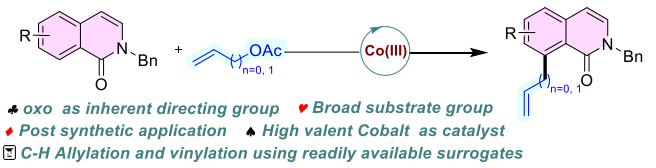
Inherent directing group enabled, Co(III)-catalyzed C-H allylation/ vinylation of isoquinolones

Sachin,[a,b] Tamanna Sharma,[a] Devesh Chandra,[a,b] and Upendra Sharma[a,b,*]

[a]C-H Activation & Phytochemistry Lab, Chemical Technology Division, CSIR-IHBT, Palampur176061, India
[b]Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India

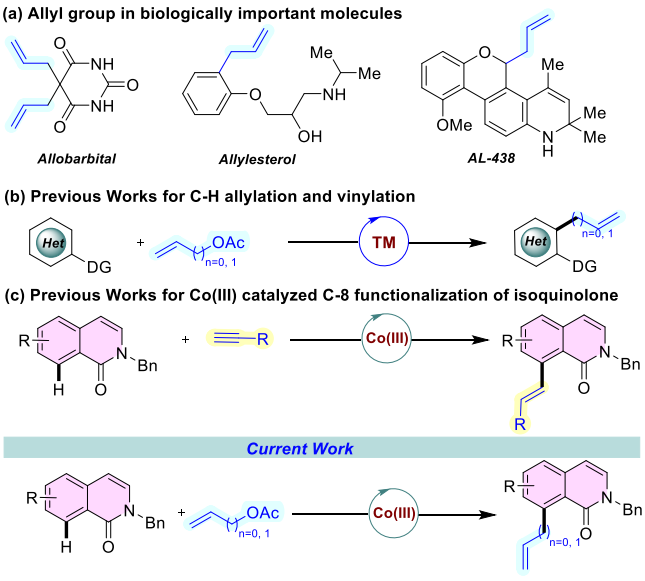
Supporting Information Placeholder

ABSTRACT: The site-selective C8-allylation and vinylation of isoquinolones has been accomplished using allyl acetate and vinyl acetates and oxo group of isoquinolone as an inherent directing group in the presence of Co(III) catalysis. A plausible mechanism for the developed reaction has also been delineated based on preliminary mechanistic studies. Broad substrate scope with good to excellent yield and post-synthetic transformations of allyl and vinyl products feature the importance of reaction.



Isoquinolones are important building blocks for synthesizing various natural products and biologically important molecules.[1] Several natural products[2a], agrochemicals,[2b] and drug molecules[2c] possess isoquinolone as active core within their structure. Unfortunately, the classical isoquinolone synthesis does not always deliver isoquinolone with the desired substitution pattern. Consequently, research in this area has shifted focus to selective functionalization of isoquinolone.[3] Classically, electrophilic metallation or radical reactions are employed to synthesize C4 functionalized isoquinolone.[4] The C3 functionalization of isoquinolone can be achieved by installing a static directing group.[5] Fortunately, the C8 functionalization of isoquinolone can be achieved *via* direct C-H functionalization, in which the oxo group of isoquinolone acts as an inherent directing group. C8-alkylation, alkenylation, and amidation of isoquinolone was reported using 4d transition metal catalyst *i.e.* Cp∗Rh(III), Cp∗Ir(III), and (*p*-cymene)Ru(II).[6] In 2021, our group developed a protocol for C8 alkenylation of isoquinolone using Cp∗Co(III)[7] and continuing our interest in direct C8 functionalization of isoquinolone, we became interested in the allylation and vinylation of isoquinolone. Electronic and coordinating flexibilities of allyl and vinyl groups allow the post-synthetic modifications into a diverse array of organic molecules and polymers.[8] Moreover, allyl and vinyl frameworks are also the common structural features of several natural and medicinally relevant scaffolds.[9] Oxo-directed C-H functionalization using high valent cobalt catalysis generally faces a problem due to the low stability of cobaltacycle species.[10] Utilizing allyl acetate as an allyl surrogate increases the challenges in ß-elimination step (ß-OAc *vs* ß-H).[11] Hence, we aim to overcome these challenges associated with oxo-directed C-H functionalization using high-valent cobalt catalysis (**Scheme 1**). In continuation of our work on cobalt-catalyzed C-H functionalization,[12] herein we report cobalt-catalyzed, inherent directing group enabled C(8)-H allylation and vinylation of isoquinolones using readily available surrogates.

