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Rhodium-Catalyzed Methylenation of Aldehydes

Hélène Lebel* and Valérie Paquet

Contribution from the Département de Chimie, Université de Montréal, C. P. 6128, Succursale Centre-Ville, Montréal, Québec, Canada H3C 3J7

Received August 25, 2003; E-mail: lebelhe@chimie.umontreal.ca

Abstract: The rhodium-catalyzed methylenation of aldehydes using trimethylsilyldiazomethane and triphenylphosphine produces a variety of terminal alkenes in excellent yields. These mild and nonbasic reaction conditions allow the conversion of enolizable substrates (keto aldehydes and nonracemic α-substituted aldehydes) to terminal alkenes without epimerization. Optimization of the reaction conditions led to the conclusion that a variety of rhodium(I) sources can be used as catalysts. The effect of the solvent on the reaction has also been studied, and it indicates that although the THF is the best solvent, other solvents may be used. The reactivity of the system is very much dependent on the nature of the phosphine reagent. The use of an easily removable phosphine is also described. Spectroscopic studies indicate that the reaction proceeds via an unusual mechanism which leads to the in situ formation of the salt-free phosphorus ylide, methylenetriphenylphosphorane.

Introduction

Since the pioneering work of Wittig,[1] the synthesis of alkenes by the olefination of carbonyl compounds has received considerable attention due to the simplicity, convenience, and efficiency of this methodology.[2] In addition to phosphorus ylides,[3] other related stoichiometric processes involving sulfur[4] and silicon[5] ylides have been developed. Furthermore, several stoichiometric systems using transition metals, such as titanium[6] and chromium,[7] have been reported for the olefination of carbonyl derivatives.[8] Despite significant advantages (i.e., high selectivities and yields, mild conditions, and a broad spectrum of keto precursors), several drawbacks remain for these olefinations, including the use of stoichiometric amounts of expensive and/or toxic metals. Recently, a few approaches to transition metal-catalyzed olefinations have been disclosed. Various transition metals, including Mo,[9] Re,[10] Fe,[11] and Ru[11c,12] catalyze the addition of ethyl diazoacetate to aldehydes in the presence of triphenylphosphine or triethyl phosphite, leading to the formation of (*E*)-conjugated esters.[13] Two different mechanistic pathways, which rely on the formation of a metal carbene intermediate, were proposed for these processes. In the first place, the nucleophilic carbene reacts with the carbonyl compound to produce the desired alkene and the corresponding metal-oxo species, which are then be reduced by the phosphorus reagent (Scheme 1).

Alternatively, the phosphorus reagent attacks the metal carbene, thus forming a phosphorus ylide species that adds to the carbonyl derivative (Scheme 2).

The extension of these methodologies to other diazo reagents or their precursors has been quite a challenge. Our interest in

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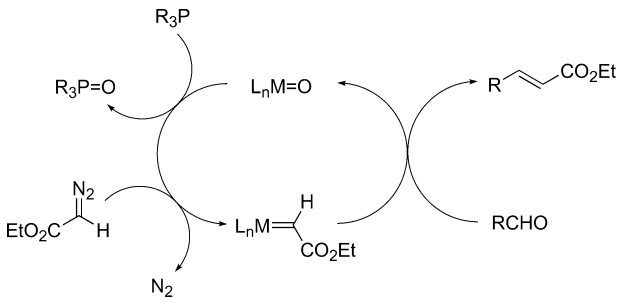
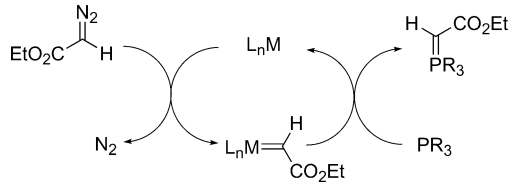
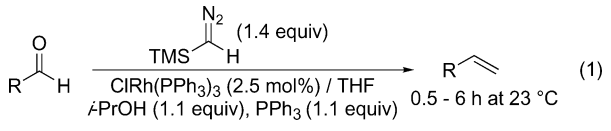
Scheme 1



Scheme 2



de novo synthesis of alkenes prompted us to study the reactivity of trimethylsilyldiazomethane[14] toward carbonyl compounds in the presence of a variety of transition metal complexes. Indeed, we have shown that the Wilkinson's complex efficiently catalyzes the methylenation of aldehydes with trimethylsilyldiazomethane in the presence of triphenylphosphine and 2-propanol (eq 1).[15,16]



More recently Aggarwal has shown that the reaction of tosylhydrazones with aryl aldehydes in the presence of an iron porphyrin complex and trimethyl phosphite was also feasible, leading to aryl-substituted alkenes with exceptionally high *E*-selectivity.[11f,17]

The methylenation reaction of carbonyl derivatives is a very important transformation in organic synthesis,[2a] as terminal alkenes are precursors for a variety of reactions, including the ring-closing metathesis reaction.[18] Although the Wittig reaction has been quite reliable for this transformation, several drawbacks including the low reactivity of the reagent with hindered carbonyl derivatives as well as the possible epimerization of base-sensitive substrates are still associated with it.[19] Several stoichiometric *gem*-dimetallic reagents derived from titanium/aluminum (Tebbe,[20] Petasis[21]),[6] titanium/zinc (Nozaki,[22] Oshima–Lombardo[23]), chromium/zinc (Takai–Utimoto,[24] Nysted[25]), boron/lithium[26] or lithium/silicon (Peterson[27]) have been developed to overcome these problems.[28,29] More recently, *gem*-dizinc species have successfully been used in methylenation reactions.[30] However, the rhodium-catalyzed methylenation reaction developed in our group is still the only existing catalytic process and a powerful means that leads to terminal alkenes. The required reagents for the rhodium-catalyzed methylenation are readily available. The reaction conditions do not require the use of a base and are mild enough to be compatible with sensitive and enolizable substrates, thereby allowing the synthesis of a variety of functionalized alkenes in excellent yields.[31]

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Furthermore, the chemoselectivity of the reaction is remarkable, since different carbonyl substrates can be discriminated between based upon their stereoelectronics. The synthesis of fluoromethylalkenes under similar reaction conditions has also been achieved in high yields.[32] In this paper, we report the scope of the rhodium-catalyzed methylenation process focusing on the optimization of the reaction conditions and the functional group compatibility. Furthermore, our mechanistic investigation through spectroscopic studies reveals that methylenetriphenylphosphorane is the active species.

