Hydrogen Transfer-Mediated Multicomponent Reaction for Direct Synthesis of Quinazolines by a Naphthyridine-Based Iridium Catalyst

HIGHLIGHTS
- Use of abundant ammonia and alcohols
- Good substrate and functional group compatibility
- New naphthyridine-based Ir catalyst
- Strategy merging hydrogen transfer and annulation
Hydrogen Transfer-Mediated Multicomponent Reaction for Direct Synthesis of Quinazolines by a Naphthyridine-Based Iridium Catalyst

Zhenda Tan,1 Zhongxin Fu,2 Jian Yang,1 Yang Wu,1 Liang Cao,1 Huanfeng Jiang,1 Juan Li,2,* and Min Zhang1,3, *

SUMMARY
Selective linkage of renewable alcohols and ammonia into functional products would not only eliminate the prepreparation steps to generate active amino agents but also help in the conservation of our finite fossil carbon resources and contribute to the reduction of CO2 emission. Herein the development of a novel 2-(4-methoxyphenyl)-1,8-naphthyridine-based iridium (III) complex is reported, which exhibits excellent catalytic performance toward a new hydrogen transfer-mediated annulation reaction of 2-nitrobenzylic alcohols with alcohols and ammonia. The catalytic transformation proceeds with the striking features of good substrate and functional group compatibility, high step and atom efficiency, no need for additional reductants, and liberation of H2O as the sole by-product, which endows a new platform for direct access to valuable quinazolines. Mechanistic investigations suggest that the non-coordinated N-atom in the ligand serves as a side arm to significantly promote the condensation process by hydrogen bonding.

INTRODUCTION
Mass mining and consumption of fossil resources have resulted in a call for the development of new catalytic transformations, enabling production of functional chemicals from renewable resources with high step and atom efficiency (Goldemberg, 2007; Michlik and Kempe, 2013a, 2013b; Kozlowski and Davis, 2013). Among various alternative feedstocks, alcohols are a category of oxidized hydrocarbons that can be extensively derived from biomass including abundantly available lignocellulose via degradation (Zakzeski et al., 2010; Sun et al., 2018; Vispute et al., 2010). N-heteroarenes represent a class of highly important compounds, and they have been extensively employed for the development of valuable products, such as bioactive molecules, pharmaceuticals, agrochemicals, dyes, ligands, sensors, and materials (Boyarskiy et al., 2016; Preshlock et al., 2016; Bandini, 2011). Consequently, the linkage of alcohols into N-heteroaromatic frameworks is of high importance, as it not only helps in the conservation of our finite fossil carbon resources but also contributes to the reduction of CO2 emission.

Over the past decade, the strategy of acceptorless dehydrogenative coupling (ADC) proceeded to renew the construction of N-heteroarenes. In this strategy, dehydrogenation is involved in the activation of alcohols via in situ formation of carbonyl intermediates, and H2 and/or H2O are generally generated as the by-products. Since 2013, significant progress has been made in this regard by the groups of Milstein (Srimani et al., 2013a, 2013b; Daw et al., 2016, 2017), Kempe (Michlik et al., 2013a, 2013b; Deibl et al., 2015; Hille et al., 2014, 2017; Deibl and Kempe, 2017; Kallmeier et al., 2017), Beller (Zhang et al., 2013a, 2013b), Kirchner (Mastalir et al., 2016), and others (Pan et al., 2016; Xu et al., 2017; Elangovan et al., 2015; Chen et al., 2014). However, it is important to note that these transformations mainly rely on the utilization of specific amines, whereas the synthesis of N-heteroarenes by combining alcohols with ammonia, an abundant and renewable nitrogen source, has been rarely explored, although the related transformations would eliminate prepreparation steps to generate active amino agents, and result in high step and atom efficiency. For instance, the Beller group has reported a Ru-catalyzed synthesis of pyrroles from ammonia, vicinal diols, and ketones (Scheme 1, Equation 1) (Zhang et al., 2013a, 2013b). Milstein and the co-workers have presented a synthesis of pyrroles and pyrazines from alcohols and ammonia (Scheme 1, Equation 2) (Daw et al., 2018).

In recent years, the so-called hydrogen-borrowing reaction has emerged as an appealing tool in achieving the alkylation of amines (Wang et al., 2014; Xiao et al., 2019; Kaloglu et al., 2016; Elangovan et al., 2016) and activated carbon nucleophiles (Blank and Kempe, 2010; Elangovan et al., 2015; Deibl and Kempe, 2017).
Interesting, the synthesis of various alkylamines from alcohols and ammonia has also been nicely demonstrated (Scheme 1, Equation 3) (Ye et al., 2014; Pingen et al., 2010; Imm et al., 2010, 2011; Gunanathan and Milstein, 2008; Yamaguchi et al., 2008; Kawahara et al., 2010). In such transformations, the alcohols serve as both the hydrogen suppliers and coupling agents. So, there is no need for external reductants such as high-press H2 gas. Despite these significant advances, the construction of functional N-heteroarenes involving alcohols and ammonia feedstocks through hydrogen autotransfer as a substrate-activating strategy remains a new subject to be explored. However, such a concept would encounter the challenges of difficult proton exchanges and selectivity control, as well as catalyst deactivation by the lone pair of electrons on the nitrogen of excess ammonia (Klinkenberg and Hartwig, 2011).

Among various N-heteroarenes, quinazolines constitute a class of structurally unique compounds, which have been found to exhibit diverse biological and therapeutic activities (Parhi et al., 2013; Ugale and Bari, 2014; Juvale et al., 2013; Ple et al., 2004), and have been extensively applied for the discovery of various functional products (Zhao et al., 2013; Zhang et al., 2011). However, the existing approaches for accessing such compounds generally require preinstalled reactants (Lin et al., 2014; Malakar et al., 2012; Portela-Cubillo et al., 2008; Yan et al., 2012; Zhang et al., 2010). In this context, the search for direct synthesis of quinazolines from easily available substrates, preferably abundant and sustainable ones, would be of great significance. Enlightened by our recent work on the synthesis and functionalization of N-heterocycles (C. Chen et al., 2017; Chen et al., 2018a, 2018b; X.-W. Chen et al., 2017; Liang et al., 2018, 2019; Xie et al., 2017, 2018, 2019), we wish herein to present, for the first time, a synthesis of quinazolines from 2-nitrobenzyl alcohols (Rajendran et al., 2015; Pasnoori et al., 2014), alcohols, and ammonia by a new iridium complex featuring a 2-(4-methoxyphenyl)-1,8-naphthyridyl ligand. In such a transformation, the hydrogen generated from dehydrogenation of alcohols and dehydroaromatization process is utilized for substrate activation through transfer hydrogenation (TH) of the nitro group, and there is no need for addition of external reductants.

RESULTS AND DISCUSSION

We initiated our investigations by choosing the synthesis of quinazoline 3aa from o-nitrobenzene methanol 1a, alcohol 2a, and ammonia as a model reaction. First, we tested the combinations of several metal
catalysts (i.e., Ru, Mn, Co, Fe, and Ni) with various phosphine ligands such as Xantphos, DPPE, DPPB, DPPP, Binap-dp, DPEphos, and Xphos (see Table S1), the privileged catalyst systems employed for the ADC and hydrogen-borrowing reactions. However, the low yields of product (<10%) disclosed that they were not suitable systems for the current synthetic purpose. When complex [IrCp*Cl]2 was employed, 15% yield of 3aa was obtained. A further optimization of other reaction parameters involving solvents, bases, and temperatures (Table S2) slightly improved the yield to 18% by using t-BuONa as the base at 140°C. Enlightened by our recent synthesis of naphthyridines (Chen et al., 2017a, 2017b, 2018a, 2018b; Xiong et al., 2016), we believed that such compounds might serve as a class of useful N-ligands with tunable coordination modes, and the preparation of a suitable naphthyridyl-Ir complex might offer a solution to obtain the desirable catalytic efficiency. Thus, we prepared 9-cyclometalated iridium complexes, involving 8-naphthyridyl (Ir-1–Ir-8) and 1,2-phenylpyridyl (Ir-9) ones. Then, their catalytic performance toward the model reaction was evaluated (Table 1, entries 1–9). In comparison, complexes bearing a 1,8-naphthyridyl ligand (entries 1–7) exhibited appealing activity, and Ir-3 (as confirmed by single-crystal X-ray diffraction, CCDC: 1848110, for detail, see Figure S101 and Tables S5–S10) was shown to be a preferred candidate, whereas complex with a 1,5-naphthyridyl or 2-phenylpyridyl ligand only resulted in low product yield (entries 8–9). The results imply that the N-atom at position 8 in 1,8-naphthyridyl ligands plays a crucial role in affording a satisfactory product yield. Further optimization showed that the presence of iridium is essential in affording the product (entry 10), and the gaseous ammonia is relatively superior to other nitrogen sources (entries 11–15). A decrease of base amount to 30% resulted in a diminished yield (entry 16), and 40% t-BuONa was sufficient for the reaction (entry 17). The time-conversion profile at 2, 4, 8, and 16 h showed that the satisfactory product yield is due to the catalyst robustness (entry 18). Based on the results, the optimal (standard) conditions are as indicated in entry 17 of Table 1.

With the optimal reaction conditions established, we then examined the generality of the synthetic protocol. (2-Nitrophenyl)methanol 1a was further employed to couple with various primary alcohols (2a–2t, Scheme S1) and ammonia. As illustrated in Scheme 2, all the reactions proceeded smoothly and furnished the desired quinazolines in moderate to excellent yields upon isolation (Scheme 2, 3ab–3at). Apart from the alkyl-substituted benzyl alcohols, other functional groups such as –OMe, –OH, –NH$_2$, –Cl, –Br, –CF$_3$, –CO$_2$Me, –COPh, –CN, and –C=C– are well tolerated in the transformation. The retention of these functionalities offers the potential for the elaboration of complex molecules via further chemical transformations. Moreover, except for the strong electron-withdrawing group –CF$_3$, the electronic property of these substituents has little influence on the reaction, whereas the relatively lower product yields using ortho-substituted benzyl alcohols might relate to the steric hindrance (3ac and 3ae). Furthermore, heteroaryl methanols (2o and 2p) were also amenable to the transformation and resulted in the 2-heteroaryl-substituted quinazolines (3ao and 3ap) in good yields, and the obtained products have the potential to be applied as hemilabile bidentate ligands in organometallic chemistry and catalysis. Interestingly, cinnamyl alcohol 2q underwent smooth hydrogen transfer-mediated annulation, affording the 2-alkenyl quinazoline 3aq in 46% yield. The relatively low product yield is due to partial formation of 2-alkyl quinazoline via reduction of the alkenyl group. The relatively low product yield of 3aq is due to the partial formation of 2-alkyl quinazoline via reduction of the alkenyl group. Aliphatic alcohols, such as methanol (2r), heptan-1-ol (2s), and cyclopropyl carbino (2t), were efficiently transformed into the 2-non-substituted and 2-alkyl quinazolines (3ar, 3as, and 3at) in moderate yields.

Subsequently, we turned our attention to the transformation of different 2-nitrobenzyl alcohols 1. First, various related substrates (1b–1l) in combination with different primary alcohols 2 and NH$_3$ were tested. As shown in Scheme 3, all the reactions smoothly delivered the multi-substituted quinazolines in moderate to excellent isolated yields. The electronic property of the substituents on the aryl ring of substrates 1 significantly influenced the product yields. In general, 2-nitrobenzyl alcohols 1 with electron-donating groups afforded the products in higher yields (3ba–3ca and 3ea–3fi) than with electron-deficient ones (3ga–3ia). This phenomenon is rationalized as the catalyst has better stability toward the electron-rich aniline intermediates, arising from the TH of nitro group of substrates 1. Gratifyingly, secondary alcohols, such as 1j and 1k, also underwent smooth annulation to give the 2,4-disubstituted quinazolines in good yields (3ja, 3jf, and 3ka). Similar to the results described in Scheme 2, a wide array of functionalities such as –Me, –OMe, –F, –Cl, –Br, –CN, –Ph, and ester are well tolerated in the transformation (Schemes 2 and 3). Noteworthy, the halogen groups did not undergo hydrodehalogenation, showing that the developed catalytic system exhibits unique chemoselectivity.
| Entry | Catalyst | NH₃ Source | Yields of 3aa[^b] |
|-------|----------|------------|------------------|
| 1     | Ir-1     | NH₄OAc     | 72               |
| 2     | Ir-2     | NH₄OAc     | 75               |
| 3     | Ir-3     | NH₄OAc     | 82               |
| 4     | Ir-4     | NH₄OAc     | 61               |
| 5     | Ir-5     | NH₄OAc     | 67               |
| 6     | Ir-6     | NH₄OAc     | 71               |
| 7     | Ir-7     | NH₄OAc     | 68               |
| 8     | Ir-8     | NH₄OAc     | 15               |
| 9     | Ir-9     | NH₄OAc     | 21               |
| 10    | –        | NH₄OAc     | –                |
| 11    | Ir-3     | NH₄Cl      | 5                |
| 12    | Ir-3     | HCOONH₄    | Trace            |
| 13    | Ir-3     | NH₃⋅H₂O    | Trace            |
| 14    | Ir-3     | (NH₄)₂SO₄  | 22               |
| 15    | Ir-3     | NH₃ (g)    | 88[^b]          |
| 16    | Ir-3     | NH₃ (g)    | 81[^b,d]        |
| 17    | Ir-3     | NH₃ (g)    | 88[^b,c]        |
| 18    | Ir-3     | NH₃ (g)    | (12, 40, 65, 84)^[^d] |

[^a]: Unless otherwise stated, the reaction was performed with 1a (0.5 mmol), 2a (0.5 mmol), Ir (1 mol %), t-BuONa (50 mol %), NH₃ sources (1.0 mmol) in toluene (1.5 mL) for 24 h under Ar protection.

[^b]: Gas chromatography yields with the use of hexadecane as an internal standard.

[^c]: 4 bar of NH₃.

[^d]: t-BuONa (30 mol %).

[^e]: t-BuONa (40 mol %).

[^f]: Conversions for 2, 4, 8, and 16 h.
To demonstrate the significance and practicality of the developed synthetic methodology, a gram-scale synthesis of compound 3aa could be achieved by performing the reaction with 8 mmol of 1a and 9 mmol of benzyl alcohol 2a, which still afforded a good isolated product yield (78%) even with lower catalyst loading (Scheme 4, Equation a, 0.2 mol%). Furthermore, compound 3ia, a key ingredient used as a herbicide with the activity on Toll-like receptors, 20 could be prepared through the reduction of commercially available acifluorfen acid to 2-nitrobenzyl alcohol 1l (Scheme S3) followed by the annulation reaction of 1l with alcohol 2a and ammonia (Equation b), and such a synthesis is far superior to the reported multi-step synthetic protocol (Mc Gowan et al., 2012; Munro and Bit, 1987; Sumida et al., 1995). Moreover, the extended π-conjugated system like compound 5ja was successfully prepared by the halocyclization (Tan et al., 2016) of compound 3ja and further Sonogashira coupling (Equation c), which offers a valuable basis for further development of optoelectronic materials.

To gain mechanistic insights into the catalytic transformation, a time-concentration profile of the model reaction is depicted in Figure 1 (also see Data S1). Substrates 1a and 2a with ammonia were converted into 3aa in maximum yield within 24 h. 2-Aminobenzaldehyde 1a-4 and 1,2-dihydroquinazoline 3aa-1 were observed during the reaction, but they were consumed up after completion of the reaction (Figure 1). The subjection of compound 1a-4 with benzaldehyde 2a-1 and NH₃ or direct treatment of 3aa-1 under the standard conditions afforded product 3aa in almost quantitative yields (see Equations 1 and 2 of Scheme S2, also see Data S1). These results support the fact that compounds 1a-4, 2a-1, and 3aa-1 are
the reaction intermediates. Furthermore, both the iridium catalyst and base play crucial roles in the dehydrogenation of 3aa-1 to product 3aa (Equation 2). An iridium hydride complex (Ir-H) was obtained from the reaction of equimolar Ir-3 and benzyl alcohol, which can efficiently catalyze the reaction to afford 3aa, showing that Ir-H as a catalytic species is involved in the reaction (Equations 3 and 4, Scheme S2, also see Data S2 and Figure S98).

With the above-mentioned preliminary experimental evidence in hand, the mechanism was further scrutinized by density functional theory calculations (geometry optimizations using B3LYP and single-point energy calculations using M06). For details, see Figures S99 and S100, Tables S3 and S4, Schemes S4–S8, and Data S4. The calculated free energy profile for the first TH (first TH) of 1a to 2-nitrosobenzaldehyde 1a-2 is shown in Figure 2. Initially, the anion exchange between Ir-3 and t-BuONa generates the alkoxy complex Ir-O1. One of the arms in 1,8-naphthyridyl ligand of Ir-O1 dissociates, allowing the Ir center to coordinate with the hydroxyl group of 1a. O–H bond cleavage occurs via transition state TS1 with an energy barrier of 21.4 kcal/mol to give Ir-alkoxide complex IN2, which then undergoes β-hydride elimination by overcoming an energy barrier of 28.0 kcal/mol (TS2) relative to IN2, and generates complex Ir-H and o-nitrobenzaldehyde 1a-1. The nitro group of 1a-1 further acts as a sacrificial hydrogen acceptor of Ir-H through two transition states TS3 and TS4. Finally, 2-nitrosobenzaldehyde 1a-2 is generated with the regeneration of Ir-O1. In addition, the base-promoted intramolecular Meerwein-Ponndorf-Verley-Oppenauer-type transfer hydrogenation (MPV-O TH) is calculated to have an energy barrier of 33.1 kcal/mol (see Scheme S4), which is 3.5 kcal/mol higher than the overall barrier of the pathway shown in Figure 2. Thus, the MPV-O TH pathway is kinetically unfavorable.

The calculated free energy profiles for the second TH of 2-nitrosobenzaldehyde 1a-2 to 2-(hydroxyamino) benzaldehyde 1a-3 and the third TH of 1a-3 to 2-aminobenzaldehyde 1a-4 are shown in Figures S99 and
S100 (also see Tables S3 and S4, Schemes S5–S8 and Data S4). In consideration that both 2-aminobenzaldehyde 1a-4 and benzaldehyde 2a-1 can condense with ammonia, two plausible pathways toward the formation of imines were investigated. For the reaction of 2a-1 and ammonia (black line in Figure 3), ammonia approaches benzaldehyde through the C–N bond linkage (TS14) giving IN18. The TH of the ammonia using other ammonia as the proton-transferring shuttle then takes place via TS15 and leads to IN20. The calculated free energy barrier of transition state TS15 is 22.8 kcal/mol relative to IN16. After rearranging to more stable IN21 featuring two hydrogen bonds, the dehydration occurs via TS16, giving the imine complex IN22. Meanwhile, we performed calculations for the dehydration without the hydrogen-bonding between the OH group and the non-coordinated N-atom in the ligand (green line in Figure 3). The calculated free
energy of transition state TS16° is −58.4 kcal/mol, which is higher than that of TS16. Therefore, the non-coordinated N-atom in the 1,8-naphthyridyl ligand plays a crucial role in the reaction, as it serves as a side-arm to significantly promote the dehydration by hydrogen bonding. An alkoxyl anion ligand rebounds to Ir center to give imine 2a-2 with regeneration of the Ir-O2 catalyst. The reaction of 1a-4 and ammonia (purple line in Figure 3) follows similar mechanisms to those for 2a-1. The relevant mechanistic details are therefore not discussed again, for simplicity. The highest energy point for the reaction of 1a-4 and ammonia is TS16°, which is energetically less favorable by 1.8 kcal/mol compared with that of TS16 for the reaction of 2a-1 and ammonia. Therefore, from a kinetic point of view, the reaction of 1a-4 and ammonia is less kinetically favorable.

