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Bromoform Activation. $TiCl_4$–Mg-Promoted $CHBr_2^-$ and CBr_3^- Transfer to a Variety of Aldehydes and Ketones

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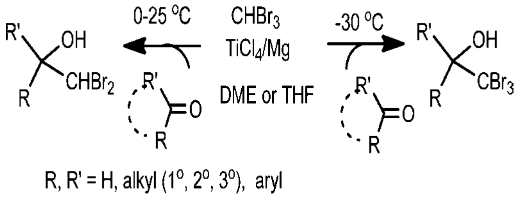
ABSTRACT



$TiCl_4$–Mg can mediate addition of $CHBr_3$ to a variety of aldehydes and ketones to form dibromomethyl carbinols and also be used to effect CBr_3 transfer to carbonyl groups to form tribromomethyl carbinols. The successful application of $TiCl_4$–Mg-promoted coupling of $CHBr_3$ with various carbonyl compounds, especially in the case of highly enolizable ketones such as 2-indanone and *β*-tetralone, highlights the extraordinary reactivity and selectivity and the weakly basic nature of this system.

Polyhalomethyl carbinols are valuable building blocks for further structural elaboration as well as interesting substances in their own right. While the carbonyl addition of polyhalomethyl anions generated in situ from a combination of polyhalomethane with strong bases such as *n*-BuLi or lithium dicyclohexylamide at −78 °C and KOH at 0 °C constitutes one of the fundamental approaches for synthesis of polyhalomethyl carbinols,[1] this process does not generally extend to highly enolizable ketones and aldehydes bearing α-protons, since complex mixtures result from extensive aldol side reactions.[1b] The other main approaches to the synthesis of polyhalomethyl carbinols, which avoid the use of strong base, involve an improvement in polyhalomethyl anion generation, which is derived from either the desilylation of polyhalomethylsilanes[2] mediated by fluoride ion or the decarboxylation of sodium trihaloacetate promoted by trihaloacetatic acid.[3] However, these two mild and efficient approaches to polyhalomethyl carbinols do not generally extend to ketones. The significant limitation on the general utility of polyhalocarbanion species arises from their low chemoselectivity and high thermolability. Compared with the polyhalomethyllithium and sodium reagents, the higher thermostability and selectivity of polyhalomethyltitanium compounds make their easy availability by synthesis important.[4] By far, either dihalomethyl- or trihalomethyltitanium compounds have been generated by adding the titanium derivatives to the extremely thermolabile polyhalomethyllithium compounds at very low temperatures (≤−70 °C).[4] Can the dibromomethyltitanium and tribromomethyltitanium reagents be generated directly via oxidative addition of the C−Br bond to $TiCl_4$–Mg bimetallics? Earlier work in our laboratories established the feasibility of CH_nX_m–$TiCl_4$–Mg system as highly nucleophilic methylene and halomethylene carbenoids to effect carbonyl-olefination.[5] In searching for new strategies based upon the concept of simple oxidative

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(1) (a) Taguchi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 3010. (b) Wyvratt, J. M.; ZHazen, G. G.; Weinstock, L. M. *J. Org. Chem.* **1987**, *52*, 944.

(2) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1985**, *107*, 4085.

(3) (a) Corey, E. J.; Link, J. O.; Shao, Y. *Tetrahedron Lett.* **1992**, *33*, 3435. (b) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906.

(4) Kauffmann, T.; Fobker, R.; Wensing, M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 943.

(5) (a) Yan, T.-H.; Tsai, C.-C.; Chien, C.-T.; Cho, C.-C.; Huang, P.-C. *Org. Lett.* **2004**, *6*, 4961. (b) Yan, T.-H.; Chien, C.-T.; Tsai, C.-C.; Lin, K.-W.; Wu, Y.-H. *Org. Lett.* **2004**, *6*, 4965. (c) Lin, K.-W.; Yan, S.; Hsieh, I.-L.; Yan, T.-H. *Org. Lett.* **2006**, *8*, 2265. (d) Tsai, C.-C.; Hsieh, I.-L.; Cheng, T.-T.; Tsai, P.-K.; Lin, K.-W.; Yan, T.-H. *Org. Lett.* **2006**, *8*, 2261. (e) Lin, K.-W.; Tsai, C.-H.; Hsieh, I.-L.; Yan, T.-H. *Org. Lett.* **2008**, *10*, 1927. (f) Bhorge, Y. R.; Chang, C.-T.; Chang, S.-H.; Yan, T.-H. *Eur, J. Org. Chem.* **2012**, 4805. (g) Bhorge, Y. R.; Chang, S.-H.; Chang, C.-T.; Yan, T.-H. *Tetrahedron* **2012**, *68*, 4846.

