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Intermolecular C–H Amidation of (Hetero)arenes to Produce Amides through Rhodium-Catalyzed Carbonylation of Nitrene Intermediate

Si-Wen Yuan[a],+, Hui Han[a],+, Yan-Lin Li[a], Xueli Wu[c], Xiaoguang Bao[c],*, Zheng-Yang Gu[a,b],*, and Ji-Bao Xia[a],*

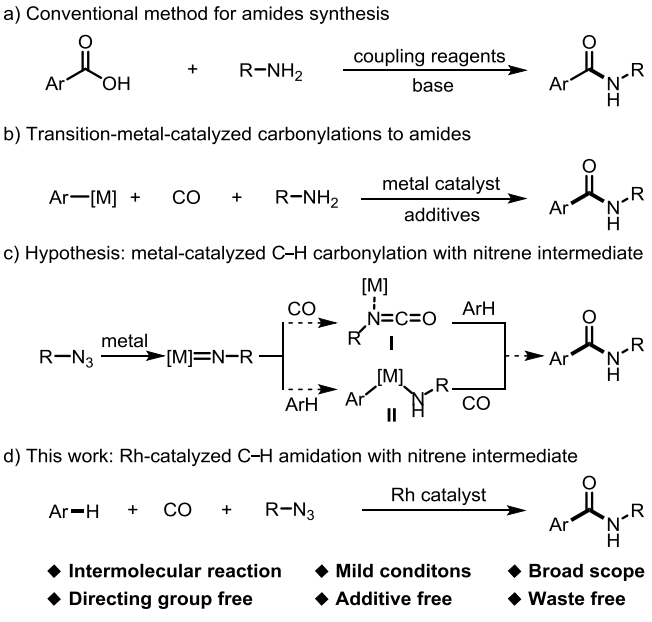
Dedicated to Professor Li-Xin Dai on the occasion of his 95 birthday

Abstract: Amide bond formation is one of the most important reactions in organic chemistry due to the widespread presence of amides in pharmaceuticals and biologically active compounds. But existing methods for amides synthesis are reaching their inherent limits. In this communication, we describe a novel rhodium-catalyzed three-component reaction to synthesize amides from organic azides, carbon monoxide, and (hetero)arenes via nitrene intermediate and direct C–H functionalization. Notably, the reaction proceeds in an intermolecular and green fashion with N_2 as the only by-product, without directing groups and any additive. The computational and mechanistic studies showed that the amides are formed through the key Rh-nitrene intermediate.

Amide linkages not only constitute one of the most essential connections in peptides and proteins, but also have an important role in pharmaceutical and chemical industries.[1] They are the basis for some of the most widely used synthetic polymers. Recently, applications of amide molecules have significantly increased in the areas of materials, agrochemicals, drugs and biologically active compounds.[2] Furthermore, amides are one of the most reliable and useful synthetic intermediates for accessing other types of compounds, such as amines, isonitriles, hetorocycles.[3] Therefore, the developments of green, waste-free, and novel catalytic methods for amide synthesis are in great demand.

Traditionally, the most common method for the synthesis of amides is condensation reaction of amines with carboxylic acids using various coupling reagents (Scheme 1a).[4] The breadth and reliability of these reactions has made it a mainstay in the synthetic organic repertoire for the assembly of amides. However, the production of large quantities of waste is the major concern using stoichiometric activating agents, such as thionyl chloride, EDC (1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide), and T3P (*n*-propylphosphonic acid anhydride), etc. Development of catalytic amidation reactions has drawn long-standing attention to chemists.[5] In the last few decades, transition-metal-catalyzed carbonylation of aryl halides and related compounds with carbon monoxide (CO) and amines via aryl–metal species has rapidly evolved to have tremendous impact since the pioneering work of Heck and co-workers in 1974 (Scheme 1b).[6] Then, many excellent works have been achieved by the groups of Beller,[7] Buchwald,[8] Jiao,[9] Li[10] and others.[11] This strategy has become a powerful tool to synthesize amides, owing to the unique ability of CO serving as an excellent carbonyl source. But the current methods are reaching their inherent limits, and it is necessary to develop new methods for amide synthesis.

