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C–H Activation

Rhodium(III)-Catalyzed Three-Component Reaction of Imines, Alkynes, and Aldehydes through C–H Activation

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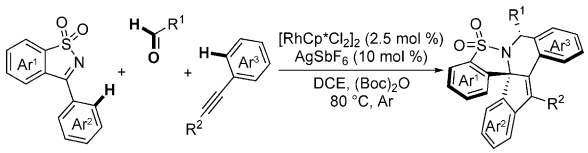
Abstract: An efficient rhodium(III)-catalyzed tandem three-component reaction of imines, alkynes and aldehydes through C–H activation has been developed. High stereo- and regioselectivity, as well as good yields were obtained in most cases. The simple and atom-economical approach offers a broad scope of substrates, providing polycyclic skeletons with potential biological properties.

Multicomponent reactions (MCRs) are very efficient approaches for the synthesis of complex structures from simple precursors.[1] These processes usually exhibit a high atom economy, synthetic convergence, and remarkable chemo-, stereo-, and regioselectivity.[2] Since the first preparation of α-aminonitriles by Strecker through condensation of aldehydes with ammonia and hydrogencyanide in the mid-19th century, MCRs have found numerous application in modern synthetic chemistry and drug-discovery research.[3] On the other hand, transition-metal catalysis has emerged as one of the most powerful strategies in organic synthesis.[4] In particular, MCRs proceeding under transition-metal catalysis have received increasing attention among synthetic chemists.[5] For instance, the sp C–H atom of terminal alkynes can be easily captured by different metal catalysts, which then undergo MCRs with aldehydes and amines.[6] Recently, Hu reported metal-catalyzed novel MCRs by trapping protic onium ylide with electrophiles.[7] However, MCRs initiated by selective sp^2 C–H activation are rarely studied, and most of them are limited to the "A+B+B" variant featuring two of the same or very similar components.[8] For "A+B+C" multicomponent reactions with three different components it is much more challenging to tame the selectivity and reactivity of the two-component coupling pathways.

Rhodium-catalyzed oxidative C–H activation has witnessed exciting progress over the past decades owing to its high efficiency, selectivity, and functional-group tolerance.[9] Despite the significant developments, revealing new reactions under rhodium catalysis is still highly desirable.[10] Previously, a number of efficient metal-catalyzed [3+2] annulation reactions for the formation of aminocyclopentene derivatives has been disclosed.[11] We wondered if the active intermediate generated from *N*-sulfonyl ketimines and alkynes could be irreversibly trapped by a third coupling partner, which might offer an opportunity to discover novel A+B+C MCRs. Herein, we found a highly efficient Rh^{III}-catalyzed three-component reaction of imines, alkynes, and aldehydes through sp^2 C–H activation.[12] More importantly, this reaction provides a new methodology to access unusual complex building blocks for the preparation of diverse biologically active compounds (Scheme 1).[13]



Scheme 1. Three-component reactions of imines, alkynes, and aldehydes through Rh^{III}-catalyzed sp^2 C–H activation.

In an initial attempt, cyclic *N*-sulfonyl ketimine **1a**, benzaldehyde (**2a**) and diphenyl acetylene (**3a**) were tested under the early [3+2] reaction conditions.[11a] Despite good conversion regarding the A+B variant, we detected the A+B+C product **5a**, albeit in a very low yield (Table 1, entry 1). Acid additives facilitated the three-component reaction pathway, but it was difficult to reach good reproducibility, regardless of the steric effect, acidity, or dosage of the acids (Table 1, entries 2–6).[14] To our delight, excellent yields and robust reproducibility were obtained by employing di-*tert*-butyl dicarbonate $(Boc)_2O$ as an additive. In addition, the reactivity was not affected when the amount of catalyst $[Cp^*RhCl]_2$ was reduced to 2.5 mol% in the presence of $(Boc)_2O$ (Table 1, entries 7 and 8). Among other anhydrides screened, Ac_2O and trifluoroacetic acid (TFAA) also proved to be appropriate for the reaction (Table 1, entries 9–11). However, varying the ratio of $(Boc)_2O$ only improved the yield of the two-component byproduct **4a** (Table 1, entries 12–15). It is worth noting that other solvents, such as toluene, methanol, AcOH, and DMF, turned out to be ineffective for the MCR (Table 1, entries 16–19). The reaction temperature was also very essential for producing **5a** selectively (Table 1, entries 20 and 21). Furthermore, the reaction could be carried out

