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Merrifield Resin-Assisted Routes to Second-Generation Catalysts for Olefin Metathesis

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Phosphine-scavenging resins can significantly facilitate the synthesis of highly active Ru metathesis catalysts, including the second-generation Grubbs, Hoveyda, and indenylidene catalysts (**GII**, **HII**, **InII**). These catalysts are customarily prepared by ligand exchange of the corresponding first-generation catalysts with the *N*-heterocyclic carbene (NHC) H_2IMes. The PCy_3, coproduct is conventionally removed by pentane extraction, but the partial solubility of the desired Ru products can cause product losses of over 20%. Sequestration of the PCy_3 coproduct with CuCl is more efficient, but is undesirable given the potential for non-innocent copper residues. Use of the arylsulfonic acid resin Amberlyst-15 delivers near-quantitative catalyst yields, but the high acidity of the resin leads to problems with reproducibility and decomposition. An alternative approach is described, in which a neutral Merrifield resin (crosslinked polystyrene with pendant *p*-$C_6H_4CH_2I$ groups; **MF-I**) is used to sequester PCy_3 as the covalently-tethered benzylphosphonium salt. Addition of **MF-I** following complete ligand exchange effects quantitative uptake of free PCy_3 (and any residual free NHC) within 45 min at RT: the clean products are isolated by filtration, in ca. 95% yield. These yields compare well with those obtained via the Amberlyst-15 route, without the challenges due to resin acidity. The efficacy of this methodology is demonstrated in the synthesis of isotopically-labelled derivatives of **HII**, in which the H_2IMes ligand bears a ^{13}C-label at the carbene carbon, or perdeuterated mesityl rings.

Introduction

Olefin metathesis offers powerful, versatile methodologies for the catalytic assembly of carbon-carbon bonds.[1,2] Ruthenium metathesis catalysts bearing an *N*-heterocyclic carbene (NHC) ligand, long embraced for synthetic purposes in academia, have now begun to see uptake in pharmaceutical manufacturing.[3] Despite prominent recent advances highlighting the potential of alternative ligand sets, particularly cyclic (alkyl)(amino) carbenes,[4] the "second-generation" Grubbs and Hoveyda catalysts **GII** and **HII** (Figure 1) continue to dominate current use. Clean, reproducible, high-yield routes to such complexes, as well as indenylidene analogue **InII**, are therefore of interest.

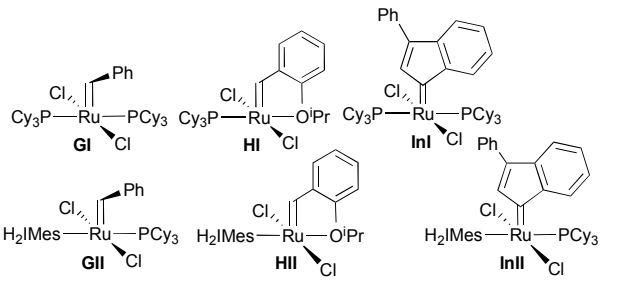
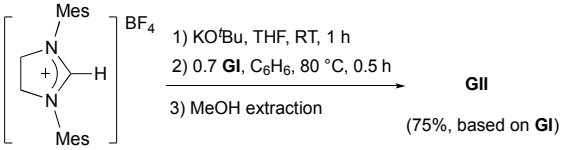


Figure 1. Metathesis catalysts discussed. Top: first-generation Ru catalysts, precursors to (bottom) the second-generation catalysts in dominant use.

These catalysts are typically accessed via ligand exchange reactions, in which a PCy_3 ligand present in the corresponding first-generation complex is replaced with H_2IMes. Classically, such routes rely on in situ generation and installation of H_2IMes•HX (X = Cl or HBF_4) with a strong base such as KO^{t}Bu, NaH, or potassium *t*-amylate ($KOCMe_2Et$).[5] Depicted in Scheme 1 is the original, still widely cited, synthesis of **GII** via this approach.[5c]



Scheme 1. Synthesis of **GII** via in situ liberation and installation of H_2IMes.

The continuing popularity of in situ NHC generation is

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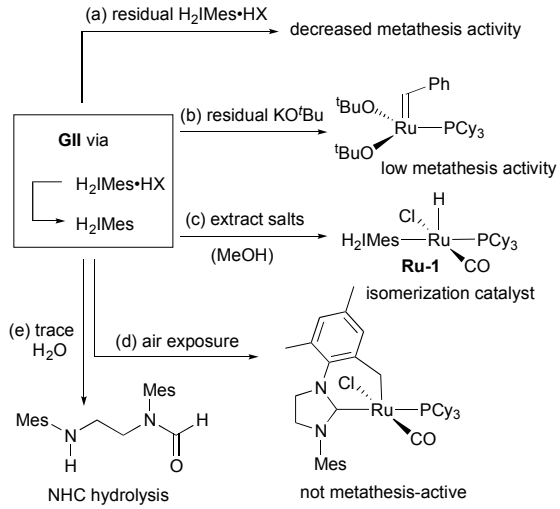
surprising, given problems pointed out in early reports.[6,7] The metathesis activity of **GII**, for example, was reported to be reduced by unreacted NHC•HX (Scheme 2a; this reagent is used in excess to ensure full conversion of **GI**), as well as residual alkali metal salts, likewise used in excess.[6] In the specific case of KO^{t}Bu, the side-reaction with **GI** generates Ru(O^{t}Bu)$_2$(PCy$_3$)(=CHPh) (Scheme 2b),[6] a complex known to exhibit minimal metathesis activity.[8] Quenching excess base with methanol is also problematic, as this generates Ru hydride contaminants,[6,7] including isomerization-active[9] **Ru-1**: Scheme 2c. (Such hydrides may plausibly originate in the conversion of methanol to methoxide ion, which reacts with **GI** and **GII** much more rapidly than does methanol itself).[10] Further, loss of the benzylidene ligand has been observed on adventitious admission of air during synthesis of **GII**[6] (Scheme 2d). Unintended exposure to air is a perennial risk for Schlenk reactions carried out at reflux, underscoring the convenience and reliability of the room-temperature, glovebox operations below.

