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BiBr$_3$-Catalyzed benzylation of alcohols. Stereochemistry and mechanistic investigations

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Abstract—We have investigated the benzylation of optically active aliphatic alcohols (octan-2-ol and butan-2-ol) as well as *cis* and *trans* 2-methylcyclohexanol or (*S*)-(−)-menthol, catalyzed by bismuth (III) bromide in the presence of (−) or (±)-1-phenylethanol (PeOH). Under mild conditions, aliphatic alcohols provided an equimolar mixture of diastereomeric ethers while alicyclic alcohols gave rise to ethers with retention of configuration. To explain these results, we assumed that BiBr$_3$, acting as Lewis acid, would lead to the formation of a 6-fold coordinated bismuth intermediate involving two molecules of 1-phenylethanol and one molecule of aliphatic alcohol. We have proposed a mechanism to explain these BiBr$_3$-promoted etherification reactions. © 2001 Elsevier Science Ltd. All rights reserved.

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1. Introduction

In a series of preliminary studies, we have established the general usefulness of bismuth (III) reagents for the halogenations of alcohols,[1] the halogen exchange reactions[2] of halides with various BiX$_3$ and more recently, the protection of aliphatic alcohols as benzylic ethers.[3]

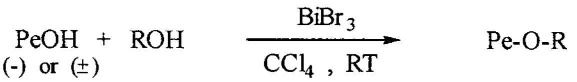
Therefore, we showed that BiBr$_3$ was very efficient in promoting the benzylation of aliphatic alcohols (primary, secondary and tertiary) by various benzylic alcohols (benzyl alcohol, 1-phenylethanol and 2-phenylpropan-2-ol). This was achieved under good yield, under mild conditions.[3]

In this paper, we extended our investigation, by studying the reaction mechanism of the noteworthy catalytic activity of BiBr$_3$ for the benzylation of alcohols. In order to do so, we extended the examples to a series of optically active alcohols—both benzylic and aliphatic. Concerning the benzylic alcohols, we have chosen the 1-phenylethanol (PeOH) for the following reasons:

(i) it provides the possibility of introducing a chiral center in the corresponding unsymmetrical ether;
(ii) regardless of the aliphatic alcohol, its reactivity was slightly lower than that observed with the 2-phenylpropan-2-ol, but significantly higher than that of benzyl alcohol;[3]
(iii) ethers derived from 1-phenylethanol proved to be stable under acidic conditions, but were easily cleaved by hydrogenolysis.[3]

2. Results and discussion

The stereochemistry of the reaction and the mechanistic examination were investigated under the same previous experimental conditions[3] using alternatively (−) or (±)-1-phenylethanol (PeOH) as benzylic alcohol, and (+) or (±)-octan-2-ol and butan-2-ol as aliphatic alcohols. Reactions were run in the presence of BiBr$_3$. The general scheme was as follows:



$$\underset{(-)\ \text{or}\ (\pm)}{\text{PeOH}} + \text{ROH} \xrightarrow[\text{CCl}_4\ ,\ \text{RT}]{\text{BiBr}_3} \text{Pe-O-R}$$

ROH = (-) or (±)-octan-2-ol, (-) or (±)-butan-2-ol

For each reaction, optical rotations of isolated phenylethyl ethers (PeOR) were measured. These results are reported in Table 1.

In any case, the ether is obtained by the condensation of two chiral alcohols. One alcohol molecule undergoes a C–O bond breaking and can be considered as the substrate. The other alcohol molecule retains its oxygen atom and plays the role of a nucleophilic reactant. Only the alcohol substrate is able to undergo a configuration change (partial or complete inversion), unless the reaction proceeds with retention of configuration.

The data reported in Table 1 calls for the following remarks:

(i) entry 1: in this case, a symmetrical ether was formed as a mixture of two diastereoisomers in a 50/50 ratio. This result indicates that there is a total racemisation of the alcohol substrate and therefore yields the two ethers (*S*,*S*) and (*S*,*R*);

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Table 1. Optical rotations of phenylethylethers obtained using $BiBr_3$ in CCl_4[3]

