ARTICLE

Lipids as Versatile Solvents for Chemical Synthesis

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Development of safe, renewable, cheap and versatile solvents is a longstanding challenge in chemistry. We show here that vegetable oils and related systems can become prominent solvents for organic synthesis. Suzuki-Miyaura, Hiyama, Stille, Sonogashira and Heck cross-couplings proceed with quantitative yields in a range of vegetable oils, fish oil, butter and waxes used as solvents. Appropriate methodologies for high-throughput screening and sustainable isolation techniques applicable for vegetable oils and related lipids are presented.

Introduction

Solvents are indispensable for chemical sciences and industry. They have a decisive role in numerous processes from the manufacture of life-saving drugs to the production of paints, coatings and personal computers. In 2020, the production of organic solvents surpassed 28 million metric tons.[1] Nevertheless, the large consumption of solvents comes with a considerable burden with respect to sustainability, environment, safety, and health.[2d]

In the pharmaceutical industry, solvents can exceed 80% of the total mass of materials needed for the production of a target compound.[3] Thus, the choice of solvent greatly influences the life cycle impact of a pharmaceutical product. Research to minimize the negative impact resulting from the use of solvents has focused on the development of solvent-free methodologies,[4] identification and use of highly recommended green solvents (water, butanol, and polyethylene glycol (PEG)),[2c,5] and the discovery of new "greener" solvents for example biomass-derived solvents (2-methyltetrahydrofuran (2MeTHF), cyrene and limonene).[2a-c,6] Unfortunately, the available alternatives are still not sufficient to cover the whole range of solvent properties provided by non-green, "traditional" solvents.[2d] For example, the use of water as solvent is often hampered by its pronounced reactivity and reduced miscibility with organic matter even though, supercritical water can act as a non-polar solvent (above 374 °C, 218 atm).[5a,b] Thus, good substitutes for halogenated solvents are lacking,[2d] and society is still facing an overreliance on hazardous solvents.[2d]

We became interested in vegetable oils and lipids as a potential new class of solvent as they fulfil a number of criteria for a green solvent (Figure 1). Vegetable oils are readily available, renewable, biodegradable, safe and cheap.[7] Vegetable oils, being a mixture of triglycerides, are aprotic, which should make them chemically more inert than for example water and butanol. They can be heated under air to 200 °C without noticeable decomposition,[8] and should be recyclable after use. Finally, vegetable oils have a good dissolving power as their polarity can be adjusted by addition of phospholipids or other amphiphiles derived from vegetable oils.[9]
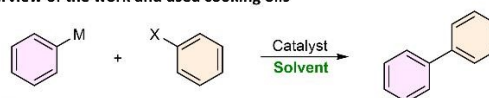
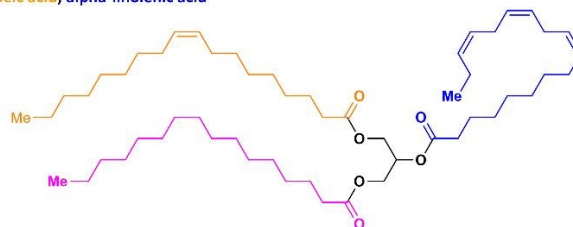**Fig. 1** Vegetable oils and related lipids as solvents for transition metal-catalyzed transformations (picture taken by A.G.).

At present renewables can hardly compete with non-renewable fossil-derived chemicals, mostly due to excessive

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Green Chemistry Accepted Manuscript

availability of fossil resources and economic reasons. Application of food grade virgin vegetable oils as solvent for chemical synthesis can be a matter of debates due to constant increase of population and demand on food. However, in the future we will need substitutions to non-renewable fossil-derived chemicals and solvents. For some applications, food grade oils may be the best alternative. New sources of lipids will become available e.g. from waste oil after food production or lipids from algae that can find value as solvents rather than food ingredient.

Vegetable oils have been used as green solvents for the extraction of bioactive compounds, e.g. carotenoids and astaxanthin from shrimp waste and phenolic compounds from plant material.[10] Many commercial drugs are sold in oil solutions.[11] One example of oils as solvent for a multi-component condensation reaction was published recently.[12] The application of vegetable oils as solvent in homogeneous catalysis has to the best of our knowledge not been reported.

Here we show that food-grade and waste lipids are excellent solvents for transition metal-catalyzed cross-coupling reactions, which are among the most frequently used transformations in modern medicinal chemistry and patent literature.[13] Our lipid-based protocols provide excellent yields for Suzuki-Miyaura, Hiyama, Stille, Sonogashira and Heck couplings.

Results and discussion

Initial studies on Suzuki-Miyaura coupling performed in rapeseed oil proved the viability of our concept on applicability of lipids as solvents. We could isolate the product, but the yield was low (ESI, Table S1, entries 1-3). In order to optimize the reaction conditions, we considered methods that would allow high-throughput screening of reactions in vegetable oils and related solvents.

Preliminary analysis of the properties of cooking oils and waxes showed a marked difference from traditional solvents, indicating that the reactions performed in oils cannot be examined and analyzed by traditional methods used for common solvents (for detailed description of used lipids see ESI, Figures S1-S16). For instance, the majority of lipids, except triacetin and tributyrin, have no boiling point, which is an advantage for reactions requiring high temperature, but can be a challenge for analysis and purification of reaction mixtures.

