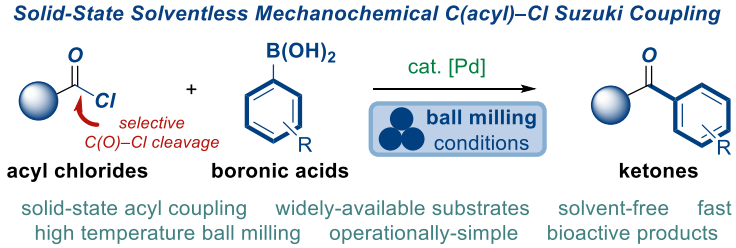
Mechanochemical Synthesis of Ketones via Chemoselective Suzuki–Miyaura Cross-Coupling of Acyl Chlorides

Jin Zhang,*[,†] Pei Zhang,[†] Yangmin Ma,[†] and Michal Szostak*[,‡]

[†]*College of Chemistry and Chemical Engineering, Key Laboratory of Chemical Additives for China National Light Industry, Shaanxi University of Science and Technology, Xi'an 710021, China*

[‡]*Department of Chemistry, Rutgers University, 73 Warren Street, Newark, New Jersey 07102, United States*

Supporting Information



ABSTRACT: The direct synthesis of ketones via acyl Suzuki-Miyaura cross-coupling of widely available acyl chlorides is a central transformation in organic synthesis. Herein, we report the first mechanochemical solvent-free method for highly chemoselective synthesis of ketones from acyl chlorides and boronic acids. This acylation reaction is conducted in the solid state, in the absence of potentially harmful solvents, for a short reaction time and shows excellent selectivity for C(acyl)–Cl bond cleavage.

The direct acylation reactions are cornerstone methodologies in organic synthesis that are among the most common transformations in the synthesis of pharmaceuticals, agrochemicals and functional materials.[1] The inherent value of acyl transfer reactions stems from the fact that the product ketones are widely represented in various facets of organic synthesis, including a wide range of bioactive natural products and pharmaceuticals, while functional group manipulations of the carbonyl group at the ipso position render these methods an attractive entryway to many important products in both academic and industrial research.[2,3] In this context, Suzuki-Miyaura cross-coupling of widely available acyl chlorides represents a central strategy for the synthesis of ketones (Figure 1A).[4] Among the advantages compared with traditional stoichiometric methods are chemoselectivity, functional group tolerance and atom economy inherent to palladium-catalyzed cross-couplings. This method takes an advantage of wide availability of acyl chlorides, avoiding the need for the synthesis of prefunctionalized precursors, while operating under catalytic regimen. The utilization of acyl Suzuki-Miyaura has witnessed applications in drug discovery, natural product synthesis and polymer synthesis.[5-8] However, despite the importance of this method, a broadly applicable solid-state synthesis of ketones by this manifold represents a challenge.

As part of research program in acyl-transfer reactions,[9] we have been attracted to the recent breakthroughs in solid-state mechanochemical synthesis using automated ball milling.[10] One of the key advantages of automated ball milling is the translation of the liquid-state organic synthesis to solid-state that avoids the use of harmful organic solvents, reduces operational reaction time and offers precise control over energy input. The development of solid-state mechanochemical methods has attracted additional attention due to operational simplicity in reaction handling and the capacity to open new reaction pathways not available in solution. In light of these advantages, it is not surprising that mechanochemistry has been identified as one of the top 10 technologies that "will change our world,"[11] and the field is a burgeoning area of research that may transform synthetic approaches to produce valuable molecules in drug, polymer and functional material research.[12,13] Herein, we report the first mechanochemical solvent-free method for highly chemoselective synthesis of ketones from acyl chlorides and boronic acids (Figure 1B). Most importantly, this acylation reaction is conducted in the solid state, in the absence of potentially harmful solvents, for a short reaction time and shows excellent selectivity for C(acyl)–Cl bond cleavage, including compatibility with various electrophilic functional groups.[2b,c] Of general interest, the Ito's protocol for ball milling at high temperature has been successfully applied in challenging cases.[14] We expect that this approach will facilitate the development of solid-state C(acyl)-transfer reactions of widely available acyl electrophiles.

