ChemComm

Chemical Communications

This article can be cited before page numbers have been issued, to do this please use: J. Tomlinson, M. J. Muldoon and P. Dingwall, *Chem. Commun.*, 2026, DOI: 10.1039/D6CC03341E.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

ChemComm

View Article Online
DOI: 10.1039/D6CC03341E

COMMUNICATION

Anti-Markovnikov Hydration of Terminal Alkynes Mediated by N,N'-Bidentate-Ligated Ruthenium Catalysts: a Comparative Mechanistic Study

That'Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Jake Tomlinson,[a] Mark James Muldoon [a] and Paul Dingwall*[a]

Mechanistic studies of the *anti*-Markovnikov hydration of terminal alkynes mediated by *N,N'*-bidentate-ligated ruthenium catalysts are reported. Electronically-asymmetric 2-(2-pyridyl)-benzoxazoles show higher activity compared to standard 2,2'-bipyridyl ligands. Detailed *in situ* NMR has allowed for the quantification of active catalytic species, and new mechanistic insights were obtained from kinetic and isotopic labelling studies.

The addition of water to terminal alkynes is an atom-economical and chemically green method of generating valuable carbonyl compounds from feedstock chemicals. Many transition metal catalysts are known to react with Markovnikov selectivity, forming methyl ketones (Figure 1).[1] The *anti*-Markovnikov hydration of terminal alkynes is dominated by Ru^{II} piano-stool complexes, generally featuring the $[RuCp]^+$ fragment (Cp = cyclopentadienyl),[2] although other transition metals have been reported to also perform this transformation.[3] Previously reported Ru catalysts have featured functionalised monodentate or bidentate arylphosphanes.[2a,4] Bifunctional arylphosphane ligands containing N-heterocycles which can form hydrogen bonding networks to assist substrate/catalyst binding,[2c,2e,5] or catalyst self-assembly via adenine/thymine base-pair analogous ligands,[6] have also shown high activity for this transformation.

In 2014, Herzon, Li and Zeng reported a highly selective and efficient catalyst featuring a 2,2'-bipyridyl (Bpy) ligand; [Ru-(CF_3-Bpy)] ((CF_3-Bpy) = 5,5'-bis(trifluoromethyl)-2,2'-bipyridine), which afforded product at 2 mol% loading at room temperature,[2f] building upon previous systems developed by the group for the reductive hydration of terminal alkynes.[7] Muldoon and co-workers have previously reported a series of electronically asymmetric 2-(2-pyridyl) benzoxazole (PBO) ligands, in a study examining palladium catalysed *tert*-butyl hydroperoxide mediated Wacker-type oxidation reactions,[8] finding them excellent catalysts for this challenging reaction.

We wondered whether PBO type ligands would be useful for alkyne hydration chemistry. This would further expand and diversify the limited pool of *N,N'*-bidentate ligands available for ruthenium-mediated alkyne hydration. While studying rates, the opportunity was taken to investigate the kinetics of the reaction and re-evaluate currently proposed mechanisms; these have been largely inferred from phosphane-based systems owing to the only relatively recent application of *N,N'*-bidentate ligands to this chemistry.[4-5,9]

A series of PBO ligands functionalised at the *meta*-position on the pyridyl ring were prepared, all in a single synthetic step

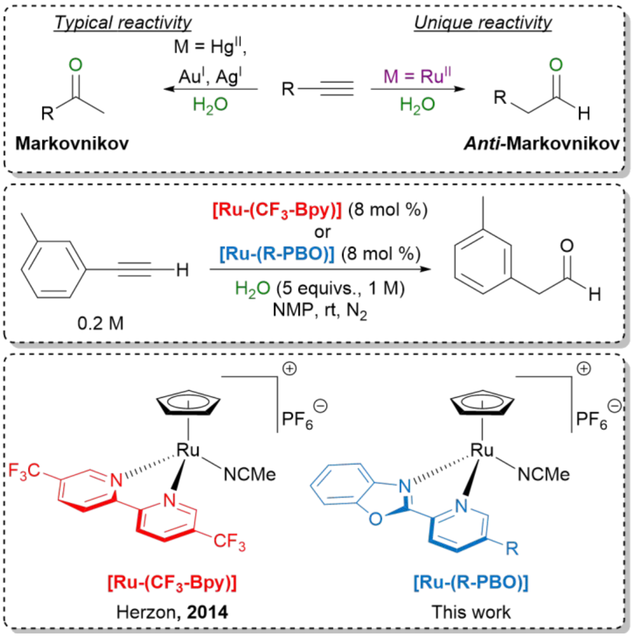

Fig 1 General scheme for transition metal mediated alkyne hydration showcasing regioselectivity of metals, reaction scheme for this work and catalysts studied.

