

Atom-Economical Synthesis of *N*-Arylamides Utilizing Isopropenyl Esters with Heterogeneous Acid Catalysts

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Cite This: *ACS Omega* 2023, 8, 44861–44866

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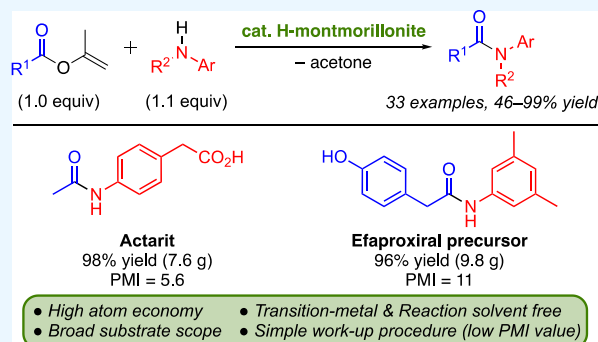
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ABSTRACT: Existing methods for the catalytic synthesis of *N*-arylamides are limited by a narrow substrate scope, high catalyst costs, and complicated purification processes of products. To overcome these limitations, this study developed an ecofriendly method for the synthesis of *N*-arylamides using isopropenyl esters. Isopropenyl esters activated using heterogeneous acid catalysts reacted smoothly even with less reactive arylamines to afford *N*-arylamides in high yields. This method exhibits a wide substrate scope and is applicable for the synthesis of various *N*-arylamides (33 examples, 46–99% yield). The developed method enabled the obtainment of high-purity products with a facile workup procedure and showed excellent process mass intensity values due to the reduction of chemical waste.

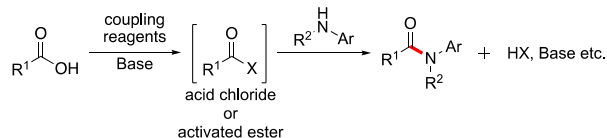


INTRODUCTION

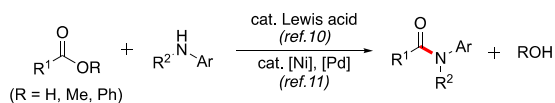
N-Arylamides are important compounds for functional chemicals such as pharmaceuticals, agrochemicals, and electronic materials as well as their synthetic intermediates.^{1–3} Classical amidation reactions using acid chlorides or active esters have been widely used (Scheme 1a) in the industrial synthesis of *N*-arylamides.^{4,5} An excess of coupling reagents and bases is used in the classic amidation reactions,^{6,7} and large

Scheme 1. Various Approaches for Synthesizing *N*-Arylamide

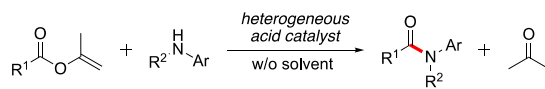
(a) Conventional method for *N*-arylamide synthesis



(b) Catalytic amidation of carboxylic acids & esters



(c) This work



- Atom economical (high RME values)
- Transition metal and reaction solvent free
- Wide substrate scope
- Insensitive to water
- Simple work-up procedure (low PMI values)

quantities of chemical waste are generated. Therefore, these methods are not considered to be environmentally friendly. The most straightforward and cost-effective approach for the synthesis of *N*-arylamides is the catalytic amidation reaction between carboxylic acids or their esters and arylamines (Scheme 1b).^{8,9} However, arylamines are less nucleophilic than other amines, and such molecular transformations can be challenging. Recently, several methods have been reported, including Lewis-acid-catalyzed electrophilic activation¹⁰ and nickel- or palladium-catalyzed cross-coupling.¹¹ Nevertheless, existing reactions still have problems, such as a narrow substrate scope, high catalyst costs, and complicated purification processes of the products.

