DOI: 10.1002/adsc.201701378
Advanced Synthesis & Catalysis

Iridium/Chiral Diene-Catalyzed Enantioselective (3+2) Annulation of Aromatic Ketimines with 1,3-Enynes *via* C–H Activation

Midori Nagamoto,[a] Kana Sakamoto,[b] and Takahiro Nishimura[b,*]

[a] Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan
[b] Department of Chemistry, Graduate School of Science, Osaka City University, Sumiyoshi, Osaka 558-8585, Japan
E-mail: tnishi@sci.osaka-cu.ac.jp

Received: October 25, 2017; Revised: November 21, 2017; Published online: January 4, 2018

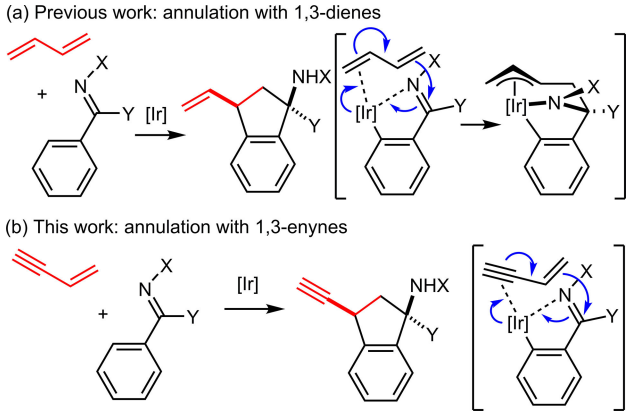
Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.201701378

Abstract: An iridium/chiral diene complex efficiently catalyzed enantioselective (3+2) annulation between 1,3-enynes and cyclic *N*-acyl ketimines generated *in situ* from 3-aryl-3-hydroxyisoindoin-1-ones. The reaction gave the corresponding aminoindane derivatives in high yields with high regio-, diastereo-, and enantioselectivity.

Keywords: Iridium; C–H activation; enynes; annulation; chiral dienes

Transition metal-catalyzed direct functionalization of aromatic compounds *via* C–H activation has been developed as one of the most powerful methodologies for atom- and step-economical synthesis.[1] The regioselective functionalization has been realized by using directing groups, some of which can be transformed through the catalytic process to give complicated molecules.[2–7,8a–c] In this context, there have been successful reports on formal (3+2) annulation reactions of aromatic imines or ketones with C–C multiple bonds giving indene or indane derivatives catalyzed by Re,[2] Rh,[3] Ru,[4] Ir,[5,8a–c] and Co[6] complexes. The asymmetric annulation[1k] has also been achieved by Rh[3c,f] and Ir[5c,8b] catalysis.

Recently, we reported the iridium-catalyzed (3+2) annulation of aromatic ketimines with 1,3-dienes giving 1-aminoindane derivatives (Scheme 1a).[8] A remarkable feature of this annulation is the high regio- and diastereoselectivity: the more electron-rich or sterically hindered alkene moiety of the 1,3-diene participated in the C–C bond formation. The reaction is proposed to proceed *via* an aryliridium(I) species intramolecularly coordinated with an imine moiety, which undergoes oxidative cyclization with 1,3-dienes forming π-allyliridium(III) species followed by reductive elimination. We next focused on the use of 1,3-enynes, which should react with the aryliridium(I) in a similar manner with 1,3-dienes as shown in Scheme 1b. Here we report an iridium-catalyzed enantioselective (3+2) annulation of aromatic ketimines with 1,3-enynes to give 3-alkynyl-1-aminoindane derivatives.



Scheme 1. Ir-Catalyzed (3+2) Annulation.

