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# Cyrene: a bio-based solvent for the Mizoroki–Heck reaction of aryl iodides†

Naya A. Stini, ‡[a,b] Petros L. Gkizis ‡[a,b] and Christoforos G. Kokotos *[a,b]

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The development of greener and more sustainable methods, as well as the adaptation of already existing protocols to more environmentally friendly procedures, has become crucial for organic synthesis. The introduction and utilization of greener solvents is a very promising alternative, especially when they can replace toxic organic solvents in the known and widely used organic reactions. Cyrene has appeared to be an excellent alternative solvent for a number of organic reactions. In this work, the development of a new, greener and more economical protocol for the Mizoroki–Heck reaction is described, using Cyrene as the green solvent and Pd/C as the palladium catalyst source. A wide substrate scope for the coupling of aryl iodides with acrylamides, acrylates, acrylic acid, acrylonitrile and styrene was demonstrated. The recyclability of Cyrene and the leaching of palladium in the final product were examined in order to enhance the industrial applicability of this protocol. Furthermore, the synthesis of the natural product piperlotine A is reported.

## Introduction

Over the last decade, many researchers worldwide, both in industry and academia, have put great effort into developing green and sustainable protocols that can be easily adjusted in industry. Furthermore, those efforts were targeted to serve the basic principles of green chemistry,[1] and the main concern was to reduce the amount of produced waste and/or use easily recyclable solvents, minimizing the environmental footprint.[2] In addition, the global increase in biodiesel production is directly linked to the increased production and use of biomass-based solvents, such as 2-methyl-tetrahydrofuran (2-Me-THF),[3] glycerol,[4] γ-valerolactone (GVL)[5] *etc.*

Cross-coupling reactions are generally recognized as an important tool in the arsenal of scientists.[6] Numerous C–H functionalization strategies have been developed over the years, offering a powerful alternative in organic synthesis.[7] Even though cross-coupling reactions require small amounts of metal catalyst, thus meeting the principles of green chemistry, many methodologies have been developed in targeting greener and more sustainable procedures. One of the major issues in cross-coupling reactions is the amount of waste generated by the procedure. It is generally admitted that the largest percentage of the produced wastes derives from solvents, so many protocols have been developed using easily recyclable and/or bio-based solvents.[8]

In 2011, Budarin *et al.* introduced an alternative green solvent, derived from levoglucosenone (LGO), under the trade name Cyrene (dihydrolevoglucosenone or 6,8-dioxabicyclo [3.2.1]octanone).[9] This novel biomass-derived solvent attracted the interest of many researchers, since it is considered a sustainable replacement for popular polar organic solvents, such as *N*,*N*′-dimethylformamide (DMF) and *N*-methyl-2-pyrrolidone (NMP), which are described as hazardous, both for the environment and human health.[10] The use of Cyrene instead of hazardous organic solvents manifests the idea presented by Anastas and coworkers, under the title of the Twelve Principles of Green Chemistry.[1] The first introduction of Cyrene as a plausible reaction medium was in 2014, when Sherwood and coworkers introduced it in literature as the reaction medium both in the Menshutkin reaction and in a fluorination reaction.[11] Since then, Cyrene has found numerous applications in organic synthesis.[9b] More specifically, Cyrene has been employed as the reaction medium in several protocols. The dimerization reaction of sinapic ester[12] and the difluoromethylation reaction of heteroarenes or terminal alkynes[13] highlighted the beneficial use of Cyrene instead of other hazardous solvents. In many syntheses of different classes of molecules, such as isothiocyanates,[14] ureas,[15] bipyridines[16] and benzothiazoles,[17] Cyrene outperformed all other suitable

[a]*Laboratory of Organic Chemistry, Department of Chemistry, National and Kapodistrian University of Athens, Panepistimiopolis 15771, Athens, Greece. E-mail: ckokotos@chem.uoa.gr*
[b]*Center of Excellence for Drug Design and Discovery, National and Kapodistrian University of Athens, Panepistimiopolis 15771, Athens, Greece*

