Carbonyl Coupling Reactions Catalytic in Titanium and the Use of Commercial Titanium Powder for Organic Synthesis

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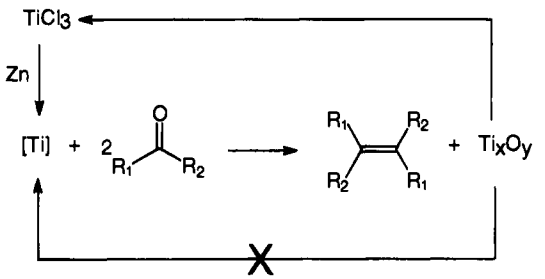
Abstract: The high thermodynamic stability of titanium oxides formed as the inorganic byproducts in McMurry-type reactions has so far prevented the development of a catalytic procedure for such reductive carbonyl coupling processes. Similarly, a tightly bound oxide layer passivates the surface of commercial titanium, which is unreactive toward organic substrates under conventional conditions. This paper outlines a way to overcome both of these problems. Thus, oxoamides **1a**−**h** can be reductively cyclized to indoles **2a**−**h** using only catalytic amounts of low-valent titanium if the reaction is carried out in the presence of a chlorosilane. Specifically, the method is based upon the in situ generation of an activated titanium species from $TiCl_3$ and Zn in the presence of the substrate, followed by regeneration of titanium chloride from the titanium oxides formed via ligand exchange with the admixed chlorosilane. Its proper choice is crucial for obtaining both good turnover numbers and clean conversions. Depending on the product structure, (TMS)Cl, $ClMe_2SiCH_2CH_2SiMe_2Cl$ (**5**), or $ClMe_2Si(CH_2)_3CN$ (**6**) was found to be best suited. Similarly, chlorosilanes also effect the activation of commercial titanium powder which may then be used as a performant off-the-shelf reagent for various types of carbonyl and acetal coupling reactions, for the deoxygenation of epoxides and for the reductive cyclization of oxoamides or oxoesters to indoles, benzofurans, and 2-quinolones. Under these conditions retinal can be reductively dimerized to β-carotene in good yield. Moreover, the titanium/chlorosilane reagent combination exhibits a strong template effect, allowing macrocyclization reactions without recourse to high dilution. Up to 36-membered rings have been closed in that way. ^{29}Si NMR studies provide some insight into the elementary steps responsible for the degradation of the surface oxide layer on titanium by the chlorosilane. The effect of Lewis acid additives on the course of the coupling processes is discussed.

Introduction

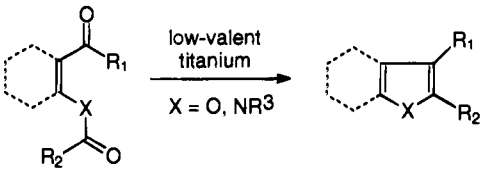
Low-valent titanium [Ti] as reagent combines a high reducing ability with a pronounced oxophilicity. This alliance undoubtedly constitutes the driving force for the reductive coupling of carbonyl compounds to alkenes (Scheme 1). Generally referred to as the "McMurry reaction",[1] this transformation has witnessed its potential in many natural product syntheses, in the formation of strained olefins, and by providing ready access to cycloalkenes independent of the ring size.[2] Moreover, we have recently been able to extend its scope beyond aldehydes and ketones as the traditional starting materials by reductively cyclizing oxoesters[3] (X = O) or oxoamides (X = NR^3) to aromatic heterocycles according to Scheme 2.[4,5]

This "organic chemistry" of titanium, however, has evolved only after techniques of metal high activation have been devised,[6] since a tightly bound and very compact oxide coating

Scheme 1



Scheme 2



renders commercial titanium powder remarkably resistant toward any kind of chemical attack. Reactive forms of metallic or low-valent titanium must therefore be prepared *in situ* by reduction of titanium halides with strong reducing agents (*i.e.*, K, Li, Na, $LiAlH_4$, C_8K, Zn) under inert atmosphere.[1,2a,7] Although these methods have reached a high degree of sophistication and were applied to organic synthesis with considerable success, there remains the inconvenience that (i) the reagent must be prepared batchwise immediately prior to use, (ii) more or less hazardous compounds are necessary for this purpose, and (iii) subtle changes in the reagent preparation may have great impact on

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(1) (a) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513−1524. (b) Lenoir, D. *Synthesis* **1989**, 883−897. (c) Betschart, C.; Seebach, D. *Chimia* **1989**, *43*, 39−49. (d) Robertson, G. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 563−611.

(2) Up to 36-membered carbocyclic rings have been closed; *cf.* (a) Fürstner, A.; Seidel, G. *Synthesis* **1995**, 63−68. (b) Eguchi, T.; Terachi, T.; Kakinuma, K. *Tetrahedron Lett.* **1993**, *34*, 2175−2178.

(3) For carbocycle synthesis via oxoester cyclizations see: McMurry, J. E.; Miller, D. D. *J. Am. Chem. Soc.* **1983**, *105*, 1660−1661.

(4) (a) Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991−6010. (b) Fürstner, A.; Jumbam, D. N., Weidmann, H. *Tetrahedron Lett.* **1991**, *32*, 6695−6696. (c) Fürstner, A.; Jumbam, D. N. *J. Chem. Soc., Chem. Commun.* **1993**, 211−212. (d) Fürstner, A.; Jumbam, D. N.; Seidel, G. *Chem. Ber.* **1994**, 1125−1130. (e) Fürstner, A.; Ernst, A. *Tetrahedron* **1995**, *51*, 773−786. For a related approach to benzofurans see: (f) Banerji, A.; Nayak, S. K. *J. Chem. Soc., Chem. Commun.* **1990**, 150−151.

(5) Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215−5229.

(6) For a review see: Fürstner, A. *Angew. Chem.* **1993**, *105*, 171−197; *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 164−189.

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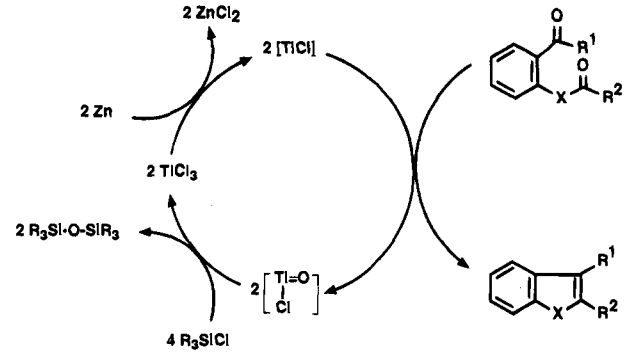
its performance. Finally, it must be mentioned that the high stability of the titanium oxides formed as the inorganic byproducts in any such reaction is not only the thermodynamic sink which drives the conversion, but is also responsible for the fact that all McMurry-type processes reported so far are (over)stoichiometric in titanium.[1] We now present a simple way to overcome these major obstacles: by using chlorosilanes as additives we have not only been able to devise the first carbonyl coupling reactions which are catalytic in titanium, but have also found a convenient way for safely activating commercial titanium powder as an off-the-shelf reagent.

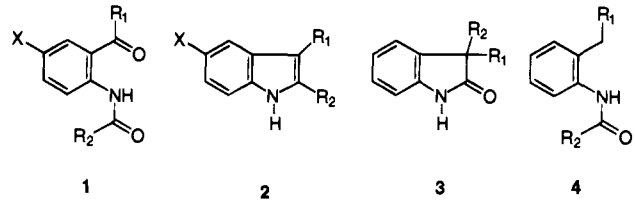
Results and Discussion

Carbonyl Coupling Reactions Catalytic in Titanium. Conventionally, McMurry-type reactions are performed in two consecutive steps:[1] first, the active species [Ti] is prepared by the reduction of $TiCl_x$ ($x = 3, 4$) with a strong reducing agent in an ethereal solvent, and only then the substrate is added to the slurry thus obtained. In contrast to this established way, we have recently outlined a shortcut and simplified procedure in which [Ti] is prepared from $TiCl_x$ ($x = 3, 4$) *in the presence of the starting material*.[5] By further exploring this—still stoichiometric—"instant method", which is highly tolerant toward many functional groups and can be performed even in non-ethereal solvents, we saw a chance for developing the first carbonyl coupling reactions which are catalytic in titanium. Rather than aiming at the direct reduction of the titanium oxides or oxychlorides formed in the carbonyl coupling step, we intended to regenerate $TiCl_x$ ($x = 3, 4$) thereof. This might be achieved by reaction with an admixed chlorosilane, which exhibits a pronounced oxophilicity and is particularly prone to nucleophilic attack. Assuming that the recovered titanium chloride slips into another "instant" coupling event as formally depicted in Scheme 3,[8] this will maintain a catalytic cycle in which a disiloxane accumulates as the final oxygen trap.

