ORGANOMETALLICS
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New Ruthenium(II) Indenylidene Complexes Bearing Unsymmetrical N-Heterocyclic Carbenes

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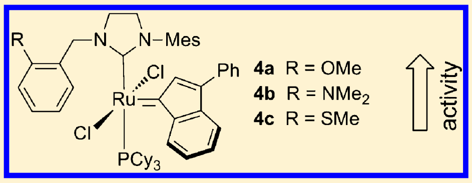
Supporting Information

ABSTRACT: New robust and air-stable ruthenium(II) indenylidene second-generation precatalysts with unsymmetrical N-heterocyclic carbene (NHC) ligands were synthesized. These complexes were studied using ring-closing metathesis (RCM) of diethyl diallylmalonate (**5**; DEDAM) as a model substrate. Two new complexes containing OMe and NMe_2 groups in the NHC ligand, namely [1-(2,4,6-trimethylphenyl)-3-(2-methoxybenzyl)-2-imidazolidinylidene]-dichloro(3-phenyl-1*H*-inden-1-ylidene)(tricyclohexylphosphine)ruthenium(II) (**4a**) and [1-(2,4,6-trimethylphenyl)-3-(2-*N*,*N*-dimethylaminobenzyl)-2-imidazolidinylidene]dichloro(3-phenyl-1*H*-inden-1-ylidene)(tricyclohexylphosphine)ruthenium(II) (**4b**), show increased activity in comparison to the parent [1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(3-phenyl-1*H*-inden-1-ylidene)(tricyclohexylphosphine)ruthenium(II) (Umicore **M2**). Interestingly, the complex [1-(2,4,6-trimethylphenyl)-3-(2-thiomethylbenzyl)-2-imidazolidinylidene]dichloro(3-phenyl-1*H*-inden-1-ylidene)(tricyclohexylphosphine)ruthenium(II) (**4c**), bearing a SMe substituent, showed very low activity in the model RCM reaction with diethyl diallylmalonate (**5**). Application of the active complexes for metathesis reactions with a broad spectrum of olefins in commercial-grade solvents in air was examined.



Olefin metathesis is a versatile tool in organic chemistry for the formation of carbon–carbon double bonds.[1] In this respect it was widely acknowledged by a Nobel Prize to R. R. Schrock, Y. Chauvin, and R. H. Grubbs.[2–4]

Olefin metathesis still attracts a great deal of attention from organic chemists not only in academia[5] but also in industry.[6] The state of the art of olefin metathesis catalysts open up new vistas for more efficient methods in tedious natural product synthesis.[7] Nowadays, there are a great number of precatalysts known with various NHC ligands designed for olefin metathesis, and many of them are commercially available.[8] It is well-known that modifications on the NHC's moiety can induce profound changes in the reactivity pattern of the resulting precatalysts.[9] Moreover, the unsymmetrical NHC ligands allow diversification of the steric bulkiness in the vicinity of the ruthenium and therefore change the catalytic properties of the resulting complexes.[10−12] The range of the ruthenium metathesis precatalysts developed up to this point is broad, but there is still need for more complexes which are air-stable and remain robust in solvents of commercial-grade purity. Therefore, we turned our attention to ruthenium indenylidene precatalysts, since they are robust and efficient in the olefin metathesis reactions.[13] We expected that formal replacement of one of the traditional mesityl groups in the NHC ligand by a flexible benzyl group bearing a donor substituent might allow additional coordination of the latter to the metal.

