Single-Electron-Transfer Catalysis

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# Oxidative Catalysis Using the Stoichiometric Oxidant as a Reagent: An Efficient Strategy for Single-Electron-Transfer-Induced Tandem Anion–Radical Reactions**

*František Kafka, Martin Holan, Denisa Hidasová, Radek Pohl, Ivana Císařová, Blanka Klepetářová, and Ullrich Jahn**

***Abstract:*** *Oxidative single-electron transfer-catalyzed tandem reactions consisting of a conjugate addition and a radical cyclization are reported, which incorporate the mandatory terminal oxidant as a functionality into the product.*

Single-electron-transfer (SET)-mediated transformations are a very convenient strategy for the synthesis of complex molecules. In such processes radical ions are generated from neutral precursors, whereas organometallic or carbocationic intermediates lead to radicals. SET-mediated reactions can be classified according to the overall change of the oxidation state as redox-neutral, oxidative, or reductive. Redox-neutral processes are often transition-metal-catalyzed cross-coupling reactions involving alkyl halides or sulfur electrophiles,[1,2] transition-metal-catalyzed atom-transfer radical reactions,[1,3] the more recently rediscovered homolytic aromatic substitutions,[1,4] tetrathiafulvalene-promoted radical reactions[5a] and cycloaddition reactions,[1] in which the catalytic SET oxidant or reductant is regenerated at the end of the catalytic cycle by the reverse electron transfer. The majority of the known SET-induced reactions are, however, overall reductive[1,5] or oxidative,[1,6] which means that at least two equal SET steps occur sequentially in the process. They require stoichiometric amounts of SET oxidants or reducing agents to proceed. Catalytic versions are rare; notable are reductive titanium-(III)-catalyzed reactions,[1,7] photoredox-catalytic transformations,[1,8] and some Minisci-type reactions.[1] However, even though they are catalytic in the SET-active species, they always require sacrificial reductants or oxidants to achieve turnover, such as metals, *t*BuOOH, and amines, which end as waste after completion of the reaction (Figure 1).[9]

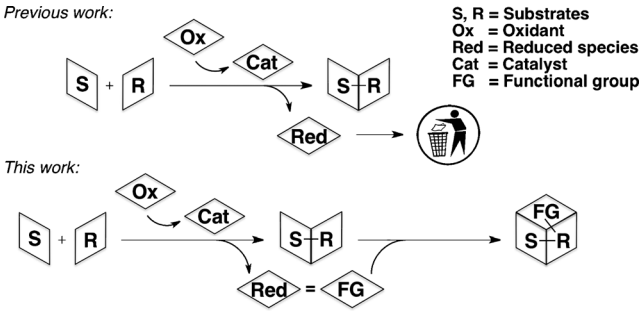


***Figure 1.*** Conventional oxidative transformation, in which the stoichiometric reduced species is wasted; in contrast, in oxidative catalysis it serves as a reagent.

We hypothesized that it would be more environmentally sustainable to use the sacrificial reduced or oxidized species resulting from promotion of the SET steps productively to introduce useful functionality into the target molecules. This gives the redox reagent a double function and renders the overall transformation redox-economic and complexity generating. Such a strategy can be considered complementary to recently introduced "borrowing-hydrogen" and related two-electron-transfer processes.[10]

We report here that catalytic oxidative SET is indeed possible and can be applied to tandem processes consisting of asymmetric organometallic conjugate addition, radical cyclization, and oxygenation steps. The reactions proceed with catalytic amounts of cheap ferrocene and 2,2,6,6-tetramethyl-*N*-oxopiperidinium hexafluorophosphate as the stoichiometric oxidant. The resulting reduced species TEMPO serves subsequently as an oxygenating agent introducing a useful protected alcohol functionality.

It is known that ferrocenium hexafluorophosphate ($\mathbf{1}^+$) does not oxidize TEMPO (**2**) and thus the equilibrium is on the left (Scheme 1).[11] Therefore the opposite process should proceed spontaneously and allow the catalytic SET oxidation. Indeed, an instantaneous and quantitative reaction to $\mathbf{1}^+$ and **2** occurred when ferrocene (**1**) and the *N*-oxopiperidinium hexafluorophosphate $\mathbf{2}^+$ were mixed.

