

Micellar Catalysis for a Sustainable Hydroaminomethylation Process in Water

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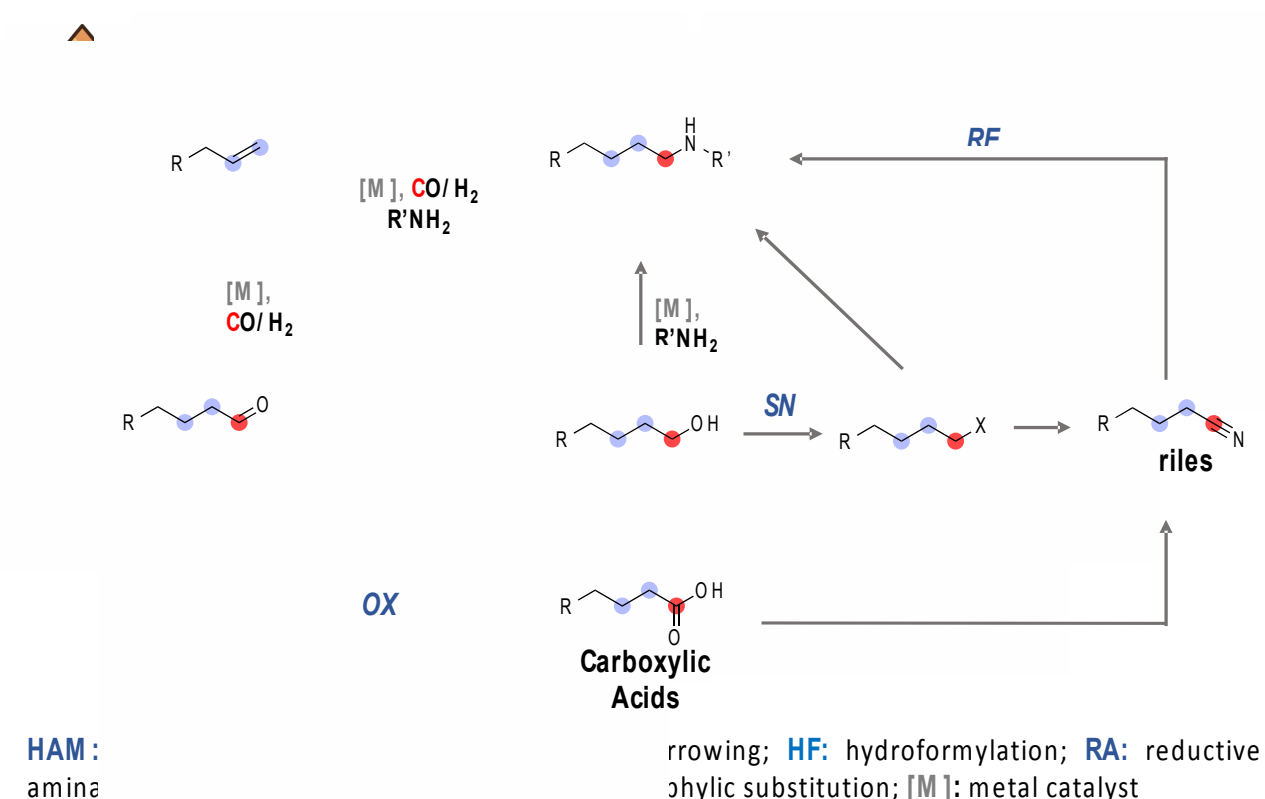
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Abstract

Hydroaminomethylation (HAM) is one of the most interesting atom-economic processes for the production of amines. Herein we report the use of combined micellar and microwave catalysis for the HAM of aniline with allylbenzene by using water as the reaction medium in high yield and regioselectivity with a full recovery of the catalyst in the water/micellar media that can be reused several times without drastic impacts on the reaction yields. The final amine is obtained as a pure product by directly eluting the reaction mixture from SCX cartridges with ethanolic ammonia. Finally, the Life Cycle Assessment of the microwave assisted micellar catalyzed process is reported confirming the sustainability of the developed methodology with respect to similar protocols. A possible extension of the proposed protocol to other substrates is also successfully explored.

Aromatic amines are very important functional groups for the synthesis of Active Pharmaceutical Ingredients (API),^{1,2} pesticides, fine chemicals, dyes, and pigments.³ Amines market is projected to be worth USD 24 Billion by 2030, with a Compounded Average Growth Rate (CAGR) of around 7.35% during the 2022 - 2030 period.⁴ The amines market is actually fluctuating as a consequence of the geopolitical situation including the war in Ukraine and the COVID related shutdown in China.⁵ Moreover, the amines market is expected to tremendously grow in the next years because of the increasing demands of these compounds with important actors as BASF SE, Lonza Corporation, and DowDuPont involved all over the world.⁴ This is directly related to the growing applications of amines in the manufacturing of agrochemicals (including crop protective agents),

API, cosmetics, and different materials including dyes. In this scenario, the impact of amine synthesis in the environment will proportionally grow with the increase of their demand. Nowadays, sustainability can be really considered as the key driver for innovation with many efforts in the chemical and pharmaceutical sectors towards cost reduction and intensification of robust eco-friendly synthetic processes.⁶ As summarized in Scheme 1, most of the approaches used for the synthesis of amines (*i.e.* reductive amination, nucleophilic substitution, hydrogen borrowing) start from compounds obtained by hydroformylation (HF) of alkenes followed by further decoration.



Scheme 1 General approaches to the synthesis of substituted amines.

These protocols mostly suffer from low atom economy and the use of impacting toxic organic solvents (*i.e.* toluene, CH_2Cl_2). During the years many efforts have been devoted towards the development of more eco-friendly approaches to the preparation of aryl amines by using sustainable media such as water in Fe-catalyzed reductive aminations,⁷ applying micellar catalysis in the alkylation of amines by alcohols,⁸ in Ullmann type reactions,⁹⁻¹³ and in Buchwald–Hartwig amination.¹⁴⁻¹⁷

Despite these reactions improvements, the purposed methodologies are still poorly atom economic and usually involve the introduction of the aromatic moiety in products obtained by HF.⁹⁻¹⁸ In this context, hydroaminomethylation (HAM) has the potential for becoming a very eco-friendly approach to the synthesis of substituted amines, however finding only a very limited application in anilines synthesis.¹⁹⁻²³ HAM is particularly suitable for the sustainable large-scale production of amines.^{24,25} As a tandem transformation composed by an HF (the most applied catalytic process in industry), followed by an imine formation and hydrogenation, HAM needs to be carefully optimized to have good chemo- and regioselectivity (linear/branched intermediate aldehydes from HF) avoiding possible side reactions such as olefin hydrogenation and isomerization, aldol condensation and alike. HAM is fully atom-economic being able to incorporate all the atoms of the starting materials and gaseous reagents inside the final product with water as the sole by-product.

