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# Synthesis of 2-Substituted Benzofurans and Indoles Using Functionalized Titanium Benzylidene Reagents on Solid Phase

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Titanium(IV) benzylidenes bearing a masked oxygen or nitrogen nucleophile in the ortho position were generated from thioacetals, using low-valent titanocene complex, $Cp_2Ti[P(OEt)_3]_2$. Methylene acetal, alkyl ether, silyl ether, fluoro, tertiary amino, and *N*-alkyl, *N*-benzyl, *N*-prenyl, and *N*-silyl *tert*-butyl carbamate groups were tolerated in the titanium alkylidene reagents (Schrock carbenes). Aryl−chlorine bonds were stable to the titanium benzylidene functionality, but there was poor chemoselectivity for the reduction of the thioacetal in the presence of an aryl chloride. The titanium benzylidenes converted Merrifield and Wang resin-bound esters into enol ethers. The oxygen nucleophile was masked as a TMS ether, and when the resin-bound enol ethers bearing this ortho substituent were treated with 1% TFA in dichloromethane, benzofurans were released from resin in high yields. The chameleon catch strategy ensured excellent purity. In a similar way, *N*-alkylated and *N*-silylated *tert*-butyl carbamates were used for the synthesis of *N*-alkyl and *N*-Boc indoles, respectively. These traceless solid-phase syntheses of heterocycles are believed to involve post-cleavage modification rather than cyclative termination.

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,[3,4,5] and Takai,[6] although Grubbs,[7] Matsubara[8] and Takeda[9,10] have introduced interesting alternatives. The reagents of Takai and Matsubara are probably 1,1-bimetallics, but 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**). Such Schrock carbenes are nucleophilic at the carbene carbon atom and electrophilic at titanium, and their reactivity toward carbonyl groups is dominated by their high-energy HOMOs.[11]

The Tebbe and Grubbs reagents allow only methylenation of esters via active species **1** ($R^1 = R^2 = H$). Thus, although the Tebbe reagent is known to tolerate a wide range of functionality in its ester substrates, no functionality is tolerated in the titanium reagent itself. The method of Petasis is more general and involves generating titanium alkylidenes **1** ($R^1 = H$, $R^2 = H$,[3] aryl,[4] silyl[5]) 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 beta to the titanium atom in active species **1**.

In Takeda's method,[9] titanium alkylidenes (with or without hydrogen atoms beta to the titanium atom) are generated by reducing thioacetals with a low-valent titanium complex, $Cp_2Ti[P(OEt)_3]_2$, **2**, freshly prepared by the reduction of titanocene dichloride with magnesium in the presence of triethyl phosphite and 4 Å molecular sieves. Thioacetals are easily synthesized under mild conditions, so Takeda's procedure seemed ideal for mak-

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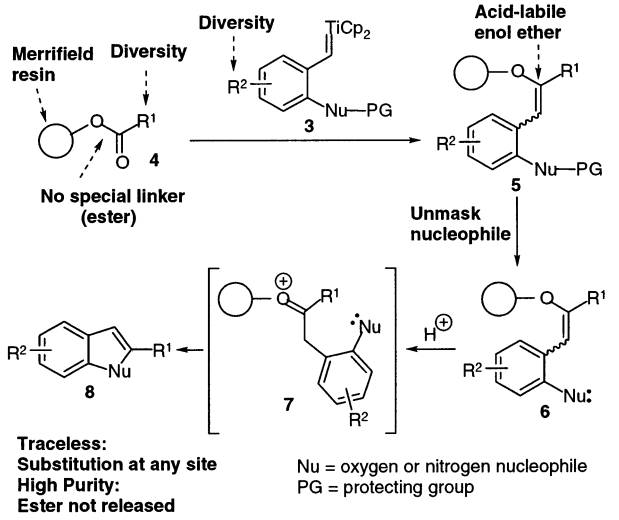
ing functionalized titanium alkylidene reagents. Takai reagents,[6] which we have used to make enol ether substrates for anionic oxy-Cope rearrangments,[12] have a similar generality but have to be made from synthetically less accessible 1,1-dihaloalkanes.

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)[12,13] or ring-closing metathesis (useful in the synthesis of polyethers)[14−16] or acid-induced rearrangement[17] or another reaction of the enol ether moiety.[18] However, none of these strategies relies on the titanium reagent introducing any functionality other than the enol ether. In order for there to be useful functionality in the titanium reagent **1** itself, the functionality must not react under the conditions used to generate the titanium(IV) alkylidene moiety and must survive long enough for alkylidenation of the ester to be carried out. The second of these conditions is less severe when the desired alkylidenation is intramolecular.[19] Prior to our work, a few titanocene alkylidenes **1** ($R^1$ = OMe,[20] SPh,[20] $SiMe_3$[5,21]) functionalized at the alpha carbon had been used in intermolecular alkylidenation reactions. However, the only synthetic strategy that exploited additional functionality introduced during the alkyidenation step was that of Mortimore and Kocienski.[22] They employed a Takai reagent bearing a masked oxygen nucleophile in a synthesis of spiroketals. We here report our related strategy for the traceless synthesis of benzofurans and indoles on solid phase (Scheme 1).

**SCHEME 1**




Solid-phase synthesis is used for the automated parallel synthesis of drug candidates and potential agrochemicals.[23] Substrates are attached to a resin, and following a series of reactions, the products are cleaved from the polymer support. The key advantages of solid-phase synthesis are that compounds not attached to the resin can be washed away following each reaction and that the resin is easily handled. Thus, using directed sorting techniques that combine parallel and split-and-pool synthesis, large numbers of discrete compounds can be synthesized. Unfortunately, many methods of solid-phase synthesis leave polar functionality in the products at the site where the resin was attached, and this may contribute to their physiochemical and biological properties and so distort structure−activity relationships. Hence, linkers have been developed that allow compounds to be released from resin with no trace of the site of attachment to resin.[24,25] The resulting specialized resins are generally rather expensive and limited to a particular class of

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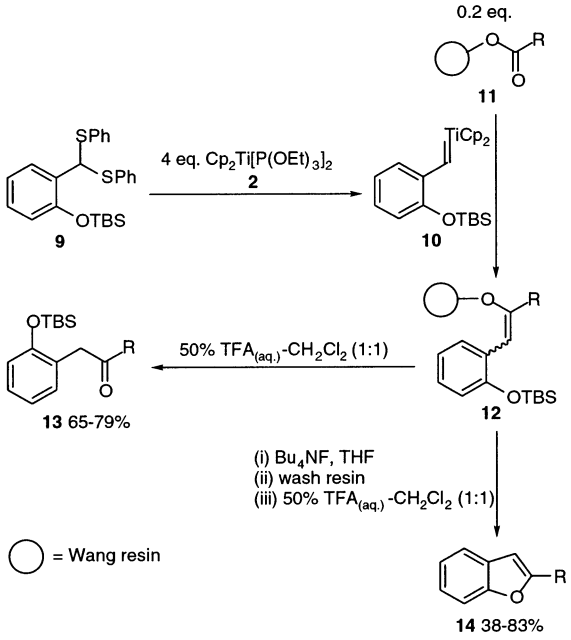
compounds. Another problem with solid-phase synthesis is that resin-bound side products are generally released from resin during the cleavage step and so contaminate the target compounds. Furthermore, cleavage from the resin, like deprotection, is generally an extra step in a synthetic sequence.

We aimed to develop novel functionalized titanium reagents that would allow a general traceless synthesis of benzofurans and indoles using inexpensive resin (Merrifeld or Wang resin) and a very simple linker (an ester moiety). The titanium reagents would switch the nature of the linker before cleavage and so ensure the high purity of the products released. Titanium benzylidenes **3,** having a masked nucleophile in the ortho position, would benzylidenate resin-bound esters **4**. The acid-stable esters **4** would thus be converted into acid-sensitive enol ethers **5**. The masked nucleophile would then be unmasked to give enol ethers **6**. Treatment with acid should then lead to the formation of oxonium ion **7** and release from the resin with concomitant cyclization to give bicyclic heterocycles **8**. If Merrifield resin[26] were used, treatment with mild acid would not affect any unreacted esters **4**, thus ensuring high purity of the compounds released.

A similar "chameleon catch strategy" was introduced by Barrett and co-workers,[27] 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, would rely on the introduction of a masked nucleophile by the titanium reagent. Furthermore, our approach might allow cyclative termination, whereby only resin-bound compounds with the unmasked nucleophile would be released from resin. The proposed solid-phase synthesis of bicyclic heterocycles would be traceless,[25] in that, theoretically, substituents would be 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.[28]

We have already reported our first success with the above strategy.[29] Thioacetal **9** was treated with 4 equiv of low-valent titanium complex **2** (freshly generated by reduction of titanocene dichloride with magnesium) to generate a benzylidenating reagent, presumably titanium benzylidene **10**, with a masked oxygen nucleophile in the ortho position (Scheme 2). Five equivalents of this reagent converted Wang resin-bound esters **11** into enol ethers **12,** and the workup consisted of simply washing the resin with various solvents. Cleavage from the resin using 50% aqueous TFA in dichloromethane (DCM) (5:8 by volume) for 30 min gave pure ketones **13** in good overall yield. Alternatively, enol ethers **12** were treated

**SCHEME 2**




with tetrabutylammonium fluoride. The resin was washed with various solvents and then treated with 50% aqueous TFA−DCM (5:8) for 30 min. This gave benzofurans **14** in moderate to good yield, following aqueous washes to remove remaining tetrabutylammonium salts (which could not be completely removed from the resin prior to cleavage). Although no chromatography was necessary, the aqueous washes were inconvenient and led to reduced and variable yields. Furthermore, the use of Wang resin[30] did not preclude the release of carboxylic acids in the event of alkylidenation of esters **11** being incomplete. We here report an improved procedure for the solid-phase synthesis of benzofurans, using a greater variety of titanium benzylidene reagents. We also give full details of the solid-phase synthesis of indoles[31] that we have recently reported in a preliminary communication.

**Benzofuran Synthesis.** 2-Substituted benzo[*b*]-furans[32,33] are widely distributed in nature and have a range of biological activities,[34] for example, as insulin-sensitivity enhancers,[35] inhibitors of tubulin polymerase,[36] antagonists of the $A_1$ adenosine receptor,[37] inhibitors of testosterone 5α-reductase,[38] and inhibitors of 5-lipoxygenase.[39] Of particular recent interest is BPAP **15**, which

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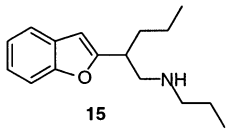
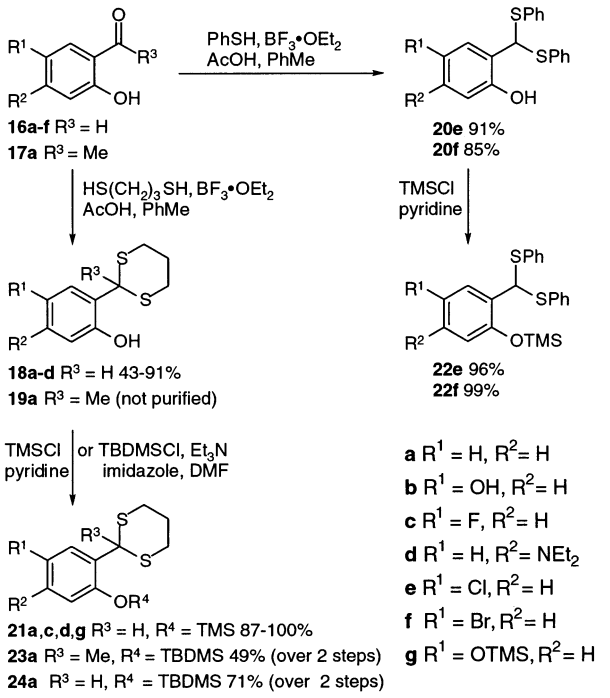



**FIGURE 1.** BPAP.

enhances impulse propagation mediated by the release of catecholamines and serotonin in the brain and so may slow progression of Parkinson's and Alzheimer's disease (Figure 1).[40] There are many methods for the synthesis of benzo[*b*]furans,[32,41] but the approach we describe here is new. Other routes to benzofurans involving alkylidenation of esters form the C=C bond rather than the C−O bond in the ring-closing step. Thus, benzofurans have been made by intramolecular alkylidenation of aryl esters using phosphonium ylides[42] and by intermolecular alkylidenation of aryl esters using a titanium reagent followed by ring-closing metathesis.[14] Solution-phase, acid-induced cyclizations of methoxymethyl-protected, *tert*-butyldimethylsilyl-protected, or free phenolic hydroxyl groups with enol ethers have been reported. However, the enol ether substrates were made by cross-coupling reactions between aryl iodides and 2-ethoxyvinylmetals (boronates,[43] stananes,[44] or copper reagents[45]) or by benzannulation, using Fischer carbene complexes of chromium.[46,47] The forcing conditions used in most of these acid-induced cyclizations[43,44,45] (polyphosphoric acid or *p*-toluenesulfonic acid and heat) seem rather harsh in the light of our results (see below). Despite the importance of solid-phase synthesis, there are very few published methods for the solid-phase synthesis of benzo[*b*]furans.[23,48,49,29] Apart from our own work on 2-substituted benzofurans,[29] only 3-substituted benzo[*b*]furans have been made in a traceless way.[48] The alternative approach of using solid-supported reagents has been applied to the synthesis of 3-aryl- and 3-amino-benzo[*b*]furans, including some 2,3-disubstituted compounds.[50] Interestingly, a polymer-bound benzo[*b*]furan is the side product of releasing a new photolabile safety catch linker.[51]

**SCHEME 3**




To make benzofurans, we needed to prepare a titanium benzylidene **2** with a masked oxygen nucleophile in the ortho position. Takeda's procedure involves generating titanium alkylidenes from thioacetals, so 2-hydroxybenzaldehydes **16a**−**d** and 2-hydroxyacetophenone **17a** were converted into the corresponding 1,3-dithianes **18a**−**d** and **19a**, respectively, by adapting Barton's procedure[52] to use fewer equivalents of thiol (Scheme 3). Only electron-rich aldehyde **16d** gave poor yields (<50%). 1,3-Dithianes are more easily formed and more stable than the corresponding diphenyldithioacetals, and this is helpful when the starting aldehyde is electron rich. However, diphenyldithioacetals should be more easily reduced using low-valent titanium, so halosalicylaldehydes **16e**−**f** were converted into the corresponding diphenyldithioacetals **20e**−**f** so that selective reduction of the thioacetal could be attempted. The high yields of thioacetals **20e**−**f** are notable because other authors have found that the formation of thioacetals in the presence of phenols is often difficult and large excesses of thiols are generally used.[53] An alkylidenating agent with a free phenolic hydroxyl could not be generated, so this group had to be protected. Ideally, removal of the protecting group, release from resin, and cyclization should all occur under the same conditions, and the side products of deprotection should be volatile. Consequently, we chose to protect phenols **18** and **20** as the corresponding trimethylsilyl (TMS) ethers **21** and **22**. Thioacetal **23a** was prepared from thioacetal **19a** to determine whether our route would allow access to 3-substituted benzo-

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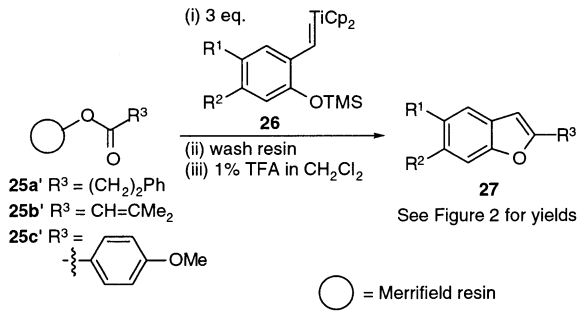
**SCHEME 4**




furans, and thioacetal **24a** was prepared for comparison.

