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One-pot synthesis of tripodal tris(2-aminoethyl)amine derivatives from seven molecular components

Ann Almesåker [a], Janet L. Scott [a,*], Leone Spiccia [a,*], Christopher R. Strauss [b]

[a] School of Chemistry and ARC Special Research Centre for Green Chemistry, Monash University, Wellington Road, Clayton, Victoria 3800, Australia
[b] QUILL Centre, The Queen's University of Belfast, Belfast, Northern Ireland BT9 5AG, United Kingdom

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ABSTRACT

Complex tripodal tris(2-aminoethyl)amine (tren)-based ligands have been prepared in a single-pot reaction of tren with 3 equiv each of cyclohexenone and a benzaldehyde derivative (i.e., from seven components and three molecular types). The highest yield of product was obtained for *p*-nitrobenzaldehyde, the most electrophilic aldehyde used.

Ligands for metal complexation generally have simple structures and are formed by straightforward organic reactions. The construction of complex ligands, such as those with highly protected metal-binding sites, often requires multi-step syntheses. Usually, overall yields are low and several purification steps are involved. The assembly of complex ligands from multi-component reactions is less common, although in some cases, organic methodology is available.[1,2]

Tris(2-aminoethyl)amine (tren) is a commercially available tripodal amine, which has found wide application as a ligand in the preparation of metal complexes.[3–5] Due to the tripodal arrangement of donor atoms, tren and a variety of N-functionalised derivatives have been commonly employed in the preparation of trigonal bipyramidal metal complexes.[6] More elaborate or extended tren ligands have been formed via substitution,[7,8] or via condensation reactions with aldehydes.[9–11] Metal complexes prepared therefrom have been employed in catalysis and in oxygen binding studies.[6,10,12,13] They have also been used to stabilise redox active oxoanions, such as thiosulfate,[14] and to prepare cyano-bridged heteropolynuclear clusters with ferromagnetic properties.[15,16] Less well explored are aryl-substituted tren ligand structures, although some have been employed in the formation of transition metal amido complexes,[17–23] which have been demonstrated to act as catalysts in dinitrogen reduction (Mo, V and Cr complexes)[20,21] and which have been tested in alkene epoxidation reactions (Fe and Mn complexes).[17] Aryl-substituted tren-based ligands are generally synthesised via aryl substitution reactions using commercially available ArF compounds in 28–99% yields.[18,24] A different pathway to these aryl-substituted tren compounds involves Pd-mediated aromatic coupling, which is limited to commercially available ArBr compounds, affording the products in 27–90% yields.[19,25] More extended tren structures have been prepared via a two-step synthesis of the starting ArBr compound followed by Pd-mediated aromatic coupling in lower but acceptable overall yields of 36–45%.[25] Given the versatility and demonstrated utility of these ligands, considerable benefit would be derived from new synthetic strategies that would broaden the range of accessible aryl-substituted tren ligands.

Herein, a straightforward methodology to highly substituted aryl tren compounds is demonstrated. A single-pot, multi-component synthetic protocol that utilises a non-enolisable aldehyde, cyclohexenone (or substituted cyclohexenone derivatives) and a primary or secondary amine to form substituted anilines[26] has been employed to assemble an aryl tren ligand scaffold from seven molecular components (three molecular types).

The reaction of a central tren unit bearing three primary amine moieties with 3 equiv each of cyclohexenone and of an aromatic aldehyde provides access to a series of functionalised tripodal ligands (Scheme 1). The resultant tripodal structures with extended arms offer a highly protected binding pocket within the tren unit which could be exploited in the preparation of metal complexes with novel geometries and properties. The flexibility of the multi-component reaction allows for introduction of great structural diversity, by variation of the aldehyde or cyclohexenone components, as demonstrated here with a range of aldehydes. A correlation has been found between the degree of activation (electrophilicity) of the aldehyde and the yield of product.

Initial attempts to combine the seven reacting molecules [tren + benzaldehyde (x3) + cyclohexenone (x3)] to produce trisubstituted tren-derivatives yielded only trace quantities of the envisaged tripodal ligand after 24 h. In contrast, the simpler multi-component reaction utilising mono-amines (i.e., combining one equivalent each of the amine, benzaldehyde and cyclohexenone) has previously been shown to yield the corresponding substituted anilines in moderate to good yields (50–90%).[26] The reaction involving tren is inherently more complex requiring that reaction

* Corresponding authors. Tel.: +61 3 9905 4526; fax: +61 3 9905 4597 (L.S.).
E-mail addresses: janet.scott@sci.monash.edu.au (J.L. Scott), leone.spiccia@sci.monash.edu.au (L. Spiccia).