In fact, heating a mixture of substrate **1a**, Zn dust, a catalytic amount of $TiCl_3$, and an excess of R_3SiCl in MeCN or DME as solvent afforded the desired indole derivative **2a** in yields comparable to those previously obtained in stoichiometric reactions.[4,5] Table 1 comprises the results of the optimization of the reaction conditions. (TMS)Cl as the cheapest of all chlorosilanes works fine when 5−10 mol % $TiCl_3$ is present (entries 1−3). Since the excess (TMS)Cl as well as the hexamethyldisiloxane formed can be easily removed *in vacuo*, the workup of the reaction mixtures is particularly convenient. It is not surprising to find that a bis(chlorosilane) such as $ClSi(Me)_2CH_2CH_2Si(Me)_2Cl$ (**5**) leads to better turnover numbers due to intramolecular siloxane formation. With this additive only 2 mol % $TiCl_3$ is necessary for complete conversion (entry 8). On the other hand, increased steric bulk of the chlorosilane hampers the oxygen transfer from titanium to silicon and hence the overall conversion (Table 1, entry 5). Importantly, a control experiment showed that the reagent combination Zn/(TMS)Cl without any $TiCl_3$ also promotes conversion of substrate **1a** but leads to a completely different product distribution (Table 1, entry 4).[9] In this case, indole **2a** is obtained as a minor product only, while the formation of the oxindole **3a** *via* pinacol/pinacone rearrangement and simple Clemmensen reduction of **1a** to amide **4a** become the major pathways. It must therefore be concluded that low-valent titanium [Ti] prepared and recycled *in situ* is indeed the actual catalyst for the reductive indole synthesis described above.

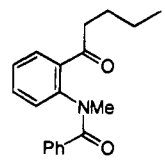
Scheme 3



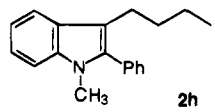


1 2 3 4

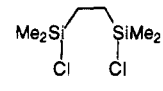
	R1	R2	X
a	Ph	Ph	H
b	Ph	CF_3	H
c	Ph	$(CF_2)_2CF_3$	H
d	Ph	COOEt	Cl
e	Ph	$(CH_2)_{14}CH_3$	H
f	Ph		H
g	Me	Ph	H



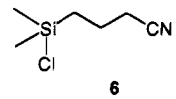
1h



2h



5



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The competition between the titanium-catalyzed indole formation and such uncatalyzed zinc-induced reductions defines the scope of the present method. As can be seen from the results in Table 2, all products bearing an aryl group at C-3 of the indole formed were obtained in high yields in these catalytic carbonyl coupling reactions (Table 2, entries 1−5). The steric and electronic properties of the reacting amide group are of minor importance, which is in accordance with the mechanistic rationale for such titanium-mediated processes previously described.[5] Cyclization of **1f** (ee = 93%) to **2f** (ee = 90%) proves the stereochemical integrity of a preexisting chiral center α to the reacting amide under the reaction conditions.

(7) Leading references: (a) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041−1044. (b) Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* **1973**, 2147−2148. (c) McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708−4709. (d) McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748−3749. (e) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3255−3266 (f) Baumstark, A. L.; McCloskey, C. J.; Witt, K. E. *J. Org. Chem.* **1978**, *43*, 3609−3611. (g) Fürstner, A., Weidmann, H. *Synthesis* **1987**, 1071−1075. (h) Fürstner. A.; Csuk, R.; Rohrer, C.; Weidmann, H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1729−1734. (i) Clive, D. L. J.; Zhang, C.; Murthy, K. S. K.; Hayward, W. D.; Daigneault, S. *J. Org. Chem.* **1991**, 56, 6447−6458.

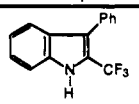
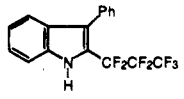
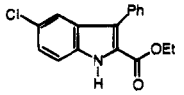
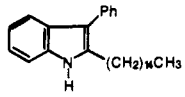
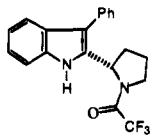
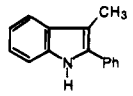
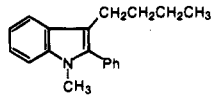
(8) The composition of the reactive intermediates in this catalytic cycle is not yet clear. Even the inorganic part of conventional McMurry reactions is still controversially discussed. While Ti(0) has been anticipated to be the actual coupling agent,[1] thorough investigations have recently revealed that the reduction of $TiCl_n$ ($n = 3, 4$) with either Mg or $LiAlH_4$ definitely does not lead to Ti(0) species. Likewise, it has been shown that titanium suboxides Ti_xO_y rather than TiO_2 are the inorganic byproducts formed; *cf.* (a) Aleandri, L. E.; Bogdanovic, B.; Gaidies, A.; Jones, D. J.; Liao, S.; Michalowicz, A.; Roziere, J.; Schott, A. *J. Organomet. Chem.* **1993**, *459*, 87−93. (b) Aleandri, L. E.; Becke, S.; Bogdanovic, B.; Jones, D. J.; Roziere, J. *J. Organomet. Chem.* **1994**, *472*, 97−112. See also ref 12a.

Table 1. Optimization of the Conversion **1a** → **2a** Using Catalytic Amounts of Titanium[a]

entry	[$TiCl_3$] (mol %)	R_3SiCl (amt (equiv))	amt of Zn (equiv)	product distribution (GC)[b] (%)			
				1a	**2a**	**3a**[c]	**4a**[d]
1	10	(TMS)Cl (5)	5	1.3	92 (80)[f]	6	–
2	10	(TMS)Cl (2.5)	3	4.5	85	11	–
3	5	(TMS)Cl (3)	3	14	85	<1	–
4	0	(TMS)Cl (5)	5	4	19	46	29
5	10	(*i*-Pr)$_3$SiCl (5)[e]	5	29	52	6	–
6	8	(EtO)$_3$SiCl	5		91 (71)[f]		
7	10	**5** (2.5)	5		86[f]		
8	2	**5** (2.5)	5		85[f]		

[a] All reactions were carried out in MeCN at reflux; reaction time 15–30 min unless otherwise stated. [b] Refers to GC yields in the crude reaction mixtures unless otherwise stated. [c] Identified by GC/MS anaylsis. [d] Identified by GC/MS and by comparison with an authentic sample. [e] After 6 h of reaction time. [f] Isolated yield.

Table 2. Reductive Indole Syntheses Catalytic in Titanium[a]

entry	sub-strate	[$TiCl_3$]	R_3SiCl	isolated yield	product
1	**1b**	10%	TMSCl	88%	
2	**1c**	11%	TMSCl	73%	
3	**1d**	10%	TMSCl	79%	
4	**1e**	10%	TMSCl	77%	
5	**1f**[b]	17%	TMSCl	67%	
6	**1g**	5%	TMSCl	--[c]	
7	**1g**	5%	(EtO)$_3$SiCl	43%	
8	**1g**	8%	**6**	82%[d]	
9	**1h**	8%	**6**	67%[d]	

[a] All reactions were carried out in MeCN at reflux unless stated otherwise with Zn dust as the stoichiometric reducing agent; *cf.* Experimental Section; reaction time 15–30 min. [b] **1f**, ee = 93%; **2f**, ee = 90%. [c] Only *N*-(2-ethylphenyl)benzamide (**4g**) as the product of the Clemmensen reduction was obtained in 54% isolated yield. [d] In DME at reflux.