Based on all the above-mentioned findings, a plausible reaction pathway for the formation of product 3aa is illustrated in Scheme 5. In the first TH process, the Ir-catalyzed dehydrogenation of 1a via alkoxyl anion exchange of Ir-O1 with 1a gives IN2, which is followed by β-H elimination to form the 2-nitrobenzaldehyde 1a-1 and the Ir–H species. The successive TH to the nitro group of 1a-1 and t-BuOH-assisted dehydration forms 2-nitrosobenzaldehyde 1a-2 and regenerates the Ir-O1 species. In the second TH process, the anion exchange of Ir-O1 with 2a gives a benzylxy complex Ir-O2. The subsequent β-H elimination of Ir-O2 followed by TH to the nitroso group and alcoholysis with 2a delivers 2-(hydroxyamino)benzaldehyde 1a-3 and regenerates complex Ir-O2, respectively. In the
third TH process, the Ir-H and benzaldehyde 2a-1 are generated via β-H elimination of Ir-O2. Subsequently, the Ir-promoted dehydration of 1a-3 forms a nitrene complex IN13, and the TH using 2a as the proton-transferring shuttle generates 2-aminobenzaldehyde 1a-4 (Qu et al., 2014; Hou et al., 2017). Next, the successive formation of imine 2a-2 via the condensation of benzaldehyde 2a-1 with NH3 and the cyclization between 2a-2 and 1a-4 affords the dihydroquinazoline 3aa-1. Finally, the iridium alkoxy complex-catalyzed dehydroaromatization of 3aa-1 gives rise to product 3aa, and the in situ-generated Ir-H and alcohol further take part in the TH of the nitro group.

**Conclusion**

In summary, we have prepared a series of cyclometalated iridium complexes. Among them, Ir-3 featuring a 2-(4-methoxyphenyl)-1,8-naphthyridyl ligand exhibits the best catalytic performance toward the hydrogen transfer-mediated annulation of 2-nitrobenzyl alcohols with readily available alcohols and ammonia, which allows direct synthesis of a wide array of valuable quinazolines. Mechanistic investigation suggests that the non-coordinated N-atom in the ligand serves as a side arm to significantly promote the condensation step by hydrogen bonding. The catalytic transformation proceeds with the striking features of good substrate and functional group compatibility, liberation of H2O as the sole by-product, high atom and step efficiency, and no need for additional reductants. The developed chemistry paves the avenues for further development of hydrogen transfer-mediated coupling reactions by design of catalysts bearing N-side arm ligands.

**METHODS**

All methods can be found in the accompanying Transparent Methods supplemental file.

**DATA AND SOFTWARE AVAILABILITY**

The crystallography data have been deposited at the Cambridge Crystallographic Data Center (CCDC) under accession number CCDC: 1848110 (Ir-3) and can be obtained free of charge from www.ccdc.cam.ac.uk/getstructures.

**SUPPLEMENTAL INFORMATION**

Supplemental Information can be found online at https://doi.org/10.1016/j.isci.2020.101003.
ACKNOWLEDGMENTS

We thank the National Key Research and Development Program of China (2016YFA0602900), National Natural Science Foundation of China (21971071), and the foundation of the Department of Education of Guangdong Province (2017KZDXM085) for financial support.

AUTHOR CONTRIBUTIONS

Z.T. and M.Z. conceived and designed the study. Z.T., J.Y., Y.W., and L.C. performed the experiments and mechanism study and analyzed the data. Z.F. and J.L. performed DFT calculations and analyzed the data. Z.T., Z.F., H.J., J.L., and M.Z. co-wrote the paper. Z.T. and Z.F. contributed equally to this work.

DECLARATION OF INTERESTS

The authors declare no competing financial interests.

Received: February 10, 2020
Revised: March 9, 2020
Accepted: March 17, 2020
Published: April 24, 2020

REFERENCES

Bandini, M. (2011). Heteroarenes as high performance organic semiconductors. Chem. Soc. Rev. 40, 1358–1367.

Blank, B., and Kempe, R. (2010). Catalytic alklylation of methyl-N-heteroaromatics with alcohols. J. Am. Chem. Soc. 132, 924–925.

Boyarsky, V.P., Ryabukhin, D.S., Bokach, N.A., and Vasilyev, A.V. (2016). Alkenylation of arenes and heteroarenes with alkynes. Chem. Rev. 116, 5894–5986.

Chen, M., Zhang, M., Xiong, B., Tan, Z., Lv, W., and Jiang, H. (2014). A novel ruthenium-catalyzed alkylation of methyl-N-heteroaromatics from 2-aminoaryl methanols and benzonitriles. Org. Lett. 16, 6028–6031.

Chen, M., Zhang, M., Xiong, B., Tan, Z., Lv, W., and Jiang, H. (2014). A novel ruthenium-catalyzed dehydrogenative synthesis of 2-arylquinazolines from 2-aminoaryl methanols and benzonitriles. Angew. Chem. Int. Ed. 53, 14232.

Chen, X.-W., Zhao, H., Chen, C.-L., Jiang, H.-F., and Zhang, M. (2017a). Hydrogen-transfer-mediated alpha-functionalization of 1,8-naphthyridines by a strategy overcoming the over-hydrogenation barrier. Angew. Chem. Int. Ed. 56, 14377–14380.

Chen, X., Zhao, H., Chen, C., Jiang, H., and Zhang, M. (2017b). Direct access to nitrogen-Bi-heteroarenes via iridium-catalyzed hydrogen-evolution cross-coupling reaction. Org. Lett. 19, 3390–3393.

Chen, X., Zhao, H., Chen, C., Jiang, H., and Zhang, M. (2018a). Transfer hydrogenative para-selective aminoalkylation of aliphatic derivatives with N-heteroarenes via ruthenium/acid dual catalysis. Chem. Commun. 54, 9067–9070.

Chen, X., Zhao, H., Chen, C., Jiang, H., and Zhang, M. (2018b). Iridium-catalyzed dehydrogenative alpha-functionalization of (Het)eraryl-fused cyclic secondary amines with indoles. Org. Lett. 20, 1171.

Daw, P., Ben-David, Y., and Milstein, D. (2017). Direct synthesis of benzimidazoles by dehydrogenative coupling of aromatic diamines and alcohols catalyzed by cobalt. ACS Catal. 7, 7456–7460.

Daw, P., Ben-David, Y., and Milstein, D. (2018). Acceptorless dehydrogenative coupling using ammonia: direct synthesis of N-heteroaromatics from diols catalyzed by ruthenium. J. Am. Chem. Soc. 140, 11931–11934.

Deibl, N., and Kempe, R. (2016). General and mild cobalt-catalyzed C-alkylation of unactivated amides and esters with alcohols. J. Am. Chem. Soc. 138, 10786–10789.

Deibl, N., and Kempe, R. (2017). Manganese-catalyzed multicomponent synthesis of pyrimidines from alcohols and amides. Angew. Chem. Int. Ed. 56, 1663–1666.

Deibl, N., Ament, K., and Kempe, R. (2015). A sustainable multicomponent pyrimidine synthesis. J. Am. Chem. Soc. 137, 12804–12807.

Elangovan, S., Sortais, J.-B., Beller, M., and Dancel, C. (2015). Iron-catalyzed alpha-alkylation of ketones with alcohols. Angew. Chem. Int. Ed. 54, 14483–14486.

Elangovan, S., Neumann, J., Sortais, J.-B., Junge, K., Darcel, C., and Beller, M. (2016). Efficient and selective N-alkylation of amines with alcohols catalyzed by manganese pincer complexes. Nat. Commun. 7, 12641.

Goldenberg, J. (2007). Ethanol for a sustainable energy future. Science 315, 808–810.

Gunaranathan, C., and Milstein, D. (2008). Selective synthesis of primary amines directly from alcohols and ammonia. Angew. Chem. Int. Ed. 47, 8661–8664.

Hille, T., Irgang, T., and Kempe, R. (2017). Synthesis of meta-functionalized pyridines by selective dehydrogenative heterocondensation of beta- and gamma-amino alcohols. Angew. Chem. Int. Ed. 56, 371–374.

Hou, C., Jiang, J., Li, Y., Zhao, C., and Ke, Z. (2017). When bifunctional catalyst encounters dual MLC modes: DFT study on the mechanistic preference in Ru-PNNH pincer complex catalyzed dehydrogenative coupling reaction. ACS Catal. 7, 786–795.

Imm, S., Baehn, S., Neubert, L., Neumann, H., and Beller, M. (2010). An efficient and general synthesis of primary amines by ruthenium-catalyzed amination of secondary alcohols with ammonia. Angew. Chem. Int. Ed. 49, 8126–8129.

Imm, S., Baehn, S., Zhang, M., Neubert, L., Neumann, H., Klackowsky, F., Pfeffer, L., Haas, T., and Beller, M. (2011). Improved ruthenium-catalyzed amination of alcohols with ammonia: synthesis of diamines and amino esters. Angew. Chem. Int. Ed. 50, 7599–7603.

Juvale, K., Gallus, J., and Wiese, W. (2013). Investigation of quinazolines as inhibitors of breast cancer resistance protein (ABCG2). Bioorg. Med. Chem. 21, 7858.

Kallmeier, F., Duzdiec, B., Irgang, T., and Kempe, R. (2017). Manganese-catalyzed sustainable synthesis of pyrroles from alcohols and amino alcohols. Angew. Chem. Int. Ed. 56, 7261–7265.

Kaloglu, N., Özdemir, I., Gürbüz, N., Achard, M., and Bruneau, C. (2016). Benzimidazolium sulfonate ligand precursors and application in ruthenium-catalyzed aromatic amine alkylation with alcohols. Catal. Commun. 74, 33–38.

Kawahara, R., Fujita, K., and Yamaguchi, R. (2010). Multialkylation of aqueous ammonia with alcohols catalyzed by water-soluble Cp*Ir-ammine complexes. J. Am. Chem. Soc. 132, 15108–15111.
Klinkenberg, J.L., and Hartwig, J.F. (2011). Catalytic organometallic reactions of ammonia. Angew. Chem. Int. Ed. 50, 86–95.

Kozloski, J.T., and Davis, R.J. (2013). Heterogeneous catalysts for the guerbet coupling of alcohols. ACS Catal. 3, 1588–1600.

Liang, T., Tan, Z., Zhao, H., Chen, X., Jiang, H., and Zhang, M. (2018). Aerobic copper-catalyzed synthesis of benzimidazoles from diaryl- and alkylamines via tandem triple C-H aminations. ACS Catal. 8, 2242.

Liang, T.Y., Zhao, H., Gong, L.Z., Jiang, H.F., and Zhang, M. (2019). Synthesis of multisubstituted benzimidazolones via copper-catalyzed oxidative tandem C-H bond functionalization and alkyl deconstructive carbofunctionalization. iScience 15, 127–135.

Lin, J.P., Zhang, F.H., and Long, Y.Q. (2014). Quinazolines in water starting from o-bromobenzylbromides and benzamidines. ACS Catal. 5, 86–95.

Malacar, C.C., Baskakova, A., Conrad, J., and Lin, J.P., Zhang, F.H., and Long, Y.Q. (2014). Sustainable synthesis of benzimidazoles from diaryl- and further diseases and their preparation. PCT Int. WO2012156498.

Mastalar, M., Glatz, M., Pittnerau, E., Allmaier, G., and Kirchner, K. (2016). A sustainable synthesis of quinolines and pyrimidines catalyzed by manganese-carbon-supported cobalt oxide nanocatalysts. Angew. Chem. Int. Ed. 55, 14967–14971.

Neumann, H., and Beller, M. (2016). Manganese-catalyzed hydrogen-autotransfer C-C bond formation: alpha-alkylation of ketones with primary alcohols. Angew. Chem. Int. Ed. 55, 14967–14971.

Pingen, D., Muller, C., and Vogt, D. (2010). Direct amination of secondary alcohols using ammonia. Angew. Chem. Int. Ed. 49, 8130–8133.

Pie, P.A., Green, T.P., Hennequin, L.F., Curwen, J., Fennell, M., Allen, J., Lambertvan der Brent, C., and Costello, G. (2004). Discovery of a new class of antiinfluenza inhibitors with high affinity and specificity for the tyrosine kinase domain of c-Src. J. Med. Chem. 47, 871.

Portela-Cubillo, F., Scott, J.S., and Walton, J.C. (2008). (2-Amino)alkalaialone O-phenyl oximes: versatile reagents for syntheses of quinazolines. Chem. Commun. 2935–2937.

Preshlock, S., Tredwell, M., and Gouverneur, V. (2016). F-18-labeling of arenes and heteroarenes in the PNP-Ir system. J. Am. Chem. Soc. 138, 4974–4981.

Rajendran, S., Raghunathan, R., Hevis, I., Krishnan, R., Ugrinov, A., Sibi, M.P., Webster, D.C., and Sicaviru, J. (2015). Programmed photodegradation of polymeric/oligomeric materials derived from renewable bioresources. Angew. Chem. Int. Ed. 54, 1159–1163.

Sriramani, D., Ben-David, V., and Milstein, D. (2013a). Direct synthesis of pyridines by dehydrogenative coupling of beta-aminocarboxylates with secondary alcohols catalyzed by ruthenium pincer complex. Angew. Chem. Int. Ed. 52, 4012–4015.

Sriramani, D., Ben-David, V., and Milstein, D. (2013b). Direct synthesis of pyridines and quinolines by coupling of gamma-amino-alcohols with secondary alcohols liberating H-2 catalyzed by ruthenium pincer complexes. Chem. Commun. 49, 6632–6634.

Sumida, M., Niwata, S., Fukami, H., Tanaka, T., Wakabayashi, K., and Boger, P. (1995). Synthesis of novel diphenyl ether herbicides. J. Agric. Food Chem. 43, 1929–1934.

Sun, Z.-H., Fridrich, B., Santi, A., Elangovan, S., and Weckhuysen, B.M. (2010). The catalytic processing of pyrolysis oils. Science 330, 1222–1227.

Wang, D., Zhao, K., Xu, C., Miao, H., and Ding, Y. (2014). Synthesis, structures of benzoaxazoli- indum(8)-complexes, and applications on C-C and C-N bond formation reactions under solvent-free conditions: catalytic activity enhanced by noncoordinating anion without silver effect. ACS Catal. 4, 3910–3918.

Xiao, M., Yue, X., Xu, R., Tang, W., Xue, D., Li, C., Lei, M., Xiao, J., and Wang, C. (2019). Transition-metal-free hydrogen autotransfer diastereoselective N-alkylation of amines with racemic alcohols. Angew. Chem. Int. Ed. 58, 10528–10536.

Xie, F., Xie, R., Zhang, J.-X., Jiang, H.-F., Du, L., and Zhang, M. (2017). Direct reductive quinolyl beta-C-H alkylation by multispherical cavity carbon-supported cobalt oxide nanocatalysts. ACS Catal. 7, 4790.

Xie, F., Chen, Q.-H., Xie, R., Jiang, H.-F., and Zhang, M. (2018). MOF-derived nanocobalt for oxidative functionalization of cyclic amines to quinazolines with 2-aminoarylmethanes. ACS Catal. 8, 5869.

Xie, R., Xie, F., Zhou, C.J., Jiang, H., and Zhang, M. (2019). Hydrogen transfer-mediated selective dual C-H alkylation of 2-arylquinolinones by doped TiO2-supported nanocobalt oxides. J. Catal. 377, 449.

Xiong, Z., Zhang, S.D., Jiang, H.F., and Zhang, M. (2016). Hydrogen-transfer-mediated direct beta-alkylation of aryl-1,8-naphthyridines with alcohols under transition metal catalyst free conditions. Org. Lett. 18, 724–727.

Xu, Z., Wang, D.-S., Yu, X., Yang, Y., and Wang, D. (2017). Tunable triazole-phosphine-copper catalysts for the synthesis of 2-aryl-1H-benzo[d]imidazoles from benzyl alcohols and diamines by acceptorless dehydrogenation and borrowing hydrogen reactions. Adv. Syn. Catal. 359, 3332–3340.

Yamaguchi, R., Kawai, S., Asai, C., and Fujita, K. (2008). Selective synthesis of secondary and tertiary amines by Cp*Ir(III)-catalyzed multialkylation of ammonium salts with alcohols. Org. Lett. 10, 181–184.

Yan, Y.Z., Zhang, Y.H., Peng, C.T., Zha, Z.G., and Wang, Z.Y. (2012). Selective iodine-catalyzed intermolecular oxidative amination of Cp(3d)-H bonds with ortho-carbonyl-substituted anilines to give quinazolines. Angew. Chem. Int. Ed. 51, 8077.

Ye, X., Plessow, P.N., Brinks, M.K., Schelweis, M., Schaub, T., Rominger, F., Paciello, R., Limbach, M., and Hofmann, P. (2014). Alcohol amination with ammonia catalyzed by an acyclic-based ruthenium pincer complex: a mechanistic study. J. Am. Chem. Soc. 136, 5923–5929.

Zakzeski, J., Brujinincs, P.C.A., Jongerius, A.L., and Weckhuysen, B.M. (2010). The catalytic valorization of lignin for the production of renewable chemicals. Chem. Rev. 110, 3552–3599.

CellPress

iScience 23, 101003, April 24, 2020 11
Zhang, J.T., Yu, C.M., Wang, S.J., Wan, C.F., and Wang, Z.Y. (2010). A novel and efficient methodology for the construction of quinazolines based on supported copper oxide nanoparticles. Chem. Commun. 46, 5244.

Zhang, Y.L., Sheets, M.R., Raja, E.K., Boblak, K.N., and Klumpp, D.A. (2011). Superacid-promoted additions involving vinyl-substituted pyrimidines, quinoxalines, and quinazolines: mechanisms correlated to charge distributions. J. Am. Chem. Soc. 133, 8467.

Zhang, M., Neumann, H., and Beller, M. (2013a). Selective ruthenium-catalyzed three-component synthesis of pyrroles. Angew. Chem. Int. Ed. 52, 597–601.

Zhang, M., Fang, X., Neumann, H., and Beller, M. (2013b). General and regioselective synthesis of pyrroles via ruthenium-catalyzed multicomponent reactions. J. Am. Chem. Soc. 135, 11384–11388.

