EXPANDING THE "ROMP TOOLBOX" FOR TISSUE ENGINEERING: ASSESSING THE DESIGN CRITERIA FOR RU-PSEUDOHALIDE INITIATORS

*Sebastien Monfette, Jay C. Conrad, Kenneth D. Camm and Deryn E. Fogg**

Department of Chemistry, and Center for Catalysis Research & Innovation
University of Ottawa
10 Marie Curie, Ottawa, ON, Canada K1N 6N5

Introduction

Living ring-opening metathesis polymerization (ROMP) offers powerful routes to designer materials, with applications ranging from biomedicine to microelectronics.[1,2] Of particular interest are ruthenium initiators that tolerate exposure to trace oxygen and water without deleterious effects on polymer properties. Despite the large number of ruthenium metathesis catalysts, however, remarkably few are capable of living ROMP (**Figure 1c**). For the controlled assembly of oligomers relevant to corneal tissue engineering,[2b] even these few suffer from key limitations: in particular, they are difficult to remove from the target materials, and they exhibit too great an extreme of reactivity. Ru-pseudohalide catalysts offer potential solutions to both issues: replacement of the chloride atoms facilitates fine-tuning of reactivity (which could enable access to initiators intermediate between the extremes of **1** and **2a**), while the polarity of the aryloxide ligand facilitates chromatographic removal of Ru residues.[3] No systematic study of the pseudohalide initiators in context of ROMP has thus far been undertaken. Here we report the ROMP behaviour of nine RuXX'(IMes)(py)(=CHPh) initiators. Analysis of the roles of ligand geometry, the electronegativity and charge properties of the donor atom, and the capacity of the aryloxide substituents to mediate ligand-ligand interactions, aid in elucidating optimal design criteria.

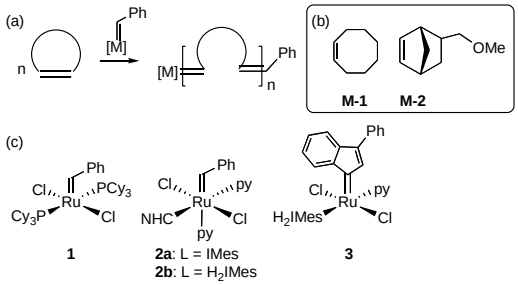

Figure 1. (a) Generic ROMP reaction. (b) Monomers investigated in this study. (c) Ru initiators capable of living ROMP.

Experimental

General considerations and materials. All reactions were carried out in a glovebox under N_2 at ambient drybox temperatures (22-24 ˚C). Dry, oxygen-free CH_2Cl_2, C_6H_6 or hexanes were obtained using a Glass Contour solvent purification system and stored over Linde 4 Å molecular sieves. Pentane (Fisher) and $CDCl_3$ (Cambridge Isotopes) were distilled from Na and CaH_2, respectively, freeze–pump–thaw degassed, and stored over Linde 4Å molecular sieves. Ampoules of THF-d_8 (Cambridge Isotopes), perfluorothiophenoxide and thallium ethoxide (Aldrich) were used as received. Cyclooctene (Aldrich) was distilled, degassed as above, and stored under N_2. Monomer **M-2** was prepared as reported and purified as for cyclooctene. Octafluorobinaphtholate was prepared as reported.[4] Initiators **2a**,[3] **4**,[5] **5**,[3] **8a**,[6] **8b**,[7] **9a**[6] and **9b**[6] were synthesized as previously described.

