

C–H Activation

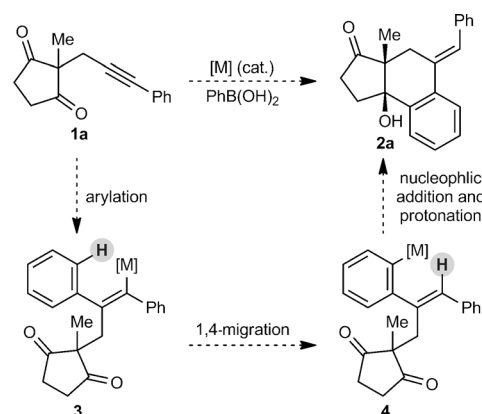
Iridium-Catalyzed Arylative Cyclization of Alkynones by 1,4-Iridium Migration**

Benjamin M. Partridge, Jorge Solana González, and Hon Wai Lam*

Abstract: 1,4-Metal migrations enable the remote functionalization of C–H bonds, and have been utilized in a wide variety of valuable synthetic methods. The vast majority of existing examples involve the 1,4-migration of palladium or rhodium. Herein, the stereoselective synthesis of complex polycycles by the iridium-catalyzed arylative cyclization of alkynones with arylboronic acids is described. To our knowledge, these reactions involve the first reported examples of 1,4-iridium migration.

Since the early reports of 1,4-palladium migration^[1a–d] and 1,4-rhodium migration,^[2a,b] numerous catalytic reactions involving 1,4-metal migration have been developed.^[1–5] Such processes enable the remote functionalization of C–H bonds, allowing the introduction of metal centers at positions that would otherwise be difficult to metalate. To date, reactions involving the 1,4-migration of palladium,^[1] rhodium,^[2] platinum,^[1q] nickel,^[4] and cobalt^[5] have been achieved. The demonstration of the ability of other metals to undergo 1,4-migration would be valuable, as their distinct properties may offer new opportunities for the development of useful synthetic methods. Herein, we describe the preparation of highly functionalized polycycles by the iridium-catalyzed arylative cyclization of alkynones. One of the key steps in this transformation is a 1,4-iridium migration, which, to our knowledge, has not been described previously.

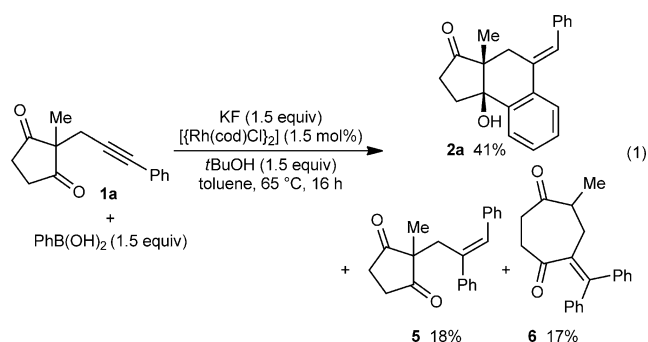
During a program aimed at the stereoselective synthesis of complex polycycles by the desymmetrization of cyclic 1,3-diketones,^[6,7] we became interested in developing an arylative cyclization of substrates such as **1a** (Scheme 1). We envisaged that in the presence of a suitable metal complex, an arylboron



Scheme 1. Proposed arylative cyclization of alkynones.

reagent could be employed in an arylmetalation of the alkyne moiety of **1a** to give alkenylmetal species **3**. This intermediate could then undergo an alkenyl-to-aryl 1,4-migration to provide intermediate **4**, which could then participate in the nucleophilic attack of one of the ketones to give tertiary-alcohol-containing tricycle **2a**.

In view of the success of rhodium catalysis in related transformations,^[2d–g,i,k–q] the reaction of **1a** with PhB(OH)₂ in the presence of [{Rh(cod)Cl}₂] (1.5 mol %), KF (1.5 equiv) as a mild base, and *t*BuOH (1.5 equiv) as a proton source was examined [Eq. (1)]. Heating the reaction in toluene at 65 °C



for 16 hours did indeed provide tricycle **2a** in 41 % yield. However, **2a** was accompanied by the simple alkyne hydroarylation product **5** (18 % yield) and the ring-expansion product **6** (17 % yield), which is formed by initial arylation of the alkyne with the opposite regioselectivity, followed by

