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# An Analogue of Grubbs Third-Generation Catalyst with Fluorophilic Pyridine Ligands: Fluorous/Organic Phase-Transfer Activation of Ring-Closing Alkene Metathesis

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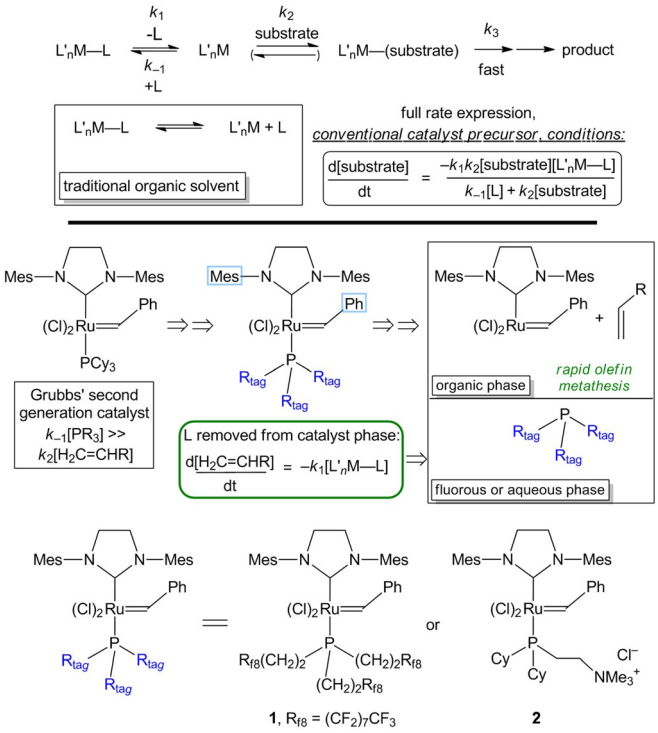
The title catalyst $(H_2IMes)[3,5\text{-}NC_5H_3(CH_2CH_2R_{f8})_2]_2(Cl)_2Ru(=CHPh)$ [$H_2IMes$ = 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene, $R_{f8} = (CF_2)_7CF_3$] was prepared from the fluorous pyridine $3,5\text{-}NC_5H_3(CH_2CH_2R_{f8})_2$ (2.1 equiv.) and the pyridine complex $(H_2IMes)(NC_5H_5)_2(Cl)_2Ru(=CHPh)$. $3,5\text{-}NC_5H_3(CH_2CH_2R_{f8})_2$ was synthesized by a Heck reaction of 3,5-dibromopyridine and the fluorous alkene $H_2C{=}CHR_{f8}$ [2.4 equiv.; $Pd(OAc)_2$ (cat.), $n\text{-}Bu_4N^+$ $Br^-$/NaOAc (2.0 equiv.)], followed by hydrogenation. The catalyst shows dramatic rate accelerations in the ring-closing metatheses of α,ω-dienes under fluorous/organic liquid/liquid biphasic conditions [e.g., perfluoro(methyldecalin)/$CD_2Cl_2$] relative to rates under monophasic organic conditions (e.g., $CD_2Cl_2$). These catalysts require initial dissociation of the pyridine ligands to generate the active species, which can either combine with an alkene (productive) or recombine with a pyridine (unproductive). In the case of $(H_2IMes)[3,5\text{-}NC_5H_2(CH_2CH_2R_{f8})_2]_2(Cl)_2Ru(=CHPh)$, fluorophilic $3,5\text{-}NC_5H_3(CH_2CH_2R_{f8})_2$ transfers to the fluorous phase, in accord with its $CF_3C_6F_{11}$/toluene partition coefficient [93.9:6.1 vs. 39.8:60.2 for $(H_2IMes)[3,5\text{-}NC_5H_3(CH_2CH_2R_{f8})_2]_2(Cl)_2Ru(=CHPh)$], which decreases the fraction of unproductive events.




**Scheme 1.** Phase-transfer activation of catalysts: general principles and phosphine-containing metathesis catalysts studied previously. Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl.

