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Water Control over the Chemoselectivity of a Ti/Ni Multimetallic System: Heck- or Reductive-Type Cyclization Reactions of Alkyl Iodides

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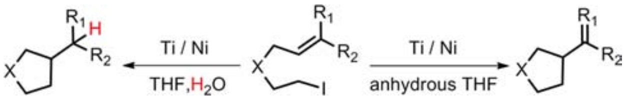
ABSTRACT



A versatile Ti/Ni multimetallic protocol is described for the efficient catalysis of two different reactions, namely a Heck- and reductive-type cyclization of alkyl iodides, in the absence or presence of water, respectively. Noteworthy, the versatility of Ti(III) chemistry allows an oxidative ending step under reductive conditions to give Heck-type products, and the good H-atom transfer capabilities of Ti(III)-aqua complexes ensure reductive-type cyclizations.

The chemical inertness of water toward carbon-centered radicals has been recently revised. We and other groups[1] have demonstrated that water becomes an excellent hydrogen-atom donor in the presence of titanocene(III) complexes. This unexpected reactivity has been mainly used to replace other more unsuitable hydrogen-atom transfer (HAT) reagents.[2] Nevertheless, the varying chemoselectivity of titanocene(III) complexes under anhydrous and aqueous conditions can also be used to develop conceptually novel processes. Thus for example, titanocene(III) complexes could control the fate of a common intermediate depending on the presence or absence of water in the reaction. To check this working hypothesis we focused our attention on Ni-catalyzed cyclization reactions of alkyl halides and simple alkenes since they have become an interesting synthetic tool in recent years (Scheme 1).[3] It is generally accepted that substrates type-**I** are able to cyclize under Ni-catalysis by radical intermediates to yield type-**II** radicals. A subsequent coupling with a radical acceptor is required as the ending step.[3] Although direct reduction of the transient radical **II**, yielding an alkane **III**, would be the equivalent of a tin-free radical cyclization, it is practically unknown in nickel catalysis.[4,5] On the other hand, oxidation of such intermediates **II** could yield an alkene **IV** as the

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[1] (a) Jin, J.; Newcomb, M. *J. Org. Chem.* **2008**, *73*, 7901–7905. (b) Cuerva, J. M.; Campaña, A. G.; Justicia, J.; Rosales, A.; Oller-López, J. L.; Robles, R.; Cárdenas, D. J.; Buñuel, E.; Oltra, J. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5522–5526. (c) Paradas, M.; Campaña, A. G.; Jiménez, T.; Robles, R.; Oltra, J. E.; Buñuel, E.; Justicia, J.; Cardenas, D. J.; Cuerva, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 12748–12756. (d) Gansäuer, A.; Cangönül, A.; Behlendorf, M.; Kube, C.; Cuerva, J. M.; Friedrich, J.; van Gastel, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3266–3270. (e) For another precedent of water acting as a HAT reagent: Spiegel, D. A.; Wiberg, K. B.; Schacherer, L. N.; Medeiros, M. R.; Wood, J. L. *J. Am. Chem. Soc.* **2005**, *127*, 12513–12515.

[2] (a) Jiménez, T.; Campaña, A. G.; Bazdi, B.; Paradas, M.; Arráez-Román, D.; Segura-Carretero, A.; Fernández- Gutiérrez, A.; Oltra, J. E.; Robles, R.; Justicia, J.; Cuerva, J. M. *Eur. J. Org. Chem.* **2010**, 4288–4295. Other remarkable HAT reagents have been also described: (b) Gansäuer, A.; Klatte, M.; Brändle, G. M.; Friedrich, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 8891–8894 and references cited therein.

[3] For selected references, see: (a) *Modern Organonickel Chemistry*; Tamaru, Y., Ed.; Wiley-VCH: 2005. (b) Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510–511. (c) Phapale, V. B.; Buñuel, E.; M. García-Iglesias, M.; Cárdenas, D. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 8790–8795. (d) Hu, X. *Chem. Sci.* **2011**, *2*, 1867–1886. (e) Wu, F.; Lu, W.; Qian, Q.; Ren, Q.; Gong, H. *Org. Lett.* **2012**, *14*, 3044–3047.