To overcome these limitations and to develop a novel, environmentally benign amidation reaction for the synthesis of *N*-arylamides, we focused on amidation reactions using isopropenyl esters (Scheme 1c).¹² Using isopropenyl esters has several advantages: (i) isopropenyl esters are moderately reactive. Amidation reaction involving highly nucleophilic alkyl amines proceeds efficiently without the use of catalysts or additives.¹³ (ii) The enol coproduced by the reaction is quickly tautomerized to acetone, and it is unnecessary to consider the reverse reaction, unlike in the reactions of other esters. (iii) Acetone is the only coproduct; therefore, the product is easily

Received: August 17, 2023

Revised: October 17, 2023

Accepted: October 20, 2023

Published: November 13, 2023



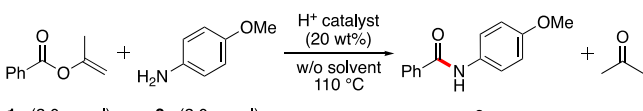
purified; moreover, the reaction has high atom economy. (iv) Isopropenyl esters can be prepared with 100% atom economy from the addition reactions of carboxylic acids with propyne.¹²

We hypothesized that further electrophilic activation of isopropenyl esters with appropriate acid catalysts would enable the esters to react readily with a range of arylamines.¹⁴ Furthermore, *N*-arylamide synthetic reaction systems that use heterogeneous acid catalysts (that can be easily separated and recovered after the reaction) would be environmentally benign and versatile. In this study, we investigated a novel method for synthesizing *N*-arylamides using heterogeneous acid-catalyzed activation of isopropenyl esters.

RESULTS AND DISCUSSION

The reaction of isopropenyl benzoate (**1a**, 2.0 mmol) with *p*-anisidine (**2a**, 2.0 mmol) at 110 °C for 15 h under solvent-free conditions was used as a model to screen various heterogeneous acid catalysts (Table 1). The reaction in the

Table 1. Optimization of the Reaction Conditions



entry	catalyst	time [h]	3aa [%] ^a	conv. [%] ^b
1		15	17	17
2	SO ₄ /ZrO ₂	15	27	30
3	Amberlyst 15DRY	15	41	46
4	Nafion-H	15	45	52
5	H-ZSM-5	15	27	28
6	H-Y Zeolite	15	66	75
7	H-beta Zeolite	15	58	62
8	H-mordenite	15	73	78
9	H-mont	15	77	85
10	Fe-mont	15	74	85
11	Cu-mont	15	60	68
12	Zn-mont	15	66	77
13	Zr-mont	15	73	80
14	Sn-mont	15	66	75
15	H-mont	24	81	88
16 ^c	H-mont	24	88 (86) ^d	96
17	PTSA-H ₂ O ^e	15	47	84

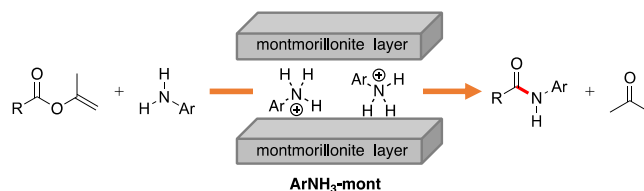
^aYield of **3aa** was determined via gas chromatography (GC) analysis using *n*-tetradecane as an internal standard. ^bConversion of **1a** was determined via GC analysis. ^c**2a** (2.2 mmol) was used. ^dIsolated yield. ^e5 mol % was used.

absence of a catalyst afforded the corresponding amide, **3aa**, in a low yield (17%, entry 1). When SO₄/ZrO₂, a representative solid super acid, was used, there was a slight improvement in the yield, suggesting that acid catalysis can promote the reaction (entry 2). Moderate yields were obtained when the strong acid ion-exchange resin Amberlyst 15DRY (41%, entry 3) and Nafion-H (45%, entry 4) were used. The H⁺-exchanged zeolites exhibited high catalytic activity (58–73%), except for H-ZSM-5 (27%), which has a small pore size (entries 5–8). The layered clay mineral H⁺-exchanged montmorillonite (H-mont) afforded **3aa** in 77% yield (entry 9).¹⁵ The effect of metal-ion-exchanged montmorillonites (Mⁿ⁺-mont) such as Fe^{III}-, Cu^{II}-, Zn^{II}-, Zr^{IV}-, and Sn^{IV}-mont catalysts was then investigated. However, lower yields (entries 10–14) were obtained compared with those obtained using H-mont. The

conditions were optimized for the reaction using the H-mont catalyst. The desired **3aa** was obtained in 88% yield (entry 16) after optimizing the reaction conditions when using the H-mont catalyst (entries 9, 15, and 16). In contrast, PTSA, a typical homogeneous acid catalyst, produced **3aa** in 47% yield and several byproducts, including benzoic acid (3% yield) and dihydroquinoline (12% yield) (entry 17).¹⁶