3-Hydroxy-3-phenylisoindolin-1-one (**1a**), which *in situ* generates a cyclic *N*-acylketimine by dehydration,[9] was treated with 1.5 equivalent of 1,3-enyne **2** in the presence of $[IrCl(cod)]_2$ (5 mol% of Ir, cod = 1,5-cyclooctadiene), 1,4-diazabicyclo[2.2.2]octane (DABCO, 5 mol%), and $NaBAr^F_4$ [10 mol%, Ar^F = 3,5-$(CF_3)_2C_6H_3$] in toluene at 80 °C for 20 h, which are the standard reaction conditions for the Ir-catalyzed annulation of aromatic ketimines with 1,3-dienes (Table 1).[8a,b] The reaction with **2a** bearing a *tert*-butyldimethylsilyl group at the alkyne terminus gave the desired annulation product **3aa** in 87% yield with complete regio- and diastereoselectivity, where the alkene moiety of **2a** participated in the C–C bond formation (entry 1). The 1,3-*cis* relative stereochemis-

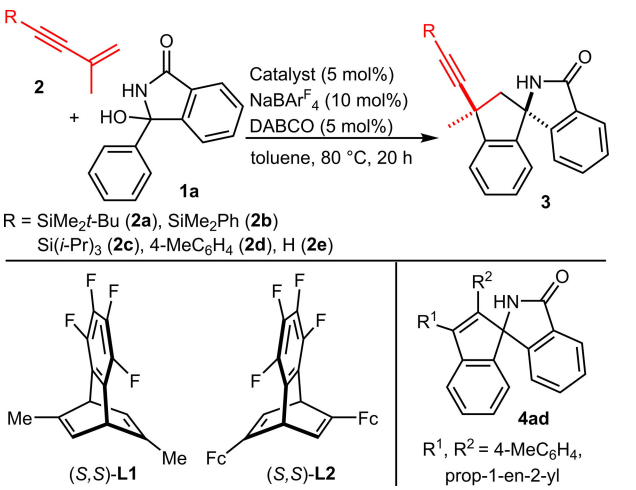
try is similar to that observed in our previous studies on the annulation with 1,3-dienes.[8] The present reaction was found to be highly sensitive to the substituents at the alkyne terminus: the use of enyne **2b** bearing a dimethylphenylsilyl group significantly decreased the yield of **3ab** (entry 2). 1,3-Enyne **2c** substituted with a sterically bulky triisopropylsilyl group did not participate in the reaction (entry 3).[10] The reaction of **2d** bearing a 4-methylphenyl group gave only a small amount of the desired annulation product **3ad**; instead, indene derivative **4ad** was formed in 30% yield as a mixture of regioisomers (entry 4). A terminal alkyne moiety in **2e** inhibited the reaction (entry 5). The present reaction requires a chelating diene ligand as an iridium/cyclooctene complex did not exhibit any catalytic activity (entry 6). This result encouraged us to develop an asymmetric reaction by using chiral diene ligands,[11] and we tested chiral diene ligands based on tetrafluorobenzobarrelene (tfb) frameworks.[12] An iridium complex with (*S*,*S*)-**L1**, which is substituted with methyl groups, exhibited high enantioselectivity giving **3aa** with >99.5% ee (entry 7). Sterically bulky ferrocenyl groups of (*S*,*S*)-**L2** significantly decreased the yield and ee (entry 8). No reaction took place in the presence of an iridium/binap catalyst or a rhodium/cod complex (entries 9 and 10).

The results obtained for the asymmetric (3+2) annulation of hemiaminals **1** with **2a** are summarized in Scheme 2. Hemiaminals **1b–e** having *para*-substituted aryl groups reacted with 1,3-enyne **2a** to give the corresponding annulation products **3ba–ea** with >99% ee. The reaction of **1c** bearing a methoxy substituent gave only a trace amount of **3ca** under the standard reaction conditions, and the use of 15 mol% of DABCO increased the yield to 39%. The reaction of **1e** needed a longer reaction time presumably because an electron-withdrawing chloro group retarded dehydration of **1e** to generate the reactive ketimine. Hemiaminals **1f–h** bearing *meta*-substituted aryl groups reacted at the less sterically hindered *ortho*-position to give the corresponding annulation products **3fa–ha** as single regioisomers with >99.5% ee.[13]

The alkyne moiety of aminoindane **3aa** obtained here was capable of some transformations: desilylation and Huisgen cycloaddition gave triazole **5** without any loss of ee. The absolute configuration of **5** was determined to be 1*R*,3*S* by X-ray crystallographic analysis (Scheme 3).[14]

