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Synthesis and RCM Reactions Using a Recyclable Grubbs−Hoveyda Metathesis Catalyst Activated by a Light Fluorous Tag

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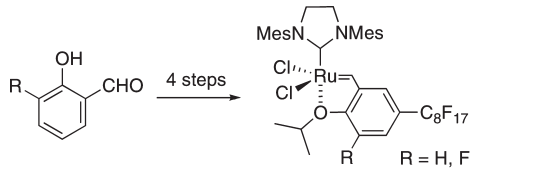

Grubbs-Hoveyda 2nd generation catalyst activated by a light-fluorous tag

A recyclable Grubbs−Hoveyda second-generation catalyst activated by a light fluorous tag was prepared. The modified light fluorous catalyst exhibited higher catalytic activity than the parent or the previously reported light fluorous variant for RCM reactions and could be routinely recovered. The light fluorous tag incorporated in the catalyst served as both an activator as well as a handle for separation and recovery with fluorous solid-phase extraction.

Olefin metathesis is among the most powerful and popular methods for carbon−carbon bond formation today,[1] and an assortment of environmentally sustainable metathesis catalysts are now available.[2] We have reported that a light fluorous Grubbs−Hoveyda second-generation metathesis catalyst **1b** is readily recovered from reaction mixtures by fluorous solid phase extraction[3] (FSPE) and can be routinely reused.[4] Although **1b** shows similar catalytic activity to the original Grubbs−Hoveyda second-generation catalyst **1a** for RCM reactions, we have been interested in improving the catalytic activity of light fluorous RCM catalysts by tuning the ligand structure.[5] Grela et al. reported that electron-withdrawing groups on the aromatic ring of the ligand increased the catalytic activity[6] of Grubbs−Hoveyda catalysts.[7] This observation has been verified by others,[8] and we planned to incorporate this design feature into our catalyst in the hopes of increasing activity. It was envisioned that a light fluorous tag directly attached to the aromatic ring of the ligand will serve as both an electron-withdrawing group and a handle for FSPE. Thus Grubbs−Hoveyda catalyst **2a** with no ethylene spacer between the aromatic ring and the fluorous tag was prepared. Concurrently catalyst **2b** was prepared based on Blechert's report that increased steric hindrance *ortho* to the isopropoxy group on the ligand enhanced reaction rates for metathesis reactions.[9] (See Figure 1).

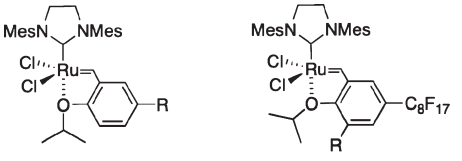

FIGURE 1. Grubbs−Hoveyda catalyst (GH 2nd) and light fluorous Grubbs−Hoveyda catalysts.

The synthesis of catalysts **2a** and **2b** is shown in Scheme 1. The direct perfluoroalkylation[10] of **3a** and **3b** under mildly basic conditions with V-70 L (2,2′-azobis-(2,4-dimethyl-4-methoxyvaleronitrile)[11] provided mono perfluoroalkylated compounds **4a**[12] and **4b** in 36 and 12% yields respectively. Isopropyl ether formation, followed by Wittig olefination provided ligand precursor **5a-b** in 78 and 75% yield respectively over the two steps. Trans-metathesis[13] with standard second-generation Grubbs catalyst provided the modified light fluorous Grubbs−Hoveyda catalyst **2a** and **2b** as dark-green crystals (**2a**: mp 182.0−183.0 °C; **2b**: mp 158.0−159.0 °C). These two catalysts required no special storage or handling and were stable to air and in solution for several months. (see ^{1}H NMR spectra in the Supporting Information).

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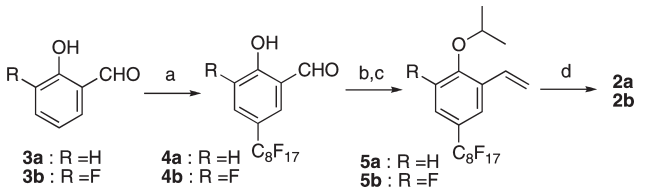
SCHEME 1. Synthesis[a] of the Modified Light Fluorous Grubbs−Hoveyda Catalyst 2a and 2b



[a]Reagents and conditions: (a) 1.0 equiv V-70 L, 1.5 equiv $C_8F_{17}I$, 8.0 equiv Cs_2CO_3, DMF, rt, **4a**: 36%, **4b**: 12%. (b) 5.0 equiv ^iPrI, 8.0 equiv K_2CO_3, DMF, 70 °C. (c) 4.0 equiv $[Ph_3PCH_3]Br$, 8.0 equiv NHMDS, THF, −78 °C, **5a**: 78%, **5b**: 75% (2 steps). (d) 1.0 equiv Grubbs second-generation catalyst, 1.1 equiv CuCl, CH_2Cl_2, rt, **2a**: 66%, **2b**: 58%.

