Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue



Check for updates

Cite this: Chem. Sci., 2020, 11, 2759

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 12th December 2019
Accepted 5th February 2020

DOI: 10.1039/c9sc06309a

rsc.li/chemical-science

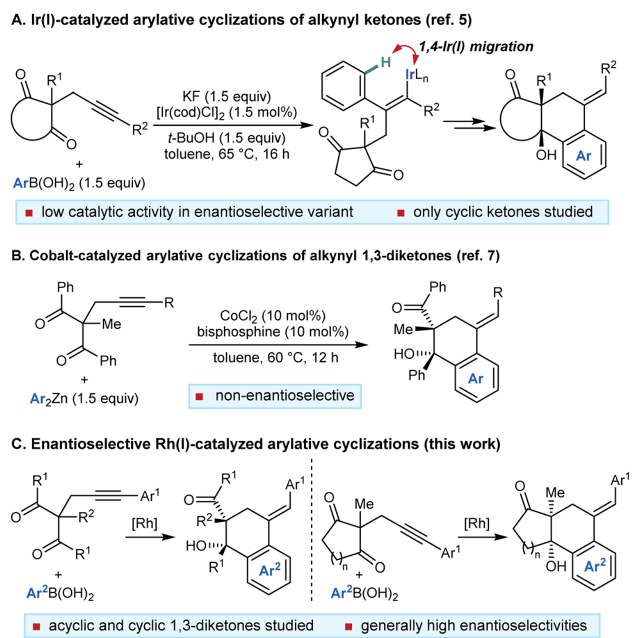
# Catalytic enantioselective arylative cyclizations of alkynyl 1,3-diketones by 1,4-rhodium(I) migration†

Alistair Groves,[ab] Jinwei Sun,[abc] Hal R. I. Parke,[ab] Michael Callingham,[ab] Stephen P. Argent,‡[b] Laurence J. Taylor‡[b] and Hon Wai Lam *[ab]

The enantioselective synthesis of densely functionalized polycarbocycles by the rhodium(I)-catalyzed reaction of arylboronic acids with 1,3-diketones is described. The key step in these desymmetrizing domino addition–cyclization reactions is an alkenyl-to-aryl 1,4-Rh(I) migration, which enables arylboronic acids to function effectively as 1,2-dimetalloarene surrogates.

The functionalization of remote C–H bonds offers a powerful method to develop new synthetic methods and achieve transformations that would otherwise be highly challenging.[1] Within this field, 1,4-migration of rhodium(I) between two carbon centers[2–4] has proven to be highly effective for the catalytic functionalization of remote C–H bonds, which has been used to impressive effect in a range of valuable synthetic methods.[4]

We have described catalytic arylative cyclizations from the reaction of alkynyl ketones with arylboronic acids, which produce densely functionalized polycarbocycles through a key step involving an alkenyl-to-aryl 1,4-metal migration (Scheme 1A).[5] This desymmetrization reaction forms two new carbon–carbon bonds with complete diastereocontrol over two new stereocenters and a trisubstituted alkene. In the non-enantioselective variant of this process, rhodium(I) catalysis was only moderately successful because of the formation of significant quantities of side-products, and the highest yields were obtained using iridium(I) catalysis.[5,6] Although preliminary attempts towards an enantioselective variant using chiral bisphosphine–iridium complexes successfully gave products in high enantioselectivities, only modest catalytic activities were observed.[5] Furthermore, only cyclic ketones were employed in that study.[5] Yan and Yoshikai have reported related cobalt-catalyzed arylative cyclizations of acyclic 1,3-diketones with diarylzinc reagents; however, enantioselective reactions were not described (Scheme 1B).[7] Therefore, to increase synthetic utility, there remains a need to discover more effective chiral catalysts that address these limitations by promoting high-yielding and highly enantioselective arylative cyclizations of a wider range substrates,[8] including acyclic 1,3-diketones. Here, we report that a chiral bisphosphine–rhodium complex promotes the diastereo- and enantioselective reaction of arylboronic acids with alkynyl 1,3-diketones, for which both acyclic and cyclic 1,3-diketones are effective substrates.




Scheme 1 Catalytic arylative cyclizations involving 1,4-metal migration.