The synthesis of indoles bearing an alkyl group at C-3, however, posed more serious problems. Since the necessary oxoamides exhibit a lower propensity for ring closure,[5] their uncatalyzed reductions by Zn/(TMS)Cl rival the titanium-catalyzed indole formation (Table 2, entry 6). This problem may in principle be overcome by switching from R_3SiCl to $(RO)_3SiCl$ as additive. Although the conversion is then very clean, the workup of the reaction mixture becomes troublesome since the sol–gel formed from the excess of the chlorosiloxane tends to include the indole. As a result, the isolated yields were rather low (Table 2, entry 7) and extensive chromatography was necessary to avoid siloxane impurities in the product. We therefore tried to refine the chlorosilane-based approach.[10] By ligating the chlorosilane to the active titanium species, we expected to entropically bias the crucial oxygen transfer from titanium to silicon. This must accelarate the titanium-catalyzed process which then may better compete with the undesirable Clemmensen-type pathway. Since nitriles are known to be reasonably good ligands to titanium in all oxidation states,[11] $NC(CH_2)_3SiMe_2Cl$ (**6**) as additive might combine the necessary oxophilicity with a sufficient affinity for titanium. In fact, this commercially available reagent turned out to be well suited for catalytic McMurry-type indole syntheses in all cases as evidenced by entries 8 and 9 in Table 2. The fact that the titanium-catalyzed conversion of **1g** with (TMS)Cl in MeCN follows the Clemmensen path while that with $NC(CH_2)_3SiMe_2Cl$ (**6**) in DME exclusively affords indole **2g** clearly features the advancement achieved by tethering the chlorosilane and the cyano function.

Although further investigations on the precise mode of action and on the scope of this approach are necessary, this process constitutes the first carbonyl coupling reaction which is truely catalytic in titanium.[12] Its concept may also be applicable to reactions induced by various other metals.

Organic Syntheses with Commercial Titanium Powder. Titanium is remarkably resistant toward corrosion due to a thin but tightly bound and very compact oxide coating of its surface.

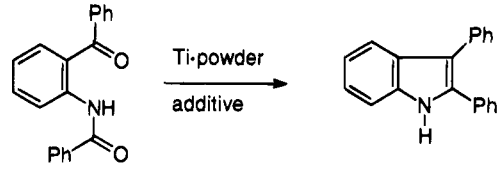
(9) For leading references on the use of R_3SiCl/Zn in organic synthesis see the following *inter alia*. Reduction of ketones to alkenes *via* carbenes: (a) Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1973**, 935. (b) Hodge, P.; Khan, M. N. *J. Chem. Soc., Perkin Trans. 1* **1975**, 809–811. (c) Smith, C. L.; Arnett, J.; Ezike, J. *J. Chem. Soc., Chem. Commun.* **1980**, 653–654. Carbonyl coupling reactions: (d) Banerjee, A. K.; Sulbaran de Carrasco, M. C.; Frydrych-Houge, C. S. V.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1803–1805. (e) Afonso, C. A. M.; Motherwell, W. B.; O'Shea, D. M.; Roberts, L. R. *Tetrahedron Lett.* **1992**, 33, 3899–3902. Carbocycle formation: (f) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821–2824. Pinacolizations: (g) So, J. H.; Park, M. K.; Boudjouk, P. *J. Org. Chem.* **1988**, *53*, 5871–5875. Cyclopropanations: (h) Motherwell, W. B.; Roberts, L. R. *J. Chem. Soc., Chem. Commun.* **1992**, 1582–1583. Reduction of sulfoxides: (i) Schmidt, A. H.; Russ, M. *Chem. Ber.* **1981**, 822–824. Reduction of enediones to 1,4-diketones: (j) Vankar, Y. D.; Kumaravel, G.; Mukherjee, N.; Rao, C. T. *Synth. Commun.* **1987**, *17*, 181–187.

(10) Several other substitutes for (TMS)Cl have been screened with only limited success comprising *inter alia* (TMS)CN, Cl_3SiH, Et_3SiH, $Me_3SiSiMe_3$, Et_3P, Ph_3P, $(EtO)_2P(O)Cl$, $Cl_3SiOSiCl_3$, Ph_2SiCl_2, $(Me_3SiO)_3SiCl$, $ClMe_2SiOSiMe_2OSiMe_2OSiMe_2Cl$, chlorinated silica.

(11) See the following for leading references. (a) TiX_2·2MeCN: Fowles, G. W. A.; Lester, T. E. *Chem. Commun.* **1967**, 47–48. (b) $TiCl_3$·3MeCN: Clark, R. J. H.; Machin, D. J.; Nyholm, R. S. *J. Chem. Soc.* **1963**, 379–387. (c) Substitution of PMe_3 by MeCN in $Cp_2Ti(PMe_3)_2$: Kool, L. B.; Rausch, M. D.; Alt, H. G.; Herberhold, M.; Thewalt, U.; Wolf, B. *Angew. Chem.* **1985**, *97*, 425–426. (d) $TiOCl_2$·2MeCN: Fowles, G. W. A.; Lewis, D. F.; Walton, R. A. *J. Chem. Soc. A* **1968**, 1468–1473.

(12) (a) Although a recent study on partially reduced TiO_2 single crystals was directed toward catalysis, these authors admit that "carbonyl metathesis has still not been accomplished catalytically"; *cf.* Idriss, H.; Libby, M.; Barteau, M. *Catal. Lett.* **1992**, *15*, 13–23. However, these and related model studies provide valuable insight into the nature of the actual coupling agent. Further reading: Idriss, H.; Pierce, K. G.; Barteau, M. *J. Am. Chem. Soc.* **1994**, *116*, 3063–3074. (b) Recently, a low-valent titanium *catalyzed* method for nitrogen fixation based upon the joint use of $TiCl_4$(cat.), Li (50 equiv), and (TMS)Cl (50 equiv) has been reported; *cf.* Mori, M.; Kawaguchi, M.; Hori, M.; Hamaoka, S. I. *Heterocycles* **1994**, *39*, 729–739.

Table 3. Reductive Indole Synthesis **1a** → **2a** Using Commercial Titanium Powder: Optimization of the Reaction Conditions[a]



1a **2a**

entry	amt of Ti (equiv)	R_3SiCl (amt (equiv))	solvent	method[a]	time (h)	yield (GC) (%)
1	3	(TMS)Cl (3)	DME	A	19	≥99 (92)[b]
2	3	(TMS)Cl (3)	THF	A	21	99
3	12	(TMS)Cl (12)	CH_3COOEt	B	25	>99
4	6	(TMS)Cl (6)	MeCN	B	8	1.2
5	10	(TMS)Cl (10)	toluene	B	67	2.3
6	4	(TMS)Cl (0.05)	DME	A	48	6.6
7	1	(TMS)Cl (1)	THF	B	56	5
8	2	(TMS)Cl (2)	THF	B	56	65
9	10	Et_3SiCl (10)[c]	THF	B	1.5[c]	>95
10	10	$Ph_2MeSiCl$ (5)	DME	A	15	>90
11	10	**5** (2.5)	DME	A	15	>90

[a] All reactions were carried out at reflux under Ar. Method A: substrate **1**, Ti dust, and chlorosilane are suspended in the given solvent and heated together in one pot for the time indicated. Method B: the Ti powder is preactivated by heating it for ~40 h together with the chlorosilane in the given solvent prior to the addition of oxoamide **1a**; In these cases only the time for the conversion **1a** → **2a** is reported. [b] Isolated yield.[c] Ti powder preactivated with Et_3SiCl instead of (TMS)Cl for ~70 h prior to the addition of the substrate.