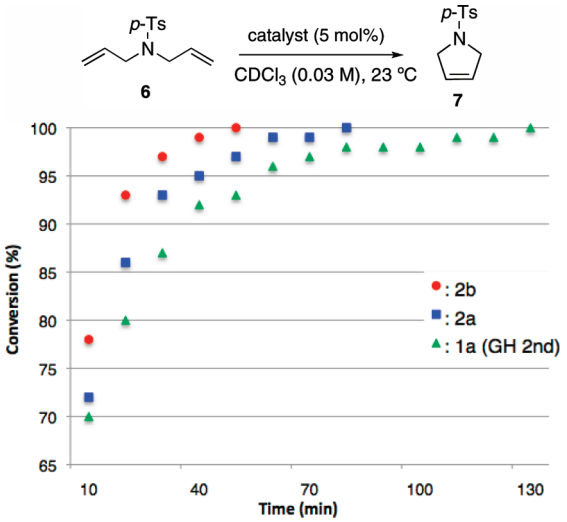


FIGURE 2. Comparison of catalytic activity for RCM of **6** in $CDCl_3$.

The relative turnover rates of catalysts **1a**, **2a**, and **2b** were determined by comparing the RCM reaction rates of these catalysts in the conversion of *N,N*-diallyl-*p*-toluenesulfonamide **6** to *N*-*p*-tosyl-2,5-dihydro-1*H*-pyrrole **7**. The reactions were conducted with $CDCl_3$ as solvent to allow for NMR monitoring of reaction aliquots. Three reactions, each with catalyst **1a**, **2a**, and **2b** respectively, were set up under identical conditions with identical catalyst loadings. At given time points the % conversion of the reaction was determined by recording ^{1}H NMR spectra of reaction mixtures and calculating the relative integrals of the corresponding methylene protons of product **7**. A plot of % conversion versus time is shown in Figure 2. It is apparent that **2b** has the highest activity among the three catalysts because it reaches 100% conversion after 50 min, whereas it takes catalysts **2a** and **1b** 80 and 130 min, respectively, to reach the same conversion in the RCM reaction of **6**. After the reaction, the RCM product **7** was isolated in almost quantitative yield using either **2a** or **2b**. Furthermore, we compared the catalytic activity between **1a** and **2b** using other bulky substrate diethyl 2-allyl-2-(2-methylallyl)malonate, **8**.[14] As a result, **2b** showed a higher catalytic activity than **1a** in this case, too (Figure 3).[15] Although the catalytic activity of **2a** was lower

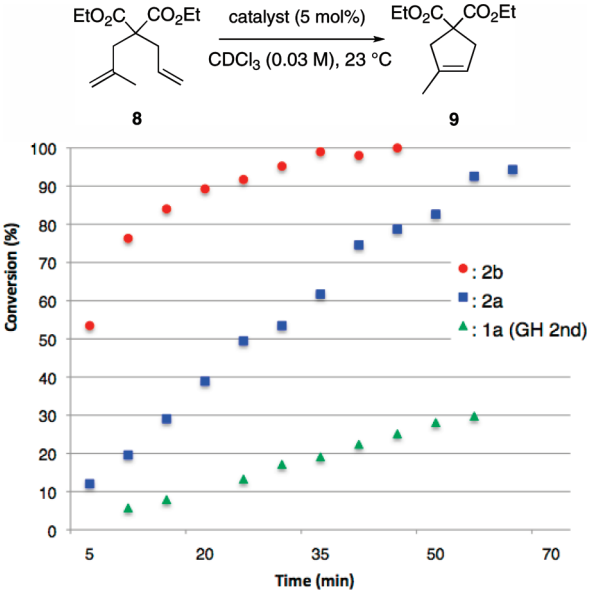
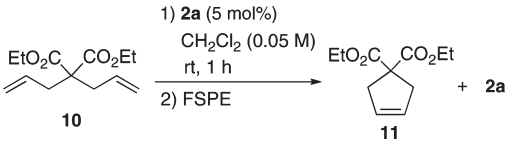


FIGURE 3. Comparison of catalytic activity for RCM of **8** in $CDCl_3$.