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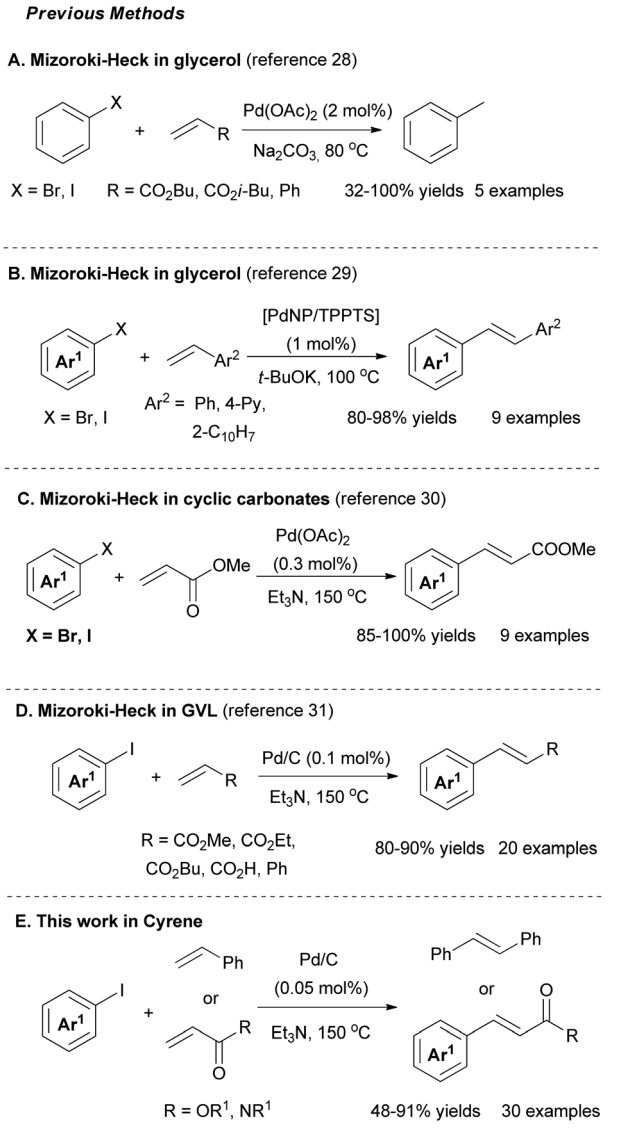
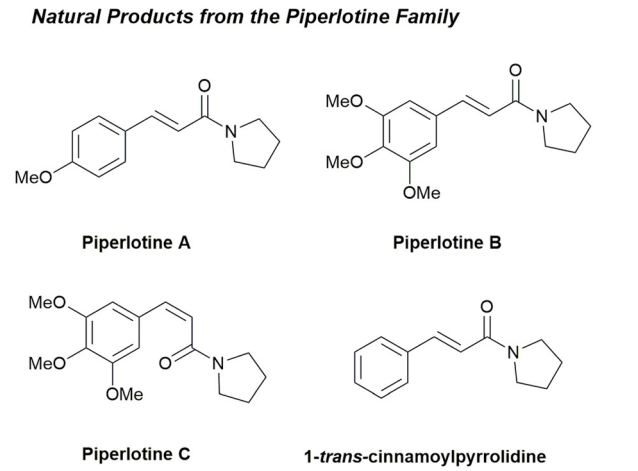
‡Equal contribution.

