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Research Article

Copper-Catalyzed Hydroboration of Enamides with Bis(pinacolato)diboron: Promising Agents with Antimicrobial Activities

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We reported in this study the hydroboration of enamides in methanol at room temperature catalyzed by copper complexes. Under such conditions, a Gram-scale reaction with a high yield was also completed. Hydroboration of 3-methylene, 2-(alkyl and phenylisoindolin-1-one 5 with bis(pinacolato)diboron yields the respective compounds 6 in good yields with high-to-moderate enantioselectivity (58% ee). Furthermore, the antimicrobial properties of the synthesized compounds were tested against four indicator microorganisms: the two Gram-positive bacteria L. *monocytogenes* ATCC 1911 and *S. aureus* ATCC 6538, the Gram-negative bacterium S. *typhimurium* ATCC 14028, and the fungus *C. albicans* (ATCC 90028). The MIC values of compounds 5-6 range from 0.312 to 2.5 (μg/mL) against *L. monocytogenes*, from 2.1 to 0.136 (μg/mL) against *S. aureus*, and from 0.126 to 0.923 (μg/mL) against *S. typhimurium*.

1. Introduction

Boron chemistry is one of the most salient subjects in organic chemistry. It is gaining popularity due to its intrinsic scientific value and practical programs. Considerable work has been placed on locating effective and straightforward approaches to manufacturing organoboron reagents, which constitute a vital reagent family in organic synthesis [1]. The conventional C-B formation by increasing borane reaction with alkenes or alkynes was achieved under pretty severe conditions. Transition metal-catalyzed hydroboration of unsaturated molecules has recently been identified as a beneficial method for synthesizing alkyl boronic acid derivatives [2]. Several transition metals, including platinum [3], gold [4], palladium [5], rhodium [6], iron [7], and nickel, have been applied to catalyze hydroboration procedures of unsaturated molecules [8]. Cu salts were widely proposed as catalysts for move-coupling reactions, essential in synthetic organic chemistry due to their low cost and toxicity [9]. The copper-catalyzed reaction has many advantages. It does, however, have some downsides, such as low conversion efficiency [10]. Previously, the researchers had developed mild conditions for copper-catalyzed borylation of primary and secondary alkyl halides [11] and similarly described the

copper-catalyzed hydroboration of styrenes activated with electron-withdrawing groups [12]. Herein, we attempt to present a low-cost, low-toxicity, high-conversion-efficiency copper-catalyzed borylation reaction of enamides in methanol at room temperature. In addition, the obtained compounds 5-6 were tested against four indicator microorganisms: the two Gram-positive bacteria *L. monocytogenes* ATCC 1911 and *S. aureus* ATCC 6538, the Gram-negative bacterium *S. typhimurium* ATCC 14028, and the fungus *C. albicans* (ATCC 90028) for their antimicrobial activity. Their MIC were also determined.

2. Experimental

2.1. General Information. Chemicals were purchased from Sigma Aldrich and used without further purification. All solvents were purified and dried with the MBraun SPS 800 solvent purification system. ^{1}HNMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, and m = multiplet signal. IR spectra were recorded on a 398 spectrophotometer (Perkin-Elmer). Melting points were determined with Kofler bench at Isste of Borj cedria (Hammam-Lif, University of Carthage, Borj Cedria, Tunisia).

2.2. General Procedure for the Synthesis of 4. A 10 mL microwave vial equipped with a magnetic stir bar was loaded with ortho-acetyl benzoic acid (5 mmol), primary amines (5.5 mmol), APTS (20 mg), and toluene (5 mL). The reaction mixture was heated and stirred in the microwave reactor at 150°C for 1 h. After the reaction was complete, the mixture was cooled to room temperature. The residue was dissolved in 20 mL of dichloromethane and was successively washed with water, 5% $NaHCO_3$, and brine. The organic phase was dried over anhydrous $MgSO_4$ and then was evaporated to give a crude product. The crude product was purified by silica gel chromatography (acetone-petrol ether (30 : 70)) to give products 4.

2.2.1. 2-(4-m-Ethoxybenzyl)-3-methyleneisoindolin-1-one (4a). Yield (%) = 77; IR(cm^{-1}): 1707(CO), 1381(C-N). ^{1}H NMR (300 MHz, DMSO) δ (ppm): 3.65 (s, 3H), 4.71–4.71 (d, J = 4.71 Hz, 1H), 4.83 (s, 3H), 5.03–5.04 (d, J = 5.04 Hz, 1H), 6.72–6.74 (d, J = 6.73 Hz, 2H), 7.10–7.13 (dJ = 7.11 Hz, 2H), 7.37–7.56 (m, 3H),7.76 7.78 (d, J = 7.77 Hz, 1H), ^{13}CNMR (300 MHz, DMSO) δ (ppm), 42.66 (CH_2), 55 (CH3), 89.97 (C), 114.11 (2CH), 119.95 (CH), 123.32 (CH), 128.60 (2CH), 129.53 (C), 136.50 (CH), 136.50 (C), 141.62 (C=C), 158.97 (COCH3), 167.27 (C=O).

2.2.2. 2-(Dimethylamino)-3-methyleneisoindolin-1-one (4b). Yield (%) = 62; IR (cm^{-1}): ^{1}H NMR (300 MHz, DMSO) δ (ppm): 2.86 (s, 6H), 5.01 (s, 1H), 5.13 (s, 1H), 7.26–7.40 (m, 2H), 7.45–7.48 (d, J = 8.3 Hz, 1H), 7.59–7.61 (dJ = 7.5 Hz, 1H). ^{13}CNMR (75 MHz, DMSO) δ (ppm) 43.51 ($2CH_3$), 89.57 (CH2), 119.97 (CH), 128.43 (C), 129.08 (CH), 131.70 (CH), 134.13 (C), 140.00 (C), 165.51 (C=O).

