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Rhodium-Catalyzed Direct Annulation of Aldehydes with Alkynes Leading to Indenones: Proceeding through *in Situ* Directing Group Formation and Removal

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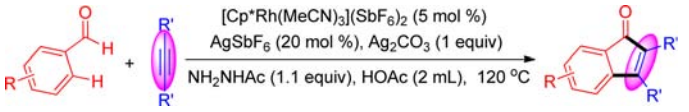
ABSTRACT



The Rh-catalyzed direct annulation of an aldehyde with an alkyne leading to indenone was achieved. The *in situ* temporal installation of acetylhydrazine enables the annulation of the *ortho* arene C−H bond with alkynes to form ketone hydrazone. Subsequently, the *in situ* directing group removal takes place since ketone hydrazone is more susceptible toward hydrolysis than aldehyde hydrazone. Notably, this procedure tolerates a series of functional groups, such as methoxyl, acetylamino, fluoro, trifluoromethyl, methoxycarbonyl, chloro, and bromo groups.

Indenone frameworks are ubiquitous in pharmaceutical and material sciences.[1] Yoshikai reported the cobalt-catalyzed self-coupling of aromatic aldimines for the synthesis of indenone.[2] Kuninobu and Takai described the ruthenium-catalyzed trimerization of aryl aldehyde for the construction of the indenone framework.[3] The annulation of alkynes with *ortho* bifunctionalized arenes is a powerful strategy leading to indenones (Scheme 1, eq 1).[4] However, on one hand, the prefunctionalization of a substrate is time and cost consuming, and on the other hand, many polysubstituted *ortho* bifunctionalized arenes are not commercially or readily available. Alternatively, transition-metal-catalyzed annulation of the arene C−H bond with alkyne has been widely reported for the construction

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(1) (a) Huebner, C. F.; Donoghue, E. M.; Plummer, A. J.; Furness, D. A. *J. Med. Chem.* **1966**, *9*, 830. (b) Jeffrey, J. L.; Sarpong, R. *Org. Lett.* **2009**, *11*, 5450. (c) Barberá, J.; Rakitin, O. A.; Ros, M. B.; Torroba, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 296. (d) Morinaka, K.; Ubukata, T.; Yokoyama, Y. *Org. Lett.* **2009**, *11*, 3890. (e) Anstead, G. M.; Wilson, S. R.; Katzenellenbogen, J. A. *J. Med. Chem.* **1989**, *32*, 2163. (f) Froimowitz, M.; Wu, K.-M.; Moussa, A.; Haidar, R. M.; Jurayj, J.; George, C.; Gardner, E. L. *J. Med. Chem.* **2000**, *43*, 4981.

(2) Gao, K.; Yoshikai, N. *Chem. Commun.* **2012**, *48*, 4305.

(3) Kuninobu, Y.; Matsuki, T.; Takai, K. *Org. Lett.* **2012**, *12*, 2948.

(4) Annulation with *ortho*-ester-containing phenylboronic acids: (a) Tsukamoto, H.; Kondo, Y. *Org. Lett.* **2007**, *9*, 4227. With 2-iodoarenenitriles: (b) Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276. With 2-halo benzaldehyde: (c) Larock, R. C.; Doty, M. J. *J. Org. Chem.* **1993**, *58*, 4579. (d) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Adv. Synth. Catal.* **2002**, *344*, 172. With 2-bromo phenylboronic acids and CO: (e) Harada, Y.; Nakanishi, J.; Fujihara, H.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 5766. With 2-bromophenylboronic acids and formaldehyde: (f) Morimoto, T.; Yamasaki, K.; Hirano, A.; Tsutsumi, K.; Kagawa, N.; Kakiuchi, K.; Harada, Y.; Fukumoto, Y.; Chatani, N.; Nishioka, T. *Org. Lett.* **2009**, *11*, 1777. With iodobenzaldimine: (g) Liu, C.-C.; Korivi, R. P.; Cheng, C.-H. *Chem.—Eur. J.* **2008**, *14*, 9503. With 2-cyano phenylboronic acid: (h) Miura, T.; Murakami, M. *Org. Lett.* **2005**, *7*, 3339.

