

Mechanochemical Ruthenium-Catalyzed Hydroarylations of Alkynes under Ball-Milling Conditions

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(5) Supporting Information



ABSTRACT: Under solventless grinding conditions, mechanochemical ruthenium-catalyzed hydroarylations of alkynes with acetanilides lead to trisubstituted alkenes. Only catalytic amounts of pivalic acid or copper acetate are required, and without the need for external heating, the reaction times are shorter than those of their solution-based counterpart. Mechanochemical oxidative annulations through palladium-catalyzed intramolecular amination convert the products into *N*-acetylindoles.

T ransition-metal-catalyzed hydroarylations of alkynes by C-H bond functionalization have attracted much attention in recent years.¹ Aromatics with directing groups undergo regio- and stereoselective *ortho*-alkenylations in a highly atom-economical manner. As catalysts for such cross-coupling reactions, rhodium,² ruthenium,³ and cobalt complexes⁴ have proven particularly effective. Typically, these catalytic systems, and in particular those of ruthenium, require a stoichiometric amount or even an excess of an organic acid for activation.⁵ In addition, long reaction times and high temperatures are often indispensable for the hydroarylation to proceed.

In the past decade, mechanochemical activation by milling, grinding, shearing, cavitation, or pulling has led to remarkable advances in organic synthesis.⁶ Specifically, ball-milling techniques allowed the improvement of traditional transformations and the discovery of new chemical reactivity using little or no organic solvent.⁷ In this context,⁸ we recently reported the first mechanochemical rhodium(III)-catalyzed C-H bond functionalization of acetanilides in ball mills.⁹ Iridium catalysis was utilized in analogous benzamide amidations with sulfonyl azides.¹⁰ Encouraged by these results, we wondered if mechanochemical conditions would also allow the use of less expensive ruthenium complexes for solventless C-H bond functionalizations. To verify this idea, we decided to investigate ruthenium-catalyzed hydroarylations of alkynes with acetanilides in a mixer mill. To render this catalytic process even more synthetically attractive, a subsequent a subsequent mechanochemical conversion of the resulting trisubstituted alkenes into indoles by palladium-catalyzed intramolecular aminations was envisaged. The results of this study are presented here.

To begin, we adopted the reaction conditions reported by Manikandan and Jeganmohan¹¹ with *N*-phenylacetamide (1a) and diphenylacetylene (2a) as starting materials and a mixture of $[\text{RuCl}_2(p\text{-cymene})]_2$ (5.0 mol %), pivalic acid (5.0 equiv),

and AgSbF₆ (20 mol %) as catalytic system.¹² To our delight, the solventless mechanochemical conditions proved suitable, and the hydroarylation reaction (at 30 Hz) provided exclusively the E-isomer of 3aa in 70% yield. Interestingly, the milling period was only 198 min (3.3 h), which was significantly shorter than the required time in solution (for details, see the SI).¹³ Further screening revealed that the amount of pivalic acid could be reduced to catalytic quantities (20 mol %), while the yield of 3aa increased to 82% after the same milling time (Table 1, entry 1). In the absence of either the silver salt or PivOH, the product was not formed (Table 1, entries 2 and 3). Substituting $AgSbF_6$ for tetrafluoroborate ($AgBF_4$) led to a drop in the yield of 3aa from 82% to 25% (Table 1, entries 1 and 4). Replacing PivOH with an acetate-containing additive $[Cu(OAc)_2 \cdot H_2O, AgOAc, Fe(OAc)_2, and NaOAc]$ led to variable results (Table 1, entries 5-8). In all cases, 3aa was formed, albeit in different amounts. The most effective additive was $Cu(OAc)_2 \cdot H_2O$, giving 3aa in 80% yield (Table 1, entry 5). This result was unexpected because in solution the use of this copper salt predominantly led to indoles by C-H functionalization followed by oxidative annulation.^{12d} Thus, the use of the mechanochemical conditions allowed alteration of the product portfolio by interrupting the reaction path commonly observed in solution. Further tuning of the reaction conditions showed that the milling time could be reduced from 198 to 99 min without significantly affecting the yield of **3aa** (83%, entry 9). In addition, carrying out a 2-fold scale-up of the C-H hydroarylation proved possible, and in the mixer mill the reaction afforded product 3aa in 71% yield (Table 1, entry 10). At this stage, a few observations of the mechanochemical hydroarylation reaction leading to 3aa in the mixer mill shall be highlighted because they differ from their solution-based

