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Palladium-Catalyzed [3 + 3] Cycloaddition of Trimethylenemethane with Azomethine Imines

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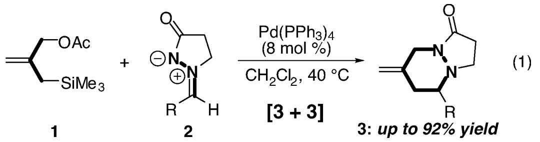
Intermolecular cycloaddition reactions are powerful methods for the convergent construction of cyclic materials from relatively simple organic fragments, and achieving such transformations by the use of transition-metal catalysts is highly desirable in view of efficiency of the process and mildness of the reaction conditions. For the construction of six-membered cyclic compounds, [4 + 2] cycloadditions (e.g., the Diels−Alder reactions) are most widely used in the literature.[1] An alternative approach is the use of [2 + 2 + 2] cycloaddition reactions as often used in the preparation of aromatic ring systems.[2] Although a [3 + 3] cycloaddition strategy is another legitimate approach toward the formation of six-membered rings, it has been much less studied[3] and only a few examples of transition-metal-catalyzed [3 + 3] cycloadditions have been reported to date.[4,5] Here we describe the development of a new palladium-catalyzed [3 + 3] cycloaddition of trimethylenemethane (TMM) with azomethine imines to produce highly functionalized hexahydropyridazine derivatives under simple and mild conditions (eq 1).

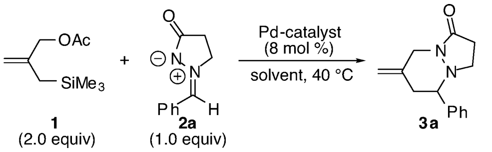


In 1979, Trost reported the use of Pd−TMM complexes in the context of [3 + 2] cycloaddition reactions.[6] Since then, he has made a significant contribution to the development of this attractive chemistry, showing the high utility of Pd−TMM complexes as a source of a three-carbon unit in a cyclic framework.[7,8] On the other hand, their use in [3 + 3] cycloadditions is very limited. To the best of our knowledge, they have only been used in the couplings with aziridines to furnish piperidine derivatives so far.[5]

1-Alkylidene-3-oxopyrazolidin-1-ium-2-ides (e.g., **2** in eq 1), developed by Dorn and Otto in 1968,[9] are isolable and stable azomethine imines and have been used as 1,3-dipoles in the context of [3 + 2] cycloadditions, giving five-membered nitrogen-containing heterocycles.[10,11] Unfortunately, however, these useful 1,3-dipoles have never been engaged in a single-step formation of six-membered rings to date.[12]

Initially, we examined the reaction of (2-(acetoxymethyl)-2-propenyl)trimethylsilane (**1**) with azomethine imine **2a** in the presence of a catalytic amount of $Pd(PPh_3)_4$ at 40 °C (Table 1) and found that the choice of solvent has a significant impact on the reaction progress. Thus, desired [3 + 3] cycloadduct **3a** was obtained in high yield by the use of dichloromethane (82% yield; entry 5) in contrast to any other solvents we employed (entries 1−4). We also found that the use of $Pd(OAc)_2/PPh_3$ or $CpPd(\eta^3\text{-}C_3H_5)/PPh_3$ as a catalyst in dichloromethane produced cycloadduct **3a** in comparably high yield (77−82% yield; entries 6 and 7).

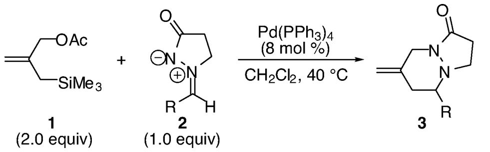
Table 1. [3 + 3] Cycloaddition of (2-(Acetoxymethyl)-2-propenyl)trimethylsilane (**1**) with Azomethine Imine **2a**



entry	Pd catalyst	solvent	yield (%)[a]
1	$Pd(PPh_3)_4$	toluene	<2
2	$Pd(PPh_3)_4$	MeOH	<2
3	$Pd(PPh_3)_4$	THF	14
4	$Pd(PPh_3)_4$	$ClCH_2CH_2Cl$	57
5	**$Pd(PPh_3)_4$**	**CH_2Cl_2**	**82 (81)**[b]
6	$Pd(OAc)_2/4\ PPh_3$	CH_2Cl_2	82
7	$CpPd(\eta^3\text{-}C_3H_5)/4\ PPh_3$	CH_2Cl_2	77

[a] Determined by ^1H NMR against an internal standard ($MeNO_2$). [b] Isolated yield in parentheses.

Table 2. Palladium-Catalyzed [3 + 3] Cycloaddition: Scope of Azomethine Imines



entry	R	product	yield (%)[a]
1	Ph (**2a**)	**3a**	81
2	4-MeC_6H_4 (**2b**)	**3b**	74
3	4-$CF_3C_6H_4$ (**2c**)	**3c**	92
4	3-ClC_6H_4 (**2d**)	**3d**	90
5	2-FC_6H_4 (**2e**)	**3e**	88
6	2-MeC_6H_4 (**2f**)	**3f**	70
7	3-pyridyl (**2g**)	**3g**	75
8	1-cyclohexenyl (**2h**)	**3h**	71
9	*t*-Bu (**2i**)	**3i**	20

[a] Isolated yield.