In a series of papers, we have employed analogues of Grubbs second-generation alkene metathesis catalysts with "phase tagged" phosphines to develop the concept of "phase-transfer activation".[1–4] This protocol is designed to enhance the effectiveness of metal-based catalyst precursors in which a ligand (L) must initially dissociate to generate the active species (Scheme 1, top).[5,6] This step is often reversible, with catalyst/ligand recombination faster than subsequent catalyst/substrate binding (i.e., $k_{-1}[L] \gg k_2[substrate]$). Per the rate expressions displayed in Scheme 1, this retards the reaction velocity relative to the opposite limit, in which the initial dissociation is rate determining (i.e., $k_{-1}[L] \ll k_2[substrate]$).

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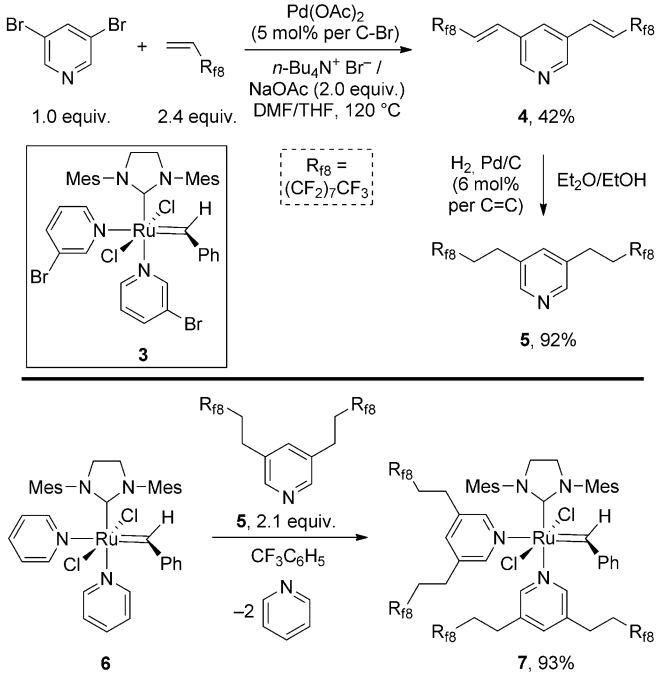
If the first limit is applicable, protocols that decrease the concentration of dissociated ligand in the reactant phase should afford more active catalyst systems. Accordingly, there are literature reports of various additives that can accelerate rates of alkene metatheses with Grubbs first- and second-generation catalysts,[7] for which reversible initial phosphine dissociation has been established.[5] With most of these, some type of binding interaction with the dissociated phosphine is possible. However, additives can also introduce deactivation pathways involving the ruthenium fragment. Thus, our strategy has been to prepare analogues in which the phosphine ligand carries an affinity label or tag for an orthogonal phase.[1–4] The idea is that when catalysis is subsequently effected under liquid/liquid (Scheme 1, middle)[1–3] or liquid/solid[4] biphasic conditions, the dissociated ligand will phase transfer to the second phase. In the idealized limit, this provides a rate acceleration per the expression in the green box.

In efforts to date, we have prepared analogues of Grubbs second-generation catalysts with fluorophilic phosphine li-

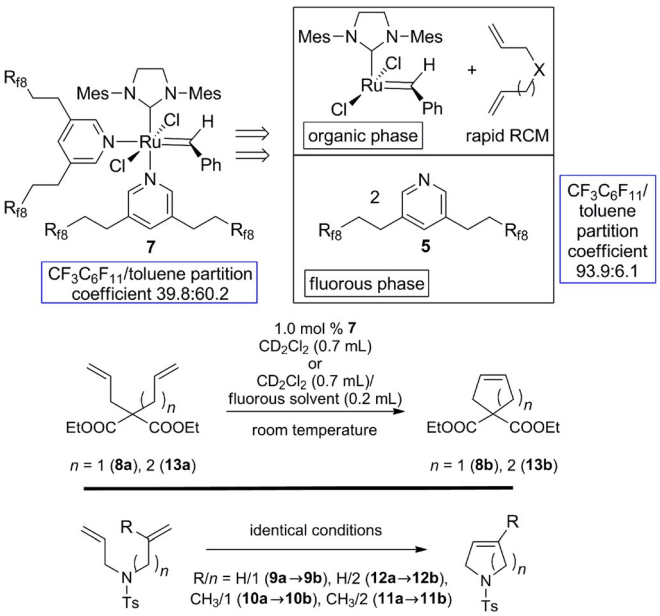
gands,[1,3] as exemplified by **1**, and hydrophilic ligands, as exemplified by **2** (Scheme 1, bottom).[2] Both **1** and **2** gave marked rate enhancements in reactions conducted under organic/fluorous or organic/aqueous conditions, as opposed to reactions conducted under organic monophasic conditions. To confirm the generality of this concept and to extend the range of useful applications, we sought to study the rates of alkene metathesis of Grubbs third-generation catalyst (i.e., compound **3**; Scheme 2),[8] which features pyridine ligands, and analogues with phase-labeled pyridines.




