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Letter

Unexpected Insertion of Nitrogen into a C−C Bond: Access to 2,3-Disubstituted Quinazolinone Scaffolds

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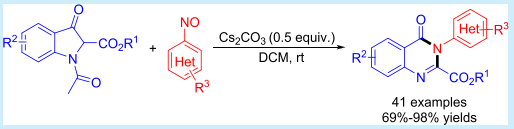
ABSTRACT: A novel, practical, highly efficient, and transition metal free nitrogen insertion reaction for the synthesis of 2,3-disubstituted quinazolinone derivatives was developed. Diverse functionalized 3-indolinone-2-carboxylates and nitrosoarenes with a wide range of substituted nitrosobenzenes, nitrosopyridines, dibenzofuranyl, or dibenzothienyl nitroso compounds worked smoothly to give 2,3-disubstituted quinazolinone derivatives in good to excellent yields (69−98%). A gram-scale reaction was achieved, and an afloqualone analogue was synthesized under the mild reaction conditions.



Quinazolinone structural units are widespread in natural products and synthetic pharmaceuticals.[1] As shown in Figure 1, tryptanthrin and sclerotigenin are the natural alkaloids that incorporate quinazolinone motifs with significant biological activities.[2] Afloqualone is a commercial oral muscle relaxant drug.[3] Idelalisib is used as a PI3Kδ inhibitor and has been approved for the treatment of relapsed chronic lymphocytic leukemia (CLL).[4] Raltiterxed is a clinical medication for the treatment of colorectal cancer.[5] Due to the prospects for application, continuous effort has been spent to develop new methodologies for the construction of quinazolinone derivatives.[6] In addition to the traditional formation of quinazolinones via Niementowski reaction[7] and cyclocondensation and cascade reactions,[8] other strategies such as methods involving a transition matel catalyst or an oxidant have emerged in recent years.[9] For instance, the copper- or palladium-catalyzed N-arylation reactions of N-substituted *o*-bromobenzamides or *o*-bromobenzoates with various benzylamines,[10] amides,[11] or amidines[12] were reliable protocols for obtaining 2,3-disubstituted quinazolinones. The N-substituted anthranilamides with aldehydes,[13] alcohols,[14] methylarenes,[15] or (*o*-azaaryl)methanes[16] through oxidative heterocyclizations or amination of the sp^3 C−H bond to synthesize 2,3-disubstituted quinazolinones were applied successfully. Alper and Wu described palladium-catalyzed cyclocarbonylation to give 2,3-disubstituted quinazolinones.[17] Deng and Chu developed the hydrogen transfer reaction of N-substituted *o*-nitrobenzamides with benzylic alcohols under iron or ruthenium catalysis.[18] Chiba and co-workers described transition metal free access to 2,3-disubstituted quinazolinones utilizing 5-aryl-4,5-dihydro-1,2,4-oxadiazoles in the presence of O_2.[19] From the viewpoint of the construcaton of 2,3-disubstituted quinazolinones, transition metal free, concise, and elegant strategies are still in great demand.

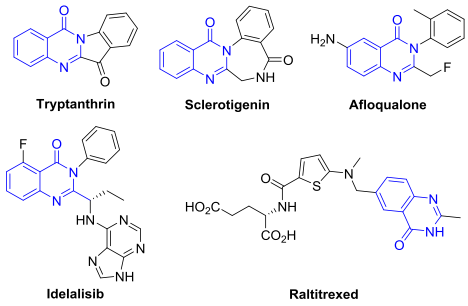


Figure 1. Bioactive quinazolinone scaffolds.

The Michael, aza-Michael, and Robinson annulation reactions of 3-indolinone-2-carboxylates with nitroolefins,[20] azodicarboxylates,[21] and cyclohexenone[22] have been reported extensively in recent years. However, the nitrogen insertion reaction of 3-indolinone-2-carboxylates remains unexplored, although insertion of nitrogen into a carbon−carbon bond as a key step has been demonstrated as a powerful strategy for the preparation of heterocyclic or carbocyclic compounds.[23] Herein, we disclose an interesting and unexpected nitrogen insertion reaction to afford 2,3-disubstituted quinazolinones.