Results and Discussion

Rhodium Catalysts. After surveying a variety of ruthenium and rhodium complexes, we found that the Wilkinson's complex is a superb and readily available catalyst for the methylenation of aldehydes with trimethylsilyldiazomethane in the presence of stoichiometric amounts of triphenylphosphine and 2-propanol at room temperature.[15a] An investigation of other rhodium complexes shows that the requisite catalyst may also be generated in situ from a number of rhodium sources, due to the presence of an excess of triphenylphosphine in the reaction mixture (see the Supporting Information for details). For instance, rhodium(III) chloride hydrate[33] may react directly with triphenylphosphine under the methylenation reaction conditions. Rhodium(I) dimer complexes, such as chloro[1,5-cyclooctadiene]- and chloronorbornadienerhodium(I) dimer, are also suitable precursors for the in situ generation of the Wilkinson's catalyst. In comparison, the corresponding cationic complexes derived from silver tetrafluoroborate and sodium tetraphenylborate were less reactive, and the olefination reaction took place only at 50 °C. Formally, the rhodium(0) complex $Rh(NO)(PPh_3)_3$ seems also to be an active catalyst, although a very long latent period was observed prior to the beginning of the olefination reaction. This latent period and the many color variations of the reaction mixture are consistent with the hypothesis that a redox process initially occurs, leading to an active rhodium(I) species. In contrast, no reaction was observed with the rhodium(II) acetate dimer, although this complex has found many applications in carbene chemistry.[34]

Reaction Conditions. THF is the best solvent for the rhodium-catalyzed methylenation of aldehydes, and the reaction conditions do not require the use of an anhydrous solvent. When a reaction was performed in ACS reagent-grade THF out of a freshly opened bottle, similar results for methylenation of 6-(*tert*-butyldimethylsilyloxy)-1-pentanal were obtained (see the Supporting Information for details).[35] The reaction is also tolerant toward other oxygenated solvents, such as ether and dioxane, although longer reaction times are required. The reaction was much slower in toluene, due to the low solubility of the rhodium catalyst in this solvent. The methylenation reaction could be successfully performed in dichloromethane, although, surprisingly, no reaction was observed with 1,2-dichloroethane.

Trimethylsilyldiazomethane has been used as a safer alternative to diazomethane in many one-carbon homologation processes.[36] Although commercially available, trimethylsilyldiazomethane is easily synthesized according to the Shioiri procedure that gives a 2.0 M hexanes solution of the reagent.[37,38] We have slightly modified the procedure, as we found that when increasing the concentration of $TMSCHN_2$ in hexanes (thus decreasing the amount of hexanes), the methylenation reaction was faster. Indeed chlorotris(triphenylphosphine)rhodium(I) is not soluble in hexanes, and the presence of this solvent is detrimental for the methylenation reaction. We also observed higher reactivity if we distilled the $TMSCHN_2$ and prepared a THF solution (see the Supporting Information for details). Other solvents, such as dichloromethane and ether, provided similar reactivity as that of the hexane solution. Finally, a commercially available ethereal solution of trimethylsilyldiazomethane could also be used, although 1.7−2.0 equiv of the reagent were required to reach completion. Alternatively, the commercial solution may be concentrated to produce a 6.0 M solution that is almost as active as the THF solution. The methylenation of various substrates with both the commercially available etheral solution of trimethylsilyldiazomethane and the freshly prepared reagent provided similar results (see Table 4 in the Supporting Information).

We have briefly investigated other diazoalkane reagents under the same reaction conditions. Diazomethane and ethyldiazoacetate led to product formation, albeit in low yields, whereas phenyldiazomethane did not react at all. The terminal alkene was the only product observed with bis(trimethylsilyl)diazomethane and trimethylsilyl(trimethylstannyl)diazomethane, which indicated a complete desilylation and destannylation prior to the olefination reaction. Other silylated diazoalkane reagents, such as trimethylsilyldiazoethane and trimethylsilylethyldiazoacetate, gave very low conversion for the olefination of cinnamaldehyde.

Phosphine. One of the major drawbacks in the utilization of triphenylphosphine-derived ylides in olefination methodologies is the purification of the desired product from a stoichiometric amount of triphenylphosphine oxide generated as a byproduct.[39] This is also the case in our rhodium-catalyzed methylenation reaction as methylenetriphenylphosphorane is produced as the active reagent (vide infra). We sought another phosphorus

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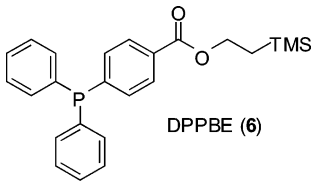
(35) The reaction is tolerant toward a certain amount of water, and up to 1 equiv of water could be added to the reaction mixture without affecting the yield. However, the addition of 5 equiv of water completely inhibits the methylenation reaction.
(36) (a) Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, *21*, 4461−4462. (b) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, *21*, 4619−4622. (c) Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 3249−3255. (d) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475−1478. (e) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Heterocycles* **1981**, *15*, 975−979. (f) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 119−124. (g) Aoyama, T.; Toyama, S.; Tamaki, N.; Shioiri, T. *Chem. Pharm. Bull.* **1983**, *31*, 2957−2959. (h) Aoyama, T.; Terasawa, S.; Sudo, K.; Shioiri, T. *Chem. Pharm. Bull.* **1984**, *32*, 3759−3760. (i) Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1986**, *27*, 2005−2006. (j) Shioiri, T.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1988**, *29*, 6295−6296. (k) Shioiri, T.; Aoyama, T.; Shioiri, T. *Synthesis* **1988**, 228−229. (l) Shioiri, T.; Aoyama, T.; Iwamoto, Y.; Nishigaki, S.; Shioiri, T. *Chem. Pharm. Bull.* **1989**, *37*, 253−256.
(37) (a) Mori, S.; Sakai, I.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 3380−3382. (b) Shioiri, T.; Aoyama, T.; Mori, S. *Org. Synth.* **1990**, *68*, 1−7.
(38) As trimethylsilyldiazomethane is nonexplosive and nonmutagenic, the very careful operations used for the preparation of diazomethane are not necessary.

