Check for updates

CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Weakly Coordinating Ketone-Directed Cp*Co(III)- and Cp*Rh(III)-Catalyzed C–H Amidation of Arenes: A Route to Acridone Alkaloids

Authors: Sourav Sekhar Bera, Md Raja Sk, and Modhu Sudan Maji

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: *Chem. Eur. J.* 10.1002/chem.201805376

Link to VoR: http://dx.doi.org/10.1002/chem.201805376

Supported by
ACES

WILEY-VCH

10.1002/chem.201805376

WILEY-VCH

FULL PAPER

Weakly Coordinating Ketone-Directed Cp*Co(III)- and Cp*Rh(III)-Catalyzed C–H Amidation of Arenes: A Route to Acridone Alkaloids

Sourav Sekhar Bera, Md Raja Sk, and Modhu Sudan Maji*

Abstract: Weakly coordinating, ketone-directed, regioselective mono-amidation of aromatic ketones, chalcone, carbazole, and benzophenones are achieved employing high-valent cobalt- and rhodium-catalysis to access numerous biologically important molecular building blocks. This amidation proceeds smoothly with varieties of ketones as well as with several amidating partners. The application of the products to the syntheses of heterocycles acridones, indoles, quinoline, quinolones, quinolinones, and quinazolines is also described. The total syntheses of acridone based alkaloids, namely toddaliopsin A, toddaliopsin D, arborinine, and formal syntheses of acronycine and noracronycin have also been accomplished applying this method. The mechanistic study reveals this amidation reaction follows a base assisted intermolecular electrophilic substitution (BIES) pathway.

Introduction

Ortho amido aromatic ketones are important structural motif found in many biologically active molecules[1] and also used as a one of the key intermediate for synthesizing diverse array of heterocycles such as acridones, indoles, quinolines, quinolones, quinolinones, quinazolines, etc (Figure 1).[2] To this point, installation of carbon-nitrogen bond in arenes has been a topic of intensive research. Traditional approaches involve Photo-Fries rearrangement of aryl acetamides[3] and nitration of the aryl ketones followed by the reduction,[4] suffers from harsh reaction conditions and poor regioselectivity, restricting their broad applicability. Though C–N-coupling reactions have been developed as a powerful protocol for the synthesis of aryl amines, requirement of pre-functionalized aryl halides or aryl boronic acids has again led the chemists to search for other alternatives.[5] In this context, transition-metal-catalyzed directed C–H amidation represents a burgeoning field owing to its step- and atom-economy, as well as rich with fixed regioselectivity.

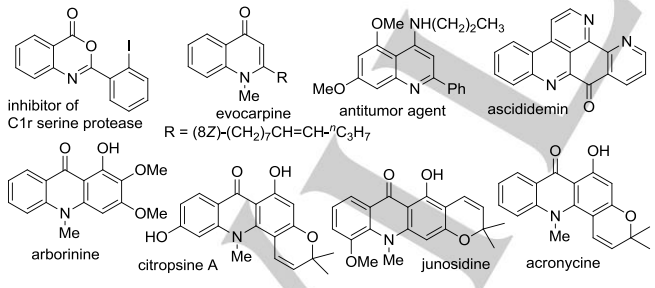
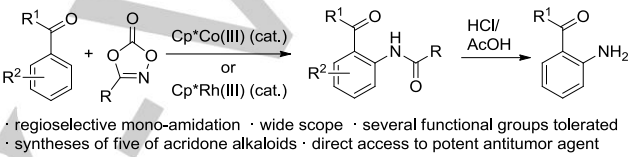


Figure 1. 2-Amino-Ketone Derived Bioactive Molecules.

[a] S. S. Bera, M. R. Sk, and Dr. M. S. Maji
Department of Chemistry, Indian Institute of Technology
Kharagpur, Kharagpur 721302, W. B., India.
E-mail: msm@chem.iitkgp.ac.in



Scheme 1. Cobalt and Rhodium-Catalyzed Ketone-Directed Amidation with Dioxazolones.

In the past decades, with the incessant advancement in C–H activation,[6] considerable efforts have been devoted toward directed C–H amidation on arenes using different transition metals like Rh,[7] Ir,[8] Ru,[9] Pd[10] and Cu.[11] Although strongly coordinating groups likes pyridyl, amide, imine, imidazole, oxazoline have ample success for the amidations,[7-11] the use of weakly coordinating directing groups are still rare.[12,13] Among the few reports on ketone-directed amidations, a palladium catalyzed amidation[12a] using *para*-tolunesulphonamide as an amidating agent and Ru-catalyzed amidation[12b,c] employing tosyl azide as nitrogen source are notable. Recently the field has perceived a substantial shift toward earth abundant first-row transition metals, e.g., cobalt catalysis, because of their higher abundance, lower prices and less-toxicity.[14-16] However, where low Lewis basicity of the ketones was itself a drawback, inferior reactivity of the base-metal cobalt makes the process more challenging for generating a durable metallacycle. Additionally, enolizable alpha proton is also an issue for promoting simple ketones in directed *ortho* C–H functionalizations. Recently, we have developed a simple ketone-directed allylation for the first time, using the base metal cobalt catalyst.[17] Here, inspired by the Chang's pioneering dioxazolone chemistry,[18] we also wish to reveal our result on ketone-directed C–H amidation of aromatic ketones, chalcone, carbazole and benzophenones (Scheme 1). To compare the reactivity of Cp*Co(III)-catalyst with its Rh-congener, we also developed an alternative amidation method by employing Cp*Rh(III)-catalyst and found a complementary reactivity for several ketones. The importance of this C–H amidation strategy is further demonstrated by the construction of several key heterocycles and the total syntheses of acridone based five alkaloids.