Initially, methyl 1-acetyl-3-oxoindoline-2-carboxylate **3a** and nitrosobenzene **4a** were examined as the reactants in the presence of a catalytic amount of DABCO in DCM at room temperature. To our delight, the reaction proceeded effectively, affording the desired 2,3-disubstituted quinazolinones **5aa** in 82% yield (Table 1, entry 1). With an increase in the amount of DABCO, a slight enhancement of the yields was detected (entries 2 and 3 vs entry 1). Subsequently, by screening various

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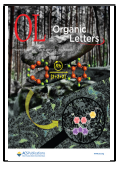

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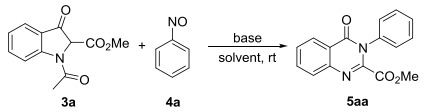
Table 1. Optimization of Reaction Conditions[a]



3a 4a 5aa

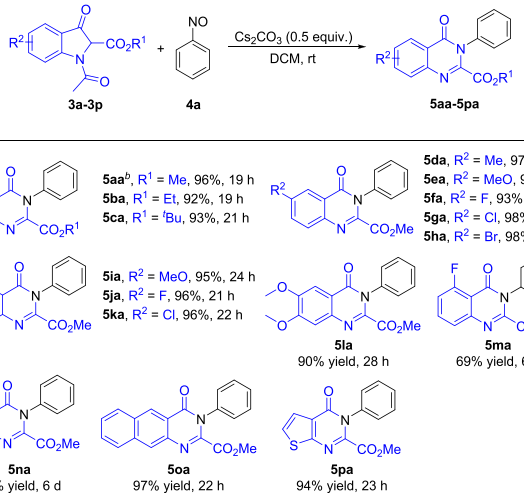
entry	base	solvent	yield (%)[b]
1[c]	DABCO[d]	DCM	82
2	DABCO	DCM	87
3[e]	DABCO	DCM	87
4[f]	DMAP	DCM	76
5[f]	Et_3N	DCM	78
6[f]	DIPEA	DCM	76
7[f]	DBU	DCM	91
8	K_2CO_3	DCM	75
9	Cs_2CO_3	DCM	96
10	Cs_2CO_3	$CHCl_3$	94
11	Cs_2CO_3	DCE[g]	90
12	Cs_2CO_3	THF	81
13	Cs_2CO_3	MTBE[h]	44
14	Cs_2CO_3	toluene	21
15	Cs_2CO_3	CH_3CN	87
16[i]	Cs_2CO_3	DCM	96
17[j]	Cs_2CO_3	DCM	96
18[k]	Cs_2CO_3	DCM	92

[a]Reaction conditions: **3a** (0.10 mmol), **4a** (0.15 mmol), and base (0.5 equiv) in the indicated solvent (0.5 mL) at rt for 22 h, unless otherwise noted. [b]Isolated yield of product **5aa**. [c]With 0.2 equiv of DABCO. [d]DABCO = 1,4-diazabicyclo[2.2.2]octane. [e]With 1.0 equiv of DABCO. [f]With 1.0 equiv of base. [g]DCE = 1,2-dichloroethane. [h]MTBE = methyl *tert*-butyl ether. [i]With 1.3 equiv of **4a**. [j]With 1.2 equiv of **4a**. [k]With 1.1 equiv of **4a**.

bases such as DMAP, Et_3N, DIPEA, DBU, K_2CO_3, and Cs_2CO_3 (entries 4–9, respectively), we found that Cs_2CO_3 was the best choice, giving product **5aa** in 96% yield (entry 9). Different solvents such as $CHCl_3$, DCE, THF, MTBE, toluene, and acetonitrile were tested with Cs_2CO_3 as the base (entries 10–15, respectively). The results revealed that the reaction yields apparently reduction when MTBE or toluene was used as the solvent (entry 13 or 14, respectively). To further improve the reaction efficiency, the ratios of nitrosobenzene **4a** and **3a** were investigated (entries 16–18). The yields of product **5aa** could be maintained when the amount of nitrosobenzene **4a** was decreased to 1.2 equiv of **3a** (entry 17). Finally, the optimal reaction conditions were found to be **3a** (0.1 mmol), **4a** (0.12 mmol), and Cs_2CO_3 (0.5 equiv) as the base in DCM at room temperature for 22 h, affording product **5aa** in 96% yield.

With the optimal conditions in hand, the substrate scope of the nitrogen insertion reaction was examined. As shown in Scheme 1, a series of 2,3-disubstituted quinazolinones could be obtained in good to excellent yields. We found that ethyl (**3b**) or *tert*-butyl (**3c**) ester proceeds with an efficiency similar to that of **3a**, giving products **5ba** and **5ca** in 92% and 93% yields, respectively. Regardless of whether electron-donating or electron-withdrawing groups were at position 5 or 6 of 3-oxoindolines, the corresponding 2,3-disubstituted quinazolinones (**5da**–**5ka**) were efficiently obtained in excellent yields (93–98%). In the case of 4-fluorine and 7-methyl derivatives (**3m** and **3n**, respectively) as the reactants, because of the effect of steric hindrance, the nitrogen insertion reaction required longer times and afforded products **5ma** and **5na** in relatively low yields (69% and 85%, respectively). Upon

