Dalton Transactions

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/dalton

Journal Name

ARTICLE

Received 00th January 20xx,

Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Tuning the Redox Properties of the Titanocene(III)/(IV)-Couple for Atom-Economical Catalysis in Single Electron Steps

A. Gansäuer,[a] S. Hildebrandt,[a] E. Vogelsang,[a] and R. A. Flowers II[b]

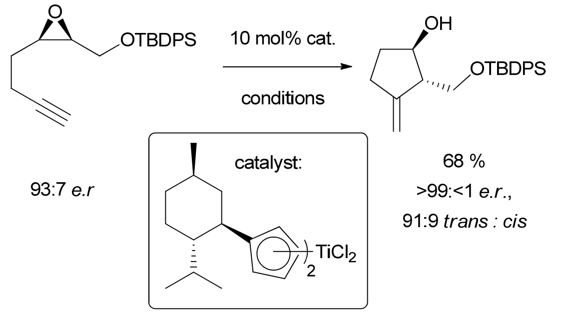
Radical-based transformations are an attractive target for the development of catalytic processes due to ease of radical generation, high functional group tolerance and selectivity of bond-forming reactions. In spite of these appealing features, the potential of radicals as key intermediates in catalysis remains largely untapped. Herein we present recent work that exploits the innate ability of titanocene-based catalysts to undergo both oxidative addition and reductive elimination in single-electron steps. We further demonstrate that tuning the redox properties of the titanocene-based catalyst can be used to develop efficient catalytic free radical processes including tetrahydrofuran synthesis, and radical arylation.

Introduction

Chemical reactions involving carbon-centred radicals are highly attractive due to their chemoselectivity, the opportunities for C-C bond formation, and ease of generation.[1,2] Originally, radical reactions were conducted as chain processes. These very powerful reactions usually feature free radicals as intermediates and proceed under substrate control. An alternative approach to performing radical reactions is to mediate radical generation and trapping by metal complexes. Usually, both steps occur via single electron transfer (SET) from the metal and therefore proceed under reagent control because their reactivity as well as chemo- and stereoselectivity can be influenced by the choice of the metal and its ligands.

Recent developments with SmI_2, the most popular SET reagent, highlight this important aspect and its topicality. It has been shown that the redox-potential of SmI_2 can be substantially varied (-0.89 V to -1.75 V vs. SCE) by additives such as HMPA, H_2O, and mixtures of amines and H_2O.[3] This redox modulation, sometimes resulting in change in mechanism[4] has not only enabled the discovery of unusual reactions, but also the development of reaction sequences that allow a dramatic increase in molecular complexity.[5]

From the point of view of sustainability, catalytic reactions are more desirable than stoichiometric processes. In the field of reagent-controlled catalysis with radicals, titanocene(III) catalysed reactions have emerged as a powerful synthetic tool.[6] A typical example of a regiodivergent ring-opening that is based on enantioselective openings of *meso*-epoxides is shown in Scheme 1.[7]



conditions:
10 mol% catalyst, Mn (2 eq.), Coll*HCl (1.5 eq.), 1,4-C_6H_8 (4.35 eq.)

Scheme 1: Regiodivergent epoxide opening.

Other unusual reactions that can be catalysed using the protic reagent combination Coll*HCl/Zn or Mn (Coll = 2,4,6-Me_3Py) are radical cyclizations to yield small rings.[8] By employing the silylating combination Coll*Me_3SiCl/Zn or Mn many very mild epoxypolyene cyclizations proceeding via radicals have been realized.[9] Furthermore, redox-umpolung reactions based on Ti(III) catalysis have recently been developed.[10] Thus, catalysis of radical reactions under reagent control can be readily carried out.[11] However, from a conceptual point of view these reactions suffer from generation of a considerable amount of waste and hence their low overall atom-economy.

