

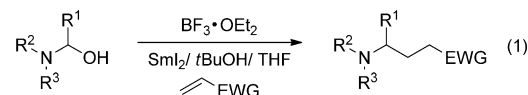
Umpolung of Hemiaminals: Titanocene-Catalyzed Dehydroxylative Radical Coupling Reactions with Activated Alkenes**

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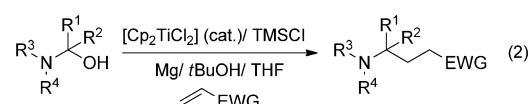
Bis(cyclopentadienyl)titanium(III) chloride (Nugent's reagent)^[1] is an efficient single-electron reductant and has been used as a versatile tool in organic synthesis,^[2,3] owing to the ease of handling, its functional-group compatibility, and a broad array of reactions that can be effected under relatively mild conditions. Today, [Cp₂TiCl] is used as a catalyst for several types of radical reactions by employing a catalytic amount of [Cp₂TiCl₂] as a catalyst precursor and a metal (such as Mn, Zn, Al, In, Mg, and Sm)^[4] as a co-reductant in the presence of TMSCl or protic acids. Among the [Cp₂TiCl]-catalyzed radical reactions, reductive epoxide opening reaction,^[5] first demonstrated by Nugent and Rajan-Babu,^[1] then by Gansäuer et al.,^[5b,c] has been the subject of intensive studies and found applications in natural product synthesis.^[6] In this reaction, a [Cp₂TiCl]-initialized homolysis of C–O bonds is involved. As an extension of this feature, Barrero and co-workers recently described a deoxygenation of alcohols usually mediated by a stoichiometric amount of [Cp₂TiCl]. In addition, catalytic examples have also been reported.^[7] In view of these precedents, the [Cp₂TiCl]-catalyzed dehydroxylative coupling reactions of alcohols and other hydroxy-containing compounds, such as sugars, hemiacetals, and hemiaminals seemed possible.

It is known that umpolung of hemiaminals can provide radical carbon intermediates in α position to amino groups through dehydroxylation and one-electron reduction of the corresponding carbenium ions.^[8] We have recently developed a SmI₂-mediated dehydroxylative radical cross-coupling reaction of hemiaminals with activated alkenes [Scheme 1,

Previous work:



This work:



formation of quaternary carbon centers in α position to amino groups possible

Scheme 1. Dehydroxylative radical coupling reactions of hemiaminals with activated alkenes. Cp = cyclopentadienyl, EWG = electron-withdrawing group, TMS = trimethylsilyl.

Eq. (1)],^[9] which was assumed to proceed through a SmI₂-based single-electron reduction of N-acyliminium ions. This methodology provides a useful and efficient strategy for C–C bond formation at the carbon atoms in α position to amino groups, and can be employed for the synthesis of alkaloids and other pharmaceuticals.^[10] Based on these considerations, it would be particularly interesting and valuable to develop transition-metal-catalyzed dehydroxylative radical coupling reactions of hemiaminals under mild conditions, which have not been reported so far. We envisioned that the singular ability of [Cp₂TiCl] to cleave a C–O bond might help us to achieve this goal.

Herein we report titanocene-catalyzed dehydroxylative radical coupling reactions of hemiaminals with activated alkenes [Scheme 1, Eq. (2)]. This novel reaction was performed by using a [Cp₂TiCl₂](cat.)/Mg/TMSCl reduction system^[11] in the presence of *tert*-butanol. An application of this radical methodology has been demonstrated by an efficient synthesis of ($\pm$)-9,10-diepi-stemoamide.