Scheme 1. Scope of the Reactions of 3-Indolinone-2-carboxylates[a]



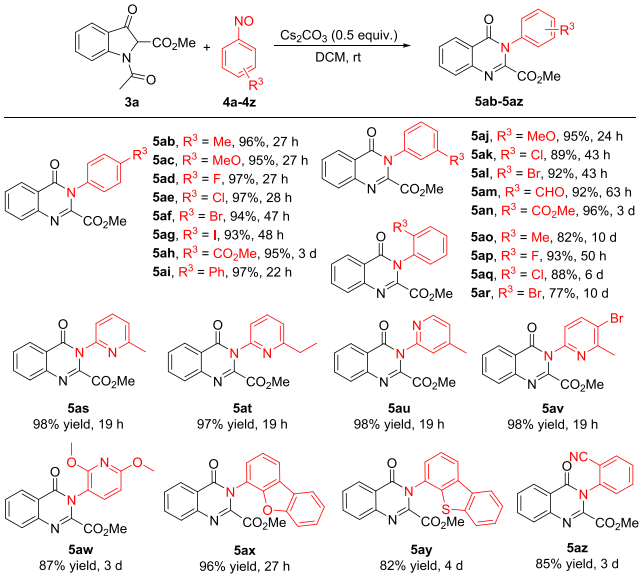
3a-3p 4a 5aa-5pa

[a]Reaction conditions: **3a**–**3p** (0.40 mmol), **4a** (0.48 mmol), and Cs_2CO_3 (0.20 mmol) in DCM (2.0 mL) at rt for the determined time. [b]X-ray of **5aa**.

application of heteroaromatic and polyaromatic fused compounds **3p** and **3o** to the reaction conditions presented here, the reaction gave the desired products **5pa** and **5oa** in 94% and 97% yields, respectively.

To further estimate the efficiency of the methodology, a wide range of nitroso compounds were applied using this strategy. As described in Scheme 2, the nitrogen insertion reactions of nitrosoarenes with diverse substituents at the *para* or *meta* position of the phenyl ring afforded the corresponding products **5ab**–**5an** in 89–97% yields. It is worth mentioning that reactants bearing a strong electron-witdrawing substituent like an ester group or a formyl group on the aromatic ring demanded longer times to complete the reaction. The reaction

Scheme 2. Scope of the Reactions of Nitrosoarenes[a]



3a 4a-4z 5ab-5az

[a]Standard reaction conditions: **3a** (0.40 mmol), **4a**–**4z** (0.48 mmol), and Cs_2CO_3 (0.20 mmol) in DCM (2.0 mL) at rt for the determined time.

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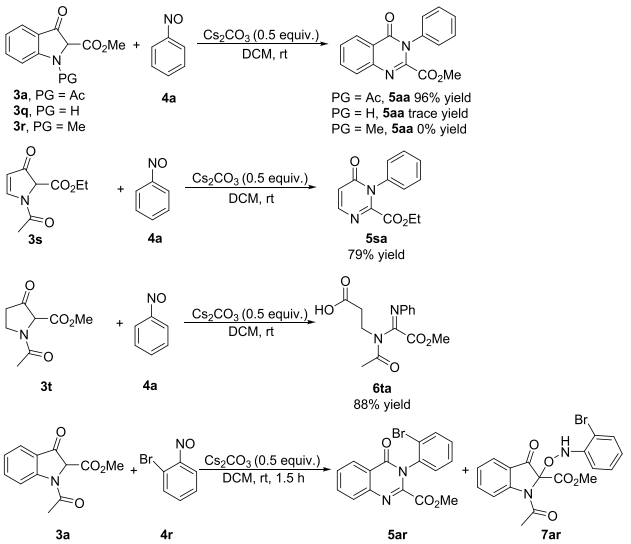
yields and times were sensitive to the steric hindrance of the substituents on the nitrosoarenes. The introduction of methyl, chlorine, bromine, and cyano at the *ortho* position of the nitrosoarene aromatic rings led to decreases in the yields of the corresponding products **5ao**−**5ar** and **5az**. To expand the reactant scope of the nitrogen insertion reaction, we paid attention to nitrosoheteroaryl compounds. A series of monosubstituted or disubstituted nitrosopyridines could also perform well in the reaction system, giving products **5as**−**5aw** in 87−98% yields. In addition, in the case of dibenzofuranyl and dibenzothienyl nitroso compounds were applied under the standard reaction conditions, and the reaction proceeded smoothly giving products **5ax** and **5ay** in 96% and 82% yields, respectively.