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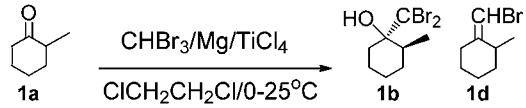
addition, we turned our attention to the concept of a polyhalomethyltitanium synthesis based upon a titanium–magnesium bimetallic-mediated oxidative addition of the halides. Effecting such elaborations by use of $TiCl_4$–Mg may have the advantages of (1) extending the addition to various carbonyl compounds such as aldehydes and enolizable ketones and (2) enhancing synthetic efficiency by elaboration of bromoform to both dibromomethyl- and tribromomethyltitanium reagents. Herein we record protocols whereby the $TiCl_4$–Mg-promoted direct coupling of bromoform with carbonyl compounds can be directed not only to dibromomethyl carbinols, which served as the precursors of terminal alkynes[6a] and acetylenic alcohols[6b,c] as well as important intermediates for ketone homologation and ring expansion,[7] but also to tribromomethylcarbinols, which are important building blocks for synthesis of conjugated ketones[8a] and α- and β-bromoenol ethers.[8b]

Initial studies centered on the $TiCl_4$–Mg-promoted $CHBr_2$-transfer reactions. The direct coupling of 2-methylcyclohexanone **1a** with $CHBr_3$ promoted by $TiCl_4$–Mg was chosen to test the feasibility of the process (Table 1). When **1a** (1.0 mmol) and $CHBr_3$ (0.3 mL, 3.3 equiv) are treated with $TiCl_4$ (1 equiv) and magnesium powder (5 equiv) in $ClCH_2CH_2Cl$–DME (1 mL) at 0–25 °C, 1-(dibromomethyl)-2-methylcyclohexanol **1b** was indeed produced but only in less than 30% conversions after 3 h (entry 1). The desired dibromomethylcarbinol **1b** was found to be admixed with a trace of vinyl bromide **1d**. Increasing the amount of Mg dramatically improved the dibromomethylcarbinol formation, with the yield varying from 35% to 50% (entries 2 and 3). Most revealing was the effect of the electron-pair-donor (EPD) additives on this process. Replacing DME with THF proves most satisfactory, giving an 85% yield of adduct **1b** (entry 4). A NOE difference experiment indicates a diequatorial orientation of dibromomethyl and methyl substituents in **1b**, substantiating a highly stereocontrolled $HCBr_2$ transfer. More gratifyingly, the reaction directly scales up; thus, dibromomethylcarbinol **1b** was obtained in 75% yield on a 10-mmol scale using 6 mmol of $TiCl_4$ and 55 mmol of Mg. It seemed reasonable to expect that the direct coupling of C–Br bond with a presumed $TiCl_4$–Mg complex accounts for the generation of an active diibromomethyltitanium species and the formation of 1-(dibromomethyl)-2-methylcyclohexanol **1b**. Notably, addition to a substituted cyclohexanone **1a** takes place with complete stereoselectivity. Assuming that steric hindrance to attack is controlling, the stereochemistry possessing the methyl group *trans* to the CBr_3 unit is assigned. Having established the feasibility of the $HCBr_2$-transfer reaction, its generality with respect to the structure of the ketone was established. Reaction of cyclopentanone and cycloheptanone with $CHBr_3$ under the standard conditions gave the desired adducts **2b** (85%) and **3b** (82%), respectively (Table 2, entries 1 and 2). Changing the ketone to acyclic ketones **4a** and **5a** led to equally gratifying results (entries 3 and 4) with formation of dibromomethyl alcohols **4b** and **5b**. The $CHBr_2$ transfer onto the unsaturated ketone **6a** was equally effective by replacing THF with DME (entry 5). The aromatic ketones **7a** and **8a** also gave satisfactory results with $CHBr_3$–Mg–$TiCl_4$–THF (entries 6 and 7). On the other hand, using the readily enolizable ketones[9] also gave satisfactory results. Thus, either 2-indanone **9a** or β-tetralone **10a** reacted efficiently with $CHBr_3$-derived dibromomethyltitanium reagent to give the desired coupling products **9b** (71%) and **10b** (62%), respectively (entries 8 and 9). The successful application of $TiCl_4$–Mg-promoted $CHBr_2$ transfer to the readily enolizable 2-indanone and β-tetralone highlights the weakly basic nature of this system. More gratifyingly, increasing the degree of steric hindrance at the carbonyl group does not impede coupling reaction. Thus, reacting 2,6-dimethylcyclohexanone **11a** and camphor-derived ketoester **12a** with $CHBr_3$–Mg–$TiCl_4$–THF produced the adducts **11b** and **12b**, respectively (entries 10 and 11). Notably, the ester group was completely unaffected. Aldehydes, which are particularly prone to reduction to give alcohols, can also lead to equally gratifying results by replacing THF with DME. Thus, in the reaction of aliphatic aldehydes (1 mmol) with $CHBr_3$, use of 1 mmol of $TiCl_4$, 10 mmol of Mg, and 1 mL of DME also led to smooth coupling, giving the desired adduct in 73–75% yield (entries 12 and 13). The unsaturated aldehyde gave an analogous result (entry 14). Exposing the aromatic aldehydes to the $CHBr_3$–$TiCl_4$–Mg–DME system also gave

