



Click amidations, esterifications and one-pot reactions catalyzed by Cu salts and multimetal-organic frameworks (M-MOFs)

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ABSTRACT

Amides and esters are prevalent chemicals in Nature, industry and academic laboratories. Thus, it is not surprising that a plethora of synthetic methods for these compounds has been developed along the years. However, these methods are not 100% atom economical and generally require harsh reagents or reaction conditions. Here we show a “spring-loaded”, 100% atom-efficient amidation and esterification protocol which consists in the ring opening of cyclopropanones with amines or alcohols. Some alkyl amines react spontaneously at room temperature in a variety of solvents and reaction conditions, including water at different pHs, while other alkyl amines, aromatic amines and alcohols react in the presence of catalytic amounts of simple Cu²⁺ salts or solids. A modular reactivity pattern (alkyl amines >> alkyl alcohols >> phenols >> aromatic amines) enables to design orthogonal and one-pot reactions on well-defined catalytic Multimetal-Organic Frameworks (M-MOFs, M= Cu, Ni, Pd), to easily functionalize the resulting cinnamides and cinnamic esters to more complex molecules. The strong resemblance of the amidation and esterification reaction conditions here reported with the copper-catalyzed azide-alkyne cycloaddition (CuAAC) allows to define this fast, clean and flexible protocol as a click reaction.

1. Introduction

Click reactions are extremely fast and regioselective couplings between two different functional groups, generally boosted by a favorable release of energy (ΔH^0 typically < -40 kcalmol⁻¹). These reactions operate under ambient conditions at different pHs, in the presence of other organic and inorganic (iclick) functional groups, and in many conventional solvents, including water [1–3]. This combination of high specificity and reaction condition ubiquity makes click reactions of great utility for the design and construction of bio-orthogonal reactions [4–6] and chemical libraries,[7,8] to name a couple of current applications Fig. 1. shows the CuAAC reaction, a very representative click reaction [9,10].

Amide and ester bonds are present at the core of chemistry. However, it is difficult to find a fast and full-atom economy protocol for the

synthesis of these paramount functional groups. A paradigmatic example is the synthesis of cinnamides and cinnamic esters, also shown in Fig. 1, which still requires classical methods such as Claisen-type condensations and Wittig-type alkylations of aldehydes [11–15], (trans)amidations and esterifications of preformed cinnamic esters and acids [16], or the intermolecular Heck coupling of acrylamides and acrylates [17–20]. However, these protocols start from a preformed amide or ester, typically use a high excess of reagent (i.e. strong base or amine/alcohol) to shift the equilibrium towards the desired carboxylate derivative, and, in many cases, do not tolerate sensitive functional groups in the molecule.

Cyclopropanones are highly energetic but stable aromatic ketones, with an increasing number of synthetic protocols in the last years [21–27]. The strained carbonyl group but not the conjugated alkene is expected to preferentially react with hard nucleophiles, in clear contrast

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to typical enones [22,28–30]. Besides, cyclopropanones will not suffer equilibrium shifts as esters or acids do after amine and alcohol addition, since the strongly thermodynamically favored strain release of the cyclopropane ring ($-67 \text{ kcal}\cdot\text{mol}^{-1}$) will drive the reaction irreversible towards the desired cinnamyl derivative [31]. This reactive hypothesis has, to our knowledge, been little explored in the open literature [32, 33], only for phenols [34] and, in some cases, to generate imines and trigger cyclic rearrangements [22,35,36], or for bio-orthogonal functionalization with phosphines [37]. With all these precedents in mind, and inspired by the archetypical click reaction (CuAAC), Fig. 1 also shows the novelty of this work, which consists in the ring-opening of cyclopropanones with amines and alcohols, which can also be named as hydroamination and hydroalkoxylation of cyclopropanones, respectively, as a potentially feasible and full-atom economy alternative reaction for a general synthesis of cinnamides and cinnamic esters. Besides, our work here will show that not only simple Cu^{2+} salts but also Cu^{2+} -containing metal-organic frameworks (MOFs) are catalytically competent for the reactions, and that other catalytic metals can be incorporated in the MOF structure and engage different reactions in one-pot.

2. Materials and methods

All chemicals were of reagent grade quality. Reagents and solvents were obtained from commercial sources and were used without further purification otherwise indicated. $\text{Ni}^{\text{II}}_2\{\text{Ni}^{\text{II}}_4[\text{Cu}^{\text{II}}_2(\text{Me}_3\text{mpba})_2]_3\} \cdot 54\text{H}_2\text{O}$ (NiCuMOF) and $[\text{Pd}_4]_{0.5}@\text{Na}_3\{\text{Ni}^{\text{II}}_4[\text{Cu}^{\text{II}}_2(\text{Me}_3\text{mpba})_2]_3\} \cdot 56\text{H}_2\text{O}$ (PdCuMOF) were prepared as reported previously (see main text). Cyclopropanones were prepared according to reported procedures (see SM). No unexpected or unusually high safety hazards were encountered.

Synthesis of $[\text{Pd}^{\text{II}}(\text{NH}_3)_4]\text{Ni}^{\text{II}}\{\text{Ni}^{\text{II}}_4[\text{Cu}^{\text{II}}_2(\text{Me}_3\text{mpba})_2]_3\} \cdot 52\text{H}_2\text{O}$ (PdNiCuMOF). Well-formed dark green prisms of PdNiCuMOF, which were suitable for X-ray diffraction, were obtained by immersing crystals of NiCuMOF (ca. 5 mg, 0.0015 mmol) for 24 h in 5 mL of $[\text{Pd}(\text{NH}_3)_4]\text{Cl}_2$ aqueous solutions (0.003 mmol). Alternatively, a multigram scale procedure was also carried out by using the same synthetic procedure but with greater amounts of both, a powder sample of compound PdNiCuMOF (5 g, 1.45 mmol) and $[\text{Pd}(\text{NH}_3)_4]\text{Cl}_2$ (1.067 g, 2.9 mmol), with the

same successful results and a high yield (4.91 g, 96%). Anal.: calcd (%) for $\text{Cu}_6\text{Ni}_5\text{PdC}_{78}\text{H}_{176}\text{N}_{16}\text{O}_{88}$ (PdNiCuMOF) (MW: 3527.45): C, 26.56; H, 5.03; N, 6.35. Found: C, 25.68; H, 5.01; N, 6.34. IR (KBr): $\nu = 3011$, 2956 and 2917 cm^{-1} (C–H), 1607 cm^{-1} (C=O).

General procedure for the synthesis of cinnamates or cinnamides. 0.7 mmol of the corresponding cyclopropanone were inserted in a glass vial with either $\text{Cu}(\text{OAc})_2$ (1–2 mol%) or NiCuMOF (10 mol%), toluene (0.5 M final dilution respect to the cyclopropanone reactant) and the corresponding alcohol or amine (0.35 mmol). The solution was left overnight at 100 °C and at the end was quenched with water (5 ml). Then, the mixture was extracted with EtOAc ($3 \times 5 \text{ ml}$) and the organic layers were washed with water (5 ml) and brine (5 ml). Afterwards, the organic phase was dried over MgSO_4 , filtered and concentrated under vacuum. The resulting mixture was purified by either thin-layer chromatography (TLC) or flash chromatography with the appropriate AcOEt/*n*-hexanes mixture.

3. Results and Discussion

3.1. Hydroamination and hydroalkoxylation of cyclopropanones with catalytic Cu^{2+} salts

3.1.1. Hydroamination reaction

Table 1 shows the results for the reaction between diphenylcyclopropanone 1a and *n*-octylamine 2a under ambient conditions, followed by gas chromatography (GC). The coupling reaction proceeds to the desired cinnamide 3a in quantitative yields after 2–3 h, with similar reaction rates for all solvents tested ($\sim 0.03 \text{ s}^{-1}$), including water at pHs between 4.8 and 14.0, and brine, which supports the potential applicability of this reaction in biological systems [6,38,39]. The addition of catalytic amounts of $\text{Cu}(\text{OAc})_2$ or the increase of the reaction temperature shortens the reaction time to just few minutes (reaction rate $\sim 0.15 \text{ s}^{-1}$), while keeping a complete selectivity towards cinnamide 3a. Notice that, under the heating reaction conditions, all reagents and catalyst are fully soluble. These results showcase the generality of the reaction under a plethora of reaction conditions, in line with typical click reactions.

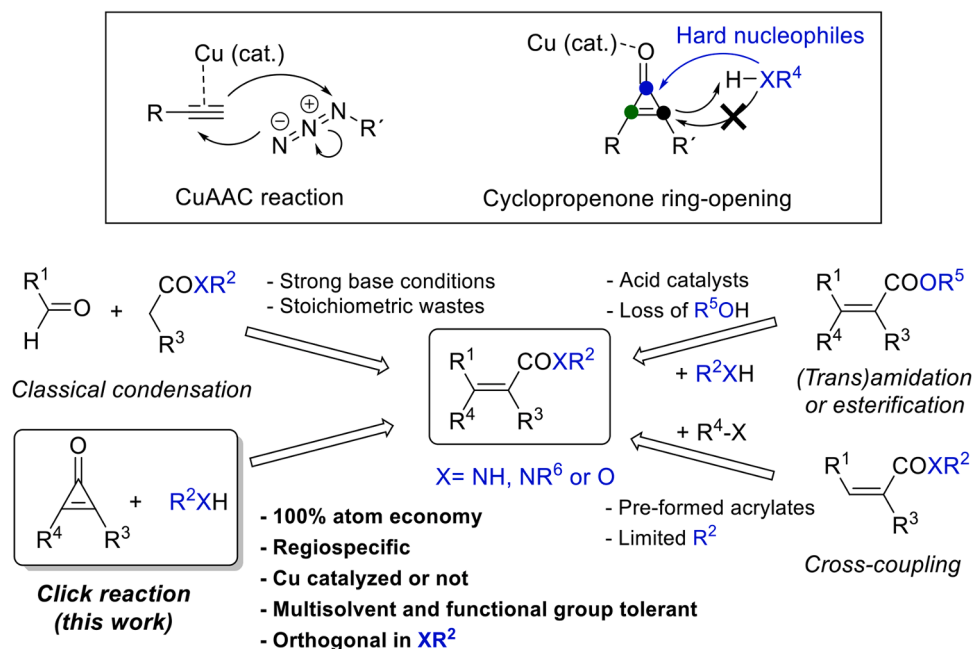


Fig. 1. Huisgen (or CuAAC) reaction and its parallelism with the here reported cyclopropanone ring-opening (click reaction), and comparison with the main synthetic methods for cinnamides and cinnamates.