As shown in Scheme 4, the asymmetric annulation of **1a** with several 1,3-enynes **2** proceeded to give the corresponding annulation products **3**. The reaction of enyne **2f** gave **3af** in 96% yield with 98% ee, where its nonconjugated alkene moiety was inert under the reaction conditions. Annulation with **2g** and **2h** bearing a phenethyl group and an allylic methoxy

Table 1. Ir–Catalyzed Annulation of **1a** with **2**.[a]

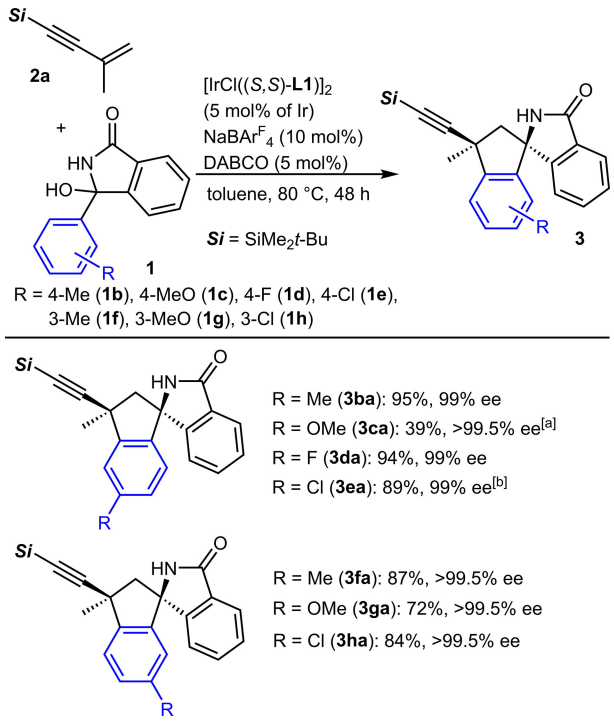


Entry	**2**	Catalyst	Yield [%][b]	Ee [%]
1	**2a**	$[IrCl(cod)]_2$	87 (**3aa**)	–
2	**2b**	$[IrCl(cod)]_2$	3 (**3ab**)[c]	–
3	**2c**	$[IrCl(cod)]_2$	0	–
4	**2d**	$[IrCl(cod)]_2$	3 (**3ad**)[c,d]	–
5	**2e**	$[IrCl(cod)]_2$	0	–
6	**2a**	$[IrCl(coe)_2]_2$	0	–
7[e]	**2a**	$[IrCl((S,S)\text{-}\mathbf{L1})]_2$	92 (**3aa**)	>99.5
8	**2a**	$[IrCl((S,S)\text{-}\mathbf{L2})]_2$	12 (**3aa**)	58
9	**2a**	$[IrCl(coe)_2]_2$/(*R*)-binap	0	–
10	**2a**	$[RhCl(cod)]_2$	0	–

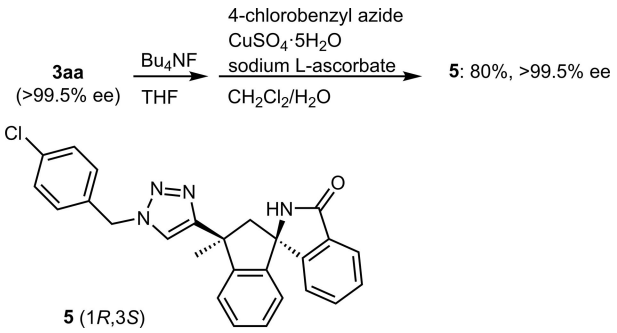
[a] *Reaction conditions*: **1a** (0.10 mmol), **2** (0.15 mmol), catalyst (5 mol% of Ir), NaBAr$^F_4$ (10 mol%), and DABCO (5 mol%) in toluene (0.40 mL) at 80 °C for 24 h. coe = cyclooctene. (*R*)-binap = (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.
[b] Isolated yield.
[c] NMR yield.
[d] **4ad** (30%, mixture of regioisomers) was observed.
[e] For 48 h.

group gave **3ag** and **3ah**, respectively, with high enantioselectivity albeit in modest yields. It should be noted that 1,3-enyne **2i** bearing a sterically hindered trisubstituted alkene moiety participated in the reaction to give **3ai** in 91% yield with 99% ee.