[a]The GlaxoSmithKline Carbon Neutral Laboratories for Sustainable Chemistry, University of Nottingham, Jubilee Campus, Triumph Road, Nottingham, NG7 2TU, UK. E-mail: hon.lam@nottingham.ac.uk

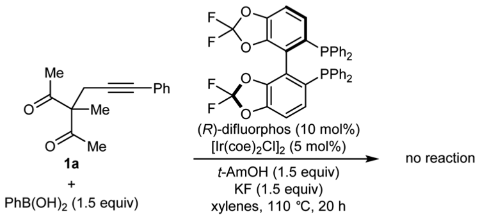
[b]School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK

[c]Jiangsu Collaborative Innovation Center of Atmospheric Environment and Equipment Technology, Jiangsu Key Laboratory of Atmospheric Environment Monitoring and Pollution Control, School of Chemistry and Materials Science, Nanjing University of Information Science and Technology, Nanjing, Jiangsu 210044, China

† Electronic supplementary information (ESI) available: Experimental procedures, full spectroscopic data for new compounds, and crystallographic data for **2j** and **5g**. CCDC 1959877 and 1959878. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc06309a

‡ To whom enquires regarding X-ray crystallography should be addressed.

Our experiments began with the arylative cyclization of alkynyl 1,3-diketone **1a** with $PhB(OH)_2$ (eqn (1) and Table 1). Application of conditions identical to those described in our



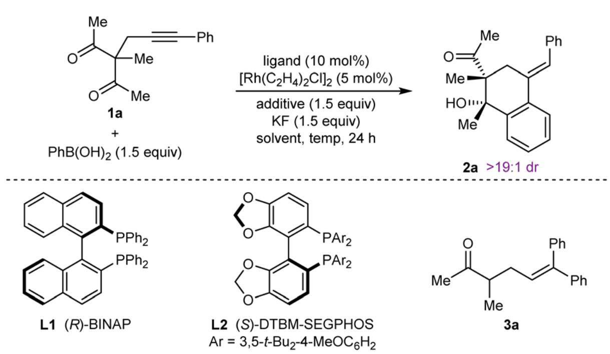

(1)

previous study,[5] using an iridium–(*R*)-difluorphos complex, led to no reaction and only unreacted starting material was recovered (eqn (1)). Pleasingly, however, reaction of **1a** with $PhB(OH)_2$ (1.5 equiv.) in the presence of $[Rh(C_2H_4)_2Cl]_2$ (5 mol%), (*R*)-BINAP (**L1**, 10 mol%), and KF (1.5 equiv.) in THF/$H_2O$ (9 : 1) at 70 °C for 24 h gave arylative cyclization product *ent*-**2a** in 54% yield (as determined by $^1H$ NMR analysis using 1,4-dimethoxybenzene as an internal standard) as a single diastereomer (>19 : 1 dr) in 80% ee (Table 1, entry 1).[9] Higher enantioselectivity was obtained using (*S*)-DTBM-SEGPHOS (**L2**), which gave **2a** in 52% NMR yield and 91% ee (entry 2). Changing the protic additive from $H_2O$ to *t*-AmOH (1.5 equiv.) further increased the enantioselectivity (entry 3). The yield of **2a** was increased further by raising the temperature to 80 °C (entry 4) and using 2.0 equivalents of $PhB(OH)_2$ (entry 5). Conducting the reaction on a larger scale using 0.30 mmol of **1a** gave **2a** in 78% yield and 98% ee (entry 6). This experiment also gave a side-product **3a** in 5% yield.[10] It should be noted that the use of $PhB(OH)_2$ free from triphenylboroxine is very important for good results, as otherwise lower enantioselectivities are observed.[11] Finally, repeating the conditions of entry 5 but using $[Ir(coe)_2Cl]_2$ in place of $[Rh(C_2H_4)Cl_2]$ led to no reaction, and only unreacted starting material was recovered (entry 7).

With effective conditions identified (Table 1, entry 6), the scope of this process with respect to the alkynyl acyclic 1,3-diketone **1** was investigated in reactions with $PhB(OH)_2$ (Table 2). Arylative cyclization products **2a–2r** were obtained as single observable diastereomers (>19 : 1 dr as determined by $^1H$ NMR analysis of the crude reaction mixtures) in 27–82% yield and 56–99% ee. Side-products analogous to **3a** (see Table 1) were generally detected but not isolated. Changing the α-substituent $R^2$ between the two ketones from methyl (**2a**) to ethyl (**2b**), *n*-butyl (**2c**), benzyl (**2d**), or 4-methoxybenzyl (**2e**) is tolerated. The low yield of **2c** results from a low conversion as significant unreacted starting material was observed. The process is also compatible with a range (hetero)aryl groups $Ar^1$ at the alkynyl position, such as 4-substituted phenyl (**2f–2i**), 2-fluorophenyl (**2j**), 3,5-dimethylphenyl (**2k**), 3,4-(methylenedioxy)phenyl (**2l**), 2-naphthyl (**2m**), 1-naphthyl (**2n**), 2-thienyl (**2o**), and 2-pyridyl (**2p**) groups. Finally, the ketone substituents can also be varied from methyl to ethyl (**2q**) or phenyl groups (**2r**), although the enantioselectivity dropped substantially in the latter case.

