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Palladium-Catalyzed Reactions with *N,N'*-diallyloxycarbonylhydrazines

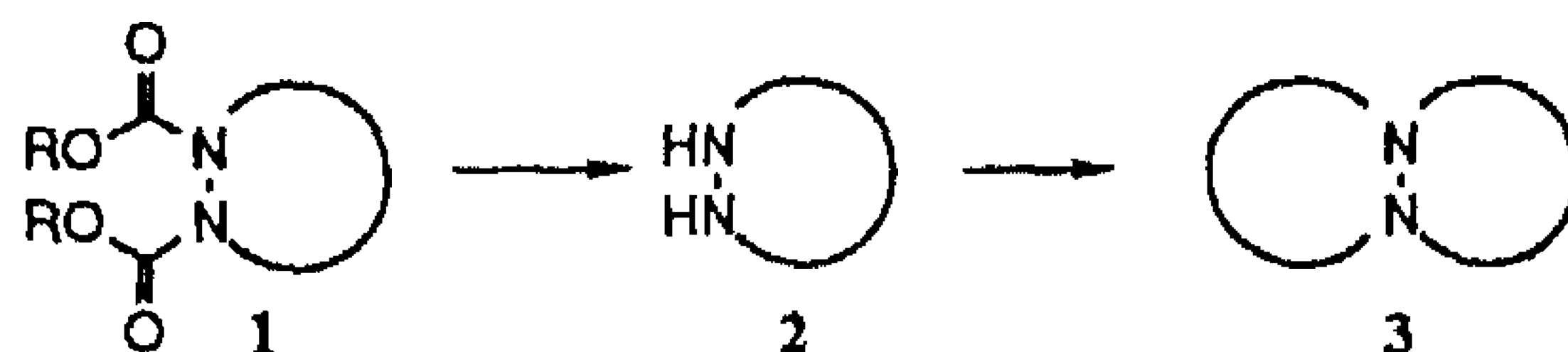
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Key Words: allyloxycarbonyl, palladium(0), tributyltin hydride, hydrazides, hydrazines

Abstract: *N*-allyloxycarbonyl-protected hydrazines react with a Pd(0)-catalyst and tributyltin hydride to a versatile intermediate ditincarbamate which can be converted either into the corresponding deprotected or acylated hydrazines.

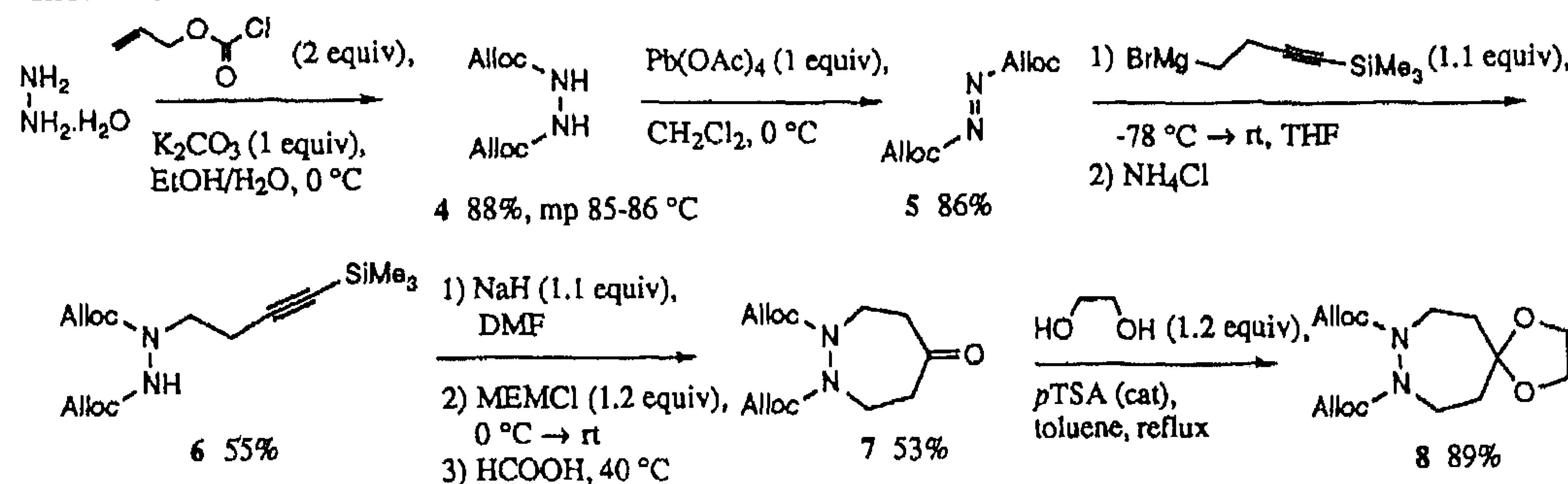
In a previous communication we reported the synthesis of various cyclic hydrazine compounds **1** via an intramolecular *N,N'*-diacylhydrazonium ion cyclization.¹ This work led to products in which both nitrogens are protected with alkyloxycarbonyl groups (R = Me, Et). Deprotection of these residues was not successful upon use of standard conditions (Me₃SiI, CH₃CN; KOH, MeOH), probably due to air-sensitivity of the corresponding free hydrazines.



