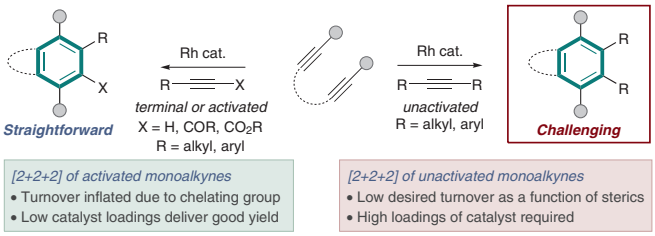
Compatibility Assessment of Unactivated Internal Alkynes in Rhodium-Catalyzed [2+2+2] Cycloadditions

John M. Halford-McGuff
Aidan P. McKay
Allan J. B. Watson*

EaStCHEM, School of Chemistry, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9ST, UK, aw260@st-andrews.ac.uk



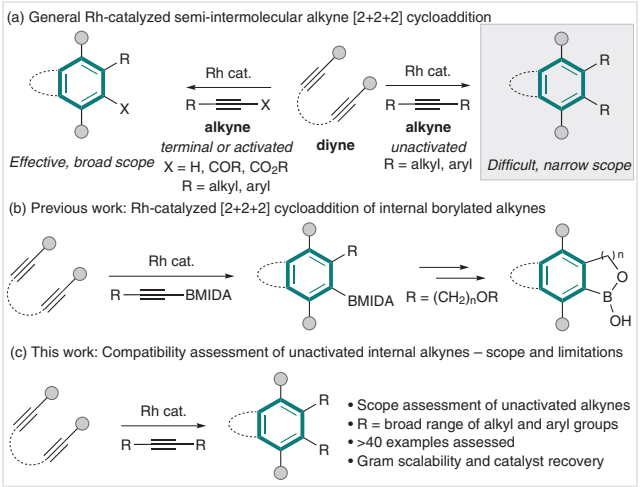
Received: 13.02.2024
Accepted after revision: 11.03.2024
Published online: 11.03.2024 (Accepted Manuscript), 28.03.204 (Version of Record)
DOI: 10.1055/a-2285-0007; Art ID: ST-2024-02-0036-L

Abstract Functionalized 1,2,4,5-tetrasubstituted benzenes are synthetically difficult or laborious to access. The Rh-catalyzed [2+2+2] cycloaddition of a diyne and internal alkyne offers a seemingly straightforward route to these scaffolds; however, this has been largely restricted to alkynes bearing activating (coordinating) functional groups, with very few examples of unactivated alkynes. In this work, we disclose an assessment of Rh-catalyzed [2+2+2] cycloadditions employing unactivated internal alkynes, focusing on the structural diversity and compatibility of both alkyne and diyne components. The limitations of this method are disclosed, with exceptionally bulky alkynes and specific functional groups undergoing side reactions. Furthermore, the practicalities of gram-scale reactions and catalyst recovery/reuse are demonstrated.

Key words cycloaddition, catalysis, rhodium, alkynes, arenes

The [2+2+2] cycloaddition of alkynes is a widely used multicomponent reaction, which generates highly complex arene scaffolds with unmatched atom economy.[1–11] First disclosed by Berthelot in 1890,[12] the process involves the confluence of three alkynes to generate (hetero)arenes. Reppe improved on Berthelot's discovery by utilizing nickel catalysis, greatly reducing the thermal requirements, and initiating the development of transition-metal-catalyzed [2+2+2] cycloaddition.[13]

The Rh-catalyzed [2+2+2] reaction has become broadly useful and inspired a range of practical methodologies.[7,8] These reactions are classified in three main ways: intramolecular, semi-intramolecular, and intermolecular (often termed mono-, bi-, and trimolecular reactions). Each offer distinct benefits and drawbacks: for instance, the intramolecular variant offers complete chemoselectivity and regiochemical control; however, the starting materials are complex. The fully intermolecular reaction, whilst the most modular, has issues with regioselectivity and chemoselectivity.[11] In contrast, the semi-intramolecular reaction of an alkyne and diyne (Scheme 1a) strikes the balance of being modular and using starting materials that are generally accessible both commercially and synthetically.



