

Titanium(IV) chloride and oxy-compounds promoted Baylis–Hillman reaction

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Abstract—The Baylis–Hillman reaction of aryl aldehydes with α,β -unsaturated ketones in the presence of titanium(IV) chloride can be promoted by oxy-compounds at room temperature, although they are not as effective as amines, chalcogenides, or quaternary ammonium salts. The oxy-compounds can be simple alcohols, ethers, and ketones. For aryl aldehydes having a strong electron-withdrawing group on the phenyl ring such as nitrobenzaldehyde or *p*-trifluoromethylbenzaldehyde, the chlorinated compound **1** is obtained as the major product. However, for other aryl aldehydes, the elimination compound **3** was formed predominantly. We also found that $\text{TiCl}_4 \cdot 2\text{THF}$ or $\text{TiCl}_4 \cdot 2\text{Et}_2\text{O}$ complex is very effective for this reaction to give the chlorinated products in high yields at low temperature. A plausible mechanism is proposed. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Recently, the Baylis–Hillman reaction has become a very hot field for synthetic chemists because the resulting adducts may have several functional groups available for numerous further transformations.^{1–12} The combination of Lewis base such as chalcogenides, amines or quaternary ammonium halides with Lewis acid TiCl_4 can significantly speed up this reaction and give the corresponding chlorinated products.^{13–15} Based on those previous results, we further attempt to explore new Lewis bases and disclose the reaction mechanism of this interesting reaction. Herein we wish to report the full details of TiCl_4 and oxy-compounds (ROH, ROR, RC(O)R) which promoted Baylis–Hillman reaction, along with a plausible mechanism based on the previous finding and our own results.

2. Results and discussion

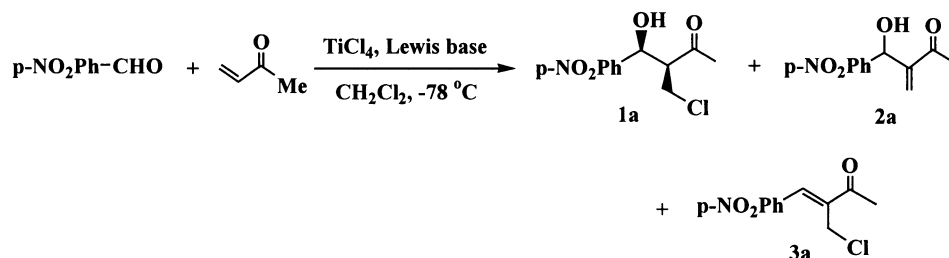
According to our previous results,^{13–15b} we initially attempted the reaction of *p*-nitrobenzaldehyde with methyl vinyl ketone in the presence of TiCl_4 (1.4 equiv.) at -78°C . No reactions occurred (Scheme 1, Table 1, entry 1). However, after adding 20 mol% (0.20 equiv.) of methanol as a Lewis base, the reaction took place to give the chlorinated product **1a** exclusively in 30% yield (Scheme 1, Table 1, entry 2). The reaction rate was much slower than

that using amines, chalcogenides or quaternary ammonium halides as Lewis base.^{13–15b} Raising the reaction temperature to 10°C could significantly speed up the reaction and gave a higher yield of **1a** (Table 1, entry 3). Secondary and tertiary alcohols also can catalyze the reaction, but in a slower rate (Table 1, entries 4, 5). Other oxy-compounds such as ketones or ethers can promote the reaction as well (Table 1, entries 6–11), whereas sterically bulky oxy-compounds such as benzophenone or triphenylphosphine oxide afforded lower yields of **1a** (Table 1, entries 10, 11). We found that, with a prolonged reaction time, the other products **2a** (Baylis–Hillman olefin) and elimination compound **3a** would be produced at the same time (Scheme 1). Acetone ($\text{Me}_2\text{C}=\text{O}$), a very common ketone, is very effective for this reaction as the Lewis base. The ^1H NMR spectroscopic data and HPLC analysis showed that only one diastereoisomer (*syn/anti*) was formed from *p*-nitrobenzaldehyde in the reaction. Its relative configuration was assigned as *syn* based on X-ray analysis of the crystal structure of **1a**.^{14,15b}