Table 1

Ring-opening of diphenylcyclopropenone **1a** with *n*-octylamine **2a**. ^a Cu(OAc)₂ (2 mol%) as a catalyst. ^b pHs were set to the indicated values with HOAc/KOAc mixtures, except for pH 11.5 (Na₂CO₃) and pH 14 (KOH). GC yields.

Entry	Solvent	T (°C)	Time (min)	3a (%)
1	Toluene	25	210	94
2 ^a		25	10	91
3		50	210	99
4		75	60	99
5		100	10	98
6	<i>n</i> -Hexane	25	135	>99
7	DCM			71
8	Diethyl ether			>99
9	CH ₃ CN			93
10	DMF			>99
11	EtOH			36
12	Water			99
13 ^a	Water		10	99
14 ^b	Water pH 2.4		135	22
15 ^b	Water pH 4.8			99
16 ^b	Water pH 9.3			92
17 ^b	Water pH 11.5			99
18 ^b	Water pH 14.0			99
18	Brine			82

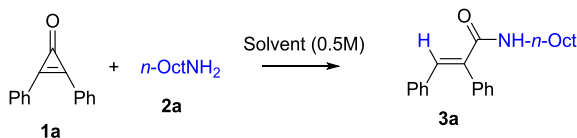


Fig. 2 shows that three different cyclopropenones **1a–c** and different alkyl amines **2a–g** react in the presence of catalytic Cu(OAc)₂ (2 mol%) to give cinnamides **3a–i** in moderate to good yields. In these cases, the presence of the Cu catalyst was needed not only to boost the reaction rate but also to increase the selectivity towards the cinnamide products, otherwise parasite reactions take over. *Cis*-olefins are exclusively formed because the reaction goes through a concerted addition of the amine to the double bond, with the Cu²⁺ catalyst coordinating the carbonyl rather than the alkene group, thus by-passing any final dehydrometalation reaction (see Fig. 8 ahead).

3.1.2. Hydroamination vs hydroalkoxylation reaction

Fig. 2 also shows that aniline **4a**, octyl alcohol **5a** and phenol **6a** react with **1a** only when Cu(OAc)₂ is added in catalytic amounts, to give 25%, >99% and 60% yield of cinnamyl derivatives **7a**, **8a** and **9a**, respectively. Other Cu²⁺ and Cu⁺ salts were similarly effective for the hydroalkoxylation of **1a** with **5a** (Table S1). Notice that no reductant agents such as ascorbic acid are required, in contrast to the most representative CuAAC reaction protocol. The activation energy (E_a) for the coupling of each nucleophile with **1a** catalyzed by a 5 mol% of Cu(OAc)₂ was calculated by kinetic measurements at different temperatures (25, 50, 75 and 100 °C), based on the initial rates of the reaction, and the results show that the $E_a = <1.0, 11.1, 13.9$ and $34.8 \text{ kcal}\cdot\text{mol}^{-1}$ for octylamine **2a**, phenol **6a**, aniline **4a** and octyl alcohol **5a**, respectively. This reactive trend (alkyl amines >> phenols > aromatic amines >> alkyl alcohols) roughly follows the expected nucleophilicity of each partner and is inversely proportional to the corresponding pK_a (35, 18, 31 and 30, respectively). Notice that the E_a values do not mathematically correlate with the pK_a values, it is just an estimation, and that the E_a calculated for the uncatalyzed reaction of **1a** with **2a** is $5.0 \text{ kcal}\cdot\text{mol}^{-1}$, thus the addition of catalytic Cu²⁺ decreases at least five times the E_a of the reaction. These significant reactivity differences among nucleophiles suggest that the hydroamination and hydroalkoxylation of cyclopropenones can be carried out in a modular way, by simply adjusting the amount of catalyst and reaction conditions Fig. 3. shows that, by using ethanolamine as a bidentate nucleophile, we could obtain the hydroaminated/alkoxyated product **10b** after two consecutive hydroadditions to cyclopropenones **1b** and **1a**, respectively,

employing or not Cu(OAc)₂ as a catalyst. This result confirms the orthogonality of the hydroamination / hydroalkoxylation reaction of cyclopropenones under the present reaction conditions.

Fig. 4 shows that aromatic amines are less reactive and require a 10 mol% of Cu catalyst to engage reasonably well in the cyclopropenone-opening reaction, as shown for aromatic cinnamides **7a–i**.

3.1.3. Hydroalkoxylation reaction

Fig. 5 shows the results for the hydroalkoxylation of cyclopropenones catalyzed by a 2 mol% of Cu(OAc)₂ (results in parentheses). As it can be seen, water [hydration reaction, product (**8b**)], different benzyl alcohols (**8f–h**), allyl alcohol **8i**, and different propargyl, alkenyl, amine, ketal and halogen-substituted alkyl alcohols (**8i–p**), and also alcohols containing complex natural products such as estradiol (**8q**), cholesterol (**8r**) and sphingomyelin (**8s**), gave good yields of the corresponding esters with cyclopropenone **1a**. Complementary, cyclopropenones bearing a methyl instead of a phenyl group (**1b**), only one phenyl group (**1d**) and *p*-nitrosubstituted phenyl rings (**1e**) were also reactive with a variety of alcohols, including alkyl (**8t**, **8w**, **8y–z**), alkenyl (**8u**, **8aa**), tertiary amine-substituted (**8v**), ketal protected (**8x**) and alkenyl (**8ab**) alcohols. These results strongly suggest that the reactivity and chemoselectivity of alcohols is enhanced respect to most of the amines (compare with the above results) in the presence of the Cu²⁺ catalyst. In view of this, we envisioned the preparation of a Cu²⁺ supported catalyst, able to perform the reaction, with improved recyclability/reusability.

3.2. Metal organic frameworks (MOFs) as suitable solid catalysts for the hydroalkoxylation of cyclopropenones

3.2.1. Synthesis and characterization of Cu²⁺-MOFs

Aiming at confirming that the described catalytic activity of Cu²⁺ cations can be extended to heterogeneous catalysis and intending to extend such results to one-pot catalysis, we used a type of porous materials –the so-called Metal-Organic Frameworks (MOFs) [40–44] whose potential in catalysis has already been widely demonstrated [45–49] to encapsulate such catalytically active metal species. In particular, we have prepared novel Multimetal-Organic Frameworks (M-MOFs) [50–54] containing three potential different metal active sites (Cu, Ni, Pd), located in both, the framework and also hosted in their channels.

Fig. 6 shows the porous crystal structure of the starting [Ni(H₂O)₆]²⁺-MOF of formula Ni^{II}₂{Ni^{II}₄[Cu^{II}₂(Me₃mpba)₂]₃} · 54H₂O; Me₃mpba⁴⁻ = *N,N'*-2,4,6-trimethyl-1,3-phenylenebis(oxamate) (NiCu-MOF, Fig. 6a) [55], the new crystal structure of MOF [Ni(H₂O)₆]²⁺/[Pd(NH₃)₄]²⁺-MOF with formula: [Pd^{II}(NH₃)₄]²⁺{Ni^{II}₄[Cu^{II}₂(Me₃mpba)₂]₃} · 52H₂O after the PS cation exchange (PdNiCuMOF, Fig. 6b), and also the structure of the previously reported MOF where all Ni²⁺ cations are substituted by Pd²⁺ ones and then reduced to form [Pd₄]²⁺ nanoclusters with formula [Pd₄]_{0.5}@Na₃{Ni^{II}₄[Cu^{II}₂(Me₃mpba)₂]₃} · 56H₂O (PdCuMOF, Fig. 6c) [56]. The previously reported ox-amato-based [57–61] three-dimensional (3D) NiCuMOF possesses accessible Cu²⁺ sites, which are located in the anionic coordination framework and Ni²⁺ cations situated in the channels (Fig. 6a). Synchrotron single crystal X-ray crystallography (SC-XRC) could be employed to un-derpin [Ni(H₂O)₆]²⁺ and [Pd(NH₃)₄]²⁺ cationic complexes inside the new nanoporous PdNiCuMOF material, and its crystal structure unambiguously shows that the [Pd(NH₃)₄]²⁺ and [Ni(H₂O)₆]²⁺ units are hosted in the two types of channels present in the anionic framework (Fig. 6b).

