

Deep Eutectic Solvent as a Sustainable Medium for C–C Bond Formation Via Multicomponent Radical Conjugate Additions

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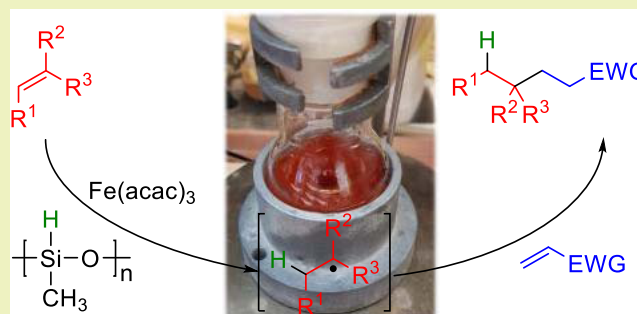
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Supporting Information

ABSTRACT: Deep eutectic solvents (DESs) have been used for the first time as a sustainable medium in radical-mediated molecular organic synthetic protocols. This study reports an efficient protocol for the C–C bond formation through radical conjugate addition of simple olefins (di- and trisubstituted). An inexpensive and abundant iron catalyst [Fe(acac)₃] together with nontoxic silane (poly(methylhydrosiloxane) (PMHS)) was employed, using choline chloride/ethylene glycol (1:2) as a solvent under air and mild reaction conditions. Different functional groups were well tolerated, and also, the reaction could be carried out on a gram scale with excellent yields.

KEYWORDS: deep eutectic solvent, iron catalyst, poly(methylhydrosiloxane), radical coupling, sustainable synthesis



INTRODUCTION

Radical reactions have gained widespread application for the construction of C–C bonds, mainly through the conjugate addition of carbon-centered radicals into unsaturated electrophiles.^{1–5} The development of new methodologies devoted to creating C–C bonds in an efficient and sustainable manner would be desirable in the area of green chemistry since it allows the generation of complex molecules of interest as agrochemicals, pharmaceuticals, and polymers.⁶

Among the plethora of carbon radical precursors, olefins represent ideal starting materials since they can be found in a variety of feedstock chemicals and in complex natural compounds, and compared to other radical precursors, are typically bench-stable.

Having this in mind, the application of hydrogen-atom transfer (HAT) to generate carbon-centered radicals from olefins is considered a robust strategy to develop new bond-forming reactions in organic synthesis (Scheme 1).⁷

The groups of Drago⁸ and Mukaiyama^{9,10} were pioneers in the use of HAT with alkenes, as radical precursors, by employing nontoxic first-row metals to access the corresponding hydration products. Later, many researchers have expanded the scope of this process to include other electrophiles.^{11–43} However, the potential of these reactions to form C–C bonds was not demonstrated until relatively recently, when the Baran group developed a unique method for the direct coupling of unactivated olefins to electron-deficient olefins, both as intra- or intermolecular reactions in the presence of an iron catalyst and phenylsilane as a reducing agent.^{44–48} In light of this, a number of other related methodologies have been subsequently reported.^{49–61} However, to date, most of the

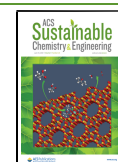
published methods are far from being environmental benign since these reported procedures employ: (i) toxic and volatile organic solvents, (ii) expensive, air- and moisture-sensitive reducing agents, and (iii) complex and expensive metal catalysts. Thus, the development of efficient HAT reactions, operating under sustainable and green conditions, is still highly sought.

Deep eutectic solvents (DESs) are an emerging class of green solvents, generally referred to combinations of two or more components that form, through electrostatic and strong hydrogen bond interactions, a eutectic liquid mixture at nearly room temperature.^{62,63} These solvents have high thermal stabilities, low volatility, and nonflammability. Most of the components used in their synthesis are naturally occurring, biodegradable, and biorenewable. Furthermore, there are supposed to exist more than one million possible mixtures, affording the possibility of designing a solvent for each different application. Due to their high versatility, tunability, and sustainability, their use as a medium to carry out metal-catalyzed organic transformations has attracted the interest of organic chemists over the last years.^{64–66} However, the change of a typical organic solvent by a DES in a reaction is challenging *per se* due to the high density of hydrogen bonds