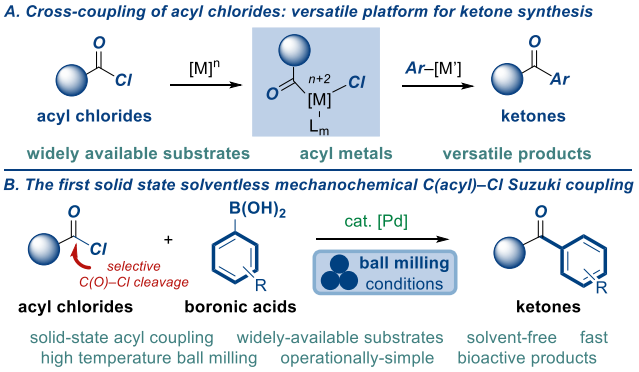
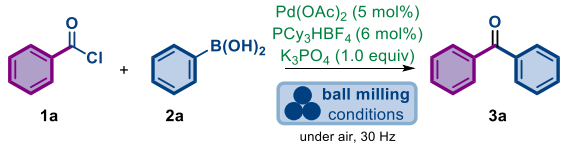


Figure 1. (a) Cross-coupling of acyl chlorides: general platform for ketone synthesis. (b) This study: the first mechanochemical solid-state Suzuki-Miyaura cross-coupling of acyl chlorides.

The proposed Suzuki-Miyaura cross-coupling of acyl chlorides was first examined using benzoyl chloride (**1a**) as the model substrate. The optimization reactions were carried out in stainless steel milling bowl vessels (5 mL volume) loaded with one stainless steel grinding ball (5 mm diameter) in a mixer mill (Retsch MM400) at oscillating frequency of 30 Hz. Selected optimization results are presented in Table 1. After extensive optimization, we identified a combination of $Pd(OAc)_2$ (5 mol%) and PCy_3HBF_4 (6 mol%) as the preferred catalyst system in the presence of K_3PO_4 (1.0 equiv) as a base under solid-state solventless conditions (entry 1). As expected, control experiments indicated that all reaction components are required for the reaction to occur (entries 2-4). Evaluation of different phosphane ligands revealed that although other ligands can be used, such as dppp, dppf, Xantphos, DavePhos, electron-rich PCy_3HBF_4 provided the optimal efficiency (entries 5-8 vs. entry 1). Likewise, an extended screen of bases revealed K_3PO_4 to be the preferred base under these mechanochemical conditions, while $NaHCO_3$, Na_2CO_3, K_2CO_3, Cs_2CO_3, NaF, KF, CsF or AgF were generally much less effective (entries 9-16 vs. entry 1). It is noteworthy that the model reaction could be performed at stoichiometric loading of aryl boronic acid and base with high efficiency (entry 17). Finally, although the initial reactions were performed for 30 min, the reaction time could be further reduced to 10 min without decrease in yield (entry 18), consistent with highly efficient solid-state coupling. We have also tested addition of 1,5-cyclooctadiene and ZrO_2 balls (not shown); however, these changes had no effect on the reaction efficiency. The influence of ball milling details has also been checked; changing the frequency (Hz) to 25 Hz and 20 Hz had a negative impact on the reaction (62% and 59%, respectively), while adding SiO_2 resulted in 80% yield. The reaction at 3 mol% Pd loading resulted in 45% yield.

With the optimized conditions in hand, the scope of this solventless C(acyl)–Cl Suzuki–Miyaura cross-coupling was examined. As shown in Schemes 1-2, this method is very general in respect to both acyl chlorides and boronic acids, including various electronically- and sterically-differentiated substrates as well as an array of sensitive functional groups that would be problematic in the traditional nucleophilic addition of organometallic reagents. As such, as

Table 1. Optimization of the Reaction Conditions[a,b]



entry	deviation from standard conditions	yield (%)
1	None	92
2	Without $Pd(OAc)_2$	<2
3	Without PCy_3HBF_4	<2
4	Without K_3PO_4	<2
5	Dppp instead of PCy_3HBF_4	20
6	Dppf instead of PCy_3HBF_4	28
7	Xantphos instead of PCy_3HBF_4	19
8	DavePhos instead of PCy_3HBF_4	20
9	$NaHCO_3$ instead of K_3PO_4	<2
10	Na_2CO_3 instead of K_3PO_4	18
11	K_2CO_3 instead of K_3PO_4	30
12	Cs_2CO_3 instead of K_3PO_4	<2
13	NaF instead of K_3PO_4	<2
14	KF instead of K_3PO_4	5
15	CsF instead of K_3PO_4	<2
16	AgF instead of K_3PO_4	<2
17	Ph-$B(OH)_2$ (1.0 equiv), K_3PO_4 (1.0 equiv)	85
18	10 min instead of 30 min	92

