

Recent developments in C-H functionalization *via* C-H bond activation using ball milling and transition-metal catalysts

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This paper is respectfully dedicated to Professor George A. Kraus

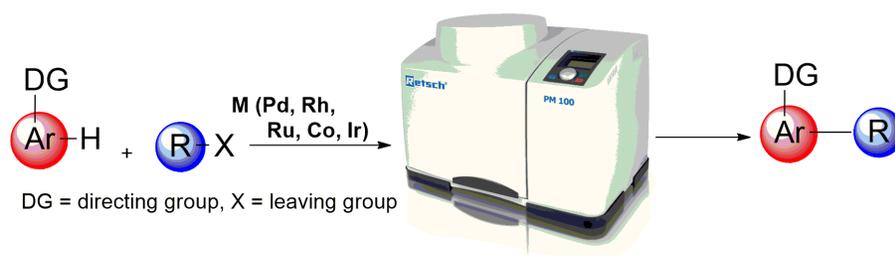
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Abstract

The inert C-H bond functionalization *via* bond activation in the presence of transition metals using ball milling is reviewed. The use of several transition metals, such as Pd, Rh, Ru, Co, and Ir are covered in this review for a variety of important functionalizations, including halogenation, amidation, alkynylation, and dehydrogenative coupling, among others. These reactions are performed under mild conditions, usually without any solvent, and in relatively short reaction times.



Keywords: C-H functionalization, C-H bond activation, ball milling, green chemistry, mechanochemistry

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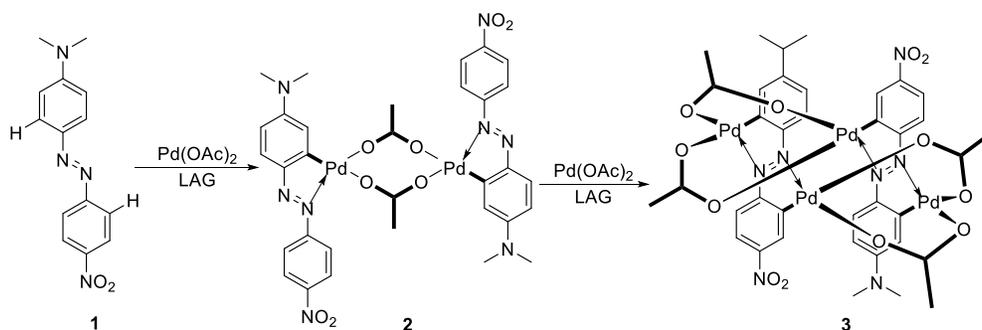
1. Introduction

The sustainable and environmentally-benign synthesis of organic molecules is of considerable interest.¹⁻³ In recent years, significant efforts have been made towards the development of more environmentally-friendly procedures which have more efficiency, cost effectiveness, and minimal chemical waste. The application of mechanical energy to induce organic reactions via grinding, ball milling, shearing and kneading, collectively referred to as mechanochemistry,⁴⁻⁶ has emerged as a powerful tool in organic synthesis. Ball-milling reactions are typically operated in a stainless-steel jar with a number of balls (as required for a particular reaction) rotating at high speed (60–800 rpm), using none or a minimum amount of organic solvent, at close to ambient temperature.⁷ Therefore, ball-milling-induced reactions are, in general, cost effective, efficient and 'greener'. Several methods have been reported so far for the synthesis of carbon-carbon and carbon-heteroatom bond formation under ball milling via cross-coupling reactions such as Suzuki, Sonogashira, Glaser and others.^{8,9}

The transition-metal-catalyzed C-H functionalization via C-H bond activation has been successfully used for the synthesis of organic molecules, including complex natural products and drugs, as the process eliminates the pre-functionalization step, and, therefore, contributes to step and atom economy.¹⁰⁻¹⁷ The use of an inert C-H bond towards the generation of a functional group is advantageous, as these bonds are the most abundant chemical moieties in organic molecules. Thus, a one-step conversion of a C-H bond to the desired functionality reduces the number of synthetic steps, thereby saving reagents, and minimizing the use of solvents and time.¹⁸ Selective activation of a particular C-H bond in an organic molecule out of several similar ones, however, is a challenging task. Therefore, directed C-H bond functionalization using an activating group and a suitable transition metal is of current interest.¹⁹⁻²² The reaction usually occurs through the formation of an organometallic-metallacycle intermediate that drives the reaction forward. As the ball-milling-induced reactions are operated under relatively mild conditions, the C-H functionalization via metallacycle intermediate is expected to proceed smoothly by this technique. We provide here a short review on C-H bond functionalization via inert C-H bond activation under ball milling addressing only the recent developments beyond a related review on this topic in 2017.²³