The larger octagonal pores –also accessible for catalysis (*vide infra*)–host both [Ni(H₂O)₆]²⁺ and [Pd(NH₃)₄]²⁺ units with the latter stabilized in sites close to the walls of the network. This evidence further supports an intrinsic stabilizing effect of MOF's confined space. The small square hindered channels retains only [Ni(H₂O)₆]²⁺ as in the structure of the precursor NiCuMOF, confirming the lesser accessibility of these pores for cation exchange. The tetra-ammonium Pd(II) monomers exhibit

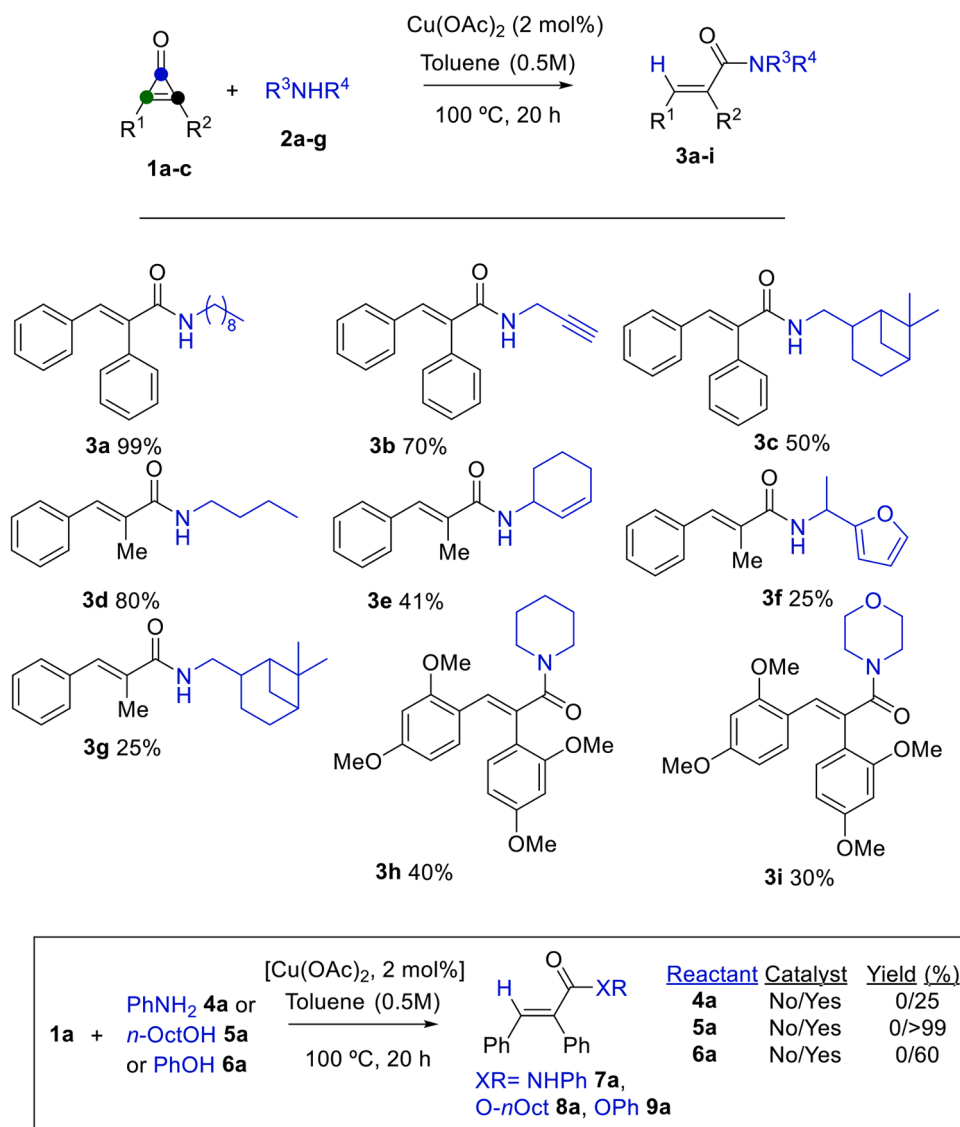


Fig. 2. Ring-opening of cyclopropanones **1a–c** with alkyl amines **2a–g** in the presence of $\text{Cu}(\text{OAc})_2$ (2 mol%). The inset at the bottom shows the ring-opening of cyclopropanone **1a** with different nucleophiles. Isolated yields.

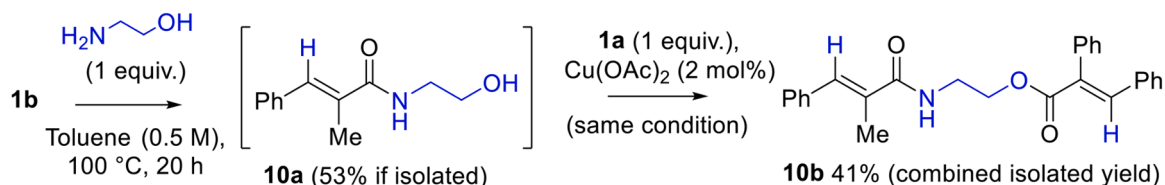


Fig. 3. Modular reactivity using ethanolamine as a bidentate nucleophile.

Pd–NH₃ bond distances [1.86(2) to 1.98(2) Å], very similar to those previously reported [56]. The larger octagonal hydrophilic channels of the MOF contain a much larger accessible void space (size of ca. 2.2 nm), which makes them as the first candidate to cation exchanges, leaving the small square channels fully occupied by the $[\text{Ni}(\text{H}_2\text{O})_6]^{2+}$ monomers exactly as in NiCuMOF (Fig. 6a and b). Apart from electrostatic interactions between Pd(II) units and the anionic framework, all $[\text{Pd}(\text{NH}_3)_4]^{2+}$ cations are hydrogen-bonded through the carboxylate oxygen atoms of the framework and ammonia molecules of the Pd(II) environment $[\text{N}_{\text{ammonia}} \cdots \text{O}_{\text{oxamate}}$ varying in the range 2.93(2)–3.07(2) Å] to the anionic framework which further fixes and stabilizes them

within the pores (dashed lines in Fig. 6b, see also Figs. S1–S6).

These direct crystallographic visualizations of the postsynthetic incorporation –within the channels of the MOF– of $[\text{Pd}(\text{NH}_3)_4]^{2+}$ cations, with a stoichiometrically-guided to be partial (50% of nickel) cation exchange, unquestionably underlines how the interplay between hydrophilic channels and the vastly solvated confined nanospace governs the exchange process, ensuring the maintenance of all kind of species, and safeguarding the final captured moieties stabilizations. Once more, synergies between MOF's crystallinity and cutting-edge crystallographic methods afford precious insights into the unorthodox chemistry with can be performed within confined spaces of MOFs.

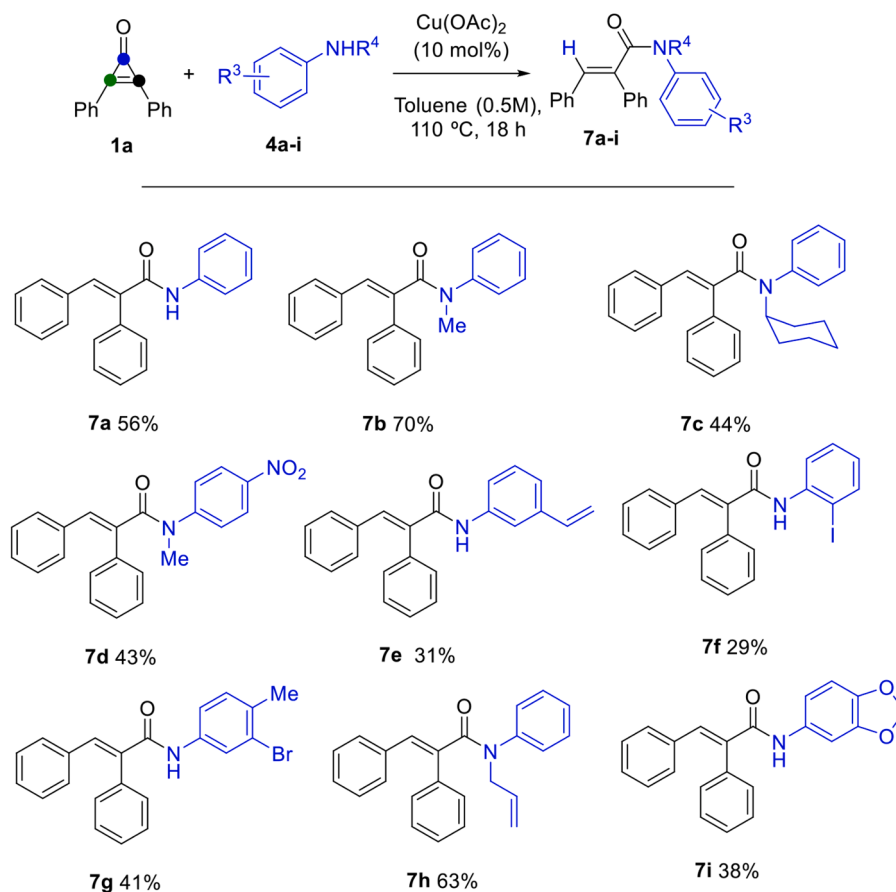


Fig. 4. Ring-opening of cyclopropanones **1a** with aromatic amines **4a-i** catalyzed by $\text{Cu}(\text{OAc})_2$ (10 mol%). Isolated yields.

The chemical identity of **PdNiCuMOF** was further established by elemental analyses (C, H, S, N), inductively coupled plasma-mass spectrometry (ICP-MS), X-ray photoelectron spectroscopy (XPS) (Fig. 7a), electronic microscopy, powder X-ray diffraction (PXRD) (Fig. 7b), thermo-gravimetric (TGA) analyses (Fig. S7) and single crystal X-ray diffraction (Table S2).

Fig. 7a shows the XPS spectra of **PdNiCuMOF**. The Pd3d line is the typical doublet with binding energies (BE) for the Pd3d_{5/2} and Pd3d_{3/2} peaks of 338.6 and 343.0 eV, respectively, typical of Pd²⁺ cations, which is in good agreement to other reported values [56].

The experimental powder X-ray diffraction (PXRD) patterns of **PdNiCuMOF**, together with those of the previously reported **NiCuMOF** [55] and **PdCuMOF** [56] for the sake of comparison, can be observed in Fig. 7b. In each case, the experimental patterns (solid lines) are identical to the theoretical ones (bold lines), confirming the purity and homogeneity of the samples. The solvent contents of **PdNiCuMOF** were confirmed by thermogravimetric analysis (TGA) (Fig. S7).

Fig. 7c shows the N₂ adsorption isotherm at 77 K of **PdNiCuMOF** (blue line) compared to those of compounds **NiCuMOF** and **PdCuMOF** (red and green lines, respectively), which confirms its permanent porosity. Remarkably, the permanent porosity for **PdNiCuMOF** is higher than **NiCuMOF** and approximately double that of **PdCuMOF**. This feature suggests higher accessible surface and structural stability for **PdNiCuMOF**. In contrast, the presence of the bulkier tetranuclear Pd clusters in **PdCuMOF** (Fig. 6c) may preclude access of the reactants to Cu²⁺ sites during the catalytic experiments.