Attempts to analyze the reaction mixtures by GC/MS were not successful, however, NMR-based screening turned out to be a prosperous strategy. Most of the signals of pure vegetable oils in ^{1}H NMR appear as separated multiplets in the aliphatic region. Accordingly, we assumed that the solvent signals may not be overlapping with part of the signals of the product and internal standard, making the latter quantifiable even for crude mixtures in oils diluted with CCl_4 or $CDCl_3$ (ESI, Figures S20-S27). Gratifyingly, our assumption worked out, and we got a crude ^{1}H NMR spectrum where the signals of reaction components and
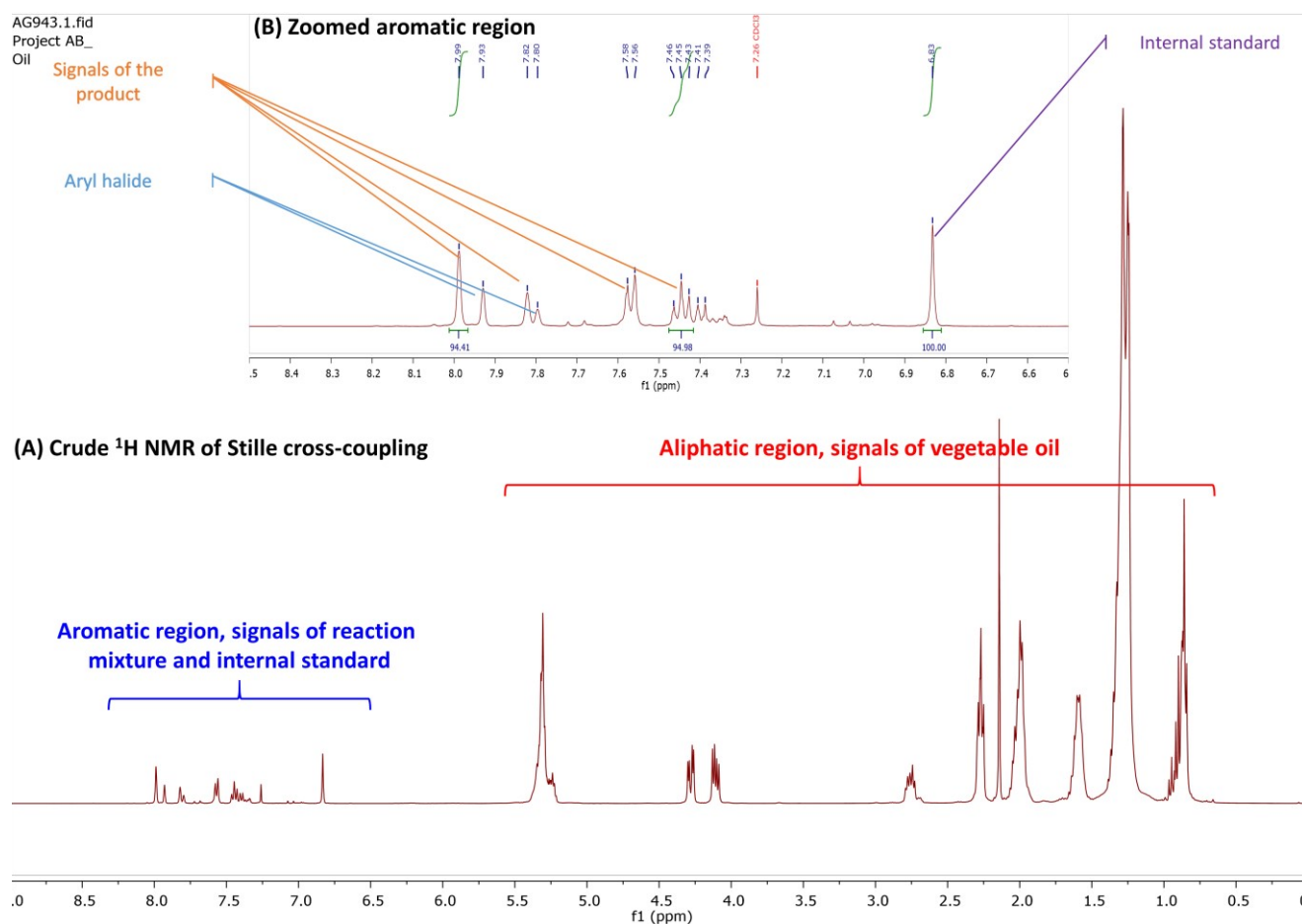

