

Key Role of Ti(IV) in the Selective Radical–Radical Cross-Coupling Mediated by the Ingold-Fischer Effect

Raffaele Spaccini, Nadia Pastori, Angelo Clerici, Carlo Punta,* and Ombretta Porta*[†]

Dipartimento di Chimica, Materiali e Ingegneria Chimica “G. Natta”, Politecnico di Milano, via Mancinelli 7, I-20131 Milano, Italy

Received September 30, 2008; E-mail: carlo.punta@polimi.it

Abstract: We report an innovative approach for the selective synthesis of polyfunctional derivatives by cross-combination of different radicals generated under mild conditions. The coordinating effect of Ti(IV) plays a key role in the reaction mechanism: due to its chelating action on the hydroxyl groups, it promotes the homolytic C–C bond cleavage of α,β -dihydroxy ketones by enhancing the captodative effect and the consequent stabilization of the corresponding α -hydroxy- α -carbonyl radicals. When these radicals are generated in the presence of stoichiometric amounts of TiCl₄ and 2,2'-azo-bis-isobutyronitrile (AIBN) is employed as a source of α -cyanoisopropyl radicals, the selective radical–radical cross-coupling is observed, affording the corresponding β -hydroxynitriles in high yields. This innovative methodology allows application of the well-known Ingold–Fischer effect to a wider range of stabilized carbon-centered radicals, whose formation derives from the chelating action of Ti(IV).

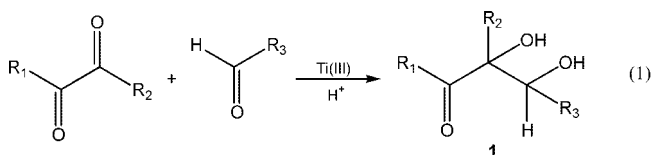
Introduction

For a long time free radical chemistry was thought to be useless for selective synthesis of complex molecules in high yields, because of the erroneous concept that the enthalpic effect was the main driving force in free radical processes. Thus, high reactivity had to be always associated to low selectivity. More recently the synthetic potentiality of radical reactions greatly increased and a wide range of selective free-radical routes has been developed by considering also the key role of polar and steric effects.^{1–3}

An intriguing example of the potential of free radical chemistry is shown by the use of the Ingold–Fischer “Persistent Radical Effect” (PRE)^{4,5} as a synthetic tool for the preparation of clean products in high yields. The PRE principle permits us to explain the highly specific C–C bond formation by a cross-coupling between radicals when two species are generated at similar rates and one is more persistent than the other, that is with a lifetime significantly greater than that for a methyl radical under the same conditions.⁶

The PRE allowed development of a large number of selective reactions involving radicals both highly stabilized^{7,8} and bearing crowded substituents.⁹

A few years ago Porta and co-workers¹⁰ reported the reduction of α,β -dicarbonyl compounds by TiCl₃, in the presence of an aldehyde, heading the stereoselective synthesis of α,β -dihydroxy ketones **1** (eq 1).



More recently, the same research group reported the results of a study on the reactivity of methyl mandelate **2** in the presence of a Ti(IV)/base system: the oxidative dimerization led to **3** in good yields¹¹ (Scheme 1, path a), whereas when the same reaction was conducted in the presence of an aldehyde, the aldol addition occurred, leading to **4** in high yields¹¹ (Scheme 1, path b).

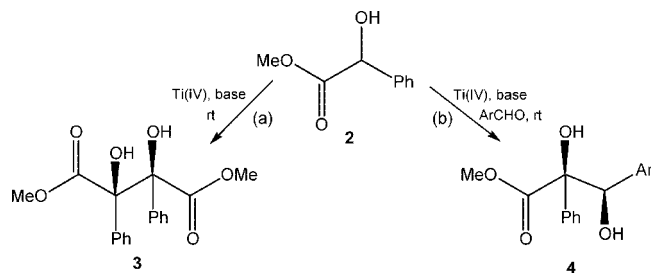
Homolytic cleavage of the C–C bond makes compounds **1**, **3**, and **4** potential good sources of radical species driven by the *captodative effect*,¹² that is the effect on the stability of a carbon-centered radical determined by the combined

[†] Deceased May 3, 2008.

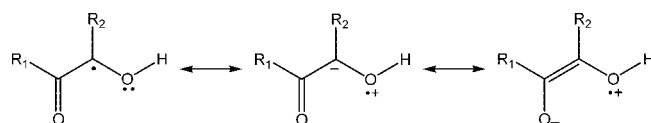
- (1) (a) Barton, D. H.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1960**, *82*, 2640–2641. (b) Viehe, D. H. G.; Janousek, Z.; Merényi, R. *Substituent Effects in Radical Chemistry*; NATO ASI series C 189; Dordrecht, 1986. (c) Minisci, F. *Free Radicals in Synthesis and Biology*; NATO ASI series C 260; Dordrecht, 1988. (d) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: London, 1991. (e) Togo, H. *Advanced Free Radical Reactions for Organic Synthesis*; Elsevier: 2004.
- (2) Renaud, P.; Sibi, M. P. *Radicals in Organic Synthesis*; Wiley VCH: 2001.
- (3) Mayr, H.; Ofial, A. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1844–1854.
- (4) Fischer, H. *J. Am. Chem. Soc.* **1986**, *108*, 3925–3927.
- (5) Daikh, B. E.; Finke, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 2938–2943.
- (6) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1976**, *9*, 13–19.