The process is not limited to the use of $PhB(OH)_2$, as shown by the arylative cyclizations of **1a** with different arylboronic acids to give **2s–2x** in 88–96% ee (Table 3). Various 4-substituted phenylboronic acids containing methyl (**2s**), methoxy (**2t**), fluoro (**2u**), or chloro groups (**2v**) reacted successfully. When 3-methylphenylboronic acid was employed, 1,4-Rh(I) migration occurred to the least sterically hindered site, *para* to the methyl

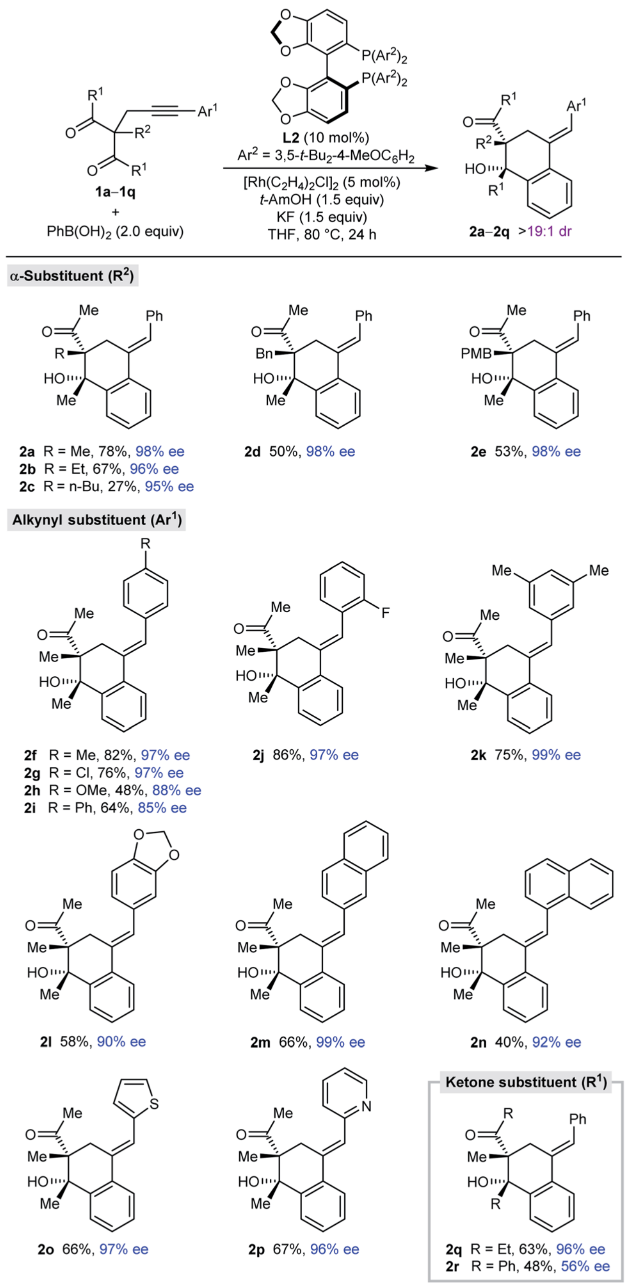
Table 1 Evaluation of reaction conditions[a]




| Entry | Ligand | Additive | Solvent | Temp. (°C) | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | **L1** | — | THF : $H_2O$ (9 : 1) | 70 | 54 | −80[d] |
| 2 | **L2** | — | THF : $H_2O$ (9 : 1) | 70 | 52 | 91 |
| 3 | **L2** | *t*-AmOH | THF | 70 | 54 | 95 |
| 4 | **L2** | *t*-AmOH | THF | 80 | 67 | 96 |
| 5[e] | **L2** | *t*-AmOH | THF | 80 | 70 | 96 |
| 6[e,f] | **L2** | *t*-AmOH | THF | 80 | 78 (5)[g] | 98 |
| 7[e,h] | **L2** | *t*-AmOH | THF | 80 | n.r.[i] | — |