Scheme1. Approaches to allylation and vinylation.



We initiated our study by taking *N*-benzylisoquinolone (**1a**) and allyl acetate (**2a**) as a model substrates. Initially, 32% of desired allylated product **3a** was obtained using $CoCp*(CO)_2I_2$ (10 mol%), $AgSbF_6$ (20 mol%) and $Cu(OAc)_2$ (0.5 equiv) in DCE at 120°C (Table S1, ESI). Encouraged by the preliminary results, solvent, oxidant, and temperature effects were investigated (**Table 1**).

Table 1. Initial optimization studies.

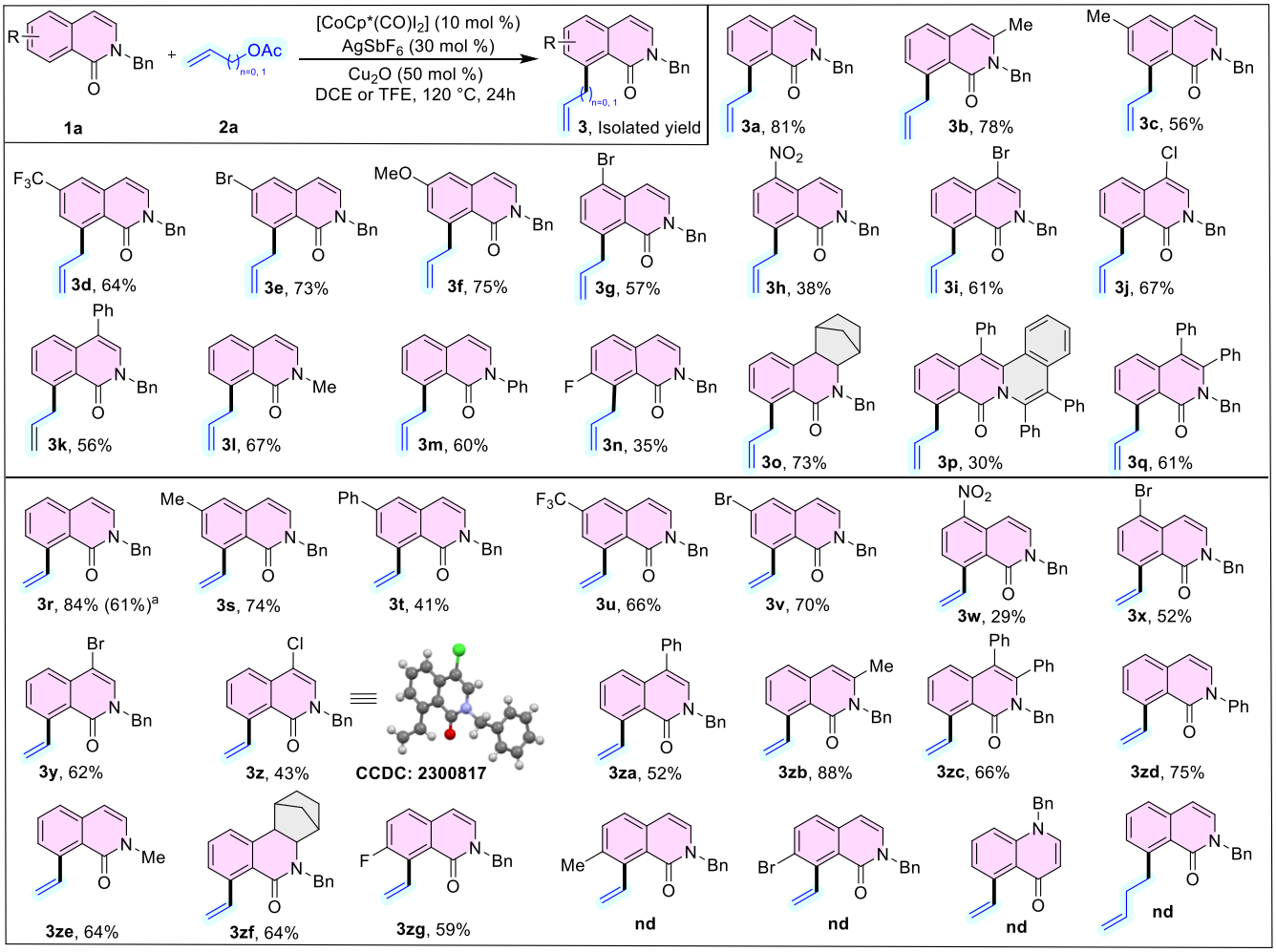
S.N	Deviation from the standard condition	Yield
1	$Cu(OAc)_2$ instead of Cu_2O	61%
2	Ag_2CO_3 instead of Cu_2O	28%
3	Ag_2O instead of Cu_2O	32%
4	TFE instead of DCE	54%
5	HFIP instead of DCE	26%
6	20 mol% $AgSbF_6$	70%
8	100°C instead of 120°C	72%
9	60°C instead of 120°C	54%
10	40°C instead of 120°C	5%
12	Without $CoCp*(CO)I_2$	nd