reagent that will lead to an easily removable byproduct, thus facilitating purification of the desired alkene. We found that the variation of the phosphine reagent has a profound effect on the methylenation reaction (Table 1). This is not surprising as not only will this reagent be incorporated in the phosphorus ylide, but the phosphine also serves as the ligand for the rhodium complex. Indeed, when we tried tributylphosphine, we observed a rapid exchange to generate $RhCl(PBu_3)_3$, which was completely inactive and did not form the desired phosphorus ylide (entry 2). In the case of trimethyl phosphite, it is known that an excess of these ligands leads to the displacement of the chloride with the formation of a catalytically inert cationic rhodium species $[LRh(P(OMe)_3)_4^+]$ (entry 3).[40] We then searched for substituted triphenylphosphine reagents which could provide active rhodium catalysts. Unfortunately, ylides derived from tri(*p*-methoxyphenyl)phosphine and tri(*p*-trifluoromethylphenyl)phosphine were unstable and rapidly decomposed without providing any of the desired alkene (entries 4 and 5). In comparison, the methylenetri(*p*-fluorophenyl)phosphine reacted with cinnamaldehyde affording the corresponding diene after 5 h (entry 6). Formation of the methylene phosphorus ylide was also observed with other diphenyl *para*-substituted phosphines (entries 7−11). However, the reactivity of these ylides is profoundly affected by *para* substitution. For example, the ylide derived from ethyl 4-diphenylphosphanylbenzoate (**5**) is not reactive enough to entirely convert cinnamaldehyde into the corresponding terminal alkene (entry 10). Conversely, the 4-diphenylphosphanylbenzoic acid 2-trimethylsilanylethyl ester (DPPBE) (**6**) recently developed by Yoakim and coauthors for the Mitsunobu reaction[41] provided an active methylene phosphorus ylide (entry 11). The reaction between the phosphine **6**



DPPBE (**6**)

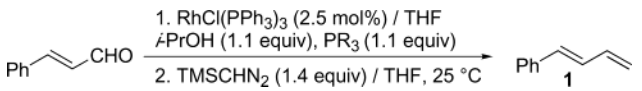
and the Wilkinson's catalyst produced a rhodium complex that contains two triphenylphosphine ligands and one DPBBE (**6**) ligand. In the presence of trimethylsilyldiazomethane and 2-propanol, this complex catalyzed the formation of a methylene ylide derived from phosphine **6**. In contrast to what we observed with phosphines **4** and **5**, the methylene ylide derived from phosphine **6** reacted efficiently with cinnamaldehyde leading to diene **1**. This initial exchange of phosphines with the Wilkinson's catalyst liberated one out of three triphenylphosphines, which is converted into triphenylphosphine oxide during the methylenation reaction. If the presence of any triphenylphosphine oxide is undesired, the use of chloro(1,5-cyclooctadiene)rhodium(I) dimer as the precatalyst to generate in situ the $RhCl(DPPBE)_3$ provides similar results (entry 12).

(39) A number of polymer-supported triphenylphosphine reagents have been developed to overcome this problem: (a) Bernard, M.; Ford, W. T. *J. Org. Chem.* **1983**, *48*, 326−332. (b) Sieber, F.; Wentworth, P.; Toker, J. D.; Wentworth, A. D.; Metz, W. A.; Reed, N. N.; Janda, K. D. *J. Org. Chem.* **1999**, *64*, 5188−5192. (c) Charette, A. B.; Boezio, A. A.; Janes, M. K. *Org. Lett.* **2000**, *2*, 3777−3779. (d) Charette, A. B.; Janes, M. K.; Boezio, A. A. *J. Org. Chem.* **2001**, *66*, 2178−2180.

(40) Wu, M. L.; Desmond, M. J.; Drago, R. S. *Inorg. Chem.* **1979**, *18*, 679−686.

(41) Yoakim, C.; Guse, I.; O'Meara, J. A.; Thavonekham, B. *Synlett* **2003**, 473−476.

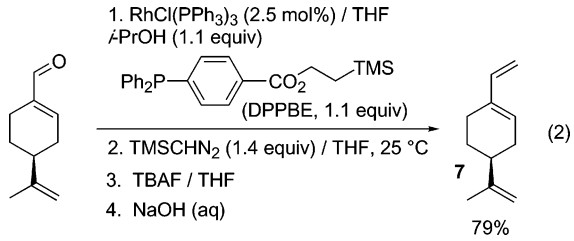
Table 1. Rhodium-Catalyzed Methylenation of 6-(*tert*-Butyldimethylsilyloxy)-1-pentanal Using Various Phosphines



entry	PR_3	conv[a] (%)
1	PPh_3, 0.5 h	≥98
2	PBu_3, 16 h	0
3	$P(OMe)_3$, 16 h	0
4	P(*p*-MeOPh)$_3$, 16 h	0
5	P(*p*-CF_3Ph)$_3$, 16 h	0
6	P(*p*-FPh)$_3$, 5 h	≥98
7	PPh_2(*p*-TMSPh) (**2**), 3 h	83
8	PPh_2(*p*-MOMOPh) (**3**), 2 h	37
9	PPh_2(*p*-MeO_2CPh) (**4**), 16 h	20
10	PPh_2(*p*-EtO_2CPh) (**5**), 16 h	15
11	DPPBE[b] (**6**), 2 h	≥98
12	DPPBE[b,c] (**6**), 2 h	≥98

[a] Determined by GC. [b]DPPBE: 4-diphenylphosphanylbenzoic acid 2-trimethylsilanylethyl ester. [c]$[Rh(COD)Cl]_2$ was used as catalyst.

The use of phosphine **6** greatly simplifies purification of the alkene. For instance, the methylenation reaction of perillaldehyde was carried out on a 5 mmol scale in the presence of DPPBE (**6**). After the reaction was found to be completed by TLC analysis, the reaction mixture was treated with TBAF in THF to cleave the trimethylsilanylethyl ester moiety (eq 2). A basic workup with NaOH easily removed the corresponding acid, and the pure diene **7** could be simply obtained after distillation with 79% yield.[42]



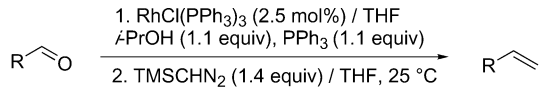
Scope of Aldehydes. The rhodium-catalyzed methylenation reaction is compatible with a number of functional groups. Aliphatic aldehydes are very reactive, and usually the methylenation reaction is complete within 1 h (Table 2).

