

Ethylene-linked bis(phenol) ligands: efficient synthesis, Ti(IV) coordination chemistry, and Lewis acid catalysis

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Abstract

We report herein an efficient synthesis of a series of chelating bis(aryloxy) ligands that can be diverged at a late stage to generate a variety of structures. Based on structural differences between linked and unlinked analogs of six-coordinate acid–base adducts of $(ArO)_2TiCl_2(dmpe)$, a hypothesis predicted that a difference between the two structure types would be apparent when the compounds shuttled between four- and six-coordinate structures. Comparing their efficiencies in the Lewis acid accelerated Diels–Alder reaction, however, did not support this notion.

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1. Introduction

Extensive experimental evidence has reinforced the paradigm that chelating ligands are most efficient at transferring their stereochemical information to transition metals and subsequently to their catalyzed reactions (e.g. BINAP, TADDOL, tartrate esters and *ansa*-metallocenes) [1]. Moreover, the chelate effect can be a significant stabilizing influence on complexes prone to ligand redistribution. For these and other reasons we recently had the need to synthesize a series of chelating aryloxy ligands for use in Ti chemistry [2]. While methylene, and oxo linkages were relatively well known we found that simple ethylene linked structures were rare, and that the reported method for their synthesis was not amenable to delivering the quantity or structural variability that we desired [3]. This note reports a new synthetic approach to ethylene-bridged bis(phenol) ligands that introduce the *ortho*-substituents at a late stage for maximum structural variability, the coordina-

tion chemistry of the 6,6'-dimethyl and diisopropyl ligands with Ti, and a comparative analysis of their activity as Lewis acid catalysts.

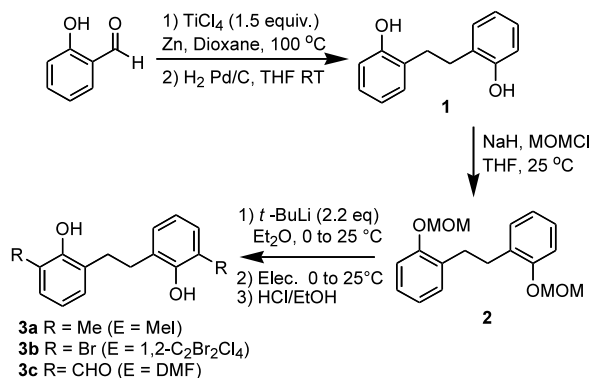
2. Ligand synthesis

Our ligand synthesis was designed to be high yielding, inexpensive and amenable to late stage diversification (Scheme 1). McMurry coupling [4] of salicylaldehyde under Mukaiyama conditions [5] ($TiCl_4$, Zn) affords the crystalline 2,2'-ethylenebis(phenol) (80:20 *trans:cis* ratio, 48% yield), which was hydrogenated over Pd/C to give the diphenol **1** in 94% yield. The diphenol was protected without purification as the methoxymethyl ether with NaH and chloromethyl methyl ether, and purified by distillation (78%). Orthometallation of **2** (2.2 equivalents *tert*-BuLi, 0→25 °C) followed by MeI afforded multi gram quantities of **3** (R = Me, 95% yield), after acidic workup and chromatography. Orthometallated **2** could also be quenched with other electrophiles like 1,2-Br₂Cl₄C₂ or DMF to provide the 6,6'-Br₂, **3b**, and 6,6'-diformyl, **3c**, diphenols, respectively. Orthometallation with an electrophilic quench offers viable routes to a wide variety of additional *ortho* functional groups (e.g. acetates, acids, and boronic acids), making this synthetic scheme highly applicable to the synthesis

