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Couplings of Benzylic Halides Mediated by Titanocene Chloride: Synthesis of Bibenzyl Derivatives

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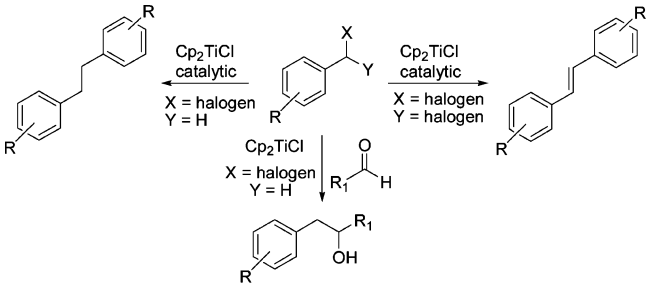

Titanocene monochloride catalyzes the homocoupling of benzylic halides and benzylic *gem*-dibromides to give the corresponding bibenzyl and stilbenyl systems. Exposure of benzylic bromides to Ti(III) in the presence of aldehydes gave rise to the Barbier-type products. Examples of the utility of the herein described processes are included.

Compounds containing the bibenzyl moiety as the core of their structure constitute an interesting group of molecules. These molecules have been used as key intermediates both for the synthesis of dyes, paints, and resins, and for the preparation of a number of natural products as stilbenyl or bibenzyl derivatives. A number of biologically important compounds such as the well-known resveratrol and derivatives,[1] combretastatins[2] and isocombretastatins,[3] or lunularic acid[4] are included among this group of compounds.

Different methods have already been developed to achieve the synthesis of compounds of this type, among them, the homocoupling of benzylic halides mediated mostly by equimolecular quantities of reducing systems such as Ni,[5] Mg,[6] In,[7] Mn/$CuCl_2$,[8] Zn/Cu,[9] SmI_2,[10] $CrCl_2$,[11] Ti(III)citrate/vitamin B_{12} cat.,[12] and salts and carbonyl complexes of Ni, Mn, or Fe.[13] The Pd/C-catalyzed[14] coupling of benzylic chloride, 1-(dichloromethyl)-, and 1-(trichloromethyl)benzene leading to the corresponding bibenzyl systems with uneven yields has also been described. McMurry coupling reaction of different benzaldehydes was used to synthesize a series of stilbenoids.[15] There has also been a very recent description of the stereoselective synthesis of hydroxystilbenoids by ruthenium-catalyzed cross-metathesis.[16] One precedent of the reaction of benzylic and allylic halides using equimolecular quantities of Ti(III) to give the corresponding homocoupling products has been reported by Yanlong et al.[17] Heterocoupling of benzylic halides with benzaldehyde or derivatives has also been reported to be achieved using conventional methods such as Wittig synthesis,[18] condensation via sulfones,[19] and either SmI_2-,[10] $CrCl_2$-,[11] or Mn-mediated[20] carbon−carbon bond forming processes, among others.

As a result of our research into the use of Cp_2TiCl in the synthesis of bioactive natural products, we have recently developed novel processes of homocoupling of allylic halides[21] and vinylepoxides catalyzed by titanocene chloride.[22] Subsequently, we wanted to explore the feasibility of accomplishing Ti(III)-mediated homo- and heterocoupling of benzylic halides. Thus, considering the mechanism proposed for the reaction with allylic halides and vinylepoxides, we surmised that titanocene could well intervene efficiently in the homocoupling of benzylic halides (Scheme 1). Following this mechanistical proposal,

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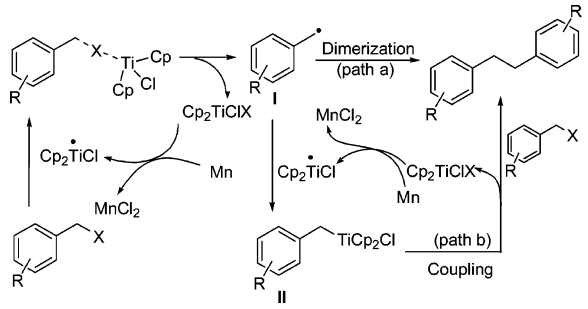
SCHEME 1