Zhao, D., Shen, Q., Zhou, Y.R., and Li, J.X. (2013). KOtBu-mediated stereoselective addition of quinazolines to alkynes under mild conditions. Org. Biomol. Chem. 11, 5908.
Supplemental Information

Hydrogen Transfer-Mediated Multicomponent Reaction for Direct Synthesis of Quinazolines by a Naphthyridine-Based Iridium Catalyst

Zhenda Tan, Zhongxin Fu, Jian Yang, Yang Wu, Liang Cao, Huanfeng Jiang, Juan Li, and Min Zhang
Copies of product NMR spectra

**Figure S1.** $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of Ir-1, related to Table 1.

**Figure S2.** $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of Ir-1, related to Table 1.
Figure S3. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of Ir-2, related to Table 1.

Figure S4. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of Ir-2, related to Table 1.
Figure S5. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of Ir-3, related to Table 1.

Figure S6. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of Ir-3, related to Table 1.
Figure S7. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of Ir-4, related to Table 1.

Figure S8. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of Ir-4, related to Table 1.
Figure S9. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of Ir-5, related to Table 1.

Figure S10. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of Ir-5, related to Table 1.
**Figure S11.** $^{19}$F-NMR (400 MHz, CDCl$_3$) spectrum of Ir-5, related to Table 1.

**Figure S12.** $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of Ir-6, related to Table 1.
Figure S13. $^{13}$C-NMR (400 MHz, CDCl$_3$) spectrum of Ir-6, related to Table 1.

Figure S14. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of Ir-7, related to Table 1.
Figure S15. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of Ir-7, related to Table 1.

Figure S16. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of Ir-8, related to Table 1.
Figure S17. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of Ir-8, related to Table 1.

Figure S18. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of Ir-9, related to Table 1.
**Figure S19.** $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of Ir-9, related to Table 1.

**Figure S20.** $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3aa, related to Scheme 2.
Figure S21. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3aa, related to Scheme 2.

Figure S22. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ab, related to Scheme 2.
Figure S23. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of $3ab$, related to Scheme 2.

Figure S24. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of $3ac$, related to Scheme 2.
Figure S25. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ac, related to Scheme 2.

Figure S26. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ad, related to Scheme 2.
Figure S27. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ad, related to Scheme 2.

Figure S28. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ae, related to Scheme 2.
Figure S29. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ae, related to Scheme 2.

Figure S30. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3af, related to Scheme 2.
Figure S31. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3af, related to Scheme 2.

Figure S32. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ag, related to Scheme 2.
Figure S33. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ag, related to Scheme 2.

Figure S34. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ah, related to Scheme 2.
Figure S35. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ah, related to Scheme 2.

Figure S36. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ai, related to Scheme 2.
Figure S37. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ai, related to Scheme 2.

Figure S38. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3aj, related to Scheme 2.
Figure S39. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3aj, related to Scheme 2.

Figure S40. $^{19}$F-NMR (100 MHz, CDCl$_3$) spectrum of 3aj, related to Scheme 2.
**Figure S41.** $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ak, related to Scheme 2.

**Figure S42.** $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ak, related to Scheme 2.
Figure S43. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3al, related to Scheme 2.

Figure S44. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3al, related to Scheme 2.
Figure S45. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3am, related to Scheme 2.

Figure S46. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3am, related to Scheme 2.
Figure S47. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3an, related to Scheme 2.

Figure S48. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3an, related to Scheme 2.
Figure S49. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ao, related to Scheme 2.

Figure S50. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ao, related to Scheme 2.
Figure S51. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ap, related to Scheme 2.

Figure S52. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ap, related to Scheme 2.
Figure S53. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3aq, related to Scheme 2.

Figure S54. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3aq, related to Scheme 2.
Figure S55. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ar, related to Scheme 2.

Figure S56. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ar, related to Scheme 2.
Figure S57. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3as, related to Scheme 2.

Figure S58. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3as, related to Scheme 2.
Figure S59. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3at, related to Scheme 2.

Figure S60. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3at, related to Scheme 2.
Figure S61. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ba, related to Scheme 3.

Figure S62. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ba, related to Scheme 3.
Figure S63. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3bd, related to Scheme 3.

Figure S64. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3bd, related to Scheme 3.
Figure S65. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ca, related to Scheme 3.

Figure S66. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ca, related to Scheme 3.
Figure S67. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3da, related to Scheme 3.

Figure S68. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3da, related to Scheme 3.
Figure S69. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ea, related to Scheme 3.

Figure S70. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ea, related to Scheme 3.
Figure S71. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3eg, related to Scheme 3.

Figure S72. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3eg, related to Scheme 3.
Figure S73. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3fa, related to Scheme 3.

Figure S74. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3fa, related to Scheme 3.
Figure S75. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3fi, related to Scheme 3.

Figure S76. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3fi, related to Scheme 3.
Figure S77. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ga, related to Scheme 3.

Figure S78. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ga, related to Scheme 3.
**Figure S79.** $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3gk, related to Scheme 3.

**Figure S80.** $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3gk, related to Scheme 3.
**Figure S81.** $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ha, related to Scheme 3.

**Figure S82.** $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ha, related to Scheme 3.
Figure S83. $^{19}$F-NMR (400 MHz, CDCl$_3$) spectrum of 3ha, related to Scheme 3.

Figure S84. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ia, related to Scheme 3.
Figure S85. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ia, related to Scheme 3.

Figure S86. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ja, related to Scheme 3.
Figure S87. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ja, related to Scheme 3.

Figure S88. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3jl, related to Scheme 2.
Figure S89. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3jl, related to Scheme 3.

Figure S90. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3ka, related to Scheme 2.
Figure S91. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 3ka, related to Scheme 3.

Figure S92. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 3la, related to Scheme 2.
Figure S93. $^{13}C$-NMR (100 MHz, CDCl$_3$) spectrum of 3la, related to Scheme 3.

Figure S94. $^{19}F$-NMR (100 MHz, CDCl$_3$) spectrum of 3la, related to Scheme 3.
Figure S94. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 4ja, related to Scheme 4.

Figure S95. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 4ja, related to Scheme 4.
Figure S96. $^1$H-NMR (400 MHz, CDCl$_3$) spectrum of 5ja, related to Scheme 4.

Figure S97. $^{13}$C-NMR (100 MHz, CDCl$_3$) spectrum of 5ja, related to Scheme 4.
Transparent Methods.

All the obtained products were characterized by melting points (m.p), $^1$H-NMR, $^{13}$C-NMR and infrared spectra (IR). Melting points were measured on an Electrothermal SGW-X4 microscopy digital melting point apparatus; $^1$H-NMR and $^{13}$C-NMR spectra were obtained on Bruker-400 and referenced to 7.26 ppm for chloroform solvent with TMS as internal standard (0 ppm). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), multiplet (m); TLC was performed using commercially prepared 100-400 mesh silica gel plates (GF254), and visualization was effected at 254 nm; Unless otherwise stated, all the reagents were purchased from commercial sources (Energy Chemical, J&K Chemic, TCI, Fluka, Acros, SCRC), used without further purification. 1,8-naphthyridines were prepared by the condensation cyclization of 2-aminonicotinaldehyde with ketones in the presence of t-BuOK (Chen et al., 2017). 2-Nitrobenzyl alcohol 1l was prepared by the reduction of Acifluorfen Acid (Rajendran et al., 2015). All calculations were performed for reactants in solution using the solvent model density (SMD) (Marenich et al., 2009) method (solvent = toluene) and employing the Gaussian 09 package (Frisch, M. J. Gaussian 09, Revision C.01; Gaussian, Inc: Wallingford, CT, 2010.). All stationary points were optimized without any constraints at the B3LYP level of theory. (Becke, 1993; Lee et al., 1988; Stephens et al., 1994) Frequency calculations at the same level of theory were also performed to identify all stationary points as minima (zero imaginary frequencies) or transition states (one imaginary frequency), and to calculate the free energies. Intrinsic reaction coordinate calculations were performed to verify the transition-state structures. (Fukui, 1970; Fukui, 1981) The LANL2DZ effective core potential method (Hay et al., 1985; Wadt et al., 1985) with an extra f-polarization function ($\zeta_f = 0.938$) (Ehlers et al., 1993) was used as the basis set for Ir, while the 6-31G(d) (Krishnan et al., 1980; McLean et al., 1980) basis set was used for all other atoms (C, H, N, O, Na and Cl). To obtain better accuracy, energies of the optimized geometries were recalculated using M06 (Zhao et al., 2005; Zhao et al., 2008; Zhao et al., 2009) single point calculations with a larger basis set, employing the LANL2TZ(f) (Roy et al., 2008) basis set for Ir and the 6-311++G** basis set for all other atoms. Empirical D3 dispersion corrections were included for the M06 functional. (Grimme et al., 2010) The final Gibbs free energies reported herein ($\Delta G_{sol}$) represent the M06 single point energies with Gibbs free energy corrections.

Optimization of reaction conditions.

Table S1. Screening of different metal catalysts and ligands. Related to Table 1. Related to the first paragraph of “RESULTS AND DISCUSSION” in the main text.
| Entry | Catalyst | Ligand | Additive | Solvent | Temperature | N source | Yields of 3aa |
|-------|----------|--------|----------|---------|-------------|----------|---------------|
| 1     | Cat 3    | L1     | t-BuOK   | toluene | 130         | NH₄OAc   | 5%            |
| 2     | Cat 3    | L2     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 3     | Cat 3    | L3     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 4     | Cat 3    | L4     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 5     | Cat 3    | L5     | t-BuOK   | toluene | 130         | NH₄OAc   | <5%           |
| 6     | Cat 3    | L6     | t-BuOK   | toluene | 130         | NH₄OAc   | <5%           |
| 7     | Cat 3    | L7     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 8     | Cat 1    | L3     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 9     | Cat 2    | L3     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 10    | Cat 4    | L3     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 11    | Cat 5    | L3     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 12    | Cat 6    | L3     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 13    | Cat 7    | L3     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 14    | Cat 8    | L3     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 15    | Cat 9    | L3     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 16    | Cat 10   | L3     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 17    | Cat 11   | L3     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 18    | Cat 12   | L3     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 19    | Cat 13   | L3     | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 20    | Cat 4    | L6     | t-BuOK   | toluene | 130         | NH₄OAc   | <5%           |
| 21    | Cat 4    | -      | t-BuOK   | toluene | 130         | NH₄OAc   | trace         |
| 22    | Cat 3    | L1     | t-BuONa  | toluene | 130         | NH₄OAc   | 5%            |
| 23    | Cat 3    | L1     | NaOH     | toluene | 130         | NH₄OAc   | <5%           |
| 24    | Cat 3    | L1     | KOH      | toluene | 130         | NH₄OAc   | <5%           |
| 25    | Cat 3    | L1     | NaOCH₃   | toluene | 130         | NH₄OAc   | <5%           |
| 26    | Cat 3    | L1     | t-BuOK   | p-xylene | 130         | NH₄OAc   | <5%           |
| 27    | Cat 3    | L1     | t-BuOK   | chlorobenzene | 130         | NH₄OAc   | <5%           |
| 28    | Cat 3    | L1     | t-BuOK   | t-amyl alcohol | 130         | NH₄OAc   | <5%           |
| 29    | Cat 3    | L1     | t-BuOK   | DMF      | 130         | NH₄OAc   | <5%           |
| 30    | Cat 3    | L1     | t-BuOK   | toluene | 130         | HCOONH₄  | trace         |
| 31    | Cat 3    | L1     | t-BuOK   | toluene | 130         | HCOONH₄  | trace         |
The reaction was performed with 1a (0.5 mmol), 2a (0.5 mmol), catalyst (1 mol%), ligand (3 mol%), additive (50 mol%), NH₃ sources (1.0 mmol) in solvent (1.5 mL) for 24 h under Ar protection. b GC yield by using hexadecane as an internal standard.

Table S2. Optimization of reaction conditions with Ir catalysts. Related to Table 1. Related to the first paragraph of “RESULTS AND DISCUSSION” in the main text.

| Entry | Catalyst | Additive | Solvent   | Temperature | N source | Yields of 3aa a, b |
|-------|----------|----------|-----------|-------------|----------|--------------------|
| 1     | [IrCl₂]₂ | t-BuOK   | toluene   | 130         | NH₄OAc   | 15                 |
| 2     | [IrCl₂]₂ | t-BuOK   | p-xylene  | 130         | NH₄OAc   | trace              |
| 3     | [IrCl₂]₂ | t-BuOK   | chlorobenzene | 130     | NH₄OAc   | -                  |
| 4     | [IrCl₂]₂ | t-BuOK   | t-amyl alcohol | 130   | NH₄OAc   | 14                 |
| 5     | [IrCl₂]₂ | t-BuOK   | DMSO      | 130         | NH₄OAc   | 10                 |
| 6     | [IrCl₂]₂ | t-BuOK   | DMF       | 130         | NH₄OAc   | 15                 |
| 7     | [IrCl₂]₂ | t-BuOK   | 1,4-dioxane | 130       | NH₄OAc   | trace              |
| 8     | [IrCl₂]₂ | t-BuONa  | toluene   | 130         | NH₄OAc   | 16                 |
| 9     | [IrCl₂]₂ | NaOH     | toluene   | 130         | NH₄OAc   | 15                 |
| 10    | [IrCl₂]₂ | NaOAc    | toluene   | 130         | NH₄OAc   | 11                 |
| 11    | [IrCl₂]₂ | Cs₂CO₃   | toluene   | 130         | NH₄OAc   | 12                 |
| 12    | [IrCl₂]₂ | NaOMe    | toluene   | 130         | NH₄OAc   | 9                  |
| 13    | [IrCl₂]₂ | -        | toluene   | 130         | NH₄OAc   | 10                 |
| 14    | [IrCl₂]₂ | t-BuONa  | toluene   | 120         | NH₄OAc   | 11                 |
| 15    | [IrCl₂]₂ | t-BuONa  | toluene   | 140         | NH₄OAc   | 18                 |
| 16    | [IrCl₂]₂ | t-BuONa  | toluene   | 150         | NH₄OAc   | 15                 |
| 17    | Ir-1     | t-BuONa  | toluene   | 140         | NH₄OAc   | 72                 |
| 18    | Ir-2     | t-BuONa  | toluene   | 140         | NH₄OAc   | 75                 |
| 19    | Ir-3     | t-BuONa  | toluene   | 140         | NH₄OAc   | 82                 |
| 20    | Ir-4     | t-BuONa  | toluene   | 140         | NH₄OAc   | 61                 |
| 21    | Ir-5     | t-BuONa  | toluene   | 140         | NH₄OAc   | 67                 |
| 22    | Ir-6     | t-BuONa  | toluene   | 140         | NH₄OAc   | 71                 |
| 23    | Ir-7     | t-BuONa  | toluene   | 140         | NH₄OAc   | 68                 |
Typical procedure for the synthesis of complexes Ir-1 – Ir-5, Ir-7, Ir-8 and Ir-9.
Under N₂ atmosphere, [Cp' IrCl₂]₂ (0.2 mmol), NaOAc (0.6 mmol) and 2-substituted 1,8-naphthyridine (0.4 mmol, Chen et al., 2017) and dichloromethane (5 mL) were introduced in a Schlenk tube, successively. Then the Schlenk tube was closed and the resulting mixture was stirred at 60 °C for 12 h. After cooling down to room temperature, the reaction mixture was filtered through celite, eluting with CH₂Cl₂, dried over MgSO₄ and filtered. The solvent was evaporated to give a crude solid followed by the addition of 1 mL of diethyl ether with washing for three times.

Typical procedure for the synthesis of complex Ir-6.
Under N₂ atmosphere, [Cp' IrCl₂]₂ (0.2 mmol), and 2-(pyridin-2-yl)-1,8-naphthyridine (0.4 mmol) and dichloromethane (5 mL) were introduced in a Schlenk tube, successively. Then the Schlenk tube was closed and the resulting mixture was stirred at 60 °C for 12 h. After cooling down to room temperature, the reaction mixture was filtered through celite, eluting with CH₂Cl₂, dried over MgSO₄ and filtered. The solvent was evaporated to give a crude solid followed by the addition of 1 mL of diethyl ether with washing for three times.

Typical procedure for the synthesis of 3aa.
A vial was charged with (2-nitrophenyl)methanol 1a (0.5 mmol), Ir-3 (1 mol %), t-BuONa (40 mol %) in succession. The vial was transferred into the autoclave. Once sealed, the autoclave was purged with argon gas, and then was injected with phenylmethanol 2a (0.5 mmol) in toluene (1.5 mL) under Ar atmosphere. Then the autoclave was aerated with NH₃, pressurized to 4 bar, heated up and kept at 140 °C for 24 h under thorough stirring. After the reaction, the autoclave was cooled to room temperature, depressurized, and the resulting mixture was purified by preparative TLC on silica to get 2-phenylquinazoline 3aa.

Scheme S1. Substrates employed for the synthesis of quinazolines. Related to Scheme 2, 3 & 4. Related to the second and third paragraph of “RESULTS AND DISCUSSION” in the main text.
The Control Experiments. Related to the fifth paragraph of “RESULTS AND DISCUSSION” in the main text.

Scheme S2. Control experiments. Related to Scheme 5. Related to the fifth paragraph of “RESULTS AND DISCUSSION” in the main text.
Data S1. The Experimental Procedure for the Time-Concentration Profile. Related to Scheme 5. Related to the fifth paragraph of "RESULTS AND DISCUSSION" in the main text.

A vial was charged with (2-nitrophenyl)methanol 1a (0.5 mmol), Ir-3 (1 mol %), t-BuONa (40 mol %) in succession, which was then transferred into the autoclave. Once sealed, the autoclave was purged with argon gas, and then was injected with phenylmethanol 2a (0.5 mmol) in toluene (1.5 mL) under Ar atmosphere. Then the autoclave was aerated with NH₃, pressurized to 4 bar, heated up and kept at 140 °C for 0−24 h (1, 2, 4, 8, 12, 16, 20 h) under thorough stirring. After the reaction, the autoclave was cooled to room temperature, depressurized, and added hexadecane (25 mg) as an internal standard. The yield was determined by the GC-MS. For 1a-4, MS (El, M/z): 121.08 [M]+; ¹H NMR (400 MHz, CDCl₃) δ 9.85 (s, 1H), 7.46 (dd, J = 7.8, 1.6 Hz, 1H), 7.29 (t, J = 8.3 Hz, 1H), 6.73 (t, J = 7.8 Hz, 1H), 6.62 (d, J = 8.2 Hz, 1H), 6.05 (s, 2H). For 3aa-1, MS (El, M/z): 208.12 [M]+; ¹H NMR (400 MHz, CDCl₃) δ 8.15 (s, 1H), 7.50-7.53 (m, 2H), 7.31-7.45 (m, 3H), 7.14-7.21 (m, 2H), 6.70 (s, 1H), 6.56-6.63 (m, 2H), 5.97 (s, 1H).

Data S2. Preparation of Cyclometalated Iridium Hydride Ir-H. Related to Scheme 5. Related to the fifth paragraph of "RESULTS AND DISCUSSION" in the main text.

