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# Ti-Catalyzed Radical Alkylation of Secondary and Tertiary Alkyl Chlorides Using Michael Acceptors

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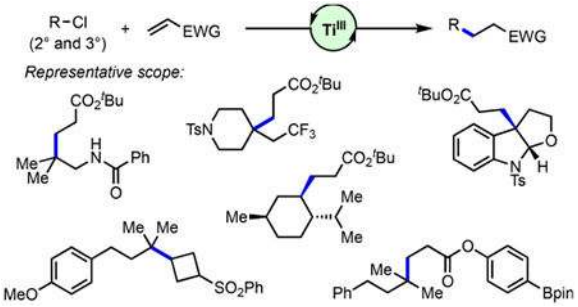
## Abstract

Alkyl chlorides are common functional groups in synthetic organic chemistry. However, the engagement of unactivated alkyl chlorides, especially tertiary alkyl chlorides, in transition-metal-catalyzed C–C bond formation remains challenging. Herein, we describe the development of a $Ti^{III}$-catalyzed radical addition of 2° and 3° alkyl chlorides to electron-deficient alkenes. Mechanistic data are consistent with inner-sphere activation of the C–Cl bond featuring $Ti^{III}$-mediated Cl atom abstraction. Evidence suggests that the active $Ti^{III}$ catalyst is generated from the $Ti^{IV}$ precursor in a Lewis-acid-assisted electron transfer process.

## Graphical Abstract




## INTRODUCTION

Carbon–chlorine bonds are prevalent structural units in organic molecules. In particular, alkyl chlorides are frequently found in natural products[1] and synthetic intermediates.[2] These

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b08605.

Experimental procedures and characterization data (PDF)

Crystallography data for **45** (CIF)

The authors declare no competing financial interest.

Crystallography data for **45** were deposited in the Cambridge Structural Database (CCDC 1833922).

compounds can be readily prepared from common functional groups including alkenes,[3] alcohols,[4] ketones,[5] epoxides,[6] and alkanes.[7] Nevertheless, methods that engage alkyl chlorides in organic synthesis are largely confined to the two-electron regime via canonical $S_N2$ and Grignard reactions. New protocols that can selectively activate and functionalize alkyl chlorides may further expand the use of these electrophiles in complex target synthesis.[8] Recent advances in radical chemistry have enabled the use of common functional groups (e.g., carboxylates,[9] alcohols,[10] alkenes,[11] and alkanes[12]) in C–C bond forming reactions. Inspired by these seminal contributions and given our research interests in Ti radical catalysis, we aimed to develop a new approach for the activation and alkylation of unactivated 2° and 3° alkyl chlorides by employing the rich redox chemistry of Ti complexes.

In principle, three strategies may be envisioned for the activation of alkyl chlorides to form the corresponding carbon-centered radicals or their equivalents (Scheme 1A). First, metal oxidative insertion[13] to the C–Cl bond can form metal–alkyl intermediates. In this context, first-row transition metals including Ni,[14] Co,[15] Fe,[16] and Cu[17] have been shown to be capable of engaging alkyl chlorides in C–C bond forming reactions. However, these methods are not suitable for transforming 3° R–Cl[18] because the corresponding metal–alkyl species are susceptible to unproductive side reactions (e.g., via $\beta$-H elimination). Indeed, current examples using such a strategy are limited to the use of special 3° alkyl chlorides that cannot undergo $\beta$-H elimination due to geometric constraints. Recently, Fu et al. reported a Cu-catalyzed photochemical cyanation reaction,[17] which constitutes a rare example in which a simple, unactivated 3° R–Cl was employed toward C–C formation. However, it was noted in the report that this method currently cannot be generalized to other tertiary substrates.

A second strategy relies on the direct, single-electron reduction of the alkyl chloride electrophile using a chemical reductant or a photocatalyst.[19] This possibility is hampered by the very negative reduction potential of unactivated R–Cl ($E \leq -2.5$ V vs $Fc^{+/0}$).

The third strategy entails metal-promoted Cl atom abstraction[20] to form the corresponding carbon-centered free radical. This pathway is the reversal of atom transfer radical addition but is challenged by the relatively high dissociation energy of C–Cl bonds (e.g., BDE of $^t$Bu–Cl is ca. 85 kcal/mol).

We were interested in using the third strategy for the activation of alkyl chlorides, as it could allow the engagement of 3◦ R–C, an underexplored class of electrophiles,[21] in C–C forming reactions (Scheme 1B). In theory, $Ti^{III}$ is a well-suited catalyst for such a process because (1) $Ti^{III}$ compounds are versatile catalysts[22] in the reductive activation of common functional groups (e.g., carbonyls[23] and epoxides[24]) and (2) $Ti^{IV}$ shows great affinity with highly electronegative, “hard” anions, making Cl atom abstraction thermodynamically favorable (e.g., BDE of $Ti^{IV}$–Cl in $TiCl_4$ is 96 kcal/mol).[25] This activation would lead to the formation of a carbon-centered radical that can participate in subsequent reactions in the presence of a radical acceptor. In a related study, Kambe achieved an elegant alkene carbomagnetization through the activation of 3◦ R–Cl.[26] This reaction, however, relies on the formation of highly reducing $Ti^{II}$ species generated in the presence of $^n$BuMgCl, thus limiting the reaction scope to only unfunctionalized substrates. Huang recently reported the

reductive addition of α-hydroxylactams to Michael acceptors using the Nugent–RajanBabu reagent.[20b] This reaction was proposed to undergo the intermediacy of α-chlorolactams, a highly activated class of electrophiles; it also required the use of $Mg^0$ to achieve high efficiency, which limited the functional group compatibility.

In this article, we report the development of a Ti-catalyzed alkylation of unactivated alkyl chlorides using Michael acceptors. In particular, 3° R–Cl, a largely untapped class of electrophiles in transition metal catalysis, was successfully engaged in C–C bond formation. Our new method displays a reaction scope and functional group compatibility that are complementary to existing protocols for accessing similar types of products.

## RESULTS AND DISCUSSION

### A. Reaction Discovery and Catalyst Optimization

Our initial attempts to achieve the radical activation and addition of 3° alkyl chloride **1** to acrylate **2** proved challenging using the Nugent–RajanBabu reagent ($Cp_2TiCl_2$) or its derivative, $Cp^*_2TiCl_2$. We hypothesize that the active site of these titanocenes is likely hindered by the pair of cyclopentadienyl ligands, rendering it difficult for the sterically demanding 3° R–Cl to approach (Scheme 2). We recently demonstrated the use of $Cp^*TiCl_3$—a catalyst frequently employed in polymerization reactions[27] but is underexplored in radical chemistry— in the [3+2] cycloaddition of alkenes with *N*-acylaziridines[28a] or cyclopropyl ketones.[23b] The removal of a Cp* ligand decreased the steric profile of these catalysts but maintained their redox properties. As such, the cyclization of a carbon-centered radical onto the Ti-bound (aza)enolate can occur smoothly (see Scheme 2). In contrast, bulkier $Cp^*_2TiCl_2$ provided the open-chain product instead.[28b]

Indeed, the use of $Cp^*TiCl_3$ as the catalyst provided a positive lead result in the reductive C–C coupling between **1** and acrylate **2** (Table 1). Upon optimization, the desired alkylation product **3** was obtained in 70% yield using Zn as the stoichiometric reductant, $Et_3N{\cdot}HCl$ as the proton source in toluene, and a reaction time of **1** h (entry 1). The unsubstituted $CpTiCl_3$ complex proved inferior (entry 2), presumably due to the less negative reducing potential of the corresponding $Ti^{III}$ active catalyst ($E_{1/2}$ = −0.79 V, compared with −1.12 V with $Cp^*TiCl_3$; see discussion below and the SI). As previously discussed, titanocene complexes $Cp^*_2TiCl_2$ ($E_{1/2}$ = −1.55 V) and $Cp_2TiCl_2$ ($E_{1/2}$ = −1.19 V) were substantially less reactive (entries 3, 4).