Discussion

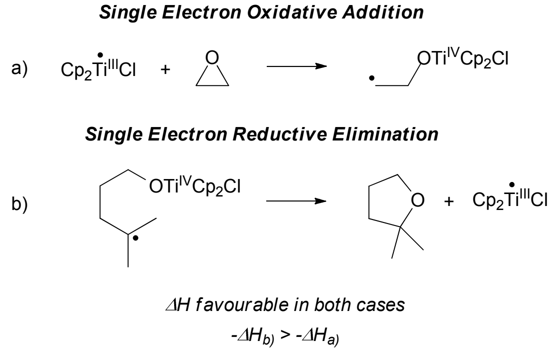
To address this shortcoming and to increase the overall efficiency of catalysis with radicals, the concept of catalysis in single electron steps was introduced.[12] To understand the underlying idea, it is important to recognize that epoxide opening by Ti(III) to provide a β–titanoxy radical can be viewed

---

[a] Kekulé-Institut für Organische Chemie und Biochemie
Universität Bonn, Gerhard-Domagk-Str. 1, 53121 Bonn (Germany)
E-mail: andreas.gansaeuer@uni-bonn.de

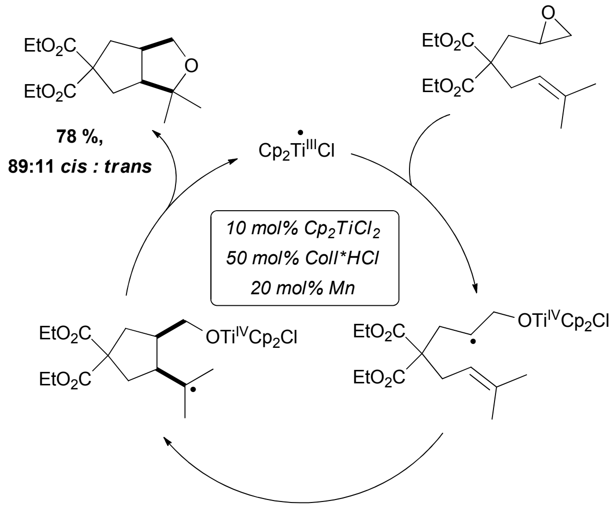
[b] Department of Chemistry
Lehigh University, Bethlehem, PA 18015 (USA)
E-mail: rof2@lehigh.edu

as a single electron oxidative addition. After electron transfer, the oxidized titanocene(IV) attached to the radical is formed. The titanocene has oxidatively added to the epoxide! A DFT computational study of this step revealed that the energy of ring opening was surprisingly low.[13] Thus, the formation of the supposedly strong Ti-O bond and the release of ring strain barely compensate the unfavourable formation of the C-centred radical from the 'Ti-radical'. This finding suggests that without the release of ring strain, a pendant radical, such as a δ–titanoxy radical, should be able to homolytically cleave a titanocene(IV)-O bond. As a consequence, a tetrahydrofuran and a titanocene(III) complex would be generated. This second step formally constitutes a single electron reductive elimination because the titanocene(III) is formed from the substrate radical with concomitant formation of the C-O bond. These points are illustrated in Scheme 2.



Scheme 2: A single electron oxidative addition and reductive elimination.

Upon oxidative addition and reductive elimination all that is required to complete a catalytic cycle is the transformation of a β–titanoxy radical to a δ–titanoxy radical. This 'radical translocation' can be realized by 5-exo and 6-exo[14] (and in principle by any) cyclizations. The catalytic cycle that results in an atom-economical reaction is shown in Scheme 3.[15]



Scheme 3: Catalysis with a 'classical' 5-exo cyclization as 'radical translocation' step.

In the titanocene catalysed reactions, Mn (or Zn) is required for the initial reduction of Cp_2TiCl_2 to Cp_2TiCl. The role of Coll*HCl was initially unclear. Later it was established that it serves to provide a resting state for the catalyst.[16]

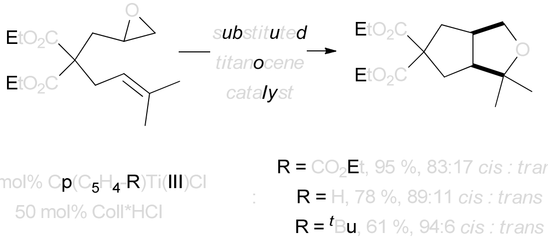
The successful reaction demonstrates that single electron reductive elimination can be incorporated into catalytic cycles featuring radicals as key intermediates. Thus, the titanocene(III)/(IV) redox couple can shuttle between the two oxidation states rather efficiently as anticipated from the DFT calculations.

The success of the catalytic reaction raises two interesting questions:

Can the performance of the reaction be improved by modifying the redox properties of the catalyst?

Can the catalytic cycle shown in Scheme 3 be used as a blueprint for the design of other atom-economical reactions based on our concept of catalysis in single electron steps?

