Transition-Metal Catalysis

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Dual Ti–Ru Catalysis in the Direct Radical Haloalkylation of *N*-Acyl Oxazolidinones**

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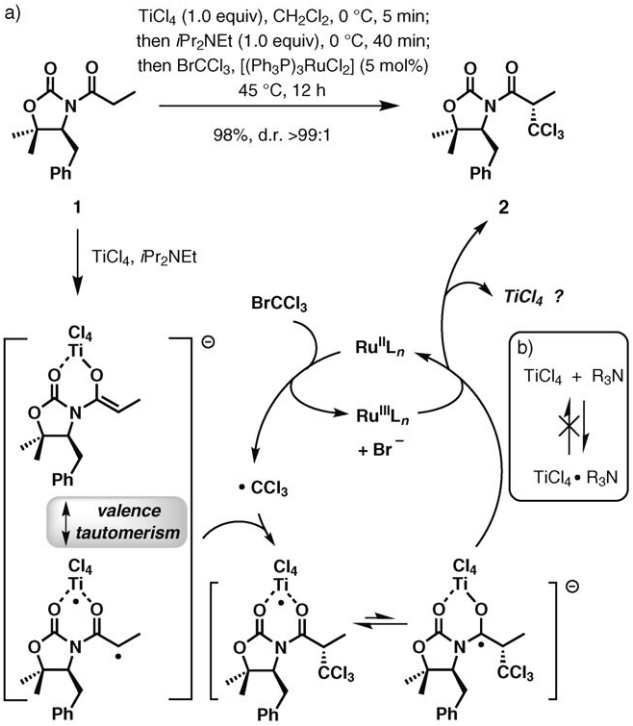
Titanium enolates have found widespread use in organic synthesis as a result of their unique reactivity and ease of preparation from inexpensive and nontoxic titanium reagents under mild conditions that are compatible with a range of functional groups.[1] The most prevalent application of titanium enolates is for stereoselective aldol reactions.[2] Several examples of the alkylation of titanium enolates with strongly electrophilic reagents have also been reported.[3] Recently, we described a different mode of alkylation of titanium enolates in which they serve as efficient radical acceptors for haloalkyl radicals generated by a ruthenium-catalyzed redox process.[4] It has been postulated that the enolate serves as an electroactive ligand for the titanium center,[5] whereby it facilitates the radical addition process and participates in the ruthenium catalytic cycle. The utility of this method in the synthesis of a range of chloroleucine-derived natural products has been illustrated.[4,6] One intriguing aspect of the reaction that emerged during our investigations is the possibility of the catalytic generation and alkylation of the titanium enolate species. Herein, we describe the development of a haloalkylation process that is catalytic in both ruthenium and titanium and thus constitutes the first example of a catalytic enolate alkylation involving titanium enolates.

During an examination of the putative mechanism of the trichloromethylation process outlined in Scheme 1,[4,5] we directed our attention toward the function of titanium tetrachloride. This mechanism suggests that $TiCl_4$ should be regenerated at the completion of the reaction, which creates potential for the development of a catalytic process. According to the seminal studies by Evans et al., initial complexation of the substrate and titanium tetrachloride is prerequisite to the addition of the amine base and the ensuing enolization.[3a] If the order of the reagent addition is reversed, enolization is precluded by the apparently irreversible formation of an unreactive $TiCl_4$–amine adduct. Thus, the potential interception of the regenerated $TiCl_4$ by the amine base would be a major challenge in the catalytic recovery of the reagent.



Scheme 1. Radical trichloromethylation based on valence tautomerism in titanium enolates: a) an initial overview of the mechanism; b) potential sequestering of $TiCl_4$ by the amine.

Preliminary experimentation revealed that indeed the haloalkylation reaction could reach completion with a substoichiometric amount of titanium tetrachloride under the original reaction conditions with diisopropylethylamine (Hünig base). On the other hand, the conversion decreased precipitously when less than 0.3 equivalents of $TiCl_4$ were used (Table 1, entries 1–4). We hypothesized that the decline in conversion at around 0.3–0.4 equivalents of $TiCl_4$ could be attributed to one of the following factors: 1) the possible formation of higher-order titanium enolates with a 2:1 or 3:1 ligand-to-metal ratio, in which case no catalytic turnover of $TiCl_4$ would occur, or 2) inefficient catalytic recovery of the titanium reagent and, possibly, a strong inhibitory effect by the amine.