- (7) Bravo, A.; Björsvik, H.-R.; Fontana, F.; Liguori, L.; Minisci, F. *J. Org. Chem.* **1997**, *62*, 3849–3857.
- (8) Recent reviews on the subject: (a) Studer, A. *Chem.—Eur. J.* **2001**, *7*, 1159–1164. (b) Fischer, H. *Chem. Rev.* **2001**, *101*, 3581–3610. (c) Studer, A. *Chem. Soc. Rev.* **2004**, *33*, 267–273.
- (9) (a) Frenette, M.; Aliaga, C.; Font-Sanchis, E.; Scaiano, J. C. *Org. Lett.* **2004**, *6*, 2579–2582. (b) Focsaneanu, K.-S.; Aliaga, C.; Scaiano, J. C. *Org. Lett.* **2005**, *22*, 4979–4982.
- (10) Clerici, A.; Porta, O. *J. Org. Chem.* **1989**, *16*, 3872–3878.
- (11) Clerici, A.; Pastori, N.; Porta, O. *J. Org. Chem.* **2005**, *70*, 4174–4176.

Scheme 1. Reactivity of Methyl Mandelate–Ti(IV)-enediolate: Oxidative Homocoupling (Path a) versus Aldol *syn*-Diastereoselective Condensation (Path b)



Scheme 2. Captodative Effect in α -Hydroxy- α -carbonyl Radicals



action of a captor (electron-withdrawing; in this case the carbonyl group) and a dative (electron-releasing; in this case the hydroxyl group) substituent, both attached to the radical center (Scheme 2).

Here we report the interesting results obtained by employing derivatives **1** and **3** as sources of stabilized radicals in the presence of Ti(IV). The coordinating effect of the metal ion¹³ induces an increased stabilization onto the new radicals, due to an enhanced captodative effect. This observation prompted us to develop a new one-pot multicomponent route for the synthesis of polyfunctional derivatives of high added value.

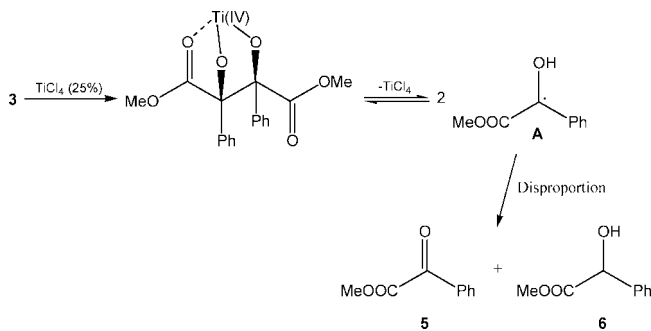
Results and Discussion

The effect of Ti(IV) on dimethyl 2,3-dihydroxy-2,3-diphenyl butanedioate **3** in benzene was first investigated. In the absence of the transition metal, no cleavage was observed at 80 °C, and compound **3** was recovered unreacted after 3 h. Nevertheless, when a catalytic amount (25%) of TiCl₄ (1 M solution in CH₂Cl₂) was added to the reaction mixture, the homolysis of **3** occurred and the starting derivative was quantitatively converted to methyl phenylglyoxylate **5** and methyl mandelate **6** within a few minutes (Scheme 3).

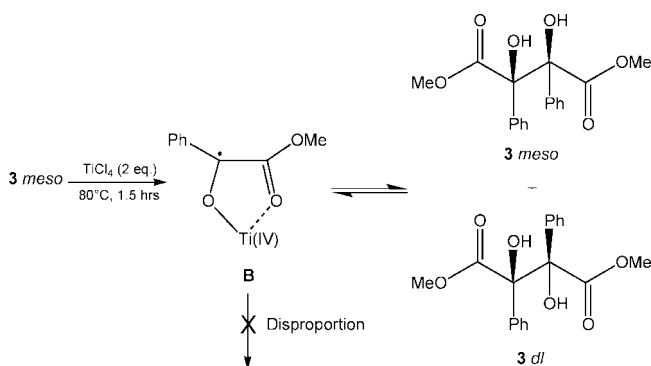
The formation of products **5** and **6** arises from the disproportionation of radicals **A**, generated *in situ* by the chelating action of Ti(IV) on the dimer **3** (Scheme 3).¹¹

The low enthalpy of dissociation of the dimer in the presence of Ti(IV) appears to result from structural features in the radical, which stabilize the radical center and lower the energy. The carboxy group is not a particularly strong radical stabilizing function in itself,¹⁴ and notwithstanding the presence of a hydroxyl group enhancing the stabilization (Scheme 2), it is not sufficient to undergo homolytic cleavage at 80 °C. The higher stability of the radical in the presence of Ti(IV) derives from the complexation of the hydroxyl group, which leads to the formation of a covalent bond between the oxygen atom and

Scheme 3. Homolytic Cleavage of the C–C Bond in Dimethyl 2,3-Dihydroxy-2,3-diphenyl Butanedioate **3**, Catalyzed by Ti(IV)



Scheme 4. Stereochemical Equilibration of Isomer **3-meso** in the Presence of 2 equiv of TiCl₄



the transition metal (radical **B**, Scheme 4). The new O–Ti(IV) bond is significantly more polar than the corresponding O–H one, and this induces an enhanced captodative effect on the carbon-centered radical, due to the stabilization of the positive charge on the oxygen atom, according to the resonance structures reported in Scheme 2.

In addition, the possible coplanarity of the carbomethoxy group with the radical center due to Ti(IV) chelation could facilitate the electron delocalization in the radical.

To verify the stabilizing role of Ti(IV), 2 equiv of TiCl₄ were added to a solution of the stereoisomer **3-meso** in benzene and the mixture was heated at 80 °C for 1.5 h. In this case no disproportionation was observed, which is consistent with the formation of the O–Ti(IV) bond, but the C–C bond cleavage occurred with stereochemical equilibration of the isomer, leading to a mixture of *meso* and *dl* in a 2.4:1 ratio (Scheme 4).