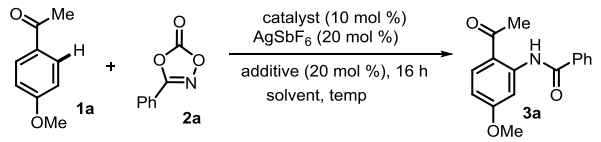
Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/chem.201805376

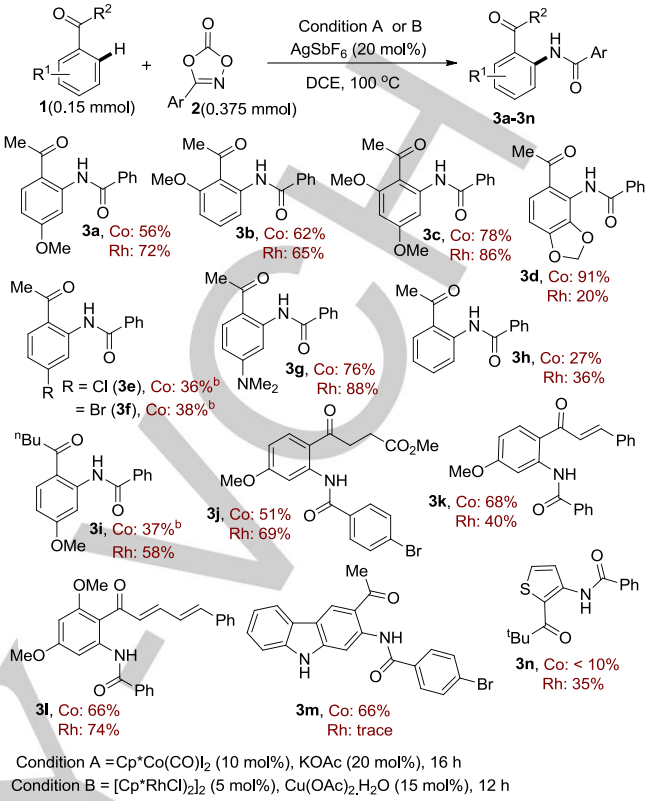
Results and Discussion

Table 1. Optimization of the Reaction Conditions[a]



Entry	Solvent	Catalyst	Additive	Temp	Yield [%][b]
1	DCE	$Cp^*Co(CO)I_2$	none	80	26
2[c]	DCE	$Cp^*Co(CO)I_2$	$Cu(OAc)_2·H_2O$	80	19
3	DCE	$Cp^*Co(CO)I_2$	$Cu(OAc)_2·H_2O$	80	36
4	dioxane	$Cp^*Co(CO)I_2$	$Cu(OAc)_2·H_2O$	80	28
5	DCE	$Cp^*Co(CO)I_2$	NaOAc	80	38
6	DCE	$Cp^*Co(CO)I_2$	KOAc	80	45
7	DCE	$Cp^*Co(CO)I_2$	AgOAc	80	40
8	DCE	$Cp^*Co(CO)I_2$	KOAc	100	49
9	DCE	$Cp^*Co(CO)I_2$	$Mn(OAc)_2·4H_2O$	100	24
10	DCE	$Cp^*Co(CO)I_2$	$Zn(OAc)_2·2H_2O$	100	49
11[d]	DCE	$Cp^*Co(CO)I_2$	KOAc	100	56
12[d],[e]	DCE	$[Cp^*RhCl_2]_2$	KOAc	100	65
13[d],[e],[f]	DCE	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2·H_2O$	100	72
14[d],[e],[f]	DCE	$[Cp^*RhCl_2]_2$	NaOAc	100	59

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.375 mmol) and 1.0 mL of DCE were used. [b] Isolated yields. [c] 1.0 equiv additive. [d] 2.5 equiv **2a** was used. [e] 5 mol% $[Cp^*RhCl_2]_2$ and 12 h reaction time. [f] 15 mol% additive was used.



Scheme 2. Scope of Different Ketone Derivatives.[a],[b] [a] Isolated yields. [b] 15 mol% of $Cp^*Co(CO)I_2$ was used.

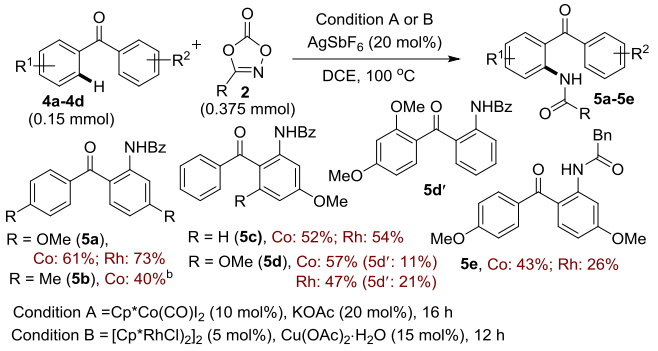
We have commenced our optimization using ketone **1a** and amidating agent **2a**. Conducting the reaction in 1,2-dichloroethane solvent by employing 10 mol% of $Cp^*Co(CO)I_2$ catalyst and 20 mol% of $AgSbF_6$ afforded **3a** in 26% yield (Table 1, entry 1). Usages of $Cu(OAc)_2·H_2O$ as an additive improved the yield (entry 3). Among different acetate additives (entries 5–10), KOAc and $Zn(OAc)_2·2H_2O$ provided better results at 100 °C. To compensate the slow decomposition of **2a** at 100 °C, 2.5 equiv of **2a** was found to be optimal amount providing **3a** in 56% yield (entry 11). In contrast, benzoyl- and tosyl-azide failed to provide any amidation products. Next, to compare the reactivity of Co-catalysis with its Rh-congener, a reaction was conducted using $[Cp^*RhCl_2]_2$ under our optimized conditions, and 65% of **3a** was isolated (entry 12). Upon using 15 mol% of $Cu(OAc)_2·H_2O$, the best yield of **3a** was isolated under Rh-catalysis (72%, entry 13).