Although it is well-known that titanium forms hexa- or octacoordinated complexes,[7] higher-order titanium enolates such as those depicted in Scheme 2 have not been documented. We monitored the enolization reaction with the Hünig base (1.1 equiv) and varying amounts of titanium

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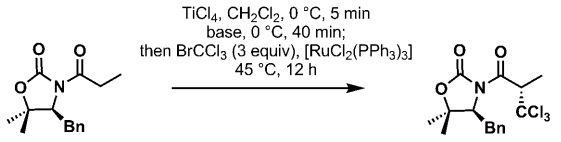
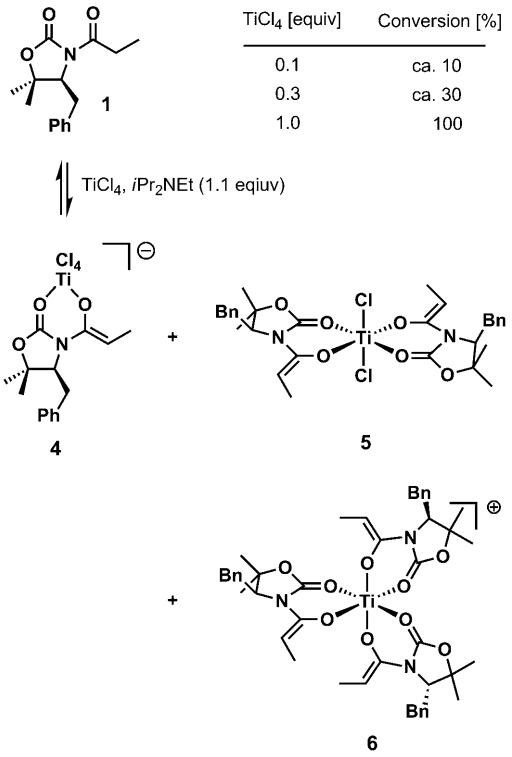
Table 1: Influence of the amine on the course of the catalytic trichloromethylation reaction.



1 2

Entry	$TiCl_4$ [mol%]	Amine (equiv)	Conversion [%][a]
1	40	iPr_2NEt (1.1)	>95
2	30	iPr_2NEt (1.1)	75
3	20	iPr_2NEt (1.1)	50
4	10	iPr_2NEt (1.1)	14
5	30	iPr_2NEt (3.0)	47
6	30	iPr_2NEt (4.5)	28
7	30	Et_3N (1.1)	76
8	30	Et_3N (3.0)	100
9	10	Et_3N (3.0)	75
10[b]	10	Et_3N (3.0)	74
11	10	Et_3N (4.5)	76
12	30	PMP (1.1)	100
13	10	PMP (1.1)	100

[a] Conversion was determined by ^1H NMR spectroscopy of the crude mixture of products. [b] The reaction time was 48 h. PMP = 1,2,2,6,6-pentamethylpiperidine.