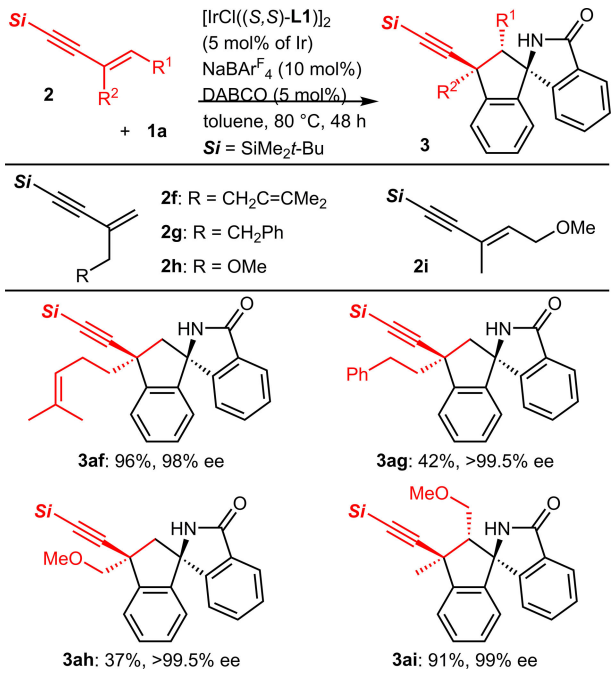
Interestingly, the reaction of enyne **2j** in Scheme 5a gave **4aj** as a sole product, where the alkyne moiety participated in the C–C bond formation with high regioselectivity, presumably because the less hindered alkene moiety preferentially coordinated to the iridium in the oxidative cyclization step as shown in the bracket of Scheme 5a.[15] The present reaction requires conjugated 1,3-enynes as the use of 1,4-enyne **2k** instead of 1,3-enyne resulted in no reaction (Scheme 5b). This result is consistent with the mechanism involving oxidative cyclization (*vide infra*).



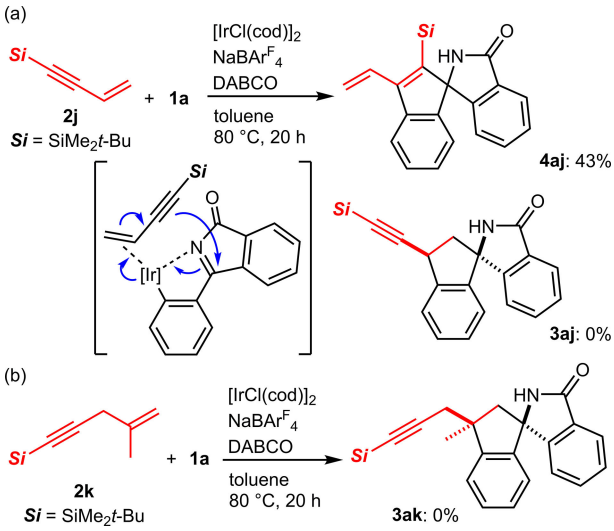
Scheme 2. Asymmetric (3+2) Annulation of Hemiaminals **1** with **2a**. *Reaction conditions*: **1** (0.20 mmol), **2a** (0.30 mmol), [IrCl((*S*,*S*)-**L1**)]$_2$ (5 mol% of Ir), NaBAr$^F_4$ (10 mol%), and DABCO (5 mol%) in toluene (0.80 mL) at 80 °C for 48 h. Isolated yields are shown. [a] Performed with DABCO (15 mol%). [b] For 72 h.



Scheme 3. Transformation of **3aa**. ORTEP illustration of **5** drawn at 50% probability level.