[*] Ing. F. Kafka,[+] Ing. M. Holan,[+] M.Sc. D. Hidasová, Dr. R. Pohl, Dr. B. Klepetářová, Dr. U. Jahn
Institute of Organic Chemistry and Biochemistry
Academy of Sciences of the Czech Republic
Flemingovo náměstí 2, 16610 Prague (Czech Republic)
E-mail: jahn@uochb.cas.cz
Homepage: http://www.uochb.cz/web/structure/616.html
Dr. I. Císařová
Department of Inorganic Chemistry, Faculty of Science
Charles University in Prague
Hlavova 2030/8, 12843 Prague (Czech Republic)
[+] These authors contributed equally to this work.

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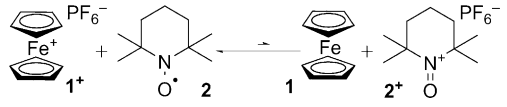
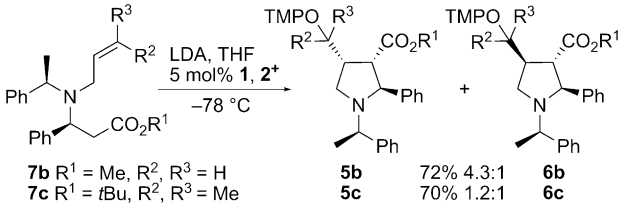


***Scheme 1.*** Equilibrium of the **1**/**2** redox pair.

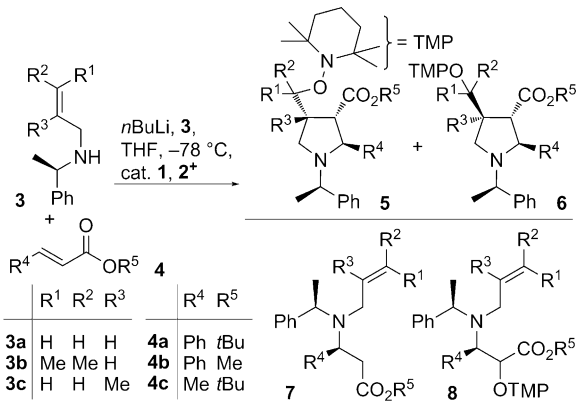
These catalytic oxidative conditions were applied to asymmetric tandem lithium amide conjugate addition/radical cyclization/oxygenation sequences leading to the tetrasubstituted pyrrolidines **5** and **6** (Table 1). The asymmetric conjugate addition step was performed with *N*-allylic 1-phenylethylamines **3** in analogy to Davies' original conditions,[12,13] followed by addition of ferrocene (**1**) and salt $\mathbf{2}^+$ in portions not exceeding the amount of **1** at −78 °C. The oxygenated pyrrolidines were isolated in mostly good yields (Table 1, entries 1–7), which are in the same range as those of the stoichiometric version of the sequence using $\mathbf{1}^+$ and TEMPO (**2**) (not shown). In contrast, the addition/cyclization sequence with the corresponding methallylamine **3c** was slow at −78 °C, giving only 25% yield of **5**/**6f** (entry 8); however, increasing the reaction temperature to −20 °C improved the yield significantly (entry 9). In most cases small amounts of the aza-Michael adduct **7** were detected (entries 1–6), whereas acyclic TEMPO coupling products **8** were found as side products only in reactions with crotonate **4c** (entries 5 and 7–9) and in the case of slower cyclizations, such as those leading to pyrrolidines **5**/**6f** (entries 8 and 9). The diastereoselectivity of the addition was high for all substrates. The cyclic products were formed with exclusive 2,3-*trans* diastereoselectivity, whereas a moderate 3,4-*cis* diastereoselectivity was observed for allyl and methallylamines (entries 1–3 and 5–9). However, no 3,4 diastereoselectivity was found for cyclizations with a prenyl group (entry 4). The amount of ferrocene could be as low as 1 mol%, but 5–10 mol% was more practical because it allowed an easy monitoring; after consumption of the enolate, **1** is oxidized to the blue ferrocenium compound indicating completion. It must be mentioned as an advantage that the oxygen atom is introduced in a stable protected form and it has been shown that the piperidinyloxy group can be carried through multiple subsequent manipulations thus reducing the effort for protection steps.[14]

The catalytic system **1**/$\mathbf{2}^+$ is also applicable in oxidative radical cyclizations of the enolates derived from enantiomerically pure *N*-allylic β-amino esters **7** (Scheme 2). Pyrrolidines



***Scheme 2.*** Catalytic oxidative cyclizations of β-amino esters **7**. LDA = lithium diisopropylamide, TMP = 2,2,6,6-tetramethylpiperidin-1-yl.

