A Practical Larger Scale Preparation of Second-Generation Hoveyda-Type Catalysts

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1. Introduction

Finding a subtle balance between the stability of the catalyst (and its insensitivity to impurities) and its high activity has been called one of the "Holy Grails" of catalysis. This is especially visible in the field of olefin metathesis: a fairly old reaction that has long remained as a laboratory curiosity without significance in advanced organic chemistry.[1] New ruthenium catalysts **1** and **2** (Figure 1), which combine high catalytic activity with fairly good stability, however, have revolutionized the field.[2−4] As a result, recent years have seen a tremendous development of research efforts in Ru catalyst design, driven by the fascinating challenge to improve the already impressive performances of the original Grubbs precatalyst **1** and **2**.

We have recently found that the 5-nitro-substituted Hoveyda-type[5] catalyst **4b** possesses a dramatically enhanced reactivity in model ring-closing (RCM), cross, (CM), and enyne metathesis.[6] Interestingly, the air and thermodynamic stability of **4b** is not reduced as compared with the parent Hoveyda−Grubbs complex **3b**.[7] As a result, **4b** has found successful applications in the synthesis of alkaloids,[8a,b] antitumor,[8c,d] antiviral,[8e,f] and antifungal agents,[8g] and a porphyrin-fullerene dyad[8h] as well as porphyrin,[8i] sulfone,[8j] and azulene-containing building blocks,[8k] chiral phosphine ligand precursors,[8l] and other ruthenium complexes.[8m]

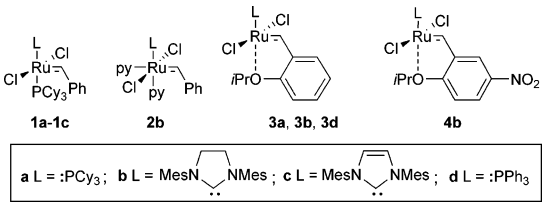

Figure 1. Selected ruthenium metathesis catalyst. *i*-Pr = isopropyl; Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl; py = 2-bromopyridine.

The first preparations of complex **4b** employed the metathesis−ligand exchange reaction between **1b**, CuCl, and 2-isopropoxy-5-nitrostyrene (**5**)[6] or 1-isopropoxy-4-nitro-2-propenylbenzene (**6**)[9] (59−83% yield; Scheme 1, route a). As syntheses from the relatively expensive **1b** would be costly on a larger scale, we later adopted a two-step, one-pot process[10] using the cheaper first-generation alkylidene **1a** as a Ru source.[7] In this procedure, solid **1a** is stirred with 4,5-dihydroimidazolium salt **7**·BF_4 in the presence of potassium *tert*-pentanolate in *n*-hexane. The in situ generated **1b** was then treated in the same flask with a solution of 2-isopropoxy-5-nitrostyrene (**5**) and CuCl, providing, after flash chromatography, complex **4b** in good yield (67−72%, Scheme 1, route b). Unfortunately, this procedure was found to be very sensitive to the quality of reagents and solvents, reaction scale, and some subtle experimental setup. As a result, our attempts to scale up of this process (>200 mg per batch) were unsuccessful and led to a drastic decrease of yield and purity of the resulting catalyst.

2. A Larger Scale Preparation of the Nitro-catalyst 4b

We were prompted to develop a new, easily scalable synthesis of **4b**, which can be performed even by less experienced chemists. We assumed that the first-generation Hoveyda catalyst **3a** is a better ruthenium source than the less stable **1a**. In a second step, a novel metathesis−exchange reaction between **3b**

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(1) Astruc, D. *New J. Chem.* **2005**, *29*, 42.

(2) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vols. 1−3.

(3) General reviews, see refs 1 and 2 and: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Schrock, R. R. *Top. Organomet. Chem.* **1998**, *1*, 31. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (e) For selected key papers on achiral and chiral molybdenum catalysts, see: Hoveyda, A. H.; Schrock, R. R. *Chem.−Eur. J.* **2001**, *7*, 945. (f) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *38*, 4555. (g) Schrock, R. R. *Pure Appl. Chem.* **1994**, *66*, 1447. (h) Murdzek, J. S.; Schrock, R. R. *Organometallics* **1987**, *6*, 1373.