This inertness is essential for all technological applications of this metal. However, such an effective shielding against any kind of attack is of course detrimental from the purely chemical point of view. This explains why commercial titanium powder has never been successfully applied to organic synthesis.[13]

From our studies directed toward carbonyl coupling reactions catalytic in titanium (vide supra) we gained the insight that titanium oxides react reasonably well with chlorosilanes. We therefore assumed that the latter may also lend themselves to the degradation of the oxide layer passivating commercial titanium.[14]

In a first run a mixture of oxoamide **1a** as the model compound, titanium powder and (TMS)Cl in DME was refluxed. A slow but remarkably clean conversion with the *exclusive* formation of 2,3-diphenylindole (**2a**) was observed. The conversion in three different runs was reproducibly >99% in GC, and the isolated yield of 92% favorably compares to the best results previously obtained using highly activated titanium samples.[4,5] Table 3 comprises the results of an optimization of the reaction conditions. DME, THF, and ethyl acetate were found suitable solvents, while the conversion was negligible in toluene and MeCN after the same periods of time. This is somewhat unexpected since MeCN is an appropriate medium for the same transformation with the catalytic $TiCl_3$/Zn/(TMS)-Cl-system described above. By varying the substrate:Ti:(TMS)-Cl ratio, it became evident that (over)stoichiometric amounts of (TMS)Cl are necessary for high yields. Small quantities, just meant to destroy the passivating oxide layer once, were insufficient (Table 3, entry 6). Although a further fine-tuning of the relative proportions of the substrate to Ti and (TMS)Cl seems feasible, all preparative runs compiled in Table 4 were carried out with ≥3 equiv of Ti and (TMS)Cl each. (TMS)Cl may be substituted by other chlorosilanes as evident from entries 9–11 in Table 3.

The coupling reactions can be performed either by heating all components in one pot as described above (method A) or in two steps by reacting the titanium powder with (TMS)Cl prior to the addition of the substrate (method B). If **1a** is added after such an activation phase of ≥40 h to the slurry of Ti and (TMS)-Cl, the reductive indole formation takes place quantitatively in less than 30 min. Control experiments, in which the suspension was carefully filtered under Ar after such a pretreatment, revealed that neither the "activated" titanium nor the greenish filtrate alone showed any appreciable activity for reductive coupling. This clearly evidences that *titanium and the chlorosilane have to be simultaneously present.* While the titanium acts as the reducing agent, the chlorosilane must permanently clean its surface from newly formed oxide coatings in statu nascendi. This may also explain why promotors other than (TMS)Cl such as iodine, 1,2-dibromoethane, $ZnCl_2$, etc., which are well known for entraining different metal-induced reactions,[15] had no appreciable effect on commercial titanium. Curiously and contrary to our expectations, ultrasound (bath as well as horn generators) did not speed up the activation of Ti by (TMS)Cl but led to complete failures under otherwise identical conditions.

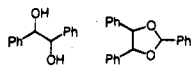
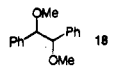
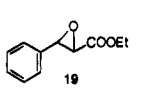
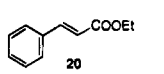
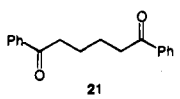
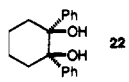
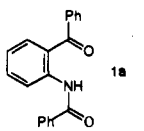
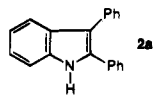
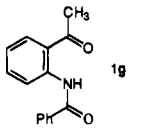
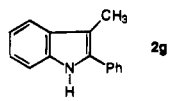
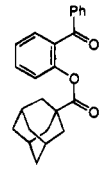
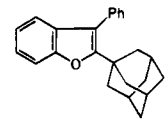
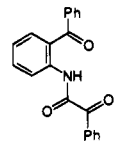
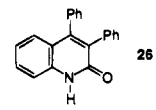
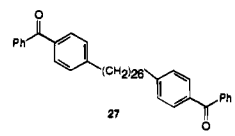
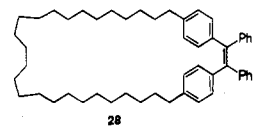
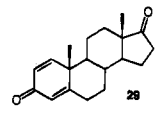
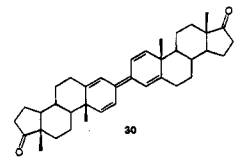
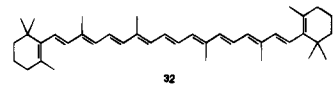
Although at first glance an activation period of ≥40 h may seem inappropriately lengthy, the preparative runs summarized in Table 4 show that patience is rewarded by very clean conversions and excellent yields in the subsequent organic reactions. We found that this procedure nicely applies to a range of different titanium-mediated transformations, including conventional McMurry alkene syntheses, deoxygenation reactions, and heterocycle formations. Thus, benzophenone (**7**) and 9-fluorenone (**9**) reacted without incident and gave tetraphenylethene (**8**) and the overcrowded 9,9′-bisfluorenylidene (**10**),[5] respectively. Benzaldehyde (**14**), after short reaction times, afforded a mixture of pinacol **15** and the benzaldehyde acetal **16** thereof. However, (*E*)-stilbene (**12**) becomes the only product isolated in 90% yield on prolonged heating. This indicates acidic reaction conditions (acetal formation/cleavage) and therefore suggests that an acetal itself may also be a suitable starting material for coupling reactions. In fact, benzaldehyde dimethyl acetal (**17**) was smoothly dimerized to compound **18**

(13) A failed attempt to use commercial titanium powder as the McMurry coupling agent is reported in ref 7e.

(14) For some leading references on the use of (TMS)Cl in combination with metals other than titanium see ref 9 and the following: (a) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, 53, 2390–2392. (b) Takai, K.; Kakiuchi, T.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2671–2673. (c) Jhingan, A. K.; Maier, W. F. *J. Org. Chem.* **1987**, *52*, 1161–1165. (d) Acyloin condensations in the presence of (TMS)Cl: Rühlmann, K. *Synthesis* **1971**, 236–253.

(15) An overview is provided by Blomberg, C. *The Barbier Reaction and Related One-Step Processes*; Springer: Berlin, 1993.

Table 4. Reactions Induced by Commercial Titanium/(TMS)Cl (3–5 equiv of each)[a]

entry	substrate	method	time (h)	product	isolated yield
1	benzophenone (7)	A	72	tetraphenylethene (8)	83%
2	9-fluorenone (9)	B	4	9,9'-bisfluorenylidene (10)	94%
3	*trans*-stilbene oxide (11)	B	0.5	(*E*)-stilbene (12)	81%
4	*cis*-stilbene oxide (13)	B	0.75	(*E*)-stilbene (12)	60%
5	PhCHO (14)	B	77	(*E*)-stilbene (12)	90%
6	PhCHO (14)	A	3	 15 16	28%(15) 35%(16)
7	$PhCH(OMe)_2$ (17)	B	1	 18	88%[b]
8	 19	A	6	 20	77%
9	 21	A	28	 22	60%[c]
10		A	12[d]		79%[c]
11		B	0.5[e]		----
12	 1a	A	19	 2a	92%
13	 1g	A	146	 2g	64%
14		B	77		54%
15		A	29[i]		81%
16		B	2.5[g]		97%[h]
17	 23	A	16	 24	91%
18	 25	B	2.5	 26	73%
19	 27	B	6	 28	90%
20	 29	B	1	 30	84%[j]
21	retinal (31)	B	0.75	 32	85%[k]

[a] Method A: substrate, titanium dust, and (TMS)Cl are suspended in DME and heated together in one pot for the time indicated. Method B: the Ti powder is preactivated by heating it with (TMS)Cl in DME for ~40 h prior to the addition of the substrate; in these cases only the time for the coupling reaction is indicated. [b] D/L:*meso* ≈ 1:1. [c] One diastereoisomer only; its stereochemistry has been assigned as *cis* by comparison with literature data.[23] 1,2-Diphenylcyclohexene (10%)[7g] was formed as the byproduct. [d] In the presence of $Ti(O\text{-}i\text{-}Pr)_4$ (1 equiv). [e] In the presence of $ZnCl_2$ (20 mol %). [f] In the presence of catalytic amounts of $Ti(O\text{-}i\text{-}Pr)_4$ (10 mol %). [g] In the presence of $(i\text{-}Pr\text{-}O)_3TiCl$ (9 mol %). [h] Refers to GC yield. [i] (*E*):(*Z*) = 1:1. [j] A large excess of both Ti dust and (TMS)Cl (30 equiv of each) has been used and turned out not to be detrimental to the unprotected keto function (*cf.* procedure in the Experimental Section). [k] The product contains traces (~5% as estimated by ^{13}C NMR) of the (*Z*)-isomer at the newly formed double bond.

