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Photocatalytic carbanion generation – benzylation of aliphatic aldehydes to secondary alcohols†

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We present a redox-neutral method for the photocatalytic generation of carbanions. Benzylic carboxylates are photooxidized by single electron transfer; immediate CO_2 extrusion and reduction of the *in situ* formed radical yields a carbanion capable of reacting with aliphatic aldehydes as electrophiles giving the Grignard analogous reaction product.

Photocatalysis is a fast growing field in chemistry, enabling novel transformations previously unattainable under thermal conditions.[1] The formation of carbon–carbon bonds is at the core of organic synthesis[2] and many photocatalytic methods have been reported over the last two decades, the majority of which involve the generation of one or more radical species as key intermediates.[3] In contrast, photocatalytic C–C bond formations involving anionic species as key intermediates are rare,[4] although the reaction between a carbanion and a carbon electrophile, *e.g.* the Grignard reaction,[5] is the most typical C–C bond forming reaction. Thus, photocatalytic methods to generate und utilize carbanion intermediates are desired in order to expand the limits of photocatalytic transformations from open shell to closed shell reactivity.

Commonly used photocatalysts, however, are only known to transfer a single electron to a substrate at once (SET), forming the corresponding radical and are not able to transfer two electrons in one step to generate the corresponding carbanion.[3] Thus, the most intuitive way to photocatalytic carbanion generation is by two subsequent SETs, *i.e.* a consecutive two-fold reduction.[6] There are a few literature examples illustrating the synthetic applicability of this strategy.[4a,b] These include the carbanion formation from 1,2-dibromomalonates giving cyclopropanes after addition to electron poor alkenes[4a] and the carbanion formation from tetraalkyl ammonium salts followed by their addition to aromatic aldehydes (Scheme 1a).[4b] The latter transformation reported by Yu *et al.* is especially interesting, as it is similar to the commonly used Grignard reaction. However, this method seems to be limited to aromatic aldehydes.

Beside the generation of a carbanion *via* a consecutive two-fold reduction, redox-neutral carbanion formations are proposed in several reports as well, typically by the reduction of a radical intermediate during the regeneration of the photocatalyst. However, this carbanion is in most cases simply protonated[7] and examples where it is synthetically used are scarce.[4c–i,8] These include the formation of a C–S bond with benzenesulfonothioates as electrophiles[4e] and intramolecular ring closures *via* an S_N2 reaction (Scheme 1b).[4f–i]

To the best of our knowledge, there is so far no report for a redox-neutral photocatalytic carbanion generation followed by its intermolecular reaction with an aliphatic aldehyde or ketone as electrophile (Scheme 1c). As mentioned above, aldehydes and ketones are in this regard especially interesting electrophiles, as the corresponding transformation is analogous to the widespread Grignard reaction. Additionally, substituted carbonyl compounds are poor radical traps for an intermolecular radical addition and forming the desired product using established photocatalytic protocols for radical addition to double bonds is generally not successful.[9] An exception to this is the photocatalytic radical addition enabled by *in situ* Brønsted acid activation yielding 3-alkoxy alcohols as reaction products reported by Glorius *et al.*[10] Mainly aromatic carbonyl compounds could be used as radical traps.
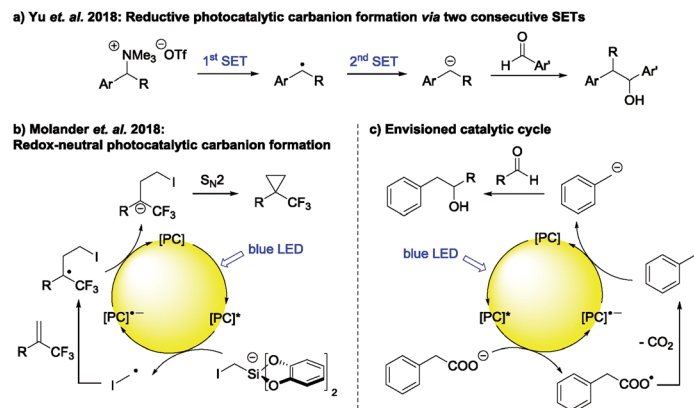
Inspired by the above mentioned reports, we envisioned a photocatalytic cycle, in which a carbanion is formed from readily available carboxylic acids. Here, the *in situ* formed carboxylate is oxidized to the corresponding radical. This intermediate is prone to CO_2 exclusion, forming the carbon centered radical, which may be converted to the corresponding carbanion by SET from the reduced photocatalyst. The desired product is then formed by addition of the carbanion to an aldehyde as electrophile (Scheme 1c). Herein we describe our efforts to realize this catalytic cycle.

