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Photocatalytic carbanion generation from C–H bonds – reductant free Barbier/Grignard-type reactions

Although Grignard- and Barbier-reactions have been developed more than 100 years ago, they are still among the most widely used transformations in synthetic organic chemistry. However, they require prefunctionalized starting materials and stoichiometric amounts of metal reductants, leading to the formation of undesired waste products. To overcome these drawbacks, we developed a redox-neutral photocatalytic version of Grignard-type reactions by employing a combination of photo- and hydrogen atom transfer (HAT) catalysis to generate benzylic carbanions, which can react with electrophiles such as aldehydes or ketones, yielding homobenzylic alcohols as products.

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Photocatalytic carbanion generation from C–H bonds – reductant free Barbier/Grignard-type reactions†

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We report a redox-neutral method for the generation of carbanions from benzylic C–H bonds in a photocatalytic Grignard-type reaction. The combination of photo- and hydrogen atom transfer (HAT) catalysis enables the abstraction of a benzylic hydrogen atom, generating a radical intermediate. This radical is reduced in situ by the organic photocatalyst to a carbanion, which is able to react with electrophiles such as aldehydes or ketones, yielding homobenzylic secondary and tertiary alcohols.

Introduction

Novel catalytic methods generally aim to produce a desired chemical compound from ever-simpler starting materials, maximizing the atom and step economy.1 Hence, the functionalization of C–H bonds has received great attention, as it illustrates the most straightforward retrosynthetic path for the synthesis of a targeted product.2 There are several methods for C–H functionalizations summarized in comprehensive reviews.3 A prominent example is the C–H activation by metal insertion,3c–f comprising cases of very high and catalyst controlled regioselectivity.4 Another prevalent method is hydrogen atom transfer,3g which is used to generate carbon centred radicals for subsequent functionalization from unreactive C–H bonds by the abstraction of a hydrogen atom.

Recently, the combination of hydrogen atom transfer (HAT) and photocatalysis has evolved into a powerful method yielding carbon radicals under mild conditions without the need of a sacrificial oxidant or reductant.5 With this approach, several impressive examples for C–C and C–X bond formations were reported, utilizing C–H bonds in order to arrive at the desired product in high or even full atom economy.6 While photocatalysis, especially in combination with HAT catalysis, mainly revolves around the generation and subsequent reaction of radical species,7 some groups have recently proposed the generation of carbanions as crucial intermediates in photocatalytic transformations.7a,k The formation of carbanionic intermediates is of particular interest as they are the reactive intermediates in the widely used Grignard and Barbier reactions (Scheme 1a).8 However, these reactions produce stoichiometric amounts of metal salt waste9 and require organohalide starting materials which often have to be prepared.10 In our previous report we aimed to overcome those drawbacks by using carboxylates to generate carbanionic intermediates in a photocatalytic reaction (Scheme 1b).8g However, only aldehydes were efficient electrophiles and CO2 was released as a stoichiometric by-product. Developing this method further, we wondered if C–H bonds could directly be activated to form the desired Grignard analogous products, maximizing the atom economy.

The most straightforward C–H activation giving potential access to carbanion intermediates from unfunctionalized starting materials is the deprotonation of the respective C–H bond. However, with a pKa value of approximately 43 (in DMSO),11 even benzylic C–H bonds would require the use of

Scheme 1 (a) Grignard reaction. (b) Photocatalytic carbanion generation from carboxylates and addition to aldehydes. (c) Envisioned photocatalytic carbanion generation from C–H bonds for Grignard-type reactions in full atom economy.
highly active bases like n-BuLi (pK_a approx. 50) exceeding e.g. LDA (pK_a = 36 in THF) in reactivity, which limits the functional group tolerance and gives rise to potential side reactions. Additionally, many of these strong bases can directly add to carbonyl compounds or be quenched by the deprotonation of the more acidic proton in alpha position of the carbonyl (pK_a of acetone = 26 in DMSO), which may also be the case for the desired benzyl anion. Additionally, waste products resulting from the use of metal bases again diminish the atom economy. The generation of carbanions by the combination of HAT- and photocatalysis could overcome these issues and illustrates a valuable method for a redox-neutral, waste-free synthesis of Grignard-type products without the use of metals or strong bases (Scheme 1c).

In a recent report, our group could show the applicability of this concept for the photocarboxylation of benzylic C–H bonds via carbanionic intermediates. In this work, we aim to extend this method to the synthesis of secondary and tertiary homo-benzylic alcohols from unfunctionalized starting materials and aldehydes or ketones in a photocatalytic two-step deprotonation reaction.