According to Xiao’s reference method (Wang et al., 2013) under N₂ atmosphere, Ir-3 (1 equiv.) and HCOOH/Et₃N (F/T) azeotrope (4 equiv.) in methanol were introduced in a Schlenk tube, successively. The solution was left overnight; Crystals of Ir-H were collected after removing the liquid with syringe and washed with MeOH. 42% yield as red crystals; ¹H NMR (400 MHz, Tol) δ 7.20 (s, 1H), 7.05 (s, 1H), 7.01 (d, J = 8.4 Hz, 1H), 6.56 (d, J = 15.5 Hz, 2H), 6.34 (d, J = 7.8 Hz, 1H), 6.29 (d, J = 9.1 Hz, 1H), 6.05 (d, J = 7.8 Hz, 1H), 3.22 (s, 3H), 1.30 (s, 15H), -15.19 (s, 1H).

Figure S98. ¹H NMR spectrum of complex Ir-H in toluene-d₈. Related to Scheme 5. Related to the fifth paragraph of “RESULTS AND DISCUSSION” in the main text.
The details of the synthetic utility. Related to the fourth paragraph of “RESULTS AND DISCUSSION” in the main text.

Scheme S3. The synthetic utility of the developed chemistry. Related to Scheme 4.

(a) Gram scale hydrogen transfer cyclization with 0.2 mol % catalyst loading

\[
\begin{align*}
\text{1a (8 mmol)} & \rightarrow \text{Ph-OH} & \rightarrow \text{NH}_3 & \rightarrow \text{1l (8 mmol)} \\
\text{2a (9 mmol)} & & & \\
\text{toluene, 140 °C, 24 h} & & & \\
\text{3aa, 78% yield (1.28 g)} & & &
\end{align*}
\]

(b) Direct access to a herbicide 3la

\[
\begin{align*}
\text{Ph} & \rightarrow \text{OH} \\
\text{F}_3\text{C} & \rightarrow \text{Cl} \\
\text{11} & \rightarrow \text{OH} \\
\text{2a} & \rightarrow \text{NH}_3 \\
\text{toluene, 140 °C, 24 h} & & & \\
\text{3la, 68% yield} & & &
\end{align*}
\]

(c) Derivatization of 3ja : Access to extended pi-conjugated system

\[
\begin{align*}
\text{3ja} & \rightarrow \text{Br} \rightarrow \text{N} \rightarrow \text{Ph} \\
\text{5 equiv LiBr} & \rightarrow \text{130 °C} \\
\text{chlorobenzene, 130 °C} & \rightarrow \text{Br} \rightarrow \text{N} \rightarrow \text{Ph} \\
\text{5 mol% PdCl}_2 & \rightarrow \text{phenylethylene} \\
\text{5 mol% Cul} & \rightarrow \text{DMF, 100 °C} \\
\text{5ja, 68% yield} & & &
\end{align*}
\]

(1) Preparation of 1l: To a solution of 5-(2-chloro-4-(trifluoromethyl)phenoxy)-2-nitrobenzoic acid (Acifluorfen Acid, 2 mmol) in THF under N₂ atmosphere, BH₃·THF (1.0 M in THF. 2 mmol, 2 mL) was added at 0 °C over 1 hour. The resulting mixture was allowed to warm to room temperature over 32 hours. After reaction, THF was removed under vacuum; the reaction mixture was quenched with water, and extracted with EtOAc. The combined organic layer was dried with anhydrous sodium sulfate and solvent were removed under reduced pressure to give crude product. Crude product was purified by column chromatography to get 1l.

(2) Synthesis of a herbicide 3la

A vial was charged with 1l (0.5 mmol), Ir-3 (1 mol %), t-BuONa (40 mol %) in succession. The vial was transferred into the autoclave. Once sealed, the autoclave was purged with argon gas, and then was injected with phenylmethanol 2a (0.5 mmol) in toluene (1.5 mL) under Ar atmosphere. Then the autoclave was aerated with NH₃, pressurized to 4 bar, heated up and kept at 140 °C for 24 h under thorough stirring. After the reaction, the autoclave was cooled to room temperature, depressurized, and the resulting mixture was purified by preparative TCL on silica to get the product 3la.

(3) Synthesis of herbicide 4ja

The mixture of 3ja (0.5 mmol), benzylamine (1 mmol), lithium bromide (3 mmol), and CuBr₂ (0.1 mmol) in chlorobenzene (3 mL) was stirred at 120 °C for 32 h using an O₂ balloon. After being cooled to room temperature, the resulting mixture was extracted with chloroform, washed with 5% Na₂CO₃ solution, dried with anhydrous sodium sulfate, and then concentrated by removing the solvent under vacuum. Finally, the residue was purified by preparative TLC on silica to give the product 4ja.

(4) Synthesis of functionalized multi conjugate N-heteroaromatic 5ja

Under N₂ atmosphere, 4ja (0.5 mmol), ethynylbenzene (0.65 mmol), PdCl₂ (5 mol %), Cul (20 mol %), PPh₃ (10 mol %), N(C₆H₅)₃ (1.5 mmol), and DMF (1.0 mL) were introduced in a Schlenk tube, successively. Then the Schlenk tube was closed, and the resulting mixture was stirred at 90 °C for 12 h. After being cooled to room temperature, the resulting mixture was extracted with chloroform, washed with 5% Na₂CO₃ solution, dried with anhydrous sodium...
sulfate, and then concentrated by removing the solvent under vacuum. Finally, the residue was purified by preparative TLC on silica to give the product 5ja.

**Scheme S4.** MPV-O TH pathway. Related to Figure 2. (Values shown are relative free energies in kcal/mol.) Related to the sixth paragraph of “RESULTS AND DISCUSSION” in the main text.

The calculated free-energy profile for the 2nd TH of 1a-2 to 1a-3 is shown in Figure S99. The reaction begins with coordination of 2a to the Ir center of Ir-O1 to form intermediate IN8, which is an endergonic process. Subsequent O–H deprotonation via four-centered transition-state TS6 with an energy barrier of 23.3 kcal/mol relative to Ir-O1 gives Ir–alkoxide intermediate Ir-O2 and t-BuOH. From Ir-O2, C–H cleavage via transition state TS7 gives Ir–benzaldehyde IN9 with an energy barrier of 27.0 kcal/mol relative to Ir-O2. Intermediate IN9 would then dissociate to give Ir-H together with the benzaldehyde. The next step is the TH from Ir-H to 1a-2. We calculated two possible pathways: hydrogen migration to N atom via TS8’ (blue line) and hydrogen migration to O atom via TS8” (red line). The results show that the barrier (24.7 kcal/mol) for hydrogen migration to O atom is higher than that (19.6 kcal/mol) for hydrogen migration to N atom, therefore the hydrogen migration to N atom is kinetically favorable. Previously, it has been shown that such a H-transfer could be facilitated by a transferring shuttle such as water or alcohol proton shuttle. We performed calculations for hydrogen migration to N atom when using benzyl alcohol 2a as the proton transferring shuttle (black line). The calculated free energy of transition state TS8 for the hydrogenation assisted by 2a is -12.2 kcal/mol, which is lower than that of TS8’. Therefore, the hydrogen migration to the N atom using 2a as the proton transferring shuttle constitutes a preferred mode. The relative instability of TS8 compared with TS8’ can be attributed to the ring strain associated with the four-membered ring in TS8’. IN10 then isomerizes to the less stable intermediate IN11 by coordination of 2a to the Ir center and dissociation of one of the arms of the 1,8-naphthyridyl ligand. The TH is accomplished via transition state TS9 with an energy barrier of 23.0 kcal/mol relative to IN10, which generates the 2-(hydroxyamino)benzaldehyde 1a-3 and complex Ir-O2.

**Figure S99.** Calculated energy profiles for transformation of 2-nitrosobenzaldehyde 1a-2 to 2-(hydroxyamino)benzaldehyde 1a-3. Values shown are relative free energies in kcal/mol. Related to Figure 2 & Figure 3. Related to the seventh paragraph of “RESULTS AND DISCUSSION” in the main text.
Figure S100. Calculated energy profiles for transformation of 2-(hydroxyamino)benzaldehyde 1a-3 to 2-aminobenzaldehyde. Values shown are relative free energies in kcal/mol. Related to Figure 2 & Figure 3. Related to the seventh paragraph of “RESULTS AND DISCUSSION” in the main text.

As shown in Figure S100 (3rd TH), Ir-O2 is transformed to IN9 through β-H elimination. The identified transition state is denoted as TS10 and the calculated energy barrier is 25.8 kcal/mol. A molecule of 1a-3 enters and then the benzaldehyde dissociates to yield intermediate IN12. Subsequently, IN12 undergoes dehydration by passing transition state TS11, affording an Ir-nitrene intermediate IN13. Binding of IN13 with benzyl alcohol 2a via a hydrogen bond affords intermediate IN14. From IN14, the TH using 2a as the proton transferring shuttle takes place via TS12 to give complex IN15, in which 2a is bound to Ir. The hydrogen of 2a is transferred to the nitrogen atom via TS13 with a very small barrier of 1.8 kcal/mol. The iridium 2-aminobenzaldehyde IN16 is generated with the formation of alcohol anion, which is stabilized by the hydrogen bonding by alcohol 2a.

Scheme S5. Hydrogen migration to N atom using t-BuOH as the proton transferring shuttle. Values shown are relative free energies in kcal/mol. Related to Figure 2 & Figure 3. Related to the seventh paragraph of “RESULTS AND DISCUSSION” in the main text.
**Scheme S6.** Other possible pathway started from IN12. Values shown are relative free energies in kcal/mol. Related to Figure 2 & Figure 3. Related to the seventh paragraph of “RESULTS AND DISCUSSION” in the main text.

**Scheme S7.** Other possible pathway started from IN19. Values shown are relative free energies in kcal/mol. Related to Figure 3. Related to the seventh paragraph of “RESULTS AND DISCUSSION” in the main text.

**Scheme S8.** Other possible pathway started from IN21. Values shown are relative free energies in kcal/mol. Related to Figure 3. Related to the seventh paragraph of “RESULTS AND DISCUSSION” in the main text.

**Table S3.** Energies (in Hartree) for all TS and intermediates. Related to Figure 2, Figure 3, Figure S99, Figure S100 and Scheme S4, Scheme S5, Scheme S6, Scheme S7 & Scheme S8.

| Geometry | $E_0$  | $E$    | $H_{413.15}$ | $G_{413.15}$ | $E_{(sol,M06)}$ |
|----------|--------|--------|--------------|--------------|-----------------|
| Ir-O1    | -1490.293732 | -1490.229403 | -1490.228095 | -1490.402536 | -1489.75506     |
| 1a       | -551.134366   | -551.117956  | -551.116647  | -551.187508  | -551.0114631    |
| IN1      | -2041.416957  | -2041.333032  | -2041.331723  | -2041.557112  | -2040.745557    |
|   | TS1   | TS2   | TS3   | TS4   | TS5   | NaOH  | H2O   | t-BuOH | t-BuONa |
|---|-------|-------|-------|-------|-------|-------|-------|--------|---------|
|   | -2041.408804 | -2041.85907 | -1807.877623 | -2041.404858 | -2041.870208 | -1807.901263 | -1807.877623 | -2041.458380 | -395.263703 |
| IN2 | -1807.908586 | -1807.855907 | -1807.877623 | -2041.404858 | -2041.870208 | -1807.901263 | -1807.877623 | -2041.458380 | -395.263703 |
| IN3 | -1807.908586 | -1807.855907 | -1807.877623 | -2041.404858 | -2041.870208 | -1807.901263 | -1807.877623 | -2041.458380 | -395.263703 |
| IN-H | -1807.908586 | -1807.855907 | -1807.877623 | -2041.404858 | -2041.870208 | -1807.901263 | -1807.877623 | -2041.458380 | -395.263703 |
| IN4 | -1807.908586 | -1807.855907 | -1807.877623 | -2041.404858 | -2041.870208 | -1807.901263 | -1807.877623 | -2041.458380 | -395.263703 |
| IN5 | -1807.908586 | -1807.855907 | -1807.877623 | -2041.404858 | -2041.870208 | -1807.901263 | -1807.877623 | -2041.458380 | -395.263703 |
| IN6 | -1807.908586 | -1807.855907 | -1807.877623 | -2041.404858 | -2041.870208 | -1807.901263 | -1807.877623 | -2041.458380 | -395.263703 |
| 1a-2 | -474.748119 | -474.748119 | -474.748119 | -474.748119 | -474.748119 | -474.748119 | -474.748119 | -474.748119 | -474.748119 |
| H2O | -76.390125 | -76.390125 | -76.390125 | -76.390125 | -76.390125 | -76.390125 | -76.390125 | -76.390125 | -76.390125 |
| 1a-2 | -474.748119 | -474.748119 | -474.748119 | -474.748119 | -474.748119 | -474.748119 | -474.748119 | -474.748119 | -474.748119 |
| 2a | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 |
| 2a | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 |
| 2a | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 | -346.636496 |
| TS6 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 |
| TS7 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 |
| TS8 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 |
| TS9 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 |
| TS10 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 |
| TS11 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 |
| TS12 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 |
| TS13 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 | -1836.91314 |
Calculated imaginary frequencies of all transition states species

Table S4. Calculated imaginary frequencies of all transition states species for substrate.
Related to Figure 2, Figure 3, Figure S99, Figure S100 and Scheme S4, Scheme S5, Scheme S6, Scheme S7 & Scheme S8.

| Species | Frequency |
|---------|-----------|
| TS1     | -584.09   |
| TS2     | -743.09   |
| TS3     | -425.57   |
Crystallographic data of complex Ir-3.

Figure S101. Molecular structure of Ir-3 is displayed with thermal ellipsoids set at 50% probability (Hydrogen atoms are omitted for clarity. CCDC: 1848110). Related to Table 1.

| TS  | Energy (kcal/mol) |
|-----|-------------------|
| TS4 | -715.20           |
| TS5 | -1746.69          |
| TS6 | -737.34           |
| TS7 | -686.33           |
| TS8 | -901.67           |
| TS8' | -860.06          |
| TS8'' | -679.02         |
| TS8-1 | -860.46        |
| TS9 | -757.76           |
| TS10 | -686.33          |
| TS11 | -593.96          |
| TS11' | -627.49         |
| TS12 | -563.41           |
| TS13 | -1148.07          |
| TS14 | -144.35           |
| TS14' | -140.97         |
| TS15 | -57.07            |
| TS15' | -316.98         |
| TS15-1 | -1654.38       |
| TS15-2 | -829.31         |
| TS16 | -697.59           |
| TS16' | -281.04           |
| TS16'' | -716.03        |
| TS16-1 | -1584.06        |
| TS16-2 | -832.94          |
| TS16-3 | -1062.09         |

Table S5. Crystal data and structure refinement for Ir-3. Related to Table 1.

| Identification code | Ir-3 |
|---------------------|------|
| Empirical formula   | C_{25}H_{26}ClIrN_{2}O |
| Formula weight      | 598.13 |
Temperature/K: 100.00(10)
Crystal system: orthorhombic
Space group: P2₁2₁2₁
a/Å: 9.0070(4)
b/Å: 14.7851(8)
c/Å: 16.1262(6)
α/°: 90
β/°: 90
γ/°: 90
Volume/Å³: 2147.52(17)
Z: 4
ρ calc \(g/cm^3\): 1.850
μ/mm⁻¹: 6.361
F(000): 1168.0
Crystal size/mm³: 0.13 × 0.12 × 0.11
Radiation: MoKα (λ = 0.71073)
2Θ range for data collection/°: 5.052 to 49.994
Index ranges: -10 ≤ h ≤ 9, -12 ≤ k ≤ 17, -19 ≤ l ≤ 15
Reflections collected: 14026
Independent reflections: 3783 \([R_{int} = 0.0488, R_{sigma} = 0.0487]\)
Data/restraints/parameters: 3783/12/277
Goodness-of-fit on F²: 1.033
Final R indexes \([I>=2σ (I)]\): R₁ = 0.0294, wR₂ = 0.0519
Final R indexes \([all\ data]\): R₁ = 0.0356, wR₂ = 0.0545
Largest diff. peak/hole / e Å⁻³: 1.03/-0.77
Flack parameter: -0.027(7)

**Table S6.** Fractional Atomic Coordinates \((×10^4)\) and Equivalent Isotropic Displacement Parameters \((Å^2×10^3)\) for Ir-3. Ueq is defined as 1/3 of the trace of the orthogonalised Uu tensor. Related to Table 1.

| Atom | x    | y    | z    | U(eq) |
|------|------|------|------|-------|
| C(1) | 671(10) | 6964(7) | 59(6) | 25(2) |
| C(2) | 698(10) | 7845(8) | -244(6) | 29(3) |
| C(3) | 1351(10) | 8496(7) | 223(6) | 24(2) |
| C(4) | 2021(9) | 8266(6) | 992(5) | 18(2) |
| C(5) | 1950(8) | 7340(6) | 1227(5) | 14(2) |
| C(6) | 2747(10) | 8882(6) | 1519(5) | 23(2) |
| C(7) | 3433(9) | 8583(6) | 2212(5) | 20(2) |
| C(8) | 3393(7) | 7652(5) | 2427(6) | 15.3(18) |
| C(9) | 4163(9) | 7236(6) | 3116(5) | 16(2) |
| C(10) | 5133(9) | 7695(7) | 3643(5) | 18(2) |
Table S7. Anisotropic Displacement Parameters (Å²×10³) for Ir3. The Anisotropic displacement factor exponent takes the form: \(-2\pi^2[a^{2}U_{11}+2hka^{*}b^{*}U_{12}+…]\). Related to Table 1.

| Atom | U₁₁   | U₂₂   | U₃₃   | U₂₃   | U₁₃   | U₁₂   |
|------|-------|-------|-------|-------|-------|-------|
| C(1) | 15(5) | 35(7) | 25(6) | -4(5) | -8(4) | 6(4)  |
| C(2) | 31(6) | 36(8) | 20(6) | 5(5)  | -10(4)| 6(5)  |
| C(3) | 29(6) | 21(7) | 21(6) | 10(5) | -2(4) | 3(5)  |
| C(4) | 15(5) | 18(6) | 21(5) | 7(4)  | 5(3)  | 4(4)  |
| C(5) | 6(4)  | 25(6) | 12(5) | 3(4)  | 3(3)  | 3(4)  |
| C(6) | 22(5) | 14(5) | 31(5) | 4(4)  | 2(4)  | -1(4) |
| C(7) | 21(5) | 9(5)  | 31(6) | 1(4)  | -4(4) | 1(4)  |
| C(8) | 15(4) | 16(5) | 16(5) | -4(5) | 1(4)  | -1(3) |
| C(9) | 19(5) | 13(6) | 16(5) | 0(4)  | 9(4)  | -3(4) |
| C(10)| 16(5) | 18(6) | 19(5) | -5(4) | 3(4)  | 2(4)  |
| C(11)| 15(5) | 29(7) | 16(5) | -7(5) | -1(4) | -6(4) |
| C(12)| 14(5) | 29(7) | 11(5) | 3(4)  | 5(3)  | -1(4) |
| C(13)| 11(4) | 18(6) | 19(5) | -5(4) | 0(3)  | -4(4) |
| C(14)| 9(4)  | 14(5) | 11(5) | -4(4) | 5(3)  | -1(4) |
| C(15)| 23(5) | 28(6) | 21(5) | 1(4)  | -10(4)| -4(5) |
| Atom   | Atom | Length/Å | Atom   | Length/Å |
|--------|------|----------|--------|----------|
| C(16)  | C(2) | 1.391(14)| C(14)  | 2.024(8) |
| C(17)  | N(1) | 1.331(11)| C(15)  | 1.429(9) |
| C(18)  | C(3) | 1.356(14)| C(16)  | 1.418(12)|
| C(19)  | C(4) | 1.420(12)| C(17)  | 1.443(12)|
| C(20)  | C(5) | 1.422(12)| C(18)  | 1.494(13)|
| C(21)  | C(6) | 1.406(12)| C(19)  | 2.160(8) |
| C(22)  | C(5) | 1.343(11)| C(20)  | 1.514(13)|
| C(23)  | N(2) | 1.391(10)| C(21)  | 2.139(9) |
| C(24)  | C(7) | 1.352(12)| C(22)  | 1.505(12)|
| C(25)  | C(8) | 1.402(12)| C(23)  | 2.154(9) |
| C(26)  | C(9) | 1.447(12)| C(24)  | 1.391(13)|
| C(27)  | N(2) | 1.357(10)| C(25)  | 1.391(13)|
| C(28)  | C(10)| 1.396(12)| C(26)  | 1.418(13)|
| C(29)  | C(14)| 1.418(13)| C(27)  | 1.499(12)|
| C(30)  | C(11)| 1.372(12)| C(28)  | 2.263(9) |
| C(31)  | C(12)| 1.406(13)| C(29)  | 2.517(12)|
| C(32)  | C(13)| 1.383(12)| C(30)  | 2.288(9) |
| C(33)  | C(14)| 1.386(12)| C(31)  | 2.417(2) |

