# "Site Selective" Formation of Low-Valent Titanium Reagents: An "Instant" Procedure for the Reductive Coupling of Oxo Amides to Indoles

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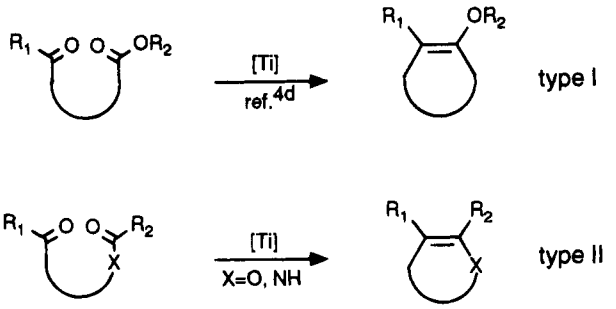
Aromatic acylamido carbonyl compounds are readily cyclized to indole derivatives upon treatment with low-valent titanium reagents of the formal oxidation states 0, +1, and +2. Other strong reducing agents such as $SmI_2$ and low-valent zirconium, niobium, and tungsten complexes are also capable of effecting such intramolecular alkylidenation reactions of amides. From the preparative point of view these heterocycle syntheses are best effected with an *active titanium species which is prepared in the presence of the carbonyl compound* upon coordination of $TiCl_n$ ($n$ = 3, 4) to the oxo amide substrate and reduction of this complex with zinc dust ("instant" method). This procedure turned out to be as effective as the titanium–graphite-based methodology previously described but is much easier to perform as all hazardous reagents are avoided. "Instant" cyclizations can also be run in nonethereal solvents such as DMF, ethyl acetate, or acetonitrile and turned out to be compatible with many functional groups. The method was used to cyclize oxo amide **15** to (+)-aristoteline, and it applies nicely to the synthesis of strained indole derivatives, the formation of benzo[*b*]furans, conventional McMurry reactions of aldehydes and ketones, and the dimerization of alkynes. Metals such as zirconium can also be activated in situ by reduction of $ZrCl_4$ in the presence of a carbonyl compound. On the basis of the results obtained with substrates bearing appropriate structural probes a mechanism for such intramolecular keto–amide coupling processes is proposed. Carbonyl dianions, formed upon two-electron reduction of the keto group, are the most likely reactive intermediates. Electrochemical investigations support this mechanistic interpretation.

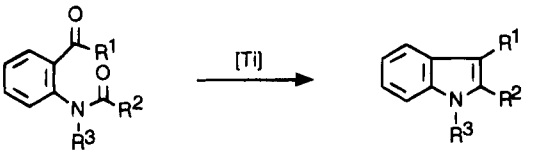
## Introduction

The biological prevalence of indole derivatives and the wide range of their pharmacological activities are responsible for the interest in new methods for the synthesis of this heterocyclic system. While the classical approaches are based upon typical organic reactivity patterns,[1] transition metal-assisted indole formations are rapidly gaining importance.[2] In this context we have outlined a new entry into aromatic heterocycles based upon intramolecular, titanium-induced type II alkylidenation reactions (Scheme 1).[3] When suitably substituted acylamido carbonyl compounds are treated with activated titanium as the reagent, the respective indoles are obtained by formation of their C2–C3 bond (Scheme 2). This approach must be discussed in the context of the McMurry reaction and has clearly disproved the alleged inertness of amides in that type of transformation.[4] Zindoxifene and a variety of structural analogues of this tumor-inhibiting drug were prepared by that method.[3d] More strikingly, the selectivity observed in the titanium-induced reduction of the tricarbonyl compound **1** to salvadoricine **2** indicated that the driving force for such

**Scheme 1**




**Scheme 2**




oxoamide cyclizations may even exceed that of a conventional diketone coupling process (Scheme 3).[3c]

McMurry reactions are generally performed in two consecutive steps:[4] first the active titanium species is prepared by reduction of $TiCl_n$ ($n$ = 3, 4) with a strong reducing agent, and then the carbonyl compound is added to the slurry thus obtained. In our original report on reductive indole synthesis we have employed titanium on graphite as the reagent.[5] For the preparation of this compound, however, the pyrophoric potassium–graphite laminate ($C_8K$) has to be used. Although $C_8K$ can be prepared on a rather large scale, is reasonably easy to handle, and has recently found a number of interesting

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(1) Reviews: (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970. (b) Brown, R. K. In *Indoles*; Houlihan, W. J., Ed.; Wiley: New York, 1972; p 227–559. (c) Robinson, B. *The Fischer Indole Synthesis*; Wiley: New York, 1982. (d) Clark, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195–221. Recent important advancements: (e) Smith, A. B.; Visnick, M.; Haseltine, J. N.; Sprengeler, P. A. *Tetrahedron* **1986**, *42*, 2957–2969. (f) Maruoka, K.; Oishi, M.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 7638–7639. (g) Houlihan, W. J.; Parrino, V. A.; Uike, Y. *J. Org. Chem.* **1981**, *46*, 4511–4515. (h) Augustine, R. L.; Gustavsen, A. J.; Wanat, S. F.; Pattison, I. C.; Houghton, K. S.; Koletar, G. *J. Org. Chem.* **1973**, *38*, 3004–3011. (i) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W. *J. Am. Chem. Soc.* **1974**, *96*, 5495–5508. (j) Blechert, S. *Liebigs Ann. Chem.* **1985**, 673–682.

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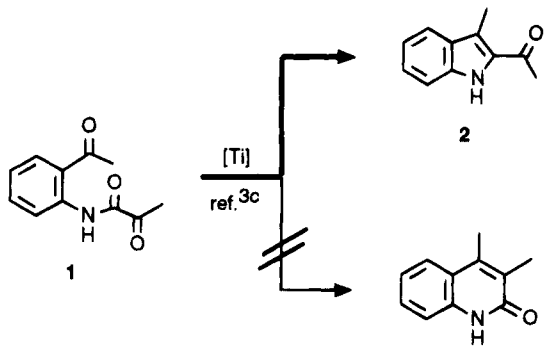
**Scheme 3**




applications to synthesis,[6] a protocol that avoids this compound without losing the performance of the graphite-based reagents would clearly improve our approach. In fact, a systematic screening among different titanium reagents paved the way for a much more practical but equally efficient procedure and provided new insight into the mechanistic features of such intramolecular oxoamide coupling reactions. Our results are discussed below.

## Results and Discussion

**Screenings.** The debate on the actual nature of the "low-valent titanium species" employed for McMurry reactions is not yet over. It was common practice to assume that metallic titanium particles are formed upon reduction of $TiCl_3$ with strong reducing agents such as K, Li, Mg, Zn, $LiAlH_4$, etc. in a Rieke-type activation process.[4] In two cases, however, more detailed investigations recently revealed that this is not the case. Thus, Bogdanovic *et al.* have unequivocally proved that reduction of $TiCl_3$ with $LiAlH_4$ affords $[TiHCl{\cdot}THF_{1/2}]_n$, whereas Mg as the reducing agent leads to $[TiCl(MgCl){\cdot}n$THF] or $[Ti(MgCl)_2{\cdot}n$THF] depending on the conditions.[7] These species constitute active principles for McMurry reactions. In the same context it should be mentioned that titanium on graphite exists in two different "modifications". While we[3,5] and others[8] have described and successfully applied a reagent obtained by reduction of $TiCl_3$ with 3 equiv of $C_8K$ (thus formally a Ti(0) species), Clive *et al.* have reported that titanium–graphite prepared by using just 2 equiv of $C_8K$ per $TiCl_3$ (formally a Ti(I) species) gave most favorable results in a case in which other McMurry procedures failed to afford any coupling products.[9] These data support the impression that depending on the mode of preparation different "McMurry agents" exist which are suited for reductive carbonyl coupling processes.[6]

This puzzling situation called for a more detailed investigation as to which oxidation state of titanium is capable of inducing the oxo amide cyclization to indoles. Using *N*-benzoyl-2-aminobenzophenone (**3a**) as a model substrate we compared the performance of several well-defined titanium species in forming 2,3-diphenylindole (**4a**). From Table 1 it is evident that Ti(0) is neither indispensable nor necessarily the best choice. A diversity of reagents[10] with the formal oxidation states 0, +1, and +2 turned out to mediate the reductive coupling. Although the yields were quite different, none of the reagents tested failed to afford indole **4a**. It should also be pointed out that such McMurry-type reactions are not restricted to heterogeneous reagents, but can also be carried out with soluble titanium complexes such as, *e.g.*, $Cp_2Ti(PMe_3)_2$ or $Ti(arene)_2$ (arene = toluene, biphenyl), which have scarcely been employed for such purposes so far.[11]

Although we have originally used $TiCl_3$/3 $C_8K$,[3,5,8] a reinvestigation showed that $TiCl_3$/2 $C_8K$ as proposed by Clive *et al.*[9] is in fact more generally applicable and leads to more reliable results. We therefore strongly recommend its use in any of these reductive cyclization reactions. At present one can only speculate why some

(2) Reviews: (a) Hegedus, L. S. *Angew. Chem.* **1988**, *100*, 1147–1161. (b) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1988**, *27*, 2225–2249. Leading references and recent developments: (c) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856–5866. (d) Krolski, M. E.; Renaldo, A. F.; Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1988**, *53*, 1170–1176. (e) Jackson, P. M.; Moody, C. J. *Tetrahedron* **1992**, *48*, 7447–7466. (f) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689–6690. (g) Izumi, T.; Soutome, M.; Miura, T. *J. Heterocycl. Chem.* **1992**, *29*, 1625–1629. (h) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1992**, *33*, 3915–3918. (i) Chen, H. G.; Hoechstetter, C.; Knochel, P. *Tetrahedron Lett.* **1989**, *30*, 4795–4798. (j) Hsu, G. C.; Kosar, W. P.; Jones, W. D. *Organometallics* **1994**, *13*, 385–396. (k) Caubere, C.; Caubere, P.; Renard, P.; Bizot-Espiart, J.-G.; Jamart-Gregoire, B. *Tetrahedron Lett.* **1993**, *34*, 6889–6892. (l) Couture, A.; Deniau, E.; Gimbert, Y.; Grandclaudon, P. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2463–2466. (m) Gray, M.; Parsons, P. J.; Neary, A. P. *Synlett*, **1993**, 281–282. (n) Kita, Y.; Tohma, H.; Inagaki, M.; Hatanaka, K. *Heterocycles* **1992**, *33*, 503–506. (o) Ito, Y.; Kobayashi, K.; Seko, N.; Saegusa, T. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 73–84. (p) Hegedus, L. S.; Sestrick, M. R.; Michaelson, E. T.; Harrington, P. J. *J. Org. Chem.* **1989**, *54*, 4141–4146. (q) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003–4018. (r) Hegedus, L. S.; Allen, G. F.; Bozoll, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800–5807. (s) Crotti, C.; Cenini, S.; Rindone, B.; Tollari, S.; Demartin, F. *J. Chem. Soc., Chem. Commun.* **1986**, 784–786. (t) Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Synthesis* **1990**, 215–218. (u) Tidwell, J. H.; Senn, D. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 4685–4686.

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(7) (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. (c) $TiH_2{\cdot}n$-$MgCl_2(THF)_2$: Bogdanovic, B.; Becker, B. Unpublished results.

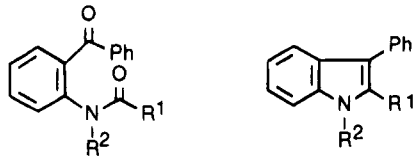
(8) (a) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Organomet. Chem.* **1985**, *280*, 307–312. (b) Burger, P.; Brintzinger, H. H. *J. Organomet. Chem.* **1991**, *407*, 207–213. (c) Pittner, S.; Huttner, G.; Walter, O.; Zsolnai, L. *J. Organomet. Chem.* **1993**, *454*, 183–198.

(9) (a) Clive, D. J. L.; Zhang, C.; Murthy, K. S. K.; Hayward, W. D.; Daigneault, S. *J. Org. Chem.* **1991**, *56*, 6447–6458. (b) Clive, D. J. L.; Murthy, K. S. K.; Zhang, C.; Hayward, W. D.; Daigneault, S. *J. Chem. Soc., Chem. Commun.* **1990**, 509–511. (c) Clive, D. J. L.; Murthy, K. S. K.; Wee, A. G. H.; Prased, J. S.; da Silva, G. V. J.; Majewski, M.; Anderson, P. C.; Evans, C. F.; Haugen, R. D.; Heerze, L. D.; Barrie, J. R. *J. Am. Chem. Soc.* **1990**, *112*, 3018–3028.

(10) (a) For $Ti(toluene)_2$ and for soluble Ti(0) clusters from $TiCl_4$ + $K[BEt_3H]$ see: Bönnemann, H.; Korall, B. *Angew. Chem.* **1992**, *104*, 1506–1508. (b) $Cp_2Ti(PMe_3)_2$: Binger, P.; Müller, P.; Benn, R.; Rufinska, A.; Gabor, B.; Krüger, C.; Betz, P. *Chem. Ber.* **1989**, *122*, 1035–1042. (c) Kool, L. B.; Rausch, M. D.; Alt, H. G.; Herberhold, M.; Thewalt, U.; Wolf, B. *Angew. Chem.* **1985**, *97*, 425–426. (d) Electrochemically generated titanium-clusters: Reetz, M. T.; Helbig, W. Unpublished results. (e) $Ti(biphenyl)_2$: Blackburn, D. W.; Britton, D.; Ellis, J. E. *Angew. Chem.* **1992**, *104*, 1520–1523. This complex is very sensitive toward oxygen, but rather stable to deaerated water. We thank Prof. K. Jonas and co-workers, Mülheim, for providing a sample of this compound.

(11) Review: Dang, Y.; Geise, H. J. *J. Organomet. Chem.* **1991**, *405*, 1–39.