As we were interested in the isolation of the free hydrazines **2** and subsequent alkylation to the bicyclic hydrazines **3**, we turned our attention to the allyloxycarbonyl (Alloc) group as a protecting group, for this group is well-known to be cleaved under relatively mild conditions using a palladium(0) catalyst in the presence of a nucleophile.^{2,3} In this reaction, the palladium catalyst will react with the Alloc moiety to form a π -allylpalladium complex, which is attacked by the nucleophile to give carbon dioxide and the free amine.

As model systems for these deprotection reactions both ketone **7** and dioxolane **8** were chosen and synthesized as shown in Scheme 1.

Scheme 1

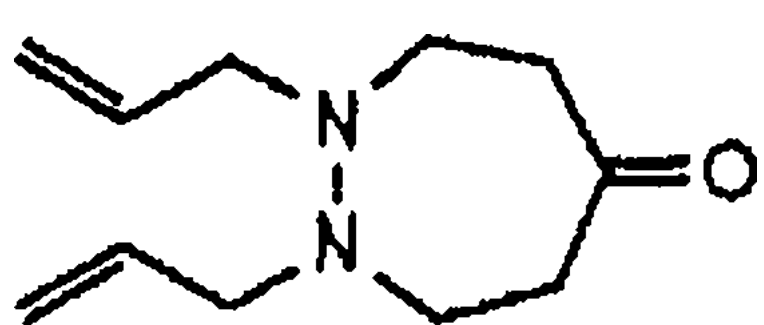
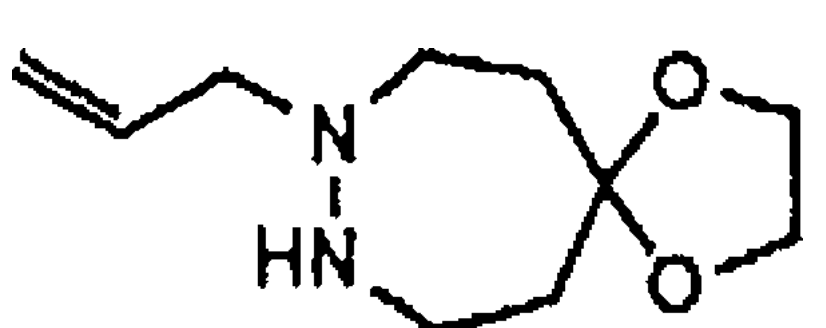
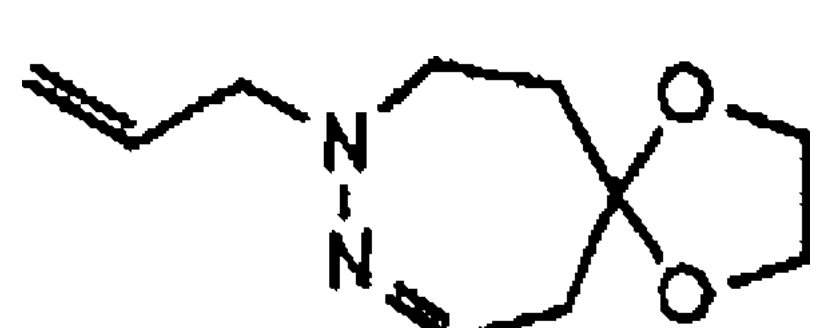
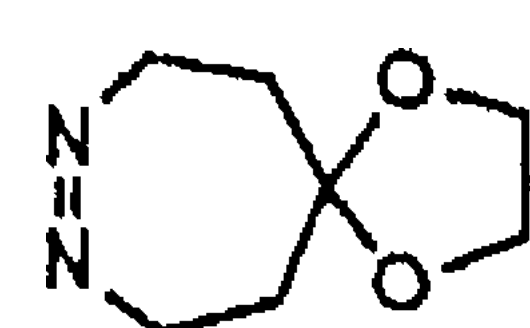