Porous polypropylene reactor vessels loaded with Merrifield resin[26] were treated with cesium carboxylate salts to give resin-bound esters **25**.[54] Thioacetals **21** were added to 4 equiv of freshly prepared $Cp_2Ti[P(OEt)_3]_2$ **2** to give titanium reagents, presumably titanium benzylidenes **26**, which benzylidenated esters **25**. The resulting resins were washed to remove excess reagent and side products and then treated with 1% TFA−DCM for 1 h to give benzofurans **27** in high yield (based on starting Merrifield resin) and excellent purity with no purification necessary (Scheme 4, Figure 2, see the Supporting

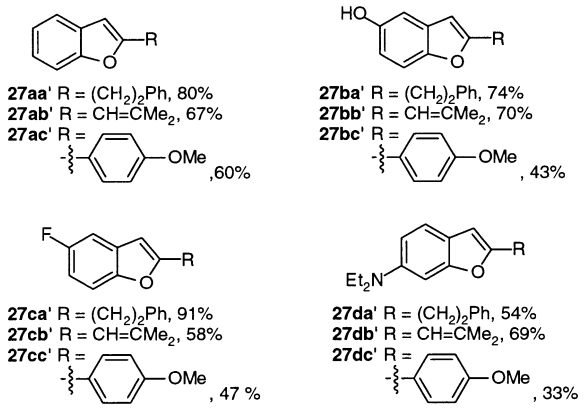



**FIGURE 2.** Yields of benzofurans based on loading of commercial chloromethylpolystyrene−1% DVB (Merrifield resin).

Information for $^1$H NMR spectra of the compounds as they are released from resin (i.e., without purification)). Thioacetal **21d**, which has a diethylamino group, gave ketones under these conditions, e.g., resin-bound ester **25a′** was converted into tertiary ammonium salt **28da′**, which could be neutralized with sodium carbonate to give ketone **29da′** (Figure 3). Clearly electron-poor phenol

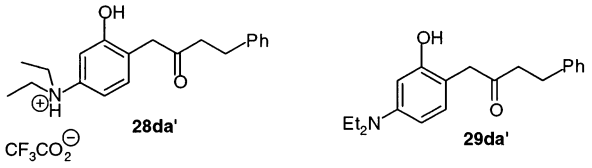



**FIGURE 3.**

**28da′** does not cyclize under the mildly acidic conditions employed. However, benzofurans **27da′**, **27db′**, and **27dc′**

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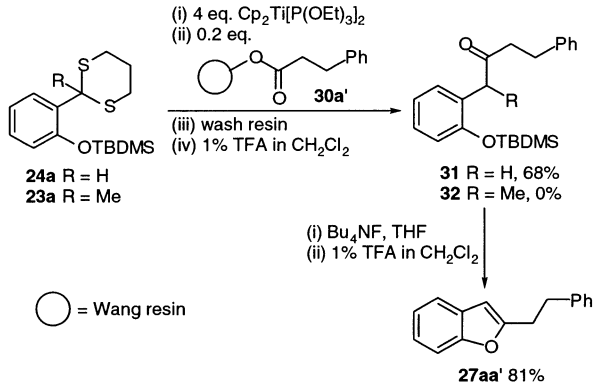
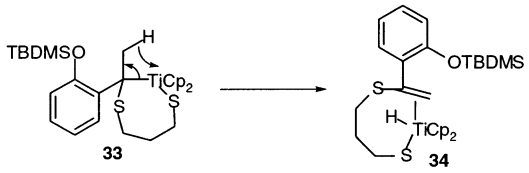
**SCHEME 5**




**SCHEME 6**

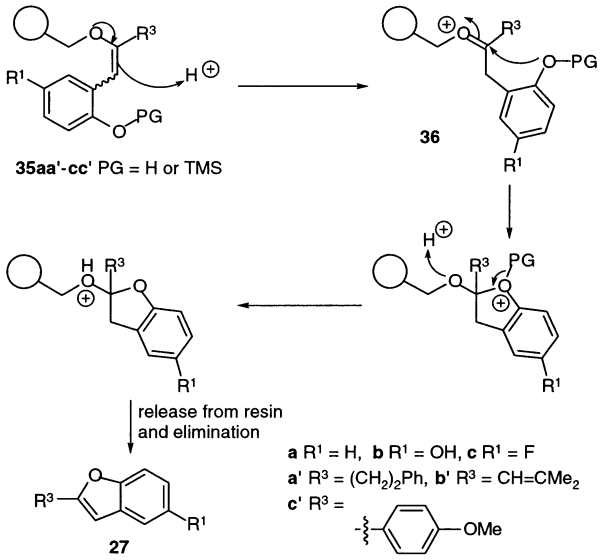



were produced (yields in Figure 2) when the resin cleavage was carried out for 3 h with 1% TFA, and the resulting material was treated with 10% TFA in DCM for 50 min, followed by neutralization with solid sodium carbonate. Unfortunately, chloro- and bromo-benzofurans could not be made cleanly using this titanium chemistry as dehalogenation competed with titanium benzylidene formation, even when fewer equivalents of titanium complex **2** were employed and complex **2** was added to thioacetals **22** rather than vice versa. Indeed, reaction of ester **25a′** with the titanium reagent derived from thioacetal **22e** and 4 equiv of $Cp_2Ti[P(OEt)_3]_2$ **(2)** gave, after cleavage, pure benzofuran **27aa′** in 25% yield.

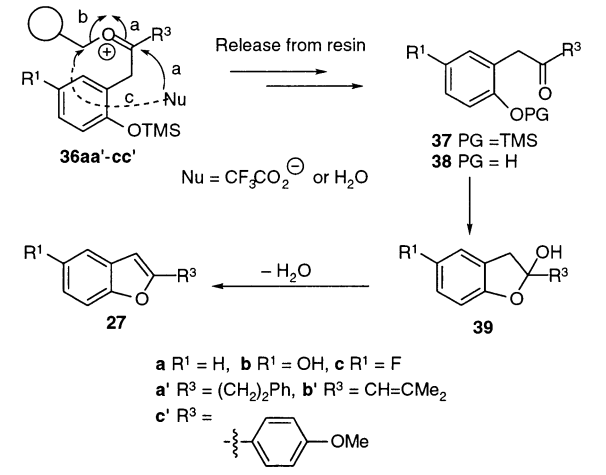
Wang resin-bound ester **30a′** was converted into ketone **31** in 68% yield (based on resin loading) using the titanium reagent derived from thioacetal **24a** (Scheme 5). Treatment of ketone **31** with tetrabutylammonium fluoride followed by 1% TFA−DCM gave benzofuran **27aa′** in good yield. These mildly acidic conditions contrast with the harsh conditions reported in the literature for similar solution-phase cyclizations.[43,44,45] Unfortunately, the reaction sequence using dithiane **23a**, derived from acetophenone **17a**, failed to give any ketone **32**. This lack of success may be due to beta elimination from the intermediate benzyltitanium complex **33** to give 18-electron complex **34** (Scheme 6). Ours is the first reported attempt to generate a titanium benzylidene from a thioketal, but Takeda has suggested that beta elimination is the reason that thioketals are generally less efficient than thioacetals at generating titanium alkylidenes using $Cp_2Ti[P(OEt)_3]_2$.[10] The problem has been overcome using 1,1-dichloroalkanes in place of thioketals, but no benzylic examples have been reported.[10]

Release of benzofurans **27aa′**−**cc′** from resin could either involve cyclative termination (Scheme 7) or postcleavage modification (Scheme 8). In the cyclative cleavage pathway, protonation of enol ethers **35** to give oxonium ions **36** is followed by intramolecular addition. An elimination reaction then gives the benzofurans **27**. The postcleavage modification route involves release of

**SCHEME 7. Cyclative Termination Pathway**




**SCHEME 8. Postcleavage Modification Pathway**




ketones **37** or **38** by acetal hydrolysis (arrows a), $S_N1$ (arrow b), or $S_N2$ (arrows b and c), followed by cyclization and elimination. The solid-phase synthesis of ketones **28da′** and **31** (Figure 3 and Scheme 5) shows that cyclative termination is not necessary for release. Furthermore, the conversion of ketone **31** into benzofuran **27aa′** using 1% TFA (Scheme 5) shows that cyclization of ketones **38** under mild conditions is feasible. Finally, treatment of resin-bound enol ether **35aa′** with 1% TFA–DCM for only 30 min gave a 1:2:6 mixture of TMS-protected phenol[55] **37aa′**, hemiacetal[56] **39aa′**, and benzofuran **27aa′** (Scheme 8). Thus, all the evidence indicates that cyclative termination is not involved in the formation of any of the benzofurans **27**, and Krchnák and Holladay's classification of our benzofuran-forming reaction as a postcleavage modification is correct. [23]

**Indole Synthesis.** We next turned our attention to the solid-phase synthesis of 2-substituted indoles. Although naturally occurring indole alkaloids[57] are derived from tryptophan and are almost invariably 3-substituted, 2-substituted analogues are of current interest for their potential as therapeutic agents. 2-Substitued analogues of melatonin,[58] which regulates circadian rhythms and sleep processes, of serotonin,[59] which is involved in regulation of the nervous system including neurotransmission, and of tryptophan itself[60] have been investigated recently. Other bioactive 2-substituted indoles include the natural and synthetic bisindoles,[57,61] which have antimicrobial and anticancer properties, the antihyperlipoproteinemic drug fluvastatin,[62] selective inhibitors of serine proteases such as urokinase-type plaminogen activator[63] and factor Xa,[64] and cyclooxygenase-2 inhibitors.[65]

There are many ways of synthesizing indoles,[66,67] but only a few methods have been used on solid phase.[23,68] Solid-phase syntheses of indoles have involved palladium-mediated heteroannulation of alkynes,[69,70,71] intra-

(55) Identification of TMS ether **37** was based on the following signals in the $^1$H NMR spectrum of the crude mixture: 0.40 (9H, s), 2.73 (2H, t, 7.5), 2.85 (2H, t, partly obscured), 3.61 (2H, s).

(56) Identificaion of hemiacetal **39** was based on the following signals in the $^1$H NMR spectrum of the crude mixture: 1.91 (1H, broad s), 2.85–2.93 (4H, m), 3.72 (2H, s).

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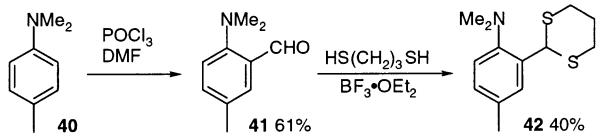
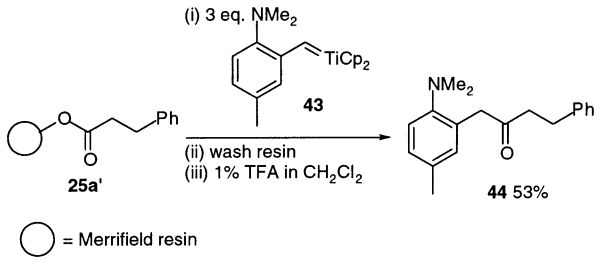
**SCHEME 9**




**SCHEME 10**

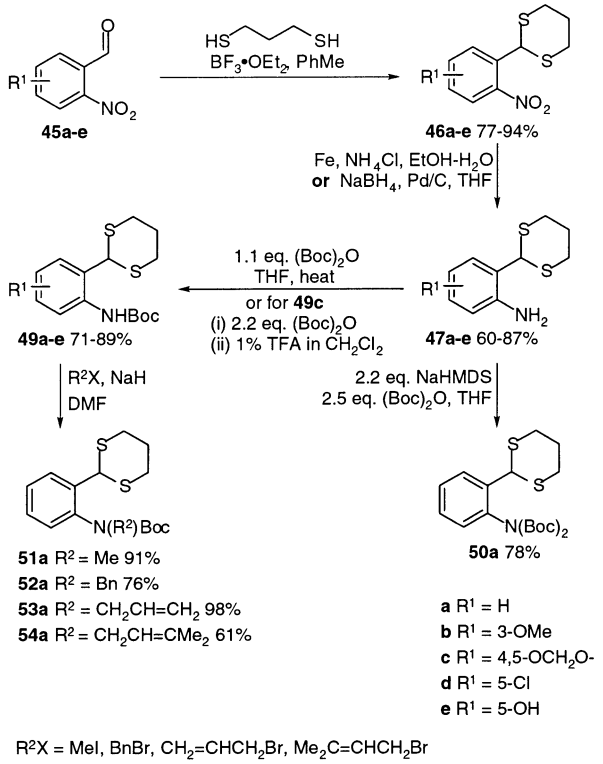



molecular Heck reaction,[72] intramolecular Wittig reaction,[73] reduction and cyclization of nitro compounds,[74] and the Nenitzescu,[75] modified Madelung,[76] and Fischer[77] indole syntheses. Traceless, solid-phase synthesis of 2-substituted indoles has been achieved by combining an *N*-sulfonate linker with palladium-mediated heteroannulation of alkynes[70] and by intramolecular Wittig reaction of a polymer-bound phosphonium salt.[73] Very recently, a traceless solid-phase synthesis of 2,3-disubstituted indoles was achieved using the modified Madelung indole synthesis.[76] The approach we describe here is both a novel strategy for the construction of indoles and the first example of a chameleon catch approach to this class of compounds.