Results and discussion

We chose ethylbenzene (1a) as model substrate, because its benzylic C–H bonds have a low bond dissociation energy (BDE = 85.4 kcal mol⁻¹) and benzylic radicals can be converted into the corresponding carbanion by single electron transfer (SET) using a reduced photocatalyst. Acetone (2a) was chosen as electrophile, as ketones do not bear a carbonyl hydrogen, which has shown to be prone to C–H abstraction by electrophilic radicals.

Product formation was observed using a combination of 4CzIPN (A) as photocatalyst and (iPr)₃SiSH as HAT catalyst. Together with K₂CO₃ as base and dry MeCN as solvent, the coupling product (3a) between 1a and 2a was detected in traces (Table 1, entry 1). A higher yield of 21% was obtained by adding ground 4 Å molecular sieves to the reaction (Table 2, entry 2). Increasing the amount of 2a by using it as a co-solvent in a 1 : 1 mixture with dry acetonitrile gave a yield of 49% (Table 1, entry 3). Reducing the amount of (iPr)₃SiSH and molecular sieves gave a slightly enhanced yield (Table 1, entry 4). Using 3DPA2FBN (B) as a photocatalyst increased the yield to 50% when 10 eq. 2a were used and 86% when acetone was used as a co-solvent (Table 1, entries 5 and 6). The reaction improved slightly by reducing the loading of photocatalyst B to 3 mol% and the amount of K₂CO₃ to 10 mol% (Table 1, entry 7). Control experiments showed, that the yield is significantly lower when the reaction is performed without base (Table 1, entry 8) and no product was detected in absence of light, photocatalyst or HAT catalyst (Table 1, entries 9–11).

![Chemical Structure](image)

**Table 1** Optimization of the reaction conditions for the photocatalytic HAT-reaction of ethylbenzene with acetone as an electrophile

| Entry | Amount of 2a | Photocatalyst (mol%) | Amount of (iPr)₃SiSH | Amount of base | Additive | Yield [%] |
|-------|--------------|----------------------|----------------------|----------------|----------|-----------|
| 1     | 10 eq.       | 4CzIPN (5)           | 20 mol%              | 20 mol%        | —        | 3         |
| 2     | 10 eq.       | 4CzIPN (5)           | 20 mol%              | 20 mol%        | 4 Å MS (100 mg) | 21       |
| 3     | Co-solvent (1 : 1) | 4CzIPN (5)     | 20 mol%              | 20 mol%        | 4 Å MS (100 mg) | 49       |
| 4     | 10 eq.       | 4CzIPN (5)           | 10 mol%              | 20 mol%        | 4 Å MS (50 mg) | 30       |
| 5     | 10 eq.       | 3DPA2FBN (5)         | 10 mol%              | 20 mol%        | 4 Å MS (50 mg) | 50       |
| 6     | Co-solvent (1 : 1) | 3DPA2FBN (5)     | 10 mol%              | 20 mol%        | 4 Å MS (50 mg) | 86       |
| 7     | 10 eq.       | 3DPA2FBN (3)         | 10 mol%              | 20 mol%        | 4 Å MS (50 mg) | 59       |
| 8     | 10 eq.       | 3DPA2FBN (5)         | 10 mol%              | —              | 4 Å MS (50 mg) | 27       |
| 9     | 10           | —                    | 10 mol%              | 20 mol%        | 4 Å MS (100 mg) | 0        |
| 10    | 10           | 4CzIPN (5)           | 10 mol%              | 20 mol%        | 4 Å MS (100 mg) | 0        |

