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SYNTHETIC APPROACHES AND N-FUNCTIONALIZATION OF 1,4,7-TRIAZACYCLONONANES: A REVIEW

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ABSTRACT

Several synthetic approaches have been developed by researchers toward the synthesis and functionalization of 1,4,7-Triazacyclononanes (TACN) in the last decade. Results obtained in this qualitative study have shown that different approaches described in the literature used often protective groups that make it possible to vary the nature of the functions grafted onto the macrocycle according to the intended application. However, the existing methods require harsh reaction conditions (acid treatment) at the final step for the deprotection step. Unfortunately, results compiled in this review paper have shown that despite the increased interest in TACN and its derivatives in the last decade, only a few synthetic methodologies have been reported in the literature, of which some have been reviewed in this current work, with a special emphasis on their advantages and disadvantages as well as the N-functionalization of TACN and its derivatives therefore.

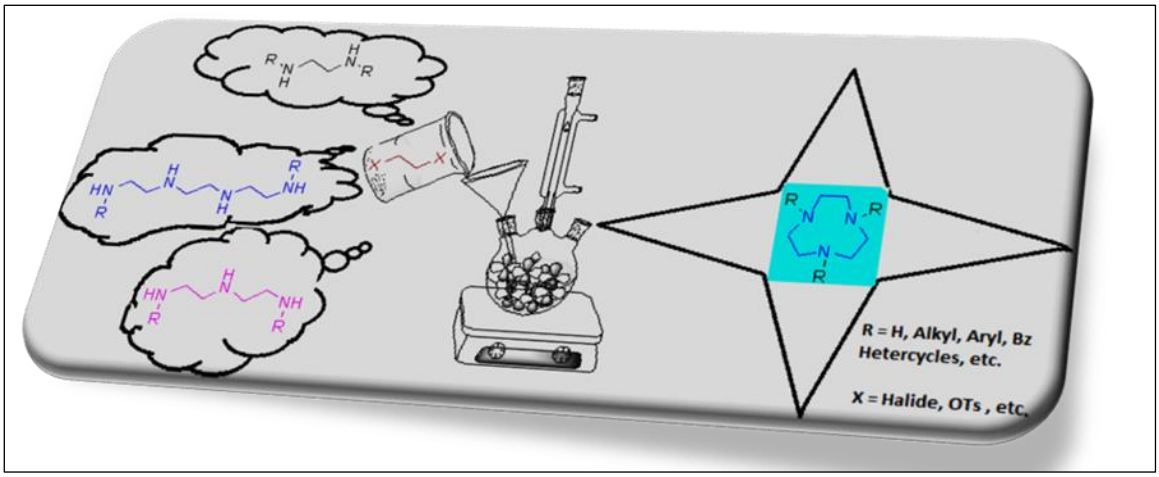
Research Methods: In this bibliographic survey, our approach focused on the literature on synthetic approaches and n-functionalization of 1,4,7-triazacyclononanes. Several results were retrieved from articles, dissertations, and theses addressing this study. These results were retrieved using Google, which was considered our search engine. In short, it was the documentary technique that was used. We have covered almost all reports in this review with a detail of synthetic Figures and respective pathways with different reagents and conditions.

Regarding the results, Results obtained in this qualitative study have shown that different approaches described in the literature used often protective groups that make it possible to vary the nature of the functions grafted onto the macrocycle according to the intended application. However, the existing methods require harsh reaction conditions (acid treatment) at the final step for the deprotection step. In general, these approaches were mostly multi-steps and resulting in poor yields. Apart from a direct commercial and economic impact, the adoption of green chemistry principles would have many benefits, including minimization of waste, reduction in eco-pollution, and the potential for

higher yields through the use of fewer synthetic steps. Unfortunately, results compiled in this review paper have shown that despite the increased interest in TACN and its derivatives in the last decade, only a few synthetic methodologies have been reported in the literature, of which some have been reviewed in this current work, with a special emphasis on their advantages and disadvantages as well as the N-functionalization of TACN and its derivatives therefore.

Keywords: 1,4,7-Triazacyclononane, Synthetic Approaches, N-functionalization, Derivatives, Advantages, Disadvantages.

Graphical abstract



1 INTRODUCTION

The synthesis of 1,4,7-triazacyclononane (TACN) and its derivatives has attracted much attention recently as they metal complexes have been found so useful in numerous applications, ranging from catalysis to molecular imaging, thus, several metal complexes have been prepared. The knowledge of their ability to stabilize high oxidation states of metal ions, has led to the development of several complexes as oxidation catalysts, etc. Numerous metal complexes, including Mn^{II-V}, Fe^{II}, Fe^{III}, Ru^{II-IV} and Ru^{VI}, Co^{III}, Ga^{III}, Cu^{II}, and Zn^{II} have been prepared.[1] For example, the ligand 1,4,7-trimethyl-1,4,7-triazacyclononane (MeTACN)[2] has been subject of many studies because of the catalytic activity of its binuclear manganese tris-oxo $[(MeTACN)_2Mn_2O_3]^{2+}$. MeTACN–Mn^{IV} complexes have been used widely as bleaching agents in laundry formulations[2b] and as catalysts in olefin polymerization[3] and olefin epoxidation with hydrogen peroxide in water[4] or organic solvents[5] as well as in other oxidation processes.[6] Protein orientation at interfaces,[7] metalloenzyme models,[8] and magnetic molecule clusters[9] are other examples of domains in which TACN derivatives have been exploited.

Research has shown that the interest in these macrocyclic molecules has continued to grow in the past decades in the field of nuclear medicine, particularly in the development of radiopharmaceuticals for diagnosis (imaging) and therapy (radioimmunotherapy).[10] TACN derivatives provide versatile platforms for obtaining efficient bifunctional chelating agents (BFCA) capable of strongly coordinating a radio-metal such as ^{111}In, $^{66/67}Ga$, $^{64/66}Cu$, and ^{90}Y for positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging, or radiotherapy applications) and ensuring the attachment of the targeting vector. TACN has also revealed to be an efficient chelator for the preparation of ^{99m}Tc radiopharmaceuticals.[10e] Derivatives bearing additional coordinating groups, such as carboxylates[11] and phosphinates,[12] have been particularly used in the development of BFCAs with optimal properties for Cu^{II} and Ga^{II} chelation.

However, despite the interest in TACN and its derivatives, to date, only a few synthetic approaches have been reported in the literature. Some of these are herein reviewed and discussed, with emphasis on their advantages and disadvantages. Literature has described several approaches to access this interesting ligand and its derivatives. The previously and currently used synthetic approaches can be classified into three different categories viz:

- Those designed to synthesize the unfunctionalized TACN (as H_3-TACN)
- Those designed to synthesize the functionalized f-TACN (as R_3-TACN), by using the commercially available unfunctionalized TACN as their starting. This category would be because of challenges encountered with the synthesis of the H_3-TACN), and/or
- Those designed to synthesize/access the functionalized-TACN (R_3-TACN) from scratch.

Therefore, the current review aimed to discuss mainly these three categories of synthetic approaches, with emphasis of their advantages and disadvantages. This would lay a foundation and open doors in future for a development of novel, improved, cost-effective and shortest synthetic approach(es) to access unfunctionalized-TACN (H_3-TACN), and symmetrically or unsymmetrically functionalized-TACN (R_3-TACN) directly, and thus with a desired stereochemistry.

2 SYNTHESIS OF TACN AND ITS *N*-FUNCTIONALIZED DERIVATIVES

In 1937 Peacock and Gwan[13] reported the first triaza macrocyclic compound 1,4-ditosyl-l,4,7-triazacyclononane, and proposed the ditosylate of TACN as a by-product 3 from the reaction (Figure 1) between N',N'-di-(p-tolylsulphony)-N',N'-bis-beta-chloroethy)ethylene diamine 1 and ethanolic ammonia.

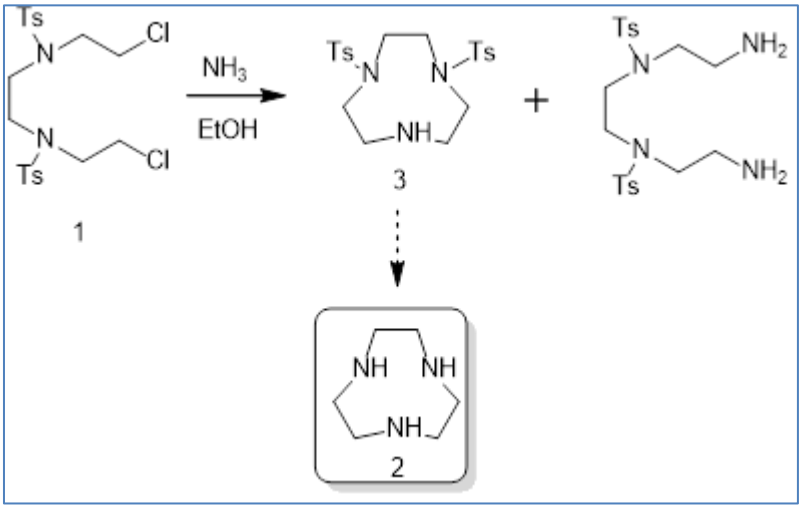


Figure 1: Proposed route to 1,4-ditosyl-TACN.[13]

In 1972 Koyama and Yoshino [14] reported the first synthesis of 1,4,7-tritosyl derivative **5**. They presented a high dilution route to triazamacrocycles via the cyclisation of tritosyl triamine salts **4** and dibromo alkanes in DMF (Figure 2). Richman and Atkins [15] modified this synthesis (Figure 3) to provide a simple route to 9 to 21 membered macrocycles containing 3 to 7 nitrogen atoms. Their strategy utilized sulphonate ester leaving groups as opposed to the previous halide moieties, improving overall yields of cyclic products.