We had shown that a titanium benzylidene could be generated from thioacetal **21d**, which has a tertiary amino group. However, our strategy for the synthesis of indoles would require an amino group (or a protected amino group) in the ortho position, and this might coordinate to titanium and interfere with the formation or reaction of the titanium benzylidene. To test this, *N*,*N*-dimethyltoluidine **40** was formylated[78] and the resulting aldehyde **41** was converted into thioacetal **42** (Scheme 9). Titanium benzylidene **43** was generated from thioacetal **42** and used to benzylideneate Merrifield resin-bound ester **25a′** (Scheme 10). Following washing of the resin, ketone **44** was released in good yield and high purity using 1% TFA−DCM.

Next we synthesized anilines **47** by converting readily available *o*-nitrobenzaldehydes **45** into thioacetals **46** and reducing the nitro groups (Scheme 11). The combination of sodium borohydride[79] and Pd/C is known to reduce nitro groups in the presence of thioacetals, phenolic

**SCHEME 11**




hydroxyls, and aryl bromides.[80] However, diazine-*N*-oxides, such as **48** (Figure 4, see Supporting Information

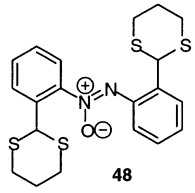



**FIGURE 4.**

for crystal structure), were formed as side products under these conditions, and they were not reduced to the desired anilines **47** when reexposed to the same reaction conditions. The use of lower concentrations of the nitro compounds and more reducing agent limited the formation of diazine-*N*-oxides but could not completely prevent their production during the reduction of electron-rich nitro compounds. The problem was overcome by using iron/ammonium chloride[81] as the reducing agent.

We failed to generate an effective alkylidenating agent from aniline **47a,** so the key challenge was to find a suitable nitrogen protecting group that would be unaffected 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 **47** were converted into *tert*-butyl

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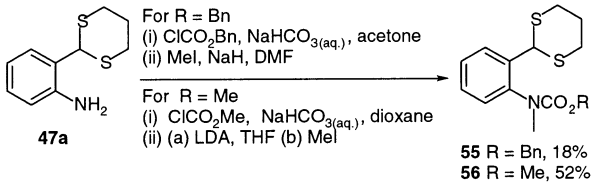
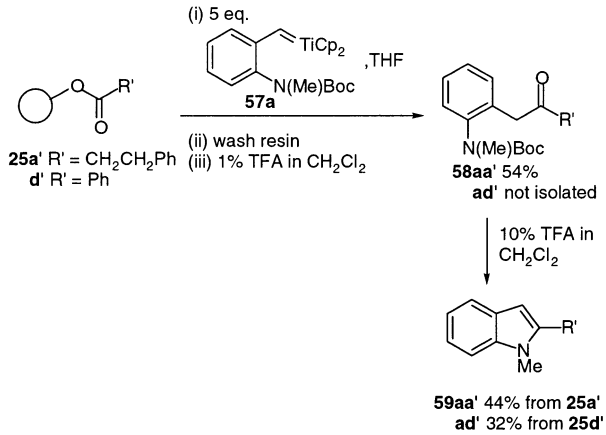
**SCHEME 12**



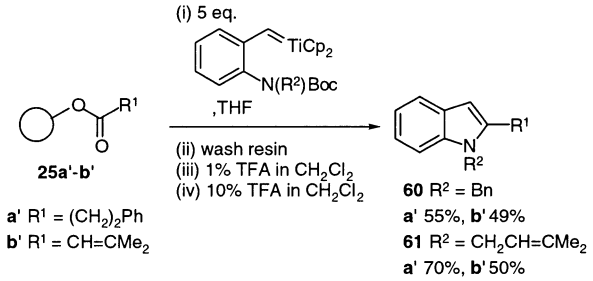

**SCHEME 13**




carbamates **49** using Boc anhydride.[82] Unstable, electron-rich aniline **47c** always gave a mixture of mono and diprotected compounds, even when the conditions chosen for carbamate formation did not lead to complete consumption of the amine **47c**. Consequently, nitro compound **46c** was reduced, diprotected, and then monodeprotected[83] to give carbamate **49c** without purifying the intermediates. Imide **50a** was also synthesized. Treatment of carbamate **49a** with LDA generated its lithium salt, which was insoluble in THF, and reaction of this with methyl iodide in dichloromethane gave tertiary carbamate **51a** in 53% yield. However, a more effective alkylation procedure used sodium hydride to deprotonate carbamate **49a** in the presence of appropriate alkylating agents to give tertiary carbamates **51a**, **52a**, **53a,** and **54a**. *O*-Benzyl carbamate **55** and *O*-methyl carbamate **56** were prepared from aniline **47a** in a similar way (Scheme 12).

Separately, each of the thioacetals **49a**, **50a,** and **51a** was added to 4 equiv of $Cp_2Ti[P(OEt)_3]_2$ in THF, and the resulting solutions were each added to 0.2 equiv of ester contained within a porous polypropylene reactor. (0.279 mequiv reactor$^{-1}$ of ester derived from Merrifield resin with a loading of 1.86 mequiv g$^{-1}$). The reactors were washed (5 × THF, 5 × alternately MeOH and dichloromethane, MeOH and finally ether), dried under vacuum, and then treated with 1% trifluoroacetic acid in dichloromethane. The solvent was then removed, and the products resulting from each attempted benzylidenation were identified. Thioacetals **49a** and **50a** gave only trace amounts of impure *N*-Boc indole, while thioacetal **51a** gave ketone **58aa′** cleanly in good yield (with respect to resin-bound ester, Scheme 13), presumably via titanium benzylidene **57a**. Clearly, the *N*-Boc group is not very

**SCHEME 14**




susceptible to benzylidenation. When the procedure was repeated and the resulting ketone **58aa′** was immediately treated with 10% TFA in dichloromethane, indole **59aa′** was the sole product following aqueous workup (see Supporting Information for $^1$H NMR spectrum). No further purification was necessary. Repeating the procedure using resin-bound ester **25d′** gave indole **59ad′**. In a similar way, *N*-benzyl and *N*-prenyl indoles **60** and **61** were made using the titanium reagents derived from thioacetals **52a** and **54a** (Scheme 14). However, *N*-allyl thioacetal **53a** failed to give indoles. This is not surprising, as Takeda and co-workers have shown that titanium alkylidenes generated from thioacetals bearing terminal or disubstituted alkenes undergo ring-closing metathesis but trisubstituted alkenes are not very susceptible to this reaction.[84] *O*-Benzyl carbamate **55** and *O*-methyl carbamate **56** also failed to give indole products. Thus, steric hindrance must contribute to the lack of reactivity of the *N*-Boc group toward the Schrock carbene.

It is evident from the crystal structures of carbamates **49a, 51a,** and **54a** (Figures 5−7) that the carbonyl group

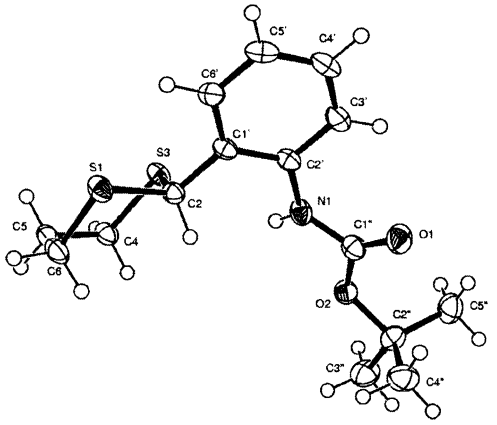



**FIGURE 5.** Crystal structure of secondary carbamate **49a**.

of tertiary carbamate **51a** and **54a** will be less electrophilic than that of carbamate **49a**, as the nitrogen lone pair is less conjugated to the aromatic ring. The degree of conjugation is determined by the torsion angle C1′−C2′−N1−C1″ (or C3′−C2′−N1−C1″). The C1′−C2′−N1−C1″ torsion angles in the crystal structures of tertiary carbamates **51a** and **54a** are 78.71(16)° and 77.30(16)°, respectively, as compared to 36.3(3)° for C3′−C2′−N1−C2″ in secondary carbamate **49a**. Indeed, in solution,

(82) Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507−6511.
(83) Wensbo, D.; Annby U.; Gronowitz, S. *Tetrahedron* **1995**, *51*, 10323−10342.
(84) (a) Fujiwara, T.; Takeda, T. *Synlett* **1999**, 354−356. (b) Fujiwara, T.; Kato, Y.; Takeda, T. *Tetrahedron* **2000**, *56*, 4859−4869. (c) Fujiwara, T.; Kato, Y.; Takeda, T. *Heterocycles* **2000**, *52*, 147−150.

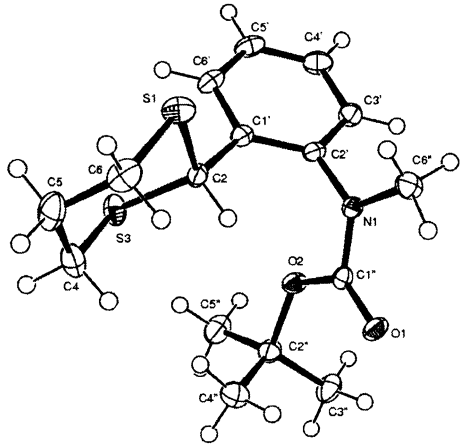


**FIGURE 6.** Crystal structure of tertiary carbamate **51a**.

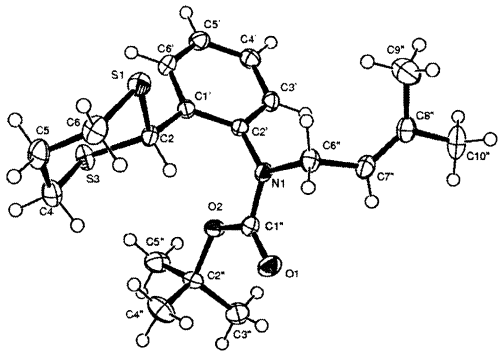


**FIGURE 7.** Crystal structure of tertiary carbamate **54a**.

there is restricted rotation about the Ar−N bonds of all the tertiary carbamates **51**−**56**, making C4 and C6 ($CH_2S$) of the dithiane moiety nonequivalent in the $^{13}C$ NMR spectra, with two signals appearing in the chemical shift range of 31−33 ppm. Furthermore, the benzylic hydrogen atoms of carbamates **52a** and **55** and the allylic hydrogen atoms of carbamates **53a** and **54a** are inequivalent in the $^1H$ NMR spectra of these compounds, confirming that they are diastereotopic. Interestingly, each crystal of dithiane **51a** is homochiral (though of course the material as a whole is racemic), while carbamate **54a** produces racemic crystals. The carbonyl group of secondary carbamate **49a** is electronically more electrophilic than those of tertiary carbamates **51a**−**54a,** since its aromatic ring and carbamate group are closer to coplanar. It is also less sterically hindered. Since Schrock carbenes are nucleophilic reagents (i.e., their reactivity is dominated by their HOMOs),[11] the greater electrophilicity of carbamate **49a** (combined with the lower steric hindrance to nucleophilic attack) would make it more susceptible to alkylidenation when the titanium benzylidene is generated. This may explain the failure of thioacetal **49a** as a substrate for the Takeda reaction. However, a more plausible explanation is that organotitanium intermediates are quenched by intramolecular proton transfer from the nitrogen atom of the carbamate. If a nitrogen anion were formed, it would be stabilized by conjugation with both the carbonyl group and the aromatic ring. Furthermore, in the crystal structure of thioacetal **49a** (Figure 5) the N−H bond is orientated toward the benzylic carbon atom. A similar conformation

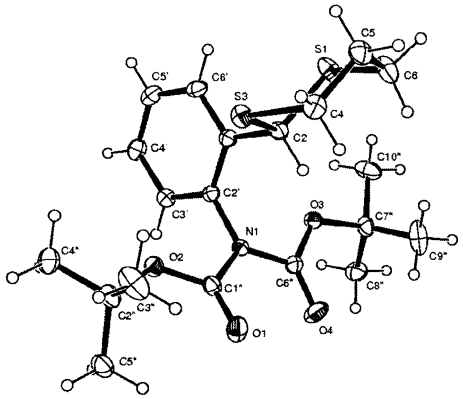


**FIGURE 8.** Crystal structure of imide **50a**.

must be energetically accessible in solution for this and other secondary carbamates **47,** as C4 and C6 of the dithiane are equivalent in their $^{13}C$ NMR spectra.