After treatment of hydrazine hydrate with 2 equiv of allyl chloroformate in the presence of a base,⁴ the resulting hydrazo compound **4** was oxidized with Pb(OAc)₄ in cold CH₂Cl₂.⁵ Purification of the azoester **5** was effected by taking up the residue in pentane and filtering off the lead salts. Introduction of the butyne moiety via a

Grignard addition,^{1,6} subsequent alkylation with MEMCl and cyclization in formic acid led to the desired ketone 7. The keto function was protected as a dioxolane by using ethylene glycol in refluxing toluene and *p*TSA (cat).

Deprotection of both 7 and 8 by using standard conditions (10% Pd(PPh₃)₄, 0.6 equiv PPh₃, excess of nucleophile, THF, rt)^{2,3} led to various products⁷ as shown in Table I.

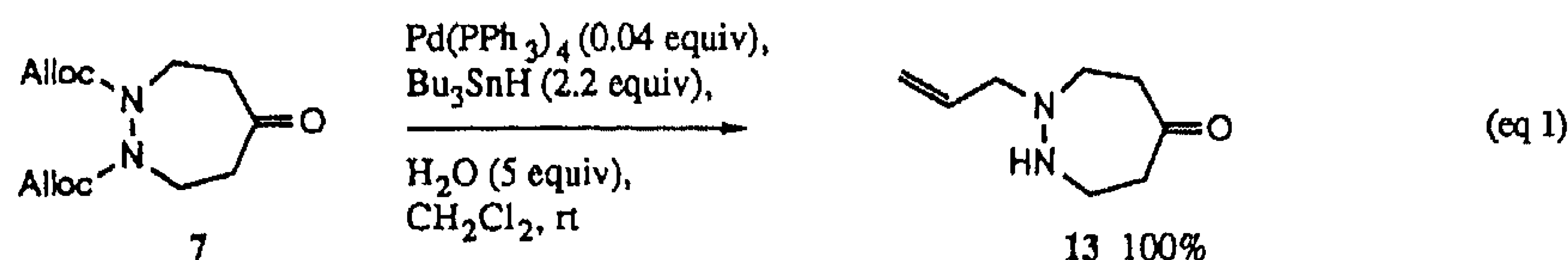
Table I

entry	Alloc compound	nucleophile	solvent	products (yield)
1	7	HCOOH (10 equiv)	THF	 9 (49%)
2	8	<i>n</i> -BuNH ₂ (10 equiv)	THF	 +  10 + 11 (20-55%)  12 (12-50%)
3	8	<i>n</i> -BuNH ₂	<i>n</i> -BuNH ₂	12 (49%)