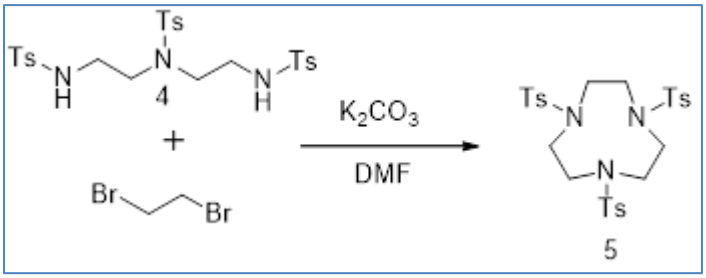


Figure 2: High dilution synthesis of 1,4,7-tritosyl-TACN.[14]

The tosyl groups in this preparation had three functions viz., i) activation of the primary amine functional group by increasing the acidity of the amino protons and stabilizing the resulting anion; ii) protection of the secondary amine group; and iii) conversion of the hydroxyl group of diols to good leaving groups.[15]

Hydrolysis of the tosylated cyclic polyamines **5** may be achieved by several methods including electrochemical reduction, reduction with either sodium amalgam in buffered methanol solution or lithium aluminium hydride. The most common methods of detosylation for cyclic triamines are reductive cleavage of the tosyl group with hydrobromic acid (HBr) in acetic acid or simply heating in concentrated sulphuric acid at 100-110°C for 2-3 days. However, this method as described by Richman and Atkins[15] suffers from many drawbacks, including, the use of tosyl groups to preorganize the intermediates to favor the intramolecular cyclization which was found to suffer from low atom-economy.[16] Moreover, the method requires long reaction times and although the macrocyclization step is generally efficient, harsh conditions are required to remove the tosyl groups. This method has also been extended to the synthesis of C-functionalized TACN derivatives by using bis-electrophilic synthons that are functionalized on a carbon atom.[17]

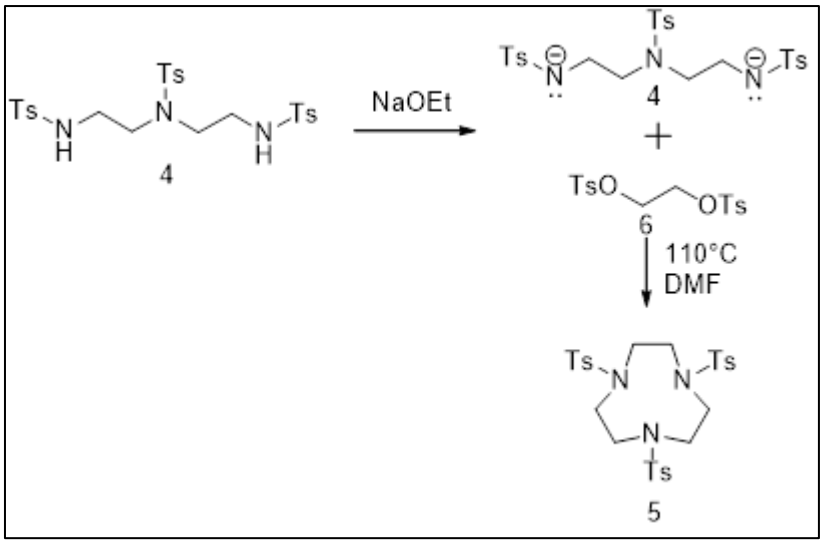


Figure 3: Richman-Atkins preparation of 1,4,7 tritosyl-TACN.[15]

Such C-functionalized macrocycles are of special interest for the synthesis of bifunctional chelating agents (BFCAs) because the targeted biomolecule can be attached to a carbon atom of the TACN derivative with the three nitrogen atoms remaining available for further functionalization with coordinating arms. This approach, however, requires the preparation of a sophisticated C-functionalized precursor that must be resistant to the deprotection conditions. A method allowing functionalization of a carbon atom starting from MeTACN and involving a bicyclic pyrazinium salt as key intermediate has been reported in the literature.[18] However, this method requires the preliminary synthesis of MeTACN by the method of Richman and Atkins and is limited to the synthesis of C-functionalized MeTACN.

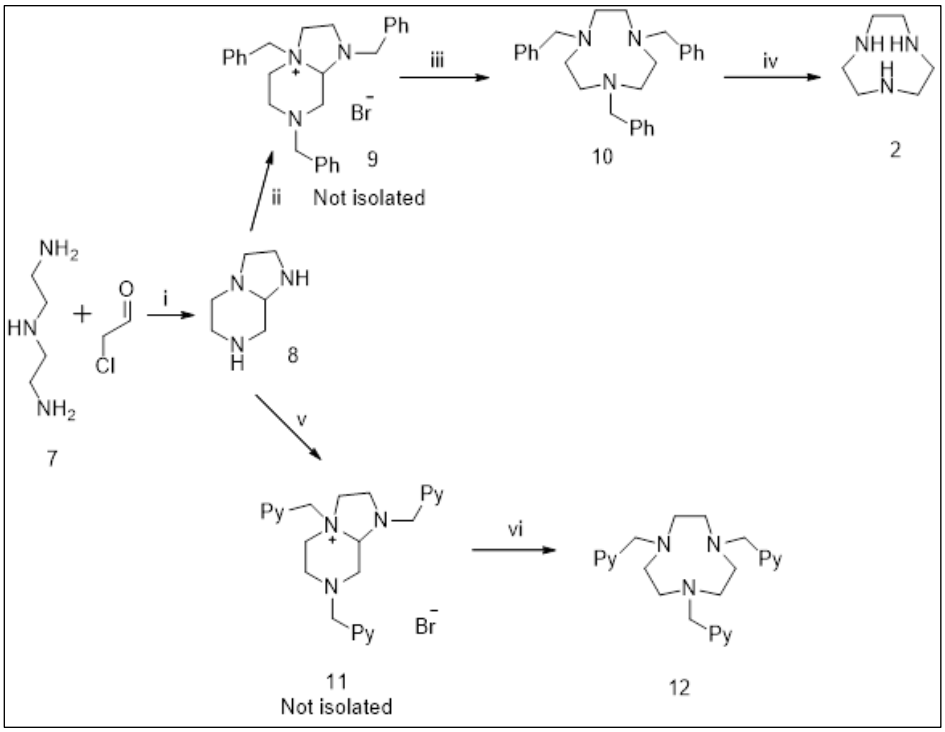


Figure 4: Synthesis of TACN and N-functionalized TACN.[16] Reagents and conditions: i) 2 equiv. K_2CO_3, CH_3CN, room temp.; ii) 3 equiv. BnBr, 4 equiv. K_2CO_3, CH_3CN, 10 °C, 24 h; iii) 1 equiv. $NaBH_4$, EtOH, –10 °C, 12 h; iv) H_2, Pd/C, CH_3CO_2H, room temp., 3 d; v) 3 equiv. 2-(bromomethyl)pyridine hydrobromide, 10 equiv. K_2CO_3, CH_3CN, 10 °C, 12 h; vi) 1 equiv. $NaBH_4$, EtOH, –10 °C, 12 h.

A methodology using the "aminal tool" has been developed by the research group of P. Désogère and co-workers in 2014[16] to easily synthesize TACN and its N- and C-functionalized derivatives. The process involves three different steps viz., i) the synthesis of an aminal intermediate from the commercially available linear diethylenetriamine; ii) functionalization of the secondary amines and quaternization of the tertiary amine with a suitable electrophilic reagent,

and iii) double-ring-opening by nucleophilic attack.[16] In this approach, amino-containing intermediate **8** was easily obtained by addition of chloroacetaldehyde to diethylenetriamine **7** in the presence of potassium carbonate (Figure 4).

Next, 3 equiv. of benzyl bromide were added to compound **8** to yield the expected ammonium salt **9**, which was not isolated but was treated with $NaBH_4$, a hydride nucleophilic agent, to undergo ring-opening which resulted in the formation of compound **10** in 37% yield after recrystallization in water. Finally, the benzyl groups of **10** were cleaved by hydrogenolysis to give TACN **2** in 95% yield after recrystallization. The authors claimed this process to be very efficient, scalable, and reproducible with no tedious chromatographic work-up steps.[16] In addition, it would give access to TACN in three steps from the commercially available linear diethylenetriamine **7** in 25% overall yield hence it has been patented.[19] It was also claimed that this approach could be used for the preparation of N-functionalized TACN by using the desired electrophilic reagent for the synthesis of the ammonium salt. For example, the addition of 3 equiv. of a pyridine derivative instead of benzyl bromide gave access to compound **12** in three steps starting from the linear amine without the need for a protection/deprotection step (Figure 4).

P. Désogère and co-workers also investigated the synthesis of new C-functionalized TACN derivatives. Thus, the addition of sodium cyanide to the quaternized ammonium salt yielded compound **8** in 63% yield (Figure 5). The nitrile **13** was reduced with $LiAlH_4$ to give **14**, followed by a hydrogenolysis to remove benzyl groups, affording the C-aminomethyl-TACN **15**.[16]

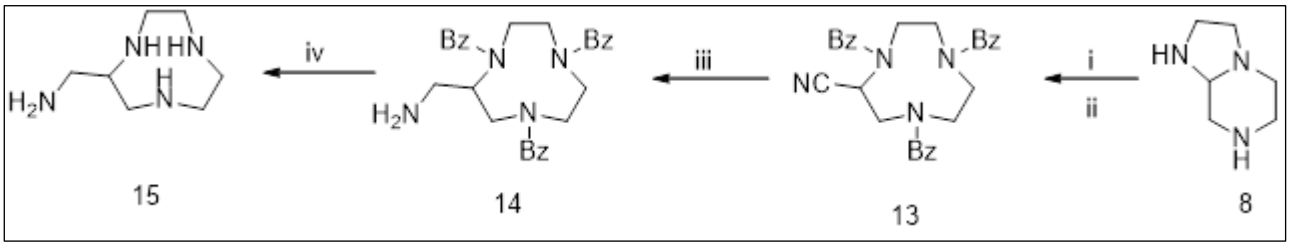


Figure 5: Synthesis of C-aminomethyl-TACN.[16] Reagents and conditions: i) 3 equiv. BnBr, 4 equiv. K_2CO_3, CH3CN, 10 °C, 6 h; ii) 1 equiv. NaCN, room temp., 3 d; iii) 1.1 equiv. $LiAlH_4$, THF, –78 °C, 12 h; iv) H_2, Pd/C, CH_3CO_2H/H_2O/THF, room temp., 10 d.

The protected and non-protected C-aminomethyl-TACNs **14** and **15**, respectively, represent highly valuable building blocks for the preparation of BFCAs.[16] By applying this synthetic approach, a wide range of new promising BFCAs can be generated from these precursors by functionalization of the secondary and/or primary amino groups. Therefore, to introduce various grafting functional groups, P. Désogère and co-workers used a protection/deprotection sequence starting from the synthon **6** (Figure 6).[16] The addition of 1 equiv. of Boc_2O to **14** followed by selective removal of the benzyl group by hydrogenolysis gave access to compound **17** in good yield. Such a strategy allowed discrimination between primary and secondary nitrogen atoms and enabled the introduction of various pendant coordinating arms for metal chelation prior to functionalization of the primary amine for further bioconjugation.

