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Highly Efficient Synthesis of Terminal Alkenes from Ketones

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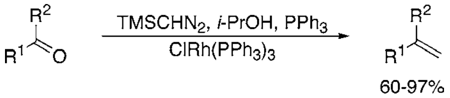
ABSTRACT



The rhodium(I)-catalyzed methylenation of ketones using trimethylsilyldiazomethane proceeds to give the corresponding alkenes in good yields (60–97%). The use of an excess of 2-propanol and 1,4-dioxane as a solvent were instrumental to obtain the desired alkenes in high yields. Superior results were achieved with the rhodium(I)-catalyzed methylenation in comparison with the standard Wittig reaction.

The synthesis of terminal alkenes from carbonyl derivatives is a very important reaction in organic synthesis.[1] The Wittig reaction[2] has been quite reliable for this transformation, although low reactivity with hindered carbonyl derivatives often required an excess of reagent.[3] Conversely, numerous stoichiometric *gem*-bimetallic reagents have been shown to react readily with ketones, leading to the corresponding alkene in high yields.[4] The development of a process using a catalytic amount of a transition metal complex to achieve methylenation reaction has been recently accomplished by our group.[5] Indeed, we showed that rhodium(I) complexes efficiently catalyzed the methylenation of a variety of aldehydes with trimethylsilyldiazomethane in the presence of triphenylphosphine and 2-propanol. However, the use of this strategy with more hindered substrates, such as ketones, has been so far limited to ketones containing an electron-withdrawing group, such as fluorine.[6] In this communication, we wish to report our efforts that led to the development of an efficient procedure for the synthesis of alkenes from various ketones.

On the basis of our previous work with fluoromethyl ketones,[6] we initially postulated that substitution of methyl ketones with other electron-withdrawing groups, such as acetoxy and benzoxy groups, could provide the desired alkene under our typical reaction conditions. However, allyl acetate **1** and allyl benzoate **2** were isolated only with moderate yields, and the formation of a silylated phosphonium salt derived from the ketone was also observed (Table 1, entries 1 and 3).[7] We hypothesized that increasing the amount of 2-propanol in the reaction mixture could diminish the Lewis acid character of the silyl reagent. Indeed, the presence of 10 equiv of 2-propanol, 1.6 equiv of trimethyl-

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[1] Kelly, S. E. Alkene Synthesis. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, p 729.

[2] (a) Wittig, G.; Geissler, G. *Liebigs Ann. Chem.* **1953**, *580*, 44−57. (b) Wittig, G.; Schöllkopf, U. *Chem. Ber.* **1954**, *87*, 1318−1330.

[3] For selected examples, see: (a) Noguchi, H.; Aoyama, T.; Shioiri, T. *Tetrahedron* **1995**, *51*, 10531−10544. (b) Mehta, G.; Islam, K. *Synlett* **2000**, 1473−1475. (c) Kim, D.; Lee, J.; Chang, J. Y.; Kim, S. *Tetrahedron* **2001**, *57*, 1247−1252. (d) Enders, D.; Voith, M. *Synlett* **2002**, 29−32. (e) Bailey, W. F.; Daskapan, T.; Rampalli, S. *J. Org. Chem.* **2002**, *68*, 1334−1338. (f) Tanaka, M.; Imai, M.; Yamamoto, Y.; Tanaka, K.; Shimowatari, M.; Nagumo, S. J.; Kawahara, N.; Suemune, H. *Org. Lett.* **2003**, *5*, 1365−1367. (g) Pirrung, M. C.; Liu, H. *Org. Lett.* **2003**, *5*, 1983−1985. (h) Bagal, S. K.; Adlington, R. M.; Baldwin, J. E.; Marquez, R.; Cowley, A. *Org. Lett.* **2003**, *5*, 3049−3052.

[4] (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611−3613. (b) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392−6394. See also: (c) Tour, J. M.; Bedworth, P. V.; Wu, R. L. *Tetrahedron Lett.* **1989**, *30*, 3927−3930. (d) Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579−5580. (e) Lombardo, L. *Org. Synth.* **1987**, *65*, 81−89. (f) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668−2670. (g) Nysted, L. N. U.S. Patent 3,865,848, 1975; *Chem. Abstr.* **1975**, *83*, 1406q. (h) Matsubara, S.; Sugihara, M.; Utimoto, K. *Synlett* **1998**, 313−315.