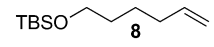
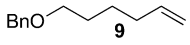
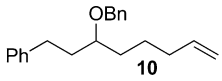
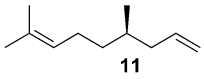
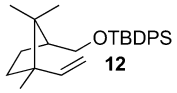
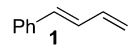
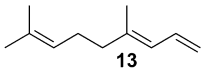
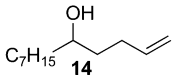
Terminal aliphatic alkenes were obtained with 74% to 98% yields, and the reaction conditions were compatible with silyloxy and benzyloxy groups (entries 1−4). In addition, high yields were observed with hindered substrates (entry 5) as well as for the formation of dienes (entries 6 and 7). In general, faster reactions and higher yields were produced with the rhodium-catalyzed methylenation reaction conditions than with the phosphonium salt and a base (entries 1, 6, and 7). Hemiacetals were more problematic substrates, as the silylation of the closed form was a faster reaction under the normal reaction conditions.[43] However, when using an excess of 2-methyl-1-propanol, we circumvented this problem, and the desired alkene alcohol **14** was isolated with 63% yield (entry 8).

When we surveyed more functionalized aldehydes, we were pleased to find that our reaction conditions are compatible with acetonides, epoxides, and carbamates (Table 3).

(42) If necessary, it is possible to avoid the use of TBAF, by performing a hydrolysis under basic conditions or a cleavage using strong acid, such as trifluoroacetic acid. See ref 41.

Table 2. Rhodium-Catalyzed Methylenation of Aliphatic Aldehydes

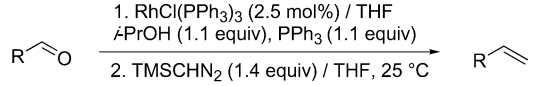


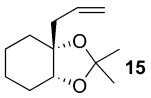
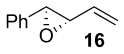
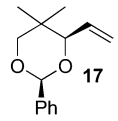
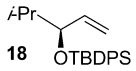
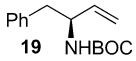
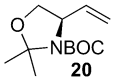
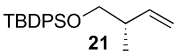
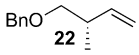
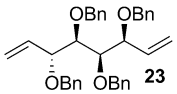
Entry	Product	Time[b]	Yield[a]	Wittig Yield[b]
1	 **8**	1 h	87%	71% (7 h)
2	 **9**	0.5 h	74%	---
3	 **10**	1 h	98%	---
4	 **11**	7 h	84%	---
5	 **12**	7 h	79%	---
6	 **1**	0.5 h	88%	82% (2 h)
7	 **13**	2 h	90%	77% (6 h)
8[c]	 **14**	1 h	63%	---

[a] Isolated yield. [b]Standard Wittig reaction: PPh_3CH_3Br, NaHMDS/THF, 25 °C. Reaction time in parentheses. [c]2-Methyl-1-propanol was used instead of 2-propanol.

Moreover, the stereochemical integrity of adjacent chiral centers is maintained for enolizable aldehydes. Indeed, the methylenation of enantioenriched α-alkoxy and α-amino aldehydes (95% ee) led to the corresponding alkenes with good yields while preserving an ee superior to 90% (entries 4−6). In addition, methylenation of silyl-protected 3-hydroxy-2-methyl propionaldehyde, an α-alkyl-substituted aldehyde, provided the desired alkene **21** in 72% yield and 94% ee (entry 7).[44] When using a less hindered protecting group, such as a benzyl, we observed some erosion of the enantioselectivity, as the desired alkene **22** was recovered with 84% ee (entry 8). These results are somewhat superior to the standard Wittig reaction conditions, since, in the presence of Ph_3PCH_3Br and NaHMDS, alkenes **21** and **22** were recovered with 90% and 80% ee, respectively. We have also looked at the methylenation of dialdehydes derived from sorbitol that have been reported by Fürstner as difficult substrates.[45] When using the Tebbe reagent, Fürstner obtained the best results for the synthesis of alkene **23** that was isolated with 42% yield. In comparison, our methodology provided the desired diene **23** with 50% yield when 2-methyl-1-propanol was used instead of 2-propanol (entry 9). All of these examples show that, in general, we observe similar or higher yields with the rhodium-catalyzed methylenation than with other methylenation procedures.

Table 3. Rhodium-Catalyzed Methylenation of α-Substituted Aldehydes



Entry	Product	Time	Yield[a] (ee)	Lit. Yield (ee)
1	 **15**	1.5 h	79%	79%[19g]
2	 **16**	1 h	86%	---
3	 **17**	5 h	74%	84%[19c]
4[b]	 **18**	3 h	89% (95%)	75%[19f]
5[b]	 **19**	16 h	53% (95%)	45-53%[19a]
6[b]	 **20**	4 h	86% (92%)	81%[c]
7[b]	 **21**	3 h	72% (94%)	73%[c] (90%)
8[b]	 **22**	3 h	78% (84%)	53%[c] (80%)
9[d]	 **23**	2 h	50%	42%[45]

[a] Isolated yield. [b]The starting material was 95% ee. [c]Standard Wittig reaction: PPh_3CH_3Br, NaHMDS/THF, 25 °C. Reaction time in parentheses. [d]2-Methyl-1-propanol was used instead of 2-propanol.

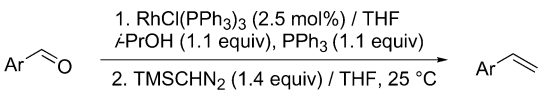
At the outset, the results for the methylenation of aryl aldehydes were quite disappointing (Table 4). Although the conversions were very high, the isolated yields of the corresponding styrene derivatives were somewhat low. The purification of the alkene from the small remaining amount of triphenylphosphine was difficult, and in some cases, higher yields could be achieved with the standard Wittig reaction (entries 1−4). However, we were able to improve the synthesis of styrene **28** to reach 60% yield, whereas the highest yield