TABLE 1. Reuse of Modified f-GH Catalyst 2a in the RCM of Diethyl 2,2-Diallylmalonate



cycles	1	2	3	4[a]	5
RCM product (%)	95	100	95	96	82
recovered catalyst (%)	97	100	91	95	100

[a]The reaction was conducted for 1.5 h.

than known activated catalyst,[6a] **2b** showed similar activity in the RCM reaction of **8**.

The purification and recycling features of **2a** were examined using diethyl 2,2-diallylmalonate **10** as the substrate (Table 1).[16] The recovered catalyst exhibited a ^{1}H NMR spectrum similar to that of fresh catalyst and was used directly in the second cycle with appropriate adjustments of all other components to maintain the same 5 mol % catalyst ratio. This process was repeated through five cycles. The ^{1}H NMR spectra of product **11** in each case was clean, and resonnaces corresponding to the free ligand resonances could not be observed in all cases by ^{1}H and ^{19}F NMR. The yield of the product was high (95−100%) in each iteration, while the yield of the recovered catalyst ranged from 91% to 100%. At the end of the fifth cycle, about 84% of the original catalyst was recovered. Although the recovered catalyst was no longer pristine by ^{1}H NMR, we expect that it was still active because the ^{1}H NMR was similar to that of the catalyst after the fourth cycle. If desired, it could be repurified by chromatography or recrystallization prior to reuse. Unfortunately, catalyst **2b** could not be recovered and reused because it was not stable to the FSPE protocol. We assume that the coordination ability of the ligand was lower than that of **2a** for the aqueous conditions in the presence of fluorous silica gel.

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In summary, we have prepared two modified Grubbs−Hoveyda second-generation catalysts (**2a** and **2b**) activated by a light fluorous tag. Although, catalyst **2b** was not recoverable by FSPE, **2b** exhibited higher catalytic activity than **1a** and **2a**. Catalyst **2a** on the other hand could be routinely recovered using FSPE in each iteration, and it was reused up to five times with minimal loss in reactivity. We have shown that the fluorous tag serves two purposes: (1) to provide a purification handle through FSPE and (2) to improve the catalytic activity through the electron-withdrawing nature of the perfluoroalkyl chain. At present, we believe that catalyst **2a** is one of the most effective light fluorous Grubbs−Hoveyda catalyst available to date.

Experimental Section

General Procedure for Perfluoroalkylation. To a solution of salicylaldehyde (300 mg, 2.46 mmol) and perfluorooctyl iodide (2.01 g, 3.68 mmol) in DMF (16 mL) was added V-70 L (758 mg, 2.46 mmol) and cesium carbonate (6.41 g, 19.7 mmol) at room temperature. The mixture was stirred for 20 h at ambient temperature. After the addition of aq HCl (1.0 M), the reaction mixture was extracted with diethyl ether. The organic layer was concentrated, and the three regioisomers of perfluoroctylated compounds (*ortho*, *para*, *and ortho*/*para dialkylated*) were purified by column chromatography over silica gel eluting with AcOEt/hexane, 1:20 to furnish **4a** in 36% yield.

2,2′-Azobis(2,4-dimethyl-4-methoxyvaleronitrile). This is commercially available, and the abbreviation in brackets [V-70] is its trade name. This compound is a mixture of diastereomeric isomers whose melting points are 58 and 107 °C and should be stored below −10 °C to prevent any decomposition. V-70 L is the isomer, with the lower melting point. The typical procedure to separate the diastereomers is described below: V-70 (5.0 g) in Et_2O (25 mL) was stirred at 10 °C for 30 min to precipitate the V-70H (1.8 g; no V-70 L was observed by ^{1}H NMR). Subsequently, the filtrate was cooled to −10 °C for 2 days to give crystallized V-70 L (0.7 g; 100% by ^{1}H NMR); V-70 L: mp ∼58 °C (dec); ^{1}H NMR ($CDCl_3$) δ 3.21 (s, 6H), 2.42 (d, J = 11 Hz, 2H), 2.26 (d, J = 11 Hz, 2H), 1.64 (s, 12H), 1.29 (s, 12H).