solvents, offering a greener approach. Its industrial applicability was demonstrated when it was utilized in a large-scale Baylis–Hillman reaction.[18] Furthermore, Cyrene has found a significant place in materials chemistry. Applications in graphene dispersion,[19] membrane fabrication,[20] MOF synthesis,[21] ROM polymerization[22] and lignin processing[10] are mentioned in the literature. Peptide chemistry has also exploited the properties of Cyrene for the replacement of toxic polar solvents that are widely used for amide synthesis.[23] Additionally, numerous research groups exploit it as a compatible solvent for biocatalysis.[24,25] Watson and coworkers were the first who successfully utilized Cyrene as the reaction medium in palladium cross-coupling reactions.[26] In 2016, they studied the Sonogashira reaction using $Pd(PPh_3)Cl_2$ as the palladium catalyst and extensively evaluated the influence of different bases and temperatures on the effectiveness of Cyrene as the reaction medium. In 2018, they studied the Suzuki–Miyaura reaction using $Pd(dppf)Cl_2$ as the catalyst and employed water as a co-solvent to enhance the fluidity of the reaction.[26]

The Mizoroki–Heck cross-coupling reaction is a powerful catalytic method for $C_{sp^2}$–$C_{sp^2}$ bond formation.[27] Generally, aryl halides are coupled with alkenes in the presence of a palladium catalyst.[27] The significance of the Mizoroki–Heck reaction in pharmaceutical industry led many researchers to develop more sustainable versions using bio-based solvents. In 2007, Wolfson and coworkers employed glycerol as solvent for the Mizoroki–Heck reaction, using $Pd(OAc)_2$ as the catalyst (Scheme 1A),[28] while Gomez and coworkers reported a similar procedure, replacing $Pd(OAc)_2$ with palladium nanoparticles stabilized by TPPTS (PdNP/TPPTS) (Scheme 1B).[29] Both methodologies suffered from a narrow substrate scope. In 2014, Clark and coworkers explored the use of cyclic carbonates as an alternative green solvent for the Mizoroki–Heck cross-coupling reaction (Scheme 1C).[30] The great disadvantage of this process, apart from the poor substrate scope, is the prolonged reaction time (24 h). γ-Valerolactone (GVL), another bio-based solvent, has been employed in the Mizoroki–Heck cross-coupling reaction by Vaccaro and coworkers (Scheme 1D).[31] The authors reported the use of commercially available Pd/C as the catalyst and a broad substrate scope, affording the desired products of the substrate in good to excellent yields. The major issue in this protocol appeared to be the level of Pd content detected in the solvent, which in some cases might pose difficulties in the recycling procedure. In addition, the Mizoroki–Heck cross-coupling reaction offers easy access to the construction of the cinnamic backbone, which appears in a variety of naturally occurring products with important medicinal activity.[32] Cinnamic acid derivatives, such as cinnamoyl acids, esters, amides or hydrazides have received much attention in medicinal chemistry. For example, cinnamic amide derivatives from the methanolic extract of *Piper lolot* were found to present anticancer activity (Scheme 2).[33] Furthermore, these cinnamic derivatives showed potent inhibitory activity on platelet aggregation,[34] which is related to the prevention of clot formation in blood.[35]




**Scheme 1** Previous sustainable protocols for the Mizoroki–Heck cross-coupling reaction, and this work.




**Scheme 2** Natural products bearing the cinnamic moiety.

Herein, we present a more sustainable, economical and "greener" approach for the Mizoroki–Heck cross-coupling reaction, employing palladium on carbon as a cheap catalyst alternative and Cyrene as the green solvent. A variety of cinnamate and cinnamide derivatives were prepared. Additionally, we applied our protocol towards the synthesis of naturally occurring products from the piperlotine family, piperlotine A and 1-*trans*-cinnamoylpyrrolidine (Scheme 2). To the best of our knowledge, this is the first reported synthetic approach applying the Mizoroki–Heck conditions for their synthesis.