With both the optimized conditions in hand for cobalt and rhodium catalysis, we applied this directed amidation on a series of electronically and sterically diversified ketones. Aryl moiety bearing electron-donating groups reacted efficiently to give amides **3a-3c** in 56-86% yields under the cobalt and rhodium catalysis (Scheme 2). Acetophenone stitched with a 1,3-dioxole group at the 3,4-position reacted through the more hindered C–H bond due to weak coordinating nature of the 1,3-dioxole oxygen to provide **3d** in 91% yield under cobalt catalysis, while rhodium failed to provide encouraging result. Acetophenones bearing electron withdrawing groups responded only under cobalt catalysis to afford **3e** to **3f** in 36-38% yields. On introduction of electron-donating amino group, ketone showed excellent reactivities to provide **3g** with 76% and 88% yields under both the catalysis. Simple acetophenone afforded 36% of **3h** under rhodium catalysis. *n*-Butyl ketone **1i** and ketone bearing a coordinating ester group **1j** furnished the corresponding amides **3i** and **3j** in 37-69% yields. Chalcones, an important structural motif found in many natural products and bioactive molecules, converted to the corresponding amide **3k** in good to moderate yields (Co: 68%, Rh: 40%). Gratifyingly, conjugated dienone also survived under both the reaction conditions and provided **3l** in comparable yields (68–74%). Though Co-catalyzed amidation of 3-acetyl-carbazole was quite efficient to provide **3m** in 66% yield, but did not react well under rhodium catalysis. Surprisingly 2-acetyl-thiophene was not reactive enough and 2-*tert*-butyl thiophene provided **3n** in only 35% yield under Rh-catalysis. Overall, we can conclude that for the electron-donating substrates both Rh- and Co-catalysis showed comparable reactivities, but Rh-catalysis does not react well for electron-deficient substrates rendering this cobalt-catalyst a more versatile one.

Accepted Manuscript

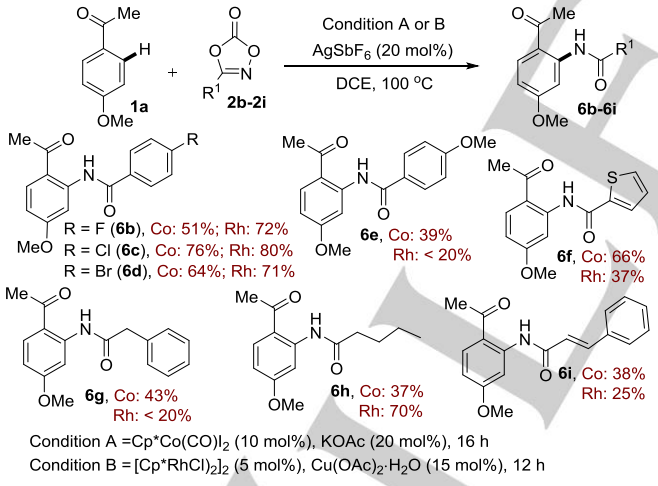
This article is protected by copyright. All rights reserved.

10.1002/chem.201805376



Scheme 3. Scope of Benzophenone Derivatives.[a],[b] [a] Isolated yields, [b] 15 mol% of $Cp^*Co(CO)I_2$ was used.

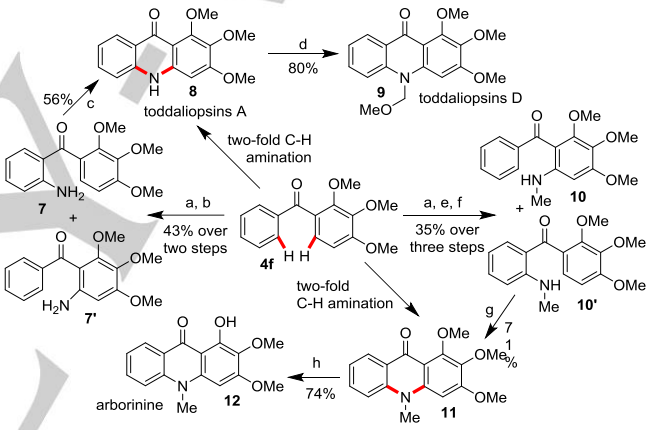
After investigating acetophenones derivatives, we switched our focus to benzophenones (Scheme 3). Symmetrical benzophenones reacted smoothly under cobalt and rhodium conditions to provide the products **5a** and **5b** with moderate to good yields (40-73%). Unsymmetrical ketone **4c** also responded well to afford single regioisomeric amide **5c** predominantly in 52-54% yields arising from the C–H amidation of the electron-rich arene. Another unsymmetrical ketone **4d** was also introduced under cobalt catalysis to achieve **5d** and **5d′** in 5.2:1 ratio with the overall yield of 68%. In contrary, in presence of rhodium, we got the similar yield but with reduced selectivity (2.2:1). The amidating agent **2g** also reacted with **4a** to provide **5e** in modest yield.



Scheme 4. Scope of Different Amidating Agents.[a] [a] Isolated yields.

The scope of the amidating agent **2** was next investigated (Scheme 4). Fluoro, chloro, and bromo substituted dioxazolones **2b-2d** were all viable for the amidation giving **6b-6d** in 51-80% yields under the cobalt- and rhodium-catalysis. Incorporation of electron donating substituent decreased the yield of the reaction significantly for cobalt-conditions (**6e**, 39%), and was very inefficient for Rh-conditions. Same trend was observed for the amidating agent **2f** bearing electron-rich thiophene ring (Co: 66%, Rh: 37%). Interestingly for dioxazolone bearing aliphatic group, a reverse trend was observed as rhodium provided superior results over cobalt (**6h**, 70% vs 37%). Alkenyl dioxazolone was also reactive albeit lower yield of **6i**.

