Titanocene-Catalyzed [2+2] Cycloaddition of Bisenones and Comparison with Photoredox Catalysis and Established Methods

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Abstract: Cp₂Ti(TFA) is a broadly applicable catalyst for the [2+2] cycloaddition of bisenones by inner-sphere electron transfer. The attractiveness of this mechanism is shown by comparison with outer-sphere ET methods. DFT calculations show that the reaction proceeds through a unique unfavorable 5-exo (the rate-determining step) and a favorable 4-exo cyclization.

Catalysis in single electron steps[1] or metalloradical catalysis (MRC)[2] is a strategy for merging the advantages of radical chemistry, such as the ease of radical generation, high functional group tolerance, and mildness of reaction conditions with those of transition metal catalysis, such as control of selectivity and efficiency. The titanocene(III)/titanocene(IV) couple has been successfully applied in catalysis in single electron steps because of its efficient shuttling between the two neighboring oxidation states, other ligands for titanium (salen) and other metal complexes (Sm) have been successfully used in a similar manner.[3] The use of epoxides as radical precursors highlights one important advantage of catalysis in single electron steps. The requirement of substrate binding by the catalyst prior to ET allows highly regioselective epoxide opening by an inner-sphere electron transfer (ET).[4] In analogy, in MRC with cobalt–carbene radicals, reductive eliminations have been carried out enantioselectively.[5]

Photoredox catalysis (PRC) that has been used in a myriad of applications is an exceptionally successful approach to enable radical reactions by electron transfer.[6] The conceptual differences to catalysis in single electron steps and PRC is that ET from the photoexcited complexes typically occurs without substrate coordination to the catalyst through outer-sphere electron transfer and, hence, without catalyst control of radical generation.

For highlighting the differences of inner- and outer-sphere electron transfer reagents in catalytic radical chemistry, we analyzed the [2+2] cycloaddition of bisenones as a case example (Scheme 1).

The Krische group was the first to report the reaction.[7] They reported cobalt catalysts in the presence of silanes for a cycloaddition through hydro- and cyclometallation, and electrochemical methods, arene radical anions, and Me₂CuLi for outer-sphere ETs to the bisenones. In a landmark paper, Yoon and his group showed how the reaction can be carried out under PRC with Ru(bpy)₂Cl₂ as photoredox catalyst.[8] They reported cobalt catalysts in the presence of silanes for a cycloaddition through hydro- and cyclometallation, and electrochemical methods, arene radical anions, and Me₂CuLi for outer-sphere ETs to the bisenones. In a landmark paper, Yoon and his group showed how the reaction can be carried out under PRC with Ru(bpy)₂Cl₂ as photoredox catalyst.[8] The addition of LiBF₄ (2 equiv) to activate the substrates for outer-sphere ET was essential, as well as iPr₂NEt (2 equiv) for the reductive quenching of photoexcited Ru.

Herein, we show that the catalytic intramolecular [2+2] cycloaddition of bisenones can also be carried out through inner-sphere ET from Cp₂Ti(III)X catalysts after complexation of the substrates. As will be shown, this allows a broader substrate scope and often higher stereoselectivity than in the outer-sphere ET methods. Our results of the initial catalyst and condition screening for substrate 1a are summarized in Table 1.

The reaction can be carried out under titanocene catalysis (10 mol% Cp₂TiX at 65°C in THF with Cp₂TiX prepared through zinc reduction of Cp₂TiX₂)[9] It is essential that more electron deficient ligands X than Cl are used. With Cp₂TiCl,
none of the desired 2a was obtained. Cp₂TiOMs (-OMs = -O₃SCH₃) gave 2a in 45% yield and our best catalyst Cp₂Ti(TFA) (-TFA = -O₂CCF₃) resulted in an isolated yield of 78% of 2a in THF. A slightly better yield (85%) was obtained with 15 mol% of Cp₂Ti(TFA).

Curiously, the weakest reductant Cp₂Ti(TFA) [E° for the anodic oxidation of Cp₂TiX from CV experiments (THF vs. Fc/Fc+): X = Cl: -0.83 V; X = OMs: -0.62 V, X = TFA: -0.58 V] gives the most active catalyst! This is rather surprising as the results from the established methods suggest that an easier initial ET to the bisenone leads to higher yields.

In all cases, 2a was obtained exclusively as the diastereomer shown. 1,4-THF, 1,4-dioxane and EtOAc as solvent gave essentially identical results. For reasons of comparability, all reactions were run for 12 h. However, the same yield was obtained after 8 h (entry 7) and no further attempts were undertaken to investigate even shorter reaction times.