This reaction has been recently reviewed by Kalck and Urrutigoity²⁰ and what becomes evident from a careful reading is that several authors are developing new HAM processes indicating them as sustainable without a real analysis of the developed process.

The original HAM version discovered by Reppe in the early 50's involved stoichiometric iron carbonyls.^{26,27} However, it was only since the 90's that this transformation started to be studied especially by Breit's and Eilbracht's groups in its Rh catalyzed version still using comparably harsh conditions ($T > 120$ °C) and non eco-friendly solvents (*i.e.* DMF, THF).²⁸⁻³⁶ Kalck and Urrutigoity³⁷ indicated how efficiently two-phase systems (*i.e.* BuOH-toluene)³⁸⁻⁴³ can work for catalyst separation from organic products in HAM reactions with implications for potential scalable applications, although. However, none of the papers explores the use of two phase systems in large scaler scale than 10 mmols and no methods for the catalysts recycle are evaluated. On the other hand, it has been generally assumed that it is not possible to perform HAM reactions in H₂O as the sole solvent, because of its negative impact on the imine/enamine formation. Vorholt and co-workers efficiently explored the use of water and different alcohols as co-solvents (*i.e.* *n*BuOH, *i*BuOH, *t*BuOH, *i*PrOH) in the HAM of water-soluble aliphatic amines (*i.e.* diethanolamine) and octene ([Rh(cod)Cl]₂, soluble sulfoxantphos, H₂O/ROH, 50 bar of syngas (CO/H₂: 1/3), and 100 °C, 6 h).⁴⁴ Again an excess of amine (3:1 with respect to 1-octene) is required as well as the use of column chromatography using classic organic solvents; the possible catalyst recycling was evaluated with not very excellent results. More recently, Zhang developed an intriguing protocol

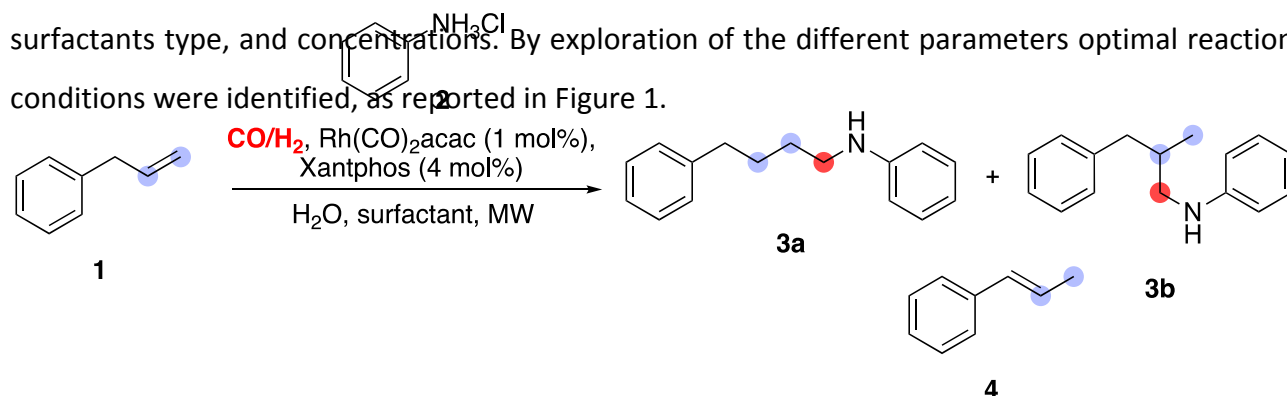
on the same substrates by using water as the sole solvent and expensive tailor-made water-soluble ligands limiting further industrial development of this protocol.⁴⁵

Micellar catalysis demonstrated to be effective to improve the possibility to perform transformations in water,⁴⁶⁻⁵⁴ actually finding many applications in chemical industry including API production,⁵⁵⁻⁵⁸ and recently drawing the attention of Glorius⁵⁹ and Schwarze⁶⁰ as a promising approach towards greener syntheses.

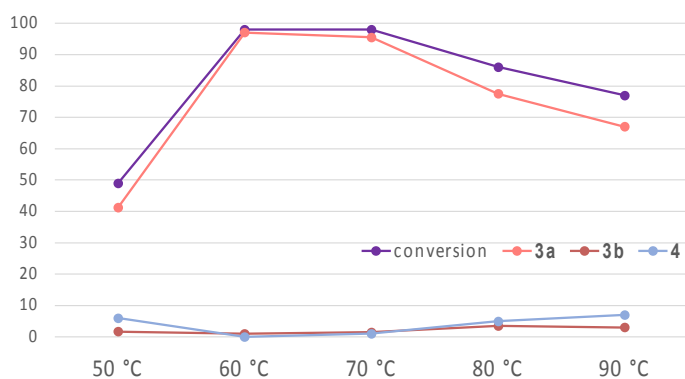
Following our interesting results on hydroformylation protocols⁶¹⁻⁶³ including a micellar catalyzed green version,⁶⁴ and on microwave-assisted HAM,⁶⁵ we recently proposed a microwave-assisted micellar catalyzed HAM of anilines (not limited to primary ones) with different olefins (not limited to styrenes) in water.⁶⁶ In this very efficient process in terms of substrate scope, reaction yields and regioselectivities obtained, we figure out that the combination of micellar and microwave (MW) catalysis is responsible for a new reaction mechanism involving a double bond carbonylation followed by reductive amination/reduction furnishing linear amines in very high yields and regioselectivities. Starting from these findings and considering that the water medium is not always synonymous with sustainability regardless of its employment, we here report our efforts towards the optimization of a sustainable process for application on larger scales quantifying the real environmental impact of the methodology. In particular, we present an improvement of the previously reported methodology entirely avoiding the use of organic solvents and implementing a full recovery of the water micellar phase retaining both the catalyst and the commercially available ligand. Looking not only to the classical greenness of our process on the basis of the 12 principles of Green Chemistry but also moving towards Circular Chemistry,⁶⁷ a Life Cycle Assessment (LCA)^{68,69} of this and other protocols used for the synthesis of (4-phenylbutyl)aniline is also reported to confirm the sustainability of the optimized HAM procedure on a comparative basis already at the lab scale. As especially in food industry the sustainability of MW heating is object of many discussions, with significant discrepancy over its real impact in terms of energy consumption due to lack of standardization,⁷⁰ we here report a careful analysis of the role of MW in the proposed protocol. We demonstrate that the energy consuming and environmental impact of MW heating in this protocol is impacting only for the 6.5% on the sustainability of the transformation, confirming that the proposed methodology can be considered as the most sustainable available so far for the synthesis of (4-phenylbutyl)aniline.

