ARTICLE

A Jackpot C-H Activation Protocol Using Simple Ruthenium Catalyst in Deep Eutectic Solvents

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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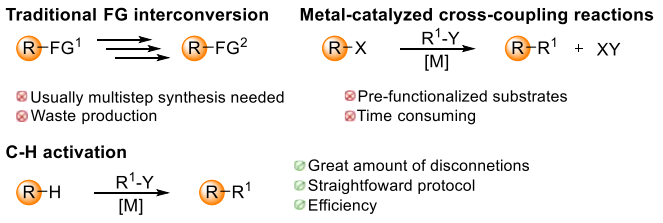
Deep eutectic solvents (DESs) have been used for the first time as a sustainable medium in a ruthenium-catalyzed C-H activation reaction. This study describes an efficient, simple and straightfoward protocol for the direct C-H activation of a broad range of aromatic substrates and reaction with several olefins and alkynes, affording interesting heterocyclic systems as products. A simple, robust and commercially available ruthenium catalyst was used along with different DESs under different reaction conditions. This methodology was compatible with the use of either internal or external oxidant (oxygen from air) using a catalytical amount of copper salts for the last case. Different functional directing groups were well tolerated obtaining promising results, that were comparable and even better that those reported in literature. Also, the reaction medium could be recycled up to 3 consecutive times and this transformation could be carried out on a gram scale with excellent yield. Several green chemistry mass metrics, such as reaction mass efficiency, process mass intensity and optimun efficiency, as well as qualitative parametres were calculated and compared with those of the classical protocols, showing the advantages of using DES for C-H activation processes.

Introduction

Efficiency, selectivity and greenness are fundamental aspects to be considered when developing a successful methodology according to the definition of Sustainable Chemistry.[1] In this context, the transition-metal catalysed activation of inert and ubiquitous C-H bonds has emerged as a powerful strategy for the design and development of environmentally benign synthetic procedures. Even though significant limitations regarding the scope and selectivity are still present, this methodology allows the direct transformation of C-H bonds avoiding the use (or synthesis) of pre-functionalized reagents, providing a more straightforward and sustainable protocol (Scheme 1).[2-4]



Scheme 1. Traditional functional group interconversion and metal-catalysed cross-coupling reactions *versus* C-H activation

Consequently, this strategy has being applied efficiently for the synthesis of pharmaceuticals, natural compounds, agrochemicals and other useful products.[5-7] Various transition-metal catalysts have been used in this transformation, with complex designed Ru(II) catalysts showing their efficiency.[8-10] Due to the limitless presence of C-H bonds in all organic molecules, an important challenge of this transformation is the selective C-H activation at a single and strategic position in the presence of other C-H bonds in the molecule, being the use of directing groups (DG) generally required for site-selective functionalizations.[11-12] A broad range of functional groups have been employed in different C-H activations as directing groups such as amides, pyridines, carboxylic acids, ketones, etc.[13-15]

Recent trends towards improving the sustainability of C-H activation reactions include the use of earth-abundant metal catalysts[16] or electrochemical protocols,[17-18] among others.[19-21] However, the main drawbacks of all these methodologies are the use of expensive and complex metal catalyst; the need of starting materials with a specific and complex structure; the employment of toxic and hazardous organic solvents; the utilization of expensive salts in stoichiometric amounts, such as Ag(I) derivative ones, producing potentially toxic metal waste; and the use of stoichiometric amounts of bases for activating the unreacted C-H bond which usually leads to the generation of undesired waste products. Hence, the development of benign and environmentally friendly C-H activation methodologies remains in demand.

There are a few reports describing C-H activation reactions in sustainable reaction media such as water or biomass-derived solvents.[21-24] Regarding Deep Eutectic Solvents (DESs), emerging sustainable solvents with unique and tunable properties,[25-30] only two examples reported their used as reaction media (Scheme 2).[31-32] However, in these procedures some disadvantages in terms of sustainability are present: the

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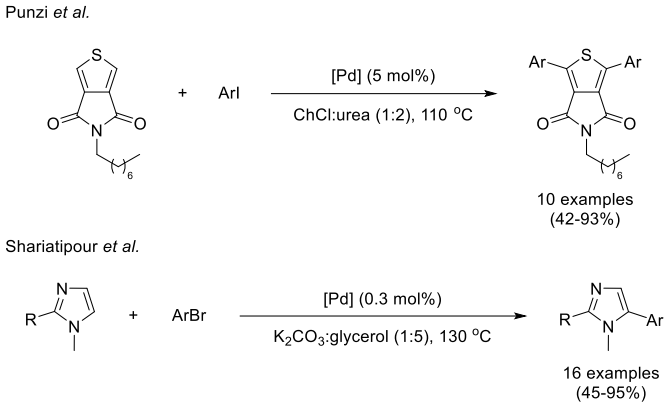
† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

use of complex and expensive palladium catalysts and ligands, several additives, high temperatures are required together with quite specific and structurally complex starting materials, being successfully applied to a narrow scope of substrates. Thus, the development of versatile, readily accessible, simpler, waste-free and environmentally-friendly C-H activation reactions would be of great interest.



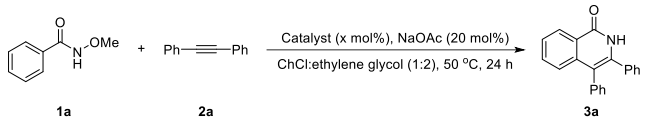
Scheme 2. Previously reported C-H activation reactions in DESs

Herein, we demonstrate the broad potential of DESs to replace volatile organic solvents, since a versatile, simple and efficient methodology for ruthenium-catalyzed C-H activation reactions has been developed in a sustainable reaction medium using a robust and readily commercially available catalyst. The adjustable and unique properties of DESs allowed the use of a broad range of suitable substrates and even exploit native DGs for the C-H activation transformation.

Results and Discussion

Our investigation started with the optimization of the catalytic system for the reaction between *N*-methoxybenzamide (**1a**) and diphenylacetylene (**2a**) as model reaction to yield interesting product **3a** (Table 1).