[4] (a) Duñach, E.; Esteves, A. P.; Freites, A. M.; Madeiros, M. J.; Olivero, S. *Tetrahedron Lett.* **1999**, *40*, 8693–8696. (b) Kim, H.; Lee, C. *Org. Lett.* **2011**, *13*, 2050–2053.

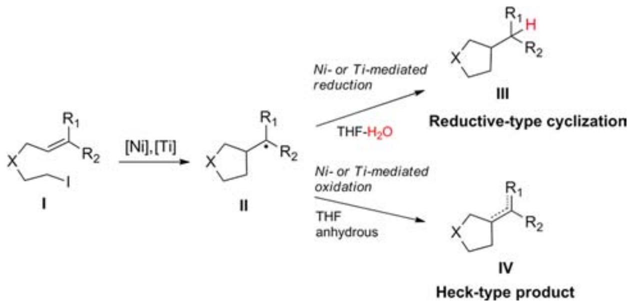
[5] For selected references using other transition metals in related reactions, see: (a) Ekomié, A.; Lefèvre, G.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Ollivier, C.; Jutand, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 6942–6946. (b) Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2012**, *4*, 854–859.

10.1021/ol3028913

final compound, which would be reminiscent of a Heck-type reaction using alkyl halides as reactants. It is worth noting that despite the enormous effort carried out in the development of Heck-type reactions, the use of alkyl halides presenting β-hydrogens as organic electrophiles[6] is considerably less advanced.[7] The success of this new approach is also based on the chemical compatibility of titanocene(III) complexes with palladium and nickel catalysts[8] and its facility to oxidize different carbon-center radicals type-**II** under highly reductive reaction conditions.[9]

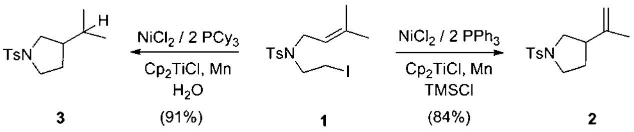
In this work, we report new cyclization reactions of primary and secondary alkyl iodides and simple alkenes with different substitution patterns based on the combination of Ti and Ni catalysts. Control toward the final ending step is obtained just by carrying out the reaction in the presence of water or in anhydrous media, yielding tin-free reductive radical cyclizations or Heck-type reactions respectively. This protocol expands significantly the scope of both reactions and improves considerably the reaction conditions reported to date, also showing that free radical and transition metal chemistries are complementary, reducing the limitations of both methodologies and giving rise to new reactivities.

Scheme 1. Working Hypothesis



To check our working hypothesis we initially treated the prenyl derivative **1** (1 mmol) with a mixture of different Ni catalysts (20 mol %) and phosphorated ligands (40 mol %) with diverse electronic and steric characteristics (PPh_3, $P(2\text{-furyl})_3$, $P(p\text{-F-Ph})_3$, $P(t\text{Bu})_3$, $P(Me)_2Ph$, $P(p\text{-MeO-Ph})_3$, $P(C_6F_5)_3$, $P(Cy)_3$, $P(Ph)_2t\text{Bu}$, $P(Ph)_2Me$, $P(OPh)_3$, $P(OEt)_3$) and *in situ* generated Cp_2TiCl (2 mmol)[10−12] in THF (0.02 M) at room temperature in the presence (10 mmol) and absence of water (Scheme 2). In this latter case, we found that the addition of trimethylsilyl chloride (4 mmol) also improved the reaction yields. Finally, our working hypothesis could be verified. After 16 h, the Heck-type product **2** was isolated in high yield (84%) using simple PPh_3 as a ligand. Only minor amounts of **3** could be obtained under these reaction conditions (9%), which presumably derived from a HAT reaction from the solvent (THF).[13] This side reaction was also observed in the Co-catalyzed Heck-type reaction of closely related alkyl iodides.[7c] In the presence of water the excellent HAT capability of the complex $Cp_2TiCl{-}H_2O$ ensured a reductive ending, thus selectively obtaining the corresponding alkane **3** in high yield (91%).[14] In this latter case, $P(Cy)_3$ gave the best yields.