Starting from our previously reported protocol,⁶⁵ where an excess of aniline hydrochloride (1.2 equiv.) with respect to allylbenzene **1** (1 equiv.) was treated with 8.8 bar of Syngas (CO/H₂ in 1:1

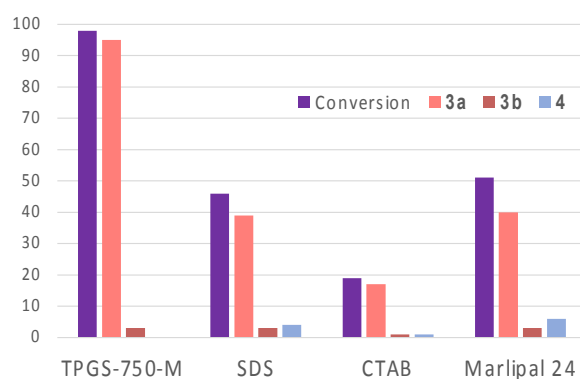
ratio) in the presence of $[\text{Rh}(\text{acac})(\text{CO})_2]$ (1 mol%) and Xantphos in an aqueous solution with 2.5 wt% of TPGS-750-M and irradiated for two cycles of 30 minutes at 70 °C, we decided to optimize the reaction conditions firstly by varying the stoichiometry, the temperature, the time, the surfactants type, and concentrations. By exploration of the different parameters optimal reaction conditions were identified, as reported in Figure 1.



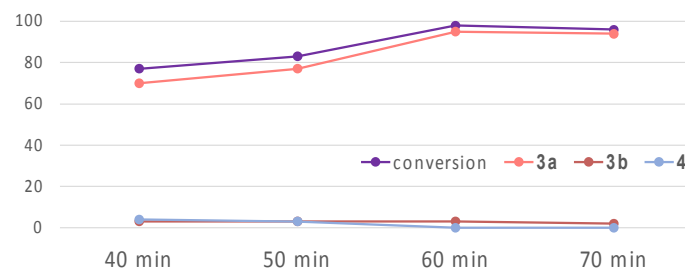
A. Temperature



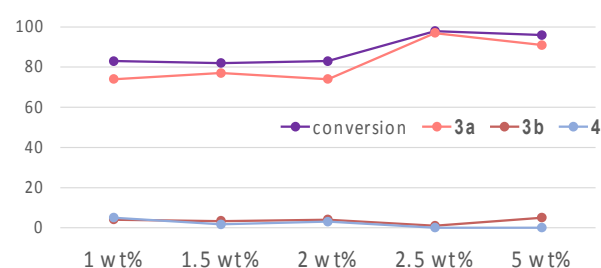
C. Different Surfactants



B. Time



D. Surfactant concentration



E. Quantity of the catalyst

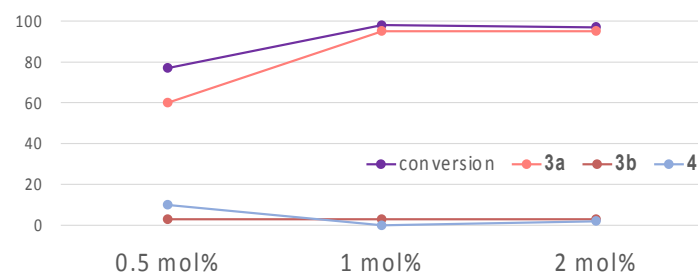


Figure 1. Allylbenzene **1** (1 mmol), PhNH_2Cl **2** (0.75 mmol), CO/H_2 (8.8 bar), $\text{Rh}(\text{CO})_2\text{acac}$ (0.0075 mmol), xantphos (0.03 mmol), H_2O (3 mL), MW at different: (A) temperature (Table S1), (B) time (Table S2), (C) use of different surfactants (Table S3), (D) concentrations of TPGS-750-M (Table S4), and (E) Quantity of the Catalyst (Table S5). Conversions are determined by GC/MS.

This allowed us to determine that a 60 minutes irradiation of the reaction mixture at 60 °C in the presence of 2.5wt% of TPGS-750-M are beneficial for our purposes and that good results can be obtained by using an excess of allylbenzene **1** (1 equiv.) with respect to aniline (0.75 equiv.) (more details in Table S6, GC-MS and NMR of the crude mixture are reported in SI). This finding is important with respect to the possible catalyst and water/micellar phase recovery, which would include the excess of **1** (0.25 equiv.) that would directly be subjected to a further HAM cycle by the addition of another 0.75 equiv. of allyl benzene **1** and 0.75 equiv. of aniline hydrochloride. With the aim to improve/evaluate the sustainability of the process a scale-up on 10 g of allylbenzene **1** (1 equiv.) with aniline hydrochloride **2** (0.75 equiv.) was set up. We found that it is possible to completely avoid classical purifications processes by directly filtering the reaction mixture on SCX ion exchange column (sulfonic acid group bonded to the surface of the silica particle, giving strong cation/amine-exchange selectivity) and flushing it with EtOH.⁷¹ The water phase contains the catalyst, the ligand, the surfactant and the excess of allyl benzene **1** and can be reused at least five times after EtOH removal *in vacuo*, by adding the starting materials **1** (0.75 eq.) and **2** (0.75 eq.) without affecting reaction yield and regioselectivity (Figure 2). The amine **3** is obtained as a pure compound after washing the SCX column with 30% NH₃ solution in EtOH and evaporating the solvent under reduced pressure.