Table 1. Optimization of the ruthenium catalyst



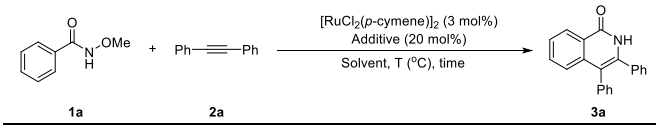
1a 2a 3a

Entry	Catalyst (x mol%)	Yield (%)[b]
1	$[RuCl_2(p\text{-cymene})]_2$ (1 mol%)	64
2	$[RuCl_2(p\text{-cymene})]_2$ (2 mol%)	69
3	$[RuCl_2(p\text{-cymene})]_2$ (3 mol%)	88
4	$[RuCl_2(p\text{-cymene})]_2$ (5 mol%)	57
5	$RuCl_3{\cdot}xH_2O$ (3 mol%)	0
6	$Ru(acac)_3$ (3 mol%)	0

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), NaOAc (20 mol%), catalyst (1-5 mol%) at 50 °C in 0.5 mL of solvent; [b] Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

Isoquinolone derivatives are remarkable structural motifs present in many natural products[33-34] with pharmacological and biological activities such as antitumor,[35] anti-inflammatory,[36] antihypertensive,[37] and so on.[38] Besides that, the selection of substrate **1a** with an internal oxidizing N-O bond facilitates the recovery of the initial oxidation state of the ruthenium catalyst, according to the stablished mechanism (Scheme 3).[39] Initial attempts pointed out $[RuCl_2(p\text{-cymene})]_2$ as a highly efficient catalyst for this C-H activation reaction in DESs (entries 1-4), with only 3 mol% of catalyst loading being required to achieve the best result (entry 3). Other simple ruthenium catalysts were tested with no success (entries 5-6).

Table 2. Optimization of the reaction conditions.[a]



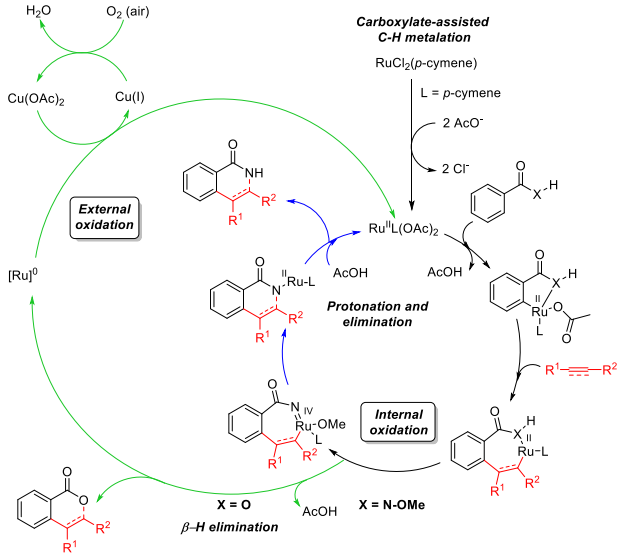
1a 2a 3a

Entry	Solvent	Additive	T (°C)	time (h)	Yield (%)[b]
1	ChCl:urea (1:2)	NaOAc	50	24	5
2	AcChCl:urea (1:2)	NaOAc	50	24	45
3	AcChCl:acetamide (1:2)	NaOAc	50	24	19
4	ChCl:glycerol (1:2)	NaOAc	50	24	41
5	Ph_3PMeBr:glycerol (1:2)	NaOAc	50	24	44
6	ChCl:ethylene glycol (1:2)	NaOAc	50	24	88
7	ChCl:ethylene glycol (1:2)	NaOAc	30	24	43
8	ChCl:ethylene glycol (1:2)	NaOAc	70	24	>99
9	ChCl:ethylene glycol (1:2)	NaOAc	90	24	>99
10	ChCl:ethylene glycol (1:2)	NaOAc	70	8	55
11	**ChCl:ethylene glycol (1:2)**	**NaOAc**	**70**	**16**	**>99**
12	ChCl:ethylene glycol (1:2)	-	70	16	0
13	ChCl:ethylene glycol (1:2)	Na_2CO_3	70	16	9
14	ChCl:ethylene glycol (1:2)	$NaHCO_3$	70	16	8
15	ChCl:ethylene glycol (1:2)	NaOH	70	16	14
16	ChCl:ethylene glycol (1:2)	Na_3PO_4	70	16	10

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), additive (20 mol%), $[RuCl_2(p\text{-cymene})]_2$ (3 mol%) in 0.5 mL of solvent; [b] Yield determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

Once the best catalyst was established, other reaction parameters were evaluated (Table 2). Choline chloride (ChCl):ethylene glycol gave the best results (88% yield, entry 6), among all the DESs tested (entries 1-6). Then, both temperature and reaction time were optimized, leading to product **3a** in quantitative yields at 70 °C after 16 h (compare entry 6 with entries 7-9 and entries 10-11). The absence of the basic additive (NaOAc) or a change to other sodium bases resulted in a significant drop in the reaction yield (entries 12-16), which

seems to indicate the important role of the acetate in the possible carboxylate-assisted C-H metalation pathway.



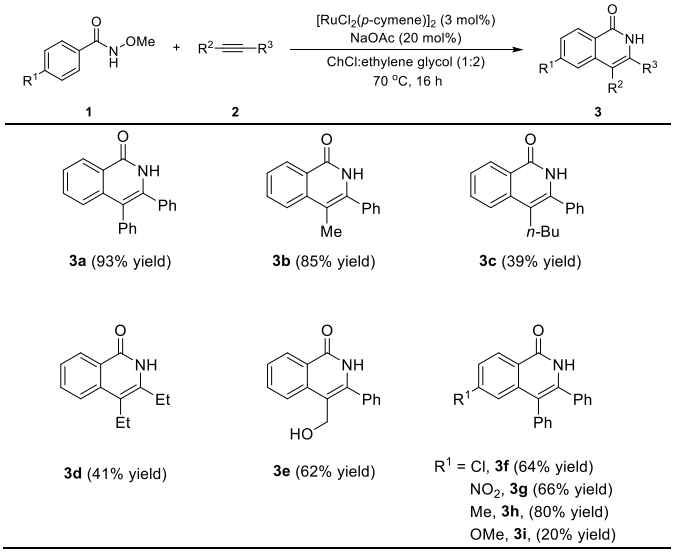
Scheme 3. General mechanism for C-H activation

In order to prove the versatility of the process, the scope of the reaction was evaluated using different disubstituted alkynes as substrates (Table 3). In general, good to excellent yields were obtained when internal alkynes with aromatic substituents were used, with moderate yields being achieved for aryl-alkyl or alkyl-alkyl substituted alkynes. Electron-withdrawing substituents at *para* position in reagent **1** seems to favour the reaction outcome, with strong electron-donating substituent (R^1 = OMe) giving the expected product **3i** in 20% yield providing the importance of the deprotonation step in the mechanism (Scheme 3). Also, the crude of the reaction was analysed by ^{1}H-NMR, where no by-products were observed. With longer reaction times, the presence of an electron donating group in the substrate, lead to a slight increase for the formation of **3i** (see ESI). As expected, this seems to indicate that decreases the reaction rate.