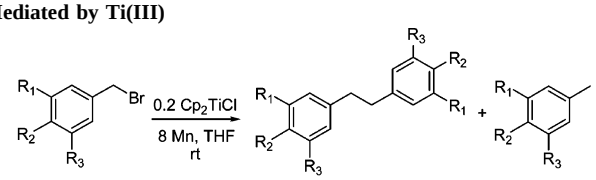


Cp_2TiClX should be released after a SET process; consequently, the excess of Mn present in the medium should permit the regeneration of Ti(III), and thus the process would be susceptible to catalysis by titanium. In this sense, voltammetric and kinetic analyses of the nature of reducing species in titanocene halide-promoted reactions carried out by Skrydstrup and Daasbjerg suggest path b as the most likely process taking place in this coupling reaction.[23]

We started our study by making benzyl bromide (**1a**) react with 0.2 equiv of Cp_2TiCl_2 and 8.0 equiv of Mn in dry and deoxygenated THF (*c* 0.07 M)—conditions which had been previously reported to promote homocoupling reactions of allylic bromides in short reaction times (10−20 min).[21] Under these conditions, the reaction was completed after 8 h, and bibenzyl (**2a**) was obtained in a 73% yield (Table 1, entry 1). The marked lesser reactivity of **1a** when compared to that of allylic bromides could be attributed to the higher stability of the intermediate benzylic radical (**I**, Scheme 1). When the molar concentration of **1a** was increased around 10 times (*c* 0.8 M), a remarkable increase of the reaction rate was noticed (Table 1, entry 2). Furthermore, whereas no reaction was detected after 24 h when benzyl chloride (**1b**) was forced to react under diluted conditions (Table 1, entry 3), a 52% yield of bibenzyl (**2a**) was obtained when the concentration was increased up to 0.8 M (Table 1, entry 4). Additionally, 2-(bromomethyl)naphthalene (**3**) behaved similarly, and a 60% yield of 1,2-bis(naphtyl)ethane (**4a**) was obtained when the concentration used was 0.07 M (Table 1, entry 5).

With the aim of widening the scope of this reaction, the influence of different oxygenated substituents on the aromatic ring was then tested. Thus, the presence of an electron-donating substituent as the methoxy group in *para* position to the bromomethyl moiety made the corresponding methoxybenzyl derivative **5** react within a few minutes to afford **6a** in a 77% yield (Table 1, entry 6). On the other hand, an electron-withdrawing substituent as the carboxymethyl group slowed down the homocoupling process (57%) (Table 1, entry 7), and more concentrated experimental conditions (*c* 0.8 M) were needed to reach satisfactory results (72%) (Table 1, entry 8). Furthermore, good yields were also detected when two or three methoxy groups were present in the starting benzylic bromide (Table 1, entries 9−12). The formation of **12a**, a dimer isolated from *Frullania brittoniae* spp. *Truncatifolia*[24] and comprised in a patented antitumoral composition, constituted a direct synthetic application of this process.

TABLE 1. Homocoupling Reactions of Benzylic Bromides Mediated by Ti(III)



1a R_1 = R_2 = R_3 = H — **2a** — **2b**
5 R_1 = H, R_2 = OMe, R_3 = H — **6a**
7 R_1 = H, R_2 = COOMe, R_3 = H — **8a**
9 R_1 = R_2 = OMe, R_3 = H — **10a** — **10b**
11 R_1 = R_2 = R_3 = OMe — **12a**

entry	benzylic halide	*c* (M)	time	compounds (yield)[a]
1	**1a**	0.07	8 h	**2a** (73%)
2	**1a**	0.8	2 h	**2a** (74%)
3	**1b**	0.07	24 h	
4	**1b**	0.8	8 h	**2a** (52%)[b]
5	**3**	0.07	20 h	**4a** (60%)
6	**5**	0.07	5 min	**6a** (77%)
7	**7**	0.07	7 h	**8a** (57%)[c]
8	**7**	0.8	30 min	**8a** (72%)
9	**9**	0.07	75 min	**10a** (74%)
10	**9**	0.8	35 min	**10a** (70%)
11	**11**	0.07	8 h	**12a** (40%)[d]
12	**11**	0.8	35 min	**12a** (70%)
13[e]	**1a**	0.07	25 min	**2a** (12%) + **2b** (85%)[f]
14[g]	**1a**	0.07	20 min	**2a** (3%) + **2b** (89%)[f]
15[e]	**9**	0.07	15 min	**10a** (15%) + **10b** (83%)

[a] Isolated yield after column chromatography. [b] A 30% yield of starting material was recovered. [c] A 23% yield of starting material was recovered. [d] A 37% yield of starting material was recovered. [e] Conditions: 1.0 equiv of Cp_2TiCl_2, 8.0 equiv of Mn, 5.0 equiv of 1,4-cyclohexadiene, THF, rt. [f] Calculated by NMR. [g] Conditions: 1.0 equiv of Cp_2TiCl_2, 8.0 equiv of Mn, 5.0 equiv of *t*-BuSH, THF, rt.