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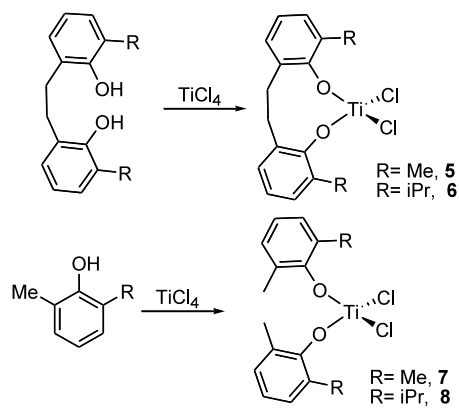
Scheme 1.

of additional ligand variants [6]. Attempts to quench the dianion with *iso*-propyl iodide were unsuccessful, and so the 6,6'-*i*Pr₂-derivative **4** was obtained by a different procedure [7]. A 4-vinyl version of **3** was also readily obtained by selective bromination (Br_2 , >98%) and Heck coupling [8] to give vinyl-**3** (52% yield).

The $(\text{ArO})_2\text{TiCl}_2$ Lewis acid complexes containing the new diaryloxy ligands were synthesized using the conditions of Okuda (ligand + TiCl_4 in pentane) [4]. This methodology proved amenable to both monodentate and bidentate phenols, and provided good yields of linked and unlinked variants of 2,6- Me_2 and 2,6- Me ,*i*Pr complexes (Scheme 2). The dichlorides **5–7** were isolated by crystallization/precipitation in moderate to good yields as red to brown solids. Catalyst **8** was isolated as a viscous brick red liquid, the physical characteristics of which made purification difficult and necessitated accurate reagent stoichiometry. Each complex was utilized as a catalyst for the Diels–Alder reaction (*vide infra*).

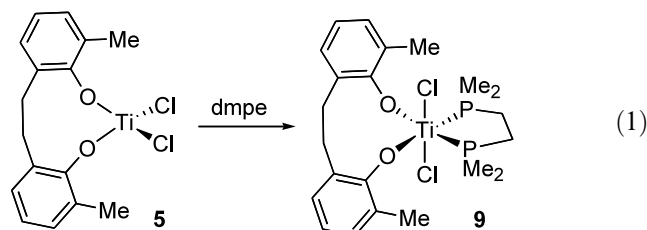
3. Results and discussion

Previous experiments have shown that stable, isolable dmpe adducts could be obtained from tetrahedral



Scheme 2.

$(\text{ArO})_2\text{TiCl}_2$ complexes like **7**, but that unknown 1:2 Ti:dmpe adducts (up to 25%) always accompanied formation of the desired product [9]. Surprisingly, the linked analog **5** reacted smoothly with dmpe to provide the desired adduct **9** free of byproducts, and in good yield (Eq. (1)). The 4-vinyl analog of **9** [10] provided X-ray quality crystals for analysis.



As expected, the six-coordinate compound (vinyl-**3**) $\text{TiCl}_2(\text{dmpe})$ had a distorted octahedral geometry [11] (Fig. 1) that was similar to its unlinked analog in most regards [10], but had a ligand conformation that differed because of the ethylene link. Like (2,6-dimethylaryloxy)₂ $\text{TiCl}_2(\text{dmpe})$, the aryloxy oxygen atoms are *trans* to the phosphorus atoms with most bond distances and angles being nearly identical. The orientations of the phenyl rings, however, are quite different as they orient perpendicular to the O–O–Ti–P–P plane in the unlinked case and are skewed almost parallel to the plane in the linked case, a natural consequence of the linkage (Fig. 2). This structural difference results in significantly different projections of the ortho methyl groups relative to the neutral-ligand binding plane. Contrasting these orientational differences are the nearly superimposable structures of the linked and