(5) (a) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2012**, *14*, 764. (b) Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* **1996**, *61*, 6941. (c) Shi, Z.-Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.-T.; Cui, Y.-X.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572. (d) Muralirajan, K.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2011**, *50*, 4169. (e) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 18326. (f) Zhou, F.; Han, X.-L.; Lu, X.-Y. *Tetrahedron Lett.* **2011**, *52*, 4681. (g) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474. (h) Chen, J.; Song, G.; Pan, C.; Li, X. *Org. Lett.* **2010**, *12*, 5426. (i) Chidipudi, S. R.; Khan, I.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 12115. (j) Kuram, M. R.; Bhanuchandra, M.; Sahoo, A. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4607. (k) Wang, C.-M.; Sun, H.; Fang, Y.; Huang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 5795.

(6) (a) Kuninobu, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2005**, *127*, 13498. (b) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202.

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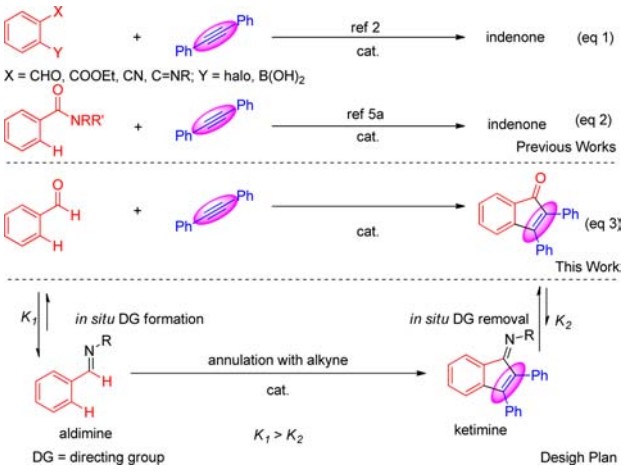
of benzo five-membered heteroarenes.[5] In 2005, Takai pioneered the carbocyclization of imines with alkynes toward indenamines.[6] Subsequently, Shi, Li, Zhao, Cramer, Glorius, Cheng, Jeganmohan, Miura, and Li independently reported the construction of indene frameworks via C−H activation, insertion of aryl metal to alkyne, and nucleophilic addition of the formed alkenyl metal intermediate to a carbonyl or iminyl group.[7] However, to the best of our knowledge, only one example was reported by Shi on the direct annulation of the C−H bond of benzimide with alkynes leading to indenone (Scheme 1, eq 2).[7a]

Undoubtedly, the direct annulation of an aryl aldehyde as commercially available starting material with alkynes is the most straightforward and atom-economical pathway toward indenones (Scheme 1, eq 3). However, aldehydes are characterized by their poor effect as a directing group in C−H bond functionalization.[8] To solve this problem, the introduction of proper directing groups, such as iminyl and hydrazonyl, is required. However, except for the introduced directing groups being part of the final product, the subsequent removal of the directing groups is required.[9] To circumvent it, the introduction of a temporal directing group may solve this drawback.[10] Indeed, the Rh-catalyzed annulation of aromatic imines with alkynes leading to indenone imine was achieved in Miura's group.[7i] We envisaged the inherent difference between the equilibrium constant of aldimine (before the annulation) and ketimine (after the annulation) could enable the *in situ* directing group formation and removal (Scheme 1, eq 3).[11] Jun developed a new strategy of metal−organic cooperative catalysis (MOCC) in the functionalization of C−H adjacent to a carbonyl group by temporal installation of a 2-aminopyridyl group.[12] Herein, we report employing this strategy in the annulation of the arene C−H bond neighboring a formyl group with an alkyne leading to indenone, proceeding through *in situ* directing group formation and removal.