To illustrate the reaction mechanism, control experiments were conducted. As mentioned above, substrate **3a** bearing an acyl group on the nitrogen worked well with nitrosobenzene **4a** under the standard reaction conditions, giving product **5aa** in 96% yield. However, unprotected 3-oxoindoline **3q** afforded only a trace of **5aa**, and *N*-methyl-protected 3-oxoindoline **3r** did not afford product **5aa** (as shown in Scheme 3). The

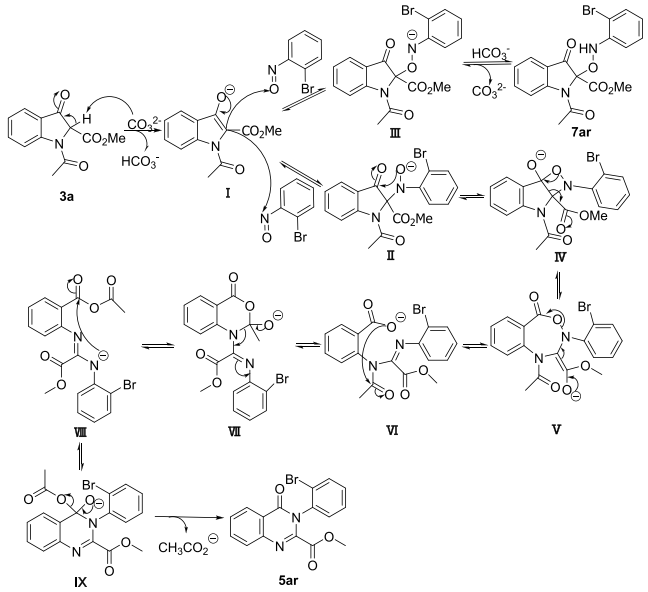
Scheme 3. Control Experiments



results of the reaction indicated that no protection group and the methyl protection group were not compatible for the nitrogen insertion reaction. To further explore the mechanism of the reaction, we synthesized compounds **3s** and **3t**.[24] Substrate **3s** provided nitrogen insertion product **5sa** in 79% yield, and reactant **3t** gave ring-opening compound **6ta** in 88% yield under the standard reaction conditions. These results hinted that the conjugated structure was vital in the process of ring closure. Furthermore, when substrate **3a** reacted with *o*-bromonitrosobenzene **4r** under the optimized reaction condition for 1.5 h, compound **7ar** and product **5ar** were detected. It is worth mentioning that if compound **7ar** is left for a long time, it could convert into ring expansion product **5ar** but with a dramatic decrease in the yield. The configurations of **5sa**, **6ta**, and **7ar** were confirmed by X-ray diffraction analysis.

A possible reaction mechanism was proposed on the basis of the results of control experiments, as depicted in Scheme 4. Initially, enolization of substrate **3a** was achieved in the presence of Cs_2CO_3. Subsequently, the enolate anion of **3a** N-

Scheme 4. Proposed Reaction Mechanism

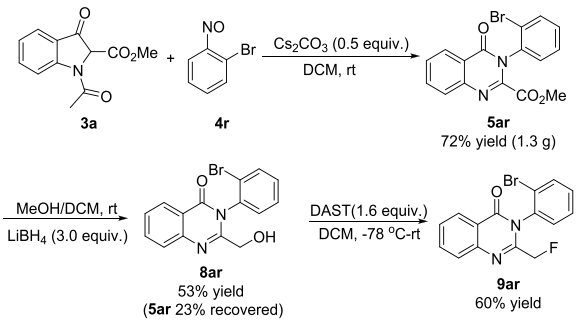


selectively attacked nitrosoarene. Meanwhile, the O-addition product perhaps existed. In particular, when *o*-bromonitrosobenzene was involved in the reaction, compound **7ar** could be detected, separated and verified by X-ray diffraction, because of the stetric hindrance. Because compound **7ar** did not convert into a stable product and the addition reaction was reversible, **7ar** could revert to the original materials, and the substrate underwent the N-selective addition reaction again. Intermediate **II** could transform into **VI** through O-nucleophilic addition, and cleavage of the C2−C3 and N−O bonds. Complex **VI** underwent an addition−elimination reaction that led to the formation of amidine compound **VIII**. Afterward, the intramolecular substitution reaction of anhydride and amidine in **VIII** afforded the desired compound **5ar**.