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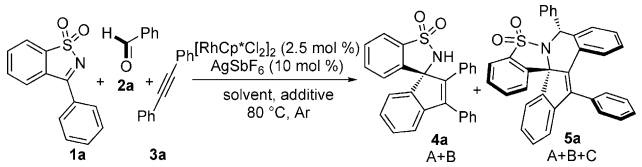
Table 1. Optimizations of the reaction conditions.[a]



Entry	Additive/[equiv]	Solvent	Time [h]	Yield [%][b] **4a**	Yield [%][b] **5a**
1[c]	–	DCE	40	85	10
2	AcOH/0.2	DCE	40	–	90
3[c]	PivOH/0.2	DCE	36	–	94
4[c]	1-adamantoic acid/0.2	DCE	20	–	81
5	AcOH/1	DCE	35	34	60
6	CF_3CO_2H/1	DCE	17	5	91
7[c]	$(Boc)_2O$/1	DCE	40	–	98
8	**$(Boc)_2O$/1**	**DCE**	**40**	–	**97**
9	Ac_2O/1	DCE	40	–	86
10	TFAA/1	DCE	40	–	91
11	Ms_2O/1	DCE	40	10	47
12	$(Boc)_2O$/0.2	DCE	28	50	50
13	$(Boc)_2O$/0.5	DCE	28	50	50
14	$(Boc)_2O$/1.5	DCE	40	57	40
15	$(Boc)_2O$/2	DCE	40	60	35
16	$(Boc)_2O$/1	toluene	40	60	–
17	$(Boc)_2O$/1	MeOH	40	95	–
18	$(Boc)_2O$/1	AcOH	40	96	–
19	$(Boc)_2O$/1	DMF	40	n.r.	n.r.
20[d]	$(Boc)_2O$/1	DCE	40	87	10
21[e]	$(Boc)_2O$/1	DCE	40	94	–
22[f]	$(Boc)_2O$/1	DCE	65	–	92
23[g]	$(Boc)_2O$/1	DCE	72	–	93

[a] Reaction conditions unless otherwise specified: **1a** (0.05 mmol), **2a** (0.1 mmol), **3a** (0.075 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), additive, solvent (1.0 mL), 80 °C, under Ar atmosphere. [b] Isolated yield. [c] $[Cp^*RhCl_2]_2$ (5 mol%) and $AgSbF_6$ (20 mol%) were added. [d] 60 °C. [e] 40 °C. [f] Reaction performed on a 1 mmol scale of **1a**, **2a** (2 mmol), **3a** (1.5 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $(Boc)_2O$ (1 mmol), DCE (10 mL) in a sealed vessel (25 mL) under Ar atmosphere at 80 °C; 467 mg of **5a** were isolated. [g] Reaction performed on a 10 mmol scale of **1a**, **2a** (20 mmol), **3a** (15 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $(Boc)_2O$ (10 mmol), DCE (100 mL) in a sealed vessel (250 mL) under Ar atmosphere at 80 °C; 4.72 g of **5a** were isolated. n.r. = no reaction.

on larger scales, providing **5a** in excellent isolated yields (Table 1, entries 22 and 23). The structure of the three-component product **5a** was characterized by X-ray crystallography (Figure 1).[15]

Under the optimized conditions, the scope of aldehydes in the Rh^{III}-catalyzed three-component reaction was examined (Table 2). Benzaldehydes bearing electron-withdrawing or -donating substitutions at the *ortho*-, *meta*- or *para*-position all reacted smoothly under this catalytic system, giving the corresponding polycyclic skeletons with moderate to excellent yields (**5a**–**5k**). Importantly, aryl iodide was well-tolerated and no cross-coupling on the iodide was detected (**5e**). Heteroaryl aldehydes exhibited reduced reactivity to capture the A + B intermediate. When thiophene-2-carbaldehyde was employed as the third coupling partner, **5l** was obtained in 23% yield, while pyridine-2-carbaldehyde failed to anticipate in the A + B + C reaction pathway (**5m**). In addition, aliphatic aldehydes were ap-