**Scheme 2.** Syntheses of a fluorous pyridine ligand and the fluorous analogue **7** of Grubbs third-generation catalyst **3**.

A variety of fluorous pyridines are known,[9,10] and therefore, fluorous analogues of **3** were targeted. The 3,5- or "*meta*"-disubstituted pyridine 3,5-$NC_5H_3(CH_2CH_2R_{f8})_2$ [**5**; $R_{f8}=(CF_2)_7CF_3$] was prepared earlier and was found to exhibit a perfluoro(methylcyclohexane) or $CF_3C_6F_{11}$/toluene partition coefficient of 93.9:6.1.[9,11] This represents a high degree of fluorophilicity, suitable for phase-transfer activation, as sketched in Schemes 1 and 3. The synthesis involved the palladium-catalyzed coupling of 3,5-dibromopyridine with the fluorous zinc reagent $IZnCH_2CH_2R_{f8}$. However, the yield was only 31%. As an alternative, a Heck reaction with the fluorous alkene $H_2C{=}CHR_{f8}$ was investigated. A variant of the "Jeffery conditions" (Scheme 2) was employed.[12] Workup afforded the bis(alkene) *trans*,*trans*-3,5-$NC_5H_3(CH{=}CHR_{f8})_2$ (**4**) in 42% yield. Subsequent hydrogenation gave **5** in 92% yield or 39% overall yield.

In an adaption of a procedure of Emrick,[13] **5** (2.1 equiv.) and bis(pyridine) complex **6** (1.0 equiv., Scheme 2)[8a] were combined in the hybrid solvent α,α,α-trifluorotoluene, $CF_3C_6H_5$, which commonly dissolves both lipophilic and fluorophilic sol-




**Scheme 3.** Ring-closing metatheses catalyzed by **7** under fluorous/organic liquid/liquid biphasic and organic monophasic conditions.

utes.[14] The perfluoroalkyl segments in **5** render it less basic than pyridine. Thus, to drive the reaction, a series of freeze/pump/thaw cycles were conducted with fresh charges of $CF_3C_6H_5$. Although most of the pyridine volatilized, trace amounts of **5** remained, affording a 93% yield of **7** of approximately 95% purity, as assayed by the signal for Ru=C*H*Ph in the $^1$H NMR spectrum. Nonetheless, the $CF_3C_6F_{11}$/toluene partition coefficient (39.8:60.2) could be determined by $^{19}$F NMR spectroscopy, as described in the Supporting Information. This shows the complex to be predominantly lipophilic, suited for phase-transfer activation as in Schemes 1 and 3.

The feasibility of phase-transfer activation was assayed with α,ω-dienes **8a**–**13a**, shown in Scheme 3. Three are 1,6-dienes that yield known five-membered ring products (see compounds **8b**–**10b**), and three are 1,7-dienes that yield known six-membered ring products (see compounds **11b**–**13b**). Reactions were conducted under side-by-side conditions in NMR tubes in either $CD_2Cl_2$ (0.7 mL) or $CD_2Cl_2$/fluorous solvent mixtures (0.7 mL/0.2 mL unless noted) with 1 mol% catalyst loadings. As in previous studies,[1–3] the volume of the organic solvent was kept constant, which ensured a greater catalyst concentration in the monophasic experiment, as some catalyst partitioned into the non-organic phase in the biphasic experiment. Hence, rate accelerations under biphasic conditions were guaranteed to be meaningful. Finally, it deserves emphasis that the educts and products remained localized in the organic phase (≥98%).[11]

