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Novel Functionalized Titanium(IV) Benzylidenes for the Traceless Solid-Phase Synthesis of Indoles†

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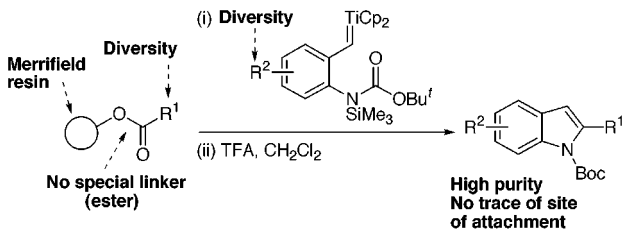
ABSTRACT



Titanium(IV) benzylidenes bearing a masked nitrogen nucleophile in the *ortho* position converted Merrifield resin-bound esters into enol ethers. An unusual nitrogen protecting group, *N*-silylated *tert*-butyl carbamate, was employed. One percent TFA released *N*-Boc indoles in high yield and purity. *N*-Methyl indoles were also prepared. Cyclative termination was not required to release the chameleon catch. The first example of a carbonyl group within a titanium alkylidene reagent is reported.

A variety of titanium reagents will alkylidenate esters to give enol ethers. The most commonly used are those developed by the groups of Tebbe[1] (and applied by Pine, Grubbs, Evans and co-workers[2]), Petasis,[3] and Takai,[4] although Grubbs,[5] Matsubara,[6] and Takeda[7] have introduced interesting alternatives. The reactive agents produced under the conditions of Tebbe, Petasis, Grubbs, and Takeda are believed to be titanocene(IV) alkylidenes ($Cp_2Ti{=}CR^1R^2$, **1**). Tebbe and Grubbs reagents allow only methylenation of esters via active species **1** ($R^1 = R^2 = H$). The method of Petasis is more general and involves generating titanium alkylidenes **1** ($R^1 = H$, $R^2 = H$,[3a] aryl,[3b] silyl[3c]) by thermolysis of dialkyltitanocenes. However, organolithiums or Grignard reagents are used to make the dialkyltitanocenes, and this limits the functionality that may be present in the alkylidenating reagent **1**. Furthermore, the method does not allow the generation of titanium alkylidenes that have hydrogen atoms β to the titanium atom in active species **1**. In Takeda's method,[7] a wide range of titanium alkylidenes (with or without hydrogen atoms β to the titanium atom) can be generated by reducing thioacetals with a low valent titanium complex,

† Dedicated to Prof. T. H. Chan on the occasion of his 60th birthday.
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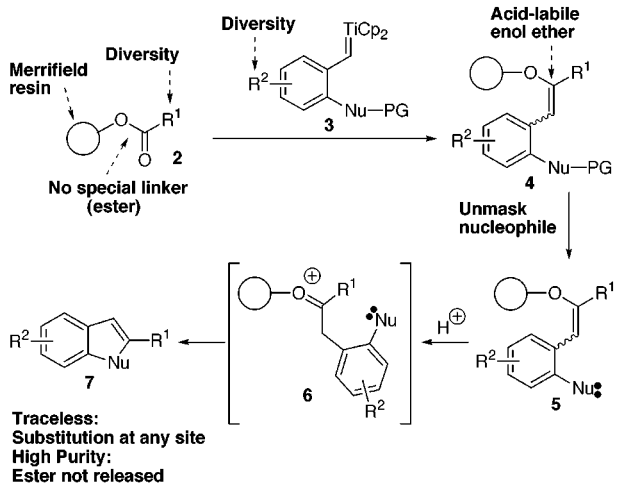
$Cp_2Ti[P(OEt)_3]_2$. Takai reagents,[4] which are probably 1,1-bimetallics, have a similar generality but have to be made from 1,1-dihaloalkanes, which are synthetically less accessible than thioacetals.