The influence of redox properties on the catalyst performance was investigated first.[12] We discovered that the use of titanocenes with cyclopentadienyl ligands containing electron withdrawing substituents lead to substantially higher yields of the desired product (Scheme 4).

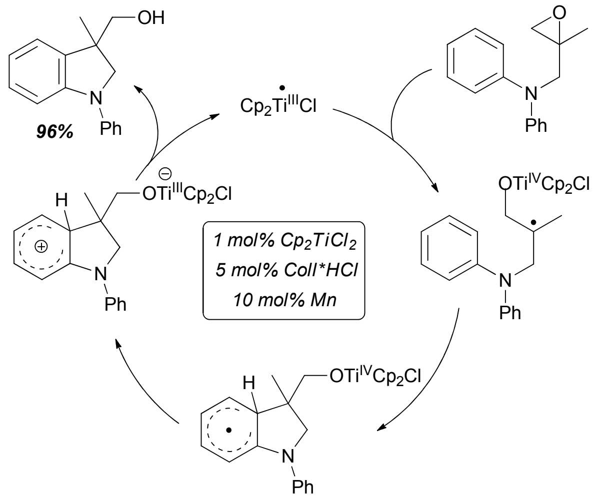


Scheme 4: Influence of ligand substitution on the performance of tetrahydrofuran formation.

This result can be attributed to two interconnected factors. First, the efficiency of the reductive elimination is enhanced by a stabilization of the titanocene(III) complex through the electron withdrawing ligands. Second, the main side-reaction of the reductive elimination, the β–hydrogen atom abstraction to yield an olefin is becoming less favourable because of a destabilization of the titanocene(IV) complex by the electron withdrawing ligand. These results clearly demonstrate that tailoring the catalyst's redox properties is essential for increasing the efficiency of the overall process.

In principle, it should be possible to devise novel atom-economical and catalytic reactions based on the use of single electron oxidative additions and reductions. To date, we have achieved this goal with a novel epoxide hydrosilylation[17] and a radical arylation of epoxides.[18] The latter reaction (Scheme 5) will be the focus of discussion for two reasons. First, its efficiency strongly depends on the redox-properties of the catalyst. Second, a more straightforward approach to generating electron deficient catalysts than the use of cyclopentadienyl ligands with electron withdrawing substituents was discovered during the study of the reaction.

In the Ti(III)-catalysed radical arylation, single electron oxidative addition proceeds via the epoxide opening. The radical translocation occurring through addition of the epoxide derived radical to the electron rich arene is exothermic and only somewhat slower than a 5-exo cyclization and therefore facile. Finally, the single electron reductive elimination is comprised of two steps, back electron-transfer through the oxidation of the radical σ–complex by the pendant titanocene(IV), and the rearomatization by proton abstraction.

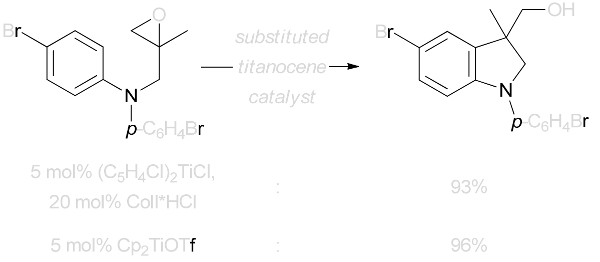


Scheme 5: Catalytic cycle for the radical arylation of epoxides.

The turnover-limiting and only endothermic step of the catalytic cycle is the back electron transfer from the radical σ-complex to the pendant Ti(IV).[19] As might be anticipated, this step can be accelerated and rendered thermodynamically more favourable by the use of catalysts with cyclopentadienyl ligands containing electron withdrawing substituents. Of the catalysts investigated $(C_5H_4Cl)_2TiCl$ turned out to be the most versatile. This is especially important for arenes with electron deficient substituents that lead to even more unfavourable back electron transfers. The introduction of more electron withdrawing substituents, such as $–CO_2Me$ or –CN, provided unstable catalysts.[19]

While this approach was effective, the use of the ring substituted titanocenes has two disadvantages. First, the reaction requires Coll*HCl for catalyst stability and efficient turn-over.[16] Second, the synthesis of the ring substituted titanocenes can be tedious. To avoid these issues, we employed $[Cp_2Ti]^+$ as a catalyst.[20] The advantage of using $[Cp_2Ti]^+$ is that it has a redox potential similar to $(C_5H_4Cl)_2TiCl$ as determined by cyclic voltammetry. Additionally, the cation can either be generated by dissolving $Cp_2Ti(OTf)$ in THF[21] or by the reduction of Cp_2TiCl_2 with Zn in CH_3CN as $[Cp_2Ti(CH_3CN)_2]_2[ZnCl_4]$.[22] The generation of the cation is enabled by its strong solvation and formation of the only weakly coordinating $[ZnCl_4]^{2-}$.