(D/L:*meso* ≈ 1:1) by Ti/(TMS)Cl.[16] Both *trans*- as well as *cis*-stilbene oxides (**11** and **13**) were reduced to (*E*)-stilbene (**12**) as the only product. Since a control experiment confirmed that (*Z*)-stilbene does not isomerize to the thermodynamically more stable (*E*)-isomer under reaction conditions, a nonsynchronous cleavage of the C–O bonds of the epoxide rings must happen. Homolytic rupture of oxirane rings by low-valent titanium is well precedented in the literature.[17] Likewise, the glycidate **19** was reduced to ethyl cinnamate (**20**) without problems.

Most gratifyingly, intramolecular carbonyl coupling reactions with Ti/(TMS)Cl as the reagent system were found to proceed particularly well. In addition to the formation of 2,3-diphenylindole (**2a**) from oxoamide **1a** (Table 3), oxoester **23** was readily converted into benzo[*b*]furan **24** and the trifunctional substrate **25** gave the respective 2-quinolone **26** in good yield.[18] Most strikingly, however, derivative **27**[2a] gave the 36-membered alkene **28** in 90% isolated yield, although it was added at once to the refluxing Ti slurry and no precautions at all were taken for providing high dilution conditions. That this essentially quantitative macrocyclization takes place even at a 0.02 M concentration must be attributed to an *exceptional template effect exerted by the chemically activated titanium surface.*

The indications previously gathered for a close relationship between the redox potential of the carbonyl compound and the ease of its conversion[5] have been confirmed by the present study. While diaryl ketones react smoothly even when crowded alkenes such as **10** are formed, aryl alkyl ketones were found to couple very slowly and dialkyl ketones are inert. The same holds true in the aldehyde series. In line with such a likely correlation between the electronic properties and the reactivity of a given substrate is the observation that all α,β-unsaturated carbonyl compounds get readily converted on exposure to Ti/(TMS)Cl. Simple enones or enals, however, such as 2-cycloheptenone, 2-cyclopentylidenecyclopentanone, and citral led to product mixtures, since the trienes initially formed undergo subsequent cycloaddition reactions as evidenced by GC/MS analyses. Nevertheless, this reactivity pattern could be successfully exploited for a completely chemo- and regioselective transformation of androsta-1,4-diene-3,17-dione (**29**) at the enone site without the unprotected ketone group interfering in this McMurry process.[19,20] Moreover, the dimerization of retinal (**31**) to β-carotene (**32**) under standard conditions did not pose

(16) For similar reductive coupling reactions of acetals see: Ishikawa, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2059–2063.

(17) (a) McMurry, J. E.; Silvestri, M. G.; Fleming, M. P.; Hoz, T.; Grayston, M. W. *J. Org. Chem.* **1978**, *43*, 3249–3255. (b) RajanBabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986–997 and references cited therein.

(18) For a [Ti]-induced synthesis of coumarins and quinolones see: Fürstner, A.; Jumbam, D. N.; Shi, N. *Z. Naturforsch. B* **1995**, *50B*, 326–331.

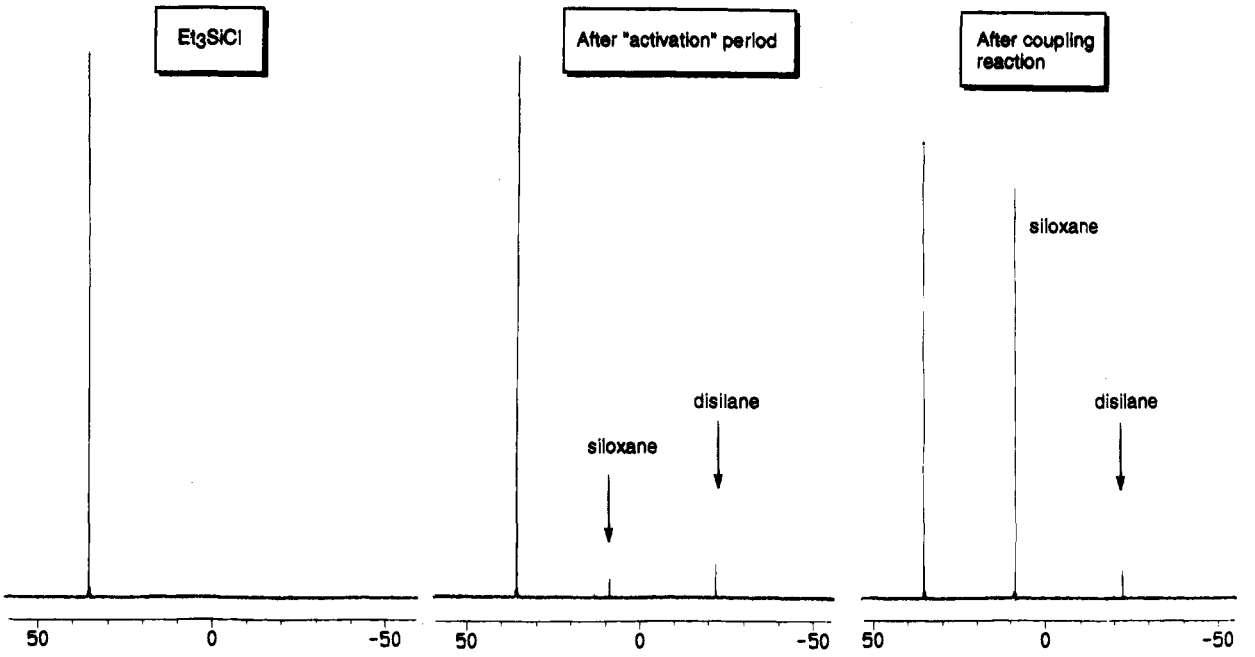


Figure 1. −50 → +50 ppm region of the ^{29}Si NMR spectra of (a) Et_3SiCl, (b) the reaction mixture after the activation phase (Ti, Et_3SiCl, THF-d_8, 70 h, reflux), and (c) the reaction mixture after the coupling reaction **1** → **2**.

particular problems. This example may well highlight another advantage of using commercial titanium powder as the coupling agent: it is the only procedure in which *only titanium compounds* are involved, while all other metal salts are excluded (this contrasts, *e.g.*, favorably all processes based on the reduction of $TiCl_3$ with Zn in which substantial amounts of $ZnCl_2$ are formed); since titanium salts are of little pharmacological concern, this method may be well suited for application to pharmaceutical chemistry.

Attempts were made to lower the redox potentials of those substrates which react reluctantly or not at all with Ti/(TMS)-Cl by complexation to an appropriate Lewis acid. Oxoamide **1g**, *e.g.*, afforded indole **2g** upon treatment with titanium dust very slowly (Table 4, entries 13 and 14). Addition of either $(i\text{-PrO})_4Ti$[21] (entry 15) or $(i\text{-PrO})_3TiCl$ (entry 16) to the reaction mixture, however, significantly accelerated the conversion. The same positive effect was experienced during the cyclization of 1,6-diphenylhexane-1,6-dione (**21**) to pinacol **22** (*cf.* entries 9 and 10). Stronger Lewis acids such as $ZnCl_2$, however, were inappropriate because they catalyzed intramolecular aldol condensation of this particular substrate (entry 11). Pentadecan-8-one, which was recovered unchanged after prolonged exposure to Ti/(TMS)Cl, was reduced by this reagent combination to the corresponding alcohol (33% isolated yield) in the presence of catalytic amounts of $(i\text{-PrO})_4Ti$. These results may raise the question of whether (TMS)Cl itself not only activates the titanium but also acts as a Lewis acid facilitating the electron transfer from the metal to the substrate.[22] Although we cannot rigorously exclude this hypothesis, the fact that the ^{13}C NMR shifts as well as the IR bands of the carbonyl groups in **1a** do not change in the presence of (TMS)Cl (5 equiv) makes such an effect rather unlikely.

^{29}Si NMR experiments shed some light onto the mode of action of the Ti/R_3SiCl reagent combination (Figure 1). After refluxing commercial titanium powder with Et_3SiCl (δ +35.4 ppm) in THF-d_8 for 70 h, resonances due to small amounts of $Et_3SiOSiEt_3$ (δ +8.9 ppm) as well as of the respective disilane $Et_3SiSiEt_3$ (δ −22.9 ppm) were observed. This indicates that redox reactions coincide with the destruction of the oxide layer by the chlorosilane during the activation phase. NMR inspection of the same mixture after addition of **1a** and its complete conversion to indole **2a** clearly showed that during the coupling step, however, only the peak due to the disiloxane gains intensity at the expense of the chlorosilane, while the disilane signal does not increase any further.