3.2.2. Hydroalkoxylation of cyclopropanones with Cu²⁺-MOFs

The isolated yields of different esters in Fig. 5 (without parentheses) show that **NiCuMOF** catalyzes the click reaction of cyclopropanone **1a** with water (**8b**), phenols (**9a-d**), benzyl (**8c,d** and **8f-h**), phenethyl

(**8e**), allyl (**8i**), homopropargyl (**8j**) and linear primary alcohols containing sensitive functionalities (**8l-m**), secondary alcohols either linear or cyclic (**8n-o**), and natural products such as geraniol (**8p**). Bigger products do not penetrate in the microporous MOF solid. The alcohol is added in all cases selectively across the cyclopropanone bond in good to excellent yields, with easy-to-migrate alkenes and chiral carbon-oxygen bonds remaining untouched during the course of the reaction. Remarkably, we observed that the catalytic activity of the framework Cu²⁺ cations persisted in **PdNiCuMOF** but not in **PdCuMOF**, in line with the higher accessibility to the Cu²⁺ sites for the former, observed during the characterization measurements (vide supra). Other Ni and Pd catalysts including NiX₂ (X=OAc, NO₃, SO₄) and PdCl₂(PPh₃)₂, Pd(PPh₃)₄, Pd[P(o-tolyl)₃]₄, PdOAc₂(SPhos)₂, and also oxime palladacycles, were tested without success (yield <1%), strongly supporting that the Cu²⁺ cations of the MOFs are the catalytic active species for the hydroalkoxylation reaction. The fact of having the Cu²⁺ in the solid framework and using non-polar toluene as solvent of the reaction, precludes a significant leaching of the active species (Fig. S8), which allowed to reuse **NiCuMOF** at least five times without significant depletion in the final yield of product **8o** after 18 h reaction time (75% after 5 uses), however, accompanied by a significant decrease of the initial rate from use to use (kinetic points for the initial 1 h reaction time, Fig. S8). These results illustrate the advantages of using a Cu²⁺-containing solid catalyst for the hydroalkoxylation of cyclopropanones.

3.3. Proposed mechanism for the Cu²⁺-catalyzed hydroalkoxylation of cyclopropanones

Fig. 8 shows a plausible mechanism for the click amidations and esterifications on the basis of kinetic, isotopic, and reactivity experiments.

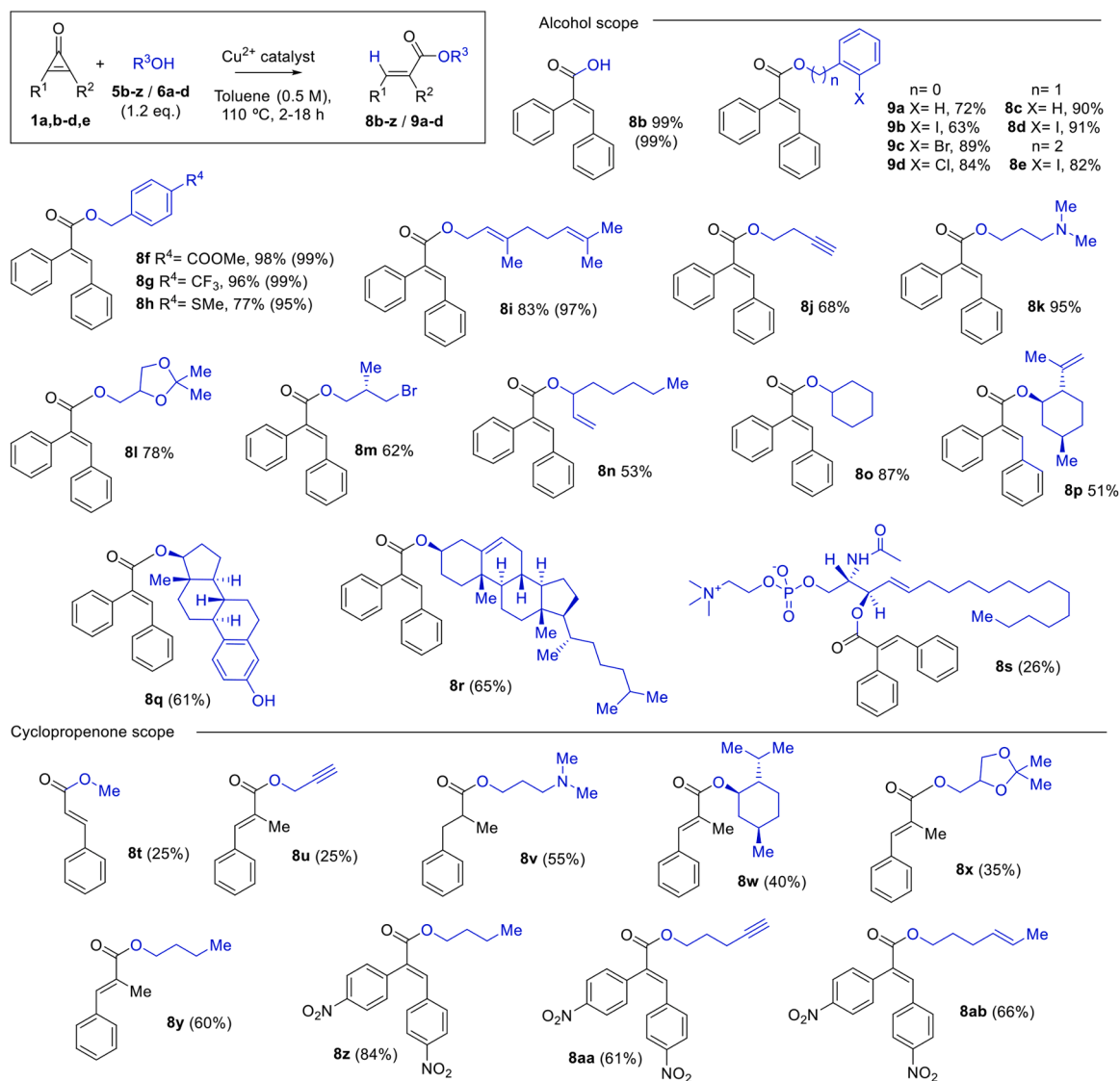


Fig. 5. Synthesis of cinnamate products by hydroalkoxylation of cyclopropenones, catalyzed by either soluble $\text{Cu}(\text{OAc})_2$ (2 mol%, yields between parentheses) or insoluble NiCuMOF (10 mol%, yields without parentheses). Isolated yields. The major product for non-symmetric cyclopropenones is shown.

A kinetic isotopic effect (KIE)= 1.1 was calculated when CD_3OD was used as a reagent, which discards any role of the H atom during the rate-limiting step of the reaction. Considering that no inverted KIE value is found and the fact that the H atom of MeOH adds untouched on the final cinnamate product in the presence of additional D_2O , and complementary, the D atom of CD_3OD adds untouched when H_2O is present in the reaction mixture, a concerted rather than a stepwise addition across the C—C bond must be accepted.

3.4. One-pot hydroalkoxylation of cyclopropenones / cross coupling reactions

3.4.1. One-pot cyclopropenone hydration / Chan–Lam coupling reaction catalyzed by NiCuMOF

The presence of different catalytically active metal sites in NiCuMOF and PdNiCuMOF invites to carry out consecutive reactions where each metal catalyzes one step, *i.e.* one-pot hydroalkoxylation / cross coupling reactions Fig. 9. shows that the one-pot cyclopropenone hydration / Chan–Lam coupling reaction proceeds with catalytic amounts of NiCuMOF to give the corresponding aromatic esters **12a–d**, after formation of intermediate **8b** (Fig. S9). The Chan–Lam coupling is severely inhibited after exchanging Ni^{2+} by either Fe^{3+} or Pd^{2+} in the MOF (Table S3)[60],

which confirms the catalytic action of Ni^{2+} for the coupling [62]. Besides, the direct coupling of the boronic acid with neither the alkene moiety of **8b** [63] nor of **1a**, [64] to give products **13a–d**, occurs, and the latter only occurred in great extent when Pd^{2+} was the exchanged cation (PdNiCuMOF , Table S3). KOH was the base of choice from all the bases tested (Table S3). Notice that despite Cu^{2+} is traditionally active as a catalyst for the Chan–Lam reaction [65], the Cu^{2+} cations, from the framework in NiCu@MOF , can not accommodate two different aromatic molecules in its rigid metal coordination sphere and neither perform redox switches, thus being merely inactive for the coupling. Thus, NiCuMOF acts here as a bifunctional solid metal catalyst where Cu^{2+} catalyzes the hydration reaction and Ni^{2+} the Chan–Lam coupling.

3.4.2. One-pot cyclopropenone hydration / Mizoroki–Heck coupling reaction catalyzed by PdNiCuMOF

In view that PdNiCuMOF is catalytically active for the direct coupling of **1a** and **11a** to give **13a** (89%, entry 3 in Table S3), we tested a one-pot cyclopropenone hydration / Mizoroki–Heck coupling reaction. In this approach, the direct coupling of the alkene with the cyclopropenone cannot occur, thus giving an opportunity for the one-pot reaction to proceed.