To survey the applicability of this methodology, the C-H activation of an arene bearing the DG directly attached to an oxygen atom was tested in order to synthesize benzofuran derivatives. Benzofuran scaffolds are common structural motifs in bioactive compounds present in several drugs, with interesting physiological and chemotherapeutic properties.[40-42] Thus, applying the same reaction conditions to starting material **7,** the corresponding disubstituted benzofuran **8** was obtained with good yield (Scheme 4).

One of the main advantages of the use of DESs as reaction media lies in the possible recyclability of the solvent which is a crucial point for the sustainability of the process.[43] Once the reaction was finished, the organic compounds were extracted with a biomass-derived solvent (2-MeTHF)[44] and the remaining DES mixture was reused, after being dried under vacuum. A new batch of fresh reagents **1a**, **2a**, ruthenium catalyst and NaOAc was added, observing that this process could be repeated up to 3 consecutive cycles without a significant loss of yield (Figure 1). However, and probably due to the presence of huge amounts of different salts which may modify the intrinsic structure of DES, the yield dropped down to around 50% after the fifth cycle.

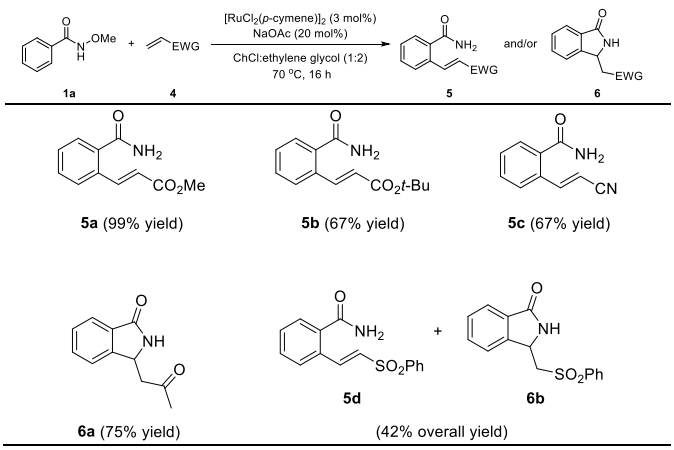
Table 3. Scope of the C-H activation reaction using disubstituted alkynes.[a]



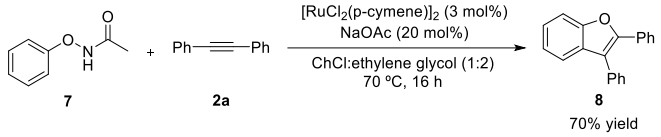
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), NaOAc (20 mol%), [$RuCl_2$(*p*-cymene)]$_2$ (3 mol%) in 1.0 mL of ChCl:ethylene glycol (1:2) at 70 °C for 16 h; isolated yield after flash column chromatography or precipitation with Et_2O.

To enlarge the scope of the reaction, we attempted to explore other more challenging types of substrates, which could be efficiently coupled without an internal oxidant motif required to increase the low oxidation state of the final ruthenium species.[45] This external oxidant strategy has also a broader substrate applicability (Scheme 3). Thus, the use of containing native DGs molecules were tested since they will increase the atom economy of the process and reduce the overall generated waste.

Table 4. Scope of the C-H activation reaction using electron poor olefins.[a]



[a] Reaction conditions: **1a** (0.2 mmol), **4** (0.24 mmol), NaOAc (20 mol%), [$RuCl_2$(*p*-cymene)]$_2$ (3 mol%) in 1.0 mL of ChCl:ethylene glycol (1:2) at 70 °C for 16 h; isolated yield after flash column chromatography.



Scheme 4. C-H activation of *N*-phenoxyacetamide and diphenylacetylene

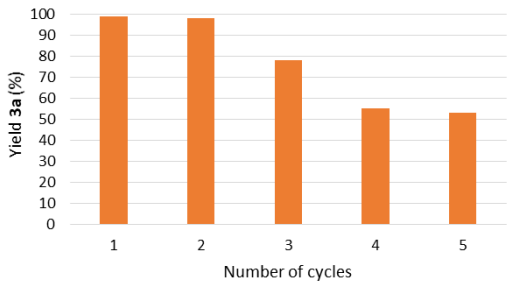
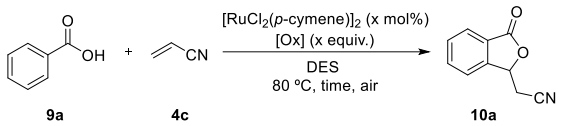


Figure 1. Recyclability of the C-H activation reaction in ChCl:ethylene glycol (1:2).

A brief optimization for the reaction between benzoic acid (**7a**) and acrylonitrile (**4c**) was performed (Table 5). Among all tested DESs (entries 1-10), betaine:HFIP mixture afforded the desired product with excellent conversion (entry 10). Then, both catalyst loading and reaction time were optimized, with only 2 mol% of ruthenium catalyst after 12 h being required to achieve almost quantitative yield (compare entries 10-13). Changing the standard $Cu(OAc)_2$ oxidant for $CuCl_2$ in the presence of NaOAc, resulted in a significant drop in the reaction yield (entry 14). Less amount of metallic oxidant intermediate was essayed, being possible to reduce the catalyst loading to only 10 mol% (compare entries 13 with 15-18), being the oxygen of the air, the final oxidant of the process. In the absence of the metallic oxidant intermediate a significant drop in the conversion of the desired product **10a** (entry 19) was observed, evidencing the need of some metallic intermediate to re-oxidize the ruthenium(0) species. To prove the potential of the DES used versus VOCs, the reaction was performed in reflux HFIP obtaining only traces of the product **10a** (entry 20). A similar result was obtained when the reaction was performed at higher temperature in a pressure tube (entry 21). These results demonstrate that the use of DESs, is ideal to perform this reaction and avoids the air pollution, due to their volatility even including a low boiling point component.

To survey the scope and versatility of catalyst in this C-H transformation, several olefins bearing electron-withdrawing groups were evaluated (Table 6). Remarkably, without any further purification step, excellent yields were obtained when benzoic acid (**9a**) was reacted with different electron poor olefins. Surprisingly, a mixture of both acyclic (**11**) and cyclic (**10b**) products were achieved when methyl acrylate was used as a substrate. As in the previous case, electron-withdrawing substituents at *para* position in reagent **4** seems also to favour the reaction. The presence of a strong electron-donating substituent (R = OMe) in the aromatic ring, gave the expected product (**10f**) only in 50% yield. These results seem to highlight the importance of the deprotonation step in the mechanism stablished (Scheme 3).

