



Cite this: *Chem. Commun.*, 2016, 52, 5876

Received 15th February 2016,
Accepted 29th March 2016

DOI: 10.1039/c6cc01398h

www.rsc.org/chemcomm

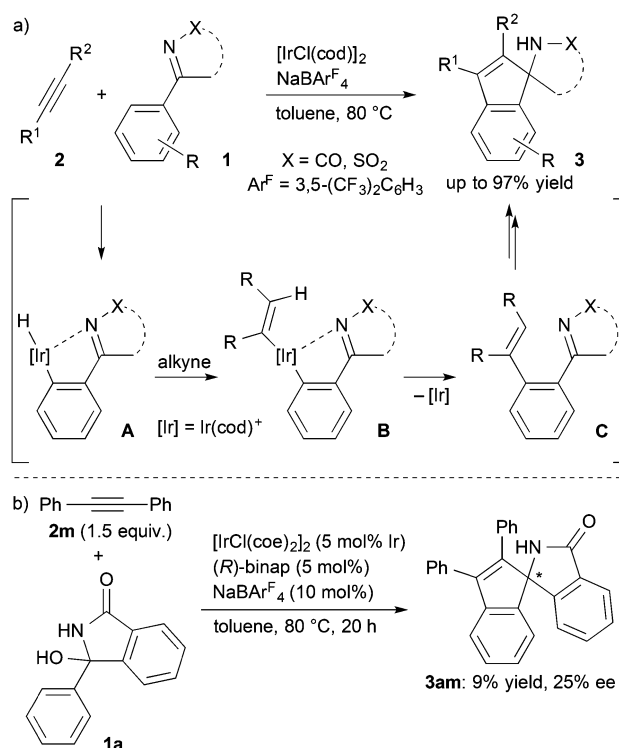
Iridium-catalyzed asymmetric [3+2] annulation of aromatic ketimines with alkynes *via* C–H activation: unexpected inversion of the enantioselectivity induced by protic acids†

Midori Nagamoto, Daisuke Yamauchi and Takahiro Nishimura*

A cationic iridium/binap catalyst enabled the asymmetric [3+2] annulation of cyclic *N*-acyl ketimines with internal alkynes *via* C–H activation to give spiroaminoindene derivatives with high enantioselectivity. The stereochemical course of this annulation was switchable by acid additives.

Transition metal-catalyzed direct functionalization of aromatic C–H bonds has enabled a short-step synthesis of various useful compounds.¹ The regioselective functionalization has been achieved by use of directing groups, which are often involved in the reactions leading to cyclic compounds through the catalytic process.² In this regard, there have been several successful reports on the formal [3+2] annulation reactions of aromatic imines or ketones with C–C multiple bonds giving indene or indane derivatives in the presence of Re,³ Ru,⁴ Rh,⁵ and Ir catalysts.⁶ The asymmetric annulation reaction has also been reported by means of Rh^{5c,d} and Ir^{6c} catalysis giving chiral 1-aminoindane derivatives with high enantioselectivity.

Recently, we reported that a cationic iridium(cod) complex catalyzes a [3+2] annulation of aromatic ketimines with alkynes *via* C–H activation to give spiroaminoindenes (Scheme 1a).⁷ Mechanistic studies revealed that the reaction proceeds *via* sequential *ortho*-alkenylation and intramolecular cyclization. For the development of the asymmetric reaction, we envisioned two possible asymmetric induction methods in light of the tandem reaction mechanism, which involves the intramolecular cyclization of the alkenylated intermediate **C** as the enantio-determining step. One is the transfer of a transient axial chirality of intermediate **C** to the chiral annulation product **3**,⁸ and the other is the use of the cationic iridium species as a chiral Lewis acid to invoke the enantioselective cyclization of intermediate **C**.⁹ We tested several chiral ligands for the Ir-catalyzed annulation