We began our study with the treatment of hemiaminal **1**^[12] and methyl acrylate (2.0 equiv) with [Cp₂TiCl₂] (0.025 equiv), Mg powder (2.0 equiv), and TMSCl (2.0 equiv); the desired cross-coupling product **2a** was obtained in 54% yield (Table 1, entry 1). The influence of other reaction factors, including Lewis acids, protic additives, and metals, was systematically investigated. TMSCl played a pivotal role in this reaction. The use of *t*BuOH gave the fastest reactions and highest yields (Table 1, entry 3 versus entry 2). After extensive trials, the optimized coupling conditions were defined as carrying out the reactions in THF with [Cp₂TiCl₂] as a catalyst precursor (0.025 equiv) and magnesium turnings as a co-reductant (5.0 equiv) in the presence of TMSCl (4.0 equiv) and *t*BuOH (4.0 equiv). Using this catalytic system, the

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Table 1: Titanocene-catalyzed dehydroxylative cross-coupling of hemiaminal **1** with methyl acrylate (optimization of the reaction conditions).^[a]

Entry	Me ₃ SiCl [equiv]	Metal ([equiv])	tBuOH [equiv]	t [h]	Yield ^[d] [%]
1	2	Mg ^[b] (2)	—	10	54
2	4	Mg ^[b] (2)	—	5	74
3	4	Mg ^[b] (2)	4	2	91
4	4	Mg ^[c] (5)	4	2	93
5	4	Sm (2)	4	2	85
6	4	Mn (2)	4	5	72
7	4	Zn (2)	4	5	64
8	4	Al (2)	4	20	17

[a] All reactions were carried out with **1** (1.0 mmol), methyl acrylate (2.0 mmol), and [Cp₂TiCl₂] (0.025 equiv) in THF (5.0 mL) at room temperature. [b] Mg powder. [c] Mg turnings. [d] Determined after separation by column chromatography. Bn = benzyl.

desired cross-coupling product **2a** was obtained in 93 % (Table 1, entry 4). Although a larger number equivalents of Mg turnings (5.0 equiv) is needed compared with Mg powder (2.0 equiv; Table 1, entry 3) because of the smaller specific surface area of the latter, the use of the former has several advantages: 1) Mg turnings are cheap and readily available; 2) Mg turnings are much more convenient to handle and recycle than Mg powder (about 3.5 equivalents of Mg turnings were recovered after the reaction and the reuse of them in the same reaction gave the same result); 3) the progress of the reaction can be easily assessed from the color of the reaction mixture, because Mg turnings do not form a suspension (in contrast to Mg powder). The color of the solution changes from orange to green once [Cp₂TiCl₂] is reduced to [Cp₂TiCl], then turns back to orange after the addition of the substrate, and to green again when the reaction is complete.

Using the optimized conditions, we explored the scope of this titanocene-catalyzed cross-coupling reaction. The coupling reactions of hemiaminals **1** and **5**^[9] were performed with a variety of α,β-unsaturated compounds (Tables 2 and 3). In general, the desired 5-substituted γ-lactams **2** and 2-substituted pyrrolidine **6** were obtained, respectively, in yields ranging from 45 to 94 %. Compared with the previously reported SmI₂-mediated reaction,^[9,10a] the reaction proceeded smoothly at room temperature (versus −40 °C with the SmI₂-mediated reaction), the concentration of hemiaminal can be much higher (0.2 mol L^{−1} versus 0.02 mol L^{−1} in SmI₂-mediated reaction), and the titanocene-catalyzed reaction provided the products in significantly higher yields in most cases (Table 2, entries 2–4 and Table 3, entry 2). To our delight, functional groups, such as esters, Weinreb amides, nitriles, and ketones, were well tolerated under the reaction conditions. It is of particular significance that the method is suitable for α,β-unsaturated ketones (Table 2, entries 5 and 6 and Table 3, entry 5) and Weinreb acrylamide (Table 2, entry 7). These groups are more readily reduced than hemiaminals and do not lead to cross-coupling products under SmI₂-mediated conditions.^[9,10] All of these results indicate that [Cp₂TiCl₂] (cat.) /

Table 2: Titanocene-catalyzed dehydroxylative cross-coupling of hemiaminal **1** with activated alkenes.