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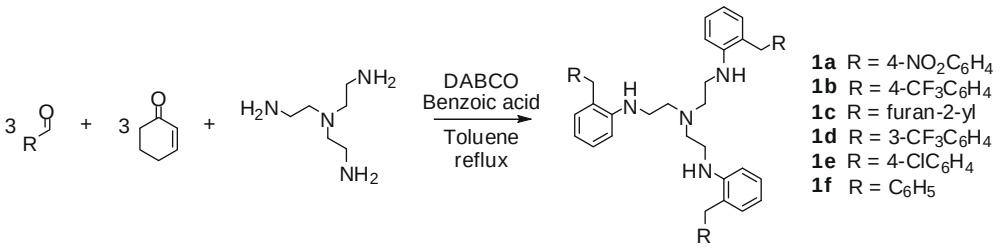


Scheme 1. Seven components assembled in a multi-component reaction to yield tripodal ligands with aromatic pendant 'arms'.

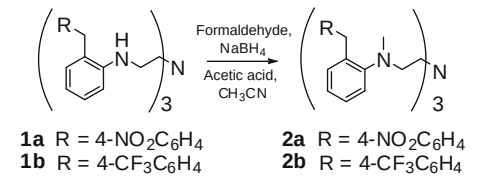
takes place at each of the three primary amines, and as a consequence formation of the product is more difficult. Nevertheless, the choice of more electrophilic aldehyde components, which bear electron-withdrawing substituents, and careful attention to adequate mixing in the early stages of the reaction to aid redissolution of poorly soluble intermediate Schiff bases (amongst other components), have allowed the isolation of several new tren derivatives.[27] The yields of compounds **1a**–**f** are low, but acceptable for **1a**–**c**, for such a complex single-pot reaction, Table 1. In this small sample, a correlation between the product yield and the Hammett constant of the corresponding acid of the benzaldehyde derivatives was observed, Table 1. In reactions involving poorly activated aldehydes, and thus slow conversion to product, by-products proliferated, complicating purification. Notwithstanding this, compounds **1d**–**f** are included in Table 1 to illustrate the marked trend in reactivity.

As the by-products detected using mass spectrometry included Schiff bases (as has been previously described[26]) and/or products of the reversible Michael reaction, it was expected that longer reaction times might allow slow accumulation of the desired products. As is common for many reactions with a final aromatisation step, the products of almost all the expected equilibrium reactions (including Schiff bases, Michael products and tautomeric dienamines) can be detected, but the desired product slowly accumulates via the one irreversible step: aromatisation. However, it seems that the poor solubility of many of these intermediates militates against full conversion to the desired product. Careful analysis of ^{1}H NMR spectra of samples withdrawn at intervals during reactions revealed that in all cases conversions to the desired products were limited by by-product competition. For example, ^{1}H NMR spectra of samples of the reaction mixtures of **1a** taken at 2 h intervals show an increase in the signal due to the benzyl CH_2 protons (3.72 ppm) of the final aromatised product, Figure 1a. Using the signals due to DABCO as an internal standard it was possible to plot conversion versus time, Figure 1b, showing the limitation of conversion to product. In all cases, the time at which the integrated area of these diagnostic benzyl CH_2 ^{1}H NMR signals reached a plateau was used to define the reaction end point and, thus, the reac-

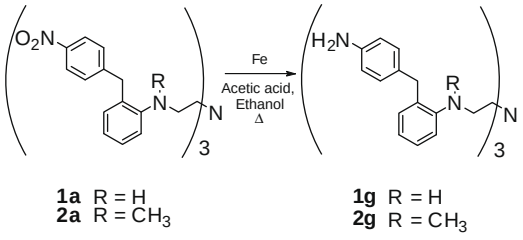
Table 1
Tren-based ligands prepared via a one-pot multi-component reaction

Ligand	Time (h)	Yield (%)	Hammett constant[28]
1a	8	32 (57)[a]	0.78
1b	13	18 (27)[a]	0.54
1c	6	14 (19)[a]	—[b]
1d	11	(19)[c]	0.42
1e	9	(4)[c]	0.23
1f	24	Trace[c]	0

[a] Yield of analytically pure material isolated after recrystallisation (yield after column chromatography; purity (NMR) >95%).
[b] No value available.
[c] Analytically pure material not isolated.



Scheme 2.



Scheme 3.

