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IN(+3) AS A CHEMOSELECTIVITY SWITCH FOR TMM-PDL$_2$ CYCLOADDITIONS TO YNONES

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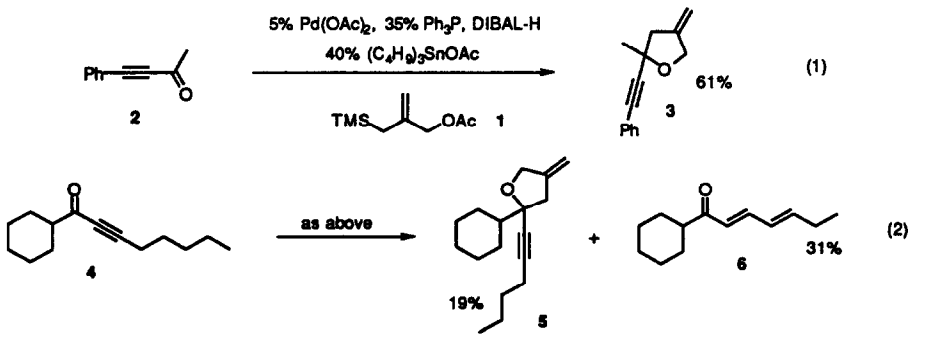
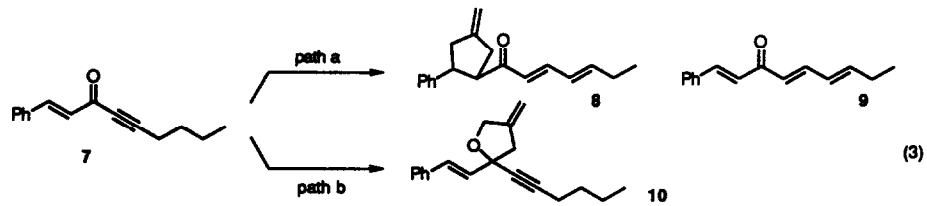
Summary: The previous inability to effect palladium catalyzed cycloadditions of 2-trimethylsilylmethallyl acetate to the carbonyl group of ynones is rectified by the employment of indium acetylacetonoate as a co-catalyst.

The presence of a tetrahydrofuran sub-unit in so many interesting natural products[1] makes their accessibility a continuing challenge. Among the most efficient methods for the synthesis of cyclic compounds are cycloadditions wherein more than one bond is formed in a single reaction.[2,3] In defining the reactivity of the palladium complex of trimethylenemethane as a reactive intermediate,[4] we have explored its reactivity with heteroatom unsaturation - C=O and C=N. Initial studies revealed insufficient reactivity under the standard conditions wherein the carbonyl or simple imine partner was exposed to 2-trimethylsilylmethallyl acetate (**1**) in the presence of a catalytic amount of a Pd(0) complex which led to two step protocols of Lewis acid mediated additions of the corresponding allylstannane followed by Pd(0) catalyzed cyclization to give both tetrahydrofurans and pyrrolidines.[5] Using imines bearing electron withdrawing groups on either the carbon or nitrogen as substrates permits direct cycloaddition of **1** with simple palladium catalysis.[6] In contrast to imines, subsequent studies reveal direct cycloaddition of **1** to carbonyl partners does occur[7] but that use of trimethyltin acetate as a co-catalyst improves the reaction.[8] Because recent work suggests that indium (+3) may be a more effective co-catalyst,[9] we re-examined a class of carbonyl partners, the ynones, whose cycloadditions proved problematical. Whereas the ynone **2** gives a good yield of cycloadduct **3**[10] under our normal conditions in the presence of tri-n-butyltin acetate as a co-catalyst, the ynone **4** undergoes preferential isomerization to the dienone **6** -- a reaction that subsequently could be optimized to provide dienones.[11]

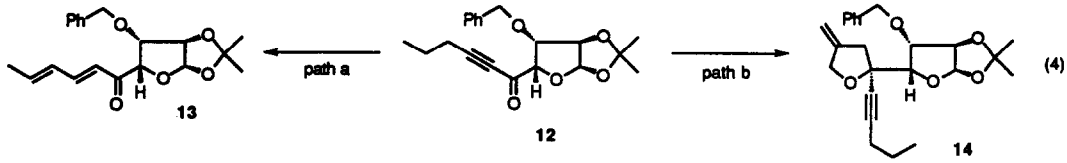


The reaction of ynone **7** proved particularly interesting (eq. 3). Cycloaddition with 2-trimethylsilylmethallyl pivalate in the presence of a Pd(0) complex prepared from 5% $Pd(OAc)_2$, 35% $(nC_4H_9)_3P$, DIBAL-H in toluene at 100° gave a 25% yield of the dienone **9** and a 38% yield of a cycloadduct **8** derived therefrom by addition to the enone. The dienone **9** can be isolated in 83% yield by heating the ynone **7**



