The Conversion of Carbonyl Compounds into Pentadienylamines by a Julia–Kocienski Olefination Procedure

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Dedicated to Professor Sir Jack Baldwin, FRS in celebration of his 70th birthday

Abstract: Julia–Kocienski olefination has been successfully employed to convert carbonyl compounds into the corresponding Boc-protected 1,3-pentadienyl amines in a C_4N homologation process. Good to excellent yields are achieved in THF using MHMDS as base to deprotonate the precursor 1-phenyl-1*H*-tetrazol-5-ylsulfone reagent. The nature of the metallic countercation dramatically affects the stereoselectivity of the newly formed alkene: good levels of 2*E*,4*E*-stereoselectivity are achieved using KHMDS whereas LiHMDS gives a predominance of the 2*E*,4*Z*-dienyl product.

Key words: 1,3-pentadienyl amines, modified Julia olefination, alkenes, 1-phenyl-1*H*-tetrazol-5-yl sulfones

The 5-aminopenta-1,3-dienyl moiety is found in a number of naturally occurring compounds with interesting biological activities (Figure 1). These include the antibiotics griseoviridin (**1**),[1] and virginiamycin M_1 (**2**),[2] the antibiotic aurodox (**3**),[3] and the antitumour, antibiotic oxazolomycin family [e.g., oxazolomycin A (**4**)[4] and neooxazolomycin (**5**)[5]], as well as more recently discovered examples.[6]

For our own synthetic approach to the oxazolomycin family,[7] we required a procedure for the homologation of aldehydes such as **6** into the corresponding penta-1,3-dienyl *N*-Boc amines **7**, as shown in Scheme 1. Initially, we investigated the Horner–Wadsworth–Emmons reagent **8**, developed by Connell and Helquist,[8] and applied to a wide range of aliphatic aromatic, and heteroaromatic carbonyl compounds to afford the desired homologated products with a high *E*,*E*-stereoselectivity in moderate to good yields (47–74%). However, in our hands, applying this