One problem with generating $[Cp_2Ti(CH_3CN)_2]^+$ in acetonitrile is that the coordinated solvent is not easily replaced by the epoxide substrates. As a consequence, epoxide coordination to $Ti(III)^+$ and ring-opening becomes turn-over limiting. As summarized in Scheme 6, $[Cp_2Ti]^+$ in THF is a highly efficient catalyst for the radical arylation. It is substantially more robust than $(C_5H_4Cl)_2TiCl$ and does not require additives. Thus, the exploitation of weakly coordinating anions as ligands combined with solvent effects results in an efficient and straightforward approach to electron deficient ET reagents.



Scheme 6: Radical arylation of epoxides by $[Cp_2Ti]^+$ in THF.

Other catalytic radical reactions have been developed using this principle even though the terms (single electron) oxidative addition and reductive elimination were not used. Conceptually related examples to our processes are the reactions employing 'cobalt(III)-carbene radicals'[23] or 'cobalt(III)-nitrene radicals'.[24] These Co(II)-porphyrin catalysed transformations include cyclopropanations,[23a,b] aziridinations,[24b] ketene[23c] and chromene[23d] synthesis, and C-H bond amination.[24a,c]

Radical generation through single electron oxidative addition occurs via reaction of diazo compounds or azides with Co(II)-porphyrins. It has been demonstrated experimentally and computationally that 'nitrene-radical' formation from an azido formate is strongly dependent on the electronic properties of the porphyrin ligand. In line with the interpretation of this step being the single electron oxidative addition, electron withdrawing substituents disfavour radical formation. The 'carbene-radicals' and nitrene-radicals may add to olefins, alkynes, or CO in the radical translocation step. The single electron reductive eliminations occur via homolytic substitution involving the weak Co(III)-C bond or via 'rebound-like' steps.

Conclusions

In summary, we have shown how atom-economical radical reactions can be designed using the concept of catalysis in single electron steps. Examples include a tetrahydrofuran synthesis, hydrosilylation of epoxides, and radical arylation of epoxides. The key mechanistic issue in catalysis in single electron steps is that oxidative additions and reductive eliminations can be carried out to generate radicals or can be carried out with radicals if the metal can efficiently shuttle between neighbouring oxidation states. This requires a precise adjustment of the redox properties of the catalyst. Our examples of catalysis in single electron steps rely on the use of the titanocene(III)/(IV) couple. The titanocene catalysts proved to be especially well suited for the realization of atom-economical catalysis in single electron steps because their electronic (and steric) properties can be tailored in a straightforward manner.

Acknowledgements

We gratefully acknowledge generous support by the SFB 813 ("Chemistry at Spin Centers"), the Jürgen Manchot Stiftung (fellowship to S. H.), the Studienstiftung des deutschen Volkes (fellowship to E. V.), and the National Science Foundation (CHE-1123815).

Notes and references

1 a) S. Z. Zard, *Radical Reactions in Organic Synthesis*, Oxford University Press, Oxford, 2003; b) P. Renaud and M. P. Sibi, *Radicals in Organic Synthesis*, Wiley-VCH, Weinheim, 2001; c) D. P. Curran, N. A. Porter and B. Giese, *Stereochemistry of Radical Reactions*, Wiley-VCH, Weinheim, 1996.

2 a) U. Jahn, *Top. Curr. Chem.*, 2012, **320**, 121-189; b) U. Jahn, *Top. Curr. Chem.*, 2012, **320**, 191-322; c) U. Jahn, *Top. Curr. Chem.*, 2012, **320**, 323-451.