2.2.3. 2-Cyclohexyl-3-methyleneisoindolin-1-one (4c). Yield (%) = 38; IR (cm^{-1}): ^{1}H NMR (300 MHz, DMSO) δ (ppm): 1.10–1.38 (m, 3H), 1.60–1.82 (m, 5H), 2.10–2.22 (m, 2H), 3.95–4.04 (m, 1H), 4.90–4.91 (d, J = 2.3 Hz, 1H), 5.11–5.12 (dJ = 2.3 Hz, 1H), 7.33–7.46 (m, 2H); 7.53–7.60 (m, 1H), 7.68–7.71 (m, 1H). ^{13}C NMR (75 MHz, DMSO) δ (ppm) 26.3 ($3CH_2$), 34.1 ($2CH_2$), 65.03 (CH), 89.57 (CH_2), 129.70 (2CH), 131.75 (2CH), 133.3 (C), 139.5 (C), 166.7 (C=O).

2.2.4. 2-Benzyl-3-methyleneisoindolin-1-one (4d). Yield (%) = 68; IR (cm^{-1}): ^{1}H NMR (300 MHz, DMSO) δ (ppm): 4.81–4.82 (d, 1H), 5.03 (s, 2H), 5.16–5.17 (d, 2H), 7.24–7.36 (m, 5H), 7.51–7.61 (m, 2H), 7.68–7.70 (d, J = 7.3 Hz, 1H), 7.90–7.93 (d, J = 7.1 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ (ppm) 43.16 (CH_2), 89.97 (CH_2), 119.92 (CH), 123.35 (CH), 127.13 (2CH), 127.38 (CH), 128.66 (2CH), 129.52 (CH), 132.07 (CH); 131.4 (2C), 143.8 (C); 165.08(C).

2.3. Synthesis of Compounds 5. A mixture of enamides (0.2 mmol), bis(pinacolato)diboron (1, 5eq), cesium carbonate (0.1eq), and [(SIMes)CuCl] (10 mol%) in MeOH (mL) was stirred 2 h at room temperature. The reaction was quenched with H_2O (50 mL) and extracted with Et_2O (3 × 30 mL). The organic phase was washed with H_2O (2 × 30 mL) and brine (30 mL) and then was dried (Mg_2SO_4) and filtered. The solvent was removed by vacuum to afford pure 5(a–e).

2.3.1. 2-(4-Methoxybenzyl)-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)isoindolin-1-one(5a). Yield (%) = 65; IR (cm^{-1}): ^{1}H NMR (300 MHz, DMSO) δ (ppm): 0.63–0.74 (m, 2H), 1.94–1.96. (s, 12H), 3.58 (s, 3H), 4.05–4.10 (d, 1H), 4.37–4.41 (m, 1H), 5.13–5.18 (d, 1H), 6.67–6.70 (d, J = 8.7 Hz, 2H), 7.09–7.11 (d, J = 8.7 Hz, 2H), 7.24––7.34 (m, 3H), 7.70–7.72 (d, J = 7.3 Hz, 1H).

^{13}C NMR (75 MHz, DMSO) δ(ppm) 24.33 ($4CH_3$), 42.53 (CH2), 54.81 (CH_3), 55.62 (CH), 81.08 (2C), 113.73–130.94 (Carom); 146.87 (C), 158.85 (C); 167.62(C).

2.3.2. 2-(Dimethylamino)-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)isoindolin-1-one (5b). Yield (%) = 40; IR (cm^{-1}): ^{1}H NMR (300 MHz, DMSO) δ (ppm): 0.75–0.79 (m, 1H), 1.16–1.19 (d, 13H), 2.92 (s, 6H), 4.56–4.61 (m, 1H), 7.29–7.45 (m, 3H), 7.66–7.68 (d, J = 7.4 Hz, 1H).

^{13}C NMR (75 MHz, DMSO) δ (ppm) 24.81 ($4CH_3$), 25.03 ($2CH_3$), 44.18 (CH_2), 98.82 (CH), 83.47 (2C), 122.32 (CH); 122.94 (CH); 127.85 (CH); 131.50 (CH); 145,94 (2C); 166.22 (C).

2.3.3. 2-Cyclohexyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-ylmethyl)-2,3-dihydro-isoindol-1-one (5c). Yield (%) = 46, ^{1}H NMR (300 MHz, DMSO) δ (ppm): 0.78–0.84 (m, 2H), 1.07–1.11 (d, 12H), 1.52–1.65 (m, 6H), 1.84–1.91 (m, 4H), 3.96–4.01 (m, 1H), 4.64–4.68 (m, 1H); 7.39–7.48 (m, 3H); 7.67–7.70 (d, J = 7.69 Hz, 1H). ^{13}C NMR (75 MHz,

DMSO) δ (ppm) 24.90 ($4CH_3$), 30.81 (CH2), 31.22 (2CH2), 34.05 (2CH2), 53.72 (CH_2), 57.17 (CH); 64.36 (CH); 83.64 (2C); 122, 12–130.99 (4CHarom); 147.52 (2C); 168.25(C).