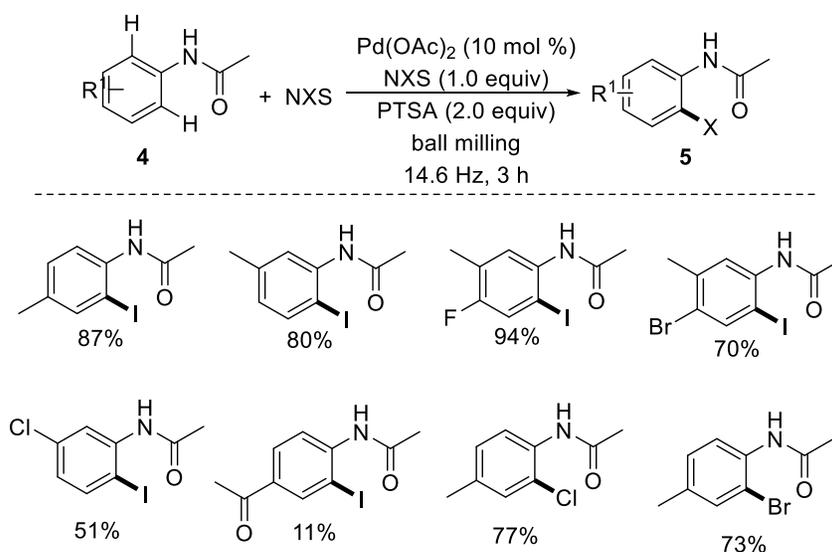
2. Pd-Catalyzed C-H Functionalization

In 2014, Ćurić and co-workers first reported the C-H bond activation of an azobenzene molecule through mechanochemical cyclometallation. Liquid-assisted grinding (LAG)²⁴ of a mixture of 4'-(*N,N*-dimethylamino)-4-nitroazobenzene (**1**) and Pd(OAc)₂, with glacial acetic acid as an additive, led to the formation of a dimeric monopalladacycle complex (**2**) which, on continued grinding with LAG in the presence of an excess of palladium acetate, provided the dicyclopalladated complex (**3**) (Scheme 1). When the molar ratio of azobenzene to palladium acetate was 1:1, the reaction produced the mono-palladated complex (**2**); however, the dicyclopalladated complex (**3**) was formed when two equivalents of Pd(OAc)₂ were added to **2**. This method of C-H bond activation using Pd(II) under ball milling demonstrates the feasibility of the mechanochemical process.



Scheme 1. Palladium-metal-mediated C–H bond activation of azobenzene under mechanochemical conditions.

Very recently, Wang's group reported the mechanochemical C-H bond halogenation of acetanilides (**4**) with *N*-halosuccinimides (NXS) under ball milling (Scheme 2).²⁵

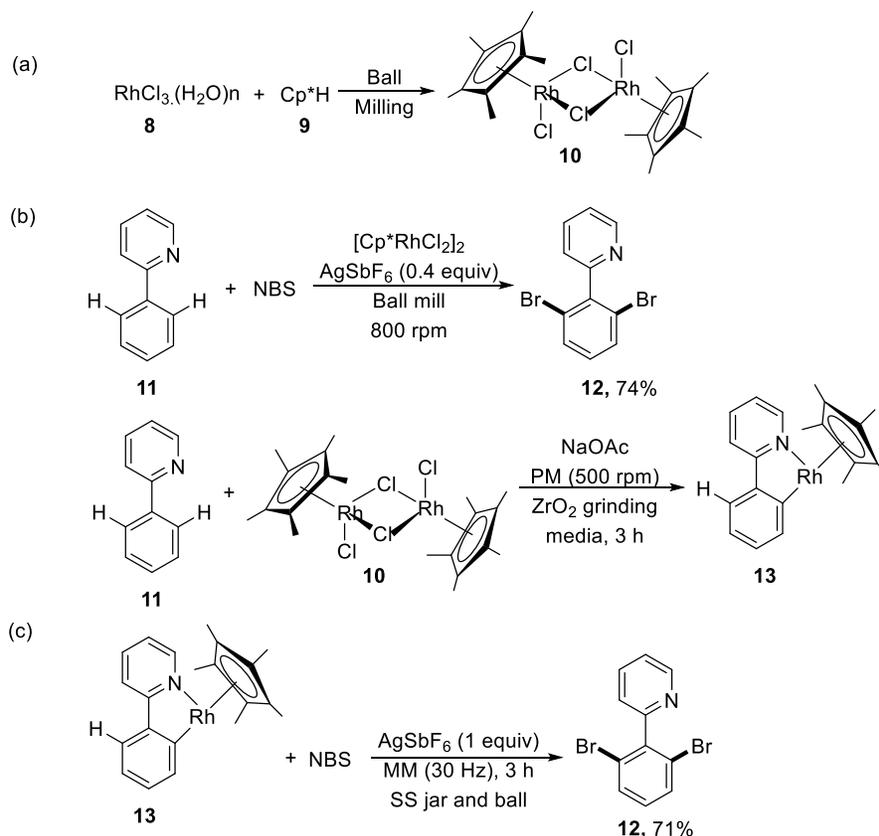


Scheme 2. Mechanochemical Pd-catalyzed *ortho*-halogenation of acetanilides.