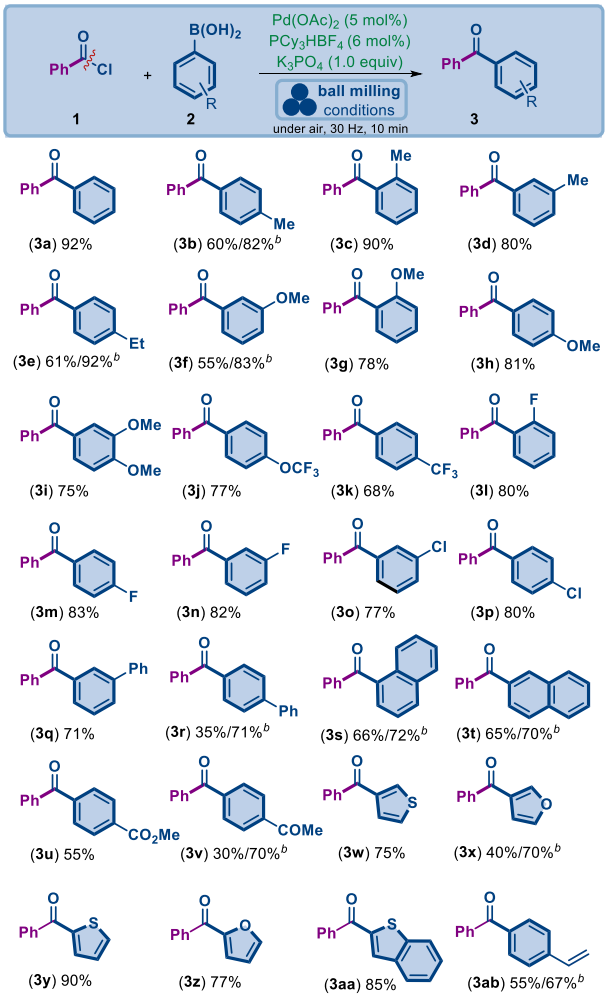
[a]Conditions: **1a** (1.0 equiv), Ph-$B(OH)_2$ (**2a**, 1.5 equiv), $Pd(OAc)_2$ (5 mol%), phosphane ligand (6 mol%), base (1.0 equiv), ball mill (30 Hz), 30 min. [b]Entry 17: Ph-$B(OH)_2$ (1.0 equiv), K_3PO_4 (1.0 equiv).

shown in Scheme 1, various aryl boronic acid substituted with electron-neutral (**3a–3e**), electron-rich (**3f–3j**) and electron-deficient functional groups (**3k–3p**) were excellent substrates. Steric-hindrance at the ortho-position (**3c**, **3g**) is well-tolerated in this coupling. Medicinally-relevant fluorinated functional groups (**3j–3n**) provided the coupling products in high yields, demonstrating potential utility in drug discovery research. Further, the reaction is fully chemoselective for the C(acyl)–Cl coupling in the presence of $C(sp^2)$–Cl bonds, providing handles for further functionalization (**3o–3p**). The method can also be used for the synthesis of ketones bearing conjugated polyarenes (**3q–3t**) (*vide infra*), which are important precursors in materials research. We were pleased to find that electrophilic functional groups, such as esters (**3u**) and ketones (**3v**) are tolerated. Furthermore, we found that the reaction conditions are compatible with heterocyclic boronic acids, such as thienyl and furyl substituted at either 3- or more sensitive to protodeboronation 2-position (**3w–3aa**) as well as 4-vinyl substitution (**3ab**), providing further handle for functionalization.

Next, we evaluated the scope of aroyl chlorides in this mechanochemical solid-state Suzuki–Miyaura cross-coupling (Scheme 2). As shown, various electron-neutral (**3b–3d**), electron-rich (**3h–3t**), and electron-deficient (**3ad–3m**) aroyl chlorides as suitable substrates for this reaction. Importantly, steric hindrance at the ortho-position (**3c**, **3ad**) as well as conjugated naphthyl substrates (**3t**) are

well tolerated. Notably, the reaction is fully chemoselective for the C(acyl)–Cl coupling in the presence of C(sp^2)–Cl (**3o–3p**) and C(sp^2)–Br (**3ae**) electrophiles, providing useful handles for functionalization. Furthermore, heterocyclic substrates, such as 2-thienyl (**3y**) and 2-

Scheme 1. Boronic Acid Scope of the Mechanochemical Suzuki–Miyaura Cross-Coupling of Acyl Chlorides[a]



