

Mechanochemical Regulation of Unstable Acyl Azide: Ir(III)-Catalyzed Nitrene Transfer C–H Amidation under Solvent-Free Ball Milling Conditions

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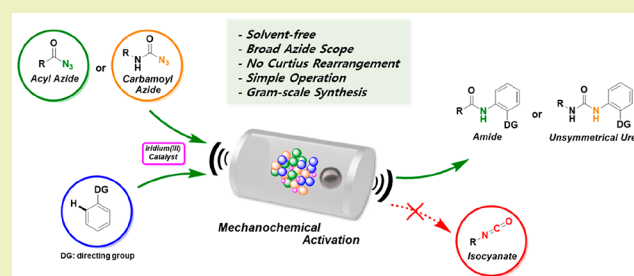
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ABSTRACT: In this study, we investigate the mechanochemical activation of acyl azide for direct C–H amidation with excellent C–N bond selectivity, fast rate, enhanced reactivity, solvent-free condition, and broad scope. Thermally unstable acyl azide, prone to Curtius rearrangement, was found to be controllable under mechanochemical ball milling conditions. Investigation of the mechanochemical process window of acyl azide led us to define highly selective Cp*Ir(III)-catalyzed acyl azide activation to acyl nitrene species and direct C–H amidation protocol. In addition to the expected merits of mechanochemistry, the newly developed high-speed ball milling method allows for carbamoyl azide utilization, which showed a limited scope under thermal solution conditions, registering to a list of mechanochemically preferred reactions.

KEYWORDS: Ball milling, Acyl azides, Carbamoyl azide, C–H amidation, Solvent-free synthesis



INTRODUCTION

Organic azides are versatile organic molecules that are used in many chemical applications. In the chemical synthesis, the organic azide functionality enables it to be a key nitrogen source for various N-containing compounds.^{1–3} Generally, the escape of nitrogen gas caused by external energy inputs triggers the reaction. However, the control of extremely reactive intermediates has been an issue in the design of chemical processes of azides.^{4,5} Recently, the development of various transition-metal catalysts has enabled control of the reactivity and selectivity of azides under mild conditions.^{6–8} However, acyl azide, extremely thermally unstable, remains problematic. For example, benzoyl azides or carbamoyl azides quickly undergo Curtius rearrangement to isocyanate around 50 °C, which significantly limits its process window.^{9–11}

In recent decades, mechanochemical transformation using ball milling has garnered attention from the synthetic community. Because of its many advantages such as solvent-free synthesis, enhanced rate, and unique selectivity, mechanochemistry becomes a significant option in chemical synthesis.^{12–14} Many reports have claimed that the high efficiency of mechanochemical ball milling reactions is due to the high temperature elevation at the collision spot.^{15,16} While mechanochemical azide transformations have been reported only with relatively stable alkyl and sulfonyl azides,^{17–19} Užarević and co-workers reported an interesting observation that acyl azide does not undergo Curtius rearrangement under high-speed ball milling conditions.^{20,21} Thermally unstable acyl azides are mechanochemically stable. They utilized this

attribute for the synthesis of amides from acyl azide, avoiding isocyanate formation. However, the formation of active acyl nitrene species from acyl azide under solvent-free mechanochemical conditions remains unexplored. There are limited reports on similar transformations utilizing dioxazolones and Rh(III) and Co(III) catalysts in mechanochemical acyl nitrene formation and its application.^{22–24}

Selective acyl nitrene transfer reactions of acyl azides have been realized in solution by transition metal catalysts such as Rh(III), Ir(III), and Ru(II).^{25–33} As mentioned, a low ceiling temperature has limits to its scope. Given the unexpected stability of acyl azide under high-speed ball milling conditions, a mechanochemical system could provide better control and a broader synthetic spectrum for the nitrene transfer reactions of acyl azide than thermal reactions in solution. Here, we developed an Ir(III)-catalyzed mechanochemical direct C–H amidation using acyl azide. In addition to the anticipated highly efficient and selective C–N bond formation over C–C bond formation, direct C–H amidation of the previously unsuccessful substrate under solution conditions was realized (Scheme 1).

