Towards Sustainable C–H Functionalization Reactions: The Emerging Role of Bio-Based Reaction Media

Stefano Santoro,^{*,[a]} Assunta Marrocchi,^[a] Daniela Lanari,^[b] Lutz Ackermann,^[c] and Luigi Vaccaro^{*,[a]}

Abstract: In the last decade, transition-metal catalyzed C–H functionalization reactions have progressed enormously, becoming a useful tool in organic synthesis and a practicable alternative to well-established methodologies. Very recently, research efforts have also been devoted to developing more sustainable C–H functionalization protocols, in order to increase their applicability. One of the most promising approaches in this sense is represented by the substitution of common reaction media with bio-based solvents. In the present contribution a general perspective on the benefits of this approach is given, followed by key literature examples.

Introduction

C–H activation reactions gained enormous attention in recent years, growing from the status of a laboratory curiosity to an established technique that is being increasingly used in the preparation of target materials.^[1] With the growing concerns about environmental pollution and depletion of natural resources, synthetic organic chemists are facing the challenge of designing “greener” methodologies which should ideally allow for maintaining the ability to rapidly access complex molecular targets while reducing the associated environmental burden.^[2] In this perspective C–H functionalization strategies already represent a potential advancement compared to related traditional cross-coupling reactions.^[3] In fact, the possibility to directly convert a relatively inert C–H group into a desired moiety without the need to prior install a more reactive functionality (traditionally a halide, pseudo-halide or metal), should reduce the number of synthetic steps necessary to access the target molecule.^[4] However, this theoretical advance may be counterbalanced by a series of common and relevant limitations. These include the almost ubiquitous need for a directing group^[5] on the substrate that undergoes the C–H activation event. The use of a directing group is also mandatory to induce regioselectivity. Other environmental issues associated with C–H functionalization, which are however in common with traditional cross-coupling reactions, are the need for polluting and/or toxic transition metals and (over)stoichiometric amounts of additives (most often bases and/or oxidants) and the frequent use of toxic polar aprotic solvents as reaction media.

As often occurs in chemical research, advances in methodological development are paralleled by efforts to make the novel methods more sustainable, in view of their potential applications.^[6] In the realm of C–H functionalization reactions this aim is pursued through different strategies: a) development of processes that do not require the presence of a directing group;^[7] b) reduced use of additives, or replacement of waste-generating additives with “greener” alternatives;^[8] c) recovery and reuse of the catalyst, often by moving from homogeneous to heterogeneous conditions;^[9] d) replacement of polluting transition metal catalysts with more environmentally-friendly alternatives;^[10] e) reduced use of solvents and/or replacement of common reaction media with more sustainable alternatives.^[11]

Recent investigations based on Life Cycle Assessment (LCA) have indeed demonstrated that the use of solvents is responsible for most of the waste generated and for the largest part of the environmental footprint in chemical production, particularly for complex organic molecules such as active pharmaceutical ingredients.^[12] Moreover, it has been shown that the choice of the solvent and the amount used are fundamental for improving the sustainability of chemical syntheses.^[13]

Regarding the choice of a reaction medium and its impact on the sustainability profile of a process, different strategies can be applied: i) reducing the amount of the required solvent or performing the reaction without solvent;^[14] ii) use of a reaction medium that can be easily and efficiently recovered at the end of the process, and reused for consecutive reactions;^[15] iii) replacement of traditional solvents with safer and more sustainable alternatives, i.e. solvents whose preparation, use and disposal is associated to the generation of less waste compared to traditional solvents.^[16] Most of the traditional solvents that find wider application as reaction media in organic chemical transformations are produced from non-renewable fossil resources and their use is thus inevitably environmentally unsustainable. However, the use of bio-based solvents, i.e. chemicals deriving from renewable biomasses possessing adequate physico-chemical properties to be used as solvents, is emerging as a possible alternative.^[11,17] Obviously, the use of a solvent derived from renewable resources does not imply a reduced waste generation, since this depends also on the defined synthetic route that should also include a strategy for their disposal. However, at least bio-based solvents represent a clear advance in respect to traditional solvents. Examples of biomass-derived solvents that are finding increasing use in organic chemistry are glycerol and its derivatives,^[18] most commonly ethers or carbonates, lactic acid and derivatives,^[19] 2-methyltetrahydrofuran (2-MeTHF),^[20] γ -valerolactone (GVL)^[21] and dihydrolevoglucosenone (Cyrene).^[22]

Bio-based solvents have found considerable application in organic synthesis, and their use has been recently reviewed.^[11,17] However, examples of C–H functionalization reactions performed in bio-based solvents are sporadic and only started appearing recently in the literature. In this contribution, selected examples are presented and commented.