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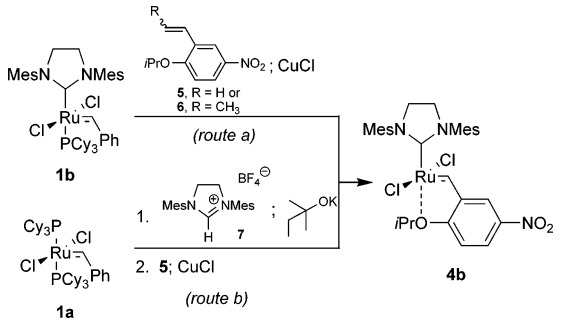
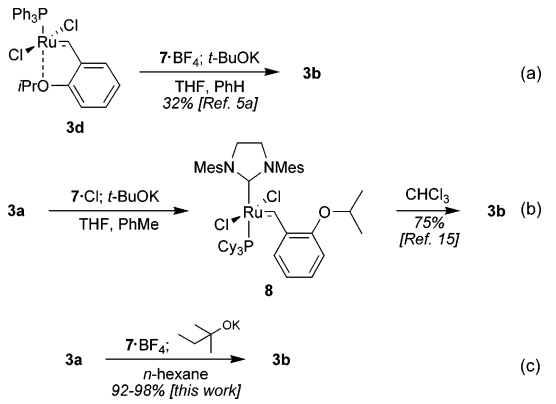
Scheme 1. Published Low-Scale Preparation of 4b



Scheme 2. Preparation of 3b from First-Generation Complexes

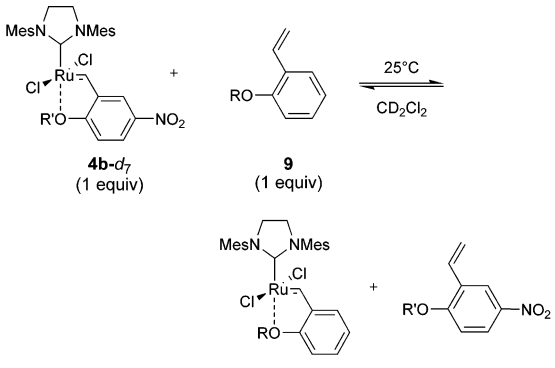


and 2-isopropoxy-5-nitrostyrene (**5**) was envisaged leading to formation of **4b**.

In the first step of our new procedure the second-generation complex **3b** is prepared from **3a** by a ligand exchange with the in situ deprotonated salt **7**·BF_4. The in situ methods for preparation of second-generation ruthenium catalysts, in which all ingredients, that is, a NHC ligand precursor, complex **1a**, and a strong base (typically *t*-BuOK),[11,12] are mixed together in an appropriate solvent (THF, benzene, toluene, or hexane), sometimes lead to undesired results, such as diminished yields and formation of significant amounts of byproducts. According to Fürstner[13] and Nolan,[14] at least one of the contaminants is a ruthenium hydride or alkoxide species, which may be responsible for various side reactions. In this context it is worth noting that a similar process using **3d** and **7**·BF_4 as starting materials has been previously described by Hoveyda et al. as being low yielding (Scheme 2a).[5a] Blechert has reported a more useful two-step preparation of **3b** from **3a** in 75% overall yield (Scheme 2b).[15] Treatment of **3a** with 1.2 equiv of **7**·Cl and 1.2 equiv of *t*-BuOK in THF/toluene at 80 °C leads first to the formation of a pink intermediate, **8**, still bearing the PCy_3 moiety. The formation of desired product **3b** was achieved by stirring isolated **8** at room temperature in $CHCl_3$ for 2 h. The final product **3b** was separated from the liberated phosphine and decomposition products by flash chromatography using CH_2Cl_2 as the eluent.[15]

After a detailed optimization, we decided to use a less polar solvent (*n*-hexane) and a more soluble base: potassium *tert*-pentanolate. Instead of $CHCl_3$, solid CuCl was selected as a more effective phosphine scavenger. These modifications, adopted in part from the excellent preparation method for **1b**,**c**, described by Nolan,[14] allowed us to develop *a high-yielding one-pot process* (Scheme 2c). In addition, the observation that ruthenium-containing, highly colored reaction byproducts are soluble in methanol allowed us to purify the crude reaction mixture by simple crystallization *without the need to use tedious chromatographic separation*. As a result, Hoveyda−Grubbs second-generation complex **3b** can be straightforwardly obtained from **3a** in a multigram scale in a high yield (92−98%, up to 15 g per batch).[16]