2.3.4. 2-Benzyl-3-((4,4,5,5-tetramethyl-1,3,2-dioxazolidin-2-yl)methyl)isoindolin-1-one (5d). Yield (%) = 42; IR(cm^{-1}): ^{1}H NMR (300 MHz, DMSO) δ (ppm): 0.78–0.88 (m, 2H), 1.01–1.04 (d, 12H), 4.16–4.21 (d, 1H), 4.46–4.50 (m, 1H), 5.26–5.32 (d, 1H), 7.15–7.24 (m, 5H); 7.34–7.44 (m, 3H); 7.78–7.81 (d, J = 7.3 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ (ppm).

24.85 ($4CH_3$), 43.63 (CH2), 56.23 (CH2), 83.64 (2C), 122.56131.44Carom); 132.26 (C); 137.55 (C); 147.28 (C); 168.33 (C).

2.4. Synthesis of Compounds 6. A mixture of enamides (0.2 mmol), bis(pinacolato)diboron (1, 5eq), cesium carbonate (0.1eq), and [(SIMes)CuCl] (10 mol%) in MeOH (mL) was stirred 2 h at room temperature. The reaction was quenched with H_2O (50 mL) and extracted with Et_2O (3×30 mL). The organic phase was washed with H_2O (2×30 mL) and brine (30 mL) and then was dried (Mg_2SO_4) and filtered. The solvent was removed by vacuum to afford pure 5(a–e).

2.4.1. 2-(4-Methoxybenzyl)-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)isoindolin-1-one (6a). Yield (%) = 65; IR (cm^{-1}): ^{1}H NMR (300 MHz, DMSO) δ (ppm): 0.63–0.74 (m, 2H), 1.94–1.96. (s, 12H), 3.58 (s, 3H), 4.05–4.10 (d, 1H), 4.37–4.41 (m, 1H), 5.13–5.18 (d, 1H), 6.67–6.70 (d, J = 8.7 Hz, 2H), 7.09–7.11 (d, J = 8.7 Hz, 2H), 7.24–7.34 (m, 3H), 7.70–7.72 (d, J = 7.3 Hz, 1H).

^{13}C NMR (75 MHz, DMSO) δ (ppm) 24.33 ($4CH_3$), 42.53 (CH2), 54.81 (CH_3), 55.62 (CH), 81.08 (2C), 113.73–130.94 (Carom); 146.87 (C), 158.85 (C); 167.62(C).

2.4.2. 2-(Dimethylamino)-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)isoindolin-1-one (6b). Yield (%) = 40; IR (cm^{-1}): ^{1}H NMR (300 MHz, DMSO) δ (ppm): 0.75–0.79 (m, 1H), 1.16–1.19 (d, 13H), 2.92 (s, 6H), 4.56–4.61 (m, 1H), 7.29–7.45 (m, 3H), 7.66–7.68 (d, J = 7.4 Hz, 1H).

^{13}C NMR (75 MHz, DMSO) δ (ppm) 24.81 ($4CH_3$), 25.03 ($2CH_3$), 44.18 (CH_2), 98.82 (CH), 83.47 (2C), 122.32 (CH); 122.94 (CH); 127.85 (CH); 131.50 (CH); 145,94 (2C); 166.22 (C).

2.4.3. 2-Cyclohexyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-ylmethyl)-2,3-dihydro-isoindol-1-one (6c). Yield (%) = 46, ^{1}H NMR (300 MHz, DMSO) δ (ppm): 0.78–0.84 (m, 2H), 1.07–1.11 (d, 12H), 1.52–1.65 (m, 6H), 1.84–1.91 (m, 4H), 3.96–4.01 (m, 1H), 4.64–4.68 (m, 1H); 7.39–7.48 (m, 3H); 7.67–7.70 (d, J = 7.69 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ (ppm) 24.90 ($4CH_3$), 30.81 (CH2), 31.22 (2CH2), 34.05 (2CH2), 53.72 (CH_2), 57.17 (CH); 64.36 (CH); 83.64 (2C); 122, 12–130.99 (4CHarom); 147.52 (2C); 168.25(C).

2.4.4. 2-Benzyl-3-((4,4,5,5-tetramethyl-1,3,2-dioxazolidin-2-yl)methyl)isoindolin-1-one (6d). Yield (%) = 42; IR (cm^{-1}): ^{1}H NMR (300 MHz, DMSO) δ (ppm): 0.78–0.88 (m, 2H), 1.01–1.04 (d, 12H), 4.16–4.21 (d, 1H), 4.46–4.50 (m, 1H), 5.26–5.32 (d, 1H), 7.15–7.24 (m, 5H); 7.34–7.44 (m, 3H); 7.78–7.81 (d, J = 7.3 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ (ppm).

24.85 ($4CH_3$), 43.63 (CH2), 56.23 (CH2), 83.64 (2C), 122.56131.44Carom); 132.26 (C); 137.55 (C); 147.28 (C); 168.33 (C).

3. Material and Methods

3.1. Antibacterial Activity

3.1.1. Bacterial Strains, Media, and Growth Conditions. Reference strains used for the antibacterial activity assays included *Micrococcus luteus* (*M. luteus*) LB 14110, *Staphylococcus aureus* (*S. aureus*) ATCC6538, *Listeria monocytogenes* (*L. monocytogenes*) ATCC 19117, *Salmonella typhimurium* (*S. typhimurium*) ATCC 14028, *Pseudomonas aeruginosa* (*P. aeruginosa*) ATCC 49189, and *Candida albicans*. The bacterial strains were cultured overnight in Luria-Bertani (LB) medium: peptone 10 (g/l), NaCl 5 (g/l) at pH 7.2, and yeast compound 5 (g/l). The bacteria were cultured under aerobic conditions with continuous agitation (200 rpm). The incubation temperatures were as follows: *M. luteus* at 30°C; *S. aureus*; *L. monocytogenes*; *S. typhimurium*; and *P. aeruginosa* at 37°C for ATCC 6538 and ATCC 19117. The cultures were diluted 1 : 100 in LB media and incubated for 5 h under constant agitation (200 rpm) at a suitable temperature.