Instrumentation. ^{1}H NMR (300 MHz) spectra were recorded on a Bruker Avance-300 spectrometer: chemical shifts are reported relative to TMS (^{1}H, ^{13}C) at 0 ppm and $C_6H_5CF_3$ (^{19}F) at –63.72 ppm. Polymer molecular weights and polydispersities were measured on a Wyatt Technology DAWN light-scattering GPC instrument equipped with an Optilab DSP refractometer, using the system and column configuration previously described.[6]

General procedure for ROMP kinetics. To a solution of cyclooctene (50 μL, 0.39 mmol) in $CDCl_3$ (3.85 mL) was added **4** (10 μL, 1.95 μmol) from a 0.195 M stock solution in $CDCl_3$. After vigorously stirring for one minute, 0.75 mL of the solution was transferred to an NMR tube and set to spin at a rate of 20 Hz in the NMR probe. Conversions were determined at regular time intervals by monitoring the integrated intensities of olefinic signals for the monomer and polymer in time-arrayed ^{1}H NMR experiments. Turnover frequencies were determined at 50% conversion (TOF_{50}), as the solution became slightly viscous at higher conversions.

Representative synthesis of poly(M-2). A solution of **M-2** (97 mg, 0.70 mmol) in 1 mL CH_2Cl_2 was added to initiator **8a** (5.2 mg, 70 μmol, 1 mol%) in 6 mL CH_2Cl_2, stirred vigorously until ROMP was complete by ^{1}H NMR analysis, and treated with 0.5 mL ethyl vinyl ether. The resulting solution was stripped, reprecipitated (CH_2Cl_2-methanol), dried under vacuum, weighed, and analyzed by light-scattering GPC. For yields, see Table 1.

Synthesis of Tl(SC_6F_5). A solution of HSC_6F_5 (1.0 mL, 7.5 mmol) in 20 mL C_6H_6 was treated with Tl(OEt) (1.53 g, 7.5 mmol, 1 equiv) in 2 mL C_6H_6 and stirred overnight. The white precipitate was collected by filtration, washed with hexanes and dried under vacuum. Yield 1.15 g (76%).

Synthesis of 6. To a solution of **2a** (200 mg, 0.28 mmol) in 20 mL C_6H_6 was added Tl(SC_6F_5) (223 mg, 0.56 mmol, 2 equiv). After 15 min, the suspension was filtered through Celite. The filtrate was stripped to dryness, reprecipitated from 10 mL of pentane (–78 ˚C), and the solid was collected by filtration and dried overnight. Yield 55 mg (20%; limited by high solubility). **6a**: ^{1}H NMR (C_6D_6): δ 19.19 (s, 1H, RuC*H*), 8.54 (s, $^3J_{HH}$ = 7.53, 2H, Ar*H*), 7.60 (br s, 2H, Ar*H*), 7.23 (t, $^3J_{HH}$ = 7.1, 1H, Ar*H*), 6.42 (br s, 1H, Ar*H*), 6.19 (br s, 2H, Ar*H*), 5.84 (br s, 1H, Ar*H*), 5.41 (s, 2H, NC*H*), 2.85–2.34 (br s, 12H, CH_3), 2.34–1.97 (br s, 6H, CH_3). A proportion of the cis isomer **6b** crystallized from a solution of **6a** left to stand in C_6D_6 for 5 days (**6a**:**6b** ratio 3:1). **6b**: ^{1}H NMR (C_6D_6): δ 18.20 (s, 1H, RuC*H*). ^{19}F{^{1}H} (C_6D_6): δ –56.2 (d, $^3J_{FF}$ = 26.82, 2F), –88.6 (t, $^3J_{FF}$ = 21.74, 1F), –91.0 (t, $^3J_{FF}$ = 22.3, 2F).