We examined the scope of the reaction by varying the substituents of the bisenone system next (Table 2). With R¹ = R² = aryl, the desired products are obtained in high yields and essentially as single diastereoisomers [d.r. > 99:1 except 2b (96:4)]. An exception is 1f with two NO₂ substituents that are reduced by Cp₂Ti(TFA) resulting in catalyst deactivation. Yields are higher than in the cobalt-catalyzed reactions developed by Krische and slightly lower than in Yoon’s excellent PRC. Our diastereoselectivities are as high as in Krische’s cobalt-catalyzed reactions and higher than under Yoon’s conditions (> 91:9 and 91:9 for 2i).

Substrates with only one aryl group (1g–i) worked well. Substrates with R¹ and R² being alkyl (1j and 1m–p) give the desired products in yields between 70% and 88% as single isomers except 1j where the d.r. is only slightly lower (d.r. 96:4). The two substrates that are not turned over (1k and 1l) because both bulky substituents R seem to prevent binding of the active titanocene(III) catalyst. One coordinating carbonyl group (1m, 1n) is mandatory for successful catalysis. This strongly suggests that an inner-sphere SET occurs with Cp₂Ti(TFA) that leads to the broadest substrate scope in the [2+2] cycloaddition, as none of the previously described systems provide products with two alkyl substituents (2j and 2m–p).

After the groundbreaking work with Ru(bpy)₃Cl₂ by Yoon and co-workers, many other PRC catalysts have been devised. To further study the difference in reactivity between titanocene(III)-mediated inner-sphere electron transfer and PRC-mediated outer-sphere electron transfer in the [2+2] cycloaddition, we decided to investigate the performance of two more reducing iridium complexes [6f] (with respect to Ru(bpy)₃Cl₂ after reductive quenching) and the less reducing organic dye 4CzIPN [6g] (with respect to Ru(bpy)₃Cl₂ after reductive quenching).

Table 1: Identification of suitable reaction conditions for the titanocene-catalyzed [2+2] cycloaddition of 1a.[a]

| Entry | Solvent | Catalyst (mol %) | Yield [%][b] |
|-------|---------|-----------------|-------------|
| 1     | THF     | Cp₂TiCl₂ (10)   | n.r.        |
| 2     | THF     | Cp₂Ti(OMs)₂ (10) | 45[1]      |
| 3     | THF     | Cp₂Ti(TFA)  (10) | 78         |
| 4     | THF     | Cp₂Ti(OMs)₂ (15) | 85         |
| 5     | THF     | Cp₂Ti(TFA)  (15) | 85         |
| 6     | ethyl acetate | Cp₂Ti(TFA)₂ (15) | 85         |
| 7     | dioxane | Cp₂Ti(TFA)  (15) | 85[1]      |

[a] Reaction conditions: Ti catalyst (10–15 mol %), Zn (30 mol %), 0.05 M 1a in solvent, 65 °C. [b] Yield of the isolated product, only diastereomer shown formed (d.r. > 99:1). [c] Yield determined by 1H NMR spectroscopy against an internal standard (trimethoxybenzene). [d] Yield after 8 h.

Table 2: Substrate scope of the titanocene-catalyzed [2+2] cycloaddition of bisenones.

| Substrate | Product | Yield[%][c] | d.r.[b] |
|-----------|---------|-------------|---------|
| Ar¹ = Ar² = 4-MeOC₆H₄H₂ | 2b | 80 | 99:1, 12 h |
| Ar¹ = Ar² = 4-CIC₆H₄H₂ | 2c | 88 | >99:1, 12 h |
| Ar¹ = Ar² = 2-naphthylone | 2d | 90 | >99:1, 12 h |
| Ar¹ = 4-NCO₆H₄H₂, Ar² = Cp₂TiH₂ | 2e | 88 | >99:1, 16 h |
| Ar¹ = 4-NO₂C₆H₄H₂ | 2f | 0  | none, 12 h |

[a] Reaction conditions: 0.05 M 1 in 1,4-dioxane, 80 °C. [b] Yield of the isolated product. [c] The diastereomeric ratio was determined by 1H NMR spectroscopy. [d] The reaction was carried out with 0.05 M 1h in THF at 65 °C. [e] The reaction was carried out with 20 mol % Cp₂Ti(TFA)₂.
redditive quenching) to understand the influence of the PRCs redox potential on the [2+2] cycloaddition under Yoon’s conditions (Table 3) to ensure a fair comparison.

