Domino Radical Cyclization

Titanium-Mediated Domino Radical Cyclization/ β Elimination of Phosphine Oxides**

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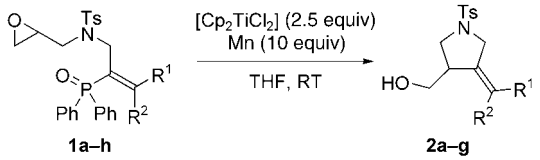
Radical reactions involving organophosphorus radicals have a long history.[1] In particular, the stability of P-centered radicals has facilitated the use of phosphorus hydrides as surrogates for tin hydrides.[2–6] Furthermore, the addition of phosphinyl,[7] phosphinoyl,[8–12] and phosphonyl[13,14] radicals, as well as their sulfur-containing counterparts,[15–17] to alkenes is a widely used method for the preparation of organophosphorus compounds and polymers.

In contrast, little is known about the β elimination of P-centered radicals, and the use of such pathways in synthesis. It has been shown that phosphinyl radical additions are reversible.[18] Radicals derived from phosphinates have been exploited for the preparation of aromatic compounds,[19] and phosphonyl radical eliminations for the synthesis of ketones,[20] although in both cases the systems were significantly biased to favor the elimination pathway. The first case was a rearomatization, and the second involved a highly reactive acyl phosphonate, with restoration of a C=O bond. To the best of our knowledge, this process has yet to afford simple olefinic compounds.

In the course of previous work, we observed a by-product arising from a radical addition/β elimination domino reaction on a vinylic phosphine oxide.[21] As far as we could tell, this was the first example of such a process. In the meantime, we had developed an efficient method allowing the preparation of enantiopure alkylidenecyclopentanes from sulfoxides through a formal asymmetric intramolecular vinylation of a prochiral radical.[22] Because sulfinyl radicals are very special β-eliminating moieties, the elimination rate of which is close to the diffusion limit,[23] the observed side reaction led us to speculate that a phosphine oxide might be a viable, kinetically different alternative to a sulfoxide and afford a novel reaction sequence. Intermolecular (but achiral),[24,25] and semi-intermolecular[26] versions involving sulfones and sulfides as leaving groups have also been reported, but none involving phosphine oxides.

In 1988, Nugent and RajanBabu reported that [Cp_2TiCl] was able to transfer one electron to oxiranes with formation of β-titanoxy radicals, which could be used further in syntheses.[27] This seminal work was made even more useful when Gansäuer et al. rendered this reaction catalytic,[28] and soon thereafter asymmetric.[29] Since then, a few titanium-mediated domino reactions have been reported,[30] but as far as we are aware, no vinylation protocol relying on the inter- or intramolecular addition/elimination sequence has been reported. Furthermore, the mediator is not an hydride-transfer agent, and we felt this would be advantageous. Thus, because the radical β elimination of phosphinoyl radicals was still uncharted territory, we decided to investigate it more closely, and report herein our preliminary results.

We first carried out the reaction with substrates derived from dimethyl malonate and the preformed titanium(III) complex, but encountered problems with lactonization. We then replaced the *gem*-diester group with a tosyl-protected nitrogen atom (**1a**), and obtained the desired domino product *exo*-isopropylidenepyrrolidine **2a** at room temperature as the sole product in good yield (Scheme 1; Table 1, entry 1).



Scheme 1. Titanium-mediated preparation of alkylidenepyrrolidines. Ts = toluenesulfonyl.

The reaction exhibits good versatility, affording access to tetrasubstituted (entries 1 and 4–8) and trisubstitued (entries 2 and 3) *exo*-alkylidenepyrrolidines. In the case of the trisubstituted olefins **2b** and **2c**, β elimination proceeds with retention of configuration, as evidenced by NOE studies (entry 2). However, in the case of oxirane **1c**, 25% of the *Z* isomer was also observed. At this time we do not understand this result. Vinyl phosphine oxide **1g** led either to **2g** or to **3**, depending on the workup conditions: stronger acidic hydrolysis deprotected the ketal.

Since the titanium(III) reagent is an organometallic compound, we wanted to confirm that the observed products were being formed via a domino radical reaction pathway. The reaction of cyclopropyl-substituted precursor **1h** led to the ring-opened product **4** as a single diastereomer, the relative configuration of which was determined by X-ray crystallography. It is derived from pseudo-chair cyclization transition state **A**, which leads to opening of the cyclopropyl ring (Scheme 2). This strongly suggests that the cyclization is radical in nature. While there is no reason for totally stereoselective ring opening, we did not observe any *Z*-olefinic product by NMR spectroscopy.[31]

To gather data on the elimination step, we designed several experiments. First, we carried out the tin-mediated