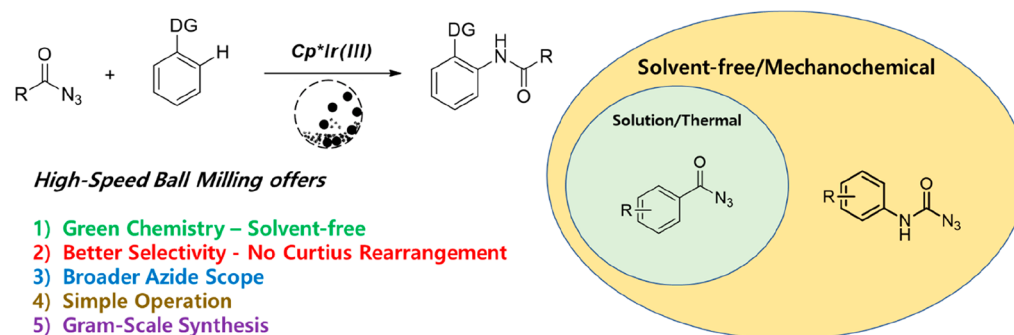
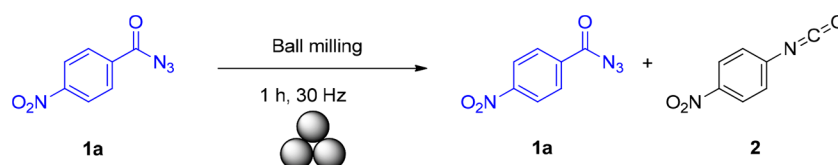
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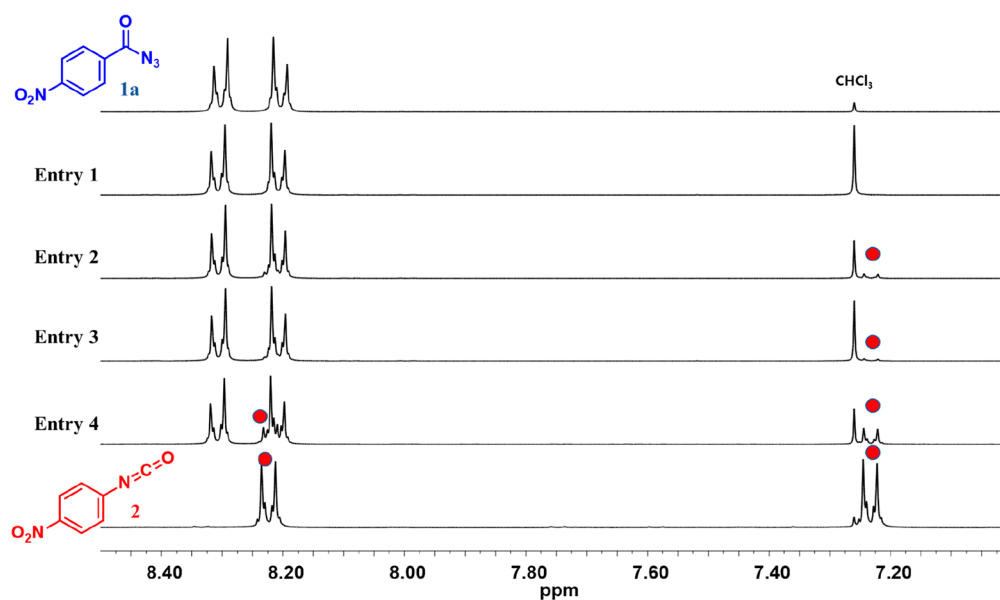