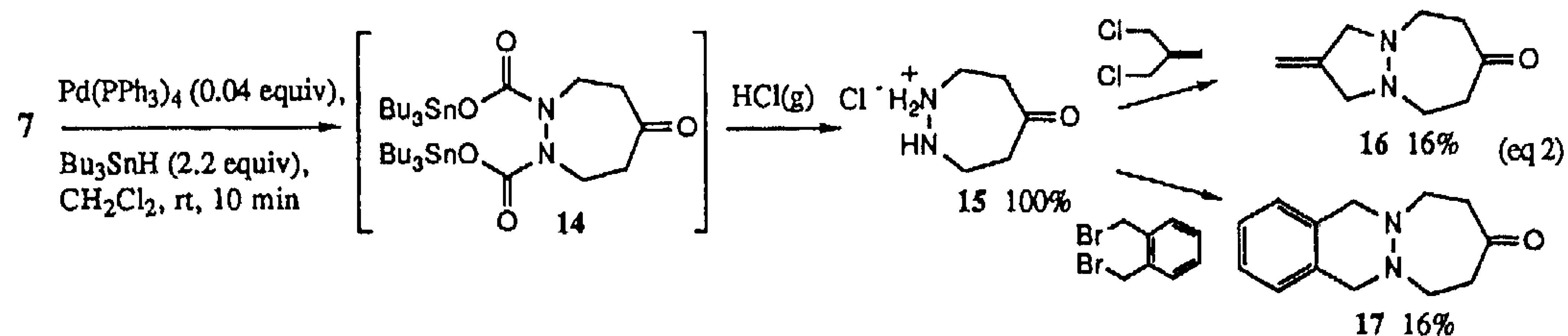
Depending on the nucleophile that was used, either diallylhydrazone 9 was formed (entry 1), or a mixture of allylhydrazone 10, allylhydrazone 11 and azocompound 12⁸ (entry 2). If the reaction and work-up were carried out under an inert atmosphere, oxidation of allylhydrazone 10 to allylhydrazone 11 could be prevented and 10 and 12 were the only isolated products. If the reaction was carried out in pure *n*-BuNH₂ azocompound 12 was the only product that could be detected (entry 3).

The formation of these products can be explained by assuming a very rapid reaction of deprotected hydrazine with the π -allylpalladium complex. Only if a large excess of another nucleophile was used (*n*-BuNH₂ as solvent), formation of allylated products could be avoided, but under these conditions the initial formed free hydrazine is further oxidized to azocompound 12.

In order to prevent *N*-allylation as a side reaction, Guibé and co-workers⁹ used Bu₃SnH, which acts as a very fast hydride-donor. Rapid reaction with the π -allylpalladium complex gives a tributyltin carbamate and propene, which evolves from the reaction mixture. The tin carbamate is cleaved *in situ* with a proton donor (water or acetic acid) that is *already present* in the reaction mixture to give the free amine, carbon dioxide and a tin salt. In our case, use of the exact Guibé conditions led to allylhydrazone 13 in quantitative yield (eq 1). This product can only be explained by assuming a very fast reaction between deprotected hydrazine and π -allylpalladium complex that is still present in the reaction mixture.

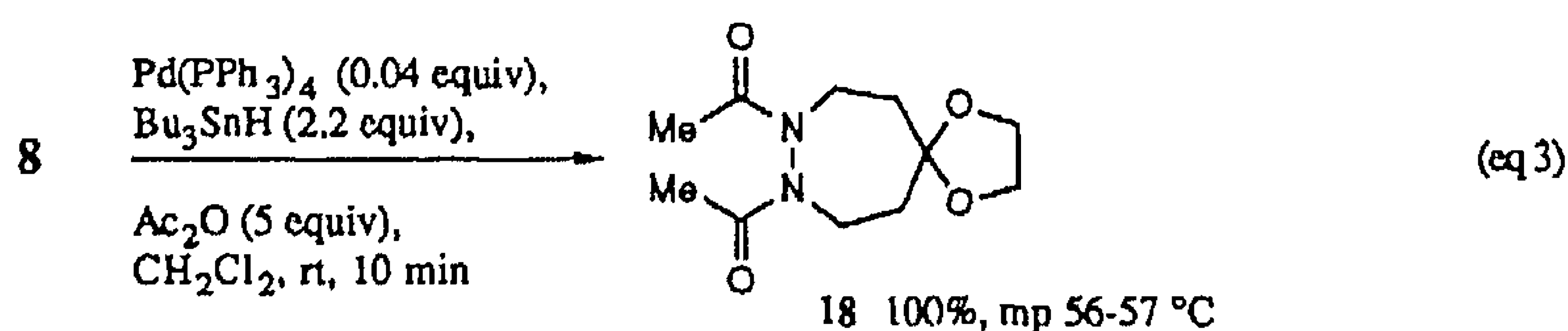


This result made clear that, before cleavage, the π -allylpalladium complex should first be converted completely into the intermediate tin carbamate. Therefore we used a modification of the Guibé method in which the intermediate ditin carbamate was treated with a proton donor *after* complete reaction of Bu₃SnH¹⁰ with the palladium complex.