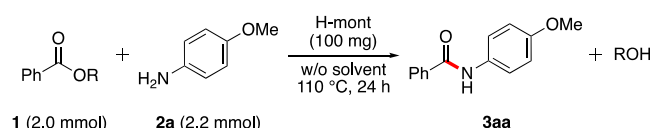
To gain insights into the active catalytic species, the spent catalyst was analyzed. Powder X-ray diffraction analysis showed that the interlayer distance increased from 0.26 nm before use to 0.54 nm. This meant the presence of the chemical species in the interlayer. In addition, elemental analysis, thermogravimetry analysis (TG), and thermal desorption and pyrolysis-gas chromatography-time-of-flight mass spectrometry (TDP-GC-TOFMS) analyses indicated that arylamine **2a** was immobilized as an arylammonium species (ArNH₃⁺) in the montmorillonite interlayer. Furthermore, similar analytical results for ArNH₃-mont (Ar = *p*-anis), which was prepared by another method, strongly supported this observation. Hence, we concluded that the catalytically active species was an arylammonium-immobilized montmorillonite (ArNH₃-mont) with appropriate Brønsted acidity¹⁷ and a large reaction space¹⁸ (Scheme 2).

Scheme 2. ArNH₃⁺-Immobilized Montmorillonite Catalyst



To evaluate the advantages of using isopropenyl esters, we attempted amidation reactions of benzoic acid and its esters under the optimized conditions (Table 2). The amidation of

Table 2. Reactivity of 1a and Its Analogs

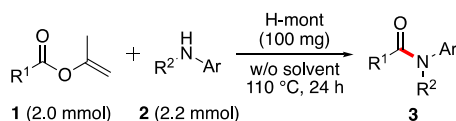


entry	R	3aa [%] ^a	RME [%] ^b
1	isopropenyl (1a)	88	66
2	H	12	11
3	Me	1	1
4	Ph	83	57
5	Vinyl	54	43

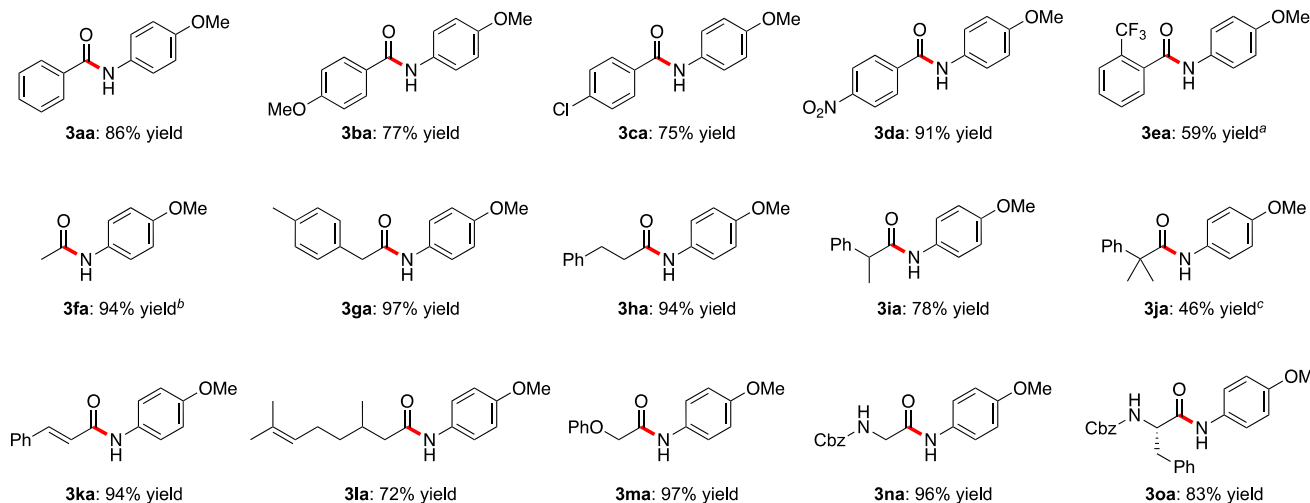
^aYield of **3aa** was determined via GC analysis using *n*-tetradecane as an internal standard. ^bReaction mass efficiency.

