Letter

Rhodium-Catalyzed Transarylation of Benzamides: C-C Bond vs C-N Bond Activation

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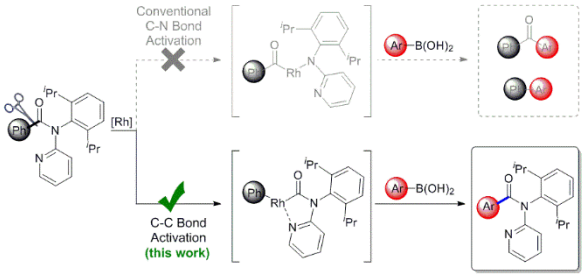
ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.9b05214 • Publication Date (Web): 25 Feb 2020



- *Rhodium-catalyzed transarylation of benzamides through direct C(O)-C(aryl) bond activation*
- *C-C bond vs C-N bond activation study (Exp & DFT)*
- *Wide scope (> 30 examples)*

Rhodium-Catalyzed Transarylation of Benzamides: C-C Bond *vs* C-N Bond Activation

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ABSTRACT: A rhodium-catalyzed transarylation of benzamides *via* selective C-C bond activation with arylboronic acids was described, which was distinct from the conventional metal-catalyzed C-N bond activation. This transformation exhibited good functional group compatibility with yields up to 88%, offering a practical approach for the construction and functionalization of benzamides. Preliminary experimental and computational studies revealed the selectivity of metal insertion into C-C bond or C-N bond was greatly affected by substituents on amide's N atom.

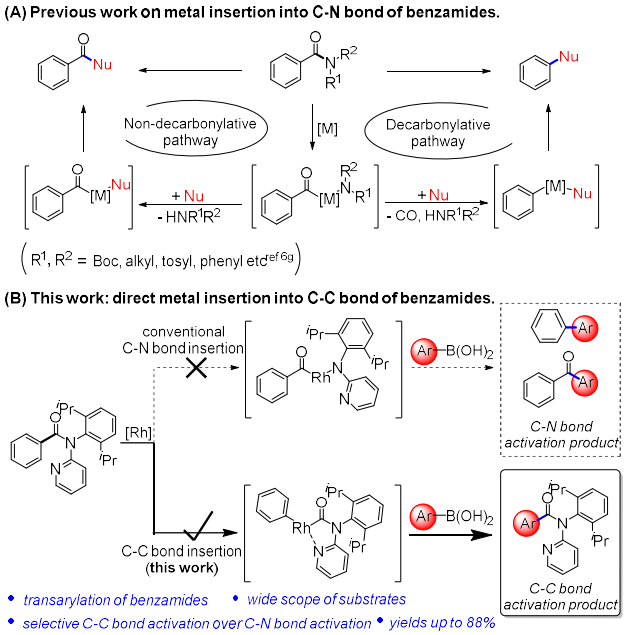
KEYWORDS: *Amide, C-C activation, C-N activation, arylation, rhodium catalysis, DFT*

Transition metal-catalyzed C-C bond activation is one of important and thorny research areas in organic chemistry over the past few decades. Compared with the well-developed C-H bond activation, C-C bond activation is facing more difficulties: the stability of C-C σ bond; the difficulty for a metal to interact with a C-C bond that is usually surrounded by more dominant C-H bonds; the incompatibility of other functional groups etc.[1] However, C-C bond activation still draws significant attention owing to its ubiquitous presence in nature, which may pave more powerful and straightforward pathways to reconstruct molecular skeletons. In recent years, transition metal-catalyzed C-C bond activation has been reported in succession, especially focusing on small ring compounds driven by relief of strain force.[2] Meanwhile, ketone, alcohol, amine and nitrile compounds have also been employed as unstrained substrates.[3] However, other important scaffolds are still underdeveloped.[4]

Amide is one of the most important structural motifs found in peptides, pharmaceutically molecules, agrochemicals and functional materials.[5] Recently, remarkable progress has been made in the metal-catalyzed C(O)-N bond activation of amides, while the direct C(O)-C bond activation is rarely reported.[6] By precisely regulating the substituents on N atom, various functionalization of amides *via* C-N bond activation could be realized.[6g] Typically, these reactions are divided into two approaches including non-decarbonylation and decarbonylation pathways, wherein the amine group acts as leaving group in both (Scheme 1A). Although decarbonylation process could fulfill the scission of C(O)-C bond macroscopically, this transformation always results in the inevitable loss of carbonyl unit and deconstruction of amide structure, along with the liberation of stoichiometric amount of hazardous carbon monoxide.

On the other hand, to the best of our knowledge, selective metal insertion into C(O)-C bond instead of C(O)-N bond with the retention of benzamide scaffold has not been reported yet. Inspired by the reports about the effects of substituents on amide's N atom on the selective C-N bond activation, in continuation of our work on C-C and C-H bond activation,[7] we herein report a general approach for catalytic selective activation of C(O)-C(aryl) bond of benzamides by introducing proper directing and steric groups onto N atom to guide the transition metal exclusive insertion into the target C-C bond and exchange aryl groups with arylboronic acids (Scheme 1B).