With 1a high yields of 2a were obtained with all catalysts. However, none of the three photoredox catalysts (PRCats) led to the formation of 1j. This indicates that the success of the reaction is not only dependent on the redox potential of the catalyst. The coordination between the catalyst and the substrate is mandatory for the efficient transformation. Thus, of all catalysts reported or investigated here, Cp2Ti(TFA) is the only complex to efficiently transform the alkyl substituted bisenones (1j and 1m–p) to the desired products. Complexation of the substrate to enforce an inner-sphere SET seems mandatory. Curiously, it is the least reducing of all catalysts investigated by Krische, Yoon, and us.

To understand the substrate scope of titanocene catalysis and the counterintuitive dependence of catalyst performance on its redox potential, we studied the proposed mechanism reaction of the [2+2] cycloaddition of 1j by computational means. The anticipated catalytic cycle (for all substrates) is shown in Scheme 2.

The reaction starts with an inner-sphere ET to the enone complexed to Ti III that delivers the stabilized radical A. This step constitutes the oxidative addition. Enones have been used as radical precursors in Cp2TiCl-mediated and -catalyzed umpolung reactions.[11] Radical generation is followed by a 5-exo cyclization of the stabilized radical anion A to yield B. Radical C is formed by a 4-exo cyclization of the enoyl radical in B to the titanocene enolate. From C, the product is liberated and the catalyst regenerated by back electron transfer from the ketyl radical to TiIV and dissociation of 2*Cp2TiIIIX. Both steps formally constitute a reductive elimination. As an alternative for closing the cycle, one can also imagine a direct intermolecular reduction of 1 by C in a process reminiscent of a chain reaction. While this option cannot be strictly ruled out, we believe the high dilution necessary and the exergonic nature of the reductive eli-

![Table 3: Investigation of other photoredox catalysts under previously reported conditions.](image)

| Entry | R       | PRCat                  | Yield of 2 [%][a,b] |
|-------|---------|------------------------|---------------------|
| 1     | C6H5, 1a| [Ir{dF(CF3)ppy}2(dtbpy)]PF6 | 88                  |
| 2     | Me, 1j  | [Ir{dF(CF3)ppy}2(dtbpy)]PF6 | 0                   |
| 3     | C6H5, 1a| fac-Ir(ppy)            | 90                  |
| 4     | Me, 1j  | fac-Ir(ppy)            | 0                   |
| 5     | C6H5, 1a| 4CzIPN                 | 85                  |
| 6     | Me, 1j  | 4CzIPN                 | 0                   |

[a] Reaction conditions: (PRCat, 5 mol %), LiBF4 (2 equiv), tBuN (2 equiv), 1 in CH2CN, blue LEDs, room temperature, 1 h. [b] The yield was determined by 1H NMR spectroscopy against the internal standard 1,3,5-trimethoxybenzene. ppy = 2-phenylpyridine.

In order to validate this mechanistic proposal, we studied the reaction of 1j to 2j computationally for Cp2Ti(TFA) in 1,4-dioxane. The conformational spaces of all minimum structures and transition states were therefore examined and all final structures were investigated on the PW6B95-D4/def2-QZVP+COSMO/[1,4-dioxane]/r2SCAN-3c level of theory.[12]

At 353.15 K, the ΔG353.15 of the overall reaction is –4.1 kcal mol−1. This relatively low value is due to the strain of the four-membered ring. The oxidative addition is thermo-
cyclization via the ideally preorganized TS[4-exo] leading to B cyclization occurs at least in part via B reported earlier by Streuff.\cite{11b–d} He noted that in titanocene-catalyzed 
 reactions in titanocene catalysis. \cite{16} However, an observation important for the interpretation of our results has been reported earlier by Streuff.\cite{11b–d} He noted that in titanocene-catalyzed reductive cross-coupling reactions of enones only acrylonitriles lead to fast conjugate radical additions due to a favorable HOMO–LUMO gap. With other acceptors, such as acrylates or acrylamides, the conjugate additions were too slow and dimerization or over-reduction of the enone substrates occurred.

In accordance, we suggest that in the [2+2] cycloadditions, only the weakly reducing Cp3Ti(TFA) is unable to reductively intercept radical A. This provides sufficient lifetime to A to allow the pivotal 5-exo cyclization to B. The computational analysis of the reaction of 1j with Cp3TiCl supports this notion. The potential energy surface is similar to that for the Cp3Ti(TFA) with the 5-exo cyclization being rate-determining (see the Supporting Information, Scheme S1 for details).