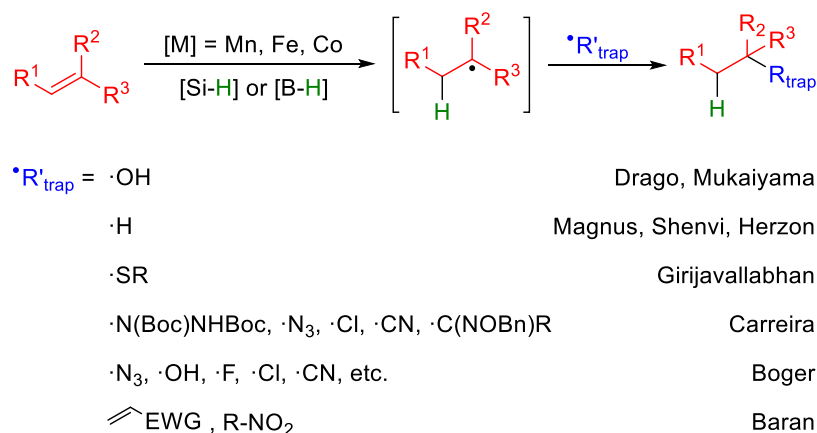
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Scheme 1. Pioneering Olefin Radical Hydrofunctionalization Reaction



and the ionic character of this neoteric medium that has a big influence on the stability of catalysts and intermediates.

Although DESs have been applied in several organic transformations, the field of radical-mediated organic reactions remains unexplored, with only a few examples related to polymer material synthesis.^{67–72} Herein, we have developed an unprecedented, practical, and sustainable methodology for the multicomponent reductive coupling of a broad range of olefins (including 1,2-disubstituted ones) via radicals, which utilizes (i) a readily available and inexpensive iron catalyst, (ii) poly(methylhydrosiloxane) (PMHS), a cheap, nontoxic, and air- and moisture-stable silane as an effective reducing agent,⁷³ and (iii) DESs as a sustainable reaction medium.

RESULTS AND DISCUSSION

Our initial investigations started by optimizing the reaction conditions, using 1-methylcyclohexene (**1a**) and methyl acrylate (**2a**) as a model reaction (Table 1). Different silanes were used as reducing agents, achieving higher yields when using alkoxy silanes instead of phenyl derivatives (entries 1–6). PMHS was selected due to its intrinsic advantages of air and moisture stability, low cost, and nontoxicity. After that, the optimal amount of silane was set at 5.5 equiv (entries 7–10). The reaction time was also evaluated, being noticed that the maximum yield was obtained after 2 h. The increase of the reaction time gave poorer results (see entries 9, 11, and 12). As expected, the reaction failed without a catalyst (entry 13). When 5 mol % $\text{Fe}(\text{acac})_3$ was used, a 78% yield was obtained (entry 14), with better results being obtained using 10 mol % iron catalyst (91% yield, entry 15). However, the further increase of this amount did not produce any significant change (compare entries 6, 9, 14, and 15). The reaction temperature had an important impact: a drop in the yield was observed when the reaction was carried out at 30 °C (entry 16). The amount of the solvent was reduced to study a possible effect in the reaction. Its decrease resulted in a negative impact on the yield (entry 17), seeming to have a crucial role in the reaction amount of the solvent, as it was previously pointed out for similar processes performed under alcohol solvent conditions.⁴⁸ Other metal catalysts were tested but no catalytic activity was observed (entries 18–24).

