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# An expedient approach to enhance Mizoroki–Heck coupling reaction by infrared irradiation using palladacycle compounds

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**An alternative and environmentally friendly strategy to promote the Mizoroki–Heck cross-coupling reaction by the use of infrared irradiation using palladacycles as precatalysts is reported. Coupling products are obtained in high yield and short reaction time. A comparison with the classical use of reflux conditions, and commercial sources of palladium complexes, shows the advantages of this new alternative for promoting coupling reactions. Copyright © 2015 John Wiley & Sons, Ltd.**

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**Keywords:** palladacycles; Mizoroki–Heck reaction; infrared irradiation

## Introduction

Methodologies based on non-conventional sources of heating such as microwaves, ultrasound, flow chemistry and micro-reactors have attracted growing attention in recent years.[1] In particular, microwave irradiation under controlled conditions is an invaluable technology that has enormous applications in various areas, including academic and industrial research.[2] This methodology has been applied in organic synthesis and catalysis,[3] and cross-coupling reactions are no exception.[4] The Mizoroki–Heck coupling reaction involving palladium complexes as catalysts is by far one of the most powerful synthetic strategies for generating new C–C bonds.[5] This coupling reaction has a wide variety of applications including total synthesis of natural products,[6] fine chemicals syntheses,[7] bioorganic chemistry,[8] material science and industrial applications,[9] among others. One of the principal features of this reaction is the great tolerance to a diversity of functional groups such as amines, hydroxyls, aldehydes, ketones, carboxylic acids, esters, nitriles, etc., without protection–deprotection methodologies.[10] A diversity of catalyst or precatalyst systems based on palladium compounds with a broad range of structural features exists, with emphasis on properties such as thermal and moisture stability[11] and always enhancing catalytic aspects related to efficiency and activity.

In this context, cyclopalladated complexes are important starting materials in organometallic chemistry.[12] Palladacycles have attracted great interest due to their applications in many areas, including organic synthesis,[13,14] material science,[15] biologically active compounds[16] and as building blocks in macromolecular chemistry.[17] Cyclopalladated complexes exhibit a superior catalytic efficiency in cross-coupling reactions.[18] In particular, the phospha-palladacycles have found application in a wide variety of palladium-catalyzed reactions.[19] Phosphine ligands, especially the electron-rich phosphines, are often toxic and sensitive to air and moisture; also phosphinite palladacycles exhibit better activity than structurally similar phosphite and phosphine complexes.[14a)] Consequently, the search for easily handled, active, thermally stable and low-cost catalysts has caused the development of phosphine-free palladium catalysts such as palladium complexes bearing nitrogen-donor ligands.[20] In addition, extensive studies have shown the efficiency and robustness of palladacycles in performing Mizoroki–Heck coupling reaction.[21]

Infrared irradiation is an energy source typically used for spectroscopic applications and its use as non-conventional heating has been scarcely explored in comparison to microwaves. Some examples in organic synthesis show that infrared irradiation efficiently promotes condensation reactions,[22] oxidation reactions,[23] heterocyclic compound syntheses[24] and Diels–Alder reactions,[25] among others. To the best of our knowledge, there is no precedent in the literature regarding the use of infrared irradiation in C–C coupling reactions.

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We herein report a comparative study of the Mizoroki–Heck reaction promoted by this non-conventional heating, using various air-stable palladacycle complexes.

## Experimental

### General considerations

All operations were carried out in open atmosphere. Column chromatography was performed using 70–230 mesh silica gel. All reagents and solvents were obtained from commercial suppliers and used without further purification. All compounds were characterized using IR spectra, recorded with a Perkin-Elmer 283B or 1420 spectrophotometer, by means of film and KBr techniques, and all data are expressed in wavenumbers ($cm^{-1}$). Melting points were obtained with a Melt-Temp II apparatus and are uncorrected. NMR spectra were measured with a Varian Eclipse +300 and Varian +500 MHz, using $CDCl_3$ and DMSO-$d_6$ as solvents. Chemical shifts are in ppm ($\delta$), relative to tetramethylsilane. MS-FAB and MS-EI spectra were obtained with a JEOL SX 102A. The values of the signals are expressed in mass/charge units ($m/z$), followed by the relative intensity with reference to a 100% base peak.