Scheme 2. Reductive- and Heck-Type Cyclization of **1**



Remarkably, these reaction conditions could be successfully applied to other starting materials. The wide variety of products obtained for the reductive-type cyclization are summarized in Table 1.

The reductive cyclizations took place in moderate to excellent yields covering a broad range of starting materials yielding the corresponding cyclic structures. Therefore, the radical cyclization is faster than the HAT from Ti(III)-aqua complexes to the acyclic transient radicals, even despite the fact that those complexes are present in stoichiometric

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(6) Heck-type reactions using alkyl halides that lack β-hydrogens are known: Matsubara, R.; Gutierrez, A. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2011**, *133*, 19020–19023 and references cited therein.

(7) (a) Levedev, S. A.; Lopatina, V. S.; Petrov, E. S.; Beletskaya, I. P. *J. Organomet. Chem.* **1988**, *344*, 253–259. (b) Terao, J.; Watanabe, H.; Miyamoto, M.; Kambe, N. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2209–2214. (c) Affo, W.; Ohmiya, H.; Ikeda, Y.; Nakamura, T.; Yorimitsu, H.; Oshima, K.; Imamura, Y.; Mizuta, T.; Miyoshi, K. *J. Am. Chem. Soc.* **2006**, *128*, 8068–8077. (d) Firmansjah, L.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 11340–11341. (e) Bloome, K. S.; Alexanian, E. J. *J. Am. Chem. Soc.* **2010**, *132*, 12823–12825. (f) Bloome, K. S.; McMahen, R. L.; Alexanian, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 20146–20148. (g) Weiss, M. E.; Kreis, L. M.; Lauber, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 11125–11128. (h) Zhou, W.; An, G.; Zhang, G.; Han, J.; Pan, Y. *Org. Biomol. Chem.* **2011**, *9*, 5833–5837. (i) Liu, C.; Tang, S.; Liu, D.; Yuan, J.; Zheng, L.; Meng, L.; Lei, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 3638–3641. (j) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773–8787.

(8) (a) Campaña, A. G.; Bazdi, B.; Fuentes, N.; Robles, R.; Cuerva, J. M.; Oltra, J. E.; Porcel, S.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7515–7519. (b) Millán, A.; Campaña, A. G.; Bazdi, B.; Miguel, D.; Álvarez de Cienfuegos, L.; Echavarren, A. M.; Cuerva, J. M. *Chem.—Eur. J.* **2011**, *17*, 3985–3994. (c) Millán, A.; Álvarez de Cienfuegos, L.; Martín-Lasanta, A.; Campaña, A. G.; Cuerva, J. M. *Adv. Synth. Catal.* **2011**, *353*, 73–78. (d) Millán, A.; Martín-Lasanta, A.; Miguel, D.; Álvarez de Cienfuegos, L.; Cuerva, J. M. *Chem. Commun.* **2011**, *47*, 10470–10472.

(9) Justicia, J.; Álvarez de Cienfuegos, L.; Campaña, A. G.; Miguel, D.; Jakoby, V.; Gansäuer, A.; Cuerva, J. M. *Chem. Soc. Rev.* **2011**, *40*, 3525–3537.

(10) For seminal papers, see: (a) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986–997. (b) Gansäuer, A.; Bluhm, H.; Pierobon, M. *J. Am. Chem. Soc.* **1998**, *120*, 12849–12859.