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- [a] Prof. S. Santoro, Prof. A. Marrocchi, Prof. L. Vaccaro
Laboratory of Green Synthetic Organic Department
Dipartimento di Chimica, Biologia e Biotecnologie
Università degli Studi di Perugia
Via Elce di Sotto, 8
06123 Perugia (Italy)
E-mail: stefano.santoro@unipg.it;
luigi.vaccaro@unipg.it
- [b] Dr. D. Lanari
Dipartimento di Scienze Farmaceutiche, Università di Perugia, Via
del Liceo, 1, 06123 Perugia, Italy
- [c] Prof. Dr. L. Ackermann
Institute for Organic and Biomolecular Chemistry
Georg-August-Universität Göttingen
Tammannstr. 2, 37077 Göttingen, Germany
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Examples of C–H Functionalization in Bio-Based Reaction Media

One of the most promising bio-based solvents is, in our view, γ -valerolactone (GVL). This chemical is derived from lignocellulosic biomasses and is highly soluble in water, which eases its biodegradation. Moreover, GVL has a low toxicity, and indeed it has been often used as a food additive and in the flavor and perfume industries. Furthermore, GVL possesses particularly interesting physico-chemical properties: high boiling (207 °C) and flash (96 °C) points, low vapor pressure, good chemical stability and polarity similar to that of common dipolar aprotic solvents ($\epsilon = 36.5$; as a comparison dielectric constants of DMF, DMA, NMP and CH_3CN are 36.7, 37.8, 32.0 and 37.5, respectively). For these reasons GVL has been proposed as a “greener” alternative to these petroleum-derived and generally toxic solvents that, despite their highly unfavorable sustainability profile, still find wide use in organic synthesis.^[21]

In recent years, GVL has been used in several transition metal catalyzed processes such as, among others, the palladium-catalyzed Hiyama,^[23] Mizoroki-Heck^[24] and Sonogashira^[25] cross-coupling reactions, platinum^[26] and rhodium-catalyzed^[27] hydroformylations and palladium-catalyzed aminocarbonylation reactions.^[28] In some cases, the use of GVL in combination with a heterogeneous palladium catalyst resulted in additional benefits, such as limited metal-leaching, compared to the use of traditional dipolar aprotic media.^[24,25]

The first reported example of a C–H functionalization performed in GVL was a palladium-catalyzed Catellani reaction (Scheme 1),^[29] i.e. a palladium/norbornene catalyzed cross-coupling cascade reaction which allows a rapid poly-functionalization of aryl halides.^[30] The reaction could be promoted by different heterogeneous palladium sources and two of them, commercially available PdEncatTM 30 and $\text{Pd}/\text{Al}_2\text{O}_3$, were used to explore the substrate scope. In most of the cases the final step is a Mizoroki-Heck-like reaction, which results in the substitution of the halide moiety with an olefinic group. In one case, however, it has been demonstrated that using benzyl alcohol instead of an olefin results in a hydrogenolysis as the terminal step, with the final formation of *meta*-difunctionalized arenes.

The nature of the catalytically-active species for the two heterogeneous catalysts was also investigated by means of hot-filtration tests, mercury-poisoning tests and by measuring the amount of palladium leached into the crude product by inductively coupled plasma optical emission spectrometry. All the experiments suggest that $\text{Pd}/\text{Al}_2\text{O}_3$ catalyzes the reaction either by genuinely heterogeneous catalysis or by a “release and catch” mechanism,^[31] while PdEncatTM 30 is likely to release homogeneous palladium in solution, which is ultimately responsible for the catalytic activity. Finally, it is worth-mentioning that the amount of palladium released by $\text{Pd}/\text{Al}_2\text{O}_3$ is extremely low (~ 2 ppm), and that the catalyst could be reused for four consecutive reaction runs without noticeable loss of activity.