***Table 1:*** Catalytic tandem aza-Michael addition/radical cyclization/oxygenation reactions.[a]



| | $R^1$ | $R^2$ | $R^3$ | | $R^4$ | $R^5$ |
|---|---|---|---|---|---|---|
| **3a** | H | H | H | **4a** | Ph | *t*Bu |
| **3b** | Me | Me | H | **4b** | Ph | Me |
| **3c** | H | H | Me | **4c** | Me | *t*Bu |

| Entry | 3 | 4 | 1 [mol%] | 5 + 6, yield [%] | d.r. 5:6 | Other products, yield [%] |
|---|---|---|---|---|---|---|
| 1 | **3a** | **4a** | 10 | **5a** + **6a**, 75 | 6:1 | **7a**, 16 |
| 2 | **3a** | **4a** | 1 | **5a** + **6a**, 71 | 5:1 | **7a**, 16 |
| 3 | **3a** | **4b** | 1 | **5b** + **6b**, 71 | 3.8:1 | **7b** + **8b**,[b] < 5 |
| 4 | **3b** | **4a** | 5 | **5c** + **6c**, 72[c] | 1.3:1 | **7c**, 22 |
| 5 | **3a** | **4c** | 2 | **5d** + **6d**, 49 | 3:1 | **7d**, 9; **8d**, 27 |
| 6 | **3a** | **4c** | 5 | **5d** + **6d**, 56 | 2.3:1 | **7d**, 12 |
| 7 | **3b** | **4c** | 10 | **5e** + **6e**, 56 | 2.3:1 | **8e**, 19 |
| 8 | **3c** | **4c** | 5 | **5f** + **6f**, 25 | 3.3:1 | **8f**, 33 |
| 9[d] | **3c** | **4c** | 5 | **5f** + **6f**, 52 | 2.4:1 | **8f**, 17 |

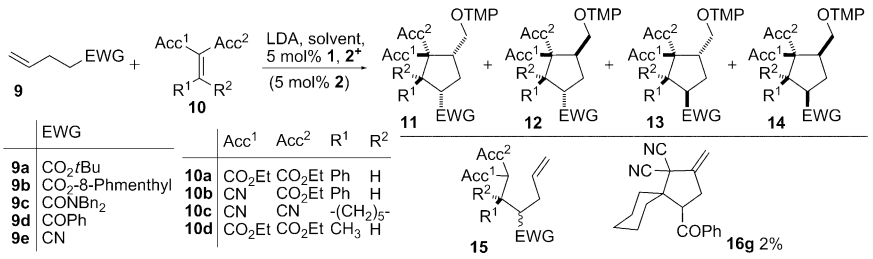
[a] Standard conditions: **3** (1.1 mmol), *n*BuLi (1.1 mmol), −78 °C, 30 min, **4** (1 mmol), 30 min, **1**, $\mathbf{2}^+$. [b] Inseparable mixture. [c] Performed on a 3 mmol scale. [d] LiCl (1 mol%) present, **1** and $\mathbf{2}^+$ added at −20 °C.

**5** and **6** were isolated in good yield and the diastereoselectivity was similar to that in the tandem process.

The new conditions were applied to catalytic oxidative tandem reactions consisting of Michael addition, radical cyclization, and oxygenation steps (Table 2). Esters, amides, ketones, and nitriles **9** are applicable as Michael donors and acceptors **10** bearing ester or cyano functions were used (entries 1–8). Substrates **9a–d** gave products **11a–d** with very high or even exclusive diastereoselectivity (entries 1–4). Enantiomerically pure 8-phenylmenthyl ester **9b** provided the product **11b** as a single enantio- and diastereomer showing a way to render the sequence asymmetric (entry 2). Some Michael adduct **15** was recovered when HMPA was used as an additive to ensure formation of the (*Z*)-enolate (entries 1, 2, and 4). It apparently resulted from hydrogen-transfer reactions, since enolate formation was always complete. Pent-4-enenitrile **9e** also reacted similarly providing tetrasubstituted cyclopentane derivative **11e** with orthogonal carbonyl functionalities in good yield and only slightly lower diastereoselectivities (entry 5). Even a fourth contiguous stereocenter can be introduced with good diastereoselectivity using benzylidenecyanoacetate **10b** (entry 6). Michael acceptors with aliphatic β-substituents, such as malononitrile **10c** and malonate **10d**, afforded the products in good yield but with lower diastereoselectivity (entries 7 and 8). Since the concentration of available TEMPO (**2**) is very low for oxygenative termination at the beginning of the sequences, the addition of 5 mol% **2** was beneficial to prefent formation of by-products such as **16g** (entries 3, 4, and 6–8).