The reaction of diallyl malonate (**8a**) and **7** under monophasic conditions in $CD_2Cl_2$ cleanly gave ring-closing metathesis product **8b**, as assayed by $^1$H NMR spectroscopy and plotted in Figure 1 (■). No byproducts were evident other than ethylene, so conversions were calculated from the relative **8a**/**8b** integrations. Upon conducting analogous reactions under bi-

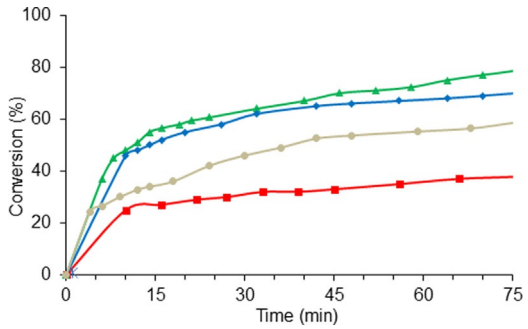



**Figure 1.** Rates of formation of **8b** (room temperature, $[8a]_0 = 0.010$ M, 1 mol% **7**). Solvent systems: ■ $CD_2Cl_2$ (0.7 mL, monophasic); ● $CD_2Cl_2$/FC-77 (0.7 mL/0.2 mL, biphasic); ◆ $CD_2Cl_2$/perfluoro(methylcyclohexane) (0.7 mL/0.2 mL, biphasic); ▲ $CD_2Cl_2$/perfluoro(methyldecalin) (0.7 mL/0.2 mL, biphasic).

phasic conditions with the use of $CD_2Cl_2$/FC-77 (Figure 1, ●),[15] $CD_2Cl_2/CF_3C_6F_{11}$ (Figure 1, ◆), and $CD_2Cl_2$/perfluoro(methyldecalin) (Figure 1, ▲), progressively faster rates were observed (Figure 1). Faster rates were also noted if $CD_2Cl_2$/perfluorotoluene mixtures, which are monophasic, were employed. Perfluorinated arenes are not considered fluorous owing to their much greater polarities,[16] but they have often been observed to enhance the rates of ruthenium-catalyzed metatheses.[17,18]

A separate experiment (Figure S1, Supporting Information) showed that the analogous reaction of Grubbs-third generation catalyst **3** in $CD_2Cl_2$ was faster than that with fluorous analogue **7**. Comparisons involving other substrates are incorporated into the figures that follow. The initial rate with **3** was very close to that of the $CD_2Cl_2$/perfluoro(methyldecalin) biphasic system in Figure 1. However, upon changing the solvent ratio from 0.7 mL/0.2 mL to 0.5 mL/0.2 mL, which compensated for the appreciable partitioning of **7** into the fluorous phase, the biphasic system became faster.

Rate profiles for ring-closing metatheses of *N*,*N*-diallyl sulfonamide **9a** to **9b** under three different conditions are depicted in Figure 2. As above, the biphasic $CD_2Cl_2$/perfluoro(methyldecalin) system (Figure 2, ▲) gave a much faster rate than the monophasic $CD_2Cl_2$ system (Figure 2, ■). A preparative reaction performed by using 100 mg of **9a** gave **9b** in 83% yield.

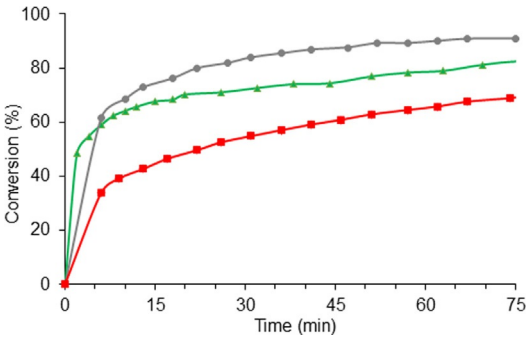



**Figure 2.** Rates of formation of **9b** (room temperature, $[9a]_0 = 0.010$ M). Solvent/catalyst systems: ■ $CD_2Cl_2$ (0.7 mL, monophasic), 1 mol% **7**; ● $CD_2Cl_2$ (0.7 mL, monophasic), 1 mol% **3**; ▲ $CD_2Cl_2$/perfluoro(methyldecalin) (0.7 mL/0.2 mL, biphasic), 1 mol% **7**.