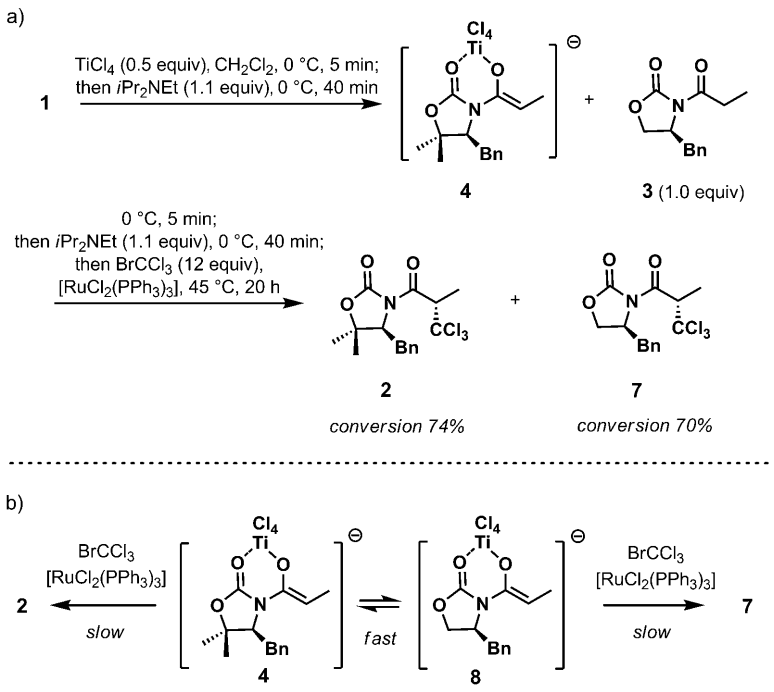
Scheme 2. Hypothetical formation of higher-order enolates during the enolization of **1** with substoichiometric $TiCl_4$. Bn = benzyl.

tetrachloride by NMR spectroscopy and found no conclusive support for the existence of higher-order titanium enolates; however, it was evident that the degree of enolization diminished proportionally with decreasing substoichiometric amounts of $TiCl_4$. Thus, whereas complete enolization was observed with 1.0 equivalent of $TiCl_4$, the conversion was approximately 10% with 0.1 equivalents of $TiCl_4$ and about 30% with 0.3 equivalents of $TiCl_4$. Notably, it could be clearly observed that more than one distinct enolate species was generated, and the relative ratios changed substantially as the amount of the titanium reagent was varied. Although the nature of the additional species is presently unclear,[8] we concluded that full conversion in the trichloromethylation reaction with a substoichiometric amount of $TiCl_4$ could not be rationalized through the implication of higher-order titanium enolates.

The next series of experiments was designed to probe the catalytic recovery of titanium tetrachloride. Specifically, we aimed to establish whether titanium tetrachloride could be efficiently transferred between different *N*-acyl oxazolidinone species once enolization was completed. The cross-over experiment in Scheme 3 was particularly illuminating and revealed a number of notable factors. When the enolization of **1** was complete ($TiCl_4$ (0.5 equiv), Hünig base (1.1 equiv), 0°C, 45 min), the *N*-acyl oxazolidinone **3** (1.0 equiv) was added along with additional Hünig base (1.1 equiv), and, after 40 min at 0°C, the ruthenium-catalyzed radical trichloromethylation was initiated under the standard conditions. With the ultimate loading of titanium tetrachloride at 0.25 equivalents, products **2** and **7** resulting from the trichloromethylation of both substrates were produced in nearly equimolar amounts, which provided conclusive support for a rapid transfer of $TiCl_4$ between different *N*-acyl oxazolidinone species in the presence of diisopropylethylamine. This experiment corroborates the feasibility of the catalytic turnover of $TiCl_4$ and suggests inhibition by the amine as a reason for its poor efficiency. It can be hypothesized that a fast equilibrium is established between titanium enolates **4** and **8** (Scheme 3b). This process is accompanied by a slow radical addition, and the distribution of products **2** and **7** is determined by the Curtin–Hammett principle.

To ascertain the influence of the amine on the efficiency of the catalytic turnover of titanium tetrachloride and to probe further the equilibrium in Scheme 1b, we carried out the trichloromethylation reaction with various amounts of the Hünig base as well as less-hindered triethylamine and more-hindered 1,2,2,6,6-pentamethylpiperidine (PMP; Table 1). An increase in the concentration of the Hünig base consistently resulted in lower conversion (Table 1, entries 5 and 6), which supports the proposed inhibitory effect of the amine.

Remarkably, both less-hindered triethylamine and more-hindered PMP proved to be superior to the Hünig base for the catalytic turnover of $TiCl_4$. Complete conversion was observed with 30 mol% of $TiCl_4$ with 3 equivalents of Et_3N, whereas conversion was 76% with 1.1 equivalents of the amine (Table 1, entries 7 and 8). The same conversion (ca. 75%) was observed with 10 mol% of $TiCl_4$ and Et_3N (3 equiv). Interestingly, no inhibitory effect was observed for triethylamine. With PMP (1.1 equiv), full conversion was observed with either 10 or 30 mol% of $TiCl_4$ (Table 1, entries 12 and 13). As with Et_3N, no inhibition of the trichloromethylation reaction was observed in the presence of excess PMP. Thus, the inhibitory effect appears to be confined to the Hünig base.