Scheme 1 (a) Prevalence of activated and terminal alkynes in Rh-catalyzed semi-intermolecular reactions and issues with unactivated alkynes. (b) Use of internal borylated alkynes in Rh-catalyzed [2+2+2] cycloadditions. (c) Broad compatibility assessment of unactivated alkynes in Rh-catalyzed [2+2+2] cycloaddition.

Mechanistic analysis in this area has been dominated by electronic arguments based on empirically observed enhanced reactivity of electron-deficient alkynes. However, alkyne electronics would not be expected to play a role in the rate-determining oxidative cyclization step.[14–16] Our

group recently disclosed evidence that the apparent electronic influence was misattributed and, instead, coordination of the electron-withdrawing groups to the Rh(III) intermediate was responsible for improved reactivity.[17] During this analysis, we noted an absence of skeletal diversity in this chemical space, which was presumably due to limitations in reaction efficiency using unactivated internal alkynes.

Our previous work has shown that the reaction requires high Rh loadings to generate the desired products in acceptable yields when unactivated alkynes are used.[17] This is due to steric parameters dominating reaction kinetics, limiting productive catalytic turnover.[17] We recently demonstrated that this can be overcome in boron-based systems to generate borylated arenes and benzoxaboroles (Scheme 1b).[18] To better explore the chemical space available and provide greater insight into reaction tolerance, we assessed the scope and limitations of this Rh-catalyzed [2+2+2] cycloaddition using unactivated alkynes (Scheme 1c).

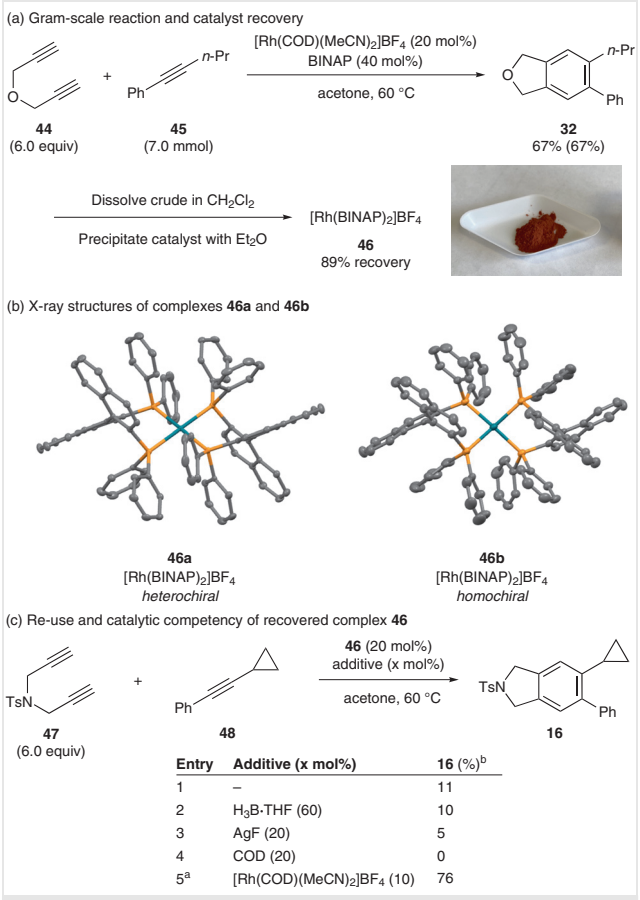
We selected general conditions based on a survey of the literature and an initial variable screen (see the Supporting Information). We avoided bespoke ligands, preferring commercial Rh sources and ligands, and selecting those with increased tolerance to air and moisture. The conditions shown in Scheme 2 were found to be widely applicable and offered improved tolerance to air and bench solvents when compared to alternative catalyst systems based on Co or Ir.