benzoic acid and methyl benzoate did not proceed well. The reaction of phenyl esters, which are considered relatively reactive, afforded **3aa** in good yields; however, it was difficult to remove the coproduced phenol. Notably, vinyl esters,¹⁹ which are the same enol esters as isopropenyl esters, produced only moderate yields of amides due to competing side reactions (e.g., the formation of quinoline, 11%).²⁰ The superiority of this protocol was also confirmed by the reaction mass efficiency (RME) value, which considers the atom

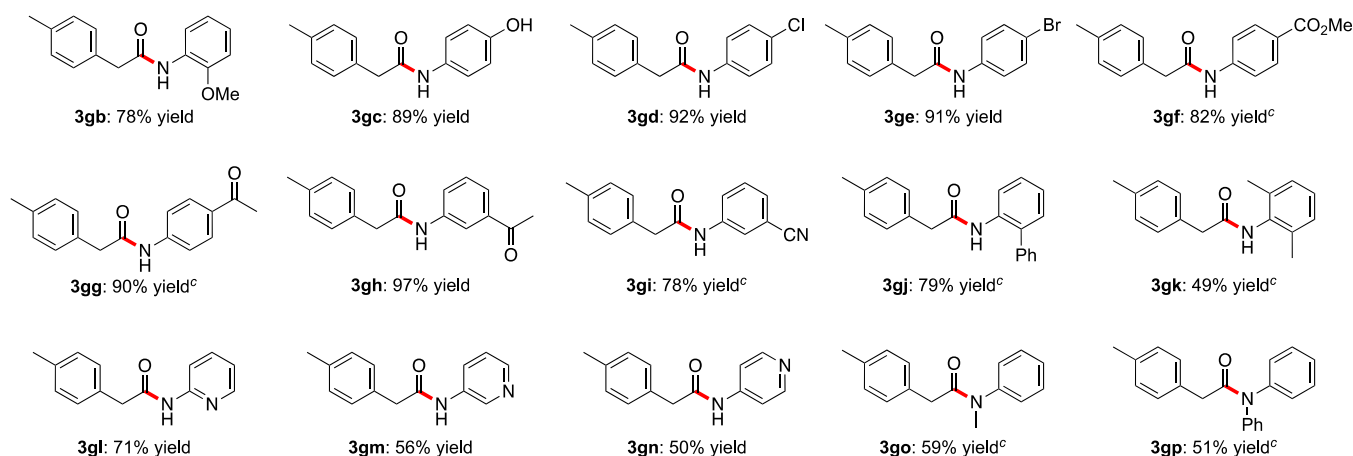
Scheme 3. Scope of Isopropenyl Esters and Arylamines



- Scope of Isopropenyl Esters -



- Scope of Arylamines -



Reaction of **1** (2.0 mmol, 1.0 equiv) and **2** (2.2 mmol, 1.1 equiv) was performed at 110 °C for 24 h in the presence of the H-mont catalyst (100 mg). Isolated yields are shown. ^aThe reaction was performed at 150 °C. ^bThe reaction was performed at 80 °C. ^cThe reaction was performed at 130 °C.

economy, yield, and stoichiometry of the reactants (Table 2).^{7,21}

The reaction scope of the isopropenyl esters was examined by using **2a** as the reaction partner under optimized conditions (Scheme 3). Isopropenyl benzoate bearing methoxy, chloro, and nitro groups at the *para*-position on the aromatic ring reacted smoothly to afford the desired products, **3ba–3da**, in 75–91% yields. Sterically bulky 2-trifluoromethylbenzoic acid isopropyl was treated at a higher temperature (150 °C), yielding **3ea** at 59%. Amidation reactions of primary and secondary aliphatic esters afforded the corresponding *N*-arylamides, **3fa–3ia**, in good-to-excellent yields. Furthermore, bulky tertiary esters produced **3ja** in a moderate yield. The amidation of cinnamate and citronellate esters afforded the corresponding amides **3ka** (94%) and **3la** (72%), respectively; there were no undesired reactions at the olefinic moiety. This