Scheme 1. Solvent-Free Mechanochemical C–H Amidation

Table 1. Stability Test of Benzoyl Azides under Ball Milling Conditions^a

| entry | jar volume (mL) | ball diameter (mm) | NMR yield ^b (%) | |
|-------|--------------------------|-----------------------------|----------------------------|----|
| | | | 1a | 2 |
| 1 | Teflon (10 mL) | stainless steel (7 mm × 2) | 98 | 0 |
| 2 | ZrO ₂ (10 mL) | ZrO ₂ (8 mm × 2) | 92 | 7 |
| 3 | stainless steel (10 mL) | stainless steel (7 mm × 2) | 91 | 5 |
| 4 | WC (10 mL) | WC (7 mm × 2) | 71 | 21 |

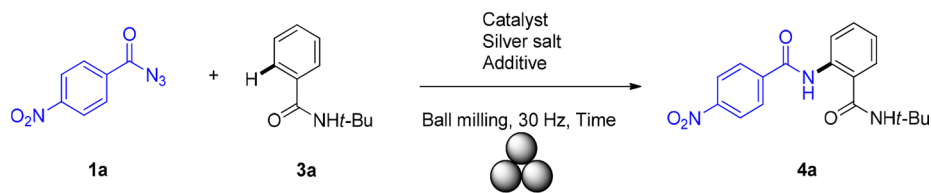
^aReaction conditions: **1a** (0.8 mmol, 154 mg) milled in each container and balls; the crude mixture was collected by chloroform (2 mL × 3) and filtered directly using Celite pads. ^bYield based on ¹H NMR analysis of the crude reaction mixture using CH₂Br₂ as the internal standard.

Figure 1. ¹H NMR spectra of the acyl azide stability test for Table 1.

RESULTS AND DISCUSSION

The stability of acyl azide under ball mill conditions was evaluated in a high-speed vibratory ball mill, MM400 (Restch) (Table 1). The density of the container and ball is directly correlated to the mechanical energy, resulting in a greater impact per collision.^{34,35} Thus, it is important to consider the azide stability in the various milling jars and balls, from low-density Teflon (2.2 g/cm³) to high-density zirconia (ZrO₂, 5.7 g/cm³), stainless steel (SS, 7.9 g/cm³), and tungsten carbide

(WC, 15.6 g/cm³). The representative *para*-nitro-benzoyl azide (**1a**) was ground in each jar and ball at the maximum frequency of MM400, 30 Hz, for 1 h. The product distribution was monitored by ¹H NMR (Figure 1) and FT-IR spectroscopy (Figure S1). The low-energy condition, Teflon jar, and SS ball resulted in no acyl azide rearrangement to isocyanate (entry 1). From the reaction in the ZrO₂ jar and balls, a sign of decomposition was detected (7%, entry 2). The small energy elevation to SS was insignificant (5%, entry 3); the use of

Table 2. Optimization of the Mechanochemical Direct C–H Amidation of Acyl Azide **1a**^a

| entry | ball mill conditions | | catalyst (mol %) | silver salt (mol %) | additive (mol %) | yield ^b (%) |
|-------|----------------------|------------|--|-------------------------|--------------------------------------|------------------------|
| | Hz | time (min) | | | | |
| 1 | 30 | 60 | [IrCp*Cl ₂] ₂ (5) | AgNTf ₂ (20) | NaOAc (20) | 44 |
| 2 | 30 | 60 | [IrCp*Cl ₂] ₂ (5) | AgSbF ₆ (20) | NaOAc (20) | 27 |
| 3 | 30 | 60 | [IrCp*Cl ₂] ₂ (5) | AgBF ₄ (20) | NaOAc (20) | <5 |
| 4 | 30 | 60 | [IrCp*Cl ₂] ₂ (5) | AgNTf ₂ (20) | AgOAc (20) | 95 |
| 5 | 30 | 10 | [IrCp*Cl ₂] ₂ (5) | AgNTf ₂ (20) | AgOAc (20) | 97 (93) ^c |
| 6 | 30 | 10 | [IrCp*Cl ₂] ₂ (5) | AgNTf ₂ (20) | Cu(OAc) ₂ (20) | 82 |
| 7 | 30 | 10 | [IrCp*Cl ₂] ₂ (5) | AgNTf ₂ (20) | | 64 |
| 8 | 30 | 60 | [IrCp*Cl ₂] ₂ (5) | AgNTf ₂ (20) | | 81 |
| 9 | 30 | 10 | [IrCp*Cl ₂] ₂ (5) | AgNTf ₂ (20) | benzoic acid (20) | 84 |
| 10 | 30 | 10 | [IrCp*Cl ₂] ₂ (5) | AgNTf ₂ (20) | 4-NO ₂ -benzoic acid (20) | 81 |
| 11 | 30 | 10 | [IrCp*Cl ₂] ₂ (5) | AgNTf ₂ (20) | 4-MeO-benzoic acid (20) | 86 |
| 12 | 30 | 10 | [IrCp*Cl ₂] ₂ (2.5) | AgNTf ₂ (10) | AgOAc (10) | 81 |
| 13 | 20 | 10 | [IrCp*Cl ₂] ₂ (5) | AgNTf ₂ (20) | AgOAc (20) | 86 |
| 14 | 30 | 60 | [RhCp*Cl ₂] ₂ (5) | AgSbF ₆ (20) | AgOAc (20) | NR |
| 15 | 30 | 60 | [RhCp*Cl ₂] ₂ (5) | AgBF ₄ (20) | AgOAc (20) | NR |
| 16 | 30 | 60 | [RhCp*Cl ₂] ₂ (5) | AgNTf ₂ (20) | AgOAc (20) | NR |

