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Eco-efficient C–H alkynylation of indoles *via* mechanochemical ruthenium catalysis

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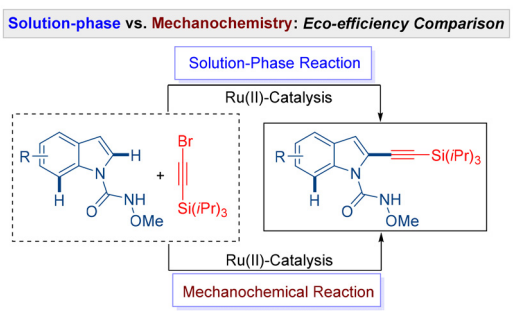
A regioselective C2-alkynylation of indoles *via* ruthenium(II)-catalyzed C–H activation using bromoalkynes is demonstrated under both solution-phase and mechanochemical conditions. The solvent-minimized mechanochemical method delivers comparable yields with reduced reaction time and improved green metrics. Broad substrate scope, gram-scale applicability, and post-functionalization showcase the synthetic utility of this approach. This work underscores the potential of mechanochemistry as a sustainable and operationally simple alternative for direct C–H functionalization of heterocycles.

Indole derivatives are ubiquitous scaffolds found in a wide array of natural products, pharmaceuticals, agrochemicals, and advanced materials, making their selective functionalization a topic of enduring interest.[1,2] Among various synthetic approaches, direct C–H activation[3] has emerged as a powerful and sustainable strategy for the late-stage modification of heterocycles, including indoles. Over the past two decades, substantial progress has been made in the regioselective functionalization of indoles through C–H functionalization.[4] In particular, alkynylated indoles serve as valuable building blocks for the construction of complex organic molecules with potential applications in medicinal chemistry and materials science.[5] However, direct C2-alkynylation of indoles has been relatively underexplored compared to C2-arylation, alkylation, and alkenylation. In this context, work by Waser,[6] Li,[7] Shi,[8] and others[9] has demonstrated the regioselective incorporation of alkynyl groups at the C2-position of indoles *via* directed transition metal-catalyzed C–H activation using hypervalent iodine–alkyne reagents. Building on these advances, Ackermann[10] and others[9c,11] developed methods employing bromoalkynes as alkynylating agents for C2-selective functionalization of indoles. Despite their efficiency, these methodologies often require volatile and toxic organic solvents, elevated temperatures, and prolonged reaction times—factors that compromise the overall greenness and sustainability of the C–H activation protocols.

In recent years, solvent-free or solvent-less mechanochemical C–H activation reactions using ball-milling techniques have emerged as an attractive alternative to conventional solution-phase methods.[12] These approaches offer several advantages, including reduced or no solvent use and significantly shorter reaction times. In this context, Bolm reported the mechanochemical C2-alkynylation of indoles using the sensitive hypervalent iodine-based reagent ethynylbenziodoxolone (EBX) as the alkyne source, catalyzed by the expensive $[Cp^*RhCl_2]_2$ in the presence of $AgNTf_2$ as an additive.[13] While efficient, the reliance on costly rhodium catalysts, silver additives, and sensitive iodine(III) reagents limits the broader applicability of this method.

To address these limitations, we sought to develop a cost-effective and sustainable mechanochemical approach for the C2-selective alkynylation of indoles (Scheme 1). Our strategy employs the inexpensive ruthenium-based catalyst[14] $[Ru(p\text{-cymene})Cl_2]_2$ and readily accessible bromoalkynes under ball-milling conditions. Furthermore, we aimed to compare the efficiency, practicality, and green chemistry metrics of this mechanochemical protocol with its solution-phase counter-



Scheme 1 Ruthenium(II)-catalyzed C2-alkynylation of indoles through solution-phase and mechanochemical strategy.