Entry	Activated Alkene	Product	Yield ^[a] [%]	d.r. ^[b]	By-product (Yield ^[a] [%])
1		2a	93		—
2		2b	93 (76) ^[c]		—
3		2c	91 (73) ^[c]	55:45 (64:36) ^[c]	—
4		2d	94 (54) ^[c]		3 (2)
5		2e	64		3 (10) 4 (25)
6		2f	45	56:44	3 (19) 4 (29)
7		2g	55		3 (8) 4 (24)
8		(E)-2h	62		3 (7) 4 (25)
9		2i	72		3 (8) 4 (16)
10		2j	92	56:44	4 (5)
11		2k	62	58:42	3 (10) 4 (22)

[a] Yields of isolated products. [b] Determined by ¹H NMR spectroscopy. [c] Results of SmI₂-tBuOH/BF₃·OEt₂-promoted reductive couplings.^[9,10a]

Table 3: Titanocene-catalyzed dehydroxylative cross-coupling of hemiaminal **5** with activated alkenes.

Entry	Activated Alkene	Product	Yield ^[a] [%]	By-product (Yield ^[a] [%])
1		6a	81	7 (7)
2		6b	86 (67) ^[b]	7 (5)
3		6c	71 (79) ^[b]	7 (8)
4		6d	74 ^[c] (88 ^[d]) ^[b]	7 (14)
5		6e	80	7 (14)

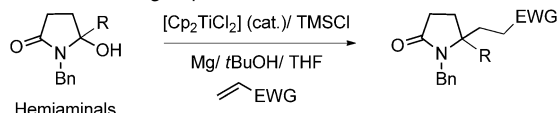
[a] Yields of isolated products. [b] Results of SmI₂-tBuOH/BF₃·OEt₂-promoted reductive couplings.^[9,10a] [c] E/Z = 55:45. [d] E/Z = 58:42. Cbz = benzyloxycarbonyl.

Mg/TMSCl is a milder and more chemoselective single-electron reducing system than SmI₂.

To further probe the applicability of this methodology, we conducted cross-coupling reactions of hemiaminals **8**, **10**, and **12** with various activated alkenes under the optimized conditions. These hemiaminals are readily available through

the addition of Grignard reagents to succinimides, and their successful coupling with activated alkenes would allow the formation of quaternary carbon centers in α position to amino groups.^[13] The desired α -amino-disubstituted γ -lactams were produced in moderate to good yields (Table 4). The coupling

Table 4: Titanocene-catalyzed formation of quaternary carbon centers in α position to amino groups from hemiaminals **8**, **10**, and **12**.

				
Entry	Hemiaminal	R	Activated Alkene	Product (Yield ^[a] [%])
1	8	Me	CH ₂ =CHCOOMe	9a (82)
2	8	Me	CH ₂ =CHCOOtBu	9b (77)
3	8	Me	CH ₂ =CHCN	9c (84)
4	10	Et	CH ₂ =CHCOOMe	11a (81)
5	10	Et	CH ₂ =CHCOOtBu	11b (72)
6	10	Et	CH ₂ =CHCN	11c (83)
7	12	Bn	CH ₂ =CHCOOMe	13a (75)
8	12	Bn	CH ₂ =CHCOOtBu	13b (68)
9	12	Bn	CH ₂ =CHCN	13c (81)

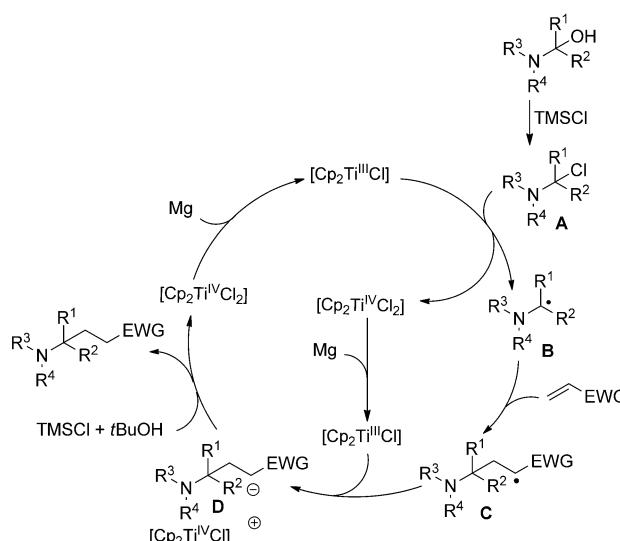
[a] Yields of isolated products.