Again, non-fluorous **3** was a superior catalyst to **7** under monophasic conditions (Figure 2, ● vs. ■). However, the initial rate appeared comparable to that of **7** under biphasic conditions (Figure 2, ● vs. ▲).

As shown in Figure 3, **7** also catalyzed the ring-closing metathesis of sulfonamide **10a** more rapidly under fluorous/organic biphasic conditions than under organic monophasic conditions (Figure 3, ▲ vs. ■). However, now **3** gave a distinctly faster rate than **7** under biphasic conditions (Figure 3, ● vs. ▲). Figure 4

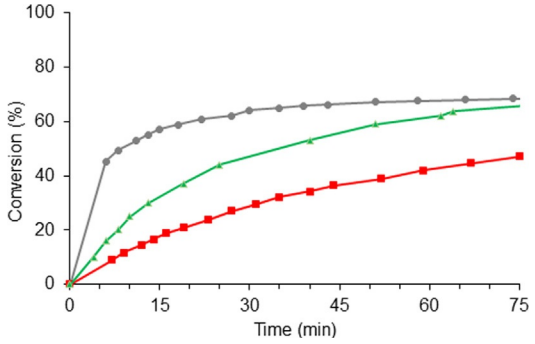



**Figure 3.** Rates of formation of **10b** (room temperature, $[10a]_0 = 0.010$ M). Solvent/catalyst systems: ■ $CD_2Cl_2$ (0.7 mL, monophasic), 1 mol% **7**; ● $CD_2Cl_2$ (0.7 mL, monophasic), 1 mol% **3**; ▲ $CD_2Cl_2$/perfluoro(methyldecalin) (0.7 mL/0.2 mL, biphasic), 1 mol% **7**.

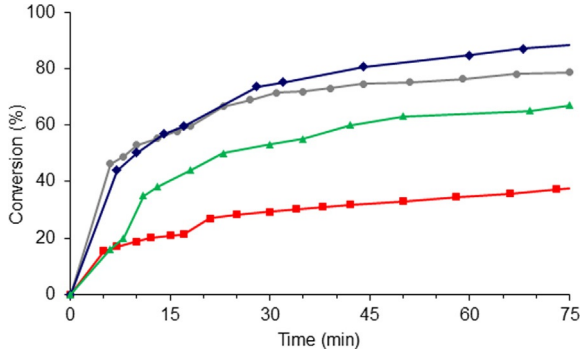



**Figure 4.** Rates of formation of **11b** (room temperature, $[11a]_0 = 0.010$ M). Solvent/catalyst systems: ■ $CD_2Cl_2$ (0.7 mL, monophasic), 1 mol% **7**; ● $CD_2Cl_2$ (0.7 mL, monophasic), 1 mol% **3**; ▲ $CD_2Cl_2$/perfluoro(methyldecalin) (0.7 mL/0.2 mL, biphasic), 1 mol% **7**; ◆ $CD_2Cl_2$/perfluoro(methyldecalin) (0.5 mL/0.2 mL, biphasic), 1 mol% **7**.

provides rate data for the homologous 1,7-diene **11a**. In that case, the initial rate under the standard biphasic conditions (0.7 mL/0.2 mL; Figure 4, ▲) was quite close to that under monophasic conditions (0.7 mL; Figure 4, ■). Hence, a parallel run was conducted with a 0.5 mL/0.2 mL solvent ratio to help compensate for the catalyst that partitioned into the fluorous phase. This showed a distinct rate enhancement (Figure 4, ◆ vs. ■).