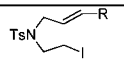
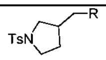
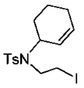
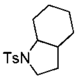
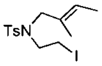
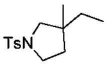
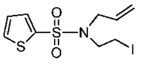
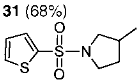
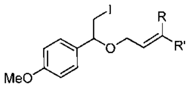
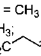
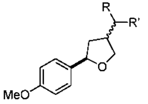
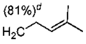
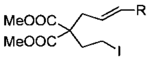
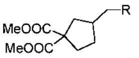
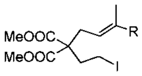
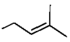
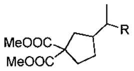
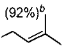
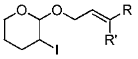
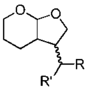
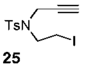
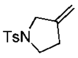
(11) Titanocene(III) chloride exists in THF as an equilibrium mixture of Cp_2TiCl and $(Cp_2TiCl)_2$; see: Enemærke, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *J. Am. Chem. Soc.* **2004**, *126*, 7853–7864. For clarity's sake we usually represent this complex as Cp_2TiCl.

(12) The corresponding control experiments showed that the nickel catalyst, the titanium catalyst, and the manganese dust are indispensable for the success of both types of reactions.

(13) We explored other solvents and obtained the Heck-type product **2** (71%) in benzene, but it resulted in being nonreproducible.

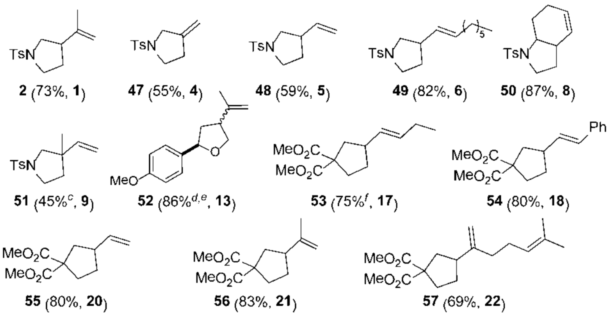
(14) Noteworthy, when deuterium oxide is used instead of water the isotopomer **3*d*** can be isolated in excellent yield (93%), confirming that the hydrogen atom comes from the added water. See Supporting Information for details.

Table 1. Ti/Ni-Mediated Reductive Radical Cyclization of Alkyl Iodides[a]

entry	alkyl iodide	cyclic product, (yield)
1	 **4** R = H **5** R = CH_3 **6** R = $(CH_2)_6CH_3$ **7** R = Ph	 **26** R = H, (93%)[b] **27** R = CH_3, (82%) **28** R = $(CH_2)_6CH_3$, (90%) **29** R = Ph, (77%)
2	 **8**	 **30** (78%)
3	 **9**	 **31** (68%)
4		 **32** (98%)
5	 **11** R = R' = H **12** R = H; R' = CH_3 **13** R = R' = CH_3 **14** R = CH_3; R' = H_2C 	 **33** R = R' = H, (98%)[c] **34** R = H; R' = CH_3, (98%)[c] **35** R = R' = CH_3, (81%)[d] **36** R = CH_3; R' = H_2C  (90)[d]
6	 **15** R = H **16** R = CH_3 **17** R = $(CH_2)_2CH_3$ **18** R = CH_2Ph **19** R = Ph **20** R = CH_2OAc	 **37** R = H, (84%) **38** R = CH_3, (85%) **39** R = $(CH_2)_2CH_3$, (87%) **40** R = CH_2Ph, (89%) **41** R = Ph, (83%) **42** R = CH_2OAc, (54%)[e]
7	 **21** R = CH_3 **22** R = H_2C 	 **43** R = CH_3, (92%)[b] **44** R = H_2C  (78%)[d]
8	 **23** R = R' = CH_3 **24** R = Ph; R' = H	 **45** R = R' = CH_3, (62%)[d] **46** R = Ph; R' = H, (78%)[f]
9	 **25**	 **47**

[a] Alkyl iodide (1 mmol), Cp_2TiCl_2 (2 mmol), $NiCl_2$ (0.2 mmol), PCy_3 (0.4 mmol), Mn dust (8 mmol), and H_2O (10 mmol) in THF at room temperature. [b] The corresponding deuterated isotopomers were also prepared.[14] [c] 85:15 mixture of *trans*/*cis* stereoisomers. [d] 50:50 mixture of *trans*/*cis* stereoisomers. [e] 20 mmol of water was used. [f] 70:30 mixture of *trans*/*cis* stereoisomers.