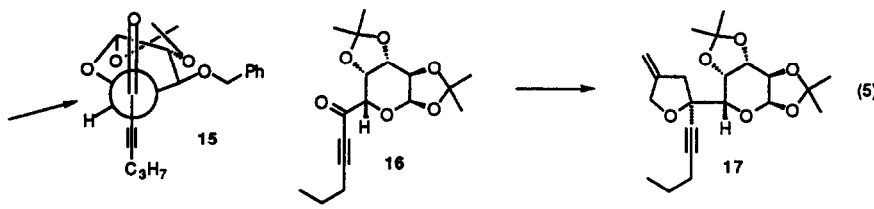
with 5% $Pd(OAc)_2$ and 17% dppp in toluene at reflux. On the other hand, adding a toluene solution of the Pd(0) catalyst prepared from 5% $Pd(OAc)_2$, 40% Ph_3P, and 12% DIBAL-H to a mixture of the ynone **7** and 10% indium acetylacetonoate (**11**) in toluene at room temperature produces a red mixture. Immersing the latter in a 65° oil bath and subsequently raising the temperature to 100° gave a 78% yield of the carbonyl adduct **10**.[10] Neither ynone isomerization (to **9**) nor C=C cycloaddition occurs in the presence of only 10% indium salt **11**.

The glucose derived substrate **12** shows identical behavior. The above catalyst (eq. 4, path a) in the absence of the indium salt **11** generates dienone **13**.[10] On the other hand, the same catalyst in the presence of

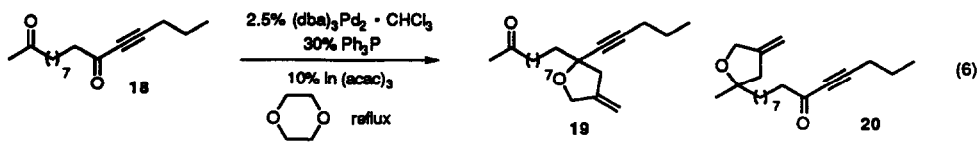


10% **11** produces the methylenetetrahydrofuran **14** accompanied by some olefin migrated cycloisomer in 85% yield. Employing 2.5% $(dba)_3Pd_2{\cdot}CHCl_3$, 30% triphenylphosphine and 10% **11** in dioxane at reflux gave an 85% yield of **14**[10] as a >95:5 ratio of diastereomers with no products derived from olefin migration. The stereochemistry is assigned based upon the Felkin-Anh model as depicted in **15** analogous to the one used to rationalize additions to the corresponding aldehyde.[7,8]

Using the same conditions as optimized for the formation of **14** (eq. 5), the mannitol derivative **16** generated the cycloadduct **17**[10] in 75% yield also as a >95:5 ratio of diastereomers. A Felkin-Anh model analogous to **15** leads to the assignment of stereochemistry as depicted.



The relative reactivity of an alkynone versus a simple ketone was explored with dione **18**. A single 1:1 cycloadduct was obtained in 72% yield (eq. 6) under the same conditions employed above (eqs. 4 and 5). A

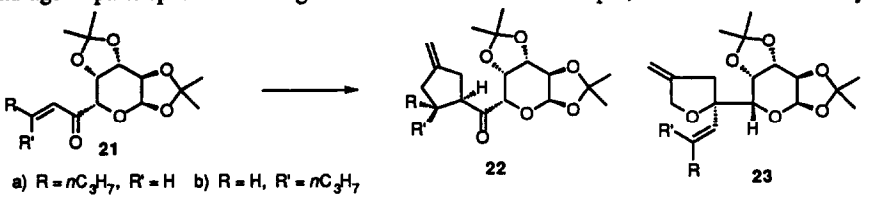


similar result was obtained using the catalyst derived from $Pd(OAc)_2$ as in eq. 3, path b. That the product was

exclusively methylenetetrahydrofuran **19**[10] and not **20** derives from interpretation of the spectral data. Infrared spectroscopy reveals the disappearance of the conjugated carbonyl group (**18**, 1662 cm^{-1}) and retention of the saturated carbonyl group (**19**, 1712 cm^{-1}). Nmr spectroscopy indicates retention of the methyl ketone (δ 2.14, 3H, s). In spite of the facts that the acetylenic ketone may be thought to be more hindered being internal in the aliphatic chain compared to the methyl ketone and that unsaturated carbonyl partners are normally less reactive than saturated carbonyl compounds towards nucleophilic addition, the carbonyl group of the ynone is the more reactive one!