To investigate the efficiency and practical utility of this method, a gram-scale reaction of **3a** and *o*-bromonitrosobenzene **4r** was carried out under the standard conditions, providing desired product **5ar** in 72% yield. Furthermore, the transformation of **5ar** is depicted in Scheme 5. The ester group of **5ar** could be selectively reduced by treatment with $LiBH_4$, giving reduction product **8ar** in 53% yield.[25] Subsequently, **8ar** was treated with the DAST reagent, affording afloqualone analogue **9ar** in 60% yield.[26]

In conclusion, we have demonstrated a highly efficient and convenient nitrogen insertion reaction for the preparation of

Scheme 5. Gram-Scale Synthesis of 5ar Followed by Transformation



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2,3-disubstituted quinazolinones from 3-indolinone-2-carboxylates and nitrosoarenes with Cs_2CO_3 as the base. The reaction proceeded smoothly under mild reaction conditions and was free of transition metals, oxidants, and peroxide. 3-Indolinone-2-carboxylates containing diverse functional groups worked well with nitrosobenzene, giving products **5aa**−**5pa** in moderate to excellent yields (69−98%). A wide range of nitroso compounds were compatible with the reaction, affording desired products **5ab**−**5az** in good to excellent yields (77−98%). Further development of this methodology is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01235.

Experimental details, characterization data, spectral data, and a description of the crystallographic data (PDF)

Accession Codes

CCDC 2075789−2075792 and 2084083 contain 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 emailing data_request@ccdc.cam.ac.uk, 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.

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■ REFERENCES

(1) (a) Khan, I.; Ibrar, A.; Ahmed, W.; Saeed, A. Synthetic approaches, functionalization and therapeutic potential of quinazoline and quinazolinone skeletons: The advances continue. *Eur. J. Med. Chem.* **2015**, *90*, 124−169. (b) Kshirsagar, U. A. Recent developments in the chemistry of quinazolinone alkaloids. *Org. Biomol. Chem.* **2015**, *13*, 9336−9352.

(2) Khan, I.; Ibrar, A.; Abbas, N.; Saeed, A. Recent advances in the structural library of functionalized quinazoline and quinazolinone scaffolds: Synthetic approaches and multifarious applications. *Eur. J. Med. Chem.* **2014**, *76*, 193−244.

(3) Ochiai, T.; Ishida, R. Pharmacological studies on 6-amino-2-fluoromethyl-3-(o-tolyl)-4(3H)-quinazolinones (afloqualone), a new centrally acting muscle relaxant. (II). Effects on the spinal reflex potential and rigidity. *Jpn. J. Pharmacol.* **1982**, *32*, 427−438.

(4) Kost, S. E. F.; Saleh, A.; Mejia, E. M.; Mostafizar, M.; Bouchard, E. D. J.; Banerji, V.; Marshall, A. J.; Gibson, S. B.; Johnston, J. B.; Katyal, S. Transcriptional Modulation by Idelalisib Synergizes with Bendamustine in Chronic Lymphocytic Leukemia. *Cancers* **2019**, *11*, 1519−1537.

(5) Chaudhary, A. P.; Shukla, A. K.; Pandey, J.; Kant, P. Study of developments of biologically active Quinazolinones derivatives: A review. *Chem. Biol. Interface* **2018**, *8*, 62−83.

(6) (a) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. Synthesis of quinazolinones and quinazolines. *Tetrahedron* **2005**, *61*, 10153−10202. (b) He, L.; Li, H.; Chen, J.; Wu, X.-F. Recent advances in 4(3H)-quinazolinone syntheses. *RSC Adv.* **2014**, *4*, 12065−12077.

(7) (a) Pereira, M.-F.; Picot, L.; Guillon, J.; Léger, J.-M.; Jarry, C.; Thiéry, V.; Besson, T. Efficient synthesis of novel pentacyclic 6,7-dihydro-5a,7a,13,14-tetraaza-pentaphene-5,8-diones. *Tetrahedron Lett.* **2005**, *46*, 3445−3447. (b) de Fatima Pereira, M.; Thiéry, V.; Besson, T. Synthesis of novel 2,3-substituted quinazolin-4-ones by condensation of alkyl or aromatic diamines with 5-(*N*-arylimino)-4-chloro-5H-1,2,3-dithiazoles. *Tetrahedron* **2007**, *63*, 847−854. (c) Kabri, Y.; Gellis, A.; Vanelle, P. Microwave-assisted synthesis in aqueous medium of new quinazoline derivatives as anticancer agent precursors. *Green Chem.* **2009**, *11*, 201−208.