Finally, no consensus exists on the reliability of the NHC•HCl salts, as compared to NHCs•HBF$_4$. Bantreil and Nolan reported lower yields for the IMes analogue of **GII** on using IMes•HCl, vs. IMes•HBF$_4$,[11] but the opposite claim has also been made.[6,12] Relevant in this context is Grela's comment that the yield of **GII** is extremely sensitive to the purity of the H$_2$IMes•HBF$_4$ reagent.[13] It should be noted that although the high crystallinity of H$_2$IMes•HBF$_4$ is a valuable aid to purification,[5a,11] this salt must be rigorously dried to remove water remaining from its synthesis, which otherwise hydrolyzes the free NHC as it is generated (Scheme 2e).[14]



Scheme 2. Exemplary problems in synthesis of **GII** via in situ liberation of H$_2$IMes.

High-yield routes to the leading Ru-H$_2$IMes metathesis catalysts (Table 1) typically utilize alternative sources of H$_2$IMes. Such sources include H$_2$IMes•CO$_2$,[15] which stands out among the many NHC adducts used to access metal-NHC derivatives for the innocuousness of the CO$_2$ byproduct.[16] Delaude and coworkers reported the synthesis of **GII** and **HII** by refluxing **GI** or **HI** with H$_2$IMes•CO$_2$, followed by chromatographic workup (Table 1, entries 1-2).[15,17]

We previously reported a convenient route involving reaction with free H$_2$IMes, and workup by addition of the acidic resin Amberlyst-15 (Figure 2a) to scavenge the PCy$_3$ byproduct.[14] This procedure offered two key advances over standard methods. First, use of the isolated free NHC (an approach pioneered by Nolan with IMes as pro-ligand)[11,18] prevents side-reactions arising from in situ liberation of the NHC.[19] Secondly, the use of Amberlyst-15 as a PCy$_3$ scavenger, originally described in a patent procedure by Verpoort and co-workers,[20] and subsequently adopted by our group and others for removal of PCy$_3$ or nitrogen bases,[14,21,22] was attractive for the simplicity and convenience of workup. Thus, workup requires only filtering off the resin once scavenging is complete, and evaporation of the filtrate.

Such straightforward purification procedures are considerably more time- and resource-efficient than removing the PCy$_3$ byproduct by column chromatography[5d] or extracting with pentane or hexanes.[5c] Amberlyst-assisted workup was initially found to improve isolated yields by 20% or more for **GII**, and ca. 15% for **HII**, vs. pentane extraction[14] (though see below). Also attractive was the elimination of concerns arising from the use of CuCl as a phosphine scavenger (Table 1, entries 2, 3, 5), as detailed below.

Table 1. Reported high-yield routes (>90%) to **GII**, **HII**, and **InII**

entry	catalyst (precursor)	NHC source	PCy$_3$ removal method	yield (scale)[a]	ref.
1	**GII** (**GI**)	H$_2$IMes•CO$_2$ (1.5 equiv)	chromatography	90% (1 g)	15
2	**HII** (**HI**)	H$_2$IMes•CO$_2$ (1.2 equiv)	1.2 CuCl chromatography	95% (0.4 g)	15
3	**HII** (**HI**)	H$_2$IMes•HBF$_4$ (1.2 equiv) + KO-CMe$_2$Et (1.3 equiv)	1.8 CuCl recrystallize from CH$_2$Cl$_2$–MeOH	92% (17.6 g)	13
4	**GII** (**GI**)	H$_2$IMes•HC$_6$F$_5$ (1.5 equiv)	chromatography	91% (0.16 g)	23
5	**HII** (**GII**)	n/a[b]	1.3 CuCl chromatography	97% (0.05 g)	24
6	**GII** (**GI**)	1 H$_2$IMes (1.1 equiv)	Amberlyst; "filter-and-strip"	96% (2.4 g)	14
7	**HII** (**HI**)	H$_2$IMes (1.1 equiv)	Amberlyst; "filter-and-strip"	98% (4 g)	14
8	**InII** (**InI**)	H$_2$IMes (1.1 equiv)	Amberlyst; "filter-and-strip"	95% (1 g)	14

[a] Scale based on mass of Ru precursor as limiting reagent. [b] Accessed by cross-metathesis (CM) of **GII** with 1,2 isoproxy-2-propenylbenzene. For strategic limitations to synthesis of **HII** via ligand exchange of **GI**, followed by metathesis of **GII**, see Scheme 5 and associated discussion.