**Chart 1**

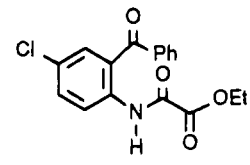


3



4

| | $R^1$ | $R^2$ |
|---|---|---|
| a | Ph | H |
| b | Ph | $CH_3$ |
| c | $(CH_2)_{14}CH_3$ | H |
| d | $(CH_2)_8CH{=}CH_2$ | H |
| e | $(CH_2)_3CH_2Cl$ | H |
| f | $(CH_2)_2CH_2Cl$ | H |
| g | $CF_3$ | H |
| h | $(CH_2)_2COOH$ | H |
| i | cyclopropyl | H |
| j | o-$BrC_6H_4$ | H |
| k | o-$IC_6H_4$ | H |
| l | 2-furanyl | H |
| m | 2-pyridyl | H |
| n | 2-benzofuranyl | H |
| o | 2-oxolanyl | H |
| p | $C(CH_3)_3$ | H |
| q | $C(CH_3)_3$ | $CH_3$ |
| r | 3,4-methylendioxyphenyl | H |
| s | $CH_3$ | tosyl |



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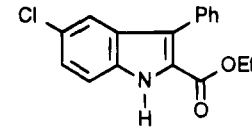

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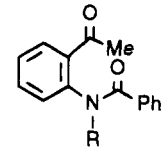
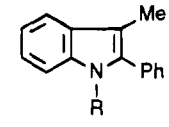
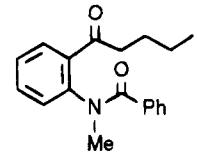


7a R = H
b R = $CH_3$



8a R = H
b R = $CH_3$



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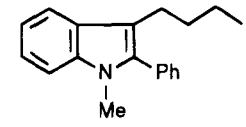

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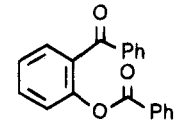

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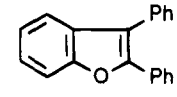

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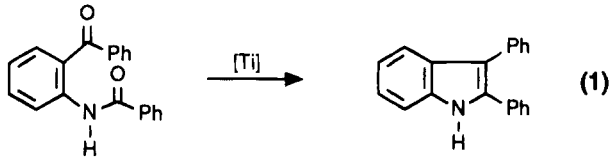
**Table 1. Screening among Different Low-Valent Titanium Species for Their Capability to Induce the Cyclization of Oxoamide 3a to Indole 4a**



3a 4a (1)

| entry | reagent | ref | formal oxidation state of [Ti] | yield[a] (%) |
|---|---|---|---|---|
| 1 | $TiCl_3 + 3C_8K$ | 3 | 0 | 90 |
| 2 | $TiCl_3 + 2C_8K$ | 9 | +1 | 90 |
| 3 | $TiCl_4 + 4K[BEt_3H]$ | 10a | 0 | 67[b,c] |
| 4 | [Ti][h] | 10d | 0 | 45[b] |
| 5 | $(C_6H_5Me)_2Ti$ | 10a | 0 | 75[d] |
| 6 | $Ti(biphenyl)_2$ | 10e | 0 | 70 |
| 7 | $[TiHCl{\cdot}THF_{0.5}]_n$ | 7 | +2 | 85[e,f] |
| 8 | $Cp_2Ti(PMe_3)_2$ | 10b,c | +2 | 79[g] |
| 9 | $[TiH_2{\cdot}nMgCl_2(THF)_2]$ | 7c | +2 | 69[c] |

[a] Isolated yields. All reactions were run in THF at reflux unless stated otherwise. [b] GC yield. [c] At ambient temperature. [d] Reaction was performed in DME. [e] The reaction was carried out at −70 → +20 °C. [f] Cyclizations of other substrates with $[TiHCl{\cdot}THF_{0.5}]_n$ at −70 → +20 °C; **7a** → **8a**, 42% isolated yield; **9** → **10**, 73% isolated yield. [g] Cyclization **9** → **10** using $Cp_2Ti(PMe_3)_2$ as reagent: 62% isolated yield. [h] Electrochemically generated Ti-clusters, cf. ref 10d.

substrates give high yields with both systems, while other ones are most sensitive to the nature of the coupling agent employed.

The reductive type II cyclizations of oxo amides are not restricted to titanium reagents. Several other strong electron donors also afforded the respective indoles upon reaction with substrates **3a** and **5** (Table 2), although the isolated yields were rather low except with $NbCl_5/Zn$ (entry 8).[12-16] The reduced reaction rate and higher cost

**Table 2. Non-Titanium Reagents for the Reductive Indole Formation**

| entry | substr | reagent[a] | time (h) | product[b] (%) |
|---|---|---|---|---|
| 1 | **3a** | $SmI_2$[d] | 1 | **4a** (31) |
| 2 | **3a** | $NbCl_3{\cdot}DME$[e] | 21 | **4a** (77)[c] |
| 3 | **3a** | $NbCl_5/Zn$ | 3 | **4a** (79)[c] |
| 4 | **3a** | $WCl_4/BuLi$ | 26 | **4a** (97)[c] |
| 5 | **3a** | Mg−graphite[5b] | 4 | **4a** (27)[f] |
| 6 | **3a** | $VCl_3/Zn$ | 20 | **4a** (55)[c] |
| 7 | **3a** | $ZrCl_4/Zn$[e] | 1.5 | **4a** (39) |
| 8 | **5** | $NbCl_5/Zn$[e] | 2 | **6** (74) |
| 9 | **5** | $WCl_4/BuLi$[e] | 23 | **6** (35) |

[a] Reactions carried out in THF at reflux unless otherwise stated. [b] Isolated yield. [c] Determined by GC analysis of the crude mixture. [d] At ambient temperature. [e] In DME at reflux. [f] Together with several unidentified byproducts.

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(13) Low-valent niobium reagents for reductive carbonyl coupling reactions: (a) Szymoniak, J.; Besancon, J.; Moise, C. *Tetrahedron* **1992**, *48*, 3867−3876. (b) Kauffmann, T.; Kallweit, H. *Chem. Ber.* **1992**, *125*, 149−151. (c) Sato, M.; Oshima, K. *Chem. Lett.* **1982**, 157−160.

(14) Vanadium reagents for pinacol-coupling reactions: (a) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014−8016. (b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Giaroni, P.; Benaglia, M. *Tetrahedron* **1991**, *47*, 5737−5758. (c) For pinacolizations with a low-valent vanadium complex prepared *in situ* in the presence of the substrate see: Kammermeier, B.; Beck, G.; Jacobi, D.; Jendralla, H. *Angew. Chem.* **1994**, *106*, 719−721 and references cited therein.

(15) Review on Sm-based reagents: Molander, G. A. *Chem. Rev.* **1992**, *92*, 29−68.

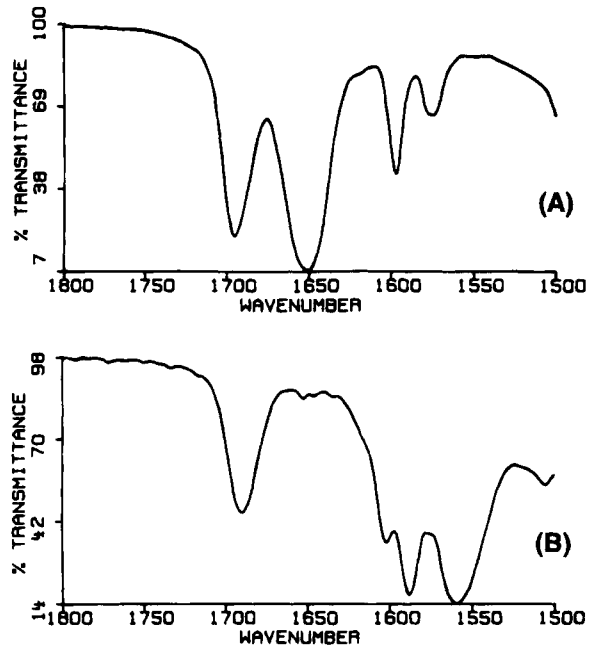



**Figure 1.** Carbonyl region of the IR spectra of oxo amide **9** in DME (A) and of a mixture of oxoamide **9** + 2 equiv of $TiCl_3$ in DME (B).

make this reagent combination less attractive than the titanium-based methodology.

**The "Instant" Method.** From the results summarized in the previous section we concluded that for a further improvement of this reductive heterocycle synthesis it was not necessary to use only Ti(0) reagents. An attractive alternative to the established procedures might be a "site selective" preparation of the active species which allows interception at the moment of formation. For this very purpose we deliberately avoided the established two-step procedure for McMurry reactions[4] but made use of the Lewis acidity of $TiCl_3$ in order to coordinate it to the substrate prior to reduction. Upon treatment with, *e.g.*, Zn dust, which itself does not affect the oxo amide, the $TiCl_3$ will be reduced within the complex unit formed *in situ*. As soon as a proper oxidation state is reached, the "active" titanium species must then efficiently induce the reductive coupling of the carbonyl groups to which it is coordinated, thus leading to the heterocyclic product.

Complex formation between substrate **9** and $TiCl_3$ can easily be monitored by IR spectroscopy (Figure 1). Upon addition of substoichiometric amounts of $TiCl_3$ to an oxo amide solution in DME two new absorptions at 1589 and 1560 $cm^{-1}$ appear, which gain intensity at the expense of the free carbonyl absorptions if the quantity of $TiCl_3$ is increased. At a **9**:$TiCl_3$ = 1:2 ratio the 1651 $cm^{-1}$ band due to free amide has completely disappeared, whereas a weak absorption at 1695 $cm^{-1}$ caused by uncomplexed ketone is still detectable. These data can qualitatively

**Table 3. Reductive Cyclization of Oxo Amides to Indoles by Low-Valent Titanium Reagents**

| | | | isolated yield[a] (%) | |
|---|---|---|---|---|
| entry | substrate | product | method A | method B |
| 1 | **3a** | **4a** | 98 | 90[e] |
| 2 | **3b** | **4b** | | 96 |
| 3 | **3c** | **4c** | 93 | 75 |
| 4 | **3d** | **4d** | 85 | 80 |
| 5 | **3e** | **4e** | 86 | 87 |
| 6 | **3f** | **4f** | | 90 |
| 7 | **3g** | **4g** | 82 | |
| 8 | **3h** | **4h** | 51 | |
| 9 | **3i** | **4i** | 84 | |
| 10 | **3j** | **4j** | 88 | 83 |
| 11 | **3k** | **4k** | 85[b] | 78[c] |
| 12 | **3l** | **4l** | 78 | 97 |
| 13 | **3m** | **4m** | 63[d] | |
| 14 | **3n** | **4n** | 94 | |
| 15 | **3o** | **4o** | low | 50 |
| 16 | **3r** | **4r** | 99 | 84 |
| 17 | **3s** | **4s** | | 86 |
| 18 | **5** | **6** | 87 | 93[e] |
| 19 | **7a** | **8a**[f] | 76 | 75[e] |
| 20 | **7b** | **8b** | | 92 |
| 21 | **9** | **10**[g] | 70 | |
| 22 | **11** | **12** | 76 | 88[e] |
| 23 | **13** | **14** | 90 | |
| 24 | **15** | **16** | 75[d] | |
| 25 | **19a** | **20a** | 88 | |

[a] Method A. "Instant" method: $TiCl_3$ (2 equiv)/Zn dust, THF. Method B. Stepwise procedure: $TiCl_3$ + $2C_8K$, THF, or DME (4 equiv of [Ti] per substrate), unless stated otherwise. [b] Contains 22% dehalogenated product **4a** (GC). [c] Contains 4.5% dehalogenated product **4a** (GC). [d] Treatment with EDTA prior to chromatography. [e] With Ti–graphite prepared using $TiCl_3$ + $3C_8K$, cf. ref 3a. [f] Obtained in 42% isolated yield with $[TiHCl{\cdot}THF_{0.5}]_n$ as the reagent (THF at −70 → +20 °C). [g] Obtained in 73% isolated yield with $[TiHCl{\cdot}THF_{0.5}]_n$ as the reagent (THF at −70 → +20 °C).

be interpreted by an equilibrium between the free ligand **9**, a complex **A**, in which only the amide is attached to the Lewis acid and species, in which both the ketone and the amide function are bound to $TiCl_3$ (either chelate **B** and/or complex **C**). The latter constitute the major component of the mixture (Scheme 4).

Addition of an excess of Zn dust to a boiling suspension of an oxo amide and $2TiCl_3$ in THF or DME leads in fact to favorable results. GC inspection of the crude reaction mixtures show very selective and clean conversions, with the GC yields being generally >90% (in several cases even >99%). The isolated yields of the respective indoles are high and are usually in the range of what can be reached with the titanium–graphite systems. Tables 3 and 4 comprise the results obtained for a representative set of oxo amides using that "instant method" and allow a comparison with the titanium–graphite based systems. N-Substitution has no effect on the yields obtained. Thus, N-alkylated or even N-tosylated indoles can be prepared as readily as N-unprotected compounds (*cf.* Table 3, entries 1/2, 17; Table 6, entries 2/3). The "instant" procedure can also be applied to the synthesis of benzo[*b*]furans from (acyloxy)carbonyl compounds,[3] as

**Scheme 4**

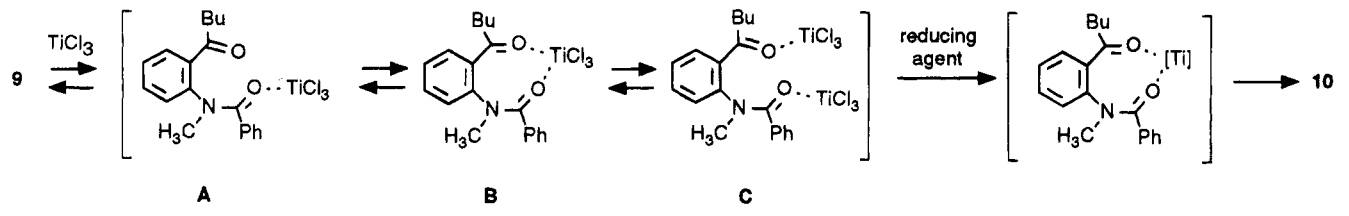


**Table 4. Screening of Different Combinations of $TiX_n$ (2 equiv)/Reducing Agent (5 equiv) for the Reductive Cyclization of Oxo Amide 3a to Indole 4a under "Instant" Conditions. The Product/Substrate Distribution Refers to GC Data of the Crude Reaction Mixtures**

| entry | $TiX_n$ | reducing agent | solvent | time (h) | $T$ (°C) | yield (%) 4a | 3a |
|---|---|---|---|---|---|---|---|
| 1 | $TiCl_3$ | Zn | DME | 1.5 | 85 | 98 | 1.2 |
| 2 | $TiCl_3$ | Zn | THF[a] | 0.2 | 25 | 98 | 1.1 |
| 3 | $TiCl_3$ | Mg | THF | 0.5 | 67 | 86 | 0.9 |
| 4 | $TiCl_4$·2THF | Zn | THF | 3.5 | 25 | 97 | 1.7 |
| 5 | $TiCl_4$·2THF | Zn | THF[a] | 3.5 | 25 | 98 | 1.1 |
| 6 | $Cp_2TiCl_2$ | Zn | THF | 2.0 | 67 | 90 | 1.0 |
| 7 | $Ti(O\text{-}i\text{-}Pr)_4$ | Zn | DME | 24 | 85 | 0 | 98 |

[a] In the presence of pyridine (1 equiv).

exemplified in entry 22. It should be pointed out that this method is operationally extremely simple, since only a mixture of the appropriate starting material with $TiCl_3$ (2 equiv) and Zn dust (5 equiv) in an inert solvent has to be refluxed until TLC shows complete conversion. Thus, any hazardous compound such as potassium or $C_8K$ is avoided, which have previously been used for the preparation of the active titanium species.[3-5] Moreover, the reaction can be run at rather high concentrations (0.1 M) without depressing the yields. These features make an up-scaling of the process a rather simple task. Furthermore, while in the titanium–graphite-induced cyclizations 4 equiv of titanium relative to the oxo amide must be employed,[3] this new procedure usually necessitates only 2 equiv of titanium per substrate. $TiCl_3$ can be replaced by other titanium salts except $Ti(O\text{-}i\text{-}Pr)_4$ (Table 4). For their *in situ* reduction without damaging the admixed substrate, Mg turnings instead of Zn dust seem to be also suitable.