With the envisioned photocatalytic cycle in mind, the coupling between phenylacetic acid (**1a**) and *n*-pentanal (**2a**) was chosen as model reaction. Compound **1a** was selected as

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Scheme 1 (a) Photocatalytic carbanion generation *via* two consecutive SETs. (b) Redox-neutral carbanion generation followed by intramolecular S_N2 reaction. (c) Envisioned catalytic cycle.

carbanion precursor, since the corresponding benzylic radical as well as the desired carbanion intermediate are stabilized by the aromatic moiety. As the photocatalyst is supposed to engage in a single electron oxidation as well as reduction, employing a catalyst with both a strong oxidation as well as reduction power is crucial. 4CzIPN is an in this regard very attractive organic photocatalyst, exhibiting an excited state redox potential of $E_{1/2}(P*/P^{•-}) = +1.35$ V *vs.* SCE and a ground state reduction potential of $E_{1/2}^{red}(P/P^{•-}) = -1.21$ V *vs.* SCE in MeCN.[11] With 4CzIPN as catalyst and Cs_2CO_3 as base, the reaction proceeded smoothly yielding the desired addition product **3a** in 73% GC-yield after 16 h (Table 1). Toluene (**4a**) was observed as a second product in 15% yield resulting from the reaction with protons as electrophile.

To increase the reaction yield, several parameters were optimized (Table 1, for the full optimization process see ESI†). A slight improvement could be realized by using DMA as solvent.

Interestingly, prior drying of the solvent over 4 Å molecular sieve did not improve the yield significantly (entries 2 and 3), whereas the addition of H_2O gave more toluene (**4a**) (entry 4). Control experiments confirmed that photocatalyst, light and base (entries 5–7) are necessary for the reaction conversion. However, the reaction can be performed in absence of base when using the preformed NBu_4^+ carboxylate salt (**5**) (entry 8), suggesting that the base merely serves to generate the carboxylate.

The reaction proceeds with various carboxylic acids (Table 2) as carbanion precursors in moderate to good yields. Halogen or –CF₃ substituted phenyl acetic acid derivatives give the desired products (**3b–h**). The presence of an additional methyl or phenyl group on the aromatic ring (**3i–l**), extended aromatic systems (**3m–n**), a Boc-protected amine (**3o**) and methoxy (**3p–r**) functional groups or additional substituents on the benzylic carbon (**3t–v**) are tolerated.

The presence of a stabilizing aromatic moiety is necessary. Aliphatic and allylic carboxylic acids yield only traces of the desired product or none at all.

Aliphatic aldehydes bearing short or long chains (**3z–ab**) react well as electrophiles. The presence of an additional methyl group at the α-carbon decreased the yield to 25% (**3ac**) and only traces of the product could be observed when pivalaldehyde was employed (**3ad**). Substituents in the β-position (**3ae**) are tolerated and even adding a second methyl group showed only a minor effect (**3af**). Aromatic aldehydes, *e.g.* benzaldehyde (**2i**), gave the corresponding product as well, but a radical–radical cross coupling of the benzyl radical and the ketyl radical similar to our previous report[12] instead of a carbanion generation cannot be excluded (Section 8, ESI†).

The formation of byproducts was investigated for selected examples (**3a–b**, **3l–n**, **3p–s**, **3w**) and an almost complete mass balance could be obtained in most cases when combining the yield of the desired (**3**) and the decarboxylated (**4**) product (Table 2). If this was not the case, *e.g.* for **3p**, an incomplete conversion of **1** was observed. Ketones, *e.g.* acetone (**6**), yield only small amounts of the tertiary alcohol (Table S9, ESI†). Using acetone (**6**) as co-solvent (1 : 1 mixture of DMA and acetone) increased the yield and **3ag** could be isolated in 32% (Table 2).