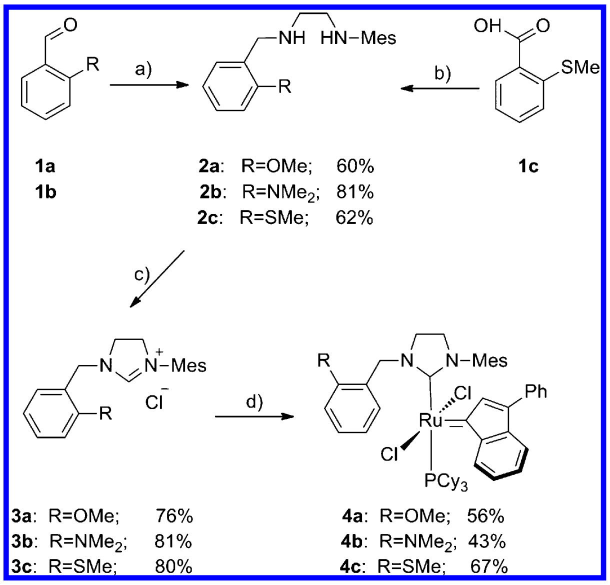
The synthesis of the new imidazolinium salts **3a**,**b** was achieved by the condensation of *N*-(2,4,6-trimethylphenyl)-1,2-diaminoethane and the respective easily accessible aldehydes. The resulting diimines were reduced in situ to diamines **2a**,**b**, which were further cyclized with triethyl orthoformate to the corresponding NHC salts.[14] Synthesis of **3c** was accomplished through the reaction of the S-methylated thiosalicylic acid **1c** with *N*-(2,4,6-trimethylphenyl)-1,2-diaminoethane using 1,1′-carbonyldiimidazole (CDI). With these NHC salts in hand, we prepared ruthenium complexes **4a**−**c**. Following the conventional route by the reaction of in situ generated carbene with commercially available dichloro(3-phenyl-1*H*-inden-1-ylidene)-bis(tricyclohexylphosphine)ruthenium(II) (**M1**), these complexes were obtained in moderate yields. Purification by silica gel chromatography and further recrystallization from a DCM/*n*-pentane mixture afforded carmine, air-stable solids (Scheme 1).

Catalytic activities of prepared precatalysts were investigated in RCM reactions with diethyl diallylmalonate (**5**) (Scheme 2, Figure 1). As a reference, commercially available Umicore **M2** precatalyst was used.

In this reaction precatalysts **4a**,**b** both show high metathetic activity and significantly outperform commercial precatalyst **M2**. Encouraged by these promising results, we decided to investigate the performance of the new precatalysts on a wider range of substrates (Table 1). In general, the reactions were monitored by GC until full consumption of the substrate. Ring-closing ene-yne metathesis (RCEYM) was investigated with the standard test substrate **7**. In this reaction precatalyst **4a** was slightly slower than its analogue **4b**; however, both showed a shorter reaction time for the conversion to the final product **8**

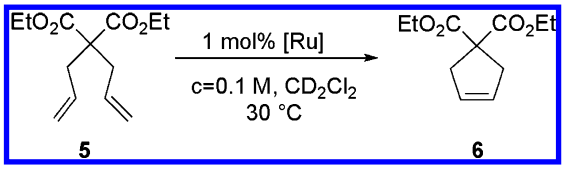
Received: August 13, 2012

Scheme 1. Synthetic Pathways for the Synthesis of the New Indenylidene Precatalysts[a]



[a]Legend: (a) *N*-(2,4,6-trimethylphenyl)-1,2-diaminoethane, HCOOH cat., MeOH, room temperature, 24 h then $NaBH_4$, MeOH, room temperature, 12 h; (b) 1,1′-carbonyldiimidazole (CDI), MeCN, 0 °C to room temperature, 3 h then *N*-(2,4,6-trimethylphenyl)-1,2-diaminoethane, 0 °C to room temperature, reflux 2 h next $LiAlH_4$, THF, 0 °C to reflux, 4 h; (c) $(OEt)_3CH$, HCl, 100 °C, 4 h; (d) $C_5H_{11}OK$, **M1**, toluene, room temperature to 65 °C, 0.5 h.