Medium size lactones are difficult-to-synthesize molecules,

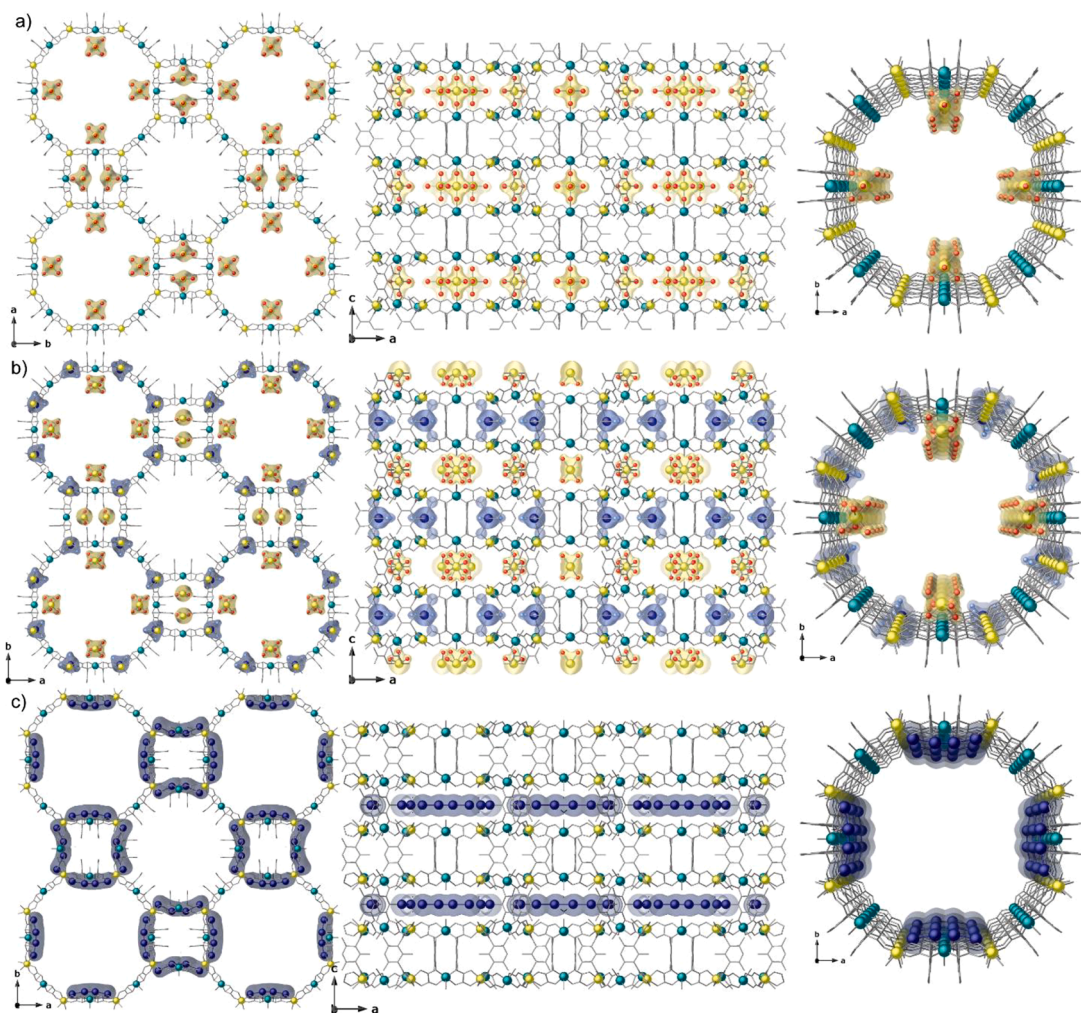


Fig. 6. Views along the *c* (left) and *b* (middle) axes of the crystal structures, determined by synchrotron X-ray diffraction, of the previously reported NiCuMOF[55] (a), the novel PdNiCuMOF (b) and the also reported PdCuMOF[56] (c). Perspective views of one single channel of NiCuMOF (a, right) and PdNiCuMOF (b, right). The ligands of the coordination 3D network are depicted as grey sticks whereas copper and nickel atoms are represented as cyan and yellow spheres. For the guest species hosted in the channels, nickel and palladium atoms and water and ammonia molecules are represented as yellow, dark blue, red and light blue spheres, respectively. Yellow and blue surfaces are used to highlight the guest Ni and Pd species, respectively, within MOFs channels.

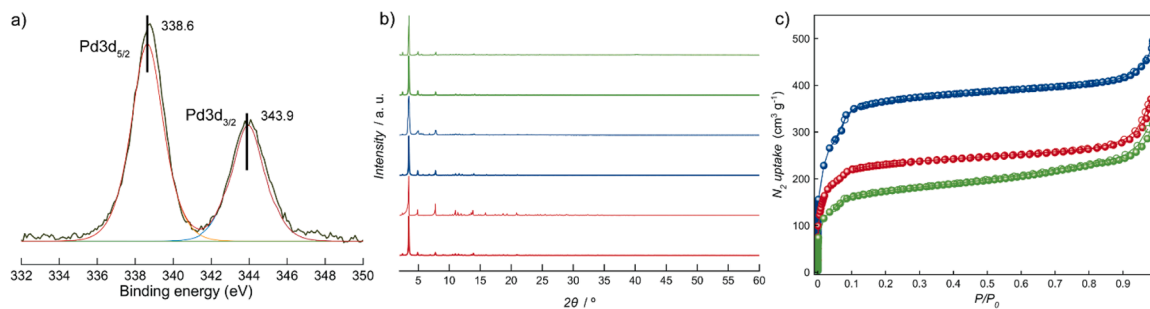


Fig. 7. (a) X-ray photoelectron spectroscopy (XPS) of PdNiCuMOF. (b) Calculated (bold lines) and experimental (solid lines) PXRD pattern profiles of NiCuMOF (red), PdNiCuMOF (blue) and PdCuMOF (green) in the 2θ range 2.0–60.0°. (c) N_2 (77 K) adsorption isotherms for the activated compounds NiCuMOF (red), PdNiCuMOF (blue) and PdCuMOF (green). Filled and empty symbols indicate the adsorption and desorption isotherms, respectively. The samples were activated at 70 °C under reduced pressure for 16 h prior to carry out the sorption measurements.

particularly by cross-coupling reactions [66–70]. The lack of straightforward, 100% atom economical and chemoselective synthetic methods for cinnamates translates into the unfeasibility of a straightforward synthesis for medium size lactones by intramolecular Heck reaction [71], since the preparation of cinnamates containing an aryl halide functionality at 5–8 carbon atom distance, ready for coupling, is difficult

to find [72–75]. Thus, the one-pot hydroalkoxylation of phenyl cyclopropenone **1d** [21,76] with *ortho*-iodo benzyl and phenethyl alcohol to give products **8ac,d**, respectively, and the corresponding intramolecular Heck reaction, to give mainly the α -coupled exo alkenyl lactone **14a**, was attempted. This product is disfavored according to the cinnamate electronics,[77] however, Fig. 10 shows that the regioirregular Heck

Proposed mechanism: Concerted addition.

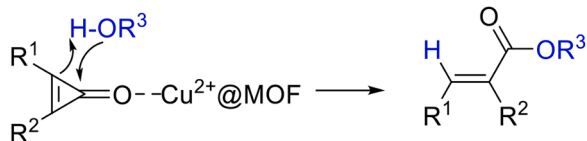


Fig. 8. Proposed mechanism for click amidations and esterifications on the basis of kinetic, isotopic and reactivity experiments.

products **14a** and **c** were the main products of the coupling when using reported conditions in solution. Then, the one-pot reactions with 10 mol % of **PdNiCuMOF** were attempted, and proceeded in reasonable yields to give the regioirregular Heck products, as also shown in Fig. 10. These last results confirm and significantly expands previous work [77,78] with sterically-hindered organopalladium complexes where the high

electron-withdrawing nature of acrylates is overridden by the severe steric effects on the catalytic Pd site, which forces the coupling to occur on the electronically-disfavored alpha position [79–83].

Considering the irrelevant role of Ni^{2+} cations in the one-pot hydroalkoxylation / Mizoroki–Heck coupling reaction, seemed reasonable to replace, completely, Ni^{2+} cations by Pd^{2+} ones in order to enhance the efficiency of the catalyst. However, when the 100% of Ni^{2+} cations hosted in the pores are replaced by Pd^{2+} cations and reduced with NaBH_4 , subnanometer Pd_4 clusters are formed, and the corresponding MOF **PdCuMOF** was not active even for the esterification, which did not proceed. This result is in line with the lack of activity of **PdCuMOF** for the hydration of the cyclopropenone, which can be ascribed to the inaccessibility of the reagents to the Cu^{2+} sites after the Pd cations have been reduced and agglomerated in clusters.

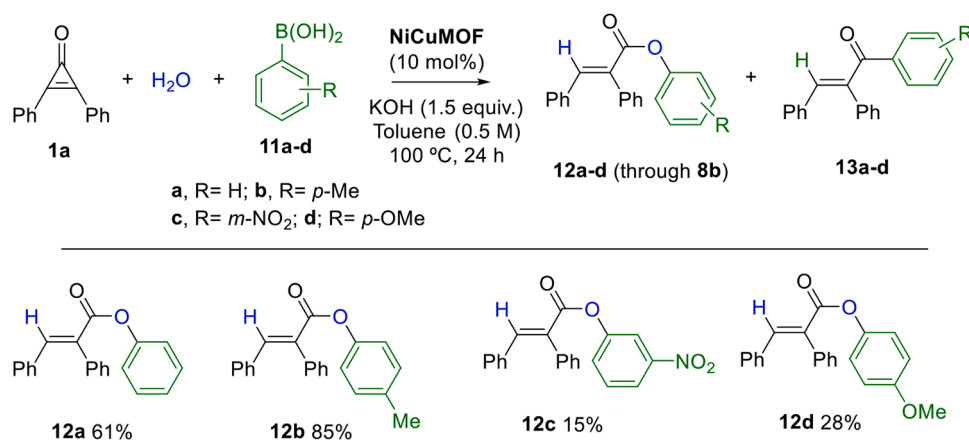


Fig. 9. NiCu@MOF-catalyzed one-pot cyclopropenone hydration / Chan–Lam reaction. Compounds **13a–d** were obtained in <10% yield in all cases.