Table 5. Optimization of the reaction conditions.[a]



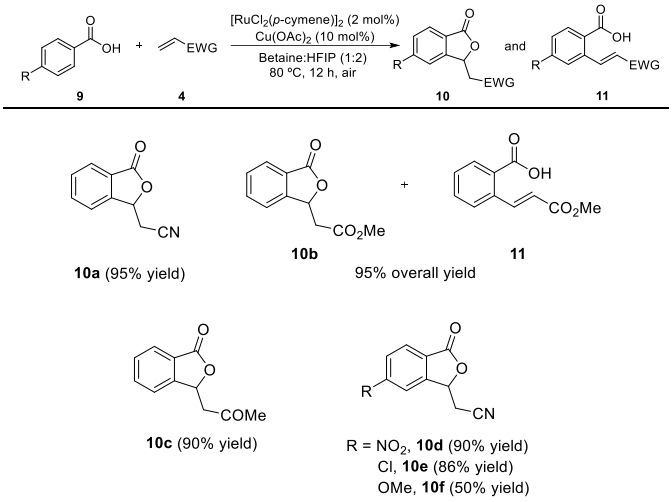
Entry	Solvent	[Ox] (equiv.)	[Ru] (mol%)	time (h)	Conv. (%)[b]
1	ChCl:glycerol (1:2)	$Cu(OAc)_2$ (2)	3	24	5
2	ChCl:urea (1:2)	$Cu(OAc)_2$ (2)	3	24	-
3	AcChCl:acetamide (1:2)	$Cu(OAc)_2$ (2)	3	24	-
4	ChCl:ethylene glycol (1:2)	$Cu(OAc)_2$ (2)	3	24	38
5	TBAB:ethylene glycol (1:2)	$Cu(OAc)_2$ (2)	3	24	-
6	MTPB:ethylene glycol (1:3)	$Cu(OAc)_2$ (2)	3	24	-
7	ChCl:1,2-propanediol (1:3)	$Cu(OAc)_2$ (2)	3	24	30
8	ChCl:resorcinol (1:2)	$Cu(OAc)_2$ (2)	3	24	-
9	L-carnitine:HFIP (1:2)	$Cu(OAc)_2$ (2)	3	24	40
10	Betaine:HFIP (1:2)	$Cu(OAc)_2$ (2)	3	24	>99
11	Betaine:HFIP (1:2)	$Cu(OAc)_2$ (2)	3	16	95[c]
12	Betaine:HFIP (1:2)	$Cu(OAc)_2$ (2)	3	12	94[c]
13	Betaine:HFIP (1:2)	$Cu(OAc)_2$ (2)	2	12	95[c]
14	Betaine:HFIP (1:2)	$CuCl_2$ (2)	2	12	36[d]
15	Betaine:HFIP (1:2)	$Cu(OAc)_2$ (1)	2	12	93[c]
16	Betaine:HFIP (1:2)	$Cu(OAc)_2$ (0.5)	2	12	95[c]
17	Betaine:HFIP (1:2)	$Cu(OAc)_2$ (0.25)	2	12	94[c]
18	**Betaine:HFIP (1:2)**	**$Cu(OAc)_2$ (0.1)**	**2**	**12**	**95[c]**
19	Betaine:HFIP (1:2)	-	2	12	28
20	HFIP	$Cu(OAc)_2$ (0.1)	2	12	traces
21[e]	HFIP	$Cu(OAc)_2$ (0.1)	2	12	traces

[a] Reaction conditions: **7a** (0.1 mmol), **4c** (0.2 mmol), [Ox] (2-0.1equiv.), $[RuCl_2(p\text{-cymene})]_2$ (3-2 mol%) in 0.25 mL of solvent at 80 °C for the corresponding time; [b] Conversion calculated by ^1H NMR of the crude of the reaction; [c] Isolated yield after flash column chromatography. [d] NaOAc (20 mol%) was added. [e] Performed at HFIP reflux. [f] Performed in a pressure tube.

In addition, the reaction using several disubstituted alkynes to synthesize isocoumarin derivatives was also essayed (Table 7) since isocoumarin scaffolds are a class of biosynthetically, structurally, and pharmacologically intriguing natural products used in drug discovery, pharmaceutical and medicinal

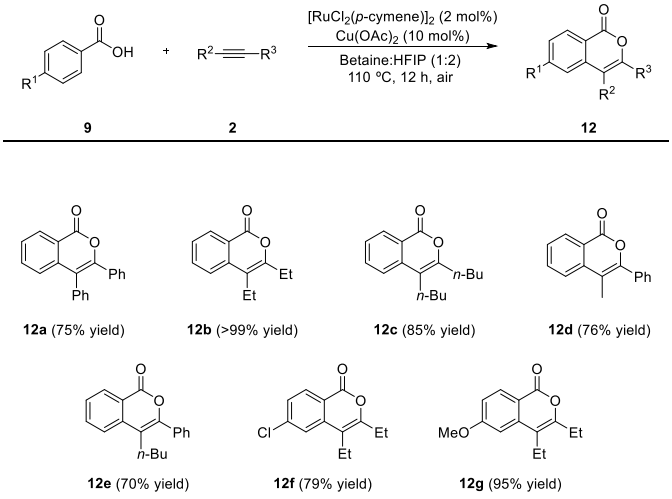
chemistry, and organic synthesis.[46] Good to quantitative yields were achieved when internal alkynes with aromatic, aryl-alkyl and alkyl-alkyl substituents were used, although an increase in the temperature was needed. Conversely to previous results, substituents in the aromatic ring at *para* position have less influence on this transformation, since similar results were obtained either bearing an electron-withdrawing group or an electron-donating one (**12f** and **12g**, respectively).

Table 6. Scope of the C-H activation reaction using electron poor olefins with benzoic acid derivatives.[a]

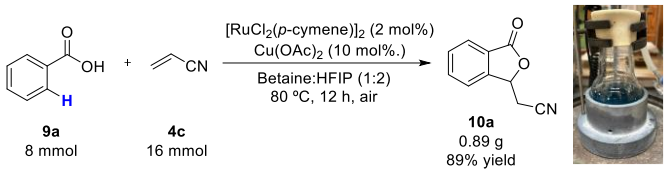


[a] Reaction conditions: **9** (0.2 mmol), **4** (0.4 mmol), $Cu(OAc)_2$ (10 mol%.), $[RuCl_2(p\text{-cymene})]_2$ (2 mol%) in 0.5 mL of betaine:HFIP (1:2) at 80 °C for 12 h; isolated yield after flash column chromatography.