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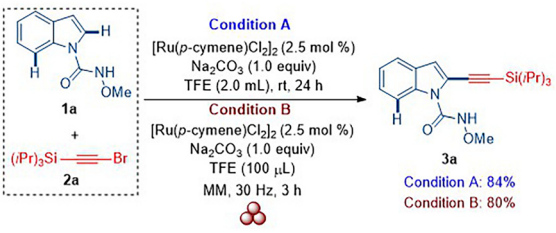
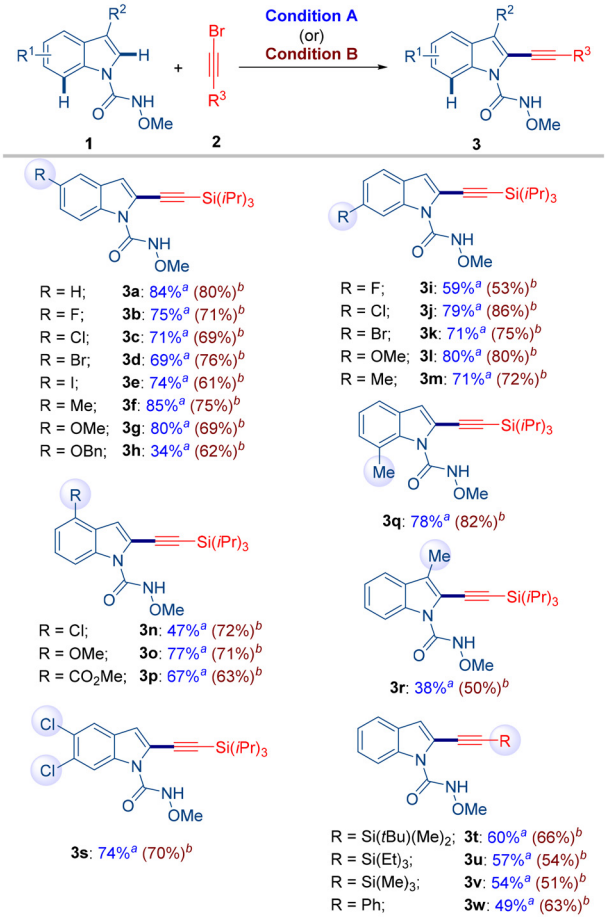
part, thereby evaluating the potential of mechanochemistry as a viable and greener alternative for C–H alkynylation.

We began our study by optimizing the reaction conditions for the synthesis of 2-alkynylated indole carboxamide **3a** from *N*-methoxy-1*H*-indole-1-carboxamide (**1a**) and (bromoethynyl) triisopropylsilane (**2a**) (Table S1). Following detailed optimization, we identified that treatment of **1a** (0.21 mmol, 1.0 equiv.) with **2a** (0.42 mmol, 2.0 equiv.) in the presence of 2.5 mol% of $[Ru(p\text{-cymene})Cl_2]_2$ and 1.0 equiv. of Na_2CO_3 in 2.0 mL of 2,2,2-trifluoroethanol (TFE) at room temperature for 24 h afforded **3a** in 84% isolated yield (Scheme 2). This reaction condition was designated as the standard solution-phase condition (Condition A). In parallel, we performed optimization studies under mechanochemical conditions to identify an optimal protocol (Table S2). Milling a mixture of **1a** (0.21 mmol, 1.0 equiv.), **2a** (0.42 mmol, 2.0 equiv.), $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol%), Na_2CO_3 (1.0 equiv.), and TFE (100 μL, used as a liquid-assisted grinding (LAG) additive) in a 5 mL stainless-steel (SS) jar with three SS balls (ϕ = 5 mm) at 30 Hz for 3 h furnished **3a** in 80% isolated yield (Scheme 2). This optimized condition was designated as the standard mechanochemical condition (Condition B).

With the optimized reaction conditions A and B established, a series of indole substrates (**1a–1s**) were subjected to alkynylation with **2a** (Scheme 3). Various indoles bearing substituents at the 4-, 5-, 6-, and 7-positions underwent smooth C2-alkynylation to afford the corresponding products (**3a–3s**) in satisfactory yields under both conditions. Notably, halogen substituents on the indole ring were well tolerated, offering potential for further diversification *via* cross-coupling strategies. The sterically hindered 3-methylindole substrate (**1r**) also participated in the reaction, albeit with reduced efficiency due to steric hindrance at the C3 position. In a similar fashion, alkynylation reactions employing bromoalkynes bearing alternative silyl groups in place of $Si(iPr)_3$ were conducted with **1a**, delivering the corresponding products (**3t–3v**) in good yields. Furthermore, (bromoethynyl)benzene (**2e**) also underwent reaction with **1a** to afford the desired product **3w** in good yield under conditions A and B. These results highlight the broad applicability of both protocols across diverse indole substrates and bromoalkyne partners. Overall, the reaction scope illustrates that both solution-phase and mechanochemical conditions deliver comparable efficiencies in most cases. However, considering the significantly shorter reaction times