amounts. This is a clear difference with respect to other protocols in which the hydrogen atom donor must be slowly added and/or that high dilutions are required. Interestingly, different kinds of cyclic radicals can be reduced: primary (from compounds **4**, **10**, **11**, **15**), secondary (from compounds **5**, **6**, **8**, **9**, **12**, **16**–**18**, **20**), tertiary (from compounds **13**, **14**, **21**–**23**), benzylic (from compounds **7**, **19**, **24**), and vinylic (from compound **25**). The reaction even takes place with challenging substrates (entries 5 and 8) that evolve to β-oxygenated transient radicals, which are known to be fragmented by Ti(III).[15] Nevertheless, under those conditions the presence of 10 equiv of water diminishes the amount of uncoordinated Ti(III),[1c,d] thus avoiding such undesired fragmentation processes. It is also worth noting that the reaction can be carried out with substoichiometric amounts of Cp_2TiCl (40 mol %) but in this case the yields are generally lower by 10–40%.[16]



2 (73%, **1**) **47** (55%, **4**) **48** (59%, **5**) **49** (82%, **6**) **50** (87%, **8**)

51 (45%[c], **9**) **52** (86%[d,e], **13**) **53** (75%[f], **17**) **54** (80%, **18**)

55 (80%, **20**) **56** (83%, **21**) **57** (69%, **22**)

[a] Alkyl iodide (1 mmol), Cp_2TiCl_2 (0.7 mmol), $NiCl_2$ (0.2 mmol), PPh_3 (0.4 mmol), Mn dust (8 mmol) and TMSCl (4.0 mmol). [b] Variable amounts of the corresponding reduced product were also isolated.[17] [c] Despite this low yield it was the main product. [d] 80:20 mixture of *trans:cis* stereoisomers. [e] 40 mmol of acetone was used as additive. [f] Mixture of four regioisomers.[17]

Figure 1. Heck-type products (yield, starting material).[a,b]

Heck-type cyclizations are more challenging reactions taking into account the potential substitution patterns in the alkene moiety. As previously mentioned, we were able to carry out a Heck-type cyclization process just with a slight modification in the reaction conditions: by using the same Ti/Ni multimetallic system but in this case under anhydrous conditions. During the optimization of this protocol, the amount of Cp_2TiCl was diminished to 70 mol % in the presence of TMSCl (4 mmol), without losing yield or chemoselectivity in the process. Using these optimized reaction conditions we studied the scope of this Heck-type reaction, and the representative results are summarized in Figure 1.

The success of the cyclization reaction depends on the substitution pattern of the alkene, as it was previously observed in other Heck-type cyclizations of alkyl halides. Thus for example, some protocols are mainly valid for monosubstituted[7g] or trisubstituted alkenes.[7f] In our case, the reaction takes place successfully when the substitution of the alkene in the β-position increases, even from a simple methyl group to a longer chain (**6**, **8**, **17**, **18**). With those substrates the reaction is synthetically useful and only minor amounts (less than 10%) of the corresponding alkane were obtained. Nevertheless, simple allyl and crotyl derivatives resulted to be more challenging starting materials and higher amounts of the reduced product were

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(15) Jiménez, T.; Morcillo, S. P.; Martín-Lasanta, A.; Collado-Sanz, D.; Cárdenas, D. J.; Gansäuer, A.; Justicia, J.; Cuerva, J. M. *Chem.—Eur. J.* **2012**, *18*, 12825–12833.

(16) We used 2,4,6-collidinium hydrochloride as a titanocene(III) regenerating agent.