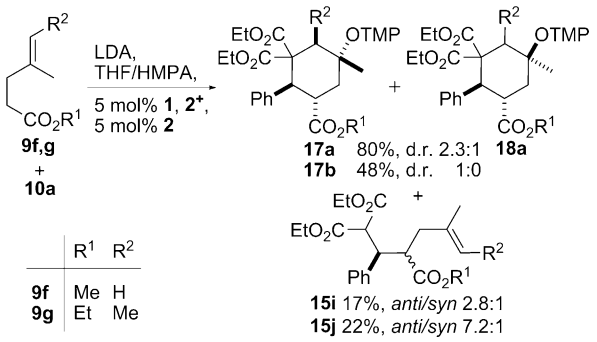
  

***Table 2:*** Catalytic tandem Michael addition/radical cyclization/oxygenation reactions.[a]

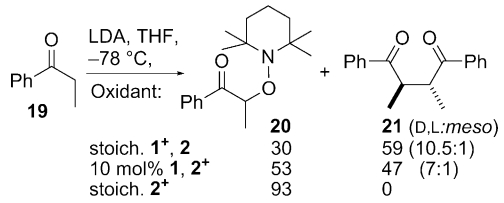



| Entry | 9 | 10 | Solvent | 2 [mol%] | 11–14, yield [%] | d.r. 11:12:13:14 | 15, yield [%] (*anti*/*syn*) |
|---|---|---|---|---|---|---|---|
| 1 | **9a** | **10a** | THF/HMPA | – | **a**, 58[b] | 40:1:1:1 | **15a**, 27 (5:1) |
| 2 | **9b** | **10a** | THF/HMPA | – | **b**, 66[b] | 1:0:0:0[c] | **15b**, 29 (1:0) |
| 3 | **9c** | **10a** | THF | 5 | **c**, 95 | 1:0:0:0 | – |
| 4 | **9d** | **10a** | THF/HMPA | 5 | **d**, 50[b] | 20:1:0:0[d] | **15d**, 11 (1:0) |
| 5 | **9e** | **10a** | THF | – | **e**, 82 | 5:1:1:0[c] | – |
| 6 | **9c** | **10b** | THF | 5 | **f**, 62[b] | 8:1:2:1 | – |
| 7 | **9d** | **10c** | THF | 5 | **g**, 64 | 2.4:1:0:0 | – |
| 8 | **9e** | **10d** | THF | 5 | **h**, 55[b] | 3:1:1.7:1 | **15h**, 8 (0:1) |

[a] Standard conditions: LDA (1.6 mmol), **9** (1.2 mmol), −78 °C, 30 min, **10** (1 mmol), −78 °C, 30 min, then warmed to −40 °C until the Michael addition step is complete, **1**, **2**$^+$. For deviations see the Supporting information. [b] Yield of isolated products after Upjohn dihydroxylation to remove **15**. [c] Traces of another diastereomer present. [d] Stereochemistry of minor diastereomer not assigned.