An example of this modification¹¹ is shown in eq 2 in which dry HCl(g) was used to cleave the ditin carbamate **14** and to protonate the resulting free hydrazine. In this way the oxidation-sensitive hydrazine was precipitated from the reaction mixture as the HCl-salt **15**. This salt could be alkylated with activated dihalides (1.5 equiv, K₂CO₃ (5 equiv), NaI (cat), butanone, rt) to give the corresponding bicyclic hydrazines **16** and **17** in rather low yields.

Remarkably, ditincarbamate **14** proved to be an extremely interesting intermediate for it could not only be cleaved by a simple proton donor, but *also by other electrophilic species* such as activated carbonyl groups to give the corresponding amides or carbamates. Thus, treatment of the intermediate ditin carbamate with an excess of acetic anhydride (eq 3) gave a quantitative yield of diamide **18**.¹²



In contrast with the deprotection reactions, the electrophile was added together with the palladium catalyst and the tributyltin hydride, without formation of *N*-allylated products. Apparently, the tin carbamate shows a much higher reactivity towards the electrophile than to the palladium complex.

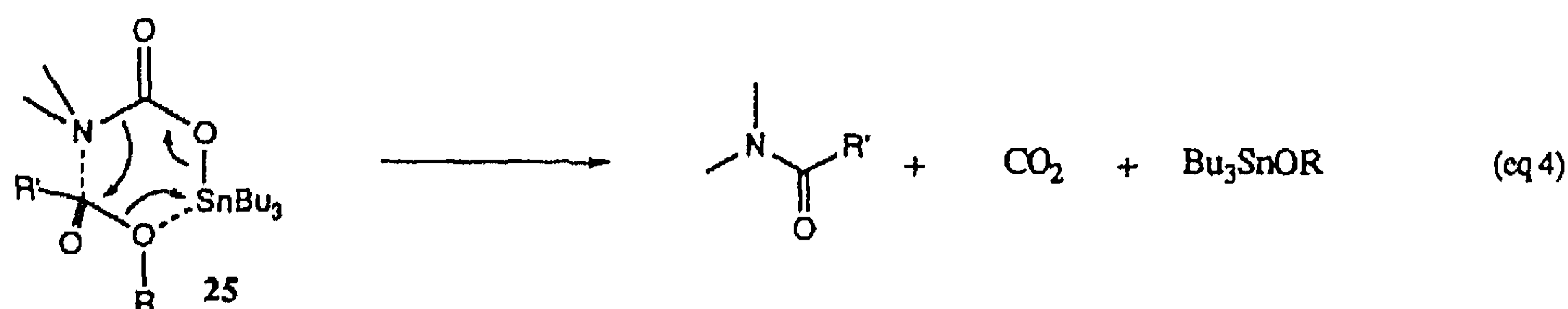
Some more examples of this acylation with activated carbonyl compounds are shown in Table II. Although an excess of the electrophile was used (entries 1 and 2), only the monosubstituted products **21** and **22** were formed, probably due to steric hindrance of the first introduced substituent. In entry 1 the Alloc group is replaced by a BOC group, which might be called a 'transprotection'. The use of activated α -amino esters¹³ such as **19** and **20** (entries 3 and 4) led to hydrazides **23** and **24**.

Table II

entry	precursor	activated carbonyl compound	equiv	product (yield)
1	7		5	 21 (87%)
2	7		2.5	 22 (62%)*
3	7	FMOC-Gly-OPFP 19	1	 23 (74%)
4	7	FMOC-L-Ala-OPFP 20	1	 24 (46%) [α] _D ²⁷ = +6.0 (c=0.5; CHCl ₃)

*After treatment of the crude mixture with HCl/MeOH.