Next, we examined other aldehydes using acetone as a Lewis base under the same reaction conditions. We found that, for aryl aldehydes having a strong electron-withdrawing group on the phenyl ring, the reaction proceeded quickly at 10°C to give **1** in high yields (Scheme 2, Table 2, entries 1, 2). However, other aryl aldehydes needed a very long time to complete the reaction and the final major products were the elimination products **3** in moderate to high yields (Table 2, entries 3–5). The *Z*-configuration of **3** has been determined by X-ray analysis.^{14,15b} The transformation among these three products **1**, **2**, and **3** has been documented before.^{14,15}

Keywords: titanium(IV) chloride; Baylis–Hillman reaction; Lewis bases; oxy-compounds.

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Scheme 1.

Table 1. Reaction of *p*-nitrobenzaldehyde with methyl vinyl ketone in the presence of TiCl_4 (1.4 equiv.) and Lewis base (0.20 equiv.) at low temperature

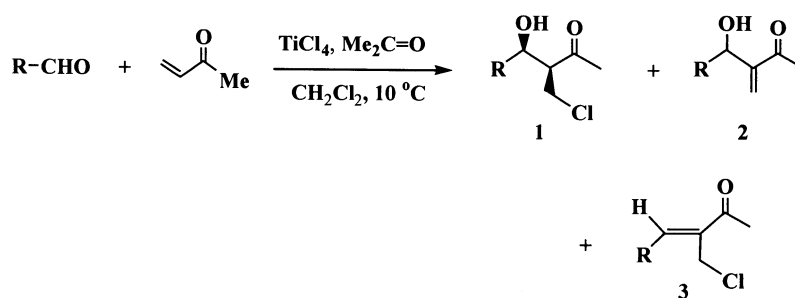
Entry	Lewis base	Temperature (°C)	Time (h)	Yield (%) ^a		
				1a	2a	3a
1	–	–78	24	–	–	–
2	MeOH	–78	24	30	0	0
3	MeOH	10	1	90	0	0
4	Me_2CHOH	10	2	87	Trace	Trace
5	Me_3COH	10	3	76	16	16
6	PhOH	10	3	60	18	18
7	PhOPh	10	6	74	Trace	Trace
8	THF	10	24	42	37	7
9	$\text{Me}_2\text{C}=\text{O}$	10	1	85	7	7
10	$\text{Ph}_2\text{C}=\text{O}$	10	20	40	30	7
11	$\text{Ph}_3\text{P}=\text{O}$	10	24	40	7	7

^a Isolated yields.

Compound **2** is derived from **1**, while compound **3** is the most stable product in this TiCl_4 -promoted reaction system. Compounds **1** and **2** can be rapidly transformed into **3** in the presence of TiCl_4 ^{14,15} at room temperature. If we prolong the reaction time at room temperature in the TiCl_4 and oxy-compound promoted reaction system, both **1** and **2** can be

completely transformed to **3**. Thus, for slow Baylis–Hillman reaction, the final product is the elimination product *Z*-olefin **3**.

In our experiments, we observed that mixing TiCl_4 with the oxy-compounds mentioned above gave an yellow solution. However, using chalcogenides, amines, or quaternary ammonium halides as Lewis bases in the same reaction system, a dark red solution was obtained.^{13–15b} These phenomena suggest that the coordination of Lewis bases such as oxy-compounds, chalcogenides, amines, or quaternary ammonium halides to TiCl_4 would take place, but the oxidation states of the Ti metal center are different. We believe that mixing TiCl_4 with the oxy-compounds gave a neutral and octahedral (six-coordinated) Ti complex (yellow color), but mixing TiCl_4 with chalcogenides, amines, or quaternary ammonium halides afforded an ionic Ti complex (dark red color) and they are the active species for the chlorination of the Baylis–Hillman adduct. In fact, some simple TiCl_4 -oxy-compound complexes such as $\text{TiCl}_4 \cdot 2\text{Et}_2\text{O}$, $\text{TiCl}_4 \cdot 2\text{POCl}_3$, and $\text{TiCl}_4 \cdot 2\text{PhCO}_2\text{Et}$ have yellow color and their crystal structures have already been disclosed before.¹⁶ For example, TiCl_4 and Et_2O can form a 1:2 complex in *cis*-configuration.^{16c} Recently, chiral titanium(IV) Lewis acids such as $[\text{TiCl}_4 \cdot (R,R)\text{-1,2-diphenyl-}$



