Preparation of α-Perfluoroalkyl Ketones from α,β-Unsaturated Ketones via Formal Hydroperfluoroalkylation

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ABSTRACT: Formal hydroperfluoroalkylation of enones is achieved in a two-step process comprising conjugate hydroboration and subsequent radical perfluoroalkylation. The 1,4-hydroboration of the enone is conducted in the absence of any transition metal catalyst with catecholborane in 1,2-dichloroethane, and the generated boron enolate is in situ α-perfluoroalkylated with a perfluoroalkyl iodide upon blue LED irradiation in the presence of an amine additive. Both reactions proceed under very mild conditions at room temperature.

Perfluoroalkyl containing organic compounds have gained great importance in various fields such as polymer chemistry, the agrochemical industry, and the pharmaceutical industry. Various agrochemicals and pharmaceuticals bear at least one fluorine atom. It is well-known that a perfluoroalkyl group, in particular the CF₃-moiety, in a bioactive compound influences the pharmacokinetics. Therefore, the development of synthetic methods for the preparation of perfluoroalkylated compounds has found significant attention in the past, and various strategies have been developed to form a C(sp³)–CF₃ bond using electrophilic, nucleophilic, and radical CF₃-sources.

Among several scaffolds, the synthesis of α-trifluoromethylated ketones has been studied, and accordingly, different approaches for their preparation have been reported. The most obvious path that is ionic enolate alkylation using CF₃I as the electrophile does not provide the targeted α-trifluoromethylated ketones. However, C(sp³)–CF₃ coupling can be achieved upon using α-halo ketones with CuCF₃ as the reagent. Moreover, radical chemistry with the reactive trifluoromethyl radical as an intermediate has been found to be highly valuable for the α-trifluoromethylation of ketones. Along these lines, Li- and Ti-enolates have been successfully used as radical acceptors for trifluoromethylation (Scheme 1a). In situ generated silyl enol ethers react efficiently with CF₃I in a radical chain reaction and different initiation protocols have been developed to run such cascades (Scheme 1b). Moreover, vinyl triflates, readily prepared upon enolate triflation, act as CF₃-radical acceptors as well as CF₃-radical precursors with SO₂ as the only byproduct of the chain reaction (Scheme 1c). All these methods use ketones as the substrates and all proceed via formation of the corresponding enolates. It is known that ketone enolates can also be generated via conjugate reduction of enones. Subsequent α-trifluoromethylation should provide the targeted α-functionalized ketones in a formal hydrotrifluoromethylation process. Surprisingly,

Scheme 1. Radical Approaches for the Preparation of α-Trifluoromethylated Ketones

a) Radical α-trifluoromethylation of ketones via their Li/Ti-enolates (ref. 9)

b) Ketone α-trifluoromethylation via its silyl enol ether (ref. 8)

c) Ketone α-trifluoromethylation via its vinyl triflate (ref. 10)

d) Reductive α-perfluoroalkylation of α,β-unsaturated ketones via catechol boron enolates (this work)

reductive enone α-trifluoromethylation has been rarely studied. Herein, we report a catalyst-free α-perfluoroalkylation of α,β-unsaturated ketones via conjugate hydroboration
with catecholborane and subsequent radical perfluoroalkylation of the in situ generated boron enolate (Scheme 1d). In contrast to the generation of silyl enol ethers or enol triflates from ketones where strong bases are generally required, the B-enolate formation via hydrosilation of enones occurs in the absence of any base under mild conditions. Moreover, regioselective enolization of dialkyl ketones is difficult, whereas enolization of an enone affords the corresponding enolate as a single regiosomer.