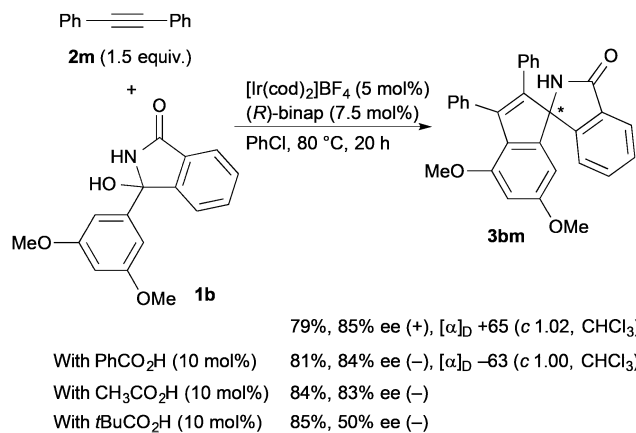
Scheme 1 Ir-catalyzed annulation of aromatic ketimines **1** with alkynes **2**.

of 3-hydroxy-3-phenylisoindolin-1-one (**1a**), which *in situ* generates an *N*-acyl ketimine by dehydration,⁷ but only low levels of the asymmetric induction were obtained (*e.g.*, 25% ee with (*R*)-binap, Scheme 1b). In contrast, it was found that the reaction of ketimines having substituted phenyl groups gave the annulation products in high yields and enantioselectivity. We also found that the stereochemical course of this annulation was switchable by acid additives. Here we report that the asymmetric [3+2] annulation of cyclic *N*-acyl ketimines with internal alkynes *via* C–H activation gives chiral spiroaminoindene derivatives.

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan. E-mail: tnishi@kuchem.kyoto-u.ac.jp

† Electronic supplementary information (ESI) available: Experimental procedures, compound characterization data, and X-ray crystallographic data of compound **3br**. CCDC 1449863. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6cc01398h



Scheme 2 Ir-catalyzed asymmetric annulation of ketimine **1b** with alkyne **2m**.

An enantiodivergent synthesis of both enantiomers has drawn a lot of attention, particularly in the field of pharmaceutical chemistry because each enantiomer often exhibits different bioactivity.¹⁰ It is an attractive and important challenge to induce both enantioselectivities using a single chiral catalyst by changing the reaction conditions such as the reaction

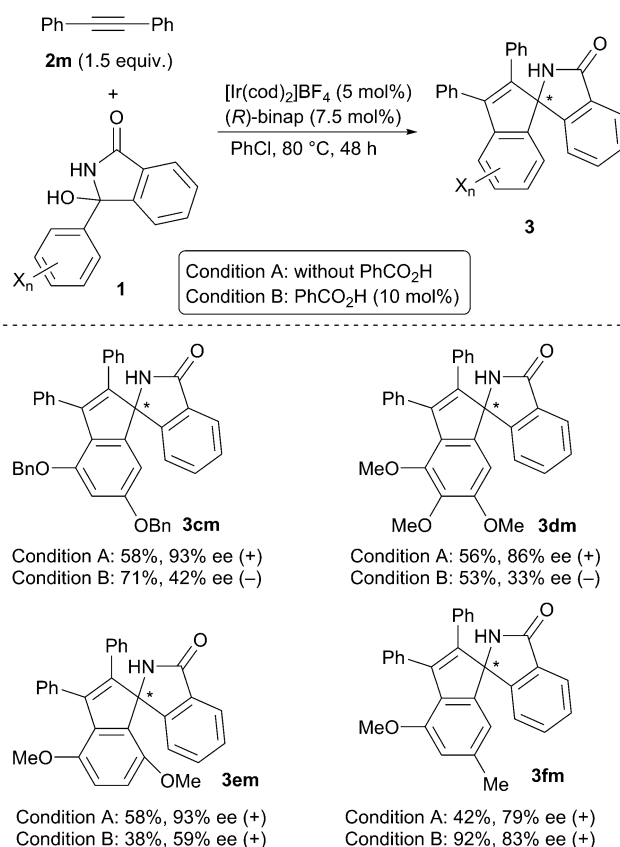
Table 1 Asymmetric annulation of **1b** with alkynes **2**^a