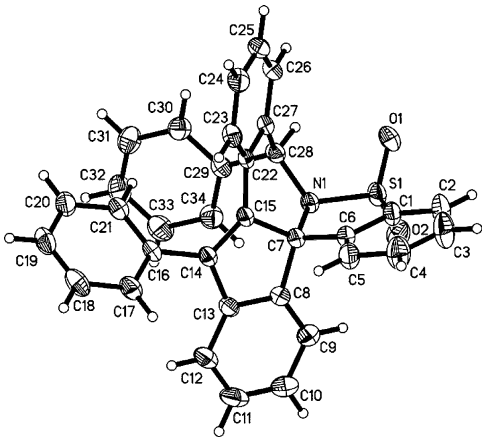
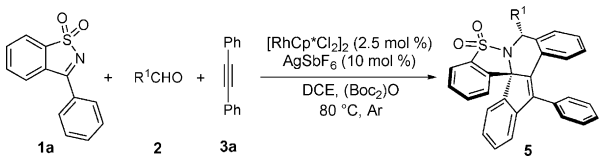
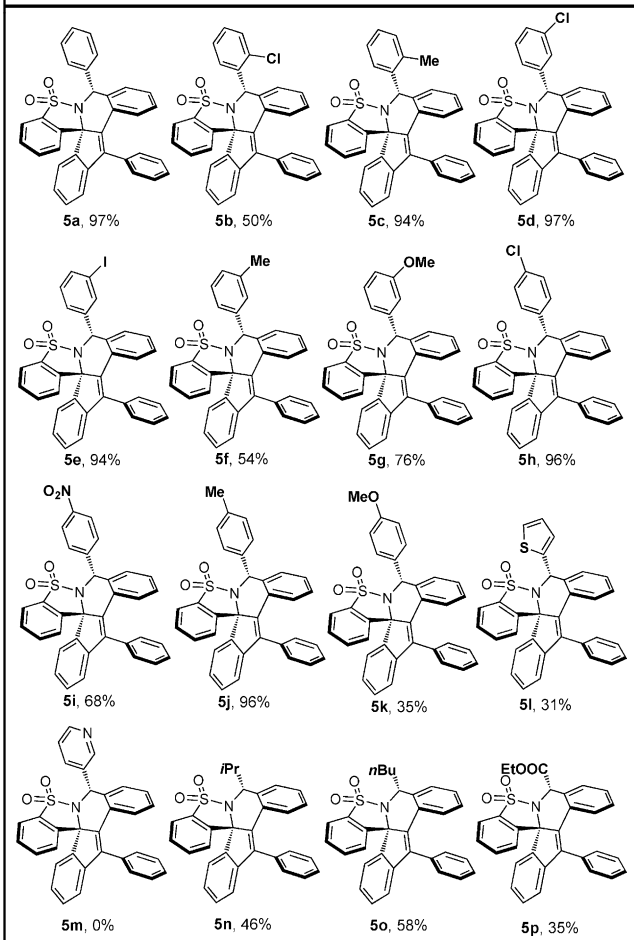


Figure 1. X-ray crystal structure of **5a**.

Table 2. Substrate scope of aldehydes.[a]



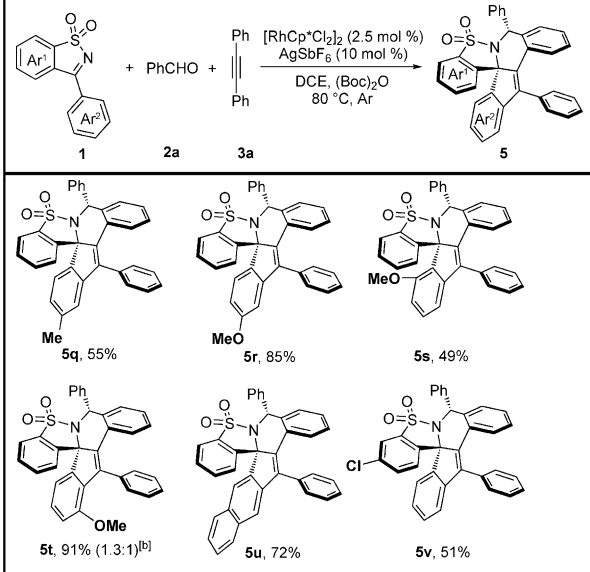


[a] Reaction conditions unless otherwise specified: **1a** (0.1 mmol), **2** (0.2 mmol), **3a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $(Boc)_2O$ (1.0 equiv), DCE (2.0 mL), 80 °C, Ar atmosphere. Yields are reported for the isolated products.

plied in the reaction, producing tetrahydroisoquinoline cores decorated with an alkyl chain (**5n**–**5p**).