Extending the reaction time to 12 h led to the quantitative conversion of **1** to **3** (entry 5). Using the optimal conditions, we conducted control experiments to elucidate the role of each reaction component. As expected, the exclusion of the Ti catalyst completely shut down the C–C coupling reactivity (entry 6). Both the reductant and the ammonium salts are required to obtain appreciable amounts of **3** (entry 7). Collidine·HCl salt instead of $Et_3N{\cdot}HCl$ as a proton source provided the product in nearly identical yield (entry 8). Notably, Mn instead of Zn is inactive (entry 9). Although Mn is more reducing than Zn, we observed no color change from red ($Ti^{IV}$) to green ($Ti^{III}$), which was apparent in the Zn-promoted reaction. This finding indicated that Mn is incapable of reducing the precatalyst in our reaction medium (see discussion below). Nonpolar and poorly coordinating solvents, such as

dichloromethane (DCM) or ethyl acetate, were compatible (entries 10 and 11), whereas MeCN and tetrahydrofuran (THF) strongly inhibited the formation of **3** (entry 12).

## B. Substrate Scope

We then explored the reaction scope under the optimal conditions. Substituted acrylates (Table 2, entries 1–8) were transformed to their corresponding products smoothly. Various functional groups, including trifluoromethyl (**4**) and tertiary amine (**12**) motifs, were also tolerated. Importantly, our protocol was compatible with aryl bromide (**14**) and aryl boronate (**16**), functional groups that would likely induce catalyst promiscuity under previous conditions reported for alkyl chloride activation (e.g., Ni catalysis[14]). Notably, primary alkyl chloride (**6**) remained untouched, presumably because primary carbon-centered radicals are more difficult to generate than their tertiary congeners. Various other Michael acceptors (entries 9–13) provided the corresponding products in good to excellent yields. Interestingly, bicyclobutanes (**28, 30**)[29] also underwent strain-relieving radical addition to provide disubstituted cyclobutenes in useful yields. Enones are currently incompatible presumably due to competing reductive transformations[30] that do not involve the alkyl chloride.

The Ti-catalyzed alkylation proceeded smoothly with an array of structurally diverse 3° alkyl chlorides (Table 3, entries 1–11). In particular, alkylated furanoindoline **45** was obtained in a synthetically useful yield from the corresponding organochloride, and the structure was identified with X-ray crystallography. Secondary alkyl chlorides also proved to be suitable substrates (entries 12–18). Achieving high yields, however, sometimes required the use of higher loadings of Zn, $Et_3N{\cdot}HCl$, or Ti catalyst as well as prolonged catalyst preactivation before substrate addition. We also investigated secondary benzyl chloride and primary alkyl chloride. (1-Chloroethyl)benzene was fully consumed, yielding 2,3-diphenylbutane via radical dimerization as the major product (ca. 50%) along with a small amount of desired alkylation adduct (ca. 15%; see SI). (3-Chloropropyl)benzene was largely unreactive and afforded the alkylation product in ca. 10% yield. Primary alkyl chlorides are frequently suitable electrophilies for metal-catalyzed C–C formation in the literature.[14–17] Therefore, our Ti-catalyzed reaction offers complementary selectivity and can be used for the selective functionalization of 2° and 3° R–Cl in the presence of their primary counterparts (see Table 2, entry 3).

## C. Tandem Chlorination and Ti-Catalyzed Alkylation.

We then demonstrated the reductive alkylation reaction on synthetically relevant scales. Four alkyl chlorides were readily prepared from common functionalities using established protocols. Deoxychlorination of alcohols[4] and hydrochlorination[3c] and chlorofunctionalization[3g,h] of alkenes led to structurally diverse alkyl chlorides in a single step in high efficiency (Scheme 3). Various other literature methods for the preparation of alkyl chlorides are provided in the SI. The resulting intermediates were then subjected to the described Ti-catalyzed conditions on a 1 mmol scale to afford the alkylation products with minimal changes in yield from the 0.1 mmol scale. In particular, owing to the large variety of alkene chlorofunctionalization reactions available in the literature, the two-step procedure comprising tandem chlorination and reductive alkylation constitutes a convenient and versatile method for the synthesis of vicinally difunctionalized products (e.g., **43, 45, 51**).

We also conducted gram-scale synthesis of **27**, which resulted in a slightly decreased but synthetically useful yield (68%) likely as a result of the heterogeneity of the reaction system. Efforts are underway to improve the efficiency of gram-scale synthesis.

To gain further insight into the compatibility of various functional groups with our reaction conditions, we examined the impact of additives (1.0 equiv) on the efficiency of the coupling process (Table 4). We found that adding benzofuran, *N*-Me indole, 4-phenylbutene, 4-octyne, 2-bromoethylbenzene, cyanobenzene, or phenyl methyl sulfide has no adverse impact on the yield of the reaction, with the additives recovered after the reaction. An aliphatic ketone has a moderate inhibition effect on the reaction, with product **3** isolated in 55% yield after 12 h. The presence of phenols, alcohols, epoxides, or pyridines, however, impedes the Ti catalysis, presumably by competitive coordination to the oxophilic metal center.

Alternative approaches to accessing the same type of products from alkyl chlorides frequently entail the generation of corresponding Grignard reagents followed by Michael addition[31] or Sn-mediated radical processes,[19a] the latter of which are often carried out in an intramolecular fashion to avoid competitive hydrogen atom transfer (HAT) and other side reactions. Our Ti-catalyzed reaction thus provides an alternative platform for accessing these products with significantly improved ease of operation, substrate scope, and selectivity. Recently, several seminal contributions in the area of radical catalysis made it possible to obtain similar Giese-type products from common functional groups (e.g., carboxylates,[9] alcohols,[10] and alkenes[11]) other than alkyl chlorides. These methods, however, cannot provide a general access to vicinally difunctionalized products as described previously. In addition, our reaction displays a different scope compared to many existing methods in terms of functional group tolerance.[32] Therefore, our Ti-catalyzed activation of alkyl chlorides provides a complementary approach to the catalytic radical reactions currently in place and allows an additional class of common functional groups (R–Cl) to be engaged in radical C–C bond formation.

### D. Mechanistic Understanding of Potential Reaction Pathways.

Spin trapping experiments support the intermediacy of carbon-centered radicals in the alkylation reaction. In the presence of 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO) and 1,4-cyclohexadiene (CHD), persistent nitroxyl radical **80** and HAT product **82** were formed, respectively (Scheme 4). The HAT reaction also constitutes an efficient alternative approach to the reduction of alkyl chlorides under Sn-/heavy metal-mediated conditions. The stereochemical infidelity of the reaction involving diastereomerically pure **66** also accords with the radical mechanism. An alternative, nonradical mechanism entails the in situ formation of an alkylzinc species from Zn and the alkyl chloride followed by Ti-catalyzed Michael addition. This possibility was ruled out using a reaction with stoichiometric Ti, wherein the Zn dust remaining after catalyst reduction was removed via filtration before addition of the alkyl chloride and acrylate. Product **3** was still formed in 40% yield.[33] Currently, a pathway involving Ti-catalyzed alkylzinc formation via a transmetalation process[34] cannot be ruled out. This mechanism, however, cannot account for the observed hydrodehalogenation in the presence of CHD.