Next, different DESs were used as solvents (Figure 1). In general, the presence of an alcohol component in the DES might favor the reaction as previously discussed. In particular, a $\text{ChCl}/\text{ethylene glycol}$ (1:2) eutectic mixture gave the best

Table 1. Optimization of the Reaction Conditions^a

entry	catalyst	silane	yield (%) ^b
1	$\text{Fe}(\text{acac})_3$ (20 mol %)	PhSiH_3 (5.5 equiv)	51
2	$\text{Fe}(\text{acac})_3$ (20 mol %)	Ph_2SiH_2 (5.5 equiv)	55
3	$\text{Fe}(\text{acac})_3$ (20 mol %)	Ph_3SiH (5.5 equiv)	0
4	$\text{Fe}(\text{acac})_3$ (20 mol %)	PhMe_2SiH (5.5 equiv)	0
5	$\text{Fe}(\text{acac})_3$ (20 mol %)	$(\text{EtO})_3\text{SiH}$ (5.5 equiv)	76
6	$\text{Fe}(\text{acac})_3$ (20 mol %)	PMHS (5.5 equiv)	89
7	$\text{Fe}(\text{acac})_3$ (30 mol %)	PMHS (1.5 equiv)	37
8	$\text{Fe}(\text{acac})_3$ (30 mol %)	PMHS (3 equiv)	45
9	$\text{Fe}(\text{acac})_3$ (30 mol %)	PMHS (5.5 equiv)	90
10	$\text{Fe}(\text{acac})_3$ (30 mol %)	PMHS (10 equiv)	49
11	$\text{Fe}(\text{acac})_3$ (30 mol %)	PMHS (5.5 equiv)	59 ^c
12	$\text{Fe}(\text{acac})_3$ (30 mol %)	PMHS (5.5 equiv)	57 ^d
13	no catalyst	PMHS (5.5 equiv)	0
14	$\text{Fe}(\text{acac})_3$ (5 mol %)	PMHS (5.5 equiv)	78
15	$\text{Fe}(\text{acac})_3$ (10 mol %)	PMHS (5.5 equiv)	91
16	$\text{Fe}(\text{acac})_3$ (10 mol %)	PMHS (5.5 equiv)	24 ^e
17	$\text{Fe}(\text{acac})_3$ (10 mol %)	PMHS (5.5 equiv)	72 ^f
18	$\text{Co}(\text{acac})_2$ (10 mol %)	PMHS (5.5 equiv)	0
19	$\text{Ni}(\text{acac})_2$ (10 mol %)	PMHS (5.5 equiv)	0
20	$\text{Pd}(\text{acac})_2$ (10 mol %)	PMHS (5.5 equiv)	0
21	FeCl_3 (10 mol %)	PMHS (5.5 equiv)	0
22	CoCl_2 (10 mol %)	PMHS (5.5 equiv)	0
23	$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (10 mol %)	PMHS (5.5 equiv)	0
24	PdCl_2 (10 mol %)	PMHS (5.5 equiv)	0

^aReaction conditions: compound **1a** (0.3 mmol), compound **2a** (0.9 mmol), silane, and the catalyst in 1.5 mL of the solvent under air at 60 °C for 2 h. ^bYield determined by GC using 4,4'-di-*tert*-butylbiphenyl (DTBB) as an internal standard. ^cReaction performed for 1 h. ^dReaction performed for 3 h. ^eReaction performed at 30 °C. ^fReaction with 1.0 mL of the solvent.

result (91% yield). Common organic solvents were also tested as reaction media (toluene, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO)), but the reaction did not take place in any case. Moreover, other previously employed solvents in this transformation were tested under our optimal reaction conditions, obtaining a 64% yield with ethanol/ethylene glycol (5:1) and a 8% yield with pure ethanol.^{44–48} Additionally, pure ethylene glycol was used as a solvent

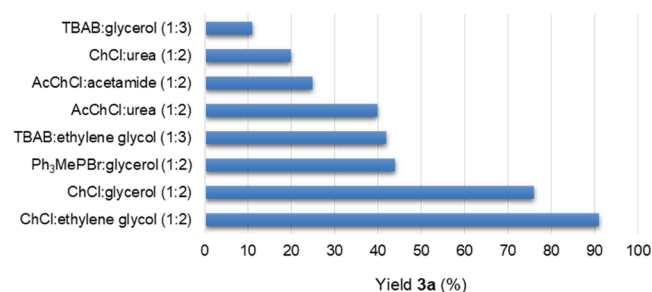
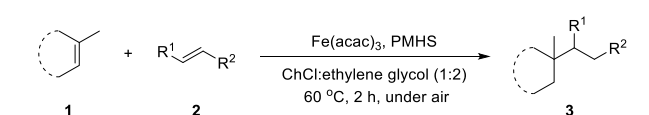