In a collaboration with the Renaud laboratory we developed TEMPO mediated oxidation of catecholboron enolates proceeding via the corresponding enoyl radicals. We further showed that catecholboron enolates are good C-radical acceptors, and based on this reactivity a boron group transfer polymerization process was developed. We therefore envisaged that catecholboron enolates can be utilized as perfluoroalkyl radical acceptors. The studies were commenced using chlorochalcone 1a as the model substrate in combination with perfluorobutyl iodide (2a) as the radical alkylation reagent. In situ generation of the boron enolate through conjugate enone reduction upon treatment of 2a with catecholborane (HBcat, 1.2 equiv) in THF for 2 h was followed by the addition of 2a (5 equiv) and subsequent blue LED irradiation for 16 h. Pleasingly, the targeted α-perfluoroalkylated ketone 3a was obtained in 29% yield (Table 1, entry 1). Increasing the amount of HBcat and 2a led to a slightly better yield (Table 1, entry 2). A further improvement was achieved upon using DMF as an additive and 3a was formed in 45% yield (Table 1, entry 3). An even better result was noted with Et3N as the additive (Table 1, entry 4). A quick solvent screening revealed that yield was improved in dioxane (Table 1, entry 5) and 1,2-dichloroethane (Table 1, entry 6). A quick solvent screening revealed that yield was improved in dioxane (Table 1, entry 5) and 1,2-dichloroethane (Table 1, entry 6). A quick solvent screening revealed that yield was improved in dioxane (Table 1, entry 5) and 1,2-dichloroethane (Table 1, entry 6). A quick solvent screening revealed that yield was improved in dioxane (Table 1, entry 5) and 1,2-dichloroethane (Table 1, entry 6). A quick solvent screening revealed that yield was improved in dioxane (Table 1, entry 5) and 1,2-dichloroethane (Table 1, entry 6). A quick solvent screening revealed that yield was improved in dioxane (Table 1, entry 5) and 1,2-dichloroethane (Table 1, entry 6).

Under the optimized conditions, the substrate scope was investigated, first varying the enone component. The studied enones were easily prepared by standard aldol condensation (see Supporting Information), and reactions were conducted with perfluorobutyl iodide as the C-radical precursor. Chalcones 1a–1i reacted well, and the corresponding products were isolated in good to very good yields (Scheme 2). Electronic effect are weak and good results were obtained for the electron-poor as well as electron-rich systems. Hence, the 4-halo chalcones 1a–1c and the nitrile 1e gave the hydrosilaneperfluoroalkylated ketones 3a–3c and 3e in 62–80% yields. Similar yields were obtained for the chalcones bearing electron-donating alkyl and the methylthio group as the para-substituent (3d, 86%; 3f, 86%; 3i, 62%), and also the unsubstituted congener 1g as well as the phenyl derivative 1h reacted well (3g, 72%; 3h, 75%). Substitution at the ortho-position of the R-aryl group in the starting chalcone (see 1j–1l) led to slightly lower yields, likely due to steric effects, and 3j–3l were isolated in 50–73% yields. As expected, a meta-substituent does not influence reaction outcome to a large extent (3m, 75%). The chalcone derived

### Table 1. Reaction Optimization

| entry | solvent | HBcat (equiv) | additive | 2a (equiv) | yield (%) |
|-------|---------|---------------|----------|-----------|-----------|
| 1     | THF     | 1.2           | −        | 5         | 29        |
| 2     | THF     | 2.2           | −        | 10        | 35        |
| 3     | THF     | 1.5           | DMF      | 5         | 45        |
| 4     | THF     | 1.5           | Et3N     | 5         | 59*       |
| 5     | dioxane | 1.5           | Et3N     | 5         | 74        |
| 6     | DCE     | 1.5           | Et3N     | 5         | 84        |
| 7     | DCE     | 1.5           | Et3N     | 2.5       | 60        |
| 8     | DCE     | 1.5           | Et3N     | 6         | 5*        |

*Reaction conditions: 1a (0.2 mmol, 1 equiv), solvent (1 mL), additive, rt, Ar, 16 h. 
*Yield were determined by NMR using 2,4,6-trimethoxybenzene as internal standard. 
*0.1 mL DMF used.
*Isolated yield based on 1a. 
*Without light.

### Scheme 2. Hydroperfluoroalkylation of Various Enones Also Varying the Perfluoroalkyl Radical Precursor

[Diagram of reaction scheme]

- 1a → 3a (80%, 72%°, R = Cl)
- 3b (71%, R = Br)
- 3c (70%, R = F)
- 3d (86%, R = SMes)
- 3e (62%, R = CN)
- 3f (86%, R = Me)
- 3g (72%, R = H)
- 3h (75%, R = Ph)
- 3i (62%, R = Bu)