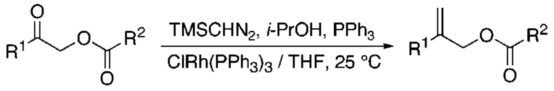
[5] (a) Lebel, H.; Paquet, V. *J. Am. Chem. Soc.* **2004**, *126*, 320−328. (b) Lebel, H.; Paquet, V. *Organometallics* **2004**, *23*, 1187−1190. (c) Grasa, G. A.; Moore, Z.; Martin, K. L.; Stevens, E. D.; Nolan, S. P.; Paquet, V.; Lebel, H. *J. Organomet. Chem.* **2002**, *658*, 126−131. (d) Lebel, H.; Paquet, V.; Proulx, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2887−2890.

[6] Lebel, H.; Paquet, V. *Org. Lett.* **2002**, *4*, 1671−1674.

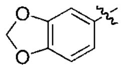
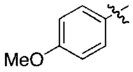
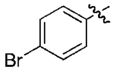
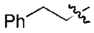
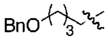
[7] This byproduct seems the result of a nucleophilic attack of triphenylphosphine onto the ketone, activated with TMSX. For a similar example, see: Lee, S. W.; Trogler, W. C. *J. Org. Chem.* **1990**, *55*, 2644−2648.

10.1021/ol049085p CCC: $27.50

Table 1. Rhodium-Catalyzed Methylenation of α-Acetoxy- or α-Benzoxymethyl Ketones (eq 1)[a]

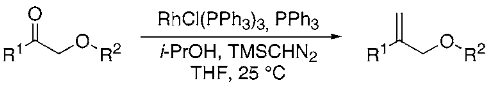


(1)

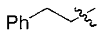
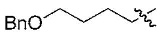
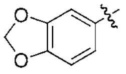
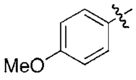
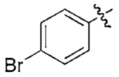
entry	R1	R2	yield[b]
1		CH_3 (**1**)	46%
2		CH_3 (**1**)	61%[c]
3		Ph (**2**)	52%
4		Ph (**2**)	82%[c]
5		Ph (**3**)	48%
6		Ph (**3**)	82%[c]
7		Ph (**4**)	74%[c]
8		Ph (**5**)	59%
9		Ph (**5**)	74%[c]
10		Ph (**6**)	84%[c]

[a] Conditions: TMSCHN$_2$ (1.6 equiv), 2-propanol (1.1 equiv), triphenylphosphine (1.1 equiv), and RhCl(PPh$_3$)$_3$ (2.5 mol %). [b] Isolated yield. [c] Using 10 equiv of 2-propanol.

Table 2. Rhodium-Catalyzed Methylenation of α-AlkoxylMethyl Ketones (eq 2)[a]



(2)

entry	R1	OR2	yield (%)[b]	yield (%) (Wittig)[c]
1		OH (**7**)	60	---
2		OMOM (**8**)	74	---
3		OBn (**9**)	84	62
4		OTHP (**10**)	83	---
5		OTES (**11**)	74	---
6		OTBS (**12**)	94	---
7		OTIPS (**13**)	97	87
8		OBn (**14**)	84[d]	82
9		OTHP (**15**)	68	72
10		OTES (**16**)	83	75
11		OTBS (**17**)	77	69
12		OTIPS (**18**)	73	73
13		OBn (**19**)	74[d]	---
14		OTHP (**20**)	83[d]	---
15		OTBS (**21**)	87[d]	86
16		OBn (**22**)	64	59
17		OTES (**23**)	79	71
18		OTBS (**24**)	84[d]	81
19		OBn (**25**)	74	67
20		OTBS (**26**)	77	82

[a] Conditions: TMSCHN$_2$ (1.6 equiv), 2-propanol (10 equiv), triphenylphosphine (1.1 equiv), and RhCl(PPh$_3$)$_3$ (2.5 mol %). [b] Isolated yield. [c] Ph$_3$PCH$_3$Br (1.1 equiv) and NaHMDS (1.1 equiv). [d] Oxidative workup using Oxone.