[a]Reaction conditions: substrate 1a (0.1 mmol), 2a (0.3 mmol), $CoCp*(CO)I_2$ (10 mol %), oxidant (0.5 equiv), solvent (0.5 mL).

Interestingly, by increasing the amount of $AgSbF_6$ up to 30 mol%, the yield of **3a** was increased to 61% (**Table 1, entry 1**). Next, screening various oxidants suggested Cu_2O to be a superior oxidant, providing **3a** in 81% yield (**Table 1, entries 2-3**). The effect of various solvents on product formation was also studied, and DCE was found to be beneficial over other solvents (**Table 1**, **entries 4-5**). Decreasing the reaction temperature resulted in a decrease of product yield (**Table 1, entries 8-10**).

With the optimized conditions, the viability of the developed protocol was investigated with a range of substituted isoquinolones (Scheme 2). 3-Methyl isoquinolone provided corresponding allylated isoquinolone (**3b**) in 78% yield. C6-substituted isoquinolone provides the corresponding allylated product (**3c-3f**) with a good to excellent yield (56-75%). C5-substituted isoquinolone was also feasible under developed reaction condition. 5-Bromoisoquinolone (**1g**) and 5-nitroisoquinolone (**1h**) provide the corresponding allylated product **3g** and **3h** in 57% and 38% yield, respectively.

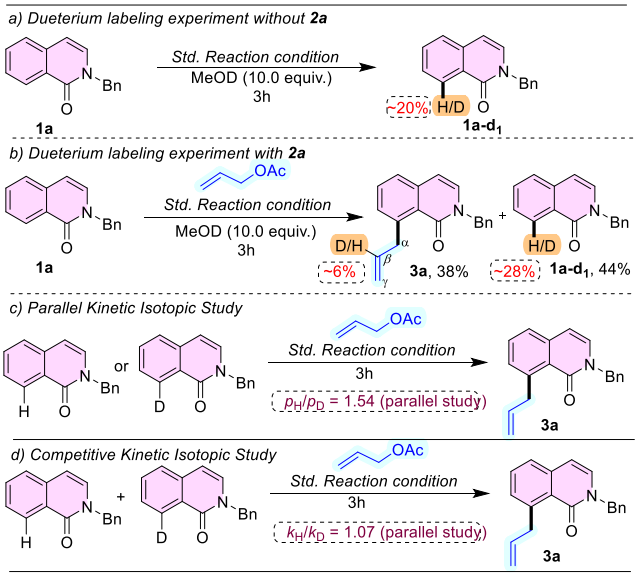
Scheme 2. Co(III)-Catalyzed allylation and vinylation of isoquinolone derivatives.