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Nł 1a	HAc + Ph	Ph [RuCl ₂ (p-cy silver salt, a ball milling, 3	mene)] ₂ additive 30 Hz, Ar	NHAc Ph 3aa
entry	silver salt	additive	t (min)	yield ^b (%)
1	AgSbF ₆	PivOH	198	82
2	AgSbF ₆		198	
3		PivOH	198	
4	AgBF ₄	PivOH	198	25
5	AgSbF ₆	$Cu(OAc)_2 \cdot H_2O$	198	80
6	AgSbF ₆	AgOAc	198	34
7	AgSbF ₆	$Fe(OAc)_2$	198	60
8	AgSbF ₆	NaOAc	198	40
9	AgSbF ₆	PivOH	99	83
10 ^c	AgSbF ₆	PivOH	99	71

^{*a*}Reaction conditions: A mixture of **1a** (81.1 mg, 0.60 mmol), **2a** (128.3 mg, 0.72 mmol), $[RuCl_2(p\text{-cymene})]_2$ (18.4 mg, 0.03 mmol, 5.0 mol %), silver salt (20 mol %), and the additive (20 mol %) was milled under argon at 30 Hz in a stainless steel milling jar (10 mL) with one ball (10 mm in diameter) of the same material. ^{*b*}After column chromatography. ^{*c*}Use of 1.2 mmol of **1a** (2-fold scale-up).

counterparts: (1) The reaction leads to E-3aa in good yields and with high positional- and diasteroselectivity. In contrast to other protocols, oxidative cyclizations toward indoles are irrelevant. (2) Presumably due to the efficient mixing during the neat grinding, the process proceeds with only catalytic amounts of the organic acid PivOH or Cu(OAc)₂·H₂O. In solution, an excess of such additives is often applied. (3) Because of the high reactant concentrations during the neat grinding, the mechanochemical hydroarylation occurs faster than in an organic solvent, and importantly, external heating is not required (99 min at 30 Hz vs i-PrOH at 100 °C for 12 h). Regarding the latter, it is worth mentioning that the dynamic nature of a high-speed ball milling process can inherently increase the temperature inside the milling container.¹⁴ Milling of organic and inorganic mixtures under similar operational conditions (milling media, time, and frequency of milling) has been reported to raise the temperature to 87 °C.^{14c,d} Therefore, in our case, such thermal effects could have complemented the mechanical milling, facilitating the mechanochemical C-H activation.

Using commercially available [RuCl₂(p-cymene)]₂ (5.0 mol %), AgSbF₆ (20 mol %), and PivOH (20 mol %), the scope of the mechanochemical hydroarylation reaction was investigated (Scheme 1). A variety of anilides 1 reacted smoothly with alkyne 2a to give the corresponding E-configured trisubstituted alkenes 3aa-la in good yields. Both electron-rich and electrondeficient para-substituted anilides exhibited high efficiency affording the products in yields ranging from 68% to 83%. This included anilides 1d-f, where the *p*-halo substituents were well tolerated. Notably, acetanilide 1g bearing a carboxyl group in the para-position of the aromatic ring could also be used, providing the corresponding product 3ga in 76% yield (Scheme 1). Similarly, para-substituted acetanilides 1h and 1i bearing CF₃ and SF₅ groups, respectively, reacted smoothly in the mixer mill to afford the alkenes 3ha and 3ia in yields of 72% and 70%. In addition, meta-substituted anilides were examined. In these cases, the hydroarylation exclusively occurred at the sterically less hindered C-H position leading to the expected products **3ja-la** in 72–85% yield (Scheme 1).

Scheme 1. Scope of Acetanilides 1 with Alkynes 2^a



"Yields in parentheses refer to results obtained with $Cu(OAc)_2 \cdot H_2O$ (20 mol %) instead of PivOH.

Next, various alkynes were applied using acetanilide 1a as a representative reaction partner (Scheme 1). Symmetric diarylalkynes with electron-donating and electron-withdrawing substituents on the arenes (2b-g) coupled with almost the same efficiency as 2a providing the corresponding products 3ab-ag in yields ranging from 65 to 74%. In addition, unsymmetrically substituted 1-phenyl alkynes 2h-j reacted well, affording alkenes 3ah-aj in yields up to 80%.