---

[a] School of Chemistry and Chemical Engineering, Queen's University Belfast, David Keir Building, Stranmillis Road, Belfast, BT9 5AG (UK)

View Article Online
DOI: 10.1039/D6CC03341E

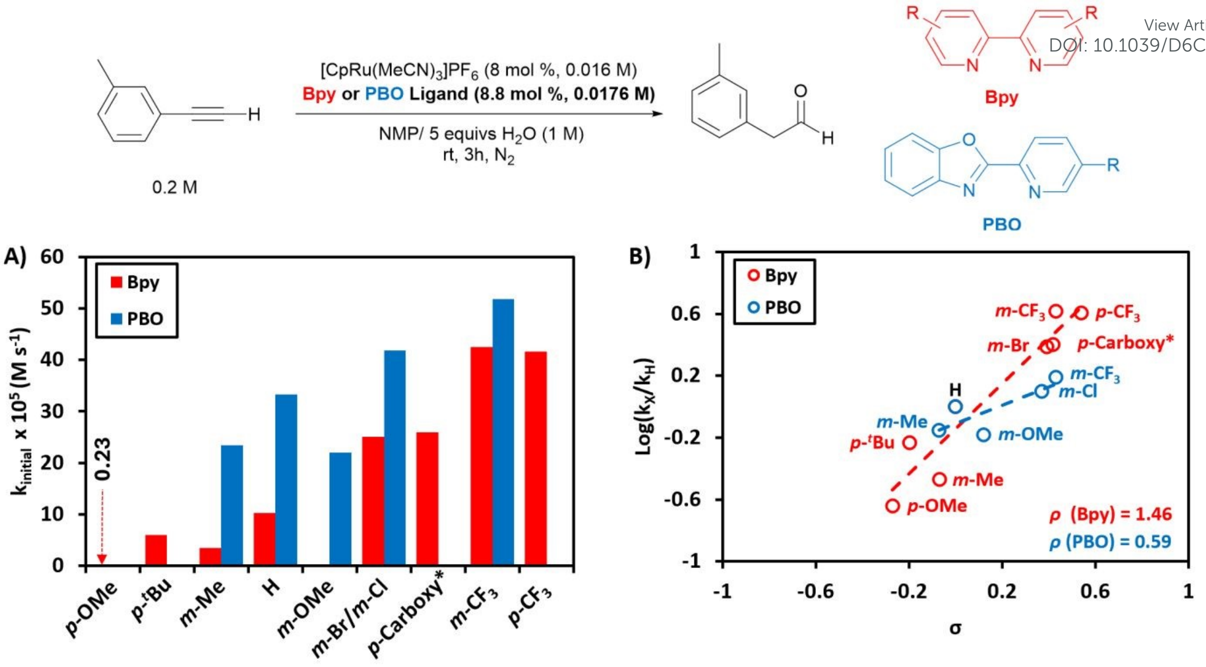

Fig 2 A) Direct comparison of initial rates for PBO vs Bpy ligands. **B)** Hammett plots for Bpy and PBO ligands showcasing relative rates based on ligand functionalisation. * σ^+ value used.

(see SI Section 9). Direct comparison of initial rates shows PBO ligands outcompete substituted Bpy ligand in all cases (Figure 2A). This is most pronounced for poorly performing electron-rich ligands: (*m*-Me)-PBO displays an increased rate of 6.7 times that of (*m*-Me)-Bpy. In contrast, the difference is smaller for the best performing ligands of each family, 2-(5-(trifluoromethyl)pyridny-2-yl)benzo[d]oxazole (5-CF$_3$-PBO) offering only a moderate rate increase of 1.2 times of CF$_3$-Bpy.