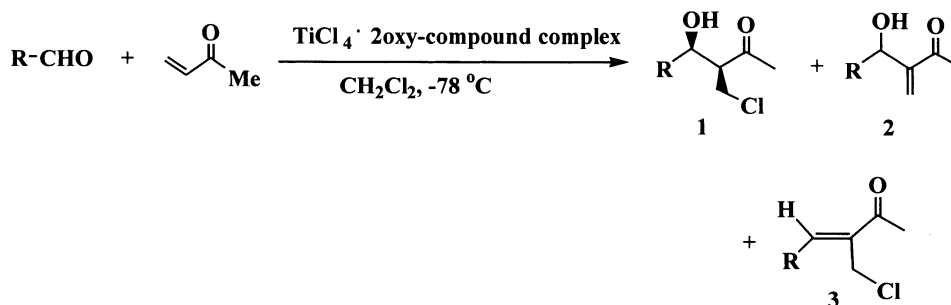
Scheme 2. b: $\text{R}=\textit{o}$ - NO_2Ph , c: $\text{R}=\textit{p}$ - CF_3Ph , d: $\text{R}=\textit{p}$ - CIPh , e: $\text{R}=\textit{p}$ - EtPh ; f: $\text{R}=\text{Ph}$.

Table 2. Baylis–Hillman reaction of aldehydes with methyl vinyl ketone in the presence of TiCl_4 (1.4 equiv.) and acetone (0.20 equiv.) at 10°C

Entry	R	Time (h)	Yield (%) ^a		
			1	2	3
1	<i>o</i> - NO_2Ph	1	71	0	0
2	<i>p</i> - CF_3Ph	3	70	Trace	0
3	<i>p</i> - CIPh	48	Trace	Trace	60
4	<i>p</i> - EtPh	50	7	Trace	36
5	Ph	60	Trace	Trace	61

^a Isolated yield.

ethane-1,2-diol dipropyl ether] and $[\text{TiCl}_3(\text{OPr}^i)\text{-}(R,R)\text{-1,2-diphenylethane-1,2-diol dimethyl ether}]$ and their use in asymmetric aldol reactions, along with their crystal structures determined by X-ray analysis, have been reported.¹⁷ All these results indicated that they are not ionic metal complexes and have octahedral structures. Thus, oxy-compounds are weak Lewis bases, unlike chalcogenides, amines, or quaternary ammonium halides which are known to form ionic titanium complexes.¹⁸ In order to further clarify the mechanism of this reaction using oxy-compounds as Lewis bases, we independently prepared the yellow $\text{TiCl}_4 \cdot 2\text{Et}_2\text{O}$ and $\text{TiCl}_4 \cdot 2\text{THF}$ complexes by



Scheme 3. a: R=*p*-NO₂Ph, b: R=*o*-NO₂Ph, c: R=*p*-CF₃Ph, d: R=*p*-ClPh, e: R=*p*-EtPh; f: R=Ph.

Table 3. Baylis–Hillman reaction of aldehydes with methyl vinyl ketone in the presence of TiCl₄·2THF or TiCl₄·2Et₂O complex (1.4 equiv.) at low temperature

Entry	Complex	R	Time (h)	Yield (%) ^a		
				1	2	3
1	TiCl ₄ ·2Et ₂ O	<i>p</i> -NO ₂ Ph	12	95	2	0
2	TiCl ₄ ·2THF	<i>p</i> -NO ₂ Ph	12	93	3	0
3	TiCl ₄ ·2THF	<i>o</i> -NO ₂ Ph	12	92	2	0
4	TiCl ₄ ·2THF	<i>p</i> -ClPh	60	0	0	60
5	TiCl ₄ ·2THF	<i>p</i> -EtPh	60	0	0	45
6	TiCl ₄ ·2THF	Ph	60	0	0	50