Entry	PeOH[a]	ROH[a]	Reaction times (min)	$[\alpha]_D$[b]	Yield[c] (%)	GC[d]
1	(−)-*S*	–	20	−36.2°[e]	95	2 (50/50)
2	(−)-*S*	(±)-octan-2-ol	45	−27.6°[e]	90	2 (50/50)
3	(−)-*S*	(+)-octan-2-ol	45	−27.6°[e]	92	2 (50/50)
4	(±)-	(+)-octan-2-ol	45	0.0°[e]	95	2 (50/50)
5	(−)-*S*	(+)-butan-2-ol	20	+5.0°[f]	95	2 (55/45)
6	(±)-	(+)-butan-2-ol	20	+13.5°[f]	92	2 (55/45)
7	(−)-*S*	(±)-butan-2-ol	20	+5.0°[f]	92	2 (55/45)

[a] The optical rotations of pure alcohols are: (−)-PeOH ($[\alpha]_D=-45°$; $c=5$, CH_3OH); (+)-octan-2-ol ($[\alpha]_D=+9.8$; $c=5$, CH_3OH); (+)-butan-2-ol ($[\alpha]_D=+12°$; $c=10$, CH_3OH), respectively.

[b] Optical rotations were determined at 25°C.

[c] Isolated yields of ether, exhibiting ^1H NMR data consistent with their assigned structures.

[d] Signals detected by GC on the completion of the reaction. In all cases, two ethers are formed as observed by GC. Percentage of both ethers is given in parentheses.

[e] $c=5$, CH_3OH.

[f] $c=10$, CH_3OH.

(ii) entries 2 and 3: in both cases, the same mixture of diastereomeric ethers (50/50) is formed with the same optical rotation. Clearly, the octan-2-ol plays the role of the alcohol substrate and is completely racemised (entry 3);

(iii) entry 4: the formation of an optically inactive ether's mixture has been observed. This result confirms the total racemisation of the octan-2-ol;

(iv) entries 5–7: the butan-2-ol presents a similar behavior to that of the octan-2-ol, except that the racemisation is not complete.

It clearly appeared that the alcohol substrate undergoes racemisation. Since this alcohol is incubated with $BiBr_3$ before 1-phenylethanol is added, we presumed that the alcohol racemisation would result from the reaction of the water, which we thought might be present in $BiBr_3$ with the ROH/$BiBr_3$ complex.

In order to test this hypothesis, we carried out the following experiment. We incubated (+)-octanol with $BiBr_3$ (1 equiv.) in CCl_4 at room temperature for 45 min. Then, we recovered octanol and measured its optical rotation. It was the same as that of the pure starting alcohol. This leads us to two possibilities: either no water is present in $BiBr_3$ or water found in $BiBr_3$ is in a too small quantity to have an effect on racemisation.

However, if we take a closer look, we can notice that the etherification reaction leads to water formation. Therefore, we foresaw that the water formed during the reaction would promote the racemisation. To check this point, we repeated the same previous experiment, except that, this time one molar equivalent of water was added after 30 min of incubation. This mixture was maintained at room temperature for 20 min, and then, the alcohol was isolated.

As in the previous experiment, the alcohol was optically proving that the water formation cannot explain the racemisation, occurring during the etherification reaction.

Furthermore, we have previously suggested[4] that the reaction of alcohols with $BiBr_3$ is inconsistent with a mechanism involving carbocation, showing that racemisation is not due to such an intermediate.

Therefore, from these results, we can presume that only the PeOH attack is responsible for the observed racemisation. This observation led us to assume that the $BiBr_3$-promoted etherification mechanism of alcohols was similar to that previously suggested for the reaction of alcohols, in the presence of $BiBr_3$.[4] In that preceding study, we showed that alcohols could yield ethers and alkenes, in appropriate cases, involving a Bi(III) intermediate. The only role of $BiBr_3$ is, an efficient catalyst for both the etherification and the elimination reactions.

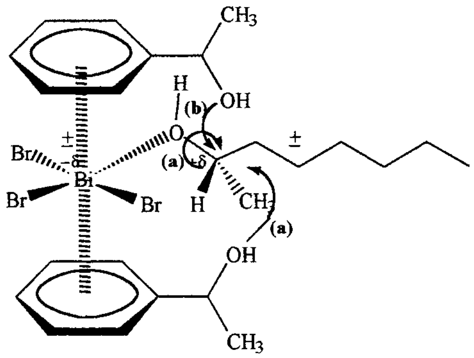
In a similar manner, we thought that this *O*-benzylation reaction in the presence of $BiBr_3$ would involve the formation of an intermediate complex, possessing several coordination-types around the bismuth atom. Thus, in such an intermediate, the bismuth atom would interact with more than one alcohol molecule.

