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On the paradox of $TiCl_4$ reducing power: pinacol coupling and two-carbon homologation of carbonyl compounds

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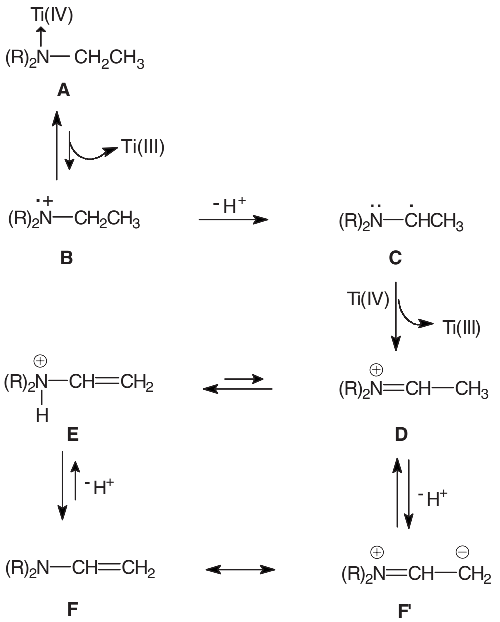
Abstract—$TiCl_4$/DIPEA/CH_2Cl_2 reducing system promotes pinacol coupling and/or reduction to alcohol of aromatic aldehydes and carbonyl compounds activated towards reduction by an electron withdrawing group. In addition, bis homologation of these substrates is observed. An inner-sphere electron transfer from $TiCl_4$ to DIPEA accounts for the products distribution.

Over the past two decades, $TiCl_4$, in conjunction with diisopropylethylamine (DIPEA) as a base and CH_2Cl_2 as a solvent, has been widely used as the system of choice for promoting aldol-type addition reactions.[1]

Pioneering studies by Evans,[1a–c] later confirmed by Tanabe,[2] firmly established that '$TiCl_4$ complexation of the enolizable substrate must precede the introduction of base, because the reaction of uncomplexed $TiCl_4$ with DIPEA leads to irreversible complexation and, as consequence, no enolization'.[1a] Since then, the order of reagent addition has always been strictly followed in promoting aldol-type addition reactions.

In this communication, we report that $TiCl_4$/DIPEA complexation is not irreversible but it is the driving force that promotes an inner-sphere electron transfer from $TiCl_4$ to DIPEA when a non-co-ordinating solvent, such as CH_2Cl_2, is used.[3] In fact, treatment of $TiCl_4$ with DIPEA (from 0.5 to 3.0 equiv) in CH_2Cl_2, at 0 °C under N_2, resulted in an instantaneous formation of the characteristic blue-violet color of $TiCl_3$. Actually, it is surprising that no one realized it before,[4] notwithstanding the numerous studies[1] conducted with $TiCl_4$/DIPEA/CH_2Cl_2 system.

The sequence depicted in Scheme 1 (R = *i*-Pr) is proposed to account for this novel and unexpected redox reaction. $TiCl_4$ is a mild oxidizing agent ($E^0 = 0.10\,V$), but following the activation of the precursor complex **A**, metal to ligand electron transfer (MLET) occurs to produce Ti(III) and aminium radical **B**.



Scheme 1.

The acidity of the protons in α to an aminium radical is greatly enhanced relative to the corresponding neutral amine and the second step can be viewed as a deprotonation of **B**. The neutral radical **C** is a good reducing

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Keywords: Titanium tetrachloride; DIPEA; Electron transfer; Pinacol coupling; Carbon homologation.

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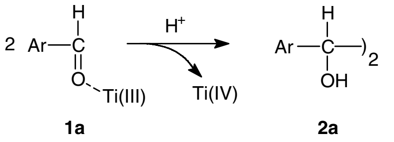
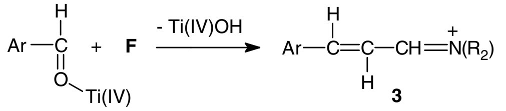
agent and reacts with a second equivalent of Ti(IV) to provide **D**. Iminium salts, as **D**, are relatively stable only in strong acidic media thus, under our reaction conditions, the equilibria involved should be by far shifted in favour of enamine **F**.[5]

Both Ti(III) and **F** (or **D**) react further with 4-Br-benzaldehyde **1a** added in one portion, after 10 min, to the blue-violet $TiCl_3$ solution. The Ti(III)-carbonyl oxygen co-ordination activates **1a** towards reductive dimerization and dimer **2a** is formed.


(1)

The Ti(IV)-carbonyl oxygen co-ordination favors the aldol condensation of **1a** with the weak nucleophilic enamine **F** and, upon metal-assisted dehydration, iminium salt **3** is obtained.[6] Basic hydrolysis of **3** furnishes *trans*-4-Br-cinnamaldehyde **4a** and diisopropylamine (Eqs. 2 and 3).