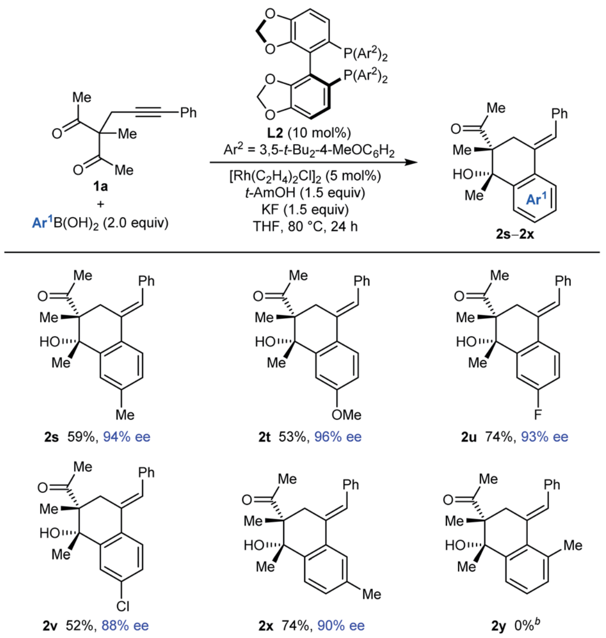
[a] Reactions were conducted with 0.05 mmol of **1a** in 1 mL of solvent. [b] Determined by $^1H$ NMR analysis using 1,4-dimethoxybenzene as an internal standard. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The major enantiomer was *ent*-**2a**. [e] Using 2.0 equivalents of $PhB(OH)_2$. [f] Using 0.30 mmol of **1a** in THF (6 mL). [g] Value in parentheses refers to the yield of side-product **3a**, which was also isolated from this experiment. [h] Using $[Ir(coe)Cl_2]_2$ in place of $[Rh(C_2H_4)_2Cl_2]$. [i] n.r. = no reaction.

Table 2 Evaluation of alkynyl acyclic 1,3-diketones **1**[a]




[a] Reactions were conducted with 0.30 mmol of **1** in THF (6 mL). Yields are of isolated products. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. PMB = *para*-methoxybenzyl.

Table 3 Evaluation of arylboronic acids with alkynyl acyclic 1,3-diketone **1a**[a]



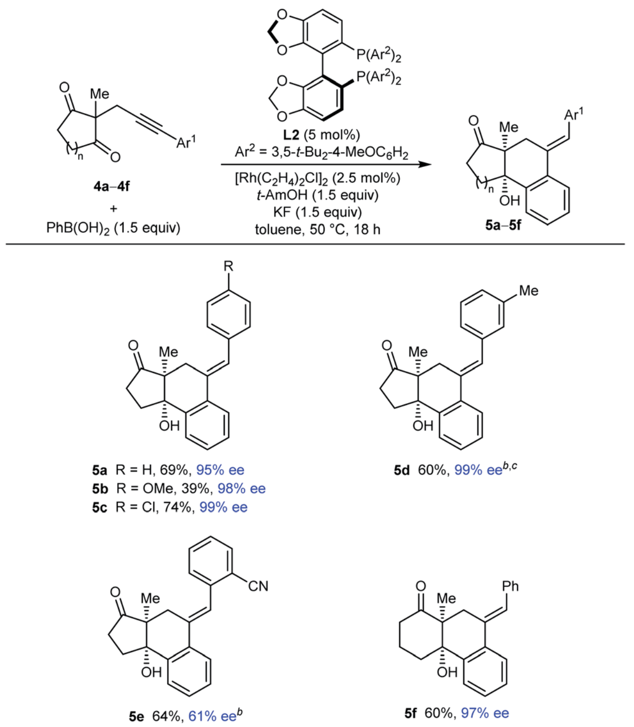

[a] Reactions were conducted with 0.30 mmol of **1a** in THF (3 mL). Yields are of isolated products. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [b] Unreacted starting material was returned along with a trace of what appeared to be alkyne hydroarylation products.

group (**2x**). However, 2-methylphenylboronic acid did not provide any of the arylative cyclization product **2y**, and returned mainly unreacted starting material along with what appeared to be small quantities of alkyne hydroarylation products.