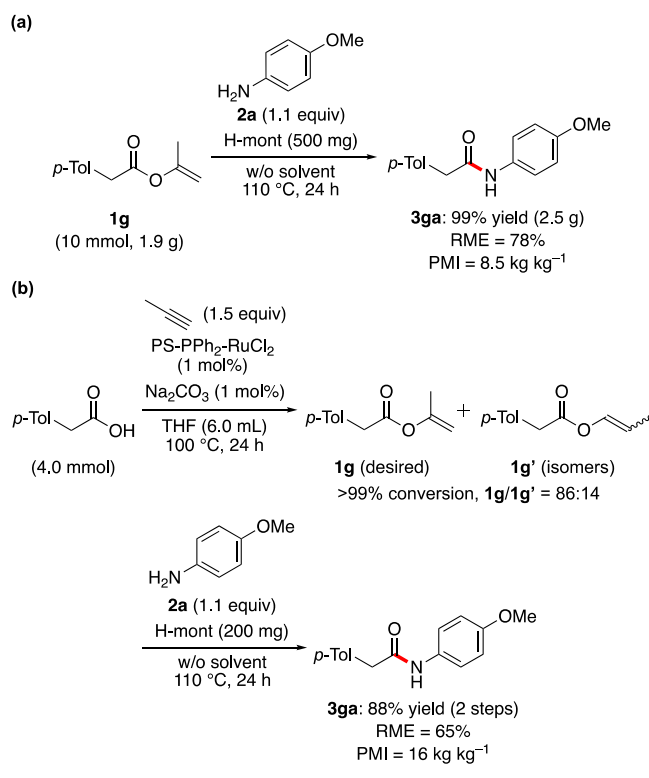
method was also applicable to the synthesis of *N*-arylamides with alkoxy (**3ma**, 97%) and amino groups (**3na**, 96%) at the α -position. Notably, the *L*-phenylalanine ester (**1o**, 97% ee), which often undergoes racemization, was also tolerated, and the reaction yielded the corresponding product (**3oa**) in 83% yield with excellent enantioselectivity (97% ee).

Next, we investigated the scope of arylamines using **1g** as the reaction partner (Scheme 3). Arylamines bearing electron-donating (methoxy or hydroxy) or halogen (chloro or bromo) groups produced **3gb–3ge** in good to high yields. Notably, this method tolerated strong electron-withdrawing groups; *N*-arylamides, **3gf–3gi**, that comprise ester, acetyl, and cyano groups at the *meta*- or *para*-position of the aromatic ring, were successfully synthesized in good-to-excellent yields. Although such substituents often hinder amidation by weakening the nucleophilicity of the arylamine, the effect was limited when

using this method. The amidation of 2-aminobiphenyl and 2,6-dimethylaniline produced lower yields because of steric hindrance, but the yields of **3gj** and **3gk** improved when the reaction temperature was increased to 130 °C. A range of aminopyridines afforded the desired products, **3gl–3gn**, in 50–71% yields. Furthermore, this method was also applicable to secondary arylamines, which have been difficult in previous methods,^{19c} and gave the corresponding tertiary amides **3go** and **3gp** in moderate yields. As described above, the developed reaction afforded 30 examples of *N*-arylamides in 46–97% yield.

The synthesis of *N*-arylamides on a multigram scale was also investigated; a 5-fold scale-up in **3ga** gave 2.5 g of the corresponding product in 99% yield without any problems (Scheme 4a). To make synthetic protocols practical and

Scheme 4. (a) Gram-Scale Synthesis of *N*-Arylamides; (b) Sequential Addition and Amidation Process