The equipment used for irradiation with IR energy was created by employing an empty cylindrical metal vessel in which an Osram lamp (bulb model Thera-Therm, 250 W, 125 V) was inserted (Fig. 1). This lamp is a special short-wave IR lamp (IR-A) for use in body care and wellness applications, with a maximum radiation at a wavelength of about 1100 nm. The lamp instantly emits a full thermal output as soon as it is switched on. For controlling the temperature, a Digi-Sense variable-time power controller was used. This time controller turned the output load on and off and then repeated the cycle. Although all the reactions were performed in open atmosphere, this arrangement also allows the use of inert conditions.

**Figure 1.** Infrared equipment.

Microwave irradiation experiments were performed using an Anton Paar Monowave 300 single-mode microwave reactor. The reaction temperature was monitored using an internal fiber-optic temperature probe (ruby thermometer) protected by a borosilicate immersion well inserted directly into the reaction mixture. Reaction times refer to the hold time at the desired set temperature and not to the total irradiation time. Pressure sensing was achieved using a hydraulic sensor integrated in the swiveling cover of the instrument. A reusable 10 ml Pyrex vial was sealed with poly(ether ether ketone) (PEEK) snap caps and standard polytetrafluoroethylene (PTFE)-coated silicone septa. Reaction cooling was performed using compressed air automatically after the heating period had elapsed.

### General experimental methods

*Synthesis of ligand* ***1***

A mixture of *N*,*N*-diphenylhydrazine hydrochloride (570 mg, 2.6 mmol) and 2-pyridinecarboxaldehyde (280 mg, 2.6 mmol) in 10 ml of methanol was stirred for 24 h at room temperature. The resulting solution was evaporated to dryness and the crude product was chromatographed on silica gel. Elution with hexane–AcOEt (99:1 v/v) allowed the product to be recovered. The pure product was obtained as a yellow solid. Yield 640 mg (84%); m.p. 94–96°C. Selected FT-IR ($\nu$, $cm^{-1}$): 3052 and 3006 (H-Csp2), 1568 (C=N), 1492 (C=$C_{Ar}$). MS-EI $m/z$ (%): 273 $[M]^+$ (77), 195 $[M - C_6H_6]^+$ (23), 168 $[M - C_{12}H_{10}N]^+$ (100). $^1$H NMR (300 MHz, $CDCl_3$, $\delta$, ppm): 7.10 (dd, 1H, H-4, $J_{H4H3}$ = 8.1 Hz, $J_{H4H5}$ = 2.7 Hz), 7.18 (d, 4H, H-8, $J_{H8H9}$ = 5.1 Hz), 7.21 (d, 2H, H-10, $J_{H10H9}$ = 5.1 Hz), 7.30 (s, 1H, H-6), 7.41 (dd, 4H, H-9, $J_{H9H8}$ = 5.1 Hz, $J_{H9H10}$ = 5.1 Hz), 7.68 (dd, 1H, H-3, $J_{H3H4}$ = 8.1 Hz, $J_{H3H2}$ = 4.8 Hz), 8.09 (d, 1H, H-2, $J_{H2H3}$ = 4.8 Hz), 8.44 (d, 1H, H-5, $J_{H5H4}$ = 2.7 Hz). $^{13}$C NMR (75 MHz, $CDCl_3$, $\delta$, ppm): 119.4 (C-2), 122.2 (C-4), 122.4 (C-8), 124.9 (C10), 129.8 (C-9), 135.8 (C-6), 136.1 (C-3), 143.0 (C-7), 148.9 (C-5), 155.3 (C-1).