Table 7. Scope of the C-H activation reaction using disubstituted alkynes with benzoic acid derivatives.[a]



[a] Reaction conditions: **9** (0.2 mmol), **2** (0.4 mmol), $Cu(OAc)_2$ (10 mol%.), $[RuCl_2(p\text{-cymene})]_2$ (2 mol%) in 0.5 mL of betaine:HFIP (1:2) at 110 °C for 12 h; [b] Isolated yield after flash column chromatography

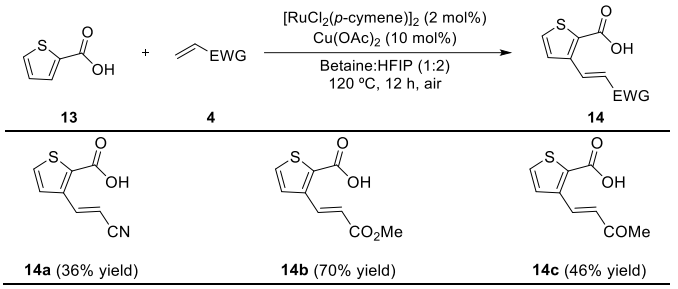


Scheme 5. Gram scale reaction

Furthermore, to prove the applicability of this methodology, the reaction was carried out on a gram scale (Scheme 3), being the desired product **10a** obtained by precipitation through addition of small amount of water in excellent yield (see ESI).

The reaction also proceeded when 2-thiophenecarboxylic acid was used as substrate. The reaction with different olefins bearing electron-withdrawing groups gave as products, heterocycles that are commonly found in drug candidates (Table 8).[47] Moderate to good yields were achieved obtaining exclusively, in all the cases, the acyclic derivative.

Table 8. Scope of the C-H activation reaction using electron poor olefins with 2-thiophenecarboxylic acid.[a]

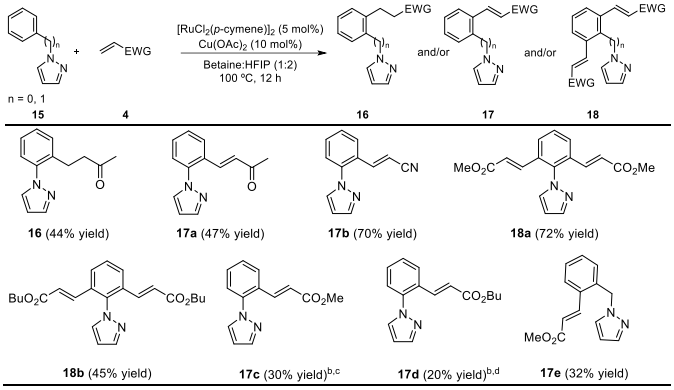


[a] Reaction conditions: **13** (0.2 mmol), **4** (0.4 mmol), $Cu(OAc)_2$ (10 mol%), $[RuCl_2(p\text{-cymene})]_2$ (2 mol%) in 0.5 mL of betaine:HFIP (1:2) at 120 °C for 12 h; isolated yield after flash column chromatography.

Among all classes of heterocycles, pyrazoles are scaffolds of vast medicinal values present in several drugs as structural core. Some arylpyrazoles have exhibited anti-inflammatory, anticancer and antimicrobial activities among others.[48] Thus, to prove the broad scope of substrates of this transformation, it was decided to test different aryl pyrazole derivatives and electron poor olefins as substrates (Table 9). A slight increase in the temperature and in catalyst loading was required for this reaction, obtaining moderate to good yields. Surprisingly, the corresponding saturated (**16**) and unsaturated compound (**17a**) were obtained with similar ratios, when methyl vinyl ketone was used as substrate. In some cases, the corresponding double addition product to 1-phenylpyrazole was observed (compounds **18a** and **18b),** when different alkyl acrylate derivatives were employed along with small amounts of the monoalkenylated derivative. Even though it is well stablished that this transformation undergoes directed double alkenylation under Pd or Rh catalysts at high temperatures, [49-50] the use of Ru catalyst has been proved to provide a mixture of both the mono and the double alkenylated product.[51] To obtain the monoalkenylated product, a single equivalent of **4** was used. However, a mixture of compounds **17** and **18** was observed.

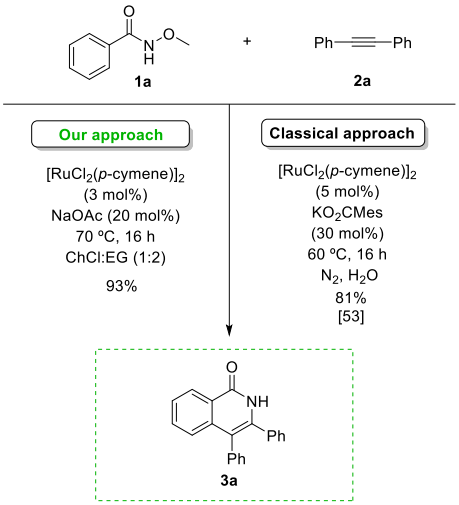
Still, it was possible to separate them, affording the corresponding monoalkenylated products with moderate yields (**17c** and **17d**). The incorporation of an additional methylene group between the pyrazole motif and the aromatic ring (**15e**), avoided the double activation, being only the monoalkenylated product observed (**17e**).

Table 9. Scope of the C-H activation reaction using electron poor olefins with 1-arylpyrazole derivatives.[a]



[a] Reaction conditions: **15** (0.2 mmol), **4** (0.4 mmol), $Cu(OAc)_2$ (10 mol%.), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) in 0.5 mL of Betaine:HFIP (1:2) at 100 °C for 12 h; isolated yield after flash column chromatography. [b] 1 equiv. of **4** was used. [c] 25% yield of **18a** was obtained. [d] 23% yield of **18b** was obtained

With the aim of gaining a clearer view of the possible impact the our methodology proposed has on the environment, several green chemistry metrics, such as atom economy (AE), reaction mass efficiency (RME), process mass intensity (PMI) and optimum efficiency (OE) were calculated.[52] Therefore, we evaluated the metrics of our methodology and the classical approach (CA) to perform a C-H activation. We appraised these metrics for the synthesis of isoquinolines[53] and benzofuran derivatives[54] since both were our model reactions. Initially, a study of the synthesis of compound **3a** was evaluated for two discrete approaches as shown in Scheme 6.



Scheme 6. Synthetic routes to synthesize compound **3a**

The metrics for these two methodologies are given in Table 10. The synthesis of the starting material **1a** has not been considered in the calculations since both methodologies synthesize the starting material following the same protocol. A few sustainable considerations that should be taken into account previously to the calculations are that the CA is performed under N_2 atmosphere, is extracted with AcOEt and could not be recycled in comparison with our proposal that is compatible with air atmosphere, uses 2-MeTHF and could be recycled at least 3 consecutive times.

