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Dichloromethane Activation. Direct Methylenation of Ketones and Aldehydes with CH_2Cl_2 Promoted by $Mg/TiCl_4/THF$

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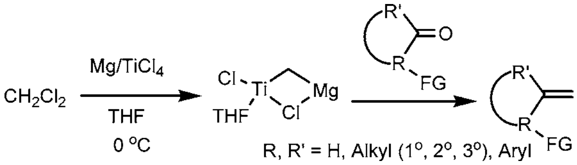
ABSTRACT



This Mg–$TiCl_4$-promoted CH_2-transfer reaction of CH_2Cl_2 represents an extremely simple, practical, and efficient methylenation of a variety of ketones and aldehydes, especially in enolizable or sterically hindered ketones such as 2,2-dimethylcyclohexanone, camphor, and fenchone.

The interest in the methylenation of carbonyl compounds, which developed strongly after the discovery of the Wittig reagents, continues to generate many exciting diverse methylenation reagents. Among such reagents, titanium methylene complexes (Tebbe-type reagents) such as Tebbe's reagent,[1a] Grubbs' titanacyclobutane,[1b] CH_2I_2− or CH_2Br_2−$TiCl_4$−zinc (cat. lead) reagent,[2] and dimethyltitanocene[3] have proven to be extraordinarily useful. To our knowledge, no metal-induced methylenations, wherein CH_2Cl_2 (DCM) serves as a CH_2 partner, have been recorded. The significant limitation on the broad utility of CH_2Cl_2 often arises from its extreme stability, and this makes it a very common solvent in organic reactions. Effecting the insertion into the unactivated C−Cl bond may require highly reactive bimetallic species. In this paper, we wish to record the critical role electron-pair-donor additives play in determining the efficiency of Mg−$TiCl_4$ in C−Cl bond activation and the first examples of the equivalent of a CH_2 transfer reaction of CH_2Cl_2 mediated by Mg−$TiCl_4$. Considering DCM's inertness in either Mg(Hg),[4] Li,[5] or low-valent titanium-promoted addition reactions, such an observation opens up fundamental questions of the importance of bimetallic complexes (intermetallics) like [TiMgClx] for olefination of carbonyl compounds.

The methylenation of adamantanone **1a** with CH_2Cl_2 was chosen to test the feasibility of the process. When **1a** and CH_2Cl_2 are treated with magnesium powder (4 equiv) and $TiCl_4$ (1 equiv) at room temperature or reflux, nothing happens. Remarkably, simply adding THF (2 mL) to the original system at 0 °C led to methylenation to give methyleneadamantane **2a** in 56% yield with starting material remaining (Table 1, entry 1). Increasing the amount of $TiCl_4$

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[3] Petasis, N. A.; Bzoweej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.

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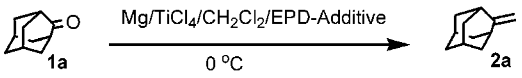
10.1021/ol0478887 CCC: $27.50

Table 1. Effect of Various EPD Additives on the Methylenation of Adamantanone 1a

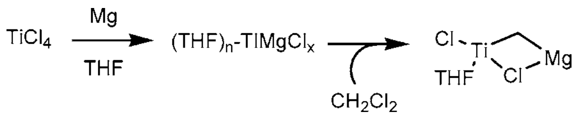


run	EPD additive	method[a] TiCl$_4$/Mg	conv (%)	yield[b] (%) 2a	yield[b] (%) 2-adamantanol
1	THF	A (1:4)	69	56	~6
		A (2:8)	100	86	~6
		B (2:8)	95	76	12
2	DME	A (2:8)	100	54	28
		B (2:8)	95	41	32
3	pyridine	A (2:8)	58	22	28
		B (2:8)	55	12	0
4	Et$_2$O	A or B (2:8)	0−38	0−30	
5	NEt$_3$, CH$_3$CN, 1,4-dioxane, furan, TMEDA	A or B (2:8)	0	-	

[a] Method A: To a solution of 2 mmol of TiCl$_4$ and 8 mmol of magnesium powder in 2 mL of CH$_2$Cl$_2$ at 0 °C was added a solution of admantanone (1 mmol) in 3−4 mL of CH$_2$Cl$_2$ and 2 mL of EPD additive. Method B: A solution of EPD additive (2 mL), CH$_2$Cl$_2$ (2 mL), TiCl$_4$ (2 mmol), and Mg (8 mmol) was stirred at 0 °C for 20 min prior to the addition of carbonyl compound. [b] Isolated yield.