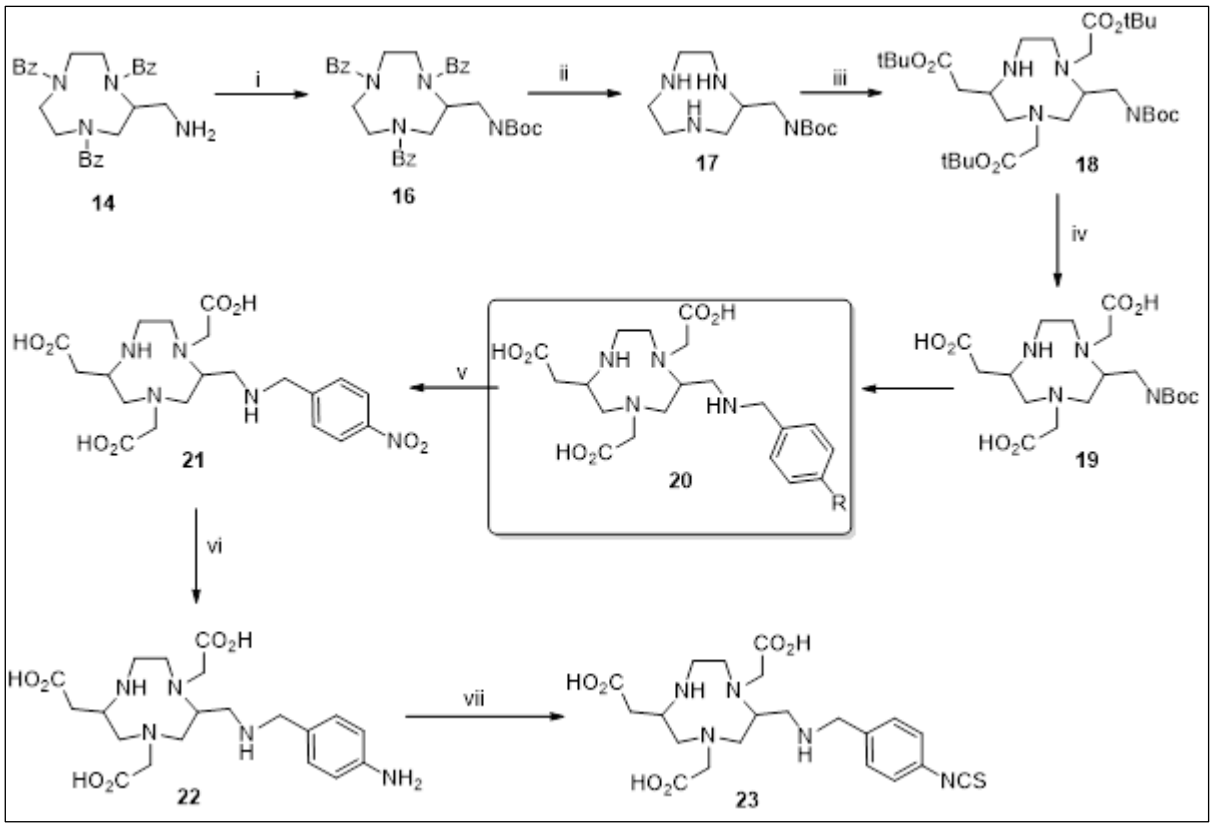


Figure 6: Synthesis of the bifunctional chelating agents MA-NOTA 19 and p-NCS-Bz-MA-NOTA 23.[16] Reagents and conditions: i) 1 equiv. Boc_2O, DCM, r.t., 12 h; ii) H_2, Pd/C, CH_3CO_2H/H_2O/THF, r.t., 2 d; iii) 3 eq. tert-butyl bromoacetate, 7 eq. K_2CO_3, DMF, 40 °C, 24 h; iv) TFA/ CH_2Cl_2, rt., 24 h; v) N-succinimidyl 4-nitrophenylacetate, DIPEA, CH_3CN, r.t., 2 h; vi) H_2, 10% Pd/C, 1 d; vi) thiophosgene, CH_2Cl_2/H_2O, 3 h, rt.

The three amines of the TACN ring of new precursor **17** were functionalized to provide compound **18** by addition of 3 equiv. of tert-butyl bromoacetate followed by cleavage of all the protecting groups to give compound **19** (MA-NOTA). Removal of the Boc protecting group, followed by treatments of **19** with N-succinimidyl 4-nitrophenylacetate, DIPEA and thiophosphogene afforded the compounds **21**, **22** and **23** respectively (Figure 6).[16] To demonstrate the potential use of compound **19** as a precursor of a new BFCA, these authors prepared a NOTA chelator, the p-NCS-Bz-MA-NOTA **23**. A pendant arm bearing a nitro functional group was introduced by using an activated ester precursor leading to compound **21**. The reaction was performed in a mixture of solvent (CH_3CN/ water) to overcome solubility challenges.[16] After reduction of the nitro group by hydrogenolysis, the desired isothiocyanate function was introduced by the addition of thiophosgene.

Bearing in mind that compound **14** (Figure 5) could also be modified without protection/deprotection steps, these authors investigated the reaction of **15** with aldehydes. Based on their previous work that revealed the versatility of using aldehyde to introduce a functional group selectively onto the amino pendant group of **22** and **23** derivatives,[20] they decided to explore this reaction by treating **15** with 1 equiv. of an aldehyde bearing an alkyne function.[16] Therefore, treatment of the precursor **15** with 4- (prop-2-ynyloxy)benzaldehyde followed by reduction with $NaBH_4$ resulted in the formation of compound **24** in 68% yield (Figure 7).

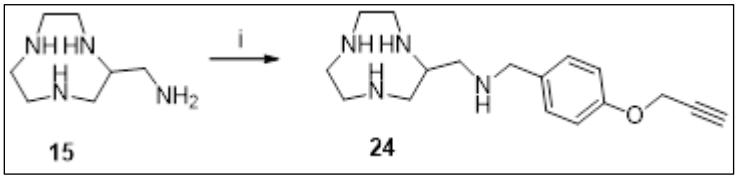


Figure 7: Synthesis of TACN precursor 24 for click chemistry.[16] Reagents and conditions: i) 4-(Prop-2-ynyloxy)benzaldehyde, EtOH, room temp., 48 h, 10 equiv. $NaBH_4$, EtOH, room temp., 12 h.

Furthermore, they also established that functionalization of the secondary amines with coordinating arms would give access to new TACN-based BFCAs for site-specific bioconjugation using click chemistry.[21] It was reported that if the reaction of an aldehyde with **15** was selective towards the primary amine, the reaction with an activated carboxylic acid

would result in a mixture of products that would be separated, hence the proposal of an alternative synthetic strategy using intermediate **19**.[16]

Coombs[22] described a slightly modified approach to access TACN and its N-functionalized derivatives from the one described by Richman and Atkins[15]. The ring closure reaction to give the tri-sulfonamide protected macrocycle, 1,4,7-tris(ptolylsulfonyl) 1,4,7-triazacyclononane **5** (Figure 8), was performed using one of the two methods (with an overall yield of 26 % by either method), viz: i) The reaction as described by Hay and Govan[23] first involves the isolation of the disodium salt of 25 by direct treatment with sodium ethoxide in ethanol. This is subsequently dissolved in DMF and reacted over 5 hours with **6**. ii) The second method is a modification to the first. Instead of isolating the disodium salt of 25 which formed in situ, by reacting the linear tri-sulfonamide with an excess of sodium hydride in DMF. After removal of unreacted sodium hydride, it was observed that the reaction proceeded as in the first method described above.

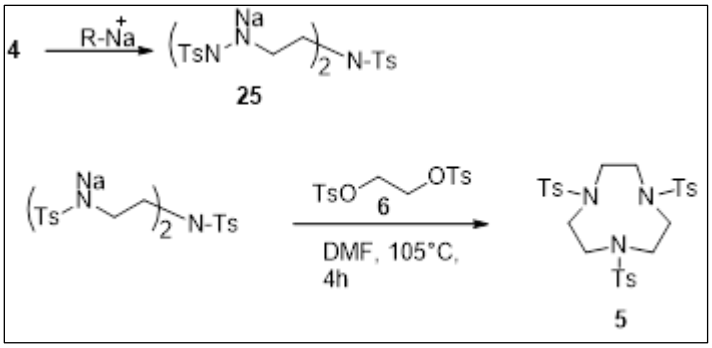


Figure 8: Synthesis of a tritosylated-TACN 5 as described by Coombs[15, 22]

It was however reported that the conversion of the cyclic tri-sulfonamide to its corresponding hydrochloride salt [H_6-TACN]Cl_3 **2**, proved difficult due to conflicting synthetic procedures and imprecise experimental details given in the literature. As the results, several approaches were attempted numerous times before isolation of their desired product, including: i) Treating the tris-sulfonamide **5** with 47% aqueous HBr and isolating the cyclic triamine as the trihydrobromide salt[24] as first described by Wieghart, a variation of this method has also been published that included the addition of a small quantity of glacial acetic acid to the aqueous HBr solution[25]. Ii) The deprotection of both linear and macrocyclic p-toluenesulfonamides, including **5**, in 50% sulfuric acid at 180°C according to another report.[26] and iii) Conversion of a sulfonamide to the corresponding amine using SmI_2.[27]

After considerable experimentation, Coombs found that the deprotection step (Figure 9) could be achieved through a modification of a fourth procedure, as described by Hay.[23]

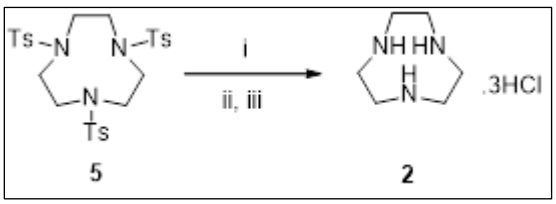


Figure 9: Deprotection of 5 to 2.[22] Reaction conditions: i) 98% H_2S0_4 ii) NaOH. iii) EtOH, HCl.

After heating a solution of **5** in concentrated (98%) H_2SO_4, the strongly acidic solution was carefully made alkaline to pH 14, and the crude hydrosulfate salt was extracted into $CHCI_3$. At a pH lower than 14, the product remained highly water-soluble and could not be extracted into the organic solvent. Consequently, this procedure would avoid the need for the continuous extraction techniques at neutral pH as reported by Hay[23] and others.[28] After removing the solvent, the residue was redissolved in ethanol, and the tri-hydrochloride salt [H_6-TACN]Cl_3 **2**, precipitated by addition of a slight excess of concentrated HCl (10 M). Recrystallisation from 2 M HCl/EtOH, afforded the trihydrochloride salt in moderate yield (55%).[22] However, the use of harsh condition renders this approach challenging.

It has been established that in order to make H_3-TACN suitable for attachment to other moieties, one or more of the three secondary amines needed to be functionalized with a spacer chain.[22] The synthesis of these substituted ligands can be approached in one of two ways viz., i) functionalization of all three N-H centers which would allow the R_3-TACN unit to be attached to up to three different units and simultaneously act as a cross-linking agent for polymeric moieties,

and ii) functionalization of a single N-H group would allow the TACN unit to be attached to just one group to produce a side-arm functionalized moiety. The synthetic methods used to produce compounds of both types are described below:

2.1 The Synthesis of Symmetrically *N*-Functionalized R_3-TACN

The functionalization of H_3-TACN has been the subject of several reviews.[29,30] Whilst much attention has been focused on the tri-Af-methyl derivative Me_3-TACN,[31] many investigations have also centered on the inclusion of three substituents which themselves contained functional groups. Figure 1 summarizes some of these substituents which include carboxylate,[32] amino,[33] hydroxyl,[34] phosphino,[35] sulfonate[36] and pyridyl[37] end groups.

