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Communication

A Cyclic Ruthenium Benzylidene Initiator Platform Enhances Reactivity for Ring-Expansion Metathesis Polymerization

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ABSTRACT: Ring-expansion metathesis polymerization (REMP) has shown potential as an efficient strategy to access cyclic macromolecules. Current approaches that utilize cyclic olefin feedstocks suffer from poor functional group tolerance, low initiator stability, and slow reaction kinetics. Improvements to current initiators will address these issues in order to develop more versatile and user-friendly technologies. Herein, we report a reinvigorated tethered ruthenium−benzylidene initiator, **CB6**, that utilizes design features from ubiquitous Grubbs-type initiators that are regularly applied in linear polymerizations. We report the controlled synthesis of functionalized cyclic poly(norbornene)s and demonstrate that judicious ligand modifications not only greatly improve kinetics but also lead to enhanced initiator stability. Overall, **CB6** is an adaptable platform for the study and application of cyclic macromolecules via REMP.

Cyclic polymers are promising building blocks for novel organic materials;[1,2] their "endless" hoop-like architectures display drastically different behaviors in solution and the solid-state compared to their linear counterparts.[3−5] Smaller hydrodynamic radii[6] and lack of chain ends contribute to unique thermal[7,8] and physical properties;[9] applications spanning biomaterials,[10] energy,[11,12] and sustainability[13,14] provide the impetus to develop improved methodologies. Acyclic ring closures[15,16] or ring-expansion polymerizations[17−19] (REP) account for most synthetic examples.[20] With advanced applications in mind, the latter is arguably more convenient as the cyclic initiator facilitates both monomer insertion and templated ring closure. Though there are myriad REP reaction classes,[21] ring-expansion metathesis polymerization (REMP)[3] remains one of the most versatile ways to access cyclic macromolecules. For acyclic polymers, advances in W, Mo, and Ru ring-opening metathesis polymerization (ROMP) initiator design[22−25] have allowed for widespread adoption of this valuable methodology. W and Mo initiators[22] are quite active and desirable for certain applications, but often initiators are derived from more air and functional group tolerant[26,27] Ru *N*-heterocyclic carbene[28,29] (NHC) complexes, such as Grubbs second (**G2**)[30−32] and third (**G3**)[33] generation scaffolds (Figure 1a). A sterically demanding NHC imparts initiator stability,[34,35] while a bulky benzylidene ensures facile ligand dissociation and thus faster initiation rates.

For cyclic polymers, W[36−41] and Mo[42] metathesis initiators can facilitate REMP of both alkene and alkyne monomers, but examples are largely limited to hydrocarbon feedstocks. Despite the overwhelming success of Ru ROMP initiators, the Ru REMP initiators developed by Fürstner[43] and Grubbs[44,45] have never been optimized to the same extent as **G2** and **G3** (Figure 1b, **UC5** and **SC5**).[44,45] Using inspiration from **G2** and **G3** design principles, there is an opportunity to develop a tunable cyclic Ru-NHC platform for REMP that improves upon the current[12,46−50] poor molecular weight control, limited stability, and slow polymerizations. Herein, we detail the first design of a more stable cyclic benzylidene initiator, **CB6** (Figure 1c), and highlight its faster polymerizations and superior molar mass control compared to the state-of-the-art.

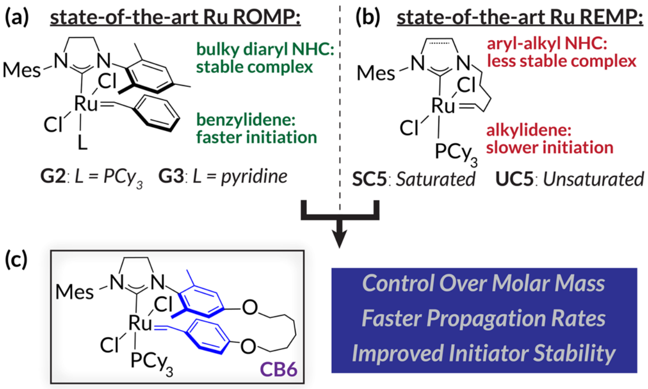

Figure 1. (a) Structural features of Ru ROMP and (b) REMP initiators alongside (c) improved cyclic benzylidene initiator, **CB6**.