We envisaged using Takeda's method to generate functionalized titanium alkylidene reagents that would allow new synthetic strategies involving conversion of esters into enol ethers. Current strategies employ alkylidenation of esters followed by sigmatropic rearrangement (particularly useful in the synthesis of macrocycles),[8] ring-closing metathesis (useful in the synthesis of polyethers),[9,10] acid-induced rearrangement,[11] or another reaction of the enol ether moiety.[12] However, none of these strategies relies on the titanium reagent introducing any functionality other than the enol ether. In their seminal paper,[13] Mortimore and Kocienski used a Takai reagent bearing a masked oxygen nucleophile in a synthesis of spiroketals. We have designed a similar strategy for the synthesis of aromatic heterocycles on solid phase (Scheme 1). Resin-bound esters **2** would be benzylide-

Scheme 1. General Strategy



nated with titanium benzylidenes **3** having a masked nucleophile in the *ortho* position. The acid-stable esters **2** would thus be converted into acid-sensitive enol ethers **4**. The masked nucleophile would then be unmasked to give enol ethers **5**. Treatment with acid should then lead to the formation of oxonium ion **6** and release from the resin with concomitant cyclization to give bicyclic heterocycles **7**. If Merrifield resin is used, treatment with mild acid would not affect any unreacted esters **2**, thus ensuring high purity of the compounds released. This "chameleon catch strategy" was introduced by Barrett and co-workers,[14] who used the Tebbe reagent to methylenate ester links to the resin. However, their choice of reagent precluded the introduction of any other functionality in the alkylidenation step. Our strategy, on the other hand, relies on the introduction of a masked nucleophile by the titanium reagent. Our solid-phase synthesis of bicyclic heterocycles would be traceless in that, theoretically, substituents are allowed at any site and would be classified as using an *O*sp^2-*C*sp^2 (benzofuran) or *N*sp^2-*C*sp^2 (indole) linker.[15]

Having successfully used the above route to make benzofurans,[16] we now report its application to the solid-phase synthesis of indoles.[17] Readily available *ortho*-nitrobenzaldehydes **8** were converted into thioacetals **9,** and the nitro group was reduced[18] to give anilines **10** (Scheme 2). However, we failed to generate an effective alkylidenating agent from aniline **10**. The key challenge was then to find a suitable nitrogen protecting group that would be unaffected

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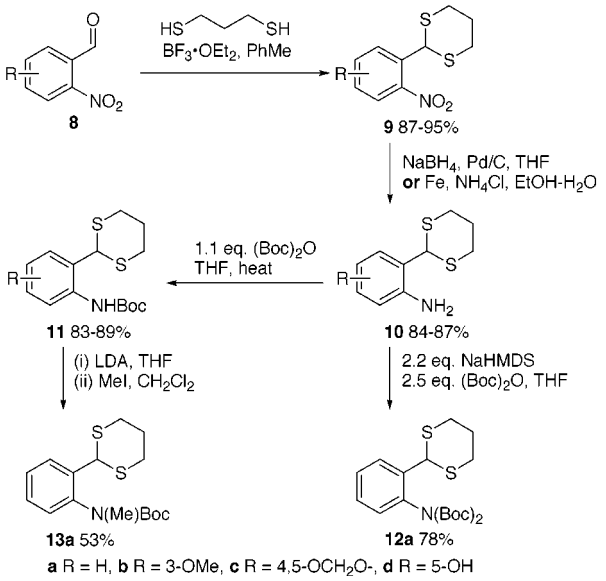
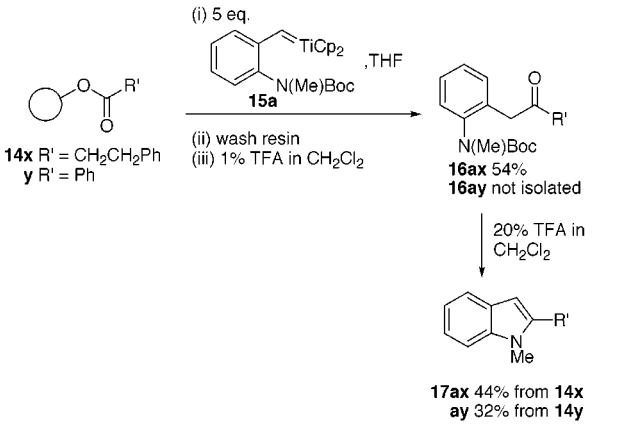
Scheme 2. Synthesis of Thioacetal Substrates