A selection of alkynes was tested, with a focus on structural diversity (Scheme 2) rather than electronic/steric variation, which has been examined previously.[17] A broad range of 35 alkynes was selected, alongside 11 different diynes. With regard to the alkyne, several *o*-substituted benzene derivatives were tolerated including Me (**1**), Ac (**2**), and free NH_2 (**3**) groups, although yields were low, likely due to steric repulsion. Heterocycles were readily incorporated, yielding complex arenes bearing thiophene (**4**), furan (**5**), indole (**6**), pyridine (**7**, **8**), and pyrimidine (**9**) motifs. Carbo- and heterocycles **10** and **11** were accommodated with ease. Carbonyls in the form of ketones (**12**), acetals (**13**), and esters (**15**) were tolerated, as well as enyne (**14**) and cyclopropane (**16**). Alcohols were particularly effective, offering excellent yields for a variety of different chain lengths and constitutional isomers (**17**–**23**). Protecting groups such as acetate (**24**) and silyl ethers (**25**) were compatible, with no observed deprotection.

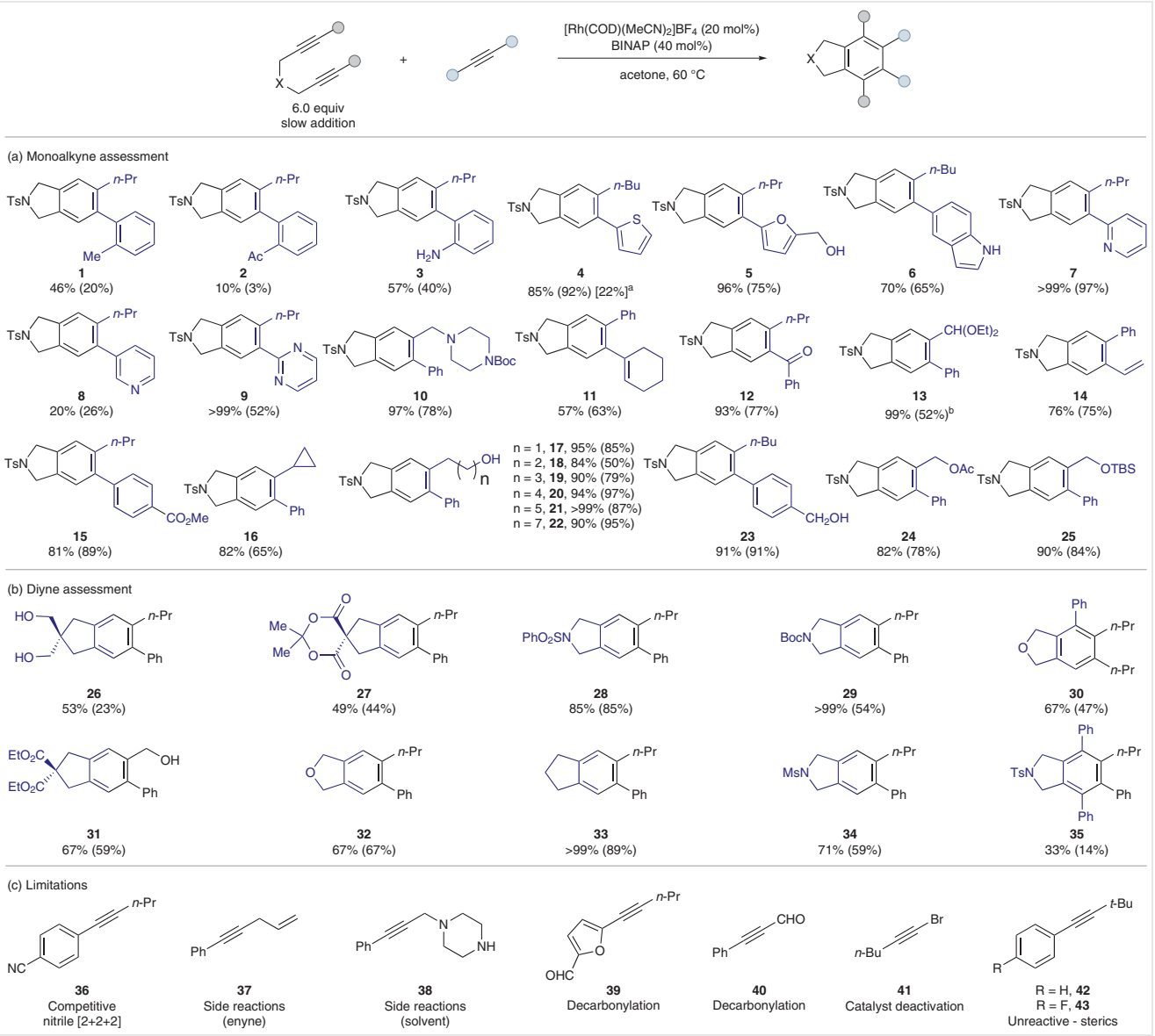
Diyne alterations were accommodated including 1,3-diol (**26**), diester (**27**, **31**), and various protected amines (**28**, **29**, **34**). Densely substituted arenes could be accessed using functionalized diynes (**30**, **35**), but with the expected lower yield due to the increased sterics. It should be noted that throughout the scope, the products from competing diyne di- and trimerization can complicate purification.