***Scheme 3.*** Catalytic tandem Michael addition/radical 6-*endo* cyclizations. HMPA = hexamethylphosphoric triamide.

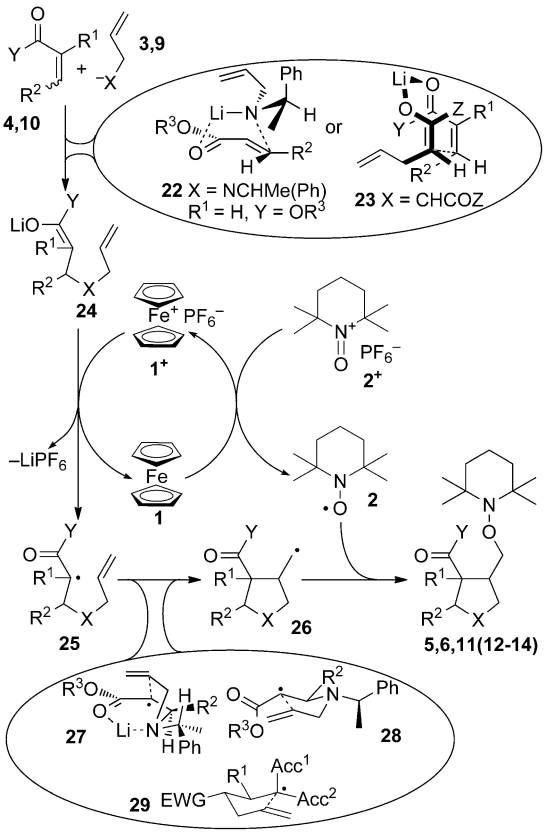



***Scheme 4.*** The behavior of the **1**/**2** redox pair toward propiophenone (**19**).

The catalytic oxidative conditions proved to be very convenient to allow slower radical cyclization steps in the presence of the fast radical trap TEMPO (Scheme 3). Esters **9f** and **9g** underwent the sequence with malonate **10a** in moderate to very good yield and diastereoselectivities, but gave in contrast to the reaction with methallylamine **3c** selectively the 6-*endo* cyclization products **17a**/**18a** and **17b**, respectively (cf. Table 1, entries 8 and 9). A significant practical advantage of all reported sequences is that stoichiometric ferrocene is not co-generated anymore. This simplifies the experimental procedures, analyses of crude mixtures, and isolation considerably.

The configuration of compounds **5e**, **11d**, **11e**, and **17b** was assigned by X-ray crystallography (Figure 2). The five-membered rings in **5e**, **11d**, and **11e** adopt half-chair conformations having the bulkier groups in pseudoequatorial positions. The cyclohexane ring in **17b** has a typical chair conformation with the substituents in 2-, 3-, and 6-position oriented equatorially. The configuration of all other compounds was assigned by NOE investigations or by analogy (see Supporting information).

Propiophenone (**19**) was subjected to the oxidant systems to demonstrate that the ferrocene-catalyzed reaction proceeds indeed identically to the stoichiometric version, since it provided a unique product spectrum of oxygenation




***Scheme 5.*** Catalytic cycle of oxidative sequences and rationale of the stereoselectivity. Stereochemistry is omitted for clarity in intermediates **24**–**26**, but shown in transition states **22**, **23**, and **27**–**29**). EWG = electron-withdrawing group.

and radical dimerization products **20** and **21** under the stoichiometric $\mathbf{1}^+/\mathbf{2}$ conditions (Scheme 4).[11b] The catalytic system $\mathbf{1}/\mathbf{2}^+$ gave a very similar product distribution, indicating the similarity of the process. Since $\mathbf{2}^+$ is also an oxidant,[15] it had to be proven that it does not act as a mediator for the same transformation on its own. Indeed, $\mathbf{2}^+$ provided exclusively oxygenated product **20** with no trace of radical-derived **21**. Thus, the similarity of the stoichiometric and catalytic results indicated that $\mathbf{2}^+$ oxidized ferrocene first to $\mathbf{1}^+$, which mediates the SET oxidation, and co-formed TEMPO served as the oxygenation reagent. Similar results were obtained for slow oxidative cyclizations of *N*-allyl-β-alaninates (see the Supporting information).

