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Ortho- and Para-Substituted Hoveyda−Grubbs Carbenes. An Improved Synthesis of Highly Efficient Metathesis Initiators[†]

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Abstract: A novel highly efficient and general route to various 3- and 5-substituted 2-alkoxystyrenes, required for the preparation of Hoveyda−Grubbs catalysts, is described.

Over the past few years, the olefin metathesis has been applied with increased frequency in organic chemistry. The tremendous success of this transformation is largely due to discovery of active, well-defined first-generation ($(\mathrm{PCy_3})_2\mathrm{Cl_2Ru{=}CHPh}$, **1**) and second-generation (**2**) ruthenium alkylidene complexes, which combine high catalytic activity with almost ideal functional group tolerance.[1] The chromatography-stable phosphane-free complex **3**, described by Hoveyda et al.,[2−4] initiates more slowly than the highly active Grubbs' benzylidene **2**.[5] Recently, we have described the similarly stable and reusable catalyst **4**, prepared from an inexpensive α-asarone.[6] Despite lower initiation activities, the use of catalysts **3** and **4** was proved to be advantageous in many cases, particularly in reactions of electron-deficient olefins.[7]

Recently, Wakamatsu and Blechert[8] have shown that the complex **5**, substituted ortho to the chelating isopropoxy ligand, initiates dramatically faster than the parent catalyst **3**, while retaining the excellent air and moisture stability. Our group has recently introduced the stable 5-nitro-substituted analogue **6**, which was shown to exhibit impressive activity in ring-closing (RCM), cross (CM), and enyne metathesis.[10] As a result, this highly active catalyst has found a successful application in target-oriented syntheses.[10c−e] The higher activity of **5** may be the result of faster initiation of the catalytic cycle as a result of a more facile release of the sterically demanding phenyl-substituted benzylidene.[9,10] Similarly, the electron-withdrawing NO_2 para to the ligating *i*-PrO in **6** would weaken O → Ru chelation and facilitate faster initiation of the catalytic cycle.[10]

To explore the synthetic potential of **5** and **6** and to study structure−activity relationships in Hoveyda-type complexes **5**−**8** (Scheme 2), a simple and general synthetic route to various 3- and 5-substituted 2-alkoxystyrenes was required.[11] The described preparation of 5-nitro-2-isopropoxystyrene, a substrate for **6**, consists of alkylation of the commercially available 2-hydroxy-5-nitrobenzaldehyde followed by Wittig reaction (49% overall yield).[10] The latter transformation is not practical for larger scale operations as it requires column chromatography to remove the triphenyl phosphine oxide

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(6) (a) Grela, K.; Kim, M. *Eur. J. Org. Chem.* **2003**, 963−966. (b) For an unique activity of a catalyst derived from **4** in living polymerization of diynes, see: Krause, J. O.; Zarka, M. T.; Anders, U.; Weberskirch, R.; Nuyken, O.; Buchmeiser, M. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 5965−5969.

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(8) (a) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403−2405. (b) For an improved synthesis of **5**, see: Dunne, A. M.; Mix, S.; Blechert, S. *Tetrahedron Lett.* **2003**, *44*, 2733−2736.

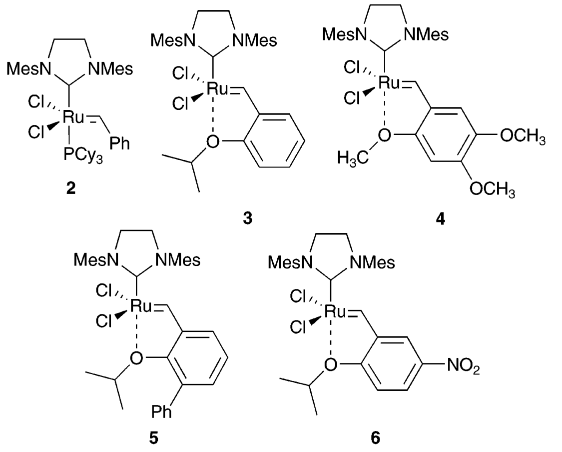
(9) Extensive studies described in ref 8 suggest that a steric bulk adjacent to the chelating isopropoxy moiety is the crucial factor securing the unusually high activity of **5**.

(10) (a) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038−4040. (b) Harutyunyan, S.; Michrowska, A.; Grela, K. A Highly Active Ruthenium (Pre)catalyst for Metathesis Reactions. In *Catalysts for Fine Chemical Synthesis*; Roberts, S., Ed.; Wiley-Interscience: New York, 2004; Vol. 3, in press. For applications of **6** in target-oriented synthesis, see the following. (c) (−)-Securinine: Honda, T.; Namiki, H.; Kaneda, K.; Mizutani, H. *Org. Lett.* **2004**, *6*, 87−89. (d) (+)-Viroallosecurinine: Honda, T.; Namiki, H.; Watanabe, M.; Mizutani, H. *Tetrahedron Lett.* **2004**, *45*, 5211−5213. (e) An artificial photosynthesis model: Ostrowski, S.; Mikus, A. *Mol. Diversity* **2003**, *6*, 315−321.

