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Oxidative annulation of acetophenones and 2-aminobenzothiazoles catalyzed by reusable nickel-doped LaMnO_3 perovskites†

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Synthesis of imidazole[2,1-*b*]benzothiazoles often suffers from the use of pre-functionalized substrates and/or homogeneous, non-recyclable catalytic systems. Herein we report a method for direct coupling of acetophenones and 2-aminobenzothiazoles in the presence of reusable perovskites, namely $\text{LaMn}_{0.95}\text{Ni}_{0.05}\text{O}_3$. Imidazole[2,1-*b*]benzothiazoles were obtained in moderate to good yields and contained an array of useful functionalities. Control experiments indicated that the perovskites played pivotal roles in halogenation and condensation steps.

Introduction

Imidazole[2,1-*b*]benzothiazoles are fused tricyclic heterocycles that are commonly found in many medicinally relevant molecules and functional materials.^{1–3} Traditional methods often rely on the annulation of α -bromo acetophenones and 2-aminobenzothiazoles.^{4,5} The first example of directly using acetophenones, without pre-functionalization of α C–H bonds, to couple with 2-aminobenzothiazoles was revealed by Hajra and co-workers.⁶ The reactions utilized catalytic amounts of FeCl_3 and ZnI_2 to facilitate the condensation. Jeong and Balwe reported a multi-component synthesis of benzo[*d*]imidazo[2,1-*b*]thiazoles from 2-aminobenzothiazoles, aldehydes, and nitromethane as a one carbon source.⁷ Feng, Ma, and co-workers recently developed a new method for copper-catalyzed, two-step annulation of ethylarenes and 2-aminopyridines.⁸ However, only one imidazole [2,1-*b*]benzothiazole was isolated. Notably, those methods utilized homogeneous catalytic systems. It is arguably more beneficial to use a heterogeneous, reusable catalyst.

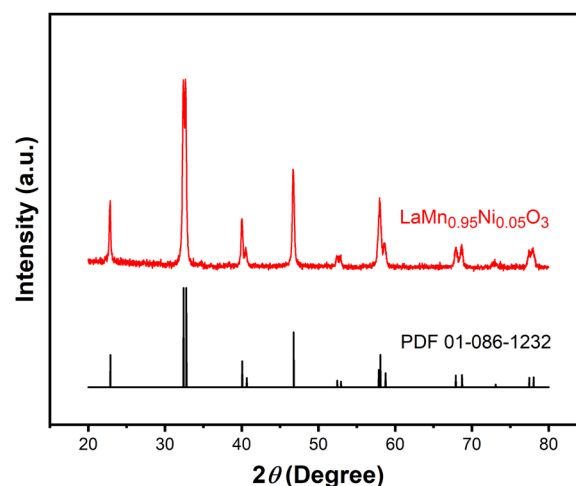
Lanthanum manganese perovskite oxide (LaMnO_3) is a well-known catalyst for oxidation reactions.^{9–11} Notably, the doping of late transition metals, such as cobalt(II) or nickel(II) ions, to LaMnO_3 was reported to increase the catalytic performances.^{12–15} Nevertheless, most of the available methods focus on the high-temperature, gas-phase oxidation. Herein we report our attempts to expand the application of nickel-doped LaMnO_3 perovskites into liquid-phase organic transformation. The annulation of 2-

aminobenzothiazoles and acetophenones occurred in the presence of catalytic amount of Ni-doped LaMnO_3 and mild conditions enough to tolerate a wide range of functionalities. Our method appears to be the first method for heterogeneously catalytic condensation toward the synthesis of imidazole[2,1-*b*]benzothiazoles.