Regarding limitations, the reaction was not tolerant of nitriles (**36**) due to competing nitrile [2+2+2] cycloaddition.[19] Whilst an enyne was tolerated to give **14**, the allyl derivative (**37**) gave a range of unidentifiable side products. It is possible that the desired product was formed and subsequently underwent further cyclization reactions, such as those disclosed by Evans and coworkers.[20] Secondary amines (**38**) were also not applicable. Aldehydes (**39**, **40**) were unsuitable due to Rh-catalyzed decarbonylation reactions, which are well documented.[21] Alkynyl bromide (**41**) lead to a complete shutdown of [2+2+2] reactivity, with full recovery of the diyne noted. Finally, exceptionally bulky alkynes (**42**, **43**) yielded no desired product due to the poor catalytic turnover resulting from steric congestion.[17]

To assess the scalability of the methodology, a gram-scale reaction (with respect to alkyne, *ca.* 7.0 mmol) was performed (Scheme 3a), giving **32** in comparable yield. In addition to demonstrating scalability, catalyst recovery was found to be feasible. Trituration of the crude reaction mixture allowed isolation of the $[Rh(BINAP)_2]BF_4$ complex **46**, with 89% recovery.



Scheme 3 (a) Gram-scale reaction and catalyst recovery. (b) SCXRD of the homochiral and heterochiral complexes **46a** and **46b** (counterion, solvent molecules and hydrogens omitted for clarity). (c) Re-use of **46** in [2+2+2] cycloaddition reactions. [a] $[Rh(BINAP)_2]BF_4$ (10 mol%) used to maintain [Rh] = 20 mol%. [b] Determined by ^1H NMR yield using an internal standard.

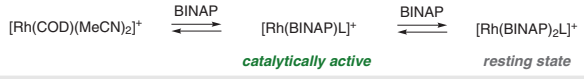


Scheme 2 Scope and limitations of Rh-catalyzed semi-intermolecular [2+2+2] cycloadditions using unactivated internal alkynes. Alkyne (0.1 mmol, 1.0 equiv), diyne (6.0 equiv added over 15 h in acetone), $[Rh(COD)(MeCN)_2]BF_4$ (20 mol%), *rac*-BINAP (40 mol%), acetone, 60 °C, 16 h. Yields determined by ^1H NMR spectroscopy using an internal standard (trichloroethylene), isolated yields in parentheses. [a] ^1H NMR yield with no slow addition. [b] Isolated as aldehyde after acid workup.