3.2. Agar Well Diffusion Assay. The agar well diffusion technique was employed to determine the antimicrobial activity of the synthesized compounds with minor modifications [13]. The growth medium (25 mL) was dispensed into Petri dishes and allowed to solidify for 15 min under ultraviolet (UV) light (265 nm wavelength). Sterile cotton was dipped into the culture of the different bacterial (adjusted to a turbidity of 0.5 McFarland standard) suspensions.

The cotton with inoculum was lightly swabbed across the agar. A sterile cork borer was used to cut wells with a diameter of 8 mm inside the agar. Stock solutions of the samples (synthesized compounds) were diluted in sterile distilled water to obtain concentrations of 500 μgmL^1. The wells were filled with the test samples and controls (100 μl). The plates were incubated for 24 hours at 37°C. Subsequently, the diameters of the zone of inhibitions around the wells were measured.

3.3. Minimum Inhibitory Concentration (MIC). MIC of the synthesized compounds and the standards ampicillin, kanamycin, and fluconazole (stock solutions at 20 mg/mL^{-1}) against the five tested bacteria and the fungus *C. albicans* were determined according to Sellem et al. [14]. The test was performed in sterile 96-well microplates with a final volume in each microplate well of 100 μL. Stock solutions of

synthesized compounds and standards were serially diluted with dimethyl sulfoxide (DMSO). To each test well, cell suspension was added to the final inoculum concentration of 10^6 CFU·mL^{-1} of indicator microorganism. The plates were then incubated at appropriate growth conditions of the corresponding indicator microorganism. The MIC was defined as the lowest concentration of the synthesized compounds and standards at which the microorganism does not demonstrate visible growth after incubation. Twenty-five μl of Thiazolyl Blue Tetrazolium Bromide (MTT) at 0.5 mg·mL^{-1} was added to the wells and incubated at room temperature for 30 min. The colorless tetrazolium salt acted as an electron acceptor and was reduced to a red-colored formazan product by the indicator microorganisms. When microbial growth was inhibited, the solution in the well remained clear after incubation with MTT.

For the antimicrobial activity determination (inhibition zones and CMIs), each experiment was carried out simultaneously three times under the same conditions. The obtained diameters of inhibition zones reported in mm and the MIC values reported in μg·mL^{-1} were quite similar, and the reported results are the average of the three experiments.

4. Results and Discussion

The addition of a methyl magnesium iodide to phthalimides 2 already synthesized by our group [15, 16] in Et_2O for 2 h gave compounds 3a–d in good yields. The resulting compounds 3 were immediately treated with PTSA in toluene at room temperature for 30 mn to yield compounds 4 in good yields Scheme 1.

The molecular structures and purity of the newly synthesized compounds were identified by NMR (^{1}H and ^{13}C), FTIR, and elemental analysis (CHN).

For the synthesis of the target compounds 4, we decided also to explore the use of 2-acetylbenzoic acid as starting material. Thus, in toluene with PTSA, 2-acetylbenzoic acid was added to a primary amine in a microwave reactor at 110°C for 1 hour, affording the corresponding 3-methylene isoindolinones with a good yield Scheme 2.

Here, we synthesized compounds 4 by both methods, the conventional heating method and the microwave irradiation technique (200 W). We remark by applying the second method, and we get a higher yield and rapid reaction time compared to the convection heating method.

The resulting compound 4 was then treated with bis(pinacolato)diboron in various catalysts, bases, and solvents to give compounds 5. We chose the reaction of (4-methoxybenzyl)-3-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)isoindolin-1-one (4e) and $B_2(pin)_2$ as a model reaction to evaluate the conditions for this Cu-catalyzed hydroboration reaction Scheme 3.

Firstly, we explored the reaction with different bases, $Ba(OH)_2$, K_3PO_4, Li_2CO_3, Na_2CO_3, K_2CO_3, Cs_2CO_3, Na_2HPO_4, and KH_2PO_4, at room temperature Table 1.

According to Table 1, we observe that the presence of a weaker base (Li_2CO_3, Na_2CO_3, and K_2CO_3), in particular cesium carbonate, gave us the best results (Ed = 48%). Then, we decide to use cesium carbonate to improve the hydroboration process.

The reactions were then tested in various solvents such as THF, Et_2O, IPrOH, CH_2Cl_2, MeOH, and toluene (entries 1–7 in Table 2).

In the case of solvents such as Et_2O and MeOH, the Ed of the hydroboration reaction was 44 and 48%, respectively (entries 1 and 2). By replacing methanol with toluene, the target compound was obtained with an Ed = 34%; thus, methanol is not only a solvent but also a hydrogen donor. By using both EtOH and i-propanol, the yields were reduced to 46% and 32%, respectively (entries 2-3). We conclude that methanol is the most suitable choice as a solvent for the hydroboration reaction.

