Asymmetric Catalysis

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Highly Active Chiral Ruthenium-Based Metathesis Catalysts through a Monosubstitution in the N-Heterocyclic Carbene**

*Sascha Tiede, Anke Berger, David Schlesiger, Daniel Rost, Anja Lühl, and Siegfried Blechert**

Asymmetric olefin metathesis has great synthetic potential as a result of its versatility in forming C–C bonds under neutral and mild conditions.[1] Stable ruthenium-based catalysts are of special interest because of their ease of handling and their functional-group tolerance.[2] All the chiral ruthenium metathesis catalysts known to date derive from α,α′-disubstituted diamines and therefore have an 3,4-disubstituted N-heterocyclic carbene (NHC) ligand (Figure 1). In complexes with monodentate ligands, such as **1** developed by Grubbs[3] as well as in the variants by Collins,[4] the transfer of chirality to the reactive metal center is accomplished through the hindered rotation of N-aryl substituents. In case of the Hoveyda complex **2**, which includes bidentate ligands, transfer is accomplished by stereocontrolled substitution of a halogen ligand with a phenol derivative, which has the drawback of significantly lowering the reactivity of the complexes.[5]

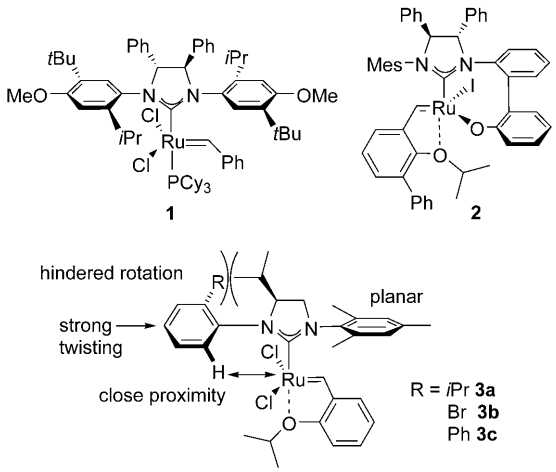

Figure 1. Chiral ruthenium metathesis (pre)catalysts **1** and **2** and our compounds **3a–c**; Mes = 2,4,6-trimethylphenyl.

[*] S. Tiede,[+] A. Berger,[+] D. Schlesiger, D. Rost, A. Lühl,[#]
Prof. Dr. S. Blechert
Institut für Chemie, Technische Universität Berlin
Strasse des 17.Juni 135, 10623 Berlin (Germany)
Fax: (+49) 30-314-29745
E-mail: blechert@chem.tu-berlin.de
Homepage: http://www.chemie.tu-berlin.de/blechert

[#] Current address: Universität Karlsruhe
Engesserstrasse 15, 76131 Karlsruhe (Germany)

[+] These authors contributed equally to this work.

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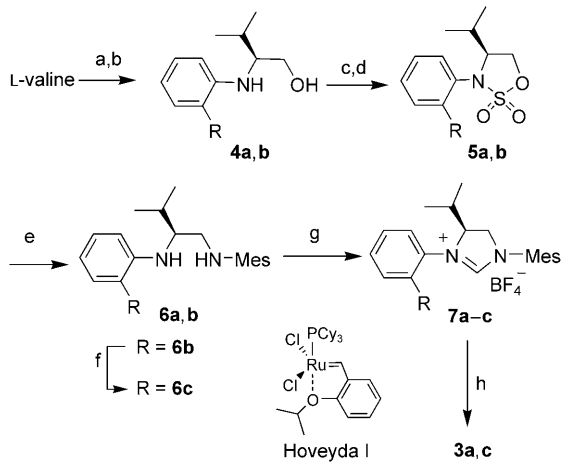
N-aryl substituted complexes are in general far more stable than their N-alkyl counterparts,[4,6] especially when insertion into the C–H bond which results in catalyst deactivation is avoided by *ortho*-substitution.[7] The 3,4-substituents in the NHC backbone have another function besides induction of chirality: they can improve the stability of ruthenium carbene complexes, as has been shown by both density functional theory (DFT) calculations[8] and experimental studies.[9] Chiral disubstituted complexes, such as **1**, show a rotation away from an orthogonal arrangement for both aryl substituents, that is not found in their achiral analogues, the Grubbs II and Hoveyda II precatalysts. This rotation should, in our opinion, have an negative impact on their reactivity.