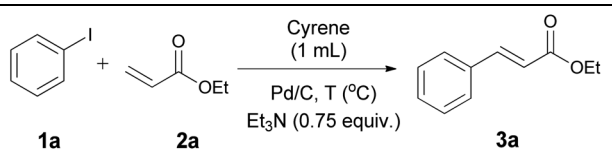
## Results and discussion

We began our investigation by employing iodobenzene (**1a**) and ethyl acrylate (**2a**) as the model reaction (Table 1). Triethylamine (0.75 equiv.) was used as the base, and commercially available palladium on carbon as the cheap catalyst approach. The catalyst choice was based on our initial aim of developing an economical procedure, replacing the more expensive and widely used catalysts such as $Pd(OAc)_2$ and $PdCl_2$, and at the same time is in line with our earlier contribution.[36] Initially, we examined the temperature range of the reaction (Table 1). According to literature, a common range of temperatures for the Mizoroki–Heck cross-coupling reaction varies from 60 to 150 °C,[37] thus we firstly performed the reaction at 50 °C (Table 1, entry 1). The reaction proved to be sluggish, leading to product formation in 5% yield. However, when the temperature was raised to 80 °C, we observed greater product formation (25% by NMR; Table 1, entry 2). This is in accordance with what is described in literature, that temperature is an important factor for the reaction and higher temperatures are likely to afford better results. Indeed, when the reaction was carried out at 150 °C, a significant increase in the yield of up to 75% was obtained (Table 1, entry 3).[38] Furthermore, prolonging the reaction time has an impact on the fluidity of the reaction mass. This can be attributed to the slight excess of acrylate that leads to polymerization pathways and to byproducts derived from Cyrene and/or acrylate. Facing the same problem in 2018, Watson and coworkers proposed the addition of a small amount of water to enhance the fluidity of the reaction.[26b] In our case, the addition of water not only did not alter the reaction's fluidity, but it also led to lower yields. This clearly indicates that water could not be used as an effective co-solvent for the developed Mizoroki–Heck cross-coupling reaction protocol.

Next, we turned our attention to optimizing the equivalents of base used in our protocol.[38] Having chosen triethylamine as the base, we observed that when using 0.5 equiv. of base, the reaction yield was significantly lower after 1 h at 150 °C. On the contrary, increasing the quantity of triethylamine (1 equiv.) increased the yield.[38] We continued employing a variety of bases (Table 2). Sodium acetate afforded a poor yield (27%), while *N*,*N*′-diisopropylethylamine (DIPEA) and $K_2CO_3$ gave comparable results to triethylamine (78% and 86%, respectively; Table 2, entries 1–4). The use of potassium carbonate, apart from affording similar results with triethylamine, offers a great advantage in general. It can be removed from the reaction mixture very easily by filtration. This is highly beneficial especially in pharmaceutical industry. On the other hand, the use of potassium carbonate in our case appeared to have a great disadvantage. In the presence of potassium carbonate, the aldol condensation of Cyrene was favoured. Thus, its use reduced the effective recyclability of Cyrene, which is not acceptable, especially in industrial scale.

Having in hand the optimum reaction conditions, a wide range of aryl iodides was evaluated in the reaction with ethyl acrylate (**2a**) (Scheme 3A). Aryl iodides bearing electron-withdrawing groups reacted well, affording the corresponding ethyl cinnamate derivatives in good to excellent yields (Scheme 3A, **3b–e**, **3i** and **3l**) after 1–2 h at 150 °C. Aryl iodides substituted with electron-donating groups reacted smoothly, affording the corresponding products in good to excellent yields (Scheme 3A, **3f–h**, **3j** and **3k**). It is worth mentioning that aryl iodides bearing a nitro or a methoxy group led to the formation of a mixture of *E*–*Z* isomers, always favoring the

**Table 1** Optimization of the reaction conditions between iodobenzene (**1a**) and ethyl acrylate (**2a**) to identify the optimum temperature for the Mizoroki–Heck reaction in Cyrene