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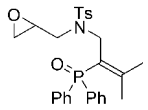
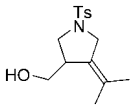
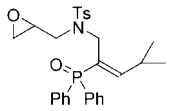
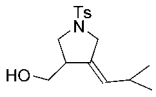
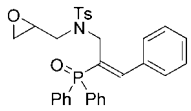
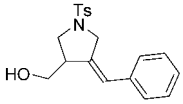
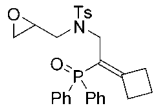
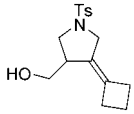
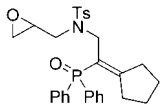
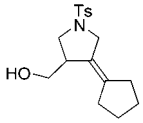
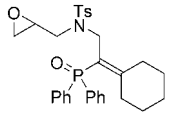
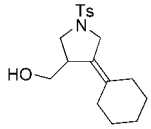
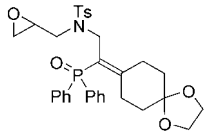
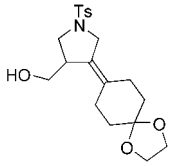
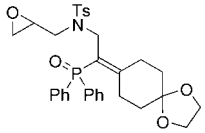
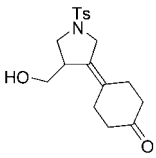
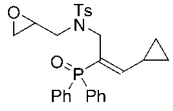
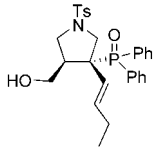
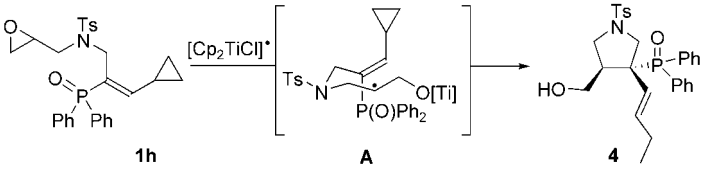
Table 1: Titanium-mediated preparation of alkylidenepyrrolidines.

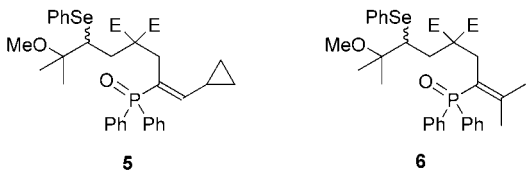
Entry	Substrate	Product	Yield [%]
1	 **1a**	 **2a**	80
2	 **1b**	 **2b**	60
3	 **1c**	 **2c**	71[a]
4	 **1d**	 **2d**	57
5	 **1e**	 **2e**	58
6	 **1f**	 **2f**	82
7	 **1g**	 **2g**	57[b]
8	 **1g**	 **3**	60[c]
9	 **1h**	 **4**	70

[a] *E*/*Z* ratio 3:1. [b] Hydrolysis with a saturated solution of NH_4Cl. [c] Hydrolysis with aqueous 1 M HCl.

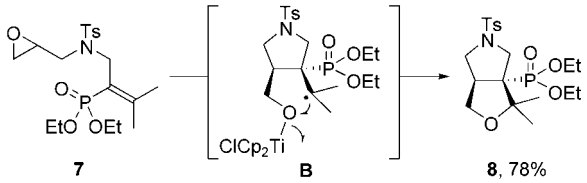


Scheme 2. Cyclization of cyclopropyl-substituted vinylic phosphine oxides.

cyclization of substrates **5** and **6** (E = CO_2Me) with triethylborane/oxygen as initiator. Diester **5** gave a cyclopropyl-ring-opened cyclopentane adduct in 75% yield as a single diastereomer. The relative configuration was assumed to be similar to that of **4**, which was further confirmed by NOE studies. This again indicates that a radical cyclization, but also that the rate of elimination of β-phosphinoyl radical is considerably slower than that of the sulfinyl leaving group, for in that case we observed no opening of the strained ring. In the case of **6**, the domino product was accompanied by roughly an equimolar amount of directly reduced material. This behavior was different from that of its sulfoxide counterpart, and can be rationalized by the increased steric bulk around the heteroatom.



We next carried out our titanium-mediated process on phosphonate derivative **7** and obtained the bicyclic product **8** (Scheme 3). Previously, we had subjected the corresponding



Scheme 3. Reaction of a vinyl phosphonate.

malonate to the classical tin-mediated reaction and observed the overwhelming formation of cyclopentane products (i.e., cyclized but not eliminated), along with a minimal (5%) amount of desired product. More interestingly, the radical termination step was not a bimolecular reduction by the tin hydride, but a dismutation of the intermediate radical. This seemed to indicate that the tertiary β-phosphono radical is rather long-lived. A similar outcome to the production of **8** was described recently by Gansäuer et al. and Trost et al.[32,33] It originates from a Ti–O bond breaking 5-*exo*-*tet* radical cyclization on the oxygen atom of intermediate **B**. Gansäuer et al. took advantage of the "relative persistence under reducing conditions [of tertiary radicals] through exclusion

of competing radical pathways". Together with our previous observations, this is important circumstantial evidence that no rapid reduction by a second equivalent of Ti^{III} reagent takes place, and that in the case of β-phosphinoyl radicals, radical elimination is observed. If this were not the case, we would much more likely have observed formation of structures like **8**, especially in the case of tetrasubstituted olefins.

In conclusion, we were able to observe for the first time a titanium-mediated intramolecular vinylation based upon the previously unknown elimination of β-phosphinoyl radicals.[34] Work to examine the full scope and limitations of this method, as well as the development of an asymmetric version, is currently underway.

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Keywords: cyclization · domino reactions · phosphorus · radical reactions · titanium

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[31] For a recent example, see A. Ogawa, I. Ogawa, R. Obayashi, K. Umezu, M. Doi, T. Hirao, *J. Org. Chem.* **1999**, *64*, 86 – 92.
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[34] Note that phosphinoyl derivatives have one additional advantage: when subjected to the titanium-mediated sequence, sulfoxides lead to both low yields and reduction to the corresponding sulfides. We did not study this further, but to some extent this precludes part of the asymmetric version, since initial reduction would eliminate any stereochemical information present on the sulfur atom.