Nitrene intermediates are among the most promising agents for selective introduction of nitrogen in molecules.[12] The chemistry of metal-nitrene intermediate has attracted significant attention due to the high reactivity in various nitrogen transfer reactions such as addition reactions,[13] radical coupling reactions,[14] as well as C–H activation reactions.[15] Organic azides have been identified as convenient nitrene precursors, which do not require any external oxidant and release N_2 as the only by-product. Our group has been interested in developing transition-metal-catalyzed C–H carbonylations to construct carbonyl compounds.[16] We hypothesize that C–H amidation of arenes would be realized with CO and azides through metal-nitrene intermediate, which has not been explored yet (Scheme 1c). The product amide could be obtained via two possible



Scheme 1. Comparison of the different approaches to amides synthesis.

[a] S.-W. Yuan, H. Han, Y.-L. Li, Dr. Z.-Y. Gu, Prof. Dr. J.-B. Xia
State Key Laboratory for Oxo Synthesis and Selective Oxidation, Suzhou Research Institute of LICP, Lanzhou Institute of Chemical Physics (LICP), Chinese Academy of Sciences, Lanzhou 730000, China
E-mail: jibaoxia@licp.cas.cn
[b] Dr. Z.-Y. Gu
College of Textiles and Clothing & Key Laboratory for Advanced Technology in Environmental Protection of Jiangsu Province, Yancheng Institute of Technology, Jiangsu, 224003, China
E-mail: zhengyang.gu@qq.com
[c] X. Wu, Prof. Dr. X. Bao
College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou, 215123, China
E-mail: xgbao@suda.edu.cn
[+] These authors contributed equally to this work.
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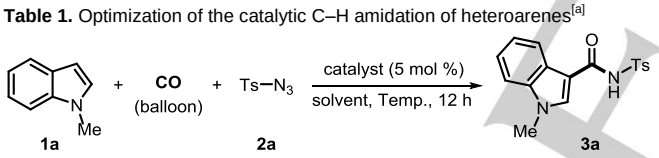
pathways. One is via isocyanate **I** derived from metal-nitrene and CO, followed by reaction with arenes. Isocyanates have been obtaiend from azides and CO under high temperatrue or via metal-catalysis.[17] The other pathway is through aryl metal intermediate **II** derived from arenes and metal–nitrene, followed by reaction with CO. This strategy provides a simple catalytic approach to amides from readily available compounds. Herein, we report a novel rhodium-catalyzed C–H amidation to synthesize amides simply from arenes, CO, and organic azides via nitrene intermediate, and it provides an efficient strategy for the synthesis of amides with broad range of substrates (Scheme 1d).

We started our research by investigating C–H amidation of *N*-methylindole (**1a**) with CO (balloon pressure) and benzenesulfonyl azide (**2a**) in the presence of various metal catalysts. To our delight, the desired amidation product **3a** was obtained in 20% yield with 5 mol % $Co_2(CO)_8$ as catalyst in MeCN at 80 °C (Table 1, entry 1). Trace amount of product could be detected with other metal catalysts, such as $Fe_2Cp_2(CO)_4$, $Ni(cod)_2$, and $Cu(OAc)_2$ (Table 1, entries 2-4). Better results were observed using $PdCl_2$ and $Pd(OAc)_2$ (Table 1, entries 5 and 6). However, trace amount of product was obtained with $Rh_2(OAc)_4$ (Table 1, entry 7). It was found that the yield of product **3a** could be increased to 92% when $[Rh(cod)Cl]_2$ was used (Table 1, entry 10). The reaction showed low reactivity at room temperature (Table 1, entry 11). We further examined other solvents, and moderate to good yields could be obtained (Table 1, entries 12-15). When the catalyst loading was reduced to 2.5 mol %, the yield of **3a** decreased to 60% (Table 1, entry 16).