as the additive. The reaction in a stainless-steel vessel with two stainless-steel balls ($d = 1.2$ cm) for 90 min at 30 Hz, provided the dimethyl 2,2'-biphenyldicarbamate product in good yield. Dimerized *N*-arylcarbamates (**7**) were obtained under the optimized conditions. In general, the *N*-phenyl-ring moiety bearing an electron-donating substituent (e.g., -Me, -OMe, -Et, and -OEt), produced higher yields of the products than those bearing electron-withdrawing substituents (e.g., -Br). The reaction did not proceed, however, with substrates bearing the relatively strongly electron-withdrawing trifluoromethyl group. Interestingly, when the reaction was performed using two different *N*-arylcarbamates [e.g., methyl (4-methoxyphenyl)carbamate and methyl *p*-tolylcarbamate] under high-speed ball milling in the presence of Pd(II) salt, the unsymmetrical 2,2'-biaryldicarbamate was obtained in 73% yield. The coupling products, 2,2'-biaryldicarbamates, were easily converted into their corresponding 2,2'-biaryldiamines on base hydrolysis. This C-H bond activation under ball milling represents a fast and environmentally-friendly method for the synthesis of 2,2'-biaryldicarbamates and 2,2'-biaryldiamines.

3. Rh-Catalyzed C-H Functionalization

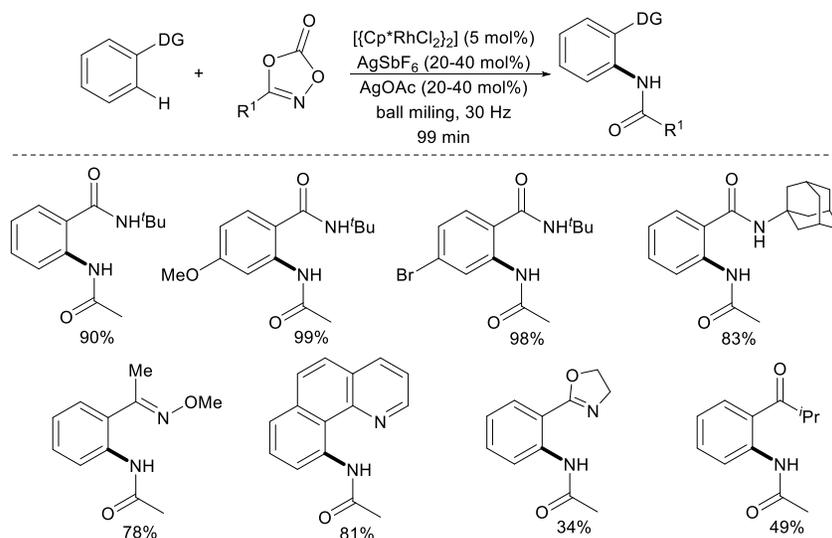
In 2015, Bolm and co-workers developed a unique protocol for the mechanochemical synthesis of pentamethylcyclopentadienyl rhodium dichloride [Cp^*RhCl_2]₂ under ball milling (Scheme 4).²⁷ When a mixture of RhCl_3 hydrate (**8**) and pentamethylcyclopentadiene (Cp^*H) (**9**) was allowed to stir under liquid-assisted grinding (LAG), the corresponding Rh(III) dimer (**10**) was obtained in good yield, and within a shorter reaction time compared to the standard solution-based protocol (Scheme 4a).



Scheme 4. Mechano-synthesis and application of [Cp^*RhCl_2]₂ for C-H bond functionalization.

The newly formed rhodium complex $[\text{Cp}^*\text{RhCl}_2]_2$ (**10**) was further applied as a catalyst for the *ortho* C-H bond halogenation of 2-phenylpyridine (**11**) in the presence of *N*-bromosuccinimide (NBS). The corresponding dibrominated 2-phenylpyridine (**12**) was formed as the major product in 74% yield (Scheme 4b). However, a higher reactivity was observed for iodination of 2-phenylpyridine using *N*-iodosuccinimide (NIS). A rhodacycle (**13**) was formed when 2-phenylpyridine (**11**) and $[\text{Cp}^*\text{RhCl}_2]_2$ (**10**) were stirred together in the presence of sodium acetate in a planetary ball mill which, on treatment with NBS and AgSbF_6 , led to the formation of the dibrominated 2-phenylpyridine (**12**) as the major product in 71% yield (Scheme 4c). This indicated that the C-H bond halogenation may occur *via* the formation of the intermediate in the original catalytic reaction under ball milling.