Synthesis of envisaged cyclic initiator **CB6** (Scheme 1) featuring both a diaryl-NHC and a tethered benzylidene commenced with alkylation of 4-hydroxybenzaldehyde and 4-bromo-3,5-dimethylphenol with dibromohexane over two steps (**2**). Wittig olefination, followed by PdBrettPhosG3-mediated[51] amination of aryl bromide **3** with **4** afforded **5**.

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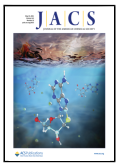

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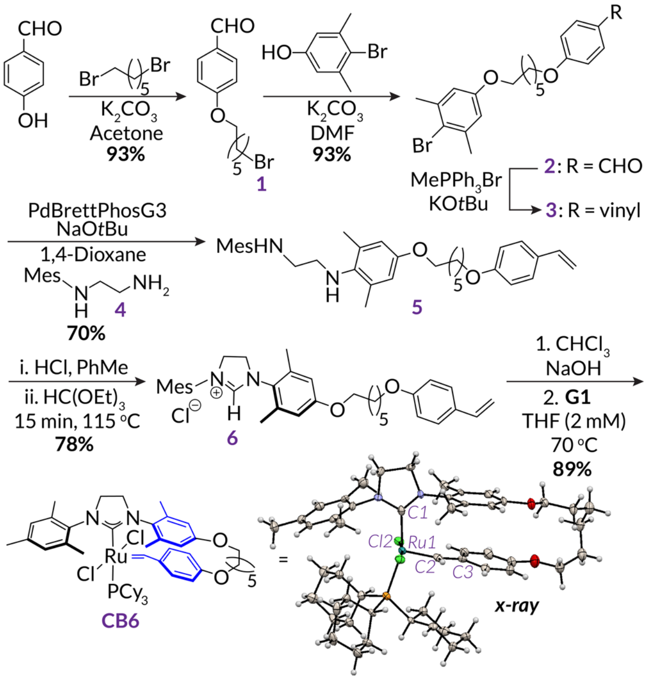
Scheme 1. Concise Synthesis of REMP Initiator CB6[a]



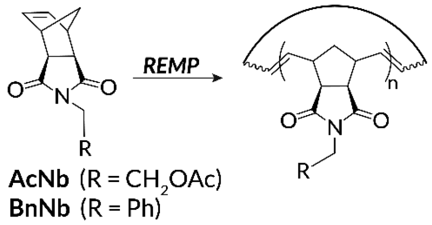
[a]X-ray structure ellipsoids shown at 50% probability.

Formation of the requisite diaryl imidazolium salt **6** could then be accomplished in one flask (HCl then triethyl orthoformate). Deprotonation of **6** with sodium hydroxide in chloroform led to a protected NHC-adduct that formed the desired initiator **CB6** upon ligand exchange and cyclization with Grubbs first generation catalyst (**G1**).[52] **CB6** could be readily purified by washing with Et_2O/pentane (Figure S1).

The structure of **CB6** was first evaluated using solution-state NMR spectroscopy; a single benzylidene ^{1}H resonance at δ = 19.4 ppm and phosphine ^{31}P resonance at δ = 28.7 ppm confirmed the presence of a lone organometallic species. For both **G2** and **CB6**, the benzylidene resonances (C2−H) appear as singlets, suggesting that these moieties are nearly orthogonal to the PCy_3 ligand and thus have a negligible $^3J_{P-H}$ value. Cyclic alkylidene complexes **SC5** and **UC5**, on the other hand, adopt geometries that orient the alkylidene hydrogens away from orthogonality ($^3J_{P-H} \approx 5-10$ Hz). Additional information was gleaned through solid-state X-ray analysis of **CB6** crystals (Scheme 1). Several stark differences exist (Figure S2) between dihedral angles in **CB6** compared to those of **G2** and representative cyclic alkylidene complexes **SC5** and **UC5**. For example, the dihedral angle (φ) outlined by Cl2−Ru−C2−C3 places the phenyl ring of **G2** off center from the chlorides by ∼12°, while the alkyl chains emanating from the Ru center in **SC5** and **UC5** are offset by ∼20° (Table S6). Remarkably, the benzylidene ring in **CB6** (Scheme 1) is almost coplanar with the chloride ligands (φ = 0.08°). Further evidence for the structural rigidity of **CB6** is revealed through density functional theory (DFT) calculations conducted at the B3LYP/6-31G(d)//LANL2DZ level of theory. **CB6** has 15 kcal/mol of strain energy (Figure S4) as assessed by homodesmotic reactions compared to the more flexible alkyl-linked **UC5** complex with just 6 kcal/mol of strain energy (Figure S5). We anticipated that these composite Ru-NHC initiator structural data would manifest themselves in faster reactions and improved molar mass control within REMP.