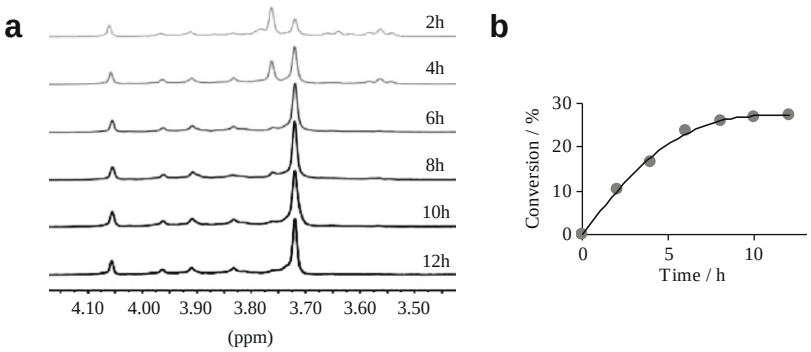


Figure 1. (a) Expansion of the ^{1}H NMR spectra of reaction mixtures of **1a** recorded every 2 h. Accumulation of the benzyl CH_2 is indicated by the increase in intensity of the signal at 3.72 ppm. (b) The conversion to product is shown over time based on the integration of ^{1}H NMR spectra using DABCO as an internal standard.

tion time for larger scale syntheses. Close examination of the ^{1}H NMR spectra of reaction mixtures of **1a** allowed detection of a signal at 4.08 ppm corresponding to 2-(4-nitrobenzyl)phenol,[29] a by-product formed by an aldol condensation between *para*-nitrobenzaldehyde and cyclohexenone followed by *iso*-aromatisation. Clearly, this by-product must be minimised to allow maximisation of conversion to the desired tripodal ligand. Previously, with mono-amines, the amine was used in excess to increase the yield and prevent side reactions such as the formation of the phenol by-product. For the reaction with the polyamine, however, a 1:3 ratio of tren to aldehyde and cyclohexenone needs to be maintained to minimise the formation of partially substituted tren products. Hence, the low availability of amine increases the risk of phenol by-product formation. This also demonstrates that yield improvement by slow addition of tren is not feasible as this would increase the formation of the phenol by-product.

To explore the scope of the multi-component reaction for preparing tren-centred tripodal structures, molecules **1a**,**b** have been further modified. Reductive N-methylation with formaldehyde in the presence of $NaBH_4$ and acetic acid in acetonitrile gives tertiary amines, **2**, in >90% yield (Scheme 2) with no need for further purification of the isolated product.

The nitro functional groups of **1a** and **2a** were also readily reduced to provide terminal $ArNH_2$ moieties of interest in the formation of supramolecular architectures or salts, or for further derivatisation and thus ligand structure diversification (while at the same time fortuitously increasing ligand solubility). Reduction of the nitro group of **1a** or **2a** in refluxing ethanol in the presence of acetic acid using iron powder as the reducing agent gave the amines **1g** and **2g** in 97% and 99% yields, respectively (Scheme 3).

The crystal structures of representative examples were examined to determine whether ligand preorganisation was evident. Single crystals of **1a** and **1b** were obtained from ethyl acetate and a 9:1 hexane/ethyl acetate mixture, respectively. In both cases, the solid-state structure reveals molecules that are highly preorganised for metal ion binding, Figure 2. The four tren nitrogen atoms are arrayed in a trigonal pyramidal geometry favourable for coordination of M^{x+} in a trigonal bipyramidal environment with one open coordination site for a small exchangeable ligand. The aromatic moieties of the arms of the putative ligands interact with each other via intramolecular π···π and CH···π interactions stabilising the tren-cleft. In the solid-state structure of **1a**, these intramolecular interactions occur between the inner aromatic ring of one arm and the outer aromatic ring of the next arm, as shown in Figure 3, forming a circular intramolecular motif of stabilising CH–π and π···π interactions. In the solid-state structure of **1b**, only CH–π interactions stabilise the cleft. The interactions occur similarly between the outer and inner aromatic rings of neighbouring arms. In this case, however, four CH···π contacts can be observed as one outer ring interacts with both the inner and outer rings of its neighbouring arm.

In conclusion, application of a one-pot, multi-component reaction combining a tripodal tetramine bearing three primary amine groups (tren) with various benzaldehydes and cyclohexenone provides a flexible approach to the preparation of a new range of aryl-substituted tren-centred ligands. Further variation of the aromatic aldehyde starting materials (of which a large number are commercially available) could allow the generation of ligands with a common tetradentate amine-binding pocket, thereby providing opportunities for further structural elaboration, utilising a single synthetic protocol. Such approaches lend themselves to automation and thus to rapid exploration of this poorly explored part of 'molecular structural space'. The ease of further structural modification of these putative ligands has been demonstrated by the