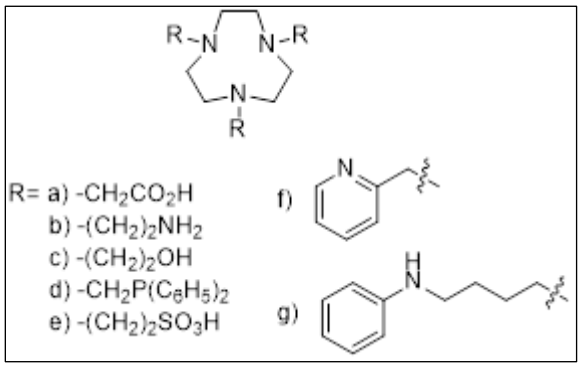


Figure 9a: Symmetrically N-functionalized-TACN derivatives.[22]

Much of the chemistry described in the literature performed on H_3-TACN uses the free base as a starting material in form of trihydrochloride salt.[22] As the presence of water is undesirable for many reactions, attempts made in the literature aimed first to neutralize the quaternary salt without resorting to the use of an aqueous solvent system. [22] It has been described that the salt could be conveniently converted into the free base by suspending it in either dry acetonitrile or dry diethyl ether, and adding either a stoichiometric quantity of triethylamine, NEt_3 or stirring with excess solid KOH.[22] It was also claimed by the authors that both $[NHEt_3]Cl$ and KCl, being insoluble in ether, were easily removed by filtration.[22] However, due to the limited solubility of $[NHEt_3]Cl$ in in MeCN solvent, KOH has often been used.

2.2 Symmetrically substituted alkenyl derivatives of H_3-TACN

Two different alkenyl chains, 1-propenyl and 1-pentenyl, have been added to H_3-TACN to form l,4,7-tris(propenyl)-l,4,7-triazacyclononane, 26, and l,4,7-tris(pentenyl)-l,4,7- triazacyclononane 27, respectively.

2.2.1 1,4,7-Tri(N-propenyl)-1,4,7-triazacyclononane, Pr_3-TACN, 26

A number of different conditions and solvent systems were used by Coombs, in attempts to synthesize 26, by reacting 2 with allyl bromide in the presence of base.[22] The development of a successful procedure proved challenging in that, each time the reaction was attempted, the only product isolated was a brown oil, soluble in CH_2CI_2. Its characterization by ^1H NMR was revealed the spectrum to present with four signals, indicating the presence of both macrocyclic and allylic protons.

However, the relative intensity ratio of the signals for the ring to allyl substituent protons was 1:1 instead of 2:1 as expected for their desired tri-substituted product,[22] which was supportive of the formation of symmetrical quaternization of the amines. Moreover, the aqueous solution of this oil immediately gave a precipitate of AgBr on treatment with acidified $AgNO_3$, also indicating that quaternization of one or more of the amine groups may have occurred.[22] The only quaternary ammonium salt of a R_3-TACN derivative that has been reported was $[Me_6\text{-TACN}][BF_4]_3$, which is formed by the extensive methylation of the tri-methyl derivative, Me3-TACN.[38] No NMR data were reported for this compound to allow comparison with the spectra of the alkenylated product that had been isolated, and further investigations were hence required to fully characterize the species isolated.[22]

After some considerable investigations, compound 26 was prepared by adopting one of the following three different synthetic methods: i) Treatment of the ethereal solution of 2, with an excess of sodium hydride afforded the product 26 in low yields.[22] ii) A modified approach from Peacock and co-workers for the synthesis of 1,4,7- tris-(3-prop-l-yne)-l,4,7-triazacyclononane was also used successfully by these authors[22,39] to access the product 26 in moderate yields; iii) In another attempt, treatments of 2 with KOH to liberate the free amine prior to treatment with a slight excess of allyl bromide, afforded also 26 in 80% yield, (Figure 10). Due to the efficiency of this later approach, the authors claimed that it was possible to use 26 directly for synthetic purposes, without further purification, although they purified their product by distillation for complete analytical characterization.

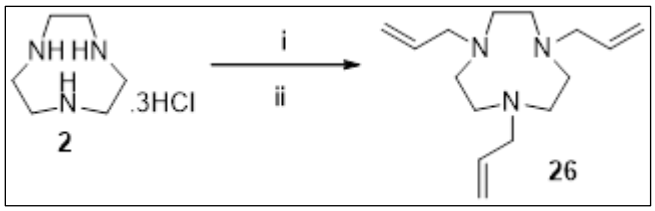


Figure 10: Synthesis of 26.[22] Reaction conditions: i) KOH, Et_2O, ii) 3-bromoprop-1-ene

The tri-substituted ligand Pr_3-TACN **26** has been mentioned in previous reports but neither its synthesis nor characterization has so far been published.[40-42] The mono-substituted ligand, PrH_2-TACN and the disubstituted ligand, Pr_2MeTACN[42] have also both been reported previously. The former was synthesized using the methodology first described by Atkins[15]. Initially, H_3-TACN is protected and the resulting orthoamide was isolated, and reacted with allyl bromide.[22] However, it was reported that the final product was isolated in low yields after deprotection by hydrolysis. The authors also reported the synthesis of Pr_2-MeTACN in two stages using an extension of this method.[22]

2.2.2 1,4,7-Tri(*N*-pentenyl)-1,4,7-triazacyclononane, Pr_3-TACN 27

The synthesis of compound 27 was attempted several times by Combs using the methodology developed by Wieghardt *et al*.[44], for the synthesis of the tri-*N*-isopropyl derivative. However, this method did not yield the desired product, and therefore it was modified for the preparation of the tris-*N*-pentenyl derivative 27. The author reported a suspension of 2 in dry acetonitrile to first convert to (H_3-TACN).3HCl by treatment with 3 equivalents of triethylamine. After removal of solid [$NHEt_3$]Cl, the filtrate was diluted with toluene and the cyclic triamine was reacted with 3 equivalents of 5-bromo-l-pentene in the presence of KOH (Figure 11). After work up, 27 was purified by conversion into its hydroperchlorate salt [Pr_3-TACNH][ClO_4], which could be easily isolated and converted back to the free amine when required.[22]

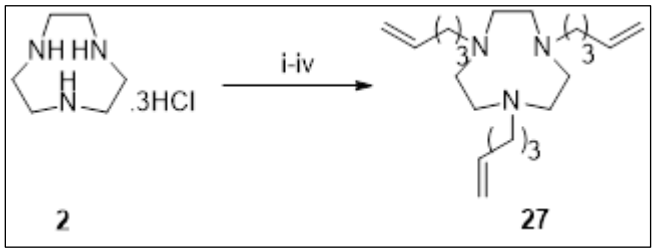


Figure 11: The synthesis of 27.[22] Reaction conditions: i) 3 equiv. NEt_3/MeCN, ii) 3 equiv. 5-bromopent-1-ene, Toluene, KOH, 95 °C, 2h, iii) $NaClO_4$/ MeOH, iv) KOH/Toluene.

2.2.3 Trisubstituted H_3-TACN containing a hydroxyl-terminated alkyl chain 28

Coombs[22] made several unsuccessful attempts to synthesize a R_3-TACN derivative containing a *N*-bonded spacer chain terminated by a hydroxyl group, which could be used to functionalize siloxanes.[22] The only tri-functionalized H_3-TACN derivative containing a primary alcohol functionality reported in the literature had been 1,4,7-tri(hydroxyethyl)triazacyclononane[34], formed in high yield by the reaction between H_3-TACN and ethylene oxide (Figure 12).

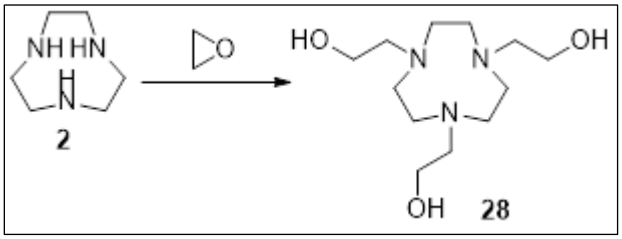


Figure 12: Synthesis of 1,4,7-tri(hydroxyethyl)triazacyclononane 28.[22]

However, ethylene oxide is difficult to handle, only available commercially in relatively large quantities, and the reaction generates a shorter spacer chain than desired for subsequent reaction with a Si-H moiety.[22] For these reasons, Coombs briefly investigated routes to longer spacer chain materials.[22] For example, a direct reaction H_3-of TACN with 1-chloro- and 1-bromo-6-hexanol (Figure 13), under the same conditions as previously developed for the synthesis of both Pr_3-

TACN and Pr_3-TACN, failed numerous times. Hence, he reported failure to obtain the desired product as result of the halohydrin being invariably isolated quantitatively after work up.[22]

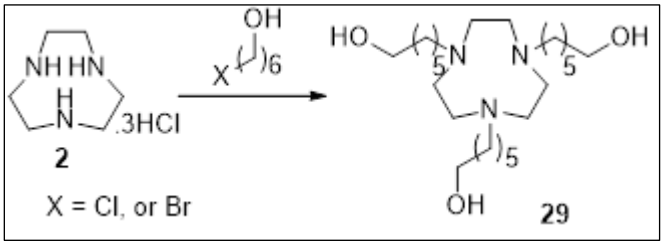


Figure 13: Attempted syntheses of a trisubstituted H_3-TACN 29 containing a primary alcohol group by Combs.[22]

The reaction between a halohydrin and the di-tosyl protected macrocycle, Ts-2H-TACN, had been reported by Sessler in 1993 for the preparation of $(Ts)_2(HO(CH_2)_3)$-TACN **29**[45] by reacting an excess of 3- bromopropanol in acetonitrile in the presence of less than one equivalent of NEt_3. This procedure, initially???? used H_3-TACN instead of the deprotected macrocycle in order to functionalize all three N-H groups. However, no reaction occurred and the halohydrin was recovered in near quantitative amounts. Subsequently, another attempted synthetic route involved the reaction of H_3-TACN with the mono-sulfonate ester of a diol.[22] As the sulfonate is a better leaving group than halide, it was found to be more susceptible to nucleophilic attack and therefore, the compound 1-tosyl-6-hexanol, **30**, was successfully synthesized by reacting 1,6-hexanediol with TsCl in Et_2O, (Figure 14).[22]

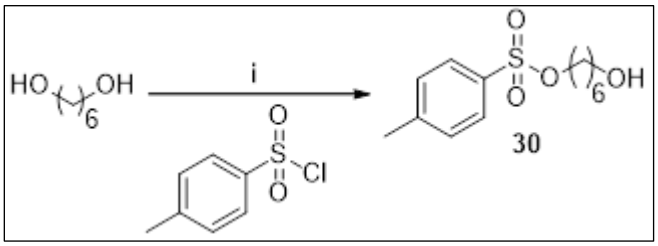


Figure 14: Synthesis of 30.[22]

Subsequently, the heating of **30** with H_3-TCN in aqueous ethanol, followed by reaction work up, and NMR spectra analysis of the final residue, characteristic signals of both the TACN and the primary alcohol moieties were observed but not in the expected intensity ratios. Thus, it was concluded that the isolated product was impure, hence the synthetic approach was abandoned.[22]

2.2.4 The synthesis of mono-substituted H_3-TACN derivatives

The synthesis of mono-substituted H_3-TACN compounds usually proceeds via a selective deprotection of Ts_3-TACN to Ts_2-H-TACN or Ts-H_2-TACN, followed by functionalization of one or two of the amines, then deprotection, of the remaining amine moieties (Figure 15).