and Mg led to complete consumption of starting material within 1 h. Thus, addition of a THF−CH$_2$Cl$_2$ solution of **2a** (1 equiv) to a mixture of TiCl$_4$ (2 equiv) and magnesium powder (8 equiv) in CH$_2$Cl$_2$ at 0 °C gave the desired methyleneadamantane **2a** (86% isolated yield, method A) in addition to a trace of the reduction product readily identified as adamantanol by its spectroscopic properties. On the other hand, stirring the THF−CH$_2$Cl$_2$ solution of TiCl$_4$−Mg at 0 °C for 20 min (method B) prior to the addition of adamantanone gave a slightly diminished yield of 76%. Other electron-pair-donor (EPD) additives including DME and pyridine gave unsatisfactory results (entries 2−3). Switching the additive to ether, NEt$_3$, acetonitrile, 1,4-dioxane, furan, or TMEDA also proved undesirable (entries 4 and 5). THF appears to be a good choice as an additive to effect methylenation of CH$_2$Cl$_2$ to the carbonyl group of **1a**. The complexation of TiCl$_4$ with THF molecules through heteroatoms seems to assist in the initial metals insertion reactions. The reaction is best envisioned as involving interception of a presumed (THF)$_n$−TiCl$_4$ complex by the magnesium powder to give active bimetallic[Ti−Mg−Clx-(THF)$_n$][6] complex followed by methylene coordinated to both the titanium and magnesium to generate a presumed [Ti−CH$_2$−Mg−Clx−(THF)$_n$] complex (Scheme 1).[7−10]

Scheme 1. CH$_2$Cl$_2$ Activation Promoted by MgTi−Bimetallic Complexes



Having established the feasibility of the methylenation, its generality with respect to the structure of the ketones was established. Reaction of *tert*-butylcyclohexanone **1b** with CH$_2$Cl$_2$ using method A gave a 81% yield of the methylenation product **2b** (Table 2, entry 1). The aromatic ketone **1c** also gave satisfactory results with CH$_2$Cl$_2$−Mg−TiCl$_4$ complex. Thus, using a 4:8 TiCl$_4$−Mg ratio, a 70% yield of **2c** was obtained (entry 2). Due to the nonbasic conditions, enolizable ketones also proved to be a satisfactory trap. Thus, either 2-indanone or β-tetralone reacted effeciently with CH$_2$Cl$_2$-derived methylenation reagent to give the desired methylenation products **2d** (84%) and **2e** (79%), respectively (entries 3 and 4).[11] To further demonstrate the scope of this methylene-forming methodology, the utility of this protocol was examined in the methylenation of sterically demanding ketones. Thus, reacting 2,6-dimethylcyclohexanone **1f** with CH$_2$Cl$_2$−Mg−TiCl$_4$ complex using method A produced the methylenecyclohexane **2f** in 85% isolated yield (Table 2, entry 5). Interestingly, using method B led to a slightly increased yield of 87%. A dramatic illustration is the comparison between Tebbe−Grubbs reagents and CH$_2$Cl$_2$−Mg−TiCl$_4$ complex wherein the former fails to effect methylenation of 2,2-dimethylcyclohexanone**1g**[12] but the latter gives 2,2-dimethylmethylenecyclohexane **2g** in 83% isolated yield. Surprisingly, increasing the degree of steric hindrance at the carbonyl group does not impede methylenation. Thus, methylenation with camphor under the standard conditions with CH$_2$Cl$_2$−Mg−TiCl$_4$ gave a 61% yield of **2h** (entry 7). Notably, performing the same reaction using method B but increasing the amount of TiCl$_4$ increased the yield to 74%. This methylenation reagent is also suitable for the methylenation of a variety of camphor derivatives bearing the carboxylic functional groups, which often interferes with methylenation of ketones (vide infra). More dramatically, in contrast to Tebbe-Grubbs reagents,[12] the CH$_2$Cl$_2$−Mg−TiCl$_4$ complex reacted efficiently even with the extremely hindered fenchone, containing a carbonyl group adjacent to two quaternary carbon atoms, to give the desired alkene **2i** in a remarkable 90% yield (Table 2, entry 8). Considering that the previous methylenation of unreactive fenchone, which is unaffected by methylenetriphenylphosphorane itself at temperatures up to 50 °C, involves activation of methylenetriphenylphosphorane by reaction with *tert*-butyllithium,[13] this convenient procedure represents an attractive alternative.

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(7) To explore what role, if any, the low-valent titanium reagents played in facilitating methylenation reagent formation, we have examined a variety of low-valent titanium compounds such as TiCl$_3$, Ti (II) species,[8] Ti(I) species,[9] and Ti(0).[9a,10] However, these reagents do not effect coupling with CH$_2$Cl$_2$ in the presence of THF.

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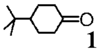
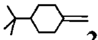
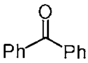
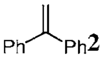
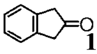
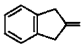
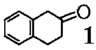
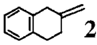
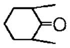
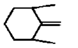
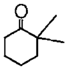
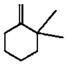
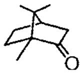
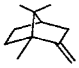
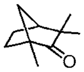
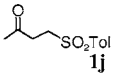
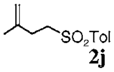
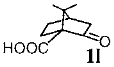
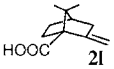
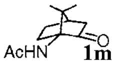
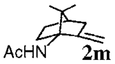
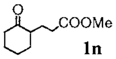
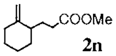
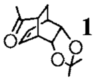
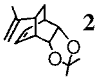
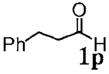
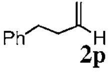
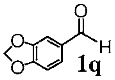
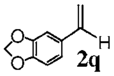
(10) McMurry, J. E.; Fleming, M. P. *J. Org. Chem.* **1976**, *41*, 896.