As activated titanium is a strong reducing agent not only for carbonyl compounds a detailed investigation of the functional group compatibility was necessary to estimate the scope and limitations of this approach to aromatic heterocycles. As can be seen from the data compiled in Table 3, both the "instant" method as well as the two-step procedure based upon titanium–graphite exhibit an advantageous profile in this respect. Thus, a variety of reducible and/or acid-sensitive sites are compatible comprising, *i.a.*, acetals, alkenes, amines, aryl halides, alkyl chlorides, ethers, and cyano, trifluoromethyl, *N*-tosyl, and cyclopropyl groups. Even free carboxylic acids and a variety of heterocyclic entities (pyridine, thiophene, furan, benzofuran, etc.) do not interfere. The great ease with which esters or amides react when positioned *ortho* to a ketone function in the substrates contrasts the *complete inertness of any remote ester or amide group in the starting materials*.[3] This striking pattern, which is obviously dictated by the vicinity of the reacting sites, must have a mechanistic implication (*vide infra*). From these results together with previous data concerning the titanium–graphite induced reactions[3] it can be concluded that such oxo amide cyclizations are distinguished by an excellent chemo- and regioselectivity.

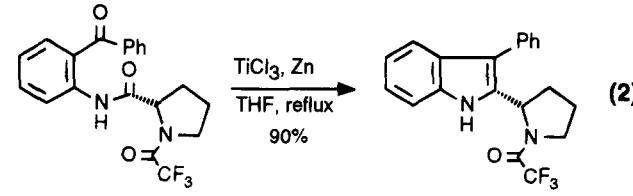
The observation that esters or amides do react only in the vicinity to a keto group but are inert otherwise led us to run the reaction in nonethereal solvents. From the results in Table 5 it can be seen that this indole synthesis is not restricted to THF or DME but can be performed equally well in ethyl acetate, DMF, or acetonitrile, which were beyond the scope of McMurry reactions so far.[4] Toluene and MeOH were found to be unsuitable. As far as we know, these are the first examples of titanium-induced coupling reactions in nonethereal and potentially reducible solvents. Moreover, the suitability of MeCN allowed us to setup a procedure for the reductive indole synthesis necessitating only catalytic amounts of titanium.[17]

**Table 5. Solvent Dependence of the Reductive Cyclization of 3a to Indole 4a with $TiCl_3$/Zn**

| entry | solvent | time (h) | yield (%) GC | isolated |
|---|---|---|---|---|
| 1 | DME | 1.5 | >99 | 92–98 |
| 2 | ethyl acetate | 0.5 | >99 | 90 |
| 3 | MeCN | 4 | 96 | 88 |
| 4 | DMF | 0.5 | 95 | 89 |
| 5 | toluene | 24 | 20[a] | |
| 6 | MeOH | 0.5 | *b* | *b* |

[a] 78% unreacted starting material detected in GC. [b] Decomposition.

An important stereochemical feature for any application of this methodology to, *e.g.*, indole alkaloid synthesis, is the integrity of a stereogenic center *alpha* to the reacting amide under the reaction conditions. We have addressed this point with the proline derivative **13** (eq 2) and found the enantiomeric purity of substrate and

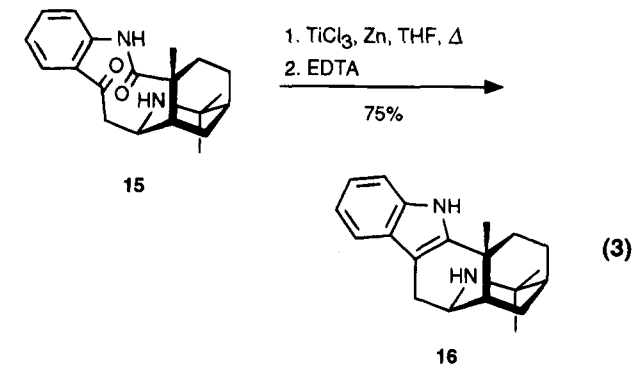



(2)

**13** (ee = 93 %) **14** (ee = 93 %)

product to be identical within the limits of detection (*cf.* Experimental Section). Once again a perfect selectivity for the coupling with the proximate amide group in **13** was encountered, whereas the remote *N*-trifluoroacetamido function in this particular compound was completely preserved.

Encouraged by these results we have applied the "instant" method to the formation of (+)-aristoteline **16**. Oxo amide **15** was reconverted to the alkaloid by means of $TiCl_3$/Zn in good yield.[18a] The product obtained was



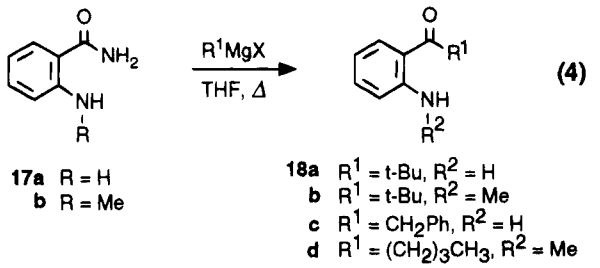

**15** (3) **16**

identical in all spectroscopic and analytical respects to an authentic sample.[18] It is, however, essential to treat the crude reaction mixture with EDTA prior to flash

(16) There is a unique report on the reductive coupling of two amides to an enediamine by means of low-valent samarium, *cf.*: Ogawa, A.; Takami, N.; Sekiguchi, M.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 8729–8730.

chromatography. This modified workup is necessary for all compounds containing a basic nitrogen atom in the vicinity of the indole nucleus (*cf.* 2-pyridylindole **4m**, Table 3, entry 13) and is thought to release such chelating products from a titanium complex formed during the reaction.

**Strained Indole Derivatives.** In order to gain more insight into scope and limitations of this indole synthesis we attempted to prepare congested derivatives by gradually increasing the size of the C-2 and C-3 substituents. While the required substrates **3p** and **3q** could be obtained from commercially available 2-aminobenzophenone by treatment with pivaloyl chloride under standard conditions, we had to optimize the access to the respective 2-aminopivalophenone derivatives **21**. Among the different routes investigated,[19] treatment of 2-aminobenzamide (**17a**) or 2-(*N*-methylamino)benzamide (**17b**)




respectively, with an excess of *tert*-butylmagnesium chloride gave good yields of the corresponding amino ketones **18a,b**. The same procedure employing either benzylmagnesium chloride or *n*-butylmagnesium chloride was used to prepare compounds **18c** and **18d**. After N-acylation with either benzoyl, mesitoyl, isopropanoyl, or pivaloyl chloride, the corresponding oxo amides **21** were subjected to reductive coupling under "instant" conditions with $TiCl_3$/Zn dust and, for comparative reasons, with titanium–graphite, where desirable.

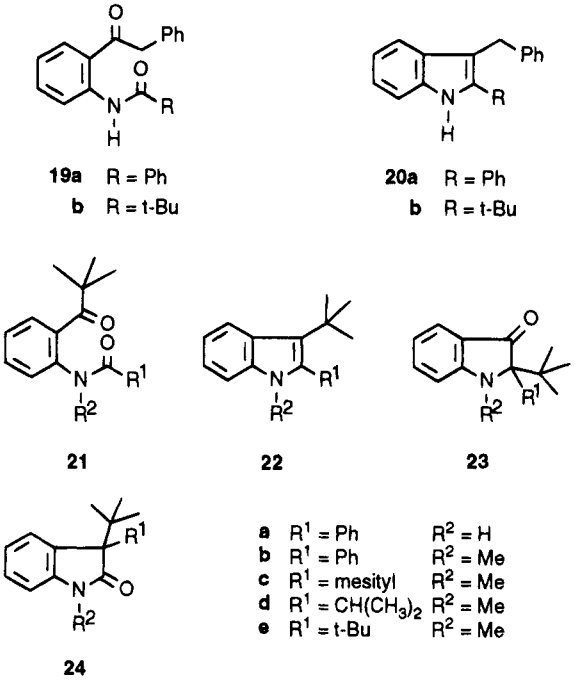
As can be seen from the results in Table 6, the neighborhood of a phenyl, mesityl, or benzyl group and a *tert*-butyl substituent at C-2/C-3 in both possible arrangements does not affect the indole formation to any noticeable extent. This is surprising as the X-ray data reveal the rather crowded situations in the enamine region of these compounds.[20]

The presence of two branched alkyl substituents at C-2/C-3, however, significantly diminished the yields obtained. Attempts to cyclize substrate **21e** to *N*-methyl-2,3-di-*tert*-butylindole (**22e**) under "instant" conditions failed and resulted in loss of one of the two *tert*-butyl groups (determined by GC/MS analyses). Titanium–graphite, however, gave this highly crowded derivative in 35% yield. In case of substrates **21d,e** substantial amounts of the rearranged derivatives, *i.e.*, pseudoindoxyls **23d,e**, have been isolated from the reaction mixtures (together with minor amounts of the oxindoles **24** which were detected by GC/MS). The formation of these byproducts provided some insight into the mechanism of the reductive heterocycle formation which is discussed below. Anyhow, although McMurry reactions were previously applied to the synthesis of strained alkenes with considerable success,[4] there is only little precedence for the formation of an alkene or arene with a 1,2-*Z*-arrangement of two *tert*-butyl groups by reductive coupling.[21]

**Table 6. Synthesis of Strained Indole Derivatives**

| entry | substrate | method[a] | time (h) | products (yield, %) |
|---|---|---|---|---|
| 1 | **3p** | A | 2 | **4p** (97) |
| 2 | **3p** | B | 3 | **4p** (79–84) |
| 3 | **3q** | B | 1 | **4q** (84) |
| 4 | **19a** | A | 22 | **20a** (88) |
| 5 | **19b** | A | 92 | **20b** (95) |
| 6 | **21a** | A | 69 | **22a** (86) |
| 7 | **21b** | A | 4 | **22b** (75)[b] |
| 8 | **21b** | B | 3 | **22b** (62) |
| 9 | **21c** | A | 67 | **22c** (88)[c] |
| 10 | **21d** | B | 22 | **22d** (36), **23d** (24)[d] |
| 11 | **21e** | B[f] | 1 | **22e** (35), **23e** (15)[d,e] |

[a] Method A: $TiCl_3$ (2 equiv)/Zn ("instant" method). Method B: titanium–graphite ($TiCl_3 + 3C_8K$). All reactions were carried out in DME at reflux temperature. [b] Pseudoindoxyl **23c** is formed in 8% yield (GC). [c] Sluggish reaction using method B. [d] Together with traces of unidentified byproducts. [e] Method A results in the loss of one of the two *tert*-butyl groups, *cf.* text. [f] With $TiCl_3$:$C_8K$ = 1:2.




(17) Fürstner, A.; Hupperts, A. Manuscript in preparation.

(18) (a) Oxoamide **15** is an undesired byproduct of oxidative degradation of aristotelin, *cf.*: Güller, R.; Borschberg, H. J. *Helv. Chim. Acta*, **1993**, *76*, 1847–1862. (b) Kyburz, R.; Schöpp, E.; Bick, I. R. C.; Hesse, M. *Helv. Chim. Acta* **1981**, *64*, 2555–2562. (c) Anderson, B. F.; Robertson, G. B.; Avey, H. P.; Donovan, W. F.; Bick, I. R. C.; Bremner, J. B.; Finney, A. J. T.; Preston, N. W.; Gallagher, R. T.; Russel, G. B. *J. Chem. Soc., Chem. Commun.* **1975**, 511–512. (d) Stevens, R. V.; Kenney, P. M. *J. Chem. Soc., Chem. Commun.* **1983**, 384–386. (e) Stoermer, D.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 564–568. (f) Review: Borschberg, H. J. *Chimia* **1991**, *45*, 329–341.

(19) Previously obtained by (a) reaction of *tert*-butylmagnesium chloride with 2-methyl-3,1-benzoxazin-4-one, *cf.* Rees, C. W.; Storr, R. C.; Whittle, P. J. *Tetrahedron Lett.* **1976**, 4647–4650. (b) Via 4-*tert*-butyl-1,2,3-benzotriazene, *cf.* Dyall, L. K. *Austr. J. Chem.* **1977**, *30*, 2669–2678. Syntheses of the 2-aminopivalophenone *via* reaction of the 2-aminobenzonitrile or *N*-methyl-*N*-methoxy-2-(*N*-methylamino)benzamide with *tert*-butylmagnesium chloride gave lower yields and less reliable results, respectively. A similar approach to aromatic amino ketones is described in: (c) Grammaticakis, P. *Compt. Rend. Acad. Sci.* **1952**, *235*, 546–547.

(20) For the X-ray structure of **22b** prepared in low yield by another procedure see: Sgarabotto, P.; Ugozzoli, F.; Greci, L.; Stipa, P.; Carloni, P. *Acta Crystallogr. C* **1989**, *C45*, 1939–1941. The X-ray structure of indole **4p** is reported in ref 3a. The structural details of further congested derivatives will be reported in due course.

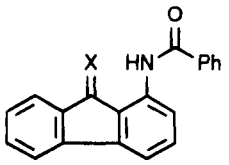
(21) (a) 3,4-Di-*tert*-butyl-3-butene: Gano, J. E.; Lenoir, D.; Park, B. S.; Roesner, R. A. *J. Org. Chem.* **1987**, *52*, 5636–5638. (b) Reduction of bis(2-*tert*-butyl-2-oxoethyl) sulfide with $TiCl_4$/Zn leads to the pinacol, which can be eliminated to 3,4-di-*tert*-butylthiophene, *cf.* Nakayama, J.; Yamaoka, S.; Hoshino, M. *Tetrahedron Lett.* **1988**, *29*, 1161–1164.

**Table 7. Reductive Dimerization (McMurry Reactions) of Aldehydes and Ketones Using $TiCl_3$ (2 equiv)/Zn Dust (5 equiv) as Reagent Combination in DME at Reflux unless Stated Otherwise ("Instant" Method)**

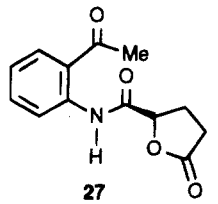
| entry | substrate | time (h) | product | yield (%) |
|---|---|---|---|---|
| 1 | benzophenone | 4[a] | tetraphenylethene | 78 |
| 2 | benzaldehyde | 1 | (*E*)-stilbene | 78 |
| 3 | cyclohexanone | 21 | cyclohexylidenecyclohexane | 57[c] |
| | | | pinacol[b] | 7[c] |
| 4 | 9-fluorenone | 2 | 9,9'-bifluorenylidene | 92 |
| 5 | decanal | 1 | eicosane-10,11-diol | 60 |
| 6 | 1,6-diphenyl-1,6-hexanedione | 3.5 | 1,2-diphenylcyclohexene | 48 |
| | | | 1,2-diphenylcyclohexane-1,2-diol | 19 |

[a] In THF at reflux. [b] Refers to (1-hydroxycyclohexyl)cyclohexanol. [c] GC yield.

**Limitations.** While *N*-formyl-2-amino ketones readily cyclize to 2-unsubstituted indoles,[3a] *N*-acylated 2-aminobenzaldehyde derivatives do pose problems in attempted "instant" cyclizations to 3-unsubstituted products. Work is in progress to overcome this important limitation. In the ketone series 9-benzamidofluorenone (**25**) failed to afford any cyclized material obviously for steric reasons. The deoxygenation product **26** was obtained instead. There is presently no reasonable explanation as to the failure with substrate **27**.