Scheme 1. Benzamides' C-N Bond and C-C Bond Activation Reactions



Analogous to the transamidation process of amides,[8] this reaction looks like a transarylation process, which not only offers a strategy for the less developed amide's C(O)-C bond activation reaction, but also complements traditional benzamides' synthetic methods owing to its potential advantages including easily available reagents, circumventing the need for protecting groups and complex ligands etc.[5] Furthermore, similar aryl-exchanged reactions of ketones were reported by Wang,[9] Johnson[10] and coworkers recently by using quinolinyl group as directing group through C-C bond activation. However, in the case of amide substrate, there exist several challenges such as: (1) selective metal insertion into C(O)-C(aryl) bond is more difficult, especially in the presence of competitive C-N and C-H bonds; (2) undesired decarbonylation after oxidative addition

would lose carbonyl unit and deconstruct the amide structure; (3) tolerance of various functional groups.

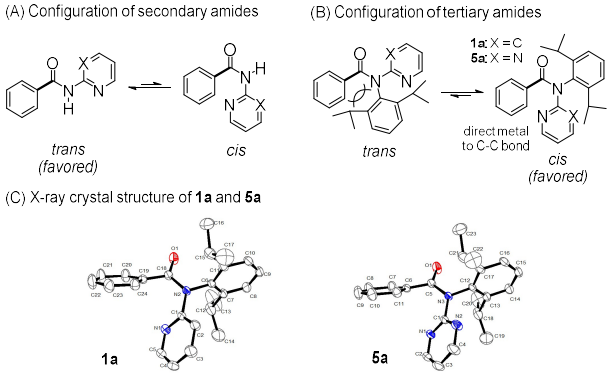


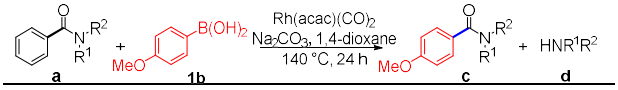
Figure 1. Configuration of *N*-substituted benzamides. ORTEP representation of **1a** (CCDC 1944056) and **5a** (CCDC 1944055) with thermal ellipsoids at a 30% probability level. H atoms are omitted for clarity.

Initially, benzamide substrates bearing primary or phenyl substituted amino group failed to afford the desired C-C bond activation products, which aroused us to introduce directing group, such as pyridyl or pyrimidyl group, onto amide's N atom. N-coordination might make metal closer to the target C-C bond and stabilize the five-membered ring intermediate. Considering that the secondary amides would favor the *trans* configuration with the directing group being far away from the C(O)-C(aryl) bond (Figure 1A),[11] the tertiary amides, which might adopt *cis* configuration if installation of proper steric groups on N atom and would force the transition metal in close proximity to the C(O)-C(aryl) bond, were designed and synthesized (Figure 1B). Indeed, the tertiary benzamide substrates **1a** and **5a**, which contained diisopropylphenyl group and pyridyl or pyrimidyl group respectively, were in the desired *cis* configuration, and their structures were confirmed by single crystal X-ray diffraction determination (Figure 1C).[12]

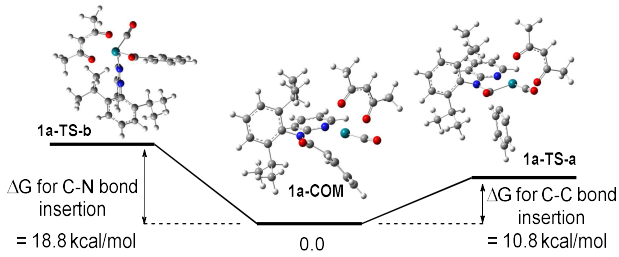
Then, we began our investigation by evaluating the effects of different substituents on the N atom of tertiary benzamides (**1a**-**8a**), together with 4-methoxyphenylboronic acid (**1b**) as substrate and $Rh(acac)(CO)_2$ as catalyst. Meanwhile, DFT methods were also employed to locate the C-C bond and C-N bond insertion transition states in oxidative addition step respectively for **1a**-**8a**.[13] Their relative activation energy ΔG and activation energy differences ΔΔG listed in Table 1 were adopted to evaluate roughly the selectivity of metal in oxidative addition process.

After extensive screening different *N*-substituents, we were delighted to find the judiciously designed *N*-(2,6-diisopropylphenyl)-*N*-(pyridine-2-yl)benzamide (**1a**) could fulfil the proposed transarylation transformation and gave 84% yield without formation of C-N bond activation product (entry 1). Computational results indicated that the activation energy ΔG of C-C insertion for **1a** was 10.8 kcal/mol, 8.0 kcal/mol lowering than that of C-N insertion, which might account for the exclusive selectivity of activation on C-C bond. Steric effect of R^2 group was an important factor affecting the selectivity. When replacing R^2 group to other less steric groups, including phenyl (entry 2), methyl substituted (entry 3) and ethyl substituted (entry 4) phenyl groups, the poorer selectivity along with smaller ΔΔG values (1.5 to 4.6 kcal/mol) were obtained, resulting in the