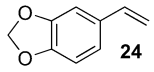
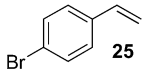
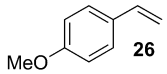
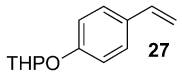
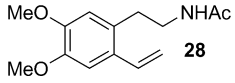
(43) For selected examples of the methylenation of hemiacetals, see: (a) Gillaizeau, I.; Charamon, S.; Agrofoglio, L. A. *Tetrahedron Lett.* **2001**, *42*, 8817−8819. (b) Nishikawa, A.; Saito, S.; Hashimoto, Y.; Koga, K.; Shirai, R. *Tetrahedron Lett.* **2001**, *42*, 9195−9198. (c) Furstner, A.; Schlede, M. *Adv. Synth. Catal.* **2002**, *344*, 657−665. (d) Jin, Y. H.; Chu, C. K. *Tetrahedron Lett.* **2002**, *43*, 4141−4143. (e) Moon, H. R.; Kim, H. O.; Lee, K. M.; Chun, M. W.; Kim, J. H.; Jeong, L. S. *Org. Lett.* **2002**, *4*, 3501−3503. (f) Ovaa, H.; Lastdrager, B.; Codee, J. D. C.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2370−2377. (g) Paquette, L. A.; Boulet, S. L. *Synthesis* **2002**, 888−894. (h) Chu, C. K.; Jin, Y. H.; Baker, R. O.; Huggins, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 9−12.

(44) Konno, K.; Fujishima, T.; Maki, S.; Liu, Z.; Miura, D.; Chokki, M.; Ishizuka, S.; Yamaguchi, K.; Kan, Y.; Kurihara, M.; Miyata, N.; Smith, C.; DeLuca, H. F.; Takayama, H. *J. Med. Chem.* **2000**, *43*, 4247−4265.

(45) Ackermann, L.; El Tom, D.; Furstner, A. *Tetrahedron* **2000**, *56*, 2195−2202.

Table 4. Rhodium-Catalyzed Methylenation of Aryl Aldehydes



Entry	Product	Time	Yield[a]	Lit. Yield
1	 **24**	1 h	74%	84% (3 h)[b]
2	 **25**	1 h	66%	---
3	 **26**	0.5 h	80%	64%[21b]
4	 **27**	1 h	93%	81%(1 h)[b]
5	 **28**	0.5 h	60%	33%[46]

[a] Isolated yield. [b]Isolated yield for the standard Wittig reaction: PPh_3CH_3Br, NaHMDS/THF, 25 °C. Reaction time in parentheses.

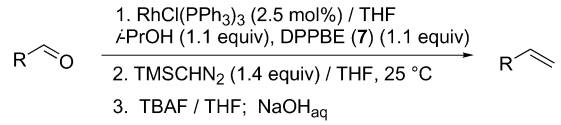
reported in the literature was 33% using the Lombardo's reagent (entry 5).[46] We have also observed some functional group compatibility issues with phenols and *p*-nitrobenzaldehyde which seem to react with trimethylsilyldiazomethane. Phenols are known to be methylated with this reagent,[36h] and the reaction using *p*-nitrobenzaldehyde quickly turned black and furnished a complex mixture of products.

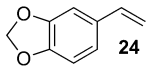
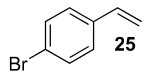
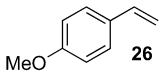
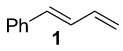
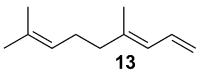
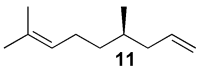
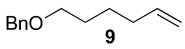
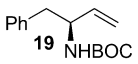
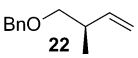
The use of an easily removable phosphine reagent, 4-diphenylphosphanylbenzoic acid 2-trimethylsilanylethyl ester (**6**), was beneficial to improve our isolated yields (Table 5). Indeed, the styrene derivatives could be produced with 77% to 90% isolated yield (entries 1−3). These reaction conditions are obviously not compatible with silyloxy groups but are quite efficient for the isolation of very greasy alkene products. For instance, the methylenation of 5-benzyloxypentanal proceeded extremely well, and no starting material could be seen by TLC or GC−MS after 0.5 h. However, the isolated yield for alkene **9** was only 74% when using triphenylphosphine (Table 2, entry 2). Conversely, this yield was improved to 89% in the presence of DPPBE (**6**) (Table 5, entry 7). In general, the methylenation reaction is slower with DPPBE (**6**) and required twice the reaction time to reach completion. Although the methylenation of chiral enantioenriched α-amino aldehydes still proceeded with retention of the stereochemical integrity, we observed a more serious loss in the enantiomeric purity with the 3-benzyloxy-2-methyl propionaldehyde, as the corresponding alkene was isolated with 79% ee after 5 h of reaction (entries 8 and 9). The longer reaction time required could certainly be one reason for this erosion.

Outstanding chemoselectivity between aldehydes and ketones was observed for the rhodium-catalyzed methylenation reaction.[47] When the keto aldehyde **29** was reacted under our

(46) Wirth, T.; Fragale, G. *Synthesis* **1998**, 162−166.

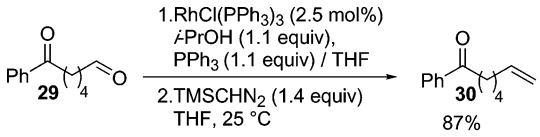
Table 5. Rhodium-Catalyzed Methylenation of Aldehydes with 4-Diphenylphosphanylbenzoic Acid 2-Trimethylsilanylethyl Ester (DPPBE)



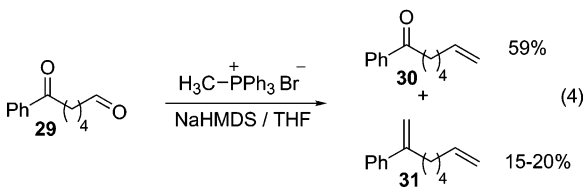
Entry	Product	Time	Yield[a] (ee)
1	 **24**	2 h 4 h[b]	81% 77%[b]
2	 **25**	2 h	77%
3	 **26**	0.5 h	90%
4	 **1**	2 h	82%
5	 **13**	2 h	77%
6	 **11**	5 h	86%
7	 **9**	0.5 h	89%
8[c]	 **19**	16 h	68% (95%)
9[c]	 **22**	5 h	76% (79%)

[a] Isolated yield. [b]$[Rh(COD)Cl]_2$ was used as catalyst. [c]The starting material was 95% ee.

standard conditions, the exclusive formation of alkene **30** in 87% yield was observed (eq 3). In comparison, under the



(3)

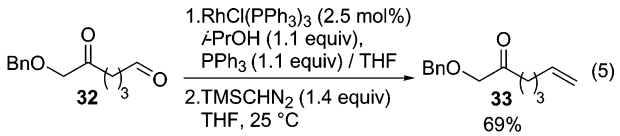


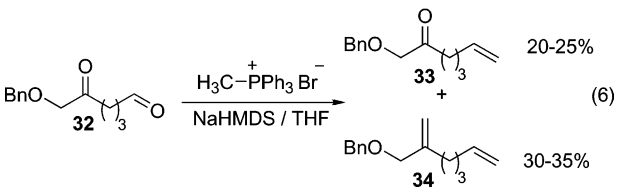
(4)

standard Wittig conditions involving the deprotonation of methyltriphenylphosphonium bromide with sodium hexamethyldisilazide, the desired alkene **30** was isolated in 59% yield along with diene **31** in 15−20% yield (eq 4).