Analogous experiments were conducted with substrates **12a** and **13a** (Scheme 3), as depicted in Figures S2 and S3. These gave rate profiles similar to those in Figures 3 and 4,

which further supports the operation of phase-transfer catalysis. The non-fluorous catalysts **3** and **6** were similarly employed under fluorous/organic biphasic conditions and organic monophasic conditions. In these cases, nearly identical rates were obtained, consistent with other studies.[1,19]

In exploratory efforts, attempts were made to prepare analogues of **7** with a single $(CH_2)_2R_{f8}$ group on each pyridine ligand.[20] However, a number of difficulties were encountered, and the fluorophilicities of the pyridines were borderline for efficient phase transfer. Nonetheless, such ligands would more closely model the electronic properties of the 3-bromopyridine ligands in **3** and would, therefore, be more likely to provide comparably reactive catalysts. In this context, an attractive goal for future research would be the synthesis of monosubstituted pyridine ligands with a single fluorous substituent consisting of a $(CH_2)_2$ spacer and 12–14 perfluorinated $sp^3$ carbon atoms. These would be sufficiently fluorophilic for efficient phase transfer but would give ruthenium catalysts more lipophilic than **7** and not as prone to partitioning into a fluorous phase.

In conclusion, the preceding results have, within the context of ruthenium-based alkene metathesis catalysts, extended the generality of phase-transfer activation from phase-tagged phosphine ligands to phase-tagged pyridine ligands. In recent studies, the applicability of this protocol to nickel-catalyzed ethylene polymerization was also demonstrated.[19] These diverse applications convincingly validate the concept posited in Scheme 1 and show that it can be reliably exploited. Finally, this work has also added to the body of fluorous alkene metathesis catalysts,[17] most of which have been investigated earlier from the standpoint of recyclability. Future reports will detail additional extensions of phase-transfer activation, for example, to catalytic reactions in aqueous solvents.

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**Keywords:** fluorous · Heck reaction · metathesis · phase-transfer catalysis · pyridine · ruthenium

[1] a) R. Corrêa da Costa, J. A. Gladysz, *Chem. Commun.* **2006**, 2619–2621; b) R. Corrêa da Costa, J. A. Gladysz, *Adv. Synth. Catal.* **2007**, *349*, 243–254.

[2] Z. Xi, H. S. Bazzi, J. A. Gladysz, *Org. Lett.* **2011**, *13*, 6188–6191.

[3] R. Tuba, R. Correa da Costa, H. S. Bazzi, J. A. Gladysz, *ACS Catal.* **2012**, *2*, 155–162.

[4] Z. Xi, H. S. Bazzi, J. A. Gladysz, *Catal. Sci. Technol.* **2014**, *4*, 4178–4182.

[5] a) For the mechanism of ruthenium-catalyzed olefin metathesis reactions, see: M. S. Sanford, J. A. Love, *Mechanism of Ruthenium-Catalyzed Olefin Metathesis Reactions in Handbook of Metathesis, Vol. 3* (Ed.: R. H. Grubbs), Wiley-VCH, Weinheim, **2003**, pp. 112–131; b) M. S. Sanford, J. A. Love, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554; c) J. A. Love, M. S. Sanford, M. W. Day, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 10103–10109.

[6] For some examples that do not involve alkene metathesis, see a) G. Bhalla, S. M. Bischof, S. K. Ganesh, X. Y. Liu, C. J. Jones, A. Borzenko, W. J. Tenn III, D. H. Ess, B. G. Hashiguchi, K. S. Lokare, C. H. Leung, J. Oxgaard, W. A. Goddard III, R. A. Periana, *Green Chem.* **2011**, *13*, 69–81; b) T. R. Younkin, E. F. Connor, J. I. Henderson, S. K. Freidrich, R. H. Grubbs, D. A. Bansleben, *Science* **2000**, *287*, 460–462; c) D. R. McAlister, J. E. Bercaw, R. G. Bergman, *J. Am. Chem. Soc.* **1977**, *99*, 1666–1668.

[7] a) M. S. Sanford, L. M. Henling, R. H. Grubbs, *Organometallics* **1998**, *17*, 5384–5389; b) E. L. Dias, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897; c) J. Huang, H.-J. Schanz, E. D. Stevens, S. P. Nolan, *Organometallics* **1999**, *18*, 5375–5380; d) M. Rivard, S. Blechert, *Eur. J. Org. Chem.* **2003**, 2225–2228; e) K. Voigtritter, S. Ghorai, B. H. Lipshutz, *J. Org. Chem.* **2011**, *76*, 4697–4702.