Table 1. Experimental and Computational Study of *N*-substituents' Effect on Selective C-N bond and C-C Bond Activation.[a,b]



Entry	-NR^1R^2	Insertion	ΔG[c]	ΔΔG[d]	Yields[e]
1	 1a	C-C	10.8	8.0	84% (83%)[f]
		C-N	18.8		0%
2	 2a	C-C	8.6	1.5	32%
		C-N	10.1		44%
3	 3a	C-C	13.3	4.6	46%
		C-N	17.9		36%
4	 4a	C-C	16.6	3.0	45%
		C-N	19.6		34%
5	 5a (Pym = 2-pyrimidyl)	C-C	11.8	4.4	68%
		C-N	16.2		21%
6	 6a	C-C	12.8	-1.1	0%
		C-N	11.7		60%
7	 7a	C-C	30.2	5.5	0%
		C-N	35.7		0%
8	 8a	C-C	29.3	-3.9	0%
		C-N	25.4		0%

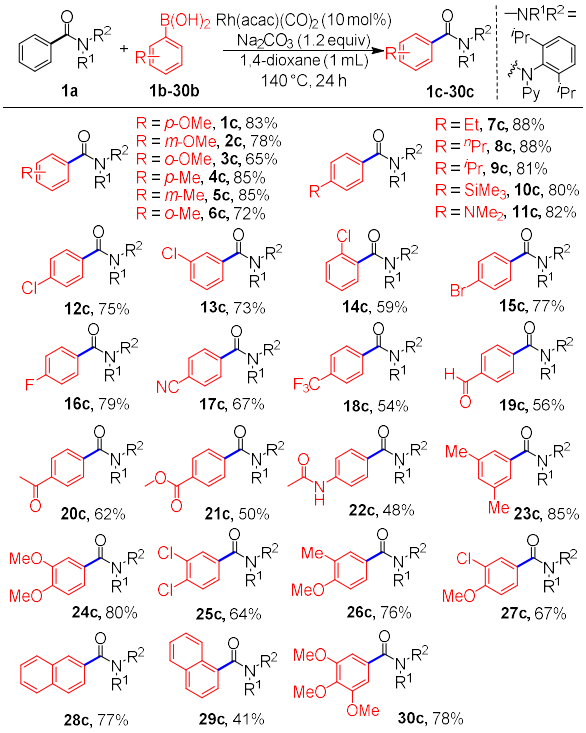


[a]The yield of amine (**d**) was monitored as the yield of C-N bond activation. [b]Reactions were carried out under nitrogen atmosphere with **a** (0.1 mmol), **1b** (0.25 mmol), $Rh(acac)(CO)_2$ (10 mol%), Na_2CO_3 (1.2 equiv) in 1,4-dioxane (1 mL) at 140 °C for 24 h. [c]Relative Gibbs free energy (kcal/mol) of Rh-complexes and the corresponding transition states associated with C-C or C-N bond insertion reactions, which was obtained at the B3LYP-D3(BJ)/[6-31G*, Lanl2dz](SMD, 1,4-dioxane) theoretical level. [d]Relative Gibbs free energy of the transition state in C-C insertion reaction was set to zero. [e]NMR yields of **c** and **d** by using CH_2Br_2 as internal standard. [f]Isolated yield.

occurrence of competitive C-N bond activation side reactions. Moreover, pyridyl group seemed to be more suitable directing group for this reaction than pyrimidyl group (entries 5-6), and the smaller ΔΔG values of pyrimidyl group might be caused by the greater effects on N atom's electron deficiency.[6] In addition, changing the directing group to phenyl group made the activation energy ΔG for both C-C bond and C-N bond insertions up to about 30 kcal/mol, thus retarding the reactions (entries 7-8). Above all, from the experimental and computational point of

view, the optimal reaction conditions consist of benzamide (0.1 mmol), arylboronic acid (0.25 mmol), $Rh(acac)(CO)_2$ (10 mol%), Na_2CO_3 (1.2 equiv) in 1,4-dioxane (1 mL) at 140 °C for 24 h under nitrogen atmosphere (see Supporting Information for details).

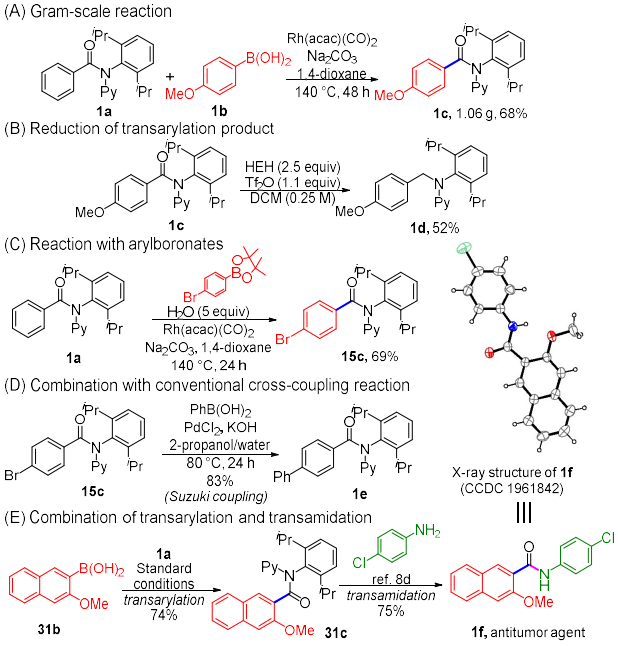
Table 2. Scope of Arylboronic Acids.[a,b]



[a]Reaction conditions: **1a** (0.1 mmol), **b** (0.25 mmol), $Rh(acac)(CO)_2$ (10 mol%), Na_2CO_3 (1.2 equiv) in 1,4-dioxane (1 mL) at 140 °C for 24 h under nitrogen atmosphere. [b]Isolated yields.