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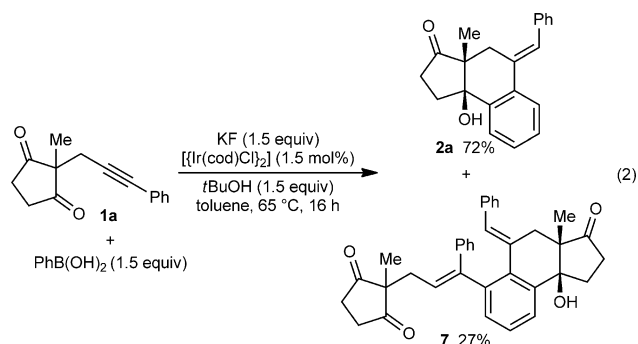
[†] These authors contributed equally to this work.

[**] We thank the ERC (Starting Grant No. 258580) and the EPSRC (Leadership Fellowship to H.W.L.) for financial support. We thank Dr. Gary S. Nichol (University of Edinburgh) and Dr. William Lewis (University of Nottingham) for X-ray crystallography, and Lorna Eades (University of Edinburgh) for ICP-MS analysis. The EPSRC National Mass Spectrometry Facility is gratefully acknowledged for providing high-resolution mass spectra.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201403271>.

a cyclization–fragmentation process, as described by Murakami and co-workers.^[8]

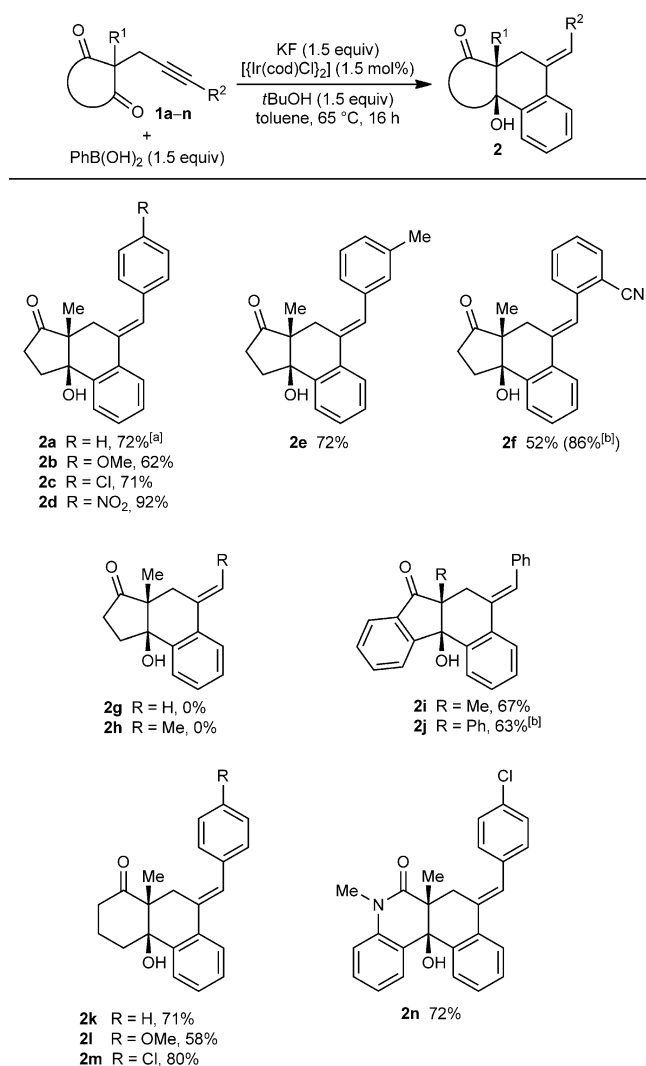
In an effort to increase the yield of **2a**, catalyst systems based upon other metals known to undergo 1,4-migrations (Pd,^[1] Pt,^[1a] Ni,^[4] and Co^[5]) were surveyed. However, no reaction was observed in these experiments. Fortunately, $[\text{Ir}(\text{cod})\text{Cl}]_2$ (1.5 mol%) was effective, and provided **2a** in 72% yield [Eq. (2)]. Interestingly, this experiment also gave



product **7** in 27% yield, the structure of which was determined by X-ray crystallography.^[9] Compound **7** is a 2:1 adduct of **1a** and $\text{PhB}(\text{OH})_2$, respectively, resulting from a complex sequence beginning with the arylmetalation of the alkyne of **1a** with the regioselectivity opposite to that seen in the formation of **2a**.^[10,11] To our knowledge, this reaction involves the first reported examples of 1,4-iridium migration. Given that the yield of **2a** was higher using an iridium- rather than a rhodium-based precatalyst, $[\text{Ir}(\text{cod})\text{Cl}]_2$ was selected for further studies.