Our reasons for postulating the existence of such an intermediate were provided by the following observations:

(i) the valence extension ability characteristic of heavy, non-metallic elements confers to bismuth (III), the potential of being a soft Lewis acid.[5] The introduction of electron withdrawing substituents (halogen atoms) onto the bismuth atom enhances the Lewis acidity of the metal center;[6,13]

(ii) bismuth trihalides readily form adducts or coordination complexes with a large variety of Lewis bases. Recently, an increasing number of complexes formed by the reaction of organic substances with bismuth (III) salts have been reported.[7] There are many reports which describe the coordination of a bismuth atom with oxygen,[8] nitrogen,[7d,9] sulfur,[10] carbonyl groups,[7b,11] silicium[12] and sulfonyl groups.[13] These results show that the coordination number around the bismuth center increases from three to nine.[7a,b,10] Furthermore, the high coordination number[7a,b,e,8d,10] makes the intermolecular interactions possible around bismuth;

(iii) in addition, it has been shown[7b,14] that BiX_3 forms donor–acceptor complexes with aromatic compounds. These arene adducts consist of sheets and have a sandwich structure in which the benzene rings are bound alternatively above and below the BiX_3 sheets. So, bismuth is centrally located above the aromatic ring by



Scheme 1.

forming a π bond. Moreover, the interactions between metal and arene are rather weak. Since the symmetrical ether formation is specific to benzylic alcohols (i.e. no reaction with aliphatic alcohols[3]), a particular interaction between $BiBr_3$ and benzylic alcohols can be expected. This interaction is most probably due to the π bond formation between the bismuth atom and the benzene ring.

These results might indicate that $BiBr_3$ can discriminate the types of the hydroxyl functions, namely aliphatic and benzylic alcohols. Besides, a similar observation[11a,15] concerning an intramolecular complex, in which the bismuth is coordinated to a carbonyl group, has been already mentioned. The authors clearly showed that $BiBr_3$ could effectively discriminate between phenyl ketones and alicyclic or aliphatic ketones.[16]

A postulated reaction mechanism for the benzylation of aliphatic alcohols is illustrated in Scheme 1.

According to experimental procedure, the initial stage of the benzylation would be the formation of a key *tetra*-coordinated complex between aliphatic alcohols and $BiBr_3$. Then, the formation of bismuth–benzene ring interactions, with two molecules of 1-phenylethanol, would lead to a 6-fold coordinated bismuth atom.

Thus, in this *hexa*-coordinated complex, the activation of aliphatic alcohols is promoted by the Lewis acid coordination with the hydroxyl group, enhancing consequently, their electrophilic activity. Besides, the existence of such a Bi–O bonded intermediate has been well demonstrated.[7c,17]

Finally, this activated oxygen atom, through coordination to bismuth, turns the carbon atom bearing this hydroxyl group into an electrophilic center. That would be likely to favor the benzylic oxygen nucleophilic attack on either side of this electron-deficient carbon atom yielding the corresponding mixture of diastereomeric ethers. Attack from side (a) involves a configuration inversion on the aliphatic alcohol, while attack from side (b) implies a configuration retention. For some reason, both attacks are equivalent with octan-2-ol, leading to an equimolar mixture of two diastereoisomers. However, in the case of butan-2-ol, one of the two attacks is slightly preponderant. So, the mechanism for the benzylation of alcohols would involve the activation of its hydroxyl function, through a complex with $BiBr_3$, followed by the nucleophilic attack of the hydroxyl group of a benzylic alcohol bonded to the same bismuth atom.

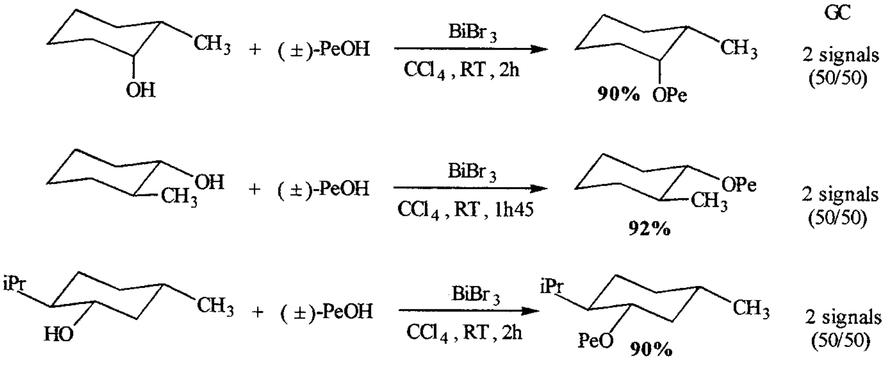
Then, this study was extended to a series of cyclic alcohols possessing a well-defined configuration namely 2-methylcyclohexanol (*cis* and *trans*) and the (*S*)-(−)-menthol. Results are illustrated in the Scheme 2.