CuCl is widely used to assist workup in the synthesis of metathesis catalysts, although Hoveyda's original report noted that it complicates chromatographic purification of **HII**.[5d] Grela and co-workers circumvented any such problems by developing a successful recrystallization procedure, used in one of the largest-scale syntheses of **HII** reported in the open literature (Table 1, entry 3).[13] More generally, copper-free scavenging protocols are desirable for deployment of metathesis catalysts in the pharmaceutical sector in compliance with current Good Manufacturing Practices

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(cGMP). Cu(I) halides mediate many catalytic transformations,[25] and copper residues are notorious for promoting unanticipated catalytic and/or redox chemistry.[26] Copper, along with iron, is indeed the one of the usual culprits in unplanned oxidations of pharmaceutical compounds catalyzed by trace metal impurities.[26d]

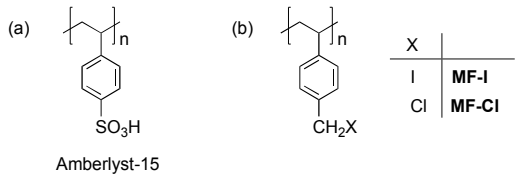


Figure 2. Molecular structures of the (a) Amberlyst and (b) Merrifield resins.

Sustained use of the alternative Amberlyst scavenging protocols, however, revealed limitations arising from the high acidity of the resin *p*-toluene sulfonic acid (pTSA)[27] groups. While the original experiments suggested that **GII** was stable toward Amberlyst-15 over 2 h in THF at RT,[14] problems with reproducibility and catalyst decomposition emerged in subsequent use, as detailed below. We therefore sought an alternative approach aimed at retaining the high yields and convenience of resin-enabled "filter-and-strip" workup, while circumventing the problems arising from the highly acidic pTSA scavenger.

Attractive from this perspective are Merrifield resins (e.g. **MF-I**, Figure 2b), benzyl halide-functionalized polystyrenes originally developed to assist solid-phase synthesis.[28,29] The Lipshutz group successfully employed in situ-generated **MF-I** to purify cross-coupling products synthesized via Ni or Pd catalysis.[30] Morris and co-workers found it advantageous to isolate the resin, which they used to sequester PPh_3 byproducts (and trace phosphine oxides) generated during synthesis of ruthenium hydride complexes.[31] Inspired by these successes, we examined the utility of the Merrifield resin **MF-I** in ligand-exchange routes to **GII**, **HII**, and **InII**, selected as the dominant metathesis catalysts in current use. Here we report the success of this approach, illustrated with synthesis of all three of these benchmark catalysts, as well as isotopically-labelled **HII**, in which the H_2IMes ligand bears a ^{13}C-label at the carbene carbon, or perdeuterated mesityl rings.

Results and discussion

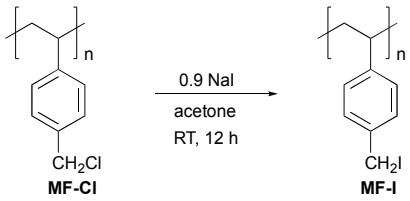
Problems with Amberlyst-15.

Initial problems with the Amberlyst-15 methodology were manifested in stoichiometric irreproducibility. Specifically, higher proportions of Amberlyst-15 were required (relative to our originally-optimized 4:1 ratio of resin pTSA groups vs. Ru),[14] to completely scavenge free PCy_3. The reaction stoichiometry is, unsurprisingly, highly sensitive to resin storage conditions. While glovebox storage maximizes convenience, the avidity of the resin for volatile base (pyridines, amines) was apparent even when Amberlyst-15 was stored in well-taped vials, and opened only after purging the glovebox atmosphere. Beyond the requirement for additional resin when using Amberlyst-15 handled under these conditions, additional, unidentified signals were evident in $^{31}P\{^1H\}$ NMR spectra of **GII** "purified" via workup with this material (Figure S9). Best practices thus involve bringing in fresh resin for each use, and ensuring that the stock supply is stored in a cabinet free of chemical vapours.

Even with clean resin, however, decomposition was occasionally apparent on treating **GII** with Amberlyst-15 in THF. In one case, 15% loss of **GII** was detected by integration of the alkylidene singlet against an internal standard, after stirring a clean sample of the catalyst with the resin in THF for 2 h. While Amberlyst-15 is much more aggressive toward **GII** alone than during workup, when free PCy_3 and **GII** are simultaneously present, this highlights undesirable potential risks.

Synthesis of the Merrifield-Iodide Resin.

Preliminary experiments indicated that the benzyl chloride resin **MF-Cl** can sequester free PCy_3, but that reaction is inconveniently slow. Even for resin that is relatively lightly (1%) crosslinked with divinylbenzene, which permits better swelling, 30% PCy_3 remained after 20 h exposure to the resin at RT in THF. We therefore abandoned direct use of **MF-Cl**, instead converting it into the more electrophilic iodide resin **MF-I** via the established[30,31] reaction with NaI. Sub-stoichiometric proportions of NaI were used (Scheme 3), to ensure that the product resin is free of residual alkali iodide, which could contribute to formation of ruthenium iodide products.[31-33]



Scheme 3. Synthesis of the Merrifield Iodide Resin.

Merrifield Resin-Assisted Synthesis of GII.

In examining the capacity of **MF-I** as an aid to workup, we first focused on the transformation of **GI** into **GII** by reaction with free H_2IMes (Scheme 4). Adding the resin once exchange is complete enables removal of both the PCy_3 byproduct, and residual free NHC (which is used in 10% excess in these reactions, to ensure complete conversion of **GI**). THF was chosen as the reaction medium: chlorinated solvents are precluded by their reactivity toward the free NHC,[14,34] while aromatic solvents limit resin swelling,[35,36] retarding the S_N2 scavenging reaction.[14] It should be noted that greater bead fragility results from the choice of lightly crosslinked resins to aid in swelling. Controlled stirring rates (ca. 240 rpm) were therefore employed, to limit mechanical damage to the beads, and conserve consistent reaction stoichiometry and rates.