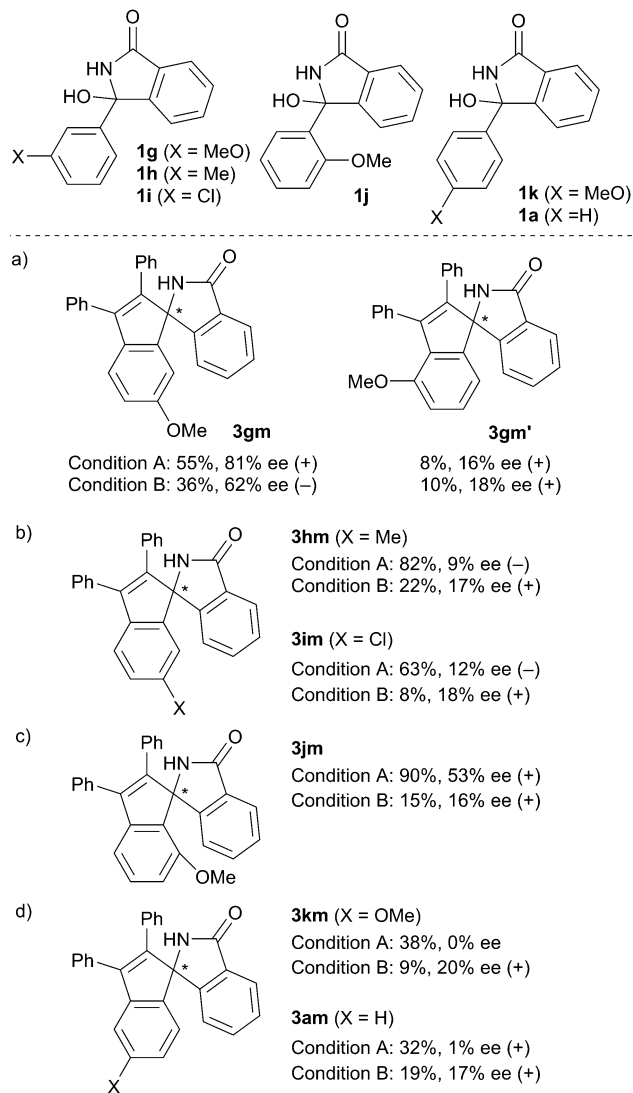
Entry	Alkyne	Condition	Yield (%)	ee (%)
1	R ¹ = R ² = Ph (2m)	A	81 (3bm)	88 (+)
2	2m	B	94 (3bm)	83 (-)
3 ^b	R ¹ = R ² = 4-MeC ₆ H ₄ (2n)	A	68 (3bn)	92 (+)
4	2n	B	89 (3bn)	76 (-)
5	R ¹ = R ² = 4-MeOC ₆ H ₄ (2o)	A	73 (3bo)	93 (+)
6	2o	B	97 (3bo)	59 (-)
7 ^b	R ¹ = R ² = 4-CF ₃ C ₆ H ₄ (2p)	A	53 (3bp)	83 (+)
8	2p	B	50 (3bp)	87 (-)
9	R ¹ = R ² = 4-FC ₆ H ₄ (2q)	A	72 (3bq)	92 (+)
10	2q	B	98 (3bq)	79 (-)
11	R ¹ = R ² = 4-ClC ₆ H ₄ (2r)	A	89 (3br)	87 (+)
12	2r	B	93 (3br)	82 (-)
13	R ¹ = R ² = 3-ClC ₆ H ₄ (2s)	A	52 (3bs)	84 (+)
14	2s	B	71 (3bs)	85 (-)
15	R ¹ = Ph, R ² = <i>n</i> -Bu (2t)	A	56 ^c (3bt)	73 (-)
16	2t	B	50 ^d (3bt)	92 (+)
17	R ¹ = R ² = <i>n</i> -Pr (2u)	A	34 (3bu)	37 (+)
18	2u	B	23 (3bu)	57 (+)

^a Condition A: **1b** (0.20 mmol), alkyne **2** (0.30 mmol), [Ir(cod)₂]BF₄ (5 mol%), and (*R*)-binap (7.5 mol%) in PhCl (0.80 mL) at 80 °C for 48 h. Condition B: with PhCO₂H (10 mol%). Isolated yields are shown and the ee was determined by chiral HPLC analysis. ^b [Ir(cod)₂]BF₄ (10 mol%) and (*R*)-binap (15 mol%). ^c Combined yield of two regioisomers (97/3). ^d Combined yield of two regioisomers (99/1).

temperature,¹¹ solvents,¹² and additives.¹³ We found that the enantiodivergent synthesis of the annulation products formed from ketimines and alkynes under Ir catalysis can be achieved by means of just a slight modification of the reaction conditions. Treatment of 3-hydroxy-3-(3,5-dimethoxyphenyl)isoindolin-1-one (**1b**) with diphenylacetylene (**2m**) in chlorobenzene in the presence of [Ir(cod)₂]BF₄ (5 mol%, cod = 1,5-cyclooctadiene) and (*R*)-binap (7.5 mol%) at 80 °C for 20 h gave the annulation product (+)-**3bm** in 79% yield with 85% ee (Scheme 2). To our surprise, the presence of a carboxylic acid inverted the enantioselectivity giving (-)-**3bm** under otherwise the same reaction conditions; the reaction in the presence of benzoic acid (10 mol%) gave (-)-**3bm** in 81% yield with 84% ee. The same inverse effect of the enantioselectivity was also observed in the presence of acetic acid (83% ee) and pivalic acid (50% ee).