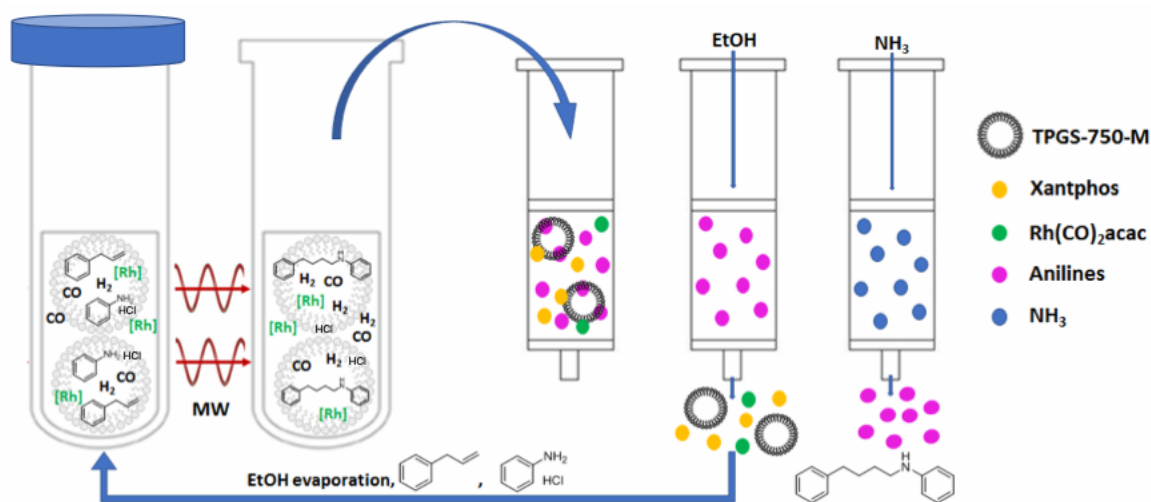
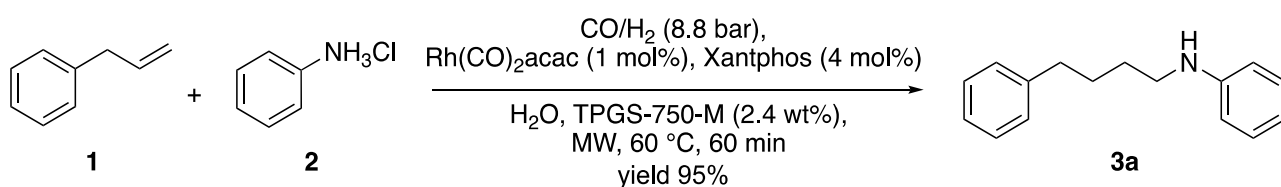


Figure 2. Catalyst and water micellar phase recovery and recycle.

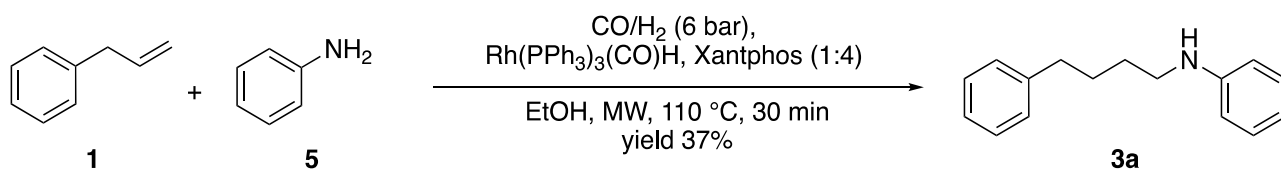
The proposed HAM protocol has been finally investigated through LCA to calculate the global environmental and energy performances to be compared with other state-of-the-art procedures. According to the ISO 14040 family standards and Guidelines,^{68,69} and the more completely

elaborated ILCD Handbook Guidelines,⁷¹ an attributional cradle-to-gate approach was implemented for the LCA calculation on the micellar catalyzed HAM of anilines as proposed in this work (Scheme 2, Process A). The functional unit chosen in this study is 1 g of the target product. The same functional unit was employed for the calculation of the environmental footprint of other processes used for the synthesis of **3a** such as: a MW assisted HAM in EtOH (Scheme 2, Process B⁶⁵), a Hydrogen Borrowing protocol (Scheme 2, Alternative 1⁷²), a cross coupling (Scheme 2, Alternative 2⁷³), and an hydroarylation (Scheme 2, Alternative 3⁷⁴). Process B is the only HAM for the synthesis of **3a** reported in the literature except for this work. The alternative procedures have been selected as they are the most efficient reported so far for the preparation of this compound.