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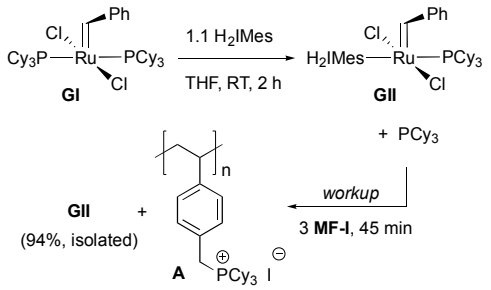
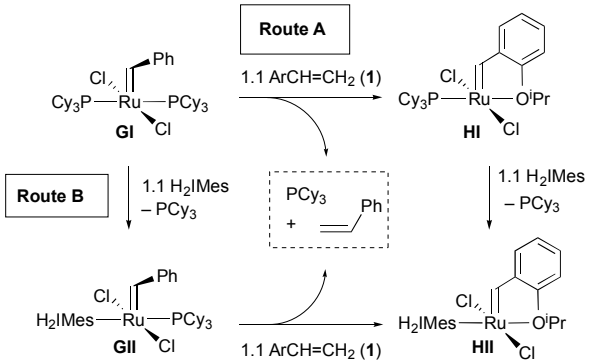


Scheme 4. Merrifield Resin-Assisted Synthesis of **GII**.

Addition of a twofold excess of **MF-I**, relative to **GI**, effected complete removal of free PCy_3 within 1.5 h, as judged by $^{31}P\{^1H\}$ NMR analysis. This period was reduced to 45 min by increasing the resin stoichiometry to 3:1. Reactions on preparative scale (3 g; Scheme 4) proceeded smoothly under these conditions, with complete reaction after 45 min. The mixture was immediately filtered through Celite to remove the phosphonium iodide-bearing resin **A**. (Minimizing exposure times of the catalyst to the resin is a precaution against salt metathesis,[31-33] the onset of which can be observed on extended reaction: e.g. 1% at 8 h; see below). The product was washed through the Celite pad with further THF, and the filtrate was evaporated. This procedure afforded clean **GII** (for spectra, see Figure S1) as a microcrystalline powder in 94% yield after drying. This is comparable to the yields obtained using the Amberlyst-15 resin. In comparison, workup by pentane extraction afforded **GII** in 75% isolated yield.[5c]

Merrifield Resin-Assisted Synthesis of HII.

The second-generation Hoveyda catalyst **HII** can be accessed from **GI** by either of the pathways shown in Scheme 5. Route A commences with synthesis of the first-generation Hoveyda catalyst **HI** via cross-metathesis of **GI** with *o*-isopropoxystyrene **1**. **HI** is then converted into the target **HII** by ligand exchange with H_2IMes. In the alternative Route B, ligand exchange of **GI** is carried out first, forming **GII**, and the styrenyl ether ligand is then installed via cross-metathesis with **1**.

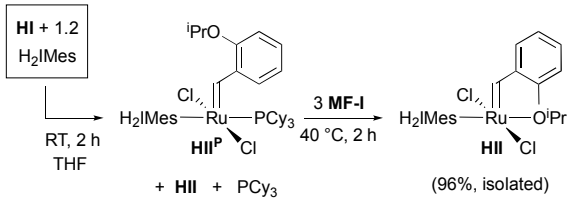


Scheme 5. Strategies for synthesis of **HII**. **Route A** (preferred): metathesis with **1**, then ligand exchange. **Route B**: ligand exchange, then metathesis. Ar = *o*-C_6H_4-O^{i}Pr.

Importantly, however, the styrene co-product of metathesis has no affinity for the resin (and nor do any stilbenes resulting from self-metathesis). To remove these byproducts, the Ru product must be purified by chromatography or extraction, either of which removes the PCy_3 coproduct along with styrene. There is thus no benefit to using the resin for post-metathesis workup (that is, after step 1 of Route A, or step 2 of Route B).

Finally, losses of 15-20% (extraction) or up to 10% (chromatography) are typically incurred in purification. Route A is therefore strategically preferable, in that maximum loss occurs in the first step, where the premium on materials and labour is least. The NHC ligand – synthesis of which is more demanding than that of **1**, even when the NHC is not isotopically labelled – is then installed in the second stage of reaction. Accordingly, the studies below focused on the capacity of **MF-I** to improve yields in the *second* step of Route A, the transformation of **HI** into **HII** via ligand exchange.

A challenge in the synthesis of **HII**, described in the original study by Blechert and co-workers,[37] is slow chelation of the ether group following reaction of **HI** with H_2IMes. The initial product is a κ^1-isopropoxystyrene intermediate with a dangling ether oxygen (**HII^P**; Scheme 6), chelation of which is inhibited by the low lability characteristic of PCy_3 trans to an NHC ligand.[38,39] Formation of **HII** is commonly driven by addition of CuCl and heating. Resin treatment proves an effective alternative. In this approach, a more specific embodiment of the strategy exemplified in Scheme 5 above, **HI** was treated with H_2IMes for 2 h at RT to effect transformation to **HII^P**. Addition of excess **MF-I** and heating for 2 h at 40 °C afforded clean **HII** as a green powder in 96% yield (Figure S2), after the usual filter-and-strip workup. In comparison, the original route gave **HII** in 85% yield after chromatographic purification.[5d]



Scheme 6. Merrifield Resin-Assisted Synthesis of **HII**.

Merrifield Resin-Assisted Synthesis of InII.