Next, we investigated the scope of the other coupling partners (Table 3). *N*-sulfonyl ketimines with substitution on both the *para*- and *ortho*-position of Ar^2 reacted with high efficiency to trigger the cascade three-component reaction (**5q**–**5s**). The coupling of *meta*-methoxy-substituted Ar^2 gave a mixture of

Table 3. Substrate scope of cyclic *N*-sulfonyl ketimines.[a]

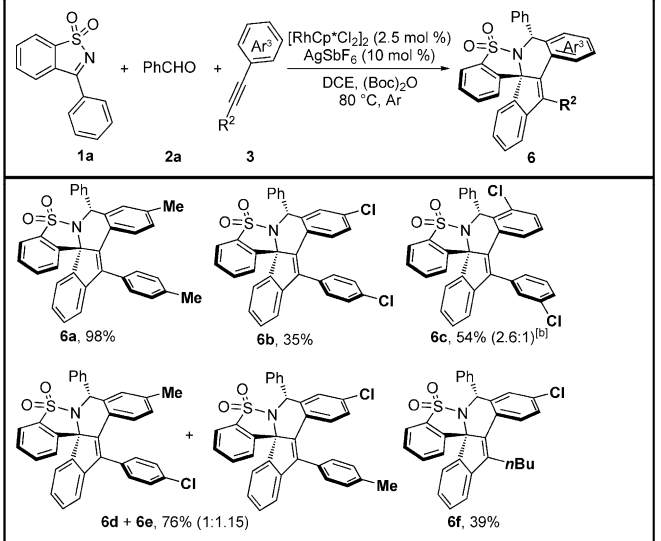


[a] Reaction conditions unless otherwise specified: **1** (0.1 mmol), **2a** (0.2 mmol), **3a** (0.15 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $(Boc)_2O$ (1.0 equiv), DCE (2.0 mL), 80 °C, Ar atmosphere. Yields are reported for the isolated products. Ratios of regioisomers are given in parentheses and were determined by ^1H NMR analysis. [b] Major isomers are shown.

regioisomers, because the initial C–H activation step can take place on two available positions. In contrast, β-naphthalene-substituted *N*-sulfonyl ketamine provided the single annulation product **5u** owing to the excellent regioselectivity of the first C–H functionalization. Ar^1 fused with a chlorine-substituted benzene ring underwent the MCR to afford **5v** in 51% yield.

To further explore the scope of this transformation, different alkynes were tested under the standard conditions (Table 4). Symmetrical diphenylacetylene with a *para*-methyl substituent underwent the cyclization reaction with **1a** and benzaldehyde (**2a**) to give the hexacyclic compound **6a** in 98% yield. *Para*-chlorine-substituted diphenylacetylene **3b** was also compatible, albeit with reduced reactivity. The reaction of 1,2-bis(3-chlorophenyl)ethyne **3c** produced regioisomers in a 2.6:1 ratio in moderate yield with prior C–C-bond formation on the *ortho*-position of the chlorine atom. Next, unsymmetrical alkynes were employed and it was found that aryl substituents with different electronic properties showed no obvious distinction when reacted with benzaldehyde (**6d** and **6e**). Besides, alkane-modified phenylacetylene provided the corresponding product **6f** in 39% yield, along with the nonreactive two-component regioisomer.

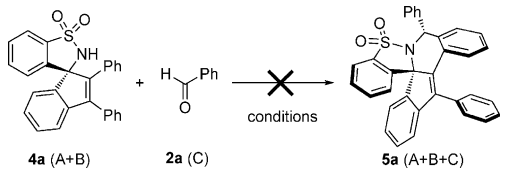
Table 4. Substrate scope of alkynes.[a]



