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A Two Catalyst System For Cycloaddition of a Trimethylenemethane Fragment to Aldehydes

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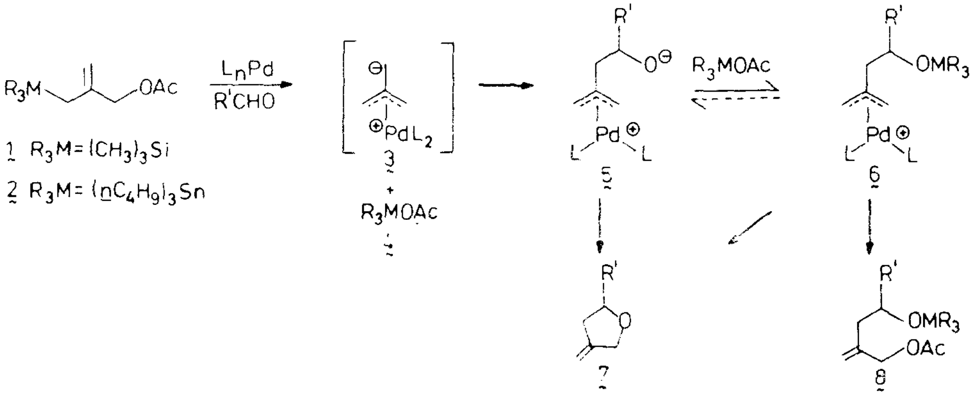
Summary: The cycloaddition of 2-trimethylsilylmethylallyl acetate to aldehydes is co-catalyzed by a Pd(o) complex and a trialkyltin acetate.

The effectiveness of ring formation by a cycloaddition strategy exemplified by the Diels-Alder reaction led us to embark on the development of cycloaddition reactions to rings other than six membered. 2-Trimethylsilylmethylallyl acetate (1) effectively adds to electron deficient olefins to form methylenecyclopentanes[1] but failed to add effectively to carbonyl groups.[2] In contrast to the silicon reagent, 2-trimethylstannyl- or 2-tri-n-butylstannylmethylallyl acetate (2) adds to the carbonyl group of aldehydes rather efficiently. Considering our interpretation invoked the intermediacy of a trimethylenemethane palladium complex devoid of either silicon or tin, the discrepancy between the two conjunctive reagents seemed most peculiar.

A possible explanation for the difference in behavior is outlined in Scheme 1. In contrast to our current thinking with respect to the mechanism of addition

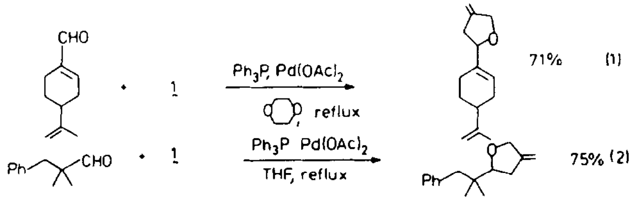
Scheme 1. A Rationale for Cycloaddition to Aldehydes



of these reagents to electron deficient olefins,[4] we envision a two step reaction here. The zwitterion 5, formed upon reaction of the TMM complex 3 with the aldehyde, may be intercepted by the silicon or tin acetate 4, a by-product of the formation of 3, faster than it cyclizes to the methylenetetrahydrofuran 7. In the case of 6 M=Si, reversal back to 5 may be very inefficient and a silyl ether is not sufficiently nucleophilic at oxygen to directly cyclize. Alternative reaction pathways for 6, M=Si, then intervene among which may be capture by acetate. Indeed, products like 8, M=Si, have been isolated.[5]

In contrast, formation of 6, M=Sn, should be more easily reversible. Furthermore, since tin ethers are excellent nucleophiles[6] towards π-allylpalladium complexes, 6, M=Sn, may directly cyclize to 7.

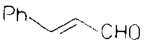
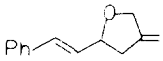
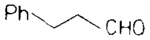
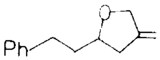
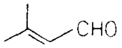
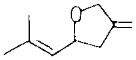
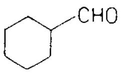
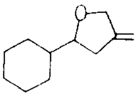
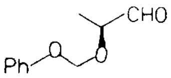
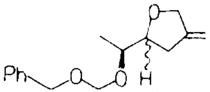
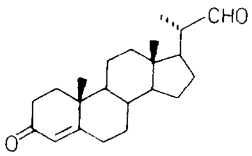
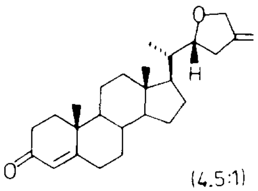
Initially, we tested this hypothesis by performing the cycloaddition of 1 with aldehydes under conditions which either remove trimethylsilyl acetate (e.g. sweeping reaction with nitrogen) or facilitate reversal of the formation of 6 (e.g. by using higher temperatures). These protocols do permit cycloaddition with non-easily enolizeable aldehydes, as exemplified in eq. 1 and 2, but slow addition of the reagent 1 is required, the reaction is less clean than the tin reaction, and the reaction fails with more easily enolizeable aldehydes.