Scheme 3. Synthesis of *N*-Methyl Indoles



by both the titanium alkylidene moiety and by the low-valent titanium used to generate it. The protecting group should also be easy to remove, and any side-products generated during deprotection should be volatile. Therefore, anilines **10** were converted into *tert*-butyl carbamates **11** using Boc anhydride.[19] Aniline **10a** was also diprotected to give imide **12a** using sodium hexamethyldisilazide as base. Methylation of carbamate **11a** was accomplished by treating its lithium salt with methyl iodide.

Separately, each of the thioacetals **11a**, **12a**, and **13a** were added to 4 equiv of $Cp_2Ti[P(OEt)_3]_2$ in THF, and the resulting solutions were added to IRORI macrokans containing 0.2 equiv of ester **14x** (0.28 mmol per kan of ester derived from Merrifield resin with a loading of 1.86 mmol g^{-1}). The kans were washed (5 × THF, 5 × alternately MeOH and dichloromethane, MeOH, and finally ether), dried under vacuum, and then treated with 1% trifluoroacetic acid (TFA) in dichloromethane. The solvent was then removed, and the products resulting from each attempted benzylidenation were identified. Thioacetals **11a** and **12a** gave only trace amounts of impure *N*-Boc indole, while thioacetal **13a** gave ketone **16ax** cleanly in good yield (with respect to resin-bound ester, Scheme 3), presumably via titanium benzylidene **15a**. Clearly, the *N*-Boc group is not very susceptible to benzylidenation. When the procedure was repeated and the resulting ketone **16ax** was immediately treated with 20% TFA in dichloromethane, indole **17ax** was the sole product following aqueous workup (see Supporting Information for ^{1}H NMR spectrum). In the same way, resin-bound ester **14y** was converted into indole **17ay**.

We then investigated the failed reactions. Thioacetals **11a** and **12a** were added to 4 equiv of $Cp_2Ti[P(OEt)_3]_2$ in THF, and the reactions were quenched in 2 M hydrochloric acid after 14 and 2.5 h, respectively. The crude mixture from thioacetal **11a** consisted mainly of *N*-Boc toluidine **18** and thiol **19** in a 2:9 ratio, while that from thioacetal **12a** was mainly toluidines **18** and **20** and carboxylic acid **21** in a 1:1:9 ratio (Figure 1). The toluidines **18** and **20** were presumably

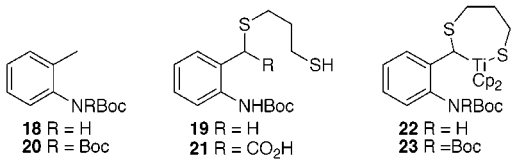


Figure 1. Products and intermediates from thioacetals **11a**−**12a**.

formed from titanium benzylidenes. Compounds **19** and **21** are probably the result of monoinsertion of titanium(II) into thioacetals **11a** and **12a** to give titanium(IV) complexes **22** and **23**, respectively. Intramolecular deprotonation of carbamate **22** would account for the formation of thiol **19**. On the other hand, migration of the *tert*-butoxycarbonyl group from the nitrogen atom of complex **23** to the benzylic carbon atom, followed by loss of the *tert*-butyl group (presumably under the acidic workup conditions), would account for the formation of compound **21**.