(11) (a) For a recent application of Ru catalysts derived from 5-nitro-2-isopropoxystyrene in polymer chemistry, see: Krause, J. O.; Nuyken, O.; Buchmeiser, M. R. *Chem. Eur. J.* **2004**, *10*, 2029−2035. (b) Recently, the concept of steric and electronic activation has been utilized by Hoveyda et al. in a preparation of chiral ruthenium complexes for asymmetric metathesis: Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502−12508.

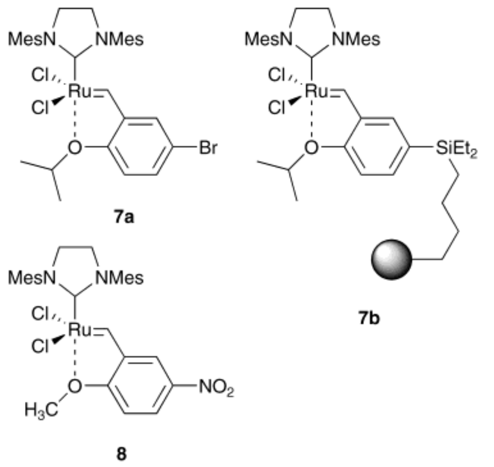
10.1021/jo049222w CCC: $27.50

SCHEME 1. Family of Modern Ruthenium Catalysts for Alkene Metathesis[a]



[a] Cy = cyclohexyl; Mes = 2,4,6-trimethyl phenyl

SCHEME 2. Selected Other Ortho- and Para-Substituted Hoveyda−Grubbs Carbenes

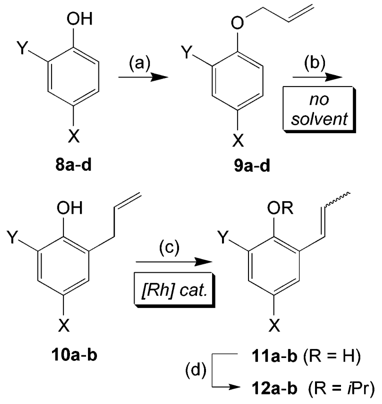


byproduct. Similarly, the optimized preparation of a starting material for **5** consists of five steps, starting from 2-hydroxybiphenylsodium salt (Kolbe−Schmitt reaction, alkylation with 12 equiv of *i*-PrBr, LAH reduction, MnO_2 oxidation, and Wittig olefination) and gives the required 2-isopropoxy-3-phenylstyrene with 16% overall yield.[8b] Therefore, we were encouraged to develop a more step- and atom-economic method that minimizes the use of large amounts of solvents and expensive reagents.

Herewith, we present a general route to various 3- and 5-substituted Hoveyda-type complexes **3**−**8**, including the highly reactive **5** and **6**, which rely on solvent-free Claisen rearrangement and catalytic C−C double bond isomerization as key steps.[12]

Our synthesis of **5**[8] begins from inexpensive 2-hydroxybiphenyl **8a**, which is readily allylated using allyl bromide and solid K_2CO_3 to give the aryl ether **9a** in 93% yield (Scheme 3). The crude product **9a** was then subjected to a rearrangement.[13] The Claisen rearrangement was achieved by heating neat **9a** at 190−195 °C. The reaction proceeded smoothly to give **10a** in 86% yield.

SCHEME 3. Preparation of Catalysts 5 and 6 Precursors[a]



		Yield (%)			
X	Y	**9**	**10**	**11** (*E*/*Z*)	**12**
a H	Ph	93	86	96 (8.8/1)	88
b NO_2	H	95	57	98 (12/1)	77

[a] Isolated yields. Reagents: (a) Cs_2CO_3 (cat.), K_2CO_3, allyl bromide, DMF, 40 °C, 1 day or NaOH, K_2CO_3, allyl bromide, acetone−water, 45 °C, 1 day; (b) 195 °C, 6 h; (c) $RhCl_3·3H_2O$ (cat.), *p*-TsOH·H_2O (cat.), 90% aq EtOH, reflux, 5 h; (d) K_2CO_3, Cs_2CO_3 (cat.), *i*-PrI, DMF, 40 °C, 1−2 days.