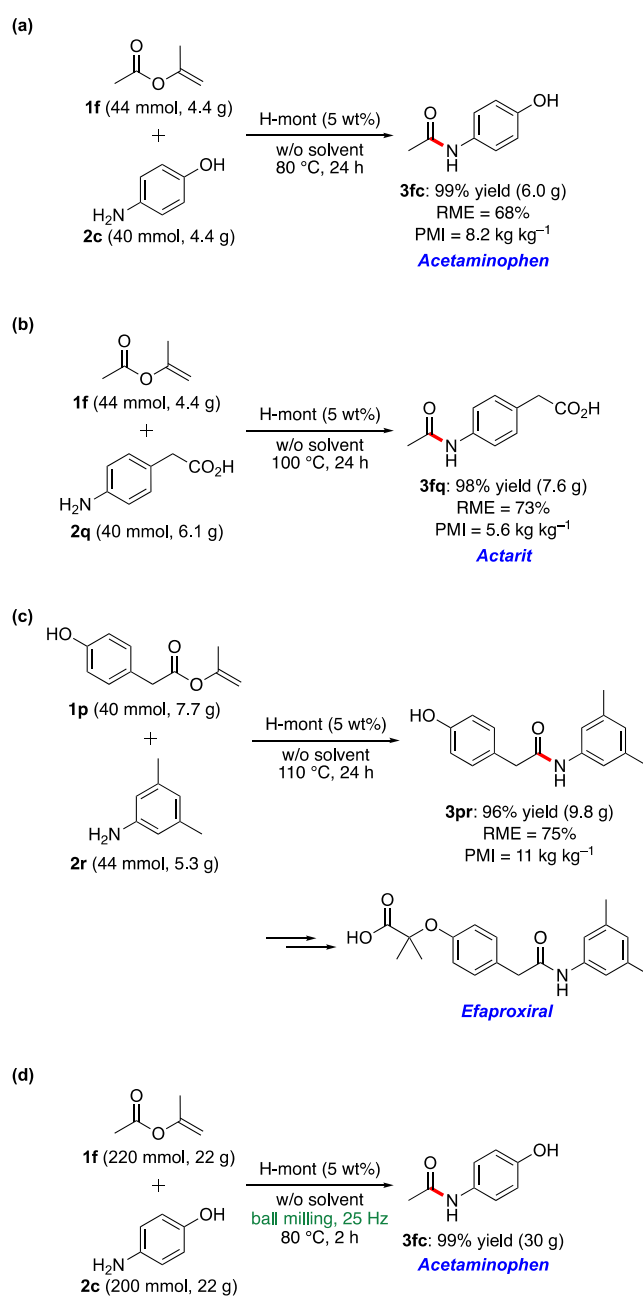
environmentally friendly, the simplicity and eco-friendliness of the workup and purification procedures are essential. This method afforded facile workup and purification procedures. After the reaction, the crude product and H-mont catalyst were easily separated by filtration with a small amount of a polar solvent (DMSO). Thereafter, water was added to the filtrate to precipitate the amide; the precipitate was subsequently filtered and washed to isolate the highly pure amide product (99% isolated yield, >99% purity based on GC analysis). To evaluate the greenness of this method, the process mass intensity (PMI) was calculated (Table S6). The PMI value in Scheme 4a is 8.5, which is better than that obtained in previous studies (Tables S11 and S12).^{6,7} Most of the products (Scheme 3) were isolated with high purity by using the procedure described above, without further extraction or column chromatography.

Isopropenyl esters can be easily prepared by the addition of carboxylic acids to propyne. Furthermore, this addition and the

amidation reaction can be performed sequentially (Scheme 4b). The reaction of carboxylic acid with propyne, in the presence of a polystyrene-immobilized ruthenium catalyst and Na₂CO₃, produced the corresponding ester, **1g**, and isomer, **1g'**. Subsequently, the crude product, **1g**, including **1g'**, obtained via filtration and concentration of the former reaction mixture, was reacted with **2a** and the H-mont catalyst to afford the desired product, **3ga**, in 88% yield (2 steps).

Finally, the developed method was employed in the multigram-scale synthesis of several pharmaceuticals, as shown in Scheme 5. In this method, the *N*-acetylation of aminophenol (**2c**) and 4-aminophenylacetic acid (**2q**) afforded the corresponding antipyretic analgesic acetaminophen (**3fc**, 6.0 g, 99% yield) and antirheumatic drug actarit (**3fq**, 7.6 g, 98% yield) in excellent yields. A simple workup, including