The nitrogen lone pair of imide **50a** is cross-conjugated with two carbonyl groups. Thus, these carbonyl groups will be susceptible to intramolecular nucleophilic attack when an organotitanium reagent is generated. Indeed, the greater electrophilicity of simple imides over amides has recently been used to improve an approach to indoles that employs the intramolecular Wittig reaction.[67c] Furthermore, the orientation of the *tert*-butoxycarbonyl groups in imide **50a** (Figure 8) would favor intramolecular nucleophilic attack. Titanium-mediated intramolecular nucleophilic acyl substitution reactions have been used to synthesize cyclopropanols, lactones, and other cyclic compounds.[85] Related zirconium-mediated acyl migrations from carbamate groups have recently been used to make $\gamma$-aminobutyric acid derivatives.[86]

To prevent intramolecular proton transfer, carbamates **49a**−**d** and **62** (prepared from phenol **49e** in 83% yield, using TMSCl and pyridine) were deprotonated and silylated to give *N*-silylated species **63** (Scheme 15). *N*-Silylation as a method of protecting carbamates (during α-lithiation) has only been reported recently,[87] but *N*-silylation followed by thermolysis is a well-established method of generating isocyanates.[88] The *N*-silylated carbamates **63** are unstable making characterization difficult. Dithiane **63a** was the only silylated carbamate for which a $^{13}C$ NMR spectrum was obtained, and in its $^{13}C$ NMR spectrum (obtained at 52 °C to allow rapid equilibration of the carbamate geometrical isomers), the C4 and C6 of the dithiane ring were, as expected, nonequivalent.

The *N*-silylated carbamates **63** were added to 4 equiv of $Cp_2Ti[P(OEt)_3]_2$ in THF, and the resulting reagents were used to benzylidenate resin-bound esters **25a′**, **25d′**, and **25e′**. The resin was washed and dried as above and

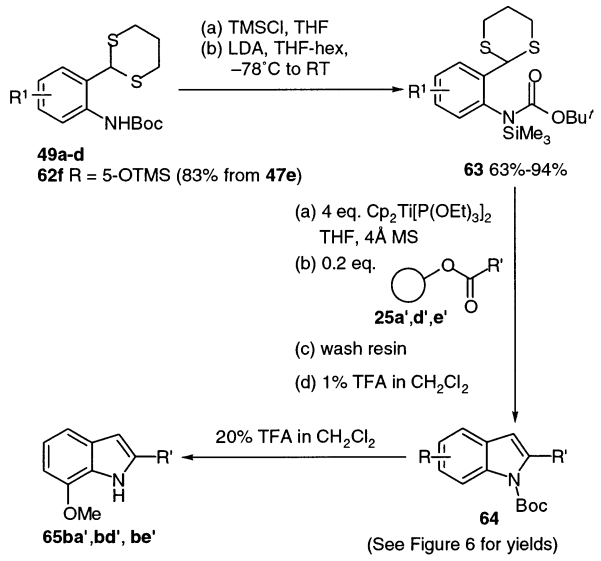
(85) For a review see the following: Sato, F.; Urabe, H.; Okamoto, S. *Chem Rev*. **2000**, *100*, 2835−2886.

(86) Ito, H.; Omodera, K.; Takigawa, Y.; Taguchi, T. *Org. Lett*. **2002**, *4*, 1499−1501.

(87) (a) Roby J.; Voyer N. *Tetrahedron Lett*. **1997**, *38*, 191−194. (b) Voyer, N.; Roby, J.; Chénard, S.; Barberis, C. *Tetrahedron Lett*. **1997**, *38*, 6505−6508. (c) Barberis, C.; Voyer, N. *Tetrahedron Lett*. **1998**, *39*, 6807−6810. (d) Barberis, C.; Voyer, N. *Synlett* **1999**, 1106−1108. (e) Barberis, C.; Voyer, N.; Roby, J.; Chénard, S.; Tremblay, M.; Labrie, P. *Tetrahedron* **2001**, *57*, 2965−2972.

(88) Chong, P. Y.; Janicki, S. Z.; Petillo, P. A. *J. Org. Chem*. **1998**, *63*, 8515−8521, and refs 8−11 therein.

**SCHEME 15**




then treated with 1% TFA to give most *N*-Boc indoles **64** in good yields and high purities after removal of solvent (Figure 9, see the Supporting Information for $^1$H NMR

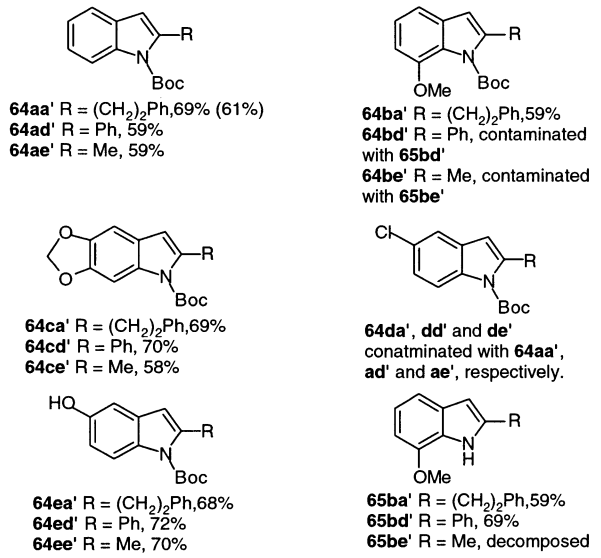



**FIGURE 9.** Yields of indoles made using 5 equiv of thioacetals **63** and based on original loading of commercial Merifield resin. Yield in parentheses resulted from the use of only 3 equiv of thioacetal **63a**.

spectra of the compounds as they are released from resin (i.e. without purification)). However, each of the 5-chloroindoles **64da′**, **64dd′**, and **64de′** was contaminated with the corresponding simple 2-substituted indoles **64aa′**, **64ad′**, and **64ae′**, respectively. The ratio of chlorinated to unchlorinated material was 2:1 in each case. Thus, it appears that the aryl−chlorine bond is stable to the titanium benzylidene functionality, but there is poor chemoselectivity for the reduction of the thioacetal in the presence of an aryl chloride. In the same way as in the benzofuran series, all attempts to reduce the thioacetal without affecting the aryl chloride failed. There was also a trace of spontaneous deprotection of the *N*-Boc 7-methoxyindole **64ba′**, and significant spontaneous deprotection of the other *N*-Boc 7-methoxyindoles **64bd′** and **64be′**, so these were fully deprotected by treating with 20% TFA in dichloromethane for 1 h. Free indoles **65ba′** and **65bd′** were isolated in high purity (Figure 9 and Supporting Information) following solvent removal, but the deprotection conditions led to substantial decomposition in the case of 2-methylindole **65be′**.

We investigated using fewer equivalents of thioacetal **49** or **50** with respect to resin-bound ester **25** (maintaining the ratio of thioacetal to low-valent titanium complex **2**) and found that using 3 instead of 5 equiv did not greatly affect the yield of indole produced. Thus, *N*-methylindole **59aa′** was made in 45% yield with 3 equiv of thioacetal **50a** and in 44% yield with 5 equiv of thioacetal **50a** (Scheme 13), while *N*-Boc indole **64aa′** was made in 61% yield with 3 equivs of thioacetal **49a** as opposed to 69% yield with 5 equiv of thioacetal **49a** (Scheme 15, Figure 9). However, yields were unsatisfactory when fewer than 3 equiv of thioacetal were used.

In all the above reactions, titanium(II) complex **2** was generated in dry THF by reduction of titanocene(IV) chloride with magnesium in the presence of triethyl phosphite. Although, in theory, only 2 equiv of titanium(II) complex **2** should be needed to generate titanium alkylidenes from thioacetals, Takeda almost invariably uses 4 equiv of titanocene dichloride with respect to thioacetal. We also found that using fewer than 4 equiv of titanocene dichloride with respect to the thioacetals gave very poor yields of benzofurans and indoles. Thus, the optimum ratio of reagents for the benzylidenation reaction appears to be 12 equiv titanocene dichloride:3 equiv of thioacetal:1 equiv of resin-bound ester.

## Conclusion

In conclusion, we have developed novel titanium(IV) benzylidene reagents that allow the traceless solid-phase synthesis of benzofurans and indoles in high purity using a chameleon catch approach. Our synthetic strategy represents a new approach to the synthesis of benzofurans and indoles. Yields range from 32 to 91% based on resin loading but are generally >50%. A range of functionality is tolerated within the titanium benzylidene reagents including methylene acetal, alkyl ether, silyl ether, fluoro, tertiary amino, and *N*-alkyl, *N*-benzyl, *N*-prenyl, and *N*-silyl *tert*-butyl carbamate groups. *N*-Allyl *tert*-butyl carbamates and methyl and benzyl carbamate groups are not tolerated. Aryl−chlorine bonds are stable to the titanium benzylidene functionality, but there is poor chemoselectivity for the reduction of the thioacetal in the presence of an aryl chloride. The optimum ratio of reagents for the benzylidenation reaction appears to be 12 equiv titanocene dichloride:3 equiv of thioacetal:1 equiv of resin-bound ester. Benzofurans and *N*-alkyl indoles are formed following cleavage from resin, but in the case of *N*-Boc indoles a cyclative termination mechanism cannot be ruled out.

## Experimental Section

All reactions were carried out under an inert atmosphere unless otherwise stated, using oven-dried or flame-dried glassware. Solutions were added via syringe unless otherwise stated. THF was freshly distilled from sodium benzophenone; dichloromethane, toluene, triethyl phosphite, and pyridine

were distilled from $CaH_2$ prior to use. Petroleum ether refers to the fraction boiling at 40−60 °C. Reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. The solid-phase reactions were carried out in normal glassware, but with the resin (particle size = 150-300 $\mu$m diamter) contained within porous polypropylene reactors that had an internal volume of 2.4 mL and a pore size of 74 $\mu$m. Purification by column chromatography was carried out using silica gel, mesh size 35−70 $\mu$m, as the stationary phase. Melting points are uncorrected. All NMR *J* values are given in Hz. Details of X-ray crystallography methods are in the Supporting Information.

**2-(2′-Hydroxyphenyl)-1,3-dithiane (18a).** $BF_3{\cdot}OEt_2$ (12.8 mL, 89.6 mmol, 1.1 equiv) was added into a solution of salicylaldehyde **16a** (10.00 g, 81.90 mmol), AcOH (80 cm $^3$), and 1,3-propanedithiol (9.00 mL, 89.6 mmol, 1.1 equiv) in PhMe (160 mL), and the resulting mixture was stirred overnight. The reaction mixture was diluted with $Et_2O$ (200 mL) and quenched by addition of water, then the organic layer was washed with water (2×), $NaHCO_3$ solution (3×), and brine (3×). The organic solution was dried over $MgSO_4$ and concentrated in vacuo to give the crude product as an off-white solid. The solid was crystallized from *i*-PrOH with some hexane to give thioacetal **18a** as fine white needles (11.1 g, 52.3 mmol). The liquor was concentrated in vacuo, and the resulting solid was crystallized from *i*-PrOH with some hexane to give dithiane[89] **18a** as fine white needles (4.77 g, 22.5 mmol). Combined yield 74.8 mmol, 91%. $R_f$ [DCM/petroleum ether (1:1)] 0.15. Mp: 132−133 °C. IR (KBr): 3317, 1499 cm$^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 1.94 (1H, ttt, $J$ = 14.1, 12.5, 3.1), 2.19 (1H, dtt, $J$ = 14.2, 4.4, 3.1), 2.92 (2H, dt, $J$ = 14.5, 3.7), 3.07 (2H, ddd, $J$ = 14.5, 12.5, 2.4), 5.41 (1H, s), 6.38 (1H, s), 6.86−6.90 (2H, m), 7.21 (1H, td, $J$ = 6.7, 1.6). $\delta_C$ (100 MHz, $CDCl_3$): 25.27, 32.02, 47.80, 117.74, 121.20, 123.99, 129.55, 130.54, 154.89. LRMS (EI$^+$): 212 ($M^{\bullet+}$), 138 [$M^{\bullet+}$ − $S(CH_2)_3$]. HRMS: calcd for $C_{10}H_{12}OS_2$ 212.0330; found 212.0332. Anal. Calcd for $C_{10}H_{12}S_2O$: C, 56.56; H, 5.70. Found: C, 56.51; H, 5.66.

**Preparation of 5-Chlorosalicylaldeyhde Diphenyldithioacetal (20e).** In a similar way, $BF_3{\cdot}OEt_2$ (8.90 mL, 70.23 mmol, 1.1 equiv) was added to a solution of 5-chlorosalicylaldehyde **(16e)** (10.00 g, 63.9 mmol), thiophenol (15.20 mL, 148.0 mmol, 2.3 equiv), and AcOH (60 mL) in PhMe (120 mL). After 4 h, the reaction mixture was diluted with DCM (200 mL) and washed with water (3×), dried over $MgSO_4$, and concentrated in vacuo to give light pink needles. The needles were crystallized from PhMe/cyclohexane (1:1) to give the thioacetal **20e** as fine white needles (20.8 g, 57.8 mmol, 91%). $R_f$ [EtOAc/hexane (1:1), $SiO_2$] 0.38. Mp: 126−127 °C. IR ($CDCl_3$ solution): 3327, 1577 cm$^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 5.60 (1H, s), 6.30 (1H, s), 6.77 (1H, d, $J$ = 9.7), 7.07−7.10 (2H, m), 7.23−7.28 (6H, m), 7.33−7.40 (4H, m). $\delta_C$ (100 MHz, $CDCl_3$): 56.32, 118.42, 125.43, 125.78, 128.44, 129.05, 129.24, 129.42, 132.85, 133.01, 152.37. LRMS (EI$^+$): 358 ($^{35}$Cl, $M^{\bullet+}$), 248 [$^{35}$Cl, ($M^{\bullet+}$) − PhSH], 110 $(PhSH)^+$. HRMS: calcd for $C_{19}H_{15}{}^{35}ClOS_2$, 358.0253; found 358.0251. Anal. Calcd for $C_{19}H_{15}ClOS_2$: C, 63.60; H, 4.18. Found: C, 63.63; H, 4.22.