Scheme 3. An Equilibration Experiment[a]



time (min)	**4b**-d_7 : **3b**
0	100 : 0
20	88 : 12
30	75 : 25
40	65 : 35
50	50 : 50
120	34 : 66
1440	25 : 75
2880	18 : 82

[a] The **4b**-d_7 to **3b** proportion was calculated from integration of ^{1}H NMR benzylidene Ru=C*H* signals: **4b**-d_7 16.46 ppm; **3b** 16.56 ppm.

The next step seemed more problematic, since it requires the replacement of the good chelating 2-isopropoxybenzylidene fragment in **3b** with the less chelating 5-nitro-2-isopropoxybenzylidene ligand. A model experiment based on mixing equimolar amounts of labeled complex[17] **4b**-d_7 with 2-isopropoxystyrene **9** revealed that the equilibrium mixture contains 82% of the more stable complex **3b** (Scheme 3). This result shows that the 2-isopropoxybenzylidene ligand bonds to ruthenium ca. 7 times stronger then the 5-nitro-2-isopropoxybenzylidene one. In order to shift this equilibrium, an excess of **5** has to be used. Another problem related to this step was the observed fast homometathesis of styrene **5** to stilbene **10** (Scheme 4). Stilbene **10** cannot react further with **3b** to generate **4b**; therefore its formation diminishes the amount of **5** available for reaction, decreasing the yield. Separation of the crystalline

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(14) Jafarpour, L.; Hillier, A. C.; Nolan, S. P. *Organometallics* **2002**, *21*, 442.

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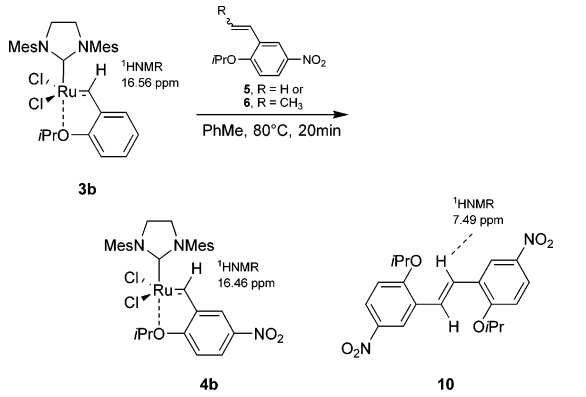
(16) The quality of the **7**·BF_4 salt used in the reaction is essential. One should make sure that this material contains no inorganic impurities and is well dried. We used a salt prepared according to Hoveyda,[5a] crystallized from 99.8% ethanol and dried under vacuum, *to obtain reproducible 98−92% yields* of **4b**. If the quality of the salt **7** is low, the reaction could not run to completion. In this case the remaining Hoveyda first-generation catalyst **3a** present after reaction has to be separated from the crude product by crystallization from a mixture of CH_2Cl_2 and methanol (1:10 v/v). After concentration to ca. one-fourth of the initial volume using a rotary evaporator green and brown crystals precipitated. These crystals were filtered off on a Büchner funnel with a glass frit and then washed with CH_3OH until only brown crystals of the Hoveyda first-generation catalyst **3a** remained on the Büchner funnel. Hoveyda second-generation catalyst **3b** remained in the solution.

(17) (a) Michrowska, A. Ph.D. Thesis, Institute of Organic Chemistry, Warsaw, 2006. (b) This complex was originally synthesized for another purpose. For the experiment shown in Figure 4, the deuterium labeling is not necessary.

Scheme 4. Preparation of 4b and Formation of Stilbene 10



stilbene byproduct is also difficult from a practical point of view. After detailed optimization it was found that the corresponding 1-isopropoxy-4-nitro-2-propenylbenzene (**6**) undergoes much slower dimerization, while it still can be used for the exchange reaction shown in Scheme 4. A 10-fold excess of **6** gives the best results, allowing conversion of ca. 80% of the Hoveyda−Grubbs catalyst **3b**.[18] The remaining unreacted **3b** and **6** can be separated and recycled.