3 a) M. Shabangi, R. A. Flowers, II *Tetrahedron Lett.*, 1997, **38**, 1137-1140; b) R. J. Enemaerke, K. Daasbjerg, T. Skrydstrup *Chem. Commun.*, 1999, 343-344; c) M. Shabangi, M. L. Kuhlman, R. A. Flowers, II *Org. Lett.*, 1999, **1**, 2133-2135; d) R. S. Miller, J. M. Seely, J. R. Fuchs, M. Shabangi, R. A. Flowers, II *J. Am. Chem. Soc.*, 2000, **122**, 7718-7722; e) R. J. Enemaerke, T. Hertz, T. Skrydstrup, K. Daasbjerg *Chem Eur. J.*, 2000, **6**, 3747-3754; f) A. Dahlen, G. Hilmersson, B. W. Knettle, R. A. Flowers, II *J. Org. Chem.*, 2003, **68**, 4870-4875; g) E. Prasad, R. A. Flowers, II *J. Am. Chem. Soc.*, 2005, **127**, 18093-18099.

4 a) A. Dahlen, G. Hilmersson *J. Am. Chem. Soc.,* 2005, **127**, 8340-8347; b) H. Faran, S. Hoz *Org. Lett.,* 2008, **10**, 865-867; c) D. V. Sadasivam, P. K. S. Antharjanam, E. Prasad, R. A. Flowers, II *J. Am. Chem. Soc.,* 2008, **130**, 7228-7229; d) K. A. Choquette, D. V. Sadasivam, R. A. Flowers, II *J. Am. Chem. Soc.,* 2010, **132**, 17396-17398; e) M. Szostak, M. Spain, D. J. Procter *J. Am. Chem. Soc.,* 2014, **136**, 8459-8466; f) M. Szostak, M. Spain, A. J. Eberhart, D. J. Procter *J. Org. Chem.,* 2014, **79**, 11988-12003; g) T. V. Chciuk, R. A. Flowers, II *J. Am. Chem. Soc.,* 2015, **137**, 11526-11531.

5 a) K. A. Choquette, R. A. Flowers *Sm and Yb Reagents* in *Comprehensive Organic Synthesis, 2nd Edition;* G. A. Molander, P. Knochel Eds.; Elsevier: Oxford, 2014 Vol 1 pp 279-343; b) M. Szostak, N. J. Fazakerley, D. Parmar, D. J. Procter *Chem. Rev.*, 2014, **114**, 5959-6039; c) M. Szostak, M. Spain, D. J. Procter *Chem. Soc. Rev.,* 2013, **42**, 9155-9183; d) D. J. Procter, R. A. Flowers, II; T. Skrydstrup, *Organic Synthesis using Samarium Diiodide: A Practical Guide*; RSC Publishing: Cambridge, 2010.

6 a) J. M. Cuerva, J. Justicia, J. L. Oller-López and J. E. Oltra, *Top. Curr. Chem.*, 2006, **264**, 63-92; b) A. Gansäuer, C.-A. Fan, J. Justicia, D. Worgull and F. Piestert, *Top. Curr. Chem.,* 2007, **279**, 25-52; c) J. Justicia, L. Á. de Cienfuegos, A. G. Camapaña, D. Miguel, V. Jakoby, A. Gansäuer and J. M. Cuerva, *Chem. Soc. Rev.*, 2011, **40**, 3525-3537.

7 a) A. Gansäuer, T. Lauterbach, H. Bluhm, and M. Noltemeyer, *Angew. Chem. Int. Ed.*, 1999, **111**, 2909-2910; b) A. Gansäuer, H. Bluhm, B. Rinker, S. Narayan, M. Schick, T. Lauterbach and M. Pierobon, *Chem. Eur. J.*, 2003, **9**, 531-542; c) A. Gansäuer, C.-A. Fan, F. Keller and J. Keil, *J. Am. Chem. Soc.*, 2007, **129**, 3484-3485; d) A. Gansäuer, L. Shi and M. Otte, *J. Am. Chem. Soc.,* 2010, **132**, 11858-11859.

8 a) A. Gansäuer, T. Lauterbach and D. Geich-Gimbel, *Chem. Eur. J.*, 2004, **10**, 4983-4990; b) J. Friedrich, M. Dolg, A. Gansäuer, D. Geich-Gimbel and T. Lauterbach, *J. Am. Chem. Soc.*, 2005, **127**, 7071-7077; c) J. Friedrich, K. Walczak, M. Dolg, F. Piestert, T. Lauterbach, D. Worgull and A. Gansäuer, *J. Am. Chem. Soc.*, 2008, **130**, 1788-1796; d) A. Gansäuer, D. Worgull, K. Knebel, I. Huth and G. Schnakenburg, *Angew. Chem. Int. Ed.*, 2009, **48**, 8882-8885; e) A. Gansäuer, K. Knebel, C. Kube, M. van Gastel, A. Cangönül, K. Daasbjerg, T. Hangele, M. Hülsen, M. Dolg and J. Friedrich, *Chem. Eur. J.,* 2012, **18**, 2591-2599.