Synthesis of **InII** was undertaken via the procedure established for the IMes analogue.[40] Accordingly, an orange-brown solution of **InI** and H_2IMes in hexanes was heated at 60 °C (Scheme 7). Within ca. 10 min, the **InII** product began to deposit as a red-brown precipitate. $^{31}P\{^1H\}$ NMR analysis of the supernatant confirmed conversion of **InI** to **InII** and free PCy_3 after 2.5 h. Also present were two minor, unidentified singlets (45.7 and –4.6 ppm in $CDCl_3$; 3% of total integration.[41]

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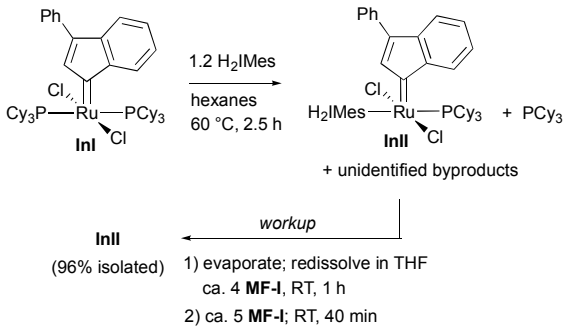

Scheme 7. Synthesis of **InII**.

To scavenge the free PCy_3, the solvent was evaporated on the Schlenk line, the residue was dissolved in THF, and a fourfold excess of **MF-I** was added. No free PCy_3 remained after stirring at RT for 1 h, as judged by NMR analysis, though traces of the byproducts remained (ca. 1% of total integration). Filtering and stirring with further **MF-I** for 40 min completely removed these species. Workup as before, by filtering through Celite to remove the resin, washing the product through with THF, and evaporating the filtrate, afforded clean **InII** as microcrystalline red-brown powder in 96% yield. In comparison, the Amberlyst route gave **InII** in 95% isolated yield; Delaude's $H_2IMes•CO_2$ route, with chromatographic workup, gave 86%,[15] and Nolan's synthesis of the IMes analogue, with pentane extraction of the PCy_3 byproduct, proceeded in 79% yield.[40]

Halide Exchange.

A potential concern at the outset of these studies was formation of Ru-iodide derivatives of the targeted metathesis catalysts, via exchange of the chloride ligands (Figure 3a). Halide exchange was observed in the Morris study, which deliberately exploited the phenomenon to synthesize the iodo catalyst RuHI(BINAP)(PPh_3).[31] In the context of metathesis, control over exchange is essential, given the impact of the anionic ligands on catalyst activity.[32,33,42]

To probe the potential for resin-induced halide exchange, the catalysts were stirred with a fourfold excess of **MF-I** at RT in THF, with dimethyl phthalate (DMT) present as an NMR integration standard. This test, carried out with the isolated catalysts in the absence of any free PCy_3, is deliberately more aggressive than the scavenging reaction, in which uptake of PCy_3 damps the reactivity of the resin, as noted above. As shown in Figure 3b, no change was observed for **InII** after 8 h. For **HII**, no change was evident at 6 h, although 1% of the known[32] mono-iodide species **HII-I** was detected at 8 h, as a singlet at 16.29 ppm. For **GII**, 1% **GII-I** was likewise present at 8 h (assigned based on its transient observation on the independently-examined reaction of **GII** with NaI, en route to known[43] **GII-I_2**). Of greater concern was the observation of an as-yet unidentified decomposition pathway for **GII**, which caused slow loss of the benzylidene signal. No decomposition was evident at 2 h, however, or – more pertinently – on the 45-minute timescale of the Merrifield-scavenging chemistry described above (see Figures S1–3). Nevertheless, this underscores the importance of removing **MF-I** promptly, particularly for **GII**, once PCy_3 scavenging is complete.

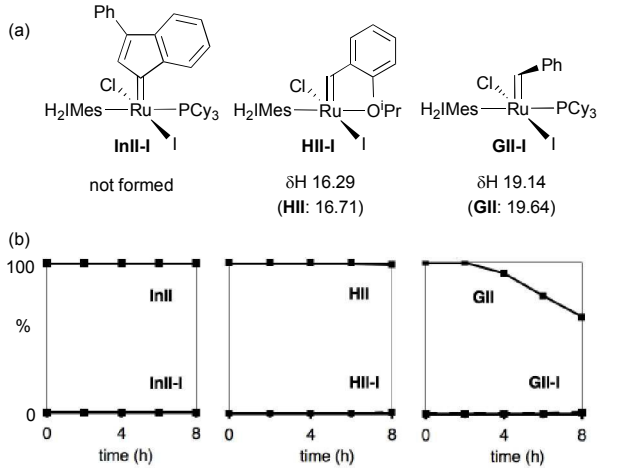

Figure 3. (a) Observed (**GII-I, HII-I**) or prospective (**InII-I**) mono-iodide species following reaction of isolated **GII**, **HII**, or **InII** with **MF-I** (4 equiv; 8 h, RT). (b) Assessing decomposition and halide exchange vs. DMT as internal standard.

Merrifield Resin-Assisted Synthesis of Isotopically-Labelled Metathesis Catalysts.

In a final set of experiments, we deployed these methodologies to aid in synthesis of isotopically labelled metathesis catalysts. We were particularly interested in derivatives of **HII** containing ^{13}C-labelled H_2IMes and d_{22}-H_2IMes, which could (respectively) report on the retention and/or activation of the NHC ligand during catalysis. The Piers group described a route to d_{22}-H_2IMes, in which the mesityl groups are fully deuterated,[44] and used this ligand to confirm that C–H activation of the Mes *o*-methyl groups is key to decomposition of the Piers catalyst, [$RuCl_2(H_2IMes)(=CHPCy_3]X$ (X = various counter-anions). ^{13}C-labelled H_2IMes, in which the label is sited at the carbene carbon, has not been reported, although a number of reports describe the corresponding *unsaturated*, ^{13}C-labelled NHCs, including ^{13}C-IMes.[45] Studies with the latter have demonstrated the potential for important insights into reaction chemistry involving the NHC ligand during catalysis. Ruthenium catalysts for olefin metathesis have been prepared with a ^{13}C label at the benzylidene,[46,47] methylidene,[48] and indenylidene[49] carbons, and at the metallacyclobutane ring carbons.[50,51] The present work is the first report of a metathesis catalyst in which the NHC ligand bears a ^{13}C-label at the carbene carbon, directly bound to the Ru center. The ^{13}C-NHC ligand can thus report directly on the stability of the Ru-NHC bond, on oxidation or attack at the NHC carbon, and (via, e.g., $^3J_{CH}$ coupling) on other spin-active ligands present on the metal.