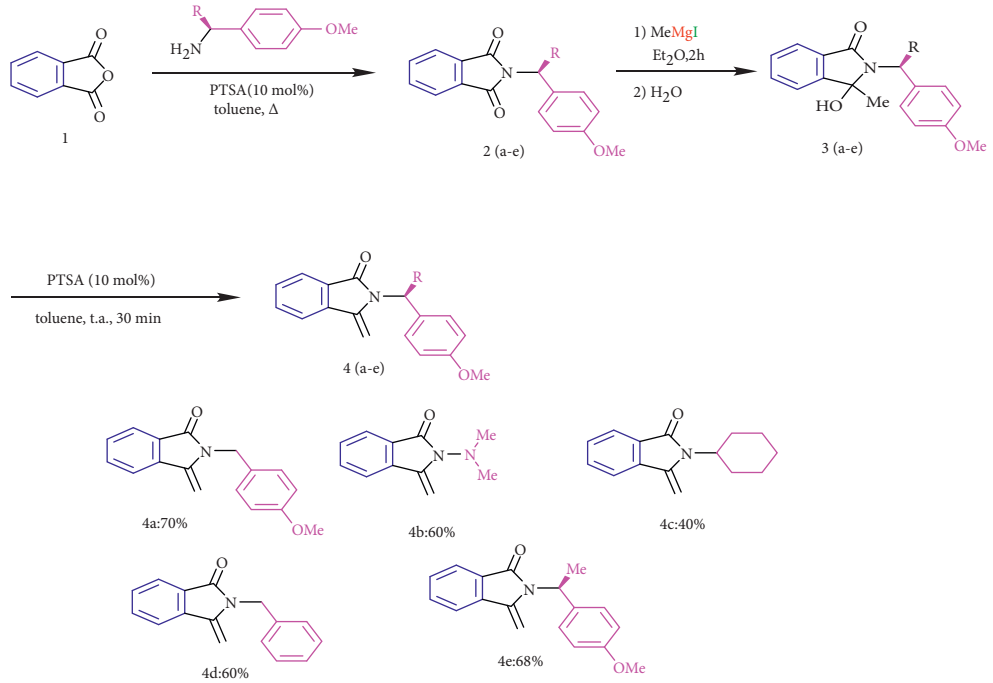
We aim to study the effect of the catalyst on the hydroboration process, and we selected the following catalysts: two commercial [(SIPr)CuCl] and [(SIMes)CuCl] and two prepared (NHCCuCl (1) and NHCCuCl (2)) in our laboratory as shown in Figure 1.

We started with the synthesis of both complexes (NHCCuCl (1) and NHCCuCl (2)). Their synthesis was performed in three steps. The first step of this reaction consisted of the addition of benzyl bromide in the basic medium at reflux to benzimidazole or imidazole. A first intermediate was isolated and purified with very good yields of 90 and 83%, respectively. The second step consisted of the condensation of benzyl chloride on the previously obtained products under reflux at toluene for 1 h in the presence of Cu_2O under microwave. The choice of the benzyl halide is important because the halogen present will act as a copper ligand in the final product. Once the N-heterocyclic carbenes were formed, the last step consisted in binding them to the metal chosen as a catalyst, here copper in toluene under microwaves at 150°C, thus allowing obtaining the two-targeted complexes [NHC-Cu-Cl] with yields of 96 and 80% after isolation of the products Scheme 4.

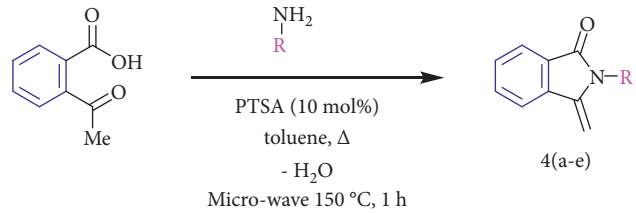
The ^{1}H NMR spectra of the benzimidazolium salts exhibit the signal for the NCHN proton at 11.5 and 11.3 ppm, respectively. In the ^{13}C NMR spectra, the characteristic signal of the imino carbon (NCHN) was detected as typical singlets at 142.5 and 143.2 ppm, respectively. These NMR values are in line with those found for other benzimidazolium salts in literature [17, 18]. The formation of the benzimidazolium salts was also evidenced by their IR spectra, which showed CN bond vibration at 1555 and 1550 cm^{-1} for the respective CN bond vibrations. All compounds showed good solubility in water and common organic solvents, such as dichloromethane, chloroform, methanol acetonitrile, and N, N-dimethylformamide.

The objective of this optimization is to significantly improve the diastereoselectivity of the reaction. The obtained results are presented in Table 3.

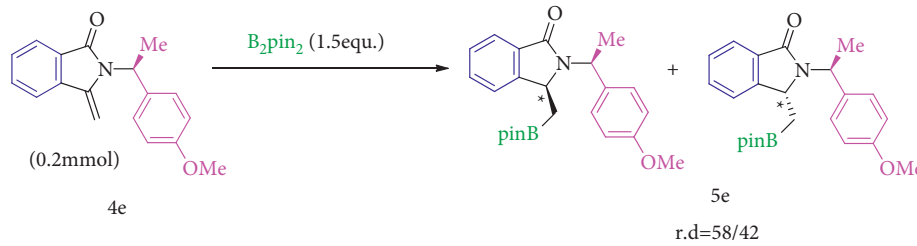
We observe that the change of catalyst influenced the reaction time. The hydroboration reaction using both commercial complexes shows a better Ed in 2 h, whereas both prepared complexes gave an Ed of 48% and 44%, respectively, in 15 mn. We now want to observe the influence of the catalyst charge on the hydroboration reaction, and the results are given in Table 4.