Fig. 2 Analysis of reaction mixtures. (A) Crude ^{1}H NMR of a Stille coupling. (B) Zoomed aromatic region of the spectra.
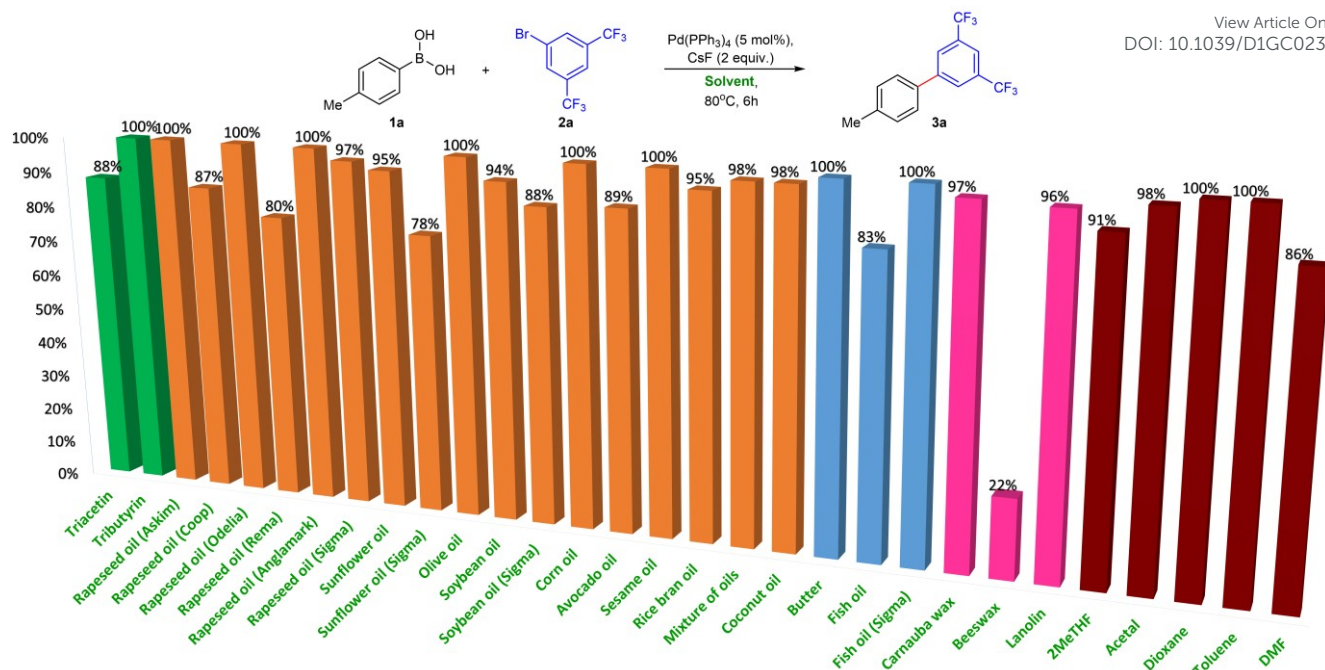
Chart 1 Screening of solvents for Suzuki-Miyaura coupling. Yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

oil were well separated and comparable. An example of such crude ^{1}H NMR is depicted in the Figure 2 for a Stille coupling.

The developed NMR screening method worked well for all reactions where at least part of the signals of the product appeared at 5.5 ppm or lower field, which is commonly the case for reagents and products containing aromatic groups. Thus, we could rapidly screen a range of parameters for optimization of the reaction conditions in lipids. Interestingly, our method for high-throughput screening in oils turned out to be more advantageous to those used for classical volatile solvents[14] as it avoids extra steps connected with evaporation and filtration (see ESI, section "General experimental procedures for optimization of cross-couplings").

With an efficient methodology for screening of reaction conditions in hand, optimized conditions for the Suzuki-Miyaura coupling[15,16] in rapeseed oil from the brand Askim were determined. For activated aryl halides, quantitative yields were observed when using $Pd(PPh_3)_4$ (for complete optimization tables see ESI, Table S1, S3). For unactivated aryl halides, excellent yields were maintained by switching to a DavePhos/Pd_2dba_3 precatalyst.

The optimized conditions were further examined for a range of lipids on the model reaction between 4-tolylboronic acid (**1a**) and 3,5-bis(trifluoromethyl)bromobenzene (**2a**) (Chart 1, ESI, Table S2). We explored the utility of vegetable oils (rapeseed oil, sunflower oil, olive oil, soybean oil, corn oil, avocado oil, sesame oil, rice bran oil, coconut oil, mixture of oils), triglycerides originating from animals (butter, fish oil), semisynthetic oils (triacetin and tributyrin)[17] as well as related natural waxes (carnauba wax, beeswax and lanolin). Most of the used lipids were food-grade and edible, which highlights their safety for the user.