Scheme 1. $\text{Pd}/\text{Al}_2\text{O}_3$ -catalyzed Catellani reaction in GVL.

Furthermore, GVL was used as reaction medium for the Pd/C-catalyzed C–H arylation of mono- and 1,4-disubstituted 1,2,3-triazoles (Scheme 2).^[32] 2,4,6-Trimethylbenzoic acid (MesCO_2H) was used as additive and, after an initial screening of reaction conditions, potassium trifluoroacetate and potassium carbonate were identified as optimal bases. A broad reaction scope was demonstrated, together with high selectivity for the reaction conducted on mono-substituted triazoles. Moreover, the reaction proved to tolerate different functionalities both on the triazole and on the aryl halide, thus enabling for subsequent product derivatization. Also in this case hot-filtration and mercury-poisoning tests and the limited amount of palladium leached into solution (≤ 5.5 ppm) suggest a genuinely heterogeneous catalysis. The catalyst could be recycled and reused for at least three consecutive reaction runs without loss of activity.

Scheme 2. Pd/C-catalyzed C–H arylation of 1,2,3-triazoles in GVL.

An example of intramolecular C–H arylation, leading to the formation in good yield of a tricyclic product, proved also viable (Scheme 3).^[32]

Scheme 3. Intramolecular Pd/C-catalyzed C–H arylation in GVL.

Another recent example of a C–H functionalization process conducted in GVL is the Pd/C-catalyzed oxidative alkenylation of aromatics, in this case acetanilides, also known as Fujiwara-Moritani or dehydrogenative Heck reaction (Scheme 4).^[33,34] A preliminary screening of reaction conditions allowed to identify benzoquinone and a polymer-bound *para*-toluenesulfonic acid as optimal oxidant and acid additive, respectively. A series of unsubstituted and substituted, either with electron-withdrawing or electron-donating groups, acetanilides was reacted with electron-poor alkenes, affording the alkenylated products in good to excellent yields. The reaction occurred in all cases with high selectivity, giving the mono-functionalized product in the *ortho* position to the acetamido directing group. The catalyst/acid mixture could be easily recovered at the end of the reaction and it could be efficiently reused for five consecutive reaction runs. A slight drop in product yield was only observed in the fifth run. The amount of palladium released into the reaction medium was measured in each reaction run and it was found to be consistently very low (≤ 4.2 ppm). Both a hot-filtration and addition of Hg(0) completely stopped the reaction. These results, taken together, suggest either a genuinely heterogeneous or a “release and catch” mechanism. Test reactions were also conducted in conventional dipolar aprotic solvents, such as DMF and NMP, which resulted in lower or comparable reactivity but with increased metal leaching in solution (80 and 31 ppm in DMF and NMP, respectively).

Scheme 4. Pd/C-catalyzed Fujiwara-Moritani reaction in GVL.

The high stability exhibited by the heterogeneous catalyst in GVL allowed scaling-up the reaction in a tailor-made Pd/C-packed flow reactor (Scheme 5). In this case, soluble *para*-toluenesulfonic acid was used as additive. The process was tested on four different substrate combinations and proved to be extremely efficient, allowing the production of more than 500 mmol of product at a 4 g/h production rate. Also in this case the amount of metal leached into solution was measured and was found to be regularly low (~ 4 ppm).^[33]

Scheme 5. Continuous flow Pd/C-catalyzed Fujiwara-Moritani reaction in GVL.

Very recently, an example of a ruthenium(II)-catalyzed oxidative C–H alkenylation of benzoic acids in GVL was reported (Scheme 6).^[35] The reaction is catalyzed by $[\text{RuCl}_2(p\text{-cymene})]_2$, with stoichiometric amounts of potassium acetate and acetic acid as additives under an ambient atmosphere of oxygen. GVL proved to be the best solvent among a series of biomass-derived alternatives (2-MeTHF, ethyl lactate and tetrahydrofurfuryl alcohol) in the terms of product yield. An extensive scope was proved and several functional groups such as ketone, aryl, alkyl, amino, ether, iodo and bromo substituents were tolerated in the reaction conditions. Aqueous hydrogen peroxide could be used instead of oxygen as terminal oxidant, at least in one example, although with a decrease in product yield (from 80% to 52%). The absence of a kinetic isotope effect suggests that the reaction begins with a fast and reversible C–H activation step, followed by alkene coordination, insertion, β -hydride elimination and intramolecular oxa-Michael addition.