Scheme 1: Protocol synthesis of compounds 4.



Scheme 2: Synthesis of enamides 4 under microwave.



Scheme 3: Optimization of the reaction of hydroboration of enamides 5e and $B_2(pin)_2$.

Table 1: Influence of the base on the hydroboration reaction[a].

Base (0, 1 equ)	Pka	t	Conv (%)	Ed[c] (%)	Yield[b] (%)
Ca $(OH)_2$	14	15 min	100	38	100
Ba $(OH)_2$	14	15 min	100	38	100
K_3PO_4	12	15 min	100	42	100
Li_2CO_3	10	15 min	100	44	100
Na_2CO_3	10	15 min	100	44	100
K_2CO_3	10	15 min	100	44	100
Cs_2CO_3	10	15 min	100	48	100
Na_2HPO_4	7	15 min	100	42	100
KH_2PO_4	2	12 h	0	ND	100

[a]Reaction conditions: 5 (0.2 mmol), $B_2(pin)_2$ (1.5 equiv) NHCCuCl (1) (10 mol%), MeOH (1 mL), and r.t. [b]isolated yield. [c]The Ed (%) was determined by ^1H NMR analysis.

Table 2: Effect of the solvent on the hydroboration reaction[a].

MeOH	Solvent (1 ml)	t	Conv (%)	Ed[c] (%)	Yield[b] (%)
—	MeOH	15 min	100	48	100
—	EtOH	15 min	100	46	100
—	i-PrOH	15 min	100	32	100
2 equ	Et_2O	2 h	100	44	100
2 equ	THF	30 min	100	42	100
2 equ	Toluene	12 h	50	34	35
2 equ	CH_2Cl_2	2 h	100	22	100

[a]Reaction conditions: NHCCuCl (1) (10 mol%), Cs_2CO_3 (0.1 equiv), MeOH (1 ml), and r.t. [b] isolated yield. [c]The Ed (%) was determined by ^{1}H NMR analysis.

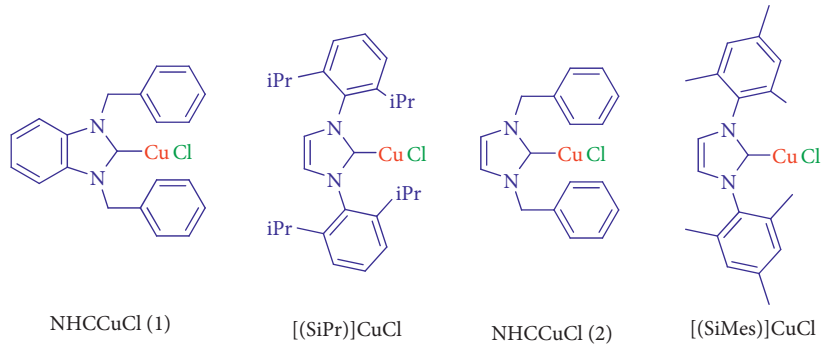
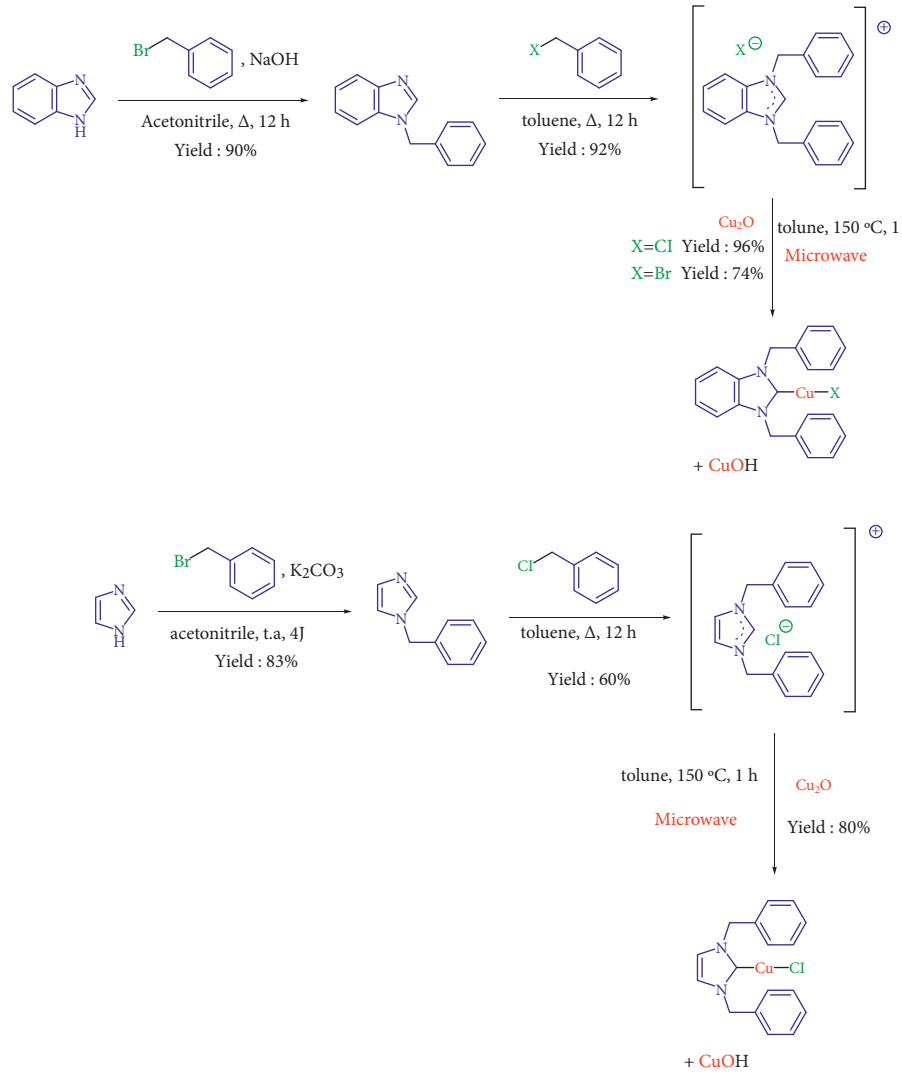


Figure 1: Structures of the Cu complexes.