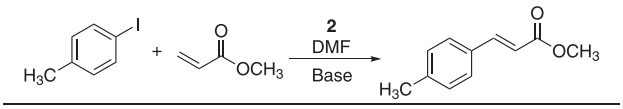
*Synthesis of complex* ***2***

A mixture of $PdCl_2$ (64 mg, 0.36 mmol) and NaCl (42 mg, 0.72 mmol) in 10 ml of methanol was stirred for 1 h. Ligand **1** (100 mg, 0.36 mmol) was added to the solution and the mixture was stirred at room temperature for 72 h, to give an orange solid, which was recovered by filtration, washed with cold methanol and finally dried in air. The pure product was obtained as an orange solid. Yield 120 mg (90%); m.p. 280°C. Selected FT-IR ($\nu$, $cm^{-1}$): 3055 (H-Csp2), 1590 (C=N), 1489 (C=$C_{Ar}$). MS-FAB+ $m/z$ (%): 413 $[M]^+$ (3), 378 $[M - Cl]^+$ (15), 273 $[M - PdCl]^+$ (15), 195 $[M - C_6H_5PdCl]^+$ (5), 168 $[M - C_6H_5N_2PdCl]^+$ (58). $^1$H NMR (500 MHz, DMSO-$d_6$, $\delta$, ppm): 5.70 (d, 1H, H-11, $J_{H11H10}$ = 6.5 Hz), 6.59 (dd, 1H, H-10, $J_{H10H11}$ = 6.5 Hz, $J_{H10H9}$ = 6.0 Hz), 6.78 (dd, 1H, H-9, $J_{H9H10}$ = 6.0 Hz, $J_{H9H8}$ = 7.5 Hz), 7.25 (d, 1H, H-8, $J_{H8H9}$ = 7.5 Hz), 7.35 (s, 1H, H-6), 7.53 (d, 1H, H-16, $J_{H16H15}$ = 7.5 Hz), 7.55 (d, 2H, H-14, $J_{H14H15}$ = 6.5 Hz), 7.62 (d, 1H, H-2, $J_{H2H3}$ = 7.5 Hz), 7.66 (dd, 1H, H-4, $J_{H4H3}$ = 7.5 Hz, $J_{H4H5}$ = 4.5 Hz), 7.73 (dd, 2H, H-15, $J_{H15H14}$ = 6.5 Hz, $J_{H15H16}$ = 7.5 Hz), 7.95 (dd, 1H, H-3, $J_{H3H2}$ = 7.5 Hz, $J_{H3H4}$ = 7.5 Hz), 8.31 (d, 1H, H-5, $J_{H5H4}$ = 4.5 Hz). $^{13}$C NMR (175 MHz, DMSO-$d_6$, $\delta$, ppm): 109.9 (C-5), 120.7 (C-3), 124.7 (C-2), 125.2 (C-11), 125.5 (C-10), 128.8(C-15), 130.6 (C-8), 131.2 (C-14, C-16), 133.9 (C-6), 134.4 (C-12), 135.4 (C-9), 140.3 (C-1), 148.4 (C-5), 156.5 (C-7), 157.1 (C-13).

*Synthesis of palladium complexes* ***3b*** *and* ***3b***

The palladium complexes **3b** and **3b** were synthesized and characterized as described in the literature.[26]

**Table 1.** Evaluation of catalytic conditions for Mizoroki–Heck cross-coupling of 4-iodotoluene with methyl acrylate using complex **2**




| Entry[a] | [Pd] (mol%) | Time (min)[b] | Base | Yield (%)[c] | TON | TOF |
|---|---|---|---|---|---|---|
| 1 | 0.1 | 60 | $K_3PO_4$ | 90 | 900 | 900 |
| 2 | 0.05 | 60 | $K_3PO_4$ | 97 | 1940 | 1940 |
| 3 | 0.01 | 60 | $K_3PO_4$ | 77 | 7700 | 7700 |
| 4 | 0.05 | 60 | $Na_3PO_4$ | 90 | 1800 | 1800 |
| 5 | 0.05 | 60 | $Li_3PO_4$ | 50 | 1000 | 1000 |
| 6 | 0.05 | 60 | $K_2CO_3$ | 86 | 1720 | 1720 |
| 7 | 0.05 | 60 | AcOK | 87 | 1740 | 1740 |

[a]All reactions were performed with 2 mmol of 4-iodotoulene, 3.3 mmol of methyl acrylate, DMF (5 ml), 2.5 mmol of base at 140°C.
[b]Reaction time based on total consumption of aryl iodide determined by TLC.
[c]Isolated yields after extraction with hexane.