The enantiodivergent synthesis of the annulation products can be achieved in the reaction of **1b** with several internal alkynes **2** (Table 1). The reactions of symmetrically substituted diaryl acetylenes **2m–2s** gave the corresponding annulation products (+)-**3bm–3bs** with 83–93% ee in the absence of benzoic acid (Condition A, odd entries of 1–14). In contrast, the reactions in the presence of benzoic acid (Condition B) gave (-)-**3bm–3bs** with 59–85% ee (even entries of 1–14). The reaction of 1-phenyl-1-hexyne (**2t**) gave **3bt** with high regioselectivity and good enantioselectivity under both Conditions A and B (entries 15 and 16). In contrast, the switch of the enantioselectivity was not

Scheme 3 Asymmetric annulation of hemiaminals **1** with **2m**.

Scheme 4 Annulation of monosubstituted hemiaminals **1** with **2m**.

observed in the reaction of 1-octyne (**2u**); the reaction gave (+)-**3bu** with moderate ee under both Conditions A and B (entries 17 and 18). The absolute configuration of (+)-**3br** obtained under Condition A was determined to be S by X-ray crystallographic analysis.¹⁴

Scheme 3 summarizes the results obtained for the reaction of several hemiaminals **1** with diphenylacetylene **2m**. The reaction of **1c**, having a 3,5-dibenzyloxyphenyl group, gave (+)-**3cm** with 93% ee under Condition A, and (-)-**3cm** with 42% ee under Condition B. The inversion of enantioselectivity was also observed in the reaction of **1d** having a 3,4,5-trimethoxyphenyl group (86% ee (+) under Condition A and 33% ee (-) under Condition B). In contrast, in the reaction of **1e** substituted with a 2,5-dimethoxyphenyl group and **1f** having a 3-methoxy-5-methyl group, the inversion of the enantioselectivity did not take place.

The reaction of hemiaminals bearing monosubstituted aryl groups was also conducted in order to gain some insights into the origin of the enantioselectivity (Scheme 4). The reaction of **1g** having a *meta*-methoxyphenyl group gave an isomeric mixture of **3gm** and **3gm'** with good regioselectivity (Scheme 4a).

The enantioselectivity of the major regioisomer **3gm**, which was formed *via* C–H activation at the less sterically hindered *ortho*-position, was much higher than that of **3gm'** under both Conditions A and B. The inversion of enantioselectivity was only observed for the major regioisomer **3gm**. It should be noted that the ee of **3gm'** was much lower than that of **3gm**, although it was expected that the methoxy group can restrict the axial rotation of the alkenylated intermediate formed *via* C–H activation at the more sterically hindered *ortho*-position. These results are consistent with the chiral Lewis acid-induced cyclization rather than the chirality transfer as the enantio-determining step. The reactions of **1h** and **1i**, having a methyl and a chloro group at the *meta*-position, respectively, gave the corresponding annulation products. The inversion of the enantioselectivity was observed in both cases, albeit with a low ee (Scheme 4b). In contrast, the inversion was not observed in the reaction of **1j** having an *ortho*-methoxyphenyl group, while a decrease of the ee was observed in the presence of the acid (Scheme 4c). The *para*-methoxy group on **1k** had no effect on the asymmetric induction in the absence of acid (Scheme 4d). The reaction of **1k** in the presence of the acid gave **3km** with 20% ee. Hemiaminal **1a** having a non-substituted phenyl group exhibited a similar reactivity and selectivity to **1k**. These results indicate that the *meta*-substituent of the aromatic rings, which undergo the C–H activation, plays some roles in the inversion of the enantioselectivity in the presence of the acid, regardless of their electronic character. Although we assume that the asymmetric induction is due to the chiral Lewis acid catalyst shown in Scheme 1, the acid additive might alter the reaction mechanism, which may result in the different stereochemical outcome.^{15,16} At this stage, the exact roles of the acid additives and the substituents on aryl group remain unclear.