Figure 1. Solvent optimization (TBAB: tetrabutylammonium bromide, ChCl: choline chloride, and AcChCl: acetylcholine chloride).

obtaining a 34% yield, demonstrating that the presence of choline chloride has a positive effect on the reaction media. This fact could be attributed to higher stability of radicals in ionic solvents as previously reported.^{74,75} Meanwhile, the reaction in FeCl₃/glycerol (3:1) failed. All of these results highlight the beneficial use of DESs in terms of reactivity and even sustainability.

Once the best conditions were found (Table 1, entry 15), the scope of the reaction was evaluated. Different acceptor olefins were probed using 1-methylcyclohexene (**1a**) as donor olefin. Olefins conjugated with esters, ketones, amides, nitriles, and sulfones proved to be competent electron-withdrawing groups in the reaction (Table 2, entries 1–5). Acyclic and

Table 2. Scope of the Reaction Using Trisubstituted Donor Olefins^a



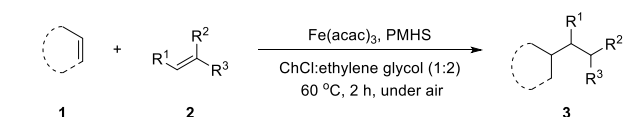
entry	compound 1	R ¹	R ²	product	yield (%) ^b
1	1-methylcyclohexene	H	CO ₂ Me	3a	91
2	1-methylcyclohexene	H	COMe	3b	75
3	1-methylcyclohexene	H	CON(Me) ₂	3c	89
4	1-methylcyclohexene	H	CN	3d	84
5	1-methylcyclohexene	H	SO ₂ Ph	3e	54 ^c
6	1-methylcyclohexene	CO ₂ Me	CO ₂ Me	3f	60
7	1-methylcyclohexene	–(CH ₂) ₂ CO–		3g	70 ^c
8	1-methylcyclohexene	–(CH ₂) ₃ CO–		3h	48 ^c
9	α-ionone			3i	95

^aReaction conditions: compound **1** (0.3 mmol), compound **2** (0.9 mmol), PMHS (5.5 equiv), and Fe(acac)₃ (10 mol %) in 1.5 mL of ChCl/ethylene glycol (1:2) under air at 60 °C for 2 h. ^bIsolated yield. ^cReaction performed for 5 h.

cyclic disubstituted acceptor olefins gave moderate to good yields (entries 6–8), observing a lower yield when using cyclohexanone as a substrate (entry 8). An intramolecular cyclization was performed using a terpenoid scaffold, α-ionone (**1b**), obtaining the corresponding cyclopropane in an excellent yield (entry 9).

More challenging donor disubstituted olefins were tested using this methodology, obtaining similar results to those using the trisubstituted ones (Table 3).^{44–48} Cyclohexene (**1c**) was

Table 3. Scope of the Reaction Using Mono- or Disubstituted Donor Olefins^a



entry	compound 1	R ¹	R ²	R ³	product	yield (%) ^b
1	cyclohexene	H	H	CO ₂ Me	3j	98
2	cyclohexene	H	H	COMe	3k	95
3	cyclohexene	H	H	CN	3l	80
4	cyclohexene	Me	CO ₂ Et	CO ₂ Et	3m	40
5	3,4-dihydro-2H-pyran	H	H	CO ₂ Me	3n	83
6	1-dodecene	H	H	CO ₂ Me	3o	80 ^c
7	phenyl vinyl sulfide	H	H	CN	3p	80 ^d

^aReaction conditions: compound **1** (0.3 mmol), compound **2** (0.9 mmol), PMHS (5.5 equiv), and Fe(acac)₃ (10 mol %) in 1.5 mL of ChCl/ethylene glycol (1:2) under air at 60 °C for 2 h. ^bIsolated yield. ^cMixture of isomers was observed. ^dReaction performed for 5 h.