First, we analyzed the performance of rapeseed oils available from distinct brands. Our studies showed that along with rapeseed oil from Askim the quantitative yields can be maintained for rapeseed oils from brands Odelia (100%),
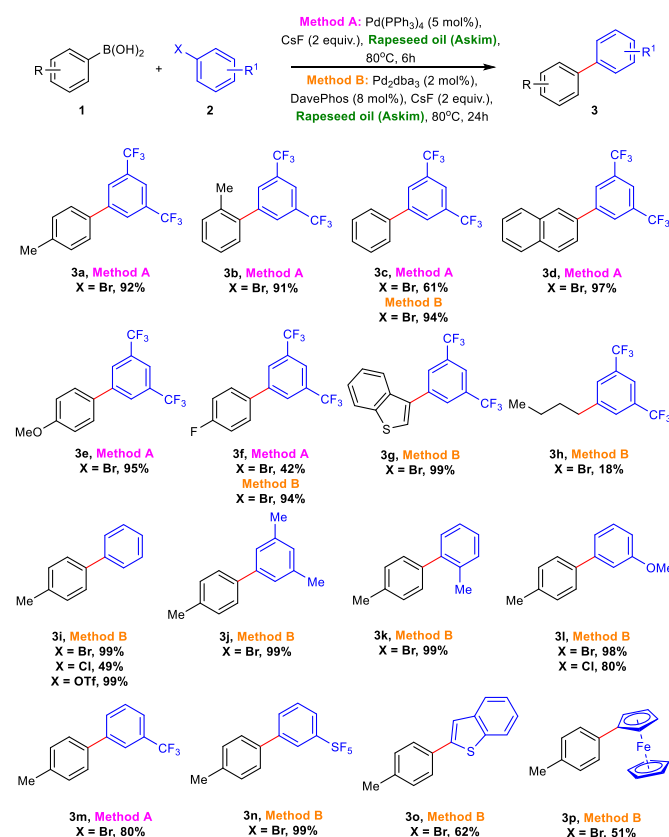
Scheme 1 Scope and limitations of Suzuki-Miyaura reaction in rapeseed oil. The yields refer to isolated products.

Anglamark (100%) and Sigma Aldrich (97%). The results obtained in rapeseed oil from Sigma Aldrich is particularly important since it is available for purchase across the globe. The yields were slightly reduced only for rapeseed oils from Coop (87%) and Rema (80%). We also explored the performance of different batches of rapeseed oil from Askim, all gave quantitative yields for biaryl (**3a**). The consistent yields in oils from different brands and production batches show that differences in production methods have little influence on the performance of diverse rapeseed oils as solvents for cross-couplings (ESI, Table S2, S5, S8, S11 and S15).

For other vegetable oils, excellent to quantitative yields were observed for the reactions carried out in sunflower oil (95%), olive oil (100%), soybean oil (94%), corn oil (100%), avocado oil (89%), sesame oil (100%), rice bran oil (95%), coconut oil (98%) and mixture of oils (98%, orange columns, Chart 1). Semisynthetic triacetin (88%) and tributyrin (100%, green columns, Chart 1) as well as triglycerides originating from animals (butter (100%), fish oil (83-100%), blue columns, Chart 1) also worked well. Noteworthy, somewhat reduced yields observed in rapeseed oil from Rema, fish oil and sunflower oil from Sigma Aldrich were increased to quantitative by the use of more active, yet expensive DavePhos/Pd$_2$dba$_3$-based catalytic system (ESI, Table S2). Among natural waxes, excellent results were obtained when using lanolin (96%) and carnauba wax (97%, pink columns, Chart 1), whereas in beeswax the product was obtained in only 22% yield.

The best reaction conditions identified for reactions performed in lipids were also examined for several traditional and green solvents (Chart 1). These studies involved 2MeTHF (91%), acetal (1,1-diethoxyethane, 98%), 1,4-dioxane (100%), toluene (100%) and DMF (86%, brown columns, Chart 1), indicating that vegetable oils and related systems can be as good as traditional solvents for cross-couplings (for other cross-couplings see ESI, Table S2, S5, S8, S11 and S15).

Inspired by the results of the solvent screening for **1a**, we examined the scope and limitations of the developed methodologies for Suzuki-Miyaura couplings in rapeseed oil (Scheme 1). Combination of different boronic acids with electron-deficient 3,5-bis(trifluoromethyl)bromobenzene (**2a**) showed excellent results with Pd(PPh$_3$)$_4$. Electron-rich and sterically hindered boronic acids also performed well, leading to corresponding biaryls in satisfactory to quantitative yields (**3a-e** 61-97%). For phenylboronic acid and 4-fluorophenylboronic acid, Pd(PPh$_3$)$_4$-catalyzed couplings gave only moderate yields (**3c** 61%, **3f** 42%), however, by changing to the DavePhos/Pd$_2$dba$_3$-based catalytic system, we could improve the yields to 94%. Challenging unstable thianaphthene-3-boronic acid also worked well, leading to biaryl (**3g**) in quantitative yield, while butylboronic acid gave only traces of arylation product (**3h**).