**25** X = O
**26** X = H, H

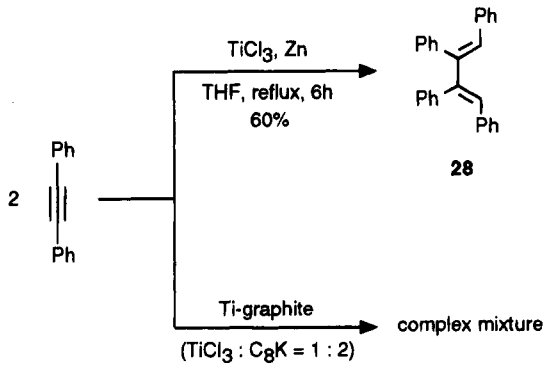



**27**

**The "Instant" Method in the Nonindole Series.** Our procedure, which essentially consists of mixing a carbonyl compound with the appropriate amount of $TiCl_3$ and Zn dust in an inert solvent and heating the suspension until TLC shows complete conversion of the substrate, is definitely not restricted to oxo amide cyclization reactions. Table 7 proves its applicability to the reductive dimerization of a set of simple aldehydes and ketones (conventional McMurry reactions). This idea is in fact not new, although it has hardly found applications in synthesis. In the three original reports on the titanium-induced reductive carbonyl dimerization to alkenes, Mukaiyama *et al.* employed such a one-pot procedure using $TiCl_4$/Zn to prepare the active species in the presence of the carbonyl compound,[22] while Tyrlik[23] and McMurry[24] both independently introduced a two-step protocol with formation of active titanium prior to its reaction with the substrate. We would like to reemphasize Mukaiyama's idea for its particular convenience. Entry 6 demonstrates that this one-step procedure may even be applied to intramolecular coupling reactions where an appropriate ring size is formed.

Among the functionalities found to be incompatible with the reductive indole synthesis the alkyne group has attracted our attention. On the one hand there is literature precedence for the reduction of diphenylacetylene to a mixture of stilbene and diphenylethane by a

**Scheme 5**




titanium slurry,[25] but on the other hand the reductive dimerization of alkynes by $Cp_2Ti(II)$ templates is well documented and has recently evolved into a powerful synthetic method for the synthesis of carbo- and heterocycles.[26,27] We therefore reexamined the reaction of tolane with low-valent titanium species. When added to a slurry of titanium–graphite ($TiCl_3$:$C_8K$ = 1:2) in THF at reflux, a complex mixture was obtained, which was not further analyzed. Reduction of $TiCl_3$ with Zn dust in the presence of the substrate ("instant" method), however, led to the formation of (*E,E*)-1,2,3,4-tetraphenyl-1,3-butadiene (**28**) in 60% isolated yield. The exclusive *cis*-arrangement of the phenyl substituents points at a titanacyclopentadiene intermediate similar to those observed in $Cp_2TiL_2$-induced (L = CO, $R_3P$, etc.) alkyne dimerizations.[26]

The principle of activating a metal in the presence of the substrate rather than in a separate operation prior to use may not be restricted to titanium. It turned out to be useful in the case of zirconium as well, which was hitherto considered to be unsuited for McMurry- and/or pinacol-type reactions. These previous failures with activated zirconium,[28] however, are rather surprising as it combines a significant reduction potential with a

(22) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041–1044.
(23) Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* **1973**, 2147–2148.
(24) McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708–4709.
(25) (a) Dams, R.; Malinowski, M.; Geise, H. J. *Rec. Trav. Chim. Pays Bas* **1982**, *101*, 112–114. (b) Dang, Y.; Geise, H. J. *Bull. Soc. Chim. Belg.* **1991**, *100*, 375–380.
(26) (a) Shur, V. B.; Burlakov, V. V.; Volpin, M. E. *J. Organomet. Chem.* **1988**, *347*, 77–83. (b) Achyutha Rao, S; Periasamy, M. *J. Organomet. Chem.* **1988**, *352*, 125–131.
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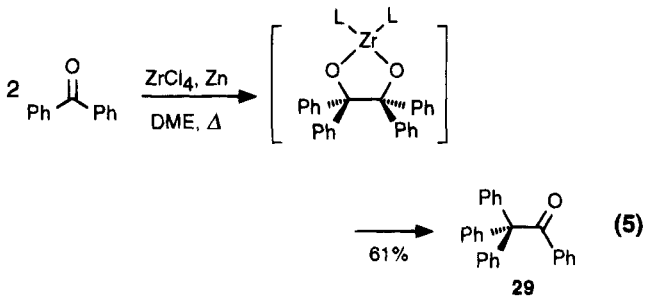
(28) Failures with activated zirconium and a variety of other transition metals as mediators for reductive carbonyl coupling reactions are reported in: (a) ref 4a as unpublished results. (b) Dams, R.; Malinowski, M.; Geise, H. J. *Bull. Soc. Chim. Belg.* **1982**, *91*, 149–152. (c) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260–265.

pronounced oxophilicity comparable to or even higher than that of titanium. Gratifyingly, the "instant" reduction of $ZrCl_4$ with Zn in the presence of benzophenone led to the clean formation of benzopinacone **29**. The




formation of this product can be explained by a tandem reaction comprising pinacol coupling as the first step, followed by a pinacol/pinacone rearrangement after the rupture of a C—O bond in the intermediate metallopinacolate (eq 5). Entry 7 in Table 2 demonstrates that an active zirconium species prepared in the presence of the oxo amide **3a** leads also to the formation of indole **4a**, although in somewhat lower yield than with titanium. These preliminary results encourage to pursue the concept of activating those metals which are thought to be unreactive or of limited use in synthesis within the coordination sphere of a suitable substrate.

## Mechanistic Considerations

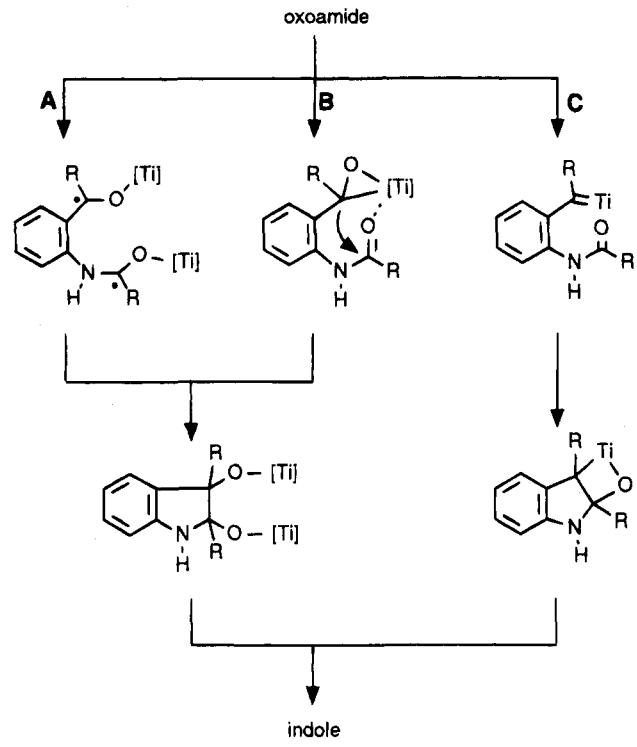
The mechanistic interpretation of heterogeneous processes is known to be particularly troublesome, and the reactions dealt with in here are no exception to the rule. One must keep in mind that different titanium species at different oxidation levels may well induce the reductive coupling reactions described above. This ambiguity as to the actual reagent is amplified by the lack of appropriate spectroscopic evidence for any reactive intermediates formed upon reaction of the "titanium species" (represented in the following by [Ti]) with the oxo amide substrates. Thus, the mechanistic picture must be put together by indirect means. The information stems mainly from the analysis of the products formed when appropriate structural probes are incorporated into the substrates. Further support comes from electrochemical investigations.

We have considered three major pathways for the intramolecular type II alkylidenation of amides or esters, respectively, that might lead to the formation of aromatic heterocycles: (i) radical anions formed upon single-electron-transfer (s.e.t.) from [Ti] to both the ketone and to the amide (ester) function (Scheme 6, path A); (ii) titanium carbenes (Scheme 6, path C); and (iii) titanium dianions obtained by the input of two electrons into the ketone without any electron transfer to the amide (ester) group (Scheme 6, path B).

Several arguments can be put forward to distinguish between these three options. Although McMurry reactions are generally considered to proceed via s.e.t. processes,[4] the mechanistic information presently available for the titanium-induced indole synthesis makes ketyl radical anions as intermediates rather unlikely. This assumption is based on the following observations:

(i) Since [Ti] does not induce acyloin condensations to any useful extent,[3a,4] it seems to be incapable of efficiently transferring electrons to esters. Because of the yet lower

**Scheme 6**




reduction potentials of amides, an s.e.t. to this functional group must be even more difficult. *N*-Phenylbenzamide was indeed recovered unchanged (>80%) when exposed to a large excess of $TiCl_3$/Zn in boiling THF for 4 h (only traces of decomposition products were detected). This finding contrasts to the ready cyclization of oxo amides to indoles. As a rule, amides undergo type II cyclizations as fast or even faster than esters.

(ii) The fact that only those esters or amides in the vicinity of the keto group undergo reductive cyclization reactions, whereas remote ones are completely inert, indicates a ketone- rather than an amide (ester)-triggered process.

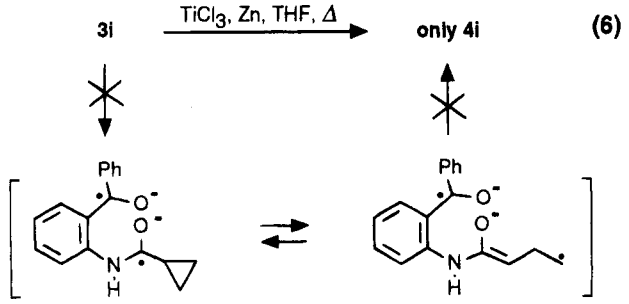
(iii) Solvents such as DMF or EtOAc should be unsuited if an amide or an ester would compete with the ketone for the electrons of the [Ti].

(iv) If an s.e.t. to the amide would take place, one might expect significant differences in reactivity depending on its electronic properties, which can be varied to a large extent by the substituents ($R^2$, $R^3$ in Scheme 2). However, all types of amides (formamides, alkanoyl-, aroyl-, and heteroaroylamides, and fatty acid amides) of a given parent amino ketone react with comparable rates.

(v) Ketyl radical anions might tend to dimerize to a certain extent. However, the yields of indoles are insensitive toward the concentration of the reaction mixture. Even at 0.1 M concentration there were no signs of any dimer formation.

(vi) Substrate **3i** was prepared bearing a cyclopropyl group as a test for a radical scenario (cyclopropylmethyl radical → homoallyl radical switch).[29] No ring-opened products were observed upon its treatment with [Ti] (eq 6).

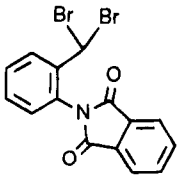
Titanium carbenes as intermediates in the heterocycle formations are suggested by the analogy to the "Tebbe-reagent", which is well-established for the alkylidenation of esters and amides.[30] Other titanium-carbenes, assumed to be formed upon reaction of aliphatic *gem*-




dibromides with low-valent titanium slurries in the presence of TMEDA, were also found to be useful for converting amides into enamines.[31] The information presently at hand does not rigorously exclude titanium carbenes but does definitely not point at such species as the reactive intermediates in type II heterocycle formations:

(i) It is well established that a titanium carbene reacts with the carbonyl group *via* an oxotitanium–cyclobutane intermediate in an ylide-like fashion (Scheme 6, path C).[30] The observation of substantial amounts of pinacole/pinacone rearrangement products (**23**) is not in accordance with such a pathway.

(ii) Attempts to form an indole upon treatment of the *gem*-dibromide **30**[38a] with a variety of titanium reagents with or without admixed TMEDA were hardly successful. Only traces of the expected indole could be detected.[32]




**30**

Dianions formed *via* two-electron reductions of carbonyl compounds have been discussed on many occasions,[33] but definite proofs for their existence are scarce.[34] Nevertheless, the mechanistic information available is best matched assuming such highly reactive intermediates (Scheme 6, path B):

(i) The fact that amides and esters react equally well, and that all kinds of amides of a given parent amino ketone cyclize with comparable rates, is in agreement with that assuption. Once a dianion of the ketone entity is formed, it will instantaneously attack either an ester or an amide kept close to it by a common titanium template. This scenario of a nucleophilic attack of the dianion onto the most proximate electrophilic site[33] is in good accordance with the observed regioselectivity of the coupling reaction, which leaves remote functional groups intact.

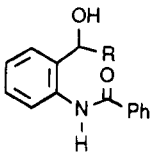
**Table 8. Cathodic Redox Potentials of Selected Carbonyl Compounds. Comparison with the Reaction Time Necessary To Achieve Quantitative Conversion of the Oxo Amide to the Corresponding Indoles Using the "Instant" Method ($TiCl_3$ (2 equiv)/Zn Dust (5 equiv))**

| substrate | 1. wave $E_{1/2}$ | 2. wave $E_{1/2}$ | reaction time (min) |
|---|---|---|---|
| benzophenone | −1.871 | −2.42 | |
| *N*-phenylbenzamide | −[a] | −[a] | |
| **5** | −1.454 | −2.09 | 105 |
| **3a** | −1.568 | −2.201 | 135 |
| **9** | −2.038 | −2.347 | 225 |
| **21b** | −2.230 | −2.349 | 270 |
| **19a** | −1.754 | −2.534 | 300 |
| **7a** | −1.876 | −2.640 | 290 |

[a] Electrochemically inactive, c.f. text.

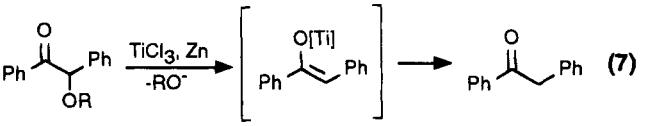
(ii) While the nature of the amide is of minor importance, the electronic properties of the ketone moiety are clearly reflected in different reaction rates (*cf.* Table 8). As a rule diaryl ketones react faster than aryl alkyl ketones.

(iii) Attempts to trap the reactive intermediate have also been carried out. Ti(biphenyl)$_2$[10e] readily effects indole formation in anhydrous THF (Table 1). When reacted with substrate **7a** in a THF/$H_2O$ (5/1) mixture, however, indole **8a** was formed in a trace amount (12%), but alcohol **33a** was isolated in 58% yield as the major product. Likewise, when the "instant" coupling of **3a** was performed in a THF/$H_2O$ (2/1) solution containing NaOAc in order to buffer the acidity of $TiCl_3$, alcohol **33b** was formed in 82% yield.




**33a** R = Me
**b** R = Ph

(iv) An acyloin entity might be used to further probe the existence of dianions by structural means. There is ample precedence for the deoxygenation of α-hydroxyketones by [Ti].[3a,35] In the case of an *O*-alkylbenzoin derivative as the substrate it is likely to be assumed that the carbonyl group rather than the ether function will be the prime site of interaction. Thus, we reinvestigated the reaction of *O*-ethylbenzoin (**31a**) under "instant" conditions as well as with titanium–graphite. In both cases, we obtained high yields of 1,2-diphenylethanone (deoxybenzoin, **32**) as the only product. Other O-unprotected as well as O-acylated benzoin derivatives (**31b,c**) as substrates behaved similarly (eq 7).[3a] An *O*-ethyl and




(7)

**31a** R = Et
**b** R = H
**c** R = Ac

**32**

(29) Review: Nonhebel, D. C. *Chem. Soc. Rev.* **1993**, 347–359 and references cited therein.

(30) For a comprehensive treatise see: Pine, S. H. *Org. React.* **1993**, *43*, 1–91. For a review on nucleophilic carbenes see: Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, 1987.