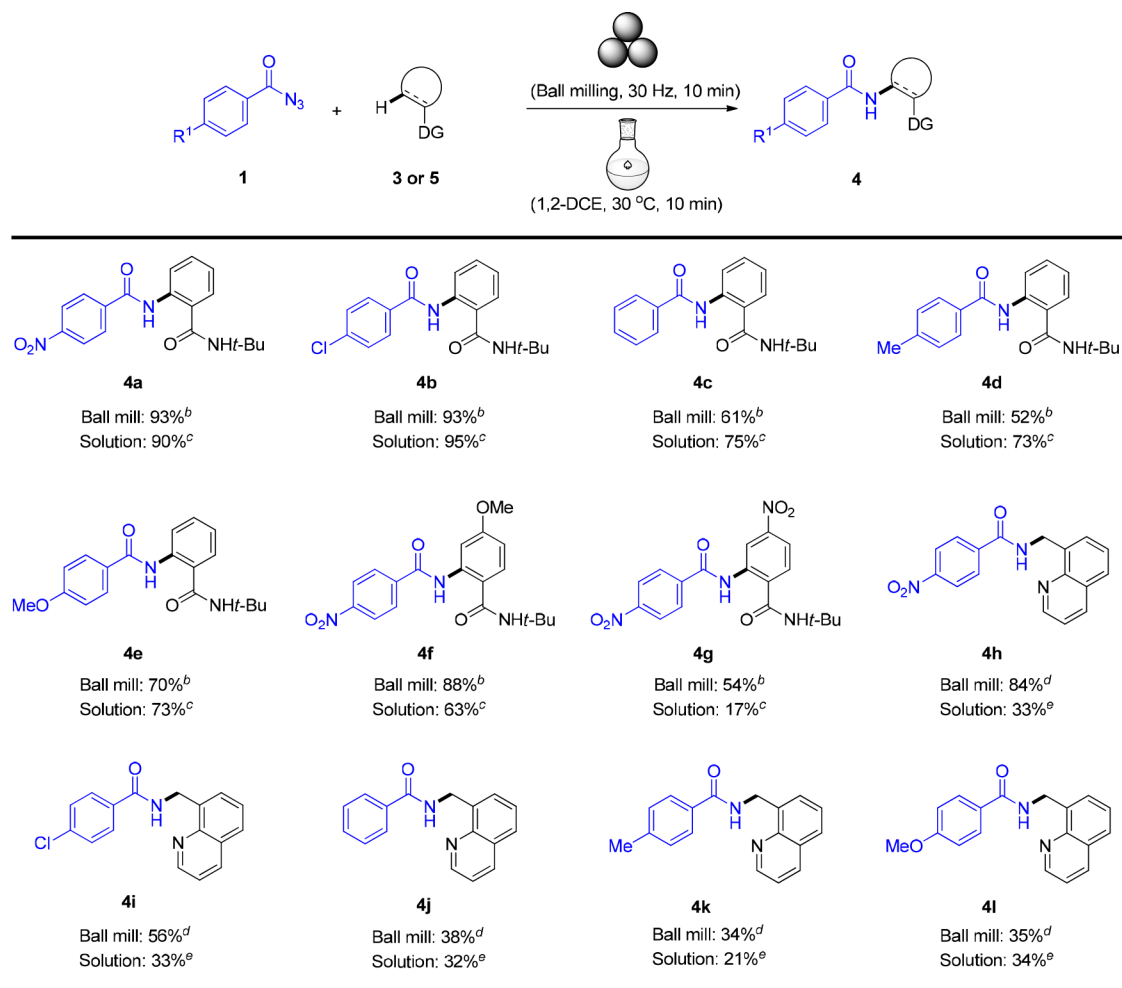
^aReaction conditions: **1a** (0.18 mmol, 35 mg), **2a** (0.1 mmol, 18 mg), catalyst (5 mol %), silver salt (20 mol %), and additives were milled in a mixer mill at 30 Hz. ^bYield based on ¹H NMR analysis of the crude reaction mixture using CH₂Br₂ as the internal standard, NR = no reaction. ^cThe isolated yield is shown in parentheses.