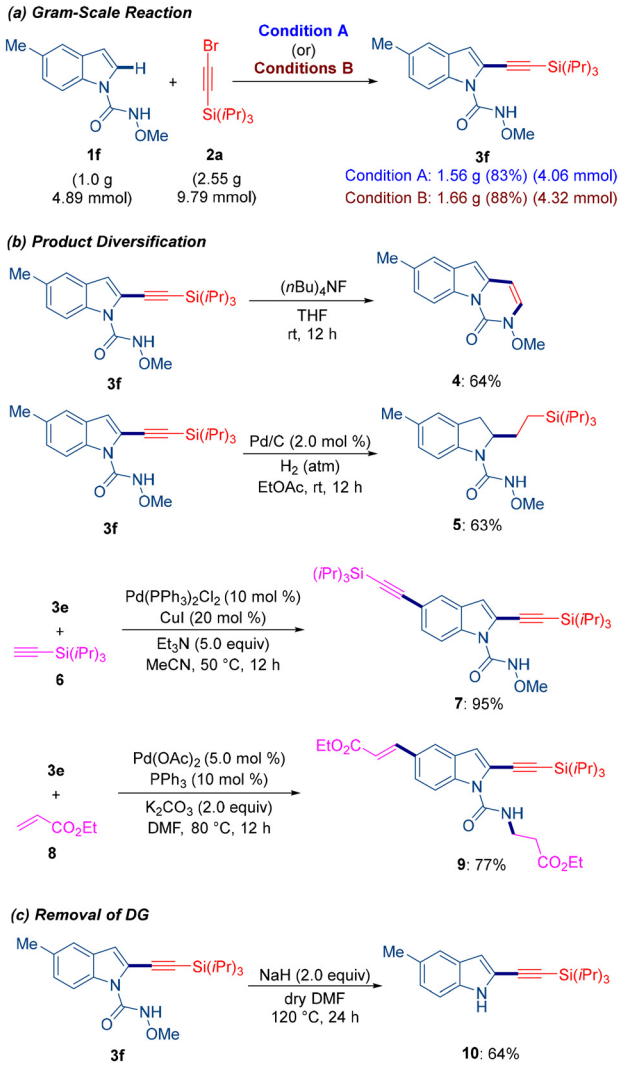
Scheme 2 Ruthenium(II)-catalyzed solution-phase or mechanochemical synthesis of C2-alkynylated indoles.



Scheme 3 Scope of ruthenium(II)-catalyzed solution-phase and mechanochemical alkynylation of indoles. [a] Condition A: **1** (0.21 mmol, 1.0 equiv.), **2** (0.42 mmol, 2.0 equiv.), $[Ru(p\text{-cymene})Cl_2]_2$ (0.005 mmol, 2.5 mol%), Na_2CO_3 (0.21 mmol, 1.0 equiv.), TFE (2.0 mL) at rt (25–28 °C) for 24 h. Yields are isolated products yield. [b] Condition B: **1** (0.21 mmol, 1.0 equiv.), **2** (0.42 mmol, 2.0 equiv.), $[Ru(p\text{-cymene})Cl_2]_2$ (0.005 mmol, 2.5 mol%), Na_2CO_3 (0.21 mmol, 1.0 equiv.), TFE (100 μL) were placed in a 5 mL SS vessel with three stainless-steel balls (ϕ = 5 mm). Ball milling conditions: 3 h at 30 Hz. Yields are isolated products yield.

and reduced solvent usage, the mechanochemical approach offers distinct advantages in terms of operational simplicity and environmental sustainability.