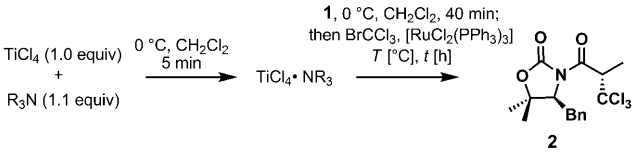
Scheme 3. a) Cross-over experiment; b) product distribution is in accord with the Curtin–Hammett principle.

We compared the original catalyst, $[RuCl_2(PPh_3)_3]$, with a more active catalyst, $[Cp^*RuCl(PPh_3)_2]$,[9] to ascertain whether the rate of trichloromethylation was limited by low catalytic turnover frequency of $TiCl_4$ or other factors associated with the radical process (Scheme 4). When the reaction was carried out at room temperature in the presence of $TiCl_4$ (20 mol%) and PMP (1.1 equiv), a substantial acceleration of the process was observed with $[Cp^*RuCl(PPh_3)_2]$ as the redox catalyst. This observation indicates that radical generation is the rate-limiting step, and both the turnover frequency of $TiCl_4$ and the addition of $\cdot CCl_3$ to the titanium enolate are relatively fast (Scheme 3b).

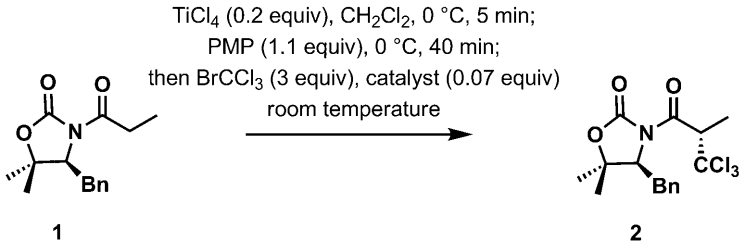
In the next series of experiments, the order of reagent addition during the formation of the titanium enolate was changed to examine the irreversibility of the formation of $TiCl_4$–amine complexes under the trichloromethylation reaction conditions. The seminal studies by Evans et al. emphasized the importance of the initial $TiCl_4$–substrate complexation; no enolate formation was observed if diisopropylethylamine or triethylamine were allowed to react with uncomplexed titanium tetrachloride first.[3a] Therefore, we were surprised to discover substantial conversion in experiments in which $TiCl_4$ and the amine were mixed prior to the addition of the substrate (Table 2). Although the conversion was lower than that observed under the original enolization conditions, these results indicate notable, albeit rather inefficient, reversibility in the formation of $TiCl_4$–amine adducts.

On the basis of the experimental results of this study, we propose the catalytic cycle depicted in Scheme 5 for the dual Ru–Ti catalysis in the direct trichloroalkylation of *N*-acyl oxazolidinones. An initial complexation of $TiCl_4$ and substrate **1**, followed by addition of the amine, produces enolate **4** along with its biradical valence tautomer **4A**.[5,10] A slow, rate-limiting electron transfer from the Ru^{II} catalyst to $BrCCl_3$ generates $\cdot CCl_3$, which adds to the electron-rich

Table 2: Influence of the inverse addition of the amines on conversion.