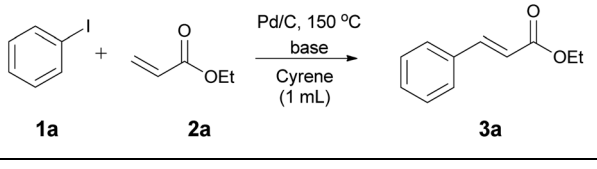



**1a** **2a** **3a**

| Entry | Temperature (°C) | Yield[a] (%) |
|---|---|---|
| 1 | 50 | 5 |
| 2 | 80 | 25 |
| **3** | **150** | **75** |

[a] Yield determined by $^1$H-NMR. The reaction was performed with iodobenzene (**1a**) (204 mg, 1.00 mmol), ethyl acrylate (**2a**) (120 mg, 1.20 mmol), and triethylamine (0.10 mL, 0.75 equiv.) in Cyrene (1 mL), with 10% w/w Pd/C (0.5 mg), at various temperatures.

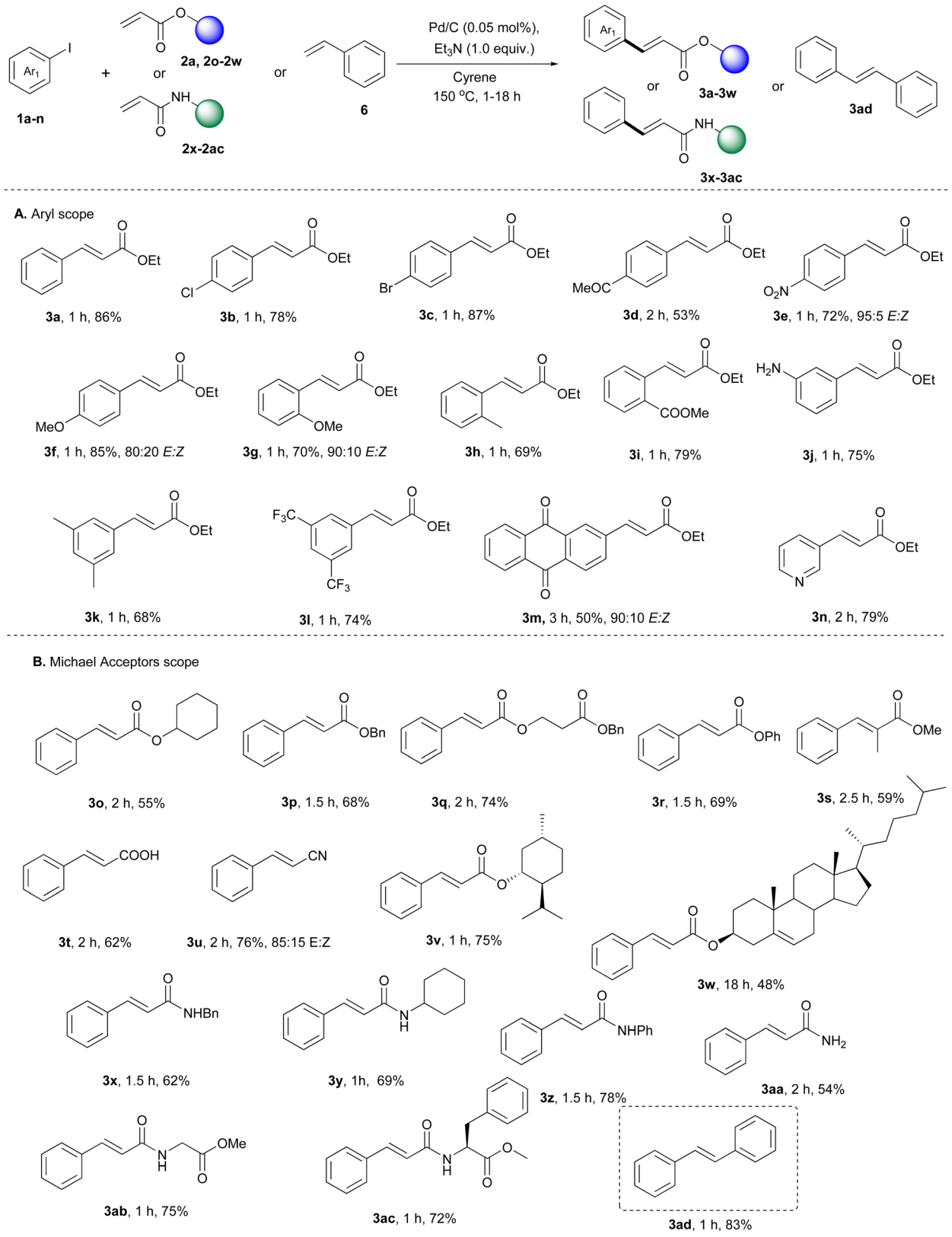
**Table 2** Optimization of the base employed in the Mizoroki–Heck reaction in Cyrene