In summary, we have shown that commercial titanium powder may simply be activated by heating with a chlorosilane and can be used as a highly performant off-the-shelf reagent for a great number of different carbonyl coupling reactions, reductions, and heterocycle syntheses. It features an excellent chemoselectivity and exhibits a strong template effect for intramolecular processes. Furthermore, it was found that chemically activated metallic titanium completely distinguishes between aromatic and aliphatic substrates. This raises once more the question of the actual nature of those titanium species prepared by reduction of $TiCl_3$ with strong reducing agents,[8,12a] which have been claimed to consist of Ti(0)[1] but do not show this particular profile. Further investigations on the preparative scope of this method, the precise mode of action of the chlorosilanes, electron microscopic studies on the morphology of (TMS)Cl-pretreated titanium, and extensions to metals other than titanium are in progress.

Experimental Section

General Procedures. For the instrumentation used see refs 2a and 5. All reactions were carried out under Ar unless stated otherwise.

(19) Examples in which unprotected ketones kinetically survive McMurry reactions are very rare; *cf.* (a) ref 4c. (b) Dauben, W. G.; Farkas, I.; Bridon, D.; Chuang, C. P.; Henegar, K. E. *J. Am. Chem. Soc.* **1991**, 113, 5883–5884. (c) Wu, Y. J.; Burnell, D. J. *Tetrahedron Lett.* **1988**, 4369–4372. (d) Ziegler, F. E.; Lim, H. *J. Org. Chem.* **1982**, *47*, 5229–5230. (e) Fürstner, A.; Ptock, A.; Weintritt, H.; Goddard, R.; Krüger, C. *Angew. Chem.* **1995**, *107*, 725–728.

(20) For the same conversion using Zn/(TMS)Cl see: Schmidt, A.; Beckert, R.; Weiß, D. *Tetrahedron Lett.* **1992**, 4299–4300.

(21) NMR inspection shows that rapid ligand exchange takes place between (TMS)Cl and $(i\text{-PrO})_4Ti$ with *in situ* formation of $(i\text{-PrO})_3TiCl$ and $Me_3SiO\text{-}i\text{-Pr}$.

(22) For discussions of the accelerating effect of chlorosilanes on reactions of carbonyl compounds with organometallics see *inter alia*: (a) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056–8066. (b) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, 6015–6018. (c) Alexakis, A.; Berlan, J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047–1050.

$TiCl_3$ was obtained from Aldrich (99% purity). Titanium powder was from Alfa, Johnson Matthey (99%); no significant differences using either a ~325 mesh or a ~100 mesh sample have been found. (TMS)-Cl was purchased from Janssen and distilled prior to use. All other chlorosilanes were purchased from Petrarch or Aldrich and used as received. The solvents were dried by distillation over the following drying agents: THF (Na/benzophenone), DME (Na/K alloy), DMF, CH_2Cl_2, MeCN (CaH_2). Flash chromatography was performed on Merck silica gel 60 (230–400 mesh). The oxoamides **1a–h** were prepared as described previously.[5]

(TMS)Cl-Mediated Indole Synthesis Catalytic in Titanium. Representative Procedure. To a suspension of $TiCl_3$ (65 mg, 10 mol %), oxoamide **1b** (1.23 g, 4.19 mmol),[5] and Zn dust (1.37 g, 21.04 mmol) in MeCN (18 mL) was added (TMS)Cl (2.29 g, 21.04 mmol) via syringe. The mixture was refluxed with a preheated oil bath for 30 min, cooled, diluted with ethyl acetate (25 mL), and filtered through a pad of silica, the filtrate was evaporated, and the residue was purified by flash chromatography with hexane/ethyl acetate (10:1) as eluent. This afforded 3-phenyl-2-(trifluoromethyl)indole (**2b**) (961 mg, 88%) as pale yellow crystals: mp 63–64 °C (lit.[5] mp 63–64 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.19 (td, 1H, J = 7.5, 1.3 Hz), 7.32–7.56 (m, 7H), 7.64 (d, 1H, J = 8.0 Hz), 8.45 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 111.7, 119.9, 121.1, 121.2 (q, J = 37 Hz), 121.3, 121.7 (q, J = 267 Hz), 125.1, 127.4, 127.6, 128.4, 130.0, 132.2, 135.0; MS *m/z* (relative intensity) 261 (100, [M$^+$]), 240 (12), 222 (10), 221 (11); IR (cm^{-1}) 3460, 1600, 1580, 1560, 1500, 1450, 1380, 1330, 1250, 1210, 1180, 1150, 1130, 1110, 780, 750, 710.

The following indoles have been obtained analogously.

2,3-Diphenylindole (2a): colorless crystals; mp 122–124 °C (lit.[4a] mp 122–124 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.38–7.66 (m, 13H), 7.93 (d, 1H), 8.18 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 111.2, 115.3, 119.9, 120.6, 122.9, 126.4, 127.7, 128.4, 128.7, 128.8, 129.0, 130.4, 132.8, 134.3, 135.3, 136.1; IR (cm^{-1}) 3413, 3059, 2977, 2873, 1602, 1504, 1483, 1455, 1439, 1329, 1251, 1100, 1071, 764, 745, 700.

3-Phenyl-2-(heptafluoropropyl)indole (2c): colorless crystals; mp 67–68 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.02 (td, 2H, J = 8.0 Hz, 1.1 Hz), 7.18–7.38 (m, 7H), 8.27 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 111.5, 113.7 (t, J = 32 Hz), 121.2, 122.7, 125.3, 127.6, 128.0, 128.2, 130.5, 132.2, 135.6; ^{19}F NMR ($CDCl_3$, 188 MHz) δ −80.8, −106.5, −126.9; MS *m/z* (relative intensity) 362 (19), 361 (100, [M$^+$]), 242 (56), 222 (48), 111 (10); IR (cm^{-1}) 3490, 3420, 3065, 1720, 1609, 1565, 1492, 1448, 1375, 1342, 1230, 1145, 1110, 1080, 1010, 985, 942, 935, 880, 770, 740, 700.

Ethyl 5-Chloro-3-phenylindole-2-carboxylate (2d): pale yellow solid; mp 174–175 °C (lit.[5] mp 174–175 °C; lit.[4c] mp 178–180 °C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.21 (t, 3H, J = 7.2 Hz), 4.28 (q, 2H, J = 7.2 Hz), 7.34–7.61 (m, 8H), 12.20 (br s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 13.7, 60.3, 114.3, 119.2, 121.6, 124.0, 124.9, 125.0, 126.9, 127.5, 127.6, 128.2, 129.5, 130.1, 132.7, 134.3, 160.8.

3-Phenyl-2-pentadecylindole (2e): syrup (lit.[4a] oil, lit.[5] mp 42–43 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (t, 3H, J = 7.3 Hz), 1.26 (br s, 26H), 2.83 (t, 2H, J = 7.5 Hz), 7.14 (m, 2H), 7.29 (m, 2H), 7.48 (m, 4H), 7.64 (d, 1H, J = 7.1 Hz), 7.91 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 22.7, 26.3, 29.4, 29.5, 29.6, 29.7, 29.9, 31.9, 110.3, 114.4, 118.9, 119.8, 121.4, 125.8, 127.9, 128.4, 129.6, 135.2, 139.5, 136.1; MS *m/z* (relative intensity) 403 (96, [M$^+$]), 207 (31), 206 (100); IR (cm^{-1}) 3390, 2922, 2858, 1620, 1605, 1498, 1460, 1330, 770, 755, 725, 703.