An alternative approach considers that 6 may be formed more irreversibly. If a tin acetate intercepts 5 kinetically faster than a silyl acetate, direct cyclization of 6, M=Sn, may proceed to the desired methylenetetrahydrofuran. Indeed, the addition of as little as 5 mol% of tri-n-butyltin acetate to a reaction of the silicon reagent 1 and an aldehyde has a profound effect on the reaction. Smooth cycloaddition occurs with all the aldehydes tested as illustrated in the Table. Varying the amount of the tin acetate from 5-200 mol% had little effect. Synthetically, we settled on 10-25 mol% for the cleanest reaction with easiest purification of products. Both di-n-butyltin diacetate and di-n-butyltin oxide are effective but offer no advantage over tri-n-butyltin acetate. Surprisingly, tri-n-butyltin chloride and trifluoroacetate apparently kill the catalyst.

Of the examples shown in the Table, all cases failed in the cycloaddition with 1 in the absence of the tin acetate co-catalyst except that of cinnamaldehyde. In this case, the tin co-catalyst increased the yield from 75% to 89% and avoided formation of an oligomeric by-product. It is interesting to note that unsaturated aldehydes only give carbonyl addition and no double bond addition. Ketones do not give

Tabel. **Synthesis of Methylenetetrahydrofurans by Tin and Palladium Co-Catalyzed Cycloadditions**[a]

Entry	Aldehyde	Product[b]	Isolated Yield
1			89%
2			71%
3			80%
4			88%
5		 (2:1)	74%
6		 (4.5:1)	94%

a) A mixture of 5 mol% of palladium acetate, 20 mol% of tri-n-butyltin acetate, and 25 mol% of triphenylphosphine is heated at reflux in THF until a clear yellow solution forms. The aldehyde (1 eq.) and silicon reagent 1 (1.2 eq) are added (concentration 0.5 M) and reflux continued until tlc indicates reaction is complete (15 min. to 5h). Sometimes 0.1 to .2 additional eq. of 1 must be added for completion of reaction. The reaction is diluted with hexane and filtered through a plug of silica gel. Evaporation and chromatography of the residue provides the pure methylenetetrahydrofuran.

b) All compounds have been characterized spectroscopically and elemental composition for new compounds established by high resolution mass spectroscopy.

cycloadducts. Entry 6 demonstrates the chemoselectivity that results. This example also demonstrates that reasonable diastereoselectivity is possible. It is surprising that as little as 5 mol% of tri-n-butyltin acetate suffices. Since eventually a full equivalent of trimethylsilyl acetate must be formed, capture of the alkoxide 5 by the tin acetate must be at least about 200 times faster than with the silyl acetate to account for this dramatic effect.

Previous attempts to catalyze the TMM-Pd reactions with Lewis acids have failed. The success herein demonstrates the feasibility of using co-catalysts provided that they don't destroy the palladium catalyst. The subtlety of this latter possibility is illustrated by the failure of the chloride or trifluoroacetate tin derivatives compared to the acetate. This new success greatly expands the versatility of the silicon reagent in synthesis. The silicon reagent, a very readily available building block, now can be used directly for additions to electron deficient olefins, aldehydes, and imines.[7] The silicon reagent is somewhat more convenient with which to work--in terms of its preparation, ease of work-up of cycloaddition reactions, and cost--compared to the tin reagent. Thus, the cycloaddition approach to methylenetetrahydrofurans now becomes even more practical.

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References

1. For a review see Trost, B.M. *Angew. Chem. Internat. Ed. Engl.* **1986**, 25, 1. For a review of an alternative approach see Binger, P.; Buch, H.M. *Topics Curr. Chem.* **1986**, 135, 0000.

2. Trost, B.M.; Bonk, P.J. *J. Am. Chem. Soc* **1985**, 107, 1778.

3. Trost, B.M.; Bonk, P.J. *J. Am. Chem. Soc.* **1985**, 107, 1985.

4. Trost, B.M.; Mignani, S.M. *Tetrahedron Lett.* **1986**, 27, 4137.

5. Trost, B.M.; Chan, D.M.T. *J. Am. Chem. Soc.* **1983**, 105, 2315, 2326

6. Keinan, E.; Sahai, M.; Roth, Z.; Nudelman, A.; Herzig, J. *J. Org. Chem.* **1985**, 50, 3558. Effectiveness of tin alkoxides in cyclization reactions have been observed in these laboratories, Tenaglia, A. unpublished observations.

7. Jones, M.D.; Kemmitt, R.D.W. *J. Chem. Soc. Chem. Commun.* **1986**, 1201.

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