This rapid reaction of tin carbamates with activated carbonyl compounds might be explained by assuming a cyclic transition state **25** (eq 4) in which the nucleophilicity of the nitrogen atom is strongly enhanced by cleavage of the Sn-O bond and concomitant formation of carbon dioxide.



In conclusion, it is stated that Alloc groups are useful protecting groups for hydrazines, for they are easily converted either into the deprotected or transprotected hydrazines. The reaction with the activated α -amino esters offers the promising possibility of peptide bond formation starting from an *N*-Alloc-protected α -amino ester and an activated α -amino ester. The results of this idea are presented in the following paper.¹⁴

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- The quality of the Bu₃SnH proved to be crucial in these reactions. For purification methods see: Klinger, R.J.; Mochida, K.; Kochi, J.K. *J. Am. Chem. Soc.* 1979, 101, 6626.
- Procedure for deprotection reactions. The reaction was carried out in an inert atmosphere of dry nitrogen. To a well-stirred solution of 41 mg (0.15 mmol) of 7 in 2 mL of dry CH₂Cl₂ were added directly after each other 7.5 mg (6 μ mol) of Pd(PPh₃)₄ and 87 μ L (96 mg, 0.33 mmol) of Bu₃SnH. After 10 min dry HCl(g) was bubbled through the gold-yellow solution so that a solid precipitated from the reaction mixture. Removal of the solvent by syringe, washing with dry ether (5 x 3 mL) afforded 24 mg (0.15 mmol, 100%) of 15 as a light yellow solid. Spectral data: IR (KBr): 3400, 2900, 1700, 1430, 1230, 1180, 1090, 740, 690. ¹H NMR (200 MHz, D₂O): 2.92 (t, *J* = 5.4 Hz, 4 H, 2 x CH₂C(O)), 3.49 (t, *J* = 5.4 Hz, 4 H, 2 x CH₂N). ¹³C NMR (50 MHz, D₂O): 43.9 (2 x CH₂C(O)), 45.7 (2 x CH₂N), 215.2 (C(O)).
- Typical procedure for acylation reactions. The reaction was carried out in an inert atmosphere of dry nitrogen. To a well-stirred solution of 355 mg (1.10 mmol) of 8 in 10 mL of dry CH₂Cl₂ were added 519 μ L (561 mg, 5.5 mmol) of acetic anhydride and directly after each other 54 mg (43 μ mol) of Pd(PPh₃)₄ and 641 μ L (705 mg, 2.42 mmol) of Bu₃SnH. After 10 min (the reaction was followed by TLC), the mixture was concentrated *in vacuo* and chromatographed (EtOAc) to yield 294 mg (1.1 mmol, 100%) of 18 (*R*_f 0.40) as a white crystalline solid, that was recrystallized from EtOAc:hexanes 1:1 (mp 56-57 °C). IR (CHCl₃): 3000, 2950, 2880, 1660, 1440, 1395, 1380, 1345, 1240, 1080, 940. ¹H NMR (200 MHz, CDCl₃): 1.68-1.79 (m, 2 H, 2 x CCHH), 1.81-2.05 (m, 2 H, 2 x CCHH), 2.02 (s, 6 H, 2 x CH₃C(O)), 3.03-3.16 (m, 2 H, 2 x NCHH), 3.93 (s, 4 H, 2 x OCH₂), 4.15-4.31 (m, 2 H, 2 x NCHH). ¹³C NMR (50 MHz, CDCl₃): 20.0 (2 x CH₃C(O)), 34.4 (2 x CCH₂), 43.1 (2 x NCH₂), 64.2 (2 x OCH₂), 108.5 (C), 171.8 (2 x C(O)). MS (EI, 70 eV): 242 (M⁺, 7), 200 (100), 157 (43), 99 (41), 43 (42). Accurate mass 242.1272 (Calcd for C₁₁H₁₈N₂O₄ 242.1267).
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