During our studies of unsymmetrically substituted NHC complexes we synthesized the first backbone-monosubstituted complexes which also bear two different N-aryl groups and studied their properties and reactivity. Our goal was to reach optimal transfer of chirality by using the C3 substituent to induce a significant twist of the monosubstituted arene ring.[10] In Addition, we employed a planar mesityl substituent to avoid steric hindrance diminishing the reactivity.[11] We herein report a new type of chiral catalyst, which is highly stable and very reactive, showing both excellent *E* selectivity and enantioselectivity in asymmetric ring-opening cross-metathesis (AROCM).

We chose L-valine as starting material, which was first coupled to an aryl halide using copper catalysis and subsequently reduced to yield **4a**,**b** (Scheme 1). 1-Iodo-2-isopropylbenzene and 1,2-dibromobenzene were used as aryl compounds. Metathesis catalysts bearing *ortho*-bromo substituents have not been described to date. The bromo substituent offers several possibilities to introduce a range of different substituents.

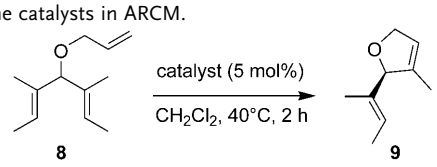
After preparation of sulfamidate[12] **5a**,**b** nucleophilic attack using boc-mesidine[13] leads to **6a**,**b**. In case of bromo-substituted diamine **6b**, a phenyl substituent can be introduced by Suzuki coupling. The phenyl is supposed to hinder the rotation around the N–aryl bond but is less sterically demanding than the isopropyl group. Synthesis of the complexes **3a–c** was by exchange of the phosphane ligand on the Hoveyda I precatalyst for the NHC group. In total, all three catalysts can be prepared in a few steps and in good overall yields.

For first studies we chose the asymmetric ring-closing metathesis (ARCM) of **8** as a model reaction, this is an especially well studied reaction type.[3a,b,4,6] Reactivity tests showed acceptable conversions using 5 mol% catalyst at 40 °C. The best enantioselectivities were achieved in CH_2Cl_2 using **3c** (Table 1). Other solvents, such as THF, 2-methyl-



Scheme 1. Catalyst synthesis: a) aryl halide, CuI, K_2CO_3, 100 °C; **a** 71 %, **b** 56 %; b) $NaBH_4$, $BF_3{\cdot}OEt_2$, 0 °C→66 °C, **a** 97 %, **b** 85 %; c) $SOCl_2$, py, −10 °C→room temperature, 12 h; **a** 86 %, **b** 70 %; d) $RuCl_3{\cdot}H_2O$, $NaIO_4$, 0 °C, 3 h; **a** 91 %, **b** 99 %; e) HN(Boc)Mes, NaH, room temperature, 12 h; TFA, room temperature, 12 h; **a** 82 %, **b** 87 %; f) $PhB(OH)_2$, 5 mol % $[PdCl_2(PPh_3)_2]$, toluene/EtOH, 120 °C, 18 h, 95 %; g) $HC(OEt)_3$, NH_4BF_4, HCO_2H, 120 °C, 18 h; **a** 67 %, **b** 71 %, **c** 92 %; h) KHMDS, Hoveyda I catalyst, room temperature, 12 h; **a** 56 %, **b** 57 %, **c** 60 %. Boc = 1,1-dimethylethoxycarbonyl; py = pyridine, TFA = trifluoroacetic acid, KHMDS = potassium hexamethyldisilazane.

Table 1: The catalysts in ARCM.



8 **9**

Catalyst	*ee* [%][a]	Conv. [%][b]
3a	59	>98
3b	50	58
3c	66	87

[a] Determined by chiral GC. [b] Determined by ^{1}H NMR spectroscopy.

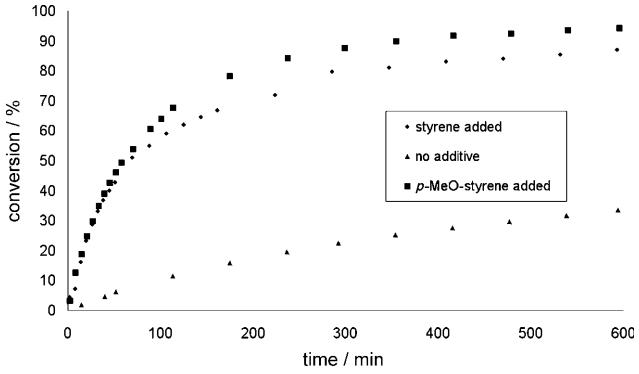
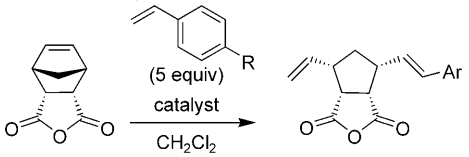


Figure 2. Influence of styrene additives on the ARCM of **8**. Conditions: room temperature, 5 mol % **3c**, and 5 equivalents additive.

