Organic LETTERS

Letter

pubs.acs.org/OrgLett

# Pd(II)-Catalyzed *ortho*-C−H Olefination/Dearomatization of *N*-Aryl Ureas: An Approach to Imine Derivatives

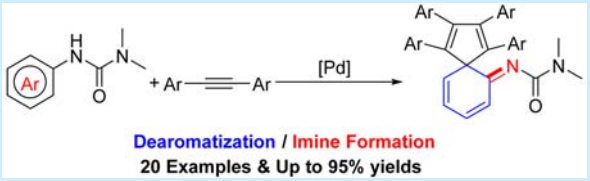
Pingping Jiang,[†,§] Yongbao Xu,[†,§] Fuxing Sun,[†] Xufei Liu,[‡] Feng Li,[†] Renfu Yu,[†] Yang Li,[†] and Qifeng Wang*[,†,‡]

[†]International Joint Research Laboratory of Nano-Micro Architecture Chemistry (NMAC), Department of Organic Chemistry, College of Chemistry, Jilin University, 2699 Qianjin Street, Changchun 130012, China

[‡]State Grid Jilin Province Electric Power Research Institute, 4433 Renmin Street, Changchun 130021, China

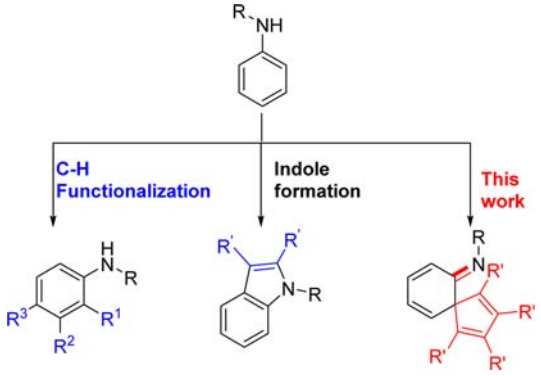
Supporting Information

**ABSTRACT:** An unprecedented approach for the synthesis of imine derivatives was achieved via a Pd(II)-catalyzed dearomatization reaction of *N*-aryl ureas with internal alkynes. The corresponding spirocyclic imine derivatives were obtained with 20 examples in good to excellent yields. Mechanistic investigation indicated that an interesting 1,3-palladium migration process led to the $\alpha$-regioselective dearomatization when 2-naphthyl ureas were used as the substrates. Fused ring products could also be obtained to further prove this migration process.




Development of synthetic approaches to imine derivatives has been attractive to organic chemists.[1,2] Among the various methods for the synthesis of imine derivatives, dearomatization of aryl amine is expected to be a very promising strategy due to its ability to introduce a three-dimensional ring system from a planar aromatic system.[3−6] In recent decades, dearomatization reactions of aromatics such as benzene,[7] indole,[8] pyridine,[9−11] phenol,[12−15] and pyrrole[16,17] have been widely investigated, which supplied abundant biologically active molecules. However, dearomatization of aryl amines or their derivatives to give imine derivatives has been rarely reported.[18−21] Scanning the literature, we noticed that the chemical transformation of aryl amine derivatives usually gave C−H functionalization products[22,23] or N-containing heterocycles (Scheme 1).[24−26] In this paper, we report the first example of the synthesis of spirocyclic imine derivatives using aryl ureas and internal alkynes as substrates with a palladium-catalyzed dearomatization strategy. This work is an essential complement for diverse chemical transformations of aryl amine derivatives. In contrast to Luan and co-workers' work in the dearomatization of free naphthols with alkynes,[27] a $\beta$-carbon palladation followed by a 1,3-palladium shift mechanism instead of a direct $\alpha$-C−H olefination process was proposed according to experimental results. Aromatic groups could be extended from naphthyl to more stable phenyl groups.