Our attention then turned to the reaction of alkynyl cyclic 1,3-diketones **4**, substrates employed in our prior study using iridium catalysis (Tables 4 and 5).[5] With toluene as the solvent, these more reactive substrates generally allowed the use of a decreased catalyst loading of 5 mol% and a lower temperature of 50 °C. Furthermore, in most cases, acceptable results were obtained using only 1.5 equivalents of the arylboronic acid. Various substrates **4a–4f** underwent arylative cyclization with $PhB(OH)_2$ to give products **5a–5f** in 39–74% yield and 61–99% ee (Table 4). Small quantities of side-products resulting from arylrhodation of the alkyne with the regioselectivity opposite to that seen in the formation of products **5** were also observed but generally not isolated (see ESI† for details). As with the acylic 1,3-diketones (Table 2), a range of aryl substituents at the alkyne are tolerated, including phenyl (**5a** and **5f**), 4-methoxyphenyl (**5b**), 4-chlorophenyl (**5c**), and 3-methylphenyl (**5d**). The lower yield of **5b** results from the formation of products of alkyne hydroarylation without cyclization. The cyclization of a 2-cyanophenyl-containing substrate **4e** proceeded smoothly using a 10 mol% catalyst loading but the product **5e** was formed in a modest 61% ee. A six-membered cyclic 1,3-diketone also underwent arylative cyclization with $PhB(OH)_2$ to give **5f** in 60% and 97% ee.

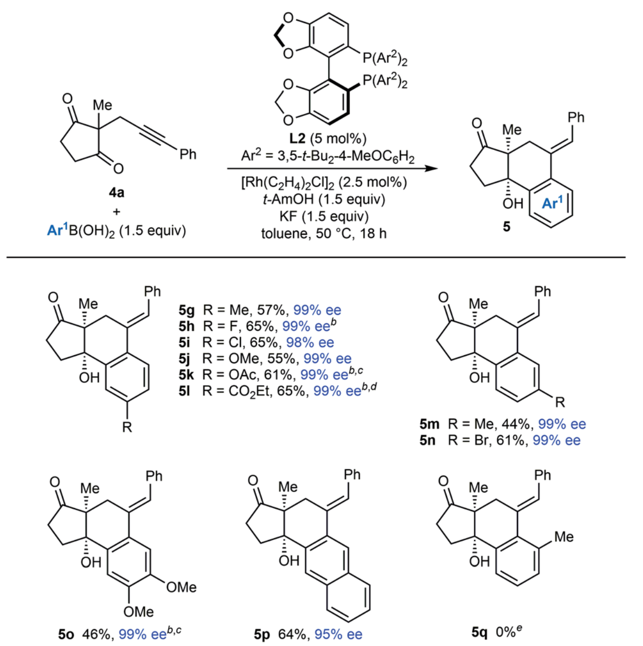
The scope of the arylative cyclization of alkynyl cyclic 1,3-diketones with respect to the arylboronic acid was then explored in reactions with substrate **4a** (Table 5). These reactions proceeded in 44–69% yield and gave products **5g–5p** in 95–99% ee. The process tolerates diverse 4-substituted phenylboronic acids containing methyl (**5g**), halide (**5h** and **5i**), methoxy (**5j**), acetoxy (**5k**), or carboethoxy groups (**5l**). 3-Substituted phenylboronic acids (**5m** and **5n**), 3,4-dimethoxyphenylboronic acid (**5o**), and 2-naphthylboronic acid (**5p**) also react effectively. Again, where 1,4-Rh(I) migration could occur to two different positions, migration

Table 4 Evaluation of alkynyl cyclic 1,3-diketones **4**[a]




[a] Reactions were conducted with 0.30 mmol of **4** in toluene (3 mL). Yields are of isolated products. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [b] Using 5 mol% of $[Rh(C_2H_4)_2Cl]_2$, 10 mol% of **L2**. [c] Using 2.0 equiv. of $PhB(OH)_2$.

Table 5 Evaluation of arylboronic acids with alkynyl cyclic 1,3-diketone **4a**[a]

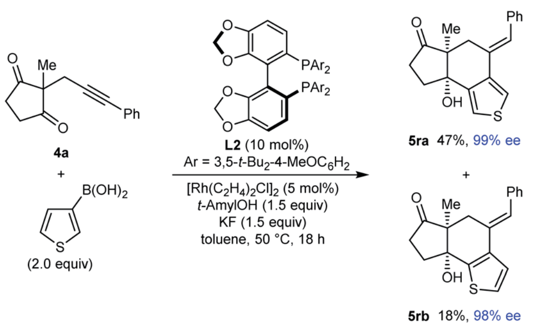



[a] Reactions were conducted with 0.30 mmol of **4** in toluene (3 mL). Yields are of isolated products. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [b] Using 5 mol% of $[Rh(C_2H_4)_2Cl]_2$ and 10 mol% of **L2**. [c] Using 2.0 equivalents of the arylboronic acid. [d] Using 2.4 equivalents of the arylboronic acid. [e] Unreacted starting material was returned.

to the sterically less-hindered side was observed (**5m–5p**). An attempt to form **5q** with 2-methylphenylboronic acid was unsuccessful, and returned only unreacted starting material.