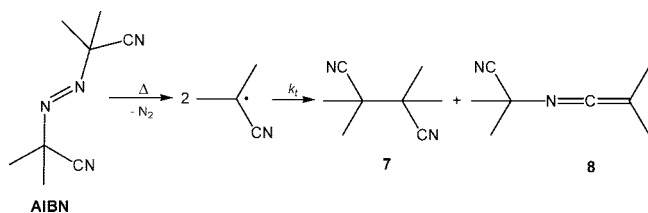
The isomerization, which derives from the equilibrium between dimer **3** and the corresponding chelated radicals, clearly shows the homolytic nature of the C–C bond cleavage. Furthermore, this result confirms the stabilizing effect of Ti(IV), the most stable radical being the least likely to disproportionate.

This equilibrium warrants a stationary concentration of radicals **B** with a relatively high lifetime in solution. Thus, the higher stabilization indirectly confers an enhanced persistent character to the new Ti(IV)-complexed radical **B** when compared with radical **A**, as the last one escapes the equilibrium undergoing fast disproportionation (Scheme 3).

This suggested that radical **B** could behave as a suitable scavenger of more transient radicals generated *in situ*, leading to the formation of C–C bonds according to the Ingold–Fischer effect and shifting the equilibrium of Scheme 4 toward the formation of new **B** radicals.

- (12) (a) Stella, L.; Janousek, Z.; Merényi, R.; Viehe, H. G. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 691–692. (b) Viehe, H. G.; Merényi, R.; Stella, L.; Janousek, Z. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 917–932. (c) Merényi, R.; Janousek, Z.; Viehe, H. G. in ref 1b, p 301.
- (13) Moreira, I. P. R.; Bofill, J. M.; Anglada, J. M.; Solsona, J. G.; Nebot, J.; Romea, P.; Urpi, F. *J. Am. Chem. Soc.* **2008**, *130*, 3242–3243.
- (14) Russell, G. A. *Free Radicals*, Vol. 1; Kochi, J. K., Ed.; Wiley: New York, 1973; p 275.

Scheme 5. Thermal Decomposition of AIBN

Table 1. Effect of Ti(IV) on the Selectivity in the Formation of Product 9^a

[Ti(IV)]/[3]	9 (selectivity %) ^b	7 + 8 (selectivity %) ^b	IBN ^c (selectivity %) ^b
0	0	100	0
0.25	25	57	18
0.50	38	50	12
0.75	77	20	3
1.00	76	22	2

^a All reactions were performed under N₂ atmosphere for 1.5 h; see Experimental Section and Supporting Information for details. ^b With the term *selectivity* we mean here the percentage of α-cyanoisopropyl radicals which lead to the formation of the different products. It has been determined by ¹H NMR with 1-biphenyl-4-yl-ethanone as an internal standard added to the crude reaction mixture. ^c IBN = isobutyronitrile.

2,2'-Azo-bis-isobutyronitrile (AIBN) resulted in being an ideal source of radicals from both a mechanistic and a synthetic point of view, according to Scheme 5.

Because of the importance of azonitriles in initiating radical reactions, α-cyanoalkyl radicals have received a great deal of study,¹⁵ including the investigation of the *cage effect* in thermal and photochemical decomposition.¹⁶ In addition, the easy introduction of cyano substituents, precursors of carboxylic groups on a wide range of organic derivatives, represents a synthetic tool for the preparation of polyfunctional derivatives.^{17–20}

AIBN (1.2 mmol) and dimer **3** *meso* (0.6 mmol) were dissolved in 10 mL of benzene in the presence of different amounts of TiCl₄ (1 M solution in CH₂Cl₂) under nitrogen atmosphere. The mixture was heated at 80 °C, and the reaction was allowed to take place for 1.5 h, which equals a one-half life period for the decomposition of AIBN at 80 °C. Thus, after 1.5 h the amount of α-cyanoisopropyl radicals, obtained by decomposition of AIBN, was equimolar with the quantity of radicals **A** deriving from dimer **3**. The results are reported in Table 1.

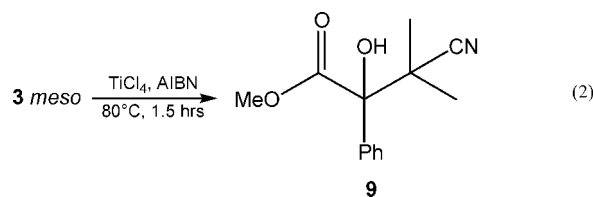
In the absence of TiCl₄, no C–C bond cleavage was observed for dimer **3**, whereas the cross-coupling product **9**

Table 2. Reactivity of **5**, **6** and **3** in the Presence of IBN^a

entry	substrate	IBN (equiv)	product 3 (selectivity %)	product 9 (selectivity %)	other products (selectivity %)
1	6	0	–	–	>98% (6)
2	5+6	0	–	–	>98% (5+6)
3	6	1	–	–	>98% (6)
4	5+6	1	–	–	>98% (5+6)
5	3	2	17 (<i>meso</i> + <i>dl</i>)	–	80% (5+6)

^a All reactions were performed under N₂ atmosphere for 1.5 h in the presence of stoichiometric amounts of TiCl₄.

was obtained, according to eq 2, when different amounts of TiCl₄ were added.



A hypothetical ionic mechanism based on the *in situ* formation of IBN, followed by a classical retro-aldol reaction, has to be excluded on the basis of the results reported in Table 2. Under the reaction conditions of Table 1, in the absence of AIBN neither **6** nor the mixture **5+6** afforded dimer **3** (entries 1 and 2, Table 2). These results are consistent with what was previously reported by our group by working at room temperature.¹¹ Thus, the isomerization of **3** *meso* (Scheme 4) may only be ascribed to a radical homocoupling. Furthermore, any attempt to obtain product **9** in the presence of IBN from **6** and **5+6** failed, and the starting materials were collected unreacted at the end of the reaction (entries 2 and 3, Table 2). Finally, when a solution containing dimer **3**, TiCl₄ (1 equiv), and IBN in benzene was refluxed for 1.5 h, no product **9** was observed, while **3** underwent disproportionation as observed in the absence of AIBN, this excluding the ionic hypothesis.