heavy WC resulted in significant isocyanate formation (21%, entry 4). These results showed that azide could undergo Curtius rearrangement by high-energy ball milling but not abruptly like with thermal activation. For the further C–H amidation reaction, we chose the combination of a Teflon jar and SS balls. We would like to emphasize that acyl azides showed a mild degradation rate under mechanochemical ball milling conditions; it still requires very careful handling with proper safety equipment.

The reaction conditions by Chang's Cp*Ir(III)-catalyzed C–H amidation in solution (Table 2, entry 1) were modified for the following procedure.^{27,28} The mixture of [Cp*IrCl₂]₂ (5 mol %), AgNTf₂ (20 mol %), NaOAc (20 mol %), *t*-butyl benzamide (**3a**) (1.0 equiv), and azide (**1a**) (1.8 equiv) was added to the Teflon jar (10 mL) with one SS ball (10 mm). After vibratory milling at 30 Hz for 1 h, the expected C–H amidation product (**4a**) was obtained in 44% yield (entry 1). Unreacted amide and azide showed no sign of decomposition to isocyanate. The silver salt for active cationic Cp*Ir(III) catalyst formation was next scrutinized. The variation of anions to SbF₆[−] (entry 2) and BF₄[−] (entry 3) showed a negative effect, giving 27 and <5%, respectively. In many C–H functionalization reactions, the additive acid or base plays a crucial role.^{36,37} We investigated a group of acetate and organic acids. Silver acetate (20 mol %) significantly improved the yield (95%, entry 4). This combination also reduced the reaction time to 10 min (97%, entry 5). However, Cu(OAc)₂ (entry 6) or no acetate (entry 7) conditions resulted in moderate yields of 82 and 64%, respectively. The milling time extension to 60 min gave 81% (entry 8). Acidic additive, benzoic acid, also helped the performance of Cp*Ir catalyst to 84% (entry 9). However, the variation of acidity showed the