**Scheme 1. Transition-Metal-Catalyzed C−H Functionalization of Aryl Amine Derivatives**




In our recent research on direct C−H *meta*-arylation of aryl ureas with aryl boronic acids, the proposed enamine intermediate inspired us to find an approach to synthesize imine derivatives.[28,29] Based on the electrophilic nature of such an intermediate, diarylacetylene was selected as one of the candidates. Our initial investigation of the reaction between 2-naphthyl urea **1a** and diphenyl acetylene **2a** under specific conditions was quite unsuccessful. Fortunately, after having tried a series of oxidants in the presence of $Pd(OAc)_2$ as the catalyst precursor and $TsOH·H_2O$ as an additive in acetic acid (see Supporting Information (SI)), we noticed the reaction proceeded well and uniquely when benzoquinone (BQ) was used as the oxidant. The product was carefully isolated and characterized by single-crystal X-ray diffraction. We were very delighted to see that a dearomatized product **3aa** was obtained (Table 1). Interestingly, in the structure, the $\beta$-C−H bond adjacent to the directing group seems to be abnormally inert in this reaction. In our continuous condition optimization, we found that the reaction did not proceed in the absence of $TsOH·H_2O$ (entry 1 in Table 1). With 1.0 equiv of $TsOH·H_2O$ as an additive, the yield estimated by $^1H$ NMR was 71% (entry 2). Increasing the stoichiometry of the oxidant to 2.0 equiv slightly decreased the yield. By using a mixture of toluene and HOAc to

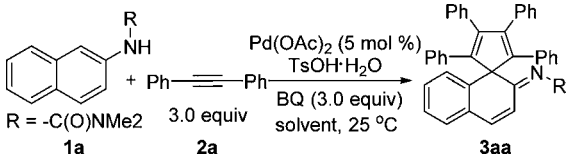
**Received:** February 4, 2016
**Published:** March 2, 2016





DOI: 10.1021/acs.orglett.6b00363
*Org. Lett.* 2016, 18, 1426−1429

**Table 1. Condition Optimization of the C−H Olefination/Dearomatization Reaction**




| entry | TsOH·H2O (equiv) | solvent | $t$ (h) | yield[a] (%) |
|---|---|---|---|---|
| 1 | 0 | HOAc | 12 | ND[b] |
| 2 | 1.0 | HOAc | 4 | 71 |
| 3 | 2.0 | HOAc | 4 | 67 |
| 4 | 2.0 | 1:1 HOAc/toluene | 4 | 53 |
| 5 | 2.0 | 1:1 HOAc/toluene | 4 | 62 |
| 6 | 2.0 | toluene | 4 | 47 |
| 7 | 2.0 | HOAc | 12 | 61 |
| 8 | 1.0 | HOAc | 12 | 73 |
| 9[c] | 1.0 | HOAc | 12 | 90 |

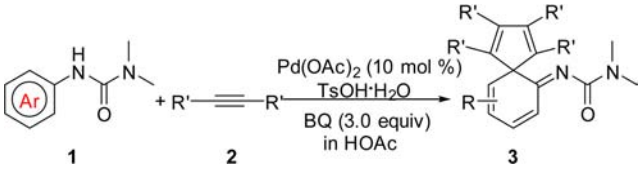
[a]Yields were calculated according to $^1$H NMR using 4-methoxyphenol as internal standard. [b]Not detected. [c]10 mol % of $Pd(OAc)_2$ was used.

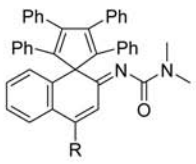
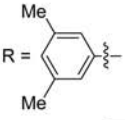
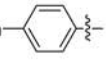
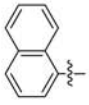
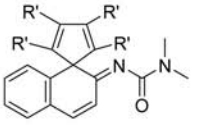
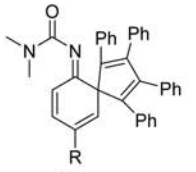
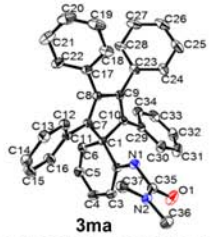
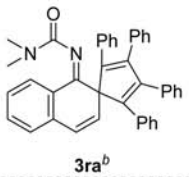
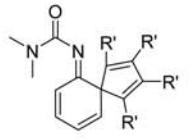
reduce the acidity of the solvent, the yield was also decreased (as estimated by $^1$H NMR in entries 4 and 5). With toluene as the solvent, the yield is only 47% (entry 6). When the reaction time was increased from 4 to 12 h, further conversion of substrate **1a** could not be observed (entry 7 vs 3 and entry 8 vs 2). With an increase of catalyst loading to 10 mol %, the yield was greatly improved to 90% (as estimated by $^1$H NMR). Thus, the reaction was optimally operated using 10 mol % of $Pd(OAc)_2$ as the catalyst precursor, 3.0 equiv of BQ as the oxidant, and 1.0 equiv of $TsOH·H_2O$ as the additive at 25 °C in HOAc under air atmosphere.