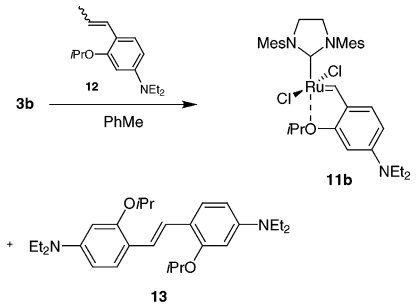
It was found that to obtain optimal conversion the reaction should be run for only a few minutes at 80 °C.[19] The crude reaction mixture after the exchange step, shown in Scheme 4, consists of the nitro-Hoveyda catalyst (**4b**), stilbene (**10**), and small amounts of unreacted Hoveyda−Grubbs second-generation catalysts (**3b**), an excess of ligand precursor (**6**), and some minor byproducts and tars.

Our goal was to avoid extensive chromatographic techniques during the isolation of product **4b**. In order to separate the resulting mixture by crystallization, a detailed cross-solubility study for all the substrates and products of this reaction was conducted (see the Supporting Information for details). As a result, we have found that nitro-catalyst **4b** can be isolated in 60% yield from the crude mixture by consecutive crystallizations from EtOAc (to remove the unreacted **3b** and **6**), from CH_2Cl_2 (to remove **10** formed in 35% yield), and finally from methanol. This sequence of crystallizations can be repeated if necessary until a product of final purity of at least 95−97% is obtained. Composition of samples after each crystallization step can be conveniently checked by ^{1}H NMR (Scheme 4).

Using the above-described procedure, we were able to obtain more than 10 g of the nitro-catalyst **4b** (97% pure according to NMR) *in a single batch*. The total yield of the pure **4b** was 55% after two steps. It is worth noting that this procedure is not sensitive to the scale of the reaction, since all the model experiments in a scale varying from 0.25 to 20 g gave similar yields of **4b**, being in the range 55−65%.

The filtrate after the crystallization from EtOAc contains the unreacted ligand **6**, small amounts of **3b** and **4b**, some amounts of stilbene **10**, and undefined products of decomposition (tars). Eventually, we become interested if it is possible to regenerate the unreacted ligand precursor **6** in order to recycle this rather expensive material. Fortunately, it was found that tars and some other byproducts can be easily separated by filtration through a short pad of silica gel eluted gravitationally with 5% → 20% v/v of ethyl acetate in cyclohexane, leading to a fraction containing mostly the regenerated **6**.[20] We found that this material can be used in preparations of the next batches of the nitro-catalysts with the same efficiency as freshly prepared **6**.

Scheme 5. Preparation of 11b[a]



3b : 12	Conversion (%)[a]	Yield 11b (%)[a]
1 : 1.1	57	28
1 : 1.5	70	51
1 : 2	76	59
1 : 3	91	70
1 : 10	n.d.	79

[a]Isolated yields of analytically pure **11b**. Conversions were calculated from ^{1}H NMR.

In a summary, starting from 19.6 g of **3b** and 69.6 g of the ligand **6**, 13.1 g of the product **4b** (60% of yield) and 21.0 g (35% of yield) of stilbene **10** were obtained without using any chromatographic techniques. In addition, by a simple filtration of the mother liquid through a short pad of silica gel it was possible to regenerate in total 36.4 g (52% of starting amount) of ligand **6** and 2.6 g (13%) of starting Hoveyda−Grubbs complex **3b** (as a mixture with **6**).[20]

3. Preparation of the Et_2N-Substituted Hoveyda Catalyst 11b

The catalyst **11b**, recently obtained in our laboratories and bearing an electron-donating Et_2N group, shows little or no activity in olefin metathesis.[21] However, in striking contrast, the in situ formed ammonium salts obtained by treatment of this complex with various Brønsted acids are of high activity.[21] As a result, **11b** was found to be a useful starting material in the preparation of some novel tunable[22a] and immobilized[22b] metathesis catalysts. Therefore, we were interested in checking if this complex can also be prepared from **3b** by a ligand exchange (Scheme 5). Since the benzylidene part of **11b** contains the electron-donating dialkylamino group, we expected that it should exhibit a much higher affinity to the ruthenium as compared with the electron-withdrawing nitro-substituted benzylidene ligand present in **4b**. Indeed, as it was found after a small-scale optimization experiment, only a 3-fold excess of the ligand precursor **12** was required to afford a high yield of **11b**. Even more fortunately, a corresponding stilbene (**13**) was formed only in minute amounts, allowing straightforward isolation of pure **11b** in good yield (70%, Scheme 5).[23]