*General procedure for Mizoroki–Heck coupling reactions under conventional thermal heating*

In a 50 ml round-bottomed flask, 4-iodotoluene (2 mmol), methyl acrylate (3.3 mmol) and base (2.5 mmol) were placed in 5 ml of DMF, and then the palladium complex **2** was added. The reaction mixture was refluxed for the time stated in Table 1 at 140°C. The reaction mixture was poured into water (10 ml) and extracted with hexane (3 × 10 ml). The combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, to give (*E*)-methyl *p*-methylcinnamate in yields stated in Table 1.

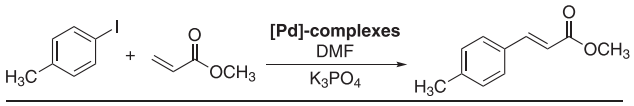
*General procedure for Mizoroki–Heck coupling reactions under infrared irradiation*

In a 50 ml round-bottomed flask, a mixture of aryl iodide (2 mmol), methyl acrylate (3.3 mmol) and base (2.5 mmol) was placed in 5 ml of DMF, and then the palladium complex was added. The reaction mixture was irradiated using an Osram lamp (bulb model Thera-Therm, 250 W, 125 V, see Fig. 1) for the time stated in Tables 2–4 at 140°C. The reaction mixture was poured into water (10 ml) and extracted with ether or hexane (3 × 10 ml). The combined organic layers were dried over anhydrous sodium sulfate. The crude product was finally purified by flash column chromatography on silica-gel to give the isolated products in yields stated in Tables 2–4.

*General procedure for Mizoroki–Heck coupling reactions under microwave irradiation*

A 10 ml microwave-transparent process vial was filled with 4-iodotoluene (2 mmol), methyl acrylate (3.3 mmol), base (2.5 mmol), 5 ml of DMF and the palladium complex. The vial was sealed with PEEK snap caps and standard PTFE-coated silicone septa. The reaction mixture was then exposed to microwave heating for the time stated in Table 2 at 160°C. The reaction mixture was poured into water (10 ml) and extracted with hexane (3 × 10 ml). The combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed *in vacuo*, to give (*E*)-methyl *p*-methylcinnamate in yields stated in Table 2.

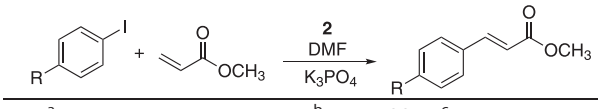
**Table 2.** Evaluation of catalytic conditions for Mizoroki–Heck cross-coupling of 4-iodotoluene with methyl acrylate using complexes **2**, **3a** and **3b**




| Entry[a] | Complex | Type of heating | Time (min)[b] | Yield (%)[c] | TON | TOF |
|---|---|---|---|---|---|---|
| 1 | **2** | Conventional[d] | 60 | 97 | 1940 | 1940 |
| 2 | **3a** | Conventional[d] | 360 | 90 | 1800 | 300 |
| 3 | **3b** | Conventional[d] | 720 | 85 | 1700 | 141 |
| 4 | **2** | Infrared[e] | 15 | 98 | 1960 | 7840 |
| 5 | **3a** | Infrared[e] | 120 | 96 | 1920 | 960 |
| 6 | **3b** | Infrared[e] | 180 | 87 | 1740 | 580 |
| 7 | **2** | Microwave[f] | 10 | 94 | 1880 | 11280 |
| 8 | **3a** | Microwave[f] | 90 | 89 | 1780 | 1186 |

[a]All reactions were performed with 2 mmol of 4-iodotoulene, 3.3 mmol of methyl acrylate, DMF (5 ml), 2.5 mmol of $K_3PO_4$ and [Pd] = 0.05 mol%.
[b]Reaction time based on total consumption of aryl iodide determined by TLC.
[c]Isolated yields after extraction with hexane.
[d]Reaction conducted at 140°C.
[e]Reaction conducted at 140°C, under infrared irradiation using an Osram lamp (bulb model Thera-Therm, 250 W, 125 V). For controlling the temperature, a Digi-Sense variable-time power controller was used.
[f]Reaction conducted under microwave irradiation at 160°C using an Anton Paar Monowave 300 single-mode microwave reactor. For further information see the Experimental section.