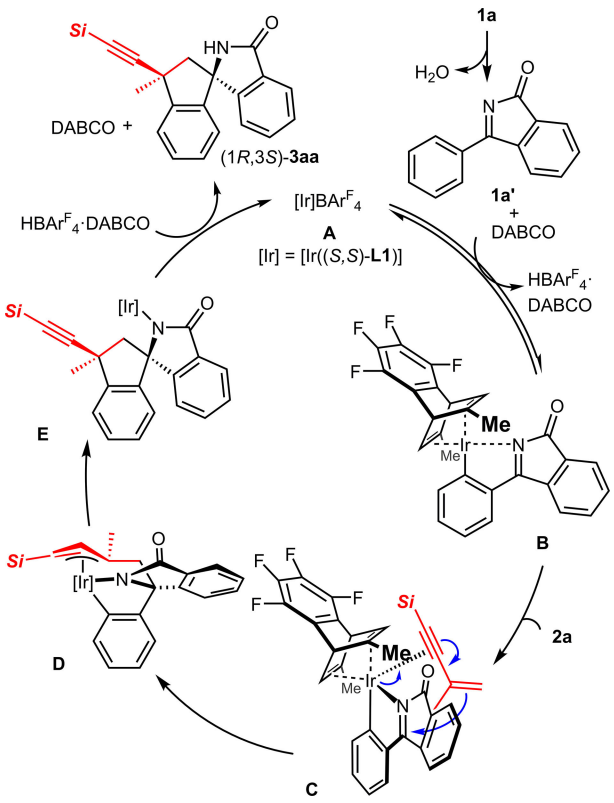
Scheme 4. Asymmetric (3+2) Annulation of **1a** with Enynes **2**. *Reaction conditions*: **1a** (0.20 mmol), **2** (0.30 mmol), [IrCl((*S*,*S*)-**L1**)]$_2$ (5 mol% of Ir), NaBAr$^F_4$ (10 mol%), and DABCO (5 mol%) in toluene (0.80 mL) at 80 °C for 48 h.



Scheme 5. Reaction with Other Enynes. *Reaction conditions*: **1a** (0.10 mmol), **2** (0.15 mmol), [IrCl(cod)]$_2$ (5 mol% of Ir), NaBAr$^F_4$ (10 mol%), and DABCO (5 mol%) in toluene (0.40 mL) at 80 °C for 20 h.

The catalytic cycle is postulated as illustrated in Scheme 6. *Ortho*-C–H activation of ketimine **1a**′, which is generated *in situ* from hemiaminal **1a** by dehydration, forms an aryliridium(I) species **B** *via* oxidative addition of the C–H bond and reductive deprotonation of the resulting aryl(hydrido)iridium (III) species by DABCO.[8a,b] 1,3-Enyne **2a** approaches the iridium center from the *re*-face of the imine moiety to avoid the steric hindrance of the methyl group on Me-tfb*. The alkynyl moiety coordinates to the iridium center to form intermediate **C**, which undergoes oxidative cyclization to form a π-propargyliridium(III) species **D**.[16] Reductive elimination and subsequent protonolysis gives (1*R*,3*S*)-**3aa** and regenerates the cationic iridium species **A**.

In conclusion, we developed the enantioselective (3+2) annulation of *N*-acyl ketimines with 1,3-eynes



Scheme 6. Plausible Catalytic Cycle.

giving aminoindane derivatives by use of an Ir/chiral diene catalyst. The reaction proceeds *via* oxidative cyclization between aryliridium(I) species and 1,3-enynes in a highly diastereo- and enantioselective manner.

Experimental Section

For detailed experimental information and the characterization of compounds, see the supporting information.

General procedure for enantioselective (3+2) annulation of ketimines with 1,3-enynes: 3-Aryl-3-hydroxyisoindolin-1-one **1** (0.20 mmol), $NaBAr^F_4$ (18.4 mg calculated as the dihydrate, 0.020 mmol, 10 mol%), DABCO (1.1 mg, 0.010 mmol, 5 mol%), 1,3-enyne **2** (for solid compounds, 0.30 mmol), and an iridium complex (0.010 mmol of Ir, 5 mol% of Ir) were placed in a Schlenk tube under nitrogen. Toluene (0.8 mL) and 1,3-enyne **2** (for liquid compounds, 0.30 mmol) were added, and the Schlenk tube was capped with a glass stopper and heated at 80 °C for 20 h with stirring. The mixture was passed through a short column of alumina with EtOAc as an eluent, and the solvent was removed on a rotary evaporator. The residue was subjected to preparative TLC on silica gel with EtOAc/hexane to give **3**.

Acknowledgements

This work was supported by JSPS KAKENHI Grant Number JP15H03810. M.N. thanks the JSPS for Research Fellowship for Young Scientists.

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