Scheme 1. Previous Pathways and Our Design Plan Leading to Indenone



With this in mind, initially, we tested the reaction of benzaldehyde **1a** with diphenyl ethyne **2a** with the combination of $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol %), NH_2NHAc (1.1 equiv), and $AgSbF_6$ (0.2 equiv) in HOAc under air at 120 °C. Pleasingly, the indenone was obtained in 45% yield (Table 1, entry 2). The reaction efficiency was slightly decreased by adding 2 equiv of $Cu(OAc)_2$ as an additive (Table 1, entry 3). However, replacing $Cu(OAc)_2$ with AgOAc increased the yield to 71% (Table 1, entry 4). To our delight, the reaction efficiency was further increased to 73% by using 1 equiv of Ag_2CO_3 under air. The yield increased to 80% under N_2 and dramatically decreased to 50% under O_2 (Table 1, entry 6). Other protic solvents such as CF_3COOH and HCOOH inhibited the reaction (Table 1, entries 7 and 8). Replacing NH_2NHAc with NH_2NHPh, NH_2Ts, or NH_2Ac resulted in no reaction or low yield (Table 1, entries 9−11). Further studies revealed other Rh catalysts, such as $[RhCl(cod)]_2$, $[RhOH(cod)]_2$, $RhCl(Ph_3P)_3$, and $Rh(acac)_3$, were totally ineffective for this annulation reaction (Table 1, entries 12−15). In the absence of $AgSbF_6$, the yield dramatically decreased to 37% (Table 1, entry 6).

With the optimized reaction conditions in hand, the substrate scope of benzaldehyde for this cyclization was studied, as shown in Figure 1. As expected, both electron-donating and -withdrawing groups such as methoxycarbonyl, methoxyl, fluoro, chloro, bromo, acetyl amino, and trifluoromethyl on the aromatic moiety of benzaldehyde were tolerated well under this procedure. Moreover, the *ortho* groups on the phenyl of **1a** had almost no effect on the annulation. For example, **3da** was isolated in 68% yield. Notably, the chloro and bromo functional groups survived well under the standard procedure, offering

(7) Li, B.-J.; Wang, H.-Y.; Zhu, Q.-L.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3948. (b) Yang, L.; Correia, C. A.; Li, C.-J. *Adv. Synth. Catal.* **2011**, *353*, 1269. (c) Sun, Z.-M.; Chen, S.-P.; Zhao, P. *Chem.—Eur. J.* **2010**, *16*, 2619. (d) Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 8181. (e) Tran, D. N.; Cramer, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 11098. (f) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2154. (g) Jayakumar, J.; Parthasarathy, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 197. (h) Chinnagolla, R. K.; Jeganmohan, M. *Eur. J. Org. Chem.* **2012**, 417. (i) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141. (j) Zhao, P.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 5506.

(8) Dubost, E.; Fossey, C.; Cailly, T.; Rault, S.; Fabis, F. *J. Org. Chem.* **2011**, *76*, 6414.

(9) For reviews, see: (a) Mousseau, J. J.; Charette, A. B. *Acc. Chem. Res.* **2013**, *46*, 412. (b) Wang, C.; Huang, Y. *Synlett* **2013**, *24*, 145. (c) Engle, K. M.; Mei, T.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (d) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450.

(10) Examples on the C−H bond functionalization involving *in situ* directing group formation and removal: (a) Bedford, R. B.; Betham, M.; Caffyn, A. J. M.; Charmant, J. P. H.; Lewis-Alleyne, L. C.; Long, P. D.; Polo-Ceron, D.; Prashar, S. *Chem. Commun.* **2008**, 990. (b) Bedford, R. B.; Haddow, M. F.; Webster, R. L.; Mitchell, C. J. *Org. Biomol. Chem.* **2009**, *7*, 3119. (c) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem,. Int. Ed.* **2003**, *42*, 112. (d) Bedford, R. B.; Limmert, M. E. *J. Org. Chem.* **2003**, *68*, 8669.