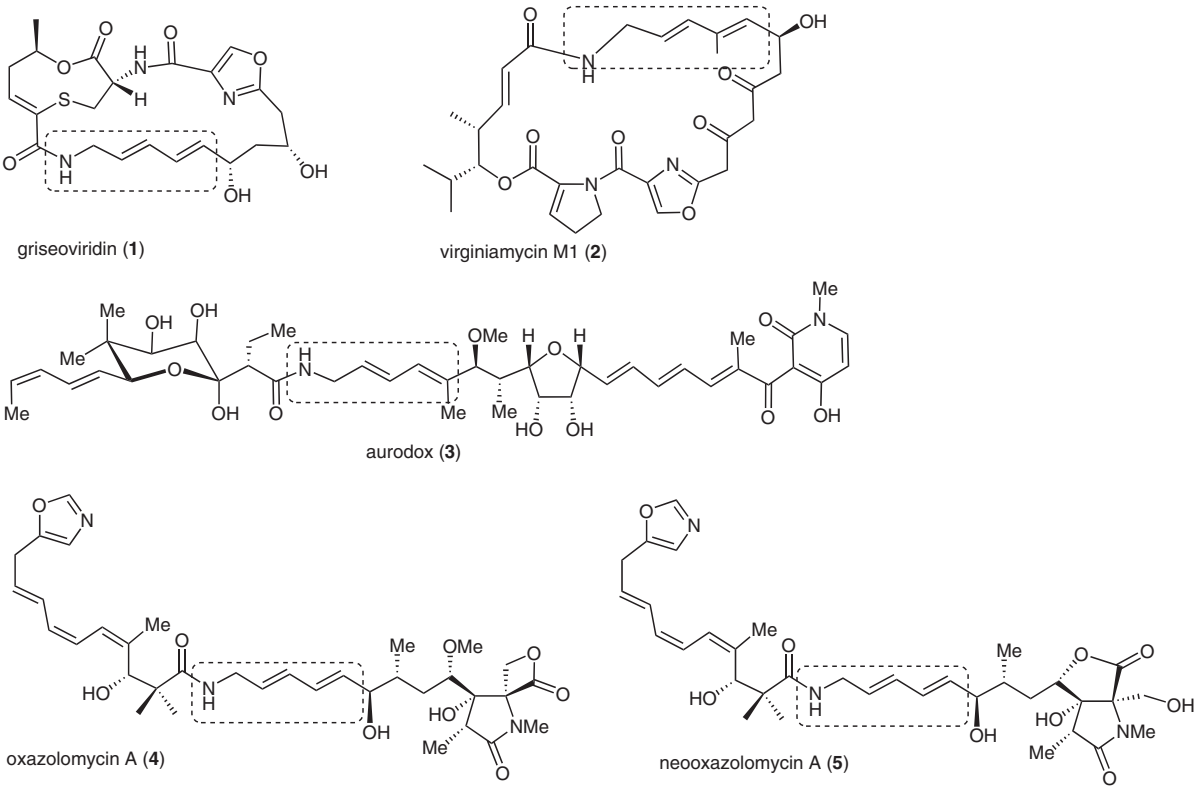

Figure 1 Natural products containing the 5-aminopenta-1,3-dienyl unit

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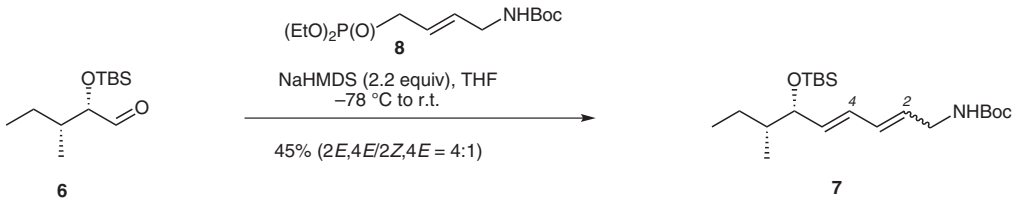
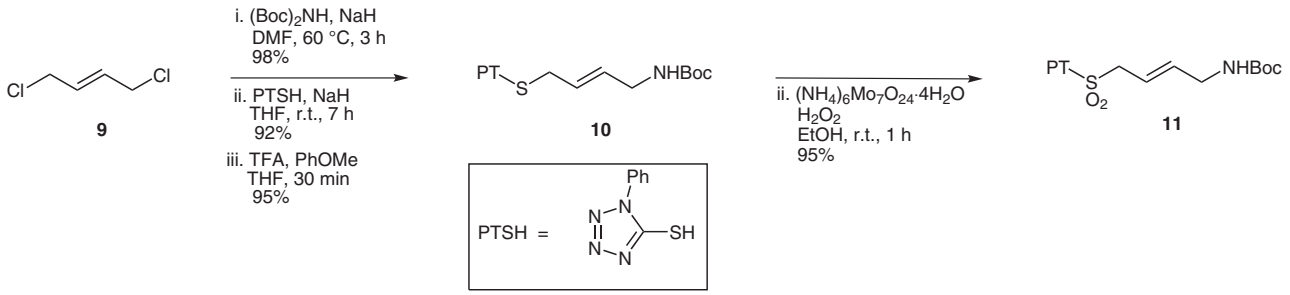


Scheme 1



Scheme 2

methodology to model aldehyde **6** gave a disappointing 45% yield of the pentadienyl amine **7** as a mixture of diene stereoisomers (Scheme 1).