Acridone derivatives, an important class of heterocycles, shows versatile bioactivities such as anti-inflammatory, anticancer, antimicrobial, antitubercular, antiparasitic, antimalarial, antiviral and fungicidal activities.[19a-c,2c] The unique semi-planar structure enables acridones to act as DNA intercalators and to inhibit topoisomerase or telomerase enzymes. Reported synthesis of acridone core structures mainly rely on the aniline derivatives.[19a,2c] Arguably the best way to accomplish these valuable alkaloids are via two-fold C−H amination of benzophenones. Here, applying our method, using simple benzophenones derivatives, a two-fold C−H amination strategy is designed to achieve the total synthesis of acridone alkaloids such as toddaliopsin and arborinine, demonstrating the applicability of our amidation reaction (Scheme 5).[19a,2c]



Scheme 5. Total Syntheses of Toddaliopsin A, Toddaliopsin D and Arborinine. Reagents and conditions: a) $[Cp^*RhCl)_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2·H_2O$ (15 mol%), 20 h; b) 4 N NaOH in 9:1 dioxane:methanol; c) KO^{t}Bu (4 equiv), DMSO; d) MOMCl (2 equiv), NaH (2.5 equiv); e) CH_3I (2.5 equiv), NaH (5 equiv); f) water, 80 °C; g) CuI (2 mol%), bpy (2 mol%), DMAc, O_2 balloon; h) BBr_3 in 1 M DCM (1.5 equiv).

The Rh(III)-catalyzed, ketone-directed, C−H amidation of **4f**, provide the key amides **5f** and **5f′** as a 3:1 mixture which upon hydrolysis under heating conditions afforded anilines **7** and **7′** in a combined yield of 43%. The ^{t}BuOK mediated second C−H amination of the mixture of **7** and **7′** delivered the toddaliopsin A **8** in 56% yield.[19b] Further methoxymethyl-protection of **8** afforded the other alkaloid toddaliopsin D **9** in 80% yield. Synthesis of arborinine was also began with amides **5f** and **5f′**. The mixture of amides **5f** and **5f′** was first methylated using methyl iodide in the presence of excess amount of sodium hydride. Pleasingly, though the majority of the methylated products underwent hydrolysis during workup to give **10** and **10′**, heating at 80 °C was required for complete conversion. The mixture of methylated amines **10** and **10′** were next subjected to the copper-catalyzed C−H amination reaction to furnish the acridone core **11** in 71% yield.[19c]

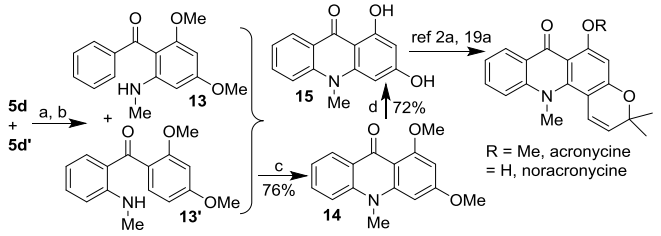
Accepted Manuscript

This article is protected by copyright. All rights reserved.

10.1002/chem.201805376

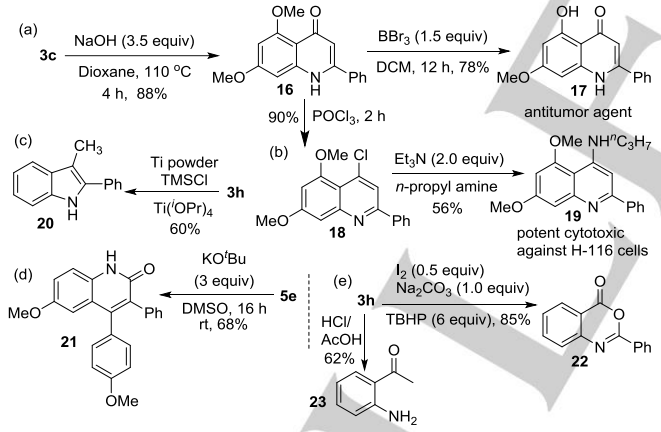
FULL PAPER

Selective demethylation of **11** completed the synthesis of arborinine **12** alkaloids in 74% yield.



Scheme 6. Formal Synthesis of Acronycine and Noracronycin. Reagents and conditions: a) CH_3I (2.5 equiv), NaH (5 equiv); b) water, 80 °C; c) CuI (2 mol%), bpy (2 mol%), DMAc, O_2 balloon; d) BBr_3 in 1M DCM (4 equiv).

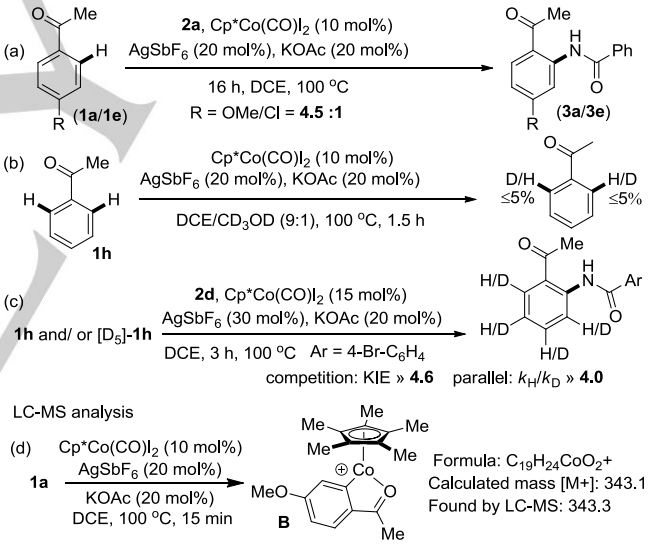
To show further applicability, formal synthesis of antitumor alkaloids acronycine and noracronycine were accomplished using our method. The products **5d** and **5d′**, obtained by Co(III)-catalyzed C−H amidation of **4d**, was first subjected to the methylation followed by hydrolysis as described for the synthesis of **10** afforded the mixture of *N*-methylated products **13** and **13′** in 50% combined yield (Scheme 6). In presence of CuI and bpy under the oxygen atmosphere, the intramolecular C−H amination provided acridone core **14** in 76% yield.[19c] Finally, treatment of **14** with BBr_3 provided the advanced intermediate **15** which has been previously utilized to synthesize acronycine and noracronycine alkaloids.[2a,19a]



Scheme 7. Applications of Amidation Products.