Scheme 2. RCM of Diethyl Diallylmalonate (5)



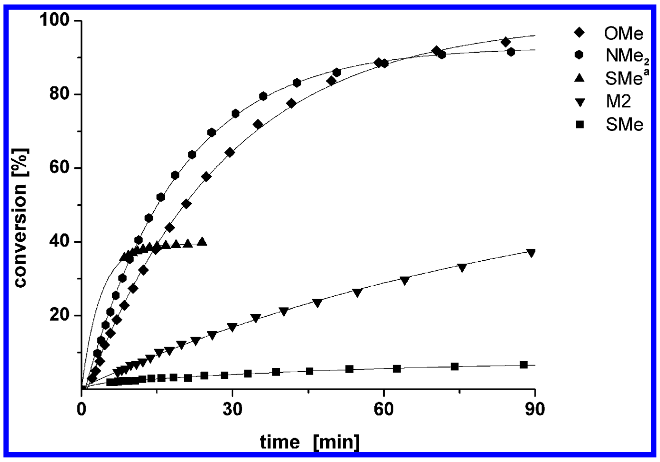


Figure 1. RCM conversion of diethyl diallylmalonate (5). Legend: (a) 60 °C in $C_6D_5CD_3$.

in comparison to the **M2** precatalyst. In general, amide-based substrate **9** required higher temperature for the full conversion to the product **10** in a reasonable time. Both new precatalysts **4a,b** in cross-metathesis of **11** and **12** showed *E* selectivity comparable to that of the **M2** precatalyst. Cyclization to the seven-membered ring in product **15** demonstrated high activity of the new complexes **4a,b**, as full conversion was achieved just in 3 h, in comparison to 8 h for the **M2** precatalyst. In principle, the new precatalysts with unsymmetrical NHC ligands **2a,b** outperform the **M2** precatalyst in the majority of tested reactions.

Blechert et al. showed that diastereoselective ring-rearrangement metathesis (DRRM) of protected cyclopentene **16** with Grubbs first-generation and Hoveyda−Grubbs first-generation precatalysts does not proceed in a diastereoselective manner, while their second-generation analogues gave poor diastereoselectivities (trans:cis d.r. = 2:1) (Scheme 3).[15] We expected that precatalysts bearing unsymmetrical NHC moieties would increase the diastereoselectivity. Therefore, we applied precatalysts **4a,b**, as well as commercially available precatalyst **M2**, to this particular reaction. Interestingly, **M2** precatalyst gave the same result (trans:cis d.r. = 2:1) as Grubbs and Hoveyda−Grubbs second-generation precatalysts. In contrast, application of the new precatalysts **4a,b** resulted in much higher diastereoselectivity for the substrate **16** (trans:cis d.r. = 4.7:1 for **4a** and trans:cis d.r. = 4.5:1 for **4b**; see Table 2). Precatalyst **4a** showed, to the best of our knowledge, the highest diastereoselectivity for the substrate **16** ever reported.[15]

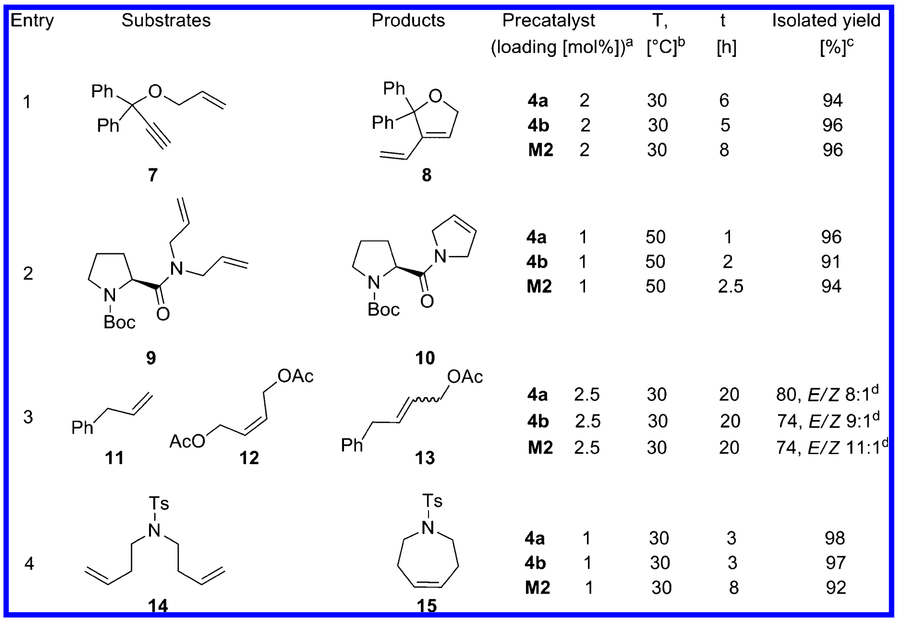
In comparison with the symmetrical ligand 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene (SIMes), the newly designed unsymmetrical NHC ligands certainly change the reactivity of indenylidene precatalysts **4a,b**. In order to find out whether the benzyl group interacts through the heteroatom with the ruthenium core, a single crystal of precatalyst **4a** was grown and analyzed by X-ray diffraction (Figure 2).