To gain an insight into the mechanism of this process, benzyl bromide (**1a**) was treated with 1.0 equiv of Ti(III) in the presence of radical reductors such as 1,4-cyclohexadiene or *t*-BuSH (5.0 equiv). In the event, the main product of both reactions was toluene (**2b**), while only minor amounts of bibenzyl (**2a**) were detected (Table 1, entries 13 and 14). This seems to denote that the initially formed benzylic radical is stable enough to be trapped by a proton donor before evolving to the benzyltitanium species. This result was confirmed after noticing that, in the reaction of bromide **9** with 1.0 equiv of Ti(III) and 5.0 equiv of 1,4-cyclohexadiene, the corresponding reduction product **10b** was obtained in a 83% yield (Table 1, entry 15). Since in our previous work on Ti(III)-mediated homocoupling of terpenic allylic halides[21] we postulated that the reacting intermediates were allyltitanium species, we considered that the result of the treatment of allylic halides with titanocene in the presence of hydrogen radical donors would add new evidence to help clarify the mechanistic nature of these two processes. Thus, when geranyl bromide was exposed to 1.0 equiv of Ti(III) in the presence of 5.0 equiv of *t*-BuSH or 1,4-cyclohexadiene, only the corresponding homocoupling product was detected in excellent yields (>90%). It could then be inferred that, in the case of terpenic allylic halides, the rate of reduction of the allylic radical to the allylic titanium is faster than any other collateral process; hence, allyltitanium species are mainly the species involved in the coupling process, while when benzylic halides are considered, the intermediacy of benzylic radicals should not be ruled out.

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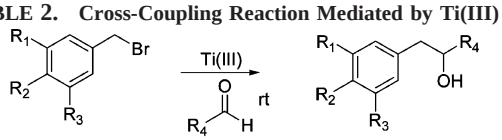
TABLE 2. Cross-Coupling Reaction Mediated by Ti(III)



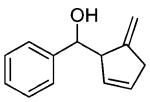
1a R_1 = R_2 = R_3 = H
5 R_1 = H, R_2 = OMe, R_3 = H
9 R_1 = R_2 = OMe, R_3 = H
9 R_1 = R_2 = OMe, R_3 = H
13 R_1 = R_2 = R_3 = H, R_4 = C_6H_5
14 R_1 = H, R_2 = OMe, R_3 = H, R_4 = C_6H_5
15 R_1 = R_2 = OMe, R_3 = H, R_4 = C_6H_5
16 R_1 = R_2 = OMe, R_3 = H, R_4 =

entry	benzylic halide	time	compounds (yield)[a]
1[b]	**1a**	3 h	**13** (38%) + **2a** (5%)
2[c]	**1a**	5 min	**13** (35%) + **2a** (24%)
3[d]	**1a**	10 min	**13** (57%) + **2a** (15%)
4[d]	**5**	5 min	**14** (50%) + **6a** (15%) + **17** (19%)
5[d]	**9**	10 min	**15** (58%) + **17** (20%)
6[d]	**9**	15 min	**16** (60%)

[a] Isolated yield after column chromatography. [b] Conditions: 0.2 equiv of Cp_2TiCl_2, 8.0 equiv of Mn, 7.0 equiv of collidine, 4.0 equiv of TMSCl, THF, rt. [c] Conditions: 2.0 equiv of Cp_2TiCl_2, 8.0 equiv of Mn, THF, rt. [d] For entries 3−6, 1.0 equiv of Cp_2TiCl_2 was used.

Encouraged by the good yields found in the homo C−C bond forming, we decided then to explore the feasibility of accomplishing crossed C−C bonds between benzylic bromides and aldehydes.