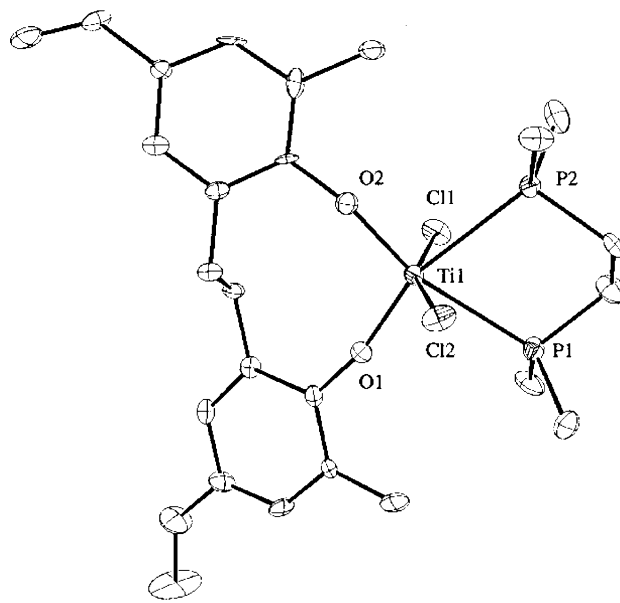


Fig. 1. ORTEP diagram of (vinyl-**3**) $\text{TiCl}_2(\text{dmpe})$. Selected bond lengths (Å) and bond angles (°): Ti–P(2) = 2.699(3), Ti–O(1) = 1.802(7), Ti–Cl(1) = 2.346(3), P–Ti–P = 74.53(8), Cl–Ti–Cl = 158.72(11), O–Ti–O = 105.5(3).

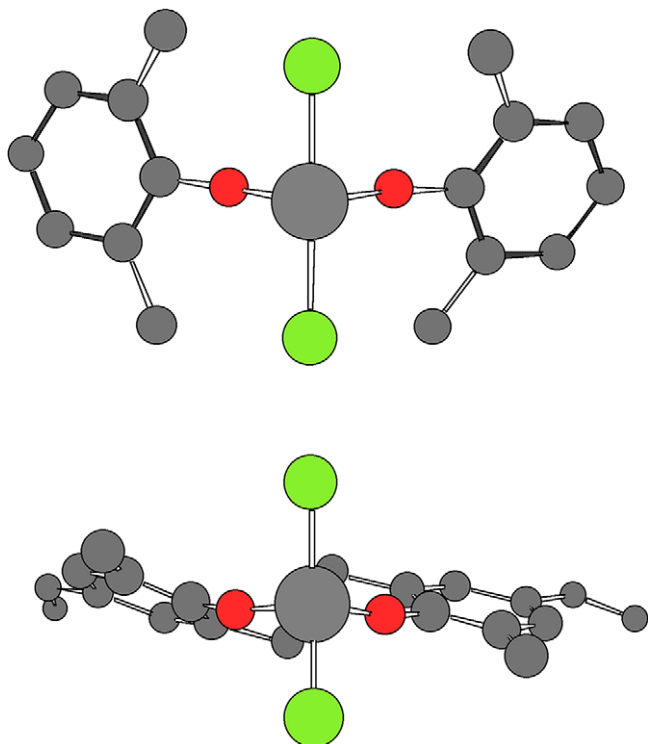
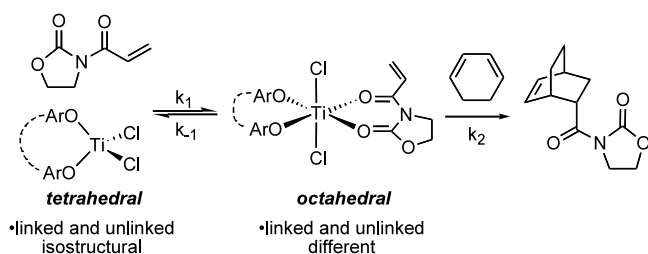


Fig. 2. CHEM3D representations of the X-ray structures of $(2,6\text{-Me}_2\text{-C}_6\text{H}_3\text{O})_2\text{TiCl}_2\text{-dmpe}$ [10] (top) and **9** (bottom) highlighting the different aryloxo rotomers. The dmpe portion is removed in both cases for clarity.

unlinked derivatives of tetrahedral (**3**) TiBr_2 complexes [4,12,13]. Thus, the linkage joining the two aryloxo ligands is structurally significant only in the octahedral form of the Lewis acid; the base-free tetrahedral forms are isostructural.