Single crystals of **4a** grown from a DCM/*n*-pentane mixture crystallize in the orthorhombic $P2_12_12_1$ space group symmetry (for the experimental details see the Supporting Information). There is one molecule of precatalyst in the asymmetric unit with the five-coordinated ruthenium atom. The **4a** molecules pack into compact layers in the crystal lattice, with the methoxy groups directed between the layers (see Figure S2 in the Supporting Information). The bond length between the ruthenium atom Ru(1) and the carbon atom C(1) is 2.059(4) Å, whereas the Ru(1)−P(1) bond is equal to 2.472(1) Å. The trigonal-bipyramidal geometry around the Ru(1) atom is distorted, with the C(1)−Ru(1)−P(1) angle equal to 160.0(1)° and the Cl(1)−Ru(1)−Cl(2) angle equal to 159.37(4)°. This led to the reduction of the space between the cyclohexyl ring of the tricyclohexylphosphine ligand and the phenyl ring of the NHC ligand. The other important structural parameters are the following: the Ru(1)−C(22) bond is 1.863(4) Å, whereas the bond lengths to the chloride atoms are 2.409(1) and 2.401(1) Å for Cl(1) and Cl(2), respectively. A high degree of freedom for the benzyl group and steric repulsion from the tricyclohexylphosphine ligand and chlorine atom are probably responsible for the lack of interaction between the oxygen atom and the metal center, at least in the solid state.

However, during the catalytic cycle after dissociation of the tricyclohexylphosphine it is feasible that such coordination takes place and influences the stability of the 14-electron catalyst.[16]

Interestingly, the sulfur-containing complex **4c** exhibits very low activity in comparison to **4a,b** in olefin metathesis of DEDAM (**5**), showing just 7% conversion after 1.5 h at 30 °C in DCM. Even after the reaction time was extended to 24 h, precatalyst **4c** showed practically no change in the conversion. However, in the same reaction this precatalyst resuscitated in

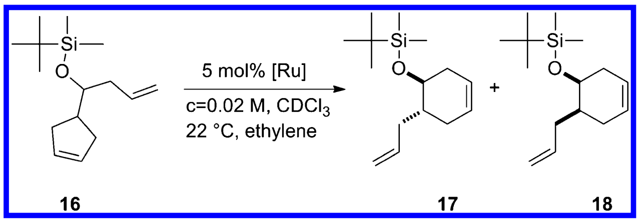
Table 1. Preparative RCM, CM, and Ene-Yne Reactions



Entry	Substrates	Products	Precatalyst (loading [mol%])^a	T, [°C]^b	t [h]	Isolated yield [%]^c
1	**7**	**8**	**4a** 2	30	6	94
			4b 2	30	5	96
			M2 2	30	8	96
2	**9**	**10**	**4a** 1	50	1	96
			4b 1	50	2	91
			M2 1	50	2.5	94
3	**11** **12**	**13**	**4a** 2.5	30	20	80, *E*/*Z* 8:1^d
			4b 2.5	30	20	74, *E*/*Z* 9:1^d
			M2 2.5	30	20	74, *E*/*Z* 11:1^d
4	**14**	**15**	**4a** 1	30	3	98
			4b 1	30	3	97
			M2 1	30	8	92

[a] 0.1 M in CH_2Cl_2 (commercial grade HPLC). [b] Reactions were performed in toluene (commercial grade HPLC) in air at 50 °C. [c] Isolated yields after flash chromatography. [d] *E*:*Z* ratio was determined by ^1H NMR spectroscopy.