Drastically different reactivity between Mn and Zn as the terminal reductant (see Table 1, entry 9) suggested that these metals do not serve simply as a reducing agent. As previously discussed, Mn is incapable of reducing Cp*$TiCl_3$ to $Ti^{III}$ in the reaction medium. Given Mn's more negative potential than Zn, we reasoned that the byproduct of the reduction process, $Zn^{2+}$, likely plays a crucial role in the activation of the Ti catalyst.[35] Indeed, in a control experiment using Mn as the stoichiometric reductant, the addition of $Zn(OTf)_2$ restored the alkylation reactivity (Table 5). Interestingly, other Lewis acids such as $Sc(OTf)_3$ and $AlCl_3$ can also promote the desired reaction.

Data from UV–vis experiments revealed that a strong Lewis acid can indeed accelerate the reduction of Cp*$TiCl_3$ by Mn. In the presence of 10 equiv of $AlCl_3$ (with respect to Ti), this reduction was nearly completed within 15 min (Figure 1). In stark contrast, with Mn alone, catalyst reduction was sluggish.

$^1H$ NMR experiments showed that in the presence of $AlCl_3$ a new Ti complex emerged. Cp*$TiCl_3$ in toluene-$d_8$ displays two C$H_3$ resonances (2.12 and 1.95 ppm) presumably arising from different aggregation states. We tentatively assign these peaks to the monomeric and Cl-bridged dimeric[36] Ti complexes.[38] Upon addition of $AlCl_3$, both resonances converged into a single signal at 1.93 ppm. We tentatively assign this species to the Cl-bridged heterometallic dimer with a composition of [Cp*$TiCl_3$][$AlCl_3$].[37] The strong Lewis acidity of $Al^{3+}$ can thus facilitate the reduction of the Ti center. The speciation of the active Ti complexes is currently underway.

The mechanism of C–Cl activation by $Ti^{III}$ was investigated using density functional theory (DFT) computation (see SI). Cyclic voltammetry data revealed that the potential required for the reduction of **1** was at least 1.1 V more negative than that of Cp*$TiCl_3$ (Figure 2). As such, an outer-sphere electron transfer from the $Ti^{III}$ catalyst to **1** is highly unlikely. Owing to the higher dissociation energy of the $Ti^{IV}$–Cl bond relative to the C–Cl bond, an inner-sphere Cl atom abstraction by $Ti^{III}$ displays an energy barrier of only 6 kcal/mol. This mechanism provides an alternative means for the activation of strong bonds that are conventionally inert to single-electron transfer.

Taken together, a catalytic cycle was proposed (Scheme 5). The Cp*$TiCl_3$ first undergoes a Lewis-acid-assisted electron transfer mediated by complex **I** to generate active Cp*$Ti^{III}Cl_2$.[38] This lower valent complex then abstracts a Cl atom from the alkyl chloride, furnishing $R^{\bullet}$ and closing the catalytic cycle. The nascent $R^{\bullet}$ then adds to the Michael acceptor to form electrophilic radical **II**, which is subsequently reduced and protonated to deliver the product, likely in a Ti-mediated process. An alternative pathway for the conversion of **II** to the product involves Cl atom transfer from the Ti catalyst to **II** followed by reduction of the resulting C–Cl bond. This pathway is less likely to operate on thermodynamic grounds because the Ti–Cl bond is substantially stronger than the C–Cl bond $\alpha$ to a carbonyl group (typically <80 kcal/mol).[39]

## CONCLUSION

To summarize, we report the Ti-catalyzed radical alkylation of unactivated secondary and tertiary alkyl chlorides with Michael acceptors. This method provides alternative means to generate carbon-centered radicals and offers a new route to C–C bond formation that is complementary to existing protocols. Future efforts are directed toward (1) understanding the structure of the active Ti catalyst and its action in activating C–Cl and other strong chemical bonds and (2) expanding the new radical reactivity of alkyl chlorides to other types of synthetically valuable reactions.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(24). For examples, see:(a) Gansauer A; Behlendorf M; von Laufenberg D; Fleckhaus A; Kube C; Sadasivam DV; Flowers RA II Angew. Chem., Int. Ed 2012, 51, 4739–4742.(b)Gansauer A; Hildebrandt S; Michelmann A; Dahmen T; von Laufenberg D; Kube C; Fianu GD; Flowers RA II Angew. Chem., Int. Ed 2015, 54, 7003–7006.(c)Zhao Y; Weix DJ J. Am. Chem. Soc 2015, 137, 3237–3240. [PubMed: 25716775]

(25). Luo Y-R Comprehensive Handbook of Chemical Bond Energies; CRC Press: Boca Raton, 2007.

(26). Nii S; Terao J; Kambe N J. Org. Chem 2004, 69, 573–576. [PubMed: 14725478]

(27). Nomura K, Liu J In Organometallic Reactions and Polymerization. Lecture Notes in Chemistry, Osakada K, Ed.; Springer: Berlin, 2014; Vol 85, pp 51–88.

(28). (a) Hao W; Wu X; Sun JZ; Siu JC; MacMillan SN; Lin S J. Am. Chem. Soc 2017, 139, 12141–12144. [PubMed: 28825816] (b)Zhang Y-Q; Vogelsang E; Qu Z-W; Grimme S; Gansauer A Angew. Chem. Int. Ed 2017, 56, 12654–12657.

(29). (a) Lopchuk JM; Fjelbye K; Kawamata Y; Malins LR; Pan C-M; Gianatassio R; Wang J; Prieto L; Bradow J; Brandt TA; Collins MR; Elleraas J; Ewanicki J; Farrell W; Fadeyi OO; Gallego GM; Mousseau JJ; Oliver R; Sach NW; Smith JK; Spangler JE; Zhu H; Zhu J; Baran PS J. Am. Chem. Soc 2017, 139, 3209–3226. [PubMed: 28140573] (b)Noyori R; Suzuki T; Kumagai Y; Takaya H J. Am. Chem. Soc 1971, 93, 5894–5896.

(30). Streuff, J. Chem. - Eur. J 2011, 17, 5507–5510.

(31). For an example, see:Chai G; Lu Z; Fu C; Ma S Adv. Synth. Catal 2009, 351, 1946–1954.

(32). For example, aryl bromides (**14**), alkyl bromides (**76**), and aryl boronates (**16**) might not be compatible with Ni-catalyzed conditions, tertiary amines (**12**) might not be compatible with photoredox conditions, alkenes (**66, 71**) might not be compatible with Fe-catalyzed hydroalkylation conditions, and alkyl halides (**6, 76**) and ketones (**74**) might not be compatible with conditions involving Mg or Grignard reagents.

(33). If the reaction goes through the proposed mechanism, the theoretical yield of reaction using 1 equiv of $Cp^*TiCl_3$ is 50%.

(34). (a) Fleury LM; Kosal AD; Masters JT; Ashfeld BL J. Org. Chem 2013, 78, 253–269. [PubMed: 23094703] (b)Fleury LM; Ashfeld BL Org. Lett 2009, 11, 5670–5673. [PubMed: 19924877]

(35). Effect of metal reductants on the electrochemical behavior of titanocenes: Enemærke RJ; Larsen J; Skrydstrup T; Daasbjerg K J. Am. Chem. Soc 2004, 126, 7853–7864. [PubMed: 15212533]

(36). For the observation of a similar dimeric half-titanocene complex, see:Paisner SN; Lavoie GG; Bergman RG Inorg. Chim. Acta 2002, 334, 253–275.

(37). $Cp^*Ti^{III}Cl_2$ can exist as a dimer in solution, as has been observed with $Cp_2Ti^{III}Cl$ (ref 35).