With the optimized reaction conditions in hand, the scope of arylboronic acids was examined as shown in Table 2. In general, the transformation exhibited broad substrate scope, good functional group tolerance and selective activation on C(O)-C(aryl) bond. For the steric effects, *m*, *p*-methoxy group substituted phenylboronic acids gave the desired products in good yields about 80% (**1c**, **2c**), while *o*-methoxy substituted product (**3c**) was obtained in a moderate yield 65%, suggesting that steric hinderance on phenylboronic acid might have a slight inhibition on the yield. Meanwhile, various alkyl-substituted substrates were well-tolerated during reaction, affording the corresponding products in good yields up to 88% (**4c**-**9c**). Trimethylsilyl (**10c**) and dimethylamino (**11c**) groups also provided the desirable yields 80% and 82% respectively. Substrates with halogen atom substituents reacted smoothly in moderate yields ranging from 59% to 79%, indicating the feasibility of combining with conventional cross-coupling methods (**12c**-**16c**). More importantly, arylboronic acids bearing electron-deficient groups, such as cyano (**17c**) and trifluoromethyl (**18c**) groups, which were inactive in quinolinyl ketone's aryl interconversion reaction,[9] resulted in 67% and 54% yields, respectively. It is worth noting that neither of the previously reported rhodium insertion into the C-H bond of the aldehyde (**19c**),[14] the C-C bond of the ketone (**20c**)[3d] or the C-O bond of the ester (**21c**)[6g] was observed in the case of arylboronic acids containing aldehyde, acetyl or ester substituents, thus avoiding the installation of protecting groups owing to their incompatibility in traditional methods. Furthermore, when substrate bearing two different amide units was treated (**22c**), the central metal exclusively inserted into the target C(O)-C(aryl) bond, rather than C-N bonds or C(O)-C(methyl) bond. In addition, coupling with di- and trisubstituted arylboronic acids delivered the corresponding poly substituted amides in moderate to good yields (**23c**-**30c**).

Scheme 2. Synthetic Applications



The utility of this transarylation reaction was further examined. Firstly, a scaled-up reaction was carried out, affording **1c** in 68% yield, indicating its feasibility on a more synthetically useful scale (Scheme 2A). Subsequent reduction of transarylation product could deliver tertiary amine (Scheme 2B).[15] In addition, replacing arylboronic acid to arylboronates with 5 equiv water could also afford the desired product **15c** in 69% yield, illustrating the compatibility of the system with water and arylboronates (Scheme 2C), and the bromo atom of the product **15c** enabled the reaction to be further concatenated with other coupling reactions for late-stage functionalization (Scheme 2D). More importantly, the combination of this transarylation process and transamidation process could realize the complete mutual conversion of amide units within two steps. For example, the reaction between **1a** and commercially available arylboronic acid **31b** smoothly provided the transarylation product **31c**, which could be further converted to **1f**,[12] an important antitumor agent, through a transamidation process with 4-chloroaniline (Scheme 2E).[8e]

At last, in order to gain insight into the possible reaction pathway, a series of control experiments were carried out as shown in Scheme 3. Initially, no reaction occurred when secondary amides (**9a** or **10a**) were treated as substrates, convincing the importance of chelation and steric effect of substituents on N atom (Scheme 3A). Meanwhile, the biaryl product (**1g**) was not detected in this transformation, which illustrated that C-C bond oxidative addition might occur prior to transmetalation process (Scheme 3B).[9-10] In addition, the fate of the leaving phenyl group of substrate was also investigated. GC-MS analysis of the