4. Summary

In conclusion, a new two-step synthesis of the nitro-substituted Hoveyda−Grubbs olefin metathesis catalyst **4b** from

(18) The use of a smaller excess of the ligand **6** is possible, but leads to lower conversions. For example, in a test reaction with 5 equiv of **6** the isolated yield of **4b** was 45−47% instead of ca. 60% obtained with 10 equiv.

(19) The crucial parameter for a successful transformation is the time of the exchange reaction, which has to be in the range 15−25 min. Prolonged heating leads to formation of larger quantities of **10**. Under these conditions the homo-dimerization of **6** is minimized and does not exceed 35% of the starting amount of **6** used.

(20) There is no need to separate the small amounts of **3b** from this fraction, as it is also a starting material for the exchange step.

(21) Gułajski, Ł.; Michrowska, A.; Bujok, R.; Grela, K. *J. Mol. Catal. A: Chem.* **2006**, *254*, 118.

(22) (a) For a short overview of other tunable Ru catalysts, see: Grela, K.; Michrowska, A.; Bieniek, M. *Chem. Rec.* **2006**, *6*, 144. (b) Michrowska, A.; Mennecke, K.; Kunz, U.; Kirschning, A.; Grela, K. *J. Am. Chem. Soc.* **2006**, *128*, 13261.

(23) This procedure was successfully used to prepare **11b** in 0.5 g scale. Mennecke, K. Private communication.

the parent first-generation Hoveyda−Grubbs complex **3a** has been developed. This method does not require extensive use of silica gel chromatography and can be easily scaled up. Other substituted Hoveyda−Grubbs catalysts, for example the diethylamino-substituted **11b**, can also be obtained by this method.

5. Experimental Part

For detailed experimental setup and for the preparation of ligand precursors **6** and **12** via Wittig reaction see the Supporting Information. All commercially available reagents were used as received.

Large-Scale Preparation of 3b. A dry, 1 L, one-necked, round-bottomed flask was equipped with a magnetic stirring bar, a rubber septum, and an argon inlet. The flask was charged under an argon atmosphere with solid **7**·BF_4 (35.28 mmol, 13.9 g) and dry *n*-hexane (400 mL). A solution of potassium *tert*-amylate in toluene (1.7 M solution in toluene, 21.6 mL, 36.75 mmol) was added from a syringe to a well-stirred suspension, and the resulting mixture was stirred under argon at room temperature for 1 h. To the resulting slightly turbid, yellowish solution was added the solid Hoveyda−Grubbs first-generation catalyst **3a** (29.4 mmol, 17.6 g) in one portion. The flask was equipped with a reflux condenser with an argon inlet at the top, and the reaction mixture was refluxed for 2 h. After this time TLC analysis indicated complete disappearance of **3a** and a formation of a new pink spot. The contents of the flask (brown liquid) are cooled to room temperature, and a solid CuCl (51.45 mmol, 5.1 g) was added slowly in three portions. The resulting mixture was refluxed for 2 h. After this time TLC analysis indicated complete conversion of the pink spot into the green one. From this point forth, all manipulations were carried out in air. The reaction mixture was then evaporated to dryness, and the resulting dark brown-green solid was redissolved in ethyl acetate (200 mL). The solution was filtrated through a Büchner funnel with a glass frit filled with Celite and then concentrated in vacuo. The dark brown residue was then dissolved in a 1:10 v/v mixture of CH_2Cl_2 and methanol (220 mL) at ambient temperature. After concentration of this solution to ca. one-fourth of the initial volume at room temperature using a rotary evaporator green crystals were precipitated. These crystals were filtered off on a Büchner funnel with a glass frit. The green crystals were washed twice with small portions of CH_3OH (∼20 mL) and dried in vacuo to give pure catalyst **3b** (25.3 mmol,15.81 g). The filtrate after crystallization was evaporated to dryness and crystallized for the second time from CH_2Cl_2 and methanol using the same protocol, giving an additional crop of **3b** (1.7 mmol, 1.08 g). The total yield of pure Hoveyda−Grubbs second-generation catalyst **3b** was 92% (27.0 mmol, 16.9 g).