(38). For studies on heterometallic dimers involving Ti, see:(a) Sekutowski DJ; Stucky GD Inorg. Chem 1975, 14, 2192–2199.(b)Folting K; Huffman JC; Bansemer RL; Caulton KG Inorg. Chem 1984, 23, 3289–3292.Higher aggregation numbers have been reported, and their formation in our reaction cannot be ruled out at this stage.

(39). By analogy, BDE(C–Cl) in 2-chloropropionic acid is 72.1 kcal/ mol. See:Lagoa ALC; Diogo HP; Minas da Piedade ME; Amaral LMPF; Guedes RC; Costa Cabral BJ; Kulikov DV; Verevkin SP; Siedler M; Epple M J. Phys. Chem. A 2002, 106, 9855–9861.

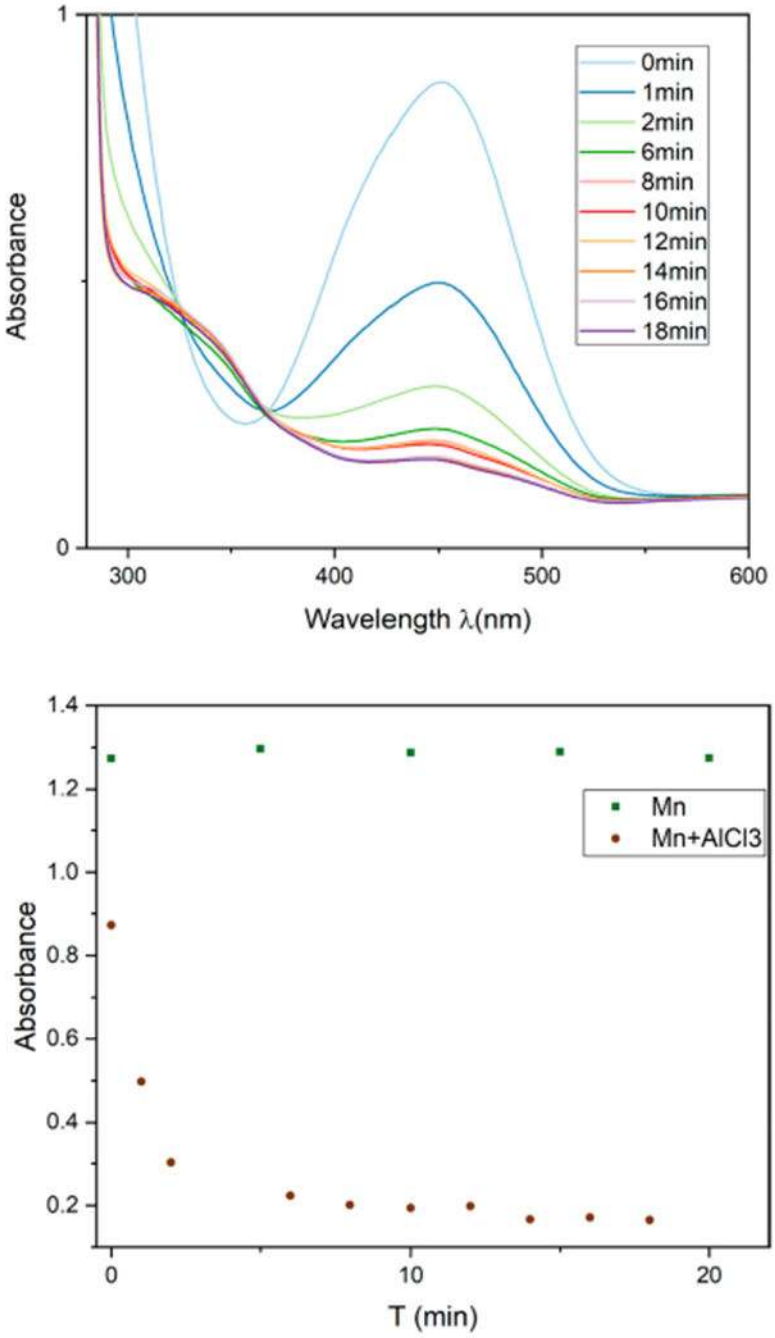



**Figure 1.**

Reduction of Cp*$TiCl_3$ by Mn in the presence or absence of $AlCl_3$. Top: UV–vis spectra showing the reduction in the presence of $AlCl_3$; the peaks at 450 and 330 nm are assigned to Cp*$TiCl_3$ and its corresponding reduced form, respectively. Bottom: Change in absorption at 450 nm showing the reduction of Cp*$TiCl_3$.