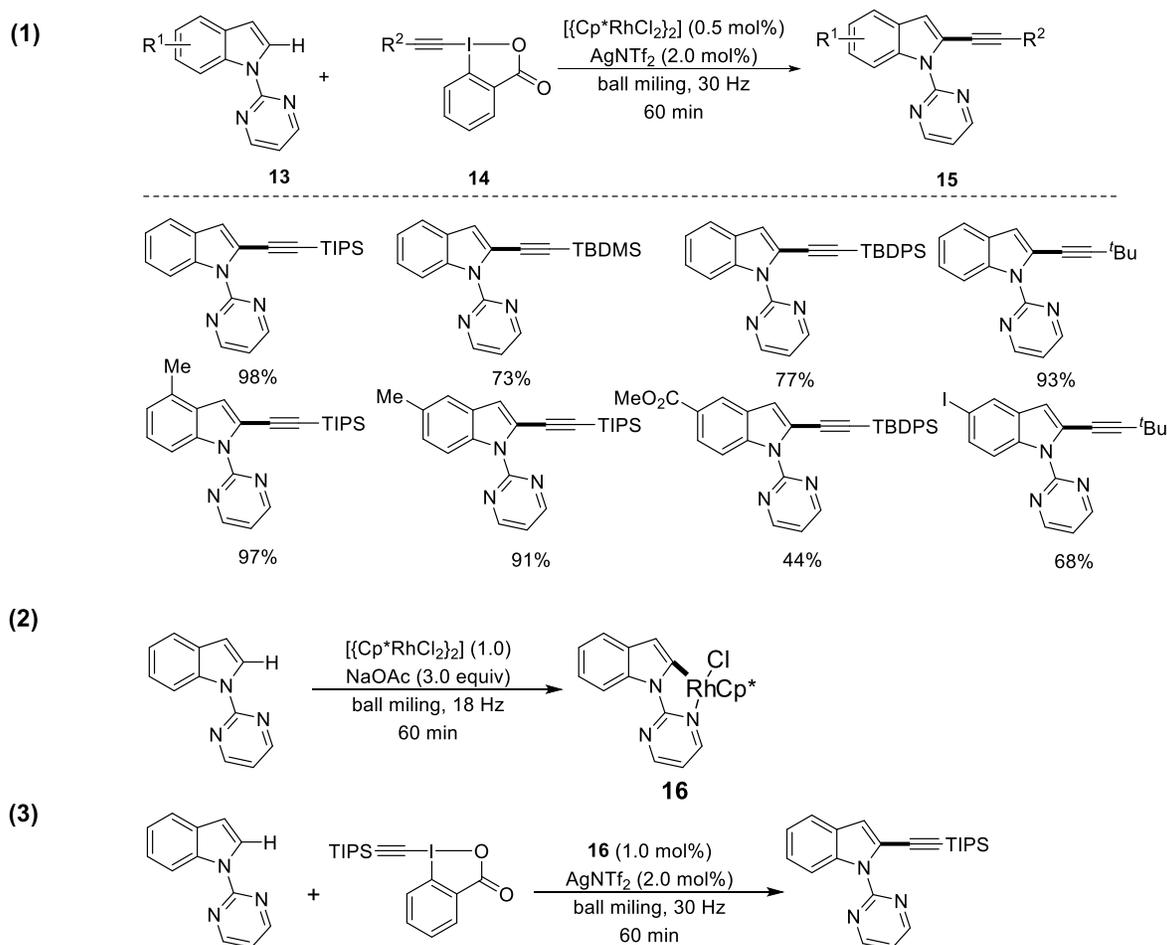
Recently, Bolm and co-workers have reported the mechanochemical C-H bond amidation of the $\text{C}(\text{sp}^2)\text{-H}$ bond using a 1,4,2-dioxazol-5-one as the amidating agent under ball milling (Scheme 5).²⁸ The reaction occurs in the presence of $[\text{Cp}^*\text{RhCl}_2]_2$, AgSbF_6 , and AgOAc under solvent-free conditions using ball milling in a 25 mL ZrO_2 milling jar with one ZrO_2 ball of 15 mm diameter at 30 Hz. It has been found that Rh is superior to other transition-metal (Ru and Ir) catalysts. Under optimized conditions, a library of amide compounds was synthesized starting from diverse, substituted-benzamide substrates as starting materials. In the case of *meta*-substituted benzamides, the reaction provides a 1.1:1 mixture of the corresponding regioisomers. In general, the reactions resulted in high yields. In the absence of any solvent, the products were obtained in shorter reaction time (99 min) at room temperature, compared to the standard solvent-based protocol for amidation (12 h). Apart from an amide as a directing group, several other directing groups (e.g., ketones, ketoximes, 2-phenylpyridine, 2-phenylpyrimidine, etc.) were used for the amidation under the optimized reaction conditions. A kinetic isotope study ($K_{\text{H}}/K_{\text{D}} = 4.4$) indicates that the C-H bond cleavage might be the rate-determining step.



Scheme 5. Rhodium catalyzed mechanochemical C-H bond amidation.