silyldiazomethane, 1.1 equiv of triphenylphosphine, and 2.5 mol % of Wilkinson's catalyst led to the formation of the desired alkene with complete conversion. Despite this, the isolated yield for allyl acetate **1** remained modest, as the product was not stable and readily decomposed in the presence of the transition metal complex, probably through the formation of a π-allyl complex (entry 2).[8] In contrast, allyl benzoate **2** was isolated with 82% yield in the presence of an excess of 2-propanol (entry 4). Similar yields were obtained for various aromatic and aliphatic allyl benzoates under those reaction conditions (entries 6, 7 and 9, 10). When we investigated other alkoxy derivatives, we were delighted to find that the beneficial effect of an excess of 2-propanol was not limited to benzoate derivatives (Table 2). Partial conversion and moderate yields were obtained with unprotected hydroxyl derivatives, as those primary alcohols are known to partially decompose the TMSCHN$_2$ reagent (entry 1).[5a] However, a number of protected α-hydroxy ketones could be reacted with good yields (entries 2−7). Typically, benzyloxymethyl and *tert*-butyldimethylsilyloxymethyl ketones provided the highest yields. The reaction conditions are compatible with both aromatic and aliphatic substrates. In general, the yields obtained with our rhodium-catalyzed methylenation reaction are similar or slightly superior to those obtained when using the typical Wittig reaction conditions with methyltriphenylphosphonium bromide and NaHMDS. We have also devised an oxidative workup using Oxone, to oxidize the remaining triphenylphosphine, which facilitates the purification of nonpolar allylic ethers (entries 8, 13−15, 18).[9]

The initial results obtained for the methylenation of aliphatic ketones, such as 4-phenyl-2-butanone, were quite disappointing (Table 3). Even in the presence of an excess of 2-propanol, the conversion into the corresponding alkene remained low, although we could clearly observe the presence of unreacted methylenetriphenylphosphorane in the ^{1}H NMR spectra.[10] Further increasing the amount of 2-propanol from 10 to 30 equiv did not help either (entry 3). It is only when we used a large excess of trimethylsilyldiazomethane that we could achieve 80% conversion (entry 4). Heating the reaction at 50 °C surprisingly did not lead to any significant increases of the conversion (entry 2). Wilkinson's catalyst does not appear to be stable at high temperature in THF and crashed out from the reaction mixture as the chloro bridged dimer. We found that the rhodium catalyst is more stable in 1,4-dioxane; thus, heating the reaction at

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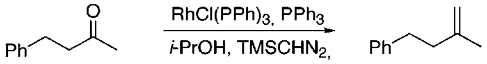
(8) (a) Takeuchi, R.; Kitamura, N. *New J. Chem.* **1998**, *22*, 659−660. (b) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581−5582.

(9) Oxone is known to oxidize readily organophosphorus derivatives, see: Wozniak, L. A.; Stec, W. J. *Tetrahedron Lett.* **1999**, *40*, 2637−2640.

(10) It was unambiguously established that methylenetriphenylphosphorane was the active methylenation reagent formed from trimethylsilyldiazomethane, 2-propanol, and triphenylphosphine in the presence of Wilkinson's catalyst. See ref 5a for details.

Table 3. Optimization of the Rhodium-Catalyzed Methylenation of 4-Phenyl-2-butanone (eq 3)[a]

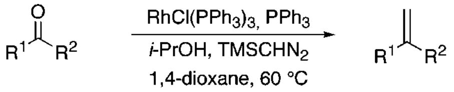


(3)

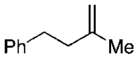
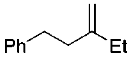
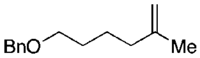
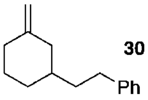
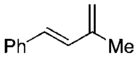
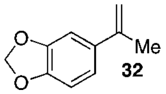
entry	solvent	temp.	*i*-PrOH (equiv)	$\mathrm{TMSCHN_2}$ (equiv)	conv.(%)[b]
1	THF	25 °C	10	1.6	33
2		50 °C	10	1.6	34
3		25 °C	30	1.6	35
4		25 °C	30	4.6	80
5	1,4-dioxane	25 °C	10	1.6	46
6		50 °C	10	1.6	80
7		50 °C	15	2.4	90
8		65 °C	15	2.4	100

[a] Conditions: $\mathrm{RhCl(PPh_3)_3}$ (2.5 mol %) and triphenylphosphine (1.1 equiv). [b] Determined by GC.

