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An Aniline-Bridged *Bis*(pyrazolyl)alkane Ligand for Dizinc-Catalysed Ring-Opening Polymerization

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We report an aniline ligand (1) with two *bis*(pyrazolyl)alkane arms, and its cationic, dizinc complexes. XRD, NMR, and modelling of the dizinc complexes resulted in an unprecedented, dynamic μ-anilide core. Compared with published μ-phenolate analogues, our μ-anilide complexes show higher activity and divergent counterion trends in ring-opening polymerization of *rac*-lactide.

The synthesis of biodegradable polymers by ring-opening polymerization (ROP) relies on main-group catalysts for their high activity.[1] However the structural and mechanistic uncertainty of simple main-group polymerization catalysts hinders their optimization and analysis.[2] The introduction of discrete main-group polymerization catalysts by Chisholm[3] and by Coates[4] significantly improved tractability in ROP. Yet Coates[4] and later Diaconescu[5] characterized a complicated role for aggregation and metal-metal cooperativity in ROP. Consequently, well-defined multimetallic catalysts based on multinucleating ligands have been studied as a source of mechanistic insight and new selectivity in ROP.[6] Notably, record ROP activities were reported with macrocyclic dizinc catalysts, by Rieger[7] and by Williams.[8] Phenolate-bridged dizinc complexes, especially those reported by Tolman and Hillmyer,[9] by Williams,[10] and by Garden,[11] have been especially prominent in this endeavour.

Our laboratory introduced binucleating *bis*(pyrazolyl)alkane ligands with BINOL[12] and phenol[13] bridging groups as sterically and electronically modular platforms for di(main group) catalysis. We first reported a versatile method for the synthesis of *bis*(pyrazolyl)alkanes by nucleophile-catalysed condensation between aldehydes and *bis*(pyrazolyl)methanones.[14] This method gives the *bis*(pyrazolyl)alkanes considerable covalent flexibility compared to existing binucleating ligands, providing improved scope for catalyst optimization and structure-activity analysis. In particular, the phenol-linked ligands PD^RH (**2**-R, Figure 1) form cationic complexes with the composition $[PD^RZn_2Et_2]^+$ (–R = –H, –Me, –Ph, –iPr) that were active, controlled, and optimizable catalysts for ROP. But we found that the cationic charge on $[PD^RZn_2Et_2]^+$ considerably reduced its activity in ROP through a coordination/insertion mechanism, which favours more nucleophilic catalysts. On this basis, we speculated that replacing the phenol with a less electronegative bridging group would improve activity.

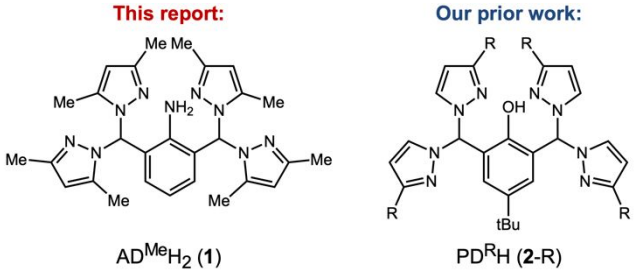

Figure 1. Binucleating *bis*(pyrazolyl)alkanes.

This manuscript reports an aniline ligand $AD^{Me}H_2$ (**1**) and a direct comparison of its coordination chemistry and catalysis to its PD^RH (**2**-R) analogues. Our work represents a rare example of a μ-anilide in a binucleating ligand. Primary amines and anilines do readily form μ-amide dizinc complexes[15] by reaction with simple organozincs[16] or with zinc amides.[17] But neither primary amines nor anilines have been used as the bridging group in a binucleating ligand for dizinc coordination chemistry despite the diversity of phenolate-binucleated dizincs.[18]

Our synthesis of $AD^{Me}H_2$ (**1**) commenced with DBU-catalysed condensation between 2-nitro-1,3-benzenedialdehyde[19] (**3**) and *bis*(3,5-dimethylpyrazolyl)methanone (**4**, Scheme 1), based on our published procedure.[14] This reaction afforded