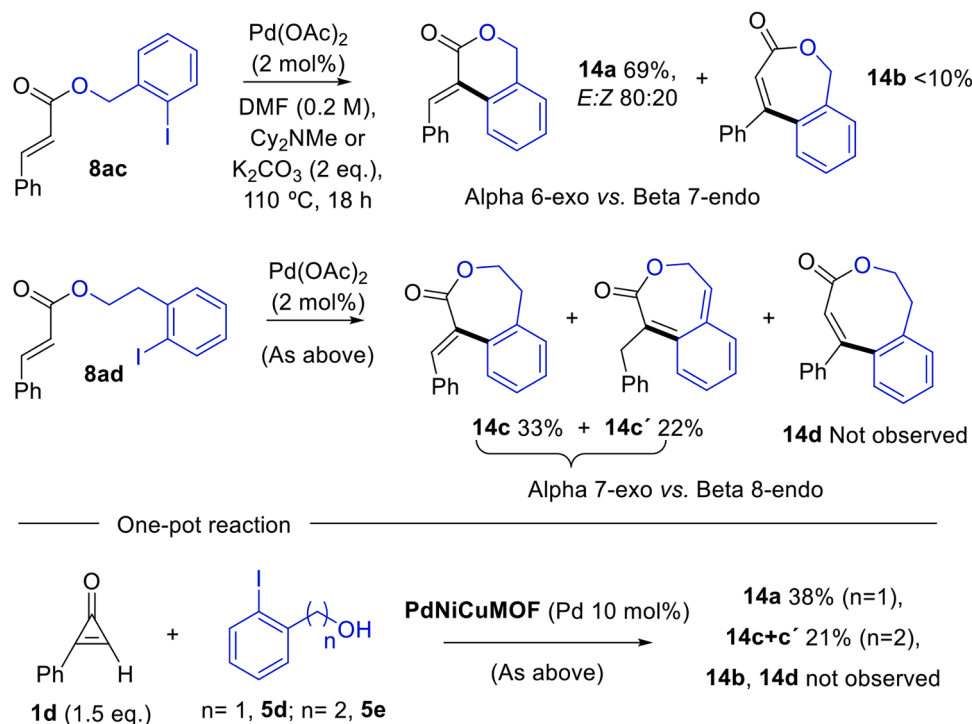


Fig. 10. Intramolecular Heck reaction of *ortho*-iodo substituted cinnamates **8ac** and **8ad** with different Pd catalysts and bases, and one-pot hydroalkoxylation of cyclopropenone **1d** / intramolecular Mizoroki–Heck reaction catalyzed by **PdNiCuMOF**.

4. Conclusions

Different Cu²⁺ salts and Cu²⁺-MOFs catalyze the hydration, hydroalkoxylation and hydroamination of cyclopropanones to give the corresponding esters and amides in high yields, with 100% atom economy, wide solvent, atmospheric and functional group tolerance, and without any additive or by-product. Multimetallic MOFs (M-MOFs) allow cyclopropanone openings / cross-coupling reactions in one-pot [84–85]. We think that the results here significantly expand the available synthetic methodologies for essential chemicals such as esters and amides, and may open a new line of research in click chemistry.

CRedit authorship contribution statement

Rossella Greco: Methodology, Resources. **Estefanía Tiburcio:** Investigation. **Brenda Palomar-De Lucas:** Resources, Methodology. **Jesús Ferrando-Soria:** Investigation. **Donatella Armentano:** Methodology, Data curation. **Emilio Pardo:** Supervision, Writing – original draft. **Antonio Leyva-Pérez:** Supervision, Writing – original draft.

Declaration of Competing Interest

The authors have no competing interests to declare.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mcat.2022.112228.

References

- J.C. Jewett, C.R. Bertozzi, Cu-free click cycloaddition reactions in chemical biology, *Chem. Soc. Rev.* 39 (2010) 1272–1279, <https://doi.org/10.1039/B901970G>.
- L. Xu, J. Dong, Click chemistry: evolving on the fringe, *Chin. J. Chem.* 38 (2020) 414–419, <https://doi.org/10.1002/cjoc.201900421>.
- H.C. Kolb, M.G. Finn, K.B. Sharpless, Click chemistry: diverse chemical function from a few good reactions, *Angew. Chem. Int. Ed. Engl.* 40 (2001) 2004–2021, [https://doi.org/10.1002/1521-3773\(20010601\)](https://doi.org/10.1002/1521-3773(20010601)).
- E.M. Sletten, C.R. Bertozzi, Bioorthogonal chemistry: Fishing for selectivity in a sea of functionality, *Angew. Chem. Int. Ed. Engl.* 48 (2009) 6974–6998, <https://doi.org/10.1002/anie.200900942>.
- R.D. Row, J.A. Prescher, Constructing new bioorthogonal reagents and reactions, *Acc. Chem. Res.* 51 (2018) 1073–1081, <https://doi.org/10.1021/acs.accounts.7b00606>, 2018.
- A. Gutiérrez-González, P. Destito, J.R. Couceiro, C. Pérez-González, F. López, J. L. Mascareñas, Bioorthogonal azide–thioalkyne cycloaddition catalyzed by photoactivatable ruthenium(II) complexes, *Angew. Chem. Int. Ed.* 60 (2021) 16059, <https://doi.org/10.1002/anie.202103645>.
- F. Musumeci, S. Schenone, A. Desogus, E. Nieddu, D. Deodato, L. Botta, Click chemistry, a potent tool in medicinal sciences, *Curr. Med. Chem.* 22 (2015) 2022–2050, <https://doi.org/10.2174/0929867322666150421110819>.
- H.D. Agnew, M.B. Coppock, M.N. Idso, B.T. Lai, J. Liang, A.M. McCarthy-Torrens, C.M. Warren, J.R. Heath, Protein-catalyzed capture agents, *Chem. Rev.* 119 (2019) 9950–9970, <https://doi.org/10.1021/acs.chemrev.8b00660>.
- F. Himo, T. Lovell, R. Hilgraf, V.V. Rostovtsev, L. Noodleman, K.B. Sharpless, V. V. Fokin, Copper(I)-catalyzed synthesis of azoles. DFT study predicts unprecedented reactivity and intermediates, *J. Am. Chem. Soc.* 127 (2005) 210–216, <https://doi.org/10.1021/ja0471525>.
- B.T. Worrell, J.A. Malik, V.V. Fokin, Direct evidence of a dinuclear copper intermediate in Cu(I)-catalyzed azide–alkyne cycloadditions, *Science* 340 (2013) 457–460, <https://doi.org/10.1126/science.1229506>.
- G.A. Grasa, T. Güveli, R. Singh, S.P. Nolan, Efficient transesterification/acylation reactions mediated by N-heterocyclic carbene catalysts, *J. Org. Chem.* 68 (2003) 2812–2819, <https://doi.org/10.1021/jo0267551>.
- M. Arthuis, A. Lecup, E. Roulland, Pd⁰-catalyzed carbonylation of 1,1-dichloro-1-alkenes, a new selective access to α -chloroacrylates, *Chem. Commun.* 46 (2010) 7810–7812, <https://doi.org/10.1039/C0CC02517H>.
- S.S. Weng, C.S. Ke, F.K. Chen, Y.F. Lyu, G.Y. Lin, Transesterification catalyzed by iron(III) β -diketonate species, *Tetrahedron* 67 (2011) 1640–1648, <https://doi.org/10.1016/j.tet.2011.01.009>.
- V. Lloret, M. Rivero-Crespo, J.A. Vidal-Moya, S. Wild, A. Doménech-Carbó, B.S. J. Heller, S. Shin, H.P. Steinrück, F. Maier, F. Hauke, M. Varela, A. Hirsch, A. Leyva-Pérez, G. Abellán, Few layer 2D pnictogens catalyze the alkylation of soft nucleophiles with esters, *Nat. Commun.* 10 (2019) 509, <https://doi.org/10.1038/s41467-018-08063-3>.
- D. Nakatake, R. Yazaki, T. Ohshima, Chemoselective transesterification of acrylate derivatives for functionalized monomer synthesis using a hard zinc alkoxide generation strategy, *Eur. J. Org. Chem.* 2016 (2016) 3696–3699, <https://doi.org/10.1002/ejoc.201600737>.
- B. Narasimhan, D. Belsare, D. Pharande, V. Mourya, A. Dhake, Esters, amides and substituted derivatives of cinnamic acid: synthesis, antimicrobial activity and QSAR investigations, *Eur. J. Med. Chem.* 39 (2004) 827–834, <https://doi.org/10.1016/j.ejmech.2004.06.013>.
- A.H.M. de Vries, J.M.C.A. Mulders, J.H.M. Mommers, H.J.W. Henderickx, J.G. de Vries, Homeopathic ligand-free palladium as a catalyst in the Heck reaction. A comparison with a palladacycle, *Org. Lett.* 5 (2003) 3285–3288, <https://doi.org/10.1021/ol035184b>.
- A. Leyva-Pérez, J. Oliver-Meseguer, P. Rubio-Marqués, A. Corma, Water-stabilized three- and four-atom palladium clusters as highly active catalytic species in ligand-free C–C cross-coupling reactions, *Angew. Chem. Int. Ed. Engl.* 52 (2013) 11554–11559, <https://doi.org/10.1002/anie.201303188>.
- E. Fernández, M.A. Rivero-Crespo, I. Domínguez, P. Rubio-Marqués, J. Oliver-Meseguer, L. Liu, M. Cabrero-Antonino, R. Gavara, J.C. Hernández-Garrido, M. Boronat, A. Leyva-Pérez, A. Corma, Base-controlled Heck, Suzuki, and Sonogashira reactions catalyzed by ligand-free platinum or palladium single atom and sub-nanometer clusters, *J. Am. Chem. Soc.* 141 (2019) 1928–1940, <https://doi.org/10.1021/jacs.8b07884>.
- A. Francais, A. Leyva, G. Etxebarria-Jardi, S.V. Ley, Total synthesis of the anti-apoptotic agents iso- and bongrekic acids, *Org. Lett.* 12 (2010) 340–343, <https://doi.org/10.1021/ol902676t>.
- R. Breslow, J. Posner, A. Krebs, Synthesis of cyclopropanones by a modified Favorskii reaction, *J. Am. Chem. Soc.* 85 (1963) 234, <https://doi.org/10.1021/ja00885a029>, –234.
- K. Komatsu, T. Kitagawa, Cyclopropenyl cations, cyclopropanones, and heteroanalogues—recent advances, *Chem. Rev.* 103 (2003) 1371–1427, <https://doi.org/10.1021/cr010011q>.
- M. Nakamura, H. Isobe, E. Nakamura, Cyclopropanone acetals: synthesis and reactions, *Chem. Rev.* 103 (2003) 1295–1326, <https://doi.org/10.1021/cr0100244>.
- F. Wang, W. Zhang, J. Zhu, H. Li, K.-W. Huang, J. Hu, Chloride ion-catalyzed generation of difluorocarbene for efficient preparation of gem-difluorinated cyclopropanes and cyclopropanes, *Chem. Commun.* 47 (2011) 2411–2413, <https://doi.org/10.1039/C0CC04548A>.
- P. Rullière, P. Cyr, A.B. Charette, Difluorocarbene addition to alkenes and alkynes in continuous flow, *Org. Lett.* 18 (2016) 1988–1991, <https://doi.org/10.1021/acs.orglett.6b00573>.
- R.D. Row, H.-W. Shih, A.T. Alexander, R.A. Mehl, J.A. Prescher, Cyclopropanones for metabolic targeting and sequential bioorthogonal labeling, *J. Am. Chem. Soc.* 139 (2017) 7370–7375, <https://doi.org/10.1021/jacs.7b03010>.
- O.J. Curnow, G.M. Fern, R.J. Pipal, Synthesis of diisopropylcyclopropanone and X-ray structure of its dichlorodimethyltin(IV) adduct, *Arkivoc* iii (2006) 43–47, <http://hdl.handle.net/10092/603>.
- J. Ciabattini, G.A. Berchtold, Cycloaddition reaction of enamines with diphenylcyclopropanone, *J. Am. Chem. Soc.* 87 (1965) 1404–1405.
- S. Cunha, A. Kascheres, A semiempirical quantum mechanical approach towards understanding of cyclopropanone reactivity, *J. Mol. Struct. THEOCHEM* 364 (1996) 45–49, [https://doi.org/10.1016/0166-1280\(95\)04453-1](https://doi.org/10.1016/0166-1280(95)04453-1).
- X. Li, C. Han, H. Yao, A. Lin, Organocatalyzed [3 + 2] annulation of cyclopropanones and β -ketoesters: an approach to substituted butenolides with a quaternary center, *Org. Lett.* 19 (2017) 778–781, <https://doi.org/10.1021/acs.orglett.6b03737>.