Figure 1 shows the plot of the ratio [Ti(IV)]/[**3**] versus the selectivity of product **9**, that is the percentage of α-cyanoisopropyl radicals indeed trapped by radicals **A** or **B**.

The selectivity in **9** linearly increased by increasing the amount of Ti(IV): for example, when 25% of Ti(IV) was employed with respect to **3**, only 25% of the desired product was recovered. The remaining starting dimer **3** underwent quantitative disproportionation, affording products **5** and **6**. α-Cyanoisopropyl radicals in excess afforded **7** and **8** (in minor yields) by homocoupling (Scheme 5) and isobutyronitrile (IBN) by disproportionation with radical **A**. When dimer **3** was reacted with a double excess of AIBN, in the presence of stoichiometric amounts of TiCl₄, product **9** was isolated with 84% yield.

These results clearly demonstrate that the scavenging effect is due to radical **B** (eq 3) deriving from the chelating action of Ti(IV), whereas radical **A** is not able to capture any radical (eq 4). In fact, the high selectivity for the cross-combination observed in the presence of stoichiometric amounts of Ti(IV) cannot be ascribed to radical **A**, because the value of the kinetic constant for the termination reaction by homocoupling of two **A** radicals is very high ($k_t \sim 5 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$),²¹ quite similar to that of two α-cyanoisopropyl radicals ($k_t = 9.4 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$, Scheme 5).²² These high values for the dimerization kinetic constants clearly show that **A** and the α-cyanoisopropyl radical are both transient radicals and cannot undergo cross-coupling

- (15) (a) Hammond, G. S.; Sen, J. N.; Boozer, C. E. *J. Am. Chem. Soc.* **1955**, *77*, 3244–3248. (b) Hammond, G. S.; Lucas, G. B. *J. Am. Chem. Soc.* **1955**, *77*, 3249–3251. (c) Van Hooft, J. P.; Tobolsky, A. V. *J. Am. Chem. Soc.* **1958**, *80*, 779–782. (d) Tanner, D. D.; Samal, P. W.; Tomoki, C.-S. R.; Henriquez, R. *J. Am. Chem. Soc.* **1979**, *101*, 1168–1175.
- (16) (a) Hammond, G. S.; Fox, J. R. *J. Am. Chem. Soc.* **1964**, *86*, 1918–1921. (b) Waits, H. P.; Hammond, G. S. *J. Am. Chem. Soc.* **1964**, *86*, 1911–1918. (c) Nelsen, S. F.; Bartlett, P. D. *J. Am. Chem. Soc.* **1966**, *88*, 143–149.
- (17) (a) Kamal, A.; Ramesh Khanna, G. B.; Ramu, R. *Tetrahedron: Asymmetry* **2002**, *13*, 2039–2051. (b) Kamal, A.; Ramesh Khanna, G. B. *Tetrahedron: Asymmetry* **2001**, *12*, 405–410.
- (18) (a) Corey, E. J.; Wu, Y. J. *J. Am. Chem. Soc.* **1993**, *115*, 8871–8872. (b) Fukuda, Y.; Okamoto, Y. *Tetrahedron* **2002**, *58*, 2513–2521.
- (19) (a) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3148–3150. (b) Mirmashhori, B.; Azizi, N.; Saidi, M. R. *J. Mol. Cat. A: Chemical* **2006**, *247*, 159–161.
- (20) Miura, Y.; Muranaka, Y.; Teki, Y. *J. Org. Chem.* **2006**, *71*, 4786–4794.

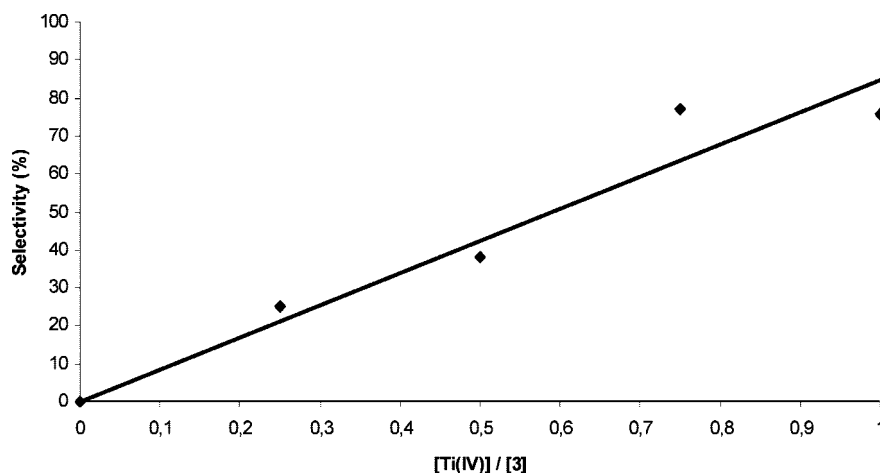


Figure 1. Effect of Ti(IV) on the selectivity in the formation of product **9**.

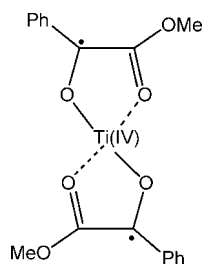
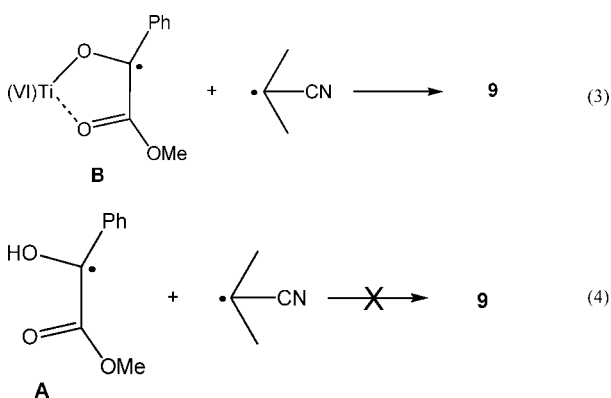


Figure 2. Possible chelating action of Ti(IV) on AIBN.

since one important condition for the Ingold–Fischer effect is the simultaneous presence of a transient and a persistent radical in solution.