This conveniently allows for the simultaneous recovery of both the metal catalyst and ligand in a single step. Single-crystal X-ray diffraction confirmed the structure of **46**, which was isolated as a mixture of the heterochiral complex **46a** ((*R*),(*R*) and (*S*),(*S*)) and homochiral complex **46b** ((*R*),(*S*)) (Scheme 3b). Compound **46a** could be isolated on reasonable scale, allowing assessment for catalytic competency in the [2+2+2] reaction under the same conditions as Scheme 2 (Scheme 3c).[22] While **46a** displays some catalytic activity, this was displayed significantly poorer [2+2+2] activity than the precatalyst–ligand mixture. This is likely due to a comparatively unfavorable dissociation of BINAP to allow rhodacycle formation with the diyne component. To facilitate BINAP dissociation, an additive screen was performed (Scheme 3c – see the Supporting Information, Table S1). Attempts to encourage BINAP dissociation *via* coordination to boron (BH_3) or Ag(I) were unsuccessful at restoring catalytic competency. Similarly, addition of 1,5-cyclooctadiene (COD) as a competing ligand to displace BINAP was unsuccessful. However, it was found that the addition of 10

mol% $[Rh(COD)(MeCN)_2]BF_4$ and 10 mol% **46** afforded catalytic activity equivalent to reactions using 20 mol% $[Rh(COD)(MeCN)_2]BF_4$ and 40 mol% BINAP (see yield of **16** in Scheme 3c *vs.* Scheme 2 (76% *vs.* 82%)). This is likely due to BINAP dissociation/equilibration from **46** to $[Rh(COD)(MeCN)_2]BF_4$, allowing for the formation of complexes of the structure $[Rh(BINAP)L]BF_4$ (where L = COD or $(MeCN)_2$), which generate vacant sites more readily than **46**.

This observation offers insight into catalyst speciation, off-cycle processes, and resting states during these Rh/BINAP-catalyzed [2+2+2] reactions. The general requirement for 1:2 Rh:BINAP stoichiometry is well-established;[7–10] however, the 1:2 complex **46** has low catalytic activity. This suggests that **46** may act as a resting state during [2+2+2] reactions, with BINAP dissociation required for Rh(I) to re-enter productive catalysis (*i.e.*, cyclometalation with the diyne). A figurative description is shown in Scheme 4. This observation is consistent with previous reports demonstrating enhanced catalytic activity of Rh(I)/BINAP complexes following COD removal *via* hydrogenation.[23]



Scheme 4 Figurative description of catalyst–ligand speciation

In summary, we have disclosed an assessment of the scope and limitations of unactivated internal alkynes in Rh-catalyzed semi-intermolecular [2+2+2] cycloadditions. A range of useful functional groups and substitution patterns can be tolerated, yielding complex arene derivatives. The limitations of the reaction have been explored and documented, with insight on competing reactions, poor reactivity, and catalyst deactivation. The scalability of the reaction has been assessed, which offers comparable yield on sub-mmol and gram scale. Lastly, while these unactivated internal alkynes require high catalyst loadings to overcome intrinsic steric constraints, almost all the catalyst and ligand can be recovered, with recyclability demonstrated.[24–26]

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

J.M.H.-M. thanks the EaSI-CAT Centre for Doctoral Training for a PhD Studentship. A.J.B.W. thanks the Leverhulme Trust for a Research Fellowship (RF-2022-014) and the EPSRC Programme Grant 'Boron: Beyond the Reagent' (EP/W0077517/1) for support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2285-0007.