The differing degrees of electronic sensitivity between each ligand family led us to construct Hammett plots for both Bpy (Figure 2B, red) and PBO (blue) ligands, based on initial rate data. For both sets of ligands, a positive Hammett ρ value was obtained, agreeing with Herzon and co-workers single timepoint yield data.[2f] Interestingly, the ρ value obtained for Bpy (1.46) is approximately double that obtained for PBO (0.59). Due to the symmetrical nature of Bpy there are twice the number of additional functional groups in comparison to PBO, conveying at least twice the electronic effect and accounting for this significantly larger slope.

Kinetic studies for Bpy and PBO systems were performed with the fastest ligand of each class, electron-poor CF$_3$-Bpy and 5-CF$_3$-PBO. Same-excess experiments revealed a small degree of irreversible catalyst deactivation for both ligands (Figure S3-4), leading to apparent catalyst orders greater than one.[10] While several factors were considered, including the formation of peroxides within the NMP solvent,[11] we believe the source of deactivation is most likely trace amounts of oxygen (see SI S3.1).

Rate data was collected using the single-scan *in situ* NMR techniques developed by Flook and Lloyd-Jones.[12] This technique has previously monitored reaction intermediates at as low as 150 μM concentrations. Pleasingly, we were able to observe catalyst speciation for both ligand systems which remained in near constant concentration over the course of the reaction (see SI Section S4). This supports that deactivation was a one-off event prior to reaction initiation, with *in situ* NMR allowing us to quantify active catalyst concentration and adjust accordingly for each kinetic experiment.[13]

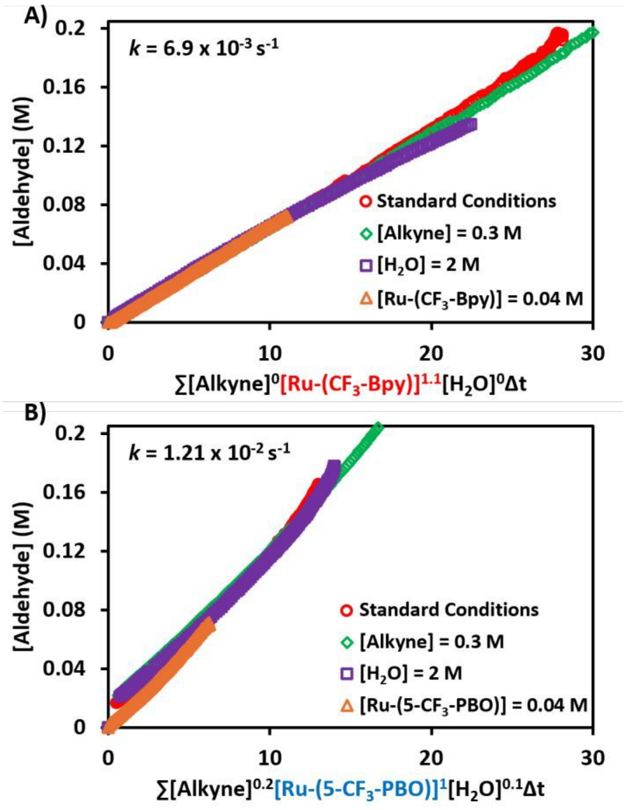

Fig 3 Full reaction orders obtained by VTNA studies for both [Ru-(CF$_3$-Bpy)] **(A)** and [Ru-(5-CF$_3$-PBO)] **(B)**. Concentration ranges, with bold indicating standard conditions: [Alkyne] = **0.2**-0.3 M, [Ru] = 0.004-**0.016** M, [H$_2$O] = **1**-2 M in NMP, room temperature, N$_2$.

View Article Online
DOI: 10.1039/D6CC03341E

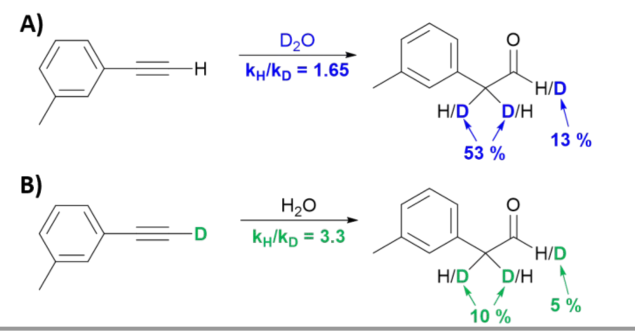

Fig 4 Results of kinetic isotope effect experiments and deuterium incorporation of isolated product. Experiments performed at standard concentrations: [Alkyne/Alkyne-*D*] = 0.2 M, [{CpRu(MeCN)$_3$}PF$_6$] = 0.016 M, [CF$_3$-Bpy] = 0.0176 M, [H$_2$O/D$_2$O] = 1 M, in NMP, room temperature, N$_2$.