9 a) J. Justicia, A. Rosales, E. Buñuel, J. L. Oller-López, M. Valdivia, A. Haidour, J. E. Oltra, A. F. Barrero, D. J. Cárdenas and J. M. Cuerva, *Chem. Eur. J.*, 2004, **10**, 1778-1788; b) J. Justicia, J. L. Oller-López, A. G. Campaña, J. E. Oltra, J. M. Cuerva, E. Buñuel and D. J. Cárdenas, *J. Am. Chem. Soc.*, 2005, **127**, 14911-14921; c) A. Gansäuer, J. Justicia, A. Rosales, B. Rinker, D. Worgull, J. M. Cuerva, and J. E. Oltra, *Eur. J. Org. Chem*., 2006, 4115-4127; d) T. Jiménez, S. P. Morcillo, A. Martín-Lasanta, D. Collado-Sanz, D. J. Cárdenas, A. Gansäuer, J. Justicia and J. M. Cuerva, J. *Chem. Eur. J.,* 2012, **18**, 12825-12833.

10 a) J. Streuff, M. Feurer, P. Bichovski, G. Frey and U. Gellrich, *Angew. Chem. Int. Ed.*, 2012, **51**, 8661-8664; b) G. Frey, H.-T. Luu, P. Bichovski, M. Feurer and J. Streuff, *Angew. Chem. Int. Ed.*, 2013, **53**, 7131-7134; c) M. Feurer, G. Frey, H.-T. Luu, D. Kratzert and J. Streuff, *Chem. Commun*., 2014, **50**, 5370-5372.

11 A. Gansäuer and H. Bluhm, *Chem. Rev*., 2000, **100**, 2771-2778.

12 A. Gansäuer, A. Fleckhaus, M. Alejandre Lafont, A. Okkel, K. Kotsis, A. Anoop and F. Neese, *J. Am. Chem. Soc.*, 2009, **131**, 16989-16999

13 a) K. Daasbjerg, H. Svith, S. Grimme, M. Gerenkamp, C. Mück-Lichtenfeld, A. Gansäuer, A. Barchuk and F. Keller, *Angew. Chem. Int. Ed.,* 2006, **45**, 2041-2044.; b) A. Gansäuer, A. Barchuk, F. Keller, M. Schmitt, S. Grimme, M. Gerenkamp, C. Mück-Lichtenfeld, K. Daasbjerg and H. Svith, *J. Am. Chem. Soc.*, 2007, **129**, 1359-1371.

14 a) A. Gansäuer and M. Pierobon, *Synlett,* 2000, 1357-1359.; b) A. Gansäuer, M. Pierobon and H. Bluhm, *Synthesis,* 2001, 2500-2520.

15 a) A. Gansäuer, B. Rinker, M. Pierobon, S. Grimme, M. Gerenkamp and C. Mück-Lichtenfeld, *Angew. Chem. Int. Ed.*, 2003, **42**, 3687-3690; b) B. M. Trost, H. C. Shen and J. P. Surivet, *J. Am. Chem. Soc.*, 2004, **126**, 12565-12579; c) D. Leca, L. Fensterbank, E. Lacôte and M. Malacria, *Angew. Chem. Int. Ed.*, 2004, **43**, 4220-4222; d) A. Gansäuer, B. Rinker, N. Ndene-Schiffer, M. Pierobon, S. Grimme, M. Gerenkamp and C. Mück-Lichtenfeld, *Eur. J. Org. Chem.*, 2004, 2337-2351.

16 A. Gansäuer, C. Kube, K. Daasbjerg, R. Sure, S. Grimme, G. D. Fianu, D. V. Sadasivam and R. A. Flowers, II, *J. Am. Chem. Soc.*, 2014, **136**, 1663-1671.

17 A. Gansäuer, M. Klatte, G. M. Brändle and J. Friedrich, *Angew. Chem. Int. Ed.*, 2012, **51**, 8891-8894.

18 A. Gansäuer, M. Behlendorf, D. von Laufenberg, A. Fleckhaus, C. Kube, D. V. Sadasivam and R. A. Flowers, II, *Angew. Chem. Int. Ed*., 2012, **51**, 4739-4742.