[a]Reaction conditions for allylation: 1a (0.2 mmol), 2a (0.6 mmol), $CoCp^*(CO)I_2$ (10 mol %), $AgSbF_6$ (30 mol%), Cu_2O (0.5 equiv), DCE (1.0 mL).[b]Reaction conditions for vinylation: 1a (0.2 mmol), 2b (0.6 mmol), $CoCp*(CO)I_2$ (10 mol %), $AgNTf_2$ (30 mol%), Cu_2O (0.5 equiv), TFE (1.0 mL), [a] at 5.0 mmol scale

4-Substituted isoquinolone also provided the allylated product (**3i-3k**) in good yields. 3,4-Isoquinolones also furnished the desired products in excellent yields. Other than *N*-benzyl, different *N*-substituted isoquinolone were also tested under the developed protocol. Pleasingly, *N*-methyl and *N*-phenyl isoquinolone provide the corresponding product (**3l-m**) in good yields. However, unmasked isoquinolone were not able to provide the allylated product. Although 7-F provided the corresponding allylated product (**3n**) in 35% yield, 7-Br and 7-methyl isoquinolone failed to react. Next, using vinyl acetate (**2b**), instead of allyl acetate provide the vinylated product (**3r**) in 37% yield, under standard reaction condition. Slight modification in standard reaction condition *i.e.*, $AgNTf_2$ instead of $AgSbF_6$ in TFE, provides **3r** in 84% yield. Under this reaction condition a range of substituted isoquinolone were diversified to yield C8 vinylated isoquinolone (**3r-3zg**).

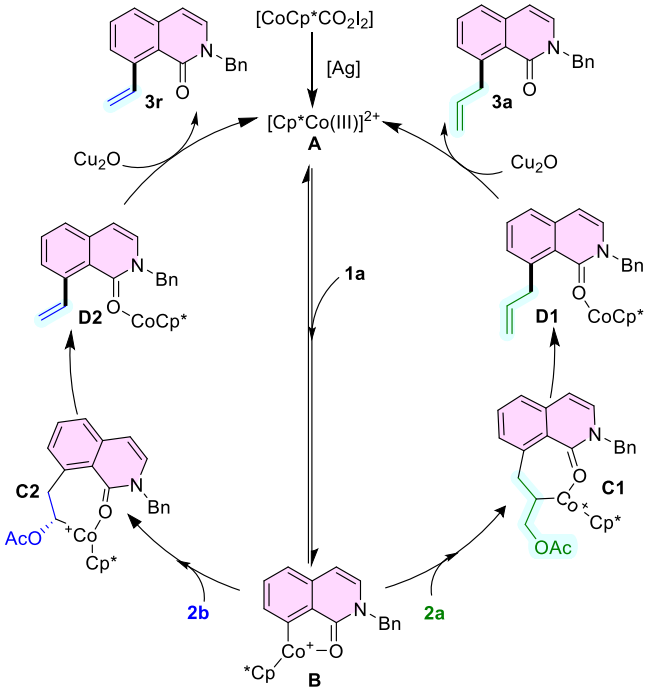
Scheme 3. Preliminary mechanistic studies.