All the products gave satisfactory ^1H NMR spectra. A marked contrast was observed between those cyclic alcohols and the aliphatic ones. Indeed, the spectroscopy data have clearly demonstrated that corresponding ethers were obtained specifically with configuration retention of the cyclic alcohols.

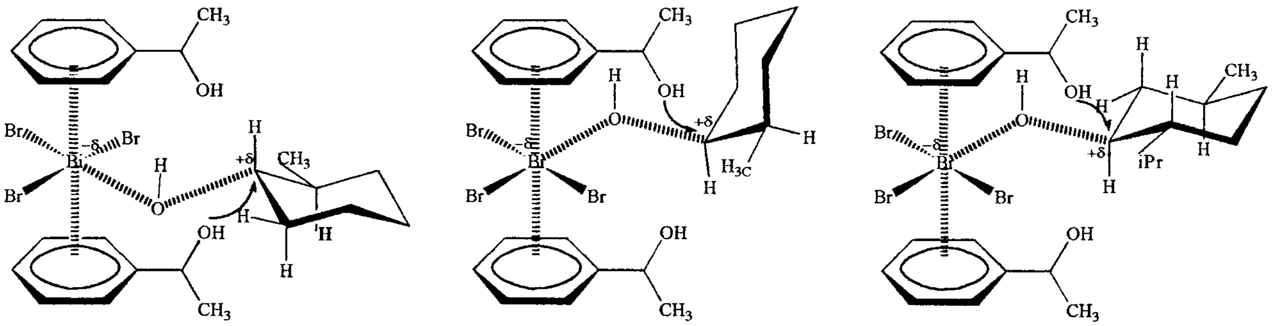
However, in each case, an equimolar mixture of diastereomers is formed (showed by GC analysis), since reactions were performed from the racemic 1-phenylethanol.

We presumed that the reaction involved the same intermediate-type as described above for aliphatic alcohols (i.e. on the one hand a Bi–O interaction with cyclic alcohols and on the other hand a bismuth–benzene ring interaction with 1-phenylethanol (Scheme 3).

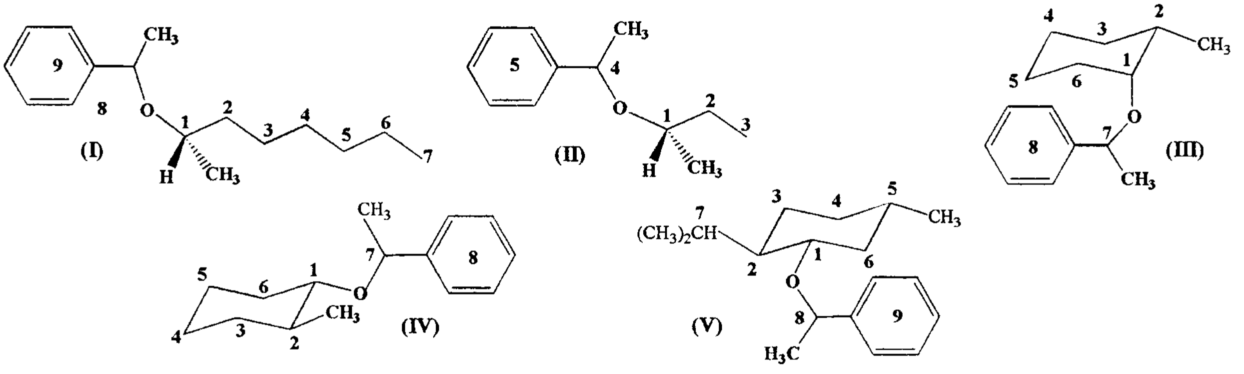
From these illustrations, we assumed that, whatever the considered cyclic alcohol, the benzylic oxygen nucleophilic would approach from the less-hindered side attack of cyclic alcohols.



Scheme 2.



Scheme 3.



Scheme 4.

Only this nucleophilic attack by the hydroxyl group of the racemic PeOH could, in such a case, explain the retention of configuration observed in the formed ethers.

