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A highly efficient olefin metathesis initiator: improved synthesis and reactivity studies

Aideen M. Dunne, Stefan Mix and Siegfried Blechert*

Institut für Chemie, Technische Universität Berlin, Strasse des 17. Juni 135, 10623 Berlin, Germany

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Abstract—The synthesis of ligand **8**, required for the preparation of catalyst **4c** has been optimised. Ligand exchange studies indicate that biphenyl-based alkylidene **4c** initiates considerably faster than its unsubstituted analogue **4a**. The performance of **4c** in ring-opening cross metathesis reactions involving substrates containing unprotected chelating atoms is also reported. © 2003 Elsevier Science Ltd. All rights reserved.

The olefin metathesis reaction is one of the most synthetically useful carbon–carbon bond forming reactions.[1] This is largely due to the discovery of active, well-defined ruthenium alkylidenes such as **1**–**4** (Fig. 1), which combine high catalytic activity with impressive functional group tolerance.[2]

The exchange of one phosphine ligand for a *N*-heterocyclic carbene (NHC) moiety (**2**, **3** and **4**) leads to 'second generation' alkylidenes possessing improved activity relative to the parent Grubbs' catalyst **1**, without an accompanying loss in stability. The chromatography-stable catalyst **4a** initiates more slowly than the phosphine-based **3**, however its use can be advantageous in certain situations, particularly in metathesis reactions involving electron-deficient olefins.[1g,3] Our group has modified the isopropoxy benzylidene component to give analogues of **4a** (**4b** and **4c**) which initiate faster than benchmark catalyst **3**, while retaining the air- and moisture insensitivity characteristic of NHC-based catalysts.[2h,i] Of particular interest is biphenyl derivative **4c**, which was shown to exhibit impressive activity in ring-closing metathesis (RCM), cross metathesis (CM), ring-opening cross metathesis (ROM-CM) and ring-opening metathesis polymerisation (ROMP) reactions.[2i]

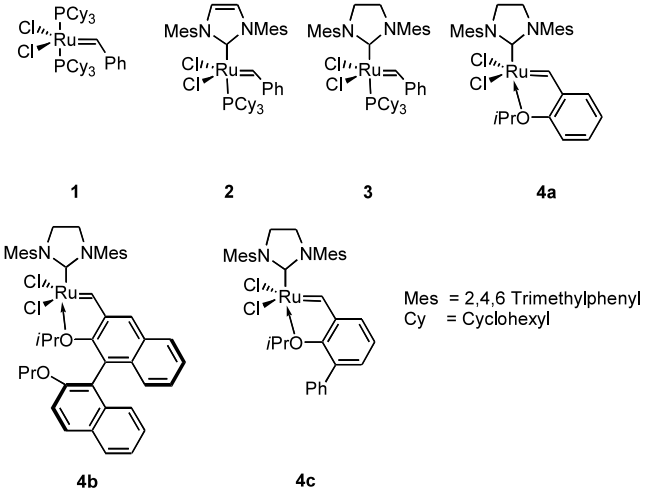

Figure 1. Olefin metathesis catalysts.

To explore the synthetic potential of **4c** further, significant amounts of catalyst were required. The original synthetic route, while suitable for small scale laboratory syntheses, was not practical for larger scale operations and was heavily reliant on column chromatography purification steps. We were thus encouraged to develop a straightforward and convenient method ideal for preparing this ligand efficiently on a large scale, using inexpensive starting materials but without using expensive and time-consuming separating techniques. With this in mind, we first attempted to carry out the alkylation of 2-hydroxybiphenyl with paraformaldehyde using the literature procedure.[4] In our hands, this reaction failed to give the desired products. We then turned our attention toward more traditional methods (Scheme 1). The oxidation of the sodium salt of 2-hydroxybiphenyl (**5**), under Kolbe–Schmitt conditions, lead to the formation, on acidic work-up, of the corresponding carboxylic acid (40%) with recovery of 2-

* Corresponding author. Tel.: +49-30-314-22255; fax: +49-30-314-23619; e-mail: blechert@chem.tu-berlin.de