Next, preliminary experiments with allyl acetate were performed to gain insight into the reaction pathway. A deuteration exchange experiment revealed reversible C-H bond activation (Scheme 3a). The standard reaction of **1a** with allyl acetate (**2a**) in the presence of MeOD provides **3a** in 38% yield with ~6% deuteration at *β*-position. However, **1a** was recovered in 44% yield accompanied by 28% deuteration at C8 position (Scheme 3b). In a parallel kinetic isotopic study, p_H/p_D value of 1.54 and in a competitive isotopic study k_H/k_D value of 1.07 were observed, respectively, suggesting C-H activation might not be a rate-determining step (Scheme 3c-d).

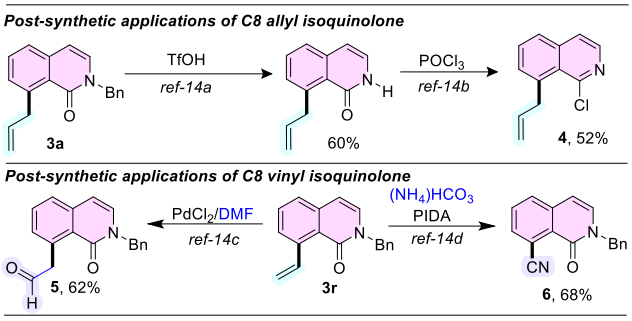
A plausible mechanism was proposed based on literature13 and preliminary experiments (Scheme 4). The reaction initiated from *in-situ* generation of cationic cobalt species (**A**) *via* $Cp^*Co(CO)I_2$ and silver salt reaction. Next, a reversible concerted metalation deprotanation (CMD) take place to form cobaltacycle (**B**). Subsequently, coordination followed by 1,2 migratory insertion of **2a** and **2b** leads to the formation of 7-membered **C1** and **C2** intermediate, respectively. The deuteration labeling experiment (Scheme 3b) also supports the 1,2-migratory insertions step. **C1** and **C2** undergoes *β*-OAc and *β*-H elimination to give **D1** and **D2,** respectively. Although both *β*-OAc and *β*-H elimination are possible from **C1** to **D1**, *β*-OAc elimination took place due to the better-leaving property of -OAc group proceeds reaction *via*. Further, Cu_2O regenerates the cationic cobalt species **A** along with the formation of products **3a** and **3r**.

Scheme 4. Plausible mechanism.



Next, the synthetic utility of the developed protocol was also examined using scale-up synthesis and post-synthetic applications of the C8-vinylated and allylated isoquinolones. The developed methodology was also feasible at 5 mmol scale, and product **3r** was obtained in 61% yield (Scheme 2). Product **3a** was further transformed into corresponding 1-chloroisoquinoline (**4**) in good yields. The vinyl group of **3r** was further transformed into synthetically important functional groups *i.e.* aldehyde and nitriles, providing 8-acetaldehyde *N*-benzyl isoquinolone (**5**) and 8-carbonitrile *N*-benzyl isoquinolone (**6**), respectively (Scheme 5).

Scheme 5. Post-synthetic applications.



In conclusion, a Co(III)-catalyzed protocol has been developed top access C8 allylated and vinylated isoquinolone derivatives. Allyl acetate and vinyl acetate serve as effective surrogates of the allyl and vinyl groups, respectively. The reaction displays a broad substrate scope and good functional group tolerance. The synthetic utility of the protocol was demonstrated by scale-up reaction and transformation of products into useful building blocks.

AUTHOR INFORMATION

Corresponding Author

*upendra@ihbt.res.in; upendraihbt@gmail.com

Personal Site: https://sites.google.com/view/u-sharma-group/home

ASSOCIATED CONTENT

Supporting Information

Notes

The authors declare no competing financial interest

ACKNOWLEDGMENT

The authors thank the Director, CSIR-IHBT for providing the necessary facilities. Mr. Sachin acknowledge CSIR, New Delhi, for the JRF. Financial support from SERB-DST (CRG/2021/000878) is also acknowledged. CSIR-IHBT communication no. for this manuscript is 0000.