Synthesis of 7. To a solution of **2a** (668 mg, 0.922 mmol) in 20 mL C_6H_6 was added $Tl_2(O_2C_{20}H_4F_8)$ (772 mg, 0.922 mmol). The reaction was stirred for 16 h, then filtered through Celite. The product was washed through with 20 mL THF, and the filtrate reduced to dryness. Yield 512 mg (66%). ^{1}H NMR (THF-d_8): δ 19.23 (s, 1H, RuC*H*), 7.85 (d, $^3J_{HH}$ = 9.3 Hz, 1H, OCC*H*), 7.81 (dd, $^3J_{HH}$ = 5.1, $^4J_{HH}$ = 3.0, 2H, ortho py), 7.51 (tt, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 3.0, 1H, para py), 7.40 (s, 2H, NC*H*), 7.35 (d, $^3J_{HH}$ = 9.3 Hz, 1H, OCC*H*), 7.16–7.11 (m, 3H, ortho and para Ph), 7.08 (d, $^3J_{HH}$ = 9.3 Hz, 1H, OCCHC*H*), 7.04 (br s, 2H, Mes Ar), 6.97 (br s, 2H, Mes Ar), 6.91 (br t, $^3J_{HH}$ = 7.2 Hz, 2H, py), 6.80 (t, $^3J_{HH}$ = 7.8 Hz, meta Ph), 6.57 (d, $^3J_{HH}$ = 9.3 Hz, 1H, OCCHC*H*), 3.64–3.58 (m, 2H, THF), 2.55 (s, 6H, Me), 2.13 (s, 6H, Me), 1.85–1.75 (br s and m overlapping, 8H, Me, THF).^{13}C{^{1}H} NMR (THF-d_8): δ 310.2 (s, Ru=*C*H), 184.6 (s, N*C*N), 172.3 (s, O*C*), 166.5 (s, O*C*), 156.3 (s, C*H*, ortho py), 155.2 (s, Ar*C*), 140.6 (s, *C*, Mes), 138.4 (s, *C*, Mes), 137.2 (s, *C*, Mes), 137.0 (m, Ar*C*), 135.7 (m, Ar*C*), 131.0 (m, Ar*C*), 130.3 (m, Ar*C*), 129.5 (m, Ar*C*), 128.8 (m, Ar*C*), 128.6 (m, Ar*C*), 128.5 (m, Ar*C*), 127.8 (m, Ar*C*), 127.4 (m, Ar*C*), 127.0 (s, *C*H, bino), 126.2 (s, *C*H, N*CC*N), 124.6 (s, *C*H, bino), 124.3 (m, Ar*C*), 123.0 (br, *C*, bino), 118.5 (m, *C*H, bino), 114.0 (m, *C*, bino), 113.8 (m, *C*, bino), 21.3 (s, *C*H_3, Mes), 18.3 (s, *C*H_3, Mes), 18.2 (s, *C*H_3, Mes). ^{19}F{^{1}H} NMR (THF-d_8): –73.09 (t, $^3J_{FF}$ = 16.0, 1F), –73.26 (t, $^3J_{FF}$ = 15.6, 1F), –80.72 to –80.87 (m, 2F), –91.47 (t, $^3J_{FF}$ = 18.7, 1F), –92.15 (t, $^3J_{FF}$ = 19.0, 1F), –98.03 (d, $^3J_{FF}$ = 19.7, 1F), –98.17 (d, $^3J_{FF}$ = 19.3, 1F). IR (Nujol, cm^{-1}) ν(C=C) 1663, 1601, 1565 cm^{-1}.

Results and Discussion

Cis-anionic ligand geometries have been found to retard initiation for both Ru-catecholate[6] and Ru-dichloride[8] catalysts, with deleterious consequences for controlled ROMP. The geometry of the new initiators is thus of key importance. Treating dichloride **2a** with two equivalents of Tl(SC_6F_5) effects quantitative transformation into a new product within 15 min at room temperature. We assign this species as trans-**6a** given the observation of only three ^{19}F resonances in the ratio of 1:2:2. Slow isomerization to cis-**6b** (driven by π-stacking of the fluorinated aromatic rings; a similar phenomenon was reported for **4**)[5] is observed in C_6D_6, as indicated by emergence of the expected six ^{19}F signals; yields of **6b** reach 25% after five days. Selective precipitation of **6b** occurred over the course of one week. For the ROMP study, crystalline **6b** was used, while the kinetic product **6a** was generated cleanly in situ by reacting **2a** with two equiv Tl(SC_6F_5) for 15 min.