Scheme 4: Protocol synthesis of Cu complexes.

Table 3: The effect of catalyst on the hydroboration reaction[a].

Cat. (10 mol%)	*T*	t	Conv (%)	Ed[c] (%)	Yield[b] (%)
NHCCuCl (1)	t.a	15 min	100	48	100
NHCCuCl (2)	t.a	15 min	100	44	100
[(SIPr)CuCl]	t.a	2 h	50	54	100
[(SIMes)CuCl]	t.a	2 h	50	58	100

[a]Reaction conditions: 5 (0.2 mmol), $B_2(pin)_2$ (1.5equiv) MeOH (1 mL), Cs_2CO_3 (0.1equi), and r.t. [b]isolated yield. [c]The Ed (%) was determined by ^1H NMR analysis.

Table 4: Effect of the catalytic charge on the hydroboration reaction[a].

[(SIMes)CuCl] (mol%)	*T*	*T*	Conv (%)	Ed[c] (%)	Yield[b] (%)
10	t.a.	2 h	100	58	100
5	t.a.	2 h	100	36	100
1	t.a.	2 h	100	38	100
0, 1	t.a.	2 h	100	38	100
0	t.a.	2 h	<5	ND	

[a]Reaction conditions: 5 (0.2 mmol), $B_2(pin)_2$ (1.5 equiv) MeOH (1 mL), Cs_2CO_3 (0.1 equiv), and r.t. [b]isolated yield. [c]The Ed (%) was determined by ^1H NMR analysis.

Table 5: Structures of compounds 6.

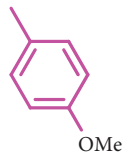
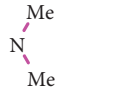
Entry	*R*	Compound	Yield (%)
1		6a	65
3		6b	40
4		6c	35
5		6d	42
6		6e	100

Table 5 shows that the conversion is always total in 2 h. However, we observed an important change in the diastereoselectivity; when we decrease the amount of catalyst, the diastereoisomeric ratio also decreases; in order to obtain interesting results in terms of selectivity, we must therefore keep a certain catalytic load during our reaction.

The scope of this copper-catalyzed hydroboration of various aryl alkene substrates with $B_2(pin)_2$was then examined under optimized conditions, as shown by the results summarized in Scheme5 and Table 5.

The results summarized in Table 5 show that we obtained compound 6 with a yield between 35 and 100%.

The mechanism proposed for this reaction of hydroboration was given in the following Scheme 6.

The hydroboration was postulated to be initiated by the Ligand-Cu-Bpin catalyst. A copper-boryl complex was integrated into the alkenes. The incorporated product was then immediately protonated by MeOH to produce the maximum product while regenerating the copper-ligand involute, which reacted with $B_2(pin)_2$ to participate in the cycle.

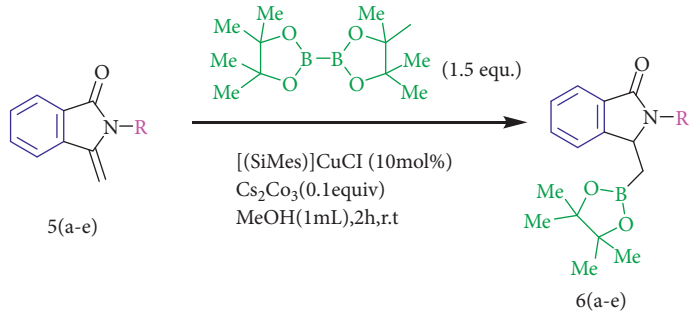
The obtained compounds 5-6 were then subject to the antimicrobial activities.

4.1. 4-Antimicrobial Activity of Phthalimides 5-6. The in vitro antimicrobial activities of compounds 5-6 were evaluated for in vitro antimicrobial activity by the well diffusion method. The synthesized compounds were screened against four indicator microorganisms: the two Gram-positive bacteria *L. monocytogenes* ATCC 1911 and *S. aureus* ATCC 6538, the Gram-negative bacterium *S. typhimurium* ATCC 14028, and the fungus *C. albicans* (ATCC 90028). As shown in Table6, all compounds exhibit considerable activity against the tested microorganisms. The results obtained by these tests showed that 5c and 5d are the most active compounds against *S. aureus* ATCC 6538 with inhibition zones of 16 and 15 mm, respectively. Additionally, 6b was found to be most active against all strains. On the other hand, compounds 5-6 were also tested for antifungal activity against *C. albicans* (ATCC 90028). All compounds 5 show that antifungal with inhibition zones of 20, 22, 23, 24, and 21 mm have antifungal activity against *C. albicans* (ATCC 90028), respectively, compared to the standard antifungal drug.