(8) (a) Lecoutey, C.; Fossey, C.; Rault, S.; Fabis, F. Efficient Room-Temperature One-Pot Synthesis of 2-Amino-3-alkyl(3-aryl)-quinazolin-4(*3H*)-ones. *Eur. J. Org. Chem.* **2011**, *2011*, 2785−2788. (b) Liu, T.; Zhu, C.; Yang, H.; Fu, H. Copper-Catalyzed Domino Synthesis of Isoquinolino[2,3-*a*]quinazolinones. *Adv. Synth. Catal.* **2012**, *354*, 1579−1584. (c) Upadhyaya, K.; Thakur, R. K.; Shukla, S. K.; Tripathi, R. P. One-Pot Copper(I)-Catalyzed Ligand/Base-Free Tandem Cyclooxidative Synthesis of Quinazolinones. *J. Org. Chem.* **2016**, *81*, 5046−5055. (d) Heravi, M. M.; Sadjadi, S.; Mokhtari Haj, N.; Oskooie, H. A.; Hekmat Shoar, R.; Bamoharram, F. F. A novel multicomponent synthesis of 4-arylaminoquinazolines. *Tetrahedron Lett.* **2009**, *50*, 943−945. (e) Wang, B.; Li, Z.; Wang, X. N.; Tan, J. H.; Gu, L. Q.; Huang, Z. S. A new approach to the facile synthesis of 2-substituted-quinazolin-4(3*H*)-ones. *Chin. Chem. Lett.* **2011**, *22*, 951−953. (f) Lygin, A. V.; de Meijere, A. *ortho*-Lithiophenyl Isocyanide: A Versatile Precursor for 3H-Quinazolin-4-ones and 3H-Quinazolin-4-thiones. *Org. Lett.* **2009**, *11*, 389−392.

(9) (a) He, L.; Li, H.; Neumann, H.; Beller, M.; Wu, X.-F. Highly Efficient Four-Component Synthesis of 4(3*H*)-Quinazolinones: Palladium-Catalyzed Carbonylative Coupling Reactions. *Angew. Chem., Int. Ed.* **2014**, *53*, 1420−1424; *Angew. Chem.* **2014**, *126*, 1444−1448. (b) Wang, L.; Wang, Y.; Chen, M.; Ding, M.-W. Reversible P(III)/P(V) Redox: Catalytic Aza-Wittig Reaction for the Synthesis of 4(3*H*)-Quinazolinones and the Natural Product Vasicinone. *Adv. Synth. Catal.* **2014**, *356*, 1098−1104. (c) Hakim Siddiki, S. M. A.; Kon, K.; Touchy, A. S.; Shimizu, K.-i. Direct synthesis of quinazolinones by acceptorless dehydrogenative coupling of *o*-aminobenzamide and alcohols by heterogeneous Pt catalysts. *Catal. Sci. Technol.* **2014**, *4*, 1716−1719. (d) Cao, L.; Huo, H.; Zeng, H.; Yu, Y.; Lu, D.; Gong, Y. One-Pot Synthesis of Quinazolin-4(3*H*)-ones through Anodic Oxidation and the Related Mechanistic Studies. *Adv. Synth. Catal.* **2018**, *360*, 4764−4773. (e) Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. A Simple and Efficient Approach to Quinazolinones under Mild Copper-Catalyzed Conditions. *Angew. Chem., Int. Ed.* **2009**, *48*, 348−351. For selected examples of 2-substituted quinazolinones, see: (f) Xu, W.; Jin, Y.; Liu, H.; Jiang, Y.; Fu, H. Copper-Catalyzed Domino Synthesis of Quinazolinones via Ullmann-Type Coupling and Aerobic Oxidative C-H Amidation. *Org. Lett.* **2011**, *13*, 1274−1277. (g) Wu, X.-F.; He, L.; Neumann, H.; Beller, M. Palladium-Catalyzed Carbonylative Synthesis of Quinazolinones from 2-Aminobenzamide and Aryl Bromides. *Chem. - Eur. J.* **2013**, *19*, 12635−12638. (h) Zhang, Z.; Wang, M.; Zhang, C.; Zhang, Z.; Lu, J.; Wang, F. The cascade synthesis of quinazolinones and quinazolines

using an α-MnO_2 catalyst and *tert*-butyl hydroperoxide (TBHP) as an oxidant. *Chem. Commun.* **2015**, *51*, 9205−9207. (i) Liu, W.; Wu, G.; Gao, W.; Ding, J.; Huang, X.; Liu, M.; Wu, H. Palladium-catalyzed oxidative C═C bond cleavage with molecular oxygen: one-pot synthesis of quinazolinones from 2-amino benzamides and alkenes. *Org. Chem. Front.* **2018**, *5*, 2734−2738. (j) Ma, Z.; Song, T.; Yuan, Y.; Yang, Y. Synergistic catalysis on Fe−N_x sites and Fe nanoparticles for efficient synthesis of quinolines and quinazolinones via oxidative coupling of amines and aldehydes. *Chem. Sci.* **2019**, *10*, 10283−10289. (k) Hu, Y.; Li, S.; Li, H.; Li, Y.; Li, J.; Duanmu, C.; Li, B. Copper-catalyzed tandem oxidative synthesis of quinazolinones from 2-aminobenzonitriles and benzyl alcohols. *Org. Chem. Front.* **2019**, *6*, 2744−2748. (l) Li, F.; Lu, L.; Ma, J. Acceptorless dehydrogenative condensation of *o*-aminobenzamides with aldehydes to quinazolinones in water catalyzed by a water-soluble iridium complex $[Cp^*Ir(H_2O)_3][OTf]_2$. *Org. Chem. Front.* **2015**, *2*, 1589−1597. (m) Zhang, F.-L.; Wang, Y.-F.; Chiba, S. Orthogonal aerobic conversion of *N*-benzyl amidoximes to 1,2,4-oxadiazoles or quinazolinones. *Org. Biomol. Chem.* **2013**, *11*, 6003−6007. (n) Zhao, P.; Yu, X.-X.; Zhou, Y.; Geng, X.; Wang, C.; Huang, C.; Wu, Y.-D.; Zhu, Y.-P.; Wu, A.-X. Splitting Methyl Ketones into Two Parts: Synthesis of 4(3*H*)-Quinazolinones via Consecutive Cyclization/Ring-Opening Reaction. *Org. Lett.* **2020**, *22*, 7103−7107.