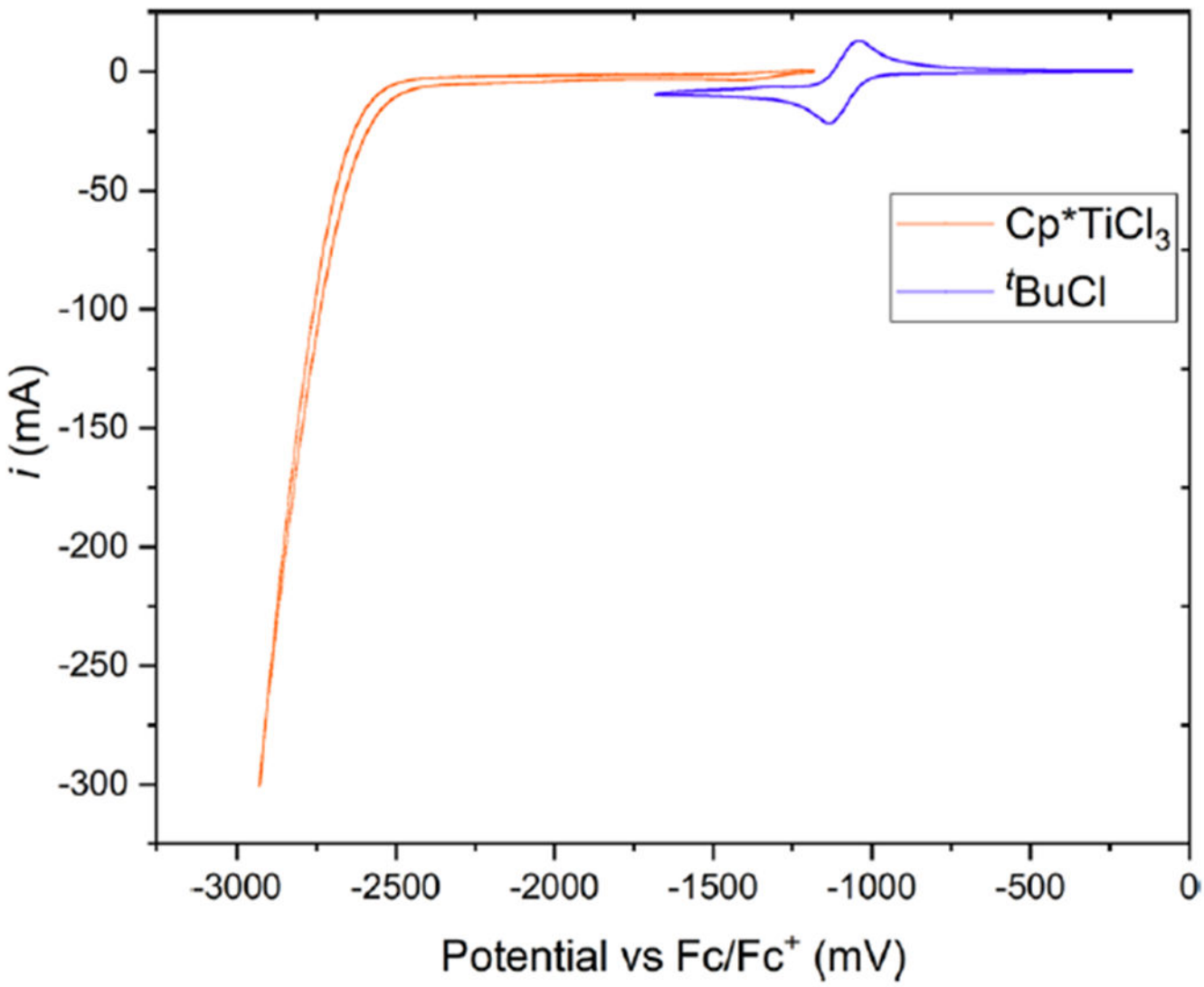
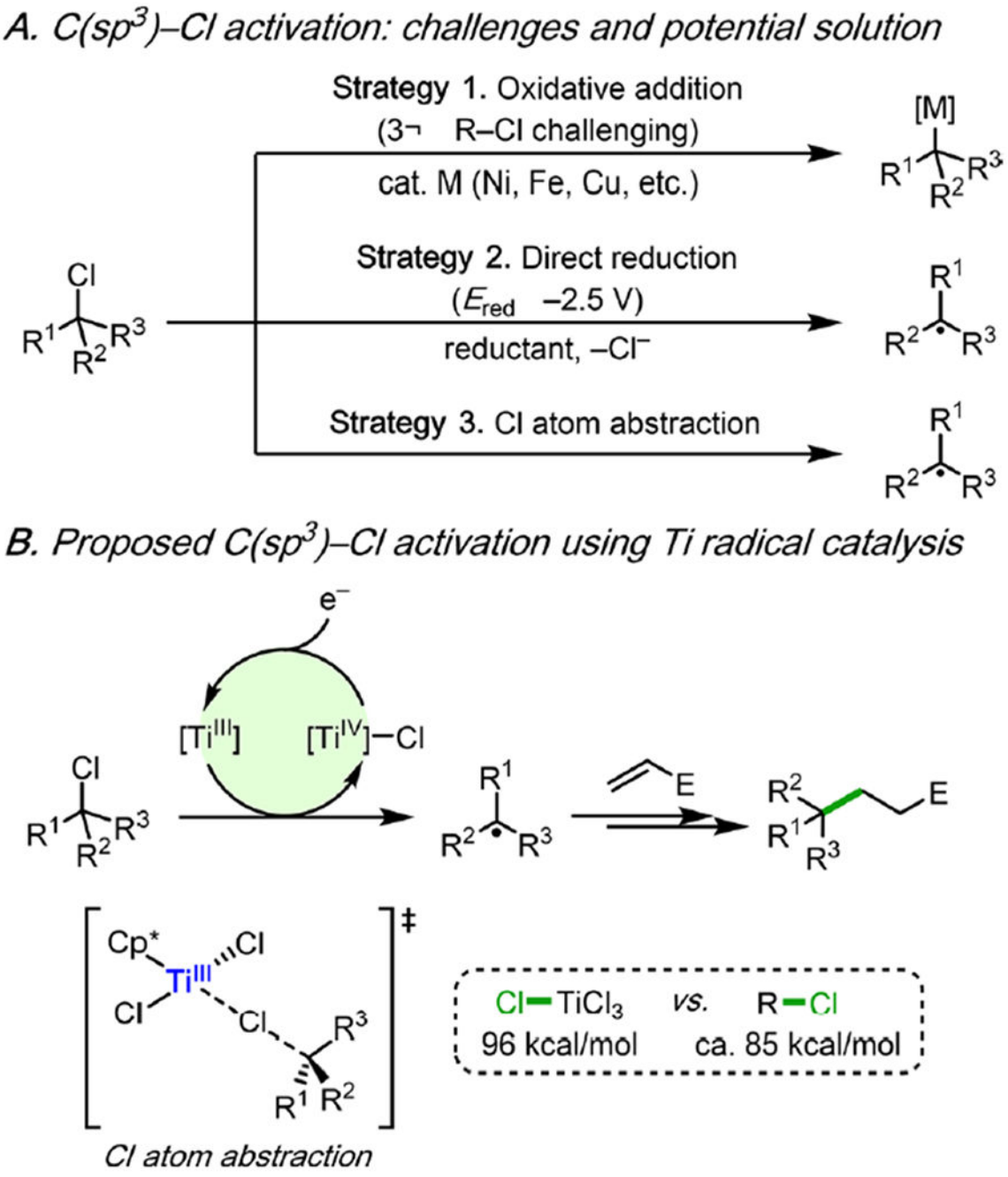
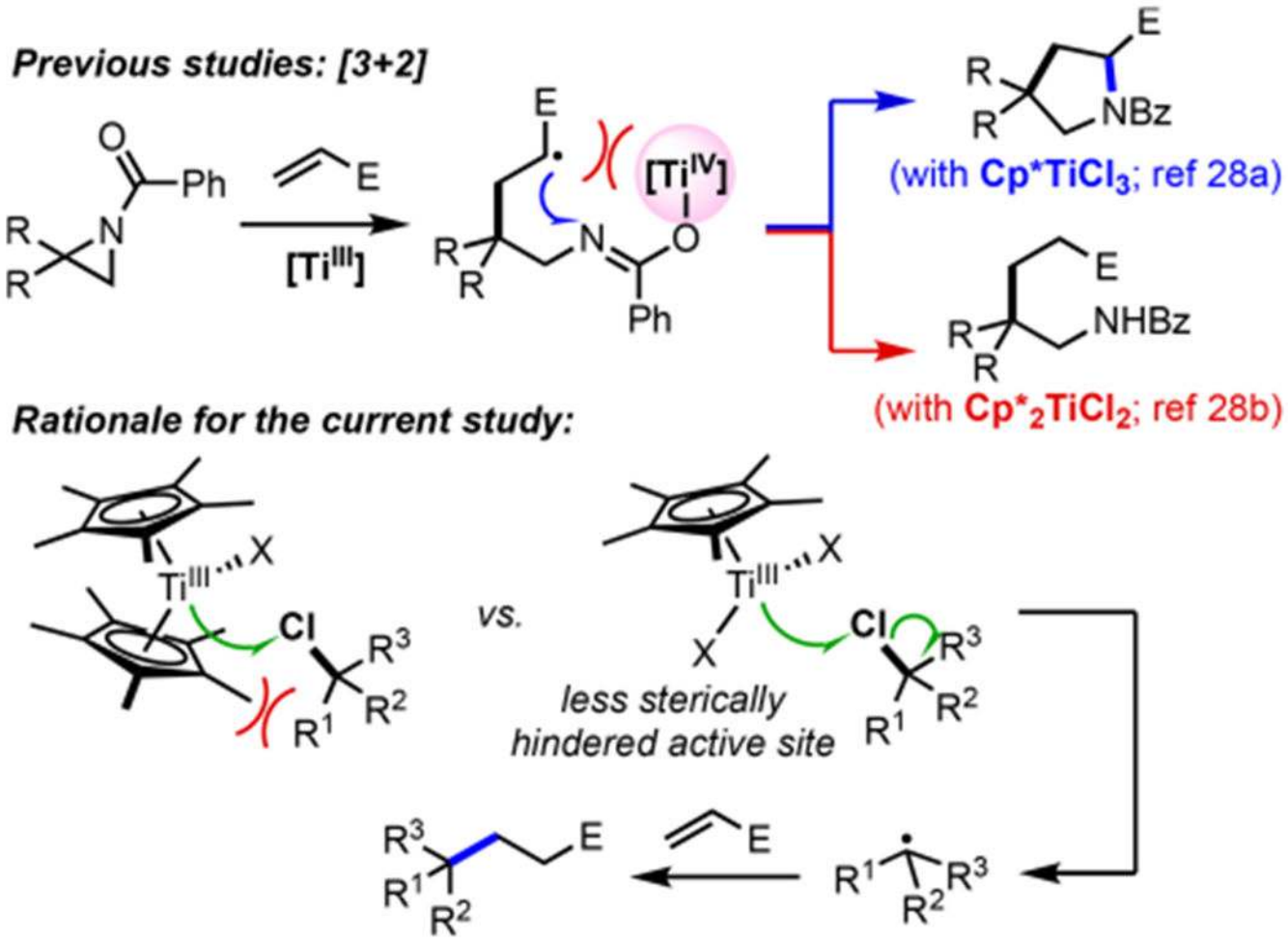