Reaction orders were obtained using Variable Time Normalisation Analysis (VTNA),[10b,14] and were found to be almost identical for each system studied (Figure 3). For both systems, first order in catalyst, and zero order in both alkyne and water were obtained, suggesting a common mechanism with an identical rate determining step.

In situ ^{19}F NMR monitoring of the hydration of 2-fluorophenylacetylene yielded resonances belonging to catalyst-bound substrate and ligand -CF$_3$ groups (Figures S10, S17). Taken together with global zero-order kinetics, the catalytic resting state is likely a product bound species found after insertion of both substrates on the catalytic cycle, with the rate determining step involving the breakdown of the intermediate to release the product aldehyde.

Deuterium labelling studies were carried out (Figure 4). Using D$_2$O as the deuterium source, the corresponding product was found to have 53 % D-incorporation at the benzylic position, with 13 % deuterium found at the terminal aldehyde proton. Using alkyne-*D* as deuterium source instead revealed not only low deuterium incorporation at the aldehyde position (5 %), but also low deuterium incorporation at the benzylic position (10 %) (Figure 4B). When the reaction was performed using both alkyne-*D* and D$_2$O, low deuterium incorporation in the final product was also observed by ^{2}H NMR, which could suggest that the NMP solvent is non-innocent and may be acting as a proton shuttle during the reaction.

H/D scrambling was observed in both systems. ^{2}H NMR of the Figure 4B completed reaction mixture found formation of HDO, indicating that isotope exchange with H$_2$O had occurred during the reaction, accounting for D incorporation at the benzylic position. We observed an increase in the degree of protonation of alkyne-*D* of Figure 4A over the course of the reaction (Figure S22) which could not be attributed to H/D exchange under ambient conditions, suggesting that H/D scrambling was occurring in the presence of Ru catalyst only, reversibly and prior to the rate determining step.

Unexpectedly, both systems resulted in observable KIEs; k_{H2O}/k_{D2O} of 1.65 and a significant $k_{Alkyne\text{-}H}/k_{Alkyne\text{-}D}$ of 3.3. The large $k_{Alkyne\text{-}H}/k_{Alkyne\text{-}D}$ KIE does appear to run contrary to observed zero order kinetics in alkyne but can be explained by a scenario in which alkyne C-H/D bond cleavage is reversible and occurs before the rate determining step,[15] providing the equilibrium concentration of the species that reacts in the rate determining step is significantly affected by the substitution of a C-H for a C-D bond. This also fits with a scenario where the rate determining step comes after semi-reversible vinylidene formation. The smaller k_{H2O}/k_{D2O} also fits into this scenario if the observed H/D scrambling produces *in situ* alkyne-*D.*

To date, the mechanism for Ru-mediated alkyne hydration has been inferred from phosphane ligand systems reported by Wakatsuki and Tokunaga (Figures 5A and S24).[4,9] While some modifications have been suggested when ligands featuring strong hydrogen-bonding networks are employed,[5a,16] mechanism A is generally cited for almost all alkyne hydration and related hydrofunctionalisation chemistry.[17] The key *anti*-Markovnikov product determining intermediate is a ruthenium-vinylidene complex (Figure 5 **A3**), which increases the electrophilicity of the terminal α-carbon giving rise to *anti*-Markovnikov selectivity. However, mechanism A is suggested to proceed *via* Ru^{IV}-hydride complexes, **A3**-**A5**, which we could not