**Table S8.** Bond Lengths for Ir-3. Related to Table 1.

| Atom | Angle/° |
|------|---------|
| C(1) | 115.0(6) |
| C(2) | 115.0(6) |
| C(3) | 115.0(6) |
| C(4) | 115.0(6) |
| C(5) | 115.0(6) |
| C(6) | 115.0(6) |
| C(7) | 115.0(6) |
| C(8) | 115.0(6) |
| C(9) | 115.0(6) |
| C(10)| 115.0(6)|
| C(11)| 115.0(6)|
| C(12)| 115.0(6)|
| C(13)| 115.0(6)|
| C(14)| 115.0(6)|

**Table S9.** Bond Angles for Ir-3. Related to Table 1.
| Atom  | Atom | Atom | Angle/° | Atom  | Atom | Atom | Angle/° |
|-------|------|------|---------|-------|------|------|---------|
| N(1)  | C(1) | C(2) | 124.8(9)| C(18) | C(19) | Ir(1) | 66.8(5) |
| C(3)  | C(2) | C(1) | 118.5(9)| C(20) | C(19) | C(18) | 109.1(8)|
| C(2)  | C(3) | C(4) | 120.0(10)| C(20) | C(19) | C(24) | 126.3(8)|
| C(3)  | C(4) | C(5) | 116.3(9)| C(20) | C(19) | Ir(1)  | 73.2(5) |
| C(6)  | C(4) | C(3) | 124.8(9)| C(24) | C(19) | Ir(1)  | 123.9(6)|
| C(6)  | C(4) | C(5) | 118.9(8)| C(16) | C(20) | C(25) | 122.8(9)|
| N(1)  | C(5) | C(4) | 123.6(8)| C(16) | C(20) | C(18) | 66.3(5) |
| C(3)  | C(2) | C(1) | 118.5(9)| C(19) | C(20) | C(16) | 107.6(8)|
| C(10) | C(9) | C(8) | 120.1(9)| C(19) | C(20) | Ir(1)  | 71.2(5) |
| C(10) | C(9) | C(14) | 120.2(8)| C(14) | Ir(1) | C(19) | 135.0(6)|
| C(14) | C(9) | C(8) | 115.6(8)| C(14) | Ir(1) | Cl(1)  | 87.6(2) |
| C(11) | C(10) | C(9) | 121.2(9)| C(14) | Ir(1) | N(2)   | 77.9(3) |
| C(10) | C(11) | C(12) | 118.8(8)| C(16) | Ir(1) | C(19) | 62.7(4) |
| C(13) | C(12) | C(11) | 120.2(8)| C(16) | Ir(1) | C(20) | 37.7(3) |
| O(1)  | C(12) | C(11) | 123.8(8)| C(16) | Ir(1) | Cl(1)  | 158.2(3)|
| O(1)  | C(12) | C(13) | 116.0(9)| C(17) | Ir(1) | C(16) | 38.5(3) |
| C(12) | C(13) | C(14) | 121.7(9)| C(17) | Ir(1) | C(18) | 39.6(3) |
| C(9)  | C(14) | Ir(1) | 115.5(6)| C(17) | Ir(1) | C(19) | 63.6(3) |
| C(13) | C(14) | C(9) | 117.7(8)| C(17) | Ir(1) | C(20) | 62.8(3) |
| C(13) | C(14) | Ir(1) | 126.8(7)| C(17) | Ir(1) | Cl(1)  | 137.3(3)|
| C(17) | C(16) | C(20) | 107.7(9)| C(18) | Ir(1) | C(16) | 65.3(4) |
| C(17) | C(16) | C(21) | 127.2(8)| C(18) | Ir(1) | C(19) | 38.2(3) |
| C(17) | C(16) | Ir(1) | 69.9(5) | C(18) | Ir(1) | C(20) | 62.7(3) |
| C(20) | C(16) | C(21) | 124.8(8)| C(18) | Ir(1) | Cl(1)  | 100.9(2)|
| C(20) | C(16) | Ir(1) | 75.9(5) | C(19) | Ir(1) | C(20) | 35.6(3) |
| C(21) | C(16) | Ir(1) | 124.8(7)| C(19) | Ir(1) | Cl(1)  | 95.9(2) |
| C(16) | C(17) | C(18) | 108.2(8)| C(20) | Ir(1) | Cl(1)  | 121.7(2)|
| C(16) | C(17) | C(22) | 126.4(9)| N(2)  | Ir(1) | C(16) | 102.8(3)|
| C(16) | C(17) | Ir(1) | 71.5(5) | N(2)  | Ir(1) | C(17) | 134.3(3)|
| C(18) | C(17) | C(22) | 125.4(9)| N(2)  | Ir(1) | C(18) | 165.8(3)|
| C(18) | C(17) | Ir(1) | 70.7(5) | N(2)  | Ir(1) | C(19) | 130.4(3)|
| C(22) | C(17) | Ir(1) | 126.1(6)| N(2)  | Ir(1) | C(20) | 103.2(3)|
| C(17) | C(18) | C(23) | 126.3(8)| N(2)  | Ir(1) | Cl(1)  | 87.94(18)|
Table S10. Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for Ir-3. Related to Table 1.

| Atom | x    | y    | z    | U(eq) |
|------|------|------|------|-------|
| H(1) | 179.5| 6529.69 | -255.38 | 30 |
| H(2) | 278.59 | 7984.1 | -755.41 | 35 |
| H(3) | 1360.63 | 9092.16 | 39.49 | 28 |
| H(6) | 2754.63 | 9494.83 | 1390.15 | 27 |
| H(7) | 3934.73 | 8990.1 | 2551.23 | 24 |
| H(10) | 5238.41 | 8317.93 | 3591.53 | 21 |
| H(11) | 6559.39 | 7557.2 | 4594.56 | 24 |
| H(13) | 4694.44 | 5220.43 | 3851.87 | 19 |
| H(15A) | 8361.16 | 6534.5 | 5061.52 | 35 |
| H(15B) | 8091.64 | 5778.45 | 5726.26 | 35 |
| H(15C) | 7080.1 | 6641.16 | 5712.29 | 35 |
| H(21A) | -1582.4 | 6440.83 | 3453.81 | 46 |
| H(21B) | -540.4 | 7050.56 | 2911.77 | 46 |
| H(21C) | -70.98 | 6787.5 | 3816.27 | 46 |
| H(22A) | 1764.71 | 5816.42 | 4502.18 | 46 |
| H(22B) | 2300.14 | 4807.76 | 4482.86 | 46 |
| H(22C) | 636.42 | 5032.8 | 4680.29 | 46 |
| H(23A) | 3268.95 | 3775.21 | 3476.79 | 36 |
| H(23B) | 2856.32 | 3335.27 | 2622.84 | 36 |
| H(23C) | 1823.73 | 3191.27 | 3394.19 | 36 |
| H(24A) | 1987.92 | 3797.17 | 1322.17 | 41 |
| H(24B) | 800.31 | 4391.11 | 865.54 | 41 |
| H(24C) | 303 | 3536.37 | 1369.29 | 41 |
| H(25A) | -2102.28 | 5849.81 | 1046.84 | 37 |
| H(25C) | -1173.12 | 6376.16 | 1574.28 | 37 |

Crystal structure determination of Ir-3. Related to Table 1. Crystal Data for C_{25}H_{36}ClIrN_{2}O (M = 598.13 g/mol): orthorhombic, space group P2_12_12_1 (no. 19), a = 9.0070(4) Å, b = 14.7851(8) Å, c = 16.1262(6) Å, V = 2147.52(17) Å³, Z = 4, T = 100.00(10) K, μ(MoKα) = 6.361 mm⁻¹, Dcalc = 1.850 g/cm³, 14026 reflections measured.
Data S3. Analytic data of the obtained compounds. Related to Table 1, Scheme 2, Scheme 3 & Scheme 4.

Complex Ir-1

Orange red solid (107.9 mg, 95% Yield); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.06 – 8.94 (m, 1H), 8.02 (t, $J = 9.2$ Hz, 2H), 7.90 (dd, $J = 20.0$, 8.6 Hz, 2H), 7.78 (d, $J = 7.7$ Hz, 1H), 7.43 (dd, $J = 7.8$, 4.2 Hz, 1H), 7.25 (t, $J = 7.1$ Hz, 1H), 7.07 (t, $J = 7.4$ Hz, 1H), 1.68 (s, 15H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.77, 167.73, 151.67, 143.45, 138.08, 136.92, 131.76, 126.42, 121.91, 121.89, 121.74, 117.94, 89.78, 9.84. IR (KBr): 3055, 2966, 2907, 1604, 1533, 1507, 1467, 1427, 1323, 1283, 847 cm$^{-1}$. HRMS (ESI): Calcd. for C$_{24}$H$_{24}$IrN$_2$ [M-Cl]$^+$: 533.1563; found: 533.1559.

Complex Ir-2

Orange red solid (105.9 mg, 91% Yield); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.97 (d, $J = 2.6$ Hz, 1H), 7.97 (d, $J = 7.7$ Hz, 1H), 7.90 – 7.82 (m, 2H), 7.78 (d, $J = 8.6$ Hz, 1H), 6.88 (d, $J = 7.8$ Hz, 1H), 2.47 (s, 3H), 1.67 (s, 15H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.66, 167.83, 154.66, 153.15, 142.97, 141.79, 137.95, 136.89, 126.32, 123.00, 121.70, 121.63, 117.82, 89.61, 21.89, 9.82. IR (KBr): 3052, 2966, 2909, 2787, 1604, 1582, 1550, 1504, 1452, 1322, 1283, 846, 798 cm$^{-1}$. HRMS (ESI): Calcd. for C$_{25}$H$_{26}$IrN$_2$ [M-Cl]$^+$: 547.1720; found: 547.1723.

Complex Ir-3

Orange red solid (112.4 mg, 94% Yield); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.96 (dd, $J = 4.1$, 1.6 Hz, 1H), 7.97 (d, $J = 7.9$ Hz, 1H), 7.85 (d, $J = 8.6$ Hz, 1H), 7.73 (dd, $J = 13.8$, 8.7 Hz, 2H), 7.57 (d, $J = 2.4$ Hz, 1H), 7.38 (dd, $J = 7.9$, 4.3 Hz, 1H), 6.65 (dd, $J = 8.6$, 2.4 Hz, 1H), 3.95 (s, 3H), 1.68 (s, 15H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 170.21, 170.13, 162.02, 154.74, 153.04, 138.73, 137.76, 136.82, 128.13, 121.39, 121.37, 119.60, 117.79, 109.29, 89.68, 55.14, 9.85. IR (KBr): 3056, 2966, 2907, 2789, 1605, 1505, 1508, 1465, 1425, 1292, 1264, 1220, 842 cm$^{-1}$. HRMS (ESI): Calcd. for C$_{25}$H$_{26}$IrN$_2$O [M-Cl]$^+$: 563.1669; found: 563.1677. Crystals suitable for a single-crystal X-ray diffraction study were grown from a concentrated solution of CHCl$_3$ layered with n-hexane in degassed NMR tube.

Complex Ir-4

Red solid (105.9 mg, 88% Yield); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.01 (dd, $J = 4.2$, 1.9 Hz, 1H), 8.01 (dd, $J = 8.0$, 1.8 Hz, 1H), 7.96 (d, $J = 2.0$ Hz, 1H), 7.83 (d, $J = 8.6$ Hz, 1H), 7.72 (d, $J = 8.7$ Hz, 1H), 7.57 (d, $J = 8.4$ Hz, 1H), 7.44 (dd, $J = 7.9$, 4.2 Hz, 1H), 6.86 (dd, $J = 8.3$, 2.0 Hz, 1H), 1.66 (s, 15H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.58, 168.96, 154.40, 153.40, 144.14, 138.44, 137.40, 137.09, 135.33, 129.04, 127.48, 122.02, 121.97,
118.11, 89.93, 9.77. IR (KBr): 3056, 2966, 2910, 2788, 1603, 1531, 1508, 1451, 1318, 1275, 1087, 1028, 842, 734 cm⁻¹. HRMS (ESI): Calcd. for C₂₄H₂₃ClIrN₂ [M-Cl]⁺: 567.1174; found: 567.1168.

**Complex Ir-5**

Brown solid (115.7 mg, 91% Yield); ¹H NMR (400 MHz, CD₂Cl₂) δ 9.15 (d, J = 2.2 Hz, 1H), 8.30 (s, 1H), 8.24 (d, J = 7.8 Hz, 1H), 8.17 (d, J = 8.6 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 7.9 Hz, 1H), 7.64 (dd, J = 7.8, 4.2 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 1.71 (s, 15H). ¹³C NMR (101 MHz, CD₂Cl₂) δ 169.18, 167.52, 154.52, 153.78, 149.13, 138.76, 137.22, 132.62 (q, JₓC-F = 3.8 Hz), 131.58, 125.96, 122.75, 118.27, 118.22, 90.28, 9.53. ¹⁹F NMR (376 MHz, CD₂Cl₂) δ -62.52. IR (KBr): 3076, 2964, 2915, 2790, 1603, 1510, 1453, 1428, 1318, 1109 cm⁻¹. HRMS (ESI): Calcd. for C₂₅H₂₃F₃IrN₂ [M-Cl]⁺: 601.1437; found: 601.1437.

**Complex Ir-6**

Brownish red solid (115.0 mg, 95% Yield); ¹H NMR (400 MHz, CDCl₃) δ 9.21 (d, J = 6.7 Hz, 1H), 9.15 – 9.07 (m, 2H), 8.96 – 8.84 (m, 2H), 8.55 (d, J = 7.2 Hz, 1H), 8.26 (s, 1H), 7.86 (s, 1H), 7.72 (d, J = 3.4 Hz, 1H), 1.52 (s, 15H). ¹³C NMR (101 MHz, CDCl₃) δ 158.81, 156.01, 155.39, 152.29, 151.76, 143.60, 141.06, 138.98, 129.84, 127.75, 125.33, 125.08, 122.11, 89.97, 9.71. IR (KBr): 3049, 2964, 2923, 2792, 1802, 1547, 1470, 1427, 1316, 1270, 1026, 845, 799 cm⁻¹. HRMS (ESI): Calcd. for C₂₃H₂₄ClIrN₂ [M-Cl]⁺: 570.1283; found: 570.1272.

**Complex Ir-7**

Brownish red solid (104.5 mg, 88% Yield); ¹H NMR (400 MHz, CDCl₃) δ 8.85 (d, J = 2.8 Hz, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.61 (s, 1H), 7.32 (dd, J = 7.7, 4.2 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 6.74 (d, J = 7.2 Hz, 1H), 3.12 – 2.85 (m, 4H), 1.63 (s, 15H). ¹³C NMR (101 MHz, CDCl₃) δ 168.92, 166.66, 153.99, 152.29, 151.76, 143.60, 141.06, 138.98, 129.84, 127.75, 125.33, 125.08, 122.11, 89.97, 9.71. IR (KBr): 3060, 2966, 2914, 2794, 1509, 1466, 1427, 1316, 1270, 1026, 845, 753, 732 cm⁻¹. HRMS (ESI): Calcd. for C₂₆H₂₆IrN₂ [M-Cl]⁺: 559.1720; found: 559.1725.

**Complex Ir-8**

Yellow solid (96.6 mg, 85% Yield); ¹H NMR (400 MHz, CDCl₃) δ 9.66 (s, 1H), 8.51 (d, J = 8.4 Hz, 1H), 8.18 (t, J = 8.0 Hz, 3H), 7.66 (dd, J = 8.4, 5.2 Hz, 1H), 7.59 – 7.45 (m, 3H), 1.51 (s, 15H). ¹³C NMR (101 MHz, CDCl₃) δ 158.56, 144.78, 143.90, 140.29, 139.31, 137.82, 130.36, 129.08, 127.68, 125.27, 122.56, 86.27, 8.89. IR (KBr): 3045, 2965, 2906, 2794, 1607, 1568, 1489, 1439, 1273, 1028, 731 cm⁻¹. HRMS (ESI): Calcd. for C₂₄H₂₄IrN₂ [M-Cl]⁺: 533.1563; found: 533.1560.

**Complex Ir-9**

Yellow solid (91.0 mg, 88% Yield); ¹H NMR (400 MHz, CDCl₃) δ 8.71 (d, J = 5.5 Hz, 1H), 7.89 – 7.78 (m, 2H), 7.67 (dd, J = 15.1, 7.7 Hz, 2H), 7.22 (t, J = 7.8 Hz, 1H), 7.17 (s, 1H), 6.95 (d, J = 7.8 Hz, 1H), 6.58 (t, J = 7.8 Hz, 1H), 6.26 (d, J = 7.8 Hz, 1H), 1.52 (s, 15H). ¹³C NMR (101 MHz, CDCl₃) δ 158.80, 166.66, 153.98, 152.29, 151.76, 143.60, 141.06, 138.98, 129.84, 127.75, 125.33, 125.08, 122.11, 89.97, 9.71. IR (KBr): 3045, 2965, 2906, 2794, 1607, 1568, 1489, 1439, 1273, 1028, 731 cm⁻¹. HRMS (ESI): Calcd. for C₂₆H₂₆IrN₂ [M-Cl]⁺: 559.1725; found: 559.1725.
7.3 Hz, 1H), 7.14 – 6.99 (m, 2H), 1.70 (s, 15H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.33, 163.36, 151.34, 144.16, 137.05, 135.81, 130.96, 123.86, 122.33, 122.07, 118.89, 88.54, 8.93. IR (KBr): 3039, 2967, 2916, 1620, 1600, 1543, 1371, 1024, 753, 734 cm$^{-1}$. HRMS (ESI): Calcd. for C$_{21}$H$_{33}$IrN [M-Cl]+: 482.1454; found: 482.1456.