Table 1. Reaction Conditions for the $TiCl_4$–Mg-Promoted $CHBr_2$ Transfer to Ketone **1a**



entry	$TiCl_4$/Mg (equiv)	EPD additive	yield[a] (%) **1b**
1	1:5	DME	$22^{b,c}$
2	1:8	DME	$35^{b,c}$
3	1:10	DME	$50^{b,c}$
4	1:10	THF	$87^{b,c}$
5	$6{:}55^{d}$	THF	$75^{b,c}$

[a] Isolated yield. [b] Plus ~50% recovered starting ketone. [c] Plus 5–7% vinyl bromide **1d**. [d] The reaction was performed on a 10 mmol scale.

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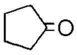
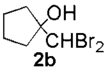
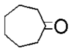
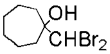
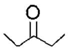
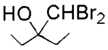
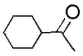
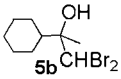
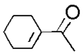
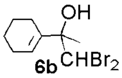
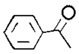
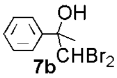
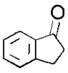
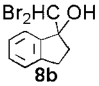
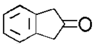
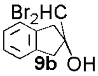
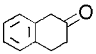
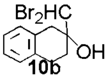
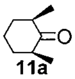
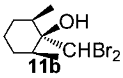
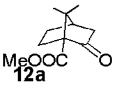
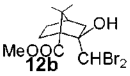
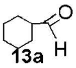
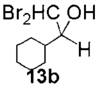
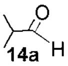
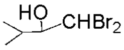
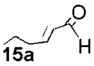
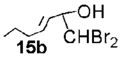
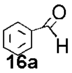
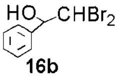
(6) (a) Wang, Z.; Yin, J.; Campagna, S.; Pesti, J. A.; Fortunak, J. M. *J. Org. Chem.* **1999**, *64*, 6918. (b) Smith, A. B., III; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925. (c) Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429.

(7) Ward, H. D.; Teager, D. S.; Murray, R. K., Jr. *J. Org. Chem.* **1992**, *57*, 1926.

(8) (a) Falck, J. R.; He, A.; Reddy, L. M.; Kundu, A.; Barma, D. K.; Bandtopadhyay, A.; Kamila, S.; Akella, R.; Bejot, R.; Mioskowski, C. *Org. Lett.* **2006**, *8*, 4645. (b) Bejot, R.; Tisserand, S.; Reddy, L. M.; Barma, D. K.; Baati, R.; Falck, J. R.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 2008.

(9) (a) Johnson, C. R.; Tait, B. D. *J. Org. Chem.* **1987**, *52*, 281. (b) Acetoacetic ester fails to react with $CHBr_3$-derived dibromomethyltitanium reagent to give the desired coupling product. (c) This $TiCl_4$–Mg–$CHBr_3$ is also suitable for the $CHBr_2$ transfer to 2-chlorocyclohexanone; see the Supporting Information.