19 A. Gansäuer, D. von Laufenberg, C. Kube, T. Dahmen, A. Michelmann, M. Behlendorf, R. Sure, M. Seddiqzai, S. Grimme, D. V. Sadasivam, G. D. Fianu and R. A. Flowers, II, *Chem. Eur. J.*, 2015, **21**, 280-289.

20 A. Gansäuer, S. Hildebrandt, A. Michelmann, T. Dahmen, D. von Laufenberg, C. Kube, G. D. Fianu and R. A. Flowers, II *Angew. Chem. Int. Ed*., 2015, **54**, 7003-7006.

21 a) K. Berhalter and U. Thewalt, *J. Organomet. Chem.*, 1991, **420**, 53-56; b) G. A. Luinstra, *J. Organomet. Chem.*, 1996, **517**, 209-215.
22 P. A. Seewald, G. S. White and D. W. Stephan, *Can. J. Chem.*, 1988, **66**, 1147-1152.
23 a) W. I. Dzik, X. Xu, X. P. Zhang, J. N. H. Reek, B. de Bruin, *J. Am. Chem. Soc.*, 2010, **132**, 10891-10902; b) H. Lu, W. I. Dzik, X. Xu, L. Wojtas, B. de Bruin, X. P. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 8518-8521; c) N. D. Paul, A. Chirila, H. Lu, X. P. Zhang, B. de Bruin, *Chem. Eur. J.*, 2013, **19**, 12953-12958; N. D. Paul, S. Mandal, M. Otte, X. Cui, X. P. Zhang, B. de Bruin, *J. Am. Chem. Soc.*, 2014, **136**, 1090-1096.
24 a) H. Lu, V. Subbarayan, J. Tao, X. P. Zhang, *Organometallics*, 2010, **29**, 389-393; b) A. I. Olivos Suarez, H. Jiang, X. P. Zhang, B. de Bruin, *Dalton Trans.*, 2011, **40**, 5697-5705; c) V. Lyaskovskyy, A. I. Olivos Suarez, H. Lu, H. Jiang, X. P. Zhang, B. de Bruin, *J. Am. Chem. Soc.*, 2011, **133**, 12264-12273.

Biographical Sketches:

Robert Flowers received his Ph.D. from Lehigh University and carried out postdoctoral studies under the guidance of Ned Arnett at Duke University. He is currently the Danser Distinguished Faculty Chair in Chemistry at Lehigh University. His research interests are in the areas of single electron transfer and mechanistic organic chemistry.

Andreas Gansäuer obtained his PhD in the group of M. T. Reetz at the MPI für Kohlenforschung. After a postdoctoral position in the group of B. M. Trost at Stanford University he completed his habilitation with R. Brückner. He is Professor of Organic Chemistry at the University of Bonn and works on titanocene synthesis and the design of new catalytic radical reactions.

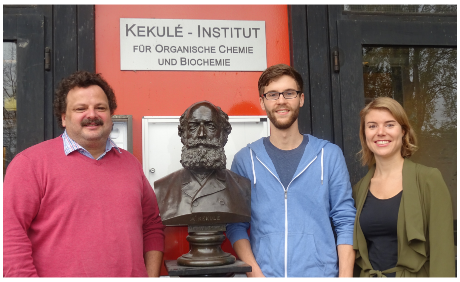
Elisabeth Vogelsang received her M.Sc. degree in chemistry from the University of Bonn in 2013. She is currently in her second year of her PhD under the supervision of A. Gansäuer, investigating novel synthesis routes to functionalized titanocenes.

Sven Hildebrandt received his M.Sc. degree in chemistry from the University of Bonn in 2014. He is currently in his first year of his PhD under the supervision of A. Gansäuer. His research interest is the development of novel catalytic radical reactions.

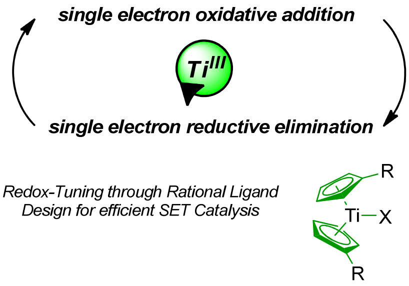
Pictures:

Bob Flowers:

Gansäuer group:



ToC-Graphic:



ToC-Text:

A concept for the design of efficient catalytic radical reactions is outlined.