**1a** **2a** **3a**

| Entry | Base | Yield[a] (%) |
|---|---|---|
| **1** | **$Et_3N$** | **96 (86)** |
| 2 | DIPEA | 78 |
| 3 | $K_2CO_3$ | 86 |
| 4 | AcONa | 27 |

[a] Yield determined by $^1$H-NMR. The reaction was performed with iodobenzene (**1a**) (204 mg, 1.00 mmol), ethyl acrylate (**2a**) (120 mg, 1.20 mmol), and base (1.0 equiv.) in Cyrene (1 mL), with 10% w/w Pd/C (1 mg), at 150 °C.




**Scheme 3** Substrate scope of different aryl iodides, acrylates and acrylamides.

*E*-isomer (Scheme 3A, **3e–3g**). We furthermore employed an aryl iodide derived from anthraquinone, which led to the corresponding cinnamate in moderate yield. In this case, the reaction time was prolonged to 3 h (Scheme 3A, **3m**). Also, the formation of the *Z*-isomer in a small percentage (10%) was detected. The position of the substituent on the benzene ring did not affect the yield of the reaction (Scheme 3A, **3g–3j**). This indicates that steric hindrance does not play a crucial role in the reaction outcome. Finally, heteroaromatic iodide (**1n**), derived from pyridine, afforded the corresponding cinnamate in good yield (**3n**). Additionally, we examined the use of bromobenzene or chlorobenzene as an alternative coupling partner in our reaction. Unfortunately, in both cases, the reaction did not take place.

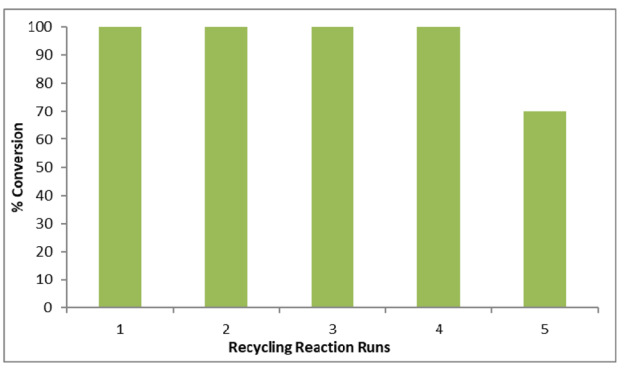
We then continued our substrate investigation with the Michael acceptor partner (Scheme 3B). A broad scope of Michael acceptors was tested in the cross-coupling reaction with iodobenzene (**1a**). Initially, a variety of acrylates was tested, affording the desired cinnamates in moderate to good yields (Scheme 3B, **3o–s**). In some cases, an increased reaction time up to 2.5 h was necessary for reaction completion. Formation of the *Z*-isomer was observed when acrylonitrile was employed (Scheme 3B, **3u**). When acrylic acid and acrylamide were used, the resulting cinnamic acid and cinnamamide were isolated in good yields (Scheme 3B, **3t** and **3aa**). It is important to mention that when these two substrates were examined, isolation by column chromatography presented some challenges, since the products co-eluted with Cyrene. To circumvent this problem, an additional purification step was required, comprising a basic extraction for the cinnamic acid, resulting in slightly lower yield (Scheme 3B, **3t**). Similar lower yield was obtained when acrylamide was employed while applying the same purification protocol (Scheme 3B, **3aa**). We further tested our protocol using acrylates derived from naturally occurring products. Menthyl acrylate afforded the desired product in excellent yield (Scheme 3B, **3v**) within 1 h, while cholesterol acrylate afforded the desired product in moderate yield after 18 h (Scheme 3B, **3w**).