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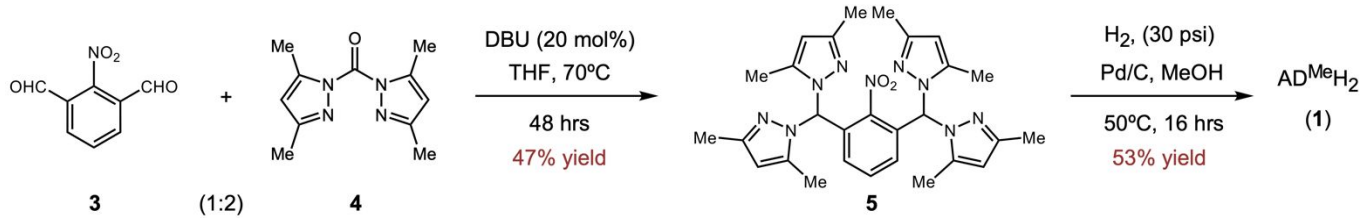
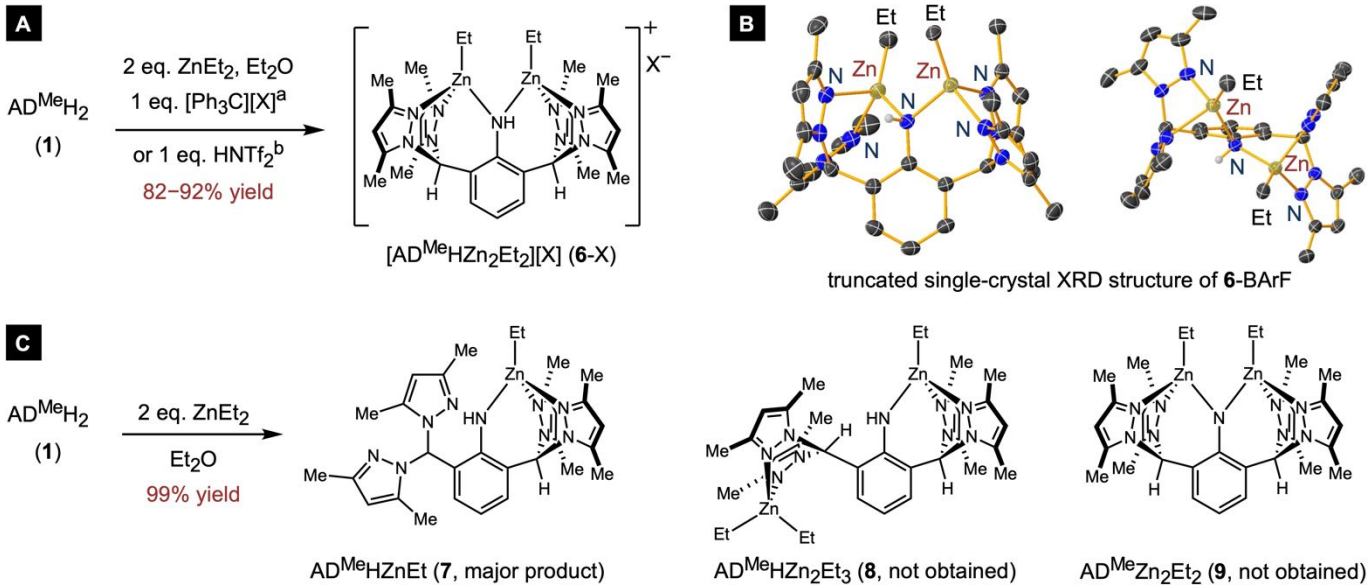
nitrobenzene-linked double *bis*(pyrazolyl)alkane **5** in 47% yield. Next, hydrogenation of **5** over palladium on carbon gave the title aniline ligand $AD^{Me}H_2$ (**1**) in 53% yield. This step required careful optimization to mitigate cleavage of the C–N(pyrazole) bonds. Nevertheless, the nitro group proved strategic for the condensation reaction, as we never successfully obtained $AD^{Me}H_2$ (**1**) by condensation with 2-amino-1,3-benzenedialdehyde. Previously,[14] we showed that electron-withdrawing groups accelerate this reaction, an effect that considerably favours the nitro group in **3**.