Large-Scale Preparation of 4b. A dry, one-necked, round-bottomed, 1 L flask was equipped with a magnetic stirring bar, rubber septum, and argon inlet. The flask was charged under argon with the compound **6** (0.314 mol, 69.57 g) and dry toluene (450 mL). To the resulting well-stirred solution the solid Hoveyda−Grubbs second-generation catalyst **3b** (31.28 mmol, 19.60 g) was added in one portion at 80 °C. The reaction mixture was stirred at the same temperature for 20 min. After this time TLC analysis indicated the formation of a new green spot of the product. At this point the reaction was immediately stopped by cooling the flask contents (dark green solution) in an ice-bath to room temperature. From this point forth, all manipulations were carried out in air. The reaction mixture was evaporated to dryness at room temperature on a rotary evaporator. The resulting dark green viscous oil was dissolved in cold EtOAc (200 mL), and the resulting dark green solution was cooled in a freezer (−30 °C) for 45 min. After this time the cold solution was filtered through a Büchner funnel with a glass frit.[24] The yellow-green solid collected on a filter was dissolved in refluxing CH_2Cl_2 (∼200 mL), and the resulting solution was cooled in a freezer (−30 °C) for 30 min. After this time a mixture of green and yellow crystals precipitated. These crystals were filtered off on a Büchner funnel with a glass frit and washed with cold ethyl acetate until only a yellow solid (30.69 mmol, 11.86 g, stilbene **10**) was left on the Büchner funnel. The filtrate was evaporated to dryness and then redissolved in a minimal amount of CH_2Cl_2. To this solution was added methanol in a volume 3 times greater than the volume of CH_2Cl_2 used. The solution was concentrated at room temperature using a rotary evaporator until deep green crystals precipitated, and the supernatant solution remained almost colorless (approximately half of the initial volume of solvent was evaporated). The supernatant solution was decanted to the round-bottom flask, and the green crystals were collected on a Büchner funnel with a glass frit. The green crystals were washed once with a small portion of methanol (∼30 mL) and once with a minimal amount of ethyl acetate (∼20 mL) and dried in vacuum to give the first crop of pure **4b**. The filtrate and the methanol solution from decantation were combined and evaporated to dryness. The residue was dissolved in refluxing CH_2Cl_2, and the above-described crystallization sequence was repeated to give the second crop of **4b**. The combined crops were subjected to a final precipitation from CH_2Cl_2/MeOH. The obtained green crystals were dried under vacuum. The total yield of the pure (97% according to NMR) **4b** was 60% (19.45 mmol, 13.06 g). Analytical data of **4b** are in agreement with those previously published in the literature.[6]

Preparation of 11b. A dry 50 mL Schlenk tube was equipped with a magnetic stirring bar and rubber septum. The flask was charged under argon with the compound **12** (0.60 mmol, 148 mg) and dry toluene (10 mL). To the resulting well-stirred solution was added the solid Hoveyda−Grubbs second-generation catalyst **3b** (0.20 mmol, 125 mg) in one portion at 80 °C. The reaction mixture was stirred at 80 °C for 60 min. After this time TLC analysis indicates the formation of a new brown spot. The reaction mixture was cooled to room temperature. From this point forth, all manipulations were carried out in air. The reaction mixture was concentrated in vacuo, and the resulting material was purified by column chromatography on silica. Elution with cyclohexane/EtOAc/Et_3N (4:1:0.1 v/v/v) removed **11b** as a brown band. Removal of the solvent, washing with a minimal amount of cold *n*-pentane, and drying under vacuum afforded **11b** as a dark brown microcrystalline solid (98 mg, 70%). Analytical data of **11b** are in agreement with those published in the literature.[21]

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Supporting Information Available: Cross-solubility chart of selected substrates and products and experimental details for the preparation of the reported compounds. This material is available free of charge via the Internet at htpp://pubs.acs.org.

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(24) From this filtrate up to 50% of **6** can be regenerated by silica gel filtration.