In summary, we have developed an asymmetric [3+2] annulation of cyclic *N*-acyl ketimines with alkynes using a cationic iridium/binap catalyst. The enantioselectivity was found to be switchable by acid additives.

This work was supported by JSPS KAKENHI Grant No. 15H03810. M. N. thanks the JSPS for a Research Fellowship for Young Scientists.

Notes and references

- (a) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda and N. Chatani, *Nature*, 1993, **366**, 529. For selected recent reviews, see: (b) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726; (c) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (d) G. Rousseau and B. Breit, *Angew. Chem., Int. Ed.*, 2011, **50**, 2450; (e) T. W. Lyons and M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147; (f) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624.
- For selected examples, see: (a) L. Ackermann and A. V. Lygin, *Org. Lett.*, 2012, **14**, 764; (b) V. S. Thirunavukkarasu, M. Donati and L. Ackermann, *Org. Lett.*, 2012, **14**, 3416; (c) L. Wang and L. Ackermann, *Org. Lett.*, 2013, **15**, 176; (d) B. Ye and N. Cramer, *Science*, 2012, **338**, 504; (e) M. P. Huestis, L. Chan, D. R. Stuart and K. Fagnou, *Angew. Chem., Int. Ed.*, 2011, **50**, 1338; (f) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133**, 6449; (g) Z. Shi, C. Grohmann and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 5393; (h) H. Wang and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 7318; (i) D. Zhao, Z. Shi and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 12426; (j) Y. Su, M. Zhao, K. Han, G. Song and X. Li,