(2)

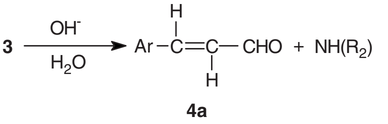
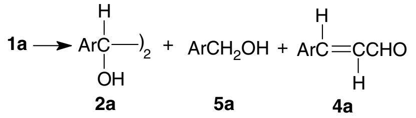

(3)

Table 1. Reduction and two-carbon homologation of 4-Br-benzaldehyde **1a** under different experimental conditions[7]



Entry (method)	**1a**:$TiCl_4$: DIPEA (equiv ratio)	Yields (%)[a]		
		2a[b]	**5a**[b]	**4a**[c]
1 (I)	1:1:1	54[d]	—	30
2 (I)	1:1:2	49[d]	21	30
3 (I)	1:1:3	37[e]	27	36
4 (II)	1:1:1	—	43	30
5 (II)	1:1:2	—	60	40
6 (II)	1:1:3	—	64	36
7 (II)	1:0.5:2	—	33	35
8 (III)	1:1:2	14[f]	51	35

[a] Yields (%) are based on the starting **1a**; the difference to 100% is unreacted **1a**; mass balance is always ⩾95%.

[b] Products distribution and *dl*/*meso* ratio were determined by ^1H NMR analysis of the crude reaction extracted with AcOEt[6] and added with an internal standard.[7]

[c] Isolated yields (^1H NMR purity ⩾95%).

[d] *dl*/*meso* ratio, 74:26.

[e] *dl*/*meso* ratio, 77:23.

[f] *dl*/*meso* ratio, >99:<1.

Thus, the net result of this unexpected process is pinacol coupling and two-carbon homologation of the starting aldehyde (Table 1, entry 1).[7]

Formation of **4a** can be viewed as a 'direct aldol reaction' of an aromatic aldehyde with acetaldehyde, a transformation that cannot be easily achieved since, under basic catalysis, acetaldol is formed instead.

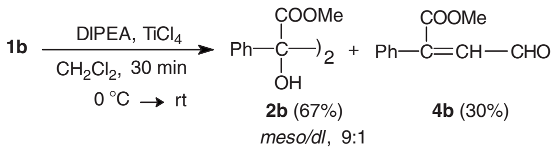
Concerning the pinacol coupling, $TiCl_4$/DIPEA/CH_2Cl_2 reducing system behaves as the $TiCl_3$/CH_2Cl_2 solution,[8] which stereo-couples aromatic aldehydes[8] but not aromatic ketones.[9] In fact, acetophenone, under the conditions of entry 2, afforded only 10% of dimers, notwithstanding the evident formation of the characteristic blue-violet $TiCl_3$ color. Self-aldol condensation of acetophenone occurred instead and 1,3-diphenyl-2-buten-1-one (58% yield *E*/*Z*, 96:4) and 1,3-diphenyl-3-hydroxy-butan-1-one (24%) are obtained. However, this result substantiates that enolization does occur even if the enolizable substrate is added last to the $TiCl_4$/DIPEA in CH_2Cl_2 solution.

4-Br-benzaldehyde, selected as a model substrate, was then investigated under different experimental conditions, by changing either the $TiCl_4$/DIPEA molar ratio or the order of reagents mixing.

As it can be seen from the data of Table 1, the yields of **4a** did not substantially change (30–40%) under all the conditions tested, whereas the distribution of the reduction products (dimer **2a** and/or 4-Br-benzyl alcohol **5a**) strongly depends on both the ratio and order of reagent addition.

Further investigation is necessary to carefully explore the observed reactivity, which may be tentatively ascribed to different types of complexation between titanium ions [Ti(III) or Ti(IV)] and the reactive intermediates involved in the redox pathways.

From our previous studies, we established[10] that an aqueous acidic $TiCl_3$ solution easily reduces carbonyl compounds activated towards reduction by an electron withdrawing group, so we applied this novel $TiCl_4$/DIPEA/CH_2Cl_2 reducing system to both PhCOCOOMe **1b** and PhCOCOPh **1c**. The results obtained, under the conditions of entry 2, are given in Eqs. 4 and 5 (yields based on the starting **1b–c**).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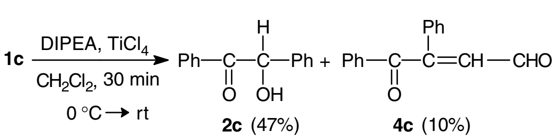
(5)

Since this novel reduction system seems to have general applicability, its extension is under investigation to both other amines and other substrates. It remains to be seen whether this attractive approach is to be successful in enantioselective and/or catalytic pinacol coupling.