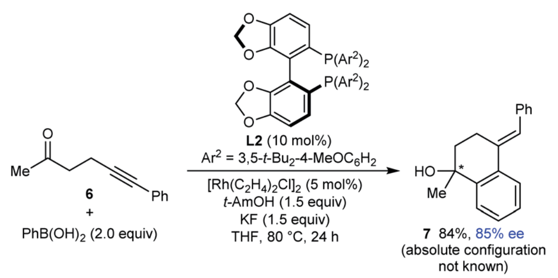
Interestingly, the reaction of substrate **4a** with 3-thienylboronic acid gave two products **5ra** and **5rb** resulting from 1,4-Rh(I) migration to different positions of the thienyl ring before cyclization (eqn (2)).

Finally, this method is not restricted to the use of 1,3-diketone-containing substrates; substrate **6** containing a single



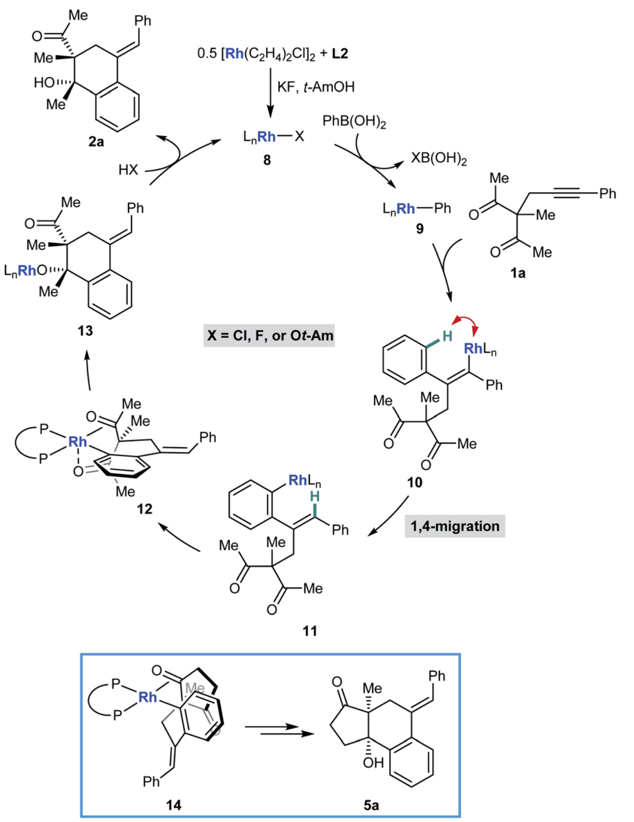

(2)

methyl ketone also underwent arylative cyclization to give **7** in 94% yield and 85% ee (eqn (3)).




(3)

Scheme 2 illustrates a possible catalytic cycle for these reactions, using **1a** and $PhB(OH)_2$ as example substrates. First, upon mixing $[Rh(C_2H_4)Cl]_2$, **L2**, KF, and *t*-AmOH, a chiral complex **8** consisting of one bisphosphine bound to one rhodium atom is formed, which could have a chloride, fluoride, or *tert*-amyl counterion. Transmetalation of **8** with $PhB(OH)_2$ gives an arylrhodium species **9**, which can then undergo migratory insertion with the alkyne of **1a** to give alkenylrhodium intermediate **10**. Alkenyl-to-aryl 1,4-rhodium(I) migration of **10** then provides arylrhodium species **11**. The relative configuration of products **2** can be explained by a tentative stereochemical model where cyclization proceeds through a conformation similar to **12**, in which: (i) rhodium(I) has




Scheme 2 Possible catalytic cycle and rationalization of diastereochemical outcomes.

a square pyramidal coordination geometry; (ii) the ketone undergoing nucleophilic attack is coordinated to rhodium such that the carbonyl group is aligned with the arylrhodium bond to enable subsequent migratory insertion; and (iii) the second ketone is coordinated to rhodium in an axial position. The relative configuration of products **5** (Tables 4 and 5) is more straightforward to rationalize; because of geometric constraints, nucleophilic addition of the arylrhodium group must occur to the same face of the cyclic 1,3-diketone as that from which the tether connecting the two reacting components projects (as in **14** to give representative product **5a**, for example). However, as to exactly how the chiral ligand controls the absolute configuration of the products is not clear at the present time.