The difference of chemoselectivity between our rhodium-catalyzed methylenation and the Wittig reaction is even more

impressive for the discrimination between an aldehyde and an alkoxy-substituted ketone. Indeed, the rhodium-catalyzed methylenation of keto aldehyde **32** with trimethylsilyldiazomethane produced exclusively alkene **33**, with no trace of diene **34** (eq 5). Conversely, a mixture of the starting material, alkene **33**





and diene **34** was observed when substrate **32** was submitted to standard Wittig methylenation conditions (eq 6). These two examples clearly illustrate that although the same reagent, methylenetriphenylphosphorane (vide infra), is generated under these two reaction conditions, its reactivity is highly affected by the other components of the reaction mixture, particularly the presence of inorganic salts, such as sodium bromide. Complexation of sodium bromide with the hydroxyketone of **32** should activate this carbonyl; thus the ketone becomes almost as reactive as the aldehyde.

Mechanistic Considerations. An outline of the two mechanisms that have been suggested for transition metal-catalyzed olefination with ethyldiazoacetate is illustrated in Schemes 1 and 2. In contrast to these olefination mechanisms, it seems unlikely that the rhodium-catalyzed methylenation reaction proceeds through a metal carbene intermediate. For instance, one would expect a reaction with rhodium(II) acetate, which is known for producing metal carbenes with diazo compounds. However, we observed that this complex is inefficient at catalyzing the olefination reaction. In addition, it is known that diazo compounds react with rhodium(I) complexes through nitrogen coordination and the adduct does not produce carbene species.[16,48] Instead of a carbene-based mechanism, we propose the following catalytic cycle: activation of trimethylsilyldiazomethane with the rhodium(I)[49] catalyst leads to the protonation by 2-propanol, followed by attack of triphenylphosphine with nitrogen extrusion to form a silylated phosphonium salt and to regenerate the catalyst (Figure 1). Desilylation by the alkoxide produces the desired methylenetriphenylphosphorane.

Spectroscopic investigations have been carried out to confirm the absence of carbene species and formation of the phosphorus ylide. First, attempts to identify the formation of a carbene species between the rhodium catalyst and trimethylsilyldiazomethane, with or without 2-propanol, were unsuccessful. In fact, NMR spectra of $RhCl(PPh_3)_3$ and $TMSCHN_2$ indicated a complex mixture of new rhodium species. Ligand exchange and formation of a *N*-coordinated diazo rhodium complex, such as **A**, seems more plausible, although a discrete species could not be identified from our NMR data. However, when we added triphenylphosphine and 2-propanol to this mixture, we clearly observed the formation of methylenetriphenylphosphorane as shown in Figure 2B. We initially observed the formation of *i*-PrOTMS (Figure 2A). The characteristic doublet of methyl-

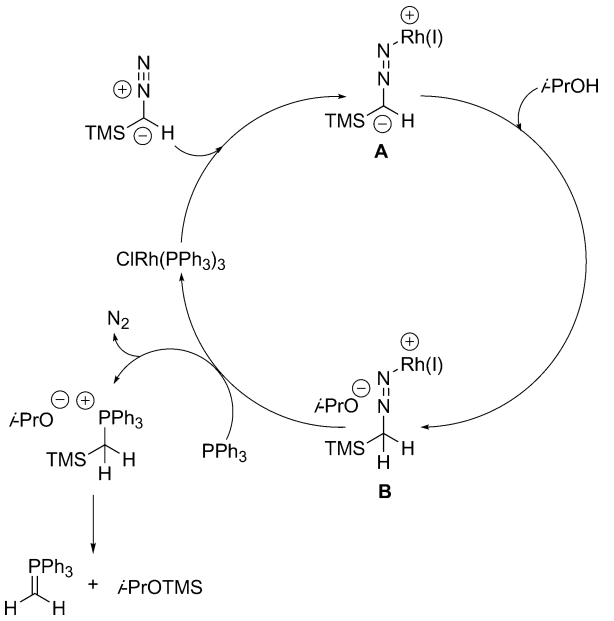


Figure 1. Proposed catalytic cycle for the rhodium-catalyzed methylenation with trimethylsilyldiazomethane, 2-propanol, and triphenylphosphine.

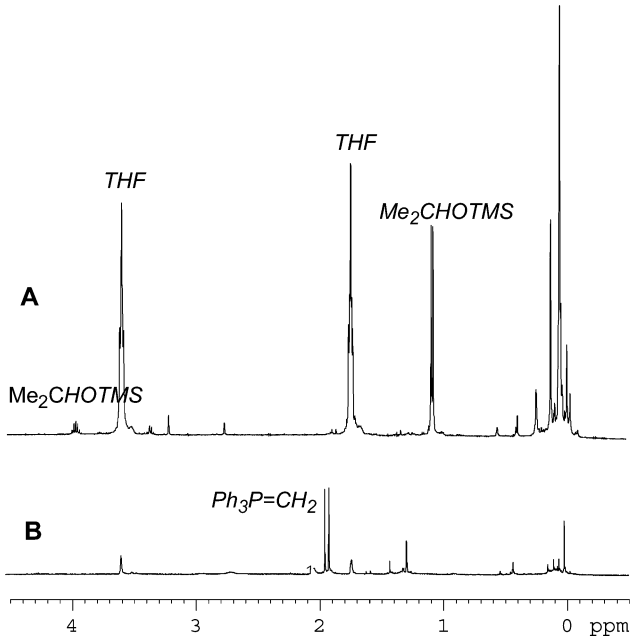


Figure 2. ^1H NMR spectra showing the formation of methylenetriphenylphosphorane in d_8-THF from trimethylsilyldiazomethane, 2-propanol, triphenylphosphine, and chlorotris(triphenylphosphine)rhodium. (A) Initial spectrum. (B) After partial evaporation under argon.