a The reaction was performed using 1 eq. (0.2 mmol) 1a in 2 mL degassed solvent. b Yields were determined with GC-FID analysis using n-decane as an internal standard. c Reaction was performed in the dark.
To test if the reaction was inhibited by the formation of the 1-Heptanol (1 eq.) 21
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Functional groups were added to the reaction separately or in combination. A yield of 62% was obtained for 10 eq. 2a, while using acetone as a co-solvent only led to 55% of the desired product 3b. Using cumene 1d decreased the yield to 29% (11% with 10 eq. 2a), presumably due to enhanced steric hindrance in the benzylic position (3d). The reaction proceeded well with isopentylbenzene 1c, yielding the corresponding product 3e in 47% and 79%, respectively. Ethylbenzene derivatives containing electron donating substituents, such as methoxy- (3f-3i) or amide-groups (3j) led to significantly increased yields of up to 87% (3f and 3j). In contrast, no product was obtained with electron deficient substrates such as 4-ethylbenzonitrile or 1-ethyl-4-(trifluoromethyl)benzene, presumably due to a kinetically more hindered hydrogen atom abstraction or the lower reactivity of the corresponding carbanion intermediate. While unsubstituted toluene did not lead to any product formation due to the bond dissociation energy of the benzylic C–H bond exceeding the capability of the hydrogen atom transfer catalyst (toluene: BDE = 89 kcal mol⁻¹, (Pr)₃SiSH: BDE = 87 kcal mol⁻¹), 4-methoxytoluene 1i gave the corresponding product 3l in 19% and 53%, respectively. Chlorine and fluorine substituents at the aromatic ring were also well tolerated in the reaction (3k and 3l) and using triethylbenzene 1m led to 87% of the triple substituted product 3m when acetone was used as a co-solvent. For this substrate, no product could be isolated when only 10 eq. 2a was used, as an inseparable mixture of single, double and triple substituted product was obtained. p-Phenyl substituted ethylbenzene could also be used in the reaction, yielding 62% of product 3n (31% with 10 eq. 2a). In contrast, 2-ethynaphthalene 1o gave only low yields of 7% and 22%, respectively (3o). Heteroaromatic substrates were also viable substrates for the reaction as moderate to good yields were obtained when 2-ethylthiophene 1p or benzofuran 1q were used (3p and 3q). Moving to ketones, the effect of steric hindrance was investigated first. A good yield can still be obtained when the carbon chain is extended at one side (3t), whereas the yield is notably affected when both sides bear longer chains (3s and 3t) or an additional group is present in α-position (3u and 3v). No ring opening products were observed when a cyclopropane ring was present in α-position, indicating that no radical processes are involved in the addition to the electrophile. The reaction proceeds well with cyclic ketones (3w and 3x), especially with cyclobutanone (3x), altogether

Table 2  Investigations of product inhibition of the reaction

| Entry | Additive | Yield [%] |
|-------|----------|----------|
| 1′    | 3DPA2FBN (5 mol%) | 41       |
| 2′    | (Pr)₃SiSH (10 mol%) | 50       |
| 3′    | 3DPA2FBN (3 mol%) | 60       |
| 4     | (0.5 eq.) | 39       |
| 5     | (1 eq.) | 11       |
| 6     | 1-Heptanol (1 eq.) | 21       |

* The reaction was performed using 1 eq. (0.2 mmol) 1a and 10 eq. 2a in 2 mL degassed solvent. * Yields were determined with GC-FID analysis using n-decane as an internal standard. * Additional catalyst was added after 14 h.

The kinetic profile of the reaction shows a quite fast linear increase of product formation in the first hours. However, after 5 hours, the conversion of starting material stops at a product yield of 50 to 55%, which increased only slightly by prolonging the reaction time (Fig. 1).

To exclude the possibility, that the termination of the reaction is caused by the decomposition of either the photocatalyst or the hydrogen atom transfer catalyst, both compounds were added to the reaction separately or in combination after several hours (Table 2, entries 1−3). However, the yield of the desired product 3a could not be increased for any of the combinations. To test if the reaction was inhibited by the formation of the product, 2-methyl-1-phenyl-2-propanol 4 was added due to its structural similarity to product 3a. Indeed, the yield decreased to 39% when 0.5 eq. 4 was added and to 11% with 1 eq. 4 (Table 2, entries 4 and 5). The addition of 1 eq. 1-heptanol also decreased the yield to 21% (Table 2, entry 6), indicating that the presence of alcohols causes the reaction to stop, presumably due to the protic hydroxy groups quenching the carbanion.