We have subsequently determined that the scope of the azomethine imine is fairly broad. Thus, with respect to the substituent on the alkylidene portion, a variety of aryl groups (Table 2, entries 1−6) as well as heteroaryl and alkenyl groups (entries 7 and 8) can be tolerated, furnishing [3 + 3] cycloadducts in high yield (70−92% yield). Unfortunately, substrates with an alkyl substituent are less effective for this [3 + 3] cycloaddition (entry 9).

Azomethine imines bearing substituents on the pyrazolidinone ring can also be used in the present [3 + 3] cycloaddition reaction with high efficiency. For example, 4,4-dimethyl-substituted dipole **2j** provides corresponding cycloadduct **3j** in 94% yield (eq 2). In addition, 5-methyl-substituted dipole **2k** is converted to the six-membered heterocycle **3k** not only in high yield (87%) but also with high diastereoselectivity (dr = 96/4; eq 3). The relative configuration of the major diastereomer was determined by X-ray crystallographic analysis, as shown in Figure 1.

We have also examined the reactions using substituted TMM precursors in combination with azomethine imine **2a**. Thus,

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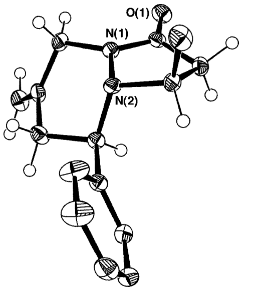
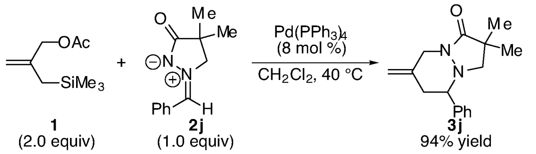
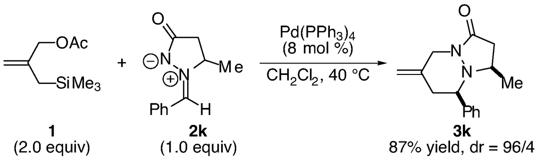


Figure 1. ORTEP illustration of **3k** with thermal ellipsoids drawn at the 50% probability level (hydrogen atoms on the methyl and phenyl groups are omitted for clarity).

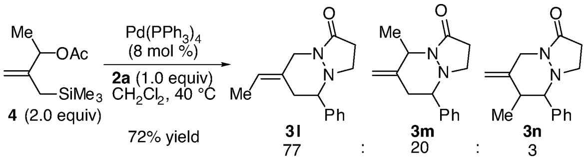


(2)

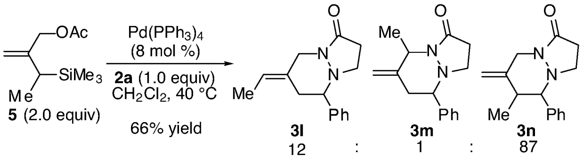


(3)

compound **4** mainly furnished two different products, **3l** and **3m**, along with a minute amount of product **3n** (**3l**/**3m**/**3n** = 77/20/3; eq 4). In contrast, the use of structural isomer **5** generated **3n** as the major product with a small amount of **3l** (**3l**/**3m**/**3n** = 12/1/87; eq 5). These results show that the substitution pattern of the TMM precursor is reflected in the product distribution in the present [3 + 3] cycloaddition with azomethine imine **2a**, indicating that the cycloaddition occurs without significant equilibration between intermediates **6** and **7** (Scheme 1). This observation strikingly contrasts to the palladium-catalyzed [3 + 2] cycloadditions of **4** or **5** with electron-deficient olefins described by Trost, which preferentially afford five-membered cyclic compounds derived from intermediate **7** regardless of the starting TMM precursor (**4** or **5**) due to the fast equilibration between **6** and **7** prior to the cycloaddition.[13]

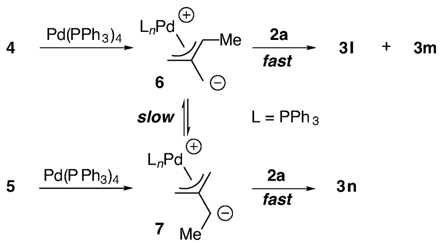


(4)

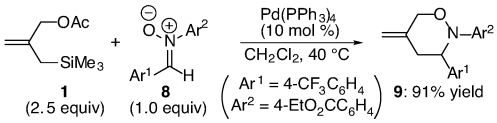


(5)

Scheme 1



These [3 + 3] cycloaddition reactions can be extended to the couplings with nitrones, as well. For example, a reaction of nitrone **8** with TMM precursor **1** provides corresponding cycloadduct **9** in 91% yield (eq 6).



(6)

In summary, we have developed a palladium-catalyzed [3 + 3] cycloaddition of trimethylenemethane with azomethine imines to produce hexahydropyridazine derivatives under mild conditions. The use of substituted TMM precursors highlights the difference of this system from previously reported [3 + 2] cycloaddition of TMMs under palladium catalysis. We have also described that the present [3 + 3] cycloadditions are applicable to couplings with nitrones.

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Supporting Information Available: Experimental procedures and compound characterization data (PDF) and X-ray data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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