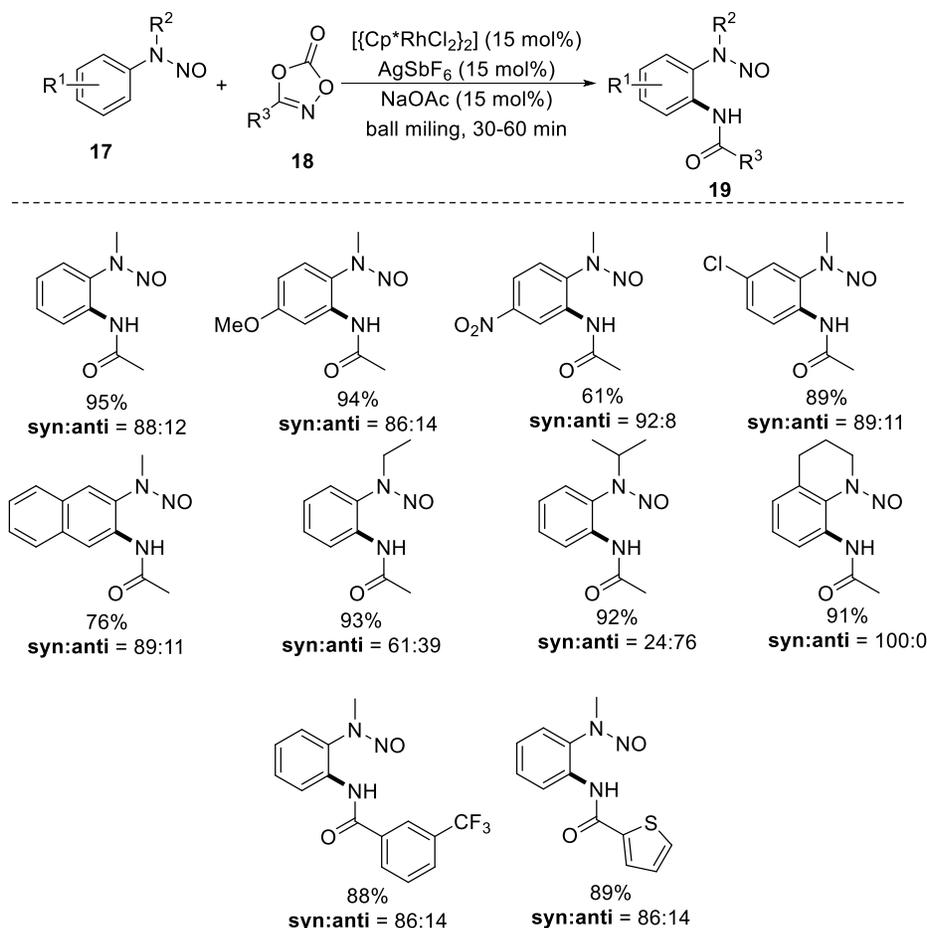
Rhodium(III)-catalyzed C-H bond alkylation of *N*-(2-pyrimidyl)indole (**13**), in which pyrimidine acts as a directing group, was reported by Bolm and co-workers (Scheme 6, Eq 1).²⁹ Functionalization of the indole moiety by an alkyne (**14**) was achieved in the presence of 0.5 mol% of $[\text{Cp}^*\text{RhCl}_2]_2$ and 2.0 mol% of AgNTf_2 under ball milling. The reaction afforded a series of C2-alkynylated indole derivatives (**15**) in good-to-excellent

yields within a short time. Both electron-donating and -withdrawing groups such as methyl, methoxy, halogens (fluoro, chloro, bromo and iodo) at the 5-position of the indole, were well tolerated under the mechanochemical reaction conditions. Interestingly, the reaction produces the silyl-protected C2-alkynated indole derivative, which can be applied further for derivatization after deprotection by the silyl group. When a mixture of *N*-pyrimidylindole (**13**) and $[(\text{Cp}^*\text{RhCl}_2)_2]$ along with NaOAc was milled for 60 min at 30 Hz under solvent-free conditions, a rhodacycle intermediate (**16**) was formed (Scheme 6, Eq 2). Next, the rhodacycle (**16**) was used as a catalyst in the presence of AgNTf₂ (2.0 mol%) for the reaction of **13** and **14** (Scheme 6, Eq. 3). After 60 minutes of milling, indole (**15**) was obtained in 96% yield. This result suggests that the reaction proceeds through the formation of **16**.



Scheme 6. Rhodium(III)-catalyzed C-H alkynylation of indoles under solvent-free conditions in a mixer mill.

Recently, Li and Wang reported the synthesis of 2-aminoanilides through C-H amidation of *N*-nitrosoanilines (**17**) under ball milling in the absence of any solvent (Scheme 7).³⁰ 1,4,2-Dioxazol-5-ones (**18**) were used as the amidating agent.



