A modification to the synthesis of Telmisartan: an antihypertensive drug

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A highly efficient approach to the synthesis of Telmisartan is described. Directed ortho-metalation of 4,4-dimethyl-2-phenyl-4,5-dihydrooxazole provided the key organozinc intermediate for a palladium catalysed biaryl coupling with 3′-(4-bromobenzyl)-1,7′-dimethyl-2′-propyl-1*H*,3′*H*-2,5′-bibenzo[*d*]imidazole which was obtained from alkylation of 1,7′-dimethyl-2′-propyl-1*H*,3′*H*-2,5′-bibenzo[*d*]imidazole. This methodology overcomes many of the drawbacks associated with previously reported syntheses.

Keywords: Telmisartan, antihypertensive drug, Negishi coupling and oxazoline hydrolysis

Telmisartan **1** is an angiotensin II receptor antagonist which is useful in the treatment of hypertension, heart disease and strokes, and bladder diseases.[1–3] Telmisartan is available in the market as an antihypertensive drug[4] under the brand name of Micardis.

The reported synthesis[5,6] of Telmisartan in Scheme 1 involves the condensation of the 7-methyl-2-propyl-3H-benzimidazole-5-carboxylic acid derivative **2** with N-methyl- benzene-1,2-diamine **3** to give the dibenzimidazole derivative **4.** Alkylation of compound 1,7′-dimethyl-2′-propyl-1*H*,3′*H*-2,5′-bibenzo[*d*] imidazole[5–7] **4** with 4′-bromomethyl-biphenyl-2-carboxylic acid *tert*-butyl ester **5** furnished ester derivative of Telmisartan **6.** Hydrolysis of the ester **6** in trifluoroacetic acid yielded Telmisartan **1** in an overall yield of around 21% containing several impurities. This process suffers from disadvantages such as (a) linear multi-step synthesis (b) poor stability of 4′-bromomethyl-biphenyl-2-carboxylic acid *tert*-butyl ester[8] **5** (c) low yield and purity obtained during the preparation of 4′-bromomethyl-biphenyl-2-carboxylic acid *tert*-butyl ester **5** arising from the formation of 20–45% of dibromo impurity **8** in a bromination step.

The intermediate 4′-bromomethyl-biphenyl-2-carboxylic acid tert-butyl ester **5,** could not be stored because of its poor stability and shorter shelf life. Therefore, it was used immediately after its preparation. Because of its high reactivity, the ester also has the disadvantage of being liable to decomposition or a side reaction in the reaction, thereby resulting in low purity.

N-Bromosuccinimide which is used for the preparation of 4′-bromomethyl-biphenyl-2-carboxylic acid tert-butyl ester **5** is unsuitable for industrial production because of its cost and reactivity. It is also difficult to control the reaction and avoid the formation of undesired 4′-dibromomethyl-biphenyl-2-carboxylic acid tert-butyl ester **8** as a dibromo impurity (Scheme 2).

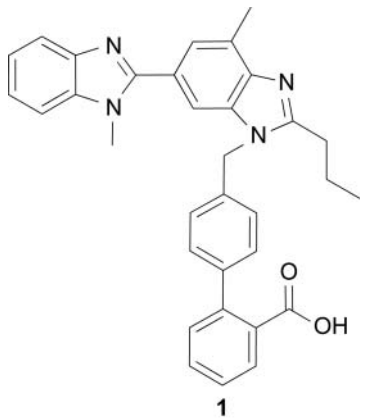

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Fig. 1

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In designing an alternative synthesis of Telmisartan our goal was to minimise the use of expensive and hazardous metals, circumvent the bromination step, and increase the overall efficiency of the synthesis. This was accomplished by reversing the order of the major bond disconnections. Alkylation of the dibenzimidazole **4** with commercially available 4-bromobenzyl bromide obviated the free-radical bromination; this offered a suitable substrate for metal-catalysed biaryl coupling via Negishi coupling and finally acid hydrolysis of intermediate **12** provided Telmisartan **1** in good yield.