We first prepared cationic anilide complexes $[AD^{Me}HZn_2Et_2]^+$, by analogy to our published synthesis of $[PD^RZn_2Et_2]^+$ complexes.[13] Thus reaction of $AD^{Me}H_2$ (**1**) with two equivalents of Et_2Zn and one equivalent of a trityl salt ($[Ph_3C][X]$) or protic acid (HX) gave us salts $[AD^{Me}HZn_2Et_2][X]$ (**6**-X; X^- = $BArF^-$, $^-NTf_2$, BF_4^-, PF_6^-, ^-OTf; $BArF^-$ = *tetrakis*(3,5-*bis*(trifluoromethyl)phenyl)borate) in good yields (82–92%, Scheme 2A). Single-crystal XRD analysis of **6**-BArF resulted in a twisted μ-anilide structure, with two pseudotetrahedral zinc atoms. Nevertheless, all four pyrazoles are NMR-equivalent at room temperature, suggesting rapid conformational interconversion. Indeed, we modelled two oppositely twisted and isoenergetic conformers of this ion **S9-4** and **S9-6**, and a transition state **S9-4** for their interconversion, obtaining a low activation energy of 5.76 kcal/mol (Section S9.3). The Zn–Zn distance 3.345 Å and the Zn-N-Zn bond angle 108.4° in **6**-BArF are both larger than those for $[PD^HZn_2Et_2][BArF]$ (3.188 Å, 102.9°)[13] and for $[ZnEt(NHMes)(THF)]_2$ (2.902 Å, 88.9°).[16a] By contrast, treating the proligand $AD^{Me}H_2$ (**1**) with two equivalents of diethylzinc without acid instead furnished the monozinc complex $AD^{Me}HZnEt$ (**7**; Scheme 2C) quantitatively. Varying the solvent and stoichiometry of this reaction never gave neutral dizinc complexes with the compositions $AD^{Me}HZn_2Et_3$ (**8**) or $AD^{Me}Zn_2Et_2$ (**9**). To understand this outcome, we modelled the reaction of a truncated analogue of **7** (**S9-1**) with dimethylzinc to give truncated analogues of $AD^{Me}HZn_2Et_3$ (**S9-2**) and $AD^{Me}Zn_2Et_2$ (**S9-3**, Section S9.2). We found that the reaction to form the trialkyl complex was exothermic (ΔH = –4.78 kcal/mol) but endergonic (ΔG = +4.58 kcal/mol), consistent with our analysis on why $PD^HZn_2Et_3$ was not formed from PD^HH and $ZnEt_2$.[13] However, our model indicated that protonolysis to generate dizinc imido **S9-3** was exergonic (ΔG = –10.51 kcal/mol). Presumably, this reaction is kinetically disfavored. Power reported that anilines do not react with organozincs to give imidos even though analogous organomagnesium compounds do.[16a,20] Reports of isolated zinc imidos remain rare.[21] As an alternative, we attempted to



Scheme 1. Synthesis of $AD^{Me}H_2$ (**1**). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.



Scheme 2. Metalation of $AD^{Me}H_2$ (**1**) with Et_2Zn: A) synthesis of cationic complexes ([a]X^- = $BArF^-$, BF_4^-, PF_6^-, TfO^-; [b]X^- = $^-NTf_2$), B) crystal structure of **6**-BArF, C) metalation without acids.

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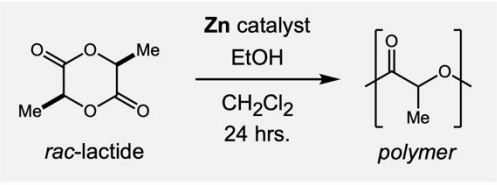
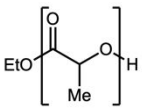
prepare imido $AD^{Me}Zn_2Et_2$ (**9**) by deprotonation of $[AD^{Me}HZn_2Et_2][BArF]$ (**6**-BArF, Section S4.2), but this approach always lead to decomposition of the zinc complex.

We next compared the dizinc catalysts $[AD^{Me}HZn_2Et_2][X]$ (**6**-X) in the ROP of *rac*-lactide (Table 1), finding **6**-NTf_2 to have the highest activity overall and the only complex that had a higher activity than Et_2Zn (entries 1–5, 8). The use of an alcohol co-initiator proved essential, as the reaction of **6**-NTf_2 on its own was much lower (entry 6). Monometallic complex $AD^{Me}HZnEt$ (**7**) was nearly unreactive until longer reaction times, in contrast to our results with the phenolate catalysts in which $PD^{H}ZnEt$ was much more reactive than its most active $[PD^{H}Zn_2Et_2]^+$ counterpart.[13] GPC analysis of the polymer produced by **6**-NTf_2 resulted in a low dispersity (*Đ* = 1.03) and a number-average molecular weight (*Mn* = 7,800 Da) lower than that expected for one chain per zinc atom (12,700 Da). Although $AD^{Me}HZnEt$ (**7**) and $ZnEt_2$ also gave low dispersities (1.08 and 1.09 respectively), the GPC trace for the polymer produced by $[AD^{Me}HZn_2Et_2][NTf_2]$ (**6**-NTf_2) was clearly more monomodal (Figure S53). End-group analysis by ^{1}H-NMR and MALDI resulted in an ethyl ester (**10**), consistent with coordination/insertion polymerization initiated by an alkoxide (Figure S47), although it would also be consistent with an activated monomer mechanism. We favor a coordination/insertion mechanism in light of our previous report.[13] The presence of nearly equal mass peaks separated by 72, half the mass of lactide, was consistent with transesterification or backbiting (Section S8.1). Stereochemical analysis of this sample resulted in Pr = 0.49, indicating no selectivity (Section S7.3). The modest selectivity obtained by $ZnEt_2$ (Pr = 0.63) suggests that **6**-NTf_2 and $ZnEt_2$ do not have the same active catalyst.