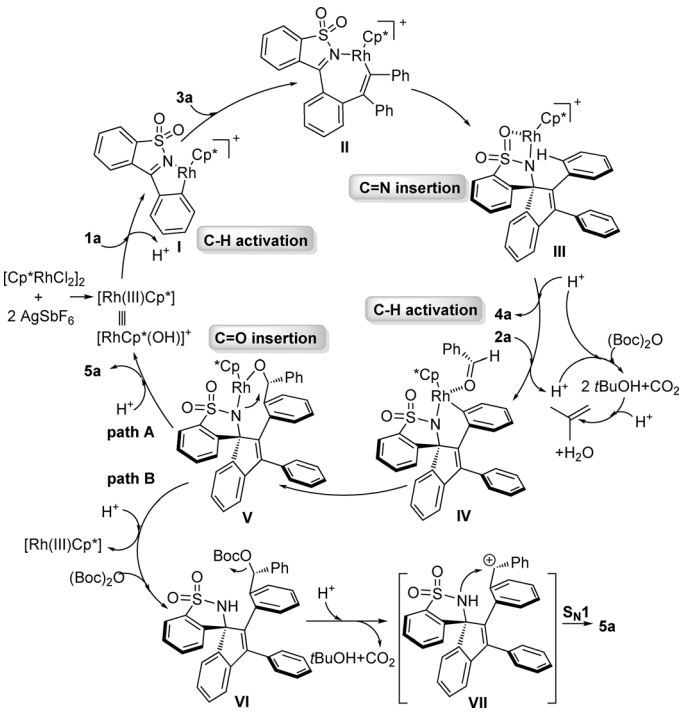
[a] Reaction conditions unless otherwise specified: **1a** (0.1 mmol), **2a** (0.2 mmol), **3** (0.15 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), $(Boc)_2O$ (1.0 equiv), DCE (2.0 mL), 80 °C, Ar atmosphere. Yields are reported for the isolated products. Ratios of regioisomers are given in parentheses and were determined by ^1H NMR analysis. [b] Major isomers are shown.

To further investigate the mechanism of the multicomponent reaction, the two-component annulation product **4a** was reacted with benzaldehyde (**2a**) under the standard conditions.[16] However, no coupling reaction was detected and unreacted starting materials were recovered. In the absence of rhodium catalyst, anhydride, or acid no further conversion of **4a** into the three-component product **5a** was observed. These experiments suggest that the aldehyde might capture the active metal intermediate of the A+B coupling before the formation of **4a** by hydrolysis. The A+B product **4a** does not turn back to the active metal intermediate and coordinates with the aldehyde to give the A+B+C product **5a** under the catalytic system (Scheme 2).

We proposed a plausible mechanism based on these results and known reports (Scheme 3). The imine nitrogen atom mediates the *ortho* C–H activation of cyclic *N*-sulfonyl ketimine **1a** by the formation of rhodacycle **I**. Subsequent regioselective insertion of the alkyne into the Rh–C bond leads to a seven-membered ring **II**, which undergoes a Grignard-type migration



Scheme 2. Conditions: a) **4a** (0.1 mmol) and **2a** (0.2 mmol) were treated under the standard conditions of the three-component reaction; b) **4a** (0.1 mmol), **2a** (0.2 mmol), and $(Boc)_2O$ (1.0 equiv) reacted in DCE (2.0 mL) at 80 °C under Ar atmosphere; c) **4a** (0.1 mmol), **2a** (0.2 mmol), and PivOH (0.2 equiv) reacted in DCE (2.0 mL) at 80 °C under Ar atmosphere.



Scheme 3. Proposed reaction mechanism.

via intramolecular C=N insertion into the Rh–C linkage to afford **III**. The second C–H activation is followed on the adjacent aryl group to form complex **IV** by chelate assistance of the aldehyde. Then, C=O insertion takes place to produce intermediate **V**, which undergoes an intramolecular cyclization in the presence of a proton source to provide product **5a** and regenerates the active rhodium species via a cyclic transition state (**path A**).[17] For the final cyclization step, another mechanistic possibility (**path B**) was speculated in which $(Boc)_2O$ may act as a protecting reagent after the protonation of intermediate **V** to give intermediate **VI**. Then, a S_N1 cyclization by generation of a bis-benzylic cation occurs to afford the final product **5a**. In this catalytic cycle (**path A**), the addition of $(Boc)_2O$ might play a very crucial role to promote the MCR and afford good reproducibility. Firstly, the proton generated from C–H activation, which tends to produce the two-component product **4a** hrough competitive hydrolysis, could be consumed by degradation of $(Boc)_2O$. Secondly, $(Boc)_2O$ itself or the degradation products (*t*BuOH/H_2O, acts as a proton source) could further participate in the final cyclization. In **path B**, the Boc group as the activating group is facilitating the ionization of the bis-benzylic secondary alcohols.