Most current methods for preparation of biaryls require either the regiospecific introduction of the desired halogen as a precursor to the organometallic reagent or the isolation of the prerequisite organometallic after directed metalation prior to cross coupling. While these methods have had some success, especially the Suzuki boronic acid cross coupling as developed by Snieckus, we felt that a methodology which eliminated the isolation and purification steps would have some useful advantages. Our approach involved the directed metalation of an appropriate carboxy protecting group followed by transmetalation with zinc chloride then a transition metal catalysed cross coupling with aryl bromides.

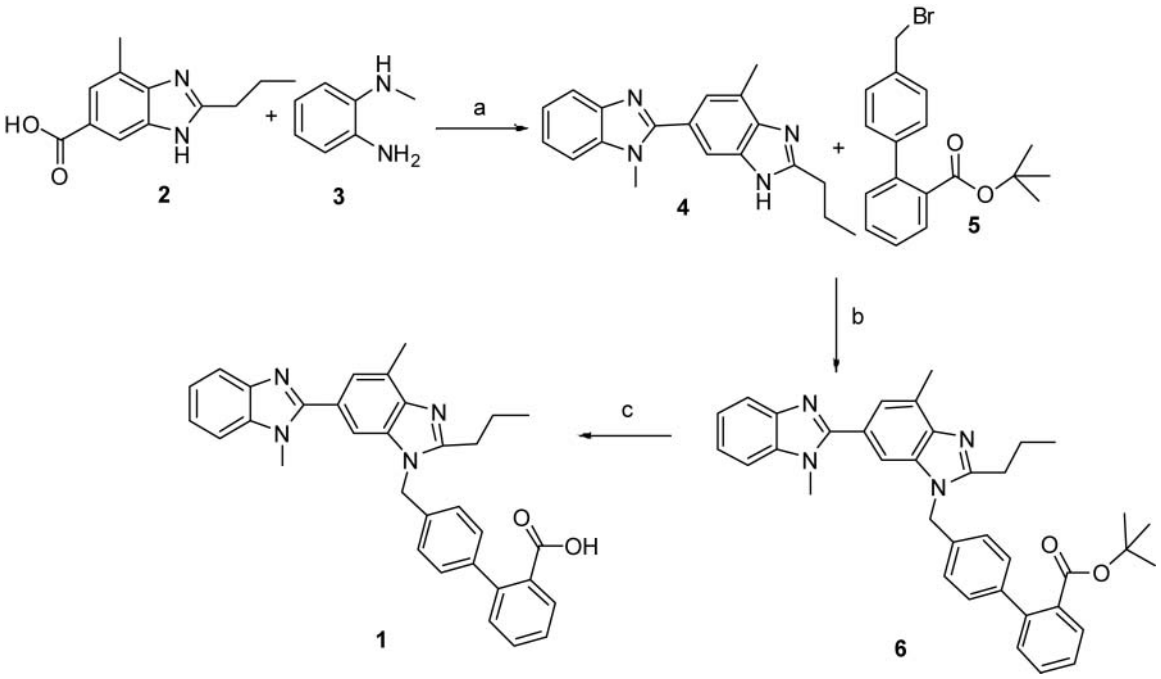
We chose the oxazoline moiety as a carboxy synthon because of its excellent ortho-metalating properties, its stability to many common reaction conditions, its use as a versatile synthetic intermediate, and the ease of recovering the parent acid under mild conditions. Aryl oxazolines were prepared by standard methods.[9] We chose to explore Negishi cross couplings[10,11] because of the great tolerance of zinc-based organometallics to a wide range of sensitive functionalities.[12,13]