Further examination of unactivated aryl halides and sulfonate esters indicated that the DavePhos/Pd$_2$dba$_3$-based precatalyst is by far the best system for Suzuki-Miyaura couplings performed in rapeseed oil (ESI, Table S3). The power
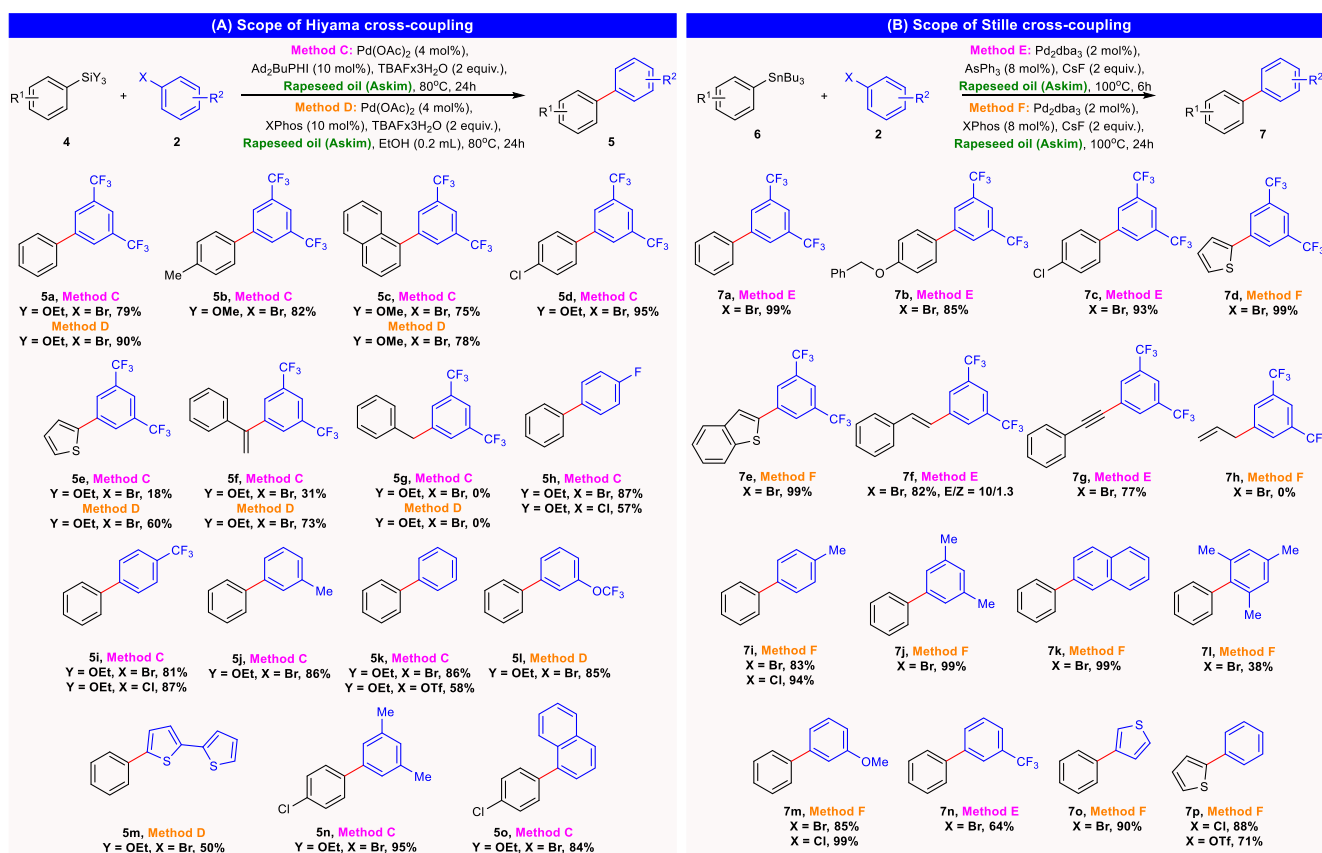
Scheme 2 Scope and limitations of Hiyama (A) and Stille (B) cross-couplings in rapeseed oil. The yields refer to isolated products.
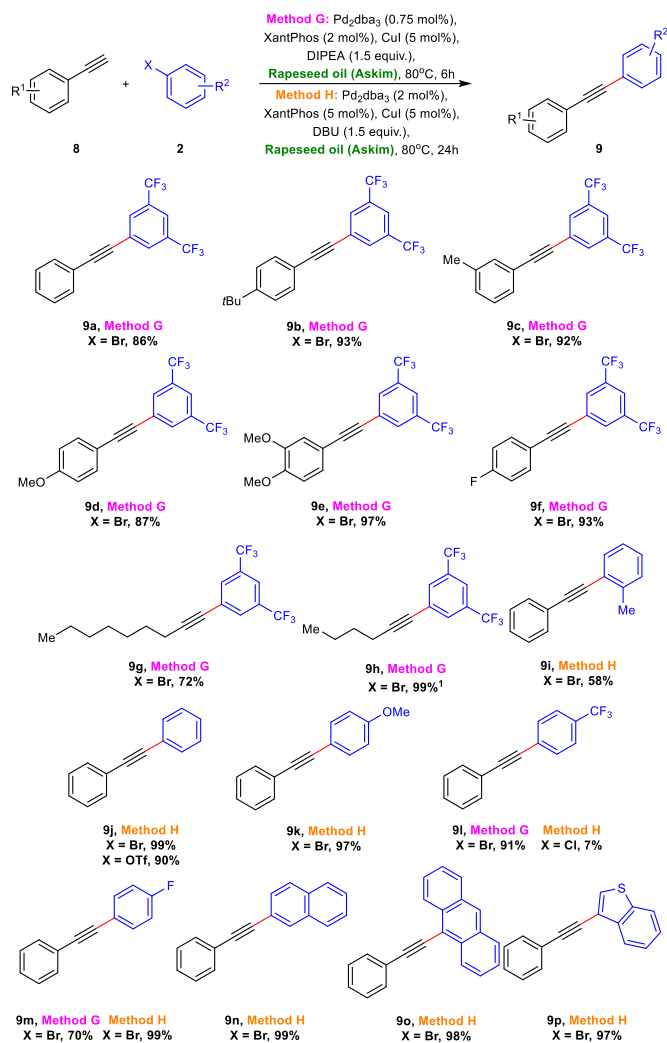
Scheme 3. Scope of Sonogashira coupling in rapeseed oil. The yields refer to isolated products. [1] The reaction was performed at 60 °C for 24h.
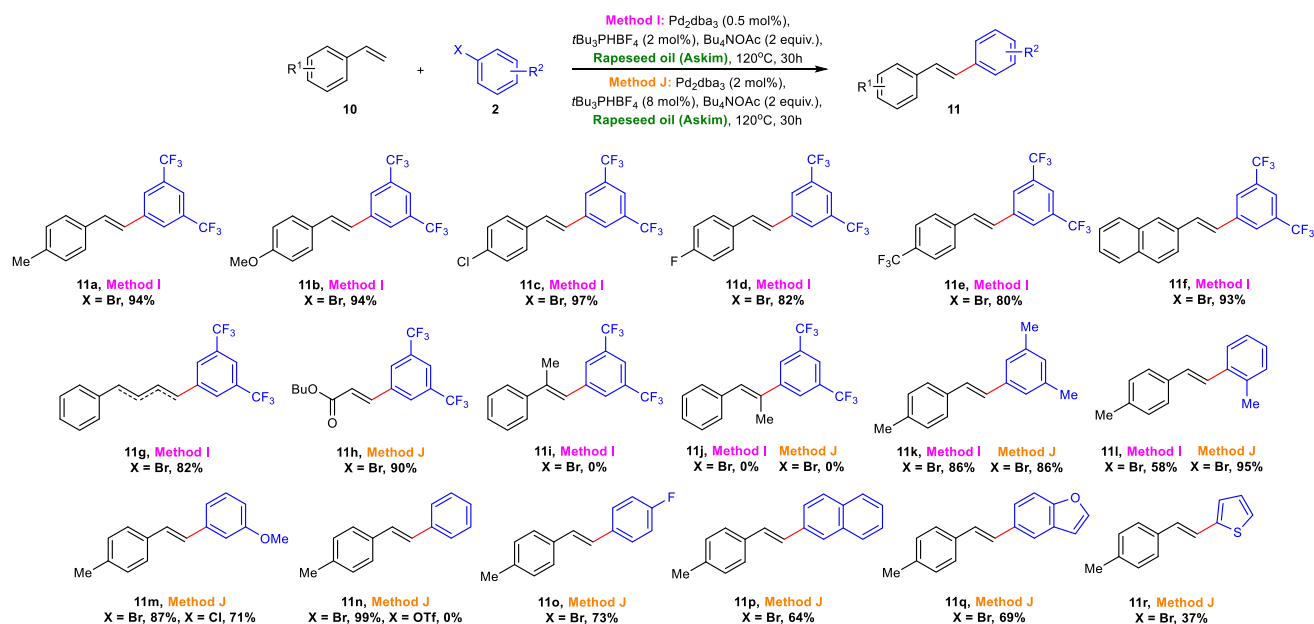
of the developed methodology was demonstrated by the successful coupling of electron-rich and sterically hindered aryl bromides, chlorides and triflates with 4-tolylboronic acid in good to quantitative yields (**3i-l** 49-99%). The reaction worked also for challenging electron-rich and unstable aryl halides, such as 2-bromobenzothiophene and bromoferrocene (**3o** 62%, **3p** 51%, Scheme 1).