References and Notes

(1) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539.
(2) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741.
(3) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209.
(4) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307.
(5) Agenet, N.; Buisine, O.; Slowinski, F.; Gandon, V.; Aubert, C.; Malacria, M. *Cotrimerizations of Acetylenic Compounds*, *In Organic Reactions, Vol. 68*; RajanBabu, T. V., Ed.; Wiley: Hoboken, **2007**, 1–302.
(6) Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev.* **2011**, *40*, 3430.
(7) Shibata, Y.; Tanaka, K. *Synthesis* **2012**, *44*, 323.
(8) *Transition-Metal-Mediated Aromatic Ring Construction*; Tanaka, K., Ed.; Wiley: Hoboken, **2013**, 3–298.
(9) Kotha, S.; Lahiri, K.; Sreevani, G. *Synlett* **2018**, *29*, 2342.
(10) Matton, P.; Huvelle, S.; Haddad, M.; Phansavath, P.; Ratovelomanana-Vidal, V. *Synthesis* **2022**, *54*, 4.
(11) Galan, B. R.; Rovis, T. *Angew. Chem. Int. Ed.* **2009**, *48*, 2830.
(12) Berthelot, M. *C. R. Hebd. Séances Acad. Sci.* **1890**, *111*, 471.
(13) Reppe, W.; Schlichting, O.; Klager, K.; Toepel, T. *Justus Liebigs Ann. Chem.* **1948**, *560*, 1.
(14) Roglans, A.; Pla-Quintana, A.; Solà, M. *Chem. Rev.* **2021**, *121*, 1894.
(15) Parera, M.; Dachs, A.; Solà, M.; Pla-Quintana, A.; Roglans, A. *Chem. Eur. J.* **2012**, *18*, 13097.
(16) Dachs, A.; Osuna, S.; Roglans, A.; Solà, M. *Organometallics* **2010**, *29*, 562.
(17) Halford-McGuff, J. M.; Slawin, A. M. Z.; Watson, A. J. B. *ACS Catal.* **2023**, *13*, 3463.
(18) (a) Halford-McGuff, J. M.; Cordes, D. B.; Watson, A. J. B. *Chem. Commun.* **2023**, *59*, 7759. (b) Halford-McGuff, J. M.; Varga, M.; Cordes, D. B.; McKay, A. P.; Watson, A. J. B. *ACS Catal.* **2024**, *14*, 1846.
(19) Varela, J. A.; Saá, C. *Chem. Rev.* **2023**, *103*, 3787.
(20) For recent reviews of transition-metal-catalyzed higher-order carbocyclization reactions, see: (a) Inglesby, P. A.; Evans, P. A. *Chem. Soc. Rev.* **2010**, *39*, 2791. (b) Yu, Z.-X.; Wang, Y.; Wang, Y. *Chem. Asian J.* **2010**, *5*, 1072. (c) Gulías, M.; López, F.; Mascareñas, J. L. *Pure Appl. Chem.* **2011**, *83*, 495. (d) Inglesby, P. A.; Evans, P. A. In *Comprehensive Organic Synthesis II, Vol. 5*; Knochel, P.; Molander, G. A.; Fürstner, A., Ed.; Elsevier: Waltham, **2014**, 656–702. (e) Kuila, B.; Kaur, M.; Singh, P.; Bhargava, G. *Eur. J. Org. Chem.* **2018**, 853. (f) Lam, H.; Lautens, M. *Synthesis* **2020**, *52*, 2427. (g) Trost, B. M.; Zuo, Z.; Schultz, J. E. *Chem. Eur. J.* **2020**, *26*, 15354. (h) Caillé, J.; Robiette, R. *Org. Biomol. Chem.* **2021**, *19*, 5702.
(21) (a) Fristrup, P.; Kreis, M.; Palmelund, A.; Norrby, P.-O.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 5206. (b) Furusawa, T.; Tanimoto, H.; Nishiyama, Y.; Morimoto, T.; Kakiuchi, K. *Chem. Lett.* **2007**, *46*, 926. (c) Bie, F.; Liu, X.; Shi, Y.; Cao, H.; Han, Y.; Szotak, M.; Liu, C. *J. Org. Chem.* **2020**, *85*, 15676. (d) Qi, X.; Zhou, R.; Ai, H.-J.; Wu, X.-F. *J. Catal.* **2020**, *381*, 215. (e) Davidson, R. T.; Kuker, E. L.; Dong, V. M. *Acc. Chem. Res.* **2021**, *54*, 1236.
(22) For further information regarding recovery of rhodium catalysts: (a) Dachs, A.; Torrent, A.; Pla-Quintana, A.; Roglans, A.; Jutand, A. *Organometallics* **2009**, *28*, 6036. (b) Garcia, L.;