Results and discussion

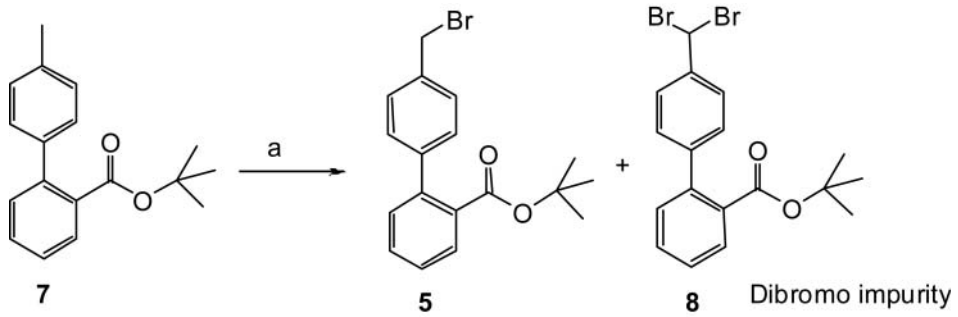
In the synthesis of Telmisartan **1**, the first stage of this synthesis was the construction of the benzylated imidazole **10** (Scheme 3). The 1,7′-dimethyl-2′-propyl-1*H*,3′*H*-2,5′-bibenzo [*d*]imidazole **4** was benzylated with 4-bromobenzyl bromide **9** in dimethylacetamide at 25–30 °C with potassium carbonate as the base to provide 3′-(4-bromobenzyl)-1,7′-dimethyl-2′-propyl-1*H*,3′*H*-2,5′-bibenzo[*d*]imidazole **10** as a white crystalline solid.

The 4,4-dimethyl-2-phenyl-4,5-dihydrooxazole **11** was metalated with 2.5M n-BuLi at 0 °C for 60 mins and transmetalated with $ZnCl_2$ in THF as the solvent. The 3′-(4-bromobenzyl)-1,7′-dimethyl-2′-propyl-1*H*,3′*H*-2,5′-bibenzo [*d*]imidazole **10** was then added together with tetrakis(triphen ylphosphine)palladium(0) and the mixture was stirred for 24 hours at 55 °C to afford the 2-(4′-((1,7′-dimethyl-2′-propyl-1*H*,3′*H*-2,5′-bibenzo[*d*]imidazol-3′-yl)-methyl)biphenyl-2-yl)-4,4-dimethyl-4,5-dihydrooxazole **12** in 55% yield. Finally oxazoline intermediate was readily cleaved by acid hydrolysis to afford Telmisartan **1**.

In summary, an extremely efficient approach to the biphenyl oxazoline structure of the Telmisartan has been developed by employing a combination of the directed ortho metalation and



Scheme 1 *Reagents and conditions:* (a) polyphosphoric acid, 150–155 °C, 4.0 h, 80%; (b) KOt–Bu, dimethyl acetamide, 75–80 °C, 3.0 h, 70%; (c) trifluoroacetic acid, DMF, 4.0 h, 70%



Scheme 2 *Reagents and conditions:* (a) N-bromosuccinimide, AIBN, CCl_4, reflux, 5.0 h, 50–75%.

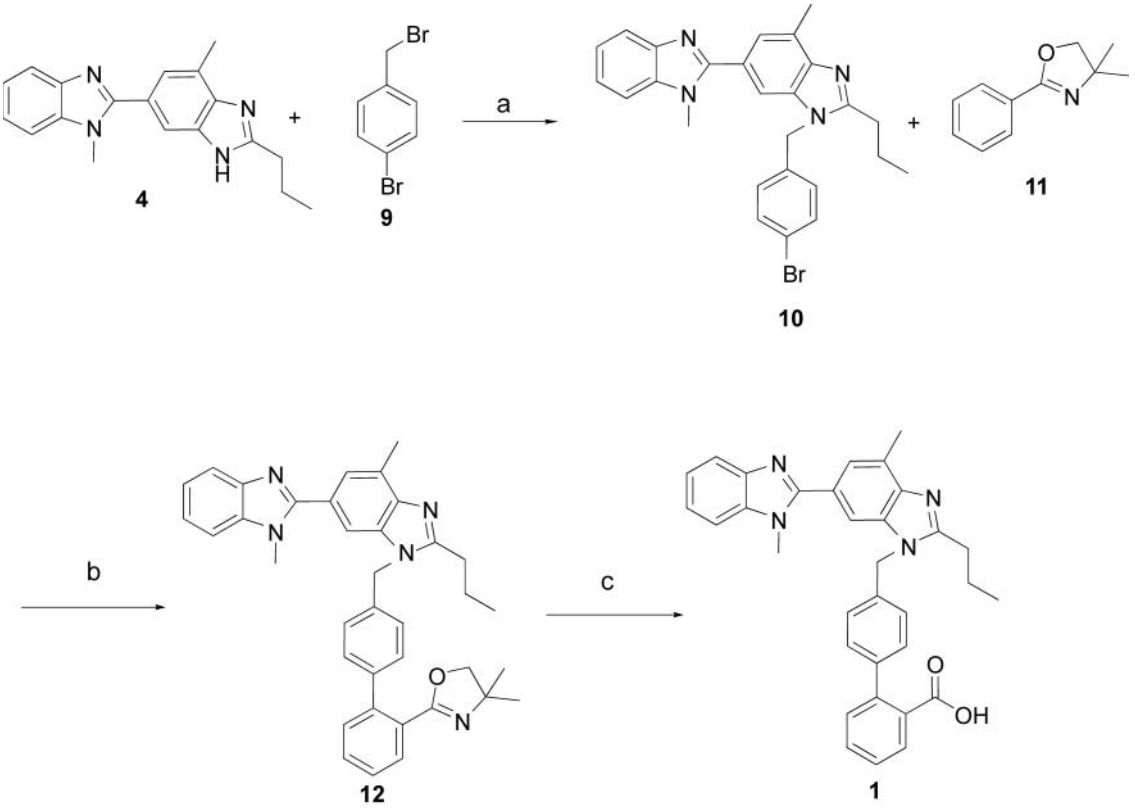
Negishi coupling methodologies. Application of this technology to the synthesis of telmisartan provided a high-yielding procedure that rivaled previous approaches.