In proof of concept experiments, we investigated the activity of initiator (I) **CB6** in REMP using two substituted norbornene-imide (Nb) monomers (M): AcNb and BnNb (Table 1). Despite ROMP polymers derived from Nb finding broad utility in drug delivery,[53] imaging,[54] self-assembly,[55] and photonic applications,[56] these monomer structures have been historically challenging[48,49,57−59] for REMP. Only Ru initiators (i.e., **UC5**) have been utilized, and in these specific cases, uncontrolled growth of high-molecular weight macrocycles was

Table 1. REMP of AcNb and BnNb[a]



M	I	$[I]_0/[M]_0$	$M_{n,theor}$ (kDa)	M_n[b] (kDa)	M_w[b] (kDa)	Đ[b]
AcNb	**UC5**	1:50	12.5	421	572	1.36
AcNb	**CB6**	1:50	12.5	43.6	65.0	1.49
AcNb	**UC5**	1:200	49.9	1220	1760	1.44
AcNb	**CB6**	1:200	49.9	183	258	1.41
AcNb	**CB6**	1:250	62.3	193	274	1.42
AcNb	**CB6**	1:320	79.8	245	348	1.42
AcNb	**CB6**	1:550	137	393	539	1.37
BnNb	**UC5**	1:100	25.3	954	1240	1.30
BnNb	**CB6**	1:100	25.3	133	182	1.37
BnNb	**UC5**	1:200	50.6	1380	1740	1.26
BnNb	**CB6**	1:200	50.6	148	213	1.44
BnNb	**CB6**	1:500	127	170	251	1.48
BnNb	**CB6**	1:800	202	200	298	1.49

[a]Polymerization reactions were stirred at 55 °C in DCE for 12 h under nitrogen. [b]Detemined by GPC-MALS-IV ($CHCl_3$, 35 °C).

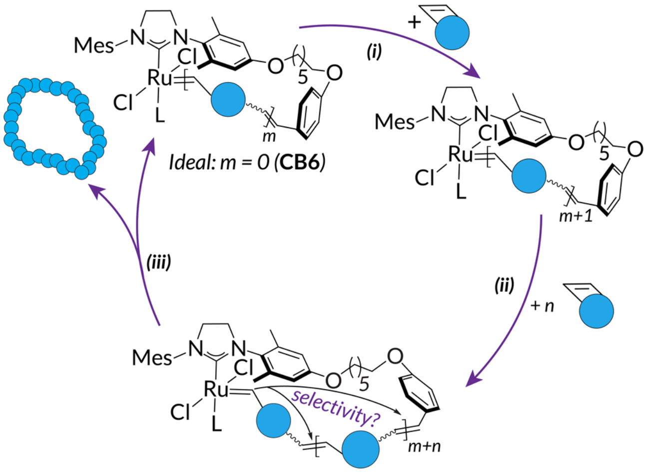


Figure 2. Accepted REMP mechanism depicting initiation (i), propagation (ii), and uncontrolled ring closure (iii).