(1) 2-phenylquinazoline (3aa)

Pale yellow solid (87.6 mg, 85% Yield), m.p.: 99-100°C (Chen et al., 2014); $^1$H NMR (400 MHz, CDCl$_3$) δ 9.38 (s, 1H), 8.51 (d, $J = 8.0$ Hz, 1H), 8.06 (d, $J = 8.4$ Hz, 1H), 7.84 (d, $J = 7.9$ Hz, 2H), 7.57 (t, $J = 7.5$ Hz, 1H), 7.33 (d, $J = 7.9$ Hz, 2H), 2.44 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 161.06, 160.52, 150.78, 138.02, 128.67, 128.62, 127.30, 127.15, 123.62. IR (KBr): 3063, 2963, 2928, 1616, 1549, 772, 704 cm$^{-1}$. MS (EI, m/z): 206.15 [M]+.

(2) 2-(p-tolyl)quinazoline (3ab)

Pale yellow solid, (82.5 mg, 75% Yield), m.p.: 98-99°C (Chen et al., 2014); $^1$H NMR (400 MHz, CDCl$_3$) δ 9.43 (s, 1H), 8.51 (d, $J = 8.0$ Hz, 2H), 8.06 (d, $J = 8.4$ Hz, 1H), 7.88 (d, $J = 7.9$ Hz, 2H), 7.57 (t, $J = 7.5$ Hz, 1H), 7.33 (d, $J = 7.9$ Hz, 2H), 2.44 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 161.17, 160.43, 150.83, 140.88, 135.35, 134.03, 129.42, 128.57, 127.12, 123.54, 21.53. IR (KBr): 3028, 2919, 2795, 1619, 1550, 724 cm$^{-1}$. MS (EI, m/z): 220.14 [M]+.

(3) 2-(o-tolyl)quinazoline (3ac)

Pale yellow solid, (63.8 mg, 58% Yield), m.p.: 45-46°C (Ma et al., 2017); $^1$H NMR (400 MHz, CDCl$_3$) δ 9.50 (s, 1H), 8.10 (d, $J = 8.2$ Hz, 1H), 8.01 – 7.87 (m, 3H), 7.66 (dd, $J = 10.8, 3.8$ Hz, 1H), 7.35 (d, $J = 5.1$ Hz, 3H), 2.61 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 164.05, 160.09, 150.42, 138.59, 137.43, 134.15, 131.32, 130.68, 129.34, 128.60, 127.55, 127.09, 125.99, 122.94, 21.05. IR (KBr): 3058, 2964, 2924, 1619, 1553, 769, 727 cm$^{-1}$. MS (EI, m/z): 220.16 [M]+.

(4) 2-(4-methoxyphenyl)quinazoline (3ad)

Pale yellow solid, (84.9 mg, 72% Yield), m.p.: 96-97°C (Chen et al., 2014); $^1$H NMR (400 MHz, CDCl$_3$) δ 9.38 (s, 1H), 8.57 (d, $J = 8.0$ Hz, 2H), 8.02 (d, $J = 8.4$ Hz, 1H), 7.84 (d, $J = 7.3$ Hz, 2H), 7.57 (t, $J = 7.5$ Hz, 1H), 7.03 (d, $J = 8.0$ Hz, 2H), 3.87 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 161.87, 160.86, 160.38, 150.84, 134.00, 130.76, 130.25, 128.41, 127.12, 126.77, 123.32, 113.99, 55.38. IR (KBr): 3055, 2969, 2833, 1605, 1585, 1407, 1247, 1162, 1028, 836, 796, 733 cm$^{-1}$. MS (EI, m/z): 236.15 [M]+.

(5) 2-(quinazolin-2-yl)phenol (3ae)

White solid, (61.1 mg, 55% Yield), m.p.: 135-136°C (Gujarappa et al., 2018); $^1$H NMR (400 MHz, CDCl$_3$) δ 9.48 (s, 1H), 8.66 (d, $J = 7.9$ Hz, 1H), 8.07 – 7.87 (m, 3H), 7.64 (t, $J = 7.3$ Hz, 1H), 7.42 (t, $J = 7.6$ Hz, 1H), 7.08 (d, $J = 8.1$ Hz, 1H), 7.01 (t, $J = 7.6$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 161.78, 160.89, 160.50, 148.10, 134.97, 133.24, 129.72, 127.56, 127.43, 127.04, 123.01, 119.19, 119.08, 117.87. IR (KBr): 3351, 3041, 1584, 1476, 1382, 1280, 1239, 759 cm$^{-1}$; MS (EI, m/z): 222.12 [M]+.

(6) 4-(quinazolin-2-yl)aniline (3af)

Pale yellow solid, (79.6 mg, 72% Yield), m.p.: 176-177°C (Saha et al., 2017); $^1$H NMR (400 MHz, CDCl$_3$) δ 9.38 (s, 1H), 8.45 (d, $J = 7.7$ Hz, 2H),
8.00 (d, J = 8.3 Hz, 1H), 7.85 (t, J = 8.3 Hz, 2H), 7.53 (t, J = 7.2 Hz, 1H), 6.80 (d, J = 7.7 Hz, 2H), 3.96 (s, 2H). 13C NMR (101 MHz, CDCl₃) δ 161.23, 160.32, 150.93, 149.03, 133.93, 130.22, 128.32, 128.28, 127.15, 126.41, 123.20, 114.80. IR (KBr): 3413, 3319, 1604, 1580, 1483, 1398, 1288, 1170, 796, 734 cm⁻¹. MS (EI, m/z): 221.14 [M⁺].

(7) 2-(4-chlorophenyl)quinazoline (3ag)
Pale yellow solid, (108 mg, 90% Yield), m.p.: 137-138°C (Chen et al., 2014); 1H NMR (400 MHz, CDCl₃) δ 9.38 (s, 1H), 8.53 (d, J = 8.0 Hz, 2H), 8.02 (d, J = 8.3 Hz, 1H), 7.85 (d, J = 7.5 Hz, 2H), 7.56 (t, J = 7.0 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H). 13C NMR (101 MHz, CDCl₃) δ 160.48, 159.98, 150.66, 136.83, 136.52, 134.22, 129.92, 128.80, 128.59, 127.43, 127.13, 123.60. IR (KBr): 3052, 2968, 1619, 1551, 1487, 1409, 846, 796, 724 cm⁻¹. MS (EI, m/z): 240.10 [M⁺].

(8) 2-(3-chlorophenyl)quinazoline (3ah)
Pale yellow solid, (91.2 mg, 76% Yield), m.p.: 149-150°C (Han et al., 2012); 1H NMR (400 MHz, CDCl₃) δ 9.44 (s, 1H), 8.62 (s, 1H), 8.50 (d, J = 6.6 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 7.7 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.50 – 7.40 (m, 2H). 13C NMR (101 MHz, CDCl₃) δ 160.56, 159.70, 150.66, 139.88, 134.80, 134.31, 130.55, 129.85, 128.68, 127.65, 127.15, 126.66, 123.77. IR (KBr): 3067, 2967, 1617, 1549, 780, 760, 716 cm⁻¹. MS (EI, m/z): 240.10 [M⁺].

(9) 2-(4-bromophenyl)quinazoline (3ai)
Pale yellow solid, (106 mg, 75% Yield), m.p.: 121-122°C (Chen et al., 2014); 1H NMR (400 MHz, CDCl₃) δ 9.42 (s, 1H), 8.49 (d, J = 8.3 Hz, 2H), 8.05 (d, J = 8.8 Hz, 1H), 7.89 (t, J = 7.2 Hz, 2H), 7.69 – 7.55 (m, 3H). 13C NMR (101 MHz, CDCl₃) δ 160.52, 160.12, 150.70, 137.00, 134.25, 131.79, 130.17, 128.64, 127.48, 127.16, 125.42, 123.66. IR (KBr): 3066, 2926, 1618, 1549, 1407, 796, 724 cm⁻¹. MS (EI, m/z): 284.03 [M⁺].

(10) 2-(4-(trifluoromethyl)phenyl)quinazoline (3aj)
Pale yellow solid, (68.5 mg, 50% Yield), m.p.: 143-145°C (Chen et al., 2014); 1H NMR (400 MHz, CDCl₃) δ 9.46 (s, 1H), 8.73 (d, J = 8.1 Hz, 2H), 8.10 (d, J = 8.8 Hz, 1H), 7.92 (t, J = 7.6 Hz, 2H), 7.77 (d, J = 8.2 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H). 13C NMR (101 MHz, CDCl₃) δ 160.60, 160.12, 150.70, 137.00, 134.25, 131.79, 130.17, 128.64, 127.48, 127.16, 125.42, 123.66. IR (KBr): 3067, 2926, 1618, 1549, 1407, 796, 724 cm⁻¹. MS (EI, m/z): 274.17 [M⁺].

(11) methyl 4-(quinazolin-2-yl)benzoate (3ak)
White solid, (101 mg, 77% Yield), m.p.: 162-163°C (Yamaguchi et al., 2016); 1H NMR (400 MHz, CDCl₃) δ 9.49 (s, 1H), 8.70 (d, J = 8.3 Hz, 2H), 8.20 (d, J = 8.3 Hz, 2H), 8.11 (d, J = 8.4 Hz, 1H), 7.94 (t, J = 9.0 Hz, 2H), 7.65 (t, J = 7.5 Hz, 1H), 3.96 (s, 3H). 13C NMR (101 MHz, CDCl₃) δ 166.95, 160.56, 160.01, 150.69, 142.15, 134.31, 131.72, 129.85, 128.78, 128.50, 127.79, 127.15, 123.77, 52.20. IR (KBr): 3062, 2968, 1720, 1619, 1549, 1286, 1113, 770, 711 cm⁻¹. MS (EI, m/z): 264.16 [M⁺].

(12) 4-(quinazolin-2-yl)benzonitrile (3al)
Pale yellow solid, (84.3 mg, 73% Yield), m.p.: 194-196°C (Yamaguchi et al., 2016); 1H NMR (400 MHz, CDCl3) δ 9.52 (s, 1H), 8.77 (d, J = 8.2 Hz, 2H), 8.14 (d, J = 8.4 Hz, 1H), 7.98 (t, J = 8.2 Hz, 2H), 7.84 (d, J = 8.2 Hz, 2H), 7.71 (t, J = 7.5 Hz, 1H). 13C NMR (101 MHz, CDCl3) δ 160.68, 159.08, 150.62, 142.13, 134.54, 132.37, 129.02, 128.82, 127.18, 127.21, 123.89, 118.89, 113.81. IR (KBr): 3065, 2968, 2225, 1616, 1546, 1429, 799 cm⁻¹. MS (EI, m/z): 231.15 [M]+.

(13) phenyl(4-(quinazolin-2-yl)phenyl)methanone (3am)

Pale yellow solid, (106.1 mg, 68% Yield), m.p.: 167-168°C (Chen et al., 2014); 1H NMR (400 MHz, CDCl3) δ 9.51 (s, 1H), 8.76 (d, J = 8.1 Hz, 2H), 8.13 (d, J = 8.3 Hz, 1H), 7.96 (dd, J = 16.0, 8.5 Hz, 4H), 7.88 (d, J = 7.5 Hz, 2H), 7.70 – 7.58 (m, 2H), 7.53 (t, J = 7.5 Hz, 2H). 13C NMR (101 MHz, CDCl3) δ 196.55, 160.63, 160.04, 150.72, 141.65, 139.06, 137.62, 134.37, 132.58, 130.36, 130.13, 128.80, 128.44, 128.37, 127.85, 127.20, 123.80. IR (KBr): 3061, 1656, 1577, 1274, 926, 861, 751, 706 cm⁻¹. MS (EI, m/z): 310.12 [M]+.

(14) 2-(naphthalen-1-yl)quinazoline (3an)

Pale yellow solid, (87.0 mg, 68% Yield), m.p.: 125-126°C (Ma et al., 2017); 1H NMR (400 MHz, CDCl3) δ 9.56 (s, 1H), 8.72 (d, J = 8.2 Hz, 1H), 8.17 (t, J = 8.0 Hz, 2H), 8.02 – 7.87 (m, 4H), 7.63 (dd, J = 17.6, 7.9 Hz, 2H), 7.58 – 7.47 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 163.49, 160.44, 150.60, 136.34, 134.35, 131.28, 130.44, 129.71, 128.68, 128.54, 127.77, 127.17, 126.91, 125.99, 125.94, 125.35, 123.16. IR (KBr): 3053, 2967, 1618, 1551, 1467, 1429, 972, 760 cm⁻¹. MS (EI, m/z): 256.13 [M]+.

(15) 2-(pyridin-3-yl)quinazoline (3ao)

White solid, (67.2 mg, 65% Yield), m.p.: 94-95°C (Ma et al., 2017); 1H NMR (400 MHz, CDCl3) δ 9.83 (s, 1H), 9.47 (s, 1H), 8.87 (d, J = 7.9 Hz, 1H), 8.75 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.93 (t, J = 8.1 Hz, 2H), 7.65 (t, J = 7.5 Hz, 1H), 7.46 (dd, J = 7.7, 4.4 Hz, 1H). 13C NMR (101 MHz, CDCl3) δ 160.65, 159.13, 151.12, 150.60, 150.20, 135.84, 134.40, 133.57, 128.64, 127.80, 127.19, 123.81, 123.43. IR (KBr): 3055, 2924, 2792, 1617, 1549, 1427, 1292, 759, 710 cm⁻¹. MS (EI, m/z): 207.13 [M]+.

(16) 2-(thiophen-2-yl)quinazoline (3ap)

Pale yellow solid, (60.4 mg, 57% Yield), m.p.: 133-134°C (Chen et al., 2014); 1H NMR (400 MHz, CDCl3) δ 9.34 (s, 1H), 8.15 (d, J = 3.6 Hz, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.86 (dd, J = 7.2, 5.1 Hz, 2H), 7.60 – 7.46 (m, 2H), 7.19 (t, J = 4.3 Hz, 1H). 13C NMR (101 MHz, CDCl3) δ 160.56, 157.88, 150.64, 143.84, 134.39, 129.98, 129.28, 128.40, 128.21, 127.29, 127.03, 123.40. IR (KBr): 3065, 2966, 2789, 1616, 1551, 1425, 713 cm⁻¹. MS (EI, m/z): 212.08 [M]+.

(17) (E)-2-styrylquinazoline (3aq)

White solid, (53.3 mg, 46% Yield), m.p.: 120-121°C (Han et al., 2012); 1H NMR (400 MHz, CDCl3) δ 9.38 (s, 1H), 8.17 (d, J = 16.0 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.89 (t, J = 7.7 Hz, 2H), 7.69 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.46 – 7.38 (m, 3H), 7.38 – 7.33 (m, 1H). 13C NMR (101 MHz, CDCl3) δ 161.33, 160.25, 150.61,
(18) quinazoline (3ar)
Brown solid, (31.2 mg, 48% Yield), m.p.: 45-46°C (Zhang et al., 2015); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 9.41\) (s, 1H), 9.35 (s, 1H), 8.06 (d, \(J = 8.7\) Hz, 1H), 7.93 (t, \(J = 7.0\) Hz, 2H), 7.68 (t, \(J = 7.4\) Hz, 1H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 160.22, 155.24, 150.00, 134.19, 128.39, 127.95, 127.19, 125.09\). IR (KBr): 3060, 2969, 1619, 1567, 1488, 1377, 754 cm\(^{-1}\). MS (EI, m/z): 232.15 [M]+.

(19) 2-hexylquinazoline (3as)
Pale yellow oil liquid (Zhang et al., 2015), (64.2 mg, 60% Yield); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 9.27\) (s, 1H), 7.90 (d, \(J = 8.5\) Hz, 1H), 7.80 (t, \(J = 7.5\) Hz, 1H), 7.51 (t, \(J = 7.0\) Hz, 1H), 3.04 (t, \(J = 7.7\) Hz, 2H), 1.84 (dt, \(J = 15.0, 7.6\) Hz, 2H), 1.40 – 1.22 (m, 6H), 0.81 (d, \(J = 6.3\) Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 167.96, 160.38, 150.38, 133.97, 127.89, 127.07, 126.89, 123.07, 40.04, 31.71, 29.23, 28.98, 22.56, 14.05. IR (KBr): 3063, 2959, 2927, 2858, 1619, 1529, 1466, 1428, 1232, 1141, 966, 753 cm\(^{-1}\). MS (EI, m/z): 214.15 [M]+.

(20) 2-cyclopropylquinazoline (3at)
Pale yellow oil liquid (Zhang et al., 2015), (52.7 mg, 62% Yield); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 9.20\) (s, 1H), 7.88 (d, \(J = 8.4\) Hz, 1H), 7.80 (t, \(J = 7.5\) Hz, 1H), 2.47 – 2.34 (m, 1H), 1.32 – 1.23 (m, 2H), 1.16 – 1.07 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 168.29, 160.22, 150.29, 133.86, 127.43, 127.00, 126.19, 123.14, 18.55, 10.60. IR (KBr): 3061, 3008, 1620, 1585, 1570, 1413, 1376, 758 cm\(^{-1}\). MS (EI, m/z): 170.10 [M]+.

(21) 6-methyl-2-phenylquinazoline (3ba)
Pale yellow solid (85.8 mg, 78% Yield), m.p.: 129-130°C (Chen et al., 2014); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 9.30\) (s, 1H), 8.52 (d, \(J = 7.3\) Hz, 2H), 7.90 (d, \(J = 8.6\) Hz, 1H), 7.65 (d, \(J = 8.7\) Hz, 1H), 7.59 (s, 1H), 7.50 – 7.35 (m, 3H), 2.48 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 160.40, 159.74, 149.36, 138.20, 137.43, 136.39, 130.41, 128.62, 128.46, 128.28, 125.79, 123.60, 21.64. IR (KBr): 3061, 2967, 2791, 1526, 1427, 831, 760 cm\(^{-1}\). MS (EI, m/z): 220.18 [M]+.

(22) 2-(4-methoxyphenyl)-6-methylquinazoline (3bd)
Pale yellow solid (100 mg, 80% Yield), m.p.: 119-120°C (Han et al., 2012); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 9.27\) (s, 1H), 8.54 (d, \(J = 8.8\) Hz, 2H), 7.90 (d, \(J = 8.6\) Hz, 1H), 7.65 (dd, \(J = 8.6, 1.7\) Hz, 1H), 7.57 (s, 1H), 7.02 (d, \(J = 8.8\) Hz, 2H), 3.86 (s, 3H), 2.50 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 161.69, 160.21, 159.64, 149.39, 136.85, 136.27, 130.90, 130.05, 128.05, 125.80, 123.30, 113.95, 55.35, 21.56. IR (KBr): 3047, 2962, 1602, 1552, 1514, 1425, 1244, 1026, 851, 827 cm\(^{-1}\). MS (EI, m/z): 250.15 [M]+.