Table 2: Test of the catalysts in AROCM.



10 >98% conversion

Entry	Catalyst	R	*T* [°C]	*t* [h]	*ee* [%][a]	*E*/*Z*[b]
1	1 mol % **3a**	H	25	1	71	19:1
2	1 mol % **3b**	H	25	1	83	19:1
3	1 mol % **3c**	H	25	1	88	>30:1
4	0.05 mol % **3c**	H	25	15	88[c]	>30:1
5	1 mol % **3c**	H	−10	12	**93**	>30:1
6	1 mol % **1**	H	25	1	76[d]	1:1[3c]
7	1 mol % **3c**	OMe	25	1	81	14:1
8	1 mol % **3c**	CF_3	25	1	68	30:1
9	1 mol % **3c**	NO_2	25	1	72	n.d.
10	1 mol % **3c**	CO_2Me	25	1	79	>30:1

[a] Determined by chiral HPLC, values refer to the *E* product. [b] Determined by GC/MS. [c] *Z* product: 65 % *ee*. [d] *Z* product: 4 % *ee*. n.d. = not determined. The best values are highlighted.

THF, C_6F_6, or toluene, did not lead to any improvements. Reactions at lower temperatures with the aim of improving enantioselectivity were prevented by the low conversions. In the course of our studies we found that addition of styrene derivatives significantly enhanced the reaction rate. Using 5 mol % **3c** at room temperature with the addition of 5 equivalents of *para*-methoxystyrene leads to a conversion from **8** into **9** of 70 % after 2 h compared to 12 % without additive (Figure 2).[14] Lower temperatures did not lead to an improvement in the *ee* values.

Much better results were achieved with ring-opening cross-metathesis (AROCM) of norbornene derivatives. To directly compare our catalysts with the Grubbs-type catalyst **1**, we used styrene as the cross-partner for our reactions. In contrast to the results of Grubbs et al.,[3c] we observed high *E* selectivities in all cases. As a first reaction we chose the AROCM of **10** (Table 2). Comparing catalysts **3a–c** (Table 2; entries 1–3), **3c** again showed the best enantioselectivity and furthermore an excellent *E* selectivity of over 30:1, while **1** shows no diastereoselectivity and in other cases led to 1.4:1 *E*/*Z* mixtures.[3c] The differences between the enantioselectivities have to be noted, too. While **3c** furnishes 88 % *ee* for the *E* isomer and 65 % *ee* for the *Z* isomer (Table 2; entry 4), **1** leads to 76 % *ee* for the *E* isomer and 4 % *ee* for the *Z* isomer (Table 2; entry 6). This great difference in enantioselectivity was rationalized by the opening of the norborne-derivative via a ruthenium benzylidene species. In our case, the formation of a methylidene species prior to the norbornene opening might occur, but no final conclusions about the mechanism can be drawn from our results.

Complete conversion of **10** could be achieved after 15 h with only 0.05 mol % catalyst loading (Table 2; entry 4).[14] Column chromatography furnished the product in 89 % yield. AROCM was also successful at low temperatures and led to an increase in enantioselectivity: using 1 mol % **3c**, 93 % *ee* was achieved with complete conversion after 12 h (Table 2; entry 5).

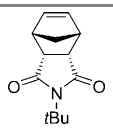
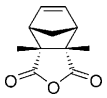
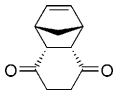
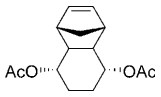
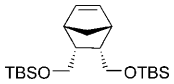
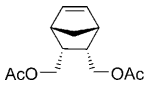
These or even longer reaction times require a high stability of the precatalyst in solution. Compound **3c** did not

show any sign of decomposition even after 12 days at 40 °C in CD_2Cl_2, while **1** started to decompose under these conditions after a few hours. Compounds **3a**,**b** were highly stable as well, which is especially notable for *ortho*-bromo precatalyst **3b**, because comparable ruthenium complexes of the Hoveyda II type bearing *ortho*-chlorophenyl substituents were not suitable for catalysis because of their instability.[15]

To study the electronic effects of the cross-partner, we used styrene derivatives with different *para* substituents (Table 2; entries 7–10).[16] Styrene was the best cross-partner. No improvement in enantiomeric excess could be detected by changing electron density of the styrene derivatives.