Table 1. Optimization of the catalytic C–H amidation of heteroarenes[a]



Entry	Catalyst	Solvent	Temp. (°C)	Yield (%)[b]
1	$Co_2(CO)_8$	MeCN	80	20
2	$Fe_2Cp_2(CO)_4$	MeCN	80	trace
3	$Ni(cod)_2$	MeCN	80	trace
4	$Cu(OAc)_2$	MeCN	80	trace
5	$PdCl_2$	MeCN	80	65
6	$Pd(OAc)_2$	MeCN	80	85
7	$Rh_2(OAc)_4$	MeCN	80	trace
8	$Cp^*Rh(MeCN)_3$	MeCN	80	40
9	$(Cp^*RhCl_2)_2$	MeCN	80	30
10	**$[Rh(cod)Cl]_2$**	**MeCN**	**80**	**92 (88)[c]**
11	$[Rh(cod)Cl]_2$	MeCN	25	10
12	$[Rh(cod)Cl]_2$	toluene	80	65
13	$[Rh(cod)Cl]_2$	THF	80	60
14	$[Rh(cod)Cl]_2$	1,4-dioxane	80	70
15	$[Rh(cod)Cl]_2$	DMF	80	80
16[d]	$[Rh(cod)Cl]_2$	MeCN	80	60

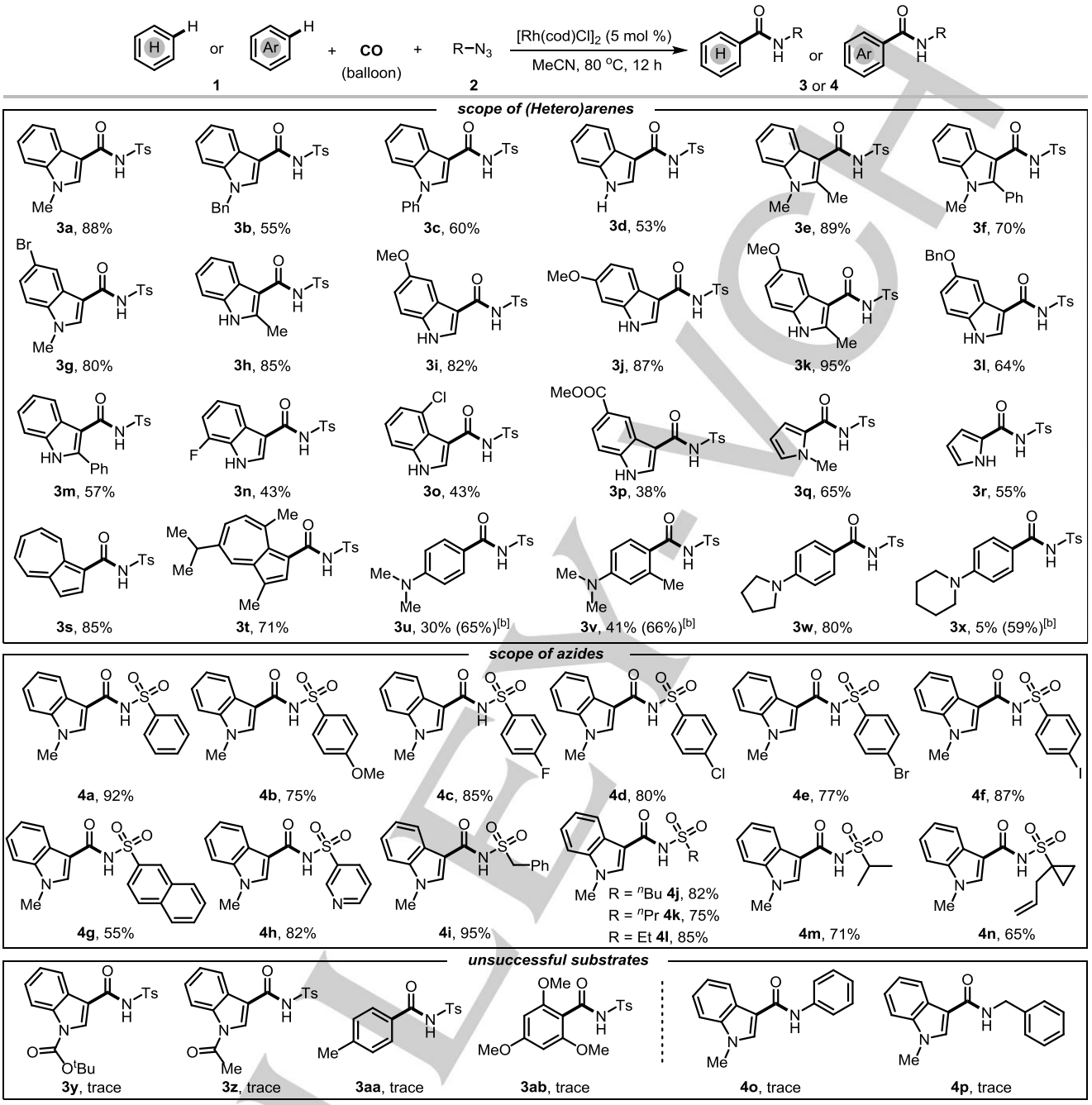
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), CO (balloon), catalyst (5 mol %), solvent (2 mL), 12 h. [b] Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c] Isolated yield. [d] 2.5 mol % $[Rh(cod)Cl]_2$.