The scope of the reaction was investigated for various ethylbenzene derivatives, ketones and aldehydes (Table 3). In most cases, good yields were obtained when the electrophile acetone was used as a co-solvent in a 1 : 1 mixture with acetonitrile, while using 10 eq. of electrophile led to moderate yields. Besides ethylbenzene 1a (41%/72%, 3a), 4- or 2-ethyltoluene were also viable substrates for the reaction (3b and 3c). Notably, 4-ethyltoluene 1b was the only substrate where using less electrophile seemed to be beneficial for the reaction, as a yield of 62% was obtained for 10 eq. 2a, while using acetone as a co-solvent only lead to 55% of the desired product 3b. Using cumene 1d decreased the yield to 29% (11% with 10 eq. 2a), presumably due to enhanced steric hindrance in the benzylic position (3d). The reaction proceeded well with isopentylbenzene 1c, yielding the corresponding product 3e in 47% and 79%, respectively. Ethylbenzene derivatives containing electron donating substituents, such as methoxy- (3f-3i) or amide-groups (3j) led to significantly increased yields of up to 87% (3f and 3j). In contrast, no product was obtained with electron deficient substrates such as 4-ethylbenzonitrile or 1-ethyl-4-(trifluoromethyl)benzene, presumably due to a kinetically more hindered hydrogen atom abstraction or the lower reactivity of the corresponding carbanion intermediate. While unsubstituted toluene did not lead to any product formation due to the bond dissociation energy of the benzylic C–H bond exceeding the capability of the hydrogen atom transfer catalyst (toluene: BDE = 89 kcal mol⁻¹, (Pr)₃SiSH: BDE = 87 kcal mol⁻¹), 4-methoxytoluene 1i gave the corresponding product 3l in 19% and 53%, respectively. Chlorine and fluorine substituents at the aromatic ring were also well tolerated in the reaction (3k and 3l) and using triethylbenzene 1m led to 87% of the triple substituted product 3m when acetone was used as a co-solvent. For this substrate, no product could be isolated when only 10 eq. 2a was used, as an inseparable mixture of single, double and triple substituted product was obtained. p-Phenyl substituted ethylbenzene could also be used in the reaction, yielding 62% of product 3n (31% with 10 eq. 2a). In contrast, 2-ethynaphthalene 1o gave only low yields of 7% and 22%, respectively (3o). Heteroaromatic substrates were also viable substrates for the reaction as moderate to good yields were obtained when 2-ethylthiophene 1p or -benzofuran 1q were used (3p and 3q). Moving to ketones, the effect of steric hindrance was investigated first. A good yield can still be obtained when the carbon chain is extended at one side (3t), whereas the yield is notably affected when both sides bear longer chains (3s and 3t) or an additional group is present in α-position (3u and 3v). No ring opening products were observed when a cyclopropane ring was present in α-position, indicating that no radical processes are involved in the addition to the electrophile. The reaction proceeds well with cyclic ketones (3w and 3x), especially with cyclobutanone (3x), altogether.
Table 3  Scope of the reaction

| Carbanion precursor: | Ketones: | Aldehydes: |
|----------------------|----------|-----------|
| ![Chemical structure](image1) | ![Chemical structure](image2) | ![Chemical structure](image3) |
| ![Chemical structure](image4) | ![Chemical structure](image5) | ![Chemical structure](image6) |
| ![Chemical structure](image7) | ![Chemical structure](image8) | ![Chemical structure](image9) |
| ![Chemical structure](image10) | ![Chemical structure](image11) | ![Chemical structure](image12) |
| ![Chemical structure](image13) | ![Chemical structure](image14) | ![Chemical structure](image15) |

The reaction was performed using 1 eq. (0.2 mmol) 1 and 10 eq. of the respective ketone in 2 mL dry, degassed MeCN. The reaction was performed using 1 eq. (0.2 mmol) 1 and 2a as co-solvent in a 1:1 mixture with dry MeCN in 2 mL degassed solvent mixture. The reaction was performed using 1 eq. (0.2 mmol) 1 and the respective ketone in the amount given in the table in 2 mL dry, degassed MeCN. The reaction was performed using 1 eq. (0.15 mmol) 5 and 3 eq. 1f in 2 mL dry, degassed MeCN.
displaying the significant influence of steric hindrance. In
terms of functional group tolerance, alkenes (3y), alkyl chlor-
ides (3z), ethers (3aa), esters (3ab) and protected amines (3ac)
are viable substrates. However, the amount of electrophile has
to be reduced in these cases, causing a decrease in yield.
Notably, if an \( \alpha,\beta \)-unsaturated system is used, the 1,4-addition
product (3ad) is obtained, while the 1,2-addition product was
not observed. As noted above, aldehydes are prone to C–H
abstraction from the carbonyl position,\(^*\) seemingly leading to
deleterious side reactions. Hence, the reaction conditions were
adapted, mainly by using an excess of the ethyl benzene instead
of the electrophile (see ESI for all optimization parameters\(^*\)).
Under the modified reaction conditions, aldehydes are feasible
substrates, but yields are generally only low to moderate (up to
43% for 6a). As with ketones, steric hindrance has a significant
effect (6a–6e). Thioethers are tolerated (6f) despite the presence
of C–H bonds in \( \alpha \)-position to the heteroatom. Further,
employing aromatic aldehydes gave the desired products as well
(6g and 6h), and the yield increased with an additional electron
withdrawing ester group (6h).