**Table 3.** Scope of Mizoroki–Heck cross-coupling using complexes **2** and infrared irradiation




| Entry[a] | R | Time (min)[b] | Yield (%)[c] | TON | TOF |
|---|---|---|---|---|---|
| 1 | $NH_2$ | 15 | 99 | 1980 | 7920 |
| 2 | $CH_3O$ | 15 | 99 | 1980 | 7920 |
| 3 | $CH_3$ | 15 | 98 | 1960 | 7840 |
| 4 | *N*-Pyrrole | 30 | 91 | 1820 | 3640 |
| 5 | H | 60 | 98 | 1960 | 7840 |
| 6 | Br | 60 | 99 | 1980 | 1980 |
| 7 | $CH_3COO$ | 30 | 95 | 1900 | 3800 |
| 8 | $CF_3$ | 150 | 99 | 1980 | 792 |
| 9 | $NO_2$ | 60 | 98 | 1960 | 1960 |
| 10 | $CH_3CO$ | 150 | 98 | 1900 | 760 |

[a]All reactions were performed with 2 mmol of 4-aryl iodide, 3.3 mmol of methyl acrylate, DMF (5 ml), 2.5 mmol of base and [complex **2**] = 0.05 mol% at 140°C.
[b]Reaction time based on total consumption of aryl iodide determined by TLC.
[c]Isolated yield after purification.

The purified product was identified by means of determination of melting point and from $^1$H NMR and $^{13}$C NMR spectra. The data obtained are consistent with those of the literature.[27]

**Table 4.** Mizoroki–Heck reaction between methyl acrylate and 4-iodotoluene promoted by infrared irradiation and commercial palladium sources

| Entry[a] | Catalytic system | Time (min)[b] | Yield (%)[c] | TON | TOF |
|---|---|---|---|---|---|
| 1 | $Pd(AcO)_2/K_3PO_4$ | 15 | 52 | 1040 | 4160 |
| 2 | $Pd(AcO)_2/Et_3N$ | 15 | 89 | 1780 | 7120 |
| 3 | $PdCl_2(PPh_3)_2/K_3PO_4$ | 15 | 82 | 1640 | 6560 |
| 4 | $PdCl_2(PPh_3)_2/Et_3N$ | 15 | 88 | 1760 | 7040 |
| 5 | $Pd(AcO)_2 + PPh_3/K_3PO_4$ | 5 | 97 | 1940 | 24250 |
| 6 | $Pd(AcO)_2 + PPh_3/Et_3N$ | 5 | 86 | 1720 | 21500 |

[a]All reactions were performed with 2 mmol of 4-iodotoulene, 3.3 mmol of methyl acrylate, DMF (5 ml), 2.5 mmol of base and [Pd] = 0.05 mol% at 140°C.

[b]Reaction time based on total consumption of aryl iodide determined by TLC.

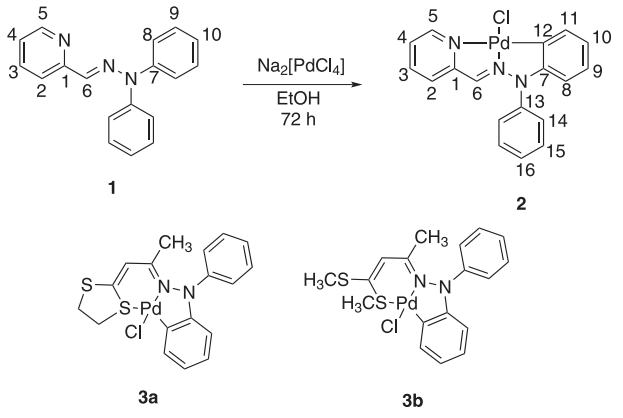
[c]Isolated yield after purification.

*Note.* The entireties of the round flasks used in each coupling reaction were meticulously cleaned with aqua regia to avoid the presence of unseen palladium catalyst.

## Results and discussion

The palladacycle complexes **3a** and **3b** were synthesized following procedures in the literature.[26] In the case of new palladacycle complex **2**, it was prepared by reaction between ligand **1** and $Na_2PdCl_4$ generated *in situ*, to give an orange crystalline solid in 90% yield (Scheme 1). This complex was fully characterized by means of conventional spectroscopic techniques.