employed as donor olefin, generating a secondary radical that efficiently reacted with poor alkenes bearing different electron-withdrawing groups such as esters, ketones, or nitriles (entries 1–3). It was observed that the intermolecular coupling is relatively insensitive to sterics since a more sterically hindered olefin gave satisfactory results (Table 3, entry 4). Cyclic enol ethers, as 3, 4-dihydro-2H-pyran (**1d**), could be used giving high regioselectivity due to the stabilizing presence of an oxygen atom adjacent to the formed radical (entry 5). Conversely, this radical stabilization was not achieved in the case of 1-dodecene (**1e**), observing a mixture of isomers with a predominant presence of the product obtained from the secondary radical intermediate.

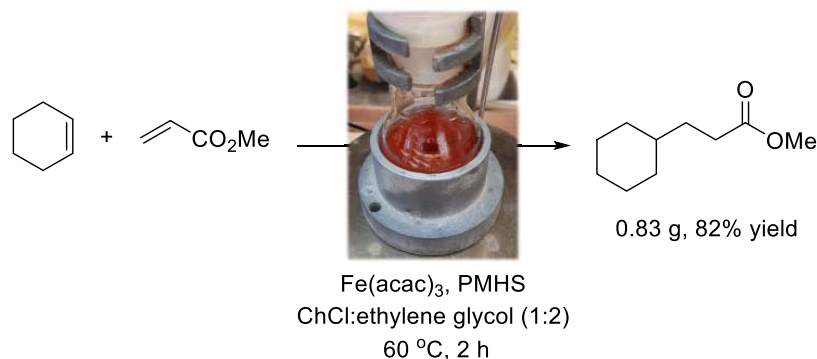
Finally, another monosubstituted donor olefin attached to a sulfur atom could be coupled with acrylonitrile (**2d**) in a good yield (Table 3, entry 7).

The possible recyclability was performed in the standard reaction by decantation of all organic compounds with 2-methyltetrahydrofuran (a renewable organic solvent), and the remaining DES and the catalyst were reused in a second cycle obtaining only 43% of compound **3a**, with the third cycle failing.

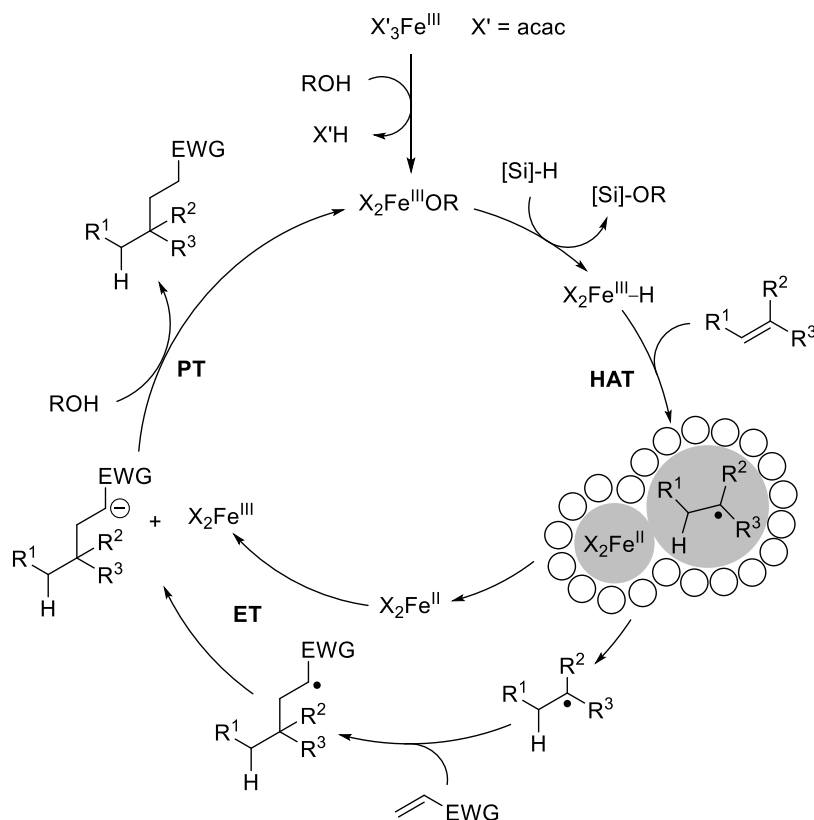
Furthermore, to prove the applicability of the methodology, the reaction was performed on a gram scale (Scheme 2). A slight decrease in the yield was observed probably due to some aggregation of silane observed during the reaction course.