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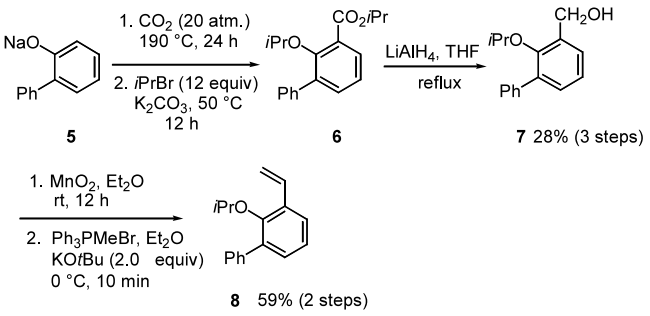
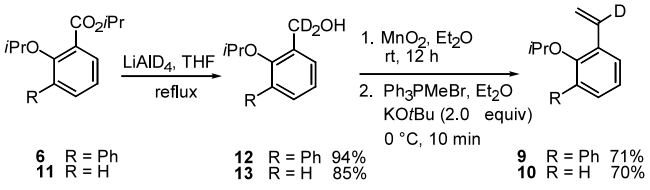


Scheme 1. Synthesis of ligand **8**.

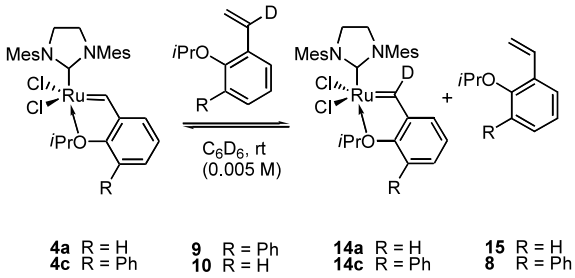
hydroxy biphenyl.[5] The crude reaction mixture was quantitatively alkylated with excess isopropylbromide, which allows the formation of the isopropylether moiety with concurrent esterification of the carboxylate group. This is desirable, as the direct reduction of the ester **6** rather than the precursor acid is thus facilitated. At this stage the crude product was purified by distillation (twice) to furnish alcohol **7**. The corresponding benzaldehyde derivative was obtained after MnO_2-oxidation of **7**, and could also be purified by distillation. Subsequent Wittig olefination and filtration of the crude product through a short silica-gel column gave styrene **8** in good yield (Scheme 1) and in multi-gram quantities. Catalyst **4c** was then prepared using standard techniques.[2i]

With more workable quantities of **4c** in hand, we wanted to estimate the relative initiation efficiency of **4a** and **4c**. Since direct observation of the intermediates in metathesis reactions by ^1H NMR spectroscopy is often difficult due to their low concentration in solution, it was decided to monitor the rates of exchange of added isopropoxystyrenes with catalysts **4a**,**c** in solution. This necessitated the synthesis of ligands **9** and **10**, which are deuterated α- to the aromatic ring (Scheme 2).

The deuterium substituents were conveniently introduced via reduction of **6** and **11** with lithium aluminium deuteride. A subsequent oxidation/olefination sequence then gave the required ligands in good overall yields. Compounds **9** and **10** were reacted in equimolar quantities with **4c** and **4a** respectively in C_6D_6.[6] As the catalyst initiates the deuterated ligands are incorporated into the alkylidene over time, as indicated by the disappearance of the alkylidene signal (δ = ca. 16.6 ppm) and appearance of signals associated with the corresponding non-deuterated styrenes (**15** and **8**) (Scheme 3). Thus the relative initiation efficiency of **4a** and **4c** can be assessed (Table 1).



Scheme 2. Synthesis of deuterated ligands **9** and **10**.



Scheme 3. Ligand exchange experiments.

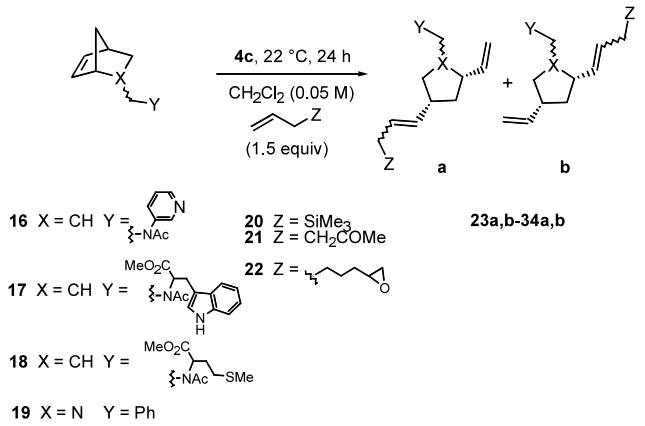
Table 1. Ligand exchange conversions via Scheme 3

Entry	Reaction	Time	Conversion[a] (%)
1	**4a**→**14a**	3 h	15
2	**4a**→**14a**	21 h	41
3	**4a**→**14a**	52 h	45[b]
4	**4b**→**14b**	19 min	33
5	**4b**→**14b**	39 min	41
6	**4b**→**14b**	137 min	53[b]

[a] Determined by NMR.
[b] Equilibrium reached.