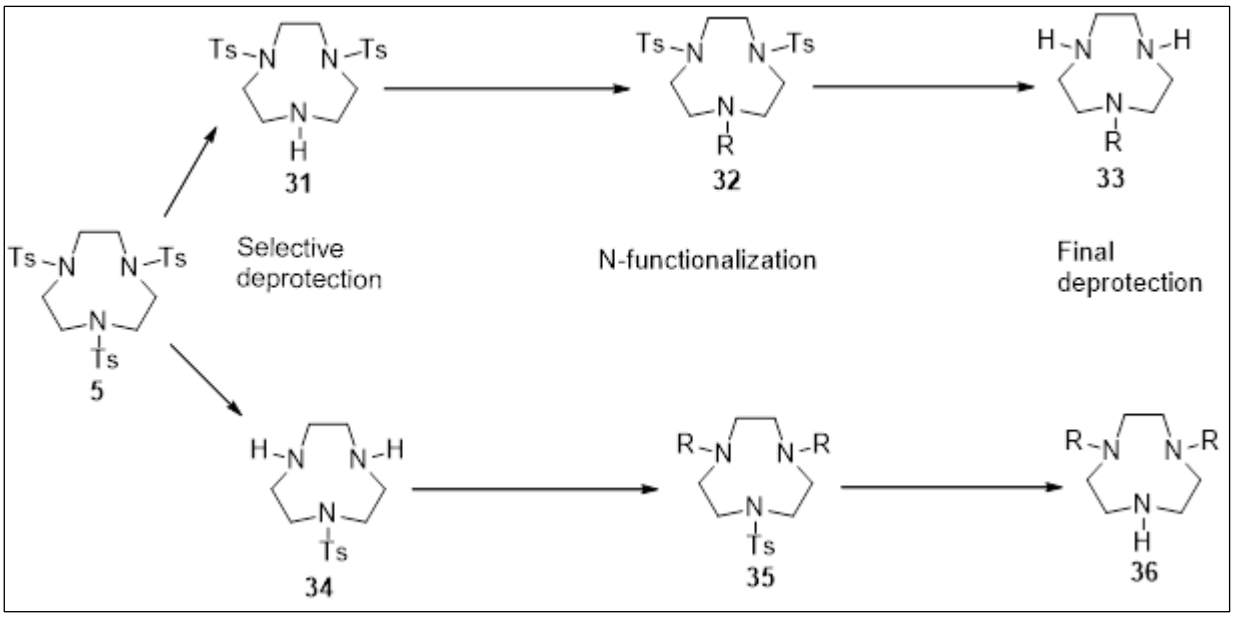


Figure 15: Selective functionalization of H_3-TACN using selective deprotection.[22]

As noted above, Sessler *et al* used this approach successfully to synthesize a mono-functionalized H_3-TACN derivative containing an alkyl chain terminated by a primary alcohol.[45] This product was subsequently used to form a bis-macrocycle as shown in Figure 16.

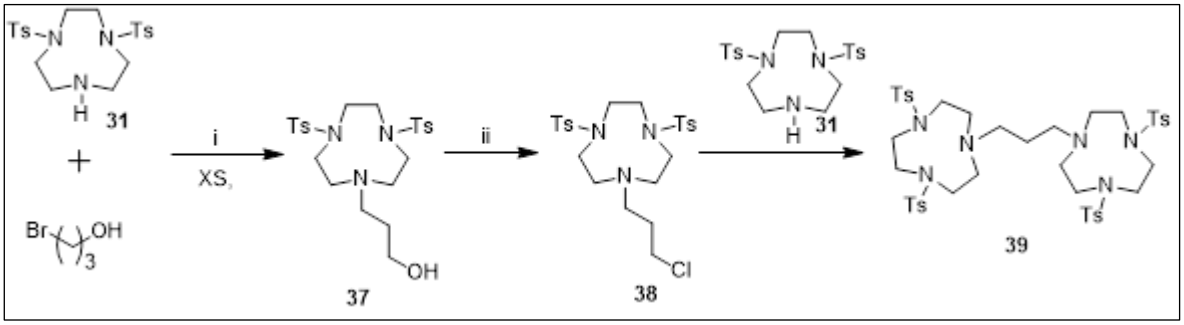


Figure 16: Sessler's reaction between Ts_2H-TACN and 3-bromopropanol for the synthesis a bis-macrocycle 39.[22,45] Reaction condition: i) MeCN, NEt_3, ii) $SOCl_2$.

As the conversion of the sulfonamide groups to secondary amines requires the use of concentrated H_2SO_4, only substituents that are not affected by these conditions can be introduced.[22] Consequently, this route is unsuitable for the selective addition of a single alkenyl or hydroxyalkyl chain to H_3TACN as either functionality would be affected under the harsh deprotection conditions needed to remove the tosyl groups.

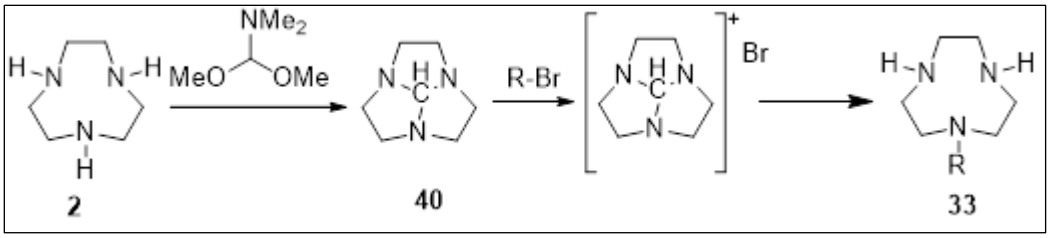


Figure 17: Selective functionalization of H_3-TACN via a cyclic ortho-amide.[22]

An alternative route to mono-functionalized derivatives involves the conversion of H_3-TACN to its ortho-amide derivative by reaction with dimethylformamide dimethylacetal.[43] The "capping" of the macrocycle then allows substitution at only one of the nitrogens to occur on reaction with an alkyl halide. A quaternary ammonium salt is formed, which on hydrolysis, affords the mono-functionalized amine **33**, (Figure 17). This method is more widely applicable, as the hydrolysis conditions are relatively mild.

The synthetic route described above had previously been attempted unsuccessfully by Combs who was unable to isolate the initial orthoamide. In a final attempt to prepare the desired mono-functionalized triaza-macrocycle by Combs, a cyclisation reaction was carried out in which the required substituent was already present on one reactant.[22] Bradshaw *et al*[46] cyclized a primary amine containing a primary alcohol functionality with a linear diamide to afford a cyclic diamide. On reduction, this gave a TACN derivative with a pendant chain containing a primary alcohol terminus as depicted in Figure 18.

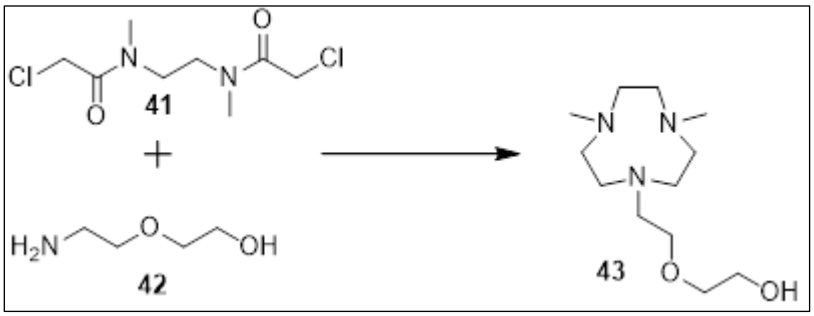


Figure 18: Synthesis of a mono-functionalized H3-TACN derivative.[22]

The first step in the synthesis of 1-(2-ethoxy)hydroxyethyl-4,7-dimethyl-1,4,7- triazacyclononane, HEDM-TACN **43**, involved the formation of the known diamide NN'-di(2-chloroacetyl)-N,N'-dimethylethylenediamine **41** in 75% yield,[47] by reacting N',N'-dimethyl-ethylenediamine with chloroacetylchloride (Figure 18), using a modified literature procedure.[34]

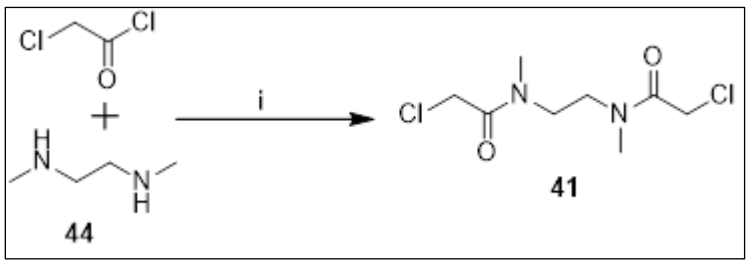


Figure 19: Synthesis of 41.[22] Reaction condition: Chloroform, 6h, reflux.