Experimental

General considerations

Commercially available chemicals were used as received unless otherwise noted. The crystal structures of the samples were determined by X-ray diffraction (XRD) using D2 Phaser-Bruker diffractometer using $\text{CuK}\alpha$ ($\lambda = 1.54184 \text{ \AA}$), operated at an accelerating voltage of 30 kV and intensity of 10 Ma, 2θ range 20° –

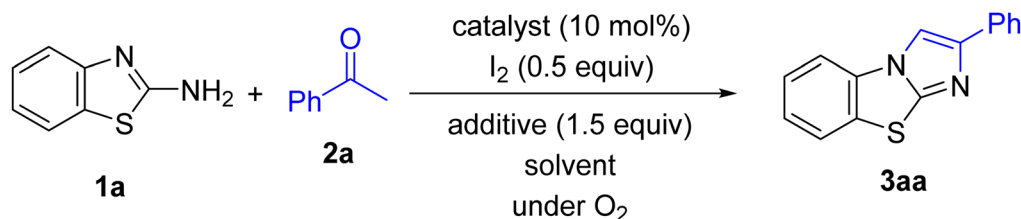

 Fig. 1 X-ray diffraction patterns of $\text{LaMn}_{0.95}\text{Ni}_{0.05}\text{O}_3$.

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Table 1 Study of reaction conditions^a

Entry	Temperature (°C)	Solvent	Catalyst	Additive	Yield of 3aa (%)
1	120	PhCl	LaMn _{0.95} Ni _{0.05} O ₃	BzOH	52
2	110	PhCl	LaMn _{0.95} Ni _{0.05} O ₃	BzOH	45
3	130	PhCl	LaMn _{0.95} Ni _{0.05} O ₃	BzOH	50
4	120	Toluene	LaMn _{0.95} Ni _{0.05} O ₃	BzOH	33
5	120	<i>p</i> -xylene	LaMn _{0.95} Ni _{0.05} O ₃	BzOH	21
6	120	DMSO	LaMn _{0.95} Ni _{0.05} O ₃	BzOH	16
7	120	PhCl	LaMnO ₃	BzOH	14
8 ^b	120	PhCl	LaMn _{0.95} Ni _{0.05} O ₃	BzOH	59
9 ^b	120	PhCl	LaMn _{0.95} Ni _{0.05} O ₃	AcOH	40
10 ^b	120	PhCl	LaMn _{0.95} Ni _{0.05} O ₃	PivOH	55
11 ^b	120	PhCl	LaMn _{0.95} Ni _{0.05} O ₃	NaHCO ₃	65
12 ^b	120	PhCl	LaMn _{0.95} Ni _{0.05} O ₃	Na ₂ CO ₃	47
13 ^{b,c}	120	PhCl	LaMn _{0.95} Ni _{0.05} O ₃	NaHCO ₃	75
14 ^{b,c}	120	PhCl	—	NaHCO ₃	10
15 ^{b,c,d}	120	PhCl	LaMn _{0.95} Ni _{0.05} O ₃	NaHCO ₃	57

^a 2a (0.15 mmol), catalyst (10 μmol), I₂ (0.05 mmol), and solvent (1 mL), under O₂, 8 h, then 1a (0.1 mmol), additive (0.15 mmol), under O₂, 12 h. Both steps were run at the same temperature. Yields are GC yields using diphenyl ether as internal standard. ^b I₂ (0.1 mmol). ^c PhCl (0.5 mL). ^d Under air for both steps. Abbreviations: BzOH = benzoic acid, AcOH = acetic acid, PivOH = pivalic acid.

80° with a step size of 0.015°. The EDX spectrum carried out on EX 350-Horiba were used to quantify the elements Ti, Si, O and N. The results of differential thermal analysis-thermogravimetric analysis (DTA-TGA) were obtained from the Labsys Evo, Setaram, which was in the environment of air at the heating rate of 5 °C min⁻¹. FESEM (Hitachi S-4800) and TEM (JEOL JEM-2100) were applied to study morphology and particle size. The nitrogen adsorption-desorption isotherms at 77 K were run on the MicroMeritics ASAP 2010. Gas chromatographic (GC) analyses were performed using a Shimadzu GC 2010-Plus equipped with

a flame ionization detector (FID) and an SPB-5 column. GC-MS analyses were carried out on a Shimadzu GCMS-QP2010 Ultra containing a ZB-5MS column. The ¹H-NMR and ¹³C-NMR spectra were recorded on Bruker AV 500 and 600 MHz spectrometers.