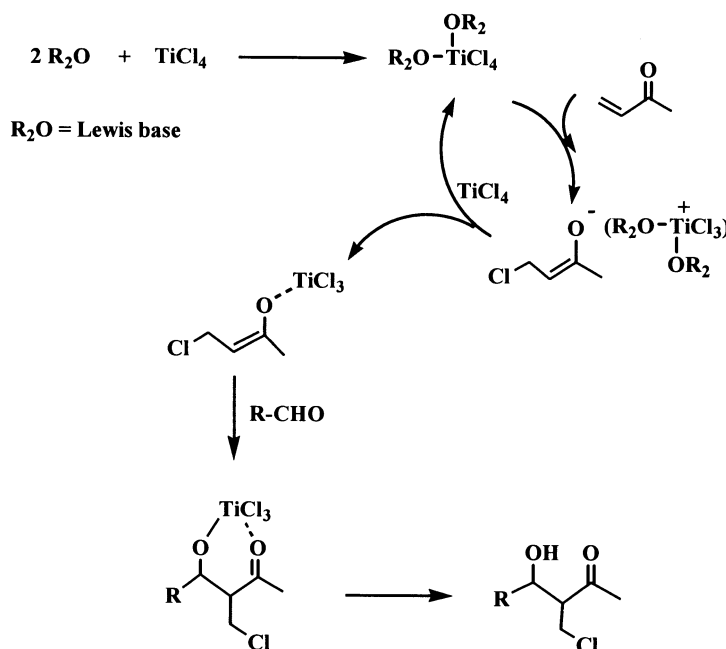
^a Isolated yield.

mixing TiCl₄ with THF and Et₂O respectively, at 0°C and utilized them directly in this reaction. We found that this yellow TiCl₄·2THF complex worked much better than that using 1.4 equiv. of TiCl₄ as a Lewis acid and 0.20 equiv. of THF as a Lewis base (Table 1, entry 8). Even at -78°C, for *p*- or *o*-nitrobenzaldehyde the reaction could be completed quantitatively within 12 h and *syn*-isomer **1a** and **1b** were formed predominantly with only traces of Baylis–Hillman olefin **2a** and **2b** (Scheme 3). For other aryl aldehydes

shown in Scheme 3, the elimination products **3** were obtained exclusively in moderate yields after 60 h at <-78°C (Table 3).

In Scheme 4 we propose a mechanism for the formation of **1** based on these previous findings and the results of our own investigations. We believe that a neutral octahedral Ti and oxy-compound complex was formed in the reaction system. The coordination of oxy-compounds to TiCl₄ activated the chloride ligand which can undergo a Michael addition to methyl vinyl ketone to give a Ti enolate. Further reaction of enolate with aryl aldehydes afforded the chlorinated products.

This finding obviously opens a way for achieving catalytic enantioselective Baylis–Hillman reaction by means of chiral oxy-compounds in a catalytic process. However, as can be seen from Scheme 4, the chiral Lewis base obviously forms only an ion pair with the enolate and it does not relate with the attack to aldehydes in the last step. Thus, it is very difficult to use this reaction process to achieve high enantioselectivity. As a matter of fact, we utilized many chiral oxy-compounds **4–7** as Lewis bases for this reaction (Fig. 1). However, only very poor enantioselectivities (3–5% ee)



Scheme 4.