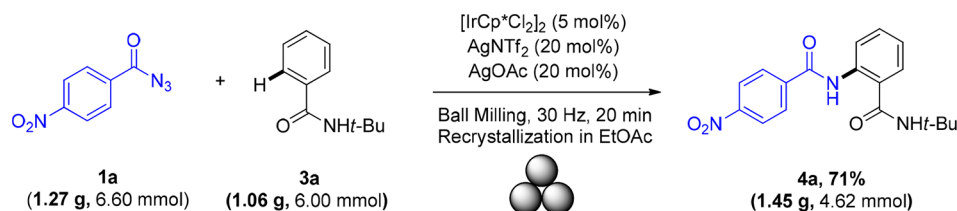
only marginal effect (entries 10 and 11). The reduction of the catalyst amount to 2.5 mol % still afforded 81% product (entry 12). Additionally, a lower frequency of 20 Hz gave an 86% yield (entry 13). Finally, the Cp*Rh(III) was evaluated. The system developed by Bolm for dioxazolone was not effective with the acyl azide (entries 14–16).²² The effective mechanical C–H activation by Cp*Rh(III) was proven by Bolm; the reaction with acyl azide might be the limiting step. The reaction progress was monitored by IR spectrometry. The direct measurement of solid reaction mixtures confirmed a fast decay of azides in the solid state (Figure S2). The spectra of 10 min reaction and after filtration were same, showing that no reaction proceeded during workup or NMR measurement in solution.

Under the optimized conditions, the substrate scope was investigated (Scheme 2). Our investigations began with a set of two comparative ball milling and solution conditions, with the same catalytic amount and time to determine and analyze the difference. The general trends of reactivity were similar, indicating that the reaction pathway was not severely affected by the activation method. Electronically different benzoyl azides reacted with benzamide **3a**. As expected, electron-withdrawing azides reacted quickly in both ball milling and solution (**4a** and **4b**). The electron-rich azides showed diminished yields (**4c**, **4d**, and **4e**). The electron density effect on benzamide was tested using electron-donating methoxy and -withdrawing nitro substitutions (**4f** and **4g**). While both amides gave the reduced yields compared to the neutral benzamide, mechanochemical ball milling showed better efficiency than solution reactions in the production of **4f** (88% over 63%) and **4g** (54% over 17%). The synthetically challenging sp³ C–H bond amidation was investigated using 8-

Scheme 2. Ir-Catalyzed sp^2 - and sp^3 -C–H Amidation with Various Acyl Azides^a

^aThe following conditions utilized a 10 mL Teflon milling jar with one stainless-steel ball of 10 mm diameter. ^b1 (0.18 mmol), 3 (0.1 mmol), [IrCp*Cl₂]₂ (5 mol %, 4 mg), AgNTf₂ (20 mol %, 8 mg), and AgOAc (20 mol %, 3 mg). ^c1 (0.18 mmol), 3 (0.1 mmol), [IrCp*Cl₂]₂ (5 mol %, 4 mg), AgNTf₂ (20 mol %, 8 mg), and AgOAc (20 mol %, 3 mg) in 1,2-dichloroethane (1,2-DCE) (0.5 mL) for 10 min at 30 °C. ^d1 (0.2 mmol), 5 (0.1 mmol), [IrCp*Cl₂]₂ (10 mol %, 8 mg), AgNTf₂ (20 mol %, 8 mg), and AgOAc (20 mol %, 3 mg). ^e1 (0.2 mmol), 5 (0.1 mmol), [IrCp*Cl₂]₂ (10 mol %, 8 mg), AgNTf₂ (20 mol %, 8 mg), and AgOAc (20 mol %, 3 mg) in 1,2-DCE (0.5 mL) for 10 min at 30 °C.

Scheme 3. A Gram-Scale Mechanochemical C–H Amidation with the Acyl Azide 1a and Benzamide 3a