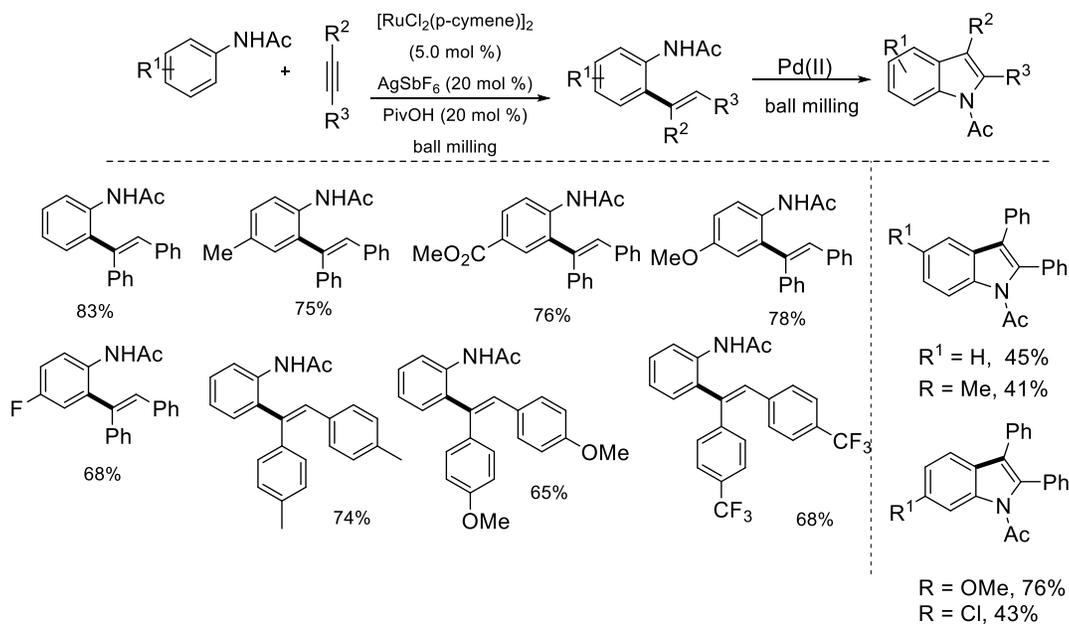
Scheme 7. Solvent-free rhodium(III)-catalyzed synthesis of 2-aminoanilides.

After several optimizations, it was observed that $[\{\text{Cp}^*\text{RhCl}_2\}_2]$ is the best catalyst for this transformation compared to other commonly employed catalysts, e.g., Pd, Co and Ir. The reaction requires the use of 1.0 mol% of $[\{\text{Cp}^*\text{RhCl}_2\}_2]$ and 15 mol% of AgSbF_6 , in the presence of NaOAc (15 mol%) as an additive, using a stainless-steel ball (10 mm in diameter) in a mixer mill at 30 Hz for 30-60 min. A range of diversely-substituted *N*-nitrosoaniline derivatives, bearing both electron-donating and electron-withdrawing groups, underwent successful *ortho*-C-H amidation with 1,4,2-dioxazol-5-ones bearing an alkyl or aryl moiety. The corresponding amidated derivatives (predominantly *syn*) (**19**) were formed in good-to-excellent yields within a short period of time. The gram-scale reactions give as good yields as mmol-scale reactions. A kinetic isotope study, with $K_H/K_D = 2.1$, indicates that the *ortho*-C-H bond cleavage might be involved in the rate-determining step. In general, the reaction provides an efficient and environmentally-benign pathway for the synthesis of 2-aminoanilide derivatives with low-catalyst loading under rhodium-catalyzed mechanochemical conditions.

4. Ru-Catalyzed C-H Functionalization

In 2017, Bolm *et al.* reported the first mechanochemical Ru(III)-catalyzed C-H bond functionalization of acetanilides under ball milling (Scheme 8).³¹ The reaction of an alkyne with acetanilide leads to the formation of tri-substituted (*E*)-alkenes in good yields in the presence of a ruthenium catalyst under solvent-free