The importance of the products amide was further demonstrated by converting them to several important heterocycles. 2-Phenyl-4-quinolone derivatives are the subject of extensive research as potent cardiovascular protectors, cytotoxic antimitotic, anti-diabetic, and antibacterial agents.[20a-b] Employing this amidation reaction, an effective 4-quinolone based anti-tumor agent **17** was synthesized from **3c** with an overall yield of 59% (Scheme 7a).[20a] The 4-amino quinoline derivative **19** which exhibits potent cytotoxicity against HCT-116 cells (IC_{50} value = 0.97 μM) and can also decrease the VEGF protein expression, was prepared in two steps from 4-quinolone **16** using $POCl_3$ and *n*-propyl amine (Scheme 7b).[20b] In one step, using titanium-powder, the amide **3h** was converted to important 2,3-disubstituted indole **20** by reductive coupling (Scheme 7c).[20c] Amide **5e** was further diversified through the synthesis of 3,4-diarylquinolinones **21** by treatment with ^{t}BuOK (scheme 7d). Synthesis of benzoxazinone core **22**, found in many drug molecules, was also accomplished from **3h** by reacting with iodine and ^{t}BuOOH (Scheme 7e).[20d] Finally, hydrolysis of **3h** afforded 2′-amino acetophenone **23**.

To understand the catalyst's mode of action, we first examined the competition between electron-rich and -deficient benzophenones. The preferential conversion of **3a** over **3e** (4.5:1) hints toward a base assisted intermolecular electrophilic substitution (BIES) mechanism.[21] A lacking of H/D scrambling at the *ortho*-position of **1h** with CD_3OD and CD_3CO_2D indicates an irreversible C–H activation step (Scheme 8b). The results from intermolecular competition experiment and parallel experiment (KIE = 4.6, k_H/k_D = 4.0, Scheme 8c) suggest that C–H activation step involves in the rate determining step. Detection of the intermediates **B** involved in the catalytic cycles have also been achieved via LC-MS analysis (Scheme 8d).[22]

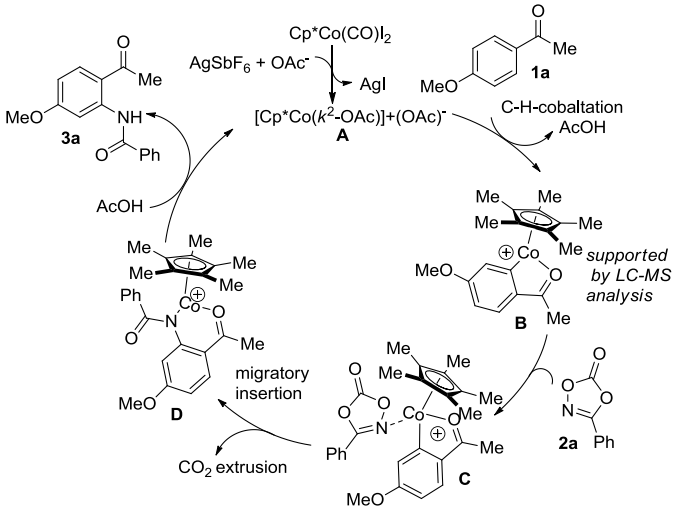


Scheme 8. Mechanistic Studies.

On the basis of our mechanistic studies and previous reports,[23] we proposed a plausible catalytic cycle where the neutral cobalt catalyst is assumed to be converted initially into a cationic species **A** in presence of a silver salt (Scheme 9). Species **A** commences a kinetically relevant, *in situ* generated acetate-assisted C−H cobaltation in acetophenone to generate metallacycle **B** which was further supported by LC-MS analysis (Scheme 8d). After the subsequent co-ordination with dioxazolones **2a**, species **C** undergoes CO_2 extrusion to form an amido inserted species **D**. Finally, in the presence of AcOH, proto-demetalation occurs to afford amidated product **3a** and regenerate active catalyst **A**.

Accepted Manuscript

This article is protected by copyright. All rights reserved.



Scheme 9. Proposed Mechanism.

Conclusions

In summary, we have developed weakly co-ordinating ubiquitous ketone-directed, high-valent cobalt and rhodium catalyzed C–H amidation using dioxazolnes as an amidating agents. The successful response from varieties of ketones and dioxazoles made the method suitable for practical applications. Total synthesis of toddaliopsin alkaloids and formal synthesis acronysin alkaloids have been achieved using amidation as key C−N bond forming step. Supremacy of this methodology was further shown by accomplishing the synthesis of important heterocycles like indole, quinoline, quinolone, quinolinone, and benzoxazinone.

Experimental Section

General Procedure for Cp*Co(III)-Catalyzed Ketone-Directed Amidation: (GP IA)

The aryl/heteroaryl ketone **1** (0.15 mmol, 1.0 equiv) was taken in a 15.0 mL screw capped sealed tube and 1.0 mL of 1,2-dichloroethane was added. Then catalyst $Cp^*Co(CO)I_2$ (7.15 mg, 0.015 mmol, 10.0 mol%), $AgSbF_6$ (10.3 mg, 0.03 mmol, 20.0 mol%) and KOAc (2.9 mg, 0.03 mmol, 20.0 mol%) were added successively to the reaction mixture and was stirred for 5 min at the room temperature. After that, the amidating agent **2** (0.375 mmol, 2.5 equiv) was added to the reaction mixture and the resultant reaction mixture was allowed to stir at 100 °C for 16 h. After completion of the reaction as indicated by TLC, the crude product was directly purified by silica gel column chromatography using petroleum ether/ ethylacetate eluent.