The iridium-catalyzed arylative cyclization of various substrates with $\text{PhB}(\text{OH})_2$ was then explored (Scheme 2). In all reactions, the 2:1 adduct was observed in approximately 10–25% yield by ^1H NMR analysis of the reaction mixtures, but these products were not isolated. Substituents at the *para*, *meta*, or *ortho* positions of the aryl group on the alkyne were tolerated (**2b–f**), though in the case where an *ortho*-cyano group was present, a higher loading of $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.5 mol%) was required for full conversion (**2f**). With *para*-substituted phenyl groups, electron-poor rather than electron-rich arenes led to higher yields of the products (compare **2b–d**), which is likely due to a more regioselective initial arylmetalation of more polarized alkynes. The relative configurations of the stereogenic centers and the *E* geometry of the alkenes in the products were assigned by analogy with **2d**, the structure of which was determined by X-ray crystallography.^[9] Substrates containing a terminal alkyne or an alkyne lacking an aryl substituent did not undergo the reaction and returned only unreacted starting material (**2g** and **2h**).

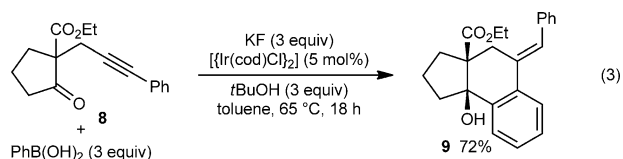
Next, variations of the pendant ketone were examined. An indane-1,3-dione reacted well to give **2i** in 67% yield. Changing the substituent at C2 (between the ketones) from a methyl to a phenyl group was tolerated, and **2j** was obtained in 63% yield using 2.5 mol% of $[\text{Ir}(\text{cod})\text{Cl}]_2$. Switching



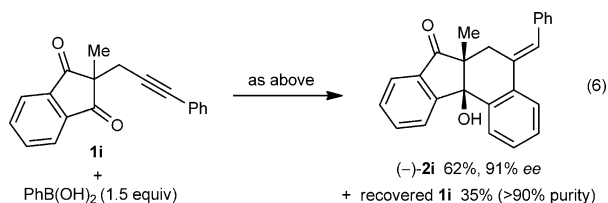
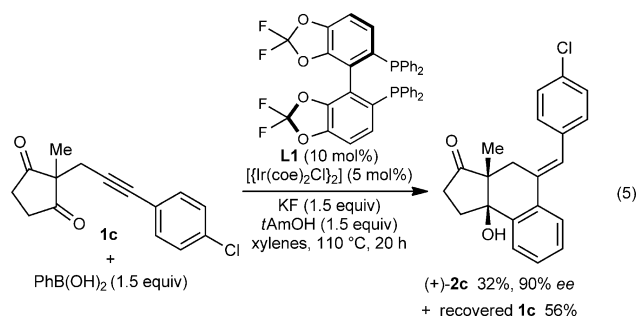
Scheme 2. Arylative cyclization of various alkynes. Reactions were conducted using 0.40 mmol of **1a–n** in toluene (4 mL). Cited yields are of isolated products. [a] Compound **7** was also isolated in 27% yield. See Equation (2). [b] 2.5 mol% of $[\text{Ir}(\text{cod})\text{Cl}]_2$ was used.

from five- to six-membered ring diketones was also possible (**2k–m**^[9]). In these cases, and in a similar fashion to the five-membered ring substrates, the reactions of substrates containing more electron-deficient arenes on the alkyne led to higher yields than those with electron-rich arenes (compare **2k–m**). A cyclic β -ketoamide was also tolerated, providing **2n** in 72% yield.

The process is not limited to cyclic 1,3-dicarbonyl substrates in which both carbonyl groups are part of the ring; the β -ketoester **8** also underwent arylative cyclization to give **9** in 72% yield [Eq. (3)]. However, substrate **8** was less



tion conditions compared with those used in the racemic reactions [Eqs. (5) and (6)].^[9,15] However, the activity of this iridium-bisphosphine complex was modest, and significant



quantities of the starting materials were returned. Interestingly, 2:1 adducts analogous to **7** were not observed in these reactions.