REFERENCES

1. (a) Ingrassia, L., Lefranc, F., Dewelle, J., Pottier, L., Mathieu, V., Spiegl-Kreinecker, S., Sauvage, S., El Yazidi, M., Dehoux, M., Berger, W. and Van Quaquebeke, E. Structure-activity relationship analysis of novel derivatives of narciclasine (an Amaryllidaceae isocarbostyril derivative) as potential anticancer agents. *J. Med. Chem.* **2009**, *52(4)*, 1100-1114. (b) Ingrassia, L., Lefranc, F., Mathieu, V., Darro, F. and Kiss, R., Amaryllidaceae isocarbostyril alkaloids and their derivatives as promising antitumor agents. *Transl. Oncol.*, **2008**, *1(1)*, 1-13.

2. Gonzalez, D., Martinot, T. and Hudlicky, T. A short chemoenzymatic synthesis of (+)-narciclasine. *Tetrahedron Lett.*, **1999**, *40(16)*, 3077-3080.

3. (a) Saeed, A. and Ashraf, Z. Efficient synthesis of some 3-substuited-1 (2 H)-isoquinolones. *Pharm. Chem. J.*, **2008**, *42(5)*, (b) Dieudonné-Vatran, A., Azoulay, M. and Florent, J.C. A new access to 3-substituted-1 (2 H)-isoquinolone by tandem palladium-catalyzed intramolecular aminocarbonylation annulation. *Org. Biomol. Chem.* **2012**, *10(13)*, 2683-2691. (c) Yang, S.H., Van, H.T.M., Le, T.N., Khadka, D.B., Cho, S.H., Lee, K.T., Lee, E.S., Lee, Y.B., Ahn, C.H. and Cho, W.J. Development of 3-aryl-1-isoquinolinamines as potent antitumor agents based on CoMFA. *Eur. J. Med. Chem.*, **2010**, *45(11)*, 5493-5497.

4. (a) Zhu, Y.Q., He, J.L., Niu, Y.X., Kang, H.Y., Han, T.F. and Li, H.Y. $AgSbF_6$-mediated selective thiolation and selenylation at C-4 position of isoquinolin-1 (2 H)-ones. *J. Org. Chem.*, **2018**, *83(17)*, 9958-9967. (b) Zhu, Y.Q., Hui, L.W. and Zhang, S.B. a palladium(0)-catalyzed C4 site-selective c-h difluoroalkylation of isoquinolin-1 (2H)-ones. *Adv. Synth. Catal.*, **2021**, *363(8)*, 2170-2176.

5. (a) Das, D. and Samanta, R. Iridium (III)-catalyzed regiocontrolled direct amidation of isoquinolones and pyridones. *Adv. Synth. Catal.*, **2018**, *360(2)*, 379-384. (b) Cui, Y., Bai, D., Liu, B., Chang, J. and Li, X. Rh (iii)-catalyzed acylation of heteroarenes with cyclobutenones via C-H/C-C bond activation. *ChemComm.*, **2020**, *56(100)*, 15631-15634. (c) Das, D., Poddar, P., Maity, S. and Samanta, R. Rhodium(III)-catalyzed C6-selective arylation of 2-pyridones and related heterocycles using quinone diazides: Syntheses of heteroarylated phenols. *J. Org. Chem.*, **2017**, *82(7)*,3612-3621. (d) Gao, F., Han, X., Li, C., Liu, L., Cong, Z. and Liu, H. Cobalt (III)-catalyzed site-selective C-H amidation of pyridones and isoquinolones. *RSC Adv.* **2018**, 57, 32659-32663. € Biswas, A., Maity, S., Pan, S. and Samanta, R. Transition metal-catalysed direct C-H bond functionalizations of 2-pyridone beyond C3-selectivity. *Chem. Asian J.* **2020,** *15(14)*, 2092-2109. (f) Zhang, L., Zheng, X., Chen, J., Cheng, K., Jin, L., Jiang, X. and Yu, C. Ru(ii)-catalyzed C6-selective C-H amidation of 2-pyridones. *Org. Chem. Front.* **2018**, *5(20)*, 2969-297.