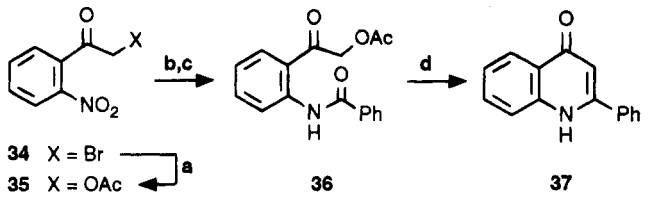
(31) For conversion of esters to enol ethers and of amides to enamines see: (a) Takai, K.; Fujimura, O.; Kataoka, Y.; Utimoto, K. *Tetrahedron Lett.* **1989**, *30*, 211–214. (b) Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410–4412. (c) Mortimore, M.; Kocienski, P. *Tetrahedron Lett.* **1988**, *29*, 3357–3360. (d) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668–2670.

(32) Fürstner, A.; Ernst, A. Unpublished results.

(33) Leading references: (a) Guijarro, D.; Mancheno, B.; Yus, M. *Tetrahedron* **1993**, *49*, 1327–1334. (b) Olivier, H.; Chauvin, Y.; Saussine, L. *Tetrahedron* **1989**, *45*, 165–169. (c) Hou, Z.; Takamine, K.; Aoki, O.; Shiraishi, H.; Fujiwara, Y.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* **1988**, 668–670. (d) Hou, Z.; Takamine, K.; Aoki, O.; Shiraishi, H.; Fujiwara, Y.; Taniguchi, H. *J. Org. Chem.* **1988**, *53*, 6077–6084. (e) Karaman, R.; Kohlman, D. T.; Fry, J. L. *Tetrahedron Lett.* **1990**, 6155–6158 and references cited therein.

(34) X-ray structures of benzophenone dianions: (a) Bogdanovic, B.; Krüger, C.; Wermeckes, B. *Angew. Chem.* **1980**, *92*, 844–845. (b) Hou, Z.; Yamazaki, H.; Fujiwara, Y.; Taniguchi, H. *Organometallics* **1992**, *11*, 2711–2714.

**Scheme 7**




[a] Key:(a) NaOAc, MeCN, reflux, 98%; (b) $H_2$ (1 atm), Pd/C (5%), EtOAc, 40 min; (c) benzoyl chloride, pyridine/$CH_2Cl_2$, 30 min, 66% (both steps); (d) $TiCl_3$, Zn, THF, reflux, 3 h, 56%.

in particular an *O*-acetyl group will be expelled as anion rather than as an ethoxy or as acyl radical. This necessitates the input of two electrons into the keto group. Although **32** readily undergoes McMurry coupling reactions, it did not spontaneously dimerize when prepared from benzoin even if a large excess of [Ti] and prolonged reaction times were applied. Thus, it must exist in a "protected" form in solution, most likely as the respective titanium enolate.

(v) Despite of the failures reported in previous attempts to intercept such enolates,[35] we prepared substrate **36** for that very purpose. In this compound the expected titanium enolate derived from the acyloin unit might react in an entropically favored intramolecular way. In fact, reaction of **36** with [Ti] prepared *in situ* according to the "instant" protocol afforded **37**[36] in 56% yield together with small amounts of several unidentified byproducts.

Electrochemical investigations were carried out to check the mechanistic proposal outlined above. Benzophenone exhibited a reversible reduction step at −1.871 V and an irreversible step at −2.42 V, while *N*-phenylbenzamide was found to be electrochemically inactive. This showed clearly that it is possible to form a ketone dianion prior to any electron transfer to an amide. Previous investigations demonstrated that the electrochemically generated dianion of benzophenone is capable of nucleophilically attacking admixed acetic anhydride with formation of 1,1-diphenyl-1-acetoxy-2-propanone.[37] This reaction can be considered as an intermolecular precedence to the pathway proposed above for the indole synthesis.

Typical cyclovoltammograms for representative oxoamides are depicted in Figure 2. Although the first reduction steps were found to be by and large irreversible, comparison of the curves in C and D show clearly that this *irreversibility is found only if the entire cathodic scenario is passed through*. For substrate **5** the one-electron reduction step on its own (curve D) is as reversible as that of benzophenone (curve A). Moreover, the results summarized in Table 8 indicate a subtle relationship between the *second* reduction potential of the substrates with the rate of the indole formation. These findings are in good agreement with the proposed mechanism. Nevertheless, these electrochemical data must be cautiously interpreted, as attempts to form

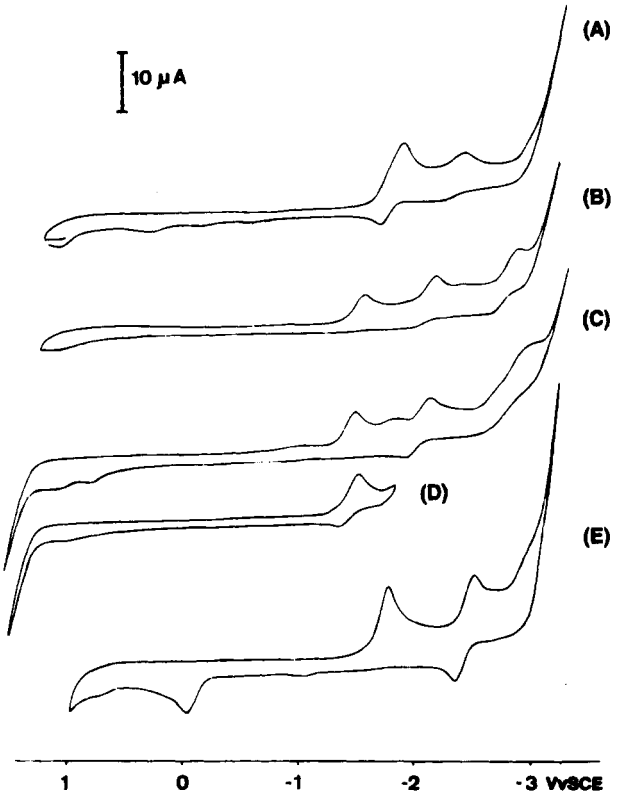



**Figure 2.** Cyclovoltamograms of different substrates ($10^{-3}$ M in 0.1 M tetra-*n*-butylammonium perchlorate (TMAP)/THF; glassy carbon electrode against SCE; scan rate 100 $mV \cdot s^{-1}$): (A) benzophenone; (B) oxo amide **3a**; (C) oxo amide **5**; (D) oxo amide **5** (first reduction step); (E) oxo amide **19a**. Comparison of the curves in C and D shows clearly that the first reduction step of **5a** becomes irreversible only after going through the entire reductive cycle but that it is itself a reversible process.

indoles from oxoamide precursors by electrochemical means failed so far.

In summary, a dianion path seems to fit all experimental results that are presently available concerning the C—C bond formation. The product distribution observed with the strained substrates **21d,e** provides some additional information about the subsequent deoxygenation step. Only if both the C-2 and the C-3 substitutents are sterically demanding any noticeable deviations from a smooth enamine-bond formation were encountered under "instant" conditions. The pseudoindoxyls **23** are obviously formed by rearrangements of the intermediate titanium pinacolates. This reaction seems to be triggered by the preferential rupture of the C—O bond at C-2 with formation of the carbocation stabilized by the vicinal nitrogen atom. Migration of the C-3 substituent with formation of the ketone function at this position leads to the product (Scheme 8).

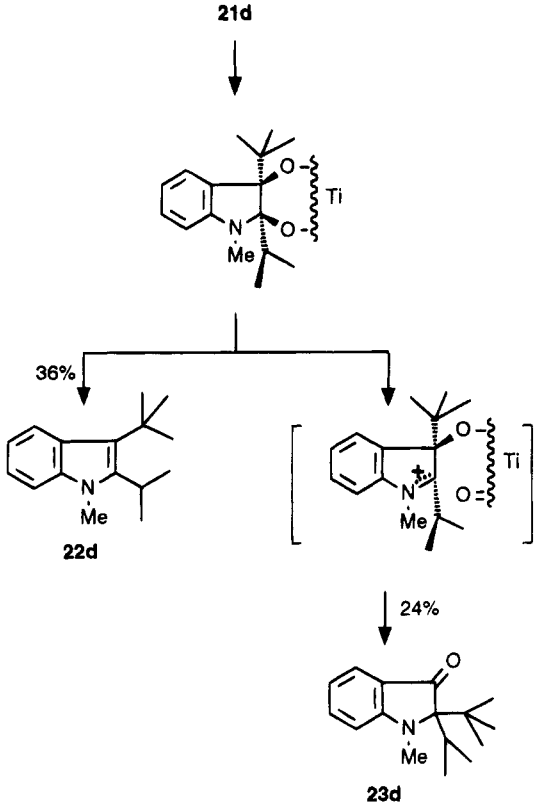
As this result is the exception to the rule it can be assumed that the deoxygenation step must be close to concerted in all those cases in which a smooth indole formation occurs. This is in agreement with previous investigations on conventional McMurry reactions of ketones or aldehydes to alkenes.[4] Even in the most congested cases C—C bond formation seems to take place without incident, whereas the subsequent deoxygenation of the intermediate pinacolates is decisive for the outcome of the reaction.

(35) McMurry, J. E.; Silvestri, M. G.; Fleming, M. P.; Hoz, T.; Grayston, M. W. *J. Org. Chem.* **1978**, *43*, 3249–3255. However, successful alkylidenation reactions via intramolecular inception of titanium ketone enolates with esters have been reported recently: Oppolzer, W.; Rodriguez, I. *Helv. Chim. Acta* **1993**, *76*, 1282–1291.

(36) Kaslow, C. E.; Lawton, W. R. *J. Am. Chem. Soc.* **1950**, *72*, 1723–1724.

(37) Curphey, T. J.; Trivedi, L. D.; Layloff, T. *J. Org. Chem.* **1974**, *39*, 3831–3834.

**Scheme 8**




## Conclusions

We have shown that the reductive cyclization of oxo amides to indoles is a very favorable process exhibiting high degrees of chemo- and regioselectivity and a good functional group compatibility. The reaction is promoted by a variety of strong reducing agents, especially by low-valent titanium species. From a preparative point of view, these intramolecular reactions are best carried out with active titanium prepared in the presence of the substrate ("instant method") by coordinating $TiCl_n$ to the oxo amide and reducing the resulting complex with zinc dust. This procedure can also be performed in several nonethereal solvents. It has been successfully applied to the synthesis of strained indoles and to the alkaloid series. Preliminary results show that it is also suitable for benzofuran synthesis, for conventional McMurry coupling reactions of aldehydes and ketones, for the dimerization of alkynes, and for the activation of metals such as zirconium. The careful analysis of the experimental results and the use of structural probes in several substrates suggest carbonyl dianions as possible intermediates in such reductive heterocycle formations. Electrochemical investigations support this mechanistic interpretation. Thus, the kinetically favored formation of a five-membered ring, the proximity of the reacting sites, the high oxophilicity of titanium, as well as the aromaticity of the products formed all contribute to the success of this type of transformation.

## Experimental Section

**General.** For the instrumentation used see ref 3d. All reactions were carried out under Ar unless stated otherwise. Graphite KS 5-44 provided by Lonza AG, Switzerland, has been used for the preparation of $C_8K$ and titanium–graphite, respectively, although other graphite samples are also suited for this purpose.[6] $TiCl_3$: Aldrich (99% purity). The solvents were dried by distillation over the following drying agents prior to use and were transferred under Ar: THF (sodium/benzophenone), DME (Na/K alloy), DMF, $CH_2Cl_2$, MeCN ($CaH_2$). Flash chromatography: Merck silica gel 60 (230–400 mesh).

**Substrates.** *tert*-BuMgCl, *n*-BuMgCl, BnMgCl, *N*-methylisatoic acid anhydride, $SmI_2$ (0.1 M in THF), (S)-(−)-*N*-(trifluoroacetyl)prolyl chloride (0.1 M in $CH_2Cl_2$), and substrates **31a**, **31b**, and **34** were purchased from Aldrich and used without further purification. Substrates **3a**, **3c**, **3p**, **5**, **7a**, and **11**, respectively, have been prepared as described in ref 3a,c. All other oxo amides were obtained analogously. A detailed description of their preparation together with the synthesis of previously unknown or insufficiently characterized oxoamines and acid chlorides as well as the full set of analytical and spectroscopic data for these compounds is given in the supplementary material.

**Method A: "Instant" Cyclization of Oxoamides to Indoles. General Procedure.** A 100-mL two-necked flask, equipped with a Teflon-coated magnetic stirring bar and a reflux condenser connected to an argon line, was charged with the keto amide (2.5 mmol), $TiCl_3$ (5.0 mmol), and zinc dust (10.0 mmol). The mixture was suspended in DME (50 mL), refluxed until TLC showed complete conversion of the substrate, cooled to room temperature, and filtered through a short plug of silica. The inorganic residues were washed with ethyl acetate (50 mL), the filtrate was evaporated, and the residue was purified by flash chromatography using 10% ethyl acetate in *n*-hexane as eluent unless stated otherwise.

**Method B: Titanium–Graphite-Induced Indole Formation. Representative Procedure.** A 50-mL two-necked flask, equipped with a Teflon-coated magnetic stirring bar and a reflux condenser connected to an argon line, was charged with graphite (1.38 g, 115 mmol) and heated to 150–160 °C while being evacuated. After the flask was flushed with Ar potassium (560 mg, 14.3 mmol) was added in pieces to the vigorously stirred graphite powder at that temperature until the bronze-colored potassium–graphite laminate ($C_8K$) was formed (10 min). When cooled to room temperature it was suspended in THF (30 mL). $TiCl_3$ (1.10 g, 7.15 mmol) was added, causing a slightly exothermic reaction, and the resulting slurry was refluxed for 1.5 h to ensure complete reduction. Keto amide **3c** (500 mg, 1.15 mmol) was added at once to that boiling suspension of titanium–graphite and heating continued for another 10 min. The mixture was allowed to cool to room temperature and filtered through a short plug of silica, the inorganic residues were washed with THF (20 mL) and ethyl acetate (50 mL), the filtrate was evaporated, and the residue was purified by flash chromatography using *n*-hexane/ethyl acetate (10/1) as eluant. This gave **4c** as a yellow solid (348 mg, 75%): mp 42–43 °C (lit.[3a] mp oil).

The same compound (0.444 g, 93%) was obtained upon reaction of keto amide **3c** (0.515 g, 1.18 mmol) with $TiCl_3$ (0.40 g, 2.6 mmol) and zinc (0.327 g, 5.00 mmol) in DME (50 mL) according to method A after 1.25 h. Spectroscopic data were in full agreement with those reported in ref 3a.

**2,3-Diphenylindole (4a).** Reaction of keto amide **3a** (0.753 g, 2.50 mmol) with $TiCl_3$ (1.68 g, 10.9 mmol) and zinc (1.30 g, 20.0 mmol) in DME (50 mL) for 1.5 h according to method A gave indole **4a** (0.658 g, 98%) as colorless crystals. All spectral and analytical data were in accordance with those reported in ref 3a.