Arduengo's now-classic synthetic route to non-labelled H_2IMes begins with cyclization of diamine **2** with triethyl orthoformate, the latter being used as both solvent and carbon source.[5a,52] As use of the labelled orthoformate as solvent is cost-prohibitive, and probe reactions in alternative

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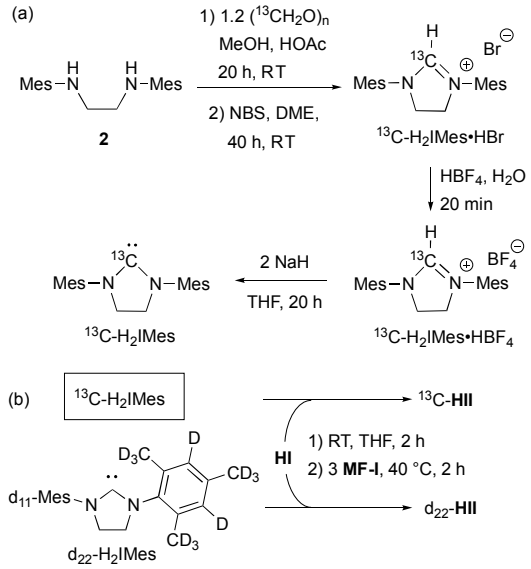
solvents proved unsatisfactory, we turned to ^{13}C-labelled paraformaldehyde, $^{13}(CH_2O)_n$, the carbon source utilized to access ^{13}C-IMes and related unsaturated NHCs.[45c–e] Thus, a suspension of diamine **2** and $^{13}(CH_2O)_n$ (1.2 equiv; Scheme 8a) in DME was stirred for 20 h at RT, after which the crude product was treated with *N*-bromosuccinimide to afford labelled imidazolinium bromide ^{13}C-H_2IMes•HBr. The latter was converted into the labelled free carbene by treatment with NaH. Ligand exchange of **HI** with ^{13}C-H_2IMes was carried out as described above, with the **MF-I** workup enabling access to clean ^{13}C-**HII** in 93% yield (Scheme 8b). The corresponding reaction with d_{22}-H_2IMes was carried out to obtain deuterium-labelled d_{22}-**HII** in 92% yield.



Scheme 8. (a) Synthesis of ^{13}C-labelled H_2IMes.[a] (b) Resin-assisted synthesis of isotopically-labelled **HII**. [a] NBS = *N*-bromosuccinimide, DME = dimethoxyethane.

Conclusions

The foregoing describes an efficient route to second-generation metathesis catalysts, in which the neutral Merrifield resin **MF-I** greatly improves the convenience and reliability of purification. Addition of resin once ligand exchange of **GI**, **HI** or **InI** with free H_2IMes is complete results in sequestration of the free PCy_3 coproduct as the covalently-tethered benzylphosphonium salt. Excess NHC is likewise removed, and the clean products can be isolated by filtration in near-quantitative yields. The high yields are due to the convenient "filter-and-strip" workup, in place of standard pentane extraction or chromatographic purification methods, which are cumbersome and reduce final yields by up to ca. 20%. The Merrifield resin-assisted synthesis improves on process reliability relative to the prior resin workup, in which the highly acidic Amberlyst-15 resin was used to sequester PCy_3: it also obviates use of CuCl, residues of which are undesirable, particularly from the perspective of deploying these catalysts in pharmaceutical manufacturing. The efficacy of the new methodology was demonstrated in the synthesis of isotopically-labelled derivatives of **HII**, bearing a ^{13}C label at the carbene carbon (^{13}C-H_2IMes), or perdeuterated mesityl rings (d_{22}-H_2IMes). Efficient access to the labelled catalysts adds powerful capabilities for the mechanistic exploration of catalyst performance, including studies of catalyst decomposition, which will be reported in due course.

Experimental

Materials and methods.

Reactions were carried out under N_2 in a glovebox at room temperature (25 ± 2 °C), unless otherwise specified. Solvents (C_6H_6, hexanes, CH_2Cl_2 and THF) were dried and degassed using a Glass Contour solvent purification system and stored under N_2 over 4 Å molecular sieves. C_6D_6, $CDCl_3$ (Cambridge Isotopes) and deionized H_2O were freeze-pump-thaw degassed (5x), and the deuterated solvents were stored under N_2 over 4 Å molecular sieves for at least 12 h prior to use. NaI (99.5% purity) and Merrifield resin **MF-Cl** (4.5 mmol/g Cl loading; 1% cross-linked with divinylbenzene; 200–400 mesh) were purchased from Sigma-Aldrich and used as received. **GI**,[53] *N,N'*-dimesitylethane-1,2-diamine **2**,[54] and free H_2IMes[55] were prepared by the reported methods. Free H_2IMes was stored in the freezer (–35 °C) under N_2. NMR spectra were recorded on an Bruker Avance 300 NMR spectrometer at 23 ± 2 °C, and referenced to the residual proton signals of the deuterated solvents (^{1}H). Chemical shifts (δ), measured in parts per million (ppm), are reported relative to TMS (^{1}H, ^{13}C) or 85% external H_3PO_4 (^{31}P) at 0 ppm.

