Chemodivergent Oxidative Annulation of Benzamides and Enynes via 1,4-Rhodium Migration

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ABSTRACT: Chemodivergent annulative couplings have been realized between N-methoxy benzamides and 1,3-enynes via Rh-catalyzed C−H activation and 1,4-Rh migration. Under Rh/copper catalyzed aerobic conditions, the nitrogen annulation occurred as the major pathway. The chemoselectivity was switched to the oxygen annulation under proper condition control with stoichiometric amounts of Cu(II) oxidant and NaOAc. Both coupling systems proceeded with a broad scope and functional group tolerance.

Scheme 1. Annulation via NH-Directed C−H Activation

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Received: January 28, 2019

DOI: 10.1021/acs.orglett.9b00363
Org. Lett. XXX, XXX, XXX−XXX

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Furthermore, the hindered site (substituted benzamides took place regioselectively at the less extendable to a thiophene group, albeit with reduced effect). The (hetero)arene ring was also functionalization of meta-substituted benzamides took place when treated with Mo(CO)₆, together with catalyzed hydrogenation of 3aa in high yield. Interestingly, reductive cleavage of the N-Ome bond in 3aa took place when treated with Mo(CO)₆, together with formal metathesis between the Mo=CO and terminal C=CH₂ bond, delivering an enone in 74% yield. Treatment of 3aa with LAH/AlCl₃ afforded the deoxygenation product in 74% yield.

This observation bodes well for development of a general approach to access iminolactones via switch of chemoselectivity. After extensive studies of the coupling of benzamide 1a and enyne 2a (see Table S1 in the Supporting Information), it was found that introduction of stoichiometric amounts of Cu(OAc)₂ (2.0 equiv) and NaOAc (2.0 equiv) favored formation of the iminolactone 4aa, and a good isolated yield (74%) was realized with 1,4-dioxane as the solvent although a small amount of the lactam product was still isolated. The generality of this iminolactone synthesis was next explored (Scheme 3). Benzamides bearing electron-donating, electron-drawing, and halogen groups at the dia, ortho, meta, and para positions were all viable substrates, and the yields were generally moderate to good. In addition, similar observations of functional group tolerance were also made with respect to the N-alloxy groups and the 1,3-ene coupling partner. In all cases, the iminolactone was the major product, with the lactam isomeric product being isolated typically in 20% yield.

Synthetic applications of a coupled product 3aa have been demonstrated in derivatization reactions (Scheme 4). Pd/C-catalyzed hydrogenation of 3aa afforded alkyl product 5 in high yield. Interestingly, reductive cleavage of the N-Ome bond in 3aa took place when treated with Mo(CO)₆, together with formal metathesis between the Mo=CO and the terminal C=CH₂ bond, delivering an enone in 74% yield. Treatment of 3aa with LAH/AlCl₃ afforded the deoxygenation product 7 in excellent yield.

The mechanism of the annulative coupling systems has been explored in a series of experimental studies (Scheme 5). H/D exchange studies under both conditions A and B revealed noticeable deuteration at the ortho’ position of products 3aa-₃₁, 3aa-₃₂, 4aa-₄₁, and 4aa-₄₂, respectively, suggesting reversibility of the ortho
C–H activation (Scheme 5a). In addition, an olefinic C–H site also underwent deuteration (14% D) under the conditions B, which suggests relevancy of 1,4-rhodium migration. To explore this C–H activation process, KIE has been studied under both coupling conditions. It follows that the lactam formation proceeded with a rather large KIE value, while the iminolactone formation proceeded with C–H activation not being involved in the turnover-determining step. Consequently, different reaction mechanisms are probably followed.

To delve into the controlling factors governing the selectivity of these systems, control experiments have been performed. It was found that the coupling of 1a and 2a under conditions A but in the presence of a stoichiometric amount of NaOAc afforded a mixture of 3aa (70%) and 4aa (20%). This observation, together with the observation of the switch of chemoselectivity of benzamide 1i (eq 1), strongly suggested correlation of iminolactone 1i with an external acetate group. Consequently, to maintain 18-electron count, the putative Rh(III) allyl moiety undergoes η3 to η1 rearrangement. Control experiments have also been performed to confirm no interconversion between 3aa and 4aa under the complementary reaction conditions.

On the basis of the experimental results and Lam’s previous reports, plausible reaction pathways are proposed in Scheme 6. Cyclometalation of benzamide 1a gives a rhodacyclic intermediate A, which undergoes regioselective migratory insertion into the alkyne unit to afford Rh(III) alkenyl B. Subsequent 1,4-Rh migration gives a Rh(III) η1 alleyl species C. In the presence of an access of NaOAc (conditions B), acetate coordination triggers allyl rearrangement to the η1 intermediate D. The intermediate D′ is proposed to undergo C–O reductive elimination to deliver product 4aa. This reductive elimination takes place as the major pathway likely because the oxygen coordination is sterically favored. Under the conditions A, the allyl intermediate D is proposed to undergo nucleophilic (internal or external) attack of the softer amide nitrogen at the η3 to produce 3aa together with a Rh(I) reductive intermediate, the reoxidation of which by Cu(II) then regenerates the active Rh(III) catalyst for the next cycle.

In summary, we have realized chemodivergent annulative couplings between N-methoxy benzamides and 1,3-enynes. Under Rh/copper catalyzed aerobic conditions, the nitrogen annulation occurred as the major pathway. In contrast, the annulation selectivity was switched to oxygen annulation under proper condition control. A broad scope of substrates has been defined for each coupling system. The flexibility of N versus O participation as a nucleophilic directing group is rather rare and may provide insight into development of important
systems that highlight the versatility of high valent-metal catalyzed C–H bond activation.

**ASSOCIATED CONTENT**

# Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00363.