Next, we evaluated the scalability of the reaction. As shown in Scheme 4a, a gram-scale reaction between **1f** and **2a** afforded the desired product **3f** in 83% yield under solution-phase conditions and 88% yield under mechanochemical conditions, demonstrating the practicality of both approaches. To showcase the synthetic utility of the alkynylated product, **3f** was treated with tetrabutylammonium fluoride (TBAF) to furnish the corresponding pyrimidoindolone derivative **4** (Scheme 4b). Furthermore, hydrogenation of **3f** using Pd/C under a hydrogen atmosphere provided the indoline derivative **5** in 63% yield. We also demonstrated the use of cross-coupling strategies for the functionalization of halogen-substituted products. For example, compound **3e** underwent a



Scheme 4 Scalable reactions and product diversifications.

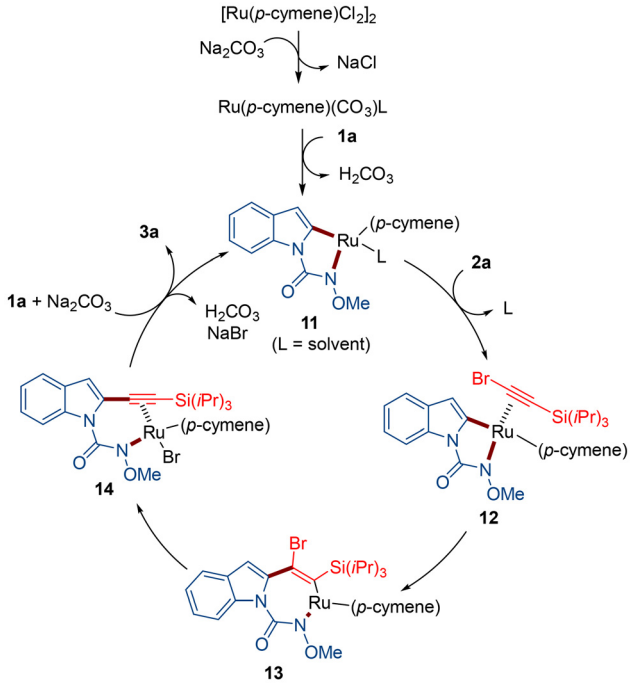


Fig. 1 Proposed mechanism.

Sonogashira coupling reaction with **6** and a Heck coupling with **8** to afford products **7** and **9**, respectively. Finally, treatment of **3f** with NaH successfully removed the *N*-methoxy carboxamide directing group, affording product **10** in good yield (Scheme 4c).

Based on the experimental results and literature precedents,[14b,c] we propose a plausible catalytic cycle involving a cyclometalated ruthenium complex **11** (Fig. 1). Coordination of alkynyl bromide **2a** to complex **11**, followed by migratory insertion, generates a seven-membered ruthenacycle intermediate **13**. This intermediate subsequently undergoes β-bromo elimination to afford species **14**. The resulting complex then reacts with another molecule of **1a** in the presence of Na_2CO_3 to release the product **3a** and regenerate the ruthenacycle intermediate **11**, completing the catalytic cycle.

After achieving a broad substrate scope and demonstrating scalability, our focus turned to evaluating the robustness of both sets of reaction conditions. Accordingly, we assessed the reaction efficiency for forming product **3a** under various sensitivity assessment parameters.[15] For Condition A, we evaluated factors such as catalyst loading, the amounts of base and alkynylating reagents, reaction time, solvent volume, and reaction scale. As shown in the radar diagram (Fig. 2a), variations in these parameters resulted in only minor deviations from the standard yield. Similarly, Condition B was also subjected to sensitivity analysis. Gratifyingly, the corresponding radar diagram (Fig. 2b) revealed minimal deviation from the standard yield, highlighting the robustness of the optimized conditions.

To evaluate the eco-friendliness of the two developed strategies, we analyzed the green chemistry metrics (GCM) for the gram-scale synthesis of compound **3f** from **1f** (1.0 g, 4.89 mmol) and **2a** (2.55 g, 9.79 mmol).[16] As shown in Table 1, both strategies exhibit satisfactory green chemistry metrics. Notably, the mechanochemical approach demonstrates superior green metrics compared to the solution-phase method. It delivers a significantly lower *E*-factor (2.33 *vs.* 19.47) and improved process mass intensity (PMI = 3.33 *vs.* 20.48), indicating reduced waste generation and material input. Moreover, enhanced mass productivity and EcoScale values further underscore its operational and environmental efficiency.