Regarding the reaction mechanism, it was determined that a radical pathway occurs since the reaction was inhibited by the use of a radical scavenger such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). A TEMPO adduct was detected by ¹H NMR (see the Supporting Information (SI)). According to the literature,^{76–78} it was presumed that initially, the solvolysis of a FeX₃ precatalyst with an alcoholic solvent generates a catalytical active iron species (X₂Fe^{III}OR). Then, this catalyst reacts with silane, leading to an iron hydride complex and an alkoxy silane compound. Note that the formation of such a weak bond (Fe–H) must be compensated

Scheme 2. Gram-Scale Reaction



Scheme 3. Proposed Reaction Mechanism



by a strong bond formation in another product (Si–O bond). One important role of ethylene glycol present in the DES might be to generate the catalytically active iron catalyst ($\text{X}_2\text{Fe}^{\text{III}}\text{OR}$), and consequently, to provide alkoxide that supplies the aforementioned driving force for Si–O bond formation. This fact could explain the higher yields observed when diol-based DESs were used as a reaction medium (see Figure 1). The next step involves the hydrogen-atom transfer (HAT) to alkene from the transient iron hydride complex to generate a carbon radical metallo-radical pair surrounded by a “cage” of solvent molecules (Scheme 3). To escape from this pocket, the solvent properties are crucial, so the “strength” of the solvent cage could be tuned through the careful selection of the reaction media.⁷⁸ In concordance with the reported importance of viscosity of solvents in the cage effect, it was noticed that the best result was obtained with the less viscous eutectic mixture but the direct correlation between viscosity and the product yield is not clear (Figure 2).^{79,80}

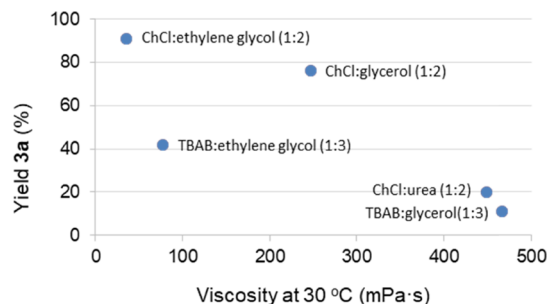


Figure 2. Plot of viscosity⁶² and yield for the radical addition model reaction in DESs.

Thus, DESs have demonstrated to be suitable media that favor the cage escape. It should be noted that homocoupling products were not observed in any case. The released radical is then trapped by an electron-poor acceptor olefin, and the

formation of a new C–C bond generates a product with a radical adjacent to the electron-withdrawing group. Finally, this radical accepts an electron (ET) and a proton from the protic solvent (PT) to afford the desired product.

CONCLUSIONS

The highly tunable properties of DESs led to the development of an efficient and sustainable methodology for C–C bond formation through an iron-catalyzed radical alkene cross-coupling reaction. The use of DESs as solvents in a radical organic synthesis transformation has been described for the first time as having notable advantages compared to previously reported methods. Furthermore, this protocol implies the use of an earth-abundant metal catalyst, an inexpensive, stable, and nontoxic silane in DESs as an environmentally friendly reaction medium under mild and air reaction conditions. A broad range of functionalities were well tolerated and even, 1,2-disubstituted olefins gave satisfactory results in comparison with previously reported methodologies. The presence of ethylene glycol and the low viscosity of DES seem to be important factors to get higher yields.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acssuschemeng.1c02193>.

Synthetic procedures, mechanism studies, and characterization data and copies of ^1H and ^{13}C NMR (PDF)

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Author Contributions

The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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