- [31] A. Greenberg, R.P.T. Tomkins, M. Dobrovolsky, J.F. Liebman, The strain energy of diphenylcyclopropanone: a reexamination, *J. Am. Chem. Soc.* 105 (1983) 6855–6858, <https://doi.org/10.1021/ja00361a018>.
- [32] A. Kascheres, J.A.R. Rodrigues, Reaction of diphenylcyclopropanone with 2-aminopyridines. Synthetic and mechanistic implications, *J. Org. Chem.* 40 (1975) 1440–1444, <https://doi.org/10.1021/jo00898a013>.
- [33] T. Eicher, R. Graf, H. Konzmann, R. Pick, Synthese und reaktionen von 2,3-diaryl- und 2,3-dialkylcyclopropanoniminen, *Synthesis* 1987 (1987) 887–892.
- [34] T. Nanda, P.C. Ravikumar, A palladium-catalyzed cascade C–C activation of cyclopropanone and carbonylative amination: easy access to highly functionalized maleimide derivatives, *Org. Lett.* 22 (2020) 1368–1374, <https://doi.org/10.1021/acs.orglett.9b04656>.
- [35] C. Kascheres, A. Kascheres, P.S.H. Pilli, Reaction of diphenylcyclopropanone with primary and secondary enamines. Synthetic and mechanistic implications, *J. Org. Chem.* 45 (1980) 5340–5343.
- [36] T.K. Heiss, J.A. Prescher, Cyclopropaniminium ions exhibit unique reactivity profiles with bioorthogonal phosphines, *J. Org. Chem.* 84 (2019) 7443–7448, <https://doi.org/10.1021/acs.joc.9b00518>.
- [37] T. Eicher, S. Böhm, H. Ehrhardt, R. Harth, D. Lerch, Zur reaktion von diphenylcyclopropanon, seinen funktionellen derivaten und imoniumsalzen mit aminen, *Liebigs Ann.* 1981 (1981) 765–788.
- [38] F. Friscourt, C.J. Fahmi, G.J. Boons, A fluorogenic probe for the catalyst-free detection of azide-tagged molecules, *J. Am. Chem. Soc.* 134 (2012) 18809–18815, <https://doi.org/10.1021/ja309000s>.
- [39] C. Favre, L. de Cremoux, J. Badaut, F. Friscourt, Sydnone reporters for highly fluorogenic copper-free click ligations, *J. Org. Chem.* 83 (2018) 2058–2066, <https://doi.org/10.1021/acs.joc.7b03004>.
- [40] O.M. Yaghi, G. Li, H. Li, Selective binding and removal of guests in a microporous metal-organic framework, *Nature* 378 (1995) 703–706, <https://doi.org/10.1038/378703a0>.
- [41] H. Furukawa, K.E. Cordova, M. O’Keeffe, O.M. Yaghi, The chemistry and applications of metal-organic frameworks, *Science* 341 (2013), 1230444, <https://doi.org/10.1126/science.1230444>.
- [42] G. Maurin, C. Serre, A. Cooper, G. Férey, The new age of MOFs and of their porous-related solids, *Chem. Soc. Rev.* 46 (2017) 3104–3107, <https://doi.org/10.1039/C7CS90049J>.
- [43] A. Kirchon, L. Feng, H.F. Drake, E.A. Joseph, H.C. Zhou, From fundamentals to applications: a toolbox for robust and multifunctional MOF materials, *Chem. Soc. Rev.* 47 (2018) 8611–8638, <https://doi.org/10.1039/C8CS00688A>.
- [44] S. Kitagawa, R. Matsuda, Chemistry of coordination space of porous coordination polymers, *Coord. Chem. Rev.* 251 (2007) 2490–2509, <https://doi.org/10.1016/j.ccr.2007.07.009>.
- [45] M. Viciano-Chumillas, M. Mon, J. Ferrando-Soria, A. Corma, A. Leyva-Pérez, D. Armentano, E. Pardo, Metal-organic frameworks as chemical nanoreactors: synthesis and stabilization of catalytically active metal species in confined spaces, *Acc. Chem. Res.* 53 (2020) 520–531, <https://doi.org/10.1021/acs.accounts.9b00609>.
- [46] R.J. Young, M.T. Huxley, E. Pardo, N.R. Champness, C.J. Sumbly, C.J. Doonan, Isolating reactive metal-based species in metal-organic frameworks – viable strategies and opportunities, *Chem. Sci.* 11 (2020) 4031–4050, <https://doi.org/10.1039/D0SC00485E>.
- [47] D. Yang, B.C. Gates, Catalysis by metal organic frameworks: perspective and suggestions for future research, *ACS Catal.* 9 (2019) 1779–1798, <https://doi.org/10.1021/acscatal.8b04515>.
- [48] A. Dhakshinamoorthy, Z. Li, H. Garcia, Catalysis and photocatalysis by metal organic frameworks, *Chem. Soc. Rev.* 47 (2018) 8134–8172, <https://doi.org/10.1039/C8CS00256H>.
- [49] J. Gascon, A. Corma, F. Kapteijn, F.X. Llabrés i Xamena, Metal organic framework catalysis: quo vadis? *ACS Catal.* 4 (2014) 361–378, <https://doi.org/10.1021/cs400959k>.
- [50] C. Castillo-Blas, F. Gándara, Metal-organic frameworks incorporating multiple metal elements, *Isr. J. Chem.* 58 (2018) 1036–1043, <https://doi.org/10.1002/ijch.201800085>.
- [51] M.J. Kalmutzki, N. Hanikel, O.M. Yaghi, Secondary building units as the turning point in the development of the reticular chemistry of MOFs, *Sci. Adv.* 4 (2018) eaat9180, <https://doi.org/10.1126/sciadv.aat9180>.
- [52] M.Y. Masoomi, A. Morsali, A. Dhakshinamoorthy, H. Garcia, Mixed-metal MOFs: unique opportunities in metal-organic framework (MOF) functionality and design, *Angew. Chem. Int. Ed. Engl.* 58 (2019) 15188–15205, <https://doi.org/10.1002/ange.201902229>.
- [53] R. Rajak, R. Kumar, S.N. Ansari, M. Saraf, S.M. Mobin, Recent highlights and future prospects on mixed-metal MOFs as emerging supercapacitor candidates, *Dalton Trans.* 49 (2020) 11792–11818, <https://doi.org/10.1039/D0DT01676D>.
- [54] Z.H. Syed, F. Sha, X. Zhang, D.M. Kaphan, M. Delferro, O.K. Farha, Metal-organic framework nodes as a supporting platform for tailoring the activity of metal catalysts, *ACS Catal.* 10 (2020) 11556–11566, <https://doi.org/10.1021/acscatal.0c03056>.
- [55] T. Granchar, J. Ferrando-Soria, H.C. Zhou, J. Gascon, B. Seoane, J. Pasán, O. Fabelo, M. Julve, E. Pardo, Postsynthetic improvement of the physical properties in a metal-organic framework through a single crystal to single crystal transmetalation, *Angew. Chem. Int. Ed. Engl.* 54 (2015) 6521–6525, <https://doi.org/10.1002/ange.201501691>.
- [56] F.R. Fortea-Pérez, M. Mon, J. Ferrando-Soria, M. Boronat, A. Leyva-Pérez, A. Corma, J.M. Herrera, D. Osadchii, J. Gascon, D. Armentano, E. Pardo, The MOF-driven synthesis of supported palladium clusters with catalytic activity for carbene-mediated chemistry, *Nat. Mater.* 16 (2017) 760–766, <https://doi.org/10.1038/nmat4910>.
- [57] T. Granchar, J. Ferrando-Soria, M. Castellano, M. Julve, J. Pasán, D. Armentano, E. Pardo, Oxamato-based coordination polymers: recent advances in multifunctional magnetic materials, *Chem. Commun.* 50 (2014) 7569–7585, <https://doi.org/10.1039/C4CC01734J>.
- [58] R. Adam, M. Mon, R. Greco, L.H.G. Kalinke, A. Vidal-Moya, A. Fernandez, R.E. P. Winpenny, A. Doménech-Carbó, A. Leyva-Pérez, D. Armentano, E. Pardo, J. Ferrando-Soria, Self-assembly of catalytically active supramolecular coordination compounds within metal-organic frameworks, *J. Am. Chem. Soc.* 141 (2019) 10350–10360, <https://doi.org/10.1021/jacs.9b03914>.
- [59] M. Mon, R. Adam, J. Ferrando-Soria, A. Corma, D. Armentano, E. Pardo, A. Leyva-Pérez, Stabilized Ru(H₂O)₆³⁺ in confined spaces (MOFs and zeolites) catalyzes the imination of primary alcohols under atmospheric conditions with wide scope, *ACS Catal.* 8 (2018) 10401–10406, <https://doi.org/10.1021/acscatal.8b03228>.
- [60] M. Tejada-Serrano, M. Mon, B. Ross, F. Gonnell, J. Ferrando-Soria, A. Corma, A. Leyva-Pérez, D. Armentano, E. Pardo, Isolated Fe(III)-O sites catalyze the hydrogenation of acetylene in ethylene feeds under front-end industrial conditions, *J. Am. Chem. Soc.* 140 (2018) 8827–8832, <https://doi.org/10.1021/jacs.8b04669>.
- [61] M.A. Rivero-Crespo, M. Mon, J. Ferrando-Soria, C.W. Lopes, M. Boronat, A. Leyva-Pérez, A. Corma, J.C. Hernández-Garrido, M. López-Haro, J.J. Calvino, E.V. Ramos-Fernandez, D. Armentano, E. Pardo, Confined Pt₁¹⁺ water clusters in a MOF catalyze the low-temperature water-gas shift reaction with both CO₂ oxygen atoms coming from water, *Angew. Chem. Int. Ed. Engl.* 57 (2018) 17094–17099, <https://doi.org/10.1021/jacs.0c12367>.
- [62] J. Wang, T. Qin, T.G. Chen, L. Wimmer, J.T. Edwards, J. Cornella, B. Vokits, S. A. Shaw, P.S. Baran, Nickel-catalyzed cross-coupling of redox-active esters with boronic acids, *Angew. Chem. Int. Ed. Engl.* 55 (2016) 9676–9679, <https://doi.org/10.1002/anie.201605463>.
- [63] W. Chen, L. Sun, X. Huang, J. Wang, Y. Peng, G. Song, Ligand-free nickel-catalyzed 1,4-addition of arylboronic acids to α,β -unsaturated carbonyl compounds, *Adv. Synth. Catal.* 357 (2015) 1474–1482, <https://doi.org/10.1002/adsc.201400761>.
- [64] L. Shan, G. Wu, M. Liu, W. Gao, J. Ding, X. Huang, H. Wu, α,β -Diaryl unsaturated ketones via palladium catalyzed ring-opening of cyclopropanones with organoboronic acids, *Org. Chem. Front.* 5 (2018) 1651–1654, <https://doi.org/10.1039/C8QO00241J>.
- [65] A. Vijayan, D.N. Rao, K.V. Radhakrishnan, P.Y.S. Lam, P. Das, Advances in carbon-element bond construction under Chan-Lam cross-coupling conditions: a second decade, *Synthesis* 53 (2021) 805–847, <https://doi.org/10.1055/s-0040-1705971>.
- [66] A. Martins, U. Marquardt, N. Kasravi, D. Alberico, M. Lautens, Synthesis of substituted benzoxacycles via a domino ortho-alkylation/Heck coupling sequence, *J. Org. Chem.* 71 (2006) 4937–4942, <https://doi.org/10.1021/jo060552l>.
- [67] M.P. Denieul, B. Laursen, R. Hazell, T. Skrydstrup, Synthesis of the benzophenone fragment of balanol via an intramolecular cyclization event, *J. Org. Chem.* 65 (2000) 6052–6060, <https://doi.org/10.1021/jo000750r>.
- [68] X. Li, B. Zhou, R.Z. Yang, F.M. Yang, R.X. Liang, R.R. Liu, Y.X. Jia, Palladium-catalyzed enantioselective intramolecular dearomative Heck reaction, *J. Am. Chem. Soc.* 140 (2018) 13945–13951, <https://doi.org/10.1021/jacs.8b09186>.
- [69] M. Lautens, J.F. Paquin, S. Pigué, Palladium-catalyzed sequential alkylation-alkenylation reactions. Application to the synthesis of 2-substituted-4-benzoxepines and 2,5-disubstituted-4-benzoxepines, *J. Org. Chem.* 67 (2002) 3972–3974, <https://doi.org/10.1021/jo0107296>.
- [70] E. Coya, N. Sotomayor, E. Lete, Intramolecular direct arylation and heck reactions in the formation of medium-sized rings: selective synthesis of fused indolizine, pyrroloazepine and pyrroloazocine systems, *Adv. Synth. Catal.* 356 (2014) 1853–1865, <https://doi.org/10.1002/adsc.201400075>.
- [71] M. Beller, A. Zapf, Intermolecular Heck reaction: palladium-catalyzed coupling reactions for industrial fine chemicals syntheses, in: E. Negishi (Ed.), *Handbook of Organopalladium Chemistry for Organic Synthesis*, John Wiley & Sons, Inc., 2002, pp. 1209–1222.
- [72] M. Alami, F. Liron, M. Gervais, J.F. Peyrat, J.D. Brion, Ortho substituents direct regioselective addition of tributyltin hydride to unsymmetrical diaryl (or heteroaryl) alkynes: an efficient route to stannylated stilbene derivatives, *Angew. Chem. Int. Ed. Engl.* 41 (2002) 1578–1580, [https://doi.org/10.1002/1521-3757\(20020503\)](https://doi.org/10.1002/1521-3757(20020503)).
- [73] D.V. Kadnikov, R.C. Larock, Palladium-catalyzed carbonylative annulation of internal alkynes: synthesis of 3,4-disubstituted coumarins, *J. Org. Chem.* 68 (2003) 9423–9432, <https://doi.org/10.1021/jo0350763>.
- [74] S.H. Kwak, S.J. Lim, H.J. Yoo, J.E. Ha, Y.D. Gong, Intramolecular Mizoroki-Heck reaction of 2-thiosubstituted acrylates for the synthesis of 3-substituted benzo[b]thiophene-2-carboxylates, *Synthesis* 48 (2016) 4131–4142, <https://doi.org/10.1055/s-0035-1562613>.
- [75] H. Madhurima, J. Krishna, G. Satyanarayana, Concise three-step strategy for the synthesis of 2-benzoxepin-3(1H)-ones, *Synthesis* 47 (2015) 1245–1254, <https://doi.org/10.1055/s-0034-1379901>.
- [76] C. He, S. Guo, L. Huang, A. Lei, Copper catalyzed arylation/C–C bond activation: an approach toward α -aryl ketones, *J. Am. Chem. Soc.* 132 (2010) 8273–8275, <https://doi.org/10.1021/ja1033777>.
- [77] F. Gánes-Portolés, R. Greco, J. Oliver-Meseguer, J. Castellanos-Soriano, M. Consuelo Jiménez, M. López-Haro, J.C. Hernández-Garrido, M. Boronat, R. Pérez-Ruiz, A. Leyva-Pérez, Regioirregular and catalytic Mizoroki-Heck