- Org. Lett.*, 2010, **12**, 5462; (k) Y. Unoh, Y. Hashimoto, D. Takeda, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2013, **15**, 3258; (l) K. Morimoto, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2011, **76**, 9548; (m) T. K. Hyster, L. Knörr, T. R. Ward and T. Rovis, *Science*, 2012, **338**, 500.
- 3 (a) Y. Kuninobu, A. Kawata and K. Takai, *J. Am. Chem. Soc.*, 2005, **127**, 13498; (b) Y. Kuninobu, Y. Tokunaga, A. Kawata and K. Takai, *J. Am. Chem. Soc.*, 2006, **128**, 202; (c) Y. Kuninobu, Y. Nishina, M. Shouho and K. Takai, *Angew. Chem., Int. Ed.*, 2006, **45**, 2766; (d) Y. Kuninobu, P. Yu and K. Takai, *Org. Lett.*, 2010, **12**, 4274.
- 4 (a) P. W. R. Harris, C. E. F. Rickard and P. D. Woodgate, *J. Organomet. Chem.*, 1999, **589**, 168; (b) R. K. Chinnagolla and M. Jeganmohan, *Eur. J. Org. Chem.*, 2012, 417; (c) P. Zhao, F. Wang, K. Han and X. Li, *Org. Lett.*, 2012, **14**, 5506; (d) J. Zhang, A. Ugrinov and P. Zhao, *Angew. Chem., Int. Ed.*, 2013, **52**, 6681; (e) C.-H. Hung, P. Gandeepan and C.-H. Cheng, *ChemCatChem*, 2014, **6**, 2692.
- 5 Rh(I): (a) Z.-M. Sun, S.-P. Chen and P. Zhao, *Chem. – Eur. J.*, 2010, **16**, 2619; (b) D. N. Tran and N. Cramer, *Angew. Chem., Int. Ed.*, 2010, **49**, 8181; (c) D. N. Tran and N. Cramer, *Angew. Chem., Int. Ed.*, 2011, **50**, 11098; (d) D. N. Tran and N. Cramer, *Angew. Chem., Int. Ed.*, 2013, **52**, 10630; Rh(III): (e) F. W. Patureau, T. Besset, N. Kuhl and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133**, 2154; (f) K. Muralirajan, K. Parthasarathy and C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2011, **50**, 4169; (g) Y. Chen, F. Wang, W. Zhen and X. Li, *Adv. Synth. Catal.*, 2013, **355**, 353; (h) L. Dong, C.-H. Qu, J.-R. Huang, W. Zhang, Q.-R. Zhang and J.-G. Deng, *Chem. – Eur. J.*, 2013, **19**, 16537; (i) M. V. Pham and N. Cramer, *Chem. – Eur. J.*, 2016, 2270.
- 6 (a) K. Tsuchikama, M. Kasagawa, K. Endo and T. Shibata, *Synlett*, 2010, 97; (b) T. Nishimura, Y. Ebe and T. Hayashi, *J. Am. Chem. Soc.*, 2013, **135**, 2092; (c) T. Nishimura, M. Nagamoto, Y. Ebe and T. Hayashi, *Chem. Sci.*, 2013, **4**, 4499; (d) Y. Ebe, M. Hatano and T. Nishimura, *Adv. Synth. Catal.*, 2015, **357**, 1425.
- 7 M. Nagamoto and T. Nishimura, *Chem. Commun.*, 2014, **50**, 6274.
- 8 For a review, see: (a) D. Campolo, S. Gastaldi, C. Roussel, M. P. Bertrand and M. Nechab, *Chem. Soc. Rev.*, 2013, **42**, 8434; for a recent example, see: (b) L. Yang, H. Zheng, L. Luo, J. Nan, J. Liu, Y. Wang and X. Luan, *J. Am. Chem. Soc.*, 2015, **137**, 4876.
- 9 The *ortho*-alkenylated *N*-sulfonylketimine was isolated in the annulation of *N*-sulfonylketimine with an alkyne, and the cyclization of it was found to proceed on a slightly acidic silica gel without the iridium catalyst; see ref. 7 for details.
- 10 For reviews, see: (a) J. Escorihuela, M. I. Burguete and S. V. Luis, *Chem. Soc. Rev.*, 2013, **42**, 5595; (b) M. Bartók, *Chem. Rev.*, 2010, **110**, 1663; (c) T. Tanaka and M. Hayashi, *Synthesis*, 2008, 3361; (d) G. Zanoni, F. Castronovo, M. Franzini, G. Vidari and E. Giannini, *Chem. Soc. Rev.*, 2003, **32**, 115; (e) Y. H. Kim, *Acc. Chem. Res.*, 2001, **34**, 955.
- 11 (a) V. S. Chen, M. Chiu, R. D. Bergman and F. D. Toste, *J. Am. Chem. Soc.*, 2009, **131**, 6021; (b) K. Manna, N. Eedugurala and A. D. Sadow, *J. Am. Chem. Soc.*, 2015, **137**, 425.
- 12 (a) J. C. Anderson, G. J. Stepney, M. R. Mills, L. R. Horsfall, A. J. Blake and W. Lewis, *J. Org. Chem.*, 2011, **76**, 1961; (b) N. Haddad, B. Qu, S. Rodriguez, L. van der Veen, D. C. Reeves, N. C. Gonnella, H. Lee, N. Grinberg, S. Ma, D. Krishnamurthy, T. Wunberg and C. H. Senanayake, *Tetrahedron Lett.*, 2011, **52**, 3718; (c) H. Yu, F. Xie, Z. Ma, Y. Liu and W. Zhang, *Org. Biomol. Chem.*, 2012, **10**, 5137; (d) R. J. Chew, X.-R. Li, Y. Li, S. A. Pullarkat and P.-H. Leung, *Chem. – Eur. J.*, 2015, **21**, 4800.
- 13 (a) T. Nishimura, X.-X. Guo and T. Hayashi, *Chem. – Asian J.*, 2008, **3**, 1505; (b) T. Inagaki, A. Ito, J. Ito and H. Nishiyama, *Angew. Chem., Int. Ed.*, 2010, **49**, 9384.
- 14 See the ESI† for the details.
- 15 For an example of the formation of hydrido-iridium(III) complexes by the reaction of iridium/bisphosphine complexes with carboxylic acids, see: T. Yamamoto, H. Tadaoka, M. Nagata, T. Hirao, Y. Kataoka, V. Ratovelomanana-Vidal, J. P. Genet and K. Mashima, *Organometallics*, 2006, **25**, 2505.
- 16 The carbometalation of the aryliridium(III) species to an alkyne and a subsequent intramolecular cyclization are alternative reaction pathways leading to the annulation product. For an example of Rh(III)-catalyzed asymmetric annulation of *N*-sulfonylketimines with alkynes involving the carbometalation step, see ref. 5i.