(11) For the direct annulation of an aromatic aldehyde with an alkyne leading to indenone in the presence of a free radical initiator in low yield, please see: Monahan, A.; Campbell, P.; Cheh, S.; Fong, J.; Grossman, S.; Miller, J.; Rankin, P.; Vallee, J. *Synth. Commun.* **1977**, *7*, 553.

(12) (a) Jun, C.-H.; Jo, E.-A.; Park, J.-W. *Eur. J. Org. Chem.* **2007**, 1869. (b) Jun, C.-H.; Lee, D.-Y.; Lee, H.; Hong, J. B. *Angew. Chem., Int. Ed.* **2000**, *39*, 3070. (c) Jun, C.-H.; Lee, H.; Hong, J. B.; Kwon, B.-I. *Angew. Chem., Int. Ed.* **2002**, *41*, 2146. (d) Jun, C.-H.; Lee, H. *J. Am. Chem. Soc.* **1999**, *121*, 880. (e) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222.

Table 1. Screening the Optimized Reaction Conditions[a]

entry	additive (equiv)	NH_2R	rhodium	solvent	yield (%)
1	–	–	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	CH_3COOH	<5
2	–	NH_2NHAc	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	CH_3COOH	45
3	$Cu(OAc)_2 \cdot H_2O$ (2.0)	NH_2NHAc	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	CH_3COOH	38
4	AgOAc (2.0)	NH_2NHAc	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	CH_3COOH	71
5	Ag_2O (1.0)	NH_2NHAc	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	CH_3COOH	68
6	Ag_2CO_3 (1.0)	NH_2NHAc	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	CH_3COOH	73(80)[b] (50)[c] (37)[d]
7	Ag_2CO_3 (1.0)	NH_2NHAc	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	CF_3COOH	<5
8	Ag_2CO_3 (1.0)	NH_2NHAc	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	HCOOH	<5
9	Ag_2CO_3 (1.0)	NH_2NHPh	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	CH_3COOH	<5
10	Ag_2CO_3 (1.0)	NH_2Ts	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	CH_3COOH	15
11	Ag_2CO_3 (1.0)	NH_2Ac	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	CH_3COOH	5
12	Ag_2CO_3 (1.0)	NH_2NHAc	$[RhCl(cod)]_2$	CH_3COOH	<5
13	Ag_2CO_3 (1.0)	NH_2NHAc	$[RhOH(cod)]_2$	CH_3COOH	<5
14	Ag_2CO_3 (1.0)	NH_2NHAc	$RhCl(Ph_3P)_3$	CH_3COOH	<5
15	Ag_2CO_3 (1.0)	NH_2NHAc	$Rh(acac)_3$	CH_3COOH	<5

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), NH_2R (0.22 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol %), $AgSbF_6$ (20 mol %), additive with indicated equivalent, and 2 mL of indicated solvent, air, 120 °C, sealed tube, 14 h. Cp* = pentamethylcyclopentadiene. [b] N_2. [c] O_2. [d] No $AgSbF_6$, N_2.

handles for further functionalization (**3fa**, **3ga**, and **3ia**). Importantly, the cyclization took place on the less hindered *ortho* position for the *meta*-substituted substrate **1f**, and no regioisomeric product of **3fa** was observed by GC-MS. Disappointingly, the salicylaldehyde derivative possessing a free phenolic hydroxyl did not work using the procedure.

Next, the substrate scope and the limitation of alkynes for this annulation were studied, as shown in Figure 2. Once again, the diaryl alkynes ran smoothly under the procedure, providing the indenones in good to excellent yields. The chloro and bromo groups in the phenyl ring of the alkynes remained untouched during this transformation. Notably, 4-octyne was applicable to the procedure, providing the annulation product **3ah** in moderate yield. 1,2-Di(thiophen-3-yl)ethyne provided the annulation product **3ai** in 32% yield. Particularly, methyl phenyl alkyne afforded 3-methyl-2-phenyl-1*H*-inden-1-one in 61% yield along with 9% of isomer. Unfortunately, dimethylacetylenedicarboxylate did not work under this procedure.