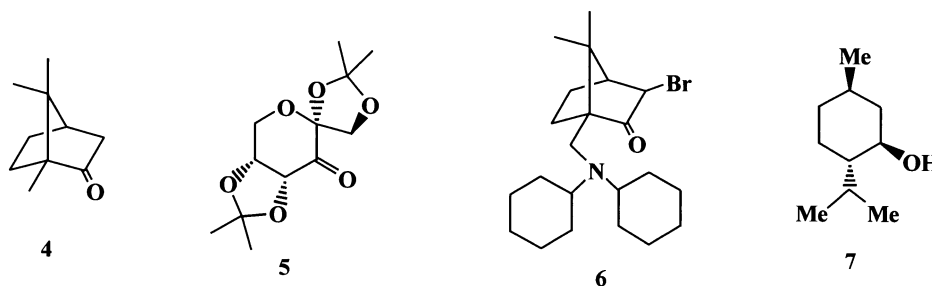
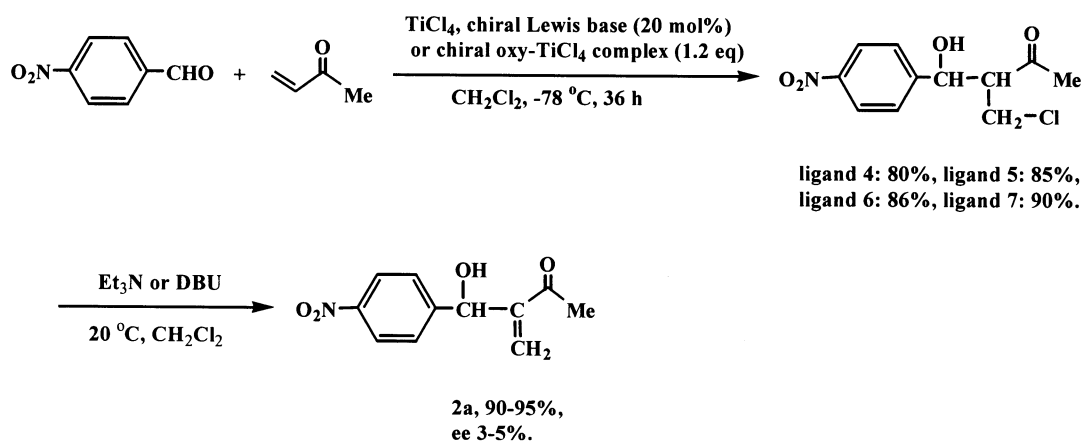


Figure 1.



Scheme 5.

have been achieved. For example, using 20 mol% of **5**,¹⁹ as a chiral Lewis base and *p*-nitrobenzaldehyde as a substrate, Baylis–Hillman olefin **2a** could be obtained in 80% yield with only 5% ee, after treating the chlorinated product **1a** with triethylamine or DBU (Scheme 5).^{13–15} Using a stoichiometric amount of **5** as Lewis base, we prepared an yellow neutral chiral oxy–Ti complex in dichloromethane and directly utilized it to the above Baylis–Hillman reaction. But a similar result was obtained. This result also partially supports the reaction mechanism shown in Scheme 4.

3. Conclusions

We have found that titanium(IV) chloride and oxy-compounds can promote the Baylis–Hillman reaction as well, although they are not as effective as amines, chalcogenides, or quaternary ammonium salts. The reaction is initiated by chloride ion from a neutral oxy–Ti complex. This finding will become a widespread concept of Lewis bases to the organic chemistry community because of the general, innocuous, and mild nature of the oxygenated organics (such as acetone and alcohols). Efforts are underway to elucidate the mechanistic details of this reaction and to define the scope and limitations of this reaction. In addition, we are planning to synthesize structurally modified chiral oxy–Ti complexes for use as chiral Lewis bases to accomplish enantioselective Baylis–Hillman reactions.

4. Experimental

4.1. General

Melting points are uncorrected. ¹H and ¹³C NMR spectra were recorded at 300 and 75 MHz, respectively. Mass spectra were recorded by EI method and HRMS was measured on a Finnigan MA+ mass spectrometer. Organic solvents used were dried by standard methods when necessary. Commercially available reagents were used without further purification. HPLC analysis was carried out by column: kromasil 4.6×150 mm and LUNA C₁₈ 4.6×150 mm, respectively. All reactions were monitored by TLC with Huanghai GF₂₅₄ silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel. The spectral data of **1a–f**, **2a**, **3a–f** and the crystal structures of **1a** and **3a** have been reported in the previous paper.^{13–15}