Experimental

All solvents and reagents were purchased from the commercial suppliers and used without further purification. All non-aqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. Organic solutions were concentrated under reduced pressure. TLC was performed on Merck precoated Silica-gel $60F_{254}$ plates. ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 and $CDCl_3$ using 400 MHz, on a Varian Gemini 400 MHz FT NMR spectrometer. The chemical shifts were reported in δ ppm relative to TMS. The IR spectra were recorded in the solid state as KBr dispersion using Perkin Elmer FT-IR spectrophotometer. The mass spectra were recorded on Shimadzu LCMS-QP 800 LC-MS and AB-4000 Q-trap LC-MS/MS. Melting points were obtained by using the open capillary method and are uncorrected.

3′-(4-Bromobenzyl)-1,7′-dimethyl-2′-propyl-1H,3′H-2,5′-bibenzo [d]imidazole **(10)**: 1,7′-Dimethyl-2′-propyl-1*H*,3′*H*-2,5′-bibenzo[*d*] imidazole **4,** (10 g, 0.03 mol) and 4-bromobenzyl bromide **9** (8.3 g, 0.03 mol) were dissolved in dimethylacetamide (50 mL). At 25–35 °C under a nitrogen atmosphere powdered potassium carbonate (4.54 g, 0.03 mol) was added portionwise over 10 mins maintaining the temperature at 25–35 °C. The resulting slurry was stirred at 25–35 °C for 8 h. The slurry was filtered and the cake was washed with dimethyl acetamide (15 mL). The filtrate was poured into water (200 mL). The product was extracted twice with ethyl acetate (50 mL) and the solvent was evaporated under vacuum at 55 °C. The residue was triturated with n-hexane (100 mL) to give a solid which was filtered and dried at 50–55 °C for 3–4 h to obtain **10** as a white crystalline powder (yield 12.5 g, 80% yield); HRMS *m/z* Calcd for $C_{26}H_{25}N_4Br$ 474.4075 [M + 1]. Found: 474.4091; ^1H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.72 (1H, s, ArH), 7.64–7.62 (2H, dd, *J* = 8.0 Hz, ArH), 7.47 (1H, s, ArH), 7.42–7.40 (2H, d, *J* = 8.0 Hz, ArH), 7.28–7.22 (2H, m, ArH), 6.94–6.92 (2H, d, *J* = 8.0 Hz, ArH), 5.52 (2H, s, $–CH_2$), 3.8 (3H, s, $–CH_3$), 2.85 (2H, t, *J* = 8.0 Hz, $–CH_2$), 2.74 (3H, s, $–CH_3$), 1.86 (2H, m, *J* = 7.6 Hz, $–CH_2$), 1.01 (3H, t, *J* = 7.6 Hz, $–CH_3$); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm): 14.2, 17.7, 21.6, 30.2, 31.2, 47.2, 109.2, 113.3, 119.7, 121.1, 123.2, 123.5, 125.6, 127.0, 128.2, 129.1, 131.2, 135.4, 135.8, 138.9, 142.6, 144.5, 153.9, 154.5.