(47) For selected examples of chemoselective methylenation, see: (a) Hsu, P.-Y.; Lee, Y.-C.; Liao, C.-C. *Tetrahedron Lett.* **1998**, *39*, 659−662. (b) Paquette, L. A.; Heidelbaugh, T. M. *Synthesis* **1998**, 495−508. (c) Nicolaou, K. C.; King, N. P.; Finlay, M. R. V.; He, Y.; Roschangar, F.; Vourloumis, D.; Vallberg, H.; Sarabia, F.; Ninkovic, S.; Hepworth, D. *Bioorg. Med. Chem.* **1999**, *7*, 665−697. (d) Faure, S.; Piva, O. *Tetrahedron Lett.* **2001**, *42*, 255−259. (e) Kim, D.; Lee, J.; Chang, J.; Kim, S. *Tetrahedron* **2001**, *57*, 1247−1252. (f) Kahnberg, P.; Lee, C. W.; Grubbs, R. H.; Sterner, O. *Tetrahedron* **2002**, *58*, 5203−5208. (g) Oesterreich, K.; Klein, I.; Spitzner, D. *Synlett* **2002**, 1712−1714.

(48) (a) Werner, H.; Schwab, P.; Mahr, N.; Wolf, J.; Werner, H. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1480−1482. (b) Werner, H.; Schwab, P.; Bleuel, E.; Mahr, N.; Steinert, P.; Wolf, J. *Chem.—Eur. J.* **1997**, *3*, 1375−1384.

(49) We suggest the formation of a rhodium(I) complex with trimethylsilyldiazomethane that has a similar coordination to that observed by Brookhart; see ref 16.

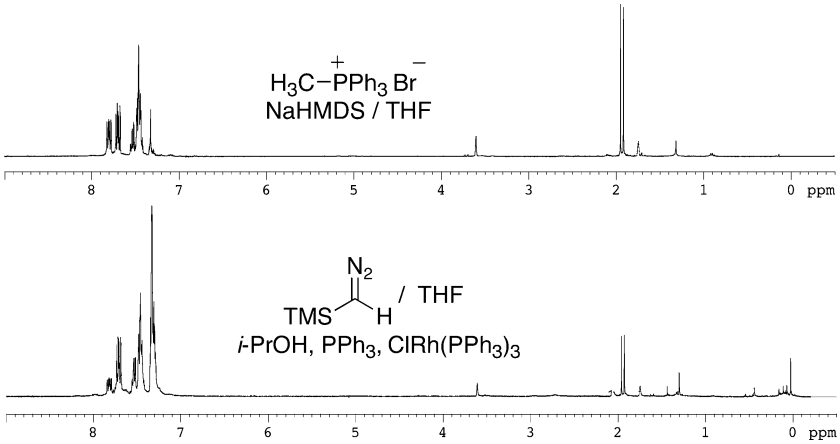
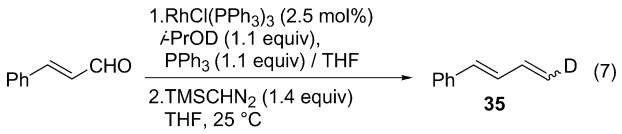


Figure 3. ^{1}H NMR spectra showing the formation of methylenetriphenylphosphorane in d_8-THF from methyltriphenylphosphonium bromide and sodium hexamethyldisilazide and from trimethylsilyldiazomethane, 2-propanol, triphenylphosphine, and chlorotris(triphenylphosphine)rhodium.

enetriphenylphosphorane could be seen after partial evaporation under argon to remove the more volatile material (Figure 2B).

A comparison of the ^{1}H NMR spectrum obtained from a mixture of methyltriphenylphosphonium bromide and sodium hexamethyldisilazide with that of our reaction mixture (trimethylsilyldiazomethane, 2-propanol, triphenylphosphine, and chlorotris(triphenylphosphine)rhodium) showed that methylenetriphenylphosphorane is the major species in both cases (Figure 3). The addition of cinnamaldehyde to that mixture led to the disappearance of the phosphorus ylide and the formation of the diene and triphenylphosphine oxide. We have also independently prepared the salt Ph_3PCH_2TMSX[50] and showed the quantitative formation of methylenetriphenylphosphorane upon treatment with sodium 2-propoxide (prepared from 2-propanol and NaHMDS). Again, addition of cinnamaldehyde led to the formation of the corresponding diene.

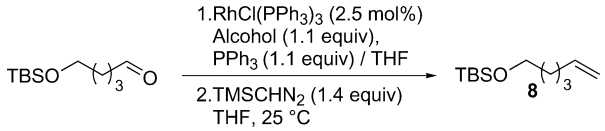
The alcohol is an essential component of the reaction, and no methylenation reaction is observed in the absence of 2-propanol. The alcohol is responsible for the desilylation reaction, as confirmed by the observation of *i*-PrOTMS from the reaction mixture. In addition, when using deuterated 2-propanol, we observed deuteration of the terminal double bond (eq 7).



(7)

We initially proposed that the first step of the catalytic cycle is the attack of triphenylphosphine on the trimethylsilyldiazomethane of complex **A** rather than protonation with the alcohol (Figure 1). However, the important observation that nitrogen evolution is not seen until 2-propanol is added to the reaction mixture led us to consider the second possibility and study in more detail the role of the alcohol. We first surveyed a variety of alcohols which demonstrated that 2-propanol was the optimal additive (Table 6).[51] When less hindered alcohols, such as methanol, ethanol, or benzyl alcohol, were used, the methylenation reaction never reached completion (entries 1−3).[52] The trimethylsilyldiazomethane seems partially destroyed under these reagents. Other secondary alcohols, such as cyclohexanol, 1-phenylethanol, or *s*-butanol, could be also used, although longer reaction time were required (entry 5−7). In the presence of more hindered alcohols, such as *tert*-butyl alcohol, a much slower reaction was observed (entry 8). Surprisingly, when 2-propanol was replaced by the more acidic phenol, no methylenation reaction was observed, although we observed the spontaneous formation of PhOTMS and PhOMe (entry 9).