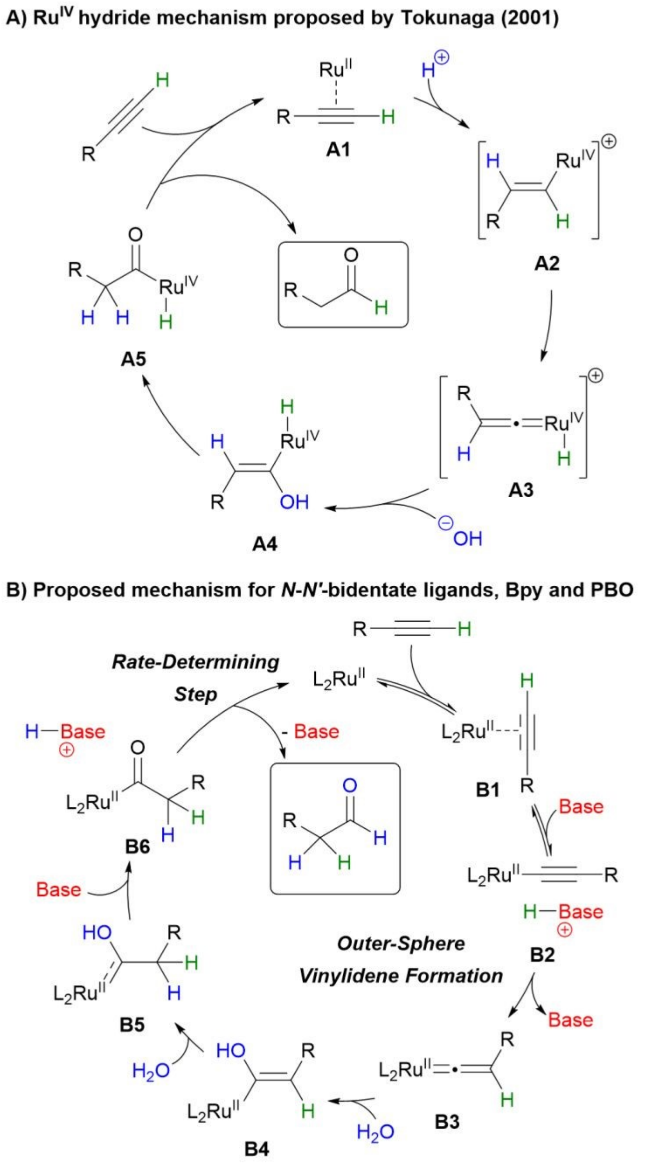

Fig 5 A) - Previously proposed mechanisms for ruthenium-catalysed *anti*-Markovnikov hydration of terminal alkynes. **B)** – Updated proposed mechanism for *N,N'*-bidentate ligand families; Bpy and PBO.

View Article Online
DOI: 10.1039/D6CC03341E

detect. Additionally, isotopic labelling studies using catalytically active complex RuCpCl(PPh_3)$_2$ found that the acetylenic proton was incorporated unambiguously as the product aldehyde proton,[9] contrary to our findings.

Our experiments, and observed differences to literature findings, prompted us to re-evaluate these mechanisms as applied to *N*,*N'*-bidentate ligands (Figure 5B). Initial coordination of the alkyne to the Ru centre (**B1**) proceeds to the product-determining vinylidene via outer-sphere deprotonation/protonation mechanism (**B2**-**B3**), as opposed to a Ru^{IV} hydride pathway **A3**, which we were unable to observe experimentally (Figure S14), facilitated by a base (H_2O, excess ligand, or solvent are potential bases with the pK_{aH} of NMP implicating it as the likely proton acceptor). η^2-coordination of the alkyne and subsequent deprotonation to form Ru-acetylide complex **B2** is likely to be reversible, in agreement with isotope labelling experiments. H/D scrambling is expected to occur on both the conjugate acid formed from the deprotonation of the alkyne (**B2**) and on the vinylidene itself (**B3**), as the pK_a of ruthenium vinylidene protons has been estimated at 11-13,[18] and have been shown to rapidly exchange with D_2O at room temperature.[19]

After formation of the vinylidene, the formal addition of water occurs via two steps. Addition of -OH via nucleophilic attack at the electrophilic vinylidene α-carbon forms Ru α-hydroxy vinyl complex (**B4**), which is protonated by a second equivalent of water to yield Ru hydroxyalkyl complex (**B5**). Deprotonation of the hydroxyl group facilitates the formation of Ru acetyl complex (**B6**), yielding the aldehyde via protonolysis, which kinetic, Hammett and spectroscopic evidence suggest as rate-determining. Global zero order kinetics and lack of deuterium incorporation at the aldehydic position strongly implicate NMP solvent involvement in proton transfer.