In summary, we have successfully development a novel Rh^{III}-catalyzed three-component reaction of imines, alkynes, and aldehydes via C–H activation, which affords a powerful method for the construction of polycyclic skeletons. This strategy allows the formation of four new bonds in a simple-to-perform, single-operation cascade C–H activation/C=N insertion, C–H activation/C=O insertion, cyclization sequence. More studies on the catalytic mechanism and further applications are under investigation in our laboratory.

Experimental Section

General procedure for the preparation of the polycyclic skeletons

N-sulfonyl ketimine **1a** (24.4 mg, 0.1 mmol, 1 equiv), benzaldehyde (**2a**, 21.2 μL, 0.2 mmol, 2 equiv), diphenyl acetylene **3a** (26.8 mg, 0.15 mmol, 1.5 equiv), $[Cp^*RhCl_2]_2$ (1.6 mg, 2.5 mol%), $AgSbF_6$ (3.6 mg, 10 mol%), and $(Boc)_2O$ (21.8 mg, 0.1 mmol, 1 equiv) were dissolved in DCE (2.0 mL) and stirred in a sealed vessel (5 mL) under the protection of Ar atmosphere at 80 °C for 40 h. TLC analysis of the mixture confirmed the formation of **5a**. Flash chromatography on silica gel (EtOAc/PE = 1:30) gave **5a** as a white solid (49.4 mg, 97%).

Acknowledgements

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Keywords: C–H activation · cyclization · multicomponent reactions · rhodium

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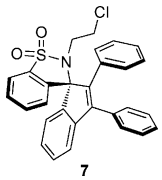
[14] For more details, see the Supporting Information.

[15] Crystallographic data for **5a**: $C_{34}H_{23}NO_2S$, $M = 509.1449$, space group: *P* 21/c, bond precision: C–C = 0.0035 A, $\lambda = 0.71073$, cell: $a = 18.3198(8)$, $b = 8.7283(4)$, $c = 20.5795(9)$ Å, $\alpha = 90^\circ$, $\beta = 110.105\ (5)^\circ$, $\gamma = 90^\circ$, $T = 293$ K, $\rho_{calcd} = 1.285$ g cm^{-3}. CCDC 1008602 contains 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

[16] **4a** can enter the catalytic cycle again to give product **5a** when **4a** is firstly deprotonated in the presence of a base. Reaction conditions with a base additive to promote the deprotonation of **4a** also failed to produce **5a**, and alkylation product **7** was separated by using DCE as the reaction solvent. Conditions: a) **4a** (0.1 mmol), **2a** (0.2 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), 1-adamantoic acid (20 mol%), K_2CO_3 (2.0 equiv), DCE (2.0 mL), 80 °C, Ar atmosphere, 49 h, **7** (90%); b) **4a** (0.1 mmol), **2a** (0.2 mmol), K_2CO_3 (2.0 equiv), DCE (2.0 mL), 80 °C, Ar atmosphere, 12 h, **7** (97%); c) **4a** (0.1 mmol), **2a** (0.2 mmol), K_2CO_3 (2.0 equiv), toluene (2.0 mL), 80 °C, Ar atmosphere, 12 h, no reaction..



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C–H Activation

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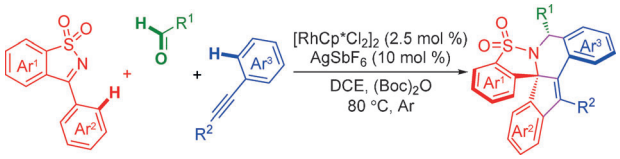
Rhodium(III)-Catalyzed Three-Component Reaction of Imines, Alkynes, and Aldehydes through C–H Activation



Efficient approach: An efficient rhodium(III)-catalyzed tandem three-component reaction of imines, alkynes, and aldehydes through C–H activation has been developed (see scheme). High stereo- and regioselectivity, as well as good yields were obtained in most cases. The simple and atom-economical approach offers a broad scope of substrates, providing polycyclic skeletons with potential biological properties.