Preparation of LaMn_{0.95}Ni_{0.05}O₃

The Ni-doped LaMnO₃ perovskites were prepared following the known sol-gel method.¹⁶ Lanthanum nitrate hexahydrate

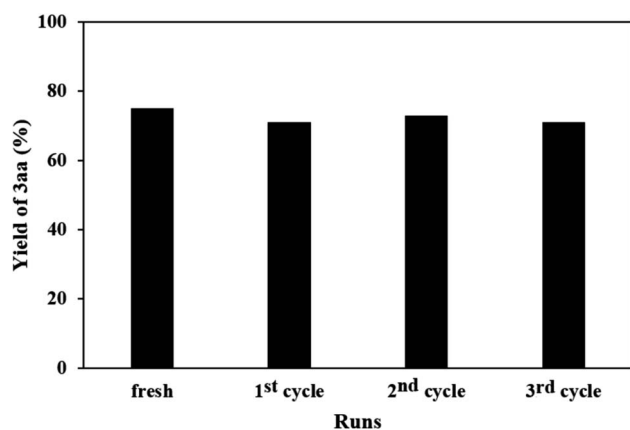


Fig. 2 Recyclability of LaMn_{0.95}Ni_{0.05}O₃ catalyst. Yield for each of reused runs was obtained after three independent attempts.

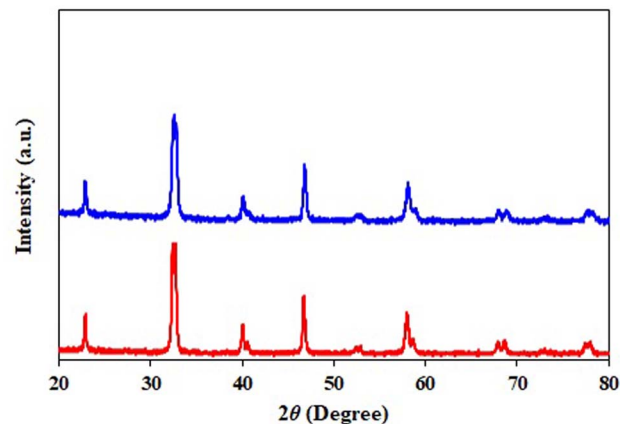


Fig. 3 X-ray diffraction patterns of fresh and reused LaMn_{0.95}Ni_{0.05}O₃ perovskites.