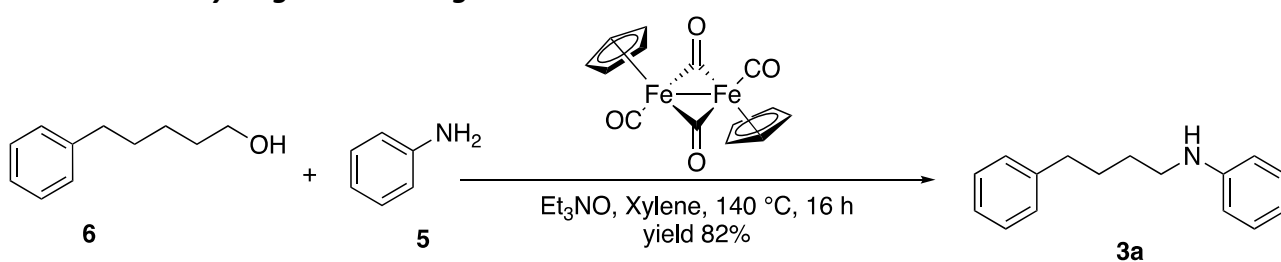
Process A: This work



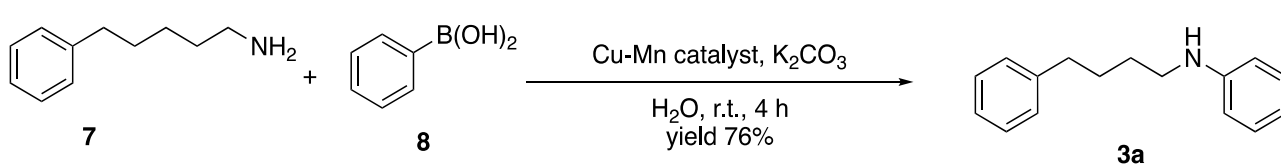
Process B: MW assisted HAM in EtOH⁶⁵



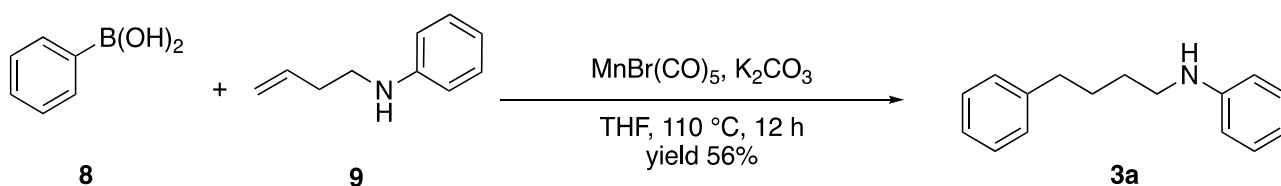
Alternative 1: Hydrogen Borrowing⁷²



Alternative 2: Cross coupling of arylboronic acids with amines⁷³



Alternative 3: Hydroarylation⁷⁴



Scheme 2. Different approaches to the synthesis of **3a**

No allocation procedure nor system expansion approach was required since all of the environmental burdens were attributed to the final product of the process, *i.e.* 1 g of the final product. The Life Cycle Inventory (LCI) data of the HAM protocol was built based on lab primary data (see Tables S7-S11 reporting the LCIs in the supporting information) and system boundaries are defined so that the foreground system is focused on the synthetic procedure, as reported in Figure 3. When needed, meta-data (conveniently customized to generate datasets for reactants, ligand, catalysts, and reaction media) and secondary data were taken from the Ecoinvent Database v. 3.6.⁷⁵ Equipment and instruments are not included in the system modelling as capital goods, but they are accounted for in terms of energy requirement for their functioning. In support of this assumption and concerning the equipment employed for the HAM protocol, a preliminary screen on the contribution of the SCX column to the environmental footprint of the targeted product confirmed that this ranges between 3% and 6%. Such a result was obtained considering the potential reusability of the SCX column for three cycles after proper reconditioning and the modelling of a waste-to energy or incineration end-of-life strategy, respectively. Although the limited equipment burden for the HAM process, the lack of information concerning the cleaning operations for the equipment used in process B and alternatives 1-3, even at a pilot scale, corroborated the decision to leave the equipment out of the LCA system modelling.

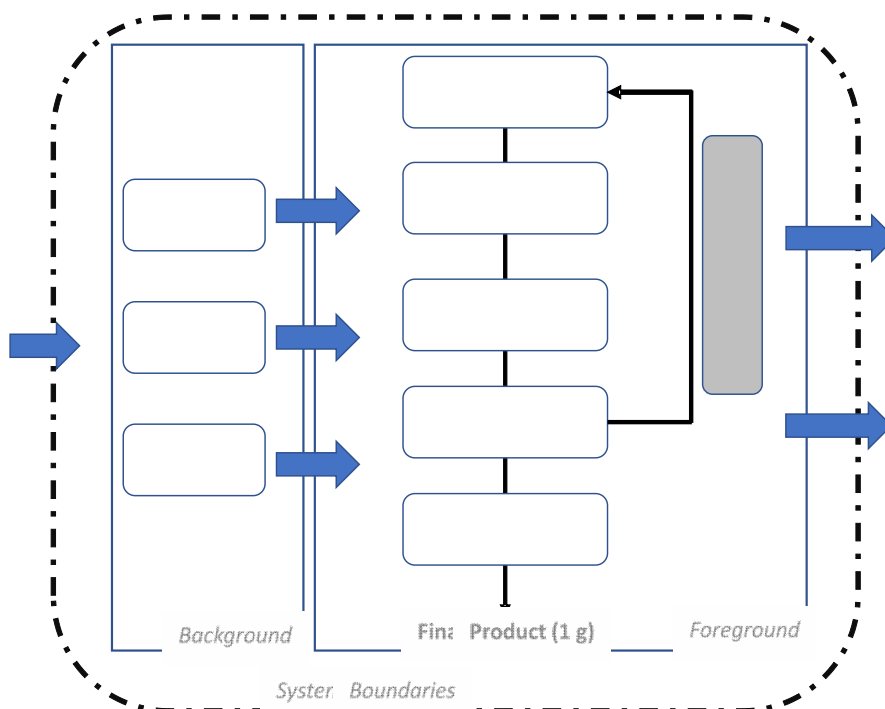


Figure 3. System boundaries of the HAM Process (Process A in this work).

The Life Cycle Impact Assessment (LCIA) method employed is the ILCD 2011 Midpoint+ method (version 1.0.9), developed by the Joint Research Centre – European Commission,⁷⁶ that allows to characterize the eco-profile of the investigated system at the midpoint level through a set of 16 impact categories and to further analyze such results at the endpoint level obtaining single scores results expressed as Eco-Points (Pt). The Cumulative Energy Demand (CED) method (version 1.09) is employed to quantify the use of the direct and indirect energy requirement during all the life cycle phases of the system expressing the results in units of Mega Joule (MJ).⁷⁷ LCA calculations are performed with software Simapro v.9.

The characterization of the environmental impacts determined by Process A is showed in Figure 4. The analysis of any single contribution highlights that electricity (MW and rotavapor consumption), catalyst and solvent (EtOH) are the major responsible for the environmental burden on all the impact categories. It is noteworthy that the recovery of the catalyst almost counterbalances its impact contribution on all the impact categories, thus highlighting the sustainability of such an approach even at the lab scale. The ligand and micellar media recovery do not contribute to the same extent to the eco-profile of Process A (details in Table S12), but this is rationally due to the very low environmental footprint of such compounds.