By considering that homolytic decomposition of **3** affords 2 equiv of radical **A**, the observed linear dependence of selectivity in product **9** on the amount of Ti(IV) would suggest that each transition metal is actually able to coordinate two **A** radicals (Figure 2), both deriving from the same chelated molecule, as shown in Scheme 3.



An excess of Ti(IV) with respect to **3** surprisingly decreased the yield of **9**. This is due to the fact that, in spite of what is usually reported for other transition metal salts, like cupric²³ and stannous²⁴ salts, Ti(IV) seems to inhibit or slow the

Table 3. Scavenger Effect of Radical **B** Determined by Studying the Cage Effect in Thermal Decomposition of AIBN at 80 °C^a

[3]/[AIBN]	9 (selectivity %) ^b	7 + 8 (selectivity %) ^b	IBN (selectivity %) ^b
0	0	100	0
0.25	50	45	5
0.50	76	22	2
1.00	85	15	0
2.00	83	17	0

^a All reactions were performed under N₂ atmosphere for 1.5 h; see Experimental Section and Supporting Information for details. ^b With the term *selectivity* we mean here the percent number of α-cyanoisopropyl radicals which lead to the formation of the different products. It was determined by ¹H NMR with 1-biphenyl-4-yl-ethanone as an internal standard added to the crude reaction mixture.

decomposition of AIBN. In fact, when a solution of AIBN in benzene was heated at 80 °C, under N₂ atmosphere, in the presence of a stoichiometric amount of TiCl₄, a white solid complex precipitated and, after 1.5 h, 83% of unreacted AIBN was recovered. This represents an important exception to the Kochi and Mog²³ statement, according to which the formation of radicals from the decomposition of AIBN at 80 °C should be independent of the presence of metal salts. Indeed, this unexpected behavior may be simply ascribed to the coordinating action of Ti(IV) on the cyano groups. The resulting complex has a low solubility in benzene, thus decreasing the concentration of AIBN in solution.

However, when 1 equiv of dimer **3** was added to the mixture, the complex was completely destroyed, as evidenced by the instantaneous disappearance of the white solid, and the reaction occurred affording **9** in good yields.

To investigate the scavenging power of radical **B**, we determined the *cage effect* of AIBN in the presence of the Ti(IV)–**3** complex. To study the *cage effect* it is important to have a scavenger which would trap all radicals that escape the cage and no others. A scavenger is presumed to meet this condition if the same *cage effect* is found over a range of scavenger concentrations and also with different scavengers. Thus, the thermal decomposition of AIBN was conducted in the presence of different amounts of 1:1 Ti(IV)–**3** complex. The results, reported in Table 3 and shown in Figure 3, point out the high persistent character of radical **B** deriving from its

(21) Fujisawa, T.; Monroe, B. M.; Hammond, G. S. *J. Am. Chem. Soc.* **1970**, *92*, 542–544.

(22) Weiner, S. A.; Hammond, G. S. *J. Am. Chem. Soc.* **1969**, *91*, 986–991.

(23) Kochi, J. K.; Mog, D. M. *J. Am. Chem. Soc.* **1965**, *87*, 522–528.

(24) Tabka, T. T.; Chenal, J.-M.; Widmaier, J.-M. *Polym. Int.* **2000**, *49*, 412–416.

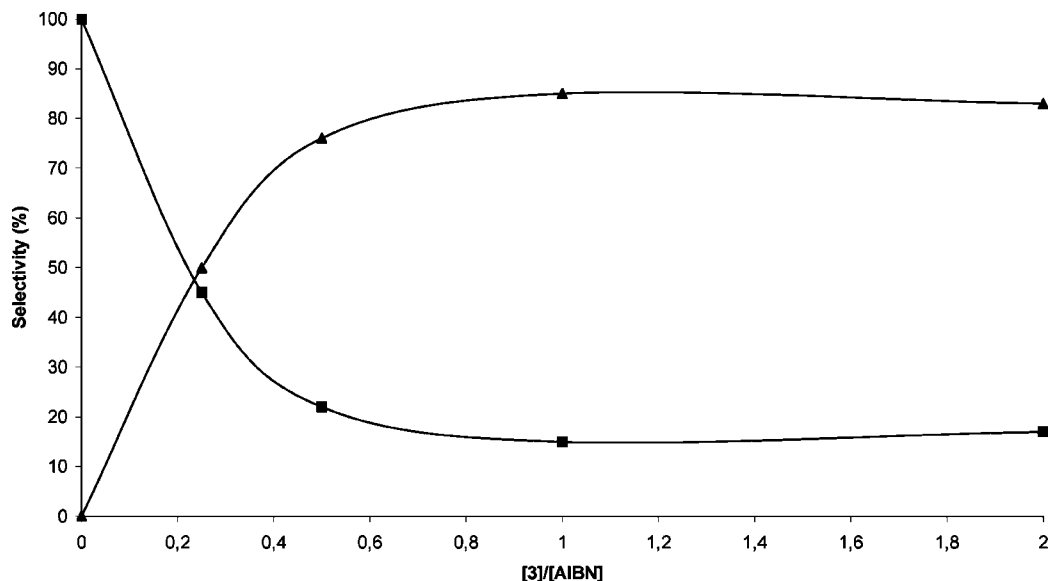


Figure 3. Scavenger effect of radical **B** determined by studying the cage effect in thermal decomposition of AIBN at 80 °C (▲ = 9; ■ = 7 + 8).