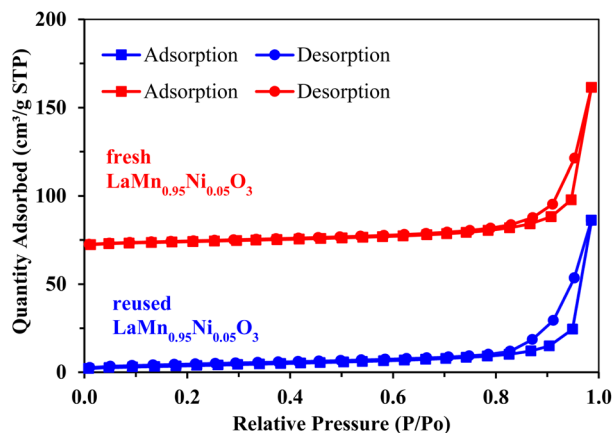
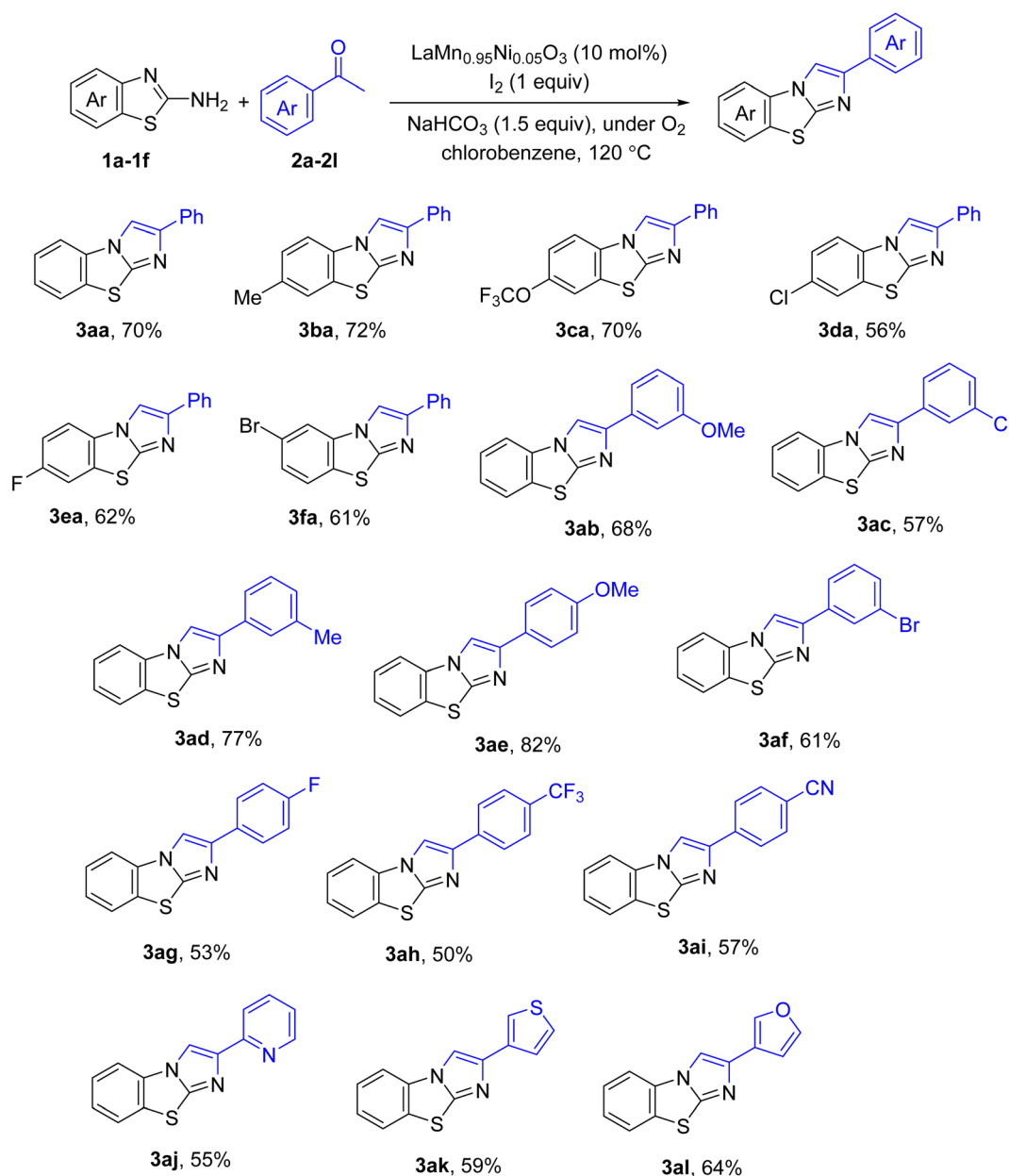


Fig. 4 Nitrogen physisorption isotherms of fresh and reused $\text{LaMn}_{0.95}\text{Ni}_{0.05}\text{O}_3$ perovskites.