Scheme 6. Ruthenium(II)-catalyzed oxidative annulation in GVL.

Moreover, GVL was identified as an effective solvent for the distal cross-dehydrogenative C–H alkenylation of challenging arylacetamidic substrates through a weak coordination by a cationic ruthenium(II) catalyst (Scheme 7).^[36] The reaction was slightly more efficient in etheric solvents, such as THF and 1,4-dioxane, which were consequently used to explore the reaction scope.

Scheme 7. Distal C–H alkenylation in GVL.

Larini, Cravotto and co-workers reported a microwave-assisted $\text{Pd}(\text{OAc})_2$ -catalyzed ligand-free C–H arylation of 2-alkyl or 2-acetylthiophenes in GVL as reaction medium (Scheme 8).^[37] The process required as little as 0.2 mol % of the catalyst, affording selectively the 5-arylated products in moderate to good yields in just 2 hours. Two different protocols were developed, depending on the electronic nature of the aryl halide. In fact, electron-poor aryl bromides or iodides reacted in the presence of potassium acetate as base, while electron-rich aryl iodides (bromides did not react) required the use of pivalic acid and potassium carbonate.

Scheme 8. Microwave-assisted $\text{Pd}(\text{OAc})_2$ -catalyzed C–H arylation of thiophenes in GVL.

The methodology was also employed for the synthesis of poly(3-hexyl)thiophene (P3HT), a polymer used in electronic devices such as flexible solar cells (Scheme 9).^[37] The polymer was obtained in high yield (75%) and molecular weight (25 kDa), showing a significant improvement over related palladium-catalyzed C–H functionalization based methodologies (in conventional organic solvents).

Scheme 9. Synthesis of poly(3-hexyl)thiophene (P3HT) in GVL.

Very recently, the first example of an electrochemical C–H functionalization reaction performed in a biomass-derived reaction medium has been reported. The reaction, a C–H amination of arylamides, is catalyzed by cost-effective $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ and occurs in GVL in mild reaction conditions (Scheme 10).^[38] The presence of a *N,O*-bidentate amide on the substrate was crucial, since substituting the 2-aminopyridine *N*-oxide with other functionalities resulted in no reactivity. A broad reaction scope was demonstrated, with several benzamides and heteroarylamides being competent substrates. The reaction is also tolerant to the presence of different functionalities, such as esters, thioethers and alkyl halides. It is noteworthy that the reaction was also tested with conventional organic solvents, including MeCN, DCE, DMSO and DMF, which resulted in no

reactivity or significantly poorer conversions as compared to the reaction conducted in GVL.

Scheme 10. Electrochemical cobalt-catalyzed C–H amination in GVL.

Another bio-based chemical that has been proposed as a replacement for commonly used organic solvents is 2-methyltetrahydrofuran (2-MeTHF). This compound can be produced from renewable lignocellulosic biomasses, either through hydrogenation of furfural or through the intermediate synthesis of levulinic acid and GVL. Other than its low carbon-footprint, 2-MeTHF has interesting chemical and physico-chemical features, such as low miscibility with water (14 g per 100 g at 23 °C), good stability towards acids and bases and higher boiling point (80 °C) compared to tetrahydrofuran. For these reasons 2-MeTHF has found relatively wide application in organic chemistry and particularly in organometallic chemistry.^[20] Still, there are to date only a few examples of C–H functionalization reactions realized in 2-MeTHF as reaction medium.

In 2014, Cook and co-workers reported an example of an iron-catalyzed C–H alkylation of aryl amides in 2-MeTHF (Scheme 11).^[39] The methodology is based on the use of 10–20 mol % of non-toxic and inexpensive iron(III) acetylacetonate [$\text{Fe}(\text{acac})_3$] as catalyst and a primary alkyl bromide, and requires the addition of 1,2-bis(diphenylphosphino)ethane (dppe) as ligand and a Grignard reagent as additive. Different directing groups were tested, and the best results were obtained with the amide derived from 8-aminoquinoline. Solvent effects were also investigated, with the best results in terms of product yield being obtained in 2-MeTHF, rather than in traditional reaction media such as toluene, THF or 1,4-dioxane. The reaction worked very efficiently on a variety of substrates, affording exclusively the products of mono-alkylation in the *ortho*-position in less than 10 minutes and in generally good yields. Moreover, the process was successfully performed on a gram scale.