Scheme 6. Effect of Ti(IV) on the Synthesis of β -Hydroxynitriles

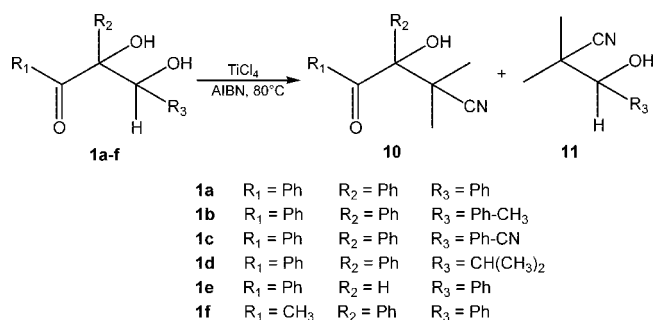


Table 4. Reactivity of α,β -dihydroxy ketones versus AIBN in the Presence of Stoichiometric Amounts of TiCl₄^a

entry	substrate	[1]/[AIBN]	10 (yield %) ^b	11 (yield %) ^b
1 ^c	1a	0.50	10a : –	11a : –
2	1a	0.50	10a : >99 (96)	11a : 48
3	1a	0.25	10a : >99	11a : 74 (71)
4	1b	0.50	10a : 87	11b : 52
5	1b	0.25	10a : >99	11b : 56 (52)
6	1c	0.50	10a : 89	11c : 51
7	1c	0.25	10a : >99	11c : 58 (54)
8	1d	0.50	10a : 82	11d : –
9	1e	0.50	10e : –	11e : –
10 ^d	1f	0.50	10f : –	11a : –
11	1f	0.50	10f : 54	11a : 43
12	1f	0.25	10f : 69 (63)	11a : 60

^a All reactions were performed under N₂ atmosphere at 80 °C for 1.5 h; see Experimental Section and Supporting Information for details. ^b Yields have been determined by ¹H NMR with 1-biphenyl-4-yl-ethanone as an internal standard added to the crude reaction mixture. Isolated yields are reported in brackets. ^c The reaction was conducted in the absence of Ti(IV). Benzoin and benzaldehyde were recovered as the sole products. ^d The reaction was conducted in the absence of Ti(IV), affording a mixture of disproportion products.

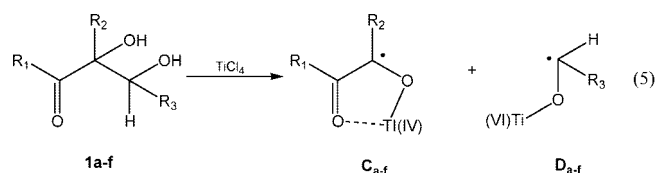
enhanced stabilization: with an equimolar concentration of **B** only 24% of α -cyanoisopropyl radicals were not trapped. A small excess of **B** was sufficient to capture all the radicals escaping from the cage, obtaining a value of 15% which is consistent with the data reported in the literature for different scavengers in benzene.¹⁹

On the basis of these intriguing results, the effect of Ti(IV) was tested on a wider range of nonsymmetric substrates (Scheme 6), with the aim to synthesize a wider range of products and to better clarify the reaction mechanism leading to the homolytic cleavage of the C–C bond.

The results are summarized in Table 4.

Substrates **1a** and **1f** underwent homolytic decomposition at 80 °C in benzene even in the absence of Ti(IV), meaning that the resulting radicals are more stable than radical **A**. This is consistent with what is described for diphenyl methyl radicals Ph₂–C[•]–R by considering the effect of R on the bond dissociation enthalpy (BDE) of the corresponding dimers. The BDE values of the dimers are 17.7, 20.0, and 21.8 kcal/mol when R = COPh, COMe, and CO₂Me, respectively.²⁵

However, the addition of Ti(IV) to solutions containing **1a** or **1f** led to cleavage of the C–C bond even at room temperature (eq 5).



The results reported in Table 3 confirmed the homolytic nature of the C–C bond cleavage. In the absence of Ti(IV) no cross-coupling was observed (entries 1 and 10). Even radical **D**, when coordinated by Ti(IV), underwent cross-combination in the presence of AIBN affording β -hydroxynitrile derivatives in good yields. Also in this case Ti(IV) plays a key role in the stabilization of the radical, though radical **D** resulted in being less stable, due to the lack of the captodative effect. In fact, by operating in stoichiometric amounts of α -cyanoisopropyl radicals, radical **C** always resulted in being a better scavenger as compared with radical **D**, affording the corresponding products in higher yields (entries 2, 4, 6, and 11). This was particularly true for radicals **C_a** and **D_{a-c}**, whereas the difference between radicals **C_f** and **D_a** was limited, due to the lower stabilization of **C_f** as compared with **C_a**. The yields could be increased by working with an excess of AIBN (entries 3, 5, 7, and 12).

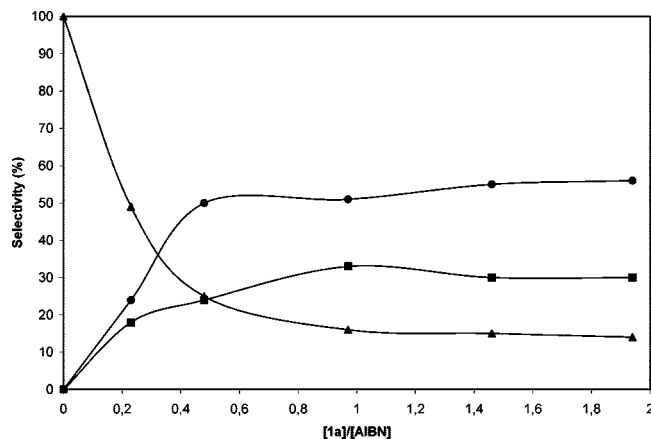


Figure 4. Scavenger effect of **1a** determined by studying the cage effect in thermal decomposition of AIBN at 80 °C (● = **10a**; ■ = **11a**; ▲ = **7 + 8**).