The 5-exo cyclization as the rate-determining step also explains why the [2+2] cycloaddition requires harsher conditions than the titanium- and samarium-catalyzed inter- and intramolecular radical redox relay reactions of cyclopropyl ketones (Scheme 4).\cite{11b}
Conflict of interest

The authors declare no conflict of interest.

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2021. https://github.com/grimme-lab/crest/releases; d) C. Bannwarth, S. Ehler, S. Grimme, J. Chem. Theory Comput. 2019, 15, 1652–1671; e) C. Bannwarth, E. Caldeweyher, S. Ehler, A. Hansen, P. Pracht, J. Seibert, S. Spicher, S. Grimme, Wiley Interdiscip. Rev.: Comput. Mol. Sci. 2021, 11, e1493; f) xtb version 6.3.3, Universität Bonn, Mulliken Center for Theoretical Chemistry, Bonn, Germany 2020. https://github.com/grimme-lab/xtb; g) CENSO version 1.0.0, Universität Bonn, Mulliken Center for Theoretical Chemistry, Bonn, Germany 2021, https://github.com/grimme-lab/CENSO/releases; h) S. Grimme, C. Bannwarth, S. Dohm, A. Hansen, J. Pisarek, P. Pracht, J. Seibert, F. Neese, Angew. Chem. Int. Ed. 2017, 56, 14763–14769; i) S. Grimme, A. Hansen, S. Ehler, J.-M. Mewes, J. Chem. Phys. 2021, 154, 064103; j) TURBOMOLE 7.4.1/7.5.1, Universit/ät Karlsruhe and Forschungszentrum Karlsruhe GmbH, Karlsruhe, Germany 2019/2020, https://www.turbomole.org; k) Klamt, A. S. Schüürmann, J. Chem. Soc. Perkin Trans. 2 1993, 799–805; l) S. Grimme, Chem. Eur. J. 2012, 18, 9955–9964; m) Spicher, S. Grimme, J. Phys. Chem. Lett. 2020, 11, 6606–6611; n) Y. Zhao, D. G. Truhlar, J. Phys. Chem. A 2005, 109, 5656–5667; o) E. Caldeweyher, S. Ehler, A. Hansen, H. Ngeuebauar, S. Spicher, C. Bannwarth, S. Grimme, J. Chem. Phys. 2019, 150, 154122; r) F. Weigend, R. Ahlrichs, Phys. Chem. Chem. Phys. 2005, 7, 5297; s) A. Klamt, J. Phys. Chem. 1995, 99, 2224–2235; t) A. Klamt, V. Jonas, T. Bürger, J. C. W. Lohrenz, J. Phys. Chem. A 1998, 102, 5074–5085; u) F. Eckert, A. Klamt, AIChE J. 2002, 48, 369–385; v) P. M. Zimmerman, J. Chem. Phys. 2013, 138, 184102; w) P. Zimmerman, J. Chem. Theory Comput. 2013, 9, 3043–3050; x) S. Dohm, M. Bursch, A. Hansen, S. Grimme, J. Chem. Theory Comput. 2020, 16, 2002–2012.

[14] a) A. Ganssäuer, T. Lauterbach, D. Geich-Gimbel, Chem. Eur. J. 2004, 10, 4983–4990; b) I. Friedrich, K. Walczak, M. Dolg, F. Piešt, T. Lauterbach, D. Worgull, A. Ganssäuer, J. Am. Chem. Soc. 2008, 130, 1788–1796; c) A. Ganssäuer, D. Worgull, K. Knebel, I. Huth, G. Schnakenburg, Angew. Chem. Int. Ed. 2009, 48, 8882–8885; Angew. Chem. 2009, 121, 9044–9047; d) A. Ganssäuer, K. Knebel, C. Kube, M. van Gastel, A. Cangonül, K. Daasbjerg, T. Hangele, M. Hülsen, M. Dolg, J. Friedrich, Chem. Eur. J. 2012, 18, 2591–2599.

[15] A. Ganssäuer, M. Behlendorf, A. Cangonül, C. Kube, J. M. Cuerva, J. Friedrich, M. van Gastel, Angew. Chem. Int. Ed. 2012, 51, 3266–3270; Angew. Chem. 2012, 124, 3320–3324.

[16] a) A. Ganssäuer, M. Pierobon, Synlett 2000, 1357–1359; b) A. Ganssäuer, M. Pierobon, H. Bluhm, Synthesis 2001, 2500–2520; c) A. Ganssäuer, M. Otte, L. Shi, J. Am. Chem. Soc. 2011, 133, 417–418.

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