Coombs reacted **41** with 2-(2-aminoethoxy)ethanol, in an equimolar (1:1) ratio in the presence of an excess of Na_2CO_3. The ring closure product l-(2-ethoxy)hydroxyethyl-3,8-dioxo-4,7-dimethyl-1,4,7-triazacyclononane **45**, was obtained in low yields.[22] In addition, the reaction performed under 2:1 molar ratio of the absolute enantiomeric excess (Aee, 44) to **41**, provided 45 in an increase yield of 34% (Figure 21). Explaining the mechanism of reaction, Bradshaw elaborated that, Na_2CO_3 was found not strong enough to deprotonate the hydroxyl terminal of Aee, but instead deprotonates the amine, which then acted as a better nucleophile than the alcohol derivatives, thus facilitating the ring closure.[46]

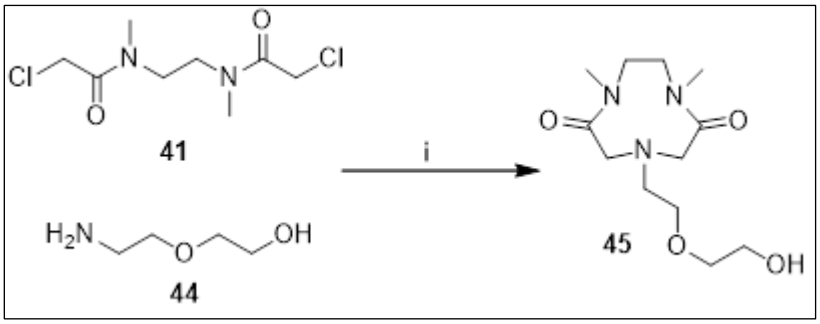


Figure 21: Synthesis of 45.[22]

It has also been reported that an organic polymer such as **48** bearing a substituted R_3-TACN could be synthesized via a ring opening metathesis polymerization (ROMP), as shown in Figure 22.[48]

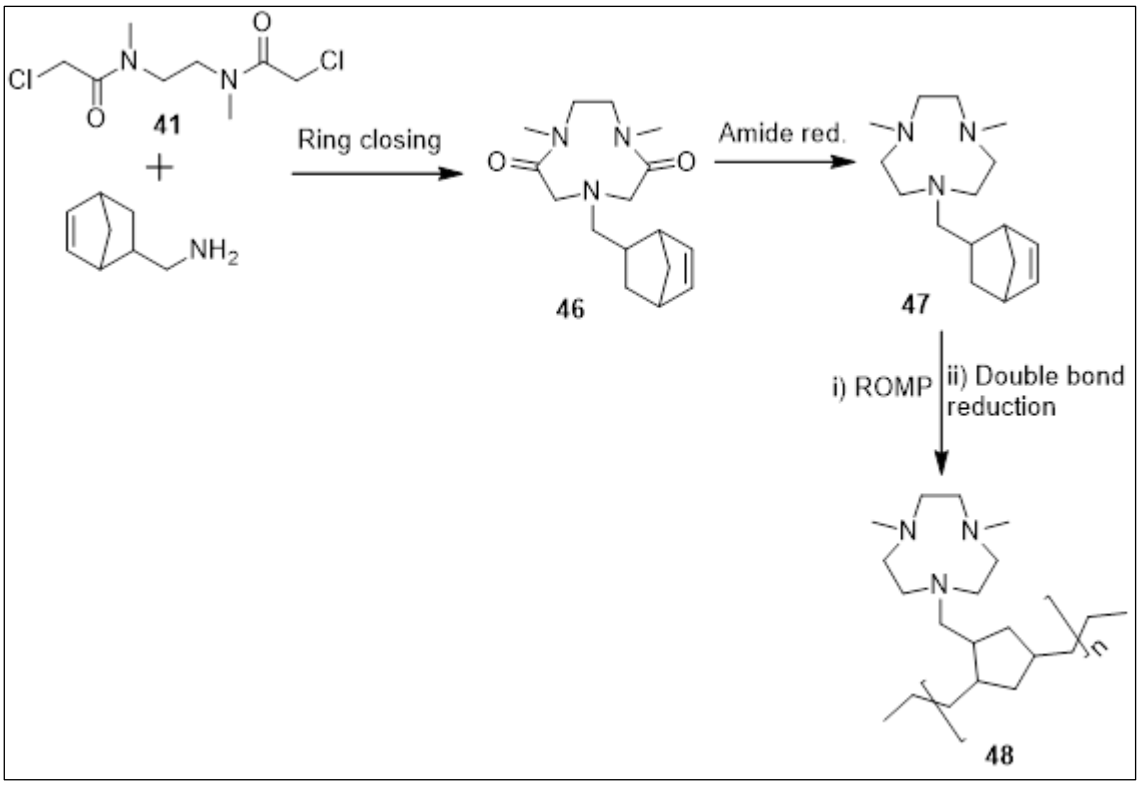


Figure 22: Functionalization of an organic polymer with R_3-TACN.[22]

Chong and Brechbiel[49] reported a convenient synthetic approach to TACN derivatives substituted with a single pendant donor group. In their approach, monosubstituted TACN with a hydroxylalkyl, an aminoalkyl, or a benzyl group were synthesized via efficient cyclization of inexpensive starting materials followed by detosylation.[49] There has been a significant interest in the synthesis of mono-substituted TACN derivatives as either intermediates or as target molecules in diverse areas of research.[50] In their continuing efforts to develop potential novel chelators for radio-immune therapy applications with yttrium or lanthanides isotopes,[51] they required an efficient entry to mono-substituted TACN derivatives bearing either an amino or a hydroxyl donor group that could be amenable to reasonably large scale production.[49] Although a few synthetic routes to mono-substituted TACNs bearing a pendant hydroxyl group have been reported,[52,53] no straightforward general synthetic route is yet available.[49]

Moreover, no example of a simple synthesis of pendant amino-armed TACNs is accessible either.[49] One of the synthetic routes to access mono-substituted TACNs involves the reaction of di-Boc protected TACN[54] with suitable alkylating agents followed by deprotection of the secondary ring amines.[55] However, unless a very reactive alkylating agent is used, the alkylation of di-protected TACN results in low yields due to the presence of the bulky Boc groups in the macrocyclic intermediate[52,54] with the orthoamide derivative 1,4,7-triazatricyclo[5.2.1.0.]decane[54,56] derived from TACN also being employed as a key intermediate for the mono-substituted TACN synthesis.[49]

In their work, Pyke and co-workers established that a general method for the preparation of hydroxylalkyl-armed TACN from the orthoamide, consists of multiple steps including the use of ethylene oxides as alkylating agents and inconvenient chromatographic purification.[52] In this regard, Chong and Brechbiel [49]pioneered the synthesis of monosubstituted TACN derivatives bearing a hydroxylalkyl, an aminoalkyl, or a benzyl group, via direct cyclization of readily available starting materials rather than starting with TACN. However, TACN is commercially available but too expensive, although it has been exclusively used as a starting material for the preparation of mono-substituted derivatives. This approach employs primary amines bearing a variety of substituents that then provide pendant arms as starting materials such as the readily available ditosylate **49.**[57] These are reacted with an N,N'-ditosyl protected ditosylate ester in the presence of Na_2CO_3 to afford the N,N'-ditosyl-protected 1,4,7-triazacyclononane macrocyclic rings **50a-g** in 81–92% yields (Figure 23).[49]

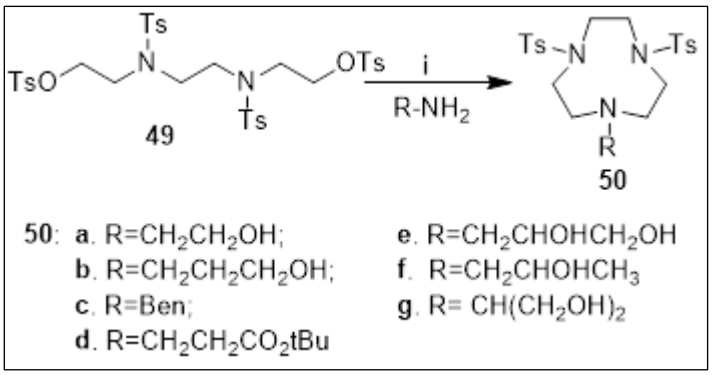


Figure 23: Synthesis of TACN macrocyclic ring 50a-g with pendant arms from a variety of primary amines.[49] Reaction conditions: i) Na_2CO_3, MeCN, reflux 24-72 h.

This cyclization approach has been claimed to be convenient, clean, and provides high yields using highly cost-effective starting materials.[49] These authors speculated that this strategy could be applied to the construction of a wide range of macrocyclic rings by using modified primary amines. Thus, the desired mono-substituted TACN having a hydroxylalkyl pendant arm (**52a** and **52b**) were obtained from deprotection of the tosyl groups in compound **51a** and **51b** (Figure 24).[58]

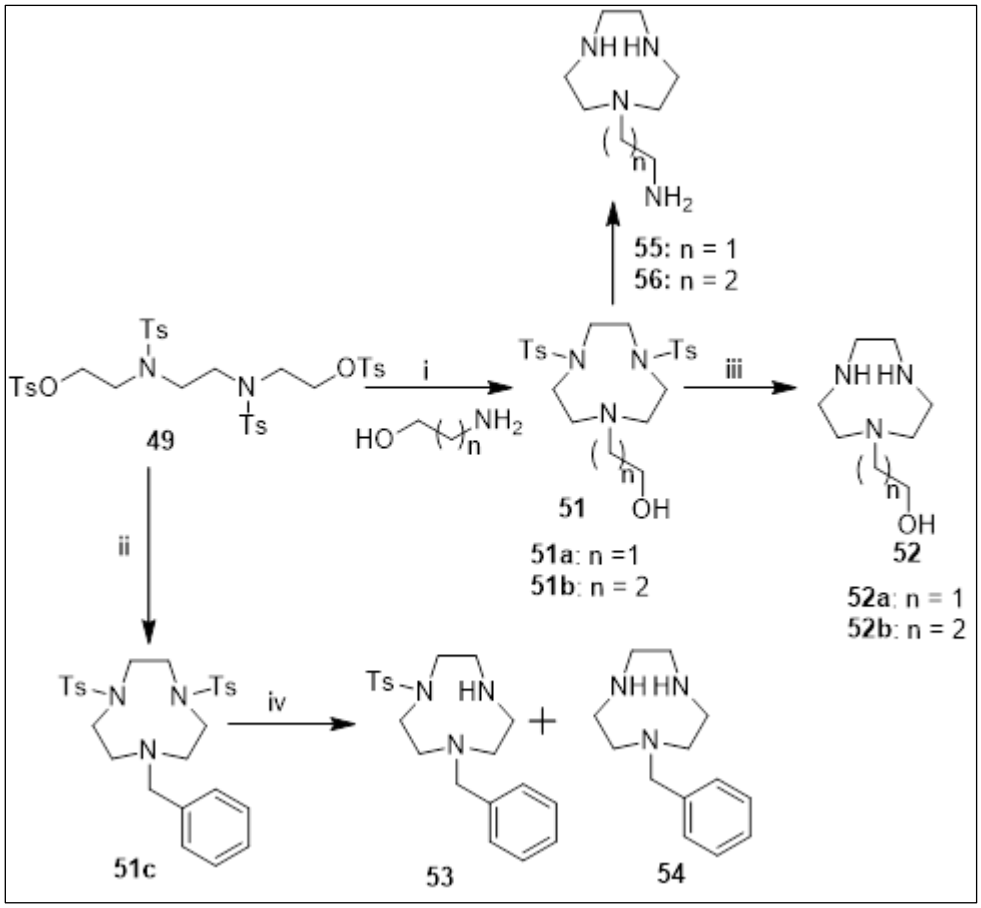


Figure 24: Synthesis of TACN macrocyclic ring with pendant arms.[49] Reaction conditions: i) $NaCO_3$, MeCN, refl., 72h; ii) $BnNH_2$, $NaCO_3$, MeCN, reflux, 72h; iii) Conc. H_2SO_4, 115 °C, 72h; iv) 30% HBr/AcOH, 90 °C, 72h.