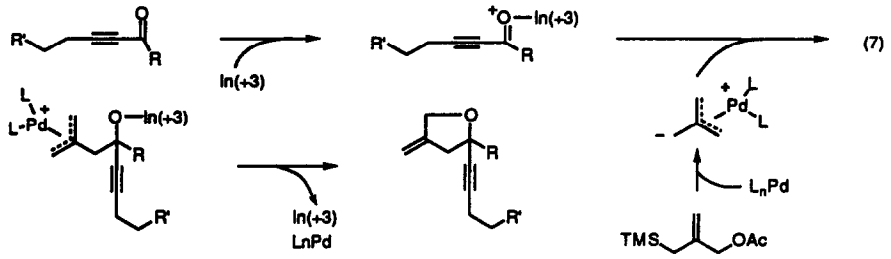
For these reactions, the choice of palladium catalyst may be important. Our most general palladium catalyst for TMM cycloadditions, palladium acetate with triisopropyl phosphite,[12] serves satisfactorily in the cycloadditions with **12** (79% yield of **14**) and **16** (78% yield of **17**) only in the presence of triphenylphosphine as ligand. The acceptor properties of triisopropyl phosphite as a ligand apparently diminishes the nucleophilic properties of the TMM-PdL_2 intermediate to make it unreactive towards a carbonyl group. Thus, in this case, triisopropyl phosphite simply serves as a mild reductant for palladium (+2). Surprisingly, this catalyst system fails to effect cycloaddition to **18**. Reducing palladium acetate with DIBAL-H to generate Pd(0) also suffices in all cases but can lead to migration of the exocyclic methylene group. For this reason, starting with a pre-reduced palladium (0) complex like $(dba)_3Pd_2{\cdot}CHCl_3$[13] is preferable. Given that the cycloaddition seems to require a more donor type of ligand, tri-o-anisylphosphine was explored with unsatisfactory results.

The dramatic effect of $In(acac)_3$ on the chemoselectivity that permits ynones to be partners considerably broadens the scope of this cycloaddition approach to methylenetetrahydrofurans. The versatility of the acetylenic linkage imparts special advantages to this method. For example, the enone **21a** mainly undergoes



double bond addition to give **22a** even in the presence of indium (+3) as a co-catalyst. The corresponding *Z* isomer **21b** suffers olefin isomerization faster than cycloaddition. Thus, direct cycloadditions to the enones **21a** or **21b** do not provide the tetrahydrofurans **23a** or **23b**. The ability to reduce acetylenes to either *E or Z* olefins provides an excellent strategy for the synthesis of either **23a** or **b** via cycloadduct **17** (eq. 5).

The rationale for the "indium effect" appears to derive from its affinity to coordinate with oxygen of the ynone thereby enhancing the electrophilicity of the carbonyl group as well as by modulating the nucleophilicity of an oxygen anion to improve its reactivity towards a π-allylpalladium intermediate. These cycloadditions involve two steps -- nucleophilic addition of the TMM-PdL_2 complex to the carbonyl group to give a zwitterion followed by collapse to product (eq. 7).[7,8,14] The remarkable chemoselectivity of the dione **18** in which the unsaturated carbonyl group is the more reactive one at first appears to be contrary to this rationale since coordination affinity of the ynone oxygen appears to be lower than that of a saturated carbonyl oxygen.[15] An explanation may lie in the low steric demands and the higher electronegativity[16] of an acetylene which may synergize to reverse the normal trend of a conjugated carbonyl group being less reactive than a non-conjugated one. The generality of this observation with respect to the addition of other nucleophiles remains to be established.



These results strongly promote the exploration of In(+3) as a catalyst to promote additions to a carbonyl group. Recent work on the use of stoichiometric organoindium compounds for carbonyl additions,[17] the catalytic effect of indium chloride on the aldol reaction,[18] and other novel indium mediated reactions,[19,20] reinforce this conclusion.

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