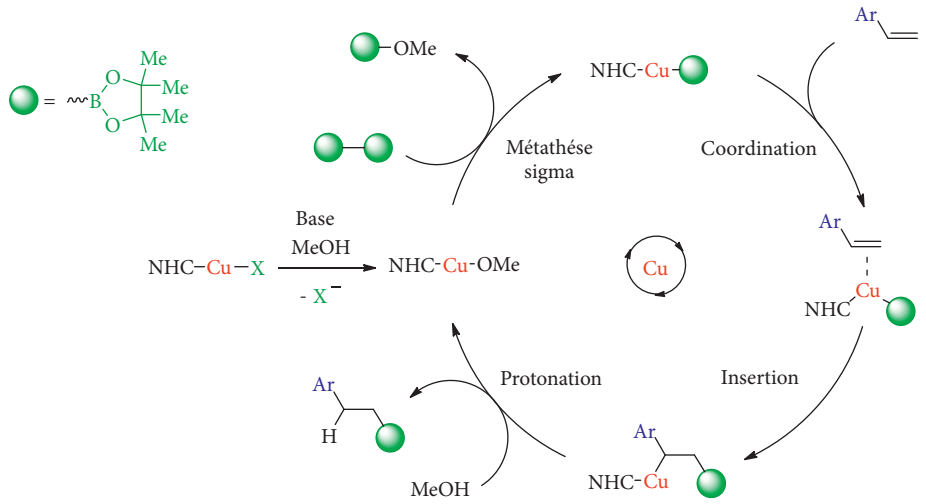
All compounds 6 have antifungal activity against *C. albicans* (ATCC 90028) with inhibition zones of 25, 22, 23, 21, and 20 mm.

The results displayed that the specific molecules have antimicrobial activity. Thus, compound derivatives 5-6 have been found to have higher and potent antimicrobial activity for a long time [18].

Minimum inhibitory concentration (MIC) of the synthesized compounds 5-6 and the standards ampicillin were assessed by microdilution method against *L. monocytogenes*,



Scheme 5: Protocol synthesis of compounds 6.



Scheme 6: Proposed mechanism for the copper-catalyzed hydroboration reaction.

Table 6: Antibacterial inhibition zones of compounds 5-6 (zone of bacterial inhibition measured in mm).

Tested compounds (300 μg/mL)[#]	*Listeria monocytogenes* ATCC 1911	*Staphylococcus aureus* ATCC 6538	*Salmonella typhimurium* ATCC 14028	*C. albicans (ATCC 90028)* (40 μg·mL^{-1})[#]
5a	10	14	11	20
5b	12	11	12	22
5c	16	16	12	23
5d	14	15	14	24
5e	13	14	11	25
6a	12	11	12	21
6b	16	16	13	22
6c	12	13	12	23
6d	13	10	10	21
6e	15	15	13	20
Ampicillin[a]	18	18	21	—
Fluconazole[b]	—	—	—	19

*Values are mean of three replicates (standard error ± 1 μg·mL^{-1}). [#]Concentration of solutions for respective activities. [a]Ampicillin was used as a standard against bacterial species (100 μg·mL^{-1}). [b]Fluconazole was used as a standard against fungi species (10 μg·mL^{-1}).

Table 7: Minimum inhibitory concentration (MIC) of compounds 5-6 expressed in mg/ml, against *L. monocytogenes*, *S. typhimurium*, and *S. aureus*.

Tested compounds (300 μg/mL)[#]	*Listeria monocytogenes* ATCC 1911	*Staphylococcus aureus* ATCC 6538	*Salmonella typhimurium* ATCC 14028
5a	0.156	0.136	0.126
5b	0.147	0.146	0.136
5c	0.312	0.211	0.310
5d	0.322	0.212	0.215
5e	0.332	0.215	0.323
6a	1.25	1.26	1.20
6b	2.5	2.23	2.3
6c	0.625	0.615	0.525
6d	1.25	1.22	0.915
6e	2.5	2.1	0.923
Ampicillin[a]	0.002		

S. Typhimurium, and *S. aureus*. *Ampicillin* was used as a standard drug for comparison (Table 7). The compound 5a is the most active notably against *S. aureus* and able to inhibit this pathogen at MIC value of 0.0048 mg/ml.

The MIC values range from 0.312 to 2.5 (μg/mL) against L. *monocytogenes*, from 2.1 to 0.136 (μg/mL) against *S. aureus*, from 0.126 to 0.923 (μg/mL) against *S. typhimurium*.

5. Conclusion

In conclusion, we have described an efficient and explicit method that has been developed for copper-catalyzed hydroboration of aryl alkenes at room temperature. The reaction can allow various functional groups; the procedure is simple to carry out as a Gram-scale reaction with less than 10% catalyst. All obtained compounds 5-6 presented significant inhibitory activity against the tested blood-borne pathogens and clinical microorganisms.

Data Availability

The data that support the findings of this study are available in the supplementary material of this paper.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

Hamida Jelali contributed to investigation. Lamjed Mansour, Jameel Al-Tamimi, and Waleed Koko contributed to biological activities. Naceur Hamdi and Sadeq M. Al-Hazmy contributed to conceptualization, original draft preparation, reviewing and editing, formal analysis, and artwork. Eric Deniau contributed to methodology, investigation, conceptualization, and original draft preparation. Mathieux Sauthier contributed to resources, reviewing and editing, visualization, formal analysis, and artwork. Naceur Hamdi contributed to supervision, data curation, validation, and project administration.

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Supplementary Materials

The structures of compounds were established through NMR (1 H and 13C). (*Supplementary Materials*)

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