Table 2. $CHBr_3-TiCl_4-Mg$-Mediated $CHBr_2$-Transfer to Various Ketone and Aldehyde Carbonyl Groups at 0−25 °C

entry	carbonyl compound	$TiCl_4/Mg$ (equiv)	coupling adduct	yield[a] %
1	 **2a**	1:10	 **2b**	85[b]
2	 **3a**	1:10	 **3b**	82[b]
3	 **4a**	1:10	 **4b**	77[b]
4	 **5a**	1:10	 **5b**	85[b]
5	 **6a**	1:10[b]	 **6b**	85
6	 **7a**	1:10	 **7b**	82
7	 **8a**	1:10	 **8b**	61
8	 **9a**	1:10	 **9b**	71
9	 **10a**	1:10	 **10b**	62
10	 **11a**	1:10	 **11b**	70
11	 **12a**	1:10	 **12b**	45
12	 **13a**	1:10[c]	 **13b**	75[b]
13	 **14a**	1:10[c]	 **14b**	73[b]
14	 **15a**	1:10[c]	 **15b**	66
15	 **16a**	1:10[c]	 **16b**	80[b]

[a] Isolated yield. [b] Plus 5−7% bromomethylenation product. [c] Reaction was performed by replacing THF with DME. [c] Assuming steric hindrance to attack is controlling.

Scheme 1. Selectivity in $CHBr_3-TiCl_4-Mg$-Mediated $CHBr_2$-Transfer Reaction

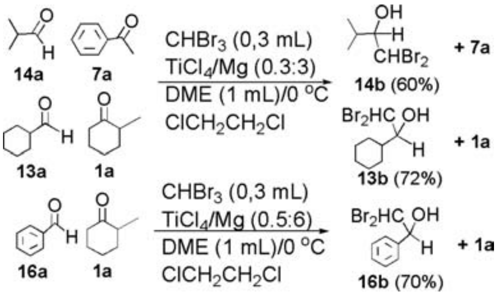
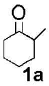
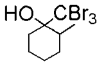
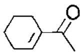
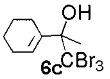
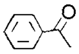
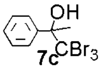
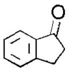
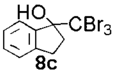
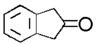
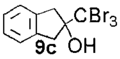
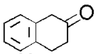
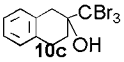
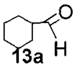
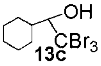
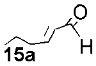
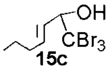
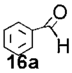
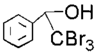
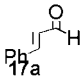
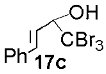
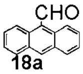
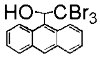
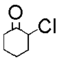
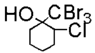


Table 3. $CHBr_3-TiCl_4-Mg-THF$-Mediated CBr_3-Transfer to Various Ketone and Aldehyde Carbonyl Groups at −30 °C

entry	carbonyl compound	$TiCl_4/Mg$ (equiv)	coupling adduct	yield[a] %
1	 **1a**	0.5:6 5:60[b]	 **1c**	89 83
2	 **6a**	0.5:6	 **6c**	86
3	 **7a**	0.5:6	 **7c**	89
4	 **8a**	0.5:6	 **8c**	86
5	 **9a**	0.5:6	 **9c**	87
6	 **10a**	0.5:6	 **10c**	85
7	 **13a**	0.5:6	 **13c**	88
8	 **15a**	0.5:6	 **15c**	88
9	 **16a**	0.5:6	 **16c**	92
10	 **17a**	0.5:6	 **17c**	86
11	 **18a**	0.5:6	 **18c**	84
12	 **19a**	0.5:6	 **19c**	60[c]

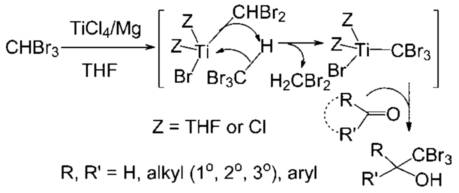
[a] Isolated yield. [b] Reaction was performed on a 25 mmol scale. [c] Reaction was performed by adding THF and DME.