Exceptional performance of vegetable oils and related lipids as solvents was further confirmed for a number of other important Pd-catalyzed transformations, including the Hiyama,[18,19] Stille,[20,21] Sonogashira[22,23] and Heck[24,25] cross-coupling reactions.

In case of Hiyama couplings in rapeseed oil (Scheme 2, A), we found that for a range of alkoxysilanes highly efficient reactions can be realized using Ad$_2$BuPHI ligand combined with Pd(OAc)$_2$. For moisture sensitive alkoxysilanes[26] high yields of Hiyama coupling can be maintained by switching to a precatalyst based on XPhos/Pd(OAc)$_2$ combined with absolute ethanol used as an additive (Scheme 2, A, **5e,f**) (for complete optimization tables see ESI, Table S4-S6).

For Stille couplings in rapeseed oil (Scheme 2, B), a relatively cheap catalytic system based on AsPh$_3$/Pd$_2$dba$_3$ performed well for activated aryl halides, whereas unactivated coupling partners required the use of XPhos/Pd$_2$dba$_3$-derived catalyst (for complete optimization tables see ESI, Tables S7-S9). Notably, for Stille cross-coupling aryl chlorides turned out to be better coupling partners than aryl bromides (**7i** 83% vs 94%, **7m** 85% vs 99%, **7p** 88%).

For the Sonogashira coupling (Scheme 3) in rapeseed oil, terminal alkynes and activated, electron-deficient aryl halides provided good to quantitative yields with XantPhos/Pd$_2$dba$_3$ as catalytic system (for complete optimization tables see ESI, Tables S10-S13). For unactivated aryl bromides and triflates generally good yields (90-99%) were obtained by increasing the catalyst loading to 2 mol% and using DBU instead of DIPEA as

Scheme 4 Scope and limitations of Heck cross-coupling in rapeseed oil. The yields refer to isolated products.