General Procedure for Cp*Co(III)-Catalyzed Ketone-Directed Amidation: (GP IB)

The aryl/heteroaryl ketone **1** (0.15 mmol, 1.0 equiv) was taken in a 15.0 mL screw capped sealed tube and 1.0 mL of 1,2-dichloroethane was added. Then catalyst $Cp^*Co(CO)I_2$ (10.7 mg, 0.0225 mmol, 15.0 mol%), $AgSbF_6$ (15.5 mg, 0.045 mmol, 30.0 mol%) and KOAc (2.9 mg, 0.03 mmol, 20.0 mol%) were added successively to the reaction mixture and was stirred for 5 min at the room temperature. After that, the amidating agent **2** (0.375 mmol, 2.5 equiv) was added to the reaction mixture and the resultant reaction mixture was allowed to stir at 100 °C for 16 h. After completion of the reaction as indicated by TLC, the crude product was directly purified by silica gel column chromatography using petroleum ether/ ethylacetate eluent.

General Procedure for Cp*Rh(III)-Catalyzed Ketone-Directed Amidation: (GP II)

The aryl/heteroaryl ketone **1** (0.15 mmol, 1.0 equiv) was taken in a 15.0 mL screw capped sealed tube and 1.0 mL of 1,2-dichloroethane was added. Then catalyst $[Cp^*RhCl_2]_2$ (4.65 mg, 0.0075 mmol, 5.0 mol%), $AgSbF_6$ (10.3 mg, 0.03 mmol, 20.0 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (4.5 mg, 0.0225 mmol, 15.0 mol%) were added successively to the reaction mixture and was stirred for 5 min at the room temperature. After that, the amidating agent **2** (0.375 mmol, 2.5 equiv) was added to the reaction mixture and the resultant reaction mixture was allowed to stir at 100 °C for 12 h. After completion of the reaction as indicated by TLC, the crude product was directly purified by silica gel column chromatography using petroleum ether/ ethylacetate eluent.

Acknowledgements

M.S.M. gratefully acknowledges SERB, Department of Science and Technology, New Delhi, India (Sanction No. EMR/2015/ 000994) for funding. S.S.B. thanks CSIR, India and M.R.S. thanks IIT Kharagpur for fellowships.

Keywords: cobalt • ketone • C–H functionalization • amidation • acridone.

[1] a) J. Sakowski, M. Bohm, I. Sattler, H.-M. Dahse, M. Schlitzer, *J. Med. Chem.* **2001**, *44,* 2886–2899; b) T. Grandifolia, *Tetrahedron Lett.* **1975**, 401–404.

[2] a) P. Magiatis, S. Mitaku, A. Pierré, G. Atassi, *Heterocycles* **2002**, *57*, 341-351; b) J. P. Michael, *Nat. Prod. Rep*. **2008**, *25*, 166–187; c) M. Gensicka-Kowalewska, G. Cholewinski, K. Dzierzbicka, *RSC Adv*. **2017**, *7*, 15776–15804; d) S. M. Prajapati, K. D. Patel, R. H. Vekariya, S. N. Panchal, H. D. Patel, *RSC Adv*. **2014**, *4*, 24463–24476; e) Y. Xia, Z.-Y. Yang, P. Xia, T. Hackl, E. Hamel, A. Mauger, J.-H. Wu, K.-H. Lee, *J. Med. Chem.* **2001**, *44,* 3932–3936; f) L. Fu, X. Huang, D. Wang, P. Zhao, K. Ding, *Synthesis* **2011**, 1547–1554.

[3] D. Elad, D. V. Rao, V. I. Stenberg, *J. Org. Chem*. **1965**, *30*, 3252–3254.

[4] H. Suzuku, T. Murashima, A. Tatsumi, I. Kozai, *Chem. Lett.* **1993**, *22*, 1421–1424.

[5] a) J. P. Wolfe, S. Wagaw, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res*. **1998**, *31*, 805−818; b) J. F. Hartwig, *Acc. Chem. Res.* **2008**, *41*, 1534–1544; c) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed*. **2009**, *48*, 6954–6971; d) J. C. Vantourout, H. N. Miras, A. Isidro-Llobet, S. Sproules, A. J. B. Watson, *J. Am. Chem. Soc*. **2017**, *139*, 4769−4779.

[6] a) F. Kakiuchi, N. Chatani, *Adv. Synth. Catal*. **2003**, *345*, 1077–1101; b) T. Gensch, M. N. Hopkinson, F. Glorius, J. Wencel-Delord, *Chem. Soc. Rev*. **2016**, *45*, 2900–2936; c) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res*. **2012**, *45*, 788–802; d) S. D. Sarkar, W. Liu, S. I. Kozhushkov, L. Ackermann, *Adv. Synth. Catal*. **2014**, *356*, 1461–1479; e) Y. Park, Y. Kim, S. Chang, *Chem. Rev*. **2017**, *117*, 9247−9301.

[7] a) J. Ryu, K. Shin, S. H. Park, J. Y. Kim, S. Chang, *Angew. Chem. Int. Ed*. **2012**, *51*, 9904–9908; (b) R.-J. Tang, C.-P. Luo, L. Yang, C.-J. Li, *Adv. Synth. Catal*. **2013**, *355*, 869–873; c) C. Grohmann, H. Wang, F.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

Glorius, *Org. Lett*. **2013**, *15*, 3014–3017; d) H. Zhao, Y. Shang, W. Su, *Org. Lett*. **2013**, *15*, 5106–5109; e) B. Zhou, Y. Yang, J. Shi, H. Feng, Y. Li, *Chem. -Eur. J*. **2013**, *19*, 10511–10515; f) B. Zhou, J. Du, Y. Yang, H. Feng, Y. Li, *Org. Lett.* **2014**, *16*, 592−595; g) J. Shi, G. Zhao, X. Wang, H. E. Xu, W. Yi, *Org. Biomol. Chem*. **2014**, *12*, 6831–6836; h) H. Wang, G. Tang, X. Li, *Angew. Chem. Int. Ed*. **2015**, *54*, 13049–13052; i) J. Wang, S. Zha, K. Chen, F. Zhang, C. Song, J. Zhu, *Org. Lett*. **2016**, *18*, 2062−2065; j) M. Jeon, N. K. Mishra, U. De, S. Sharma, Y. Oh, M. Choi, H. Jo, R. Sachan, H. S. Kim, I. S. Kim, *J. Org. Chem*. **2016**, *81*, 9878−9885; k) N. K. Mishra, Y. Oh, M. Jeon, S. Han, S. Sharma, S. H. Han, S. H. Um, I. S. Kim, *Eur. J. Org. Chem*. **2016**, 4976–4980.