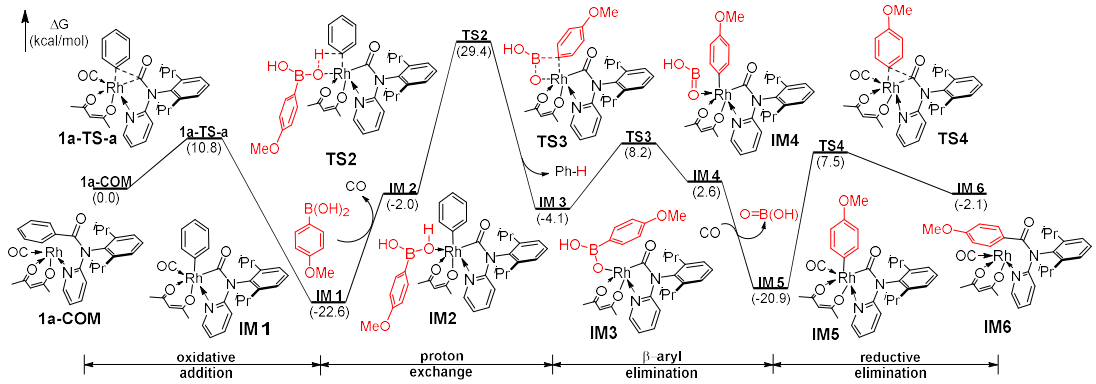
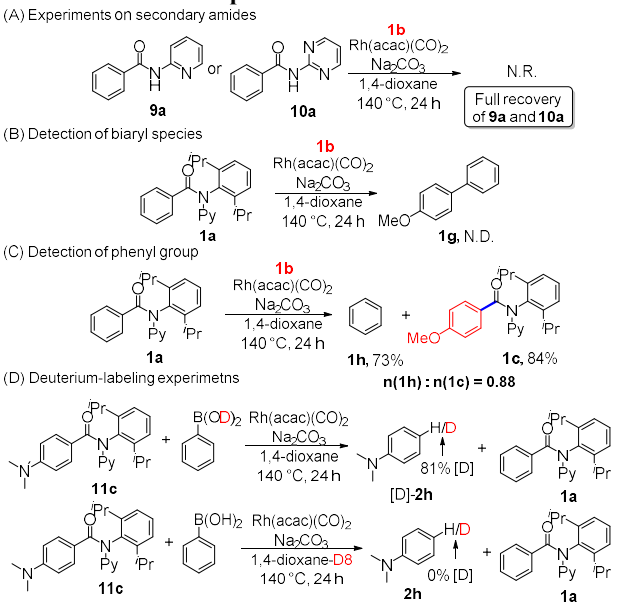


Figure. 2. DFT-computed pathway for transarylation of benzamides and DFT calculations was obtained at the B3LYP-D3(BJ)/[6-31G*, Lanl2dz](SMD, 1,4-dioxane) theoretical level.

the reaction mixture revealed that benzene (**1h**) was obtained in 73% yield, which was in 0.88 molar ratio to transarylation product **1c**, indicating that β-aryl elimination[16] might be involved in transmetalation process (Scheme 3C). According to Hartwig's work,[16a] the H source of benzene would be from the hydroxyl hydrogen of boronic acid, and our deuterium-labeling experiments further convinced that. Following treatment of **11c** with $PhB(OD)_2$ and 1,4-dioxane-D8 respectively, the deuterated ratios of the corresponding hydrogen of **2h** were approximately 81% and 0%, respectively, providing the evidence for the proton exchange between phenyl group and arylboronic acid rather than solvent (Scheme 3D).

Scheme 3. Control Experiments



Based on our work and literatures,[1-3,9-10,16] DFT calculations were performed to further probe the mechanism of this transformation, and the plausible reaction pathway was shown in Figure 2. The reaction started from ligand exchange between **IM6** and substrate **1a** to give catalyst-substrate complex **1a-COM**, which directly facilitated the C(O)-C(aryl) bond oxidative addition to generate **IM1** *via* **1a-TS-a**. Then ligand substitution converted **IM1** to **IM2**, and **IM2** underwent proton exchange to deliver **IM3** *via* **TS2** and release benzene. The proton exchange process was exergonic by 2.1 kcal mol^{-1}. Subsequently, β-aryl elimination of **IM3** *via* **TS3** gave **IM4**,[16] and **IM4** recombined with CO ligand to give **IM5**. The final reductive elimination, which required an activation energy of 28.4 kcal mol^{-1}, afforded **IM6** (*via* **TS4**) and closed the catalytic cycle.

In conclusion, we developed an example of Rh-catalyzed transarylation of benzamides to afford the aryl exchanged benzamides with arylboronic acids. Screening of the amide *N*-substituents experimentally and computationally made Rh(I) catalyst exclusively insert into C(O)-C(aryl) bond rather than conventional C(O)-N bond. In addition, this transformation provided a novel and practical methodology to construct amides, with broad substrate scope, good functional group tolerance and high selectivity. Further studies on amide's functionalization are ongoing in our research group.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

Supporting Information

Detailed experimental procedures, characterization data, copies of ^{1}H, ^{13}C and ^{19}F NMR spectra of products are reported in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENT

We are grateful to the National Natural Science Foundation of China (grant nos. 21472128) and Sichuan Science and Technology Program (NO. 2018JY560) for financial support. We also acknowledge Comprehensive training platform of specialized laboratory, College of chemistry, Sichuan University for HRMS analysis, Prof. Daibing Luo for single crystal measurements and Prof Pengchi Deng for NMR analysis.