Noteworthy was the high regioselectivity with the hydroarylation occurring exclusively at the alkyl-substituted carbon. In solution, the pyrazolyl substituent is an efficient directing group in ruthenium-catalyzed hydroarylation reactions.^{3a,15} Using the standard mechanochemical reaction conditions, solventless milling of 1-phenyl-1H-pyrazole (1m) with 2h gave dialkenylated 3mh in 80% yield (Scheme 2 (a)). Encouraged by this positive result, a competition experiment was carried out. Grinding a mixture of 1a, 1m, and 2h in the presence of the catalyst and additives for 30 min gave a mixture of 3ha/3mh in a ratio of 1:8.25 (Scheme 2 (b)). This result revealed a significantly higher reactivity of the pyrazole compared to the acetanilide. With various alkynes (used in 3fold excess), 4-pyrazolyl-substituted acetanilide 1n served as an analogous intramolecular probe (Scheme 2 (c)). The selective formation of 3nh-nk showed a dominant directing power of the pyrazolyl substituent over the amido moiety. When the same type of milling experiment was conducted with a combination of N-(4-acetylphenyl)acetamide (10) and 1phenyl-1-propyne (2h), the amido group prevailed over the ketonic carbonyl to give exclusively product 3oh in 31% yield (Scheme 2 (d)).

The mechanochemical hydroarylation was further investigated by mechanistic studies. (1) The reaction of acetanilide $1a-d_5$ with alkyne 2a gave the expected product $3aa-d_n$ in 28% Scheme 2. Competition Experiments for the Ru-Catalyzed Mechanochemical Hydroarylation



yield after 30 min of milling (Scheme 3 (a)). The significant deuterium/proton exchange at the 6 position of the arene

Scheme 3. Deuterium-Labeling Experiments under Mechanochemical Conditions



(20%) suggested that the C–H bond cleavage step was reversible. In addition, 10% of the olefinic proton of **3aa**- d_n was exchanged by deuterium.¹⁶ (2) From an experiment with an equimolar mixture of acetanilides **1a** and **1a**- d_5 under mechanochemical conditions, a kinetic isotopic effect (KIE) of 2.13 was determined (Scheme 4 (b)). This value was similar to the one (KIE = 3.35) found by performing an analogous

Scheme 4. Mechanosynthesis of Indoles



experiment in 2-propanol (at 100 °C for 1 h). We conclude that the C–H bond cleavage step is mechanistically similar. (3) An intermolecular competition experiment with substituted acetanilides 1c/1h and the alkyne 2a conducted in the mixer mill showed higher reactivity for electron-deficient acetanilide 1h than for 1c. Then a competition reaction between acetanilide (1a) and alkynes 2b/2f revealed a slightly higher preference for the more electron-deficient alkyne 2f over 2b in the hydroarylation by ball milling (see the SI for details).¹⁷

Based on the above observations, we suggest that in most parts the mechanism of the mechanochemical hydroarylation reaction is similar to the one proposed for the solution-based counterpart.⁵ It begins with a C–H bond activation of the metal-coordinated acetanilide forming the characteristic sixmembered metallacycle. Subsequent migratory insertion of the alkyne followed by protodemetalation with the organic acid liberates the product and regenerates the active catalyst, which enters the next catalytic cycle.

The aforementioned mechanochemical C–H bond functionalization strategy was complemented by the development of a palladium-catalyzed conversion of products 3 to indoles 4 by oxidative $C(sp^2)$ –H/N–H coupling in a mixer mill.^{18,19} Using Pd(OAc)₂ (10 mol %) and PhI(OAc)₂ (2.2 equiv), various indoles (4a–f) were obtained in yields ranging from 40% to 76% (Scheme 4).

In summary, we performed ruthenium-catalyzed hydroarylations of alkynes with acetanilides under mechanochemical conditions. The solventless reactions in the mixer mill proved faster than their reported solution-based counterparts, and they proceeded without external heating. The mechanochemically prepared hydroarylation products were further converted into indoles by palladium catalyzed $C(sp^2)$ –H/N–H coupling in a mixer mill.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b02973.

Experimental procedures, characterization data, NMR spectra (PDF)

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The authors declare no competing financial interest.

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