Ke and co-workers have reported a similar mechanism in their detailed theoretical study of Ru-mediated reductive hydration of alkynes.[20] Re-examining Ke's potential energy surface, an energy span analysis supports product protonolysis as a possible rate determining step (SI section S7) adding complementary theoretical support to our experimental work.

In conclusion, we have shown that PBO ligands provide a new family of *N*, *N'*-bidentate ligands for the *anti*-Markovnikov hydration of terminal alkynes. Compared to the previously reported Bpy ligands, PBO offers unanimously improved reactivity, particularly for electron-rich PBOs, where Bpy offers much poorer general performance. However, that the two best ligands of each class, CF_3-Bpy and 5-CF_3-PBO, offering similar reactivity suggests that the improved performance of PBOs may be more intricate than the electronic asymmetry of the PBO ligand scaffold, and further investigation is needed to conclusively determine the governing factors that account for the trend in reactivity shown in this study. Detailed *in situ* NMR studies have allowed for catalyst speciation to be observed during reaction monitoring. Mechanistic studies have revealed valuable information, particularly regarding the reversibility of pre-rate-determining steps and the effects of isotope labelling studies. An updated mechanism, supported by existing literature theoretical studies, has been proposed based on the experimental evidence reported.

Author Contributions - Conceptualisation and supervision were undertaken by PD and MJM. Investigation and data curation was performed by JT. All authors were responsible for writing and editing of the prepared manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

Characterisation data for all synthesised compounds and details on NMR acquisition and processing methods is included in the Supplementary Information (SI). Due to the large file sizes of the *in situ* NMR datasets generated, they are not available via a data repository but are available on request from the authors.

Notes and references

1. a) Y. Fukuda and K. Utimoto, *J. Org. Chem.*, 1991, **56**, 3729-3731; b) E. Mizushima, K. Sato, T. Hayashi and M. Tanaka, *Angew. Chem. Int. Ed.*, 2002, **41**, 4563-4565; c) N. Marion, R. S. Ramón and S. P. Nolan, *J. Am. Chem. Soc.*, 2009, **131**, 448-449; d) P. Nun, R. S. Ramón, S. Gaillard and S. P. Nolan, *J. Organomet. Chem.*, 2011, **696**, 7-11; e) J. Tauchman, M. Carvalho and P. Štěpnička, *Collect. Czech. Chem. Commun.*, 2011, **76**, 1277-1283; f) X. Li, G. Hu, P. Luo, G. Tang, Y. Gao, P. Xu and Y. Zhao, *Adv. Synth. Catal.*, 2012, **354**, 2427-2432; g) T. Tachinami, T. Nishimura, R. Ushimaru, R. Noyori and H. Naka, *J. Am. Chem. Soc.*, 2013, **135**, 50-53; h) Y. Zhou, Q. Liu, W. Lv, Q. Pang, R. Ben, Y. Qian and J. Zhao, *Organometallics*, 2013, **32**, 3753-3759; i) H. He, C. Qi, X. Hu, Y. Guan and H. Jiang, *Green Chem.*, 2014, **16**, 3729-3733; j) Z. M. Zhang, L. H. Wu, J. H. Liao, W. Q. Wu, H. F. Jiang, J. X. Li and J. W. Li, *J. Org. Chem.*, 2015, **80**, 7594-7603; k) T. Kusakabe, Y. Ito, M. Kamimura, T. Shirai, K. Takahashi, T. Mochida and K. Kato, *Asian J. Org. Chem.*, 2017, **6**, 1086-1090; l) A. Y. Rulev and D. A. Ponomarev, *Angew. Chem. Int. Ed.*, 2019, **58**, 7914-7920; m) A. Mariconda, M. Sirignano, R. Troiano, S. Russo and P. Longo, *Catalysts*, 2022, **12**.
2. a) T. Suzuki, M. Tokunaga and Y. Wakatsuki, *Org. Lett.*, 2001, **3**, 735-737; b) D. B. Grotjahn and D. A. Lev, *J. Am. Chem. Soc.*, 2004, **126**, 12232-12233; c) D. B. Grotjahn and D. A. Lev, *Catalysis of Organic Reactions*, 2005, **104**, 227-236; d) A. Labonne, T. Kribber and L. Hintermann, *Org. Lett.*, 2006, **8**, 5853-5856; e) F. Boeck, T. Kribber, L. Xiao and L. Hintermann, *J. Am. Chem. Soc.*, 2011, **133**, 8138-8141; f) L. Li, M. Zeng and S. B. Herzon, *Angew. Chem.*, 2014, **126**, 8026-8029.
3. R. Salvio and M. Bassetti, *Inorg. Chim. Acta.*, 2021, **522**, 120288.
4. M. Tokunaga and Y. Wakatsuki, *Angew. Chem. Int. Ed.*, 1998, **37**, 2867-2869.
5. a) D. B. Grotjahn, E. J. Kragulj, C. D. Zeinalipour-Yazdi, V. Miranda-Soto, D. A. Lev and A. L. Cooksy, *J. Am. Chem. Soc.*, 2008, **130**, 10860-10861; b) D. B. Grotjahn, *Chem. Lett.*, 2010, **39**, 908-914.
6. a) B. Breit, U. Gellrich, T. Li, J. M. Lynam, L. M. Milner, N. E. Pridmore, J. M. Slattery and A. C. Whitwood, *Dalton Trans.*, 2014, **43**, 11277-11285; b) F. Chevallier and B. Breit, *Angew. Chem. Int. Ed.*, 2006, **45**, 1599-1602.
7. a) L. Li and S. B. Herzon, *J. Am. Chem. Soc.*, 2012, **134**, 17376-17379; b) L. Li and S. B. Herzon, *Nat. Chem.*, 2014, **6**, 22-27.
8. M. N. Blair, M. Murray-Williams, C. Maguire, C. L. Brown, Q. Cao, H. Chai, Y. Li, R. L. O'Hagan, P. Dingwall, P. Manesiotis, C. L. Lyall, J. P. Lowe, U. Hintermair, P. C. Knipe and M. J. Muldoon, *Catal. Sci. Technol.*, 2023, **13**, 6224-6232.