**Figure 2.**

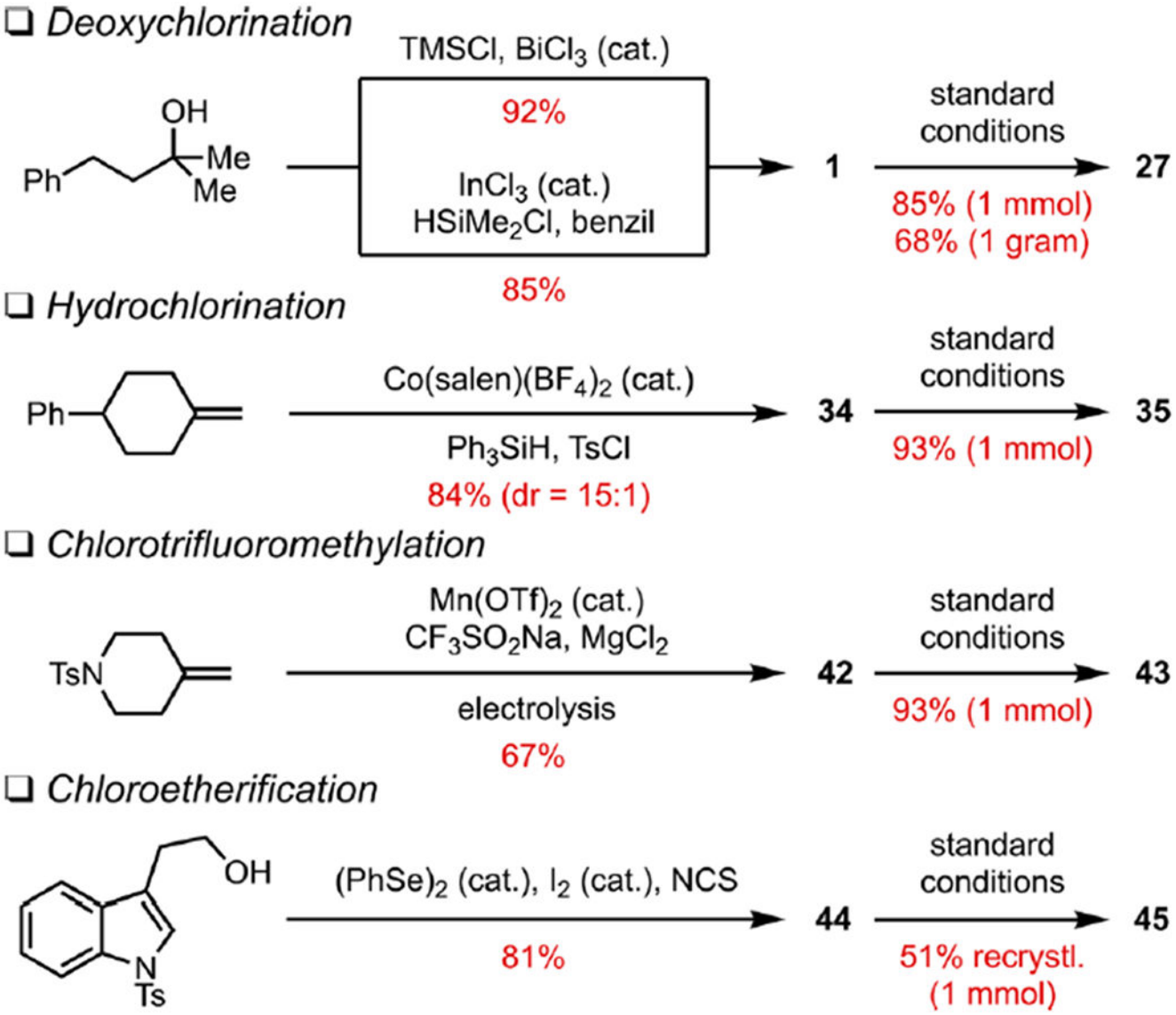
Cyclic voltammetry of $Cp^*TiCl_3$ (2 mM) and $^t$BuCl (2 mM) in DCM (0.2 M $BU_4NPF_6$) with a scan rate of 100 mV/s.