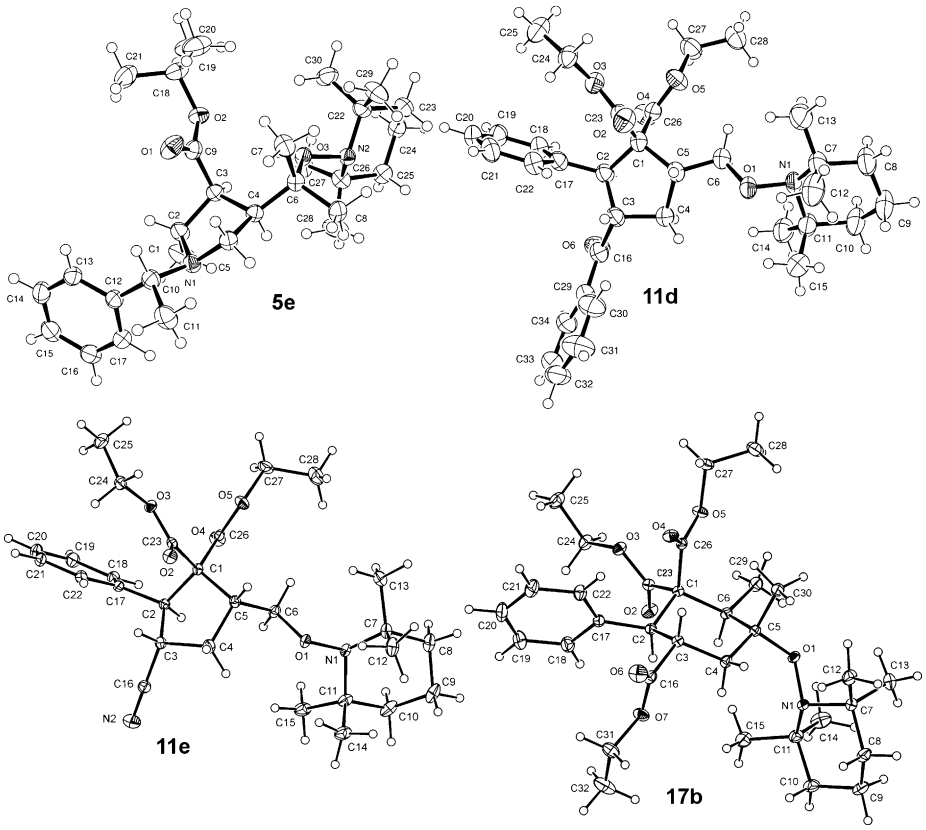



***Figure 2.*** ORTEP drawings of **5e**, **11d**, **11e**, and **17b**. The displacement ellipsoids are drawn at the 50% level for **5e** and **11d**, and at 30% for **11e** and **17b**.

The presented catalytic oxidative addition/cyclization sequences have several intriguing features (Scheme 5). The organometallic polar addition of amides **3** and enolates **9** to Michael acceptors **4** and **10** proceeds reliably and mostly with very high diastereoselectivity via transition states **22**[12,13] and **23**,[16] respectively, thus setting the first stereocenter. The subsequent cyclization step does not proceed at the oxidation state of the enolate **24**, but SET oxidation allows the switch to the much more reactive radical **25**. The catalytic SET oxidation cycle for this step begins with oxidation of ferrocene (**1**) by the stable oxopiperidinium salt $\mathbf{2}^+$ leading to the active ferrocenium oxidant $\mathbf{1}^+$ and TEMPO (**2**). The resulting radical **25** undergoes 5-*exo* (or 6-*endo*) cyclizations to give radical **26** which couples with co-generated **2** to furnish the oxygenated products **5**, **6,** or **11**. The SET oxidation with **1** as the limiting species allows generation of the initial radical in low concentration to enter the desired cyclization step. At the same time, the concentration of the final coupling species **2** also remains low, thus reducing the extent of premature coupling with the initial radical **25**. By the same token, slow 6-*endo* cyclizations proceed in good yield. The diastereoselectivity of the radical cyclization to pyrrolidines **5** and **6** can be explained either by chelated or Beckwith–Houk transition states **27** or **28**. In contrast, the radical cyclization to cyclopentane derivatives **11** must proceed through a chair-like Beckwith–Houk transition state **29**, in which all substituents are located in pseudoequatorial positions.

In summary, an efficient catalytic protocol was developed that allows the economic asymmetric preparation of highly functionalized pyrrolidines and cyclopentanes by the first SET-catalyzed tandem organometallic addition/radical cyclization/oxygenation process. It represents an example of catalysis in which the mandatory stoichiometric terminal oxidant is efficiently incorporated as a useful functionality in the product. This type of oxidative catalysis paves the way for the design of other catalytic tandem processes incorporating multiple intermediates of different redox state and multiple SET steps. Applications in target-oriented synthesis can be foreseen. Research along these lines is pursued and will be reported in due course.

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