REFERENCES

(1) (a) Dong, G. *C-C Bond Activation*, Springer, Berlin, **2014**, 1. (b) Murakami, M.; Chatani, N. Eds. *Cleavage of Carbon-Carbon Single Bonds by Transition Metals*, Wiley-VCH, Weinheim, Germany, **2016**, 1. (c) Murakami, M.; Ishida, N. Potential of Metal-Catalyzed C-C Single Bond Cleavage for Organic

Synthesis. *J. Am. Chem. Soc.* **2016**, *138*, 13759-13769. (d) Ruhland, K. Transition-Metal-Mediated Cleavage and Activation of C-C Single Bonds. *Eur. J. Org. Chem.* **2012**, *2012*, 2683-2706. (e) Wu, X.; Zhu, C. Recent Advances in Radical-Mediated C-C Bond Fragmentation of Non-Strained Molecules. *Chin. J. Chem.* **2018**, *37*, 171-182. (f) Park, Y. J.; Park, J.; Jun, C. Metal-Organic Cooperative Catalysis in C-H and C-C Bond Activation and Its Concurrent Recovery. *Acc. Chem. Res.* **2008**, *41*, 222-234.

(2) (a) Fumagalli, G.; Stanton, S.; Bower, J. F. Recent Methodologies That Exploit C-C Single-Bond Cleavage of Strained Ring Systems by Transition Metal Complexes. *Chem. Rev.* **2017**, *117*, 9404-9432. (b) Kondo, T. Ruthenium- and Rhodium-Catalyzed Strain-Driven Cleavage and Reconstruction of the C-C Bond. *Eur. J. Org. Chem.* **2016**, *2016*, 1232-1242. (c) Lu, B. L.; Dai, L.; Shi, M. Strained small rings in gold-catalyzed rapid chemical transformations. *Chem. Soc. Rev.* **2012**, *41*, 3318-3339. (d) Marek, I.; Masarwa, A.; Delaye, P. O.; Leibeling, M. Selective Carbon-Carbon Bond Cleavage for the Stereoselective Synthesis of Acyclic Systems. *Angew. Chem. Int. Ed.* **2015**, *54*, 414-429. (e) Wang, Y.; Yu, Z. X. Rhodium-Catalyzed [5 + 2 + 1] Cycloaddition of Ene-Vinylcyclopropanes and CO: Reaction Design, Development, Application in Natural Product Synthesis, and Inspiration for Developing New Reactions for Synthesis of Eight-Membered Carbocycles. *Acc. Chem. Res.* **2015**, *48*, 2288-2296. (f) Xia, Y.; Lu, G.; Liu, P.; Dong, G. Catalytic activation of carbon-carbon bonds in cyclopentanones. *Nature* **2016**, *539*, 546-550. (g) Zhang, D.-H.; Tang, X.-Y.; Shi, M. Gold-Catalyzed Tandem Reactions of Methylenecyclopropanes and Vinylidenecyclopropanes. *Acc. Chem. Res.* **2014**, *47*, 913-924.

(3) (a) Chen, F.; Wang, T.; Jiao, N. Recent Advances in Transition-Metal-Catalyzed Functionalization of Unstrained Carbon-Carbon Bonds. *Chem. Rev.* **2014**, *114*, 8613-8661. (b) Dermenci, A.; Coe, J. W.; Dong, G. Direct activation of relatively unstrained carbon-carbon bonds in homogeneous systems. *Org. Chem. Front.* **2014**, *1*, 567-581. (c) Liu, H.; Feng, M.; Jiang, X. Unstrained Carbon-Carbon Bond Cleavage. *Chem. Asian J.* **2014**, *9*, 3360-3389. (d) Song, F.; Gou, T.; Wang, B. Q.; Shi, Z. J. Catalytic activations of unstrained C-C bond involving organometallic intermediates. *Chem. Soc. Rev.* **2018**, *47*, 7078-7115.

(4) (a) Zhu, J.; Wang, J.; Dong, G. Catalytic activation of unstrained C(aryl)-C(aryl) bonds in 2,2'-biphenols. *Nat. Chem.* **2019**, *11*, 45-51. (b) Onodera, S.; Ishikawa, S.; Kochi, T.; Kakiuchi, F. Direct Alkenylation of Allylbenzenes via Chelation-Assisted C-C Bond Cleavage. *J. Am. Chem. Soc.* **2018**, *140*, 9788-9792. (c) Youn, S. W.; Kim, B. S.; Jagdale, A. R. Pd-Catalyzed Sequential C-C Bond Formation and Cleavage: Evidence for an Unexpected Generation of Arylpalladium(II) Species. *J. Am. Chem. Soc.* **2012**, *134*, 11308-11311. (d) Xu, Y.; Qi, X.; Zheng, P.; Berti, C. C.; Liu, P.; Dong, G. Deacylative transformations of ketones via aromatization-promoted C-C bond activation. *Nature* **2019**, *567*, 373-378. (e) Moselage, M.; Li, J.; Kramm, F.; Ackermann, L. Ruthenium(II)-Catalyzed C-C Arylations and Alkylations: Decarbamoylative C-C Functionalizations. *Angew, Chem. Int. Ed.* **2017**, *56*, 5341-5344.