In the next step, we investigated the substrate scope of 2-naphthyl ureas. As shown in Table 2, **3aa** was obtained in 81% isolated yield. 4-Phenyl-2-naphthyl urea gave the desired product **3da** in 82% isolated yield. With the methyl group at the *para*-, *ortho*-, or *meta*-position of the phenyl substituent, the corresponding imines **3ea**, **3fa**, and **3ga** could be obtained in 72, 84, and 90% isolated yields, respectively. 4-Methoxyphenyl group substituted substrate gave the corresponding imine **3ha** in a nearly quantitative yield. High yields were also obtained when electron-withdrawing groups such as *para*-F, -Cl, and -Ph were installed on the phenyl group, and **3ia**, **3ja**, and **3ka** were isolated in 80, 85, 83% yields, respectively. 4-(1-Naphthyl) substituted 2-naphthyl urea could convert to imine **3la** in 85% isolated yield. We also tested the scope of acetylenes **2**. 1,2-Di-*p*-tolylethyne and 1,2-bis(4-fluorophenyl)ethyne gave the desired products **3ab** and **3ac** in 65 and 87% isolated yields, respectively. The reaction proceeded very reluctantly when alkyl substituted acetylenes such as 3-hexyne or 1-phenylpropyne were used, and only a detectable amount of product was formed. This phenomenon is consistent with the limitation in the synthesis of indole and benzofuran derivatives in the literature.[24,30]

To further extend the substrate scope, we used other aryl ureas to investigate the C−H olefination/dearomatization behavior. When phenyl urea was used as the substrate, the reaction proceeded smoothly under optimized conditions in the absence of $TsOH·H_2O$, giving the corresponding imine **3ma** in 86% isolated yield. In the case of substituted phenyl ureas, the acidity of the solvent was found to be crucial for this transformation. Toluene with $TsOH·H_2O$ as the additive was proven to be a suitable solvent (see SI), and the reaction proceeded smoothly in

**Table 2. Substrate Scope Investigation of the C−H Olefination/Dearomatization of Aryl Ureas**




| substrates | yield[a] (%) | substituents | yield[a] (%) |
|---|---|---|---|
|  | | **3ga**, R =  | 90 |
| **3aa**, R = H | 81 | **3ha**, R = MeO  | 95 |
| **3da**, R =  | 82 | **3ia**, R = F  | 80 |
| **3ea**, R = Me  | 72 | 3ja, R = Cl  | 85 |
| **3fa**, R =  | 84 | 3ka, R = Ph  | 83 |
| | | **3la**, R =  | 85 |
|  | | **3ab**, R' = Me  | 65 |
| | | **3ac**, R' = F  | 87 |
|  | | **3ma**[b], R = H | 86 |
| | | **3na**[c], R = Cl | 74 |
| | | **3oa**[c], R = $CF_3$ | 72 |
| | | **3pa**[c], R = CN | 74 |
| | | **3qa**[c], R = C(O)Me | 78 |
|  | |  **3ra**[b] | 88 |
|  | | **3mb**[b], R' = *p*-F−Ph- | 82 |
| | | **3mc**[c], R' = *p*-Me−Ph- | 86 |

[a]Isolated yields. [b]In the absence of TsOH. [c]Toluene was used as solvent.

the presence of a series of functional groups such as −Cl, $-CF_3$, −CN, and −C(O)Me. Corresponding products **3na**, **3oa**, **3pa**, and **3qa** were obtained in moderate to good isolated yields. 1-Naphthyl urea was also tested, and the dearomatized product **3ra** was obtained in 88% isolated yield. The scope of alkynes was also



DOI: 10.1021/acs.orglett.6b00363
*Org. Lett.* 2016, 18, 1426−1429

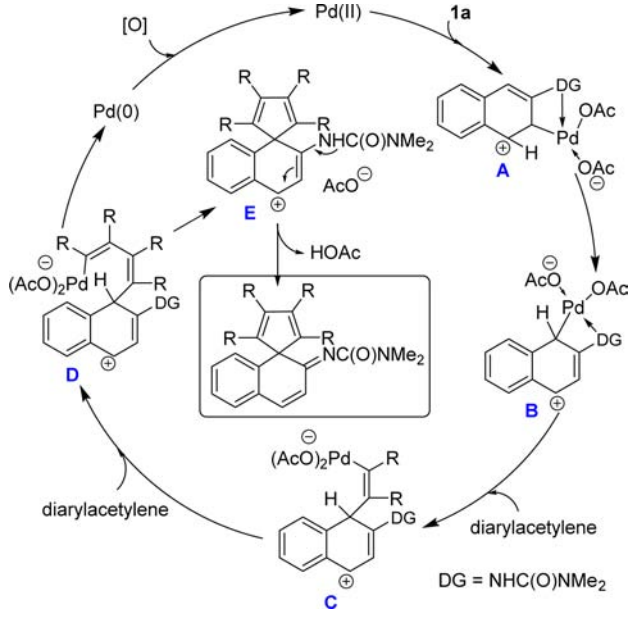
investigated, and substituted diphenyl acetylenes supplied **3mb** and **3mc** in good yields.