To gain a preliminary understanding of the mechanism, the kinetic isotope effects of benzaldehyde were studied. However, during the intramolecular kinetic isotope effect study, 88% of H on the C-7 position of indenone

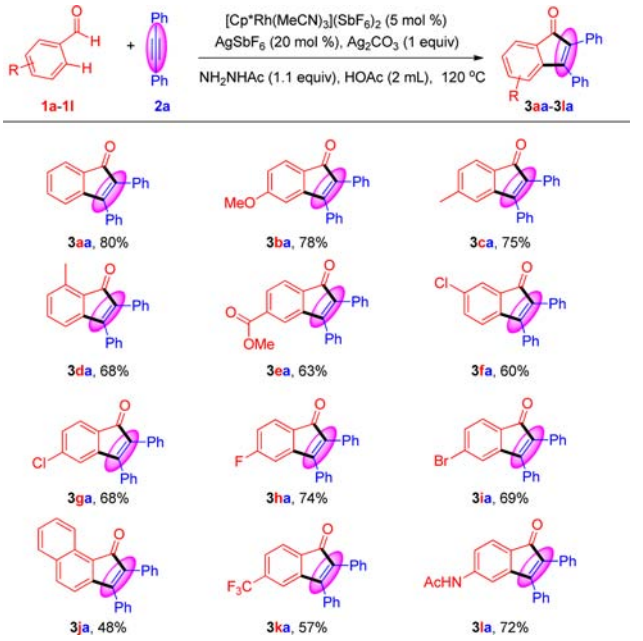


Figure 1. Substrate scope of aldehydes. Reaction conditions: **1** (0.2 mmol), diphenyl acethyne **2a** (0.3 mmol), NH_2NHAc (0.22 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.2 mmol), and 2 mL of HOAc, N_2, 120 °C, sealed tube, 14 h.

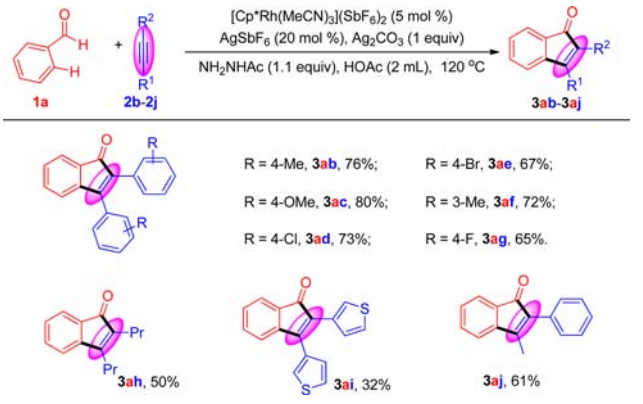
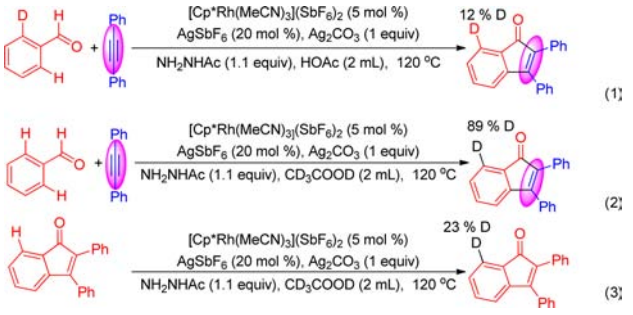


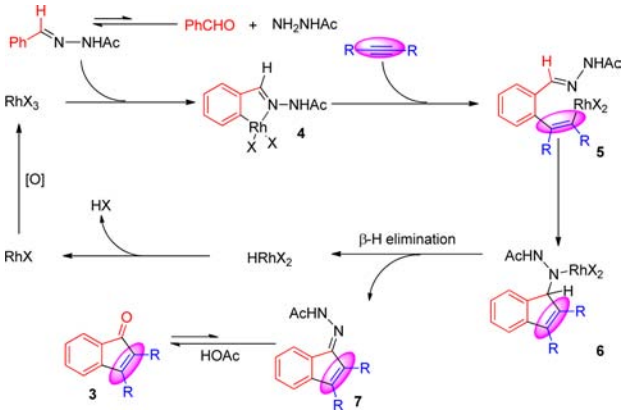
Figure 2. Substrate scope of alkynes. Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), NH_2NHAc (0.22 mmol), $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5 mol %), $AgSbF_6$ (20 mol %), Ag_2CO_3 (0.2 mmol), and 2 mL of HOAc, N_2, 120 °C, sealed tube, 14 h.