In conclusion, we have reported rhodium(I)-catalyzed arylative cyclizations of alkynyl 1,3-diketones with arylboronic acids, which involve an alkenyl-to-aryl 1,4-Rh(I) migration as a key step. By using a chiral rhodium(I) complex based upon (*S*)-DTBM-SEGPHOS, the formation of side-products observed previously[5] with $[Rh(cod)Cl]_2$ is significantly reduced, and catalytic activity is greatly increased compared with chiral iridium complexes.[5] These desymmetrization reactions provide densely functionalized polycarbocycles with high diastereo- and enantioselectivities, and notably, both acyclic and cyclic 1,3-ketones are effective substrates.[12]

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by the Engineering and Physical Sciences Research Council [grant number EP/M50810X/1]; the Leverhulme Trust [grant RPG-2016-341]; the Natural Science Foundation of Jiangsu Province [grant number BK20161307]; the Startup Foundation for Introducing Talent of NUIST (grant number 2016r044); the University of Nottingham; and GlaxoSmithKline.

## Notes and references

1 For selected reviews of remote functionalization reactions, For selected reviews: (*a*) R. Breslow, *Acc. Chem. Res.*, 1980, **13**, 170–177; (*b*) H. Schwarz, *Acc. Chem. Res.*, 1989, **22**, 282–287; (*c*) H. Jiang, L. Albrecht and K. A. Jorgensen, *Chem. Sci.*, 2013, **4**, 2287–2300; (*d*) I. Franzoni and C. Mazet, *Org. Biomol. Chem.*, 2014, **12**, 233–241; (*e*) M. Vilches-Herrera, L. Domke and A. Börner, *ACS Catal.*, 2014, **4**, 1706–1724; (*f*) G. Qiu and J. Wu, *Org. Chem. Front.*, 2015, **2**, 169–178; (*g*) A. Vasseur, J. Bruffaerts and I. Marek, *Nat. Chem.*, 2016, **8**, 209–219; (*h*) J. Bruffaerts, D. Pierrot and I. Marek, *Org. Biomol. Chem.*, 2016, **14**, 10325–10330; (*i*) H. Sommer, F. Juliá-Hernández, R. Martin and I. Marek, *ACS Cent. Sci.*, 2018, **4**, 153–165.

2 Seminal examples: (*a*) K. Oguma, M. Miura, T. Satoh and M. Nomura, *J. Am. Chem. Soc.*, 2000, **122**, 10464–10465; (*b*) T. Hayashi, K. Inoue, N. Taniguchi and M. Ogasawara, *J. Am. Chem. Soc.*, 2001, **123**, 9918–9919.

3 For an early review, see: S. Ma and Z. Gu, *Angew. Chem., Int. Ed.*, 2005, **44**, 7512–7517.

4 Selected, recent examples of 1,4-rhodium(I) migrations: (*a*) R. Shintani, S. Isobe, M. Takeda and T. Hayashi, *Angew. Chem., Int. Ed.*, 2010, **49**, 3795–3798; (*b*) K. Sasaki, T. Nishimura, R. Shintani, E. A. B. Kantchev and T. Hayashi, *Chem. Sci.*, 2012, **3**, 1278–1283; (*c*) J. Zhang, J.-F. Liu, A. Ugrinov, A. F. X. Pillai, Z.-M. Sun and P. Zhao, *J. Am. Chem. Soc.*, 2013, **135**, 17270–17273; (*d*) R. Shintani, R. Iino and K. Nozaki, *J. Am. Chem. Soc.*, 2014, **136**, 7849–7852; (*e*) H. B. Hepburn and H. W. Lam, *Angew. Chem., Int. Ed.*, 2014, **53**, 11605–11610; (*f*) T. Johnson, K.-L. Choo and M. Lautens, *Chem. Eur.–J.*, 2014, **20**, 14194–14197; (*g*) A. Masarwa, M. Weber and R. Sarpong, *J. Am. Chem. Soc.*, 2015, **137**, 6327–6334; (*h*) A. Claraz, F. Serpier and S. Darses, *ACS Catal.*, 2017, **7**, 3410–3413; (*i*) B. M. Partridge, M. Callingham, W. Lewis and H. W. Lam, *Angew. Chem., Int. Ed.*, 2017, **56**, 7227–7232; (*j*) M. Callingham, B. M. Partridge, W. Lewis and H. W. Lam, *Angew. Chem., Int. Ed.*, 2017, **56**, 16352–16356; (*k*) J. L. Ming and T. Hayashi, *Org. Lett.*, 2018, **20**, 6188–6192; (*l*) J. L. Ming, Q. Shi and T. Hayashi, *Chem. Sci.*, 2018, **9**, 7700–7704; (*m*) S.-S. Zhang, T.-J. Hu, M.-Y. Li, Y.-K. Song, X.-D. Yang, C.-G. Feng and G.-Q. Lin, *Angew. Chem., Int.*