4.1.1. Typical reaction procedure for the preparation of syn-3-(chloromethyl)-4-hydroxy-4-(4'-nitrophenyl)-2-butanone (1a). To a solution of acetone (1.45 mg, 0.025 mmol) in dichloromethane (1.3 mL), was added 1.4 M titanium tetrachloride in dichloromethane (0.5 mL, 0.7 mmol) at 10°C. After stirring for 5 min, a solution of *p*-nitrobenzaldehyde (76 mg, 0.5 mmol) in dichloromethane (1.0 mL) and methyl vinyl ketone (105 mg, 1.5 mmol, 123 μL) were added. The reaction mixture was kept for 24 h at –78°C. The reaction was quenched by addition of saturated aqueous NaHCO₃ solution (1.0 mL). After

filtration, the filtrate was extracted with dichloromethane (5.0 mL \times 2) and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash silica gel chromatography to give compound **1a** (117 mg, 91%) as a colorless solid (eluent: ethyl acetate/petroleum ether 1/4); mp 90–91°C; IR (KBr) ν 1720 cm⁻¹ (C=O); ¹H NMR (CDCl₃, 300 MHz) δ 2.20 (3H, s, Me), 2.93 (1H, br. s, OH), 3.22–3.38 (1H, m), 3.67 (1H, dd, $J=11.3$, 4.0 Hz), 3.89 (1H, dd, $J=11.3$, 9.2 Hz), 5.11 (1H, d, $J=5.6$ Hz), 7.56 (2H, d, $J=8.6$ Hz, Ar), 8.25 (2H, d, $J=8.6$ Hz, Ar); MS (EI) m/e 258 (MH⁺, 0.60), 208 (M⁺–49, 60), 71 (M⁺–186, 100); [Found: C, 51.64; H, 4.94; N, 5.35%. C₁₁H₁₂ClNO₄ requires C, 51.27; H, 4.69; N, 5.44%].

4.2. Preparation of TiCl₄·2THF or TiCl₄·2Et₂O complex

To an anhydrous THF or Et₂O solution (10 mL), was added TiCl₄ (1.0 mL) dropwise under argon atmosphere at 0°C. The reaction mixture was stirred for 20 min. After the solvent was removed under reduced pressure, bright yellow TiCl₄·2THF or TiCl₄·2Et₂O complex was obtained which was used for the next reaction without further purification.

4.3. Typical reaction procedure for the preparation of 3-(chloromethyl)-4-(4'-nitrophenyl)-3-buten-2-one (**3a**) using TiCl₄·2THF complex

To a solution of TiCl₄·2THF complex (233 mg, 0.70 mmol) in dichloromethane (1.0 mL) was added a solution of *p*-nitrobenzaldehyde (76 mg, 0.5 mmol) in dichloromethane (1.0 mL) and methyl vinyl ketone (105 mg, 1.5 mmol, 123 μ L) at –78°C. The reaction mixture was kept for 12 h at –78°C under argon atmosphere. Then, the reaction was quenched by addition of saturated aqueous NaHCO₃ solution (1.0 mL). After filtration, the filtrate was extracted with dichloromethane (5.0 mL \times 2) and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure and the residue was purified by flash silica gel chromatography to give compound **1a** (117 mg, 91%) as a colorless solid (eluent: ethyl acetate/petroleum ether 1/4).