We continued our substrate exploration using acrylamides, another interesting family of Michael acceptors. All acrylamides tested gave the desired products in good yields (Scheme 3B, **3x–z**). Two acrylamides derived from glycine and phenylalanine were also used, leading to the corresponding cinnamamides in great yields (Scheme 3B, **3ab** and **3ac**). Finally, an electron-rich olefin, styrene, was employed as the coupling partner, leading to **3ad** in 83% yield.

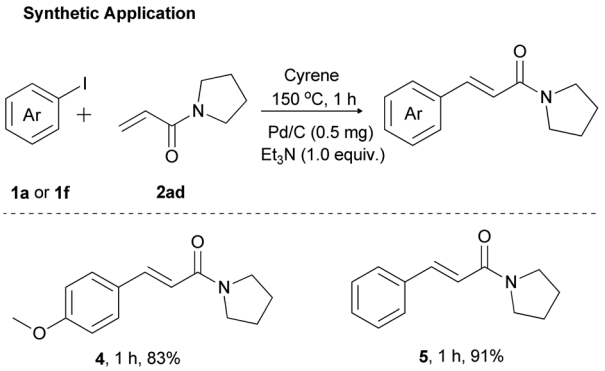
Since the Mizoroki–Heck reaction is a common practice both in academia and in industry, some crucial factors need to be checked. Our desire to develop a reaction protocol that can be easily implemented in a manufacturing plant led us to investigate some industrially important parameters. Firstly, we explored palladium leaching. We performed the developed Mizoroki–Heck cross-coupling reaction between iodobenzene (**1a**) and ethyl acrylate (**2a**) in Cyrene. The reaction was completed after 1 h at 150 °C, and we proceeded with the purification step, which comprises filtration through a Celite pad and extraction using ethyl acetate and water.[38] The palladium level in Cyrene after workup was found to be 6 ppb, whereas it was 0.25 ppb in the purified product.[38] Palladium leaching is significantly lower in Cyrene than in other solvents reported in the literature,[31] which makes it safer and more robust in the recycling procedure. To make the comparison of palladium leaching more straightforward, we carried out the reaction using our protocol, switching the solvent from Cyrene to DMF or GVL.[38] Even though the leaching was found to be lower (25 ppm in DMF, 1.1 ppm in GVL) than that reported in literature[31] for these solvents, still, the best results were obtained by employing Cyrene.[38]

Since the industrial character of a reaction protocol is directly linked to the amount of produced waste, we also examined the recyclability of Cyrene. Testing our protocol at a larger scale is crucial to prove its applicability in industry. We performed the reaction in gram scale. After the usual workup, from the aqueous layer, 70% of the used Cyrene was isolated by water thermal treatment.[38] The reaction between iodobenzene (**1a**) and ethyl acetate (**2a**) took place quantitatively up to four consecutive cycles. However, significant loss in conversion was observed at the fifth cycle (Scheme 4),[38] while after each cycle, the reaction medium was more viscous.