Roglans, A.; Laurent, R.; Majoral, J.-P.; Pla-Quintana, A.; Caminade, A.-M. *Chem. Commun.* **2012**, *48*, 9428. (c) Fernández, M.; Ferré, M.; Pla-Quintana, A.; Parella, T.; Pleixats, R.; Roglans, A. *Eur. J. Org. Chem.* **2014**, 6242. (d) Pla-Quintana, A.; Roglans, A. *Molecules* **2022**, *27*, 1332.

(23) (a) Thiel, I.; Hostmann, M.; Jungk, P.; Keller, S.; Fischer, F.; Drexler, H.-J.; Heller, D.; Hapke, M. *Chem. Eur. J.* **2017**, *23*, 17048. (b) Preetz, A.; Fischer, C.; Kohrt, C.; Drexler, H.-J.; Baumann, W.; Heller, D. *Organometallics* **2011**, *30*, 5155.

(24) The research data supporting this publication can be accessed at https://doi.org/ DOI: 10.17630/019f4d4d-d107-41d8-ad7f-3ddb244e1b3c.

(25) CCDC 23332665 (**46a**) and CCDC 2332666 (**46b**) contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

(26) **Representative Procedure for the Synthesis of 4**

An oven-dried microwave vial was charged with 2-(hex-1-yn-1-yl)thiophene (15.0 mg, 100 µmol, 1.0 equiv), $[Rh(COD)(MeCN)_2]BF_4$ (7.6 mg, 20.0 µmol, 20 mol%), and *rac*-BINAP (24.9 mg, 40.0 µmol, 40 mol%). The vial was sealed, evacuated, and backfilled with N_2. Dry acetone (0.5 mL) was introduced into the vial, and the mixture was heated to 60 °C. A solution of 4-methyl-*N*,*N*-di(prop-2-yn-1-yl)benzenesulfonamide (148 mg, 600 µmol, 6.0 equiv) in acetone (0.5 mL) was prepared and this was added *via* syringe pump to the heated Rh solution over 15 h. The mixture was allowed to stir at 60 °C for the duration of the slow addition followed by a further 1 h (16 h, total reaction time). The vial was then allowed to cool to RT, before filtering through Celite® (washing with acetone) and concentrating *in vacuo* to give a residue that was purified by flash column chromatography (silica, 0–5% Et_2O in PhMe) to yield the desired product **4** as a yellow solid (37.9 mg, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81–7.76 (m, 2 H), 7.35–7.30 (m, 3 H), 7.14 (s, 1 H), 7.08 (s, 1 H), 7.06 (dd, *J* = 5.14, 3.50 Hz, 1 H), 6.94 (dd, *J* = 3.51, 1.20 Hz, 1 H), 4.62 (s, 2 H), 4.60 (s, 2 H), 2.68–2.60 (m, 2 H), 2.41 (s, 3 H), 1.51–1.38 (m, 2 H), 1.33–1.19 (m, 2 H), 0.83 (t, *J* = 7.31 Hz, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 143.8, 143.8, 142.3, 141.6, 136.2, 133.8, 133.8, 130.0, 127.8, 127.1, 126.7, 125.5, 125.2, 123.7, 53.7, 53.9, 34.0, 33.3, 22.6, 21.6, 14.0. IR (ATR, film): 2924, 1344, 1161, 1098, 1061, 810, 702, 665, 615, 550 cm^{-1}. HRMS (ESI): *m/z* calcd for $[C_{23}H_{25}NO_2S_2 + H]^+$: 412.1400; found: 412.1391.