The overall yields of **52a** and **52b** were 89% and 94%, respectively.[49] Chong and co-workers prepared TACN derivatives **55** and **56** bearing an aminoalkyl group in high yield after conversion of the hydroxyl group in **51a** and **51b** to an amino group and subsequent detosylation.[58] Deprotection of the tosyl groups in **51c** was attempted under the same conditions used for the preparation of **52a** and **52b** to generate the mono-benzyl TACN.[49] However, the treatment of **51c** with sulfuric acid failed to afford **54**. On contrary, the acid hydrolysis of the tosyl groups using hydrobromic acid/acetic acid mixture in the presence of phenol at lower temperature (90 °C) was successful, resulting in a mixture of compounds **53** and **54** which were separated and isolated by Chong and co-workers prepared.[49]

These authors observed that while not entirely as successful in providing a single chromatography free route to the desired **54** as hoped to by the authors, the ability to access **53** as a potential intermediate for further derivatization of TACN was an attractive side benefit. The authors' approach allowed for a cost-efficient and high yield production of mono-substituted TACN in a large scale that may be employed for a variety of applications via further modification. However, the use of harsh conditions and high temperature rendered this approach challenging and therefore the need for improvement.

Other approaches towards the synthesis of cyclic tosylamines were reported by Stetter and Roos.[59] The condensation of terminal dihalides with bis-sulfonamide sodium salts under high dilution were performed to obtain moderate cyclization yield.[59] In addition, modified approaches derived from Atkins and Richman (approaches) have been also reported by McAuley et al.,[60] Graeme et al.,[61] Searle et al.,[62] and Kellogg.[63]

Pickeland co-workers[64] reported the synthesis of the first unsymmetrical ,4,7-tri-alkyl-1,4,7-triazacyclononane (R_3-TACN) derivatives containing either one or two tertiary alkyl substituents, as well as chiral derivatives where the stereogenic centers are exocyclic and alpha to the TACN nitrogen atoms. Additionally, a fast and convenient synthesis of the HCl salts of H_3-TACN and the industrially relevant binculeating ligand H_4-DTNE **39** similar to the one prepared by Sessler *et al*[45] has also been described. Though TACN and its N-substituted derivatives (R_3-TACN) have been used similarly to transition metals owing to their ideal facial coordination geometry, limitation in their application as ligands has been very laborious due to challenging approaches by which they have been synthesized.[15]

Despite multiple reports describing improved syntheses of H_3-TACN,[65] the need for a more efficient, expedient, and atom economic synthesis remains.[64] Furthermore, there have been comparatively few improvements in the syntheses of R_3-TACN derivatives, most of which are synthesized by alkylation of H_3-TACN, and several challenges associated with their preparation as follows persist including:

- The synthesis of R_3-TACN ligands where one or more of the R groups is different from the others requires laborious and time-intensive protecting group manipulation.[66]
- Unsymmetrical R_3-TACN ligands where one or two R groups are tertiary alkyl are not known.
- Current routes to chiral derivatives of R_3-TACN are very limited and have found limited success,[67] likely owing to the non-ideal chiral environment established by ligands synthesized by current routes viz., i) derivatives with chiral R groups where the chiral center is removed from the nitrogen atoms by one methylene unit,[67g,68] and ii) derivatives where chirality comes from chiral centers on the nine-membered heterocycle[67b–f,69] where such chiral groups do not project toward the coordination sphere of the ligated metal.

R_3-TACN ligands are typically synthesized via alkylation of H_3-TACN by Eschweiler–Clarke methylation to afford Me_3-TACN [70] for example, by substitution of alkyl halides[65d] or by ring-opening of epoxides.[67g,68a] The Richman–Atkins route to R_3-TACN ligands is required because the synthesis of H_3-TACN, which is derived directly from deprotection of Ts_3-TACN, precludes installing R groups prior to the formation of the nine-membered heterocycle (Figure 3).

Accordingly, R_3-TACN derivatives with tertiary alkyl R groups are inaccessible by this route, and were unreported until 2013 when Pickeland co-workers demonstrated a short and efficient synthesis of $^tBu_3$-TACN,[71a] which offer a unique steric and oxidatively robust coordination environment. [68,71b] The synthetic route employed was an extension of the so-called "crab-like" cyclization method originally reported by Izatt and co-workers,[72] and later utilized by Bolm[73] and Murray,[74] for the synthesis of Me_2-RTACN ligands (R = primary alkyl group, Figure 25). This route, involved chloroacetylation of R group (**58**), cyclization around an amine, and reduction of the diamide product with $LiAlH_4$ (Figure 25), was claimed to be suitable for the synthesis of R_3-TACN derivatives bearing tertiary alkyl R groups. This because these groups could be installed prior to cyclization (installation of tertiary alkyl groups after cyclization has not been reported because methods for alkylation of secondary amines with tertiary alkyl groups are exceptionally rare).[68,75]

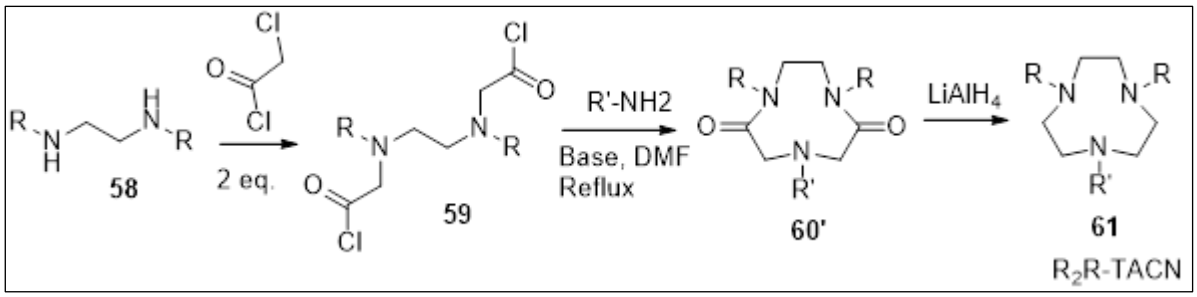


Figure 25: Synthesis of R_3-TACN derivatives by the "crab-like" cyclization and reduction.[64]

The authors demonstrated how this modified "crablike" cyclization route could be employed for the synthesis of unsymmetrical ^{t}Bu$_2$-RTACN and ^{t}Bu$_4$-DTNE ligands, as well as a rapid route to the HCl salts of H_3-TACN and H_4-DTNE that involve significantly less waste than the Richman–Atkins route. Furthermore, their method led to the first syntheses of chiral R_3-TACN ligands with chiral centers directly on the nitrogen substituent(s). A critical analysis of the factors determining the accessibility of R_3-TACN ligands by this route was described by these authors, highlighting both the scope and limitations of the methodology.[68]

These studies opened the possibility of investigating new and previously inaccessible R_3-TACN ligands in catalysis, particularly in asymmetric catalysis where advances have been hindered by the nature of the current achiral derivatives.[68]

Several routes for the synthesis of unsymmetrical R_3-TACN ligands containing no more than two identical R groups have been reported in the decades following the discovery of H_3-TACN.[68] One notable technique includes the conversion of H_3-TACN to the corresponding tricyclic orthoamide that can be alkylated only once and then deprotected to afford RH_2-TACN, where R is a primary or secondary alkyl group or a protecting group.[66a] Such derivatives can then be further elaborated, and this route has been applied for the synthesis of a derivative where all three R groups of R_3-TACN were identical.[66a,77]

However, such compounds require many steps to access. Another notable route involved the mono detosylation of Ts_3-TACN to afford Ts_2H-TACN followed by alkylation and deprotection.[66b,c,77] This route is used in the industrial production of Me_4DTNE, which alongside Me_3-TACN, are the most important industrial R_3-TACN derivatives.[64]

A promising route has been developed starting from diethylenetriamine and chloroacetaldehyde.[65c] Nonetheless, the method could not be used for the preparation of unsymmetrical R_3-TACN derivatives where at least one R group is a tertiary alkyl group because the substitution of a tertiary alkyl group with a secondary nitrogen is not feasible. Hence, this class of sterically unique and oxidatively resistant ligands have not yet been reported.[64] Pickel and co-workers established that an attempt to synthesize an unsymmetrical R_3-TACN derivative from a diethylenetriamine derivative bearing an alkyl group on the central nitrogen by a route analogous to the one shown in Figure 3 failed because of the nucleophilicity of the central nitrogen.[67b] Subsequently, the "crab-like" cyclization route to Me_2R-TACN derivatives with primary alkyl groups was developed by Izatt and co-workers[72]. The cyclization as applied to **59** involved the Me around the primary amines followed by reduction with $LiAlH_4$, and stands as the only route with promise for the incorporation of at least one tert-butyl substituent on nitrogen. Consistent with this perspective, this route was successfully applied in the first synthesis of ^{t}Bu$_3$-TACN[71] from **58**^{t}Bu, chloroacetyl chloride and ^{t}Bu-NH_2 via **59**^{t}Bu. Pickel et al. argued that the synthetic route could be applied broadly for the synthesis of ^{t}Bu$_2$R-TACN derivatives by cyclization of diamide **59**^{t}Bu, (prepared from chloroacetyl chloride and **58**^{t}Bu in 94 % yield) around various primary amines followed by reduction with $LiAlH_4$. Hence, ^{t}Bu$_2$-R-TACN derivatives by adopting this method, allowing access to the first unsymmetrical R_3-TACN derivatives bearing tertiary nitrogen substituents (Figure 26).[64]

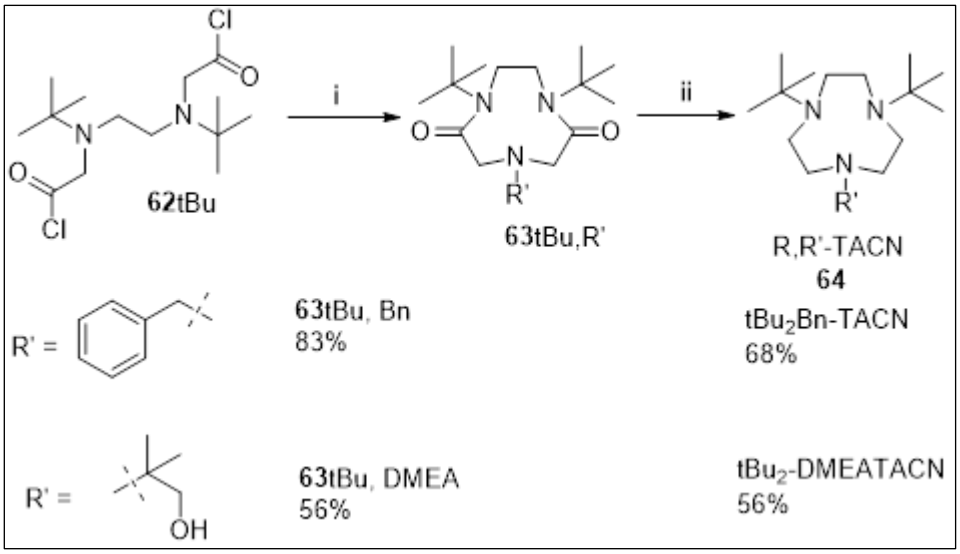


Figure 26: Synthesis of first unsymmetrical R_2R'TACN derivatives bearing tertiary nitrogen substituents by Pickel and co-workers.[64] Reaction condition: i) R'NH_2, Base, DMF, reflux; ii) $LiAlH_4$, Et_2O or THF.