With the optimal reaction conditions in hand, we first investigated the scope of various heteroarenes and arenes **1** (Table 2). It was gratifying to observe that *N*-Bn and *N*-Ph substituted indoles exhibited moderate reactivity (**3b** and **3c**, 55% and 60%). Trace amount of product could be detected when *N*-Boc or *N*-Ac substituted indole was used (**3y** and **3z**). Notably, the free (NH) indole could be tolerated for this reaction generating the C–H amidation product **3d** in 53% yield. It should be noted that urea product was not detected by reaction with N–H of indole. Other substituted *N*-methylindoles were compatible to this reaction giving the desired products in good yields, such as 1,2-dimethylindole, 1-methyl-2-phenylindole, and 5-bromo-1-methylindole (**3e-g**, 70-89%). Free (NH) indoles bearing electron-donating groups (Me, OMe) at different positions could produce the desired products **3h-k** in excellent yields (82-95%). When 5-(benzyloxy)-1H-indole **1l** was used, the product **3l** could be isolated in 64% yield. However, 2-phenyl, 7-F, and 4-Cl substituted indoles displayed lower reactivity than other indoles and the desired product **3m-o** could be obtained in 43-57% yields. Poor reactivity was also observed with indole **1p** bearing electron-withdrawing group, and product **3p** was obtained in 38% yield. Besides indoles, *N*-methylpyrrole and pyrrole were found to be appropriate substrates for this reaction, which could react to generate the corresponding products in moderated to good yields (**3q** and **3r**). Good yields were also obtained when using azulenes as substrates (**3s** and **3t**). Last but not least, electron-rich arenes also displayed good reactivity in this reaction. For example, *N*,*N*-dimethylaniline, *N*,*N*,3-trimethylaniline, 1-phenylpyrrolidine, and 1-phenylpiperidine all worked well, and the corresponding chemoselective C–H amidation products could be isolated in good yields (**3u-x**, 59-80%). Unfortunately, trace amount of products could be detected with toluene, anisole, and even 1,3,5-trimethoxybenzene as substrates under current conditions (**3aa** and **3ab**).

Then, we investigated the scope of organic azides **2**. It was found that benzenesulfonyl azides with electron-donating group (OMe) showed good reactivity, leading to the desired products **4b** in 75% yield. Generally, the halogen-substituted benzenesulfonyl azides (F, Cl, Br, I) were well tolerated, and the corresponding products could be obtained in relatively good yields **(4c-f**, 77-87%). The reaction of naphthalene-2-sulfonyl azide showed a lower reactivity, delivering the product **4g** in 55% yield. The heterocyclic 3-pyridylsulfonyl azide also worked well and the product **4h** could be obtained in 82% yield. Besides arylsulfonyl azides, alkylsulfonyl azides, such as benzylsulfonyl azide, butane-1-sulfonyl azide, propane-1-sulfonyl azide, ethanesulfonyl azide, propane-2-sulfonyl azide, and 1-vinylcyclopropane-1-sulfonyl azide also exhibited good reactivities in this transformation, producing the target products **4i-n** in 65-95% yields. Unfortunately, when we tested azidobenzene or (azidomethyl)benzene for this reaction, trace amount of the products could be detected (**4o** and **4p**).