**Scheme 1.**
Ti-Catalyzed Alkylation of Unactivated Alkyl Chlorides: Challenges and Rationale

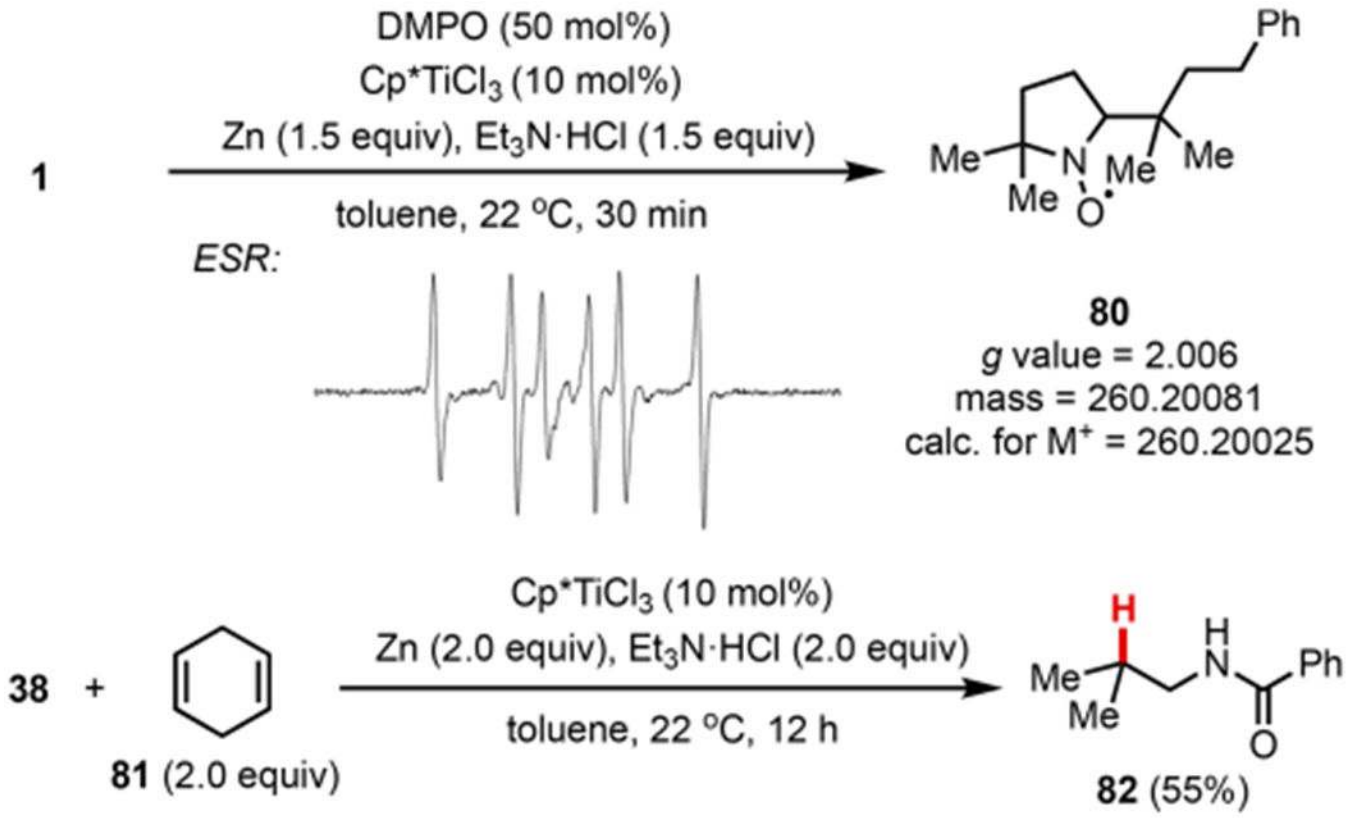



**Scheme 2.**
Rationale for Catalyst Optimization

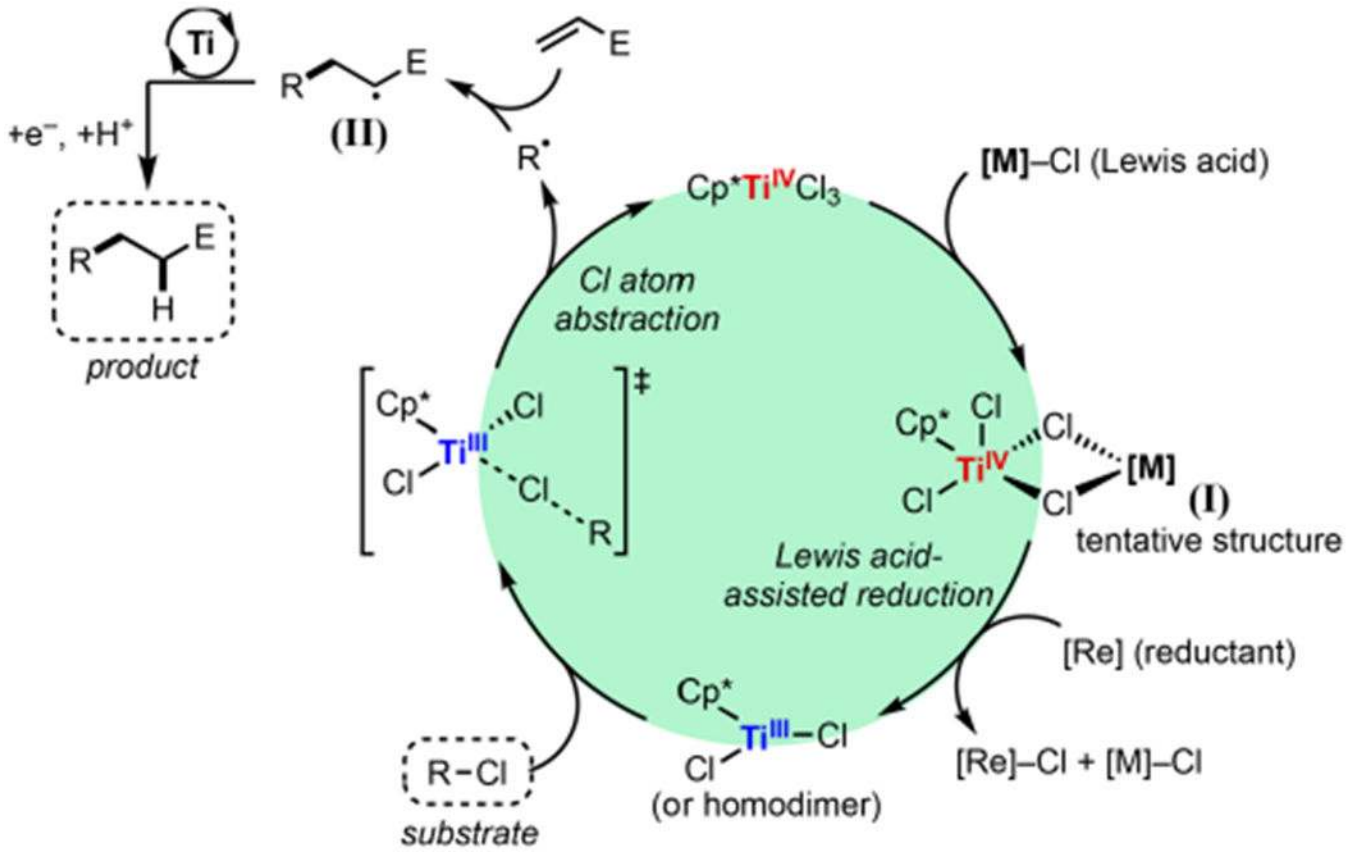



**Scheme 3.**

Synthetic Scale (1 mmol or Greater) Preparation and Ti-Catalyzed Alkylation of Alkyl Chlorides



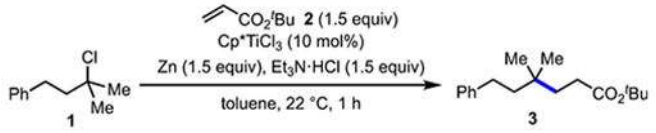

**Scheme 4.**
Spin Trapping Experiments




**Scheme 5.**
Proposed Catalytic Cycle

**Table 1.**

Ti-Catalyzed Alkylation and Control Experiments[a]



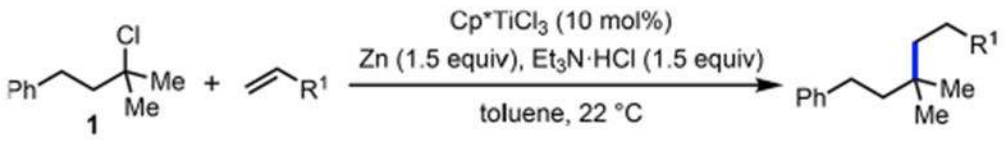

| entry | variation from standard conditions | yield (%) |
|---|---|---|
| 1 | none | 70 |
| 2 | $CpTiCl_3$ instead of $Cp^*TiCl_3$ | 10 |
| 3 | $Cp_2TiCl_2$ instead of $Cp^*TiCl_3$ | 22 |
| 4 | $Cp^*_2TiCl_2$ instead of $Cp^*TiCl_3$ | 21 |
| **5** | **12 h reaction time** | **98** |
| 6[b] | no Ti catalyst | <5 |
| 7[b] | no Zn or $Et_3N{\cdot}HCl$ | <5 |
| 8[b] | Col·HCl instead of $Et_3N{\cdot}HCl$ | 96 |
| 9[b] | Mn instead of Zn | <5 |
| 10[b] | DCM instead of toluene | 65 |
| 11[b] | EtOAc instead of toluene | 97 |
| 12[b] | MeCN or THF instead of toluene | <5 |

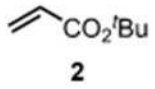
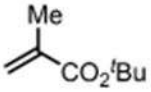
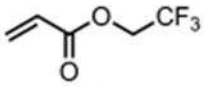
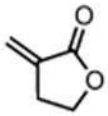
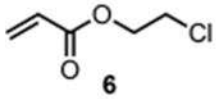
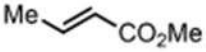
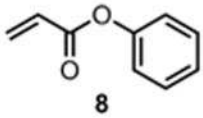
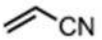
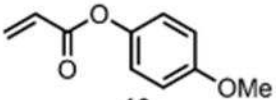
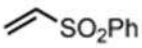
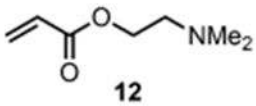
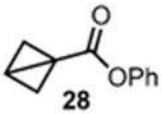
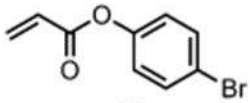
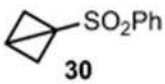
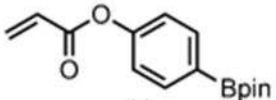
[a]All reactions were conducted on a 0.1 mmol scale with NMR yields reported.