Complex **7** was prepared in the same manner by treating **2a** with $Tl_2(O_2C_{20}H_4F_8)$. Pure **7** was obtained by crystallization from a concentrated THF solution; the crystals were used for the ROMP study.

Preliminary experiments were aimed at benchmarking the ROMP activity of pseudohalide catalysts **4-7** against that of **2a**. ROMP of cyclooctene (**M-1**) was chosen as a probe reaction, as the lower reactivity of this monomer relative to norbornene derivatives facilitates NMR screening. The results of this primary screen are shown in **Figure 3a**.

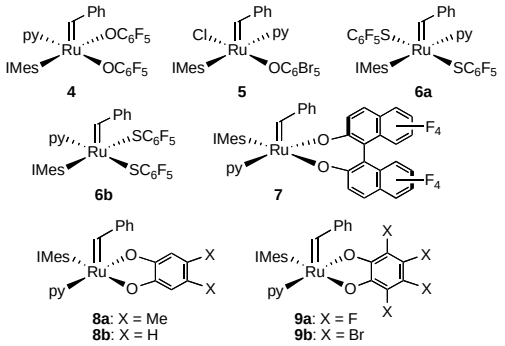

Figure 2. Ru-pseudohalide ROMP initiators explored in this study.

Several reactivity trends can be extracted. First, the ligand geometry is again found to be critical: trans-disposition of the anionic (and, correspondingly, the neutral donors) improves overall activity, as evidenced by the nearly threefold increase in TOF_{50} for **6a**, vs. **6b**. The positive correlation between trans-geometry and metathesis activity thus appears to be independent of the nature of the anionic ligands. Secondly, comparison of the *O*-bound and *S*-bound initiators, corrected for constant geometry, reveals that the latter are more reactive (TOF_{50} for **4**: 0.3; **6b**: 0.5 min^{-1}), consistent with our prior observation that less electronegative anionic donors (i.e. higher pK_a) enhance overall activity.[6] Intriguingly, however, the binaphtholate derivative **7** is the most reactive of the bis-pseudohalide initiators, despite the enforced cis-arrangement of the anionic ligands, and the presence of two O-donor atoms. An explanation may lie in the different spatial arrangement of the binaphtholate vs. monodentate aryloxide ligands. Within bis-perfluorophenoxide **4**, the fluorinated aromatic rings are essentially coplanar, minimizing steric pressure on the neighboring pyridine ligand. The greater orthogonality present in **7** may promote a greater degree of inter-ligand interaction, which facilitates pyridine decoordination. The higher reactivity of this complex is of keen interest for the use of this cis-anionic, atropisomeric ligand in asymmetric metathesis.

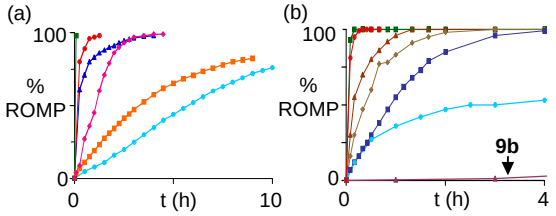

Figure 3. Activity of RuXX'(IMes)(py)(=CHPh) initiators in ROMP of (a) **M-1** and (b) **M-2**. Conditions: (a): [**M-1**] = 0.1 M in $CDCl_3$, 23 °C, M:I = 200:1. (b) [**M-2**] = 0.1 M in CH_2Cl_2, 23 °C, M:I = 100:1. **2a** (■), **4** (●), **5** (●), **6a** (◆), **6b** (■), **7** (▲), **8a** (▲), **8b** (◆), **9a** (■), **9b** (▲).