3. Conclusion

In summary, the catalytic activity of $BiBr_3$ in the field of *O*-benzylation reactions by PeOH has been extended to optically active and cyclic alcohols. $BiBr_3$ proved to be capable of realizing an outstanding catalytic process. To explain our results, we stated the hypothesis that benzylation reaction of alcohols in the presence of $BiBr_3$ should involve the formation of an intermediate, possessing a 6-fold coordinated bismuth atom. This intermediate complex would contain a bismuth–oxygen bond (ROH) and two bismuth–benzene ring interactions (PeOH). The breakdown of this intermediate would be generated by the benzylic oxygen nucleophilic attack, yielding the corresponding ether. Inasmuch as the existence of a structure of $[EX_6]$ type has been already mentioned,[18] our proposed mechanism would be reasonable.

4. Experimental

4.1. General

^{1}H NMR was recorded in a Brucker Ace-250 instrument at 250 MHz in $CDCl_3$ solutions. We used a numbering system as presented in Scheme 4. GC analysis was performed with a Delsi 330 apparatus. Optical rotations were measured using a Perkin Elmer 241 polarimeter with specific rotations determined at 20°C. All starting materials, optically active alcohols and $BiBr_3$ were commercially available (Aldrich). Benzylation reactions were performed following the general procedure previously described.[3]

4.1.1. Compound I. δ: 7.4 (m, 5H, C_6H_5), 4.6 and 4.3 (q, 1H, C8-H)*, 3.4 (q, 1H, C1-H), 1.5 (d, 3H, C8-CH_3), 1.2–1.6 (m, 10H, CH_2 (2–6)), 1.1 (d, 3H, C1-CH_3), 0.9 (t, 3H, CH_3(7)). * represents diastereomeric pairs.

4.1.2. Compound II. δ: 7.4 (m, 5H, C_6H_5), 4.6 and 4.3 (q, 1H, C4-H)*, 3.3 (q, 1H, C1-H), 1.5 (d, 3H, C8-CH_3), 1.4 (m, 2H, CH_2(2)), 1.1 (d, 3H, C1-CH_3), 0.8 (t, 3H, CH_3(3)). * represents diastereomeric pairs.

4.1.3. Compound III. δ: 7.4 (m, 5H, C_6H_5), 4.6 and 4.3 (q, 1H, C7-H), 3.3 and 3.2 (quint., 1H, J=4, 8 Hz, C1-H)*, 1.5 (d, 3H, C7-CH_3), 1 (d, 3H, C2-CH_3), 0.9–2 (m, 10H, CH_2 (2–6)). * represents diastereomeric pairs.

4.1.4. Compound IV. δ: 7.4 (m, 5H, C_6H_5), 4.6 and 4.3 (q, 1H, C7-H), 2.9 and 2.7 (dt, 1H, J=4, 10 Hz, C1-H)*, 1.5 (d, 3H, C7-CH_3), 1 (d, 3H, C2-CH_3), 0.9–1.8 (m, 10H, CH_2 (2–6)). * represents diastereomeric pairs.

4.1.5. Compound V. δ: 7.4 (m, 5H, C_6H_5), 4.6 and 4.3 (q, 1H, C8-H)*, 3.2 and 3.0 (dt, 1H, J=5, 12 Hz, C1-H)*, 2.3 (m, 2H, CH_2 (6)), 1.7 (m, 1H, C7-H), 1.5–1.6 (m, 4H, CH_2 (3 and 4)), 1.5 (d, 3H, C8-CH_3), 1 (m, 3H, C5-CH_3), 0.9 (m, 6H, C7-$(CH_3)_2$). * represents diastereomeric pairs.