Table 1 Optimization of reaction conditions[a]

Entry	Solvent	Additive (eq.)	Yield 3a[b] [%]	Yield 4a[b] [%]
1	Dry DMF	—	73	15
2	Dry DMA	—	75	11
3	**DMA**	**—**	**75 (63)[c]**	**12**
4	DMA	H_2O (3 eq.)	34	55
5[d]	DMA	—	Not detected (n.d.)	n.d.
6[e]	DMA	—	n.d.	n.d.
7[f]	DMA	—	n.d.	n.d.
8[g]	DMA	—	64 (48)[c]	12

[a] Reactions were performed with **1a** (150 μmol, 1 eq.), **2a** (3 eq.) and Cs_2CO_3 (1 eq.) in degassed solvent (2 mL) under a nitrogen atmosphere. [b] GC-yield determined with *n*-decane as internal standard. [c] Isolated yield in parentheses. [d] Reaction performed in absence of 4CzIPN. [e] Reaction performed in the dark. [f] Reaction preformed without base. [g] The preformed NBu_4^+ carboxylate salt (NBu₄PA, **5**) was used instead of **1a** in absence of Cs_2CO_3.

Table 2 Scope of the reaction[a]

Carboxylic acids:

3a
63% (12%[b])

3b X = F: 62% (15%[b]),
3c X = Cl: 53%,
3d X = Br: 32%

3e X = F: 17%,
3f X = Br: 16%

3g
43%

3h
37%

3i p-Me: 60%,
3j m-Me: 68%,
3k o-Me: 54%

3l
58% (30%[c])

3m
33% (30%[b])

3n
56% (25%[b])

3o
48%

3p p-OMe: 13% (1%[b], 75%[d]),
3q m-OMe: 63% (20%[b])

3r
35% (13%[b])

3s
61% (21%[b])

3t[e]
62%

3u
57%

3v
51%

3w
33% (48%[c])

3x
27%

3y[e, f]
35%

Aldehydes/Ketone:

3z
41%

3aa
73%

3ab
72%

3ac
25%

3ad
Traces[g]

3ae
56%

3af
41%

3ag
32%[h] (49%[b, h])

[a] Reactions were performed with **1** (150 μmol, 1 eq.) and **2** (3 eq.) in degassed DMA (2 mL) under a nitrogen atmosphere. If not noted otherwise, the numbers indicate isolated yields. [b] GC-yield of the corresponding decarboxylated side-product **4** determined by GC-FID analysis with n-decane as internal standard. [c] Isolated yield of the corresponding decarboxylated side-product **4**. [d] Recovered starting material **1** after complete reaction time. [e] Mixture of syn- and anti-product was obtained. [f] trans-Styrylacetic acid rather than α-vinylphenylacetic acid was used as starting material. [g] Observed by GC-MS, not isolated. [h] Acetone/DMA (1 : 1) was used as solvent.

Further, several electrophiles for an intermolecular S_N2 reaction were tested (Table S11, ESI†), however an efficient system could not be found and only product traces were detected in some cases.

Starting the mechanistic investigation, a photo-conversion of 4CzIPN was observed during the course of the reaction (Fig. S1, ESI†). The degradation product could be isolated and identified as 4CzBnBN (**7a**) by X-ray crystal structure analysis (Scheme 2). Compound **7a** is likely formed by radical addition of the benzyl radical to the radical anion of 4CzIPN, followed by cyanide elimination similar to reactions reported by different groups.[13]

4CzBnBN seems to be significantly more photo-stable and the product resulting from a second cyanide elimination could only be detected in traces. Performing the benzylation reaction with 4CzBnBN as catalyst gave the desired product as well (Scheme S4, ESI†), showing that 4CzBnBN is contributing and likely the main active catalyst for the carbanion formation. Ground state potentials of $E_{1/2}^{ox}(P^{\cdot+}/P)$ = +1.48 V vs. SCE and $E_{1/2}^{red}(P/P^{\cdot-})$ = −1.72 V vs. SCE in DMF were measured by CV.