In view of this disappointing result, we decided to investigate the use of the Julia–Kocienski olefination (a type of modified Julia olefination, MJO) for the transformation depicted in Scheme 1. Sylvestre Julia and his group originally reported the one-pot synthesis of alkenes using lithiated 2-benzothiazolyl sulfones (BT-sulfones) and carbonyl compounds in 1991,[9] and since then several groups have expanded the scope of this process and improved its stereoselectivity.[10–12] Solvent effects have proved to be extremely important, and major advances have come from modifying the heterocyclic activating group. The introduction of the 1-phenyl-1*H*-tetrazol-5-yl (PT) group by Kocienski et al. has proved to be particularly valuable given the enhanced stability of the metalated sulfones, the efficiency of the homologation with a range of substrates, and the high stereoselectivities observed.[10]

Herein, we report the preparation of a PT-sulfonyl reagent equivalent to the Helquist reagent **8** and its use for the conversion of carbonyl compounds into 1,3-pentadienyl *N*-Boc amines (and the corresponding deprotected amines); the dramatic effect of the metallic countercation on the stereoselectivity of the Julia–Kocienski reaction is also discussed.

The PT-sulfone **11** required for the Julia–Kocienski reaction, was easily prepared in four steps from commercially available (Fluka) *trans*-1,4-dichlorobut-2-ene (**9**; Scheme 2). Thus, treatment of dichloride **9** with di-*tert*-butyl iminodicarboxylate and NaH in DMF, followed by treatment of the product with commercially available 1-phenyl-1*H*-tetrazol-5-thiol in THF in the presence of sodium hydride, and then removal of one of the Boc protecting groups using TFA produced sulfide **10** in high overall yield with no detectable isomerisation of the double bond. Sulfide oxidation using aqueous hydrogen peroxide in the presence of a catalytic amount of ammonium molybdate tetrahydrate[13] then gave the required sulfone **11** as a crystalline solid in 96% yield,[14] without the complication of allylic rearrangements often encountered in the oxidation of allylic sulfides of this type.[15]

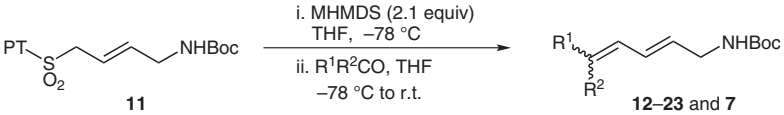
The initial evaluation study involved the treatment of sulfone **11** with sodium hexamethyldisilazide (NaHMDS) and subsequent addition of benzaldehyde (Scheme 3), using the same conditions employed by Connell and Helquist with the corresponding phosphonate reagent **8**. These conditions gave the expected alkenes **12** in 61% yield as a 1:1 mixture of alkene isomers about the newly formed double bond (in contrast to Helquist's procedure,[8] no isomerisation of the pre-existing double bond in *E*-sulfone **11** was observed under these conditions).

We went on to optimise this Julia–Kocienski olefination in terms of solvent, temperature, base, and the order of addition. The use of THF at –78 °C was preferred and it was then established that the choice of base was important (Scheme 3). According to the literature, the *trans* selectivity of the reaction involving PT-sulfones increases with the electropositivity of the countercation of the base (K > Na > Li).[10] The use of KHMDS gave diene **12** in almost quantitative yield although the *E*/*Z* ratio remained 1:1. However, greater *E*,*E*-stereoselectivity was obtained (63:37) when the preformed sulfonyl dianion was added to the benzaldehyde, and this was improved still further (72:28) when an equimolar amount of 18-crown-6 (18-cr-6) was employed.