**1-Methyl-2,3-diphenylindole (4b).** Prepared according to procedure B upon reaction of **3b** (804 mg, 2.55 mmol) with

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titanium–graphite ($C_8K$ (4.2 g, 31 mmol), $TiCl_3$ (2.4 g, 15.5 mmol)) in DME (60 mL) for 1.5 h. Standard workup followed by flash chromatography with toluene as eluant afforded the product as colorless crystals (690 mg, 96%): mp 136–138 °C (lit.[38b] mp 138 °C); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.75 (s, 3H), 7.24–7.51 (m, 13H), 7.91 (d, 1H, $J$ = 7.8 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) 31.1, 109.8, 119.9, 120.4, 122.4, 125.7, 128.2, 128.4, 128.6, 130.1, 131.4, 132.2, 135.5; MS $m/z$ (relative intensity) 283 (100, [M$^+$]), 268 (11), 114 (3).

**2-(9′-Decenyl)-3-phenylindole (4d).** Prepared according to method A with keto amide **3d** (500 mg, 1.38 mmol), $TiCl_3$ (434 mg, 2.81 mmol), and zinc (368 mg, 5.62 mmol) in THF (30 mL) for 2 h. Indole **4d** was obtained as yellow syrup (388 mg, 85%): $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.25 (br s, 10H), 1.64 (m, 2H), 2.02 (m, 2H), 2.80 (t, 2H, $J$ = 7.7 Hz), 4.89–5.04 (m, 2H), 5.70–5.90 (m, 1H), 7.08–7.50 (m, 8H), 7.63 (d, 1H, $J$ = 7.1 Hz), 7.86 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 50 MHz) 26.2, 28.8, 29.0, 29.2, 29.3, 29.8, 33.7, 110.4, 114.1, 114.2, 118.8, 119.8, 121.4, 125.8, 127.9, 128.4, 129.5, 135.1, 135.4, 136.1, 139.1; MS $m/z$ (relative intensity) 331 (91, [M$^+$]), 206 (100), 205 (12), 204 (19), 179 (16), 178 (11). It was also prepard by method B reacting **3d** (500 mg, 1.38 mmol) with titanium–graphite (graphite (1.60 g, 133 mmol), potassium (648 mg, 16.6 mmol), $TiCl_3$ (1.28 g, 8.30 mmol)) in THF (30 mL) for 15 min (365 mg, 80%).

**2-(4′-Chlorobutyl)-3-phenylindole (4e).** Prepared according to method A with **3e** (500 mg, 1.58 mmol), $TiCl_3$ (487 mg, 3.16 mmol), and zinc (413 mg, 6.32 mmol) in THF (30 mL) as reagents. Indole **4e** was obtained after 2 h as a yellow syrup (385 mg, 86%): $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.60–1.90 (m, 4H), 2.84 (t, 2H, $J$ = 7.3 Hz), 3.43 (t, 2H, $J$ = 6.1 Hz), 7.05–7.48 (m, 8H), 7.62 (d, 1H, $J$ = 7.0 Hz), 7.93 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 50 MHz) 25.5, 26.9, 31.8, 44.6, 110.5, 114.9, 119.0, 120.0, 121.7, 126.1, 127.9, 128.6, 129.6, 130.3, 134.9, 135.2; MS $m/z$ (relative intensity) 285 (32), 284 (20), 283 (98, [M$^+$]), 207 (19), 206 (100), 204 (18), 179 (11), 178 (11). Via method B: reaction of keto amide **3e** (500 mg, 1.58 mmol) with titanium–graphite (graphite (1.28 g, 107 mmol), potassium (522 mg, 13.6 mmol), $TiCl_3$ (1.03 g, 6.68 mmol)) in THF (30 mL) as described afforded indole **4e** after 10 min as a yellow syrup (397 mg, 87%). Analytical data as shown above.

**2-(3′-Chloropropyl)-3-phenylindole (4f).** Prepared according to method B using **3f** (500 mg, 1.66 mmol), graphite (1.35 g, 112 mmol), potassium (549 mg, 14.0 mmol), and $TiCl_3$ (1.08 g, 7.02 mmol) in THF (30 mL). After a reaction time of 5 min **4f** was obtained as yellow syrup (405 mg, 90%): $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.01 (m, 2H), 2.95 (t, 2H, $J$ = 7.4 Hz), 3.44 (t, 2H, $J$ = 6.3 Hz), 7.05–7.50 (m, 8H), 7.61 (dd, 1H, $J$ = 7.1, 1.2 Hz), 7.91 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 50 MHz) 23.5, 32.4, 44.2, 110.5, 115.1, 119.0, 120.0, 121.8, 126.1, 127.9, 128.6, 129.5, 133.8, 135.0, 135.2; MS $m/z$ (relative intensity) 269 (13, [M$^+$]), 269 (40), 207 (20), 206 (100), 205 (11), 204 (20), 179 (14), 178 (12).

**3-Phenyl-2-(trifluoromethyl)indole (4g).** Treatment of keto amide **3g** (500 mg, 1.71 mmol) with $TiCl_3$ (528 mg, 3.42 mmol) and zinc (447 mg, 6.84 mmol) in THF (30 mL) as described in procedure A gave indole **4g** after 4 h as yellow crystals (364 mg, 82%): mp 63–64 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 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) 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, 129.96, 132.16, 135.0; MS $m/z$ (relative intensity) 261 (100, [M$^+$]), 240 (12), 222 (10), 221 (11).

**3-(3′-Phenylindol-2′-yl)propionic Acid (4h).** The reaction of oxo amide **3h** (500 mg, 1.68 mmol) with $TiCl_3$ (521 mg, 3.38 mmol) and zinc (442 mg, 6.76 mmol) in THF (30 mL) was run according to method A for 1.5 h. After filtration the inorganic residues were washed with THF (20 mL) and ethyl acetate (50 mL, 2% v/v concd HOAc), the filtrate was evaporated, and the residue was chromatographed using $n$-hexane/ethyl acetate (4/1, 2% v/v concd HOAc) as eluant affording indole **4h** as colorless crystals (228 mg, 51%): mp 133–136 °C dec; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 2.77 (t, 2H, $J$ = 6.6 Hz), 3.17 (t, 2H, $J$ = 6.6 Hz), 7.07–7.47 (m, 8H), 7.62 (d, 1H, $J$ = 7.5 Hz), 8.57 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 50 MHz) 21.0, 34.4, 110.7, 114.8, 118.9, 119.8, 121.8, 126.1, 127.5, 128.5, 129.5, 133.9, 135.0, 135.2, 179.3; MS $m/z$ (relative intensity) 265 (92, [M$^+$]), 247 (15), 219 (12), 218 (24), 206 (100), 205 (13), 204 (28), 179 (20), 178 (15), 102 (13).

**2-Cyclopropyl-3-phenylindole (4i).** Treatment of keto amide **3i** (500 mg, 1.88 mmol) with $TiCl_3$ (590 mg, 3.83 mmol) and zinc (501 mg, 7.66 mmol) in THF (30 mL) as described in procedure A gave indole **4i** (369 mg, 84%) after 3 h as a yellow solid: mp 96–97 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 0.70 (m, 2H), 0.95 (m, 2H), 2.20 (m, 1H), 7.05–7.69 (m, 10H); $^{13}$C NMR ($CDCl_3$, 50 MHz) 7.6, 8.1, 115.1, 118.6, 120.0, 121.6, 125.7, 128.0, 128.3, 129.5, 134.7, 135.4, 136.3; MS $m/z$ (relative intensity) 233 (100, [M$^+$]), 232 (39), 230 (12), 219 (13), 218 (77), 217 (40), 206 (16), 204 (12), 109 (14).

**2-(2′-Bromophenyl)-3-phenylindole (4j).** Prepared according to method A upon reaction of keto amide **3j** (0.500 g, 1.32 mmol) with $TiCl_3$ (0.47 g, 3.0 mmol) and zinc (0.393 g, 6.00 mmol) in DME (50 mL) for 5 h. **4j** was obtained as a white solid (0.400 g, 88%): mp 137–138 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.12–7.41 (m, 11H), 7.59–7.68 (m, 1H), 7.81 (dd, 1H, $J$ = 7.6, 1.0 Hz), 8.22 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 111.0, 116.6, 119.8, 120.3, 122.8, 123.8, 125.9, 127.1, 127.3, 128.3, 129.5, 129.8, 132.9, 133.2, 133.4, 133.9, 134.7, 135.6; MS $m/z$ (relative intensity) 350 (21), 349 (95), 348 (21), 347 (92, [M$^+$]), 269 (15), 268 (74), 267 (100), 266 (20), 265 (12), 239 (11), 165 (12),134 (52). Following method B the same product was obtained (382 mg, 83%) after 3 h reaction time using the following reagents: **3j** (500 mg, 1.32 mmol), graphite (1.02 g, 85 mmol), potassium (413 mg, 10.6 mmol), and $TiCl_3$ (814 mg, 5.28 mmol) in THF (30 mL).

**2-(2′-Iodophenyl)-3-phenylindole (4k).** Reaction of keto amide **3k** (500 mg, 1.17 mmol) with $TiCl_3$ (379 mg, 2.46 mmol) and zinc (322 mg, 4.92 mmol) in THF (30 mL) according to method A gave indole **4k** (388 mg, 85%) after 2.5 h as a yellow solid. GC analysis showed that this compound contained 2,3-diphenylindole (**4a**) (22%), which could not be removed by flash chromatography: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 6.94–7.40 (m, 11H), 7.77–7.92 (m, 2H), 7.99 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 50 MHz) 99.7, 111.1, 116.1, 119.9, 120.4, 122.7, 125.9, 127.1, 128.0, 128.3, 129.4, 130.0, 132.5, 134.7, 135.4, 135.7, 138.3, 139.4; MS $m/z$ (relative intensity) 395 (100, [M$^+$]), 269 (18), 268 (64), 267 (88), 266 (18), 265 (12), 239 (11), 134 (33). The following quantities were chosen when method B was followed: **3k** (500 mg, 1.17 mmol), graphite (1.38 g, 115 mmol), potassium (562 mg, 14.4 mmol), $TiCl_3$ (1.11 g, 7.20 mmol) in THF (30 mL). Indole **4k** (360 mg, 78%) prepared that way after a reaction time of 10 min contained 4.5% (GC analysis) of 2,3-diphenylindole (**4a**).

**2-(2′-Furanyl)-3-phenylindole (4l).** Treatment of **3l** (255 mg, 0.87 mmol) with $TiCl_3$ (526 mg, 3.41 mmol) and zinc (446 mg, 6.82 mmol) in THF (15 mL) according to method A for 7 h gave indole **4l** (177 mg, 78%) as a yellow syrup: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 6.30 (br s, 2H), 7.03–7.58 (m, 10H), 8.55 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 50 MHz) 106.7, 110.8, 111.8, 114.4, 119.5, 120.3, 122.9, 125.1, 126.9, 128.5, 128.7, 130.2, 134.6, 135.4, 141.3, 147.1; MS $m/z$ (relative intensity) 259 (100, [M$^+$]), 230 (33). Reaction of **3l** (500 mg, 1.71 mmol) with titanium–graphite obtained from graphite (1.97 g, 164 mmol), potassium (802 mg, 20.5 mmol), and $TiCl_3$ (1.58 g, 10.3 mmol) in THF (30 mL) according to method B gave indole **4l** in 97% yield (429 mg) after 10 min reaction time.

**3-Phenyl-2-(2′-pyridyl)indole (4m).** A suspension of keto amide **3m** (0.444 g, 1.47 mmol), $TiCl_3$ (1.55 g, 10.0 mmol), zinc (1.31 g, 20.0 mmol), and pyridine (1.0 mL, 12.0 mmol) in DME (50 mL) was refluxed for 1 h. After cooling to room temperature and dilution with ethyl acetate (50 mL) a solution of EDTA (9.84 g, 30.0 mmol) in $H_2O$ (300 mL) was added, and the mixture was vigorously stirred for 10 min. Separation of the organic layer, evaporation of the solvent, and flash chromatography of the residue with 10% ethyl acetate in $n$-hexane as eluent gave indole **4m** (0.249 g, 63%) as a white solid: mp 149–150 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 7.02–7.12 (m, 2H), 7.22 (td, 1H, $J$ = 6.9, 1.2 Hz), 7.32–7.57 (m, 9H), 8.57 (dt, 1H, $J$ = 5.0, 1.3 Hz), 10.16 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 111.2, 117.0, 120.0, 120.1, 121.6, 121.8, 123.5, 127.1,

128.8, 129.6, 130.5, 132.0, 135.3, 135.4, 136.1, 149.0, 150.6; MS $m/z$ (relative intensity) 270 (74, [M$^+$]), 269 (100), 268 (16), 134 (14).

**2-(2′-Benzofuranyl)-3-phenylindole (4n).** Following method A the reaction of keto amide **3n** (500 mg, 1.47 mmol) with $TiCl_3$ (469 mg, 3.04 mmol) and zinc (398 mg, 6.08 mmol) in THF (30 mL) for 3 h gave indole **4n** (428 mg, 94%) as colorless crystals: mp 138–139 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 6.65 (s, 1H), 7.09–7.63 (m, 13H), 8.79 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 50 MHz) 102.8, 110.8, 111.0, 116.9, 119.8, 120.6, 121.0, 123.2, 123.6, 124.4, 127.3, 128.8, 129.1, 130.3, 134.4, 135.7, 148.6, 153.9; MS $m/z$ (relative intensity) 309 (100, [M$^+$]), 308 (15), 307 (11), 280 (14).

**2-(2′-Oxolanyl)-3-phenylindole (4o).** Prepared according to method B via reaction of keto amide **3o** (500 mg, 1.69 mmol) with titanium–graphite (graphite (1.31 g, 109 mmol), potassium (532 mg, 13.6 mmol), $TiCl_3$ (1.05 g, 6.8 mmol)) in THF (30 mL). After 20 min reaction time **4o** (220 mg, 50%) was obtained as colorless crystals: mp 135–136 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.78–2.03 (m, 3H), 2.18–2.29 (m, 1H), 3.84 (m, 1H), 4.07 (m, 1H), 5.18 (t, 1H, $J$ = 7.1 Hz), 7.04–7.50 (m, 8H), 7.64 (dd, 1H, $J$ = 7.4, 1.3 Hz), 8.54 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 50 MHz) 26.2, 33.6, 68.6, 74.1, 110.9, 114.2, 119.1, 119.9, 122.0, 126.1, 127.9, 128.4, 129.5, 134.8, 135.1, 135.7; MS $m/z$ (relative intensity) 263 (100, [M$^+$]), 262 (18), 234 (10), 233 (30), 232 (51), 220 (20), 219 (13), 218 (33), 217 (21), 207 (11), 206 (25), 204 (16), 193 (22), 186 (10), 165 (15).

**2-*tert*-Butyl-3-phenylindole (4p).** Obtained as colorless crystals (0.255 g, 97%) according to method A upon reaction of keto amide **3p** (0.299 g, 1.06 mmol) with $TiCl_3$ (0.670 g, 4.34 mmol) and zinc (0.568 g, 8.68 mmol) in 30 mL of DME for 1.5 h. The same product was prepared according to method B using keto amide **3p** (0.703 g, 2.50 mmol), $C_8K$ (4.28 g, 31.0 mmol), and $TiCl_3$ (1.50 g, 9.72 mmol) in DME (40 mL) after 3 h reaction time (0.491 mg, 79%): mp 126–127 °C (lit.[3a] mp 126–127 °C). Spectral data as reported in ref 3a.