The first step in our mechanistic hypothesis is the oxidation of the carboxylate followed by the extrusion of CO_2 to generate a benzyl radical. There are several reports describing this process with various photoredox catalysts.[14] Accordingly, the emission of 4CzBnBN could be quenched upon addition of NBu_4PA (**5**) resulting in a linear Stern–Volmer plot (Fig. S7, ESI†), confirming the interaction between the excited photo-catalyst and the substrate. The following CO_2 elimination could be monitored by in situ IR spectroscopy (Fig. 1) together with the depletion of the aldehyde in course of the reaction.
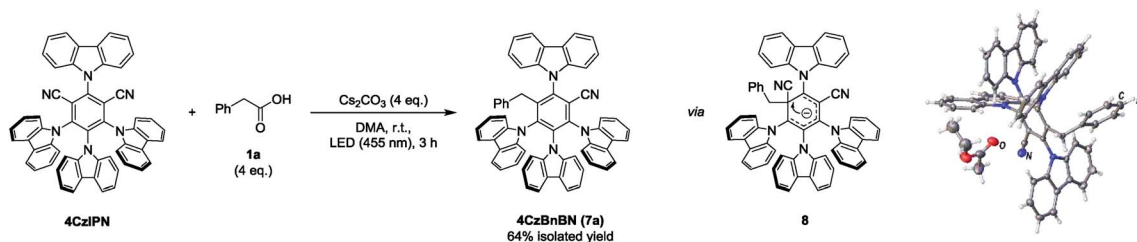
Next, deuterium labeling experiments were conducted to support the formation of an anionic intermediate during the later course of the reaction (Scheme 3a). With D_2O as electrophile, the corresponding deuterated decarboxylated starting material was isolated (**4v-d**). As a control experiment, the non-deuterated product (**4v**) was obtained when the reaction was performed in deuterated DMF in absence of D_2O. Addition of D_2O to a reaction mixture after completed irradiation did not yield any **4v-d** from **4v** via base-induced (Cs_2CO_3) H/D-exchange (Scheme S5, ESI†).

In addition to the incorporation of deuterium, a carbanion intermediate is expected to engage in an E1cb elimination if an appropriate leaving group is present in the homobenzylic position. Hence, tropic acid (**9**) was subjected to the reaction conditions (Scheme 3b). Indeed, styrene (**10**) together with the decarboxylated byproduct (**11**) was detected. To exclude styrene formation from **11** by a simple E2 elimination induced by Cs_2CO_3, **11** was directly subjected to the applied reaction conditions, yielding no styrene (Scheme S6, ESI†).
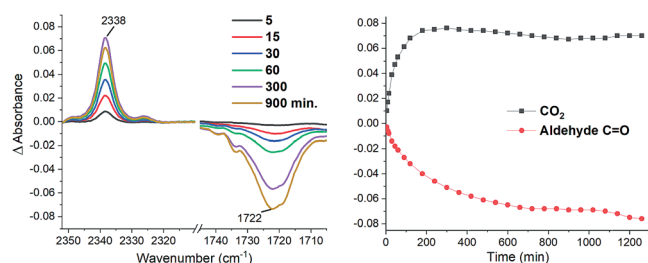
In order to thoroughly study the feasibility and selectivity of the addition of the benzyl anion (**15**) to the electrophile, a computational analysis was performed. The C=O addition and the acid–base reaction of **15** and the C_α–H was proven at the SMD(DMF)-ωB97X-D/TZVP level of theory (see Section 7.9 in the ESI†). Indeed, the reaction of the benzyl anion with the alde-hydes results to be exothermal (ΔG = −6.9 kcal mol^{-1}) and slightly kinetically favored (ΔG^* = +6.2 kcal mol^{-1}) compared to the abstraction of the acidic proton in the α position (ΔG^* = +6.8 kcal mol^{-1}). Ketones were found to be less selective towards the C=O addition of the benzyl anion compared to the aldehydes (see compound **3ag**). As a parallelism, the reaction of the benzyl anion with the ketonic C=O is almost thermoneutral (ΔG = +1.5 kcal mol^{-1}). The competing acid–base reaction is exothermal (ΔG = −12.1 kcal mol^{-1}), with comparable barriers (ΔG^* ca. 10 kcal mol^{-1}). The barriers for the reactions of **15** with DMA are higher compared to the ones of aldehydes and ketones.