References

1. Boyer, B.; Keramane, E. M.; Montero, J. L.; Roque, J. P. *Synth. Commun.* **1998**, *28*, 1737.
2. Boyer, B.; Keramane, E. M.; Arpin, S.; Montero, J. L.; Roque, J. P. *Tetrahedron* **1999**, *55*, 1971.
3. Boyer, B.; Keramane, E. M.; Roque, J. P.; Pavia, A. A. *Tetrahedron Lett.* **2000**, *41*, 2891.
4. Keramane, E. M.; Boyer, B.; Roque, J.-P. *Tetrahedron* **2001**, *57*, 1909–1916.
5. (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (b) Pearson, R. G. *J. Chem. Educ.* **1987**, *64*, 561. (c) Repichet, S.; Leroux, C.; Hernandez, P.; Dubac, J.; Desmurs, J. R. *J. Org. Chem.* **1999**, *64*, 6479 (and references cited therein).
6. (a) Reese, A. L.; McMartin, K.; Miller, D.; Wickham, P. P. *J. Org. Chem.* **1973**, *38*, 764. (b) Nakamura, E.; Shimada, J.; Kuwajima, J. *Organometallics* **1985**, *4*, 641. (c) Garrigues, B.; Gonzaga, F.; Robert, H.; Dubac, J. *J. Org. Chem.* **1997**, *62*, 4880 (and references cited therein).
7. (a) Briand, G. G.; Burford, N. *Chem. Rev.* **1999**, *99*, 2601 (and references cited therein). (b) Lange, K. C. H., Klapotke, T. M. In *The Chemistry of Organic Arsenic, Antimony and Bismuth Compounds*; Patai, S., Ed.; Wiley, Academic Press: 1994; pp. 315–366. (c) Guo, Z.; Sadler, P. J. *Angew. Chem. Int. Ed.* **1999**, *38*, 1512 (d) Di Vaira, M.; Mani, F.; Stoppioni, P. Di Vaira. *Eur. J. Inorg. Chem.* **1999**, 833. (e) Carmalt, C. J.; Clegg, W.; Elsegood, M. R. J.; Errington, R. J.; Havelock, J.; Lightfoot, P.; Norman, N. C.; Scott, A. *J. Inorg. Chem.* **1996**, *35*, 3709 (and references cited therein). (f) Suzuki, H.; Ikegami, T.; Matano, Y. *Synthesis* **1997**, 249.
8. (a) Ogama, T.; Yoshikawa, A.; Wada, H.; Ogawa, C.; Uno, N.; Suzuki, H. *J. Chem. Soc., Chem. Commun.* **1995**, 1407 (and references cited therein). (b) Kallal, K.; Coin, C.; Dunach, E.; Postel, M. *New J. Chem.* **1997**, *21*, 495. (c) Habata, Y.; Fujishiro, F.; Akabori, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 953. (d) Steward, C. A.; Calabrese, J. C.; Arduengo, A. J. *J. Am. Chem. Soc.* **1985**, *107*, 3397.
9. (a) Hancock, R. D.; Cukrowski, I.; Baloyi, J.; Mashishi, J. *J. Chem. Soc., Dalton Trans.* **1993**, 2895. (b) Cukrowski, I.; Marsicano, F.; Hancock, R. D.; Tshetlo, T. T.; Van Otterlo, W. A. L. *Polyhedron* **1995**, *14*, 1661.
10. Genge, A. R. J.; Levason, W.; Reid, G. *Chem. Commun.* **1998**, 2159.
11. (a) Komatsu, N.; Uda, M.; Suzuki, H. *Synlett* **1995**, 984. (b) Murafuji, T.; Mutoh, T.; Satoh, K.; Tsunenari, K. *J. Organomet.* **1995**, *14*, 3848.
12. (a) Breunig, H. J.; Rosler, R.; Lork, E. *Angew. Chem. Int. Ed.* **1998**, *37*, 3175. (b) Althaus, H.; Breunig, H. J.; Rosler, R.; Lork, E. *J. Organomet.* **1999**, *18*, 328.
13. Suzuki, H.; Murafuji, T.; Azuma, N. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1169.
14. (a) Franck, W.; Schneider, J.; Muller-Becker, S. *J. Chem. Soc., Chem. Commun.* **1998**, 799 (and references cited therein). (b) Schier, A.; Wallis, J. M.; Muller, G.; Schmidbaur, H. *Angew. Chem. Int. Ed.* **1986**, *25*, 757.
15. Komatsu, N.; Ishida, J. Y.; Suzuki, H. *Tetrahedron Lett.* **1997**, *38*, 7219.
16. Komatsu, N.; Uda, M.; Suzuki, H.; Takahashi, T.; Domae, T.; Wada, M. *Tetrahedron Lett.* **1997**, *38*, 7215.
17. (a) Arnauld, T.; Barton, D. H. R.; Normant, J. F.; Doris, E. *J. Org. Chem.* **1999**, *64*, 6915 (and references cited therein). (b) Zevaco, T.; Postel, M.; Benali-Cherif, N. *Main Group Chem.* **1992**, *15*, 217.
18. Fisher, G. A.; Norman, N. C. In *Advances in Inorganic Chemistry*; Sykes, A. G., Ed.; Academic Press: New York, 1994; Vol. 41, pp 248.