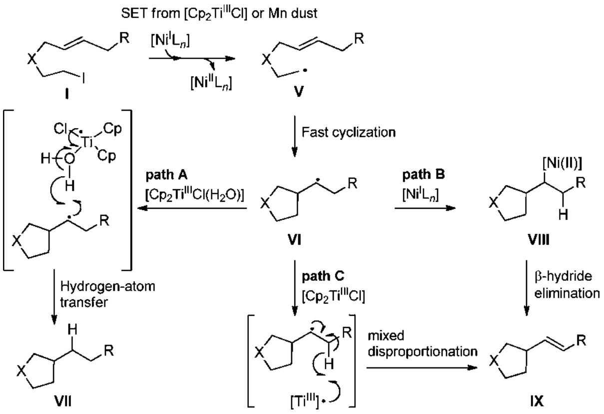
(17) See Supporting Information for details

obtained (up to 35%).[17] This different behavior can be attributed to the inability of titanocene(III) to generate alkenes from some unhindered radicals. Instead of the desirable mixed disproportionation process,[18] Cp_2TiCl irreversibly traps those radical intermediates, providing the corresponding alkane after acidic quenching. Therefore, the nickel catalyst is uniquely responsible for alkene formation and must trap the intermediates before Cp_2TiCl. In the other cases, nickel and Ti(III) can act in a synergic manner.

From a synthetic point of view, different hetero- (**2**, **47**–**52**) and carbocycles (**53**–**57**) can be prepared using this methodology. Again, the reaction with substrates that originate β-oxygenated transient radicals is more difficult to confront (from compound **13**). In this case, we found that the simple addition of acetone decreases the amount of uncoordinated Ti(III) without affecting the key oxidative ending step. We also carried out the reaction with alkenes presenting an oxygenated function in the allylic position (**20**). The reaction took place efficiently, but with this substrate the β-acetoxy elimination process is preferred instead of the usual β-hydride elimination process.[18]

All these results can be explained based on the following mechanistic hypothesis (see Scheme 3).[12] After an initial Ni-catalyzed activation step, the alkyl radical **V** is generated. At this moment, the oxidation state of the Ni-catalyst is unclear. Previously reported studies suggest that this kind of reaction is mediated by Ni(I) complexes.[3] In our case, we used Ni(II)-complexes as precatalysts, which are easily reduced to Ni(I)-active species.[19] A subsequent cyclization step originates the new radical intermediate **VI**, which can evolve by different pathways depending on the reaction conditions. In the presence of a good HAT reagent (path A), as Ti(III)-aqua complexes, the alkane **VII** is obtained. Consequently, the use of 10 equiv of deuterium oxide instead of water afforded the corresponding deuterated isotopomer. The formation of the alkene **IX** seems to be more complex and could be explained by two main mechanisms: β-hydride elimination in an alkyl-Ni intermediate **VIII** (path B) or a Ti(III)-mediated mixed disproportionation[18] of intermediate **VI** (path C). The resulting titanium and nickel hydrides are probably reintroduced in the catalytic cycle with the aid of TMSCl.[9,18]

Scheme 3. Mechanistic Hypothesis for the Ti/Ni Reductive- and Heck-Type Cyclization Reactions



In summary, we have developed an efficient protocol for the catalysis of two interesting reactions, namely a reductive- and Heck-type cyclization of alkyl iodides with a broad substrate scope. Both reactions proceed under very mild conditions and benefit from the good match between the Ti(III) free radical agent and the Ni chemistry. The bivalency of this protocol makes it unique due to its ability to catalyze two kinds of reactions, which normally proceed via two different reaction mechanisms. Moreover this hybrid organometallic–radical process allows circumventing some drawbacks of a formal Heck reaction of alkyl halides,[7] such as the compatibility with common functional groups,[7c] or harsh reaction conditions.[7f] Noteworthy, the excellent HAT capabilities of the Ti(III)-aqua complexes ensure the preference for a reductive ending step using similar reaction conditions, yielding the corresponding cyclic products in high yields.

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Supporting Information Available. General experimental details. ^1H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

[18] Justicia, J.; Jiménez, T.; Morcillo, S. P.; Cuerva, J. M.; Oltra, J. E. *Tetrahedron* **2009**, *65*, 10837–1084.

[19] Our reaction can be also catalyzed by $Ni(COD)_2$. Taking into account that $Ni(COD)_2$ is usually contaminated by other oxidized species, we cannot rule out that in that case Ni(I) is also the active species: Dible, B. R.; Sigman, M. S.; Arif, A. M. *Inorg. Chem.* **2005**, *44*, 3774–3776.