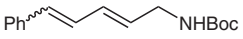
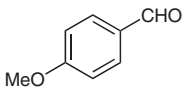
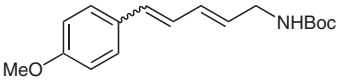
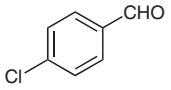
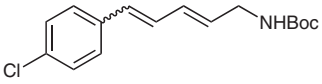
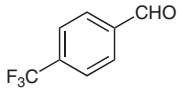
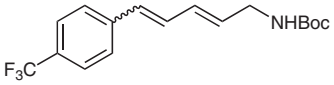
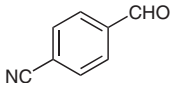
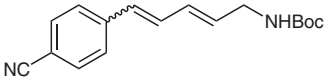
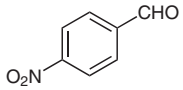
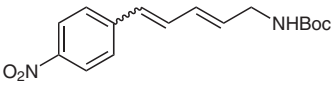
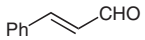
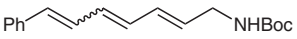
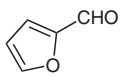
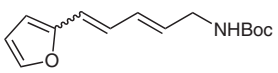
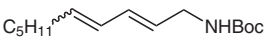
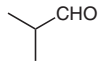
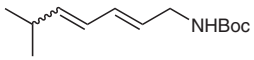
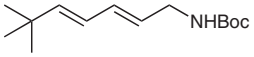
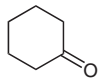
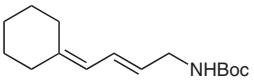
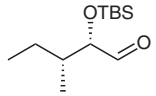
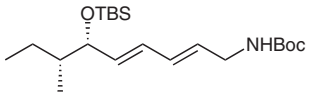
In dramatic contrast, changing to LiHMDS gave the most stereoselective process of all resulting in a predominance of the 2*E*,4*Z*-diene isomer (*E*,*E*/*E*,*Z* = 13:87).[16,17]

We next went on to examine the scope of this process with a range of aromatic, heterocyclic, vinylic, and aliphatic aldehydes (Table 1, entries 1–11).[18] In almost all cases, better yields were observed with LiHMDS compared to

Table 1 Reactions of Sulfone **11** with Aldehydes and Ketones Using KHMDS or LiHMDS

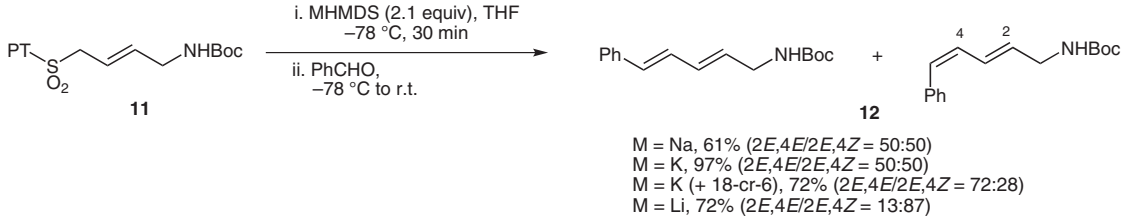


11 **12–23** and **7**

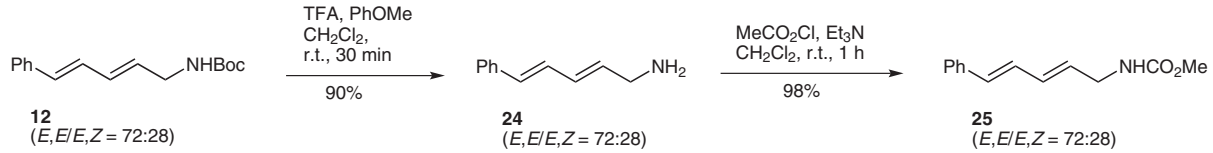
Entry	R^1R^2CO	Product	KHMDS[a,b]		LiHMDS[b]	
			2*E*,4*E*/2*E*,4*Z*	Yield (%)	2*E*,4*E*/2*E*,4*Z*	Yield (%)
1	PhCHO	 **12**	72:28	72	13:87	72
2		 **13**	70:30	75	13:87	91
3		 **14**	77:23	75	23:77	86
4		 **15**	80:20	63	16:84	82
5		 **16**	75:25	86	25:75	95
6		 **17**	80:20	67	65:35	65
7		 **18**	>95:5	59	23:77	88
8		 **19**	84:16	75	34:66	59
9	$C_5H_{11}CHO$	 **20**	71:29	78	29:71	80
10		 **21**	78:22	73	63:37	76
11		 **22**	>95:5	23	>95:5	88
12		 **23**	n/a	76	n/a	94
13[c]	 **6**	 **7**	>95:5[c]	93	–	–

[a] In all reactions using KHMDS, 1.2 equiv of 18-crown-6 was added to the mixture.
[b] Unless stated otherwise, the preformed dianion was added by cannula to the carbonyl compound.
[c] Using NaHMDS with the aldehyde added to the preformed dianion.