(*S*)-(−)-3-Phenyl-2-[*N*-(trifluoroacetyl)-2′-pyrrolidyl)indole (2f): mp 73–75 °C dec (lit.[5] mp 73–75 °C); $[\alpha]_D^{20}$ −27.9° (*c* 0.8, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz, [rotamer]) δ 1.82–2.27 (m, 4H), 3.54–3.83 (m, 2H), 5.43 (dd, 1H, J = 8.0, 5.4 Hz), [5.63 (d, 0.3H, J = 7 Hz)], 7.05–7.55 (m, 9H), 8.40 (br s, 1H), [8.79 (br s, 0.3H)]; ^{13}C NMR ($CDCl_3$, 100 MHz, [rotamer]) δ 21.6, 25.1, 32.0, 35.9, 47.6, [48.9], [55.8], 56.8, 68.3, 110.9, [111.3], 114.1, 115.3, 116.2 (q, J = 288 Hz), [119.2], 119.3, 120.1, [120.3], [122.4], 122.5, [126.6], 126.7, [128.3], 128.5, [128.6], 128.7, 129.7, 130.2, [131.0], 133.2, [134.3], [134.5], 134.7, 135.1, [135.2],156.2 (q, J = 37 Hz), [157.2]; IR (cm^{-1}) 3370, 3060, 2960, 2940, 1680, 1460, 1240, 1200, 1150, 750, 700. The determination of the enantiomeric purity of this product (ee = 90%) was performed with LC: Varian 5060, UV 100 on a Chiraspher column (250 mm, ϕ 4.5 mm) at 308 K with *n*-heptane/2-propanol (95/5) as eluent; flow, 1.0 mL/min; detection, UV 254 nm.

1,2-Bis(chlorodimethylsilyl)ethane (5)-Mediated Indole Synthesis Catalytic in Titanium. To a suspension of $TiCl_3$ (10 mg, 2 mol %), oxoamide **1a** (1.01 g, 3.36 mmol),[4a,5] and zinc dust (1.10 g, 16.83 mmol) in MeCN (5 mL) was rapidly added a solution of chlorosilane **5** (1.88 g, 8.72 mmol) in MeCN (7 mL). The resulting mixture was refluxed with a preheated oil bath under argon for 15 min, cooled, diluted with CH_2Cl_2 (25 mL), and filtered through a pad of silica. Evaporation of the yellow filtrate and flash chromatography of the residue (hexane/ethyl acetate 15:1) afforded 2,3-diphenylindole (**2a**) as colorless crystals (768 mg, 85%), which exhibited the same analytical and spectroscopic data as shown above.

4-(Chlorodimethylsilyl)butyronitrile (6)-Mediated Indole Synthesis Catalytic in Titanium. To a suspension of oxoamide **1h** (295 mg, 1.0 mmol),[5] $TiCl_3$ (13 mg, 8 mol %), and Zn dust (327 mg, 5.0 mmol) in DME (10 mL) was added compound **6** (0.81 mL, 5.0 mmol). The mixture was refluxed with a preheated oil bath for 1 h, cooled, and filtered through a pad of silica, the filtrate was evaporated, and the residue was purified by flash chromatography with hexane/ethyl acetate (10:1) as eluent. Thus, indole **2h** (177 mg, 67%) was obtained as pale yellow syrup (lit.[5] syrup): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.72 (t, 3H, J = 7.3 Hz), 1.10–1.28 (m, 2H), 1.41–1.59 (m, 2H), 2.58 (t, 2H, J = 7.6 Hz), 3.45 (s, 3H), 6.96–7.42 (m, 8H), 7.54 (dt, 1H, J = 7.4, 1.1 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.9, 22.7, 24.3, 30.7, 39.5, 109.3, 113.9, 119.0, 119.1, 121.5, 127.8, 128.3, 130.6, 132.4, 137.2, 137.9; MS *m/z* (relative intensity) 263 (29, [M$^+$]), 221 (19), 220 (100) 204 (13); IR (cm^{-1}) 3060, 2960, 2930, 2860, 1605, 1470, 1440, 1430, 1365, 1335, 1235, 755, 740, 700.

3-Methyl-2-phenylindole (2g). **2g** was prepared as described above: colorless crystals; mp 91–93 °C (lit.[4a] mp 90–92 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.52 (s, 3H), 7.18–7.61 (m, 9H), 8.06 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 9.9, 109.0, 110.9, 119.2, 119.8, 122.6, 127.8, 128.0, 128.8, 130.0, 131.6, 134.3, 136.2; IR (cm^{-1}) 3416, 3043, 2941, 2917, 1607, 1480, 1461, 1448, 1375, 1287, 1089, 740.

Representative Procedure for the Activation of Commercial Titanium (Method A). Synthesis of 2,3-Diphenylindole (2a). A 25 mL two-necked flask, equipped with a Teflon-coated magnetic stirring bar and a reflux condenser connected to an argon line, was charged with oxoamide **1a** (660 mg, 2.19 mmol), DME (10 mL), Ti powder (315 mg, 6.54 mmol), and (TMS)Cl (713 mg, 6.54 mmol). The mixture was refluxed for 19 h until TLC showed complete conversion of the substrate, cooled to room temperature, and filtered through a short pad of silica. The inorganic residues were washed with ethyl acetate (20 mL) in several portions, the filtrate was evaporated, and the residue was purified by flash chromatography using 10% ethyl acetate in *n*-hexane as eluent, affording 2,3-diphenylindole (**2a**) (543 mg) as colorless crystals. The analytical and spectroscopic data of the product were identical with those reported above.

Tetraphenylethene (8). **8** was obtained as described above: colorless crystals; mp 220–222 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.00–7.13 (m, 20H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 126.42, 127.66, 131.35, 141.00, 143.74; identical with an authentic sample.[7g]

2-(1-Adamantyl)-3-phenylbenzo[*b*]furan (24). **24** was obtained as described above; colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.61 (s, 6H), 1.90 (s, 9H), 7.03 (d, 2H, J = 4 Hz), 7.08–7.19 (m, 1H), 7.26–7.37 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.34, 36.70, 36.97, 41.54, 110.45, 115.48, 119.52, 122.20, 123.48, 127.24, 128.00, 130.93, 131.75, 134.00, 152.56, 160.42. MS *m/z* (relative intensity): 328 ([M$^+$], 100), 271 (25), 243 (11), 165 (10). IR (cm^{-1}) 2920, 2860, 1610, 1590, 1495, 1465, 1320, 1250, 1170, 1055, 980, 965, 795, 740, 700.

Method A: Titanium-Induced Carbonyl Coupling Reactions in the Presence of Lewis Acid Additives. Synthesis of *cis*-1,2-Diphenyl-1,2-cyclohexandiol (22). A suspension of titanium powder (2.40 g, 50.10 mmol), 1,6-diphenylhexane-1,6-dione (**21**) (0.667 g, 2.50 mmol),[7h] Ti(O-*i*-Pr)$_4$ (0.712 g, 2.50 mmol), and (TMS)Cl (5.46 g, 50.10 mmol) in DME (8 mL) was refluxed for 12 h under Ar and filtered through a short pad of silica, the inorganic residues were washed with THF, the combined filtrates were evaporated, and the crude residue was chromatographed (SiO_2, hexane/ethyl acetate, 10:1, as eluent). A first fraction was identified as 1,2-diphenylcyclohexene (59 mg, 10%) by comparison with an authentic sample.[7g] The slower moving fraction

consisted of *cis*-1,2-diphenylcyclohexane-1,2-diol (**22**) (0.530 g, 79%): mp 73−74 °C (lit.[23] mp 73.2−73.9 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.51−1.80 (m, 6H), 1.96 (t, 2H), 2.82 (t, 2H), 7.01−7.18 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 20.8, 34.5, 76.8, 126.7, 126.8, 127.0, 144.2.

Representative Procedure for Intermolecular Coupling Reactions with Commercial Titanium Powder (Method B): Synthesis of 9,9′-Bisfluorenylidene (10). Titanium powder (0.793 g, 16.55 mmol) was suspended in DME (10 mL), (TMS)Cl (2.0 mL, 16.6 mmol) was added, and the mixture was refluxed for 67 h under argon. 9-Fluorenone (**9**) (0.911 g, 5.06 mmol) was added at once to the boiling suspension, and reflux was continued for another 4 h. The mixture was allowed to cool to ambient temperature and filtered through a short pad of silica, the insoluble residues were rinsed with THF in several portions (ca. 100 mL), the combined filtrates were evaporated, and the residue was purified by flash chromatography (SiO_2, hexane/ethyl acetate, 10:1, as eluent), affording compound **10** (0.780 mg, 94%) which was identical to an authentic sample:[5] orange-red crystals; mp 187−189 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.15−7.35 (m, 8H), 7.68 (dd, 4H, J = 7 Hz, 1 Hz), 8.37 (d, 4H, J = 7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 119.87, 126.71, 126.83, 129.13, 138.25, 141.00, 141.30; MS *m/z* (relative intensity) 328 (100, [M$^+$]), 162 (23); IR (cm^{-1}) 3060, 1715, 1605, 1475, 1444, 1350, 1280, 940, 875, 786, 761, 743, 720, 639, 586.