- reactions, *Nat. Catal.* 4 (4) (2021) 293–303, <https://doi.org/10.1038/s41929-021-00592-3>.
- [78] P. Wucher, L. Caporaso, P. Roesle, F. Ragone, L. Cavallo, S. Mecking, I. Göttker-Schnetmann, Breaking the regioselectivity rule for acrylate insertion in the Mizoroki–Heck reaction, *Proc. Natl. Acad. Sci. USA* 108 (22) (2011) 8955–8959, <https://doi.org/10.1073/pnas.1101497108>.
- [79] I.P. Beletskaya, A.V. Cheprakov, Palladacycles in catalysis – a critical survey, *J. Organomet. Chem.* 689 (2004) 4055–4082, <https://doi.org/10.1016/j.jorganchem.2004.07.054>.
- [80] C. Nájera, Oxime-derived palladacycles: applications in catalysis, *ChemCatChem* 8 (2016) 1865–1881, <https://doi.org/10.1002/cctc.201600035>.
- [81] J. Mo, J. Xiao, The Heck reaction of electron-rich olefins with regiocontrol by hydrogen-bond donors, *Angew. Chem. Int. Ed. Engl.* 45 (2006) 4152–4157, <https://doi.org/10.1002/anie.200600799>.
- [82] L. Qin, X. Ren, Y. Lu, Y. Li, J. Zhou, Intermolecular Mizoroki–Heck reaction of aliphatic olefins with high selectivity for substitution at the internal position, *Angew. Chem. Int. Ed. Engl.* 51 (2012) 5915–5919, <https://doi.org/10.1002/anie.201201806>.
- [83] A. Fardost, J. Lindh, P.J.R. Sjöberg, M. Larhed, Palladium(II)-catalyzed decarboxylative heck arylations of acyclic electron-rich olefins with internal selectivity, *Adv. Synth. Catal.* 356 (2014) 870–878, <https://doi.org/10.1002/adsc.201301004>.
- [84] A. Dhakshinamoorthy, A.M. Asiri, H. García, Metal–organic frameworks as multifunctional solid catalysts, *Trends Chem.* 2 (2020) 454–466, <https://doi.org/10.1016/j.trechm.2020.02.00>.
- [85] A. Dhakshinamoorthy, A.M. Asiri, H. García, Mixed-metal or mixed-linker metal organic frameworks as heterogeneous catalysts, *Catal. Sci. Technol.* 6 (2016) 5238–5261, <https://doi.org/10.1039/C6CY00695G>.