[b]Reaction time: 12 h.

**Table 2.**

Alkene Scope of Ti-Catalyzed Alkylation[a]




| Entry | Alkene | Product | Yield (%) | Entry | Alkene | Product | Yield (%) |
|---|---|---|---|---|---|---|---|
| 1 |  **2** | **3** | 97 | 9 |  **18** | **19** | 98[b] |
| 2 |  **4** | **5** | 95 | 10 |  **20** | **21** | 40[d] |
| 3 |  **6** | **7** | 97[b,c] | 11 |  **22** | **23** | 50 |
| 4 |  **8** | **9** | 63 | 12 |  **24** | **25** | 68[d] |
| 5 |  **10** | **11** | 86 | 13 |  **26** | **27** | 89[d] |
| 6 |  **12** | **13** | 78[d,e] | 14 |  **28** | **29** | 89[b] *dr* = 1.6:1 |
| 7 |  **14** | **15** | 70 | 15 |  **30** | **31** | 46[b,c,g] *dr* = 2:1 |
| 8 |  **16** | **17** | 81(70[f]) | | | | |

[a]All reactions were conducted on a 0.1 mmol scale unless otherwise noted with isolated yields reported.

[b]EtOAc as the solvent.

[c] **40** instead of **1**.

[d] With 2 equiv of Zn, $Et_3N{\cdot}HCl$, and alkene.

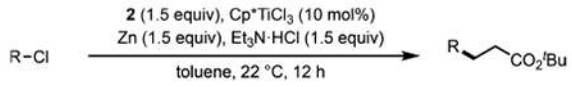
[e] 40 °C.

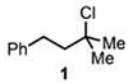
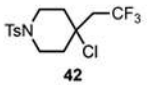
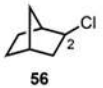
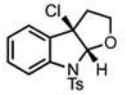
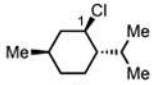
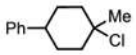
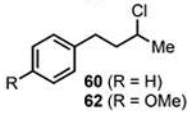
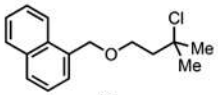
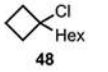
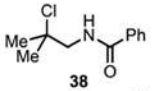
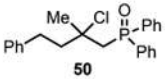
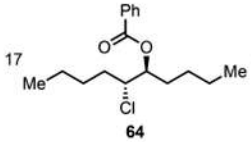
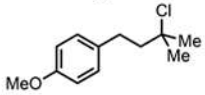
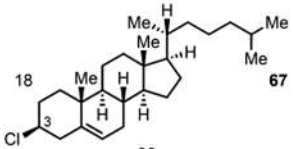
[f] 1.0 mmol scale.

[g] $AlCl_3$ (1 equiv) used as Lewis acid additive.

**Table 3.**

Alkyl Chloride Scope of Ti-Catalyzed Alkylation[a]




| Entry | Alkyl chloride | Product | Yield (%) | Entry | Alkyl chloride | Product | Yield (%) | Entry | Alkyl chloride | Product | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 |  **1** | **3** | 97 | 7 |  **42** | **43** | 74 | 14 |  **56** | **57** | 62[h–k] |
| 2 |  **32** | **33** | 67[b] | 8 |  **44** | **45** | 50[d,e] | 15 |  **58** | **59** | 75[h,i,l,m] *dr* = 1.8:1 |
| 3 |  **34** | **35** | 83 *dr* = 2.6:1[c] | 9 | $^t$Bu–Cl **46** | **47** | 75[f,g] | 16 |  **60** (R = H) **62** (R = OMe) | **61** **63** | 82[n] 73[b] |
| 4 |  **36** | **37** | 77 | 10 |  **48** | **49** | 59[f] | | | | |
| 5 |  **38** | **39** | 91 | 11 |  **50** | **51** | 63 | 17 |  **64** | **65** | 53[o] *dr* = 1.6:1 |
| 6 |  **40** | **41** | 42 | 12 |  **52** | **53** | 42[f–j] | | | | |
| | | | | 13 |  **54** | **55** | 45[j] | 18 |  **66** | **67** | 42[h,i,p] *dr* = 1.9:1 |

[a] All reactions were conducted on 0.1 mmol scale with isolated yields reported.

[b] With 2 equiv of alkene.

[c] In the major product, **2** is added trans to Ph.

[d] With 15 mol % Ti catalyst and 5 equiv of **2**.

[e] Cis-fused bicycle was formed as the observable stereoisomer.

[f] Using alkene **14** instead of **2**.

[g] Using **14** as the limiting agent with 4 equiv of R–Cl.

[h] With 20 mol % Ti catalyst for 72 h.

[i] Using 3 equiv of Zn and $Et_3N{\cdot}HCl$.

[j] Using **14** as the limiting agent with 2 equiv of R–Cl.

[k] Only one stereoisomer was isolated; the stereochemistry at C2 is tentatively assigned as exo using 2D NMR.

[l] Using 4 equiv of **2**.

[m] The configuration of C1 in the major product is *S*.

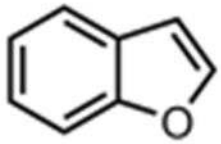
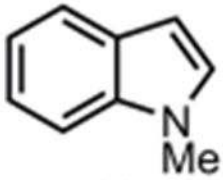
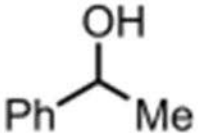
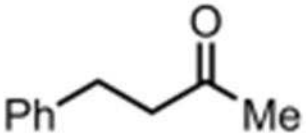
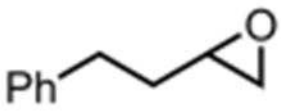
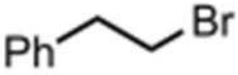
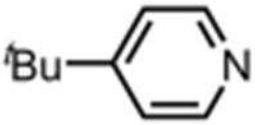
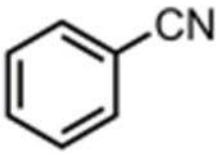
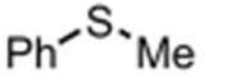
[n] 1 mmol scale with 20 mol % Ti catalyst.

[o] Using 20 mol% Ti catalyst, 3 equiv Zn, $Et_3N{\cdot}HCl$, and **2**; relative stereochemistry of the major product could not be determined.

[p] The configuration of C3 in the major product is S.

**Table 4.**

Additive Effect on the Ti-Catalyzed Alkylation[a,b]

| | | | |
|---|---|---|---|
|  |  |  |  |
| 68 | 69 | 70 | 71 |
| 88% (98%) | >99% (95%) | 22% (83%) | 90% (85%) |
|  |  |  |  |
| 72 | 73 | 74 | 75 |
| 81% (84%) | 16% (69%) | 55% (93%) | <10% (75%) |
|  |  |  |  |
| 76 | 77 | 78 | 79 |
| 96% (88%) | <5% (67%) | 76% (72%) | 90% (84%) |

[a]Yields of product **3** were determined with $^1$H NMR.

[b]Values in parentheses are recovery yields of the additives determined with GC or $^1$H NMR (see SI).

**Table 5.**

Lewis Acid Effect on the Ti-Catalyzed Alkylation[a]

| Lewis acid (1 equiv) | NMR yield (%) of 3 |
|---|---|
| none | <10 |
| $Zn(OTf)_2$ | 70 |
| $AlCl_3$ | 30 |
| $Sc(OTf)_2$ | 46 |

[a]Reaction conditions: see Table 1, entry 9 with a reaction time of 3 h.