(2.16 g, 5 mmol), manganese nitrate tetrahydrate (1.72 g, 4.75 mmol), and nickel nitrate hexahydrate (70 mg, 0.25 mmol) were mixed in a beaker containing 50 mL distilled water and 50 mL alcohol to form a homogeneous solution. Then, citric acid monohydrate (4.22 g, 20 mmol) was added and the solution was heated at 80 °C until a viscous gel was formed. The obtained gel was dried at 120 °C for 5 h (ash), pulverized, and calcined in the air at 500 °C for 3 h at a heating rate of 5 °C min^{-1} to evaporate the solvent. Finally, the resulting powder was calcined again at 800 °C for 3 h.

General procedure for studying the annulation

For a typical reaction of optimization, the mixture of acetophenone (0.15 mmol), I_2 , catalyst, and solvent was added to



Scheme 1 Scope of imidazole[2,1-*b*]benzothiazoles. Conditions: 2a-2l (0.15 mmol), I_2 (0.1 mmol), $\text{LaMn}_{0.95}\text{Ni}_{0.05}\text{O}_3$ (10 μmol), chlorobenzene (0.5 mL), under O_2 , 120 °C, 8 h, then 1a-1f (0.1 mmol), NaHCO_3 (0.15 mmol), 120 °C, 12 h. Yields are isolated yields.

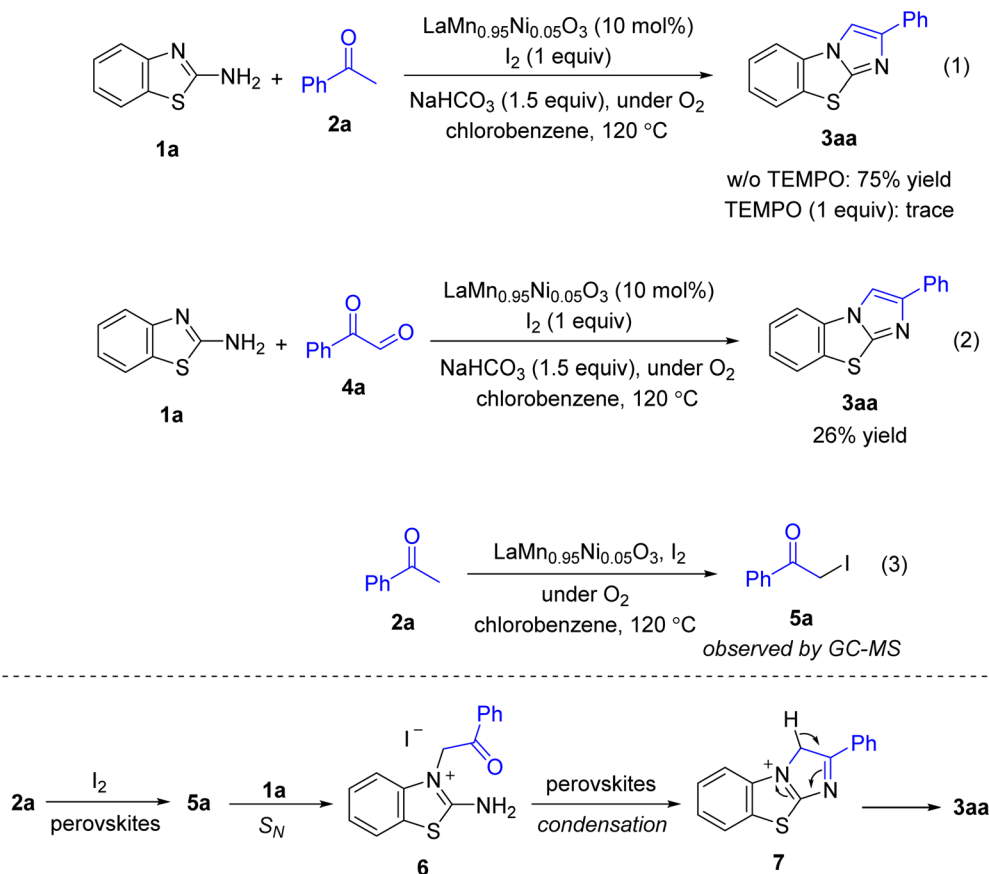
a 12 mL screw-cap vial. The reaction tube was flushed with O₂, tightly capped, and stirred at the given temperature for 12 h. Then, 2-aminobenzothiazole (0.1 mmol) and an additive were added. The tube was flushed with O₂ again, capped, then stirred at the temperature identical to the first step for an additional 8 h. The mixture was cooled to room temperature and diphenyl ether (17.0 mg, 0.1 mmol) as an internal standard was added. Organic components were extracted into ethyl acetate (2 mL), washed with Na₂S₂O₃ solution (5% in water, 1 mL), and brine (1.0 mL). The obtained organic layer was dried over anhydrous Na₂SO₄, filtered, and analyzed by GC with reference to diphenyl ether. For isolation, the aforementioned steps should be followed, except the addition of the internal standard. Purification of the last organic layer by column chromatography afforded the desired product. For studying the recyclability of perovskites, the material was removed by centrifugation after the reaction finished, then washed with solvents (methanol 3 × 3 mL, acetone 3 × 3 mL, and diethyl ether 3 × 3 mL), activated under vacuum for 12 h, and used for next runs.