(5) (a) Greenberg, A.; Breneman, C. M.; Liebman, J. F. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials*, Wiely, **2000**. (b) Marchildon, K. Polyamides – Still Strong After Seventy Years. *Macromol. React. Eng.* **2011**, *5*, 22-54. (c) Pattabiraman, V. R.; Bode, J. W. Rethinking amide bond synthesis. *Nature* **2011**, *480*, 471-479.

(6) (a) Dander, J. E.; Garg, N. K. Breaking Amides using Nickel Catalysis. *ACS Catal.* **2017**, *7*, 1413-1423. (b) Gao, Y.; Ji, C. L.; Hong, X. Ni-mediated C-N activation of amides and derived catalytic transformations. *Sci China Chem* **2017**, *60*, 1413-1424. (c) Liu, C.; Szostak, M. Twisted Amides: From Obscurity to Broadly Useful Transition-Metal-Catalyzed Reactions by N-C Amide Bond Activation. *Chem. Eur. J.* **2017**, *23*, 7157-7173. (d) Liu, C.; Szostak, M. Decarbonylative cross-coupling of amides. *Org. Biomol. Chem.* **2018**, *16*, 7998-8010. (e) Ouyang, K.; Hao, W.; Zhang, W. X.; Xi, Z. Transition-Metal-Catalyzed Cleavage of C-N Single Bonds. *Chem. Rev.* **2015**, *115*, 12045-12090. (f) Meng, G.; Shi, S.; Szostak, M. Cross-Coupling of Amides by N-C Bond Activation. *Synlett* **2016**, *27*, 2530-2540. (g) Takise, R.; Muto, K.; Yamaguchi, J. Cross-coupling of aromatic esters and amides. *Chem. Soc. Rev.* **2017**, *46*, 5864-5888. (h) Wang, Q.; Su, Y.; Li, L.; Huang, H. Transition-metal catalysed C-N bond activation. *Chem. Soc. Rev.* **2016**, *45*, 1257-1272.

(7) (a) Yan, X.; Ye, R.; Sun, H.; Zhong, J.; Xiang, H.; Zhou, X. Synthesis of 2-Arylindoles by Rhodium-Catalyzed/Copper-Mediated Annulative Coupling of *N*-Aryl-2-aminopyridines and Propargyl Alcohols via Selective C-H/C-C Activation. *Org. Lett.* **2019**, *21*, 7455-7459. (b) Yang, J.; Ji, D.-W.; Hu, Y.-C.; Min, X.-T.; Zhou, X.; Chen, Q.-A. Cobalt-catalyzed hydroxymethylarylation of terpenes with formaldehyde and arenes. *Chem. Sci.* **2019**, *10*, 9560-9564. (c) Yan, X.; Sun, H.; Xiang, H.; Yu, D.-G.; Luo, D.; Zhou, X. Palladium-catalyzed C(carbonyl)-C bond cleavage of amides: a facile access to phenylcarbamate derivatives with alcohols. *Chem. Commun.* **2018**, *54*, 8606-8609. (d) Yao, X.; Weng, X.; Wang, K.; Xiang, H.; Zhou, X. Transition metal free oxygenation of 8-aminoquinoline amides in water. *Green Chem.* **2018**, *20*, 2472-2476.

(8) (a) Lanigan, R. M.; Sheppard, T. D. Recent Developments in Amide Synthesis: Direct Amidation of Carboxylic Acids and Transamidation Reactions. *Eur. J. Org. Chem.* **2013**, *33*, 7453-7465. (b) Acosta-Guzamán, P.; Mateus-Gómez, A.; Gamba-Sánchez, D. Direct Transamidation Reactions: Mechanism and Recent Advances. *Molecules* **2018**, *23*, 2382-2398. (c) Figueiredo, R. M. d.; Suppo, J.-S.; Campagne, J.-M. Nonclassical Routes for Amide Bond Formation. *Chem. Rev.* **2016**, *116*, 12029-12122. (d) Li, G.; Ji, C.-L.; Hong, X.; Szostak, M. Highly Chemoselective, Transition-Metal-Free Transamidation of Unactivated Amides and Direct Amidation of Alkyl Esters by N-C/O-C Cleavage. *J. Am. Chem. Soc.* **2019**, *141*, 11161-11172.

(9) Wang, J.; Chen, W.; Zuo, S.; Liu, L.; Zhang, X.; Wang, J. Direct Exchange of a Ketone Methyl or Aryl Group to Another Aryl Group through C-C Bond Activation Assisted by Rhodium Chelation. *Angew. Chem. Int. Ed.* **2012**, *51*, 12334-12338.

(10) Dennis, J. M.; Compagner, C. T.; Dorn, S. K.; Johnson, J. B. Rhodium-Catalyzed Interconversion of Quinolinyl Ketones with Boronic Acids via C-C Bond Activation. *Org. Lett.* **2016**, *18*, 3334-3337.

(11) (a) Nguyen, K.; Iskandar, M.; Rabenstein, D. L. Kinetics and Equilibria of Cis/Trans Isomerization of Secondary Amide Peptide Bonds in Linear and Cyclic Peptides. *J. Phys. Chem. B* **2010**, *114*, 3387-3392. (b) Ramachandran, G.; Sasisekharan, V. Conformation of Polypeptides and Proteins. *Adv. Protein Chem.* **1968**, *23*, 283-438.