These data led us to hypothesize that the structural differences between linked and unlinked octahedral forms of otherwise similar complexes would be manifested in their Lewis acid properties. That is, although the ground state structure of linked and unlinked tetrahedral Lewis acids are nearly identical, ligand torsional strain generated upon substrate coordination would attenuate the performance of the linked ligands in a reaction like the Diels–Alder (k_1/k_{-1} , Scheme 3), which necessitates the intermediacy of an octahedral activated complex. This hypothesis was evaluated by comparing the ability of two sets of catalysts to



Scheme 3.

accelerate the Diels–Alder reaction between the two-point binding substrate 3-acryloyloxazolidinone and 1,3-cyclohexadiene.

The first catalyst set included $(2,6\text{-Me}_2\text{-C}_6\text{H}_3\text{O})_2\text{TiCl}_2$ (**7**) [14] and its linked analog **5**. The second, more sterically bulky catalyst set, included $(2\text{-}^i\text{Pr-6-Me-C}_6\text{H}_3\text{O})_2\text{TiCl}_2$ (**8**) and its linked analog (**6**). The reactions were carried out in CH_2Cl_2 at ambient temperature using 5 mol% catalyst and 15 equivalents of diene to achieve pseudo-first order conditions. Reaction progress was monitored by quenching an aliquot on silica gel and analyzed by GC. As Fig. 3 indicates, the catalysts have similar initial rates with the linked methyl complex **5** being slightly faster ($1.1 \times$) than its unlinked analog **7** ($k_{\text{obs}} = 3.4 \times 10^{-4}$ and $3.0 \times 10^{-4} \text{ s}^{-1}$, respectively). Since the linked ^iPr complex **6** was 1.2 times slower than its unlinked analog **8** ($k_{\text{obs}} = 2.4 \times 10^{-4}$ and $2.9 \times 10^{-4} \text{ s}^{-1}$, respectively), these data indicate that the conformational rigidity observed in the solid state does not translate into significant Diels–Alder rate differences.

Based on the simple mechanism in Scheme 2 and the rate of reaction, one possible explanation for the observed insensitivity to ligand structure is that cycloaddition is not turnover limiting (k_2), and that the effect that putatively diminishes the binding constant also compensates by enhancing the rate of product release (reforming the tetrahedral complex) [15]. Additional mechanistic studies will be necessary to distinguish between the reasonable mechanisms.

4. Conclusion

In summary, this paper reports a new, efficient methodology for the synthesis of ethylene-linked diphe-

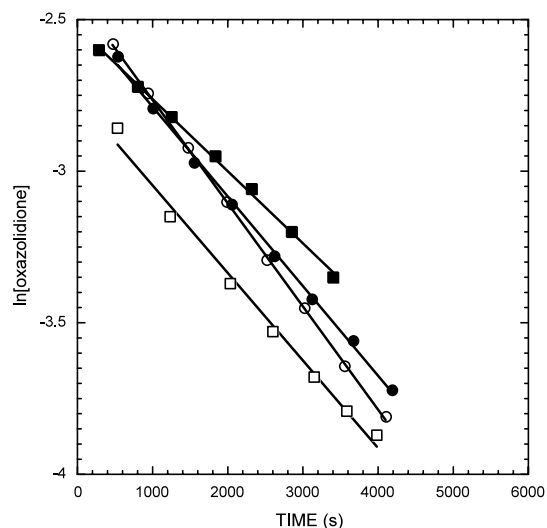


Fig. 3. Plot of $\ln[\text{oxazolidinone}]$ vs. time. ● = **7**; ○ = **5**; □ = **8**; and ■ = **6**.

nol ligands that introduces the *ortho*-substituent in the next to last step. This approach provides a highly convergent route to many ligand structures in addition to the ones reported herein. The coordination chemistry of these ligands parallels that of the unlinked cases in many ways, though octahedral coordination environments bring out their differences.