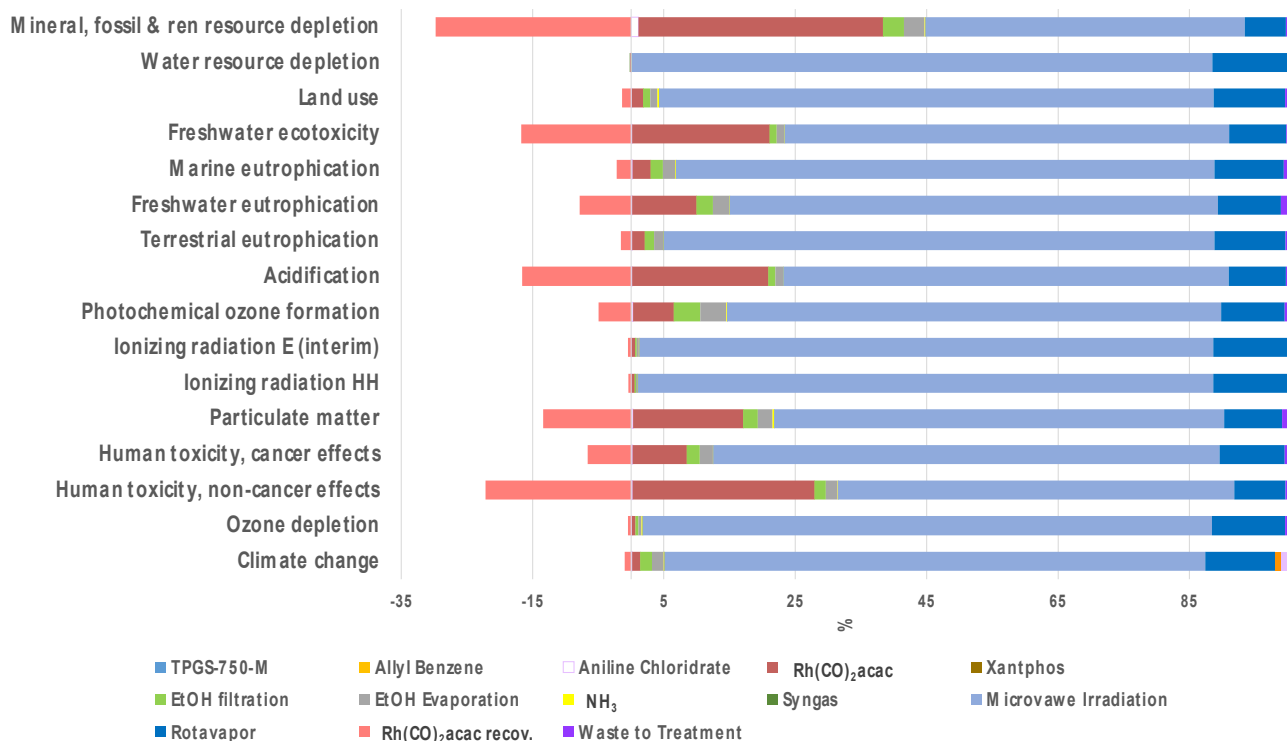


Figure 4. Summary of the characterization of the environmental impacts of the HAM process investigated in this work (Process A) expressed as a percentage of the whole environmental footprint. Method: ILCD 2011 Midpoint+ V1.10 / EC-JRC Global, equal weighting / Characterization

Figures S2-S4 reported in the Supporting Information allow to estimate the different global impact's contributions with respect to solvents and reagents (use and recovery), work-up and MW, respectively. LCA models were built also for the alternative processes and the relative environmental impacts characterization results are reported in the Supporting Information as well (see Tables S14-S18 and Figures S2-S4).

Concerning the Eco-Points calculation, the global single score results to be 1,20 mPt for process A; Figure 5 shows the contribution of any single item to the environmental impact categories confirming that the electricity consumption (0,98 mPt and 0,12 mPt, respectively) and catalyst employment (0,19 mPt) are the major inputs to the eco-profile.

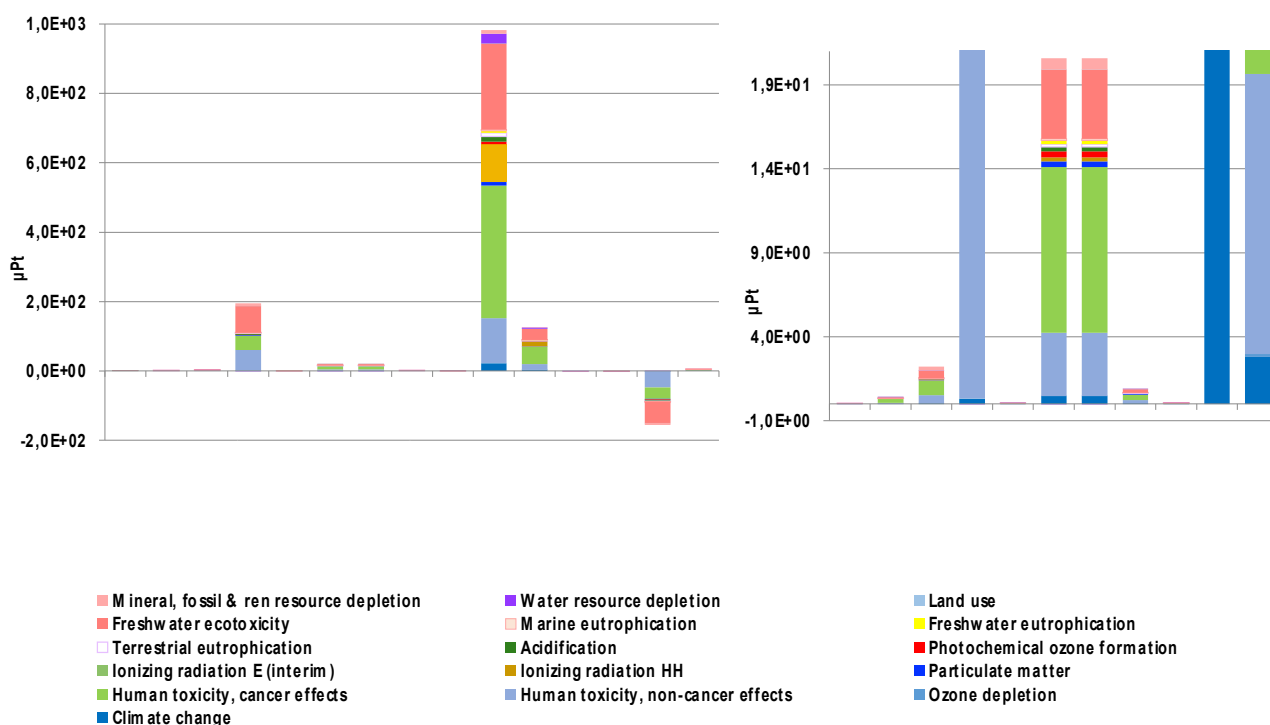


Figure 5. Single score calculation of the HAM process investigated in this work (Process A). In the Graph on the left all the parameters are reported while on the right only the less impacting ones are indicated. Method: ILCD 2011 Midpoint+ V1.10 / EC-JRC Global, equal weighting / Single score

Figure 6 shows the comparison among the endpoint results obtained for all the analysed processes in this work. The single score calculation gave the following results: 3,7 mPt for classical HAM (Process B); 12,6 mPt for Hydrogen Borrowing (Alternative 1); 10,3 mPt for Cross Coupling (Alternative 2) and 8,1 mPt for Hydroarylation (Alternative 3). In general, the eco-profiles of Alternatives 1, 2 and 3 at the endpoint level are dominated by the volumes of solvents and eluents used for filtration and chromatography, with a significant burden attributable to their treatment as a waste after the amine (**3a**) synthesis, and by the electricity consumption that is higher with respect to the corresponding MW assisted protocols A and B. This outcome is well represented in the diagrams by the contribution percentage of the toxicity categories (human health, cancer and non-cancer effects, and freshwater) to the global score with a descending trend going from

Hydrogen Borrowing (Alternative 1) to Hydroarylation (Alternative 3). In this regard, also catalyst loss plays an important role giving a sizeable contribution also to the particulate matter impact category. Although with minor absolute values, the same results are evident for the classical HAM process for which no optimization in terms of material recovery is implemented. In this case, even if the employment of MW allows for an efficient use of energy, the low process yield affects the environmental performances of the process.