Results and discussion

The results of characterization confirmed the successful preparation of the LaMn_{0.95}Ni_{0.05}O₃ perovskites (see the ESI† for

details). For example, the XRD pattern showed diffraction peaks of LaMn_{0.95}Ni_{0.05}O₃ at $2\theta = 23^\circ, 32^\circ, 40^\circ, 47^\circ, 53^\circ, 58^\circ, 68^\circ,$ and 78° (Fig. 1). The peaks exhibited the rhombohedral structure of LaMnO₃ perovskites (card PDF#01-086-1232).¹⁷ The EDX spectrum expressed that no foreign elements or initial synthetic precursors were detected (Fig. S2†). The exothermic peak at 677 °C in the TGA-DTA result was assigned for the formation of the perovskite phase (Fig. S3†). The SEM (Fig. S4†) and TEM (Fig. S5†) images showed that nanoparticles were obtained. The surface area of the LaMn_{0.95}Ni_{0.05}O₃ obtained from nitrogen physisorption isotherm was 14.538 m² g⁻¹ (Fig. S6†).

The as-prepared LaMn_{0.95}Ni_{0.05}O₃ perovskites were firstly used for the annulation of 2-aminobenzothiazole **1a** and acetophenone **2a** to afford the desired imidazole[2,1-*b*]benzothiazole **3aa**. The results of optimization studies are presented in Table 1. It should be noted that acetophenone **2a** was treated with iodine, in the presence of catalyst, prior to the addition of 2-aminobenzothiazole **1a** and the additive. The annulation should be run at 120 °C to obtain a reasonable yield (entries 1–3). Chlorobenzene was superior to other aromatic solvents such as toluene and *p*-xylene (entries 4 and 5). Polar, aprotic solvents were not suitable for the annulation (entry 6). Coupling of **1a** and **2a** in the presence of LaMnO₃ catalyst gave only 14% yield of the desired product **3aa**, somewhat confirming the crucial