Having obtained palladacycles **2**, **3a** and **3b**, we started to explore their catalytic properties as catalytic precursors in the Mizoroki–Heck cross-coupling reaction using conventional thermic conditions (Table 1). Initially, we evaluated the effect of the concentration of the palladium complex on the Mizoroki–Heck reaction between methyl acrylate and 4-iodotoluene. We chose complex **2** as a model precatalyst. The coupling reaction was conducted in refluxing DMF (5 ml) for 1 h using different concentrations of precatalyst **2**. We obtain good yields within 1 h, when 0.1 and 0.05 mol% of **2** are used (Table 1, entries 1 and 2). The influence of a base was also evaluated and five experiments were conducted using $K_3PO_4$, $Na_3PO_4$, $Li_3PO_4$, $K_2CO_3$ and AcOK. The first of these (Table 1, entry 2) gives the best results.




**Scheme 1.** Palladacycle complexes.

Once the catalyst load and base were established, we evaluated complexes **3a** and **3b** under the same catalytic conditions (Table 2, entries 1–3). The yields of coupling product are similar across the series, but complex **2** exhibits a better performance with turnover number (TON) and turnover frequency (TOF) of around $2 \times 10^3$. These results also reveal the good catalytic activity of **2** in Mizoroki–Heck cross-coupling reactions, compared with other palladacycles.[14a)] In all cases, reactions were conducted in open vessels and the coupling product was purified by simple extraction with hexane, yielding almost pure methyl *trans*-cinnamate. With the aim of testing the effectiveness of infrared irradiation for Mizoroki–Heck reaction, we performed this coupling reaction under infrared conditions using complexes **2**, **3a** and **3b** and the same reaction conditions, refluxing DMF and $K_3PO_4$ as base (Table 2, entries 4–6). We observe an important decrease in reaction time for all cases, obtaining the coupling product in excellent yields.

Comparing the activity and efficiency between complexes **2** and **3a** (Table 2, entries 4 and 5), we observe a similar activity with TONs of around $1.9 \times 10^3$, but complex **2** is more efficient as revealed in the TOF values. This behavior can be explained by the presumable hemilability of pyridine fragment of ligand **1** to palladium atom in complex **2**, providing open coordination sites[28] for the possible olefin coordination that could favor the precatalysis step giving the active specie responsible, Pd(0), of the coupling reaction.[29]

In the case of complexes **3a** and **3b**, they involve a similar coordination pattern, complex **3a** being a more rigid system. These palladacycles are very stable and the ligands strongly coordinate to palladium atom as was previously demonstrated.[26,30] We have compared the catalytic performance of complexes **2** and **3a** under microwave irradiation using the same reaction conditions (Table 2, entries 7 and 8). The results obtained no show significant differences in TON values between infrared and microwave irradiation, which means that infrared irradiation can be considered as a new alternative methodology to promote coupling reaction.

To evaluate the scope of these complexes as catalytic precursors in the Mizoroki–Heck coupling reaction assisted by infrared irradiation, a variety of activated and deactivated aryl iodides with methyl acrylate using complex **2** as a precatalyst were examined (Table 3). The results obtained show that complex **2** is highly active and efficient in catalyzing this cross-coupling reaction producing the coupling product with yields ranging from 91 to 99%. In general, the complex tested displays a good performance, being more active when aryl iodides are *para*-substituted by electron-releasing groups. This study shows that the Mizoroki–Heck reaction can be carried out using infrared radiation as a heating source, reducing reaction times and positively increasing the efficiency of this reaction.

As a further step, we also compared these findings with known palladium systems, in order to demonstrate the effectiveness of infrared irradiation in promoting the Mizoroki–Heck cross-coupling reaction (Table 4). Thus, we have tested various commercial palladium compounds in combination with triphenylphosphine (entries 5 and 6) as the most popular ligand used in this kind of reaction, using the same model reaction. These results show that infrared irradiation assisted this coupling reaction, and the catalytic system formed by $Pd(OAc)_2/PPh_3/K_3PO_4$ is the most efficient catalytic system.

## Conclusions

We report for the first time the use of an infrared-assisted methodology for conducting the Mizoroki–Heck cross- coupling reaction.

The results obtained show that this energy source can be considered as an excellent, economical and accessible alternative to promote this coupling reaction, showing advantages such as short reaction times and good yields, facilitating access to a clean, simple and economic methodology comparable to those involving microwaves.

**Acknowledgments**

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