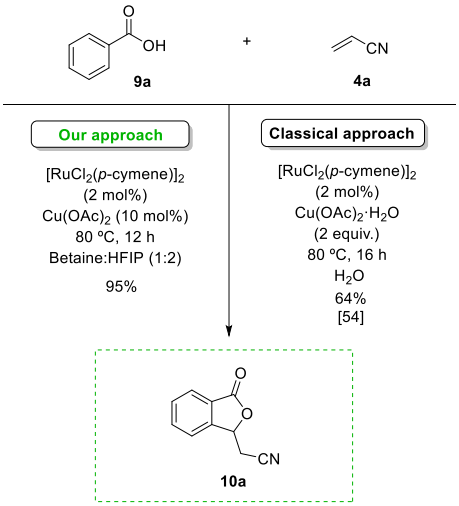
From these metrics it is clear that our approach provides slightly higher yield. As would be expected, same results were obtained in the case of the AE since both approaches use the same reagents. Our proposal does better than the classical one in terms of RME and OE. This is mainly due to the use of 1:2 equivalence of **1a**:**2a**, increasing waste production in the case of CA. A huge difference in the case of the PMI values is observed. For the case of CA, 1267 g of input material per g of product produced with the solvents and the work up step (compare PMIr with PMIs and PMIw) increasing significantly the waste generated.

Table 10. Quantitative metrics of our approach and the classical one to synthesize compound **3a**

Route	Yield (%)	AE (%)	RME (%)	OE (%)	PMI (g/g)	PMIr[a] (g/g)	PMIs[b] (g/g)	PMIw[c] (g/g)
Ours[1]	93	90	76	84	336	13	332	322
CA	81	90	47	53	1267	20	1263	1247

[a] Process mass intensity: reaction. [b] Process mass intensity: solvents. [c] Process mass intensity: work up.

Then, the metrics for the synthesis of compound **10a** were appraised for two methodologies as shown in Scheme 7.



Scheme 7. Synthetic routes to synthesize compound **10a**

Also, in this case the synthesis of the starting materials was not taken into account since both of them are commercially available. The metrics appraised for these two approaches are described in Table 11.

Table 11. Quantitative metrics of our approach and the classical one to synthesize compound **10a**

Route	Yield (%)	AE (%)	RME (%)	OE (%)	PMI (g/g)	PMIr[a] (g/g)	PMIs[b] (g/g)	PMIw[c] (g/g)
Ours[2]	95	99	72	73	559	18	556	541
CA	64	99	49	49	1835	52	5323	5332

[a] Process mass intensity: reaction. [b] Process mass intensity: solvents. [c] Process mass intensity: work up.

Our approach outperformed in terms of yield, superseding the classical one by 30%. As would be expected same results were obtained in the case of the AE since both approaches use the same reagents. Also, our proposal was superior to the classical one in terms of RME and OE by almost 25%. This could be explained because of the low yield in CA in comparison with our approach. A tremendous difference in the case of the PMI values is observed, being for the case of CA, 1835 g of input material per g of product produced (compare PMIr with PMIs and PMIw). Due to the use of an excess of solvents and due to a purification by column chromatography instead of just simply low temperature distillation of the crude of the reaction.

Finally, not only mass metrics were calculated but also qualitative parameters were evaluated since they are focused on the innate safety of the materials used. These metrics were classified by Clark *et al*[52] as green, amber, or red flags to design preferred, acceptable-some issues and undesirable conditions. The qualitative evaluation is shown in Table 12.

In the case of the synthesis of **3a**, it is clear that the flags assigned of both approaches to reagents used and the work up are in concordance with those results calculated previously, highlighting the waste produced. Regarding the solvents, the CA employs solvents as hexane and AcOEt, whereas in our synthesis 2-MeTHF is used, which is considered to be a renewable solvent.[44] In general any significant caution should be taken in the case of health and safety category.

Although none of the approaches for the synthesis of **10a** performs in a preferred manner considering the solvents and health and safety, it is worth mentioning that once HFIP is part of the DES structure its toxicity decreases, since almost no volatility was observed. Both proposals slightly outperformed the preferred energy category by 10 ºC which it can be considered as acceptable. The mass metrics calculated previously are in harmony with the qualitative ones considering the work up of the CA, which uses excess of solvents and a column chromatography to purify the desired product, in comparison with our methodology which uses a low temperature distillation or filtration.

Table 12. Qualitative appraisal of all the methodologies

Steps	Solvents	Flag	Health and safety	Flag	Reagents used	Flag	Energy	Flag	Work up	Flag
Classical approach for the synthesis of 3a										
1	Hexane, AcOEt		KO_2CMes: unknown hazards		Use excess of reagents Catalyst		60 ºC		Excess of solvents Chromatography	
Our synthesis of 3a										
1	2-MeTHF		None		Catalyst		70 ºC		Chromatography	
Classical approach for the synthesis of 10a										
1	NH_3, hexane, AcOEt		NH_3: H314, H335, H410		Catalyst		80 ºC		Excess of solvents Chromatography	
Our synthesis of 10a										
1	*HFIP 2-MeTHF		*HFIP: H314, H373, H332		Catalyst		80 ºC		Low temperature distillation or filtration	

Finally, comparing quantitative and qualitative green metrics, it is clear that, in the case of the synthesis of **3a**, our proposal significantly outperformed towards the CA, having excellent yield, AE, RME, OE and low values for PMI. Regarding the synthesis of **10a**, similar results were obtained with the qualitative metrics. However, when considering both the mass and the qualitative metrics, it is obvious that our proposal is a better option due to the higher efficiency, its excellent RMI and OE, and lower PMIs, making this approach more desirable.

Experimental Section

General

Full general statements were described elsewhere.[53]

General synthetical procedures

N-methoxyamides[54] **1** and *N*-phenoxyacetamide[55] **7** were synthesized following procedures reported in literature.

General procedure for the preparation of DESs

A mixture of hydrogen-bond donor and hydrogen-bond acceptor compound, with the previously specified molar ratio, was added in a round bottom flask under an inert atmosphere. The mixture was stirred for 30 minutes in a T range between 65 and 80 °C obtaining the corresponding DES.

General procedure for the synthesis of isoquinolones.

N-methoxybenzamide derivative **1** (0.2 mmol), alkyne **2** (0.24 mmol), NaOAc (20 mol%) and $[RuCl_2(p\text{-cymene})]_2$ (3 mol%) were stirred in 1.0 mL DES at 70 °C for 16 h. The mixture was quenched with water and extracted with 2-MeTHF (3 x 5 mL). The combined organic phases were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. Product **3** was purified by chromatography on silica gel (with 1/1 hexane/ethyl acetate elution) The compound was full characterized and the data for known ones were in concordance with the data reported in literature (see ESI).

General procedure for *N*-methoxybenzamides olefination

N-methoxybenzamide derivative **1** (0.2 mmol), electron-poor olefin **4** (0.24 mmol), NaOAc (20 mol%) and $[RuCl_2(p\text{-cymene})]_2$ (3 mol%) were stirred in 1.0 mL DES at 70 °C for 16 h. The mixture was quenched with water and extracted with 2-MeTHF (3 x 5 mL). The combined organic phases were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. Products **5** and **6** were purified by chromatography on silica gel (usually with 1/1 hexane/ethyl acetate elution). Unless otherwise stated, all the compounds were full characterized and the data for known ones were in concordance with the data reported in literature (see ESI).

