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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 sixmembered rings, it has been much less studied³ 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 sixmembered rings to date.¹²

Initially, we examined the reaction of (2-(acetoxymethyl)-2propenyl)trimethylsilane (1) with azomethine imine **2a** in the presence of a catalytic amount of Pd(PPh₃)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/PPh₃ or CpPd(η^3 -C₃H₅)/ PPh₃ as a catalyst in dichloromethane produced cycloadduct **3a** in comparably high yield (77–82% yield; entries 6 and 7).

We have subsequently determined that the scope of the azomethine imine is fairly broad. Thus, with respect to the substituent on *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 ₂ CH ₂ Cl	57
5	Pd(PPh ₃) ₄	CH ₂ Cl ₂	82 (81) ^b
6	Pd(OAc) ₂ /4 PPh ₃	CH_2Cl_2	82
7	$CpPd(\eta^3-C_3H_5)/4 PPh_3$	CH_2Cl_2	77

^{*a*} Determined by ¹H NMR against an internal standard (MeNO₂). ^{*b*} Isolated yield in parentheses.

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



entry	R	product	yield (%) ^a
1	Ph (2a)	3 a	81
2	$4 - MeC_6H_4(2b)$	3b	74
3	$4-CF_{3}C_{6}H_{4}(2c)$	3c	92
4	$3-ClC_{6}H_{4}(2d)$	3d	90
5	$2-FC_{6}H_{4}(2e)$	3e	88
6	$2-MeC_{6}H_{4}(2f)$	3f	70
7	3-pyridyl (2g)	3g	75
8	1-cyclohexenyl (2h)	3h	71
9	<i>t</i> -Bu (2i)	3i	20

^a Isolated yield.

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 sixmembered 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,



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



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



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).



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.

References

- (a) Dennis, N. Org. React. Mech. 2004, 499. (b) Fringuelli, F.; Taticchi, A. The Diels-Alder Reaction: Selected Practical Methods; John Wiley & Sons: Chichester, U.K., 2002. (c) Frühauf, H.-W. Chem. Rev. 1997, 97, 523. (d) Lautens, M.; Klute, W.; Tam, W. Chem. Rev. 1996, 96, 49.
- (2) (a) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* 2005, 4741.
 (b) Varela, J. A.; Saá, C. *Chem. Rev.* 2003, 103, 3787. (c) Saito, S.; Yamamoto, Y. *Chem. Rev.* 2000, 100, 2901.
- (3) For reviews on formal [3 + 3] cycloadditions, see: (a) Hsung, R. P.; Wei, L.-L.; Sklenicka, H. M.; Shen, H. C.; McLaughlin, M. J.; Zehnder, L. R. *Trends Heterocycl. Chem.* 2001, 7, 1. (b) Harrity, J. P. A.; Provoost, O. Org. Biomol. Chem. 2005, 3, 1349. See also: (c) van der Louw, J.; van der Baan, J. L.; Out, G. J. J.; de Kanter, F. J. J.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron* 1992, 48, 9901. (d) Ganton, M. D.; Kerr, M. A. J. Org. Chem. 2004, 69, 8554.
- (4) (a) Huang, Y.; Lu, X. Tetrahedron Lett. 1987, 28, 6219. (b) Huang, Y.; Lu, X. Tetrahedron Lett. 1988, 29, 5663. (c) Barluenga, J.; Tomás, M.; Rubio, E.; López-Pelegrín, J. A.; García-Granda, S.; Priede, M. P. J. Am. Chem. Soc. 1999, 121, 3065. (d) Young, I. S.; Kerr, M. A. Angew. Chem., Int. Ed. 2003, 42, 3023. (e) Sibi, M. P.; Ma, Z.; Jasperse, C. P. J. Am. Chem. Soc. 2005, 127, 5764.
- (5) (a) Bambal, R. B.; Kemmitt, R. D. W. J. Organomet. Chem. **1989**, 362, C18. (b) Hedley, S. J.; Moran, W. J.; Prenzel, A. H. G. P.; Price, D. A.; Harrity, J. P. A. Synlett **2001**, 1596. (c) Hedley, S. J.; Moran, W. J.; Price, D. A.; Harrity, J. P. A. J. Org. Chem. **2003**, 68, 4286. (d) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. J. Org. Chem. **2005**, 70, 207.
- (6) (a) Trost, B. M.; Chan, D. M. T. J. Am. Chem. Soc. 1979, 101, 6429. (b) Trost, B. M.; Chan, D. M. T. J. Am. Chem. Soc. 1983, 105, 2315.
- (7) For a review, see: Chan, D. M. T. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; p 57.
- (8) For examples of [4 + 3] cycloaddition with Pd-TMM, see: (a) Trost, B. M.; MacPherson, D. T. J. Am. Chem. Soc. 1987, 109, 3483. (b) Trost, B. M.; Schneider, S. Angew. Chem., Int. Ed. Engl. 1989, 28, 213. (c) Trost, B. M.; Christopher, M. M. J. Am. Chem. Soc. 1993, 115, 6636. For an example of [6 + 3] cycloaddition with Pd-TMM, see: (d) Trost, B. M.; Seoane, P. R. J. Am. Chem. Soc. 1987, 109, 615.
- (9) (a) Dorn, H.; Otto, A. Chem. Ber. 1968, 101, 3287. (b) Dorn, H.; Otto, A. Angew. Chem., Int. Ed. Engl. 1968, 7, 214.
- (10) For a review, see: Schantl, J. G. Sci. Synth. 2004, 27, 731.
- (11) For recent examples, see: (a) Suárez, A.; Downey, C. W.; Fu, G. C. J. Am. Chem. Soc. 2005, 127, 11244. (b) Pezdirc, L.; Jovanovski, V.; Bevk, B.; Jakse, R.; Pirc, S.; Meden, A.; Stanovnik, B.; Svete, J. Tetrahedron 2005, 61, 3977. (c) Panfil, I.; Urbanczyk-Lipkowska, Z.; Suwinska, K.; Solecka, J.; Chmielewski, M. Tetrahedron 2002, 58, 1199.
- (12) Self-dimerization of these dipoles is known: Dorn, H.; Kreher, T. Tetrahedron Lett. 1988, 29, 2939.
- (13) Trost, B. M.; Chan, D. M. T. J. Am. Chem. Soc. 1981, 103, 5972.

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