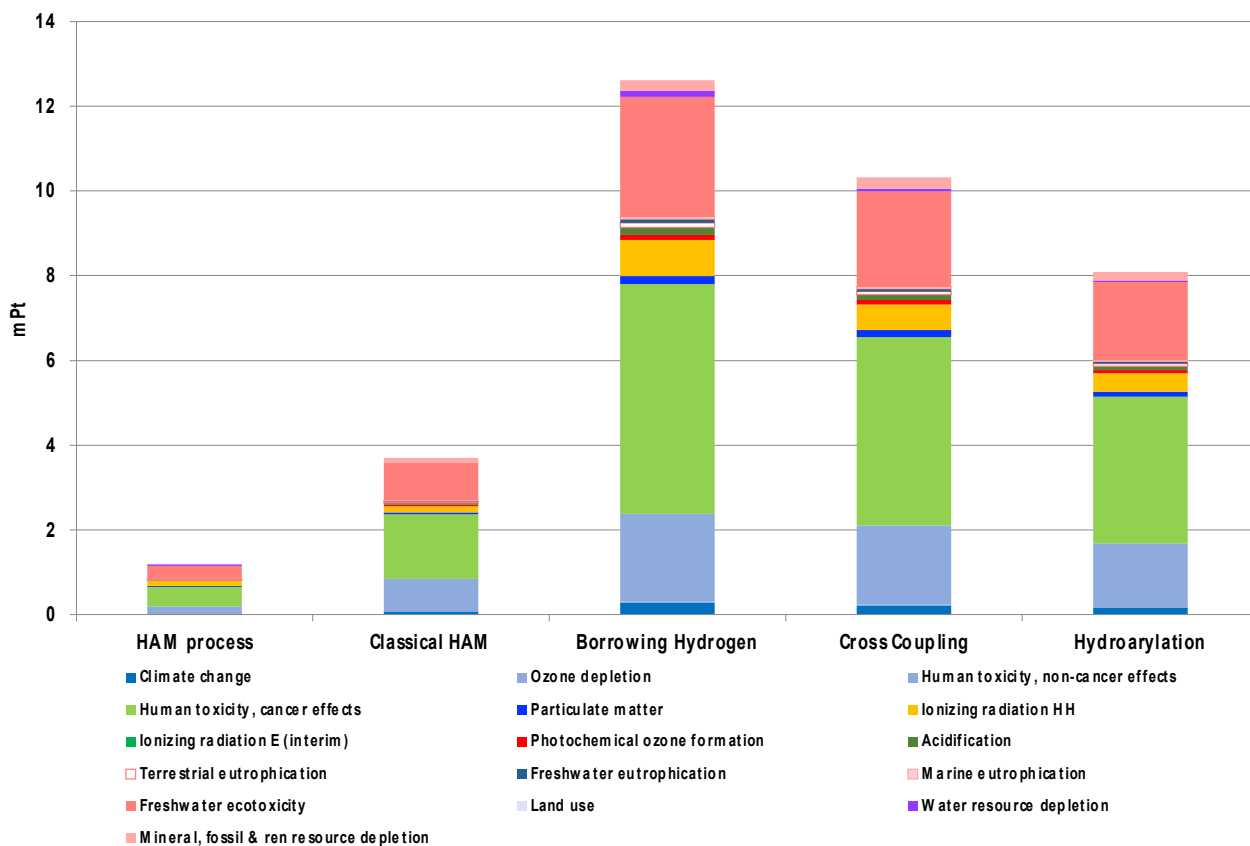


Figure 6. Single score results of all the processes investigated in this work. Method: ILCD 2011 Midpoint+ V1.10 / EC-JRC Global, equal weighting / Single score

Another important insight that can be derived from LCA calculation is the amount of direct and embedded energy (*i.e.* the energy that is used to produce a material or product) consumption relative to the micellar catalysed HAM process. In Figure 7, the CED indicator is used to show differences in terms of energy consumption among the various alternatives analysed. As expected from the inspection results of the environmental footprint, Process A performs better than all the other procedures, with a consumption of 3,5 MJ of electricity required per gram of final product, and 53,2 MJ of energy embedded in all raw materials used. The hydrogen borrowing process shows the major energy performances with a consumption of 42,8 MJ of direct energy and 321,3 MJ of energy embedded in all raw materials. Results for previously developed MW assisted HAM

in EtOH are 1,08 MJ and 176,7 MJ of direct and embedded energy, respectively. The cross coupling shows energy performances of 32,2 MJ and 298,1 MJ of direct and embedded energy, respectively. For hydroarylation results pointed out 21,9 MJ of electricity and 187,3 MJ of energy embedded in raw materials. This data shows that the HAM process, developed in this manuscript, is the most sustainable route available so far for the synthesis of **3a**.