In summary, we have reported the iridium-catalyzed arylative cyclization of alkynones with arylboronic acids.^[16] These reactions involve 1,4-iridium migration as a key step, a mode of reactivity for iridium that, to our knowledge, has not been reported previously.^[17] Efforts to exploit the 1,4-migration of iridium and other metals in new catalytic transformations are ongoing in our group.

Received: March 12, 2014

Published online: May 19, 2014

Keywords: alkynes · boron · catalysis · C–H activation · iridium

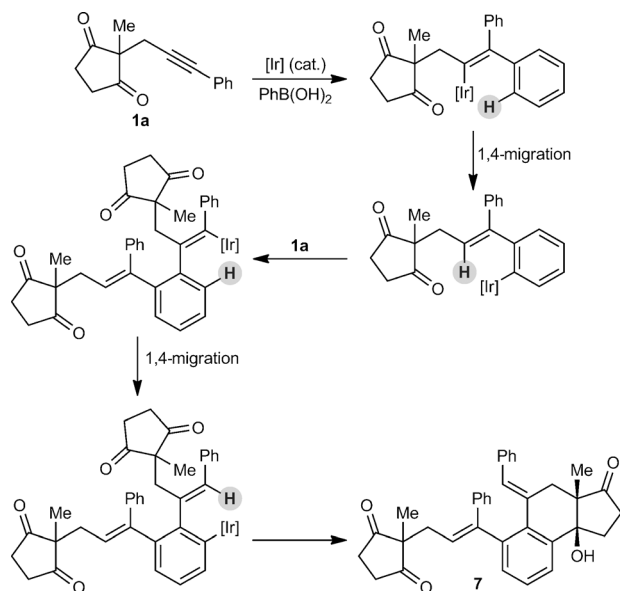
- [1] For examples of 1,4-palladium migration, see: a) G. Dyker, *Angew. Chem.* **1992**, *104*, 1079–1081; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1023–1025; b) G. Dyker, *J. Org. Chem.* **1993**, *58*, 6426–6428; c) G. Dyker, *Angew. Chem.* **1994**, *106*, 117–119; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 103–105; d) G. Dyker, *Chem. Ber.* **1994**, *127*, 739–742; e) L. Wang, Y. Pan, X. Jiang, H. Hu, *Tetrahedron Lett.* **2000**, *41*, 725–727; f) Q. Tian, R. C. Larock, *Org. Lett.* **2000**, *2*, 3329–3332; g) R. C. Larock, Q. Tian, *J. Org. Chem.* **2001**, *66*, 7372–7379; h) G. Karig, M.-T. Moon, N. Thasana, T. Gallagher, *Org. Lett.* **2002**, *4*, 3115–3118; i) M. A. Campo, R. C. Larock, *J. Am. Chem. Soc.* **2002**, *124*, 14326–14327; j) M. A. Campo, Q. Huang, T. Yao, Q. Tian, R. C. Larock, *J. Am. Chem. Soc.* **2003**, *125*, 11506–11507; k) O. Baudoin, A. Herrbach, F. Gueritte, *Angew. Chem.* **2003**, *115*, 5914–5918; *Angew. Chem. Int. Ed.* **2003**, *42*, 5736–5740; l) Q. Huang, A. Fazio, G. Dai, M. A. Campo, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 7460–7461; m) J. Zhao, M. Campo, R. Larock, *Angew. Chem.* **2005**, *117*, 1907–1909; *Angew. Chem. Int.*

Ed. **2005**, *44*, 1873–1875; n) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696; o) D. Masselot, J. P. H. Charmant, T. Gallagher, *J. Am. Chem. Soc.* **2006**, *128*, 694–695; p) J. Zhao, R. C. Larock, *J. Org. Chem.* **2006**, *71*, 5340–5348; q) A. Singh, P. R. Sharp, *J. Am. Chem. Soc.* **2006**, *128*, 5998–5999; r) J. Hitce, P. Retailleau, O. Baudoin, *Chem. Eur. J.* **2007**, *13*, 792–799; s) J. Zhao, D. Yue, M. A. Campo, R. C. Larock, *J. Am. Chem. Soc.* **2007**, *129*, 5288–5295; t) M. A. Campo, H. Zhang, T. Yao, A. Ibdah, R. D. McCulla, Q. Huang, J. Zhao, W. S. Jenks, R. C. Larock, *J. Am. Chem. Soc.* **2007**, *129*, 6298–6307; u) T. Kesharwani, A. K. Verma, D. Emrich, J. A. Ward, R. C. Larock, *Org. Lett.* **2009**, *11*, 2591–2593; v) J. Pan, M. Su, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 8806–8810; *Angew. Chem. Int. Ed.* **2011**, *50*, 8647–8651; w) H. J. Lee, K. H. Kim, S. H. Kim, J. N. Kim, *Tetrahedron Lett.* **2013**, *54*, 170–175; x) T. Piou, A. Bunescu, Q. Wang, L. Neuville, J. Zhu, *Angew. Chem.* **2013**, *125*, 12611–12615; *Angew. Chem. Int. Ed.* **2013**, *52*, 12385–12389.