satisfactory results (entry 15). The chemoselectivity was briefly explored with a series of aldehydes and ketones as summarized in Scheme 1. As expected, exposure of a mixture of aliphatic aldehyde and ketone to a 0.3 equiv of $TiCl_4$ and 3 equiv of Mg in $ClCH_2CH_2Cl$/DME at 0 °C produced exclusively the aldehyde-derived adduct. The aromatic aldehyde gave an analogous result in the presence of aliphatic ketone. Thus, using a 0.5:6 $TiCl_4$/Mg ratio proves most satisfactory, giving only a 70% yield of benzaldehyde-derived dibromomethyl alcohol **16b**. The preference for coupling of aldehydes with $CHBr_3$ ptomoted by $TiCl_4$–Mg highlihgts the chemoselectivity of the $CHBr_2$-transfer process.

Having established that $CHBr_3$–Mg–$TiCl_4$ showed promise as a generally useful $CHBr_2$-transfer reagent, we envisioned the feasibility of the $TiCl_4$–Mg-promoted CBr_3 transfer reactions. Initial studies centered on a simple 2-methylcyclohexanone **1a**. Gratifyingly, exposing **1a** to the $CHBr_3$–Mg–$TiCl_4$–THF system at −30 °C led to smooth CBr_3 transfer to give the desired adduct (Table 3, entry 1). Thus, using a 0.5:6 $TiCl_4$/Mg ratio proves most satisfactory, giving a 89% yield of the desired alcohol **1c** in addition to a trace (< 5%) of dibromomethyl alcohol adduct. Most delightfully, the reaction directly scales up; thus, tribromomethyl alcohol **1c** was obtained in 83% yield on a 25-mmol scale using a 5 equiv of $TiCl_4$ and 60 equiv of Mg. Extension of this $TiCl_4$–Mg-promoted CBr_3 transfer to other traps confirms their generality. Fortunately, the unsaturated ketones also gave satisfactory results with $CHBr_3$–Mg–$TiCl_4$–THF system (entries 2–4). Not surprisingly, in contrast to polyhalomethyllithium and magnesium reagents, this $CHBr_3$–Mg–$TiCl_4$–THF system reacted efficiently even with the readily enolizable ketones. Thus, reacting 2-indanone and *β*-tetralone with $CHBr_3$ under the standard conditions produced the desired tribromomethyl alcohol adducts **9c** (87%) and **10c** (85%), respectively (entries 5 and 6). On the other hand, the Ti–Mg–bimetallic complex promoted CBr_3 transfer onto the aldehydes was equally effective (entries 7–11). More dramatically, this $TiCl_4$–Mg-promoted CBr_3 transfer to chloro ketone containing an active methine hydrogen and chloro group was equally effective (entry 12).

The reaction is best envisioned as involving interception of a presumed $[Cl_2TiBr(CHBr_2)]$ complex by the $CHBr_3$ to generate an active $[Cl_2TiBr(CBr_3)]$ complex and CH_2Br_2 (Scheme 2). Left unanswered by this proposal is the strong dependence of the formation of polyhalomethyltitanium complex on the relative amount of $TiCl_4$ to Mg and THF. Further mechanistic work is clearly required before any definite conclusions can be reached.

Scheme 2. $TiCl_4$–Mg–Bimetallic Complex-Promoded CBr_3-Transfer Reaction of $CHBr_3$



The ability to elaborate $CHBr_3$ into unusual dibromomethyl- and tribromomethyltitanium reagents via $TiCl_4$–Mg bimetallic complex mediated transformation should prove to be a particularly valuable strategy. The successful application of $TiCl_4$–Mg-promoted coupling of $CHBr_3$ with various carbonyl compounds, especially in the case of highly enolizable ketones such as 2-indanone and *β*-tetralone, highlights the extraordinary reactivity and the weakly basic nature of this system. On the other hand, this $CHBr_3$–Mg–$TiCl_4$ seems highly selective and might become practical $CHBr_2$- and CBr_3-transfer reagents applicable to large-scale synthesis. The efficiency of this chemistry suggested several intriguing directions which are currently under active investigation.

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

Supporting Information Available. Experimental procedures and spectra data for **1b**–**16b**, **1c**, **6c**–**10c**, **13c**, and **15c**–**19c**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.