The following products have been prepared analogeously.

(*E*)-Stilbene (12): colorless crystals; mp 121−122 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.05 (s, 2H), 7.16−7.43 (m, 6H), 7.51 (d, 4H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 126.5, 127.6, 128.6, 128.7, 137.3; identical with a commercial sample.

1,2-Diphenyl-1,2-ethanediol (*meso* + D,L) (15): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.94 [2.31] (br s, 2H), 4.58 [4.72] (s, 2H), 6.99−7.23 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 79.11 [78.08], 126.99 [127.12], 127.92 [128.08], 128.13 [128.21], 139.91; MS *m/z* (relative intensity) 214 (3, [M$^+$]), 108 (100), 107 (91), 79 (62), 77 (28); IR (cm^{-1}) 3390, 3060, 3030, 2900, 1600, 1492, 1453, 1205, 1055, 1032, 1003, 915, 798, 764, 700, 622, 563.

2,4,5-Triphenyl-1,3-dioxolane (16): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.87 (s, 2H), 6.32 (s, 1H), 6.94−7.44 (m, 13H), 7.59 (dd, 2H, J = 8 Hz, 2 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 85.22, 87.14, 104.65, 126.39, 126.63, 126.87, 128.18, 128.44, 128.50, 128.55, 128.63, 129.32, 136.50, 138.10, 138.21.

1,2-Dimethoxy-1,2-diphenylethane (18). D/L:*meso* $\approx$ 1:1. The stereochemistry of the isomers has not been unambigously assigned. Faster moving fraction: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.14 (s, 6H), 4.29 (s, 2H), 7.16−7.25 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 57.1, 86.9, 127.6, 127.7, 128.0, 138.5. Slower moving fraction: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.26 (s, 6H), 4.30 (s, 2H), 6.95−7.19 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 57.1, 87.6, 127.5, 127.8, 138.2; MS *m/z* (relative intensity) 242 (0.1, [M$^+$]), 121 (100), 77 (13); IR (cm^{-1}) 3060, 3030, 2970, 2925, 2890, 2860, 2820, 1490, 1455, 1215, 1115, 1090, 970, 962, 840, 830, 768, 700, 640, 627, 595, 520.

Ethyl Cinnamate (20): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.33 (t, 3H), 4.26 (q, 2H), 6.43 (d, 1H, J = 16 Hz), 7.36 (m, 3H), 7.50 (m, 2H), 7.68 (d, 1H, J = 16 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.17, 60.30, 118.15, 127.89, 128.70, 130.04, 134.33, 144.38, 166.83. The product was identical with a commercial sample in all spectroscopic respects.

β-Carotene (32): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.96 (s, 12H), 1.18−2.00 (m, 30H), 5.90−6.80 (m, 14H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.79, 19.32, 20.81, 21.80, 29.02, 33.15, 34.32, 39.71, 125.06, 126.67, 129.38, 130.02, 130.88, 132.46, 136.01, 136.48, 137.28, 137.81, 137.95; IR (cm^{-1}) 2970, 2930, 1720, 1670, 1450, 1380, 1360, 970.

Intramolecular Dicarbonyl Coupling Reactions with Commercial Titanium (Method B): Synthesis of 1,2-Diphenyl(2,26)[36]-paracyclophan-1-ene (28). A suspension of titanium powder (0.626 g, 13.07 mmol) in DME (10 mL) and (TMS)Cl (1.59 mL, 13.07 mmol) was refluxed for 68 h. To this preactivated titanium reagent 1,26-bis-(4-benzoylphenyl)hexacosane (**27**) (147 mg, 0.202 mmol)[2a] was added at once, and the mixture was refluxed for 6 h to ensure complete cyclization of this substrate. The suspension was filtered, the filtrate was evaporated, and the residue was chromatographed (SiO_2, hexane/ethyl acetate, 20:1, as eluent), thus affording the title compound (126 mg, 90%) as colorless crystals: mp 108−109 °C (lit.[2a] mp 108−109 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.18 (s, 36H), 1.21 (s, 8H), 1.46 (br s, 4H), 2.42 (t, 4H, J = 7.5 Hz), 6.82 (m, 8H), 6.98 (m, 10H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 28.50, 28.60, 28.72, 28.92, 29.06, 29.29, 29.38, 29.61, 29.77, 31.26, 35.64, 126.18, 127.56, 128.01, 131.20, 131.42, 140.62, 140.98, 141.11, 144.12; MS *m/z* (relative intensity) 695 (61), 694 (100, [M$^+$]).

3,4-Diphenyl-2-quinolone (26). 26 was prepared according to the procedure described above: colorless crystals; mp 303-305 °C (lit.[18] mp 303−305 °C); ^{1}H NMR (DMSO-d_6, 200 MHz) δ 6.98−7.56 (m, 14H), 12.04 (br s, 1H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ 115.2, 119.9, 121.8, 126.6, 126.9, 127.2, 127.6, 128.0, 128.7, 129.5, 129.9, 130.2, 130.7, 132.0, 135.8, 136.2, 138.3, 148.2, 161.3.

Chemoselective Coupling of Androsta-1,4-diene-3,7-dione (29) Using Commercial Titanium (Method B). A 25 mL two-necked flask, equipped with a Teflon-coated magnetic stirring bar and a reflux condenser connected to an argon line, was charged with Ti powder (2.60 g, 54.28 mmol) and (TMS)Cl (5.90 g, 54.3 mmol). The mixture was suspended in DME (10 mL) and refluxed for 40 h. When a solution of androsta-1,4-diene-3,7-dione (**29**) (506 mg, 1.78 mmol) in DME (3 mL) was added at once, the green suspension immediately turned blue. Reflux was continued until TLC showed complete conversion of the substrate (1 h), the mixture was cooled to room temperature and filtered through a short plug of silica, the inorganic residues were washed with ethyl acetate (20 mL) in several portions, the filtrate was evaporated, and the residue was purified by flash chromatography using *n*-hexane/ethyl acetate (10:1) as eluent, affording compound **30** (402 mg, 84%)[20] as colorless crystals. The (*Z*)- and (*E*)-isomers ((*E*):(*Z*) $\approx$ 1:1) could not be separated by column chromatography: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.92 (s, 6H), 1.17 (s, 6H), 0.9−2.6 (m, 30H), 5.88 (dd, 2H, J = 10 Hz, 3 Hz), 6.45 (d, 2H, J = 10 Hz), 6.65 (td, 2H, J = 10 Hz, 2 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.77, 14.14, 20.53, 20.60, 20.70, 21.73, 31.36, 32.38, 32.45, 32.83, 35.54, 35.66, 41.67, 47.72, 50.90, 53.14, 53.26, 116.43, 120.67, 122.78, 136.12, 136.43, 147.21, 147.57, 220.64, 220.67; MS *m/z* (relative intensity) 538 (11), 537 (42), 536 (100, [M$^+$]), 522 (23), 521 (55), 518 (12), 503 (13), 372 (15), 371 (11), 358 (15), 357 (48), 209 (23), 208 (43), 207 (16), 195 (11), 193 (17), 151 (16), 150 (13), 147 (29), 109 (13); IR (cm^{-1}) 3040, 2940, 1740, 1658, 1455, 1440, 1372, 1240, 1200, 1090, 1042, 1005, 815, 793, 717, 675; Raman (Kr laser 6471 A) 1642, 1590, 1543.

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(23) (a) Hoffman, W. D.; McEwen, W. E.; Kleinberg, J. *Tetrahedron* **1959**, *5*, 293−304. (b) van Tilborg, W. J.; Smit, C. J. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 532−536.