In conclusion, we have developed a regioselective C2-alkynylation of indoles employing a ruthenium(II)-catalyzed C–H activation strategy under both solution-phase and mechanochemical conditions. Using readily available bromoalkynes and a cost-effective $[Ru(p\text{-cymene})Cl_2]_2$ catalyst enabled efficient functionalization across a broad range of indole substrates,

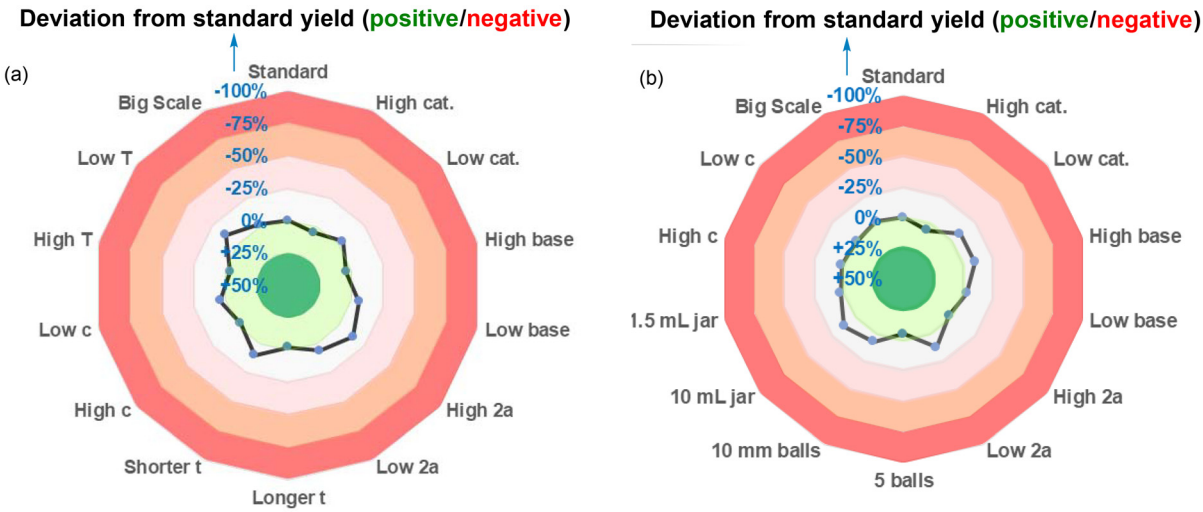


Fig. 2 Sensitivity assessment of the reaction Conditions A and B. (a) Radar diagram for Condition A. (b) Radar diagram for Condition B. c = concentration. *T* = temperature. *t* = time. cat. = catalyst.

Table 1 Quantification of green chemistry metrics (GCM) for the synthesis of compound **3f**

			Obtained value for product **3f**	
Entry	Green chemistry metrics	Ideal value	Solution phase approach	Mechanochemical approach
1	Chemical yield (CY)	100%	82.95	88.33
2	*E*-factor	0	19.47	2.33
3	Process mass Intensity (PMI)	1	20.48	3.33
4	Atom economy (AE)	100%	82.61	82.61
5	Carbon efficiency (CE)	100%	66.66	66.66
6	Reaction mass efficiency (RME)	100%	43.94	46.76
7	Optimum efficiency (OE)	100%	53.18	56.60
8	Mass productivity (MP)	100%	4.88	30.56
9	Waste intensity (WI)	0	0.95	0.70
10	Percentage conversion (PC)	100%	100	100
11	Percentage selectivity (PS)	100%	82.95	88.33
12	EcoScale	100%	68.47	73.17

with both protocols delivering comparable yields. The mechanochemical approach, in particular, demonstrated operational simplicity, shorter reaction times, and reduced solvent consumption. Scalability was confirmed through gram-scale synthesis, and the synthetic utility of the alkynylated products was exemplified through downstream transformations. Sensitivity assessments highlighted the robustness of both protocols, while green chemistry metric analysis revealed the superior environmental profile of the mechanochemical method. These findings underscore the potential of mechanochemistry as a practical and sustainable alternative for C–H alkynylation in complex molecule synthesis.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI. Supplementary information: experimental details, characterization data of the isolated products, and copies of the NMR spectra of new products. See DOI: **https://doi.org/10.1039/d5ob01198a**.

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