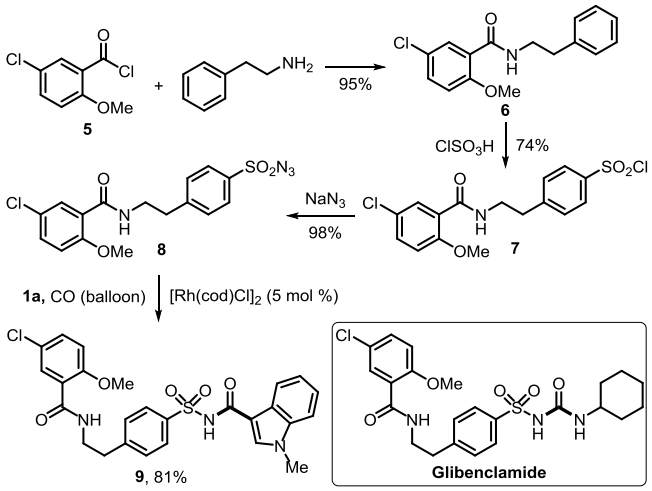
The motif of sulfonamide is a core structure widely distributed in many antibiotics, such as antidiabetic drug Glibenclamide, one of the top 200 most prescribed medication in US in 2016. To demonstrate the synthetic utility of our method, an analogue **9** of Glibenclamide was synthesized concisely from readily available chemicals (Scheme 2). Sulfonyl azide **8** was prepared efficiently by condensation of acyl chloride **5** with amine, followed by Friedel-type sulfonylation and azidation. The desired product **9** was then obtained in 81% yield by C–H amidation of **1a** under the standard conditions.

Table 2. Substrate scope of Rh-catalyzed C–H amidation of (hetero)arenes with CO and azides[a]

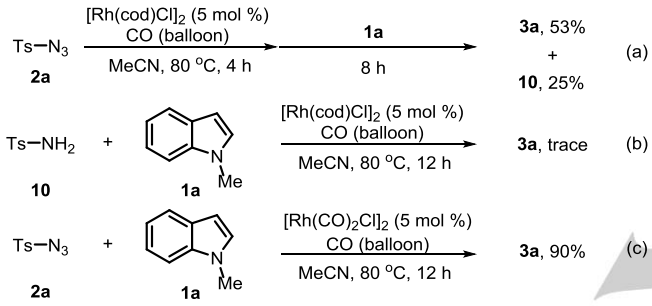


[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), CO (balloon), $[Rh(cod)Cl]_2$ (5 mol %), MeCN (2 mL), 80 °C, 12 h, isolated yield was provided. [b] With $Pd(OAc)_2$ (5 mol %).

Then, several control experiments were performed to understand the reaction mechanism. We carried out a stepwise reaction of *p*-toluenesulfonyl azide (**2a**) with CO for 4 hours under standard reaction conditions, followed by addition of *N*-methylindole (**1a**) for 8 hours, affording product **3a** and by-product *p*-toluenesulfonamide **10** in 53% and 25% yields, respectively (Scheme 3a). When we tried the reaction of by-product **10** with **1a** under standard conditions, trace amount of product **3a** could be detected, demonstrating that **10** was not the intermediate (Scheme 3b). We used the $[Rh(CO)_2Cl]_2$ as the catalyst, and product **3a** could be obtained in 90% NMR-yield, indicating that $[Rh(CO)_2Cl]_2$ might be the on-cycle catalyst (Scheme 3c). The reactions of arenes with tosylisocyanate were performed with or without $[Rh(CO)_2Cl]_2$. Excellent yields were obtained for both reactions and reaction rate was accelerated with $[Rh(CO)_2Cl]_2$, indicating that isocyanate could be the possible intermediate (details see Figure S1).



Scheme 2. The modification of Glibenclamide.



Scheme 3. Control experiments.