Scheme 3. DRRM of Cyclopentene (16)



16 **17** **18**

Table 2. Diastereoselective Ring-Rearrangement Metathesis with Different Precatalysts

precatalyst	conversion (%)^a	trans:cis^a
Gru I, Hov I^b	95	1:1
Gru II, Hov II^b	95	2:1
M2	>95	2:1
4a	>95	4.7:1
4b	>95	4.5:1

[a] Determined by ^1H NMR spectroscopy [b] Results reported by Blechert et al.[15]

toluene at 60 °C, showing 40% conversion after 25 min (Figure 1). Recently, Lemcoff studied in detail Ru−S^{II} chelation in a number of ruthenium benzylidene complexes containing thioalkyl ligands. In all cases these S-chelated complexes exhibited strongly decreased activity in metathesis (latent precatalysts).[17] Also in the case of a thio-analogue of *trans*-dichloro Hoveyda precatalyst obtained by us, very low catalytic potency was observed.[18] Therefore, we suppose that, at least in solution, there must be some interaction between the Lewis basic group in the ortho position in the benzylic arm of the NHC ligand and the ruthenium center (Scheme 4) that influences the catalyst reactivity profile. Unfortunately, despite many attempts, we were unable to grow single crystals of good quality.

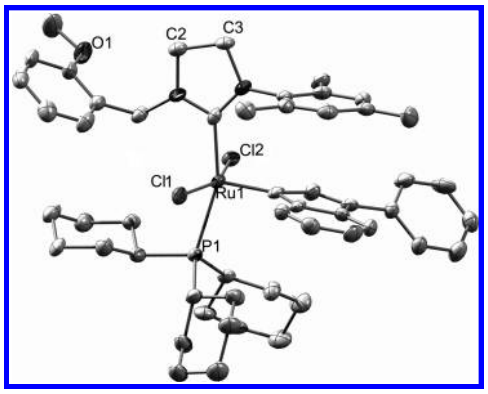
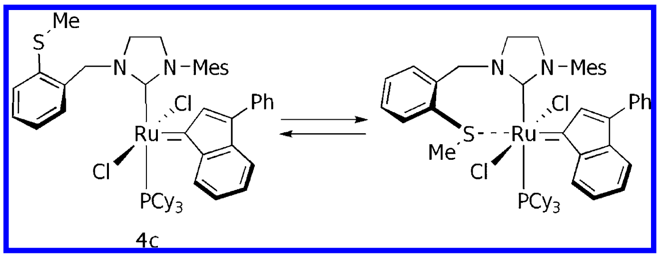


Figure 2. ORTEP representation of complex **4a**. Hydrogen atoms have been omitted for clarity. Thermal ellipsoids are shown at the 50% probability level.

Scheme 4. Possible Interaction between NHC and Ru Center of 4c in Solution



In conclusion, three new unsymmetrical NHCs have been synthesized in a convenient fashion. Three indenylidene precatalysts with those NHC ligands were prepared, and their catalytic activities have been comparatively studied for formation of a disubstituted double bond in the RCM reaction with diethyl diallylmalonate (**5**). Two complexes, containing OMe (**4a**) and NMe_2 (**4b**) substituents in the NHC ligands, were found to outperform commercially available catalyst **M2**. This trend was retained also in other RCM and RCEYM reactions performed *in air in commercial grade solvents*. Complex

4c, containing the SMe substituent, showed in contrast practically no reactivity in the benchmark reaction of **5**. To better understand the structure−reactivity relationship associated with unsymmetrical benzyl-substituted NHC ligands, the synthesis of other precatalysts and their studies will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We wish to thank the Foundation for Polish Science (TEAM Programme cofinanced by the EU European Regional Development Fund, Operational Program Innovative Economy 2007-2013. O.A. thanks Dr. M. Barbasiewicz, Dr. P. Horeglad, and Dr. W. Kośnik for fruitful discussions. O.A. is also grateful to Dr. R. Loska for the initial work.

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