(*E*)-2-(2-(Phenylsulfonyl)vinyl)benzamide + 3-((phenylsulfonyl)methyl)isoindolin-1-one (5d + 6b**):** White solid, R_f= 0.43 (Hexane/AcOEt 1/4); t_r =19.68 min;m.p. 145-150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) – an equilibrium between the acyclic and cyclic (aprox. 2:1) compounds was found: δ= 8.35 (s, 1H, NH), 8.05 (s, 2H, NH_2), 8.01 (d, *J* = 15.4 Hz, 2H, *H*C=CHSO$_2$Ph), 7.95-7.90 (m, 7H, ArH), 7.90-7.85 (m, 3H, ArH), 7.80-7.70 (m, 4H, ArH), 7.65-7.60 (m, 11H, ArH), 7.57 (d, *J* = 15.4 Hz, 2H, HC=C*H*SO$_2$Ph), 7.60-7.55 (m, 3H, ArH), 7.50-7.45 (m, 6H, ArH), 4.90 (dd, *J* = 7.8, 3.9 Hz, 1H, C*H*CH$_2$SO$_2$Ph), 4.07 (dd, *J* = 14.4, 4.1 Hz, 1H, CHC*H*$_2$SO$_2$Ph), 3.80-3.60 (m, 1H, CHC*H*$_2$SO$_2$Ph) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ= 169.7, 169.0, 144.8, 140.6, 139.9, 139.3, 138.1, 134.0, 133.6, 131.9, 131.7, 130.6, 130.0, 129.9, 129.6, 129.5, 128.9, 128.6, 127.8, 127.8, 127.5, 127.1, 123.7, 122.9, 58.2, 50.8 ppm; IR (ATR): ν = 3397, 3232, 3062, 2989, 2935, 1704, 1295, 1141, 728 cm^{-1}; MS (70 eV, EI): *m/z* (%): 145 (M^+ - SO$_2$Ph, 100%), 132 (47), 77 (21); HRMS (QTOF) calculated for M^+ -SO$_2$Ph 146.0606, found 145.9801.

General procedure for synthesis of benzofuran derivative

N-phenoxyacetamide **7** (0.2 mmol); diphenylacetylene **2a** (0.24 mmol), NaOAc (20 mol%) and $[RuCl_2(p\text{-cymene})]_2$ (3 mol%) were stirred in 1.0 mL DES at 70 °C for 16 h. The mixture was quenched with water and extracted with 2-MeTHF (3 x 5 mL). The combined organic phases were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. Product **8** was purified by chromatography on silica gel (hexane elution). The compound was full characterized, and the data were in concordance with the data reported in literature (see ESI).

General Procedure for Recycling Experiments

The reaction was performed according to the general procedure. Once the reaction was completed, the reaction mixture was cooled to room temperature, and 2-MeTHF (3 x 1 mL) was added to the reaction vessel. The biphasic mixture was stirred for 5 min, and the upper phase (VOC-phase, mainly unreacted organic reagents, and products) was separated by decantation and analysed by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. The eutectic mixture was dried under vacuum and was charged again with fresh reagents, catalyst and base, repeating the process.

General procedure for benzoic acid derivatives olefination

Benzoic acid derivative **9** (0.2 mmol), electron-poor olefin **4** (0.4 mmol), $Cu(OAc)_2$ (10 mol%) and $[RuCl_2(p\text{-cymene})]_2$ (2 mol%) were stirred in 1.0 mL DES at 70 °C for 12 h under air atmosphere. The mixture was quenched with water and extracted with 2-MeTHF (3 x 5 mL). The combined organic phases were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. Products **10** and **11** were purified by chromatography on silica gel (usually with 9/1 hexane/ethyl acetate elution). Unless otherwise stated, all the compounds were full characterized and the data for known ones were in concordance with the data reported in literature (see ESI).

2-(6-nitro-3-oxo-1,3-dihydroisobenzofuran-1-yl)acetonitrile (10e**):** Yellowish solid; R_f= 0.63 (Hexane/AcOEt 1/1); m.p. 200-203 °C; t_r = 15.60 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 8.53 (dd, *J* = 10.0, 1.6 Hz, 2H, ArH), 8.18 (d, *J* = 8.6 Hz, 1H, ArH), 5.80 (t, *J* = 5.4 Hz, 1H, C*H*CH$_2$CN), 3.16 (dd, *J* = 5.5, 3.0 Hz, 2H, CHC*H*$_2$CN) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ= 166.2, 151.9, 147.3, 127.8, 126.2, 117.9, 74.6, 29.7, 23.7 ppm; IR (ATR): ν = 2950, 2920, 2854, 2360, 1755, 1645, 1543, 1369 cm^{-1}; MS (70 eV, EI): *m/z* (%): 167 (4%), 149 (100), 104 (6), 57 (10); HRMS (QTOF) calculated for M^+ -CH$_2$CN 178.0140, found 178.0182.

General procedure for isocoumarin synthesis

Benzoic acid derivative **9** (0.2 mmol), alkyne **2** (0.4 mmol), $Cu(OAc)_2$ (10 mol%.) and $[RuCl_2(p\text{-cymene})]_2$ (2 mol%) were stirred in 1.0 mL DES at 110 °C for 12 h. under air atmosphere The mixture was quenched with water and extracted with 2-MeTHF (3 x 5 mL). The combined organic phases were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. Products **12** were purified by chromatography on silica gel (usually with 8/2 hexane/ethyl acetate elution). Unless otherwise stated, all the compounds were full characterized and the data for known ones were in concordance with the data reported in literature (see ESI).

General procedure for gram scale reaction

Benzoic acid (8 mmol), acrylonitrile (16 mmol), $Cu(OAc)_2$ (10 mol%) and $[RuCl_2(p\text{-cymene})]_2$ (2 mol%) were stirred in 16 mL DES at 70 °C for 12 h under air atmosphere. The mixture was quenched with water (20 mL) and a little amount of AcOEt (6 mL) and the desired product was isolated by filtration.

General procedure for thiophenecarboxylic acids olefination

Thiophenecarboxylic acid **13** (0.2 mmol), electron-poor olefin **4** (0.4 mmol) $Cu(OAc)_2$ (10 mol%.) and $[RuCl_2(p\text{-cymene})]_2$ (2 mol%) were stirred in 1.0 mL DES at 120 ºC for 12 h under air atmosphere. The mixture was quenched with water and extracted with 2-MeTHF (3 x 5 mL). The combined organic phases were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. Products **14** were purified by chromatography on silica gel (usually with 1/1 hexane/ethyl acetate elution). Unless otherwise stated, all the compounds were full characterized and the data for known ones were in concordance with the data reported in literature (see ESI).