Scheme 11. Iron-catalyzed C–H alkylation of aryl amides in 2-MeTHF.

McMullin, Williams, Frost and co-workers developed a ruthenium-catalyzed C–H alkenylation of aromatics in 2-MeTHF, using oxazolidinone as a directing group (Scheme 12).^[40] The reaction is catalyzed by 2.5 mol % of $[\text{RuCl}_2(p\text{-cymene})]_2$, requires a catalytic amount of AgSbF_6 and makes use of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as terminal oxidant. Other reaction media were also tested, with DCE and 1,4-dioxane resulting in low or moderate reactivity, and DME giving results comparable to 2-MeTHF, but with a worse sustainability profile. A broad reaction scope was demonstrated in 2-MeTHF, with several functionalities tolerated on the aromatic ring and on the oxazolidinone moiety, with good selectivities for the mono-alkenylation. However, only electron-poor methyl, *n*-butyl and benzyl acrylates could be used as coupling partners. The methodology could be applied in gram scale, and a thorough mechanistic investigation was conducted by means of DFT calculations and experiments.

Scheme 12. Ruthenium(II)-catalyzed C–H alkenylation of *N*-aryloxazolidinones in 2-MeTHF.

Frost and co-workers also reported a related protocol for the C–H alkenylation of *N*-arylhydantoin in 2-MeTHF (Scheme 13).^[41] The reaction was also catalyzed by $[\text{RuCl}_2(p\text{-cymene})]_2$ (5 mol %) and requires AgSbF_6 as co-catalyst and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ as terminal oxidant. The use of protic solvents (water or AcOH) was not tolerated, while conventional etheric solvents, such as THF or DME, resulted in slightly lower reactivity compared to 2-MeTHF. Various electron-donating or electron-withdrawing functionalities, including halides, were tolerated on the aromatic ring, and also the hydantoin directing group could be decorated with different alkyl groups. Also in this case, complete selectivity for the mono-alkenylation in the *ortho*-position was observed and the reaction was limited to the use of acrylates as coupling partners.

Scheme 13. Ruthenium(II)-catalyzed C–H alkenylation of *N*-arylhydantoin in 2-MeTHF.

Finally, the use of biomass-derived 2-MeTHF was not limited to proximity-induced *ortho*-selective C–H transformations. Indeed, more challenging *meta*-selective^[42] C–H functionalizations proved recently viable within an arene-ligand-free ruthenium(II/III) manifold (Scheme 14).^[43] The site-selective ruthenium catalyst enabled organometallic C–H activation through cycloruthenation, setting the stage for remote purine^[44] base diversification. The reaction could be efficiently conducted also in other solvents, with 1,4-dioxane and toluene giving comparable results to 2-MeTHF.

Scheme 14. *meta*-Selective C–H alkylation of purines in 2-MeTHF.

Conclusions and Outlook

C–H functionalization strategies represent an increasingly useful tool in order to develop more sustainable organic syntheses, due to their potential low atom- and step-economies. Still, in the endeavor of reducing the environmental impact of chemical production, it cannot be neglected that most of the impact depends on the use of solvents. Among the possible alternatives to the use of common organic solvents, mostly derived from non-renewable resources, the use of bio-based reaction media appears particularly promising. In this contribution we have presented selected recent examples relying on this strategy, with the hope that this will stimulate further research in this field. It is reasonable to anticipate that the development on new C–H functionalization reactions will be progressively paralleled by the application of these new processes in bio-derived reaction media.

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Entry for the Table of Contents (Please choose one layout)

CONCEPT

Greener C–H functionalizations: The use of bio-based chemicals as alternative reaction media allows for reducing waste-generation, thus increasing the applicability of this rapidly-growing synthetic tool.

Stefano Santoro,* Assunta Marrocchi,
Daniela Lanari, Lutz Ackermann, Luigi
Vaccaro*

Page No. – Page No.

**Towards Sustainable C–H
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