ARTICLE

base (Scheme 3, **9i-p**). Unfortunately, all attempts to find appropriate conditions for Sonogashira coupling with aryl chlorides failed (ESI, Table S13).

For Heck couplings (Scheme 4), finding successful conditions in rapeseed oil was more challenging (complete optimization tables can be found in the ESI, Tables S14-S16, see also the discussion in the section ''General considerations''). The search for optimal conditions showed that unsubstituted styrenes, acrylates and terminal olefins can be coupled with aryl halides using tBu$_3$PHBF$_4$/Pd$_2$dba$_3$ as precatalyst combined with Bu$_4$NOAc as base. Corresponding derivatives of stilbene and other internal olefins were obtained in good to quantitative yields (Scheme 4, **11a-h**, 80-97%). Notably, the Heck cross-coupling involving a terminal olefin resulted in a mixture of isomeric internal olefins (**11g**, 82%). For improved conversion of unactivated aryl halides, we increased the catalyst loading to 2 mol%, which allowed us to isolate substituted stilbenes (**11k-r**) in 37-99% yields (Scheme 4, Method J). The effect of the catalyst loading was particularly notable for sterically hindered aryl bromides (**11l** 58% vs 95%). The developed methodology was also suitable for the coupling of aryl chlorides (**11m** 71%), whereas aryl sulfonate esters were not productive coupling partners (see also ESI, Table S16).
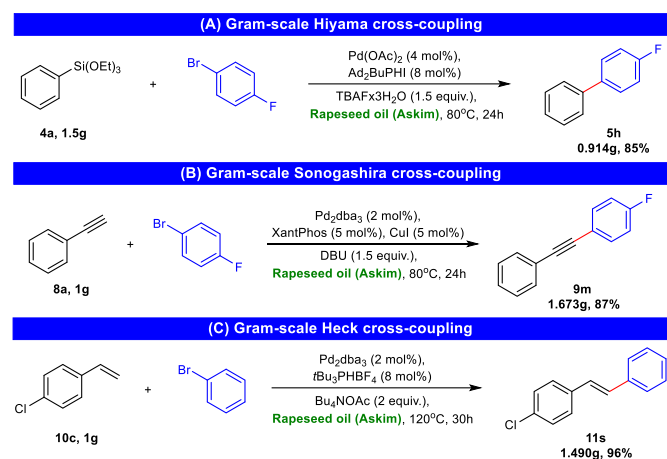
**Scheme 5** Gram-scale experiments in rapeseed oil.

Vegetable oils and related lipids possess a varying number of internal double bonds (Figure 1, B), which potentially can be involved in Heck couplings and related reactions. We analysed the stability of oils in a series of control experiments where the best conditions for cross-couplings described above were run in rapeseed oil in the presence of only 3,5-bis(trifluoromethyl)bromobenzene (**2a**). In all cases, we observed partial recovery of the starting aryl halide alongside the biaryl formed from the reductive homocoupling of the aryl halide.[27] ^{1}H, ^{13}C and ^{19}F NMR spectra of rapeseed oil before and after the control experiments were identical. The Heck cross-coupling reaction is known to be quite sensitive to steric hindrance (Scheme 4, **11i,j**),[24,25] which can be one of the reasons for the efficiency of vegetable oils and related systems as solvents.

As vegetable oils consist of esters, decomposition via saponification is another possible side reaction. In our work,

saponification was observed only in the presence of water or strong bases such as alkoxides. Considerable amount of saponification is easily detectable, as the liquid phase turns into a wax-like solid when a reaction mixture is cooled. This phenomenon was never seen for anhydrous conditions or bases like carbonates, fluorides, acetates and amines, which are commonly used for cross-coupling reactions, including the present work.

Oils were also suitable solvents for gram-scale experiments (Scheme 5). The Hiyama coupling of triethoxyphenylsilane (**4a**) and 1-bromo-4-fluorobenzene was easily scaled up to 1.5 grams of the limiting reagent, without any notable drop in the yield of the product biaryl (Scheme 5, A; **5h** 0.914 gram, 85%). Sonogashira coupling of one gram of phenylacetylene (**8a**) with 1-bromo-4-fluorobenzene led to corresponding internal alkyne (**9m**) in 87% yield (Scheme 5, B; 1.673 gram). Similarly, starting from one gram of 4-chlorostyrene (**10c**), the product of the Heck cross-coupling reaction (**11s**) can be isolated in 96% yield (Scheme 5, C; 1.490 gram).
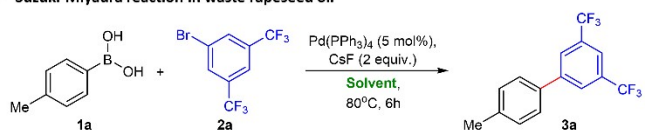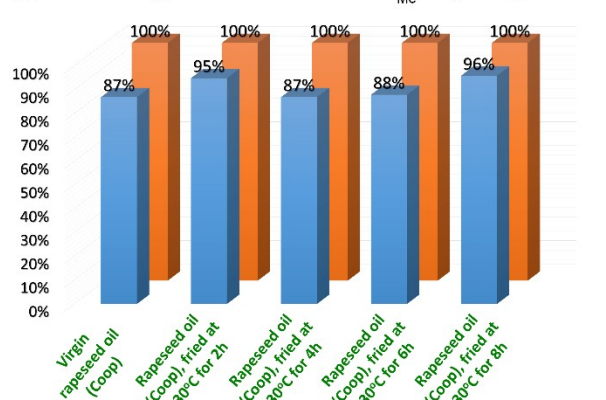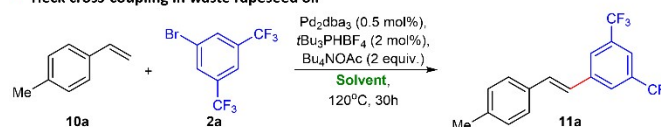
Chart 2 Application of waste rapeseed oil for Suzuki-Miyaura (blue columns) and Heck (orange columns) cross-couplings. Yields determined by ^{1}H NMR.