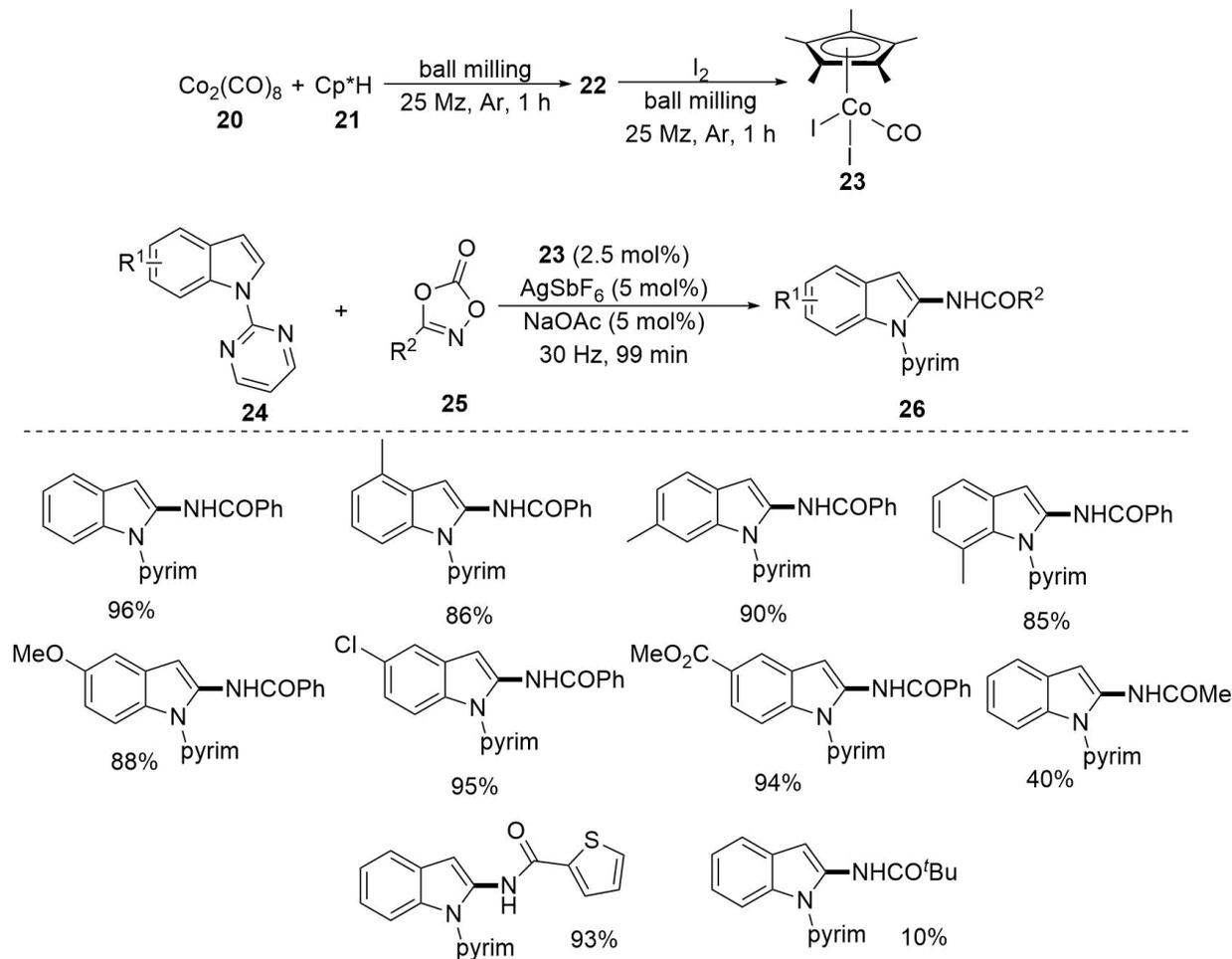
conditions. The reaction requires the use of catalytic amounts of AgSbF_6 salt as an oxidant, and pivalic acid or copper acetate as an additive. The corresponding alkene derivatives were formed within a short time. The alkene derivatives were converted into *N*-acetylindoles by palladium catalyzed $\text{C}(sp^2)\text{-H/N-H}$ coupling in the mixer mill.



Scheme 8. Mechanochemical ruthenium-catalyzed hydroarylation of alkynes under ball-milling.

5. Co-Catalyzed C-H Functionalization

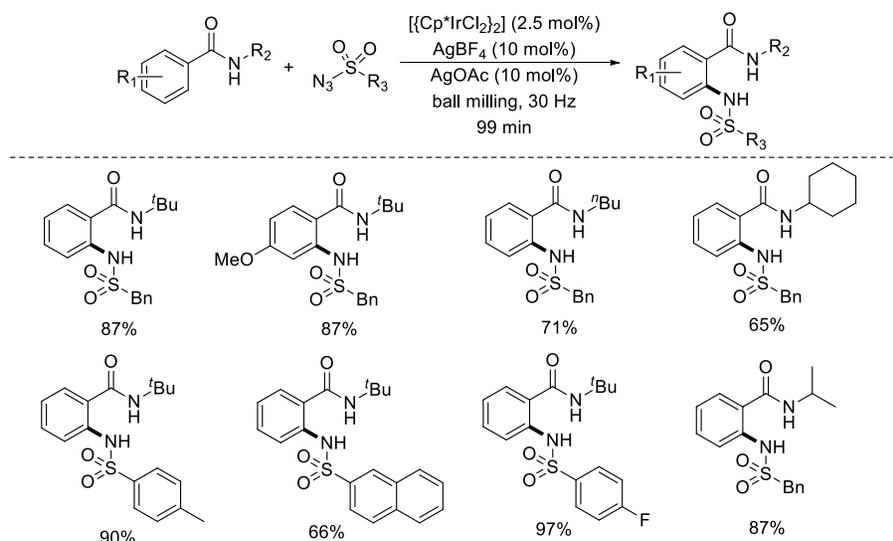
Bolm and his group developed a unique procedure for the synthesis of $[\text{Cp}^*\text{Co}(\text{CO})\text{I}_2]$ under ball milling which was then subsequently used in the amidation of indoles (Scheme 9).³² Initially, $\text{Co}_2(\text{CO})_8$ (**20**) undergoes reaction with pentamethylcyclopentadiene (Cp^*H , **21**) in dichloromethane (DCM) to generate the intermediate $[\text{Cp}^*\text{Co}(\text{CO})_3]$ (**22**). The Co(I) intermediate (**22**) then reacts with molecular iodine in diethyl ether to provide the cobalt (III) complex (**23**). The newly-formed cobalt (III) complex was applied further as a catalyst for the amidation of indoles (**24**) using 1,4,2-dioxazol-5-one (**25**) as the amidating agent under solvent-free grinding in a mixer ball mill. The mechanochemical C-H bond amidation occurs in the presence of 2.5 mol% $[\text{Cp}^*\text{Co}(\text{CO})\text{I}_2]$, 5 mol% of AgSbF_6 , and 5 mol% of NaOAc for 99 min at 30 Hz. A range of amidated indole derivatives (**26**) was synthesized starting from 1,4,2-dioxazol-5-ones and an indole moiety under the optimized conditions. It was observed that, compared to the previous solution-based protocol, this method offers a more practical and environmentally-benign access to both the cobalt(III) catalyst and 2-amidated indoles.