**2-(2′-Trimethylsilyloxyphenyl)-1,3-dithiane (21a).** TMSCl (7.20 mL, 56.7 mmol, 1.2 equiv) was added to a solution of phenol **18a** (10.0 g, 47.1 mol) in pyridine (100 mL). After 20 h, the reaction mixture was diluted with $Et_2O$ (350 mL) and washed with water (5×), 1 M $CuSO_4$, water (2×), and brine, and then dried over $Na_2SO_4$ and concentrated in vacuo to give TMS ether **21a** as a pale yellow oil (13.2 g, 46.2 mmol, 98%). IR (thin-film): 1599, 1090, 834, 766 cm$^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 0.31 (9H, s), 1.93 (1H, dtt, $J$ = 14.1, 12.5, 3.1), 2.35 (1H, dtt, $J$ = 14.1, 4.5, 2.5), 2.90 (2H, dt, $J$ = 14.4, 3.7), 3.05 (2H, ddd, $J$ = 14.4, 12.6, 2.4), 5.53 (1H, s), 6.78 (1H, dd, $J$ = 8.1, 1.0), 6.92 (1H, td, $J$ = 7.6, 1.0), 7.15 (1H, td, $J$ = 7.9, 1.8), 7.54 (1H, dd, $J$ = 7.7, 1.7); $\delta_C$ (100 MHz, $CDCl_3$). 0.29, 24.88, 32.05, 44.37, 118.84, 121.47, 128.61, 128.69, 129.44, 151.23. LRMS (EI$^+$): 284 ($M^{\bullet+}$), 381 [($M^{\bullet+}$) − $OSi(CH_3)_3$]. HRMS: calcd for $C_{13}H_{20}OS_2Si$, 284.0725; found, 284.0725. Anal. Calcd for $C_{13}H_{20}OS_2Si$: C, 54.88; H, 7.09; S 11.27. Found: C, 54.81; H, 6.97; S, 11.41.

**2-(2′-*tert*-Butyldimethylsilyloxyphenyl)-1,3-dithiane (24a).** Triethylamine (2.3 mL, 16.5 mmol) was added to a solution of phenol **18a** (3.18 g, 15.0 mmol), TBSCl (2.49 g, 16.5 mmol), and imidazole (1.12 g, 16.5 mmol) in DMF (15 mL) and was allowed to stir for 16 h. The reaction mixture was poured into saturated $NaHCO_3$ and extracted into diethyl ether (3×). The combined organics were washed with water (5×), dried over $Na_2SO_4$, and concentrated to yield a pale yellow solid (4.88 g, 16.5 mmol, 100%). Recrystallization from petroleum ether (40−60 °C) gave TBS ether **24a** as needles (3.66 g, 11.2 mmol, 75%). Mp: 77−80 °C. IR (KBr): 1089, 831 cm$^{-1}$. $\delta_H$ (400 MHz: $CDCl_3$): 0.26 (s, 6H), 1.06 (s, 9H), 1.91−1.98 (m, 1H), 2.13−2.19 (m, 1H), 2.87−2.93 (m, 2H), 3.00−3.07 (m, 2H), 5.60 (s, 1H), 6.78 (dd, $J$ = 1.1, 8.1, 1H), 6.93 (dt, $J$ = 1.1, 7.5, 1H), 7.12 (dt, $J$ = 1.8, 7.5, 1H), 7.52 (dd, $J$ = 1.7, 7.7, 1H). $\delta_C$ (100 MHz: $CDCl_3$): −4.4, 18.3, 25.3, 25.8, 32.5, 44.8, 118.8, 121.7, 129.0, 129.2, 129.8, 138.1. LRMS (EI): 326 ($M^{\bullet+}$), 269 ($M^{\bullet+}$ − $C_4H_9$), 195 ($M^{\bullet+}$ − $C_6H_{15}SiO$). HRMS: calcd for $C_{16}H_{16}OS_2Si$, 326.5973; found, 326.5976. Anal. Calcd for $C_{16}H_{16}OS_2Si$: C, 58.89; H, 7.97. Found: C, 58.83; H, 7.80.

**Merrifield Resin-Bound Esters 25.** Following the published procedure for loading Merrifield resin,[54] Six porous polypropylene reactors charged with Merrifield resin (0.311 mequiv reactor$^{-1}$, 170 mg of Merrifield resin with a loading of 1.83 mequiv (of benzylic chloride) g$^{-1}$) were stirred in DMF (150 mL) with the corresponding cesium salt (prepared by adding CsOH to the carboxylic acid, until pH 7 was achieved (9.3 mmol, 5 equiv)) at 50 °C for 15 h. The reactors were then washed with DMF (×2), with water (×2), and then alternately with MeOH and DCM (×5) before finally washing with MeOH and diethyl ether to give the desired resin-bound esters **25**, which were dried under vacuum. The same procedure was used to prepare reactors with loadings of 0.279 mequiv reactor$^{-1}$ (150 mg of 1.86 mequiv g$^{-1}$ Merrifield resin) and 0.305 mequiv reactor$^{-1}$ (164 mg of 1.86 mequiv g$^{-1}$ Merrifield resin).

**Solution-Phase Synthesis of 2-(2′-Phenylethyl)benzo[*b*]furan (27aa)′.** Ketone **31** (0.135 g, 0.38 mmol) was dissolved in THF (5 mL) and stirred under an argon atmosphere. TBAF (1.0 M in THF, 1.0 mL, 1.0 mmol) was added, and the solution was stirred for 3 h at room temperature. The solvent was then removed under reduced pressure, and the residue was taken up in diethyl ether (10 mL) and washed with water (5 × 10 mL). After drying (magnesium sulfate) the solvent was removed under reduced pressure to give the deprotected ketone as an oil. The oil was dissolved in a solution of 1% TFA in dichloromethane (5 mL) and stirred for 30 min under an argon atmosphere at room temperature. Solvent removal under reduced pressure gave the benzofuran as a solid **27aa′** (68 mg, 0.31 mmol, 81%). $R_f$ [$SiO_2$, petroleum ether 40/60 diethyl ether (1:1)] 0.58. Mp: 50−52 °C. IR ($CDCl_3$ solution): 1614. $\delta_H$ (400 MHz, $CDCl_3$): 3.08 (4H, s), 6.36 (1H, s), 7.15−7.31 (7H, m), 7.43 (1H, d, $J$ = 8.1), 7.47 (1H, dd, $J$ = 7.0, 1.5). $\delta_C$ (100 MHz, $CDCl_3$): 30.77, 34.36, 102.75, 111.15, 120.72, 122.85, 126.59, 127.44, 128.76, 128.87, 129.28, 141.30, 155.05, 158.84; LRMS (EI$^+$): 222 ($M^{\bullet+}$), 131 ($M^{\bullet+}$ − $PhCH_2^{\bullet}$). HRMS: calcd for $C_{16}H_{14}O$, requires 222.1044; found, 222.1044. IR and $^1$H NMR spectra are in good agreement with literature.[90]

**General Procedure for Solid-Phase Synthesis of Benzo[*b*]furans 27.** $Cp_2TiCl_2$ (2.79 g, 11.2 mmol, 12 equiv), Mg (0.30 g, 12.3 mmol, 13.2 equiv), and 4 Å MS (0.50 g) were heated, gently, by heat gun under reduced pressure (0.3 mmHg) for about 1 min. THF (12 mL) was added, then $P(OEt)_3$ (3.80 mL, 22.4 mmol, 24 equiv) was added to the resulting suspension. After 3 h, thioacetal **21** (0.80 g, 2.80 mmol, 9 equiv)

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(90) Grandberg, I.; Sorokin, V. I. *Chem. Heterocycl. Compd.* (*N.Y.*) **1973**, *9*, 26−30.

in THF (12 mL) was added to the mixture, and after a further 15 min, the resulting reagent was split three ways (approximately 9 mL) and added to three separate vessels, each containing a porous polypropylene reactor charged with resin-bound ester **25** (0.311 mequiv/reactor prepared from 170 mg of commercial Merrifield resin with a loading of 1.83 mequiv (of benzylic chloride) $g^{-1}$). After 21 h the reactors were washed together with THF (5×) and then alternately with MeOH and DCM (3×). Finally, the reactors were washed with MeOH and $Et_2O$ and dried in vacuo. Each reactor containing resin-bound enol ether was then shaken in 1% TFA−DCM (5 mL) for 2 h, the solution was removed, and the reactor was washed with DCM (3×); all of the DCM solutions were combined and concentrated in vacuo to give a resin-bound ester. Yields are based on the loading of the commercial Merrifield resin.

**General Procedure for Solid-Phase Synthesis of 6-Diethylaminobenzo[*b*]furans 27da′, 27db′, 27dc′.** The benzylidenation reaction and resin washing were carried out as above. Each reactor containing resin-bound enol ether was then shaken in 1% TFA−DCM (5 mL) for 3 h, the DCM solution was removed, and the reactor was washed with DCM (3×); all DCM solutions were combined and concentrated in vacuo. The resulting solid was treated with 10% TFA−DCM (10 mL) for 50 min, and the reaction was then quenched by addition of solid $Na_2CO_3$. The solid was removed by filtration, and the DCM solution was concentrated in vacuo to give diethylaminobenzofuran **27da′**, **27db′**, or **27dc′**.

**1-(4′-Diethylamino-2-hydroxyphenyl)-4-phenylbutan-2-one (29da′).** The ketone was prepared by alkylidenation of the corresponding resin-bound ester and then treating the resulting resin-bound enol ether with 1% TFA−DCM (5 mL) for 1 h. The DCM solution was decanted, and the resin was washed with DCM (3×); all DCM solutions were combined, neutralized with solid anhydrous $Na_2CO_3$, and concentrated in vacuo to give the ketone as a green oil (54 mg, 0.173 mmol, 56%). IR (Golden Gate): 3369, 1671, 1525 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 1.06 (6H, t, $J$ = 7.1), 2.82 (4H, s), 3.31 (4H, q, $J$ = 7.1), 3.58 (2H, s), 6.50 (1H, brd, $J$ = 7.4), 6.79 (1H, brs), 6.95 (1H, d, $J$ = 8.2), 7.06−7.12 (3H, m), 7.16−7.20 (2H, m). $\delta_C$ (100 MHz, $CDCl_3$): 8.11, 26.48, 41.05, 115.15, 115.43, 123.07, 125.22, 125.42, 129.10, 137.65, 153.58, 207.02. LRMS ($EI^+$): 311 ($M^{\bullet+}$), 178 [$M^{\bullet+} - C_6H_5(CH_2)_2CO^{\bullet}$]. HRMS: calcd for $C_{20}H_{25}NO_2$, 311.1885; found, 311.1884.

**Wang Resin-Bound Esters 30.** To Wang resin contained within porous polypropylene reactors (170 mg reactor$^{-1}$ of 1.7 mequiv (of benzylic hydroxyl) $g^{-1}$) swollen in THF (concentration, ca. 0.02 mol $L^{-1}$ with respect to the resin) was added the appropriate acid (5.00 equiv) and DMAP (0.90 equiv), and the mixture was stirred at room temperature. DIC (5.00 equiv) was added dropwise, and the mixture was stirred overnight. The THF was removed, and the reactors were washed with THF, alternating methanol and then DCM (5× each), MeOH, and finally $Et_2O$. The resin was dried under vacuum and retreated as above using the acid, DMAP, and DIC. Washing and drying of the resin as before yielded the desired resin-bound ester **30**.

**1-(2′-*tert*-Butyldimethylsilyloxyphenyl)-4-phenylbutan-2-one (31).** In a similar way to the general procedure for the solid-phase synthesis of benzofurans above, thioacetal **24a** (0.48 g, 1.45 mmol) was converted to a titanium benzylidene and reacted with Wang resin-bound ester **30a** in a reactor (0.29 mequiv reactor$^{-1}$ prepared from 170 mg of commercial Wang resin with a loading of 1.7 mequiv (of benzylic hydroxyl) $g^{-1}$). Cleavage with 1% TFA−DCM then gave ketone **31** as an oil (70 mg, 0.20 mmol, 68%). IR (thin film): 1714, 1601, 1584 $cm^{-1}$. $\delta_H$ (400 MHz: $CDCl_3$): 0.20 (s, 6H), 0.97 (s, 9H), 2.69 (t, $J$ = 8.0, 2H), 2.83 (t, $J$ = 7.9, 2H), 3.64 (s, 2H), 6.81 (d, $J$ = 8.1, 1H), 6.87 (dt, $J$ = 7.4, 1.0, 1H), 7.06−7.12 (m, 5H), 7.22−7.25 (m, 2H). $\delta_C$ (100 MHz, $CDCl_3$): −4.19, 18.19, 25.73, 29.71, 43.26, 45.29, 118.39, 121.25, 125.31, 126.00, 128.28, 128.36, 129.41, 131.40, 141.00, 153.74, 208.71. LRMS ($CI^+$): 355 [(M + H)$^+$], 297 [25, (M + H)$^+$ − $^t$BuH]. HRMS: calculated for $C_{22}H_{31}O_2Si$, (M + H)$^+$, requires 355.2093; found 355.2092.

**2-(*N*,*N*-Dimethylamino)-5-methylbenzaldehyde (41).** Phosphorus oxychloride (5.70 mL, 60.0 mmol) was added to DMF (14 mL) at 0 °C and was allowed to stir for 15 min. After this time, *N*,*N*-dimethyl-*p*-toluidine **(40)** (2.20 mL, 20 mmol) was added, the reaction was allowed to warm to 60 °C, and then the mixture was stirred for 16 h. The reaction was poured into NaOH (2 M) and extracted into diethyl ether (3×). The organics were washed with water (6×), dried over $Na_2SO_4$, and concentrated to yield a yellow oil (2.76 g, 16.9 mmol). Column chromatography ($SiO_2$, hexane/diethyl ether 9:1) gave aldehyde[91] **41** as a yellow oil (1.99 g, 12.2 mmol, 61%). $R_f$ ($SiO_2$, hexane/diethyl ether 9:1): 0.10. IR (KBr): 1686 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 2.31 (s, 3H), 2.87 (s, 6H), 6.97 (d, $J$ = 8.3, 1H), 7.27 (dd, $J$ = 2.2, 8.3, 1H), 6.97 (d, $J$ = 1.8, 1H). $\delta_C$ (100 MHz, $CDCl_3$): 20.3, 45.8, 118.0, 127.3, 130.4, 130.6, 135.4, 154.1, 191.6. LRMS (EI): 163 ($M^{\bullet+}$). HRMS: calcd for $C_{10}H_{13}NO$, 163.2193; found, 163.2201. Anal. Calcd for $C_{10}H_{13}NO$: C, 73.61; H, 7.98; N, 8.59. Found: C, 73.42; H, 7.97; N, 8.57.