(23) 8-methyl-2-phenylquinazoline (3ca)
Pale yellow solid (69.3 mg, 63% Yield), m.p.: 59-60°C (Gopalaiah et al., 2017); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 9.41\) (s, 1H), 8.67 (d, \(J = 6.7\) Hz, 2H), 7.79 – 7.68 (m, 2H), 7.57 – 7.44 (m, 4H), 2.86 (s, 3H). \(^{13}\)C NMR (101 MHz,
CDCl₃ δ 160.58, 159.98, 149.76, 138.42, 137.17, 133.87, 130.47, 128.60, 128.55, 126.93, 124.82, 123.55, 16.94. IR (KBr): 3064, 2967, 2791, 1528, 1468, 1427, 953, 760 cm⁻¹. MS (El, m/z): 220.17 [M⁺].

(24) 5-methyl-2-phenylquinazoline (3da)
Pale yellow solid (58.3 mg, 53% Yield), m.p.: 115-117°C (Cheng et al., 2016);
¹H NMR (400 MHz, CDCl₃) δ 9.66 (s, 1H), 8.62 (d, J = 7.6 Hz, 2H), 7.93 (d, J = 8.5 Hz, 1H), 7.77 (t, J = 7.8 Hz, 1H), 7.58 – 7.47 (m, 3H), 7.38 (d, J = 7.0 Hz, 1H), 2.79 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 160.69, 157.54, 151.28, 138.07, 135.49, 133.98, 130.54, 128.63, 128.55, 127.85, 126.85, 122.76, 17.56. IR (KBr): 3059, 2966, 2796, 1525, 1467, 1427, 755, 703 cm⁻¹. MS (El, m/z): 220.16 [M⁺].

(25) 6-methoxy-2-phenylquinazoline (3ea)
Pale yellow solid (100 mg, 85% Yield), m.p.: 120-121°C (Ma et al., 2017);
¹H NMR (400 MHz, CDCl₃) δ 9.22 (s, 1H), 8.47 (d, J = 7.2 Hz, 2H), 7.87 (d, J = 9.1 Hz, 1H), 7.42 (m, 4H), 6.99 (s, 1H), 3.81 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 159.39, 158.80, 158.25, 147.00, 138.23, 130.18, 130.13, 128.60, 128.22, 127.14, 124.47, 103.92, 55.69. IR (KBr): 3060, 2966, 2790, 1621, 1529, 1427, 755, 703 cm⁻¹. MS (El, m/z): 236.16 [M⁺].

(26) 2-(4-chlorophenyl)-6-methoxyquinazoline (3eg)
White solid (123 mg, 91% Yield), m.p.: 174-175°C (Cheng et al., 2016);
¹H NMR (400 MHz, CDCl₃) δ 9.29 (s, 1H), 8.50 (d, J = 8.6 Hz, 2H), 7.94 (d, J = 9.2 Hz, 1H), 7.53 (dd, J = 9.2, 2.7 Hz, 1H), 7.47 (s, 1H), 7.10 (d, J = 2.7 Hz, 1H), 3.94 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 158.78, 158.40, 158.33, 146.90, 136.69, 136.33, 130.08, 129.52, 128.74, 127.30, 124.51, 103.93, 55.72. IR (KBr): 3065, 2966, 2790, 1531, 1469, 1428, 1318, 1223, 948, 837 cm⁻¹. MS (El, m/z): 270.10 [M⁺].

(27) 6,7-dimethoxy-2-phenylquinazoline (3fa)
White solid (113 mg, 85% Yield), m.p.: 176-177°C (Gopalaiah et al., 2017);
¹H NMR (400 MHz, CDCl₃) δ 9.19 (s, 1H), 8.54 (d, J = 7.4 Hz, 2H), 7.57 – 7.42 (m, 3H), 7.35 (s, 1H), 7.06 (s, 1H), 4.06 (s, 3H), 4.01 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 159.92, 157.09, 156.22, 150.35, 148.61, 138.39, 130.12, 128.57, 128.14, 119.40, 106.87, 103.95, 56.44, 56.20. IR (KBr): 3065, 2966, 2790, 1531, 1469, 1428, 1318, 1223, 948, 837 cm⁻¹. MS (El, m/z): 266.13 [M⁺]. HRMS (ESI): Calcd. for C₁₆H₁₄BrN₂O₂ [M+H⁺]: 345.0233; found: 345.0235.

(28) 2-(4-bromophenyl)-6,7-dimethoxyquinazoline (3fi)
White solid, (129 mg, 75% Yield), m.p.: 157-159°C (unknown compound);
¹H NMR (400 MHz, CDCl₃) δ 9.07 (s, 1H), 8.32 (d, J = 8.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.24 (s, 1H), 6.98 (s, 1H), 3.98 (s, 3H), 3.94 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 158.90, 157.02, 156.37, 150.54, 148.53, 137.30, 131.67, 129.71, 124.78, 119.48, 106.79, 103.94, 56.46, 56.23. IR (KBr): 3071, 2965, 1615, 1498, 1421, 1230, 1154, 842 cm⁻¹. MS (El, m/z): 344.08 [M⁺]. HRMS (ESI): Calcd. for C₁₆H₁₄BrN₂O₂ [M+H⁺]: 345.0233; found: 345.0235.
(29) 6-chloro-2-phenylquinazoline (3ga)
Pale yellow solid (69.6 mg, 58% Yield), m.p.: 157-158°C (Chen et al., 2014); ¹H NMR (400 MHz, CDCl₃) δ 9.39 (s, 1H), 8.60 (dd, J = 7.4, 2.1 Hz, 2H), 8.03 (d, J = 9.0 Hz, 1H), 7.89 (d, J = 2.2 Hz, 1H), 7.82 (dd, J = 9.0, 2.3 Hz, 2H), 7.57 – 7.48 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 161.31, 159.50, 149.27, 137.61, 135.08, 132.81, 130.41, 128.70, 128.62, 125.83, 124.00. IR (KBr): 3064, 2967, 1613, 1542, 1430, 837 cm⁻¹. MS (EI, m/z): 240.10 [M⁺].

(30) methyl 4-(6-chloroquinazolin-2-yl)benzoate (3gk)
Pale yellow solid (81.9 mg, 55% Yield), m.p.: 198-199°C (unknown compound); ¹H NMR (400 MHz, CDCl₃) δ 9.44 (s, 1H), 8.70 (d, J = 7.8 Hz, 2H), 8.22 (d, J = 7.9 Hz, 2H), 8.08 (d, J = 9.1 Hz, 1H), 7.96 (s, 1H), 7.88 (d, J = 8.9 Hz, 1H), 3.99 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 166.87, 160.26, 159.58, 149.17, 141.65, 135.32, 133.42, 131.96, 130.52, 129.88, 128.50, 125.86, 124.17, 52.25. IR (KBr): 3066, 2966, 1539, 1473, 1429, 1374, 1277, 1107, 832, 765, 715 cm⁻¹. MS (EI, m/z): 298.12 [M⁺]. HRMS (ESI): Calcd. for C₁₆H₁₂ClN₂O₂ [M+H⁺]: 299.0582; found: 299.0579.

(31) 6-fluoro-2-phenylquinazoline (3ha)
Pale yellow solid (62.7 mg, 56% Yield), m.p.: 140-141°C (Malakar et al., 2012); ¹H NMR (400 MHz, CDCl₃) δ 9.42 (s, 1H), 8.59 (d, J = 7.3 Hz, 2H), 8.10 (dd, J = 9.2, 5.0 Hz, 1H), 7.67 (td, J = 8.9, 2.3 Hz, 1H), 7.58 – 7.48 (m, 4H). ¹³C NMR (101 MHz, CDCl₃) δ 160.44 (d, J_C-F = 251.0 Hz), 160.77, 151.44, 137.58, 131.18, 131.01, 130.98, 128.95, 128.73, 128.30, 122.17, 77.35, 77.03, 76.71. IR (KBr): 3056, 2967, 1531, 1430, 1373, 1286, 837 cm⁻¹. MS (EI, m/z): 224.14 [M⁺].

(32) 7-bromo-2-phenylquinazoline (3ia)
Pale yellow solid (71 mg, 50% Yield), m.p.: 125-127°C (Wang et al., 2014); ¹H NMR (400 MHz, CDCl₃) δ 9.43 (s, 1H), 8.60 (d, J = 7.3, 2.2 Hz, 2H), 8.29 (s, 1H), 7.79 (d, J = 8.6 Hz, 1H), 7.70 (dd, J = 8.6, 1.6 Hz, 1H), 7.58 – 7.48 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 161.83, 160.31, 151.44, 137.58, 131.18, 131.01, 130.98, 128.95, 128.73, 128.30, 122.17, 77.35, 77.03, 76.71. IR (KBr): 3056, 2966, 1540, 1428, 1379, 1319, 935, 759, 700 cm⁻¹. MS (EI, m/z): 284.06 [M⁺].

(33) 4-methyl-2-phenylquinazoline (3ja)
Pale yellow solid (84.7 mg, 77% Yield), m.p.: 89-90°C (Gopalaiah et al., 2017); ¹H NMR (400 MHz, CDCl₃) δ 8.63 (d, J = 7.4 Hz, 2H), 8.10 (d, J = 8.3 Hz, 2H), 7.87 (t, J = 7.7 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.56 – 7.46 (m, 3H), 3.03 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.23, 160.21, 150.43, 138.34, 133.51, 130.39, 129.27, 128.57, 126.86, 124.98, 123.03, 22.02. IR (KBr): 3063, 2966, 1616, 1547, 1430, 1338, 757, 708 cm⁻¹. MS (EI, m/z): 220.16 [M⁺].
(34) 4-(4-methylquinazolin-2-yl)benzonitrile (3jI)

Brown solid (67.3 mg, 55% Yield), m.p.: 195-197°C (Yu et al., 2017); 
\[
\text{\textsuperscript{1}}H \text{ NMR (400 MHz, CDCl}_3\text{) } \delta 8.69 (d, J = 7.7 \text{ Hz}, 2H), 8.11 – 7.99 (m, 2H), 7.84 (t, J = 7.7 \text{ Hz}, 1H), 7.74 (d, J = 7.8 \text{ Hz}, 2H), 7.58 (t, J = 7.6 \text{ Hz}, 1H), 2.97 (s, 3H). \]
\[
\text{\textsuperscript{13}}C \text{ NMR (101 MHz, CDCl}_3\text{) } \delta 168.66, 158.15, 150.20, 142.42, 133.91, 132.27, 129.40, 128.99, 127.77, 125.06, 123.28, 118.98, 113.56, 21.97. \]
IR (KBr): 3064, 2966, 2921, 2790, 2225, 1535, 1469, 1428, 854, 759 cm\textsuperscript{-1}. MS (EI, m/z): 245.15 [M]+.

(35) 2,4-diphenylquinazoline (3ka)

Pale yellow solid, (88.8 mg, 63% Yield), m.p.: 116-118°C (Cheng et al., 2016);
\[
\text{\textsuperscript{1}}H \text{ NMR (400 MHz, CDCl}_3\text{) } \delta 8.69 (d, J = 7.3 \text{ Hz}, 2H), 8.11 (dd, J = 17.7, 8.4 Hz, 2H), 7.91 – 7.80 (m, 3H), 7.61 – 7.45 (m, 7H). \]
\[
\text{\textsuperscript{13}}C \text{ NMR (101 MHz, CDCl}_3\text{) } \delta 168.34, 160.29, 152.06, 138.30, 137.76, 133.55, 130.55, 130.25, 129.95, 129.22, 128.75, 128.58, 127.03, 121.74. IR (KBr): 3060, 2966, 1559, 1536, 1440, 1338, 769, 702 cm\textsuperscript{-1}. MS (EI, m/z): 282.15 [M]+.

(36) 6-(2-chloro-4-(trifluoromethyl)phenoxy)-2-phenylquinazoline (3la)

Pale yellow solid, (136 mg, 68% Yield), m.p.: 142-143°C;
\[
\text{\textsuperscript{1}}H \text{ NMR (400 MHz, CDCl}_3\text{) } \delta 9.34 (s, 1H), 8.59 (d, J = 7.1 \text{ Hz}, 2H), 8.13 (d, J = 9.1 \text{ Hz}, 1H), 7.82 (s, 1H), 7.68 (d, J = 9.1 \text{ Hz}, 1H), 7.59 – 7.46 \text{ (m, 4H), 7.27 (s, 1H), 7.17 (d, J = 8.5 Hz, 1H).} \]
\[
\text{\textsuperscript{13}}C \text{ NMR (101 MHz, CDCl}_3\text{) } \delta 160.68, 159.57, 154.61, 154.48, 148.06, 137.80, 131.29, 130.67, 128.68, 128.62, 128.58, 128.48, 127.21, 126.69, 125.51 (q, J_{C-F} = 4.0 \text{ Hz}), 124.08, 120.96, 112.02. \]
IR (KBr): 3060, 1562, 1537, 1486, 1340, 771, 702 cm\textsuperscript{-1}. HRMS (ESI): Calcd. for C\textsubscript{21}H\textsubscript{13}ClF\textsubscript{3}N\textsubscript{2}O [M+H]+: 401.0663; found: 401.0664.

(37) 1-bromo-3,5-diphenylimidazo[1,5-c]quinazoline (4ja)

Yellow solid, (95.7 mg, 48% Yield), m.p.: 229 °C;
\[
\text{\textsuperscript{1}}H \text{ NMR (400 MHz, CDCl}_3\text{) } \delta 8.86 (d, J = 7.4 \text{ Hz}, 1H), 7.89 (d, J = 7.4 \text{ Hz}, 1H), 7.65 – 7.53 (m, 2H), 7.30 (d, J = 7.7 \text{ Hz}, 2H), 7.20 – 6.97 (m, 8H). \]
\[
\text{\textsuperscript{13}}C \text{ NMR (101 MHz, CDCl}_3\text{) } \delta 145.63, 141.80, 138.54, 133.45, 130.13, 129.28, 128.77, 128.72, 128.50, 128.48, 128.27, 127.85, 127.54, 125.61, 121.69, 118.93, 109.04. MS (EI, m/z): 399.05 [M]+.

(38) 3,5-diphenyl-1-(phenylethynyl)imidazo[1,5-c]quinazoline (5ja)

Yellow solid, (151 mg, 72% Yield), m.p.: 201-202°C;
\[
\text{\textsuperscript{1}}H \text{ NMR (400 MHz, CDCl}_3\text{) } \delta 8.95 (d, J = 7.2 \text{ Hz}, 1H), 7.92 (d, J = 7.1 \text{ Hz}, 1H), 7.70 (d, J = 6.9 Hz, 2H), 7.66 – 7.57 (m, 2H), 7.45 – 7.37 (m, 3H), 7.33 (d, J = 7.4 \text{ Hz}, 2H), 7.22 – 7.12 (m, 3H), 7.12 – 6.99 (m, 5H). \]
\[
\text{\textsuperscript{13}}C \text{ NMR (101 MHz, CDCl}_3\text{) } \delta 146.10, 142.39, 138.90, 133.52, 131.57, 131.51, 130.87, 130.08, 129.31, 129.28, 128.77, 128.66, 128.56, 128.53, 128.42, 128.05, 127.81, 127.49, 123.18, 122.46, 119.61, 116.48, 94.53, 83.93. \]
IR (KBr): 3061, 2219, 1548, 1477, 1330, 758, 697 cm\textsuperscript{-1}. HRMS (ESI): Calcd. for C\textsubscript{30}H\textsubscript{20}N\textsubscript{3} [M+H]+: 422.1652; found: 422.1649.
**Data S4. Cartesian coordinates. Related to Figure 2, Figure 3, Figure S99, Figure S100 and Scheme S4, Scheme S5, Scheme S6, Scheme S7 & Scheme S8.**

| Coordinates | Value 1 | Value 2 | Value 3 |
|-------------|---------|---------|---------|
| H 7.21318100 | 0.99233800 | 0.03877100 |
| H 6.37997500 | 2.05872500 | -1.12305800 |
| H -1.67851400 | -0.39160200 | 3.22323900 |
| H -1.83556400 | -1.46554200 | 3.38248100 |
| H -2.24044000 | -0.10304000 | 2.32981800 |
| H -2.10217300 | 0.14185100 | 4.08571700 |
| H -0.17546200 | -0.09136700 | 3.04474400 |
| H -0.05254800 | 1.43403400 | 3.06007200 |
| H -0.54687400 | 1.91010000 | 2.22561400 |
| H -0.22134000 | 1.89902400 | 3.96293500 |
| H 1.10797600 | 1.65183300 | 2.8101000 |
| H 0.59489300 | -0.65879400 | 4.25916200 |
| H 0.48000700 | -1.74796900 | 4.30631700 |
| H 1.66431600 | -0.43628700 | 4.16660900 |
| H 0.23323000 | -0.23384300 | 5.20516400 |
| O 0.36721400 | -0.76092400 | 1.92891100 |
| O -0.42448200 | 3.14518500 | 2.03556600 |
| H -1.95757700 | -3.77630200 | 1.39228600 |
| H -1.23151900 | -1.36260700 | -0.19493900 |
| H -0.11523500 | -0.55241700 | 0.03399600 |
| H -0.21816400 | 0.83818100 | 0.24400100 |
| H -1.51230800 | 1.37344000 | 0.20371000 |
| H -2.63652700 | 0.58434400 | -0.03929000 |
| H -2.49724400 | -0.78993800 | -0.24163500 |
| H -1.09027200 | -2.42641500 | -0.34030000 |
| H -1.63502700 | 2.40401500 | 0.36866500 |
| H -3.62057100 | 1.04338400 | -0.06885400 |
| H -3.36529000 | -1.41297700 | -0.43335100 |
| O 1.18923900 | -2.45142700 | 0.27175600 |
| O 1.18112600 | -1.24143000 | 0.05600700 |
| O 2.21251400 | -0.58673800 | -0.15254500 |
| O 0.95127800 | 1.77650300 | 0.51481000 |
| H 1.60035100 | 1.36103800 | 1.29404200 |
| H 0.54884600 | 2.72195700 | 0.88662200 |
| O 1.68521300 | 2.09806900 | -0.65823100 |
| H 2.15466900 | 1.2784100 | -0.89064900 |
| C -0.10681600 | 2.32991100 | -0.47845300 |
| C -2.31745800 | 4.90370600 | -0.89930900 |
| H 0.11568100 | 4.44655800 | -0.89459200 |
| N -0.31168400 | 0.47825000 | 0.02099300 |
| N -0.95899900 | 1.29188200 | -0.25047700 |
| C 1.29848200 | 1.98906600 | -0.44272700 |
| C 2.34085200 | 2.92536300 | -0.56779000 |
| C 3.68686600 | 2.53928100 | -0.45349900 |
| C 3.95908700 | 1.18780200 | -0.18614000 |
| C 2.92527000 | 0.24967000 | -0.06170500 |
| C 1.58306700 | 0.61333500 | -0.21370000 |
| H 2.12593000 | 3.97506100 | -0.74748500 |
| H 4.45634100 | 3.27670700 | -0.55401000 |
| H 3.20903300 | -0.77194100 | 0.16540300 |
| H -0.72586400 | 0.88123000 | -0.40157300 |
| C -1.42950300 | 0.59263600 | -2.42195800 |
| O -0.36028800 | 1.98362500 | -2.67713000 |
| O -0.54626200 | 2.16556900 | -3.21646400 |
| H -0.73334300 | -2.01082400 | -4.28854100 |