6. (a) Zhao, P., Niu, R., Wang, F., Han, K. and Li, X., Rhodium(III)-and ruthenium(II)-catalyzed olefination of isoquinolones. *Org. Lett.* **2012**, *14(16)*, 4166-4169. (b) Lee, S., Mah, S. and Hong, S., Catalyst controlled divergent C4/C8 site-selective C-H arylation of isoquinolones. *Org. Lett.* **2015**, *17(15)*, 3864-3867. (c) Shaikh, A.C., Shinde, D.R. and Patil, N.T. Gold vs rhodium catalysis: tuning reactivity through catalyst control in the C-H alkynylation of isoquinolones. *Org. Lett.* **2016**, *18(5)*, 1056-1059.

7. Chandra, D., Kumar, N., Parmar, D., Gupta, P. and Sharma, U. Co(iii)-catalysed regioselective linear C(8)-H olefination of isoquinolone with terminal aromatic and aliphatic alkynes. *Chem. Commun*. **2021**, *57(88)*, 11613-11616.

8. (a) Yu, M., Lou, S. and Gonzalez-Bobes, F. Ring-closing metathesis in pharmaceutical development: fundamentals, applications, and future directions. *Org Process Res Dev*, **2018**, *22(8)*, 918-946. (b) Dutta, S., Bhattacharya, T., Werz, D.B. and Maiti, D. Transition-metal-catalyzed C-H allylation reactions. *Chem*., **2021**, *7(3)*, 555-605.

9. (a) Astrain-Redin, N., Sanmartin, C., Sharma, A.K. and Plano, D. From natural sources to synthetic derivatives: The allyl motif as a powerful tool for fragment-based design in cancer treatment. *J. Med. Chem*, 2023, 66(6), 3703-3731. (b) Delplace, V. and Nicolas, J. Degradable vinyl polymers for biomedical applications. *Nat. Chem*., 2015, *7(10)*, 771-784. (c) Bazzini, P. and Wermuth, C.G., *The practice of medicinal chemistry*, 4th ed, Academic Press, 2008, pp. 319-357. DOI:10.1016/B978-0-12-417205-0.00013-4

10. (a) da Silva Júnior, E.N., Jardim, G.A., Gomes, R.S., Liang, Y.F. and Ackermann, L. Weakly-coordinating *N*-oxide and carbonyl groups for metal-catalyzed C-H activation: the case of A-ring functionalization. *Chem. Commun*. **2018**, *54(54)*, 7398-7411. (b) Martínez de Salinas, S., Sanjosé-Orduna, J., Odena, C., Barranco, S., Benet-Buchholz, J. and Pérez-Temprano, M.H. Weakly coordinated cobaltacycles: Trapping catalytically competent intermediates in Cp∗CoIII Catalysis. *Angew. Chem. Int. Ed*. **2020**, *59(15)*, 6239-6243. (c) Mandal, R., Garai, B. and Sundararaju, B. Weak-coordination in C-H bond functionalizations catalyzed by 3d metals. *ACS Catal*. **2022**, *12(6)*, 3452-3506.

11. (a) Dai, H., Yu, C., Wang, Z., Yan, H. and Lu, C., 2016. Solvent-controlled, tunable *β*-OAc and *β*-H elimination in Rh(III)-catalyzed allyl acetate and aryl amide coupling via C-H activation. *Org. Lett*. **2016**, *18(14)*, 3410-3413. (b) Otley, K.D. and Ellman, J.A. An efficient method for the preparation of styrene derivatives via Rh (III)-catalyzed direct C-H vinylation. *Org. Lett*. **2015**, *17(5)*, 1332-1335. (c) Sk, M.R. and Maji, M.S. Cobalt(III)-catalyzed ketone-directed C-H vinylation using vinyl acetate. *Org. Chem. Front*, **2020**, *7(1)*, 19-24. (d) Kalsi, D., Laskar, R.A., Barsu, N., Premkumar, J.R. and Sundararaju, B. C8-selective allylation of quinoline: a case study of *β*-hydride vs *β*-hydroxy elimination. *Org. Lett*. **2015**, *18(17)*, 4198-4201.