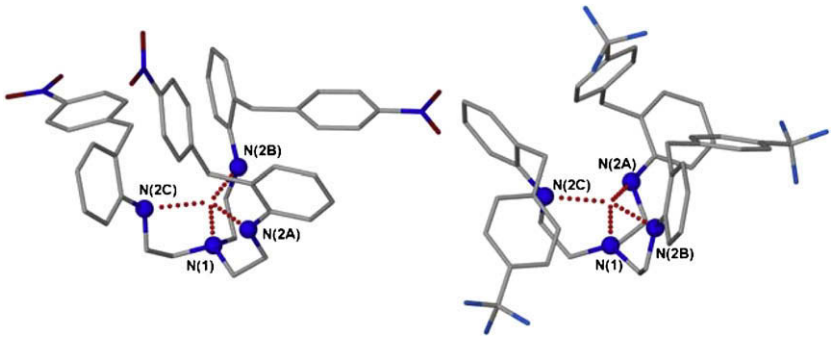


Figure 2. Structures of **1a** (left) and **1b** (right) showing the possible metal coordination site where the nitrogen atoms, shown as blue spheres, are preorganised in a trigonal pyramidal manner. Intersection of the dotted lines indicates where the metal ion might coordinate.

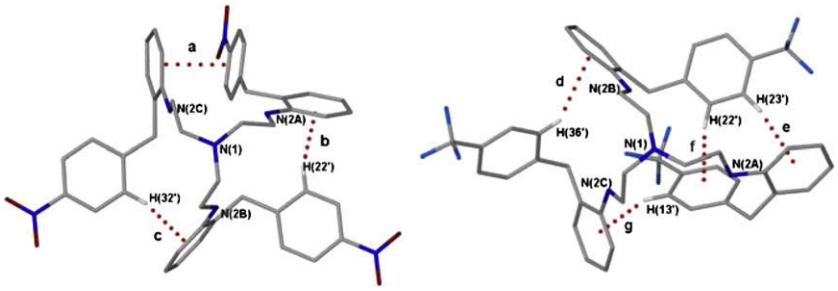


Figure 3. Molecular structures of **1a** (left) and **1b** (right) showing intramolecular interactions leading to preorganisation of the ligand in a geometry favourable for metal ion binding. Interactions are characterised by the following distances: (a) π···π 3.45 Å, (b) CH···π 2.54 Å, (c) CH···π 2.47 Å, (d) CH···π 2.81 Å, (e) CH···π 2.86 Å, (f) CH···π 2.82 Å and (g) CH···π 2.66 Å.

application of high-yielding N-alkylation and nitro reduction reactions. Studies towards the formation of metal complexes with these and related ligands are ongoing.

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Supplementary data

Experimental procedures, NMR spectra and fully numbered molecular structures are available. Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.008.

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27. *Typical synthetic procedure*: Synthesis of tris{[2-(4-nitrobenzyl) phenylamino]ethyl}amine, **1a**. A solution of tren (0.89 mL, 6.0 mmol) in toluene (30 mL) was added dropwise to a stirred solution of 4-nitrobenzaldehyde (2.72 g, 18 mmol), benzoic acid (1.10 g, 9.0 mmol), DABCO (1.01 mg, 9.0 mmol) and cyclohexenone (1.92 mL, 19.8 mmol) in toluene (40 mL). The reaction mixture was heated at reflux in a Dean–Stark apparatus. Cyclohexenone (0.59 mL, 6.0 mmol) was further added after 4 h. After 8 h, the reaction mixture was cooled to room temperature, washed with satd $NaHCO_3$ (30 mL), water (30 mL) and brine (30 mL), dried over $MgSO_4$ and then filtered and concentrated. The resulting oil was subjected to silica gel flash column chromatography (ethyl acetate/hexane 8:2). Recrystallisation of the solid from hot ethyl acetate gave 1.48 g of **1a** as a yellow solid (32%). Mp = 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63 (t, J = 6.0 Hz, 6H, NCH_2), 3.04, (m, 6H, NCH_2), 3.68 (br t, J = 5.0 Hz, 3H, NH), 3.71 (s, 6H, CH_2), 6.58 (m, 3H, Ar), 6.71 (m, 3H, Ar), 6.85 (m, 3H, Ar), 7.06 (m, 6H, Ar), 7.17 (m, 3H, Ar), 8.02 (m, 6H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.4 (CH_2), 42.2 (NCH_2), 54.0 (NCH_2), 114.1 (ArCH), 118.1 (ArCH), 123.2 (ArC), 123.8 (ArCH), 128.7 (ArCH), 129.5 (ArCH), 130.7 (ArCH), 145.8 (ArC), 146.8 (ArC), 147.2 (ArC); HR-MS (MALDI-TOF) $[M+H]^+$ calcd for $C_{45}H_{46}N_7O_6$: 780.3510, found: 780.3507.
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