2-Hydroxy-5-perfluorooctylbenzaldehyde (4a):[12] white crystals; mp 73.0−74.0 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 11.85 (s, 1H), 9.96 (s, 1H), 7.79 (m, 2H), 7.16 (t, J = 7.6 Hz, 1H); ^{19}F NMR (466 MHz, $CDCl_3$) δ −126.0 (2F), −122.6 (2F), −121.8 (2F), −121.7 (2F), −121.5 (2F), −121.3 (2F), −108.9 (2F), −80.6 (3F).

3-Fluoro-2-hydroxy-5-perfluorooctylbenzaldehyde (4b): pale-yellow crystals; mp 64.0−65.0 °C: ^{1}H NMR (270 MHz, acetone-d_6) δ 10.16 (s, 1H), 7.88 (s, 1H), 7.69 (d, 1H, J = 10.8 Hz); ^{19}F NMR (466 MHz, $CDCl_3$) δ −132.8 (1F), −126.0 (2F), −122.6 (2F), −121.7 (2F), −121.5 (4F), −121.0 (2F), −110.0 (2F), −80.6 (3F); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 195.6, 153.0, 152.8, 149.2, 127.5 (t, J = 6.6 Hz), 121.9, 120.7, 106−121 (m, C_8F_{17}); EI-MS m/z: 558 (M^+), 189; HRMS (EI) m/z calcd for $C_{15}H_4F_{18}O_2$ 557.9924, found 557.9915.

General Procedure for Wittig Reaction. To a solution of methyltriphenylphosphoniumbromide (245 mg, 0.68 mmol) in anhydrous THF (8 mL) was added sodium bis(trimethylsilyl)-amide (252 mg, 1.37 mmol) under nitrogen at −78 °C and stirred for 30 min. Then the reaction temperature rose to −10 °C and was stirred for further 30 min. A solution of 2-isopropoxy-5-perfluorooctylbenzaldehyde (100 mg, 0.17 mmol) in anhydrous THF (5 mL) was then added and stirring continued for 2 h at room temperature. After the addition of aq HCl (1.0 M), the reaction mixture was extracted with diethyl ether. The organic layer was concentrated in vacuo, and the residue was purified by column chromatography over silica gel, eluting with AcOEt/hexane, 1:10 to give **5a** (78 mg, 78%).

1-Isopropoxy-4-perfluorooctyl-2-vinylbenzene (5a): yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.65 (d, J = 2.1 Hz, 1H), 7.40 (dd, J = 8.9, 2.4 Hz, 1H), 6.97−7.08 (m, 1H), 6.94 (d, J = 8.3, 1H), 5.79 (dd, J = 17.8, 1.1 Hz, 1H), 5.33 (dd, J = 17.3, 1.1 Hz, 1H), 4.59−4.68 (m, 1H), 1.38 (d, J = 2.9 Hz, 6H); ^{19}F NMR (466 MHz, $CDCl_3$) δ −126.0 (2F), −122.6 (2F), −121.8 (2F), −121.7 (4F), −121.2 (2F), −109.7 (2F), −80.7 (3F); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 157.8, 131.1, 128.0, 127.4, 125.5 (t, J = 6.6 Hz), 120.6, 115.7, 112.9, 105−121 (m, C_8F_{17}), 71.0, 22.1; EI-MS m/z: 580 (M^+), 538, 169; HRMS (EI) m/z calcd for $C_{19}H_{13}F_{17}O$ 580.0695, found 580.0711.

3-Fluoro-1-isopropoxy-4-perfluorooctyl-2-vinylbenzene (5b): yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.21 (dd, J = 11.3, 2.2 Hz, 1H), 6.97−7.08 (m, 1H), 5.81 (dd, J = 17.8, 0.8 Hz, 1H), 5.41 (d, J = 11.3 Hz, 1H), 4.50−4.63 (m, 1H), 1.34 (d, J = 5.7 Hz, 6H); ^{19}F NMR (466 MHz, $CDCl_3$) δ −126.8 (1F), −126.0 (2F), −122.6 (2F), −121.8 (2F), −121.6 (4F), −121.2 (2F), −110.1 (2F), −80.7 (3F); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 157.4, 153.8, 146.2, 134.3, 130.4, 123.7, 120.2 (t, J = 6.7 Hz), 117.2, 105−120 (m, C_8F_{17}), 77.2, 22.6; EI-MS m/z: 598 (M^+), 556, 187; HRMS (EI) m/z calcd for $C_{19}H_{12}F_{18}O$ 598.0601, found 598.0582.