The isomerization of **10a** to **11a** was then tested. From many isomerization protocols known,[14] the reaction catalyzed by 3 mol % rhodium trichloride/*p*-TsOH·H_2O in 90% aqueous EtOH gave the best results in terms of both selectivity and yield.[15] Finally, the alkylation of **11a** was carried out with *i*-PrI in DMF, using K_2CO_3 and a catalytic amount of Cs_2CO_3, yielding the catalyst **5** precursor **12a** in 88% yield after a final chromatographic purification (Scheme 3). The styrene **12b**, a precursor for the highly active NO_2-substituted catalyst[10] **6** can be obtained with similar efficiency using the same protocol.

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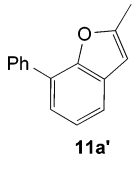
(12) See Supporting Information for experimental details.

(13) (a) For a review on Claisen rearrangement, see: Rhoadas, S. J.; Raulis, N. R. *Org. React.* **1975**, *22*, 1−252. For a similar Claisen rearrangement−isomerization protocol of phenol allyl ethers applied in total syntheses, see: (b) Baxendale, I. R.; Lee, A.-L.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1850−1857. (c) Nguyen Van, T.; Debenedetti, S.; De Kimpe, N. *Tetrahedron Lett.* **2003**, *44*, 4199−4201. (d) De Koning, C. B.; Green, I. R.; Michael, J. P.; Oliveira, J. R. *Tetrahedron* **2001**, *57*, 9623−9634.

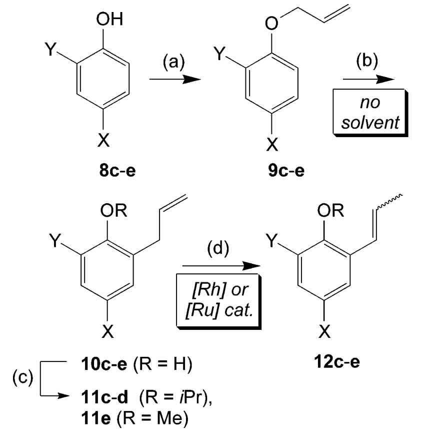
(14) Several homogeneous and supported catalysts for a C−C double bond isomerization are known, including: (a) $RhCl_3·nH_2O$ and polystyrene-supported $RhCl_3$: Setty-Fichman, M.; Blum. J.; Sasson, Y. *Tetrahedron Lett.* **1994**, *35*, 781−784. (b) Felkin's iridium catalyst: Baudry, D.; Ephritikhine, M.; Felkin, H. *J. Chem. Soc., Chem. Commun.* **1978**, 694−695. (c) Polymer-supported: Wilkinson's catalyst, $[(COD)IrCl]_2$ and 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl perhydro-1,3,2-diazaphosphorine (PS-BEMP); see ref 13a. (d) RuClH(CO)-$(PPh_3)_3$: Krompiec, S.; Kuznik, N.; Bieg, T.; Adamus, B.; Majnusz, J.; Grymel, M. *Polish J. Chem.* **2000**, *74*, 1197−1200. Krompiec, S.; Pigulla, M.; Szczepankiewicz, W.; Bieg, T.; Kuznik, N.; Leszczynska-Sejda, K.; Kubicki, M.; Borowiak, T. *Tetrahedron Lett.* **2001**, *42*, 7095−7098. (e) For recent examples of aryl-allyls isomerization using *t*-BuOK, see: ref 13c,d. (f) For a $RuClH(CO)(PPh_3)_3$ isomerization of structurally related 2-isopropoxyallylbenzenes, see: van Otterlo, W. A. L.; Pathak, R.; de Koning, C. B. *Synlett* **2003**, 1859−1861.

(15) In addition to the expected **11a** (96% of yield) a small amount of the byproduct **11a′** (4% of yield) has been obtained.



11a′

SCHEME 4. Preparation of Catalysts 3, 7a, and 8 Precursors[a]



	X	Y	9	Yield (%)		
				10	11	12 (*E*/*Z*)
c	Br	H	95	71	89	92 (15/1)
d	H	H	–	–[b]	93	71[c] (14.3/1)
e	NO_2	H	–	–[d]	96	95 (21/1)

[a] Isolated yields. Reagents: (a) K_2CO_3, Cs_2CO_3 (cat.), allyl bromide, DMF, 65−70 °C, 5 h or NaOH, K_2CO_3, allyl bromide, acetone−water, 45 °C, 1 day; (b) 195 °C, 6 h; (c) K_2CO_3, Cs_2CO_3 (cat.), *i*-PrI, DMF, 40 °C, 1−2 days or NaOH, K_2CO_3, *i*-PrI or Me_2SO_4, acetone−water, 45 °C, 20 h; (d) $RhCl_3 \cdot 3H_2O$ (cat.), *p*-TsOH·H_2O (cat.), 90% aq EtOH, reflux, 5 h. [b] 2-Allylphenol (**10d**) was used as received from Fluka AG. [c] Ruthenium isomerization conditions: $CH_2{=}CHOTMS$, **2** (cat.), CH_2Cl_2, 35 °C, 24 h (66%). [d] **10b** was used as a substrate.