Scheme 5. Multigram-Scale Synthesis of Pharmacological Active *N*-Arylamides



filtration with methanol, yielded highly pure products with excellent PMIs. Efavoxiral is an *N*-arylamide that exhibits pharmacological activity and is utilized as a radiation enhancer, for example. The precursor of efavoxiral, **3pr**, was synthesized from **1p** and **2r** in 96% yield on 40 mmol scale, with a PMI of 11, lower than that of the reported methods.²² The effect of solvents on this reaction was examined, and none of the evaluated solvents had a positive effect (Table S4). Although the absence of the solvent is ideal for green chemistry applications, there are concerns about mixing substrates and controlling reaction heat during large-scale synthesis. We considered that this problem can be solved by ball milling, a synthetic method which has received much attention in recent years.²³ Therefore, we investigated the mechanochemical synthesis of **3fc** using a ball mill on a 200 mmol scale. Two 50 mL ZrO₂ reaction jars each containing ZrO₂ balls were used to perform the desired amidation reaction, yielding 30 g (99%) of the corresponding amide (**3fc**) after only 2 h of grinding at 80 °C, easily achieving a 5-fold scale-up (Scheme 5d). In contrast, when this scale of synthesis was carried out using magnetic stirrers or stirring blades, the reaction did not proceed favorably because the generated amide crystals inhibited mixing of the substrates and catalyst.

CONCLUSIONS

In conclusion, we report an atomically economical synthetic method for the direct amidation of isopropenyl esters to obtain *N*-arylamides in high yields. H-Montmorillonite, an inexpensive and readily available heterogeneous catalyst, exhibited excellent catalytic activity for this transformation, allowing the reaction of various isopropenyl esters with arylamines. *N*-Arylamides were efficiently synthesized using the developed method, which could be further applied to the synthesis of pharmacological active *N*-arylamides. Furthermore, because the H-mont catalyst and coproduced acetone were easily removed, the reaction mixture was easily purified to a high-purity product via simple workup procedures (filtration and solvent washing). Additionally, we described the facile scale-up to a 200 mmol scale by mechanochemical synthesis using ball milling. The drawback of this method is that the isopropenyl ester must be prepared in advance. We consider the use of a flow reaction as an effective way to solve this problem. An immobilized transition metal catalyst is loaded into a column reactor into which a solution of the carboxylic acid and propene is flowed and converted into the desired isopropyl esters. The resulting isopropenyl esters are discharged from the reactor, while being separated from the catalyst. Thus, harmful transition metal contamination is minimized as long as no metal leaching occurs. To achieve this flow reaction, a highly durable catalyst is required, which we are currently developing. We plan to investigate the construction of a continuous process that can prepare isopropenyl esters from carboxylic acids by flow synthesis, followed by the continuous synthesis of *N*-arylamides by mechanochemical methods. The developed method is attractive and promising as an environmentally benign synthesis of *N*-arylamides and as an alternative to current amidation reactions, which are low yielding and generate abundant chemical waste.

EXPERIMENTAL SECTION

General Procedure for *N*-Arylamide Synthesis. In a 25 mL test tube equipped with screw cap (NICHIDEN-RIKA

GLASS Co., Ltd., tempered hard-glass test tube equipped with screw cap ST-18S) were placed isopropenyl benzoate (**1a**, 324 mg, 2.00 mmol) and *p*-anisidine (**2a**, 271 mg, 2.20 mmol). In addition, an H-mont catalyst (100 mg) was added to the mixture. After the test tube was sealed, the reaction mixture was stirred for 24 h at 110 °C. The reaction mixture was cooled to room temperature, followed by the addition of a small amount of polar solvent (DMSO) to dissolve the amide product. The resulting suspension was separated by filtration into the H-mont catalyst and the filtrate. Water was then added to the filtrate to precipitate the amide. The collected precipitate was washed with water and *n*-heptane and dried under vacuum to give **3aa** (390 mg, 86% yield, >99% pure on GC analysis) as a white solid.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge. The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.3c06080>.

Detailed experimental methods; ¹H and ¹³C NMR and HRMS data; and RME and PMI calculations (PDF)

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Author Contributions

T.I.: project conceptualization, experimental designing, data collection (experiments and formal analysis), analysis and interpretation of results, manuscript writing and editing; T.M. and T.I.: project conceptualization, project administration, manuscript review and editing. All authors reviewed the results and approved the final version of the manuscript.

Funding

This work was supported in part by a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS KAKENHI, Grant No. 21K14666).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

T.I. acknowledges support from JSPS KAKENHI (grant number 21K14666). We thank Prof. Shū Kobayashi (The University of Tokyo) for the beneficial discussions.

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