**2-*tert*-Butyl-*N*-methyl-3-phenylindole (4q).** Prepared as described in method B using keto amide **3q** (0.655 g, 2.22 mmol), graphite (3.00 g, 250 mmol), potassium (1.16 g, 30.0 mmol), and $TiCl_3$ (1.51 g, 9.78 mmol) in DME (50 mL). After 1 h reaction time indole **4q** was obtained as colorless crystals (0.478 g, 84%): mp 108–109 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 1.34 (s, 9H), 3.91 (s, 3H), 6.91–7.06 (m, 2H), 7.12–7.39 (m, 7H); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ 32.1, 33.3, 34.1, 108.2, 114.7, 119.2, 119.3, 121.5, 126.2, 127.5, 129.8, 131.7, 137.0, 138.5, 142.9; MS $m/z$ (relative intensity) 263 (58, [M$^+$]), 248 (100), 233 (29), 232 (13), 218 (18), 217 (10).

**2-[3′,4′-(Methylenedioxy)phenyl]-3-phenylindole (4r).** Treatment of oxo amide **3r** (429 mg, 1.24 mmol) with $TiCl_3$ (383 mg, 2.48 mmol) and zinc (324 mg, 4.96 mmol) in THF (30 mL) for 4 h according to method A gave indole **4r** (383 mg, 99%) as colorless crystals: mp 150–151 °C; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 5.87 (s, 2H), 6.68–6.88 (m, 3H), 7.06–7.44 (m, 8H), 7.64 (d, 1H, $J$ = 7.4 Hz), 8.01 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 50 MHz) 108.6, 108.7, 110.8, 114.4, 119.5, 120.4, 121.9, 122.5, 126.2, 126.6, 128.5, 128.7, 130.1, 133.9, 134.9, 135.6, 147.2, 147.7; MS $m/z$ (relative intensity) 313 (100, [M$^+$]), 254 (31), 127 (17). The same compound (381 mg, 84%) was obtained according to method B by reaction of **3r** (500 mg, 1.45 mmol) with titanium–graphite (graphite (1.12 g, 93 mmol), potassium (454 mg, 11.6 mmol), $TiCl_3$ (895 mg, 5.80 mmol)) in THF (30 mL) for 20 min.

**2-Methyl-3-phenyl-1-tosylindole (4s).** Prepared according to procedure B upon treatment of substrate **3s** (393 mg, 1.00 mmol) with titanium–graphite ($C_8K$ (2.1 g, 15.53 mmol), $TiCl_3$ (1.20 g, 7.77 mmol)) in DME (50 mL) for 1.2 h. Workup as described above followed by flash chromatography with toluene as eluent afforded the title compound as a white solid (311 mg, 86%): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.38 (s, 3 H), 2.70 (s, 3 H), 7.24–7.56 (m, 10H), 7.81 (d, 2H, $J$ = 8.3 Hz), 8.39 (d, 1H, $J$ = 8.6 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) 13.68, 21.65, 110.56, 114.74, 119.39, 123.75, 124.44, 126.57, 128.75, 129.56, 130.07, 133.33, 136.56, 144.94.

**Ethyl 5-Chloro-3-phenylindolecarboxylate (6).** Reaction of compound **5** (0.743 g, 2.25 mmol) with $TiCl_3$ (0.84 g, 5.5 mmol) and zinc (0.734 g, 11.2 mmol) in DME (50 mL) for 1.5 h according to method A gave indole **6** (0.586 g, 87%) as a pale yellow solid: mp 174–175 °C (lit.[3c] mp 178–180 °C). The material was identical in all spectroscopic respects to an authentic sample.[3c]

**3-Methyl-2-phenylindole (8a).** Obtained by following method A with ketoamide **7a** (0.396 g, 1.65 mmol), $TiCl_3$ (0.916 g, 5.93 mmol), and zinc (0.776 g, 11.8 mmol) in DME (20 mL). Indole **8a** was obtained after 0.75 h as a white solid (0.259 g, 76%), the spectral and analytical data of which were in accordance with those previously published.[3a]

**1,3-Dimethyl-2-phenylindole (8b).** Prepared according to procedure B upon reaction of substrate **7b** (350 mg, 1.38 mmol) with titanium–graphite ($C_8K$ (2.1 g, 15.53 mmol), $TiCl_3$ (1.20 g, 7.77 mmol)) in DME (50 mL) for 0.5 h. Workup as described followed by flash chromatography with toluene as eluant afforded the product as colorless crystals (280 mg, 92%): mp 65–67 °C (lit.[38b] mp 69 °C); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.40 (s, 3H), 3.70 (s, 3H), 7.24–7.61 (m, 8H), 7.72 (d, 1H, $J$ = 7.5 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) 9.57, 31.12, 109.46, 119.07, 119.39, 121.99, 127.99, 128.58, 130.90, 132.49, 137.54, 137.92.

**3-Butyl-1-methyl-2-phenylindole (10).** Reaction of keto amide **9** (0.200 g, 0.678 mmol) with $TiCl_3$ (1.15 g, 7.45 mmol) and zinc (0.736 g, 11.3 mmol) in DME (50 mL) according to method A gave indole **10** (0.126 g, 70%) after 4 h as a yellow syrup: $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ 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) $\delta$ 13.9, 22.7, 24.3, 30.7, 39.5, 109.3, 113.9, 119.0, 119.1, 121.5, 127.8, 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).

**2,3-Diphenylbenzo[*b*]furan (12).** Reaction of keto ester **11** (0.640 g, 2.12 mmol)[3a] with $TiCl_3$ (0.651 g, 4.21 mmol) and zinc (0.551 g, 8.42 mmol) in DME (50 mL) according to method A gave **12** (0.434 g, 76%) after 1 h as a white solid: mp 120–122 °C (lir.[3a] mp 119–122 °C). All spectroscopic data were in agreement with those reported previously.[3a]

**(*S*)-(−)-3-Phenyl-2-[*N*-(trifluoroacetyl)-2′-pyrrolidyl]indole (14).** Prepared according to method A by the reaction of keto amide **13** (250 mg, 0.64 mmol) with $TiCl_3$ (209 mg, 1.36 mmol) and zinc (178 mg, 2.72 mmol) in THF (20 mL) for 1 h. Pale brown crystals (206 mg, 90%): mp 73–75 °C dec; $[\alpha]^{20}_D$ −27.9° ($c$ 0.8, $CH_2Cl_2$); $^1$H NMR ($CDCl_3$, 400 MHz, [rotamer]) $\delta$ 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]) $\delta$ 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]. The determination of the enantiomeric purity of this product (ee = 93.0%) was performed by LC: Varian 5060, UV 100 on a Chiraspher column (250 mm, 4.5 mm) at 308 K with $n$-heptane/2-propanol (95/5) as eluent; flow: 1.0 mL/min; detection: UV 254 nm.

**(+)-Aristoteline (16).** A suspension of oxo amide **15** (24 mg, 0.074 mmol),[18a] $TiCl_3$ (45 mg, 0.29 mmol), and Zn (77 mg, 1.18 mmol) in THF (2 mL) was refluxed for 4 h. EDTA (430 mg, 1.47 mmol) was added, and the mixture stirred for 1 h at ambient temperature, diluted with THF (20 mL), and filtered through a short plug of silica. The filtrate was evaporated and the residue chromatographed (hexane/ethyl acetate/$NEt_3$ = 10/10/1), thus affording **16** as colorless crystals (16.2 mg, 75%). The product was identical in all respects with an authentic sample: mp 160–162 °C (lit.[18c] mp 164 °C, lit.[18b] mp 160–162.5 °C, lit.[18d] mp 158–159 °C); $[\alpha]^{20}_D$ +20.2 ($c$ 0.3, $CDCl_3$) (lit.[18c] +16 (MeOH); lit.[18b] +23 ($c$ 1.84, $CHCl_3$)); $^1$H NMR (400 MHz, $CDCl_3$) 1.05, 1.31, 1.53 (s, 3H each), 1.20–1.71 (m, 5H), 1.90–1.93 (m, 1H), 1.95 and 2.05 (ddAB, 2H, $J$ = 3.2, 14 Hz), 2.22–2.31 (m, 1H), 2.65 (d, 1H, $J$ = 16.5 Hz), 3.07 (dd, 1H, $J$ = 16.5, 5.8 Hz), 3.63 (dd, 1H, $J$ = 1, 5.6 Hz), 7.05 (dt, 1H, $J$ = 1.1, 7.2 Hz), 7.10 (dt, 1H, $J$ = 1.1, 7.2 Hz), 7.29 (dd, 1H, $J$ = 1, 8 Hz), 7.44 (dd, 1H, $J$ = 1, 8 Hz), 7.77 (br s, 1H, −NH); $^{13}$C NMR (100 MHz, $CDCl_3$) 25.2, 25.5, 27.5, 27.8, 28.6,

29.1, 33.2, 35.7, 36.0, 39.4, 50.6, 53.6, 104.4, 110.5, 118.2, 119.2, 121.1, 128.2, 136.2, 142.5.

**3-(Phenylmethyl)-2-phenylindole (20a).** Reaction of keto amide **19a** (0.500 g, 1.58 mmol) with $TiCl_3$ (0.551 g, 3.56 mmol) and zinc (0.466 g, 7.13 mmol) in DME (50 mL) according to method A and standard workup gave indole **20a** (0.394 g, 88%) after 22 h as colorless crystals: mp 117–119 °C (lit.[38c] mp 119 °C).

**2-*tert*-Butyl-3-(phenylmethyl)indole (20b).** Reaction of keto amide **19b** (0.395 g, 1.34 mmol) with $TiCl_3$ (0.772 g, 5.00 mmol) and zinc (0.654 g, 10.0 mmol) in DME (50 mL) according to method A gave indole **20b** (0.334 g, 95%) after 92 h as a viscous oil: $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.40 (s, 9H), 4.30 (s, 2H), 6.98 (t, 1H, $J$ = 7.5 Hz), 7.05–7.25 (m, 7H), 7.29 (d, 1H, $J$ = 7.4 Hz), 7.92 (br s, 1H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 30.4, 30.8, 32.9, 108.1, 110.2, 119.3, 121.1, 125.5, 128.1, 130.3, 133.4, 141.8, 142.7; MS $m/z$ (relative intensity) 263 (89, [M$^+$]), 249 (19), 248 (100), 206 (17), 186 (10), 170 (27), 131 (17), 91 (49).

**3-*tert*-Butyl-2-phenylindole (22a).** Obtained by reaction of keto amide **21a** (0.490 g, 1.74 mmol) with $TiCl_3$ (0.744 g, 4.80 mmol) and zinc (0.627 g, 9.60 mmol) in DME (50 mL) according to method A (0.373 g, 86%) after 69 h as a white solid: mp 103–106 °C; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.36 (s, 9H), 7.06–7.45 (m, 8H), 7.69 (br s, 1H), 7.90 (d, 1H, $J$ = 7.0 Hz); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 32.4, 33.1, 110.6, 118.9, 121.5, 121.7, 122.2, 127.4, 127.5, 128.1, 130.9, 133.4, 135.7, 136.4; MS $m/z$ (relative intensity) 249 (40, [M$^+$]), 235 (18), 234 (100).

**3-*tert*-Butyl-1-methyl-2-phenylindole (22b).** Reaction of keto amide **21b** (0.504 g, 1.70 mmol) with $TiCl_3$ (0.635 g, 4.08 mmol) and zinc (0.535 g, 8.16 mmol) in DME (50 mL) according to procedure A gave after 4 h indole **22b** as colorless crystals (0.334 g, 75%). The same product (0.384 g, 62%) was obtained by method B after 3 h reaction time using **21b** (0.701 g, 2.37 mmol), $C_8K$ (4.7 g, 34 mmol), and $TiCl_3$ (1.75 g, 11.3 mmol) in DME (50 mL): mp 164–166 °C (lit.[20] mp 171–172 °C). Spectroscopic data in accordance with those in ref 20.

**3-*tert*-Butyl-1-methyl-2-(2′,4′,6′-trimethylphenyl)-indole (22c).** This compound was prepared according to method A by treatment of ketoamide **21c** (0.503 g, 1.49 mmol) with $TiCl_3$ (2.16 g, 14.0 mmol) and zinc (1.83 g, 28.0 mmol) in DME (50 mL) for 67 h (0.399 g, 88%). Colorless crystals: mp 131–132 °C; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.29 (s, 9H), 2.00 (s, 6H), 2.36 (s, 3H), 3.22 (s, 3H), 6.93 (s, 2H), 7.12 (td, 1H, $J$ = 7.9, 1.3 Hz), 7.21 (td, 1H, $J$ = 7.9, 1.3 Hz), 7.32 (dd, 1H, $J$ = 7.6, 1.3 Hz), 7.92 (dd, 1H, $J$ = 7.9, 1.0 Hz); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 20.4, 21.2, 28.9, 31.3, 32.9, 109.2, 118.0, 119.7, 120.5, 121.9, 127.0, 127.7, 131.6, 133.3, 137.5, 137.9, 138.3; MS $m/z$ (relative intensity) 305 (27, [M$^+$]), 291 (23), 290 (100).

**3-*tert*-Butyl-2-isopropyl-1-methylindole (22d).** Prepared according to method B using keto amide **21d** (0.363 g, 1.39 mmol) and titanium–graphite (graphite (3.00 g, 250 mmol), potassium (1.21 g, 31.0 mmol), $TiCl_3$ (1.60 g, 10.4 mmol)) in DME (50 mL). After 22 h reaction time the title compound was obtained by flash chromatography as colorless crystals (0.115 g, 36%): mp 75–76 °C; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.42 (d, 6H, $J$ = 7.4 Hz), 1.57 (s, 9H), 3.77 (s, 3H), 3.81–4.03 (m, 1H), 6.97–7.28 (m, 3H), 7.96 (dt, 1H, $J$ = 7.7, 1.1 Hz); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 21.1, 25.7, 31.8, 33.1, 33.9, 108.4, 118.0, 118.4, 120.0, 122.0, 126.6, 137.5, 141.5; MS $m/z$ (relative intensity) 229 (21, [M$^+$]), 215 (18), 214 (100), 174 (16). A second, slower moving fraction was identified as pseudoindoxyl **23d** (syrup, 81 mg, 24%) by the following spectral properties: $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 0.88 (d, 3H, $J$ = 6.6 Hz), 1.00 (d, 3H, $J$ = 7.1 Hz), 1.03 (s, 9H), 2.35–2.58 (m, 1H), 3.12 (s, 3H), 6.57–6.69 (m, 2H), 7.33–7.52 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 18.0, 19.9, 27.2, 32.2, 32.6, 38.9, 78.4, 107.1, 116.1, 121.6, 123.5, 136.9, 161.2, 204.2; IR: 1690, 1620 cm$^{-1}$; MS $m/z$ (relative intensity) 245 (10, [M$^+$], 190 (13), 189 (100), 188 (97), 174 (39), 173 (11), 160 (16).