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References

- For reviews, see: (a) Ciganek, E. *Org. React.* **1997**, *51*, 201. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (c) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653.
- Brzezinski, L. J.; Rafel, S.; Leahy, J. M. *J. Am. Chem. Soc.* **1997**, *119*, 4317.
- Marko, I. E.; Giles, P. G.; Hindley, N. J. *Tetrahedron* **1997**, *53*, 1015.
- Richter, H.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 2729.
- Barrett, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1999**, 2533.
- Kunidig, E. P.; Xu, L. H.; Romanens, P.; Bernardinelli, G. *Tetrahedron Lett.* **1993**, *34*, 7049.
- Aggarwal, V.; Mereu, A.; Tarver, G. J.; MaCague, R. *J. Org. Chem.* **1998**, *63*, 7183.
- Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 1539.
- (a) Kataoka, T.; Iwama, T.; Tsujiyama, S.-I.; Iwamura, T.; Watanabe, S.-I. *Tetrahedron* **1998**, *54*, 11813. (b) Kataoka, T.; Iwama, T.; Kinoshita, S.; Tsujiyama, Y.; Iwamura, T.; Watanabe, S. *Synlett* **1999**, 197. (c) Kataoka, T.; Iwama, T.; Tsujiyama, S.; Kanematsu, K.; Iwamura, T.; Watanabe, S. *Chem. Lett.* **1999**, 257. (d) Kataoka, T.; Iwama, T.; Tsujiyama, S. *Chem. Commun.* **1998**, 197. (e) Iwama, T.; Tsujiyama, S.-I.; Kinoshita, H.; Kanamatsu, K.; Tsurukami, Y.; Iwamura, T.; Watanabe, S.-I.; Kataoka, T. *Chem. Pharm. Bull.* **1999**, *47*, 956.
- Ono, M.; Nishimura, K.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **1999**, *40*, 1509.
- (a) Nagaoka, Y.; Yomioka, K. *J. Org. Chem.* **1998**, *63*, 6428. (b) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049.
- Li, G.; Gao, J.; Wei, H.-X.; Enright, M. *Org. Lett.* **2000**, *2*, 617.
- (a) Shi, M.; Jiang, J.-K.; Feng, Y.-S. *Org. Lett.* **2000**, *2*, 2397. (b) Shi, M.; Feng, Y.-S. *J. Org. Chem.* **2001**, *66*, 406. (c) Shi, M.; Jiang, J.-K.; Cui, S.-C.; Feng, Y.-S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 390. (d) Shi, M.; Li, C.-Q.; Jiang, J.-K. *J. Chem. Soc., Chem. Commun.* **2001**, 833.
- Shi, M.; Jiang, J.-K. *Tetrahedron* **2000**, *56*, 4793.
- (a) Kataoka, T.; Kinoshita, H.; Iwama, T.; Tsujiyama, S.-I.; Iwamura, T.; Watanabe, S.-I.; Muraoka, O.; Tanabe, G. *Tetrahedron* **2000**, *56*, 4725. Shi, M.; Feng, Y.-S. *J. Org. Chem.* **2001**, *66*, 406 The crystal data of **1a** and **3a** have been deposited at the Cambridge Crystallographic Data Center and allocated the deposition numbers: CCDC 144817 for **1a** and CCDC 142973 for **3a**.
- (a) Talzi, V. P.; Ignashin, S. V.; Chudinova, I. P.; Shchupletsov, V. G. *Zh. Prikl. Khim.* **1998**, *71*, 1843. (b) Guo, G.-L.; Pan, Z.-H.; Zhang, Z.-Y. *Acta Phys. Chim. Sin.* **1986**, *2*, 278. (c) Branden, C. I. *Acta Chem. Scand.* **1962**, *16*, 1806. (d) Clark, R. J. H.; Lewis, J.; Machin, D. J.; Nyholm, R. S. *J. Chem. Soc.* **1963**, 5873.
- Ishimaru, K.; Monda, K.; Yamamoto, Y.; Akiba, K.-Y. *Tetrahedron* **1998**, *54*, 727.
- (a) Everhart, J. B.; Ault, B. S. *Inorg. Chem.* **1996**, *35*, 4090. (b) Chen, L.; Cotton, F. A. *Polyhedron* **1998**, *17*, 3727. (c) Chen, L.; Cotton, F. A.; Dunbar, K. R.; Feng, X.; Heintz, R. A.; Uzelmeir, C. *Inorg. Chem.* **1996**, *35*, 7358. (d) Cotton, F. A.; Murrell, C. A.; Petrukhina, M. A. *J. Organomet. Chem.* **1999**, *573*, 78. (e) Antler, M.; Laubengayer, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5250. (f) Bharathi, P.; Perisaamy, M. *Org. Lett.* **1999**, *1*, 857. (g) Clark, R. J. H.; Coles, M. *Chem. Commun.* **1971**, 1587. (h) Clark, R. J. H.; Coles, M. *J. Chem. Soc., Dalton* **1972**, 533.
- (a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (b) Mio, S.; Kamagawa, Y.; Sugai, S. *Tetrahedron* **1991**, *47*, 2133.