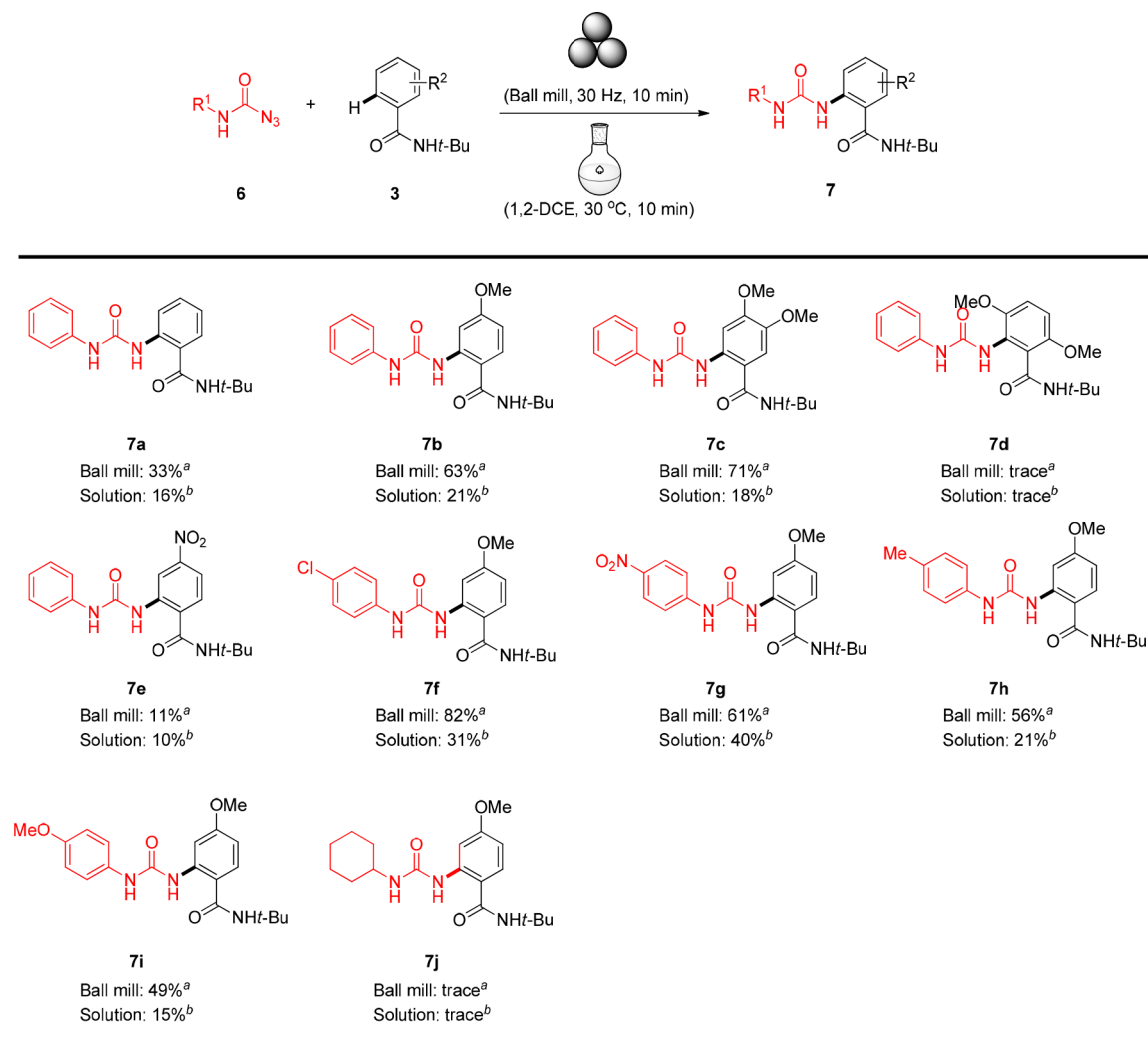


methyl quinoline (5).²⁸ Both solvent-free ball milling and solution-based reactions exhibited low efficiency. In the case of highly activated *para*-nitro-benzoyl azide (1a), a high yield was obtained exclusively in ball milling (84%), while the solution reaction gave 33% yield (4h). The other electronically poor 4-chloro-benzoyl azide showed better efficiency in ball milling than in solution (4i). However, these deviations were not viable with electron-rich acyl azides (4j, 4k, and 4l). The extended reaction time (99 min) for low yielding reactant combinations (4h, 4j, and 4l) did not show a positive effect (Table S1). The newly developed condition is applicable to other types of azides. *p*-Toluenesulfonyl azide reacted with 3a

under otherwise identical conditions and produced the corresponding tosyl amide (4m) in 70% yield, respectively.¹⁷ The reaction with diphenylphosphoryl azide (4n) gave a moderate yield (50%).