Table 4. Rhodium-Catalyzed Methylenation of Aliphatic and Aromatic Ketones (eq 4)[a]



(4)

entry	product	yield (%)[b]	yield (%) (Wittig)[c]
1	 **27**	88	81
2	 **28**	87	71
3	 **29**	78[d]	68
4	 **30**	93	59
5	 **31**	97	79
6	 **32**	87	---

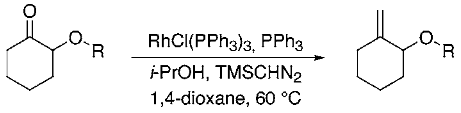
[a] Conditions: $\mathrm{TMSCHN_2}$ (2.4 equiv), 2-propanol (15 equiv), triphenylphosphine (1.1 equiv), and $\mathrm{RhCl(PPh_3)_3}$ (2.5 mol %). [b] Isolated yield. [c] $\mathrm{Ph_3PCH_3Br}$ (1.1 equiv) and NaHMDS (1.1 equiv). [d] Oxidative workup using Oxone.

50 °C in this solvent in the presence of 1.6 equiv of trimethylsilyldiazomethane led to the formation of the terminal alkene within 80% conversion (entry 6). After further optimizations, we found that the optimal reaction conditions took place in 1,4-dioxane at 65 °C with 2.5 mol % of $\mathrm{RhCl(PPh_3)_3}$, 1.1 equiv of triphenylphosphine, 15 equiv of 2-propanol, and 2.4 equiv of trimethylsilyldiazomethane (entry 8).

As outlined in Table 4, high yields (78−97%) could be obtained with a variety of aliphatic and aromatic ketones under these reaction conditions. In addition to aliphatic methyl alkenes (entries 1 and 3), alkenes derived from ethyl alkyl ketones and cyclic ketones were synthesized in high yields (entries 2 and 4).

Furthermore, an aliphatic α,*β*-unsaturated ketone led to the desired diene **31** with 97% yield. In all cases, the rhodium-catalyzed methylenation reaction with trimethylsilyldiazomethane proved to be superior to the standard Wittig reaction using $\mathrm{Ph_3PCH_3Br}$ and NaHMDS. In many cases the Wittig reaction did not reach completion, whereas the rhodium-catalyzed decomposition of trimethylsilyldiazomethane did provide the alkene with complete conversion.[11] In contrast, cyclic α,*β*-unsaturated ketones, such as cyclohexenone or cyclopentenone, did not lead to the desired alkene but instead provided 1,4-addition products.[12] For more hindered substrates, such as α-alkoxycyclohexanone derivatives, the generation of only 1.1 equiv of methylenetriphenylphosphorane was not sufficient for the methylenation reaction to reach completion. It was necessary to increase the amount of triphenylphosphine to 2 equiv to furnish the corresponding terminal alkenes with high yields (Table 5). 2-Benzyloxy- and 2-tetrahydropyranyl-2-oxy-cyclohexanones led to the formation of the corresponding allylic ether with 82% and 72% yields, respectively (entries 1 and 2). 2-Triisopropylsilyloxycyclohexanone provided the highest yield among all silyloxy derivatives (entries 3−5), as 2-*tert*-butyldimethylsilyloxymethylcyclohexanone was surprisingly

Table 5. Rhodium-Catalyzed Methylenation of α−AlkoxyCyclohexanone Derivatives (eq 5)[a]



(5)

entry	OR	yield (%)[b]	yield (%) (Wittig)[c]
1	OBn (**33**)	82	77
2	OTHP (**34**)	72	59
3	OTES (**35**)	64[d]	60
4	OTBS (**36**)	71[e]	52[f]
5	OTIPS (**37**)	89	34[g]
6	OBz (**38**)	80	68

[a] Conditions: $\mathrm{TMSCHN_2}$ (2.4 equiv), 2-propanol (15 equiv), triphenylphosphine (2.0 equiv), and $\mathrm{RhCl(PPh_3)_3}$ (2.5 mol %); oxidative workup using Oxone. [b] Isolated yield. [c] $\mathrm{Ph_3PCH_3Br}$ (2.0 equiv) and NaHMDS (2.0 equiv). [d] Standard workup. [e] 2.5 equiv of $\mathrm{PPh_3}$. [f] $\mathrm{Ph_3PCH_3Br}$ (2.5 equiv) and NaHMDS (2.5 equiv). [g] LiHMDS was used.