[8] a) M. S. Sanford, J. A. Love, R. H. Grubbs, *Organometallics* **2001**, *20*, 5314–5318; b) J. A. Love, J. P. Morgan, T. M. Trnka, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2002**, *41*, 4035–4037; *Angew. Chem.* **2002**, *114*, 4207–4209.

[9] C. Rocaboy, F. Hampel, J. A. Gladysz, *J. Org. Chem.* **2002**, *67*, 6863–6870.

[10] a) B. Huang, J. Liu, *Tetrahedron Lett.* **1990**, *31*, 2711–2712; b) B.-N. Huang, J.-T. Liu, *J. Fluorine Chem.* **1993**, *64*, 37–46; c) R. D. Chambers, C. Magron, G. Sandford, *J. Chem. Soc. Perkin Trans. 1* **1999**, 283–290; d) T. Nishimura, Y. Maeda, N. Kakiuchi, S. Uemura, *J. Chem. Soc. Perkin Trans. 1* **2000**, 4301–4305; e) K. Tanaka, H. Hara, G. Nishida, M. Hirano, *Org. Lett.* **2007**, *9*, 1907–1910; f) T. Lechel, J. Dash, P. Hommes, D. Lentz, H. Reissig, *J. Org. Chem.* **2010**, *75*, 726–732.

[11] J. A. Gladysz, C. Emnet, J. Rábai, *Partition Coefficients involving Fluorous Solvents in Handbook of Fluorous Chemistry* (Eds.: J. A. Gladysz, D. P. Curran, I. T. Horváth), Wiley-VCH, Weinheim, **2004**, pp. 56–100.

[12] a) T. Jeffery, *J. Chem. Soc. Chem. Commun.* **1984**, 1287–1289; b) M. T. Reetz, J. G. de Vries, *Chem. Commun.* **2004**, 1559–1563 and references therein.

[13] D. Samanta, K. Kratz, X. Zhang, T. Emrick, *Macromolecules* **2008**, *41*, 530–532.

[14] H. Matsubara, I. Ryu, *Fluorous Organic Hybrid Solvents for Non-Fluorous Organic Synthesis in Topics in Current Chemistry* (Volume Editor: I. T. Horváth) **2012**, *308*, pp. 1–24.

[15] FC-77 is a mixture of *n*-$C_8F_{18}$ and the cyclic ether $C_8F_{16}O$ (CAS #52623-00-4).

[16] a) R. Filler, *Fluorine-Containing Molecules* (Eds.: J. F. Liebman, A. Greenberg, W. R. Dolbier, Jr.) VCH, Weinheim, **1988**, Chap. 2; b) I. Alkorta, I. Rozas, J. Elguero, *J. Org. Chem.* **1997**, *62*, 4687–4691, and references therein; c) J. C. Collings, K. P. Roscoe, E. G. Robins, A. S. Batsanov, L. M. Stimson, J. A. K. Howard, S. J. Clark, T. B. Marder, *New J. Chem.* **2002**, *26*, 1740–1746, and references therein.

[17] a) C. Samojłowicz, A. Kajetanowicz, K. Grela, *Olefin Metathesis in Fluorous Phases and in Fluorinated Aromatic Solvents in Olefin Metathesis, Theory and Practice* (Ed.: K. Grela), Wiley, Hoboken, **2014**, pp. 537–545; b) For work since the publication of the preceding review, see Y. Kobayashi, S. Inukai, N. Kondo, T. Watanabe, Y. Sugiyama, H. Hamamoto, T. Shioiri, M. Matsugi, *Tetrahedron Lett.* **2015**, *56*, 1363–1366.

[18] A reviewer has inquired about the perfluoro(methyldecalin)/$CH_2Cl_2$ partition coefficients of **5** and **7**, as the 93.9:6.1 and 39.8:60.2 values presented in the text and graphics are for $CF_3C_6F_{11}$/toluene. Analogous measurements gave 94.9:5.1 and 56.4:43.6, respectively. Note that perfluoro(methyldecalin) is a mixture of constitutional and stereoisomers that may slightly vary from batch to batch.

[19] Z. Xi, H. S. Bazzi, J. A. Gladysz, *J. Am. Chem. Soc.* **2015**, *137*, 10930–10933.

[20] Z. Liu, Texas A&M University, **2010**, unpublished results.

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