(11) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281.

(12) Clawson, L.; Buchwald, S. L.; Grubbs, R. H. *Tetrahedron Lett.* **1984**, *25*, 5733.

(13) Corey, E. J.; Kang, J.; Kyler, K. *Tetrahedron Lett.* **1985**, *26*, 555.

Table 2. Methylenation via Activation of CH_2Cl_2

Entry	Substrate	Method $TiCl_4$/Mg (equiv)	THF (mL)	Product	yield (%)[a]
1	 **1b**	A 2/8	2.0	 **2b**	81[b]
2	 **1c**	A 4/8	1.5	 **2c**	70[c]
3	 **1d**	A 2/8	3.0	 **2d**	84[c]
4	 **1e**	A 2/8	3.0	 **2e**	79[c]
5	 **1f**	A 2/8	2.0	 **2f**	85[c]
		B 2/8	2.0		87[c]
6	 **1g**	A 2/8	1.0	 **2g**	83[c]
7	 **1h**	A 2/8	2.0	 **2h**	61[d]
		B 3/8	1.0		74[c]
8	 **1i**	A 2/8	1.0	 **2i**	90
9	 **1j**	A 2/8	2.0	 **2j**	82
10	 **1k**	A 2/8	1.0	 **2k**	88[c]
11	 **1l**	A 2/8	1.0	 **2l**	85[c]
12	 **1m**	A 4/10	2.0	 **2m**	81[c]
13	 **1n**	A 1/4	1.0	 **2n**	84
14	 **1o**	A 1/4	1.0	 **2o**	95
15	 **1p**	A 4/8	2.0	 **2p**	64[e]
16	 **1q**	A 5/10	2.0	 **2q**	75[d]

[a] Isolated yield. [b] Plus 8% dimerization product derived from ketone. [c] Plus <5% reduction product derived from ketone. [d] Plus ~8% reduction product derived from ketone. [e] Reduction product (8%) and 4-phenyl-2-butanol (22%) were produced as byproducts.

The chemoselectivity was explored with sulfonyl ketone (entry 9) and a series of keto carboxylates (entries 9−13) as summarized in Table 2. As expected, esters, amides, acids, and sulfonyl group were completely unaffected. The latter is particularly noteworthy since rapid reduction of sulfones to sulfides at low temperatures had been noted with titanium-(II) reagent previously.[14] The broad scope of this methylenation is illustrated by the tolerance of ketal (entry 14). Aldehydes, which are particularly prone to reduction to give alcohols, can also lead to good chemoselectivity by changing the amount of Mg−$TiCl_4$. Thus, in the reaction of hydrocinnamaldehyde with CH_2Cl_2 using 4 equiv of $TiCl_4$ and 8 equiv of Mg, alcohol formation was suppressed and a 8:1 ratio of methylenation vs reduction products was isolated in 71% yield (entry 15). For the methylenation of piperonal, use of 5 equiv of $TiCl_4$ and 10 equiv of Mg proves most satisfactory, giving an 83% yield of a 10:1 ratio of methylenedioxystyrene to piperonol (entry 16). In each aldehyde−methylenation, about 5% of the minor pinacol coupling product formed under these conditions.

The ability to elaborate CH_2Cl_2 into an unusual titanium methylene complex via Mg−Ti bimetallic complex (intermetallic) promoted oxidative addition of the unactivated C−Cl bond should prove to be a particularly valuable strategy. This Mg−$TiCl_4$-promoted CH_2-transfer reaction of CH_2Cl_2 represents an extremely simple, practical, and efficient methylenation of a variety of ketones and aldehydes, especially in the case of enolizable or sterically hindered ketones. These observations suggest that there may be a wealth of intermetallic species-promoted reactions of CH_2Cl_2 yet to unfold and that the THF−$TiCl_4$ complex appears to be just tight enough to accelerate reaction with Mg leading to highly active $[TiMgCl_x(THF)_n]$ intermetallic species.[15] While further mechanistic work is clearly required, the efficiency of this chemistry opens an opportunity of utilizing this strategy for other members of this class such as dichlorides and trichlorides.

Acknowledgment. We thank the National Science Council of the Republic of China for generous support.

Supporting Information Available: Experimental procedures and spectra data for **2d**−**e**,**g**,**i**−**o**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Akgun, E.; Mahmood, K.; Mathis, C. A. *J. Chem. Soc., Chem. Commun.* **1994**, 761.

(15) For $[Ti(MgCl)_2(THF)_n]$-catalyzed cleavage of ethers, see: (a) Bartmann, E. *J. Organomet, Chem.* **1985**, *284*, 149. (b) Kadam, S. M.; Nayak, S. K.; Banerji, A. *Tetrahedron Lett.* **1992**, *33*, 5129.