When R_3 was an aliphatic group (**1d**), radical **D_a** did not afford any coupling and the only product was **10a** (entry 8). **1e**, obtained by substitution of the phenyl group in R_2 with a hydrogen atom, did not undergo any C–C bond cleavage (entry 9). In both cases, the behavior has to be ascribed to the lower stabilization of the corresponding radicals due to the lack of the aromatic ring, which usually plays a well-known key role in the stabilization of carbon-centered radicals.

Figure 4 shows the scavenger effect of compound **1a** on the decomposition of AIBN. Also in this case the *cage effect* was analogous to those reported in the literature and demonstrated the high stabilized character of radicals **C_a** and **D_a**. The difference between **C_a** and **D_a** in trapping α -cyanoisopropyl radicals is also emphasized.

Conclusions

We have developed an innovative methodology for the synthesis of β -hydroxynitriles by cross-combination between stabilized radicals and the α -cyanoisopropyl radical. Our results emphasize the key role of Ti(IV) both in the production of stabilized radicals generated *in situ* from α,β -dihydroxy ketones and in the induction of a persistent character onto carbon-centered radicals, which are able to trap the α -cyanoisopropyl radicals generated by thermal decomposition of AIBN.

This methodology represents an intriguing route to the one-pot synthesis of polyfunctional derivatives in good to high yields and provides a new indication of the important role that titanium salts can play in organic synthesis.

Experimental Section

General. All materials were purchased from commercial suppliers. $TiCl_4$ was provided in CH_2Cl_2 (1 M solution). Benzene was distilled and dried on molecular sieves prior to use. α,β -Dihydroxy ketones were prepared according to the literature.^{13,14} All reactions were performed in benzene at 80 °C under nitrogen atmosphere. NMR spectra were recorded at 500 MHz for 1H and 125 MHz for ^{13}C , measured in $CDCl_3$. Chemical shifts (δ) were presented in ppm, using the $CDCl_3$ peak ($\delta = 7.26$ ppm for 1H and 77.00 ppm for ^{13}C) as an internal standard. Mass spectra were performed with a GLC-MS instrument, using a gas chromatograph equipped with an SBP-1 fused silica column (30 m \times 0.2 mm i.d., 0.2 μm film thickness) and helium as a carrier

gas. Flash column chromatography was performed by using a 40–63 μm silica gel packing.

General Procedure for the Determination of Ti(IV) Role in the C–C Bond Cleavage of **1 and **3**.** A well-stirred solution of compound **1** or **3** (0.6 mmol) in benzene (10 mL) was heated at 80.0 °C for 1.5 h under nitrogen atmosphere and in the presence of different amounts of $TiCl_4$ solution. The reaction mixture was quickly cooled at room temperature, quenched with water (20 mL), and extracted with ethyl acetate (3 \times 10 mL). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude reaction mixture was analyzed by 1H NMR upon addition of 1-biphenyl-4-yl-ethanone as an internal standard.

General Procedure for the Determination of the Cage Effect. A well-stirred solution of AIBN (1.2 mmol) in benzene (10 mL) was heated at 80.0 °C for 1.5 h under nitrogen atmosphere and in the presence of different amounts of $TiCl_4$ and **1** or **3** in a 1:1 ratio. The reaction mixture was quickly cooled at room temperature, quenched with water (20 mL), and extracted with ethyl acetate (3 \times 10 mL). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude reaction mixture was analyzed by 1H NMR upon addition of 1-biphenyl-4-yl-ethanone as an internal standard.

General Procedure for the Synthesis of β -Hydroxynitriles. A well-stirred solution of compounds **1a–f** (Table 3) or compound **3** (0.6 mmol), $TiCl_4$ (0.6 mL), and AIBN (1.2 or 2.4 mmol) in benzene (10 mL) was heated at 80.0 °C for 1.5 h under an atmosphere of nitrogen. The reaction mixture was quickly cooled at room temperature, quenched with 20 mL of water, and extracted with ethyl acetate (3 \times 10 mL). The organic phase was washed with brine, dried (Na_2SO_4), filtered, and concentrated under vacuum. The desired products were isolated by flash column chromatography and purified by crystallization (see below). The yields reported in Table 4 refer to 1H NMR with 1-biphenyl-4-yl-ethanone as an internal standard.

Characterization of the Products. 3-Cyano-2-hydroxy-3,3-dimethyl-2-phenyl-propionic Acid, Methyl Ester (9**).** White solid, purified by crystallization from ethyl acetate, mp 139–140 °C. 1H NMR ($CDCl_3$): δ_H 1.29 (3H, s), 1.45 (3H, s), 3.91 (1H, OH, s, D_2O exchange), 3.96 (3H, s), 7.36–7.38 (3H, m), 7.81–7.84 (2H, m) ppm. ^{13}C NMR ($CDCl_3$): δ_C 22.4 (CH₃), 23.1 (CH₃), 40.5 (C), 53.8 (CH₃), 79.9 (C), 123.5 (CN), 126.7 (2CH), 128.2 (2CH), 128.8 (CH), 136.7 (C), 172.8 (CO) ppm. IR (liquid film): ν_{max} 3411, 2995, 2955, 2243, 1736, 1255 cm^{-1} . MS (m/z): 233 (M^+ , <1), 165 ($M-C(CH_3)_2CN$, 12), 105 ($M-C(CH_3)_2CN-COOMe$, 100).