To learn about the reaction mechanism, we also tested the reactivity of the 3-position-capped substrate **1b** (Scheme 2). It is

**Scheme 2. Reactivity Investigation of 3- and 3,4-Site-Capped Aryl Ureas with Diphenylacetylene under Optimized Conditions**

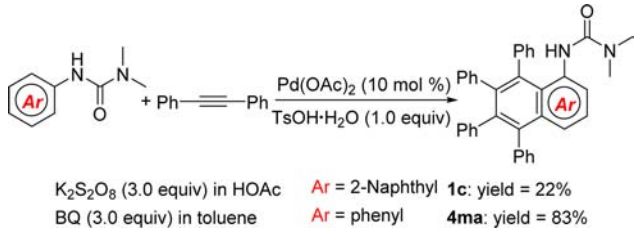

interesting that no desired products **3** were obtained. This result indicates that the $\alpha$-C−H bond cannot undergo a direct olefination/dearomatization reaction in the absence of a $\beta$-C−H bond.[27] Therefore, the only possible pathway to rationalize this information is that there is a 1,3-shift process of palladium in the dearomatized ring system after $\beta$-carbon palladation occurred. Based on this conclusion, a proposed catalytic cycle is depicted in Scheme 3. In the first step of the reaction,

**Scheme 3. Proposed Mechanism**




electrophilic attack of the directing-group-coordinated Pd(OAc)$_2$ to the 3-position of 2-naphthyl urea gives intermediate **A**.[28] A 1,3-shift of the Pd center generates intermediate **B**, which is probably thermodynamically more stable due to the stabilization of the C−Pd bond with an adjacent phenyl group. A sequential alkyne migratory insertion leads to the formation of intermediates **C** and **D**. Pd-catalyzed allyl sp$^3$ C−H olefination gives the spirocyclic intermediate **E** and released Pd(0).[31,32] Deprotonation of **E** gives the final imine derivative, and oxidation of Pd(0) regenerates Pd(II). Alternatively, **B** can also eliminate a molecule of HOAc like **E**, followed by alkyne migratory insertion and annulation to give the final product. The key step in the catalytic cycle is the formation of thermodynamically stable intermediate **B**. However, because intermediate **A** could be converted to the *meta*-arylated product, there should be any kinetic products from such an intermediate. We reinvestigated the reaction using $K_2S_2O_8$ as the oxidant, and we noticed the formation of a side product, which was isolated in 22% yield.[33] After identification with X-ray diffraction (see SI), the product was found to be compound **1c** (Scheme 4), which was consistent

**Scheme 4. Fused Ring Product Formation**




with our expectation according to the structure. It should be mentioned that **1c** could not be converted to spirocyclic imine either (Scheme 2). When phenyl urea was used as the substrate, the thermodynamic stabilities of **A** and **B** were compatible due to the absence of a phenyl group. Therefore, the fused ring products could be formed competitively. We found that **4ma** was formed exclusively in 83% isolated yield when 1.0 equiv of TsOH·$H_2O$ was used as an additive under the optimized condition (Scheme 4).

In summary, we have reported the first example for the synthesis of imine derivatives using aryl urea and diarylacetylene as substrates via a palladium(II)-catalyzed *ortho*-C−H olefination/dearomatization reaction. A series of aryl ureas could be transformed into the corresponding imine derivatives in good to excellent yields. A rationalized mechanism was proposed to shed light on the product formation. Fused ring products were also obtained to further prove the proposed intermediate.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00363.

Experimental procedures (PDF)
X-ray data for **1c** (CIF)
X-ray data for **3aa** (CIF)
X-ray data for **3ma** (CIF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: wangqifeng@jlu.edu.cn.

### Author Contributions

§P.J. and Y.X. contributed equally.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (No. 21202060), Key Scientific and Technological Project in Jilin Province (No. 20140204041GX), and Creative Program in Jilin University (Nos. 336OEP01, 336OEP06).