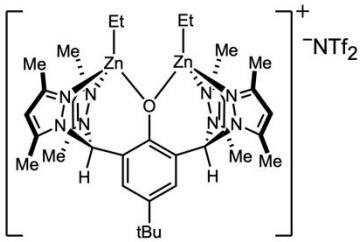
Table 1. Ring-opening polymerization of *rac*-lactide.





end-group functionalization with **6**-NTf_2 (**10**)

$[PD^{Me}Zn_2Et_2]^+$ $[NTf_2]^-$ (**11**):



Entry[a]	Zn complex	conversion (30 min)[b]	conversion (1 h)[b]	conversion (24 h)[b]	$M_{n,theo}$ (kg/mol)[c]	$M_{n,GPC}$ (kg/mol)[d]	$Đ$[d]
1.	$[AD^{Me}HZn_2Et_2][BArF]$ (**6**-BArF)	0%	0%	2%	--	--	--
2.	$[AD^{Me}HZn_2Et_2][BF_4]$ (**6**-BF_4)	0%	0%	2%	--	--	--
3.	$[AD^{Me}HZn_2Et_2][PF_6]$ (**6**-PF_6)	0%	0%	0%	--	--	--
4.	$[AD^{Me}HZn_2Et_2][OTf]$ (**6**-OTf)	0%	0%	3%	--	--	--
5.	$[AD^{Me}HZn_2Et_2][NTf_2]$ (**6**-NTf_2)	13%	21%	88%	12.7	7.80	1.03
6.[e]	$[AD^{Me}HZn_2Et_2][NTf_2]$ (**6**-NTf_2)	0%	0%	2%	--	--	--
7.	$AD^{Me}HZnEt$ (**7**)	0%	0%	85%	12.2	7.60	1.08
8.	$ZnEt_2$	0%	3%	96%	13.8	6.3	1.09
9.	$[PD^{Me}Zn_2Et_2][NTf_2]$ (**11**)	0%	1%	3%	--	--	--
10.[f]	$[PD^{H}Zn_2Et_2][NTf_2]$ (**12**)	0%	3%	98%	14.1	11.2	1.12

[a]Conditions: $[rac\text{-lactide}]_0$ = 0.5 M in CH_2Cl_2 at room temperature, catalyst was premixed with ethyl alcohol (1 equivalent w.r.t. zinc) for 24 h and then treated with *rac*-lactide (100 equivalents w.r.t. zinc). [b]Determined by ^{1}H NMR spectroscopy in $CDCl_3$. [c]Calculated from (100 × % conversion × 144.13(molecular weight of *rac*-lactide)). [d]Determined by GPC in THF (calibrated with polystyrene standards) and a correction factor of 0.58 was applied to all molecular weights. [e]Ethyl alcohol was not used in this reaction. [f]Benzyl alcohol was used in place of ethyl alcohol.

By contrast, the $BArF^-$ salt $[PD^{H}Zn_2Et_2][BArF]$ was the optimal catalyst among our published phenolate series,[13] and it showed much higher activity (95% conversion in 1 hour) than $[AD^{Me}HZn_2Et_2][NTf_2]$ (**6**-NTf_2). However, these two catalysts also have different pyrazoles and different counterions. To more rigorously compare the bridging atoms, we prepared phenolate analogues $[PD^{Me}Zn_2Et_2][NTf_2]$ (**11**) and $[PD^{H}Zn_2Et_2][NTf_2]$ (**12**). We used benzyl alcohol for polymerization with **12** because that was the cocatalyst that we used in our previous manuscript.[13] Both were less active than $[AD^{Me}HZn_2Et_2][NTf_2]$ (**6**-NTf_2), with only **12** showing appreciable activity at long reaction times. These results suggest that the μ-anilide increases ROP activity compared to the phenolate. However, we acknowledge that the divergent counterion trends complicates a straightforward comparison between these two series. Unfortunately, we did not successfully prepare a simple pyrazole analogue of $AD^{Me}H_2$ (**1**) to compare with $[PD^{H}Zn_2Et_2][BArF]$.

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In summary, this work introduces the μ-anilide core to the growing field of binucleating ligands for dizinc catalysis, and demonstrates its direct analogy to more established phenolate ligands. Our aniline ligand $AD^{Me}H_2$ (**1**) shows metalation reactivity similar to its phenol counterparts $PD^{R}H$ (**2**-R), while its dizinc complexes $[AD^{Me}HZn_2Et_2][X]$ (**6**-X) show conformational dynamics similar to our published phenolate series $[PD^{R}Zn_2Et_2][X]$. This structural homology allowed us to compare μ-phenolate and μ-anilide bridging in catalysis, resulting in an influence on counterion effects and on activity. These results will further expand the tools available for optimization and structure-activity analysis in bimetallic catalysis.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as a part of Supplementary Information.

Acknowledgements

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The data supporting this article have been included as a part of Supplementary Information.