The green metrics of the solvent-free process were evaluated (Table S3).³⁸ Solvent-free synthesis improved the atom economy of 4a synthesis from 24% (solution) to 47% (ball milling). For the case of 4h, increased synthetic efficiency by mechanochemistry made a sharp distinction: 8% (solution) and 38% (ball milling).

A gram-scale experiment maintained its high efficiency. A 20 mL Teflon milling jar with one stainless-steel ball of 12 mm, 20

Scheme 4. Ir-Catalyzed sp^2 C–H Amidation with Various Carbamoyl Azides

^aConditions: **6** (0.15 mmol), **3** (0.1 mmol), $[\text{IrCp}^*\text{Cl}_2]_2$ (10 mol %, 8 mg), AgNTf_2 (20 mol %, 8 mg), and AgOAc (40 mol %, 7 mg) were milled in a mixer mill at 30 Hz, using a 10 mL Teflon milling jar with one stainless-steel ball of 10 mm diameter. ^bConditions: **6** (0.15 mmol), **3** (0.1 mmol), $[\text{IrCp}^*\text{Cl}_2]_2$ (10 mol %, 8 mg), AgNTf_2 (20 mol %, 8 mg), and AgOAc (40 mol %, 7 mg) in 1,2-DCE (0.5 mL) for 10 min at 30 °C.

min vibration, and simple recrystallization in ethyl acetate gave 71% isolation yield (Scheme 3).

Recently, M. Kim and co-workers developed an unsymmetrical urea synthesis through Ir(III)-catalyzed C–H amidation with carbamoyl azides.³⁹ The method was only compatible with disubstituted carbamoyl azides. Monosubstituted carbamoyl azides exhibited low reactivity. Increasing the temperature for thermal activation was not applicable because of the Curtius rearrangement, which led us to investigate the mechanochemical process (Scheme 4). The first trial with electron-neutral benzamide (**3a**) with phenyl carbamoyl azide (**6a**) gave only 33% yield (**7a**), which was still as high as that of the solution. The addition of electron density to benzamide improved the reactivity. Monomethoxy benzamide reacted more efficiently (63%, **7b**), and the dimethoxy substrate showed a 71% yield (**7c**). Notably, this increase was not observed in the solution-based reactions, giving no catalytic turnover. However, the mechanochemical conditions could not overcome the steric hindrance (**7d**). The deactivation by the electron-withdrawing nitro group gave the expected low yield (11%, **7e**).

The electric variation of carbamoyl azide was evaluated. The moderately withdrawing chlorine substitution produced unsymmetrical urea **7f** with a high yield of 82%. However, further electron deficiency lowered the production (61%, **7g**). As seen in Scheme 2, enriching the electron density on the phenyl group had a negative effect on the catalytic performance (**7h** and **7i**). However, the low reactivity of aliphatic carbamoyl azide remains unsolved in ball milling (**7j**). To improve the yield, the reaction time was extended to 99 min for ball milling and 12 h for solution reactions (Table S2). However, no improvement was observed. The observed catalyst deactivation might be caused by the inhibitory effect of the urea product. The addition of product **7g** (50 mol %) at the initial mixture decreased the yield from 61 to 6%. The further investigation for overcoming product inhibition is currently in progress.

CONCLUSIONS

This study showed that unstable acyl azides behaved differently in high-speed ball milling. The high-energy impact of the balls and container did not promote the abrupt decomposition to isocyanate. Employing a $\text{Cp}^*\text{Ir(III)}$ catalyst, controlled

activation of acyl nitrene and amidation was realized mechanochemically. A comparative study of solution reactions showed that the mechanochemical reaction followed similar reactivity trends. Elimination of the solvent did not limit the reactivity with benzoyl azide; through the ball milling method, the unexpected reactivity increase of carbamoyl azide was obtained. Therefore, the current approach provides a practical and sustainable method to address the Curtius rearrangement issue of conventional solution-based acyl azides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.1c01786>.

Experimental procedures, compound characterizations, and copies of ^1H NMR, ^{13}C NMR, FT-IR, and mass spectra (PDF)

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Notes

The authors declare no competing financial interest.

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