Acknowledgements

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References

- [1] J. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley, New York, 1995.
- [2] (a) See, for example: F.G. Sernetz, R. Mülhaupt, S. Fokken, J. Okuda, *Macromolecules* 30 (1997) 1562;
(b) S. Fokken, T.P. Spaniol, H.-C. Kang, W. Massa, J. Okuda, *Organometallics* 15 (1996) 5069;
(c) D. Takeuchi, T. Nakamura, T. Aida, *Macromolecules* 33 (2000) 725;
(d) J. Okuda, S. Fokken, T. Kleinhenn, T.P. Spaniol, *Eur. J. Inorg. Chem.* (2000) 1321.;
(e) T.J. Davis, J. Balsells, P.J. Carroll, P.J. Walsh, *Org. Lett.* 3 (2001) 2161.
- [3] S. Fokken, T.P. Spaniol, J. Okuda, F.G. Sernetz, R. Mülhaupt, *Organometallics* 16 (1997) 4240.
- [4] (a) J.E. McMurry, T. Lectka, J.G. Rico, *J. Org. Chem.* 54 (1989) 3748;
(b) J.E. McMurry, *Chem. Rev.* 89 (1989) 1513.
- [5] T. Mukaiyama, T. Sato, J. Hanna, *Chem. Lett.* (1973) 1041.
- [6] (a) For examples of quenching with formyl, acetate, amide, carbinol and carboxylate precursors, see: C.A. Townsend, L.M. Bloom, *Tetrahedron Lett.* 22 (1981) 3923;
(b) For quenching with a boronic acid precursor, see: B.I. Alo, A. Kandil, P.A. Patil, M.J. Sharp, M.A. Siddiqui, V. Snieckus, P.D. Josephy, *J. Org. Chem.* 56 (1991) 3763.
- [7] (a) J.W. Anthis, I. Filipov, D.E. Wigley, *Inorg. Chem.*, in press;
(b) J.W. Anthis, PhD dissertation, University of Arizona, April 2001.
- [8] (a) For several reviews of the Heck coupling, see: N.J. Whitcombe, K.K.M. Hii, S.E. Gibson, *Tetrahedron* 57 (2001) 7449;
(b) A. Biffis, M. Zecca, M. Basato, *J. Mol. Cat. A: Chem.* 173 (2001) 249;
(c) A. de Meijere, F.E. Meyer, *Angew. Chem. Int. Ed. Engl.* 33 (1994) 2379.
- [9] A.O. Larsen, P.S. White, M.R. Gagné, *Inorg. Chem.* 38 (1999) 4824.
- [10] The 4-vinyl analog of **5** was obtained by a different route since the vinyl group is hydrohalogenated under the conditions of *Scheme 2*. It is obtained in pure form by treating the ligand first with $\text{Ti}(\text{NEt}_2)_2(\text{OiPr})_2$, and then SiCl_4 , see footnote 13.
- [11] (a) For several other examples of this octahedral distortion see: L.M. Kobriger, A.K. McMullen, P.E. Fanwick, I.P. Rothwell, *Polyhedron* 8 (1989) 77;
(b) J.R. Clark, A.L. Pulvirenti, P.E. Fanwick, M. Sigalas, O. Eisenstein, I.P. Rothwell, *Inorg. Chem.* 36 (1997) 3623.
- [12] B.P. Santora, P.S. White, M.R. Gagné, *Organometallics* 18 (1999) 2557.
- [13] S.A. Waratuke, M.G. Thorn, P.L. Fanwick, A.P. Rothwell, I.P. Rothwell, *J. Am. Chem. Soc.* 121 (1999) 9111.
- [14] A.W. Duff, R.A. Kamarudin, M.F. Lappert, R.J. Norton, *J. Chem. Soc. Dalton Trans.* (1986) 489.
- [15] Attempts to measure comparative rates and thermodynamics of binding dieneophile to linked and unlinked analogs (**5/7** and **6/8**) were frustrated by unresolvable broad peaks.