observed. Polymerizations were initiated (Figure 2i) with **CB6** by addition to monomers in DCE. Reactions were stirred under nitrogen at 55 °C; the elevated temperature, previously shown to facilitate chain-transfer[30,33] in poly(norbornene)s, was employed to promote backbiting for ring formation (Figure 2iii).[49,58] Ideally **CB6** is regenerated upon release of cyclic polymer ($m = 0$), but in actuality the ring-closure step is not well controlled and a variety of sizes are produced. Evaluation of a variety of $[\mathbf{CB6}/\mathrm{M}]_0$ ratios revealed an increase in absolute weight-average molecular weight (M_w) with increased monomer loading (Table 1) as would be expected for a controlled polymerization. Backbiting kinetics and chain-transfer equilibria[45] likely lead to the observed nonideal, albeit controlled, relationships between M_w and $[\mathrm{M}]_0$ (Figures S10 and S11). Importantly, neither monomer Lewis basicity nor steric encumbrance affected the activity of **CB6** significantly. To compare against the current state-of-the-art, analogous REMP reactions initiated with **UC5** were performed. Although saturated variants (i.e., **SC5**) are more active than unsaturated ones, the former is a capricious complex; in our hands, we were unable to isolate sufficient quantities of pure **SC5**. Hence, we opted to compare against the more widely adopted[12,18,42−44,52,54,55] unsaturated **UC5**. Previous accounts of Ru-REMP with Nb monomers led to high molecular weight products;[57,59,61] consistent results were obtained in a direct comparison of polymers produced from **CB6** with those produced from **UC5** (Table 1). Polymerizations initiated by **CB6** are more controlled and afford molar masses closer to theoretical values, suggesting improved initiator efficiency. These differences may be due in part to stark differences in kinetics (*vide infra*) and clearly demonstrate a significant advantage of **CB6** over **UC5** as a REMP initiator.

To evaluate the cyclic polymer architecture accessed from **CB6**, polymers derived from **G2** and **CB6** with the same number-average molecular weight (M_n) were analyzed by GPC-MALS-IV. A comparison between linear and cyclic polymers with identical molar masses reveals the macrocycle's smaller hydrodynamic radius (i.e., longer retention time) and lower intrinsic viscosity.[1−3,60] Indeed, plots of molar mass versus retention time for polymers initiated with **G2** and **CB6** (M_n = 183 kDa for AcNb polymers and M_n = 170 kDa for BnNb polymers) reveal that the cyclic structures have larger molar masses than linear ones at any given retention time

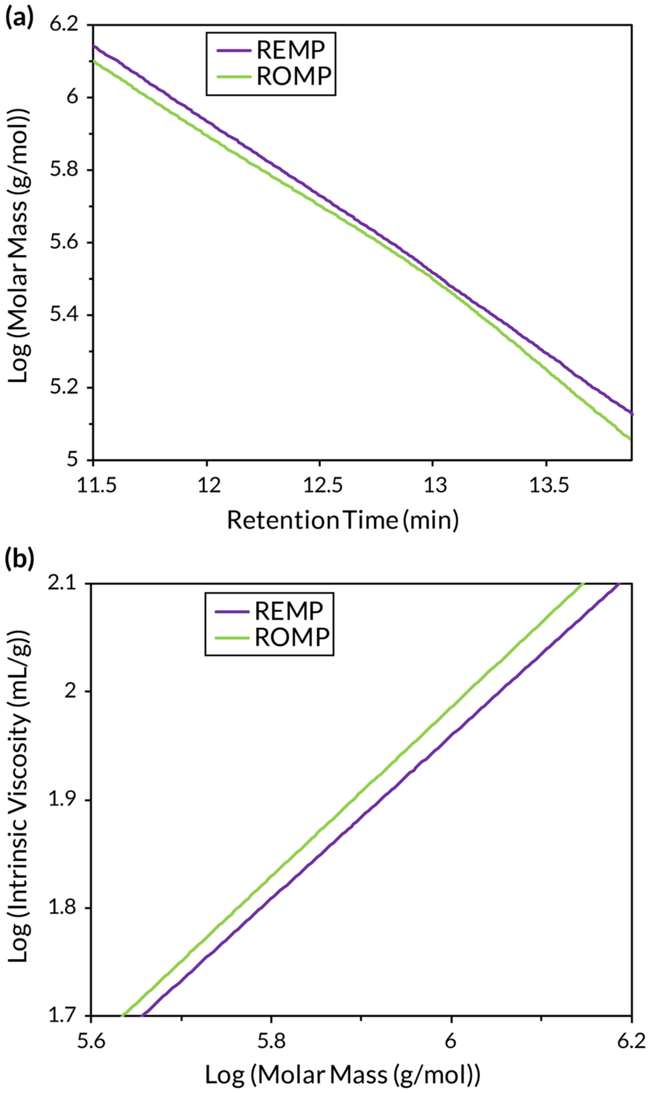


Figure 3. (a) Log(molar mass) versus retention time plot and (b) Mark−Houwink−Sakurada plot obtained for REMP (purple) and ROMP (green) of AcNb. GPC-MALS-IV data were collected in $CHCl_3$ at 35 °C.