Scheme 9. Cobalt-catalyzed C-H amidation of indoles under ball milling.

6. Ir-Catalyzed C-H Functionalization

In addition to Pd, Rh, Ru and Co catalysts, Ir catalysts have also been successfully employed for C-H bond functionalization under mechanochemical conditions. In 2016, Bolm and his co-workers developed a mechanochemical C-H amidation of amides with aryl or alkyl sulfonyl azides, using $[\text{Cp}^*\text{IrCl}_2]_2$ as the catalyst in the presence of Ag salt as an oxidant, under ball milling for the first time (Scheme 10).³³ The reactions involve the interaction of an amide derivative and sulfonyl azides in the presence of $[\text{Cp}^*\text{IrCl}_2]_2$ (2.5 mol%), AgBF_4 (10 mol%) and AgOAc (10 mol%) under ball milling. A range of diversely-substituted aromatic amides reacted with both aryl and alkyl sulfonyl azides under the optimized reaction conditions, and the corresponding *ortho*-C-H amidated derivatives were formed in good-to-excellent yields. Intermolecular-competition experiments revealed the slightly lower reactivity of electron-rich azides compared with electron-deficient ones.



Scheme 10. Mechanochemical Ir-catalyzed C-H bond amidation of amides.

3. Conclusions

Functionalization *via* C-H activation is, in itself, a green concept since it eliminates molecule pre-functionalization steps, thereby, helping to reduce the numbers and amounts of reagents and solvents used. When this is coupled with an energy- and cost-saving tool such as ball milling, its importance and value are definitely enhanced. This brief account demonstrates various types of functionalization *via* C-H activation using a variety of transition-metal catalysts under ball milling. We believe it will attract the attention of synthetic chemists and will find further applications in organic synthesis.

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Tubai Ghosh completed his B.Sc (Chemistry Hons.) from Hooghly Mohsin College, The University of Burdwan in 2010. He obtained M.Sc (2 yr) in Chemistry degree from IIT Kanpur in 2012. Currently he is working as a senior research fellow in the group of Professor B. C. Ranu at the School of Chemical Sciences, Indian Association for the Cultivation of Science, Jadavpur, Kolkata, India. His current research focuses on the transition-metal-catalyzed C-H bond functionalization.



Swapnadeep Jalal was born in Burdwan (West Bengal), India. He obtained his B. Sc. and M. Sc. degrees from The University of Burdwan, India, in 2008 and 2010, respectively. He received his Ph. D. degree from Jadavpur University (Kolkata), India in 2017. His research focuses on the synthesis of bioactive heterocyclic and polycyclic ring compounds by cross coupling reactions and alkyne/alkene carbonyl metathesis reaction using transition-metal catalyst. He is currently working under Professor B. C. Ranu, School of Chemical Sciences, IACS, Kolkata, India, as a DST-NPDF Fellow. He is also continuing as guest lecturer at P.G Department of Chemistry, Vivekananda Mahavidyalaya under The University of Burdwan, West Bengal, India since 2014.



Brindaban C. Ranu started his independent research career in 1985 at the Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Kolkata, India after completion of his graduate studies at Rice University (mentor - Professor E. Wenkert), Houston, Texas, USA and IACS, Kolkata (mentor - Professor U. R. Ghatak) and postdoctoral work at Virginia Tech, USA (mentor - Professor T. Hudlicky). His research interests include Green Synthesis and Green Catalysis. He became professor in 1996 and Senior Professor in 2006. Currently he is INSA Senior scientist. He received the Chemical Research Society of India silver medal in 2010. He was elected fellow of the Indian Academy of Sciences in 1995 and fellow of the Indian National Science Academy in 2008. He is also a recipient of J C Bose National Fellowship, DST, Govt. of India. He has published more than 275 papers.