(10) Kotipalli, T.; Kavala, V.; Janreddy, D.; Bandi, V.; Kuo, C.-W.; Yao, C.-F. Synthesis of 2,3-Disubstituted Quinazolinone Derivatives through Copper Catalyzed C−H Amidation Reactions. *Eur. J. Org. Chem.* **2016**, *2016*, 1182−1193.

(11) Xu, L.; Jiang, Y.; Ma, D. Synthesis of 3-Substituted and 2,3-Disubstituted Quinazolinones via Cu-Catalyzed Aryl Amidation. *Org. Lett.* **2012**, *14*, 1150−1153.

(12) Li, B.; Samp, L.; Sagal, J.; Hayward, C. M.; Yang, C.; Zhang, Z. Synthesis of Quinazolin-4(3*H*)-ones via Amidine *N*-Arylation. *J. Org. Chem.* **2013**, *78*, 1273−1277.

(13) Tian, X.; Song, L.; Li, E.; Wang, Q.; Yu, W.; Chang, J. Metal-free one-pot synthesis of 1,3-diazaheterocyclic compounds *via* I_2-mediated oxidative C−N bond formation. *RSC Adv.* **2015**, *5*, 62194−62201.

(14) Hu, Y.; Chen, L.; Li, B. Iron nitrate/TEMPO-catalyzed aerobic oxidative synthesis of quinazolinones from alcohols and 2-aminobenzamides with air as the oxidant. *RSC Adv.* **2016**, *6*, 65196−65204.

(15) Zhao, D.; Wang, T.; Li, J.-X. Metal-free oxidative synthesis of quinazolinones *via* dual amination of sp^3 C−H bonds. *Chem. Commun.* **2014**, *50*, 6471−6474.

(16) Liu, H.; Zhai, T.; Ding, S.; Hou, Y.; Zhang, X.; Feng, L.; Ma, C. Direct and metal-free oxidative amination of sp^3 C−H bonds for the construction of 2-hetarylquinazolin-4(3*H*)-ones. *Org. Chem. Front.* **2016**, *3*, 1096−1099.

(17) (a) Zheng, Z.; Alper, H. Palladium-Catalyzed Cyclocarbonylation of *o*-Iodoanilines with Imidoyl Chlorides to Produce Quinazolin-4(3*H*)-ones. *Org. Lett.* **2008**, *10*, 829−832. (b) Zeng, F.; Alper, H. Tandem Palladium-Catalyzed Addition/Cyclocarbonylation: An Efficient Synthesis of 2-Heteroquinazolin-4(3*H*)-ones. *Org. Lett.* **2010**, *12*, 1188−1191. (c) Zeng, F.; Alper, H. One-Step Synthesis of Quinazolino[3,2-*a*]quinazolinones via Palladium-Catalyzed Domino Addition/Carboxamidation Reactions. *Org. Lett.* **2010**, *12*, 3642−3644. (d) Chen, J.; Natte, K.; Spannenberg, A.; Neumann, H.; Langer, P.; Beller, M.; Wu, X.-F. Base-Controlled Selectivity in the Synthesis of Linear and Angular Fused Quinazolinones by a Palladium-Catalyzed Carbonylation/Nucleophilic Aromatic Substitution Sequence. *Angew. Chem., Int. Ed.* **2014**, *53*, 7579−7583. (e) Chen, J.; Feng, J.-B.; Natte, K.; Wu, X.-F. Palladium-Catalyzed Carbonylative Cyclization of Arenes by C-H Bond Activation with DMF as the Carbonyl Source. *Chem. - Eur. J.* **2015**, *21*, 16370−16373. (f) Li, H.; Li, W.; Spannenberg, A.; Baumann, W.; Neumann, H.; Beller, M.; Wu, X.-F. A Novel Domino Synthesis of Quinazolinediones by Palladium-Catalyzed Double Carbonylation. *Chem. - Eur. J.* **2014**, *20*, 8541−8544.