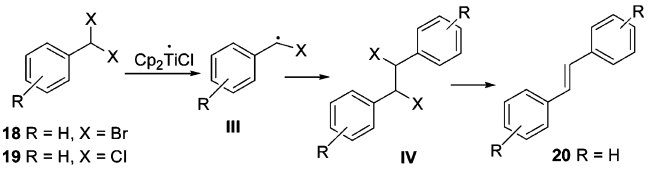
In this sense, there have been recent descriptions of Barbier-type reactions—mostly allylations—mediated by titanocene monochloride using either catalytic quantities[25] or 2 equiv of this reagent.[26] In our hands, when benzyl bromide (**1a**) was reacted with benzaldehyde using catalytic Ti(III) in the presence of the combination Mn/collidine/TMSCl, the cross-coupling adduct **13** was the main reaction product (Table 2, entry 1). On the other hand, when an excess of Ti(III) (2.0 equiv) was added to **1a** and benzaldehyde, the result was similar (Table 2, entry 2). We focused then our efforts to improve the experimental conditions for this cross-coupling. In the event, the use of only 1 equiv of Ti(III) together with the quick and simultaneous addition of the aldehyde and the corresponding benzyl bromide, as well as the employment of an excess of aldehyde due to its tendency to undergo pinacol coupling reactions in the presence of SET reagents, allowed yields of the Barbier-type adducts ranging from 50 to 60% yield (Table 2, entries 3−6). In entries 4 and 5, apart from the corresponding cross-coupling products, a byproduct possessing structure **17** could also be isolated in 19 and 20% yield, respectively. The formation of **17** seems to indicate an unprecedented transference of a cyclopentadienyl moiety from Cp_2TiCl.



17

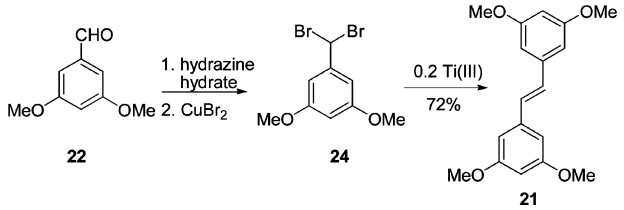
Once we had postulated the intermediacy of radical species in the reaction of benzylic bromides with Ti(III), it was envisioned that stilbene and derivatives could be prepared from the corresponding 1,1-dihalobenzyl derivatives after treatment with catalytic quantities of Ti(III) (Scheme 2). Thus, the benzyl radical initially formed (**III**), now further stabilized by the presence of the halogen atom at α, would dimerize to give the 1,2-dihalodibenzyl derivative (**IV**), which could further evolve to give rise to the formation of the corresponding stilbene derivatives via a Ti(III)-mediated reductive dehalogenation.[27]

SCHEME 2. Synthesis of Stilbene Derivatives



18 R = H, X = Br
19 R = H, X = Cl
III
IV
20 R = H

SCHEME 3. Synthesis of 3,3′,5,5′-Tetramethoxystilbene (21)



22
24
21

Thus, we caused 1,1-dibromobenzyl (**18**) to react with 0.2 equiv of Cp_2TiCl_2 and an excess of Mn (*c* 0.8 M) and found that the reaction took place after 35 min, yielding 74% of *trans*-stilbene (**20**). Under identical experimental conditions, 1,1-dichlorobenzyl (**19**) led after 18 h only to a 32% yield of **20**, with 50% of unaltered starting material being recovered. In our opinion, it deserves to be underlined the ability of catalytic quantities of Ti(III) to promote in an one-pot reaction two chemical transformations, namely, a carbon−carbon bond forming process and the reduction of 1,2-dibromides to the corresponding olefins.

At this juncture, we felt that naturally occurring 3,3′,5,5′-tetramethoxystilbene (**21**), isolated from *Centipeda minima*,[28] could be efficiently synthesized using this catalytic protocol. Compound **21** is contained in a pharmaceutical composition used in the prevention of carcinogenesis,[29] while its tetrahydroxy derivative showed significantly lower IC_{50} values against COX-2 than clinically established celecoxib.[30] This synthesis was designed starting from commercially available 3,5-dimethoxybenzaldehyde (**22**). When this compound was treated with hydrazine hydrate following the conditions described by Takeda et al.,[31] considerable quantities of the corresponding azine were formed. The reduction of the quantity of hydrazine from 20 to 2.5 equiv led efficiently to the corresponding hydrazone, which was converted into dibromide **24** by reaction with $Et_3N/CuBr_2$.[31] Gratifyingly, exposure of **24** to catalytic Ti(III) led to natural product **21** in a 72% yield (Scheme 3).

In summary, the reduction of benzylic halides and benzylic *gem*-dibromides with Cp_2TiCl resulted in good yields of the

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corresponding bibenzyls and stilbenes. Cp_2TiCl also proved to mediate the heterocoupling reaction of benzylic halides and aldehydes. The synthesis of different bibenzyls and stilbenes illustrates the utility of these processes.