Reaction conditions: 1 (0.2 mmol, 1 equiv), DCE (1 mL), HBcat (0.3 mmol, 1.5 equiv), Et3N (69 μL, 2.5 equiv), rt, Ar, 16 h. Reaction conducted on 1 mmol scale.
from 2-naphthyl aldehyde exerting weak steric effects reacted efficiently to provide 3n in 80% yield. We were pleased to find that enones derived from aliphatic aldehydes engaged in the hydroperfluoroalkylation as documented by the successful preparation of the cyclopentyl- (3o) and methyl congener (3p), albeit slightly lower yields were achieved (54–55%). Moreover, heteroaromatics are tolerated as the benzofuranyl (3q) and thienyl ketone (3s) could be prepared by this method. The latter example further shows that also the Ar-group in the enones of type 1 can be varied. Along these lines, the para-methoxyphenyl ketone 3r was obtained in an excellent 90% yield. Unfortunately, cyclic enones are not eligible substrates due to the failure of the initial conjugate hydroboration.\textsuperscript{15} Methyl styryl ketone worked, albeit the yield was moderate (3x, 24%).

We finally tested whether the perfluorobutyl iodide can be replaced by other perfluoroalkyl radical sources. Pleasingly, reaction of ICF\textsubscript{2}CO\textsubscript{2}Et with 1a under the optimized conditions gave the desired ketone 3t in 71% yield. As expected, the novel cascade can also be conducted with perfluoropropyl iodide (3u), perfluoroethyl iodide (3v), and importantly also with trifluoromethyl iodide (3w).

To check the role of the catecholboron moiety in the radical alkylation, we studied the α-perfluorobutylolation of two additional boron enolates. The enolate derived from conjugate reduction of 4-chlorochalcone (1a) with 9-borabicyclo[3.3.1]nonane (9-BBN)\textsuperscript{16} was reacted with C\textsubscript{6}F\textsubscript{5}I under the optimized condition (LED irradiation). However, only traces of the targeted 3a were identified (Scheme 3). In addition, we

|Scheme 3. Control Experiments: The Importance of the Catecholboron Moiety|

| 1a | 1) 9-BBN (1.5 equiv) | rt, 3 h | 2) C\textsubscript{6}F\textsubscript{5}I (5 equiv), NEt\textsubscript{3} blue LED |
| 4a | 1) HBPin (2 equiv) | pyridine (2 equiv) | 2) C\textsubscript{6}F\textsubscript{5}I (5 equiv), NEt\textsubscript{3} blue LED |

generated the pinacol boron enolate derived from α-iodoacetoephene (4a).\textsuperscript{17} Again, radical α-perfluorobutylolation was not efficient upon irradiation, and 5a was formed in traces only. In both cases reduction worked, but the subsequent radical C−R\textsubscript{f}-bond formation failed. These two experiments clearly show the importance of the catechol moiety at boron on its radical reactivity. Notably, the unique reactivity of the catechol entity was previously also found for the boron enolate oxidation with TEMPO.\textsuperscript{13}

The suggested mechanism for the radical perfluoroalkylation of a catecholboron enolate A is depicted in Scheme 4. In the initiation step, the perfluoroalkyl radical is generated by blue LED irradiation of the perfluoroalkyl iodide/amine complex. The electrophilic C-radical then adds to the catecholboron enolate A to generate the corresponding borylated ketyl radical B. Structure of A was confirmed for the enolate derived from 1a (Ar = Ph, R = 4-CIPh) by NMR spectroscopy (see SI). For this particular substrate, enolate generation occurred selectively and the Z-configuration was assigned based on literature precedence.\textsuperscript{15a} This highly nucleophilic radical can undergo rapid SET-oxidation by the perfluoroalkyl iodide to give the product ketone 3, IBcat and the perfluoroalkyl radical, qualifying the overall cascade as an electron catalyzed process.\textsuperscript{18} The SET-oxidation of intermediate B might be assisted with the Lewis-basic amine coordinating to the B atom of the enolate.\textsuperscript{19} Alternatively, radical B might engage in an endothermic I atom abstraction reaction from RfI followed by very fast ionic IBcat fragmentation.

In summary, we have presented formal hydroperfluoroalkylation of various aromatic enones. These transformations proceed via initial conjugate reduction of the αβ-unsaturated ketone with catecholborane and subsequent light initiated radical chain α-perfluoroalkylation of the intermediately formed catecholboron enolate. The radical alkylation works only on catecholboron enolates and analogous pinacolboron- and dialkyl boron enolates do not engage in the radical alkylation. The process works under mild conditions, and a catalyst is not required in both steps of the cascade. Importantly, the two-step procedure can be conducted in one pot, further increasing the practicality of the process. The method introduced further expands boron-based radical chemistry.
Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c04260

Notes

The authors declare no competing financial interest.

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