(Figure 3a and Figure S12). Evaluation of Mark−Houwink−Sakurada (MHS) plots for the same groups of polymers reveals that $\eta_{\mathrm{cyclic}}/\eta_{\mathrm{linear}} \approx 0.93$ for both AcNb and BnNb polymers (Figure 3b and Figure S13); as expected, the cyclic polymers have a lower intrinsic viscosity than the corresponding linear polymers ($\eta_{\mathrm{cyclic}} < \eta_{\mathrm{linear}}$). Additionally, both pairs of polymers have nearly identical MHS *a* values (0.754−0.783 for poly(AcNb) and 0.742−0.735 for poly(BnNb)), which confirms similar backbone-independent conformations. Previous works report $\eta_{\mathrm{cyclic}}/\eta_{\mathrm{linear}}$ ratios between 0.33 and 0.92;[9,37−41,62−69] it is unclear if these discrepancies are due to sample purity, backbone-related phenomena, or M_n dependence on viscosity.

Polymerization kinetics (Figure 2i,ii) of AcNb using either **UC5**, **CB6**, or **G2** were studied *in situ* using ^{1}H NMR spectroscopy (DCE-d_4, 55 °C). Reactions initiated with **UC5** showed sluggish rates as expected based on previous work by Grubbs[44,45] (Figure 4a). Excitingly, reactions initiated with **CB6** showed a drastic increase in rate compared to that of **UC5**. In under 5 min, full monomer conversion was observed

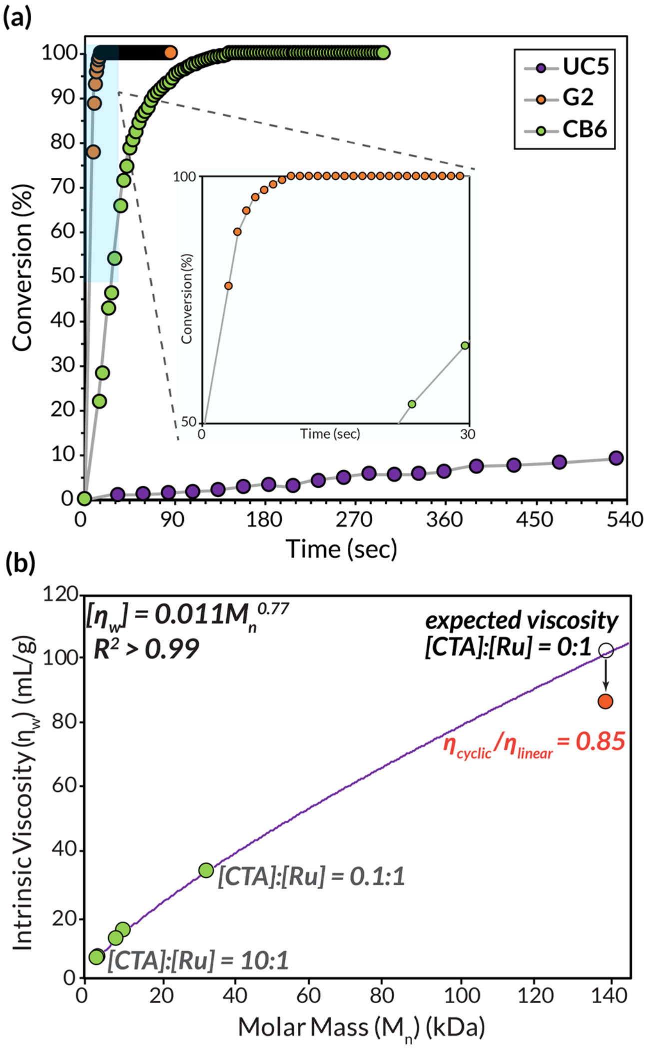


Figure 4. (a) AcNb monomer consumption ($[AcNb]_0$ = 1 mM, [I/AcNb] = 1:50) monitored by ^1H NMR spectroscopy (55 °C in DCE-d_4) and (b) Mark–Houwink–Sakurada plot obtained during REMP of AcNb with **CB6** in the presence of 3-hexene.