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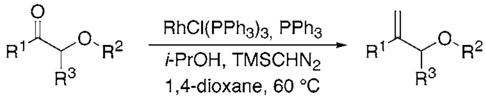
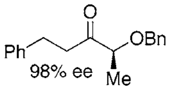
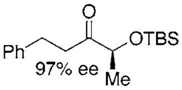
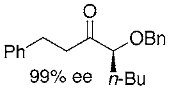
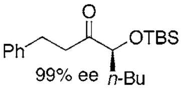
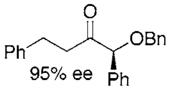
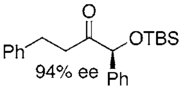
(11) The same amount of the phosphine reagent, either triphenylphosphine for the rhodium-catalyzed methylenation or methyltriphenylphosphonium bromide for the standard Wittig, were used to generate the same amount of the ylide reagent with both methods for comparison purpose. It is common practice however, to use an excess of methylenetriphenylphosphorane under standard Wittig reaction with such substrates to achieve better yields.

(12) No cyclopropane derivative was observed in these reactions. Silylated Michael addition products (as a mixture of diastereoisomers) appear to be the major products.

Table 6. Rhodium-Catalyzed Methylenation of Chiral Enantioenriched α-Alkoxyketone Derivatives (eq 6)[a]



(6)

Entry	Substrate	Product	Yield (%)[b]	ee (%)
1		(**39**)	81	97
2		(**40**)	90	95
3		(**41**)	84[c]	99
4		(**42**)	86[c]	99
5		(**43**)	87	95
6		(**44**)	81	94

[a] Conditions: $TMSCHN_2$ (2.4 equiv), 2-propanol (15 equiv), triphenylphosphine (1.5 equiv), and $RhCl(PPh_3)_3$ (2.5 mol %); oxidative workup using Oxone. [b] Isolated yield. [c] $TMSCHN_2$ (3.2 equiv), 2-propanol (20 equiv), triphenylphosphine (2.5 equiv), and $RhCl(PPh_3)_3$ (2.5 mol %); oxidative workup using Oxone.

unreactive. Here again, the comparison with the standard Wittig reaction was in favor of the rhodium-catalyzed methylenation. Whereas the generation of 2.0−2.5 equiv of methylenetriphenylphosphorane was sufficient to reach completion in the presence of Wilkinson's catalyst, only partial conversion was observed with the same amount of Ph_3PCH_3Br and NaHMDS, leading to the isolation of alkenes with modest yields.[11]

So far, the rhodium-catalyzed methylenation reaction of substituted enolizable substrates was shown to proceed without epimerization. To test the stereochemical integrity of adjacent chiral centers under the new reaction conditions, a series of chiral enantioenriched α-benzyloxy- and α-*tert*-butyldimethylsilyloxy-ketone derivatives were prepared from the chiral pool (Table 6). Substrates of entries 1 and 2 were derived from (*S*)-ethyl lactate, whereas other ketones were obtained from the corresponding diol, obtained by hydrolytic kinetic resolution of terminal epoxides[13] (entries 3 and 4) and by asymmetric dihydroxylation[14] (entries 5 and 6). When treated under the rhodium-catalyzed methylenation reaction conditions in 1,4-dioxane at 60 °C, these ketones furnished the corresponding alkenes with 81 to 90% yield. More importantly, no significant erosion of the enantiomeric excess was observed in the alkene products.[15]

In summary, we have described new reaction conditions for the synthesis of terminal alkenes from ketones. The alkene products were obtained in high yields, which are usually superior to those observed with the standard Wittig reaction condition. Moreover the stereochemical integrity of adjacent chiral centers is maintained for enolizable ketones.

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Supporting Information Available: Experimental procedures, compound characterization data, and ^1H spectra of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] Similar results could be obtained with Ph_3PCH_3Br and NaHMDS: for instance, alkene **39** was isolated with 85% yield and 97% ee.