To investigate the mechanism of the reaction, a carbanion
test system based on a molecule used by Murphy et al. to
confirm the generation of aryl anions (Scheme 2a) was used.\(^{19}\)
According to Murphy, radicals are not capable of adding to
esters. Therefore, ethyl-5-phenylpentanoate 7a was subjected to
the standard reaction conditions. The formation of the cyclic
ketone 8a indicates the presence of the anionic intermediate
7a\(^*\) (Scheme 2b).

In addition to this, fluorescence quenching studies were
performed to confirm the interaction of the excited state of the
photocatalyst with the deprotonated HAT catalyst (Pr)\(_3\)SiS\(^-\). Efficient
fluorescence quenching was observed for the photocatalysts B and C
upon addition of (Pr)\(_3\)SiS\(^-\), indicating the oxidation of the deprotonated hydrogen atom transfer catalyst
by the excited state of the photocatalyst (ESI, Fig. S3 and S4\(^\dagger\)). To
further confirm this, cyclic voltammetry measurements were
performed (ESI, Fig. S5\(^\dagger\)). Indeed, a potential of 0.67 V vs.
SCE in MeCN was obtained for a 1 : 2 mixture of (Pr)\(_3\)SiSH
and K\(_2\)CO\(_3\) which is well in the range of photocatalyst B
and C (\(E_{1/2}(3DPA2FBN*/3DPA2FBN\(^-\)) = 0.92\) V vs. SCE,
\(E_{1/2}(3DPAFIPN*/3DPAFIPN\(^-\)) = 1.09\) V vs. SCE).\(^{20}\) Lastly, the
formation of benzylic radicals (1\(^*\)) during the reaction is indicated
by the presence of small amounts of the homocoupling product 9
in the reaction mixture (ESI, Fig. S6\(^\dagger\)).

Based on these mechanistic investigations, the reaction
mechanism depicted in Scheme 3 is proposed. The photo-
catalyst is excited upon irradiation with blue light and after
deprotonation with K\(_2\)CO\(_3\), (Pr)\(_3\)SiS\(^-\) can be oxidized to (Pr)\(_3\)
SiS\(^-\) by a SET to the excited photocatalyst PC\(^*\). The generated
sulfur radical is capable of abstracting a hydrogen atom from
ethylbenzene 1a, generating the benzylic radical 1a\(^*\) (1a: BDE = 85.4 kcal mol\(^{-1}\),\(^{15}\) (Pr)\(_3\)SiSH: BDE = 87 kcal mol\(^{-1}\)).\(^{18}\)
Compound 1a\(^*\) (\(E_{1/2}(1a*/1a) = 1.60\) V vs. SCE)\(^{22}\) can be reduced
by the radical anion of the photocatalyst PC\(^-\) (\(E_{1/2}(3DPA2FBN/
3DPA2FBN\(^-\)) = −1.92\) V vs. SCE, \(E_{1/2}(3DPAFIPN/3DPAFIPN\(^-\)) =
−1.59\) V vs. SCE),\(^{20}\) thus closing the photocatalytic cycle. The
resulting benzylic anion 1a\(^-\) reacts with electrophiles like
aldehydes or ketones, leading to the desired product 3.

**Conclusions**

In summary, we have developed a method for the photocatalytic
generation of carbanions from benzylic C–H bonds, which react
with electrophiles, such as aldehydes or ketones, to generate
homobenzylic alcohols as products. The reaction represents
a formal two-step deprotonation of the non-acidic benzylic C–H
bond and could be a mechanistic alternative to classic C–C
bond forming reactions such as the Grignard or Barbier reaction,
giving the same products. However, instead of using stoichiometric amounts of a zero-valent metal and halogenated
precursor, an organic photocatalyst, catalytic amounts of a
hydrogen atom transfer reagent and visible light are used to
generate carbanionic intermediates directly from C–H bonds,
yielding the desired product in a redox neutral reaction with full
atom economy.

**Conflicts of interest**

There are no conflicts to declare.

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