Despite being a Hoveyda II type catalyst, compound **3c** initiates very easily. During the test of more substrates, **3c** again showed high *E* selectivity paired with, in some cases, excellent *ee* values (Table 3). Indications for the origin of the

Table 3: AROCM of different substrates with **3c**.[a]

Entry	Substrate	*T* [°C]	*t* [h]	*ee* [%][b]	*E*/*Z*[c]	Conv. [%][d]
1		25	20	82	24:1	>98
2		−10	72	**92**	13:1	>98
3		25	3.5	82	21:1	>98
4		−10	48	**90**	23:1	>98
5		25	120	86	19:1	61
6		25	2	76	>30:1	>98
7		−10	12	70	21:1	>98
8		−10	12	60	21:1	>98

[a] Conditions: 0.14 mmol substrate, 5 equivalents styrene and 1 mol% **3c** in 2.1 mL CH_2Cl_2. [b] Determined by chiral HPLC, best values are highlighted. [c] Determined by GC/MS. [d] Determined by ^{1}H NMR spectroscopy.

high enantioselectivity can be found in the crystal structures of **3a** and **3c** (Figure 3). The aryl substituent R does not, as might be thought, point in the direction of the ruthenium center but towards the chiral center in the backbone. The N–aryl bond in biphenyl compound **3c** is rotated about 30% more in the direction of the metal center compared to the sterically more demanding isopropyl compound **3a** (36° versus 26°). The distance between the unsubstituted *ortho*-carbon atom to the ruthenium center is only 3.158(9) Å in **3c** (**3a**: 3.231(13) Å). The mesityl moiety is as expected orthogonal to the styrene-ether unit. Despite its asymmetric N-substitution, only a single isomer of **3c** can be detected in its ^{1}H NMR spectra in C_6D_6 below 60 °C.[17]

In summary, our newly developed metathesis (pre)catalyst **3c** is highly *E* selective in AROCM. Its high stability and low initiation barrier allows reactions with very low catalyst loadings and at low temperatures. The biphenyl structure, novel to ruthenium catalysts metathesis chemistry, leads to excellent enantioselectivities in AROCM. Further studies concerning the reaction scope and catalyst immobilization are underway.

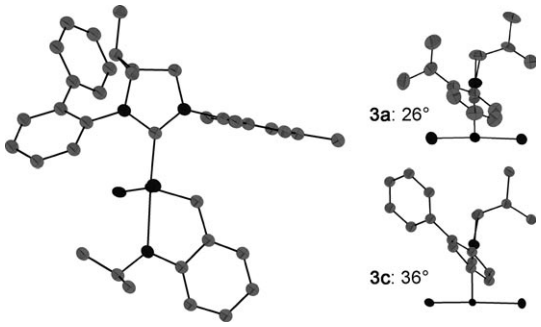


Figure 3. Left: X-ray structure of **3c**. Right: side-view of **3c** and **3a** (styrene ether and mesityl group omitted for clarity).[18]

Experimental Section

Typical AROCM procedure: **3c** (4.30 mg, 6.10 μmol, 0.05 mol%) was added to a solution of **10** (2.00 g, 12.2 mmol, 1 equiv.) and styrene (6.35 g, 61.0 mmol, 5 equiv.) in CH_2Cl_2 (174 mL, $c = 0.07$ M) under a nitrogen atmosphere. After 15 h stirring at room temperature, ethylvinyl ether (0.1 mL) was added, the solvent evaporated, and the compound was purified using column chromatography (SiO_2, cyclohexane/EtOAc). 2.90 g (10.8 mmol, 89% yield) product was obtained.

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[16] An influence of styrene additives on selectivity in ARCM has been described in Ref. [4c].

[17] Other unsymmetrically N-substituted NHC ligands with two chiral centers in their backbone show different rotational isomers (Ref. [4b]) even at room temperature

[18] Crystallographic data for **3c**: $C_{27}H_{42}Cl_2N_2ORu$, $M_r = 702.70$, $P\,21\,21\,21$ $P2_12_12_1$, $a = 8.9798(11)$, $b = 12.8985(15)$, $c = 29.555(3)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 3423.2(7)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.363$ g cm^{-3}, $\mu = 0.645$ mm^{-1}, $T = 150$ K, $\theta_{max} = 24.990$, $R_{int} = 0.153$, $R = 0.0739$, $Rw = 0.1511$. CCDC 765620 (**3c**) and CCDC 765621 ((*R*)-**3a**) contain 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.