DOI: 10.1021/acs.orglett.6b00363
*Org. Lett.* 2016, 18, 1426−1429

## REFERENCES


(1) Layer, R. W. *Chem. Rev.* **1963**, *63*, 489−510.
(2) Huang, L. B.; Arndt, M.; Goossen, K.; Heydt, H.; Goossen, L. J. *Chem. Rev.* **2015**, *115*, 2596−2697.
(3) Lopez Ortiz, F.; Iglesias, M. J.; Fernandez, I.; Andujar Sanchez, C. M.; Ruiz Gomez, G. *Chem. Rev.* **2007**, *107*, 1580−1691.
(4) Roche, S. P.; Porco, J. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068−4093.
(5) Zhuo, C. X.; Zhang, W.; You, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 12662−12686.
(6) Zhuo, C. X.; Zheng, C.; You, S. L. *Acc. Chem. Res.* **2014**, *47*, 2558−2573.
(7) Liu, L. T.; Wang, Z. H.; Zhao, F.; Xi, Z. F. *J. Org. Chem.* **2007**, *72*, 3484−3491.
(8) Luo, J.; Wu, B.; Chen, M. W.; Jiang, G. F.; Zhou, Y. G. *Org. Lett.* **2014**, *16*, 2578−2581.
(9) Wang, S. G.; You, S. L. *Angew. Chem., Int. Ed.* **2014**, *53*, 2194−2197.
(10) Sun, Z. K.; Yu, S. Y.; Ding, Z. D.; Ma, D. W. *J. Am. Chem. Soc.* **2007**, *129*, 9300−9301.
(11) Mousseau, J. J.; Fortier, A.; Charette, A. B. *Org. Lett.* **2010**, *12*, 516−519.
(12) Zheng, J.; Wang, S. B.; Zheng, C.; You, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 4880−4883.
(13) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 404−405.
(14) Seoane, A.; Casanova, N.; Quinones, N.; Mascarenas, J. L.; Gulias, M. *J. Am. Chem. Soc.* **2014**, *136*, 7607−7610.
(15) Mulcahy, J. V.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 12630−12631.
(16) Wu, K. J.; Dai, L. X.; You, S. L. *Chem. Commun.* **2013**, *49*, 8620−8622.
(17) Wang, D. S.; Ye, Z. S.; Chen, Q. A.; Zhou, Y. G.; Yu, C. B.; Fan, H. J.; Duan, Y. *J. Am. Chem. Soc.* **2011**, *133*, 8866−8869.
(18) Wang, L. F.; Fan, R. H. *Org. Lett.* **2012**, *14*, 3596−3599.
(19) Quideau, S.; Pouysegu, L.; Ozanne, A.; Gagnepain, J. *Molecules* **2005**, *10*, 201−216.
(20) Bedford, R. B.; Butts, C. P.; Haddow, M. F.; Osborne, R.; Sankey, R. F. *Chem. Commun.* **2009**, 4832−4834.
(21) Garcia-Fortanet, J.; Kessler, F.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 6676−6677.
(22) Shi, Z. J.; Li, B. J.; Wan, X. B.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C. M.; Wang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5554−5558.
(23) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593−1597.
(24) Shi, Z. Z.; Zhang, C.; Li, S.; Pan, D. L.; Ding, S. T.; Cui, Y. X.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572−4576.
(25) Stuart, D. R.; Bertrand-Laperle, M.; Burgess, K. M. N.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 16474−16745.
(26) Wurtz, S.; Rakshit, S.; Neumann, J. J.; Droge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230−7233.
(27) Gu, S. L.; Luo, L.; Liu, J. J.; Bai, L.; Zheng, H. Y.; Wang, Y. Y.; Luan, X. J. *Org. Lett.* **2014**, *16*, 6132−6135.
(28) Jiang, P.; Li, F.; Xu, Y.; Liu, Q.; Wang, J.; Ding, H.; Yu, R.; Wang, Q. *Org. Lett.* **2015**, *17*, 5918−5921.
(29) Zhang, J. C.; Liu, Q. W.; Liu, X. F.; Zhang, S. Q.; Jiang, P. P.; Wang, Y. X.; Luo, S. Y.; Li, Y.; Wang, Q. F. *Chem. Commun.* **2015**, *51*, 1297−1300.
(30) Zhu, R. Y.; Wei, J. B.; Shi, Z. J. *Chem. Sci.* **2013**, *4*, 3706−3711.
(31) Li, S. H.; Chen, G.; Feng, C. G.; Gong, W.; Yu, J. Q. *J. Am. Chem. Soc.* **2014**, *136*, 5267−5270.
(32) Wasa, M.; Engle, K. M.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680−3681.
(33) Wu, J. L.; Cui, X. L.; Mi, X.; Li, Y.; Wu, Y. J. *Chem. Commun.* **2010**, *46*, 6771−6773.




DOI: 10.1021/acs.orglett.6b00363
*Org. Lett.* 2016, 18, 1426−1429