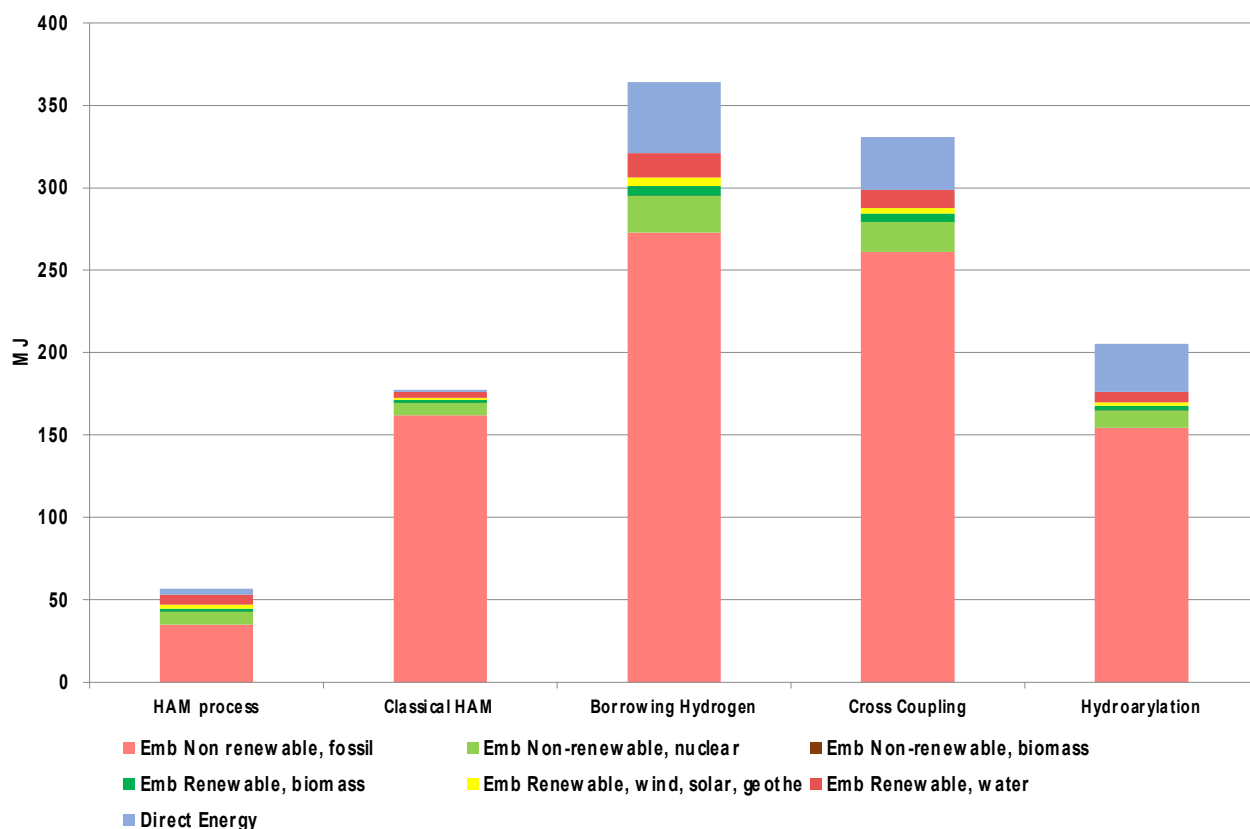
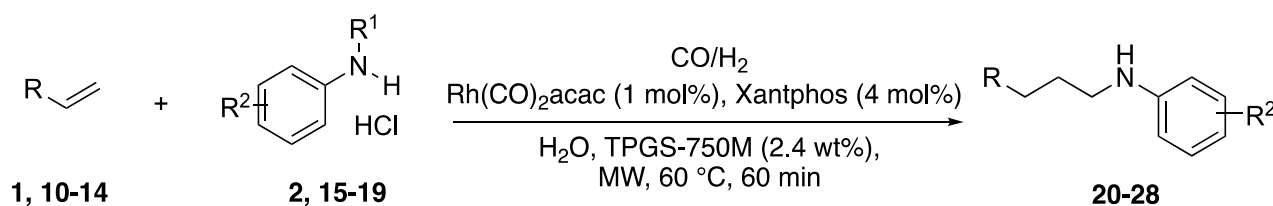
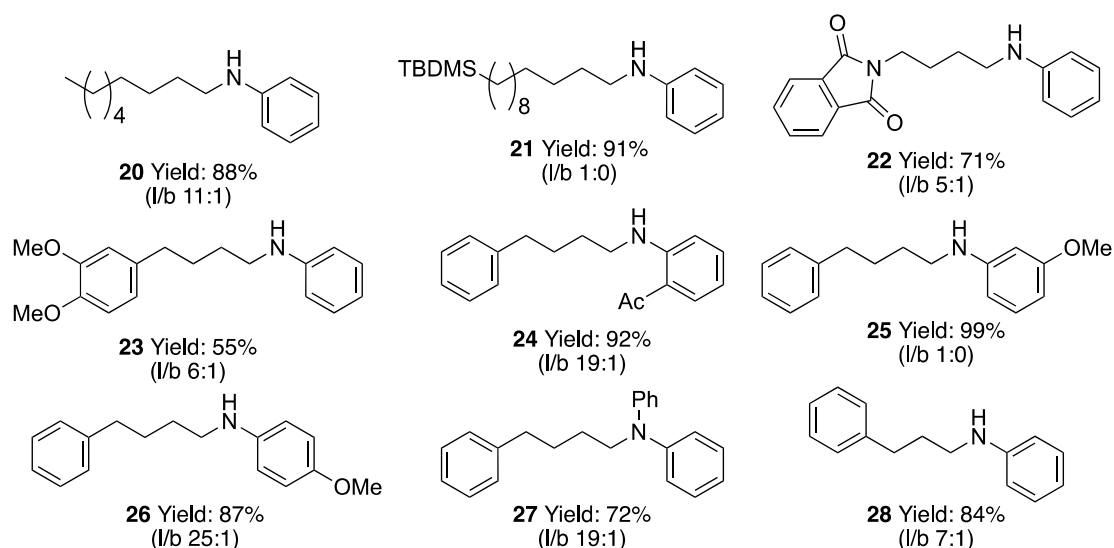


Figure 7. CED indicator results specifying contributions for embedded and direct energy values components.

With these data in hand, we applied the developed reaction conditions to different alkenes including styrenes and by using different primary and secondary anilines as summarized in Scheme 3. It is interesting to note that using the improved protocol and workup better results are obtained for all the substrates both in terms of regioselectivities and reaction yields.





Scheme 3. Substrate scope exploration in 1 g scale.

In Conclusion, we herein report a sustainable protocol for the HAM of alkenes with anilines hydrochloride. The methodology is of general applicability on different substrates. The LCA analysis of the proposed protocol applied to the synthesis of **3a**, confirmed the sustainability of the overall process with respect to the other methodologies reported so far for the synthesis of the same compound.

It is interesting to note that MW irradiation is crucial to let this transformation occur in the mild and sustainable conditions reported. Even if the energy consumption related to the use of this heating source represents the major input to the eco-profile of this protocol, its impact is limited to a 6.5% of the overall sustainability of this transformation. This is a finding of paramount importance demonstrating that energy consuming MW heating is not necessarily synonym of impacting processes if a process can benefit in terms of reaction time, temperature, pressure, and used solvents. Furthermore, the eco-impact of a MW assisted transformation can be further lowered down by using renewable energy sources to power the MW magnetron. We are convinced that this work represents an intriguing basis and a good practice for the early-stage analysis of the sustainability of catalytic process under MW or traditional heating. It is interesting to note, that during the revision of this manuscript, the biodegradable surfactant Savie has been reported by Lipshutz and coworker.⁷⁸ TPGS-750-M has been replaced with Savie on the proposed HAM protocol furnishing **3a** in very good yield and regioselectivity (Table S3), thus indicating that is probably possible to further improve the overall sustainability of this process. It will be interesting to quantify by LCA analysis how this surfactant can really impact and help in developing new sustainable processes. This work represents one of the first report in which the real

sustainability of a micellar catalyzed protocol is evaluated by using LCA analysis confirming the value of this technology for further industrial applications.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Synthesis; experimental conditions; ^1H , and ^{13}C NMR; LCA (PDF)

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ABBREVIATIONS

API: Active Pharmaceutical Ingredient; CAGR: Compounded Average Growth Rate; CED: Cumulative Energy Demand; HAM: Hydroaminomethylation; HB: Hydrogen Borrowing; HF: Hydroformylation; LCA: Life Cycle Assessment; LCI: Life Cycle Inventory; LCIA: Life Cycle Impact Assessment; MJ: Mega Joule; MW Microwave; OX: Oxidation; Pt: Eco-Points; RA: Reductive Amination; RE: Reduction; SN: Nucleophilic Substitution; SCX Strong Cation Exchange.

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TOC:

As confirmed by the LCA, HAM is used for the sustainable synthesis of amines combining micellar and microwave catalysis in water