Computational studies were carried out to obtain an in-depth understanding on the reaction mechanism.[18] The initial catalyst precursor, Rh(cod)Cl, could undergo ligand exchange with CO molecules to afford the complex of $Rh(CO)_2Cl$, which is exothermic by 7.1 kcal/mol. Thus, the thermodynamically more stable Rh(I) complex, $Rh(CO)_2Cl$, was employed for the computational study. Initially, the azide, TsN_3 (**2a**), could coordinate with the Rh(I) catalyst model to form a complex **INT1**. Next, the transition state (TS) of the dissociation of N_2 from **INT1** to generate the key Rh–nitrene intermediate is located as **TS1**, in which the cleavage N–N bond distance is lengthened to 1.84 Å (Figure 1). The calculated energy barrier for the elimination of N_2 is 31.3 kcal/mol relative to **INT1**. The triplet state of the formed Rh–nitrene intermediate (**^{3}INT2**) is found to be the ground state, which is 6.5 kcal/mol lower in energy than the corresponding singlet state (**^{1}INT2**). Subsequently, two possible mechanistic pathways were considered. For the proposed *path a*, the transition states of CO attack to the nitrene moiety of both **^{1}INT2** and **^{3}INT2** were located as **^{1}TS2** and **^{3}TS2**, respectively, which are very close in energy. The predicted $\Delta G^{\neq}$ for this pathway is ca. 12 kcal/mol relative to separated CO and **^{3}INT2**. The resulted Rh(I)-isocyanate complex (**^{1}INT3**)[19] is very exothermic. Alternatively, another substrate, indole (**1d**), might react with the nitrene moiety of the formed Rh–nitrene intermediate via H-atom abstraction (HAA) pathway prior to CO attack (*path b*). For the triplet state, the optimized TS of the intermolecular HAA from C^3–H bond of indole was shown as **^{3}TS3** in Figure 2, in which the C…H distance is lengthened to 1.37 Å while the N…H distance is shortened to 1.27 Å. The predicted energy barrier of HAA in the triplet state is very high (27.1 kcal/mol relative to separated **^{3}INT2** and **1d**). For the HAA in the singlet state, the optimized TS was shown as **^{1}TS3**, in which the C…H distance is lengthened to 1.29 Å while the N…H distance is shortened to 1.45 Å. Although the predicted $\Delta G^{\neq}$ in singlet state is much lower than the corresponding triplet state, the overall energy barrier for *path b* is still higher than that of *path a*. Therefore, computational results suggest that the generation of isocyanate is more favorable via CO attack to the nitrene moiety after the formation of the key Rh–nitrene intermediate. Based on the mechanistic and computational studies, the plausible reaction pathway was proposed in Scheme 4.

In summary, we have developed a novel rhodium-catalyzed C–H amidation to synthesize amides simply from readily available (hetero)arenes, CO, and organic azides via nitrene intermediate. This protocol provides a simple and effective strategy for the synthesis of amides with a range of substrates. No directing group on arenes and any additive are needed in this reaction. The mechanistic and computational studies showed that the formation of amides was through Rh−nitrene intermediate.

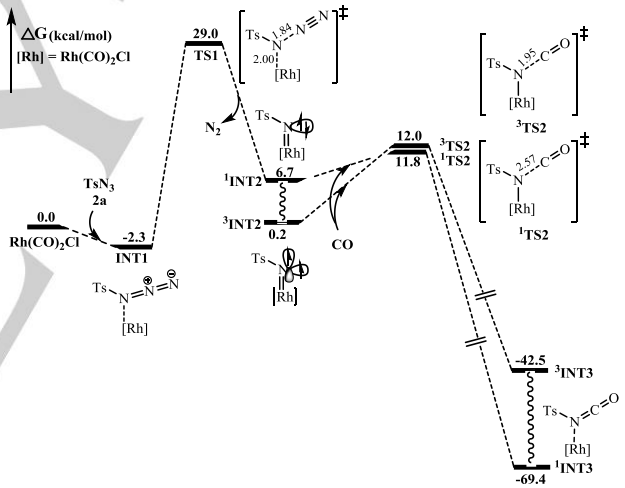


Figure 1. Energy profiles (in kcal/mol) for the formation of the Rh-nitrene intermediate and subsequent CO attack to the nitrene moiety to form isocyanate. Bond lengths are shown in Å.