Acknowledgements

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3. We did not observe this redox process when co-ordinating solvents, such as THF or MeOH, were used instead of CH_2Cl_2. With these solvents, the octahedral co-ordinative valence of the metal ion is saturated, thus hampering further $TiCl_4$ complexation with DIPEA.
4. The violet color sometimes observed was erroneously considered indicative of enolate formation.[1f]
5. Enamines without hydrogen on the nitrogen, as F, are normally stable: March, J. *Advanced Organic Chemistry*; John Wiley: New York, 1985; pp 69–70 and references cited therein.
6. When the reaction mixture is extracted with AcOEt, iminium salt **3** remains in the aqueous layer, but if the extraction is performed with CH_2Cl_2, **3** is partially isolated. Recrystallization from CH_2Cl_2/AcOEt afforded white needles: mp 218–20 °C (dec); ^{1}H NMR ($CDCl_3$): δ 1.49 (6H, d, $J = 6.5$ Hz); 1.64 (6H, d, $J = 6.5$ Hz); 4.22 (1H, septuplet, $J = 6.5$ Hz); 4.98 (1H, septuplet, $J = 6.5$ Hz); 7.55 (2H, ArH, d, $J = 8.3$ Hz); 7.58 (1H, dd, $J = 10.5$, 14.8 Hz); 7.75 (2H, ArH, d, $J = 8.3$ Hz); 8.91 (1H, d, $J = 14.8$ Hz); 9.99 (1H, d, $J = 10.5$ Hz). MS (CI): m/z 297–295 (M + 1, 40); 296–294 (M, 60); 102 (100). Treatment of **3** in $CHCl_3$ with water, under vigorous stirring for 1 h, afforded *trans*-4-Br-cinnamaldehyde **4a** in the organic layer and di-isopropylamine hydrochloride in the aqueous phase. **4a**: mp = 80 °C (ether); ^{1}H NMR ($CDCl_3$): δ 6.70 (1H, dd, $J = 7.9$, 15.9 Hz); 7.42 (1H, d, $J = 15.9$ Hz); 7.43 (2H, ArH, d, $J = 8.8$ Hz); 7.58 (2H, ArH, d, $J = 8.8$ Hz); 9.71 (1H CHO, d, $J = 7.9$ Hz). MS (CI): m/z 213–211 (M + 1, 100).
7. Method I: dropwise addition of 2.0 mL of a 1.0 M $TiCl_4$ solution in CH_2Cl_2 (2.0 mmol) to a well stirred solution of DIPEA (2.0 mmol) in CH_2Cl_2 (10 mL), cooled at 0 °C under N_2, afforded an instantaneous violet solution indicative of $TiCl_3$ formation. After 10 min, 4-Br-benzaldehyde (2.0 mmol) dissolved in CH_2Cl_2 (5 mL) was added in one portion. After further 30 min at rt, the reaction was quenched with a semisaturated NH_4Cl solution (10 mL) under vigorous stirring. The mixture was then extracted with AcOEt[6] (3 × 50 mL), the organic layers washed with water (3 × 5 mL), dried and concentrated in vacuo. ^{1}H NMR analysis of the crude mixture, added with an internal standard, afforded the yields and *dl*/*meso* ratio of **2a** (and/or **5a**) given in Table 1 (entries 1–3). The combined aqueous layers were brought to a pH≈8–9 by addition of a 10% NaOH solution and then extracted with AcOEt (3 × 50 mL). Upon usual workup, *trans*-4-Br-cinnamaldehyde **4a** was recovered (^{1}H NMR purity $\geqslant$ 95%) in the isolated yields reported in Table 1. Method II: dropwise addition of 2.0 mL of a 1.0 M $TiCl_4$ solution in CH_2Cl_2 (2.0 mmol) to a well stirred solution of **1a** (2.0 mmol) in CH_2Cl_2 (10 mL), cooled at 0 °C under N_2, afforded a yellow slurry precipitate indicative of **1a**-$TiCl_4$ complexation. After 10 min, DIPEA (2.0 mmol) was added dropwise (5 min) with a syringe affording a homogeneous green solution, and stirring was continued for additional 30 min at room temperature. Workup as above. Method III: to a well stirred solution of **1a** (2.0 mmol) and DIPEA (4.0 mmol) in CH_2Cl_2 (10 mL), cooled at 0 °C under N_2, 2.0 mL of a 1.0 M solution of $TiCl_4$ solution in CH_2Cl_2 (2.0 mmol) were added. The resulting green solution was then stirred for additional 30 min at room temperature. Workup as above. **2a** (*dl*): mp 176 °C;[8] ^{1}H NMR ($CDCl_3$): δ 4.59 (2H, s); 6.96 (4H, ArH, d, $J = 8.4$ Hz); 7.36 (4H, ArH, d, $J = 8.4$ Hz). **2a** (*meso*): mp 137 °C;[8] ^{1}H NMR ($CDCl_3$): δ 4.80 (2H, s); 7.03 (4H, ArH, d, $J = 8.4$ Hz); 7.40 (4H, ArH, d, $J = 8.4$ Hz). **5a**: mp 79–82 °C; ^{1}H NMR ($CDCl_3$): δ 2.0 (1H, OH, s, D_2O exchanged); 4.65 (2H, CH_2, s); 7.24 (2H, ArH, d, $J = 8.2$ Hz); 7.48 (2H, ArH, d, $J = 8.2$ Hz).
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