(*E*)-3-(3-methoxy-3-oxoprop-1-en-1-yl)thiophene-2-carboxylic acid (14b**)**: Yellowish solid, R_f= 0.60 (Hexane/AcOEt 3/2); m.p. 68-70 ºC ; t_r =10.52 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.68 (d, J = 15.9 Hz, 1H, CHC*H*CO_2Me), 7.55 – 7.45 (m, 1H), 7.33 (tdd, J = 6.3, 4.3, 2.1 Hz, 2H), 6.27 (d, J = 15.9 Hz, 1H, C*H*$CHCO_2$Me), 3.80 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ= 167.7, 138.3, 137.5, 128.1, 126.9, 125.1, 117.4, 51.7 ppm; IR (ATR): ν = 3089, 1720, 1530 cm^{-1}; MS (70 eV, EI): *m/z* (%): 168 (M^+-CO_2, 70%), 137 (100), 109 (47). HRMS (QTOF) calculated for M^+-CO_2 167.0167, found 167.9067.

(*E*)-3-(3-oxobut-1-en-1-yl)thiophene-2-carboxylic acid (14c**)**: yellowish solid, R_f=0.67 (Hexane/AcOEt 1/1); m.p. 65-67 ºC; 10.34 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 7.56 – 7.48 (m, 2H, ArH + C*H*CHCOMe), 7.36 (ddd, J = 5.1, 2.9, 0.6 Hz, 1H, ArH), 7.32 (d, J = 0.9 Hz, 1H, ArH), 6.55 (d, J = 16.2 Hz, 1H, CHC*H*COMe), 2.36 (s, 3H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ= 198.8, 137.8, 137.0, 128.8, 127.3, 127.1, 125.3, 27.6 ppm; IR (ATR): ν = 3089, 2919, 2857, 1712, 1658, 1511 cm^{-1}; MS (70 eV, EI): *m/z* (%): 152 (M^+-CO_2, 62%), 137 (100), 109 (59). HRMS (QTOF) calculated for M^+-CO_2 152,0218, found 152.8318.

General procedure for arylpyrazole olefination

Arylpyrazole derivative **15** (0.2 mmol), electron-poor olefin **4** (0.4 mmol), $Cu(OAc)_2$ (10 mol%.) and $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) were stirred in 1.0 mL DES at 100 ºC for 12 h under air atmosphere. The mixture was quenched with water and extracted with 2-MeTHF (3 x 5 mL). The combined organic phases were dried over $MgSO_4$, followed by evaporation under reduced pressure to remove the solvent. Products **16**, **17** and **18** were purified by chromatography on silica gel (usually with 8/2 hexane/ethyl acetate elution). Unless otherwise stated, all the compounds were full characterized and the data for known ones were in concordance with the data reported in literature (see ESI).

(*E*)-4-(2-(1H-pyrazol-1-yl)phenyl)but-3-en-2-one (17a**)**: yelowish oil, R_f= 0.49 (Hexane/AcOEt 3/2); t_r = 14.169 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.85 – 7.69 (m, 3H, ArH), 7.59 – 7.42 (m, 4H, ArH), 6.69 – 6.52 (m, 2H, C*H*C*H*$COCH_3$), 2.29 (s, 1H, CHCHCOC*H*$_3$) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ= 198.6, 141.5, 140.1, 139.4, 130.9, 130.3, 129.6, 128.7, 127.8, 126.3, 107.6, 27.2 ppm; IR (ATR): ν = 2924, 2854, 1670, 1500 cm^{-1}; MS (70 eV, EI): *m/z* (%): 212 (M+, 10%), 169 (100); HRMS (QTOF) calculated for M^+ 212.0950, found 212.1950.

Dimethyl 3,3'-(2-(1H-pyrazol-1-yl)-1,3-phenylene)(2E,2'E)-diacrylate (18a**)**: yellow solid, R_f= 0.50 (Hexane/AcOEt 7/3); m.p. 68-70 ºC ; t_r =18.03 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.85 (d, J = 1.5 Hz, 1H, ArH), 7.74 (d, J = 7.8 Hz, 2H, ArH), 7.60 – 7.45 (m, 2H, ArH), 7.11 (d, J = 16.1 Hz, 2H, C*H*$CHCO_2$Me x2), 6.62 – 6.52 (m, 1H, ArH), 6.29 (d, J = 16.1 Hz, 2H, CHC*H*CO_2Me x2), 3.73 (s, 6H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ= 166.7, 141.6, 138.9, 138.7, 133.7, 132.9, 129.8 (2C), 128.7(2C), 121.6, 107.6, 51.9 ppm; IR (ATR): ν = 3080, 2924, 2854, 1701, 1631, 1500 cm^{-1}; MS (70 eV, EI): *m/z* (%): 312 (M^+, <10%), 253 (100), 193 (75). HRMS (QTOF) calculated for M^+ 312.1115, found 312.1108.

Conclusions

We have proved that the ruthenium-catalysed C-H activation of different substrates can be achieved for the first time in DESs, under either aerobic or anaerobic conditions in a versatile and straightforward, using a robust and commercially available catalyst without the use of difficult-handle and complex metal catalyst, therefore, contributing towards the sustainability of the process. The use of DESs, as selection of green reaction media, in this kind of transformations has been described as having notable advantages compared to previously reported methods. This simple procedure was compatible with a broad range of different substrates, avoiding the pre-functionalization and the use of quite specific and complex structurally starting materials, being a direct and widely applicable protocol even at gram-scale. Besides, the methodology was compatible with different substrates, using either an internal or external oxidant, and even using DGs, obtaining interesting heterocyclic products. Moreover, in terms of sustainability, it is worthy to mention: i) the high adaptability of the DES in this transformation allowed the recyclability of the reaction at least three consecutive cycles without detrimental results; ii) it was possible to perform the reaction at gram scale and the desired product was obtained by simple precipitation without any further purification step, avoiding the solvent waste. Furthermore, in the approach using the oxygen from air as the final oxidant, the amount of metallic copper salts was reduced to catalytically amounts preventing metal squander, improving the overall sustainability of the process

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the University of Alicante (VIGROB-316FI) and the Spanish Ministerio de Economia, Industria y Competitividad (PGC2018-096616-B-100) and Conselleria de Innovación, Universidades, Ciencia y Sociedad de la Generalitat Valenciana (AICO/2021/013). NE and BS thank Generalitat

Valenciana (ACIF/2020/186 and ACIF/2017/211, respectively) for their fellowships.

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