KHMDS and, again, KHMDS gave a predominance of the newly formed *E*-alkene whereas LiHMDS generally gave a predominance of the newly formed *Z*-alkene. Three exceptions in terms of LiHMDS stereoselectivity were *p*-nitrobenzaldehyde (entry 6) and hindered, α-branched aliphatic aldehydes (entries 10 and 11) where the newly



Scheme 3



Scheme 4

formed *E*-alkene predominated. In the extreme case of pivaldehyde, only the *E*-isomer could be observed by ^{1}H NMR spectroscopy (entry 11). Cyclohexanone proved a good substrate (entry 12) but, in contrast to phosphonate reagent **8**, other ketones (acetophenone, benzophenone, pinacolone, diethyl ketone) gave little or none of the homologated products. Finally, in Table 1 (entry 13), the original reaction (Scheme 1) was repeated using sulfone **11**; we were delighted to observe that, again using Na-HMDS, the required adduct **7** was now obtained in almost quantitative yield as the *E*,*E*-isomer.

We next demonstrated that the Boc group can be readily removed (Scheme 4). Thus, treatment of *N*-Boc adduct **12** with TFA and anisole in dichloromethane produced the corresponding pentadienylamine **24** in 90% yield. Due to the highly unstable nature of this amine, it was immediately reprotected as the methyl carbamate derivative **25** for characterisation purposes. The *E*,*E*/*E*,*Z* ratio was unaltered during these functional group transformations.

In summary, the easily prepared and crystalline Boc-protected PT-sulfone **11**, when used in the Julia–Kocienski olefination, provides a simple and convenient procedure to convert a wide range of carbonyl compounds directly into their corresponding Boc-protected pentadienyl amines. The transformation proceeds in good to excellent yields with KHMDS giving good levels of *E*-stereoselectivity at the newly formed alkene (i.e., the 2*E*,4*E*-diene) and LiHMDS generally giving a predominance of the newly formed *Z*-alkene (i.e., the 2*E*,4*Z*-diene). We are currently applying this methodology to prepare natural products such as those shown in Figure 1.

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(14) **Preparation of *tert*-Butyl (*E*)-4-(1-Phenyl-1*H*-tetrazol-5-ylsulfonyl)but-2-enyl Carbamate (11)**
To a solution of the sulfide **10** (7 g, 15.6 mmol) and $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ (5.8 g, 4.7 mmol) in MeOH (130 mL) was added 30% aq H_2O_2 (48.3 mL, 468 mmol) at r.t. The solution was stirred for 1 h, and then sat. aq $Na_2S_2O_7$ solution was added to quench the excess of peroxide. After a stirring for 45 min at r.t., the reaction mixture was extracted with EtOAc (3 × 100 mL), dried ($NaSO_4$), and concentrated in vacuo; purification by silica flash column chromatography (PE–EtOAc, 1:1) gave the title sulfone **11** (5.6 g, 95%) as a white solid, mp 86 °C; R_f = 0.56 (PE–EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, *t*-Bu), 3.77 (m, 2 H, CH_2-1), 4.41 (d, *J* = 7.5 Hz, 2 H, CH_2-4), 4.63 (br s, 1 H, NH), 5.29–6.04 (m, 1 H, H-2), 6.00 (dt, *J* = 15.0, 7.5 Hz, 1 H, H-3), 7.57–7.60 (m, 5 H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.7, 42.2, 59.5, 81.5, 114.5, 125.5, 130.0, 131.8, 133.3, 141.1, 153.4, 155.9. IR (neat): ν_{max} = 3356, 2978, 1709, 1502, 1347, 1249, 1155 cm^{-1}. HRMS: *m/z* calcd for $C_{16}H_{21}N_5O_4S$ [MH$^+$]: 380.13925; found (CI): 380.1392 (0.1 ppm error).