Scheme 2 Mechanistic consideration. Conditions: equation 1: **2a** (0.15 mmol), I₂ (0.1 mmol), TEMPO (0.1 mmol), LaMn_{0.95}Ni_{0.05}O₃ (10 μmol), chlorobenzene (0.5 mL), under O₂, 120 °C, 8 h, then **1a** (0.1 mmol), NaHCO₃ (0.15 mmol), 120 °C, 12 h. Equation 2: **4a** (0.15 mmol), I₂ (0.1 mmol), LaMn_{0.95}Ni_{0.05}O₃ (10 μmol), chlorobenzene (0.5 mL), under O₂, 120 °C, 8 h, then **1a** (0.1 mmol), NaHCO₃ (0.15 mmol), 120 °C, 12 h. Equation 3: **2a** (0.15 mmol), I₂ (0.1 mmol), LaMn_{0.95}Ni_{0.05}O₃ (10 μmol), chlorobenzene (0.5 mL), under O₂, 120 °C, 8 h. Yields are GC yields.

role of doped nickel ions (entry 7). Increasing the amount of iodine resulted in a better yield (entry 8). Among the additives attempted, NaHCO₃ provided the best yield of **3aa** (entries 9–12). Decreasing the amount of chlorobenzene solvent by a half afforded a 75% yield of **3aa** (entry 13). Omitting the presence of Ni-doped LaMnO₃ perovskites gave only 10% yield of **3aa** (entry 14). The reaction under air afforded **3aa** in 57% yield, which was lower than that under O₂, confirming the crucial role of O₂ to obtain reasonable yields (entry 15).

Next, we studied the recyclability of Ni-doped LaMnO₃ perovskites. Notably, the yields of the annulation product **3aa** after three cycles were comparable (Fig. 2). The results of XRD diffractogram (Fig. 3) and nitrogen isotherm (Fig. 4) with respect to the reused Ni-doped LaMnO₃ perovskites were nearly identical to those of the fresh material, somewhat confirming that the structure of the material was still remained. Thus, the Ni-doped LaMnO₃ perovskites feature a promising reusability toward the condensation of 2-aminobenzothiazoles and acetophenones.

Scope of the substrates was next investigated. The result is shown in Scheme 1. Fluoro (**3ea**, **3ag**), chloro (**3da**, **3ac**), bromo (**3af**), and cyano (**3ai**) functionalities were all compatible with reaction conditions. Regarding acetophenones, electron-rich compounds (**3ae**) were more reactive than the electron-poor (**3ag**–**3ai**). The yields of imidazole[2,1-*b*]benzothiazoles obtained from pyridyl (**3aj**), thiophenyl (**3ak**), and furanyl (**3al**) ketones varied from 55% to 64%, showing the compatibility of heterocycles toward the annulation.

To understand the mechanism, some control experiments were carried out (Scheme 2). No product was observed if TEMPO was added (equation 1), somewhat implying the formation of radical species during the course of the reaction. Use of phenylglyoxal **4a** to couple with 2-aminobenzothiazole **1a** afforded a low yield of the product **3aa** (equation 2), confirming that oxidation of α C–H bonds to furnish the aldehyde was unlikely the key step. Meanwhile, running the first step which included acetophenone **2a**, Ni-doped LaMnO₃ perovskites, and iodine gave the iodination intermediate **5a** (equation 3). Based on the results that we observed as well as those previously reported,^{6,11} a possible mechanism was proposed (Scheme 2). Iodination of α C–H bonds in acetophenone **2a** gave the adduct **5a** followed by a nucleophilic substitution to afford **6**. Imine condensation would yield **7** which underwent a tautomerization to finally furnish the desired product **3aa**. We envisaged that Ni-doped LaMnO₃ perovskites played a crucial role in the first oxidation (**2a** → **5a**).

Conclusions

In conclusion, we have developed a method for nickel-doped LaMnO₃ perovskites mediated annulation of 2-aminobenzothiazoles and acetophenones. The reactions proceeded under mild conditions that were tolerant of many useful functionalities as well as heterocycles. Characterization of the reused material regarding the results XRD and nitrogen physorption isotherm somewhat confirmed that the structure of

the LaMn_{0.95}Ni_{0.05}O₃ was still remained, thus implying the recyclability and reusability of the perovskites.

Conflicts of interest

There are no conflicts to declare.

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