Experimental procedures, spectral data of new compounds, and crystallographic data of 4aa (PDF)

**Accession Codes**

CCDC 1888533 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

We acknowledge the financial support for this work from the National NSF of China (21525208) and the Shaanxi Normal University.

**REFERENCES**

(1) (a) Sambiagio, C.; Schönbauer, D.; Bieleck, R.; Dao-Huy, T.; Potońschig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, T.; Besser, T.; Maes, B. U. W.; Schnürch, M. Chem. Soc. Rev. 2018, 47, 6603. (b) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. Chem. Rev. 2017, 117, 9333. (c) Park, Y.; Kim, Y.; Chang, S. Chem. Rev. 2017, 117, 9247. (d) Hummel, J. R.; Boerth, J. A.; Ellman, J. A. Chem. Rev. 2017, 117, 9163. (e) Yang, Y.; Lan, J.; You, J. Chem. Rev. 2017, 117, 8787. (f) Mishra, N. K.; Sharma, S.; Park, J.; Han, S.; Kim, I. S. Acc. Chem. Res. 2017, 50, 351. (g) Wang, F.; Yu, S.; Li, X. Chem. Soc. Rev. 2016, 45, 6462. (h) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J.; Besser, T.; Maes, B. U. W.; Schnürch, M. Chem. Soc. Rev. 2018, 47, 6603. (k) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. Chem. Rev. 2017, 117, 9333.

(2) (a) Yang, Y.; Li, Y.; Cheng, Y.; Wan, D.; Li, M.; You, J. Chem. Commun. 2016, 52, 2872. (b) Ye, B.; Cramer, N. Acc. Chem. Res. 2015, 48, 1308. (c) Kuhl, N.; Schröder, N.; Glorius, F. Adv. Synth. Catal. 2014, 356, 1443. (d) Song, G.; Li, X. Acc. Chem. Res. 2015, 48, 1007. (e) Colby, D. A.; Tsal, A. S.; Bergman, R. G.; Ellman, J. A. Acc. Chem. Res. 2012, 45, 814. (f) Satoh, T.; Miura, M. Chem. - Eur. J. 2010, 16, 11212. (g) Song, G.; Wang, F.; Li, X. Chem. Soc. Rev. 2012, 41, 3651.

(3) (a) Bai, D.; Xu, T.; Ma, C.; Zheng, X.; Liu, B.; Xie, F.; Li, X. Acc. Catal. 2018, 8, 4194. (b) Xie, F.; Yu, S.; Qi, Z.; Li, X. Angew. Chem., Int. Ed. 2016, 55, 153. (c) Sun, H.; Huang, Y. Synlett 2015, 26, 2751.

(4) (a) Fukui, Y.; Liu, P.; Liu, Q.; He, Z.-T.; Wu, N.-Y.; Tian, P.; Lin, G.-Q. J. Am. Chem. Soc. 2014, 136, 15607. (b) Yu, S.; Tang, G.; Li, Y.; Zhou, X.; Lan, Y.; Li, X. Angew. Chem., Int. Ed. 2016, 55, 8696.

(5) (a) Xingwei Li: 0000-0002-1153-1558

(6) (a) Ackermann, L. Acc. Chem. Res. 2014, 47, 281. (b) He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang, C. Tetrahedron Lett. 2014, 55, 5705. (c) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. Angew. Chem., Int. Ed. 2011, 50, 1338.

(7) (a) Ma, S.; Gu, Z. Angew. Chem., Int. Ed. 2005, 44, 7512. (b) Shi, F.; Larock, R. C. Tep.Curr. Chem. 2009, 292, 125. (c) Kesharwani, T.; Verma, A. K.; Emrich, D.; Ward, J. A.; Larock, R. C. Org. Lett. 2009, 11, 2591.

(8) (a) Partridge, B. M.; Callingham, M.; Lewis, W.; Lam, H. W. Angew. Chem., Int. Ed. 2017, 56, 7227. (b) Dooley, J. D.; Lam, H. W. Angew. Chem. - Eur. J. 2014, 24, 4050. (c) Callingham, M.; Partridge, B. M.; Lewis, W.; Lam, H. W. Angew. Chem., Int. Ed. 2017, 56, 16352.

(9) (a) Lu, Q.; Cembellín, S.; Greiβle, S.; Singha, S.; Daniluc, C. G.; Glorius, F. Angew. Chem., Int. Ed. 2018, 57, 1399.

(10) (a) Partridge, B. M.; Callingham, M.; Lewis, W.; Lam, H. W. Angew. Chem., Int. Ed. 2017, 56, 7227. (b) Dooley, J. D.; Lam, H. W. Angew. Chem. - Eur. J. 2014, 24, 4050. (c) Callingham, M.; Partridge, B. M.; Lewis, W.; Lam, H. W. Angew. Chem., Int. Ed. 2017, 56, 16352.

(11) (a) Lu, Q.; Cembellín, S.; Greiβle, S.; Singha, S.; Daniluc, C. G.; Glorius, F. Angew. Chem., Int. Ed. 2018, 57, 1399.
Considering the oxidative ability of N-methoxy benzamide and N-(pivaloyloxy)-benzamide, we performed the coupling of N-methoxy benzamide/N-(pivaloyloxy)-benzamide with 1,3-enynes under redox-neutral conditions. We failed to obtain any [4 + 1]-type annulation product.

The identity of the iminolactone correlates with the characteristic C≡N and the quaternary alkyl signals in 13C NMR spectroscopy.

For discrepancy of mechanisms of allylic coupling with hard and soft nucleophiles, see: (a) Trost, B. M.; Thaisrivong, D. A. J. Am. Chem. Soc. 2008, 130, 14092. (b) Trost, B. M. Chem. Rev. 1996, 96, 395.