Considering the experimental observations, computational results and cited literature reports, the following mechanism is
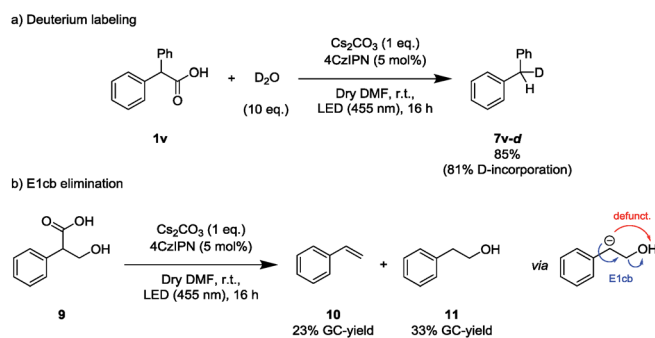
Scheme 2 Isolation of 4CzIPN photo-conversion product 4CzBnBN (**7a**). The reaction was performed with 4CzIPN (30 μmol, 1 eq.) and **1a** (4 eq.) in degassed DMA (2 mL) under a nitrogen atmosphere.
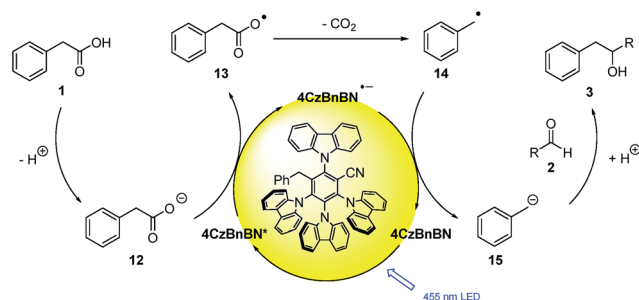

Fig. 1 *In situ* FT-IR studies. Irradiation of a solution containing NBu$_4$PA (**5**) (75 mM), **2a** (75 mM) and 4CzBnBN (3.75 mM) in dry DMA lead to the formation of CO$_2$ (2338 cm^{-1}) and the depletion of **2a** (1722 cm^{-1}).

Scheme 3 Experiments supporting the formation of a reactive anionic intermediate.

proposed (Scheme 4): the carboxylic acid **1** is deprotonated by the base (Cs$_2$CO$_3$) to give carboxylate **12**. The carboxylate ($E_{1/2}^{ox}$ (NBu$_4$PA **5**) = +1.27 *vs.* SCE[14a]) can be oxidized by the

Scheme 4 Proposed mechanism.

excited photocatalyst 4CzBnBN ($E_{1/2}^{ox}$(P*/P$^{•-}$) = +1.21 V *vs.* SCE) and the generated radical species **13** is transformed to the benzylic radical **14** by elimination of CO$_2$. The radical anion of 4CzBnBN is with a reduction potential of $E_{1/2}^{red}$(P/P$^{•-}$) = −1.72 V *vs.* SCE not able to reduce aliphatic aldehydes ($E_{1/2}^{red}$(3-methylbutanal **2g**) = −2.24 V *vs.* SCE[15]) and hence transfers an electron to the more easily reducible benzyl radical ($E_{1/2}^{red}$ = −1.43 V *vs.* SCE[16]) to form carbanion **15**. This species is capable of adding to aldehydes (**2**) forming the desired product **3** after protonation of the alcoholate.

Conclusions

In summary, a redox-neutral procedure to benzylate aliphatic aldehydes *via* the photocatalytic generation of a carbanion intermediate is presented, rendering the desired Grignard analogous products in moderate to good yields. The proposed mechanism is supported by emission quenching, *in situ* UV/VIS and *in situ* IR studies, while the presence of the reactive anionic intermediate is shown by deuterium labeling, E1cb elimination and DFT calculation.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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