**2-[2′-(*N*,*N*-Dimethylamino)-5-methylphenyl]-1,3-dithiane (42).** $BF_3{\cdot}OEt_2$ (2.6 mL, 20 mmol) was added dropwise to a solution of aldehyde **41** (1.60 g, 9.80 mmol), in 1,3-propanedithiol (2.0 mL, 20 mmol) at rt, under $N_2$. The reaction was then heated at 70 °C for 15 h. The reaction mixture was quenched into NaOH (1 M) and extracted into DCM (3×). The combined organics were then washed with water (3×), dried over $Na_2SO_4$, and concentrated to yield a yellow oil (2.09 g). Column chromatography ($SiO_2$, DCM) gave a colorless oil, which solidified (1.36 g, 5.37 mmol, 55%). Recrystallization from DCM/petroleum ether (40−60 °C) gave thioacetal **42** as needles (0.99 g, 3.92 mmol, 40%). $R_f$ ($SiO_2$, DCM): 0.45. Mp: 54−57 °C. $\delta_H$ (400 MHz: $CDCl_3$): 1.90−2.00 (m, 1H), 2.15−2.20 (m, 1H), 2.29 (s, 3H), 2.72 (s, 6H), 2.86−2.91 (m, 2H), 3.07−3.15 (m, 2H), 5.75 (s, 1H), 6.99−7.05 (m, 2H), 7.41 (s, 1H). $\delta_C$ (100 MHz: $CDCl_3$): 20.7, 25.4, 32.6, 45.7, 45.8, 119.5, 129.7, 130.0, 130.1, 133.5. LRMS (EI): 253 ($M^{\bullet+}$), 238 ($M^{\bullet+}$ − $^{\bullet}CH_3$). HRMS: calcd for $C_{13}H_{19}NS_2$, 253.4326; found, 253.4305. Anal. Calcd for $C_{16}H_{16}OS_2$: C, 61.66; H, 7.51; N, 5.53. Found: C, 61.27; H, 7.60; N, 5.24.

**1-(2′-*N*,*N*-Dimethylamino-5′-methylphenyl)-4-phenylbutan-2-one (44).** In a similar way to the general procedure for the solid-phase synthesis of benzofurans, thioacetal **44** (0.37 g, 1.45 mmol) and Merrifield resin-bound ester **25a′** gave ketone **44** as a yellow oil (0.044 g, 0.16 mmol, 53%). $\delta_H$ (400 MHz: $CDCl_3$): 2.34 (s, 3H), 2.91−2.98 (m, 4H), 3.21 (s, 6H), 4.15 (s, 2H), 6.85 (s, 1H), 7.19−7.31 (m, 7H). $\delta_C$ (100 MHz: $CDCl_3$): 20.8, 29.7, 43.9, 46.1, 47.6, 119.7, 126.0, 127.5, 128.4, 128.5, 130.0, 133.7, 140.1, 140.7, 140.9, 206.4. LRMS (EI): 281.1 ($M^{\bullet+}$), 162.1, 148.1. HRMS: calcd for $C_{19}H_{21}NO$, 281.3997; found, 281.3992.

**2-(2′-Nitrophenyl)-1,3-dithiane (46a).** 1,3-Propanedithiol (12.0 mL, 120 mmol) was added to a solution of 2-nitrobenzaldehyde **45a** (15.0 g, 99.0 mmol) and $BF_3{\cdot}OEt_2$ (13.5 mL, 120 mmol) in toluene (50 mL) under nitrogen and was stirred for 16 h at rt. The reaction mixture was quenched by adding water and then extracted into DCM (2×). The combined organics were washed with 1 M NaOH (2×) water (2×), dried over $Na_2SO_4$, and concentrated in vacuo to give a yellow solid. Recrystallization, from propan-2-ol, gave thioacetal **46a** as yellow needles (20.72 g, 86.0 mmol, 87%). $R_f$ (DCM, $SiO_2$): 0.48. Mp: 114−116 °C. IR (KBr): 1524, 1351 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 1.89−2.01 (m, 1H), 2.17−2.24 (m, 1H), 2.90−2.96 (m, 2H), 3.09−3.16 (m, 2H), 5.89 (s, 1H), 7.42 (dt, $J$ = 1.3, 8.2, 1H), 7.60 (dt, $J$ = 1.2, 7.6, 1H), 7.87−7.90 (m, 2H). $\delta_C$ (100 MHz, $CDCl_3$): 25.4, 32.7, 46.4, 125.1, 126.2, 129.5, 131.1, 133.9, 138.5. LRMS (EI): 241 ($M^{\bullet+}$), 224 ($M^{\bullet+}$ − OH). HRMS: calcd for $C_{10}H_{11}NO_2S_2$, 241.0231; found 241.0233. Anal. Calcd for $C_{10}H_{11}NO_2S_2$: C, 49.79; H, 4.56; N, 5.81. Found: C, 49.80; H, 4.49; N, 5.81.

(91) Dhanak, D.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2181−2186.

**2-(2′-Aminophenyl)-1,3-dithiane (47a).**[92] THF (150 mL) was added to a three-necked flask containing thioacetal **46a** (20.7 g, 86.0 mmol) charged with argon, and the reaction mixture was cooled using an ice bath. Pd/C (5% loading/50% water, 13.8 g), followed by $NaBH_4$ (11.13 g, 294 mmol) in three equal portions over 10 min, was added, and the reaction mixture was allowed to stir at rt for 18 h. The reaction mixture was acidified to pH 6 with 2 M HCl, and then chloroform (150 mL) was added and the mixture was stirred for 10 min. The solution was then filtered, and the organic layer was washed with water (2×), dried over $Na_2SO_4$, and concentrated to leave a yellow solid. Recrystallization from propan-2-ol gave amine[92] **47a** as needles (15.42 g, 73.0 mmol, 85%). $R_f$ ($SiO_2$, DCM): 0.14. Mp: 112−115 °C. Literature mp:[92] 114−115 °C. IR (KBr): 3434, 3340, 1623 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 1.88−1.99 (m, 1H), 2.15−2.22 (m, 1H), 2.90−2.95 (m, 2H), 3.06−3.13 (m, 2H), 4.15 (s, 2H), 5.30 (s, 1H), 6.68 (dd, $J$ = 1.0, 7.9, 1H), 6.75 (dt, $J$ = 1.1, 7.5, 1H), 7.09 (dt, $J$ = 1.5, 7.5, 1H), 7.30 (dd, $J$ = 1.4, 7.7, 1H). $\delta_C$ (100 MHz, $CDCl_3$): 25.3, 32.0, 48.7, 117.0, 119.1, 123.1, 128.5, 129.3, 144.4. LRMS (EI): 211.0 ($M^{\bullet+}$), 178.0 ($M^{\bullet+}$ − SH). HRMS: calcd for $C_{10}H_{13}NS_2$, 211.0489; found, 211.0490. Anal. Calcd for $C_{10}H_{13}NS_2$: C, 66.89; H, 5.92; N, 4.88. Found: C, 66.79; H, 5.82; N, 4.73.

**2-(2′-Amino-5′-hydroxyphenyl)-1,3-dithiane (47e).** Adapting a literature procedure,[81] we added Fe powder (7.54 g, 135 mmol) to a solution of thioacetal **46e** (12.87 g, 50.0 mmol) and $NH_4Cl$ (12.04 g, 225 mmol), in EtOH (200 mL) and water (200 mL) and heated under reflux for 2 h. After cooling, the mixture was filtered through Celite and washed with EtOAc. The dark green solution was then concentrated in vacuo. The resulting slurry was partitioned between EtOAc and brine, the organics were then washed with water (2×), dried over $MgSO_4$, and concentrated in vacuo to give amine **47e** as a yellow solid (9.87 g, 43.4 mmol, 87%), which was used in the next step. Recrystallization of a 0.30 g portion, from propan-2-ol, gave amine **47e** as needles (0.24 g, 70%). $R_f$ (EtOAc, $SiO_2$): 0.46. Mp: 156−159 °C. IR (KBr): 3441, 1583, 1520 $cm^{-1}$. $\delta_H$ (250 MHz, $C_2D_6$-SO): 1.61−1.77 (m, 1H), 2.08−2.15 (m, 1H), 2.80−2.88 (m, 2H), 3.04−3.16 (m, 2H), 4.57 (s, 2H), 5.39 (s, 1H), 6.43−6.49 (m, 2H), 6.69 (d, $J$ = 2.5, 1H), 8.51 (s, 1H). $\delta_C$ (62.8 MHz, $C_2D_6$-SO): 25.5, 31.6, 46.0, 114.8, 116.3, 117.3, 123.6, 137.5, 148.9; LRMS (EI): 257.0 ($M^{\bullet+}$), 240 ($M^{\bullet+}$ − OH). HRMS: calcd for $C_{10}H_{13}NOS_2$, 257.0180; found, 257.0178. Anal. Calcd for $C_{10}H_{13}NOS_2$: C, 52.86; H, 5.73; N, 6.17. Found: C, 52.86,; H, 5.76; N, 6.13.

**Diazine-*N*-oxide (48).** THF (150 mL) was added to a three-necked flask charged with argon and containing thioacetal **46a** (14.15 g, 58.6 mmol), and the reaction was cooled using an ice bath. Pd/C (5% loading/ 50% water, 4.38 g), followed by $NaBH_4$ (5.54 g, 147 mmol) in three equal portions over 15 min, was added, and the reaction was allowed to stir at rt for 18 h. After this time, the reaction was worked up exactly as for amine **47a** above, to leave an orange oil (13.52 g). $^1H$ NMR spectroscopy confirmed that an 18:8:2 mixture of amine **47a**/diazine-*N*-oxide **48**/starting material **46a** was obtained. Column chromatography ($SiO_2$, $CHCl_3$) gave pure starting material **46a** (0.50 g, 2.07 mmol), amine **47a** (5.21 g, 24.7 mmol), and diazine-*N*-oxide **48** (1.93 g, 4.43 mmol). The latter was recrystallized from EtOAc, to give diazine-*N*-oxide **48** as orange/yellow needles (1.59 g, 3.65 mmol). $R_f$ ($SiO_2$, $CHCl_3$): 0.25. Mp: 202−204 °C. IR (KBr): 1630 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 1.86−1.97 (m, 2H), 2.09−2.15 (m, 2H), 2.81−2.85 (m, 4H), 3.04−3.12 (m, 4H), 5.75 (s, 1H), 6.00 (s, 1H), 7.41−7.47 (m, 3H), 7.53−7.7.54 (m, 1H), 7.71 (dd, $J$ = 1.2, 7.9, 1H), 7.81−7.83 (m, 1H), 7.89 (dd, $J$ = 1.3, 7.8, 1H), 8.55−8.57 (m, 1H). $\delta_C$ (100 MHz: $CDCl_3$): 25.0, 25.1, 32.0, 32.1, 45.6, 122.0, 124.1, 128.4, 129.0, 129.1, 130.0, 130.1, 130.7, 132.1, 136.5, 138.1, 140.2, 147.8. LRMS (CI+): 435.0 [$(M + H)^+$], 417.1 [$(M + H)^+$ − $H_2O$]. HRMS: calcd for $C_{20}H_{22}N_2OS_4$, 435.0693; found, 435.0693. Anal. Calcd for $C_{20}H_{22}N_2OS_4$: C, 55.14; H, 5.09; N, 6.43. Found: C, 55.21; H, 5.05; N, 6.43. Structure confirmed by X-ray crystallography.

**2-[2′-(*N*-Boc-amino)phenyl]-1,3-dithiane (49a).** Adapting a known procedure,[44] we heated a solution of amine **47a** (3.18 g, 15.0 mmol) and $(Boc)_2O$ (3.60 g, 16.5 mmol) in THF (25 mL) under reflux and under nitrogen for 5 h. After this time, the mixture was poured into water, extracted into DCM (2×), washed with water (2×), dried over $Na_2SO_4$, and concentrated to yield a pale yellow solid. Recrystallization from propan-2-ol gave carbamate **49a** as golden plates (4.00 g, 12.8 mmol, 86%). $R_f$ ($SiO_2$, DCM): 0.32. Mp: 142−144 °C. IR (KBr): 3400, 1737 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 1.54 (s, 9H), 1.88−1.99 (m, 1H), 2.17−2.23 (m, 1H), 2.91−2.95 (m, 2H), 3.07−3.14 (m, 2H), 4.75 (s, 1H), 5.30 (s, 1H), 7.05 (dt, $J$ = 1.0, 7.6, 1H), 7.27 (dt, $J$ = 1.5, 8.6, 1H), 7.40 (dd, $J$ = 1.2, 7.7, 1H), 7.82 (d, $J$ = 7.1, 1H). $\delta_C$ (100 MHz, $CDCl_3$): 25.1, 28.4, 31.9, 48.3, 80.5, 122.9, 124.1, 128.3, 129.1, 136.1, 138.1, 153.2. LRMS (EI): 311.0 ($M^{\bullet+}$), 255.0 ($M^{\bullet+}$ − $C_4H_{10}$); HRMS: calcd for $C_{15}H_{21}NO_2S_2$, 311.1014; found, 311.1014. Anal. Calcd for $C_{15}H_{21}NO_2S_2$: C, 57.84; H, 6.80; N, 4.50. Found: C, 57.95; H, 6.80; N 4.40.