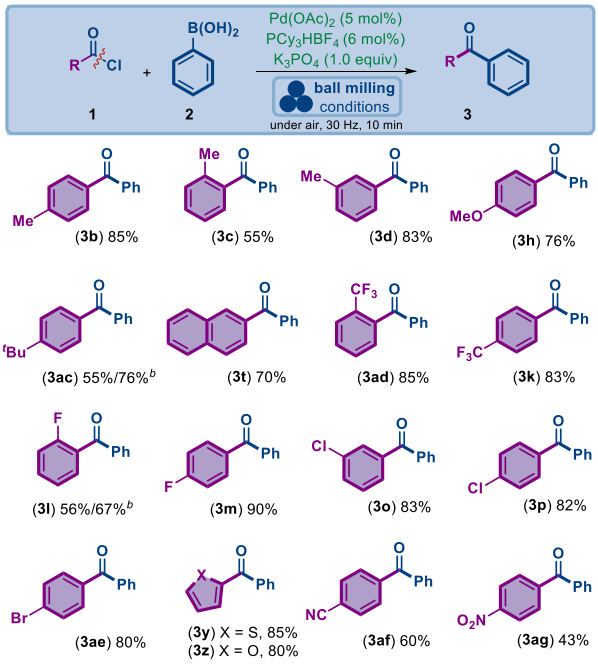
[a]Conditions: see Table 1, entry 18. [b]Preset temp. of 200 °C.

furyl (**3z**) are well tolerated. Pleasingly, the reaction is also compatible with challenging electrophilic functional groups, such as cyano (**3af**) and nitro (**3ag**) that are often used as precursors to nitrogen-containing heterocycles in medicinal chemistry. Overall, the scope of the reaction is broad enabling solid-state cross-coupling of acyl electrophiles. It should be noted that the reaction tolerates ortho-substitution (Scheme 1, **3c**, **3g**, **3l**; Scheme 2, **3c**, **3l**, **3ad**).

During the scope development, we noticed that some reactions were sluggish. To solve this problem, we were attracted to the recent study by Ito and co-workers, who demonstrated operationally-simple ball milling at high temperatures. This potentially powerful approach has a potential to provide a solution to the long-standing problem of solubility in solid-state mechanochemical synthesis. As such, we conducted select cross-couplings at higher preset temperatures according to Ito et al.[14] As shown in Scheme 3, this approach permits to markedly increase the reaction efficiency with the onset at 100 °C or 150 °C depending on the substrate class in this acyl coupling.

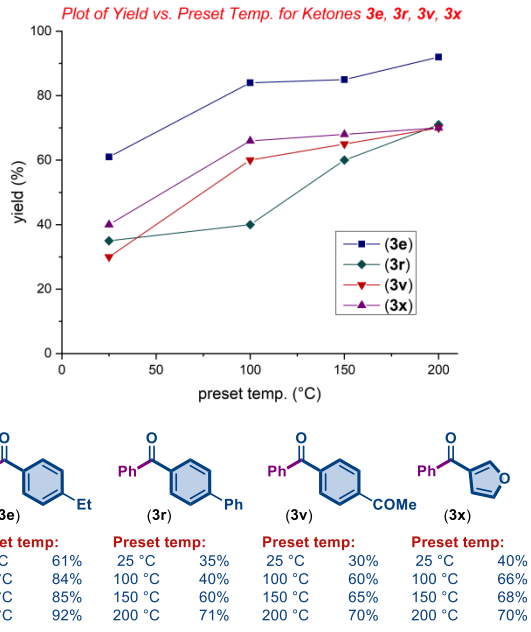
Importantly, we have also demonstrated the utility of this solid-state coupling in medical chemistry research by synthesizing potent antitubulin agents by the direct coupling of acyl

Scheme 2. Electrophile Scope of the Mechanochemical Suzuki–Miyaura Cross-Coupling of Acyl Chlorides[a]



[a,b]See Scheme 1.