- [2] For examples of 1,4-rhodium migration, see: a) K. Oguma, M. Miura, T. Satoh, M. Nomura, *J. Am. Chem. Soc.* **2000**, *122*, 10464–10465; b) T. Hayashi, K. Inoue, N. Taniguchi, M. Ogasawara, *J. Am. Chem. Soc.* **2001**, *123*, 9918–9919; c) K. Oguma, M. Miura, T. Satoh, M. Nomura, *J. Organomet. Chem.* **2002**, *648*, 297–301; d) R. Shintani, T. Hayashi, *Org. Lett.* **2005**, *7*, 2071–2073; e) T. Miura, T. Sasaki, H. Nakazawa, M. Murakami, *J. Am. Chem. Soc.* **2005**, *127*, 1390–1391; f) R. Shintani, K. Okamoto, T. Hayashi, *J. Am. Chem. Soc.* **2005**, *127*, 2872–2873; g) R. Shintani, K. Takatsu, T. Hayashi, *Angew. Chem.* **2007**, *119*, 3809–3811; *Angew. Chem. Int. Ed.* **2007**, *46*, 3735–3737; h) T. Matsuda, M. Shigeno, M. Murakami, *J. Am. Chem. Soc.* **2007**, *129*, 12086–12087; i) R. Shintani, K. Takatsu, T. Katoh, T. Nishimura, T. Hayashi, *Angew. Chem.* **2008**, *120*, 1469–1471; *Angew. Chem. Int. Ed.* **2008**, *47*, 1447–1449; j) J. Panteleev, F. Menard, M. Lautens, *Adv. Synth. Catal.* **2008**, *350*, 2893–2902; k) T. Seiser, O. A. Roth, N. Cramer, *Angew. Chem.* **2009**, *121*, 6438–6441; *Angew. Chem. Int. Ed.* **2009**, *48*, 6320–6323; l) M. Shigeno, T. Yamamoto, M. Murakami, *Chem. Eur. J.* **2009**, *15*, 12929–12931; m) R. Shintani, S. Isobe, M. Takeda, T. Hayashi, *Angew. Chem.* **2010**, *122*, 3883–3886; *Angew. Chem. Int. Ed.* **2010**, *49*, 3795–3798; n) T. Seiser, N. Cramer, *Angew. Chem.* **2010**, *122*, 10361–10365; *Angew. Chem. Int. Ed.* **2010**, *49*, 10163–10167; o) K. Sasaki, T. Hayashi, *Tetrahedron: Asymmetry* **2012**, *23*, 373–380; p) T. Matsuda, Y. Suda, A. Takahashi, *Chem. Commun.* **2012**, *48*, 2988–2990; q) K. Sasaki, T. Nishimura, R. Shintani, E. A. B. Kantchev, T. Hayashi, *Chem. Sci.* **2012**, *3*, 1278–1283; r) Y. Ikeda, K. Takano, S. Kodama, Y. Ishii, *Chem. Commun.* **2013**, *49*, 11104–11106; s) J. Zhang, J.-F. Liu, A. Ugrinov, A. F. X. Pillai, Z.-M. Sun, P. Zhao, *J. Am. Chem. Soc.* **2013**, *135*, 17270–17273.