**2-[2′-(*N*-Boc-amino)-4′,5′-methylenedioxyphenyl]-1,3-dithiane (49c).** Amine **47c** was prepared as a yellow solid (7.69 g) in the same way as amine **47e,** using Fe powder (4.70 g, 28.0 mmol), thioacetal **46c** (8.00 g, 50.0 mmol), and $NH_4Cl$ (7.49 g, 140 mmol) in EtOH (125 mL) and water (75 mL). The product was one compound by both $^1H$ NMR spectroscopy and TLC analysis and was not further purified after workup due to its instability. $R_f$ (DCM, $SiO_2$): 0.42. $\delta_H$ (400 MHz, $CDCl_3$): 1.85−1.97 (m, 1H), 2.13−2.20 (m, 1H), 2.88−2.94 (m, 2H), 3.05−3.12 (m, 2H), 5.25 (s, 1H), 5.86 (s, 2H), 6.31 (s, 1H), 6.87 (s, 1H). LRMS (EI): 255 ($M^{\bullet+}$), 180 ($M^{\bullet+}$ − $C_3H_7S^{\bullet}$). HRMS: calcd for $C_{11}H_{13}NO_2S_2$, 255.0388; found, 255.0385. A solution of amine **47c** (5.61 g, 22.0 mmol) and $(Boc)_2O$ (11.52 g, 52.8 mmol) in THF (75 mL) was heated under reflux for 15 h. After this time, the reaction mixture was poured into water and extracted into EtOAc (2×). The combined organics were washed with brine and water, dried over $Na_2SO_4$, and concentrated to give the crude imide **50c** as a green solid. The solid was dissolved in DCM (250 mL), TFA (2.6 mL, 33.0 mmol) was added dropwise, and the mixture was allowed to stir for 15 h. After this time, the reaction mixture was washed with $NaHCO_3$ (2×) then water, dried over $Na_2SO_4$, and concentrated to yield a yellow solid. Recrystallization from propan-2-ol gave carbamate **49c** as yellow needles (6.53 g, 18.4 mmol, 83% over 3 steps). $R_f$ ($SiO_2$, DCM): 0.15. Mp: 156−158 °C. IR (KBr): 3404, 1727, 1508 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 1.53 (s, 9H), 1.85−1.95 (m, 1H), 2.15−2.21 (m, 1H), 2.88 (dt, $J$ = 14.4, 3.3, 2H), 3.05−3.12 (m, 2H), 5.22 (s, 1H), 5.93 (s, 2H), 6.94 (s, 1H), 6.24 (s, 1H). $\delta_C$ (90 MHz, $CDCl_3$): 25.1, 28.4, 32.0, 47.7, 80.5, 101.5, 105.6, 107.7, 130.1, 147.9, 153.5. LRMS (EI): 355.0 ($M^{\bullet+}$), 298.0 ($M^{\bullet+}$ − $C_4H_8$), 282.0 ($M^{\bullet+}$ − $C_4H_9O$), 225.0 ($M^{\bullet+}$ − $C_6H_{10}O_3$), 192.0 ($M^{\bullet+}$ − $C_6H_{12}NO_4$). HRMS: calcd for $C_{16}H_{21}NO_4S_2$, 355.0912; found, 355.0914. Anal. Calcd for $C_{16}H_{21}NO_4S_2$: C, 54.08; H, 5.91; N, 3.94. Found: C, 54.23; H, 6.05; N, 3.86.

**2-[2′-(*N*,*N*-di-*tert*-butoxycarboxyamino)phenyl]-1,3-dithiane (50a).** A solution of NaHMDS (22.0 mL, 22.0 mmol, 1 M in THF) was added to a solution of amine **47a** (2.11 g, 10.0 mmol) and $(Boc)_2O$ (5.46 g, 25.0 mmol) in THF (50 mL) at 0 °C under nitrogen. The reaction was allowed to warm to rt and stirred for 16 h. After this time, the reaction was poured into water, extracted into DCM (2×), washed with water (2×), dried over $Na_2SO_4$, and concentrated to yield a white/yellow solid. Recrystalization from petroleum ether (40−60 °C) gave imide **50a** as needles (3.21 g, 7.80 mmol, 78%). $R_f$ (hexane/DCM 1:9, $SiO_2$): 0.10. Mp: 106−109 °C. IR (KBr): 1789 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 1.36 (s, 18H), 1.91−1.95 (m, 1H), 2.13−2.17 (m, 1H), 2.84−2.89 (m, 2H), 2.98−3.05 (m, 2H), 5.22 (s, 1H), 5.30 (s, 1H), 7.06 (dd, $J$ = 1.2, 7.8, 1H), 7.27 (dt, $J$ = 1.6, 7.5, 1H), 7.31 (dt, $J$ = 1.2, 7.5, 1H), 7.67 (dd, $J$ = 1.5, 7.7, 1H). $\delta_C$ (100 MHz: $CDCl_3$): 25.1, 27.6, 32.0, 45.8, 82.8, 128.4, 128.5,

(92) Gassman, P. G.; Drews, H. R. *J. Am. Chem. Soc.* **1978**, *100*, 7600−7610.

129.0, 136.2, 136.5, 150.9. LRMS (CI+): 412.1 [$(M + H)^+$], 312.1 [$(M + H)^+ - C_5H_8O_2$]. Anal. Calcd for $C_{20}H_{29}NO_4S_2$: C, 58.36; H, 7.10; N, 3.40. Found: C, 58.37; H, 6.97; N, 3.29. Structure confirmed by X-ray crystallography.

**General Procedure for Carbamate Alkylation to Give Carbamates 51a-54a.** NaH (60% in mineral oil (0.66 g, 16.5 mmol)) was added portionwise to a solution of carbamate **49a** (4.04 g, 13 mmol) and alkyl halide (MeI, BnBr, allyl bromide, or prenyl bromide, 16.5 mmol), in DMF at 0 °C under argon. The reaction mixture was then allowed to warm to rt and stirred for 2−3 h. After this time, the reaction mixture was carefully poured into iced water and extracted into EtOAc (2×). The combined organics were then washed with water (3×), dried over $MgSO_4$, and concentrated to yield the desired amine.

**2-[2′-(*N*-Boc-*N*-methylamino)phenyl]-1,3-dithiane (51a).** Following the above procedure, using MeI (1.10 mL, 16.5 mmol) in DMF (60 mL), and allowing to stir for 2 h gave amine **51a** as a pale yellow solid (3.85 g, 11.8 mmol, 91%), which was used in the next reaction. Recrystallization of a 0.30 g portion, from propan-2-ol, gave amine **51a** as needles (0.24 g, 73%). $R_f$ ($SiO_2$, DCM): 0.13. Mp: 103−105 °C. IR (KBr): 1688 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 1.35 (s, 9H), 1.88−1.99 (m, 1H), 2.13−2.20 (m, 1H), 2.85−3.11 (m, 4H), 3.22 (s, 3H), 5.24 (s, 1H), 7.10 (d, $J = 6.4$, 1H), 7.26−7.32 (m, 2H), 7.67 (dt, $J = 1.9$, 6.6, 1H). $\delta_C$ (100 MHz, $CDCl_3$): 25.1, 28.0, 32.1, 32.5, 37.5, 45.9, 80.2, 127.7, 128.0, 129.0, 129.2, 136.6, 140.8, 155.1. LRMS (EI): 325.1 ($M^{\bullet+}$), 269.1 ($M^{\bullet+} - C_4H_8$), 224.1 ($M^{\bullet+} - C_5H_{11}O_2$). HRMS: calcd for $C_{16}H_{23}NO_2S_2$, 325.1170; found, 325.1172. Anal. Calcd for $C_{16}H_{23}NO_2S_2$: C, 59.04; H, 7.12; N, 4.30. Found: C, 59.05; H, 7.12; N, 4.35. Structure confirmed by X-ray crystallography.

**2-[2′-(*N*-Benzyloxycarboxy-*N*-methylamino)phenyl]-1,3-dithiane (55).** Benzylchloroformate (2.20 mL, 15.0 mmol) was added dropwise to a solution of amine **49a** (3.17 g, 15.0 mmol) and $NaHCO_3$ (2.52 g, 30.0 mmol) in acetone/water (4:1, 125 mL) at 0 °C, following a published procedure for forming benzyl carbamates.[93] The reaction mixture was allowed to warm to rt and then further stirred for 2 h. After this time, the reaction mixture was concentrated in vacuo, water was added, and the mixture was extracted with EtOAc. The combined organics were washed with water (2×), dried over $MgSO_4$, and concentrated to yield a yellow oil (5.28 g). DMF (90 mL) and MeI (1.90 mL, 30 mmol) were added, and the mixture was cooled to 0 °C under argon. NaH (60% in mineral oil, (0.75 g, 18.8 mmol)) was then added portion-wise over 10 min, and the mixture was allowed to warm to rt. After being stirred for 3 h, the reaction mixture was carefully poured into iced water and extracted into EtOAc (2×). The combined organics were then washed with water (2×), dried over $Na_2SO_4$, and concentrated to yield a yellow/orange oil (1.15 g, 4.06 mmol, 58%). Column chromatography ($SiO_2$, DCM) gave carbamate **55** as a yellow solid (0.98 g, 2.73 mmol, 18% over two steps). Recrystallization of a 0.30 g portion, from propan-2-ol, yielded carbamate **55** as white flakes (0.25 g, 15%). $R_f$ ($SiO_2$, $CH_2Cl_2$) 0.25. Mp: 67−70 °C. IR (KBr): 1699 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 1.82−1.94 (m, 1H), 2.05−2.13 (m, 1H), 2.79−3.02 (m, 4H), 3.28 (s, 3H), 5.05 (d, $J = 12.7$, 1H), 5.10 (d, $J = 12.6$, 1H), 5.23 (s, 1H), 7.11 (d, $J = 7.2$, 1H), 7.23−7.34 (m, 7H), 7.71 (dd, $J = 7.6$, 1.7, 1H). $\delta_C$ (100 MHz, $CDCl_3$): 24.9, 31.9, 32.2, 38.3, 45.7, 67.0, 127.4, 127.5, 127.9, 128.1, 128.4, 129.2, 129.4, 136.5, 136.6, 139.9, 155.7. LRMS (EI): 359.1 ($M^{\bullet+}$), 268.1 ($M^{\bullet+} - C_7H_7$). HRMS: calcd for $C_{19}H_{21}NO_2S_2$, 359.1014; found, 359.1012. Anal. Calcd for $C_{19}H_{21}NO_2S_2$: C, 63.48; H, 5.84; N, 3.90; S, 17.84. Found: C, 63.46; H, 5.83; N, 4.02; S, 18.05.

**2-[2′-(*N*-Methyl-*N*-methyloxycarboxyamino)phenyl]-1,3-dithiane (56).** Methylchloroformate (0.80 mL, 12 mmol) was added dropwise to a solution of amine **49a** (2.11 g, 10 mmol) and saturated $NaHCO_3$ (0.80 mL), in dioxane (60 mL), and the reaction mixture was allowed to stir for 16 h. The reaction mixture was poured into water and extracted into diethyl ether (2×). The combined organics were then washed with water (2×) and brine, dried over $MgSO_4$, and concentrated to yield 2-[2′-(*N*-methyloxycarboxyamino)phenyl]-1,3-dithiane as a solid (2.41 g, 90%, 8.96 mmol), which was used in the next step. Recrystallization of a 0.50 g portion, from propan-2-ol, yielded 2-[2′-(*N*-methyloxycarboxyamino)phenyl]-1,3-dithiane as needles (0.36 g, 65%). $R_f$ ($SiO_2$, DCM): 0.30. Mp: 95−97 °C. IR (KBr): 3295, 1731, 1702 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 1.89−1.99 (m, 1H), 2.17−2.22 (m, 1H), 2.91−2.94 (m, 2H), 3.05−3.12 (m, 2H), 3.81 (s, 1H), 5.31 (s, 1H), 7.06 (t, $J = 7.4$, 1H), 7.30 (t, $J = 7.6$, 1H), 7.39 (d, $J = 7.6$, 1H), 7.62 (s, 1H), 7.89 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$): 25.0, 31.9, 48.8, 52.5, 122.6, 124.6, 128.6, 129.3, 136.0, 154.3. LRMS (EI): 269.1 ($M^{\bullet+}$), 163.1 ($C_{10}H_{11}S$). HRMS: calcd for $C_{12}H_{15}NO_2S_2$, 269.0544; found, 269.0544. Anal. Calcd for $C_{12}H_{15}NO_2S_2$: C, 53.57; H, 5.62; N, 5.21; Found: C, 53.43; H, 5.60; N, 5.28. LDA (3.75 mL, 7.50 mmol, 2.0 M), in THF (4.0 mL) was added dropwise to a solution of this carbamate (1.88 g, 7.00 mmol) in THF (20 mL) under argon at −78 °C, was allowed to warm to rt, and then was stirred for 1 h. The reaction mixture was cooled to −40 °C before MeI (1.80 mL, 30.0 mmol) was added, was allowed to warm to rt, and then was stirred for 1 h. The reaction mixture was poured into water and extracted with EtOAc (2×). The combined organics were then washed with water (3×), dried over $Na_2SO_4$, and concentrated to yield a yellow solid (1.79 g). Recrystallization, from propan-2-ol, yielded carbamate **56** as a solid (1.15 g, 4.06 mmol, 58%). Mp: 105−107 °C. IR (KBr): 1700 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 1.87−1.98 (m, 1H), 2.14−2.21 (m, 1H), 2.85−2.92 (m, 2H), 3.02−3.10 (m, 2H), 3.28 (s, 3H), 3.64 (s, 3H), 5.24 (s, 1H), 7.14 (d, $J = 7.1$, 1H), 7.29−7.36 (m, 2H), 7.71 (dd, $J = 7.2$, 1.8, 1H). $\delta_C$ (100 MHz, $CDCl_3$): 25.2, 32.1, 32.4, 38.4, 45.7, 53.1, 127.9, 128.5, 129.3, 129.7, 136.6, 140.1, 156.6; LRMS (EI): 283.0 ($M^{\bullet+}$). HRMS: calcd for $C_{13}H_{17}NO_2S_2$, 283.0701; found, 283.0703. Anal. Calcd for $C_{13}H_{17}NO_2S_2$: C, 55.09; H, 6.05; N, 4.94; S, 22.63. Found: C, 55.13; H, 5.98; N, 4.83; S, 22.72.