View Article Online
DOI: 10.1039/D6CC03341E

9. M. Tokunaga, T. Suzuki, N. Koga, T. Fukushima, A. Horiuchi and Y. Wakatsuki, *J. Am. Chem. Soc.*, 2001, **123**, 11917-11924.
10. a) C. Alamillo-Ferrer, G. Hutchinson and J. Burés, *Nat. Rev. Chem.*, 2023, **7**, 26-34; b) J. Burés, *Angew. Chem. Int. Ed.*, 2016, **55**, 2028-2031.
11. Q. Su and H. Matsuhashi, *Org. Proc. Res. Dev.*, 2021, **25**, 627-631.
12. A. Flook and G. C. Lloyd-Jones, *J. Org. Chem.*, 2024, **89**, 16586-16593.
13. A. Martínez-Carrión, M. G. Howlett, C. Alamillo-Ferrer, A. D. Clayton, R. A. Bourne, A. Codina, A. Vidal-Ferran, R. W. Adams and J. Burés, *Angew. Chem. Int. Ed.*, 2019, **58**, 10189-10193.
14. J. Burés, *Angew. Chem. Int. Ed.*, 2016, **55**, 16084-16087.
15. E. M. Simmons and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2012, **51**, 3066-3072.
16. A. J. Arita, J. Cantada, D. B. Grotjahn and A. L. Cooksy, *Organometallics*, 2013, **32**, 6867-6870.
17. M. Arndt, K. S. M. Salih, A. Fromm, L. J. Goossen, F. Menges and G. Niedner-Schatteburg, *J. Am. Chem. Soc.*, 2011, **133**, 7428-7449.
18. A. M. M. Beardall, D. E. Chapple, N. Henao Ruiz, P. D. Boyle and J. M. Blacquiere, *ChemCatChem*, 2024, **16**, e202400407.
19. M. Bassetti, V. Cadierno, J. Gimeno and C. Pasquini, *Organometallics*, 2008, **27**, 5009-5016.
20. Z. Ye, X. Huang, Y. Shao, J. Jiang, L.-B. Qu, C. Zhao and Z. Ke, *Catal. Sci. Technol.*, 2019, **9**, 2315-2327.

View Article Online
DOI: 10.1039/D6CC03341E

Characterisation data for all synthesised compounds and details on NMR acquisition and processing methods is included in the Supplementary Information (SI). Due to the large file sizes of the *in-situ* NMR datasets generated, they are not available via a data repository but are available on request from the authors.