- [3] For reviews of 1,4-metal migration, see: a) S. Ma, Z. Gu, *Angew. Chem.* **2005**, *117*, 7680–7685; *Angew. Chem. Int. Ed.* **2005**, *44*, 7512–7517; b) F. Shi, R. C. Larock, *Top. Curr. Chem.* **2010**, *292*, 123–164.
- [4] For an example of 1,4-nickel migration, see: A. L. Keen, M. Doster, S. A. Johnson, *J. Am. Chem. Soc.* **2007**, *129*, 810–819.
- [5] For examples of 1,4-cobalt migration, see: a) B.-H. Tan, J. Dong, N. Yoshikai, *Angew. Chem.* **2012**, *124*, 9748–9752; *Angew. Chem. Int. Ed.* **2012**, *51*, 9610–9614; b) B. Wu, N. Yoshikai, *Angew. Chem.* **2013**, *125*, 10690–10693; *Angew. Chem. Int. Ed.* **2013**, *52*, 10496–10499.
- [6] D. W. Low, G. Pattison, M. D. Wieczysty, G. H. Churchill, H. W. Lam, *Org. Lett.* **2012**, *14*, 2548–2551.
- [7] A. R. Burns, J. Solana González, H. W. Lam, *Angew. Chem.* **2012**, *124*, 10985–10989; *Angew. Chem. Int. Ed.* **2012**, *51*, 10827–10831.
- [8] T. Miura, M. Shimada, M. Murakami, *Angew. Chem.* **2005**, *117*, 7770–7772; *Angew. Chem. Int. Ed.* **2005**, *44*, 7598–7600.

- [9] CCDC 979585 (**7**), 979586 (**2d**), 979587 (**2i**), and 990617 [(+)-**2c**] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [10] A plausible mechanism for the formation of **7** is illustrated below.



- [11] Repeating the reaction shown in Equation (2) at a lower concentration of 0.04 M with respect to **1a** rather than at the standard concentration of 0.1 M gave **2a** and **7** in 74% and 15% yields, respectively. A reaction at a higher concentration of 0.4 M

gave **2a** and **7** in 79% and 17% yields, respectively. However, solubility problems were encountered with some of the other substrates at a 0.4 M concentration, so a 0.1 M concentration was used throughout this study.

- [12] For a recent review on sterically controlled iridium-catalyzed C–H borylation, see: J. F. Hartwig, *Acc. Chem. Res.* **2012**, *45*, 864–873.
- [13] For iridium-catalyzed hydroarylation of alkynes, see: K. Tsuchikawa, M. Kasagawa, Y.-K. Hashimoto, K. Endo, T. Shibata, *J. Organomet. Chem.* **2008**, *693*, 3939–3942.
- [14] For iridium-catalyzed arylation of alkenes using arylboron compounds, see: a) T. Nishimura, Y. Yasuhara, T. Hayashi, *Angew. Chem.* **2006**, *118*, 5288–5290; *Angew. Chem. Int. Ed.* **2006**, *45*, 5164–5166; b) T. Nishimura, Y. Yasuhara, T. Hayashi, *J. Am. Chem. Soc.* **2007**, *129*, 7506–7507; c) T. Nishimura, Y. Yasuhara, M. Nagaosa, T. Hayashi, *Tetrahedron: Asymmetry* **2008**, *19*, 1778–1783; d) S. B. Kim, C. Cai, M. D. Faust, W. C. Trenkle, D. A. Sweigart, *J. Organomet. Chem.* **2008**, *694*, 52–56; e) T. Nishimura, Y. Yasuhara, T. Sawano, T. Hayashi, *J. Am. Chem. Soc.* **2010**, *132*, 7872–7873; f) T. Nishimura, A. Noishiki, T. Hayashi, *Chem. Commun.* **2012**, *48*, 973–975.
- [15] The absolute configuration of (+)-**2c** was determined by X-ray crystallography. See the Supporting Information for further details.
- [16] To support the conclusion that an iridium species is the active catalyst, we performed ICP-MS analysis on a standard reaction mixture (product **2a**, Scheme 2). Although trace quantities of Fe (120 ppb), Ni (29 ppb), Cu (19 ppb), and Pd (62 ppb) were identified as being present, control experiments carried out with salts containing these metals at approximately these quantities, in the absence of $[\text{Ir}(\text{cod})\text{Cl}]_2$, did not lead to the formation of product **2a**, as determined by ^1H NMR analysis.
- [17] After this manuscript was accepted, Ishii and co-workers reported an example of 1,4-iridium(III) migration. See: Y. Ikeda, K. Takano, M. Waragai, S. Kodama, N. Tsuchida, K. Takano, Y. Ishii, *Organometallics* **2014**, *33*, 2142–2145.