Biphenyl-based catalyst **4c** underwent much faster exchange with **9** than **4a** did with **10**. Since the steric and electronic effects of *meta*-phenyl group on the benzylidene moiety are negligible, it is clear that in the case of **4c**, the energy barrier associated with spontaneous initiation at room temperature (i.e. dissociation of the Ru–O bond)[7] is considerably lower than that of **4a**. This can be reasonably attributed to a weakening of the chelation bond of **4c** as a result of steric crowding by the adjacent phenyl substituent. Since the formation of stilbenes, which would require the intermediacy of a methylidene rather than a benzylidene intermediate, was not observed on the time-scale of the experiments, these results allow some insights to be obtained concerning the relative ability of **4a** and **4c** to dissociate their chelating isopropoxyether ligands.

We were also interested in testing the ability of the fast initiator **4c** to promote the metathesis of traditionally challenging olefin substrates. It is known that unprotected amines and sulphides[8] are generally poor substrates in olefin metathesis reactions due to their tendency to coordinate to the ruthenium centre, thus trapping the catalyst in an unreactive form. However, we were pleased to find that ROM-CM reactions[9] between flexible and readily prepared norbornene and azanorbornene derivatives bearing either unprotected Lewis-basic nitrogen or sulphur atoms (**16**–**19**) and allyltrimethylsilane (**22**) proceeded with uniformly high efficiency (Scheme 4, Table 2). Pyridine, indole, unhindered sulphide and tertiary amine substituents were all found to be compatible with **4c** in these reactions, with a maximum of 0.5 mol% of initiator required for quantitative conversion of **16**–**19**. The products from these reactions were formed as an expected mixture of regioisomers,[10,11] however, no attempt at separation



Scheme 4. ROM-CM promoted by **4c**.

Table 2. Results of ROM-CM experiments

Substrate	CM Partner	Product	**4c** (mol%)	Yield (%)[a]
16	**20**	**23a,b**	0.3	72
17	**20**	**24a,b**	0.5	96
18	**20**	**25a,b**	0.3	90
19	**20**	**26a,b**	0.4	82
16	**21**	**27a,b**	3	39
17	**21**	**28a,b**	1	46
18	**21**	**29a,b**	1	50
19	**21**	**30a,b**	3	39
16	**22**	**31a,b**	1	55
17	**22**	**32a,b**	0.5	72
18	**22**	**33a,b**	0.5	68
19	**22**	**34a,b**	1	46

[a] Refers to isolated yields after chromatography.

was made, as these experiments were designed only to test the functional group tolerance of **4c** in ROM-CM processes. Less sterically encumbered CM partners **21** and **22** were not as effective as **20**; isolated yields of cross products were reduced due to the ability of **27a,b**–**34a,b** to participate in metathesis dimerisation and oligimerisation (as opposed to selective CM) processes under the reaction conditions.

Nevertheless, it is apparent that phosphine-free catalyst **4c** possesses functional group tolerance towards Lewis-basic potentially chelating functionality in ROM-CM reactions. In summary, we have developed an efficient and practical synthetic route to ligand **8**, which allows catalyst **4c** to be readily prepared in reasonable quantities. Reactivity studies have shown that despite displaying relatively high rates of exchange with deuterated ligand **9**, **4c** is a robust and synthetically useful catalyst for the ROM-CM of substrates bearing Lewis-basic chelating atoms.

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5. Due to their similar pK_a values, repeated attempts to separate **5** and its corresponding acid non-chromatographically were unsuccessful.
6. Use of CD_2Cl_2 resulted in significant catalyst decomposition. In C_6D_6, catalyst degradation in the absence of added styrene was monitored and found to be insignificant on the time-scale of the experiments.
7. The steric effect which promotes ligand dissociation would also be expected to hinder the catalyst deactivating reassociation back reaction. For a discussion of the mechanism of olefin metathesis catalysed by **3**, see: Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.
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10. All products gave satisfactory analytical data.
11. Sample ROM-CM procedure: To a stirred solution of **16** (0.30 mmol) and allyltrimethylsilane (0.45 mmol) in CH_2Cl_2 (6 mL) under N_2 was added **4c** (0.0009 mmol). The solution was stirred at rt for 24 h and the solvent removed in vacuo. The residue was purified by column chromatography to give **20** (0.22 mmol, 72%) as a light yellow oil.