Entry	Amine	*T* [°C]	*t* [h]	Conversion [%]
1	iPr_2NEt	20	12	41
2	iPr_2NEt	45	12	45
3	iPr_2NEt	50	24	57
4	PMP	20	12	57
5	PMP	45	12	63
6	Et_3N	45	12	35

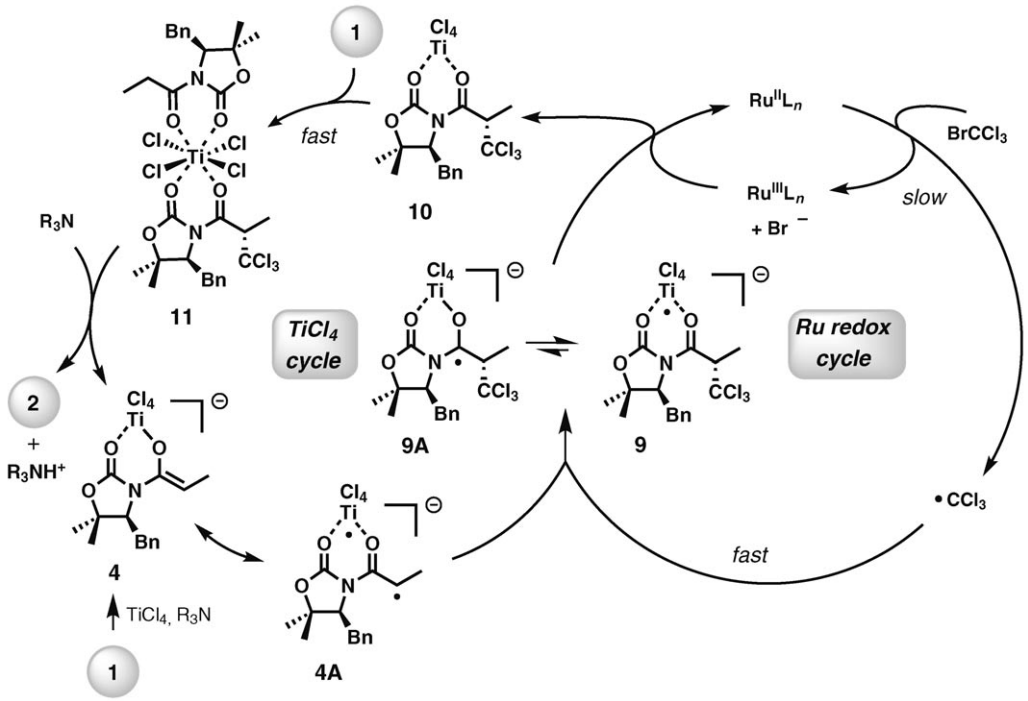


Catalyst	*t* [h]	Conversion [%]
$[RuCl_2(PPh_3)_3]$	48	76
$[Cp^*RuCl(PPh_3)_2]$	3	93

Scheme 4. Comparison between $[RuCl_2(PPh_3)_3]$ and $[Cp^*RuCl(PPh_3)_2]$ as the redox catalyst for radical generation. Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl anion.

titanium enolate to directly afford **9**, rather than the carbon-centered radical **9A**, along with the Ru^{III} counterpart.[11] Intermediate **9**, which is essentially the final product **2** complexed to a Ti^{III} center, regenerates the Ru^{II} catalyst, possibly by another single-electron-transfer event, to give the Ti^{IV} chelate **10**. At this stage, $TiCl_4$ is transferred directly and at a relatively high rate to another molecule of the substrate, potentially via an octacoordinated species, such as **11**. Alternatively, $TiCl_4$ can be intercepted by excess amine, which accounts for the inhibitory effect of the amine. It is highly unlikely that uncoordinated $TiCl_4$ is present at any time during the course of the reaction.[12]

In summary, a direct radical trichloromethylation reaction that is catalytic in both the titanium



Scheme 5. Proposed mechanism for Ti–Ru catalysis in the radical haloalkylation of titanium enolates.

and ruthenium reagents has been developed as a result of a deeper mechanistic investigation of the process. This reaction constitutes the first alkylation of titanium enolates that is catalytic in titanium and provides a foundation for expanding the scope of catalytic radical alkylation reactions of titanium enolates. Important findings include: 1) the discovery that the complexation of trialkyl amines to $TiCl_4$ appears to be reversible, especially at elevated temperatures, although the decomplexation is of limited efficiency; and 2) the observation that the turnover frequency for the catalytic transfer of $TiCl_4$ is relatively high in comparison with the rate of radical generation, even with the more reactive ruthenium catalyst $[Cp^*RuCl(PPh_3)_2]$.

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