When testing the reaction in gram scale,[38] we modified the purification procedure so that it can be easily adjusted in industry. Thus, instead of column chromatography, we added a second extraction with water. No further purification was required to obtain the isolated product in excellent yield (91%).[38] In this case, we calculated the *E*-factor as a representative factor for the "greenness" of our protocol when applied at a larger scale. To our delight, the calculated *E*-factor was lower (*E*-factor = 19)[38] than that of previously reported methods.[31] Overall, employing Cyrene as the green solvent and Pd/C as the catalyst leads to a sustainable protocol, where recycling of Cyrene is possible, while Pd leaching is far less than that reported in other solvents.[31] Thus, both organic toxic solvents can be substituted by a bio-based green solvent, and a cheap source of Pd can be employed in very low loading.




**Scheme 4** Recycling of Cyrene in the Mizoroki–Heck reaction.




**Scheme 5** Synthetic application: synthesis of naturally occurring products isolated from *Piper lolot*.

It is well stated in the literature that cinnamic acid derivatives exhibit antioxidant activity and are extensively employed in medicinal chemistry.[32] In our group, over the past years, we focused on developing green and eco-friendly synthetic protocols that are easily applied to the synthesis of naturally occurring products with excellent pharmaceutical profiles, or of pharmaceuticals.[39] In 2007, Li and coworkers isolated a new family of compounds from the methanolic extract of *Piper lolot*, including piperlotine A, piperlotine C, piperlotine D and 1-*trans*-cinnamoylpyrrolidine (Scheme 2), which showed potent antiplatelet aggregation activity.[40] Also, their cytotoxic activity and antimicrobial activity were noted.[40] Moreover, other cinnamic derivatives of the same plant are known to present anticancer activity.[33]

Having already tested our protocol in a variety of substrates, we examined for the first time a Mizoroki–Heck coupling towards the synthesis of piperlotine A (**4**) and 1-*trans*-cinnamoylpyrrolidine (**5**) (Scheme 5). Both reactions proceeded smoothly, affording the corresponding cinnamate derivatives in excellent yields.

## Conclusions

In conclusion, a green, inexpensive, fast and environmentally friendly synthetic protocol for the Mizoroki–Heck cross-coupling reaction was developed, utilizing Cyrene as the reaction medium. Cyrene is an excellent eco-friendly alternative, replacing toxic organic solvents, such as DMF or NMP, that are usually used. Palladium on carbon offers a cheap catalyst alternative to common palladium catalysts. Cyrene was introduced for the Mizoroki–Heck reaction between aryl iodides and acrylates and can be easily recovered and used up to four consecutive times, reducing the amount of produced waste and the overall cost of the procedure. Palladium levels both in the crude reaction mixture and in the final product were extremely low compared to other solvents in the literature. Finally, we managed to apply our procedure successfully towards the synthesis of the naturally occurring product piperlotine A and its derivative.

## Experimental

### General procedure for the Mizoroki–Heck cross-coupling reaction

In a screw-capped tube, aryl iodide **1** (1.00 mmol, 1.00 equiv.), acrylate **2** (1.20 mmol, 1.20 equiv.), triethylamine (TEA) (1.00 mmol, 1.00 equiv.), Cyrene (1 mL) and 10% w/w Pd/C (0.5 mg) were added consecutively. The screw-capped tube was sealed with a cap and Teflon and was left stirring at 150 °C for 1–18 h. The reaction was monitored using thin layer chromatography (TLC). After reaction completion, the reaction mixture was filtered through a Celite pad. The filtrate was diluted with EtOAc (2.5 mL), and water (2.5 mL) was added. The organic layer was separated and dried over $Na_2SO_4$. After filtration, the organic solvent was removed *in vacuo*. The desired product was isolated by column chromatography.

## Author contributions

C. G. K. conceived the study; N. A. S., P. L. G. and C. G. K. designed the experiments and analyzed the data. N. A. S. and P. L. G. performed the experiments. N. A. S., P. L. G. and C. G. K. prepared the draft of the manuscript, and C. G. K. performed the final editing. The manuscript was written through contributions of all authors.

## Conflicts of interest

There are no conflicts to declare.

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