Modified light fluorous metathesis catalyst (2a): green crystals; mp 182.0−183.0 °C: ^{1}H NMR (270 MHz, $CDCl_3$) δ 16.38 (s, 1H), 7.69−7.72 (m, 1H), 7.08−7.13 (m, 5H), 6.90 (d, J = 8.6 Hz, 1H), 4.90−4.99 (m, 1H), 4.21 (s, 4H), 2.47 (s, 12H), 2.39 (s, 6H), 1.29 (d, J = 6.2 Hz, 6H); ^{19}F NMR (466 MHz, $CDCl_3$) δ −125.9 (2F), −122.5 (2F), −121.7 (2F), −121.4 (4F), −121.0 (2F), −109.3 (2F), −80.6 (3F); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 293.5, 209.6, 154.4, 144.7, 139.1, 129.4, 127.4, 123.1, 121.2 (t, J = 6.0 Hz), 119.2, 115.5, 113.0, 107−123 (m, C_8F_{17}), 76.4, 51.5, 29.7, 21.1, 19.4; IR: 2924, 1592, 1487, 1240, 1202, 1146, 1115, 661 cm^{-1}; HRMS (FAB) m/z calcd for $C_{39}H_{39}Cl_2F_{17}N_2ORu$ 1046.1211, found 1046.1224.

Modified light fluorous metathesis catalyst (2b): green crystals; mp 158.0−159.0 °C: ^{1}H NMR (270 MHz, $CDCl_3$) δ 16.31 (s, 1H), 7.47 (d, J = 11.6 Hz, 1H), 7.07 (s, 4H), 6.92 (s, 1H), 5.39−5.45 (m, 1H), 4.21 (s, 4H), 2.47 (s, 12H), 2.39 (s, 6H), 1.26 (s, 6H); ^{19}F NMR (466 MHz, $CDCl_3$) δ −130.2 (1F), −125.9 (2F), −122.5 (2F), −121.7 (4F), −121.3 (2F), −121.1 (2F), −109.5 (2F), −80.6 (3F); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 292.2, 208.4, 153.3, 149.7, 148.1, 140.4, 139.2, 129.5, 124.3, 117.2 (t, J = 6.3 Hz), 115.3, 107−124 (m, C_8F_{17}), 82.2, 77.3, 51.5, 29.7, 22.0, 20.8; IR: 2924, 1487, 1324, 1240, 1196, 1145, 1104, 668 cm^{-1}; HRMS (FAB) m/z calcd for $C_{39}H_{38}Cl_2F_{18}N_2ORu$ 1064.1117, found 1064.0961.

1-Tosyl-2,5-dihydro-1*H*-pyrrole[13] **(7):** white crystals; mp 124.5−125.5 °C: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.72 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 5.65 (s, 2H), 4.12 (s, 4H), 2.43 (s, 3H).

Diethyl 3-methylcyclopent-3-ene-1,1-dicarboxylate[14] **(9):** pale-yellow oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.18 (m, 1H), 4.19 (q, J = 7.3 Hz, 4H), 2.96 (m, 2H), 2.90 (s, 2H), 1.71 (s, 3H), 1.25 (t, J = 7.3 Hz, 6H).

Diethyl cyclopent-3-ene-1,1-dicarboxylate[15] **(11):** colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.61 (s, 2H), 4.19 (d, J = 7.6 Hz, 4H), 3.00 (s, 4H), 1.25 (t, J = 7.6 Hz, 6H).

General Procedure for RCM and FSPE. Diethyl 2,2-diallylmalonate **10** (375 mg, 1.56 mmol) and **2a** (81.8 mg, 0.078 mmol, 0.050 equiv) were dissolved in dichloromethane (31 mL, 0.05 M) under a nitrogen atmosphere, and the mixture was stirred for 1 h at room temperature. After removal of the volatile components by rotary evaporation, the brownish mixture was submitted to separation by FSPE. A short column was packed with fluorous silica gel (2.4 g) using aq 80% MeOH as the

solvent. The crude reaction mixture was then loaded onto this column and eluted with 9.6 mL of aq 80% MeOH followed by 12 mL of THF. The evaporation of the 80% MeOH fraction and the THF fraction by vacuum centrifuge gave RCM product **11** in 95% yield (314 mg) and catalyst **2a** in 97% yield (79.7 mg).

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Supporting Information Available: Copies of ^{1}H NMR of **2a** with the passage of time, and ^{1}H NMR, ^{19}F NMR, ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.