maintained retention (Scheme 2, eq 1), indicating an H/D exchange may be involved during the procedure. Indeed, by replacing HOAc with CD_3COOD, the reaction of **1a** and **2a** resulted in 89% deuteration of the H atom on the C-7 position (Scheme 2, eq 2). However, only 23% of the deuterium atom was incorporated when indenone was subjected to the standard reaction conditions in CD_3COOD (Scheme 2, eq 3). The H/D exchange suggested a cyclorhodation step was involved in the reaction.

Scheme 2. Isotopic Labelling Study



Scheme 3. A Tentative Mechanism



Although the mechanism in detail remains unclear at this current stage, based on the well documented annulation of an arene C−H bond with an alkyne,[5−7] a proposed mechanism was outlined in Scheme 3. In the reaction procedure, there is an equilibrium reaction between benzaldehyde acetylhydrazone and aldehyde.[13] First, coordination of Rh species with benzaldehyde acetylhydrazone facilitated the *ortho* aromatic C−H bond cleavage to form intermediate **4**. This step is reversible supported by the observed H/D exchange in Scheme 2. Second, the insertion of intermediate **4** to a C−C triple bond produces the alkenyl rhodium species **5**. Subsequently, the nucleophilic addition of intermediate **5** to the C=N bond forms intermediate **6**.[14] Third, the β-H elimination of intermediate **6** delivers $HRhX_2$ species along with the intermediate **7**,[15] which transforms to indenone by protonation.[16] Finally, the reductive elimination of $HRhX_2$ followed by the oxidation by Ag(I) regenerates the Rh(III) species.

In conclusion, we have developed a Rh-catalyzed annulation of benzaldehyde with alkynes in the presence of 1.1 equiv of acetic hydrazide leading to indenones with good functional group tolerance. The important feature of the present catalytic system is the application of the strategy of *in situ* directing group formation and removal. Thus, it might open up an expedient synthetic pathway for the formyl-directing arene C−H bond functionalization. Efforts to expand the strategy to new reactions and to elucidate the mechanism in detail are underway in our laboratory.

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Supporting Information Available. Experimental procedures along with copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) The ^{1}H NMR of the mixture of benzaldehyde and NH_2NHAc in CD_3COOD confirmed the benzaldehyde acetylhydrazone was the main species. For details, see Supporting Information.

(14) For reviews in the nucleophilic addition of a C=N bond, please see: (a) Schmidt, F.; Stemmler, R.; Rudolph, J.; Bolm, C. *Chem. Soc. Rev*. **2006**, *35*, 454. (b) Robert, B. *Chem. Rev*. **1998**, *98*, 1407–1438. (c) Shu, K.; Haruro, I. *Chem. Rev*. **1999**, *99*, 1069.

(15) The intermolecular Heck-type reaction of imine, for Rh, please see: (a) Ishiyama, T.; Hartwig, J. *J. Am. Chem. Soc*. **2000**, *122*, 12043. For Pd, please see: (b) Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc*. **2006**, *128*, 14800. (c) Ohno, H.; Aso, A.; Kadoh, Y.; Fujii, N.; Tanaka, T. *Angew. Chem., Int. Ed*. **2007**, *46*, 6325. For the Heck-type intramolecular alkenylation of imine, please see ref 7i.

(16) The ^{1}H NMR of the mixture of indenone and NH_2NHAc in CD_3COOD confirmed the indenone was the dominant species. For details, see Supporting Information.

The authors declare no competing financial interest.