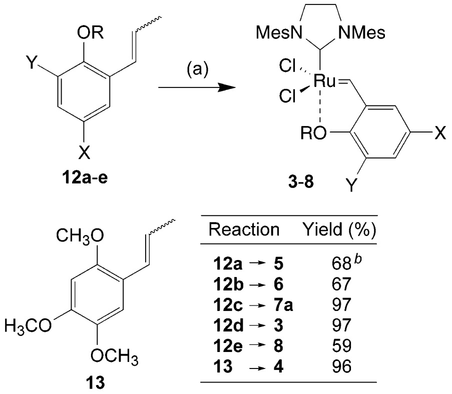
However, the electron-poor aryl-ether **9b** was substantially less prone to rearrangement (Scheme 3).[16,17]

To show the general applicability of our Claisen rearrangement−isomerization procedure, other representative styrenes **12c**−**e**, precursors for the benzylidene-modified (**7a**, **8**) and supported (**7b**)[18] catalysts, were prepared (Scheme 4). In this case, isomerizations of aryl ethers (**11c**−**e**) also proceeded smoothly, with even higher *trans* selectivity.

Nishida and co-workers recently reported that several substrates can be isomerized using a catalyst formed in situ from Grubbs' benzylidene **2** and vinyloxytrimethylsilane.[19] We have checked that this system can be used for isomerization of the 2-isopropoxy-allylbenzene **11d** (Scheme 4).[20]

Having the required precursors in hand we attempted the catalyst preparation, using the standard ligand exchange−metathesis procedure.[2b] Treatment of **12a**−**e** with **2** in CH_2Cl_2 at 40−45 °C in the presence of CuCl as a phosphane scavenger gave catalysts **3**−**8** in good to excellent yields (Scheme 5). In the case of ortho-substituted catalyst **5**, 2 equiv of styrene **12a** was required to achieve good yield. It was also observed that more electron-rich catalysts (Scheme 5, reactions **12d** → **3**, **12c** → **7a**, and **13** → **4**) can be obtained in higher yields as compared with sterically or electronically altered **5**, **6**, and **8**. Complexes **3**−**8** displayed the expected activities in a set of benchmark metathesis reactions, and their analytical data are in full agreement with those published in the literature.[2,6,8,10,18]

SCHEME 5. Preparation of Catalysts 3−6, 7a, and 8[a]



Reaction	Yield (%)
12a → **5**	68[b]
12b → **6**	67
12c → **7a**	97
12d → **3**	97
12e → **8**	59
13 → **4**	96

[a] Isolated yields. Reagents: (a) **2**, CuCl, CH_2Cl_2, 40−45 °C, 45−60 min. [b] Two equivalents of **12a** was used.

In summary, we have developed an efficient and general synthetic route, based on a solvent-free Claisen rearrangement and catalytic isomerization, which allows various catalyst precursors to be readily prepared in multigram quantities. This protocol can be used in preparation of highly active ortho- and para-substituted catalysts **5** and **6** and their chiral analogues, as well as parent Hoveyda−Grubbs carbene **3** and other systems.[11,21]

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Supporting Information Available: Full experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of **12a**−**e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] For safety reasons, Claisen rearrangement of the NO_2-bearing **9b** was carried out in a 1:1 w/w mixture with diphenyl ether, which can be then separated by a simple biphasic extraction and recycled.

[17] Claisen rearrangement of this substrate is known to give moderate yields: White, W., N.; Gwyn, D.; Schlitt, R.; Girard, C.; Fife, W. *J. Am. Chem. Soc.* **1958**, *80*, 3271−3277 (*o*-dichloro benzene, 6 h, 59%).

[18] The bromo-substituted styrene **12c** constitutes a valuable starting material for preparation of a PS-DES-supported catalyst **7b**; cf. ref 3b.

[19] Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732−4734. (b)

[20] (a) For a recent example of ruthenium isomerization catalyst formed in situ from **1**, 2-propanol, and NaOH, see: Schmidt, B. *Chem. Commun.* **2004**, 742−743. For reviews on olefin isomerization caused by ruthenium metathesis catalysts, see: (b) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865−1880. (c) Alcaide, B.; Almendros, P. *Chem. Eur. J.* **2003**, *9*, 1259−1262.

[21] (a) Recently, another example of an *o*-substituted Hoveyda-type catalyst has been described: Zaja, M.; Connon, S. J.; Dunne, A. M.; Rivard, M.; Buschmann, N.; Jiricek, J.; Blechert, S. *Tetrahedron* **2003**, *59*, 6545−6558. (b) The high activity of this catalyst has been proved: *Synlett* **2004**, 667−670.