Synthetic procedures.

Synthesis of MF-I from MF-Cl. Reaction carried out using the reported procedure,[31] using lower proportions of NaI. **MF-Cl** (4.24 g, 19.1 mmol) was suspended in acetone (20 mL), and NaI (2.28 g, 17.2 mmol; 0.9 equiv) was added. The suspension was stirred for 16 h in air, after which the resin was filtered off and washed successively with degassed H_2O (4 x 100 mL), and acetone (2 x 100 mL). Yield after drying: 6.11 g (quantitative).

Resin-Assisted Synthesis of GII by Ligand Exchange. Solid white H_2IMes (1.23 g, 4.01 mmol, 1.1 equiv) was added to a solution of **GI** (3.00 g, 3.64 mmol, 1 equiv) in 80 mL THF. A colour change from purple to red occurred on stirring for 5 min at RT. Stirring was continued for 2 h, after which conversion to **GII** was complete (NMR). **MF-I** (3.63 g, 10.9 mmol, 3 equiv) was then added to sequester free PCy_3, and the mixture was stirred for 45 min. No free PCy_3 remained after this time. The resin was then filtered off (Celite), and **GII** was washed through with THF (3 x 3 mL). The filtrate was evaporated under vacuum to afford 2.91 g of clean red **GII** (94%). NMR chemical shifts agree with values reported in C_6D_6.[38] Key values are reproduced here for convenience. ^{31}P{^{1}H} NMR (C_6D_6, 121 MHz): δ 30.1 (s, *P*Cy_3).^{1}H NMR (C_6D_6, 300 MHz): δ 19.64 (s, 1H, Ru=C*H*Ph).

Resin-Assisted Synthesis of HII by Ligand Exchange. Solid H_2IMes (1.84 g, 5.99 mmol, 1.2 equiv) was added to a brown

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solution of **HI** (3.00 g, 4.99 mmol, 1 equiv) in 30 mL THF. The solution was stirred for 2 h at RT, at which point no colour change was evident, but conversion to **HII** and **HII^P** was complete. $^{31}P\{^1H\}$ NMR (THF, 300 MHz): δ 30.6 (s, **HII^P**), 10.9 (s, PCy_3); ratio 4:1. **MF-I** (4.65 g, 14.0 mmol, 2.8 equiv) was added, and the reaction was heated at 40 °C. After 2 h, the solution was dark green, and both transformation to **HII** and sequestration of PCy_3 were complete. The mixture was filtered through Celite, and the product was washed through with THF (3 x 3 mL). The combined filtrate was stripped of solvent to afford **HII** as a spectroscopically clean green solid (2.99 mg, 96%; Figure S2). NMR values agree with those reported.[5d] That for the benzylidene proton is provided here for convenience. ^1H NMR (C_6D_6, 300 MHz): δ 16.71 (s, 1H, Ru=C*H*Ph).

Resin-Assisted Synthesis of InII by Ligand Exchange. Reaction adapted from the reported procedure for the IMes analogue.[40] Thus, solid **InI** (0.31 g, 0.33 mmol, 1 equiv) was added to a stirred solution of H_2IMes (0.12 g, 0.39 mmol, 1.2 equiv) in hexanes (40 mL), and the mixture was heated to 60 °C. After 2.5 h, the colour had changed from orange-brown to dark red, and a red-brown precipitate had deposited. No **InI** remained in the solution, but two unassigned PCy_3 derivatives were present; $^{31}P\{^1H\}$ NMR ($CDCl_3$, 300 MHz): 45.7 (s), – 4.6 (s); ratio 3:1; 3% of total integrated intensity. Evaporation of the solvent gave a dark red powder. This was re-suspended in THF (20 mL) to form a slurry, to which **MF-I** (0.47 g, 1.43 mmol, 4.3 equiv) was added. The mixture was stirred at RT for 1 h, then filtered (Celite). The product was washed through with THF (3 x 2 mL). No free PCy_3 remained in the filtrate, though traces of the byproducts remained (ca. 1% of total integration). These disappeared on adding further **MF-I** (0.59 g, 1.77 mmol, 5.4 equiv) and stirring for 40 min. The resin was separated as before. Evaporation of the filtrate gave 0.30 g **InII** as a spectroscopically clean red-brown solid (96%; Figure S3). The $^{31}P\{^1H\}$ NMR chemical shift is in good agreement with that reported in C_6D_6.[56] $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ 26.9 (s, PCy_3).

Synthesis of ^{13}C-Labelled H_2IMes•HBr. In air. ^{13}C-Paraformaldehyde (61 mg, 1.97 mmol, 1.3 equiv) was added to a solution of *N,N'*-dimesitylethane-1,2-diamine (434 mg, 1.46 mmol) in 10 mL methanol. Acetic acid (0.17 mL, 2.97 mmol; 2.0 equiv) in 2 mL methanol was added dropwise to the stirred reaction mixture. Stirring was continued for 10 h, after which the solvent was removed under vacuum to afford the cyclic product. This was dissolved in DME (6 mL) and treated with *N*-bromosuccinimide (305 mg, 1.71 mmol; 1.1 equiv). A white precipitate deposited over 40 h, which was filtered off and washed with cold DME (3x). Yield: 468 mg (82%). NMR chemical shifts are in reasonable agreement with values reported for the chloride salt in dmso-d_6,[52] with the addition of ^{13}C splitting. ^1H NMR ($CDCl_3$, 300 MHz, 298 K): δ 8.87 (d, $^1J_{HC}$ = 204 Hz, 1H, NC*H*N), 6.92 (s, 4H, Mes C*H*), 4.61 (s, 4H, CH_2), 2.37 (s, 12H, Mes *o*-CH_3), 2.26 (s, 6H, Mes *p*-CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 Hz, 298 K): δ 159.0 (N*C*HN), 140.6 (Mes *C*), 135.0 (Mes *C*), 130.1 (Mes *C*H), 52.0 (*C*H_2), 21.0 (Mes *p*-*C*H_3), 18.1 (Mes *o*-*C*H_3).