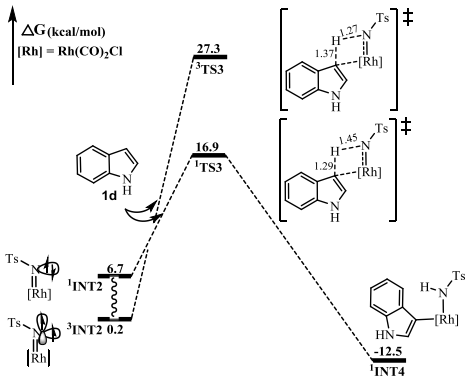
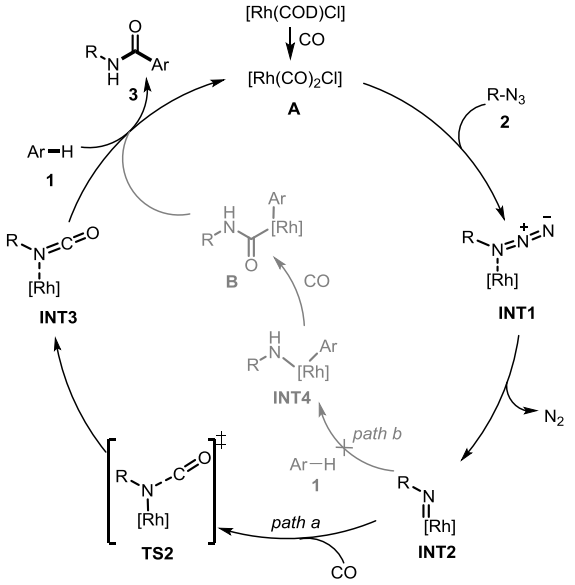


Figure 2. Energy profiles (in kcal/mol) for the HAA pathway after the formation of the Rh-nitrene intermediate. Bond lengths are shown in Å.



Scheme 4. Plausible reaction pathway.

Acknowledgements

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Keywords: carbonylation • C–H functionalization • amide • rhodium • nitrene

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[18] See Supporting Information for computational details.

[19] Alternatively, the *η*-2 binding mode of isocyanate with Rh(I) was considered computationally, which would convert to the *η*-1-isocyanate-Rh(I) complex. For related references, see: a) D. S. Glueck, J. Wu, F. J. Hollander, R. G. Bergman, *J. Am. Chem. Soc.* **1991**, *113*, 2041; b) H. Werner, U. Brekau, O. Nürnberg, B. Zeier, *J. Organomet. Chem.* **1992**, *440*, 389; c) D. J. Mindiola, G. L. Hillhouse, *Chem. Commun.* **2002**, 1840.

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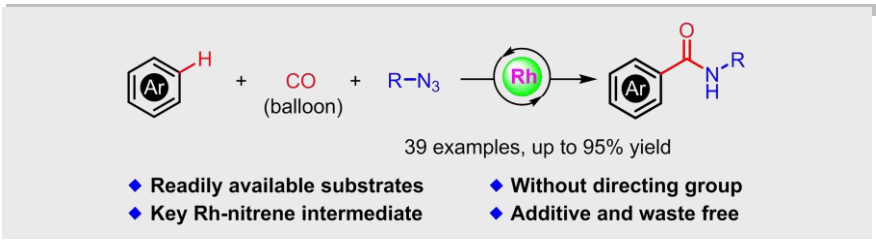

A novel rhodium-catalyzed three-component reaction has been developed to synthesize amides from organic azides, carbon monoxide, and (hetero)arenes via nitrene intermediate and direct C-H functionalization. No directing group on arenes and any additive are needed in this reaction.

Si-Wen Yuan[a],+, Hui Han[a],+, Yan-Lin Li[a], Xueli Wu[c], Xiaoguang Bao[c],, Zheng-Yang Gu[a,b],*, Ji-Bao Xia[a],**

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Intermolecular C–H Amidation of (Hetero)arenes to Produce Amides through Rhodium-Catalyzed Carbonylation of Nitrene Intermediate