seemed to be affected by the steric hindrance of R groups in the hemiaminals and electron-withdrawing groups in the activated alkenes. Reactions of hemiaminals with bulkier R groups provided products in lower yields when coupled with the same activated alkene. Furthermore, in coupling reactions of the same hemiaminal with different acrylates, the more bulky *tert*-butyl acrylate gave the product in a lower yield than methyl acrylate (Table 4, entry 2 versus entry 1, entry 5 versus entry 4, and entry 8 versus entry 7). Moreover, coupling reactions of three hemiaminals with the least hindered acrylonitrile consistently gave the highest yields (Table 4, entries 3, 6, and 9).

To further demonstrate the advantage of this titanocene-catalyzed reaction over the previously reported SmI₂-mediated reaction with regard to both efficiency and applicability,^[9,10] a large-scale synthesis of **2a** was performed. Following the established general procedure for titanocene-catalyzed cross-coupling reaction, only a 100 mL round-bottom flask was needed for the reaction, and product **2a** was eventually obtained in 83 % yield from hemiaminal **1** (2.16 g, 11.3 mmol). Comparatively, at least 450 mL of a solution of SmI₂ in THF was required for the preparation of **2a** on the same scale using the previously reported SmI₂-mediated reaction.^[10a]

We also explored the plausible mechanism of titanocene-catalyzed direct dehydroxylative cross-coupling reaction of hemiaminals with activated alkenes. NMR experiments with hemiaminal **1** in deuterated tetrahydrofuran showed that in situ chlorination of the hemiaminal occurred upon treatment with TMSCl (compare with the Supporting Information). Based on these observations, the first step of titanocene-catalyzed direct dehydroxylative reactions presumably involves the TMSCl-promoted conversion of the hemiaminal to the chlorolactam **A**, as suggested by Peterson and

Jacobsen^[14] (Scheme 2). Subsequently, chlorolactam **A** is reduced by [Cp₂TiCl] to generate α -acylaminoalkyl radical **B**,^[8a,9,10] which is then trapped by an activated alkene to give radical **C**. Further reduction of radical **C** by another [Cp₂TiCl] complex generates the tetravalent titanium salt **D**, which is

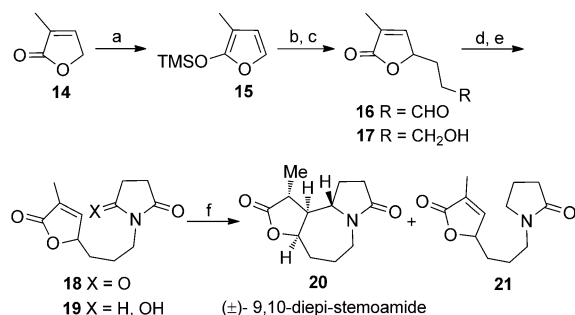


Scheme 2. Plausible mechanism for the titanocene-catalyzed dehydroxylative coupling of hemiaminals with activated alkenes.

eventually protonated to give the corresponding cross-coupling product. The beneficial effect of *t*BuOH may be ascribed to its synergistic effect with TMSCl, accelerating the chlorination of hemiaminals as well as the protonation of titanium salts **D** by in situ generation of HCl.

