-aryl rotation giving rise to a more flexible reaction pocket, resulting in a lower enantioselectivity. Owing to its properties, we believe that this novel carbene ligand is also of particular interest for a range of applications in metal-catalyzed enantioselective reactions.

Experimental Section

Typical procedure for AROCM: **10** (28.9 mg; 0.10 mmol, 1 equiv) and allyltrimethylsilane (22.8 mg; 0.2 mmol, 2 equiv) were dissolved in dry CH_2Cl_2 (0.04 M) under nitrogen atmosphere at room temperature. The mixture was degassed by "freeze-pump-thaw" cycle. **3a** (2.08 mg; 2.5 mol%, 2.5 μmol) was added and the mixture stirred for 2 h at room temperature. Ethyl vinyl ether was added in excess and the volatile compounds were removed under vacuum. The residue was purified by column chromatography (SiO_2, *c*-hexane:EtOAc, 25:1) and 36.0 mg of a clear oil were isolated (0.09 mmol, 89%).

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Keywords: agostic interactions · asymmetric catalysis · N-heterocyclic carbenes · olefin metathesis · ruthenium

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[13] Crystallographic data for **3b**: $C_{30}H_{34}Cl_2N_2ORu$, $M_r = 610.56$, $P2_1$, $a = 8.9101(4)$, $b = 15.7385(6)$, $c = 9.8022(4)$, $\alpha = \gamma = 90°$, $\beta = 94.402(4)°$, $V = 1370.52(10)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.480$ g cm^{-3}, $\mu = 0.793$ mm^{-1}, $T = 150$ K, $\theta_{max} = 25.00°$, $R_{int} = 0.0512$, $R = 0.0417$, $R_w = 0.0475$. CCDC 795016 (**3b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