**General Procedure for Synthesis of Ketone 58aa′ *N*-Alkyl-indoles 59−61.** Following the same procedure as that for the synthesis of indoles **64** below, but using thioacetal **51a**, **52a,** or **54a** (1.50 mmol, 5.0 equiv) in benzylidenation of ester **25** (0.279 or 0.305 mequiv reactor$^{-1}$, 1.0 equiv), gave ketones (such as **58aa′**). These were not isolated (with the exception of **58aa′**) but were dissolved in DCM (5 mL), stirred, and cooled to 0 °C under argon. TFA (0.5 mL, 6.50 mmol) was added, the solution was allowed to warm to rt, and stirring was continued for 1−3 h. After this time, the reaction mixture was poured into saturated $NaHCO_3$ and extracted into DCM (2×). The combined organics were then washed with saturated $NaHCO_3$ and then water, dried over $Na_2SO_4$, and concentrated under vacuum to yield an *N*-alkyl indole **59-61**.

**Both Rotamers of 1-[2′-(*N*-Boc-*N*-methylamino)phenyl]-4-phenylbutan-2-one (58aa′).** The above general procedure, using thioacetal **51a** (0.47 g, 1.45 mmol) and resin-bound ester **25a′** (0.305 mequiv), yielded ketone **58aa′** as a black oil (as a 3:2 mixture of rotamers A and B separated on NMR time scale at low temperature (55 mg, 0.16 mmol, 54%)). $\delta_H$ (360 MHz, 233 K, $CDCl_3$) 1.28 (s, $9H^A$), 1.49 (s, $9H^A$), 2.76 (t, $J = 7.2$, $2H^{A+B}$), 2.86 (t, $J = 7.8$, $2H^{A+B}$), 3.02 (s, $3H^B$), 3.05 (s, $3H^A$), 3.52−3.63 (m, $1H^{A+B}$), 3.71−3.81 (m, $1H^{A+B}$), 7.11−7.33 (m, 7H). LRMS (EI): 353.2 ($M^{\bullet+}$), 297.1 ($M^{\bullet+} - C_4H_8$), 253.2 ($M^{\bullet+} - C_5H_8NO_2$). HRMS: calcd for $C_{22}H_{27}NO_3$, 353.1991; found, 353.1987.

***N*-Methyl-2-phenethyl-indole 59aa′.** Using carbamate **51a** (0.42 g, 1.50 mmol) and resin-bound ester **25a′** (0.279 mequiv) in the above reaction sequence gave indole **59aa′** (28 mg, 0.13 mmol, 44% over three steps) as a yellow-brown oil. $R_f$ ($SiO_2$, DCM): 0.64. IR (Solt$^n$, $CDCl_3$): 3055, 1468 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 3.05 (s, 4H), 3.61 (s, 3H), 6.31 (s, 1H), 7.05−7.09 (m, 1H), 7.16 (dt, $J = 1.1$, 7.1, 1H), 7.21−7.32 (m, 6H), 7.53 (d, $J = 7.8$, 1H). $\delta_C$ (100 MHz, $CDCl_3$) 28.9, 29.3, 35.1,

(93) Gleave, D. M.; Brickner, S. J. *J. Org. Chem.* **1996**, *61*, 6470−6474.

98.8, 108.7, 119.3, 119.7, 120.7, 126.2, 128.4, 128.5, 137.4, 138.1 140.5, 141.3. LRMS (EI): 235.1 ($M^{\bullet+}$), 144.1 ($M^{\bullet+} - C_7H_7$). HRMS: calcd for $C_{17}H_{17}N$, 235.1361; found, 235.1359.

***N*-Methyl-2-phenethyl-indole 59aa′.** In a similar way, using fewer equivalents of carbamate **51a** (0.29 g, 0.90 mmol) to resin-bound ester **25a′** (0.305 mequiv) gave indole **59aa′** (31 mg, 0.13 mmol, 45% over three steps, data as above).

**2-[2′-(*N*-Boc-amino)-5′-trimethylsilyloxy-phenyl]-1,3-dithiane (62f).** TMSCl (3.1 mL, 24.0 mmol) was added dropwise to a solution of carbamate **49e** (6.54 g, 20.0 mmol) in dry pyridine (40 mL), and the mixture was stirred under argon for 15 h. After this time, the solvent was removed in vacuo and diethyl ether was added. The resulting precipitate was filtered off, and the ethereal solution was concentrated to leave a white solid. Recrystallization, from propan-2-ol, gave the desired product **62f** as a white powder (6.63 g, 16.6 mmol, 83%). Mp: 116−119 °C. IR (KBr): 3433, 1716, 1509 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 0.25 (s, 9H), 1.53 (s, 9H), 1.91−1.98 (m, 1H), 2.16−2.22 (m, 1H), 2.89−2.95 (m, 2H), 3.06−3.13 (m, 2H), 5.22 (s, 1H), 6.75 (dd, $J$ = 8.8, 2.8, 1H), 6.96 (d, $J$ = 2.7, 1H), 7.52 (s, 1H). $\delta_C$ (90 MHz, $CDCl_3$): 0.2, 25.2, 28.4, 32.0, 47.6, 80.4, 114.8, 115.9, 119.6, 120.4, 125.4, 129.2, 153.8. LRMS (EI): 399.0 ($M^{\bullet+}$), 343.0 ($M^{\bullet+} - C_4H_8$). HRMS: calcd for $C_{18}H_{29}NO_3S_2Si$, requires 399.1358; found, 399.1358.

**2-[2′-(*N*-Boc-*N*-trimethylsilyl-amino)phenyl]-1,3-dithiane (63a).** A solution of LDA (7.2 mL, 14.4 mmol, 2.0 M in THF, ethyl benzene, and heptanes) in THF (22.8 mL) was added dropwise to a solution of carbamate **49a** (3.74 g, 12.0 mmol) and TMSCl (2.0 mL, 14.4 mmol) in THF (70 mL) at −78 °C. The reaction mixture was allowed to warm to rt over 45 min and was allowed to stir for a further 1 h. After this time, the solvent was removed in vacuo, and diethyl ether was added. The resulting precipitate was filtered off, and the ethereal solution was concentrated to leave carbamate **63a** (a mixture of the two geometrical isomers and $^1H$ and $^{13}C$ NMR were carried out at 52 °C to allow rapid equilibration on the NMR time scale) as a white solid (3.95 g, 10.3 mmol, 86%). Mp: 100−103 °C; IR: 1680, 1250 $cm^{-1}$. $\delta_H$ (400 MHz, 52 °C, $CDCl_3$): 0.23 (s, 9H), 1.43 (s, 9H), 1.90−1.99 (m, 1H), 2.11−2.16 (m, 1H), 2.85−3.02 (m, 4H), 5.22 (s, 1H), 6.93 (dd, $J$ = 1.1, 7.0, 1H), 7.18−7.25 (m, 2H), 7.62 (dd, $J$ = 1.9, 7.4, 1H). $\delta_C$ (100 MHz, 52 °C, $CDCl_3$): 0.3, 25.3, 28.1, 32.7, 32.8, 46.9, 80.4, 127.4, 128.5, 129.0, 129.3, 137.2, 138.7, 156.7;. LRMS (EI): 383.2 ($M^{\bullet+}$), 327.1 ($M^{\bullet+} - C_4H_9$), 282.1 ($M^{\bullet+} - C_7H_{18}$). HRMS: calcd for: $C_{18}H_{29}NO_2S_2Si$, requires 383.1409; found, 383.1413. Anal. Calcd for $C_{18}H_{29}NO_2S_2Si$: C, 56.35; H, 7.62; N, 3.65. Found: C, 56.26; H, 7.66; N, 3.44.

**General Procedure for the Solid-Phase Synthesis of *N*-Boc-indoles 64.** Titanocene dichloride (1.51 g, 6.00 mmol, 20.0 equiv), magnesium (0.20 g, 8.2 mmol), and 4 Å molecular sieves (0.60 g) were heated briefly in vacuo and then allowed to cool before THF (6.0 mL) and triethyl phosphite (2.1 mL, 12 mmol) were added under argon. The reaction mixture was then cooled using an ice bath and stirred for 30 min. After stirring for a further 2−2.5 h, a THF (6.0 mL) solution of the thioacetal **63** (1.50 mmol, 5.0 equiv) was added, and the solution was then stirred for 15 min. The reaction mixture was syringed into a flask containing 1 reactor of resin-bound ester **25** (0.279 or 0.305 mequiv, 1.0 equiv), preswollen in THF (3 mL). The mixture was stirred under argon for 15−18 h. After this time, the reactor was removed and then washed with THF (5×), alternately with MeOH and DCM (5×), then MeOH, and finally with diethyl ether. The resin was then dried under vacuum. The reactor was then treated with 1% TFA in DCM (5 mL, 0.65 mmol) and placed on a shaker for 30 min. The DCM solution was removed, and the reactor was washed with DCM (3×). The combined DCM solutions were concentrated in vacuo to give pure *N*-Boc indoles **64**.

***N*-Boc-2-phenethyl-indole 64aa′.** The above general procedure, using thioacetal **63a** (0.58 g, 1.5 mmol) and resin-bound ester **25a′** (0.305 mequiv), yielded indole **64aa′** in excellent purity as a gray oil (0.062 g, 0.195 mmol, 69%). IR (Solt$^n$, $CDCl_3$): 1749, 1454 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 1.68 (s, 9H), 3.00 (t, $J$ = 8.4, 2H), 3.32 (t, $J$ = 8.4, 2H), 6.34 (d, $J$ = 0.6, 1H), 7.16−7.30 (m, 7H), 7.42 (dd, $J$ = 1.0, 7.7, 1H), 8.07 (d, $J$ = 8.3, 1H). $\delta_C$ (100 MHz, $CDCl_3$): 28.3, 31.8, 35.2, 83.8, 107.4, 115.6, 119.8, 122.6, 123.3, 126.0, 128.4, 129.3, 136.5, 141.5, 141.6, 150.6. LRMS (EI): 321.2 ($M^{\bullet+}$), 265.1 ($M^{\bullet+} - C_4H_8$), 220.1 ($M^{\bullet+} - C_5H_9O_2$). HRMS: calcd for $C_{21}H_{23}NO_2$, 321.1729; found, 321.1726.

**Preparation of *N*-Boc-2-phenethyl-indole 64aa′ Using 3 equiv of Thioacetal 63a.** Titanocene dichloride (0.90 g, 3.60 mmol, 12.0 equiv), magnesium (0.10 g, 4.0 mmol), and 4 Å molecular sieves (0.20 g) were heated briefly in vacuo and then allowed to cool before adding THF (5.0 mL) and triethyl phosphite (1.2 mL, 7.2 mmol) under argon. The reaction mixture was cooled using an ice bath and stirred for 30 min. After the mixture was stirred for a further 2.5 h, a THF (4.0 mL) solution of the thioacetal **63a** (0.35 g, 0.90 mmol, 3.0 equiv) was added, and the solution was stirred for 15 min. The reaction mixture was syringed into a flask containing 1 reactor of resin-bound ester **25a′** (0.305 mequiv, 1.0 equiv) preswollen in THF (6 mL). The mixture was stirred under argon for 18 h. Washing and cleavage were performed as before and yielded indole **64aa′** as a gray oil (59 mg, 0.18 mmol, 61% data as above).

**7-Methoxy-2-phenyl-1H-indole 65bd′**. Following the general procedure for the synthesis of *N*-Boc-indoles **64**, using thioacetal **63b** (0.62 g, 1.5 mmol) and resin-bound ester **25d′** (0.279 mequiv), yielded Boc-indole **64bd′**. Boc-indole **64bd′** was immediately dissolved in DCM (2.0 mL) and cooled to 0 °C with stirring, adapting a known Boc-indole deprotection method.[94] TFA acid (0.50 mL, 6.5 mmol) was added, and the mixture was allowed to warm to rt and then was stirred for 1 h. After this time, the reaction mixture was concentrated in vacuo to give indole **65bd′** as a green solid (0.043 g, 0.193 mmol, 69% over three steps). Mp: 82−85 °C. IR (KBr): 3440,-1681 $cm^{-1}$. $\delta_H$ (400 MHz, $CDCl_3$): 3.97 (s 3H), 6.63 (d, J 7.7, 1H), 6.79 (d, J 1.9, 1H), 7.01−7.05 (m, 1H), 7.22−7.33 (m, 2H), 7.39−7.44 (m, 2H) 7.64−7.56 (m, 2H), 8.57 (s, 1H). $\delta_C$ (100 MHz, $CDCl_3$): 55.3, 100.2, 102.2, 113.3, 120.5, 125.1, 127.2, 127.5, 128.9, 130.4, 132.3, 137.5, 145.9. LRMS (EI) 223.1 ($M^{\bullet+}$). HRMS: calcd for $C_{15}H_{13}NO$, 223.0997; found, 223.0998.

**Supporting Information Available:** (a) Experimental and characterization data for compounds **18b−d**, **20f**, **21c**, **21d**, **21g**, **22e**, **22f**, **23a**, **27ab′-27dc′**, **46b−e**, **47b**, **47d**, **49b**, **49d**, **49e**, **52a**, **53a**, **54a**, **59ad′**, **60a′**, **60b′**, **61a′**, **61b′**, **63b−f**, **64ad′**, **64ae′**, **64ba′**, **64ca′**, **64cd′**, **64ce′**, **64ea′**, **64ed′**, **64ee′**, **65ba′**, (b) $^1H$ NMR spectra of all compounds in experimental and supplementary Experimental Section including (i) benzofurans **27**, ketone **31,** and *N*-Boc indoles **64** as released from resin, (ii) indoles **65** after solvent removal, (iii) *N*-alkyl indoles **17** after aqueous workup (with no further purification), and X-ray crystal structure of **48**, and (c) crystallographic information files (CIF). This material is available free of charge via the internet at http://pubs.acs.org.

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