Further, we briefly examined performance of waste rapeseed oils for Suzuki-Miyaura and Heck cross-coupling reactions. Our studies included rapeseed oils, which were used for frying potatoes for 2, 4, 6 and 8 hours respectively (Chart 2). For Suzuki-Miyaura reaction the yields of biaryl (**3a**) in waste rapeseed oils varies in the range 87-96% and were in general slightly better than those observed in virgin rapeseed oil (87%). Meanwhile, for Heck cross-coupling the yield of stilbene derivative (**11a**) was quantitative in all lipids. The biaryl (**3a**) obtained in waste rapeseed oil, used for frying at 130 ^{o}C for 8

ARTICLE

hours, can be isolated by column chromatography in 93% yield. That is to say, optimal conditions found for virgin rapeseed oil without any alteration can be successfully applied for waste vegetable oils.

During our work, we identified 3 general methods applicable for the isolation of products obtained in vegetable oils. Due to the miscibility of most common solvents with oils (see ESI, Figure S28), extraction of products from oils with organic solvents is not possible. As an alternative, we profited from the fact that oils have no boiling point. Products could be isolated from oil by a short-path vacuum distillation using a Kugelrohr apparatus (ESI, Figure S29). However, products obtained in this manner were occasionally contaminated by unreacted starting materials and required further purification. Following the short-path vacuum distillation, rapeseed oil from the flask containing the reaction mixture can be filtered through a short pad of silica gel using ethyl acetate, dried, and applied for another experiment without notable drops in yields.

Table 1 Substitution of heptane with other renewable solvents for column chromatography on the instance of Heck cross-coupling.
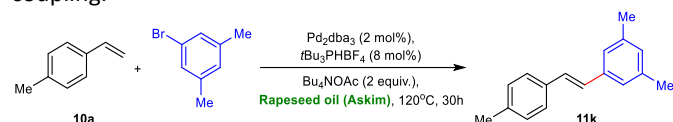
Entry	Eluent based on	Isolated yield of 11k %
1	Heptane	86
2	(−)-α-Pinene	90
3	3-Carene	91
4	Dipentene	–[1]
5	(R)-(+)-Limonene	86
6	γ-Terpinene	89
7	α-Terpinene	–[1]
8	Terpinolene	–[1]
9	Sabinene	87
10	Myrcene	–[1]
11	α-Phellandrene	–[1]

[1] The eluent partly polymerized during isolation, the product was observed along with oligomers of the eluent.

Alternatively, nonpolar products were directly separated from oils using column chromatography (ESI, Figure S29). This method was by far the fastest approach for purification. To prevent the use of large amounts of non-renewable heptane or related hydrocarbons as an eluent, we investigated the use of renewable terpenes as eluent on a reference Heck cross-coupling reaction (Table 1). Among the tested monoterpenes, dipentene, α-terpinene, terpinolene, myrcene and α-phellandrene were not useful as eluent due to partial polymerization during isolation (Table 1, entries 4, 7, 8, 10, 11), while (−)-α-pinene, 3-carene, (R)-(+)-limonene, γ-terpinene and sabinene were successful as eluents for preparative column chromatography (Table 1, entries 2, 3, 5, 6, 9). All successful eluents are readily available in kilogram scale through international suppliers. Notably, following the column chromatography, rapeseed oil can be washed out from the

column using ethyl acetate, dried, and applied for another experiment without notable drops in yields.

In a third approach, products were separated using sequential saponification of oils followed by extraction (ESI, Figure S29). The latter method has two disadvantages; the oil is lost and many functional groups do not tolerate typical conditions used for saponification (such as esters and nitriles).

Conclusions

We have shown that food grade and waste vegetable oils as well as related lipids can be use as solvents for Suzuki-Miyaura, Hiyama, Stille, Sonogashira and Heck cross-coupling reactions. Excellent yields can be achieved for a wide range of substrates. Optimal conditions can readily be found through the developed high-throughput screening methods, and isolation of products, obtained in vegetable oils, can be realized by preparative column chromatography based on fully renewable monoterpenes used as eluents. We believe that our discoveries can inspire to the use of vegetable oils as a green solvent in various reaction types.

Author contributions

A.G. directed the project, designed and carried out the experiments and analyzed the data. A.G. wrote the main manuscript text, K.H.H. and A.B. added useful advices. All authors discussed the results and reviewed the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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