Note: SCF Done: E(RM06) = -1490.22403005
SCF Done: E(RM06) = -1807.7382

Ir-H  
C 1.11652700 1.74831000 2.15599100  
C 1.91752400 2.46686300 1.17772000  
C 3.03031200 1.64524500 0.83320000  
C 1.84419500 0.52998500 2.49225900  
C 2.99756000 0.46285100 1.68169400  
C 1.67238700 3.87089400 0.70855900  
C 2.06941100 4.59069300 1.43890600  
C 2.16105900 4.07064200 2.25046800  
C 0.60760500 4.08511300 0.58358500  
C 4.15126500 1.99551400 0.10346800  
C 4.51518300 1.11405900 0.64212500  
C 3.83383900 2.73137100 0.85070900  
C 5.00815600 2.42039500 0.44067100  
C 4.09821500 -0.54899200 1.78149400  
C 3.73074300 -1.51394200 2.14246300  
C 4.58559000 -0.71800200 0.81827100  

72
| IN6 | SCF Done: E(RM06) = -2041.33327065 | C | -2.77524100 | -1.02967900 | 1.28031100 |
|-----|----------------------------------|---|-------------|--------------|-------------|
| C   | 2.49424900                      | -0.99165500 | -2.06057300  |              |
| C   | 0.19889970                      | -0.08207100 | -2.59070800  |              |
| C   | 0.24242400                      | -0.79553100 | -2.62688430  |              |
| C   | 1.85368600                      | -2.29965700 | -1.93133730  |              |
| C   | 0.49060000                      | -1.21829200 | -2.25211500  |              |
| C   | 1.73047300                      | 1.29830800  | 3.12308110   |              |
| H   | 2.57605600                      | 1.77801600  | 2.62402700   |              |
| H   | 1.95645500                      | 1.24959500  | 4.19759500   |              |
| C   | 0.85454500                      | 1.93709800  | 2.98567400   |              |
| C   | -1.05656400                     | 0.28029200  | -3.16394200  |              |
| H   | -1.16988300                     | -0.58234500 | -4.21549200  |              |
| H   | -1.90534400                     | -0.69282800 | -2.61037500  |              |
| H   | 1.12603800                      | 0.80571900  | -3.10496700  |              |
| C   | -0.52154900                     | -3.29114100 | -2.23055700  |              |
| H   | -1.50334900                     | -2.93614600 | -5.54212700  |              |
| H   | -0.22393800                     | -4.09631900 | -2.91582600  |              |
| H   | -0.62033500                     | -3.71340800 | -1.22402300  |              |
| H   | 2.53686200                      | -3.52212900 | -3.90425000  |              |
| H   | 1.93284500                      | -4.41877500 | -1.55616100  |              |
| H   | 3.51071200                      | -3.66906900 | -1.87164500  |              |
| H   | 2.69921400                      | -3.40512800 | -0.31057800  |              |
| C   | 3.98225900                      | -0.78842000 | -2.07949000  |              |
| H   | 4.25119200                      | 0.27037100  | -2.06219400  |              |
| H   | 4.46788200                      | -1.27446400 | -1.22474500  |              |
| H   | 4.41112300                      | -1.21988100 | -2.99522700  |              |
| H   | -4.26301000                     | 2.62795900  | -2.54754800  |              |
| H   | -5.23375600                     | 2.53990300  | -1.03075000  |              |
| H   | -3.39498300                     | 2.99127000  | 0.02036400   |              |
| H   | -4.75249900                     | 3.25183200  | -0.28546000  |              |
| C   | -5.19362700                     | 3.07031100  | -1.57566600  |              |
| H   | -4.59368800                     | 2.48297600  | -3.57582000  |              |
| C   | -2.82613400                     | 3.14891800  | 1.30908500   |              |
| H   | -5.42071000                     | 3.59211700  | 0.50045000   |              |
| H   | -6.22500500                     | 3.25798300  | -1.85755800  |              |
| C   | -1.49245300                     | 2.88595200  | 1.48632200   |              |
| C   | -0.69195600                     | 2.45496400  | 0.37606900   |              |
| H   | -3.45152400                     | 3.47464600  | 2.13732100   |              |
| H   | -1.02631100                     | 2.99841100  | 2.45953200   |              |
| N   | -0.99228200                     | 2.37022300  | -2.30367200  |              |
| N   | -1.21410200                     | 2.27273300  | -0.83049000  |              |
| C   | 0.78317600                      | 2.34543600  | 0.55621100   |              |
| C   | 1.37506400                      | 3.51890800  | 1.05891700   |              |
| C   | 2.75163700                      | 3.68587100  | 1.19170500   |              |
| C   | 3.57119400                      | 2.62369800  | 0.80870500   |              |
| C   | 2.99229600                      | 1.43396300  | 0.34340600   |              |
| C   | 1.61056300                      | 1.23205000  | 0.21346700   |              |
| H   | 0.73246300                      | 4.35668300  | 1.31886200   |              |
| H   | 3.15245400                      | 4.62144000  | 1.56508000   |              |
| H   | 3.68330500                      | 0.63989000  | 0.94425000   |              |
| Ir  | 1.01976500                      | -0.61855700 | -0.51665500  |              |
| O   | 4.39635100                      | 2.63351400  | 0.86052400   |              |
| H   | 5.57836600                      | 3.80846100  | 1.33432600   |              |
| H   | 5.29978700                      | 4.03318700  | 2.37266800   |              |
| H   | 6.65084700                      | 3.60491100  | 1.28933800   |              |
| H   | 5.35162600                      | 4.67827000  | 0.70321600   |              |
| O   | -0.32645200                     | -4.58403100 | 1.07587600   |              |
| C   | -4.00751500                     | -1.65456600 | 0.94772500   |              |
| Atom | X   | Y   | Z   |
|------|-----|-----|-----|
| C    | 1.62734400 | 2.72556900 | 1.19515800 |
| C    | 1.79495900 | 1.51821100 | 1.89296700 |
| C    | 3.34192600 | 1.38725900 | 2.32543000 |
| C    | 4.26977200 | 2.40904800 | 2.05147600 |
| C    | 3.91063300 | 3.56353400 | 1.37506300 |
| C    | 2.57016700 | 3.70759000 | 0.96037100 |
| H    | 0.59798400 | 2.85712600 | 0.89625900 |
| C    | 5.28682400 | 2.25845900 | 2.40397900 |
| H    | 4.63785200 | 4.34578200 | 1.17800600 |
| C    | 2.26524900 | 4.61382200 | 0.43891300 |
| C    | 3.79122600 | 0.22321000 | 0.38061200 |
| H    | 2.99676100 | -0.50127300 | 3.35006300 |
| O    | 4.94898900 | 0.01629800 | 3.44831500 |
| N    | 1.09659300 | 0.51402300 | 2.15942300 |
| N    | -0.20000500 | 0.75956000 | 1.64615100 |

71

IN10' SCF Done: E(RM06) = -1732.58402243
IN12  SCF Done: E(RM06) = -1.733.74794620
H  0.18866800  2.45044000  -2.38673200  
H  0.90029000  3.70531100  -1.55361000  
H  1.44151000  2.12961800  -1.33554700  
C  -2.45264700  5.67839100  -0.35581400  
C  -1.43625200  4.74864300  -0.13167800  
C  -1.60533900  3.41061600  -0.51126200  
C  -2.80847000  3.00789000  -1.10914200  
C  -3.82090700  3.93836100  -1.33223900  
C  -3.64619300  5.27353400  -0.95912100  
C  -2.31794300  6.71288800  -0.05223500  
C  -2.93948500  1.96415700  -1.37621800  
H  -4.75727800  3.62031600  -1.79193900  
H  -4.44074800  5.99486600  -1.12912000  
C  -0.49210600  2.40661900  -0.27301100  
H  0.12802100  2.69721500  0.58840100  
O  -0.38320870  1.14277100  -0.36011000  
H  -0.51417000  5.06338700  0.35459000  
     75  
TS14'  SCF Done: E(RM06) = -1714.41743282
    H  1.55945800  -0.18579000  2.54091400  
H  1.15700800  -1.55815900  2.37444600  
C  -0.28263600  -1.63966900  2.64812400  
C  0.35581500  0.60345900  2.68325200  
C  -0.76801100  -0.33449800  2.80316000  
C  2.07843200  -2.73985300  2.27868700  
H  3.02135100  -2.47296100  1.79281100  
H  2.31519900  -3.12968500  3.27847600  
H  1.62672800  -5.35631100  1.70661100  
C  -1.04467200  -2.91682200  2.81682800  
H  -0.91018600  -3.29125600  3.84204000  
H  -2.11578200  -2.78054700  2.65171900  
H  -0.69430700  -3.69584700  2.13635300  
C  -2.18450000  0.08022500  3.05706000  
H  -2.32063400  0.35216300  4.11288800  
C  -2.46152700  0.95467100  2.45963800  
H  -2.89054300  -0.72082400  2.82248900  
C  0.29524900  2.06001600  3.04100200  
H  0.37404600  2.19292400  4.12929000  
H  1.11308300  2.62618600  2.58427800  
H  -0.64718400  2.51975400  2.72647800  
C  2.97075800  0.29793700  3.83082000  
H  3.66073000  -0.25476500  2.03985200  
H  3.07222800  1.36067100  2.45287100  
C  3.29479300  0.15392100  3.72293400  
C  -2.49030600  -3.70466000  -0.49026600  
C  -0.56851800  -2.66794900  -1.19352300  
C  -0.47901300  -3.52768200  -2.33207700  
C  -1.47306100  -4.51902300  -2.49561600  
C  -2.49116000  -4.61092200  -1.57275300  
C  -3.28523300  -3.57296900  -0.25226100  
C  0.58887500  -3.33084200  -3.24507200  
H  -1.42176500  -5.18732500  -3.35131900  
H  -3.27779900  -5.35287300  -1.66235800  
C  1.47186300  -2.30873300  -3.03469800  
C  1.33323500  -1.46821600  -1.89345700  
H  0.68119100  -3.98289600  -4.10970100  
H  2.27745800  -2.12615700  -3.73557600  
     75
IN18'  SCF Done: E(RM06) = -1714.42821239
    H  1.75865400  -0.56907000  2.41150300  
C  1.34759800  -1.90649600  2.08791000  
H  2.56876000  -3.58101900  2.66274000  
H  1.76483500  -3.77894800  1.10047500  
H  -0.80560200  -3.34540500  2.49918600  
H  -0.56715000  -3.87618700  3.43269900  
H  -1.88749300  -3.20113600  2.46312700  
H  -1.96527600  -0.18868600  4.33277600  
H  -2.29009300  0.46116200  2.72120600  
H  -2.63517500  -1.23551200  3.06997700  
C  0.52769600  1.56972800  3.32553800
| X  | Y  | Z   |
|----|----|-----|
| 0  | 0  | 0   |
| 1  | 1  | 1   |
| 2  | 2  | 2   |
| 3  | 3  | 3   |

Note: The coordinates are given in angstroms (Å).
IN22'  SCF Done: E(RM06) = -1771.01136503
Supplemental Reference.

Chen, X. W., Zhao, H., Xiong, B., Jiang, H. F., Dixneuf, P. H. and Zhang, M. (2017). Selective synthesis of nitrogen bi-heteroarenes by a hydrogen transfer-mediated direct α, β-coupling reaction. Organic & Biomolecular Chemistry 15, 6093-6097.

Rajendran, S., Raghunathan, H., Hevus, I., Krishnan, R., Uginov, A., Sibi, M. P., Webster, D. C. and Sivaguru, J., (2015). Programmed photodegradation of polymeric/aligomeric materials derived from renewable bioresources. Angew. Chem.-Int. Edit. 54, 1159-1163.

Wang, C., Chen, H.-Y. T., Bacsa, J., Catlow, C. R. A. and Xiao, J. (2013). Synthesis and X-ray structures of cyclometalated iridium complexes including the hydrides. Dalton Transactions 42, 935-940.

Marenich, A. V., Cramer, C. J. and Truhlar, D. G. (2009). Performance of SM6, SM8, and SMD on the SAMPL1 test set for the prediction of small-molecule solvation free energies. J. Phys. Chem. B. 113, 4538–4543.

Becke, A. D. (1993). Density-functional thermochemistry. III. The role of exact exchange. J. Chem. Phys. 98, 5648–5652.

Lee, C., Yang, W. and Parr, R. G. (1988). Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. Phys. Rev. B. 37, 785–789.

Stephens, P. J., Devlin, F. J., Chabalowski, C. F. and Frisch, M. J. (1994). Ab Initio Calculation of Vibrational Absorption and Circular Dichroism Spectra Using Density Functional Force Fields. J. Phys. Chem. 98, 11623–11627.

Fukui, K. (1970). Formulation of the reaction coordinate. J. Phys. Chem. 74, 4161–4163.

Fukui, K. (1981). The path of chemical reactions - the IRC approach. Acc. Chem. Res. 14, 363–368.

Hay, P. J. and Wadt, W. R. (1985). Ab initio effective core potentials for molecular calculations. Potentials for K to Au including the outermost core orbitals. J. Chem. Phys. 82, 299–310.

Wadt, W. R. and Hay, P. J. (1985). Ab initio effective core potentials for molecular calculations. Potentials for main group elements Na to Bi. J. Chem. Phys. 82, 284–298.

Ehlers, A. W., Böhmle, M., Dapprich, S., Gobbi, A., Höllwarth, A., Jonas, V., Köhler, K. F., Stegmann, R., Veldkamp, A. and Frenking, G. (1993). A set of f-polarization functions for pseudo-potential basis sets of the transition metals Sc–Cu, Y, Ag and La–Au. Chem. Phys. Lett. 208, 111–114.

Krishnan, R., Binkle, J. S., Seeger R. and Pople, J. A. (1980). Self-consistent molecular orbital methods. XX. A basis set for correlated wave functions. J. Chem. Phys. 72, 650–654.

McLean, A. D. and Chandler, G. S. (1980). Contracted Gaussian basis sets for molecular calculations. I. Second row atoms. Z=11–18. J. Chem. Phys. 72, 5639–5648.

Zhao, Y., Schultz, N. E. and Truhlar, D. G. (2005). Exchange-correlation functional with broad accuracy for metallic and nonmetallic compounds, kinetics, and noncovalent interactions. J. Chem. Phys. 123, 161103.

Zhao, Y. and Truhlar, D. G. (2008). Acc. Chem. Res. 41, 157–167.

Zhao, Y. and Truhlar, D. G. (2008). The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. Theor. Chem. Acc. 120, 215–241.

Zhao, Y. and Truhlar, D. G. (2009). Benchmark Energetic Data in a Model System for Grubbs II Metathesis Catalysis and Their Use for the Development, Assessment, and Validation of Electronic Structure Methods. J. Chem. Theory Comput. 5, 324–333.

Roy, L. E., Hay, P. J. and Martin, R. L. (2008). Revised Basis Sets for the LANL Effective Core Potentials. J. Chem. Theor. Comput. 4, 1029–1031.

Grimme, S., Antony, J., Ehrlich, S. and Krieg, H. (2010). A consistent and accurate ab initio parametrization of density functional dispersion correction [DFT-D] for the 94 elements H–Pu. J. Chem. Phys. 132, 154104.

Chen, M., Zhang, M., Xiong, B., Tan, Z., Lv, W. and Jiang, H. (2014). A Novel Ruthenium-Catalyzed Dehydrogenative
Synthesis of 2-Arylquinazolines from 2-Aminoaryl Methanols and Benzonitriles. Organic Letters 16, 6028-6031.

Ma, J., Wan, Y., Hong, C., Li, M., Hu, X., Mo, W., Hu, B., Sun, N., Jin, L. and Shen, Z. (2017). ABNO-Catalyzed Aerobic Oxidative Synthesis of 2-Substituted 4H-3,1-Benzoxazines and Quinazolines. European Journal of Organic Chemistry (23), 3335-3342.

Han, B., Yang, X. L., Wang, C., Bai, Y. W., Pan, T. C., Chen, X. and Yu, W. (2012). CuCl/DABCO/4-HO-TEMPO-Catalyzed Aerobic Oxidative Synthesis of 2-Substituted Quinazolines and 4H-3,1-Benzoxazines. J. Org. Chem. 77, 1136-1142.

Yamaguchi, T., Sakurai, K., Yamaguchi, E., Tada, N. and Itoh, A. (2016). Magnesium iodide-catalyzed synthesis of 2-substituted quinazolines using molecular oxygen and visible light. Rsc Advances 6, 56892-56895.

Zhang, Z., Wang, M., Zhang, C., Zhang, Z., Lu, J. and Wang, F. (2015). The cascade synthesis of quinazolinones and quinazolines using an α-MnO2 catalyst and tert-butyl hydroperoxide (TBHP) as an oxidant. Chemical Communications 51 (44), 9205-9207.

Gopalaiah, K., Saini, A. and Devi, A. (2017). Iron-catalyzed cascade reaction of 2-aminobenzyl alcohols with benzylamines: synthesis of quinazolines by trapping of ammonia. Organic & Biomolecular Chemistry 15, 5781-5789.

Cheng, X., Wang, H., Xiao, F. and Deng, G.-J. (2016). Lewis acid-catalyzed 2-arylquinazoline formation from N’-arylbenzimidamides and paraformaldehyde. Green Chemistry 18, 5773-5776.

Malakar, C. C., Baskakova, A., Conrad, J. and Beifuss, U. (2012). Copper-Catalyzed Synthesis of Quinazolines in Water Starting from α-Bromobenzylbromides and Benzamidines. Chemistry-a European Journal 18, 8882-8885.

Wang, H., Chen, H., Chen, Y. and Deng, G.-J. (2014). Palladium-catalyzed one pot 2-arylquinazoline formation via hydrogen-transfer strategy. Organic & Biomolecular Chemistry 12, 7792-7799.

Yu, C., Guo, X., Xi, Z., Muzzio, M., Yin, Z., Shen, B., Li, J., Seta, C. T. and Sun, S. (2017). AgPd Nanoparticles Deposited on WO2.72 Nanorods as an Efficient Catalyst for One-Pot Conversion of Nitrophenol/Nitroacetophenone into Benzoxazole/Quinazoline. Journal of the American Chemical Society 139, 5712-5715.

Gujjarappa, R., Malty, S. K., Hazra, C. K., Vodnala, N., Dhiman, S., Kumar, A., Beifuss, U. and Malakar, C. C. (2018). Divergent Synthesis of Quinazolines Using Organocatalytic Domino Strategies under Aerobic Conditions. European Journal of Organic Chemistry (33), 4628-4638.

Saha, M., Mukherjee, P. and Das, A. R. (2017). A facile and versatile protocol for the one-pot Pd(II)(OAc)2 mediated divergent synthesis of quinazolines from 2-aminobenzylamine. Tetrahedron Lett. 58, 2044-2049.

Chen, J., Natte, K., Neumann, H. and Wu, X.-F. (2014). A convenient palladium-catalyzed carbonylative synthesis of quinazolines from 2-aminobenzylamine and aryl bromides. Rsc Advances 4, 56502-56505.