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(16) The Julia–Kocienski olefination is normally *trans*-selective due to the kinetically controlled and irreversible addition of metallated PT-sulfones to aldehydes preferentially generating *anti*-β-alkoxysulfones, which then undergo Smile rearrangement.[10,11] In the present study, it would appear that LiHMDS preferentially generates *syn*-β-alkoxysulfones resulting in a predominance of the *E*,*Z*-adducts. The reasons for this unexpected switch are not fully understood at the present time but further studies are in progress to shed light on this interesting observation.

(17) **Preparation of 1-[*N*-(*tert*-Butoxycarbonyl)amino]-5-phenylpenta-2,4-diene (12)**
To as stirred solution of PT-sulfone **11** (45 mg, 0.12 mmol, 1.2 equiv) in THF (1.4 mL) was added LiHMDS (0.26 mL 1.0 M in THF, 0.26 mmol, 2.55 equiv), or KHMDS (0.52 mL, 0.5 M in toluene, 0.26 mmol, 2.55 equiv), at –78 °C. In the KHMDS case, 18-crown-6 (34 mg, 0.13 mmol, 1.2 equiv) was also present at the outset. After 1.5 h at the same temperature, the orange mixture was added to benzaldehyde (10.6 mg, 0.1 mmol, 1.0 equiv) in THF (0.9 mL) at –78 °C via cannula. The mixture was stirred at –78 °C for 1.5 h and then for 1 h at r.t. After quenching with brine (3 mL) and stirring at r.t. for 10 min, the aqueous layer was extracted with EtOAc (3 × 8 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. Purification was performed via flash chromatography on SiO_2 using mixtures of PE and EtOAc as eluent to afford the product alkenes as mixtures of their 2*E*,4*E*/2*E*,4*Z* isomers (ratio was determined by ^{1}H NMR spectroscopy).
Using KHMDS
72% (2*E*,4*E*/2*E*,4*Z* = 72:28); NMR data for major isomer **12*E*,*E*** were comparable to those published.[8]
Using LiHMDS
72% (2*E*,4*E*/2*E*,4*Z* = 13:87) as a pale yellow solid, R_f = 0.71 (PE–EtOAc, 4:1); mp 42 °C. ^{1}H NMR (400 MHz, $CDCl_3$; major isomer): δ = 1.43 (s, 9 H, *t*-Bu), 3.81 (m, 2 H, H-1), 4.58 (br s, 1 H, NH), 5.84 (dt, 1 H, *J* = 15.0, 5.5 Hz, H-2), 6.23 (t, 1 H, *J* = 11.6 Hz, H-4), 6.23 (t, 1 H, *J* = 11.5 Hz, H-4), 6.42 (d, 1 H, *J* = 11.5 Hz, H-5), 6.69 (dddd, *J* = 15.0, 11.5, 2.5, 1.5 Hz, 1 H, H-3), 7.36–7.25 (m, 5 H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$; major isomer): δ = 28.1, 42.2, 81.5, 127.9, 128.5, 128.7, 129.4, 129.6, 130.9, 132.9, 137.6, 156.1. IR (neat): ν_{max} = 3318, 2978, 1677, 1531, 1365, 1275, 1166, 995 cm^{-1}. HRMS: *m/z* calcd for $C_{16}H_{21}NNaO_2$ [MNa]$^+$: 282.1470; found: 282.1465 (3.5 ppm error)].

(18) All novel compounds were fully characterised (sometimes as *E*,*E*/*E*,*Z* mixtures) including confirmation by high-field NMR and HRMS.