To prevent intramolecular proton transfer, carbamates **11a**−**c** and **24** (prepared from phenol **11d** in 83% yield using TMSCl, pyridine) were deprotonated and silylated to give *N*-silylated species **25** (Scheme 4). *N*-Silylation as a method of protecting carbamates (during α-lithiation) has only been reported recently,[20] but *N*-silylation followed by thermolysis is a well-established method of generating isocyanates.[21] The *N*-silylated carbamates **25** were added to 4 equiv of $Cp_2Ti[P(OEt)_3]_2$ in THF, and the resulting reagents were used to benzylidenate esters **14x** (R′ = $PhCH_2CH_2$), **14y** (R′ = Ph), and **14z** (R′ = Me). The resin was washed and dried as above and then treated with 1% TFA to give the *N*-Boc indoles **26**

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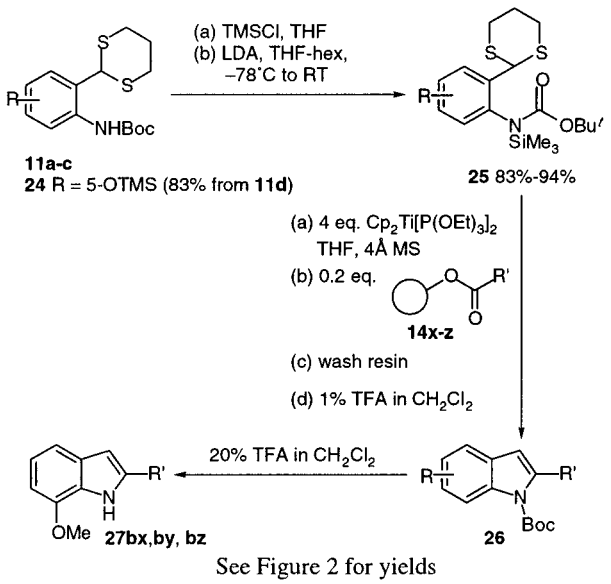
Scheme 4. Synthesis of *N*-Boc and *N*-H Indoles



See Figure 2 for yields

in good yields and high purities (except **26bx**, **26by**, and **26bz**) after removal of solvent (Figure 2, see Supporting Information for ^{1}H NMR spectra of the compounds as they are released from resin (i.e., without purification)).

There was significant spontaneous deprotection of the *N*-Boc 7-methoxyindoles **26bx**, **26by**, and **26bz**, so they were fully deprotected by treating with 20% TFA in dichloromethane for 1 h. Free indoles **27bx** and **27by** were isolated in high purity (Figure 2 and Supporting Information) following solvent removal, but the deprotection conditions led to substantial decomposition in the case of 2-methylindole **27bz**.

In conclusion, we have developed novel titanium(IV) benzylidene reagents that allow the traceless solid-phase synthesis of indoles in high purity using a chameleon catch approach. In the case of *N*-methyl indoles cyclization occurs after release from the resin, whereas in the case of *N*-Boc indoles a cyclative termination mechanism cannot be ruled out.

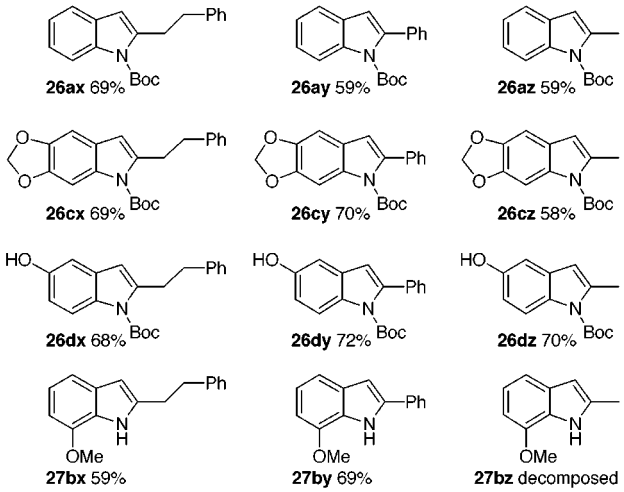


Figure 2. Yields of indoles based on resin-bound esters **14**.

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Supporting Information Available: ^{1}H NMR spectra of *N*-Boc indoles **26** as released from resin, indoles **27** after solvent removal, and *N*-methyl indoles **17** after aqueous workup (with no further purification). This material is available free of charge via the Internet at http://pubs.acs.org.

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