Experimental Section

General Procedure for the Catalytic Homocoupling Reaction of Benzylic Bromides Mediated by Ti(III). A mixture of Cp_2TiCl_2 (190 mg, 0.74 mmol) and Mn dust (1620 mg, 29.44 mmol) in thoroughly deoxygenated THF (50 mL) was stirred under an Ar atmosphere at room temperature until the red solution turned green. The corresponding benzylic bromide (3.68 mmol) in strictly deoxygenated THF (2 mL, $C_f = 0.07$ M) was then added to the Cp_2TiCl solution (TLC monitoring). Then, THF was removed, and the reaction was quenched with 1 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding coupling products (**2a**, **4a**, **6a**, **8a**, **10a**, and **12a**). The same procedure was followed when the molar concentration was 0.8.

General Procedure for the Cross-Coupling Reaction Mediated by Ti(III). A mixture of Cp_2TiCl_2 (333 mg, 1.30 mmol) and Mn dust (572 mg, 10.40 mmol) in thoroughly deoxygenated THF (18 mL) was stirred under an Ar atmosphere at room temperature until the red solution turned green. Then, the corresponding benzylic bromide (1.30 mmol, 1.0 equiv) and the corresponding aldehyde (2.60 mmol, 2.0 equiv) were added simultaneously to the Cp_2TiCl solution (TLC monitoring). THF was removed, and the reaction mixture was quenched with 1 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding alcohols (**13**, **14**, **15**, **16**, and **17**). In some cases, minor quantities of homocoupling products were obtained. Please see Table 2.

General Procedure for the Catalytic Homocoupling Reaction of Benzylic *gem*-Dihalides Mediated by Ti(III). A mixture of Cp_2TiCl_2 (61 mg, 0.24 mmol) and Mn dust (528 mg, 9.60 mmol) in thoroughly deoxygenated THF (2 mL) was stirred under an Ar atmosphere at room temperature until the red solution turned green. The corresponding benzylic *gem*-dihalide (1.2 mmol) in strictly deoxygenated THF (1 mL) was then added to the Cp_2TiCl solution (TLC monitoring). Then, THF was removed, and the reaction was quenched with 1 N HCl, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude was purified by column chromatography on silica gel to afford the corresponding stilbene derivatives (**20**, **21**).

Synthesis of 3,3′,5,5′-Tetramethoxystilbene (21). 1-(3,5-Dimethoxybenzylidene)hydrazine (23): Finely powdered 4 Å molecular sieves (2 g) were placed in a flask under argon atmosphere. MeOH (5 mL) and hydrazine hydrate (160 mg, 5.0 mmol) were added successively. After 20 min, a methanol solution (5 mL) of 3,5-dimethoxybenzaldehyde (**22**) (332 mg, 2.0 mmol) was added dropwise to the reaction mixture for 5 min at room temperature (TLC monitoring). Then, molecular sieves were filtered off and washed with *t*-BuOMe. The solvent was concentrated under reduced pressure at 0 °C to obtain 310 mg of **23**. Compound **23** was directly used in the following reaction without purification.

1-(Dibromomethyl)-3,5-dimethoxybenzene (24): Copper(II) bromide (670 mg, 3.0 mmol) was dissolved in MeOH (6 mL) under argon atmosphere. Then, Et_3N (0.15 mL) was added, and the mixture was stirred for 20 min at room temperature. Then, 1-(3,5-dimethoxybenzylidene)hydrazine (**23**) (180 mg, 1.0 mmol) was added dropwise in 3 mL of MeOH for 5 min at 0 °C (TLC monitoring). After being stirred for 5 min, the reaction was quenched by addition of 3.5% NH_3 aqueous solution, extracted with *t*-BuOMe, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to afford **24**: IR (film) 2961, 2936, 2838, 1596, 1461, 1427, 1349, 1323, 1298, 1203, 1158, 1064, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.73 (6H, s), 6.31 (1H, t, $J = 2.2$ Hz), 6.48 (1H, s), 6.62 (1H, d, $J = 2.2$ Hz), 6.63 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.0, 55.6 (2C), 101.9, 104.8 (2C), 143.8, 160.7 (2C).

3,3′,5,5′-Tetramethoxystilbene (21): According to the general procedure described for the homocoupling of benzylic *gem*-dihalides, the resulting crude was purified by column chromatography using hexane as eluent on silica gel to afford 72% of **21**[32] as a colorless solid: Mp 129−130 °C, lit.[32] 130−132 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (12H, s), 6.33 (2H, t, $J = 2.3$ Hz), 6.60 (4H, d, $J = 2.3$ Hz), 6.94 (2H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.5, 100.3, 104.8, 129.3, 139.3, 161.1.

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Supporting Information Available: Experimental procedures and spectroscopic data of new compounds and ^1H and ^{13}C NMR spectra of **2**, **4**−**17**, **20**, **21**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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