Synthesis of ^{13}C-H_2IMes•HBF_4. In air; variant on the method reported for the unsaturated salt.[11] The dibromide salt (0.460 g, 1.18 mmol) was stirred vigorously in 50 mL water to effect complete dissolution. After 20 min, a solution of HBF_4 (40% w/w in water; 0.80 mL, 4.37 mmol; 3.4 equiv) was added dropwise. The product precipitated as a white solid, which was filtered off, suspended in Et_2O, filtered again, and dried for two days to ensure complete removal of water prior to liberating the free carbene. Yield: 0.420 g (90%). ^1H NMR ($CDCl_3$, 300 mHz, 298 K): δ 7.90 (d, $^1J_{HC}$ = 205 Hz, 1H, NC*H*N), 6.96 (br s, 4H, Mes C*H*), 4.52 (s, 4H, CH_2), 2.34 (s, 12H, Mes *o*-CH_3, 2.29 (s, 6H, Mes *p*-CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz, 298K): δ 158.6 (NCHN), 141.2 (Mes *C*), 134.9 (Mes *C*), 130.2 (Mes *C*), 51.9 (*C*H_2), 21.1 (Mes *p*-*C*H_3), 17.7 (Mes *o*-*C*H_3).

Synthesis of Free ^{13}C-H_2IMes. In the glovebox, NaH (33 mg, 1.31 mmol; 3.3 equiv) was added to a suspension of ^{13}C-labelled H_2IMes•HBF_4 (156 mg (0.425 mmol) in 15 mL THF. The reaction was stirred for 18 h before filtering through Celite. The filtrate was stripped to dryness. The residue was redissolved in benzene, filtered through Celite, and stripped of solvent to yield a tan solid. Yield: 88 mg (63%). NMR chemical shifts are consistent with reported[52] values, with the addition of the ^{13}C splitting indicated. ^1H NMR (C_6D_6, 300 MHz, 298 K): δ 6.82 (s, 4H, Mes C*H*), 3.26 (s, 4H, CH_2), 2.29 (s, 12H, Mes *o*-CH_3), 2.16 (s, 6H, Mes *p*-CH_3). $^{13}C\{^1H\}$ NMR (C_6D_6, 75.5 MHz, 298 K): δ 243.5 (N*C*N), 139.2 (d, $^2J_{CC}$ = 9.7 Hz, Mes C_i), 135.8 (d, $^3J_{CC}$ = 1.3 Hz, Mes C_i), 129.4 (Mes *C*H), 50.3 (d, $^2J_{CC}$ = 75.6 Hz, CH_2), 20.5 (Mes *p*-CH_3), 17.7 (Mes *o*-CH_3).

Resin-Assisted Synthesis of ^{13}C-HII. As for the synthesis of **HII** above, but by reaction of ^{13}C-H_2IMes (8 mg, 0.013 mmol, 1.1 equiv) with **HI** (14 mg, 0.023 mmol, 1 equiv) in 2 mL THF, and workup with **MF-I** (25 mg, 0.075 mmol, 3 equiv). Yield: 14 mg, 93%. NMR chemical shifts agree with those above, barring additional splitting due to the ^{13}C label.

Resin-Assisted Synthesis of d_{22}-HII. As for **HII**, using d_{22}-H_2IMes (11.5 mg, 0.035 mmol, 1.4 equiv) with **HI** (15.1 mg, 0.025 mmol, 1 equiv) in 3 mL THF, and treating with **MF-I** (25 mg, 0.075 mmol, 3 equiv). Yield of **d_{22}-HII**: 15 mg, 92%. NMR chemical shifts agree with the values above for non-labelled **HII**, barring the absence of those due to the mesityl rings.

Control Experiments: Halide Exchange with MF-I.

Representative procedure. A solution of **GII** (10 mg, 0.01 mmol, 1 equiv) and DMT (2.3 mg, 0.01 mmol, 1 equiv) in THF (1 mL) was stirred at RT for 5 min. ^1H NMR analysis of an aliquot (stripped to dryness and suspended in C_6D_6) was used to establish the initial integration ratio of substrate to DMT. This material was evaporated, redissolved (THF) and returned to the reaction mixture. **MF-I** (16.0 mg, 0.04 mmol, 4 equiv) was added, and the reaction was stirred at RT for 8 h. Aliquots were taken every 2 h to assess loss of **GII** and formation of **GII-I**. ^1H NMR (C_6D_6, 300 MHz, at 8 h): δ 19.64 (s, 1H, Ru=C*H*Ph for **GII**, 99%), 19.43 (s, 1H, Ru=C*H*Ph for **GII-I**, 1%). A similar procedure was used for **HII** and **InII**. For **InII**, which has no benzylidene proton, an isolated signal of the indenylidene ring protons was used (see Figure S3a).

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Conflicts of interest

There are no conflicts to declare.

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