To demonstrate the synthetic value of this titanocene-catalyzed reaction, we developed an efficient six-step total synthesis of ($\pm$)-9,10-diepi-stemoamide.^[15,16] Stemoamide, one of the *Stemona* alkaloids, was isolated from the Chinese traditional medicine *Stemona tuberosa* Lour by Xu and co-workers in 1992.^[17] Recently, the groups of Khim and Cossy have independently developed an asymmetric synthesis of (–)-9,10-diepi-stemoamide^[15c] and a stereoselective synthesis of its racemate,^[15a,b] respectively, by employing a 7-*exo-trig* radical ring-closure strategy. We started our synthesis from commercially available 3-methyl-2(5*H*)-furanone **14**, which was treated with TMSOTf in the presence of Et₃N to give silyloxyfuran **15** in 78 % yield. A Mukaiyama–Michael reaction^[18] of silyloxyfuran **15** with acrolein under the catalysis of pyrrolidine–AcOH at –40 °C gave aldehyde **16** in 64 % yield, which was reduced by BH₃ in THF at –30 °C to give alcohol **17** in 93 % yield. Condensation of alcohol **17** with succinimide mediated by Ph₃P and DIAD afforded N-substituted succinimide **18** in 91 % yield. Treatment of imide **18** with NaBH₄ in methanol at –10 °C produced hemiaminal **19** in 92 % yield. Based on the above-established method, the intramolecular radical cross-coupling reaction of hemiaminal **19** underwent smoothly utilizing the catalytic system [Cp₂TiCl₂]/Mg/TMSCl to give ($\pm$)-9,10-diepi-stemoamide (**20**) in 32 % yield as the sole diastereomer, along with

hemiaminal-reduced product **21** in approximately 35 % yield (Scheme 3). The spectral data of the synthetic ($\pm$)-9,10-diepi-stemoamide (**20**) matched those reported.^[15] It is worth noting that the ring-closing reaction (**19** to **20**) does not occur under the SmI₂-mediated radical coupling conditions.^[9,10]



Scheme 3. Total synthesis of ($\pm$)-9,10-diepi-stemoamide. Reaction conditions: a) TMSOTf, Et₃N, 0 °C $\rightarrow$ RT, CH₂Cl₂, 78 %; b) acrolein, pyrrolidine, AcOH, CH₂Cl₂/H₂O, -40 °C, 64 %; c) BH₃·THF, -30 °C, 93 %; d) succinimide, DIAD, PPh₃, THF, RT, 91 %; e) NaBH₄, MeOH, -10 °C, 92 %; f) [Cp₂TiCl₂] (cat.)/Mg/TMScI, THF, 0 °C $\rightarrow$ RT, 3.5 h, **20**: 32 % and **21**: 35 %.

In summary, we have developed a novel method for umpolung of hemiaminals using the [Cp₂TiCl₂] (cat.)/Mg/TMScI catalytic reduction system in the presence of *tert*-butanol, which can be employed in the direct dehydroxylative radical coupling of hemiaminals with activated alkenes. This radical coupling was proposed to proceed through in situ chlorination of the hydroxy group by TMScI. Compared to our previously reported SmI₂-mediated reductive coupling,^[9,10] titanocene-catalyzed cross-coupling reactions show four great advantages: 1) only 0.025 equivalents of [Cp₂TiCl₂] were needed and at most 1.5 equivalents of Mg turnings were consumed, thus the required metal loading was reduced greatly; 2) the method can be used for the formation of quaternary carbon centers in α position to amino groups; 3) the method is suitable for reactions with a wide range of hemiaminals and activated alkenes, especially for α,β -unsaturated ketones and Weinreb acrylamide; 4) the reactions can be carried out at room temperature and with a much higher concentration of hemiaminal (0.2 mol L⁻¹), and therefore, the reactions can be scaled up conveniently. The power of this methodology has been demonstrated by the efficient six-step total synthesis of ($\pm$)-9,10-diepi-stemoamide (**20**) with 12.4 % overall yield, which, to the best of our knowledge, is the shortest synthetic route to this compound so far.

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