using **CB6**, while **UC5** effected <10% monomer conversion. The structural similarities between **CB6** and **G2** undoubtedly led to the difference in kinetics. For polymerizations of AcNb (Figure S15) and BnNb (Figure S16) with **CB6**, a sharp increase in M_w occurred just after full monomer consumption, followed by a quick decrease in M_w. The equilibrium-controlled molar mass[45] is nearly reached in 3 h, providing expedited kinetics compared to that of **UC5**.

In accordance with efforts to make REMP a more accessible technology, we sought to evaluate the stability of **CB6**. Solution-state stability is also important because linear impurities generated during REMP are often attributed to initiator decomposition.[70] We monitored the characteristic benzylidene peak (or alkylidene peak in the case of **UC5**) of **CB6**, **UC5**, and **G2** in degassed benzene-d_6 as a function of time (Figure S3) by ^1H NMR spectroscopy. **CB6** is less stable than benchmark **G2** but persists longer in solution than **UC5**. Perhaps more importantly, **CB6** has a significantly longer shelf life (−20 °C under nitrogen) than **UC5**. **CB6** remains unchanged by ^1H NMR spectroscopy with similar activity for at least 5 months, while **UC5** decomposes over less than 3 months (Figures S6 and S7). As a final testament to the robustness of **CB6**, REMP on the benchtop *under air* ([I/AcNb] = 1:200) afforded a cyclic poly(norbornene) as determined by GPC-MALS-IV (Figure S14), albeit with considerably higher M_n than expected, presumably due to expedited initiator oxidation. Interestingly, the measured M_n (388 kDa) was still closer to the theoretical M_n than the M_n for the identical reaction conducted under an inert atmosphere with **UC5** (Table 1).

To further confirm that **CB6** initiated REMP resulted in cyclic polymers, we performed chain-transfer experiments using 3-hexene as the chain-transfer agent (CTA). We hypothesized that adding CTA would purposefully generate linear impurities. The linear fragments should follow a MHS relationship ($\eta = KM^a$) as a function of CTA concentration; deviation from this trend at $[CTA]_0 = 0$ would only be expected if there was a change in architecture. Accordingly, ROMP of AcNb with **G2** ($[I/M]_0$ = 1:200) in the presence of CTA ([CTA]/[Ru] = 0:1–10:1) afforded linear polymers that fit the MHS relationship (Figure S17). On the other hand, REMP of AcNb with **CB6** and **UC5** using identical CTA ratios produced polymers that also fit the MHS relationship, except when CTA was omitted (Figures 4b and S18). Because cyclic polymers have lower viscosities than their linear counterparts, the observed deviations suggest a change in cyclic to acyclic architecture upon addition of CTA. In other words, lower viscosity ($\eta_{cyclic}/\eta_{linear}$ = 0.77–0.85) polymers were only generated in the absence of CTA; chain transfer results in decreased molar masses and viscosities for linear structures and topological changes when cyclic macromolecules are present.

In summary, we demonstrated the superior utility of a novel cyclic Ru-NHC complex, **CB6**, to synthesize cyclic poly(norbornene)s. Based on the drastic improvements in molecular weight control, reaction kinetics, and initiator stability, **CB6** will serve as a building block for a platform of REMP initiators. A thorough understanding of the intimate relationship between initiator structure and subsequent performance within the REMP mechanism (Figure 2) will ultimately allow for broad control over cyclic macromolecule design.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c03491.

General experimental procedures and characterization, NMR data, GPC traces, crystallography data for CCDC 2073591, and DFT experiments and coordinates (PDF)

Accession Codes

CCDC 2073591 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare the following competing financial interest(s): T-W.W. and M.R.G. are inventors on Provisional Patent Application 63/171,474.

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