**2,3-Di-*tert*-butyl-1-methylindole (22e).** This derivative was obtained via method B with substrate **21e** (1.12 g, 4.07 mmol) and titanium–graphite (graphite (6.00 g, 500 mmol), potassium (2.45 g, 62.6 mmol), $TiCl_3$ (4.89 g, 31.7 mmol)) in DME (50 mL) for 15 min and flash chromatography with hexane as eluent. Syrup (350 mg, 35%): $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.53 (s, 9H), 1.58 (s, 9H), 3.67 (s, 3H), 6.82–7.14 (m, 3H), 7.83 (d, 1H, $J$ = 7.7 Hz); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 33.7, 34.4, 34.5, 34.9, 36.1, 109.1, 119.0, 120.6, 122.5, 123.8, 128.0, 140.1, 144.6; MS $m/z$ (relative intensity) 243 (37, [M$^+$]), 229 (18), 228 (100), 198 (11), 172 (26), 57 (12). A second slower moving fraction was identified as the pseudoindoxyl **23e** (syrup, 15%) by the following spectral parameters: $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ 1.13 (s, 18H), 3.28 (s, 3H), 6.57–6.66 (m, 2H), 7.34–7.52 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 50 MHz) $\delta$ 29.1, 35.0, 40.7, 80.2, 106.8, 116.1, 121.9, 123.4, 136.7, 161.9, 203.0; IR: 1690, 1615 cm$^{-1}$; MS $m/z$ (relative intensity) 259 (9, [M$^+$]), 203 (81), 188 (72), 174 (43), 160 (20), 147 (100), 144 (11), 77 (14).

***(E,E)*-1,2,3,4-Tetraphenyl-1,3-butadiene (28).** A suspension of tolan (380 mg, 2.13 mmol), $TiCl_3$ (670 mg, 4.34 mmol), and Zn dust (570 mg, 8.68 mmol) in DME (10 mL) was refluxed for 6 h under Ar. The blue-green mixture was diluted with $CH_2Cl_2$ (50 mL) and filtered through a plug of silica, the filtrate was evaporated, and the residue was purified by column chromatography with hexane/ethyl acetate (25/1) as eluant. Thus, the product was obtained as pale yellow crystals (230 mg, 60%): mp 177–179 °C (lit.[26b] mp 176–178 °C); $^1H$ NMR (200 MHz, THF-$d_8$) 6.34 (s, 2H), 6.66–6.75 (m, 4H), 6.90–7.01 (m, 6H), 7.25–7.45 (m, 10H); $^{13}C$ NMR (50 MHz, THF-$d_8$) 127.4, 128.2, 128.4, 129.6, 130.2, 131.2, 132.5, 138.1, 140.8, 146.6; MS $m/z$ (relative intensity) 358 (69, [M$^+$]), 281 (25), 267 (100), 203 (17), 178 (21), 167 (60).

**Deoxygenation of Benzoin Derivatives.** A suspension of *O*-ethylbenzoin (**31a**) (1.08 g, 4.49 mmol), $TiCl_3$ (1.39 g, 9.00 mmol), and Zn dust (1.18 g, 18 mmol) in DME (50 mL) was refluxed under Ar for 4 h. The mixture was filtered, the solvent evaporated, and the residue purified by flash chromatography with hexane/ethyl acetate (10/1) as eluent affording **32** as yellow oil that crystallized upon standing at room temperature. Colorless crystals (750 mg, 85%): mp 54–57 °C. The product was identical to an authentic sample.

**Trapping Experiments. 1-(2′-Benzamidophenyl)ethanol (33a).** A solution of Ti(biphenyl)$_2$ (886 mg, 2.49 mmol)[10e] and keto amide **7a** (297 mg, 1.24 mmol) in THF (5 mL) and water (1 mL) was refluxed for 75 min. Evaporation of the solvent and flash chromatography of the crude product afforded indole **8a** (12%) and the slower moving alcohol **33a** (174 mg, 58%). Colorless crystals: mp 97–98 °C; IR 3440, 3280, 1655, 1590, 1530, 1440, 1320, 750, 710 cm$^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$) 1.52 (d, 3H, $J$ = 6.6 Hz), 3.85 (br s, 1H, –OH), 4.96 (q, 1H, $J$ = 6.6 Hz), 6.96–7.52 (m, 6H), 7.86 (dd, 2H, $J$ = 1.1, 7.9 Hz), 8.23 (d, 1H, $J$ = 6 Hz), 10.25 (br s, 1H); $^{13}C$ NMR (50 MHz, $CDCl_3$) 22.8, 71.2, 122.4, 124.1, 126.8, 127.1, 128.3, 128.8, 131.8, 133.0, 134.7, 136.9, 165.4; MS $m/z$ (relative intensity) 241 (20, [M$^+$]), 136 (28), 121 (22), 105 (100), 77 (55).

**2′-(Benzamidophenyl)phenylcarbinol (33b).** To a suspension of $TiCl_3$ (1.09 g, 7.03 mmol) in THF (10 mL) and water (5 mL) was added NaOAc until pH 7 was reached. Substrate **3a** (476 mg, 1.58 mmol) and zinc dust (920 mg, 14.06 mmol) were added and the mixture refluxed for 30 min. Standard extractive workup (EtOAc) followed by flash chromatography of the crude product afforded **33b** (391 mg, 82%) as colorless crystals: mp 151–152 °C; IR 3150–3480, 1660, 1580, 1530, 1440, 1310, 1250, 760, 700 cm$^{-1}$; $^1H$ NMR (200 MHz, DMSO-$d_6$) 6.84–7.65 (m, 15H), 8.25 (d, 1H); $^{13}C$ NMR (50 MHz, DMSO-$d_6$) 84.3, 121.2, 126.3, 126.6, 127.2, 127.8, 128.0, 128.6, 129.1, 131.1, 132.4, 134.3, 137.8, 144.3, 163.1; MS $m/z$ (relative intensity) 303 (15, [M$^+$]), 198 (35), 105 (100), 77 (40).

**2-Phenyl-4-quinolone (37).** A suspension of substrate **36** (540 mg, 1.82 mmol), $TiCl_3$ (560 mg, 3.63 mmol), and Zn (476 mg, 7.30 mmol) in THF (7 mL) was refluxed for 3 h, cooled, and filtered through a short pad of silica, the solvent was evaporated, and the residue was chromatographed using ethyl acetate as the eluent affording compound **37** as pale yellow crystals (225 mg, 56%): mp 247–250 °C (lit.[36] mp 252–254 °C); $^1H$ NMR (200 MHz, DMSO-$d_6$) 6.36 (s, 1H), 7.34 (dt, 1H, $J$ = 1, 8 Hz), 7.50–7.88 (m, 7H), 8.12 (dd, 1H, $J$ = 1, 8 Hz), 11.75 (br s, 1H); $^{13}C$ NMR (50 MHz, DMSO-$d_6$) 107.04, 118.67, 123.09, 124.47, 127.20, 128.77, 130.31, 131.56, 134.08, 140.45, 149.95, 177.89; MS $m/z$ (relative intensity) 221 (100, [M$^+$]), 204 (7), 193 (53), 165 (18), 89 (11).

**$Cp_2Ti(PMe_3)_2$-Mediated Cyclizations.** A solution of $Cp_2Ti(PMe_3)_2$ (670 mg, 2.03 mmol)[10b,c] and **3a** (204 mg, 0.67 mmol) in DME (50 mL) was refluxed for 10 min, cooled, and filtered through a pad of silica. The filtrate was evaporated and the residue chromatographed using hexane/ethyl acetate (10/1) as eluent affording indole **4a** (145 mg, 79%) which was identical in all respects to the samples prepared by the instant method.

Indole **10** was obtained by stirring a mixture of $Cp_2Ti(PMe_3)_2$ (790 mg, 2.39 mmol) and oxo amide **9** (226 mg, 0.76 mmol) in DME (4 mL) at ambient temperature for 2 h. Workup as described above afforded **10** (123 mg, 62%), which was identical to an authentic sample.

**$[TiHCl{\cdot}THF_{0.5}]_n$-Induced Indole Syntheses.** At −70 °C oxo amide **3a** (904 mg, 3.00 mmol) was added to a suspension of $[TiHCl{\cdot}THF_{0.5}]_n$ (896 mg, 6.67 mmol)[7b] in THF (15 mL). The mixture was allowed to warm to room temperature overnight, and the conversion was monitored by recording both the amount of $H_2$ formed and the reaction temperature. Evolution of gas started at −40 °C. For workup the mixture was filtered through a pad of silica, the solvent evaporated, and the residue purified by flash chromatography with hexane/ethyl acetate (10/1) as eluent. Thus, **4a** was obtained as colorless crystals identical in all analytical and spectroscopic properties to an authentic sample (683 mg, 85%).

**Ti(arene)$_2$-Induced Indole Formation.** A solution of oxo amide **3a** (512 mg, 1.7 mmol) and $Ti(C_6H_5Me)_2$ (653 mg, 3.5 mmol)[10a] in DME (50 mL) was refluxed for 0.5 h, cooled, and filtered through a pad of silica. Evaporation of the solvent followed by flash chromatography (hexane/ethyl acetate 10/1) afforded indole **4a** as colorless crystals (341 mg, 75%). The reaction with Ti(biphenyl)$_2$ was performed analogously in THF as solvent.

**Low-Valent Niobium-Induced Indole Formation.** A suspension of $NbCl_5$ (1.56 g, 5.7 mmol) and zinc (566 mg, 8.56 mmol) in DME (50 mL) was stirred at ambient temperature for 45 min. Substrate **5** (700 mg, 2.1 mmol) was added, the mixture refluxed for 2 h and filtered through a pad of silica, the filtrate was evaporated, and the residue was chromatographed affording **6** as pale yellow crystals (356 mg, 74%). Analytical data as reported above.

**Low-Valent Tungsten-Induced Indole Formation.** *n*-BuLi (1.6 M in hexane, 5.96 mL, 9.5 mmol) was added to a suspension of $WCl_4$ (3.11 g, 9.5 mmol) in THF (50 mL) at −78 °C, and the mixture was allowed to warm to room temperature. Substrate **5** (700 mg, 2.1 mmol) was added and the reaction refluxed for 23 h and worked up as described above affording indole **6** as pale yellow crystals (221 mg, 35%).

**$SmI_2$-Induced Indole Formation.** Substrate **3a** (301 mg, 1.0 mmol) dissolved in THF (10 mL) was slowly added to a stirred solution of $SmI_2$ (0.1 M in THF, 40 mL, 4.0 mmol) at ambient temperature. After 1 h the mixture was filtered through a pad of silica, the solvent evaporated, and the residue chromatographed affording indole **4a** as colorless crystals (90 mg, 31%) together with two unidentified byproducts.

**"Instant" Activation of Zirconium. Tetraphenylethanone (29).** A suspension of $ZrCl_4$ (1.51 g, 6.48 mmol), zinc dust (847 mg, 12.96 mmol), and benzophenone (654 mg, 3.59 mmol) in DME (50 mL) was refluxed for 5 h. For workup the mixture was filtered through a pad of silica, the solvent removed *in vacuo*, and the residue chromatographed (hexane/ethyl acetate 10/1) affording the title compound as colorless crystals (363 mg, 61%). Identified by comparison with an authentic compound. Characteristic data: $^{13}C$ NMR (50 MHz, $CDCl_3$) 70.8 (s), 126.4 (d), 127.3 (d), 127.5 (d), 127.9 (d), 130.6 (d), 130.7 (d), 131.4 (d), 137.2 (s), 142.9 (s), 198.5 (s); MS *m/z* (relative intensity) 348 (5, $[M^+]$), 332 (6), 243 (100), 165 (56), 105 (20).

The cyclization of oxo amide **3a** (466 mg, 1.55 mmol) to indole **4a** (161 mg, 39%) was performed analogously with $ZrCl_4$ (1.44 g, 6.18 mmol) and Zn (808 mg, 12.36 mmol).

**McMurry Coupling of Aldehydes and Ketones to Alkenes. Representative Procedure.** A suspension of 9-fluorenone (514 mg, 2.85 mmol), $TiCl_3$ (417 mg, 5.94 mmol), and zinc dust (777 mg, 11.88 mmol) in DME (20 mL) was refluxed for 2 h and filtered when cooled to room temperature, the solvent was evaporated, and the residue was chromatographed with hexane/ethyl acetate (15/1). Thus, 9,9'-bifluorenylidene was obtained as orange-red crystals (430 mg, 92%). The spectroscopic properties were in agreement with those reported in the literature: mp 187−189 °C (lit.[38d] mp 187−189 °C). Updated spectroscopic data: $^{13}C$ NMR (50 MHz, $CDCl_3$): 119.8, 126.7, 126.8, 129.1, 138.2, 141.0, 141.3; MS *m/z* (relative intensity) 328 (100, $[M^+]$), 162 (23).

**Tetraphenylethene.** Obtained as described above upon reaction of benzophenone (728 mg, 4.0 mmol), $TiCl_3$ (1.64 g, 10.6 mmol), and Zn (1.41 g, 21.2 mmol) in THF (50 mL) at reflux for 4 h. The product (568 mg, 78%) was identical to an authentic sample.[5a]

**(*E*)-Stilbene.** Obtained according to the procedure given above with benzaldehyde (596 mg, 5.6 mmol), $TiCl_3$ (1.25 g, 8.1 mmol), and Zn (1.06 g, 16.2 mmol) in DME (50 mL) after 1 h at reflux. Colorless crystals (391 mg, 78%). Identical to an authetic sample.

**Eicosane-10,11-diol.** Obtained as described above with decanal (1.56 g, 10.0 mmol), $TiCl_3$ (3.36 g, 21.7 mmol), and Zn (2.78 g, 43.4 mmol) in DME (50 mL). After 1 h at reflux the mixture was worked up as usual affording the title compound as colorless syrup (935 mg, 60%): $^1H$ NMR (200 MHz, $CDCl_3$) 0.9 (t, 6 H), 1.15−1.60 (m, 28 H), 2.1 (m, 4 H), 3.3 (m, 2 H); $^{13}C$ NMR (50 MHz, $CDCl_3$) 13.7 (q), 22.3 (t), 25.3 (t), 28.9 (t), 29.2 (t), 29.3 (t), 31.5 (t), 33.3 (t), 74.1 (d).

**Cyclization of 1,6-Diphenyl-1,6-hexanedione.** A mixture of 1,6-diphenyl-1,6-hexanedione (536 mg, 2.02 mmol),[5a] $TiCl_3$ (899 mg, 5.83 mmol), and Zn (763 mg, 11.66 mmol) in DME (50 mL) was refluxed for 3.5 h. Workup as described above followed by flash chromatography with hexane/ethyl acetate (15/1) afforded 1,2-diphenylcyclohexene (227 mg, 48%) and 1,2-diphenylcyclohexane-1,2-diol (92 mg, 19%). The analytical and spectroscopic data were in accordance with those reported in ref 5a,b.

**Electrochemical Investigations.** The cyclovoltamograms were recorded under aprotic conditions in THF with 0.1 M tetra-*n*-butylammonium perchlorate as the supporting electrolyte with a PAR 170 apparatus (EG&G, Munich) in a standard cell (Metrohm, Filderstadt). A three-electrode system was employed with Ag/AgCl (in standard solution) and a platinum wire as the reference and the auxiliary electrodes, respectively. Working electrode: glassy-carbon (2 mm). After the measurements the potential of the Ag/AgCl electrode was compared and normalized to SCE. The concentration of the substrates was $10^{-3}$ M. Scan rate: 100 $mV{\cdot}s^{-1}$.

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**Supplementary Material Available:** Detailed description of the preparation and the full set of analytical and spectroscopic data (IR, $^1H$ NMR, $^{13}C$ NMR, MS) of all starting materials. List of IR absorptions and of the elemental analyses of all new products (23 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; ordering information is given on any current masthead page.