(18) (a) Wang, H.; Cao, X.; Xiao, F.; Liu, S.; Deng, G.-J. Iron-Catalyzed One-Pot 2,3-Diarylquinazolinone Formation from 2-Nitrobenzamides and Alcohols. *Org. Lett.* **2013**, *15*, 4900−4903. (b) Qiao, J.; Jiang, H.; Liu, X.; Xu, C.; Sun, Z.; Chu, W. Ruthenium-Catalyzed Synthesis of Quinazolinones through Hydrogen Transfer and Cyclization. *Eur. J. Org. Chem.* **2019**, *2019*, 2428−2434.

(19) Wang, Y.-F.; Zhang, F.-L.; Chiba, S. Oxidative Radical Skeletal Rearrangement Induced by Molecular Oxygen: Synthesis of Quinazolinones. *Org. Lett.* **2013**, *15*, 2842−2845.

(20) Jin, C.-Y.; Wang, Y.; Liu, Y.-Z.; Shen, C.; Xu, P.-F. Organocatalytic Asymmetric Michael Addition of Oxindoles to Nitroolefins for the Synthesis of 2,2-Disubstituted Oxindoles Bearing Adjacent Quaternary and Tertiary Stereocenters. *J. Org. Chem.* **2012**, *77*, 11307−11312.

(21) Yarlagadda, S.; Ramesh, B.; Ravikumar Reddy, C.; Srinivas, L.; Sridhar, B.; Subba Reddy, B. V. Organocatalytic Enantioselective Amination of 2-Substituted Indolin-3-ones: A Strategy for the Synthesis of Chiral α-Hydrazino Esters. *Org. Lett.* **2017**, *19*, 170−173.

(22) Yarlagadda, S.; Sankaram, G. S.; Balasubramanian, S.; Subba Reddy, B. V. Asymmetric Robinson Annulation of 3-Indolinone-2-carboxylates with Cyclohexenone: Access to Chiral Bridged Tricyclic Hydrocarbazoles. *Org. Lett.* **2018**, *20*, 4195−4199.

(23) (a) Jeffs, P. W.; Molina, G.; Cortese, N. A.; Hauck, P. R.; Wolfram, J. Aza-Ring Expansion of *cis* -Bicyclo[4.2.0]octanones and Related Compounds. A Regiospecific Synthesis of *cis* -Octahydroindolones. *J. Org. Chem.* **1982**, *47*, 3876−3881. (b) Sahasrabudhe, K.; Gracias, V.; Furness, K.; Smith, B. T.; Katz, C. E.; Srinivasa Reddy, D.; Aubé, J. Asymmetric Schmidt Reaction of Hydroxyalkyl Azides with Ketones. *J. Am. Chem. Soc.* **2003**, *125*, 7914−7922. (c) Banerjee, R.; King, S. B. Synthesis of Cyclic Hydroxamic Acids through -NOH Insertion of Ketones. *Org. Lett.* **2009**, *11*, 4580−4583. (d) Lachia, M.; Richard, F.; Bigler, R.; Kolleth-Krieger, A.; Dieckmann, M.; Lumbroso, A.; Karadeniz, U.; Catak, S.; De Mesmaeker, A. An improved procedure for the Beckmann rearrangement of cyclobutanones. *Tetrahedron Lett.* **2018**, *59*, 1896−1901. (e) Sietmann, J.; Ong, M.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Wiest, J. M. Desymmetrization of Prochiral Cyclobutanones via Nitrogen Insertion: A Concise Route to Chiral γ-Lactams. *Angew. Chem., Int. Ed.* **2021**, *60*, 9719−9723.

(24) Zvilichovsky, G.; Gurvich, V. Ozonolysis of 2-(1,4-Cyclohexadienyl)glycine. *Tetrahedron* **1995**, *51*, 5479−5490.

(25) Vacher, B.; Funes, P.; Chopin, P.; Cussac, D.; Heusler, P.; Tourette, A.; Marien, M. Rigid Analogues of the α2-Adrenergic Blocker Atipamezole: Small Changes, Big Consequences. *J. Med. Chem.* **2010**, *53*, 6986−6995.

(26) Hamaguchi, W.; Masuda, N.; Samizu, K.; Mihara, T.; Takama, K.; Watanabe, T. Synthesis and *in Vivo* Evaluation of Novel Quinoline Derivatives as Phosphodiesterase 10A Inhibitors. *Chem. Pharm. Bull.* **2014**, *62*, 1200−1213.

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