Table 6. Rhodium-Catalyzed Methylenation of 6-(*tert*-Butyldimethylsilyloxy)-1-pentanal Using Various Alcohols



entry	alcohol	conv[a] (%)
1	MeOH; 1.5 h	58
2	EtOH; 1.5 h	63
3	BnOH; 1 h	54
4	*i*-PrOH; 1 h	≥98
5	*c*-HexOH; 2 h	≥98
6	PhCH(OH)Me; 2 h	≥98
7	*s*-BuOH; 6 h	≥98
8	*t*-BuOH; 8 h	52
9	PhOH; 6 h	0

[a] Determined by GC.

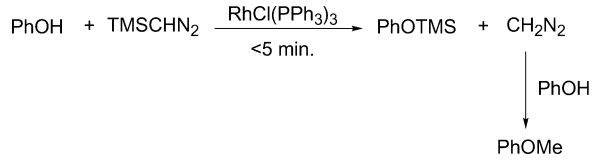
It was previously established that the reaction of $TMSCHN_2$ with an alcohol does not produce the silylated alcohol and diazomethane (eq 8).[36d] Conversely, when $TMSCHN_2$ was treated with 2-propanol in the presence of the Wilkinson's catalyst (but in the absence of the phosphine reagent), we

(50) (a) This salt was prepared from $Ph_3PCH{=}TMS$ and HCl and then treated with $NaBPh_4$ according to the following procedure: Seyferth, D.; Singh, G. *J. Am. Chem. Soc.* **1965**, *87*, 4156−62. (b) It has been shown that these salts ($TMSCH_2PPh_3X$) cannot be synthesized from the reaction between $TMSCH_2Cl$ and triphenylphosphine. In addition, they are very difficult to prepare as a single species. Indeed, the salt we prepared was a 1:1 mixture of $TMSCH_2PPh_3Cl$ and $TMSCH_2PPh_3BPh_4$, in addition to containing 30% of CH_3PPh_3X. For discussion, see: Schmidbaur, H.; Tronich, W. *Chem. Ber.* **1967**, *100*, 1032−1050.

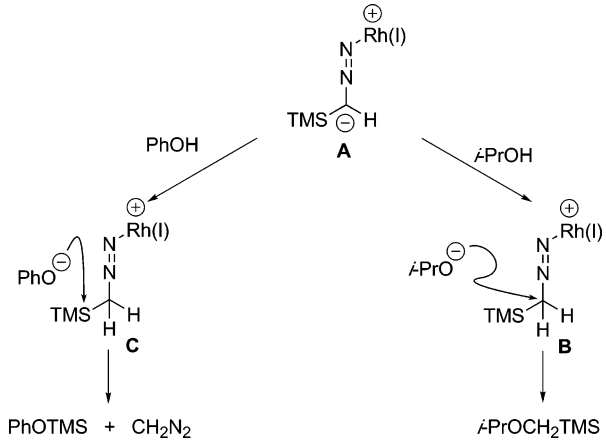
(51) All of the alcohols were purified under drying agents prior to use, although we have shown that the methylenation reaction is not strongly influenced by the presence of water; see ref 35.

(52) We based our argumentation on steric factors, as the difference in pK_a's between those alcohols and 2-propanol is minimal and cannot account for the drastic effect observed in the methylenation reaction. For instance, the pK_a of EtOH (DMSO) is 29.8; the pK_a of *i*-PrOH (DMSO) is 30.3. See: Olmstead, W. N.; Margolin, Z.; Bordwell, F. G. *J. Org. Chem.* **1980**, *45*, 3295−3299.

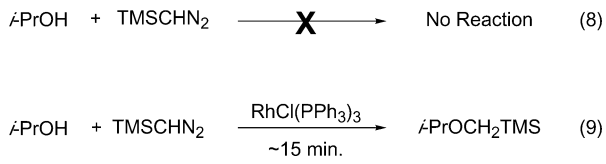
Scheme 3



Scheme 4



observed the formation of trimethylsilylmethyl(2-propyl)ether (eq 9).



In contrast, the same reaction with phenol led to trimethylsilyl(phenyl)ether and phenylmethyl ether (Scheme 3). These results suggest an initial protonation of the diazo reagent coordinated to the metal (**A**) with both alcohols, leading to an intermediate such as **B** or **C** (Scheme 4). A fast silylation reaction of the phenoxide will then occur to generate PhOTMS, prior to a reaction with triphenylphosphine. This reaction prevents the formation of the phosphorus ylide and explains why no olefination reaction was observed in the presence of phenol. The other byproduct, diazomethane, will then react with another equivalent of phenol, as illustrated in Scheme 3. In the case of 2-propanol, a similar protonation of complex **A** seems to occur initially. However, the steric hindrance of the isopropoxide precludes its silylation. In the absence of triphenylphosphine, isopropoxide attacks on the carbon of complex **B** producing *i*-PrOCH$_2$TMS after extrusion of nitrogen. We can envision that, in the presence of triphenylphosphine, this later step will take place with the phosphine reagent being more nucleophilic than the isopropoxide. These control experiments, combined with the observation that no reaction was observed between complex **A** and triphenylphosphine (in the absence of 2-propanol), indicate that the initial step in the catalytic cycle is the protonation of trimethylsilyldiazomethane from complex **A** to form complex **B**, followed by the attack of triphenylphosphine.

Conclusion

In summary, the rhodium-catalyzed methylenation of aldehydes has been presented. The reaction conditions have been optimized to lead to a very efficient procedure. The synthetic potential is highlighted by the functional group compatibility of this methodology, which allows the preparation of terminal alkenes with yields up to 99%. The reaction conditions are mild enough to be compatible with sensitive and enolizable substrates. The chemoselectivity of the reaction is remarkable in that aldehydes selectively react in the presence of ketones, whereas a much lower chemoselectivity was observed using the standard Wittig conditions. The use of an easily removable phosphine, DPPBE (**6**), has facilitated the purification of the alkenes produced. Finally, we propose that this reaction proceeds by an unusual mechanism that involves the formation of methylenetriphenylphosphorane via the activation of the trimethylsilyldiazomethane by coordination of the nitrogen with the rhodium(I) complex.

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Supporting Information Available: Characterization data for new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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