2-(4′-((1,7′-Dimethyl-2′-propyl-1H,3′H-2,5′-bibenzo[d]imidazol-3′-yl)-methyl)biphe-nyl-2-yl)-4,4-dimethyl-4,5-dihydrooxazole **(12)**: To a stirred solution of 4,4-dimethyl-2-phenyl-4,5-dihydrooxazole **11**, (3 g, 0.017 mol) in THF (30 mL) at 0 °C was added 2.5M n-BuLi in hexanes (12 mL, 0.02 mol). The mixture was stirred at 0 °C for 60 mins, then 1.0M $ZnCl_2$ in ether (41 mL, 0.03 mol) was added. The reaction mixture was warmed to the ambient temperature over 1 h, then tetrakis(triphenylphosphine)palladium (0) (0.2 g) and 3′-(4-bromobenzyl)-1,7′-dimethyl-2′-propyl-1*H*,3′*H*-2,5′-bibenzo[*d*] imidazole **10** (8.1g, 0.017 mol) were added. The mixture was stirred at 55 °C for 24 h, poured into saturated ammonium chloride (200 mL), and extracted with ethyl acetate (2 × 50 mL). The organic extracts were combined, washed with water (2 × 50 mL), brine (1 × 50 mL), dried over $MgSO_4$ and concentrated under vacuum to give residue. The obtained residue was triturated with n-hexane (50 mL) to give the solid which was filtered and dried at 50–55 °C for 3–4 h to obtain



Scheme 3 *Reagents and conditions:* (a) K_2CO_3, dimethyl acetamide, 8 h, 80% (b) n-BuLi, $ZnCl_2$, $Pd(PPh_3)_4$, THF, 24 h, 55%; (c) concentrated hydrochloric acid, reflux, 30 h, 85%.

12 as a white crystalline powder (yield 5.4 g, 55% yield); m.p. 191–193 °C (lit[7] m.p 191–193 °C) ; HRMS *m/z* Calcd for $C_{37}H_{37}N_5O$ 568.7225 [M + 1]. Found: 568.7222; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 7.78 (1H, d, *J* = 8.0 Hz, ArH), 7.68 (1H, s, ArH), 7.64 (1H, s, ArH), 7.62–7.60 (2H, d, *J* = 8.0 Hz, ArH), 7.59 (1H, d, *J* = 8.0 Hz, ArH), 7.47–7.17 (6H, m, ArH), 7.07 (2H, d, *J* = 8.0 Hz, ArH), 5.45 (2H, s, $–CH_2$), 3.82 (3H, s, $–CH_3$), 3.58 (2H, s, $–CH_2$), 2.97 (2H, t, *J* = 7.6 Hz, $–CH_2$), 2.74 (3H, s, $–CH_3$), 1.92 (2H, m, *J* = 7.6 Hz, $–CH_2$), 1.29 (6H, s, 2× $–CH_3$), 1.04 (3H, t, *J* = 7.6 Hz, $–CH_3$); ^{13}C NMR (400 MHz, $CDCl_3$) (δ ppm): 13.9, 16.7, 21.6, 27.6, 29.6, 31.6, 46.9, 67.2, 79.0, 108.8, 109.2, 119.3, 122.1, 122.2, 123.5, 123.6, 125.6, 127.0, 127.2, 128.8, 129.1, 129.7, 129.9, 130.2, 134.4, 134.8, 136.4, 140.6, 140.8, 142.6, 142.8, 154.2, 156.2, 163.1.