*Ed.*, 2019, **58**, 3387–3391; (*n*) A. Selmani, F. Serpier and S. Darses, *J. Org. Chem.*, 2019, **84**, 4566–4574; (*o*) L. O'Brien, S. N. Karad, W. Lewis and H. W. Lam, *Chem. Commun.*, 2019, **55**, 11366–11369; (*p*) A. Selmani and S. Darses, *Org. Lett.*, 2019, **21**, 8122–8126.

5 B. M. Partridge, J. Solana González and H. W. Lam, *Angew. Chem., Int. Ed.*, 2014, **53**, 6523–6527.

6 For other examples of 1,4-iridium(I) migration, see ref. 4*j* and; R. E. Ruscoe, M. Callingham, J. A. Baker, S. E. Korkis and H. W. Lam, *Chem. Commun.*, 2019, **55**, 838–841.

7 J. Yan and N. Yoshikai, *ACS Catal.*, 2016, **6**, 3738–3742.

8 For selected examples of other types of enantioselective arylative cyclizations of alkynyl electrophiles, see ref. 4*h*, *n–p* and: (*a*) R. Shintani, K. Okamoto, Y. Otomaru, K. Ueyama and T. Hayashi, *J. Am. Chem. Soc.*, 2005, **127**, 54–55; (*b*) T. Miura, M. Shimada and M. Murakami, *J. Am. Chem. Soc.*, 2005, **127**, 1094–1095; (*c*) T. Miura, T. Sasaki, H. Nakazawa and M. Murakami, *J. Am. Chem. Soc.*, 2005, **127**, 1390–1391; (*d*) R. Shintani, A. Tsurusaki, K. Okamoto and T. Hayashi, *Angew. Chem., Int. Ed.*, 2005, **44**, 3909; (*e*) J. Song, Q. Shen, F. Xu and X. Lu, *Org. Lett.*, 2007, **9**, 2947–2950; (*f*) X. Han and X. Lu, *Org. Lett.*, 2010, **12**, 108–111; (*g*) Z.-T. He, B. Tian, Y. Fukui, X. Tong, P. Tian and G.-Q. Lin, *Angew. Chem., Int. Ed.*, 2013, **52**, 5314–5318; (*h*) J. Keilitz, S. G. Newman and M. Lautens, *Org. Lett.*, 2013, **15**, 1148–1151; (*i*) Y. Li and M.-H. Xu, *Org. Lett.*, 2014, **16**, 2712–2715; (*j*) T. Johnson, K.-L. Choo and M. Lautens, *Chem. Eur.–J.*, 2014, **20**, 14194–14197; (*k*) F. Serpier, B. Flamme, J.-L. Brayer, B. Folléas and S. Darses, *Org. Lett.*, 2015, **17**, 1720–1723; (*l*) C. Clarke, C. A. Incerti-Pradillos and H. W. Lam, *J. Am. Chem. Soc.*, 2016, **138**, 8068–8071; (*m*) C. Yap, G. M. J. Lenagh-Snow, S. N. Karad, W. Lewis, L. J. Diorazio and H. W. Lam, *Angew. Chem., Int. Ed.*, 2017, **56**, 8216–8220; (*n*) S. N. Karad, H. Panchal, C. Clarke, W. Lewis and H. W. Lam, *Angew. Chem., Int. Ed.*, 2018, **57**, 9122–9125.

9 The relative and absolute configurations of **2j** and **5g** were determined by X-ray crystallography, and those of the remaining products were assigned by analogy. CCDC 1959877 and 1959878 contain the ESI crystallographic data for this paper.† Furthermore, the spectroscopic data of **2r** are consistent with those reported previously (ref. 7), which suggests the relative configurations of products **2** are identical to those reported in ref. 7.

10 Ketone **3a** appears to be the result of arylrhodation of the alkyne of **1a** with the regioselectivity opposite to that seen in the formation of arylative cyclization product **2a**, combined with a retro-Claisen condensation. However, the order of these steps is not currently known.

11 See the ESI† for purification of arylboronic acids.

12 The research data associated with this publication can be found at: http://dx.doi.org/10.17639/nott.7036.