(12) CCDC 1944056 (**1a**), 1944055 (**5a**) and 1961842 (**1f**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

(13) (a) Mujika, J. I.; Mercero, J. M.; Lopez, X. Water-Promoted Hydrolysis of a Highly Twisted Amide: Rate Acceleration Caused by the Twist of the Amide Bond. *J. Am. Chem. Soc.* **2005**, *127*, 4445-4453. (b) Kemnitz, C. R.; Loewen, M. J. "Amide Resonance" Correlates with a Breadth of C–N Rotation Barriers. *J. Am. Chem. Soc.* **2007**, *129*, 2521-2528. (c) Glover, S. A.; Rosser, A. A. Reliable Determination of Amidicity in Acyclic Amides and Lactams. *J. Org. Chem.* **2012**, *77*, 5492-5502. (d) Liu, L.; Chen, P.; Sun, Y.; Wu, Y.; Chen, S.; Zhu, J.; Zhao, Y. Mechanism of Nickel-Catalyzed Selective C-N Bond Activation in Suzuki-Miyaura Cross-Coupling of Amides: A Theoretical Investigation. *J. Org. Chem.* **2016**, *81*, 11686-11696. (e) Szostak, R.; Shi, S.; Meng, G.; Lalancette, R.; Szotak, M. Ground-State Distortion in *N*-Acyl-*tert*-butyl-carbamates (Boc) and *N*-Acyl-tosylamides (Ts): Twisted Amides of Relevance to Amide N-C Cross-Coupling. *J. Org. Chem.* **2016**, *81*, 8091-8094. (f) Pace, V.; Holzer, W.; Meng, G.; Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. Structures of Highly Twisted Amides Relevant to Amide N-C Cross-Coupling: Evidence for Ground-State Amide Destabilization. *Chem. Eur. J.* **2016**, *22*, 14494-14498. (g) Ji, C.-L.; Hong, X. Factors Controlling the Reactivity and Chemoselectivity of Resonance Destabilized Amides in Ni-Catalyzed Decarbonylative and Nondecarbonylative Suzuki-Miyaura Coupling. *J. Am. Chem. Soc.* **2017**, *139*, 15522-15529.

(14) (a) Murphy, S. K.; Park, J.-W.; Cruz, F. A.; Dong, V. M. Rh-catalyzed C-C bond cleavage by transfer hydroformylation. *Science* **2015**, *347*, 56-60. (b) Landis, C. R. Construction and deconstruction of aldehydes by transfer hydroformylation. *Science* **2015**, *347*, 29-30. (c) Tan, G.; Wu, Y.; Shi, Y.; You, J. Syngas-Free Highly Regioselective Rhodium-Catalyzed Transfer Hydroformylation of Alkynes to *α,β*-Unsaturated Aldehydes. *Angew. Chem. Int. Ed.* **2019**, *58*, 7440-7444.

(15) (a) Barbe, G.; Charette, A. B. Highly Chemoselective Metal-Free Reduction of Tertiary Amides. *J. Am. Chem. Soc.* **2008**, *130*, 18-19. (b) Sitte, N. A.; Bursch, M.; Grimme, S.; Paradies, J. Frustrated Lewis Pair Catalyzed Hydrogenation of Amides: Halides as Active Lewis Base in the Metal-Free Hydrogen Activation. *J. Am. Chem. Soc.* **2019**, *141*, 159-162. (c) Das, S.; Addis, D.; Zhou, S.; Junge, K.; Beller, M. Zinc-Catalyzed Reduction of Amides: Unprecedented Selectivity and Functional Group Tolerance. *J. Am. Chem. Soc.* **2010**, *132*, 1770-1771. (d) Asad, N.; Deodato, D.; Lan, X.; Widegren, M. B.; Phillips, D. L.; Du, L.; Dore, T. M. Photochemical Activation of Tertiary Amines for Applications in Studying Cell Physiology. *J. Am. Chem. Soc.* **2017**, *139*, 12591-12600. (e) Xie, L.-G.; Dixon, D. J. Tertiary amine synthesis via reductive coupling of amides with Grignard reagents. *Chem. Sci.* **2017**, *8*, 7492-7497.

(16) (a) Zhao, P.; Incarvito, C. D.; Hartwig, J. F. Directly Observed Transmetalation from Boron to Rhodium. *β*-Aryl Elimination from Rh(I) Arylboronates and Diarylborinates. *J. Am. Chem. Soc.* **2007**, *129*, 1876-1877. (b) Ma, G.-N.; Zhang, T.; Shi, M. Catalytic Enantioselective Arylation of *N*-Tosylarylimines with Arylboronic Acids Using C_2-Symmetric Cationic *N*-Heterocyclic Carbene Pd^{2+} Diaquo Complexes. *Org. Lett.* **2009**, *11*, 875-878. (c) Xue, L.; Ng, K. C.; Lin, Z. Theoretical studies on *β*-aryl elimination from Rh(I) complexes. *Dalton Trans.* **2009**, *30*, 5841-5850.

Graphic Abstract