[8] a) J. Ryu, J. Kwak, K. Shin, D. Lee, S. Chang, *J. Am. Chem. Soc*. **2013**, *135*, 12861−12868; b) T. Kang, Y. Kim, D. Lee, Z. Wang, S. Chang, *J. Am. Chem. Soc*. **2014**, *136*, 4141−4144; c) C. Pan, N. Jin, H. Zhang, J. Han, C. Zhu, *J. Org. Chem*. **2014**, *79*, 9427−9432.

[9] a) V. S. Thirunavukkarasu, K. Raghuvanshi, L. Ackermann, *Org. Lett*. **2013**, *15*, 3286–3289; b) M. Shang, S.-H. Zeng, S.-Z. Sun, H.-X. Dai, J.-Q. Yu, *Org. Lett*. **2013**, *15*, 5286–5289; c) M. R. Yadav, R. K. Rit, A. K. Sahoo, *Org. Lett*. **2013**, *15*, 1638–1641; d) J. Kim, J. Kim, S. Chang, *Chem. -Eur. J*. **2013**, *19*, 7328–7333; e) K. Raghuvanshi, D. Zell, K. Rauch, L. Ackermann, *ACS Catal*. **2016**, *6*, 3172−3175.

[10] a) K.-H. Ng, A. S. C. Chan, W.-Y. Yu, *J. Am. Chem. Soc*. **2010**, *132*, 12862–12864; b) K. Sun, Y. Li, T. Xiong, J. Zhang, Q. Zhang, *J. Am. Chem. Soc*. **2011**, *133*, 1694–1697; c) E. J. Yoo, S. Ma, T.-S. Mei, K. S. L. Chan, J.-Q. Yu, *J. Am. Chem. Soc*. **2011**, *133*, 7652–7655; d) X.-Y. Liu, P. Gao, Y.-W. Shen, Y.-M. Liang, *Org. Lett*. **2011**, *13*, 4196–4199.

[11] a) L. D. Tran, J. Roane, O. Daugulis, *Angew. Chem. Int. Ed*. **2013**, *52*, 6043–6046; b) M. Shang, S.-Z. Sun, H.-X. Dai, J.-Q. Yu, *J. Am. Chem. Soc*. **2014**, *136*, 3354−3357; c) J. Peng, Z. Xie, M. Chen, J. Wang, Q. Zhu, *Org. Lett*. **2014**, *16*, 4702−4705; d) H. Xu, X. Qiao, S. Yang, Z. Shen, *J. Org. Chem*. **2014**, *79*, 4414−4422; e) J. Peng, M. Chen, Z. Xie, S. Luo, Q. Zhu, *Org. Chem. Front*. **2014**, *1*, 777–781.

[12] a) B. Xiao, T.-J. Gong, J. Xu, Z.-J. Liu, L. Liu, *J. Am. Chem. Soc*. **2011**, *133*, 1466–1474; b) M. Bhanuchandra, M. R. Yadav, R. K. Rit, M. R. Kuram, A. K. Sahoo, *Chem. Commun*. **2013**, *49*, 5225–5227; c) Q.-Z. Zheng, Y.-F. Liang, C. Qina, N. Jiao, *Chem. Commun*. **2013**, *49*, 5654–5656; d) J. Kim, S. Chang, *Angew. Chem. Int. Ed*. **2014**, *53*, 2203–2207; e) Y.-F. Zhang, B. Wu, Z.-J. Shi, *Chem. -Eur. J*. **2016**, *22*, 17808–17812; f) F. W. Patureau, T. Besset, F. Glorius, *Angew. Chem. Int. Ed*. **2011**, *50*, 1064–1067.

[13] During the preparation of this manuscript, a base-metal (Mn)-catalyzed ketone-directed C–H amidation was reported: X. Kong, B. Xu, *Org. Lett*. **2018**, *20*, 4495−4498.

[14] B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Adv. Synth. Catal.* **2014**, *356*, 1491−1495.

[15] a) N. Moselage, J. Li, L. Ackermann, *ACS Catal*. **2016**, *6*, 498−525; b) T. Yoshino, S. Matsunaga, *Adv. Synth. Catal*. **2017**, *359*, 1245–1262; c) J. R. Hummel, J. A. Ellman, *J. Am. Chem. Soc*. **2015**, *137*, 490−498; d) J. Ghorai, A. C. S. Reddy, P. Anbarasan, *Chem. -Eur. J.* **2016**, *22*, 16042−16046; e) D.-G. Yu, T. Gensch, F. de Azambuja, S. Vásquez-Céspedes, F. Glorius, *J. Am. Chem. Soc*. **2014**, *136*, 17722−17725; f) H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga, M. Kanai, *J. Am. Chem. Soc*. **2014**, *136*, 5424−5431; g) S. S. Bera, S. Debbarma, A. K. Ghosh, S. Chand, M. S. Maji, *J. Org. Chem*. **2017**, *82*, 420−430; h) S. S. Bera, S. Debbarma, S. Jana, M. S. Maji, *Adv. Synth. Catal*. **2018**, *360*, 2204–2210; i) R. Mandal, B. Emayavaramban, B. Sundararaju, *Org. Lett*. **2018**, *20*, 2835−2838; j) P. G. Chirila, J. Adams, A. Dirjal, A. Hamilton, C. J. Whiteoak, *Chem. -Eur. J.* **2018**, 24, 3584–3589; k) J. Sanjose-Orduna, J. M. S. Toro, M. H. Prez-Temprano, *Angew. Chem., Int. Ed.* **2018**, *57*, 11369−11373.