3-Hydroxy-2,2-dimethyl-4-oxo-3,4-diphenyl-butyroneitrile (10a**).** White solid, purified by flash column chromatography (eluent hexane/ethyl acetate 7:3), crystallized from ethyl ether, mp 164–166 °C. 1H NMR ($CDCl_3$): δ_H 1.40 (3H, s), 1.47 (3H, s), 3.18 (1H, OH, s, D_2O exchange), 7.26–7.28 (2H, m), 7.30–7.40 (4H, m), 7.60–7.64 (4H, m) ppm. ^{13}C NMR ($CDCl_3$): δ_C 23.1 (CH₃), 23.3 (CH₃), 40.8 (C), 84.1 (C), 124.0 (CN), 126.5 (2CH), 128.3 (CH), 128.5 (2CH), 128.9 (CH), 129.9 (2CH), 132.8 (2CH), 134.8 (C), 136.1 (C), 197.8(CO) ppm. IR (liquid film): ν_{max} 3396, 3020, 2401, 2212, 1606, 1215 cm^{-1} . MS (m/z): 279 (M^+ , <1), 147 ($M-CN-PhCO$, 7), 105 (PhCO, 100).

3-Hydroxy-2,2-dimethyl-4-oxo-3-phenyl-pentanitrile (10f**).** White solid, purified by flash column chromatography (eluent hexane/ethyl acetate/methanol 7.5:2:0.5), crystallized from ethyl acetate, mp 94–96 °C. 1H NMR ($CDCl_3$): δ_H 1.31 (3H, s), 1.47 (3H, s), 1.84 (3H, s), 3.84 (1H, OH, s, D_2O exchange), 7.44–7.48 (2H, m), 7.56–7.60 (1H, m), 7.98–8.00 (2H, m) ppm. ^{13}C NMR ($CDCl_3$): δ_C 22.5 (CH₃), 22.9 (CH₃), 23.3 (CH₃), 40.5 (C), 81.4 (C), 123.7 (CN), 128.4 (2CH), 129.8 (2CH), 133.1 (CH), 136.1 (C), 203.1 (CO) ppm. IR (liquid film): ν_{max} 3444, 3020, 2235, 1670, 1597, 1459, 1216 cm^{-1} . MS (m/z): 217 (M^+ , <1), 174 ($M-CH_3CO$, 19), 148 ($M-C(CH_3)_2CN$, 7), 105 (PhCO, 100).

3-Hydroxy-2,2-dimethyl-3-phenyl-propionitrile (11a**).** White solid, purified by flash column chromatography (eluent chloroform/

hexane/ethyl ether 6:3.5:0.5), mp 70–73 °C. ^1H NMR (CDCl_3): δ_{H} 1.23 (3H, s), 1.43 (3H, s), 2.25 (1H, d, *OH*, $J = 3.28$ Hz D_2O exchange), 4.56 (1H, d, $J = 3.28$ Hz, s after D_2O exchange), 7.32–7.42 (5H, m) ppm. ^{13}C NMR (CDCl_3): δ_{C} 23.22 (CH_3), 24.26 (CH_3), 39.33 (C), 79.14 (CH), 123.89 (CN), 127.63 (2CH), 128.68 (CH) 139.20 (C) ppm. IR (liquid film): ν_{max} 3454, 2982, 2238, 1683, 1455 cm^{-1} . MS (m/z): 175 (M^+ , <1), 107 ($\text{M}-\text{C}(\text{CH}_3)_2\text{CN}$, 100).

3-Hydroxy-2,2-dimethyl-3-*p*-tolylpropanenitrile (11b). Oil, purified by flash column chromatography (eluent chloroform). ^1H NMR (CDCl_3): δ_{H} 1.22 (3H, s), 1.43 (3H, s), 2.16 (1H, s, *OH*, D_2O exchange), 2.36 (3H, s), 4.52 (1H), 7.18 (2H, d, 2CH), 7.32 (2H, d, 2CH) ppm. ^{13}C NMR (CDCl_3): δ_{C} 21.07 (CH_3), 22.90 (CH_3), 23.94 (CH_3), 39.10 (C), 78.72 (CH), 123.7 (CN), 123.34 (C), 127.17 (2CH), 129.02 (2CH), 135.97 (C) ppm. IR (liquid film): ν_{max} 3460, 2982, 2926, 2877, 2239, 1683, 1516, 1471, 1448, 1260, 1182, 1061, 1019, 818, 747, 706, 515 cm^{-1} . MS (m/z): 189 (M^+ , <1); 121 ($\text{M}-\text{C}(\text{CH}_3)_2\text{CN}$, 100); 93 (55); 77 (Ph^+ , 41).

4-(2-Cyano-1-hydroxy-2,2-dimethyl-ethyl)benzonitrile (11c). Oil, purified by flash column chromatography (eluent chloroform). ^1H NMR (CDCl_3): δ_{H} 1.27 (3H, s), 1.41 (3H, s), 2.45 (1H, d, *OH*, $J = 3.21$ Hz D_2O exchange), 4.64 (1H, d, $J = 3.21$ Hz, s after

D_2O exchange), 7.57 (2H, d, 2CH), 7.66 (2H, d, 2CH) ppm. ^{13}C NMR (CDCl_3): δ_{C} 23.46 (CH_3), 23.63 (CH_3), 39.31 (C), 78.12 (CH), 112.99 (CN), 118.73 (CN) 123.34 (C), 128.61 (2CH), 132.41 (2CH), 144.53 (C) ppm. IR (liquid film): ν_{max} 3454, 2985, 2880, 2232, 1666, 1610, 1467, 1196, 1065 cm^{-1} . MS (m/z): 181 ($\text{M}-\text{H}_2\text{O}$, <1); 132 ($\text{M}-\text{C}(\text{CH}_3)_2\text{CN}$, 100); 104 (70); 77 (Ph^+ , 49); 69 ($\text{C}(\text{CH}_3)_2\text{CN}$, 90).

Acknowledgment. Financial support from MURST (Prin 2006) and Politecnico di Milano is gratefully acknowledged. We thank Professor Francesco Minisci for fruitful chemical discussions. The authors dedicate this article to the memory of their coauthor, Professor Ombretta Porta.

Supporting Information Available: Experimental procedures and spectral data of products **9**, **10a**, **10f**, and **11a–c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA807613Q