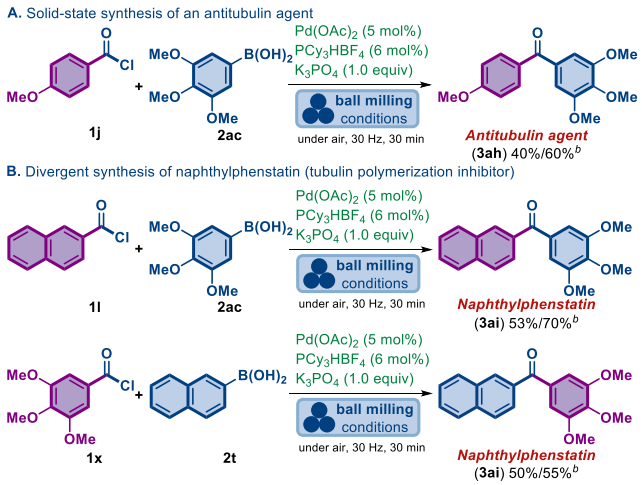
Scheme 3. Ball Milling at High Temperatures[a]



chlorides with boronic acids (Scheme 4). This coupling can be performed directly from functionalized substrates (Scheme 4A) or in a divergent way from either functionalized acyl chlorides or

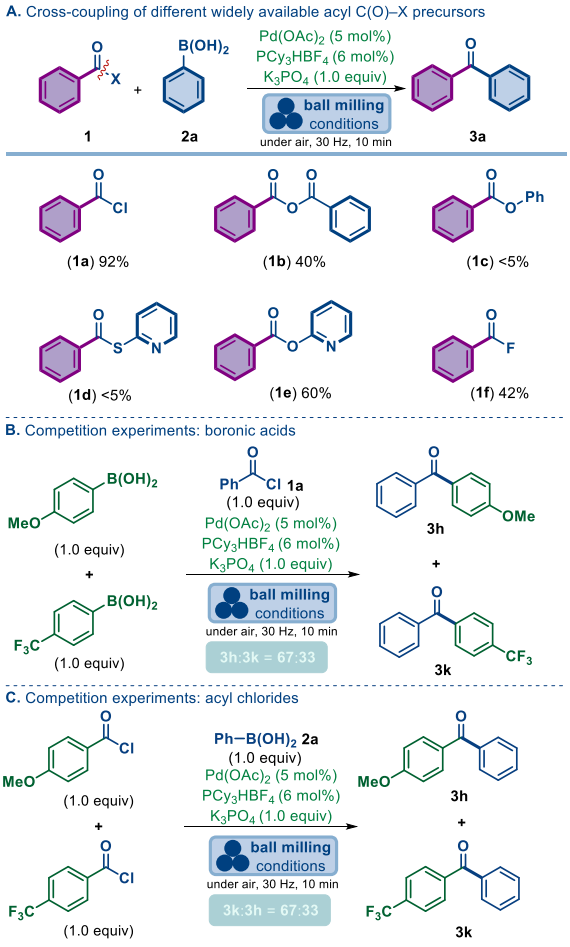
boronic acids (Scheme 4B). In view of the prevalent role of diaryl ketones in pharmaceutical research, this solid-state method provides access to synthetically useful synthons.

Scheme 4. Synthesis of Antitubulin Agents[a,b]



[a,b]See Scheme 1.

Scheme 5. Mechanistic Studies



We conducted preliminary mechanistic studies (Scheme 5). As shown in Scheme 5A, these solid-state conditions are also amenable to other common acyl electrophiles, such as anhydrides (**1b**), fluorides (**1f**) and 2-pyridyl esters (**1e**).

In contrast, phenolic esters (**1c**) and 2-pyridyl thioesters (**1d**) are recovered unchanged, consistent with the ease of oxidative addition of the C(acyl)–X bond and providing handle for chemoselective cross-coupling. Furthermore, intermolecular competition experiments revealed that electron-rich boronic acids are inherently more reactive (**3h**:**3k** = 67:33, 4-MeO:4-CF_3, Scheme 5B), while electron-deficient chlorides are more reactive (**3k**:**3h** = 67:33, 4-CF_3:4-MeO, Scheme 5C). These results are consistent with the Pd(0)/(II) catalytic cycle for acyl Suzuki–Miyaura cross-coupling.[8d,8e]

In conclusion, we have developed the first mechanochemical solvent-free method for highly chemoselective synthesis of ketones from acyl chlorides and boronic acids. This method provides solid-state synthesis of important ketone products from broadly available acyl electrophiles. Notable features of this process include the avoidance of potentially harmful solvents, short reaction time and excellent selectivity for C(acyl)–Cl bond cleavage. The method is compatible with various electrophilic functional groups and has been applied to the synthesis of potent tubulin inhibitors. This method also features the application of Ito's protocol for ball milling at high temperature that can be applied in challenging cases. We expect that this approach will facilitate the development of important solid-state C(acyl)-transfer reactions of widely available acyl electrophiles.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

zhangjin@sust.edu.cn
michal.szostak@rutgers.edu

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