12. (a) Kumar, R., Kumar, R., Chandra, D. and Sharma, U. Cp∗CoIII-catalyzed alkylation of primary and secondary C (sp^3)-H bonds of 8-alkylquinolines with maleimides. *J. Org. Chem*. **2019**, *84(3)*, 1542-1552. (b) Parmar, D., Dhiman, A.K., Kumar, R., Sharma, A.K. and Sharma, U. Cp∗Co(III)-Catalyzed selective C8-olefination and oxyarylation of quinoline *N*-oxides with terminal alkynes. *J. Org. Chem*. **2022**, *87(14)*, 9069-9087. (c) Chandra, D., Manisha and Sharma, U. Recent advances in the high valent cobalt catalyzed C-H functionalization of *N*-heterocycles. *Chem. Rec*., **2022**, *22(3)*, p.e202100271. (d) Manisha, B., Gupta, S.S. and Sharma, U. Co(III)-catalyzed C7 alkynylation of indolines with bromoalkyne. *Synth*. **2024**. DOI: 10.1055/a-2218-7534. (e) Chandra, D., Sachin and Sharma, U., 2023. Co (III)-catalyzed regioselective [4+2] annulation of *N*-chlorobenzamide with allenes and vinyl acetate. *Asian J. Org. Chem*, **2023**, e202300536.

13. (a) Sk, M.R. and Maji, M.S., Cobalt (III)-catalyzed ketone-directed C-H vinylation using vinyl acetate. *Org. Chem. Front*, **2020**, *7(1)*, 19-24. (b) Manikandan, R. and Jeganmohan, M., 2016. Temperature-controlled redox-neutral ruthenium(II)-catalyzed regioselective allylation of benzamides with allylic acetates. *Org. Biomol. Chem*., **2016**, *14(32)*, 7691-7701. (c) Gensch, T., Vásquez-Céspedes, S., Yu, D.G. and Glorius, F. Cobalt(III)-catalyzed directed C-H allylation. *Org. Lett*. **2015**, *17(15)*, 3714-3717. (d) Gupta, S.S., Gupta, S., Manisha, Gupta, P. and Sharma, U. Experimental and computational studies on Ru(II)-catalyzed C7-allylation of indolines with allyl bromide. *Chem. Eur. J*. **2023**, *29(50)*, 202301360.

14. (a) Geng, X., He, H., Shatskiy, A., Stepanova, E.V., Alvey, G.R., Liu, J.Q., Kärkäs, M.D. and Wang, X.S. Construction of phenanthridinone skeletons through palladium-catalyzed annulation. *J. Org. Chem*., **2023**, *88(17)*, 12738-12743. (b) Yang, C., Mehmood, F., Lam, T.L., Chan, S.L.F., Wu, Y., Yeung, C.S., Guan, X., Li, K., Chung, C.Y.S., Zhou, C.Y. and Zou, T. Stable luminescent iridium(III) complexes with bis (*N*-heterocyclic carbine) ligands: photo-stability, excited state properties, visible-light-driven radical cyclization and CO_2 reduction, and cellular imaging. *Chem. Sci*. **2016**, *7(5)*, 3123-3136. (c) Wright, J.A., Gaunt, M.J. and Spencer, J.B. Novel anti-markovnikov regioselectivity in the wacker reaction of styrenes. *Chem. Eur. J*. **2006**, *12(3)*, 949-955. (d) Xu, J.H., Jiang, Q. and Guo, C.C. Phenyliodonium diacetate mediated direct synthesis of benzonitriles from styrenes through oxidative cleavage of C-C bonds. *J. Org. Chem*. **2013**, *78(23)*, 11881-11886.