4′-[(1,7′-Dimethyl-2′-propyl-1H,3′H-2,5′-bibenzimidazol-3′-yl) methyl]biphenyl-2-carboxylic acid (**1**): A mixture of **12** (4.0 g, 0.007 mol) and concentrated hydrochloric acid (40 mL) was heated to reflux (100–105 °C) for about 30 h. The reaction mass was cooled to 0–5 °C. 20% Sodium hydroxide solution was added until the reaction mixture pH attained to 9–10 and further stirred at room temperature for 2 h. The required solid was filtered and washed with water (50 mL). The wet cake was dissolved in a mixture of water (60 mL) and acetonitrile (20 mL) and then heated to 60–65 °C. The pH of the resulting clear solution was adjusted to 5.0–5.5 using 5% acetic acid, and stirring was continued for 2 h. The precipitated solid was filtered and washed with water (50 mL). Dried at 70–75 °C for 4–5 h under a vacuum to obtain Telmisartan **1** as a white crystalline powder (yield 3.0 g, 85%); m.p. 260–262 °C (lit[6] mp 260–262 °C); IR (KBr, cm^{-1}) 2300–3500 (broad), 1680 (C=O); HRMS *m/z* Calcd for $C_{33}H_{30}N_4O_2$ 515.6169 [M + 1]. Found: 515.6192; ^{1}H NMR (400 MHz, $CDCl_3$) (δ ppm): 12.8 (1H, s, –COOH), 8.42 (1H, d, *J* = 8.0 Hz, ArH), 8.02 (1H, d, *J* = 8.0 Hz, ArH), 7.52–7.28 (8H, m, ArH), 7.20 (2H, d, *J* = 8.0 Hz, ArH), 7.05 (1H, s, ArH), 6.96 (1H, s, ArH), 5.42 (2H, s, $–CH_2$), 3.82 (3H, s, $–CH_3$), 2.97 (2H, t, *J* = 7.6 Hz, $–CH_2$), 2.74 (3H, s, $–CH_3$), 1.92 (2H, m, *J* = 7.6 Hz, $–CH_2$), 1.04 (3H, t, *J* = 7.6 Hz, $–CH_3$); ^{13}C NMR (400 MHz, DMSO-d_6) (δ ppm): 13.5, 16.7, 20.6, 27.6, 32.7, 47.1, 51.7, 112.0, 112.7, 114.7, 118.6, 125.3, 125.7, 125.8, 127.0, 127.4, 128.6, 129.3, 130.4, 130.6, 131.5, 132.3, 133.1, 133.2, 133.7, 134.5, 140.2, 140.5, 150.2, 157.3, 168.1.

We are grateful to SVNIT, Surat and IICT, Hyderabad for supporting this work.

Received 13 December 2009; accepted 1 February 2010
Paper 090911 doi: 10.3184/030823410X12656400473065
Published online: 1 March 2010

References

1 A.J. Battershill and L.J. Scott, *Drugs*, 2006, **66**, 51.
2 H. Norbert, N. Berthold, R. Uwe, C.A. Jacobus, M. Van, W. Wolfgang and E. Michael, U.S. Patent 1997, 5,591,762.
3 R.W. Ruth, J.C. William, D.I. John, R.C. Michael, P. Kristine, D.S. Ronald and B.M.W.M.T. Pieter, *J.Med. Chem*., 1996, **39**, 625.
4 http://www.rxlist.com/cgi/generic2/telmisartan.htm
5 U.J. Ries, G. Mihm, B. Narr, K.M. Hasselbach, H. Wittneben, M. Entzeroth, J.C.A. Meel, W. Wienen and N.H. Hauel, *J. Med. Chem.*, 1993, **36**, 4040.
6 K.S. Reddy, N. Srinivasan, C.R. Reddy, N. Kolla, Y. Anjaneyulu, S. Venkatraman, A. Bhattacharya and V.T. Mathad, *Org. Process Res. Dev.*, 2007, **11**, 81.
7 A. Sanjeev Kumar, Samir Ghosh, G.N. Mehta, R. Soundarajan, P.S.R. Sarma and Kale Bhima, *Synth. Commun*., 2009, **39**, 4149
8 D.J. Carini and J.V. Dunicia, European Patent 1988, 2,53,310.
9 M. Reuman and A.I. Meyers, *Tetrahedron*, 1985, **41,** 837.
10 E. Negishi, T. Takahashi and A.O. King, *Org. Syn*., 1987, **66,** 67.
11 E. Negishi, A.O. King and N. Okukado, *J.Org. Chem*., 1977, **42,** 1821
12 C. Jubert and P. Knochel, *J. Org. Chem*., 1992, **57,** 5425.
13 L. Zhu, R.M. Wehmeyer and R.D. Rieke, *J. Org. Chem*., 1991, **56,** 1445.