The high incidence of chain-transfer characteristic of ROMP polyoctenes obscures the primary control over polymer properties exerted by a given initiator. In polynorbornenes, such chain-transfer events are disfavored by higher bulk and rigidity. We thus explored the effect of the pseudohalide ligands on polymer chain lengths and polydispersities in ROMP of **M-2** (**Table 1**). The reactivity trends observed for **M-1** are maintained for **M-2**: that is, initiators bearing cis-disposed anionic ligands are less reactive than those featuring a trans arrangement of these ligands (**Figure 3b**). Examination of the GPC data, however, reveals poor chain-length control for all of the pseudohalide catalysts, although reasonable polydispersities are obtained for **8a/b**. Measurement of k_p/k_i ratios for **4** and **5** reveals very slow initiation relative to propagation, in comparison to **2a**, the current state of the art. For the catecholates **8-9**, very low initiation efficiency (I.E.) prevents observation of the propagating species: the GPC data demonstrate that initiation is slowest for the electron-deficient catecholates. Of note, however, these systems demonstrate that within a constant steric environment, initiation rates are less sensitive to inductive effects than propagation (Table 1).[6]

Comparison of the behaviour of **2a** and **5** demonstrates that while overall reaction rates, as indicated by TOF_{rel}, decline slightly on replacing chloride by perbromaryloxide, the I.E. is dramatically affected, decreasing by nearly an order of magnitude. That is, initiation is much more strongly affected than propagation. Of interest is the contrast with the catecholate systems. The difference may reflect the known capacity of the perbromoaryloxide ligand to chelate to the metal center via a pendant bromine, which could impede initiation. Both properties point toward detrimental effects on controlled ROMP associated with the electron-withdrawing OAr unit.

Table 1. Data for ROMP of M-2.

Init	Time (h)	Conv[a] (%)	Yield[b] (%)	M_n ($\times 10^{-3}$)[c]	PDI	k_p/k_i[d]	Rel. I.E.[e]	TOF_{rel}
2a	0.16	100	91	15.0	1.10	5	590	313
4	12	68	43	37.5[c]	1.35	114	–	5
5	0.33	100	82	138	1.48	82	64	250
8a	1.5	100	92	1300	1.12	–	7	87
8b	2.5	100	90	1500	1.13	–	6	34
9a	4	100	91	3200	1.23	–	3	14
9b	20	100	89	8800	1.7	–	1	1

[a] % Conversion to polymer at time stated (^{1}H NMR). [b] Isolated yield. [c] Average of two experiments; measured in duplicate for each; ±2-6%. Calcd: 13.8 × 10^3 Da except for **4**: 9.38 × 10^3 Da. [d] Determined by the reported method;[9] – indicates no observable propagating species. [e] Relative initiation efficiency normalized to values for the slowest-reacting catalyst. Values extracted from M_n data at 100% conversion; $IE_{rel} = [M_{n,\,calcd})/M_{n,\,exptl}]/[M_{n,\,calcd}$ for **9b**$)/M_{n,\,exptl}$ for **9b**$)]$.

Conclusions

The foregoing demonstrates a broad range of reactivity in ROMP of cyclooctene and norbornene monomers via a range of Ru-pseudohalide metathesis initiators. The goal of achieving reactivity intermediate between that of **1** and **2a** is not achieved, but key design criteria for improved performance can be extracted. These include trans-disposition of the anionic ligands in the initiator and the living polymer; use of donor atoms of lower electronegativity than oxygen (or, ideally, chloride); and incorporation of this donor within a ligand set that maintains polarity, but is not electron-withdrawing. The latter underscores the need for new pseudohalide ligands: ligand systems in which the donor atom is pendant on an aryl ring are limited by either cis-chelation, or the need for electron-withdrawing substituents to prevent π-coordination, both of which retard turnon efficiency and thus compromise control over chain lengths. Current studies focus on exploring new pseudohalide ligands that meet these criteria, promoting initiation while retaining sufficient polarity for easy polymer purification.

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