[16] a) P. Patel, S. Chang, *ACS Catal*. **2015**, *5*, 853−858; b) J. R. Hummel, J. A. Ellman, *Org. Lett*. **2015**, *17*, 2400−2403; c) J. Park, S. Chang, *Angew. Chem. Int. Ed*. **2015**, *54*, 14103–14107; d) R. Mei, J. Loup, L. Ackermann, *ACS Catal*. **2016**, *6*, 793−797; e) X. Wang, A. Lerchen, F. Glorius, *Org. Lett*. **2016**, *18*, 2090−2093; f) F. Wang, H. Wang, Q. Wang, S. Yu, X. Li, *Org. Lett*. **2016**, *18*, 1306−1309; g) Y. Liu, F. Xie, A.-Q. Jia, X. Li, *Chem. Commun*. **2018**, *54*, 4345–4348; h) P. Shi, L. Wang, K. Chen, J. Wang, J. Zhu, *Org. Lett*. **2017**, *19*, 2418−2421; i) K. Kawai, Y. Bunno, T. Yoshino, S. Matsunaga, *Chem. -Eur. J*. **2018**, *24*, 10231–10237; j) F. Wang, L. Jin, L. Kong, X. Li, *Org. Lett*. **2017**, *19*, 1812−1815; k) G. N. Hermann, C. Bolm, *ACS Catal*. **2017**, *7*, 4592−4596.

[17] M. R. Sk, S. S. Bera, M. S. Maji, *Org. Lett.* **2018**, *20*, 134–137.

[18] Y. Park, K. T. Park, J. G. Kim, S. Chang, *J. Am. Chem. Soc*. **2015**, *137*, 4534−4542.

[19] a) J. P. Michael, The Alkaloids; Elsevier, Inc., **2017**; 78, pp 1−108; b) W.-T. Wei, J.-F. Sheng, H. Miao, X. Luo, X.-H. Song, M. Yan, Y. Zou, *Adv. Synth. Catal.* **2018**, *360*, 2101–2106; c) P. C. Huang, K. Parthasarathy, C. H. Cheng, *Chem. -Eur. J.* **2013**, *19*, 460–464; d) W. R. Gutekunst, P. S. Baran, *Chem. Soc. Rev*. **2011**, *40*, 1976–1991; e) L. McMurray, F. O'Hara, M. J. Gaunt, *Chem. Soc. Rev.* **2011**, *40*, 1885–1898; f) X. Xu, Y. Liu, C.-M. Park, *Angew. Chem. Int. Ed*. **2012**, *51*, 9372–9376; g) A. Lerchen, T. Knecht, M. Koy, C. G. Daniliuc, F. Glorius, *Chem. Eur. J.* **2017**, *23*, 12149–12152.

[20] a) M. Hadjeri, E.-L. Peiller, C. Beney, N. Deka, M. A. Lawson, C. Dumontet, A. Boumendjel, *J. Med. Chem.* **2004,** *47,* 4964–4970; b) J. Ren, J. Zhao, Y.-S. Zhou, X.-H. Liu, X. Chen, K. Hu, *Med Chem Res*. **2013**, *22*, 2855–2861; c) S. A. Patil, R. Patil, D. D. Miller, *Future Med. Chem*. **2012**, *4*, 2085–2115; d) S. J. Hays, *et al*. *J. Med. Chem.* **1998**, *41*, 1060−1067.

[21] a) H. Wang, M. Moselage, M. J. Gonzalez, L. Ackermann, *ACS Catal*. **2016**, *6*, 2705−2709; b) W. Ma, R. Mei, G. Tenti, L. Ackermann, *Chem. Eur. J.* **2014**, *20*, 15248–15251; c) Y. Qiu, W.-J. Kong, J. Struwe, N. Sauermann, T. Rogge, A. Scheremetjew, L. Ackermann, *Angew. Chem. Int. Ed*. **2018**, *57*, 5828–5832; d) E. Tan, O. Quinonero, M. E. de Orbe, A. M. Echavarren, *ACS Catal*. **2018**, *8*, 2166−2172.

[22] See Supporting Information for details.

[23] E. M. Simmons, J. F. Hartwig, *Angew. Chem. Int. Ed*. **2012**, *51*, 3066−3072.

Accepted Manuscript

This article is protected by copyright. All rights reserved.

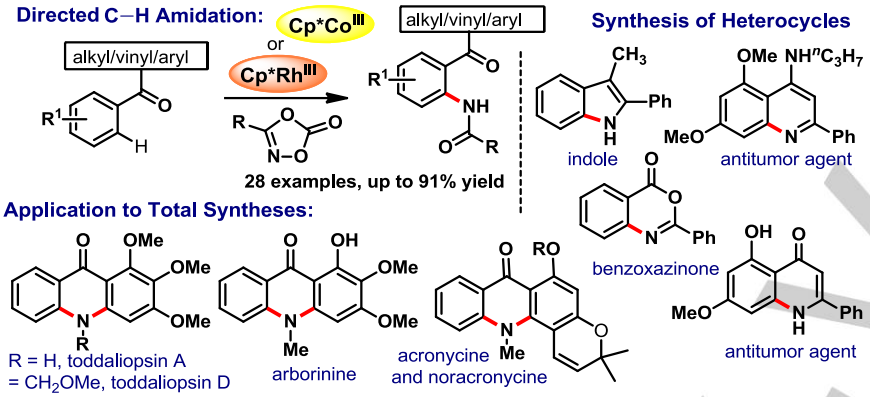
10.1002/chem.201805376

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 2:

FULL PAPER



*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title

* Co(III)- and Rh(III)-catalyzed ketone directed amidation. * Regioselective mono-amidation * Total synthesis of toddaliopsin A, toddaliopsin D and arborinine. * Formal synthesis of acronycine and isoacronycine. * Direct access to potent antitumor agent * Detection of reactive intermediates via LC-MS analysis.

Accepted Manuscript

WILEY-VCH

This article is protected by copyright. All rights reserved.