In addition to the novelty of the ligands provided through this synthetic approach developed, by Pickeland co-workers claimed thatthis route could also be amenable to the facile preparation of sterically bulky analogues of well-known and highly useful TACN derivatives that are otherwise tedious to prepare.[64] For example, that the synthesis of Me_2-pic-TACN (pic = 2-picolylamine) requires at least five days and seven steps, though this compound has nonetheless been used extensively in coordination chemistry and catalysis over the last decade.[78] In contrast, the synthesis of $^tBu_2$pic-TACN has been shown to be remarkably facile through the method by Pickel et al., proceeding in only two working days and three steps, each of which was carried out successively without purification of any intermediates (Figure 27).[64]

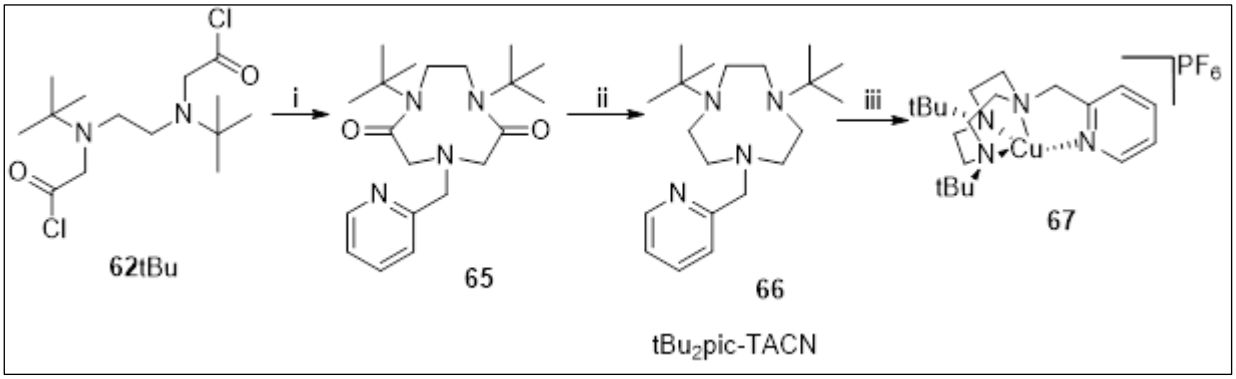


Figure 27: Synthesis of $^tBu_2$PIC-TACN 66 and [Cu(tBu_2PIC-TACN)][PF_6] 67.[64] Reaction conditions: i) 2-picolylamine, K_2CO_3, DMF, 120 °C, aqueous workup; ii) $LiAlH_4$, THF, aqueous workup; iii) [$Cu^I(MeCN)_4$)][PF_6], THF.

As an added feature of the efficiency of this method, the otherwise challenging purification of tBu_2pic-TACN, which is an oil at room temperature, was circumvented by metalation of the crude ligand with [$Cu(MeCN)_4$][PF_6] in three steps, followed by crystallization in DCM, to afford [Cu(tBu_2pic-TACN)][PF_6] **67** in 45 % yield over four steps. The authors also established that, given its ease of synthesis, tBu_2pic-TACN would be an attractive alternative to Me_2pic-TACN as a tetradentate ligand for supporting metal catalyzed oxidative transformations.[64] It was further reported that the synthesis of $^tBu_2$H-TACN through cyclization around NH_3 has been also successful. However, this required large excess of ammonia to prevent oligomerization, and the use of a pressure vessel to accommodate heated solutions of NH_4OH.[64] In their experience, $^tBu_2$H-TACN was the most readily synthesized ligand in 46 % overall yield, without any purification prior to distillation of the final product (Figure 28).

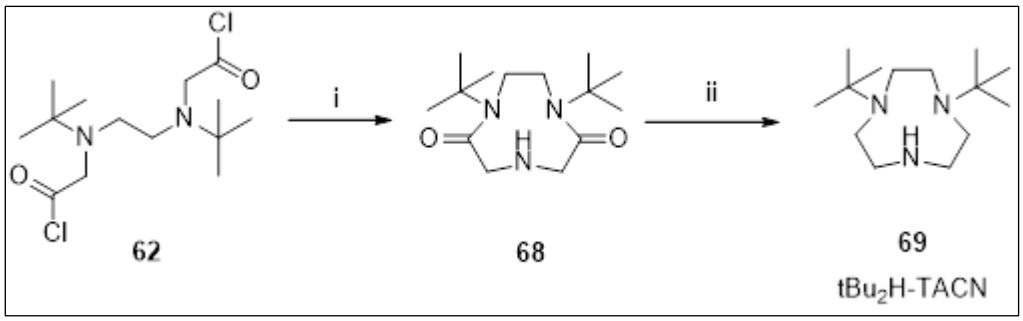


Figure 28: Synthesis of $^{t}Bu_2$H-TACN 51.[45] Reaction conditions: i) Conc. NH_4OH, MeCN, 100 °C, aqueous workup; ii) $LiAlH_4$, THF, Et_2O.

From an industrial perspective, Me_3TACN is among the most important R_3-TACN derivatives, as an effective ligand for the large-scale manganese-catalyzed H_2O_2 bleaching of wood pulp and cotton for the paper and textile industries, as well as in commercial dishwasher detergents as H_2O_2 activators, processes that together utilize more than half of global H_2O_2 production.[79] Currently, Me_3TACN is produced through Eschweiler–Clarke methylation of H_3TACN, a process that proceeds in near-quantitative yields.[64] Therefore, an improvement in the route to Me_3TACN likely requires an improved route to H_3-TACN.[64] However, the production of H_3TACN has been the subject of multiple patents in the past four decades with nearly all methods coalescing around the cyclization of twice-deprotonated Ts_3DET with $TsOCH_2CH_2OTs$ to afford Ts_3TACN as described previously by Atkins and Richman.[15,64] Deprotection of the tosyl groups generally utilizes H_2SO_4 to form $[H_6\text{-TACN}]_2[SO_4]_3$, an insoluble species that is more easily isolated when converted to $[H_6\text{-TACN}][Cl]_3$ using concentrated hydrochloric acid.[15] Generally, $[H_6\text{-TACN}][Cl]_3$ **2** is subjected to Eschweiler–Clarke methylation without isolation by addition of sufficient base to deprotonate $[H_6TACN]^{3+}$.[65d, 80,] While highly optimized, the Richman–Atkins approach still??utilizes five equivalents of tosyl protecting groups per equivalent of Me_3TACN formed, where TsO– and Me_3TACN both have molecular/ionic weights of 171 g/mol.[64] Given that $^{t}Bu_2$H-TACN **69** is so readily accessible, that Pickel *et al.*, reasoned that removal of the ^{t}Bu moieties would provide an attractive alternative route to H_3TACN.[64] After screening several conditions, the authors found the treatment of $^{t}Bu_2$H-TACN **69** with conc. HCl to provid $[H_6TACN][Cl]_3$ **2** in 89 % yield (Figure 29).[64]

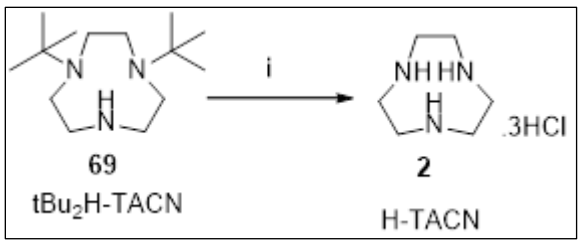


Figure 29: Synthesis of $[H_6TACN][Cl]_3$ 2 via acidic deprotection of $^{t}Bu_2$HTACN 69.[64]

Pickel, C.T *et al*. concluded that their route to $[H_6TACN][Cl]_3$ **2** was particularly attractive when compared to the conventional Richman–Atkins route for the following reasons:[64]

- Upon deprotection of $^{t}Bu_2$H-TACN, 54 % of the total mass is converted to an H_3TACN salt, compared to only 22 % in the case of Ts_3TACN (assuming quantitative yields). Therefore, the route described in their approach should be especially useful for large scale preparations of Me_3TACN, where atom economy and ease of scalability are particularly important.
- This synthesis of $[H_6TACN][Cl]_3$ **2** requires only one purification step: vacuum distillation of $^{t}Bu_2$HTACN, as crystallization of $[H_6TACN][Cl]_3$ **2** occurs spontaneously upon cooling of the reaction mixture.
- The overall synthesis of $[H_6TACN][Cl]_3$ **2** from commercially available di-tert-butylethylenediamine could be accomplished within two days, including workups and purifications.

Packel and co-workers also demonstrated the utility of this route in the practical and highly expedient synthesis of another industrially relevant TACN derivative, Me_4DTNE.

2.2.5 Synthesis of Chiral TACN derivatives with one chiral R group

One of the longest standing challenges in TACN synthesis has been the development of effective chiral derivatives for asymmetric catalysis.[64] To date, synthetic routes to chiral R_3-TACN derivatives have proceeded by one of two routes viz.:

- substitution of R_3-TACN with an epoxide[67g] or lactone[68] or
- introduction of annulet (ring) substituents during the Richman–Atkins synthesis of an R_3-TACN derivative.[67b–f,69]

TACN compounds generated by the former method possess a beta-N chiral center that is too remote to produce a significant stereo-inductive influence on the coordination sphere of a coordinated metal, while the latter have stereocenters on the TACN annulus (ring), which projects in the opposite direction of the coordination sphere.[64] These ligands have been employed in a number of reports, mainly in the pursuit of a Mn(R_3-TACN) catalyzed asymmetric olefin epoxidation[67] based on the system developed by Hage.[79] Only poor to moderate enantiomeric excess (ee's) were observed in these studies, consistent with the notion that such chiral TACN derivatives have a fundamental design flaw originating from the limitations associated with the available methods for their synthesis.[79]

Asymmetric TACN derivatives with exocylic-N alpha stereocenters represent the ideal design for maximizing the stereo-inductive influence of the TACN framework on the metal coordination sphere.[64] To date, TACN derivatives of this type are unknown in the literature, likely due to the challenges associated with asymmetric functionalization of R_3-TACN or its mono or di-protected analogues.[64] It was recognized by Pickel, C. T. *et al*., that by employing the "crab-like" cyclization strategy, an amine with an alpha-N stereocenter could be incorporated into the TACN ring during the cyclization step, obviating the need for a direct asymmetric functionalization of TACN. Therefore, **62**tBu was treated with sec-phenethyl, exobornyl, and menthylamine under their previously established cyclization conditions to provide the corresponding asymmetric diamides.[64] Reduction of the diamides with $LiAlH_4$ furnished the first series of chiral TACN derivatives with non-annulet, alpha-N stereocenters (Figure 30).[64]

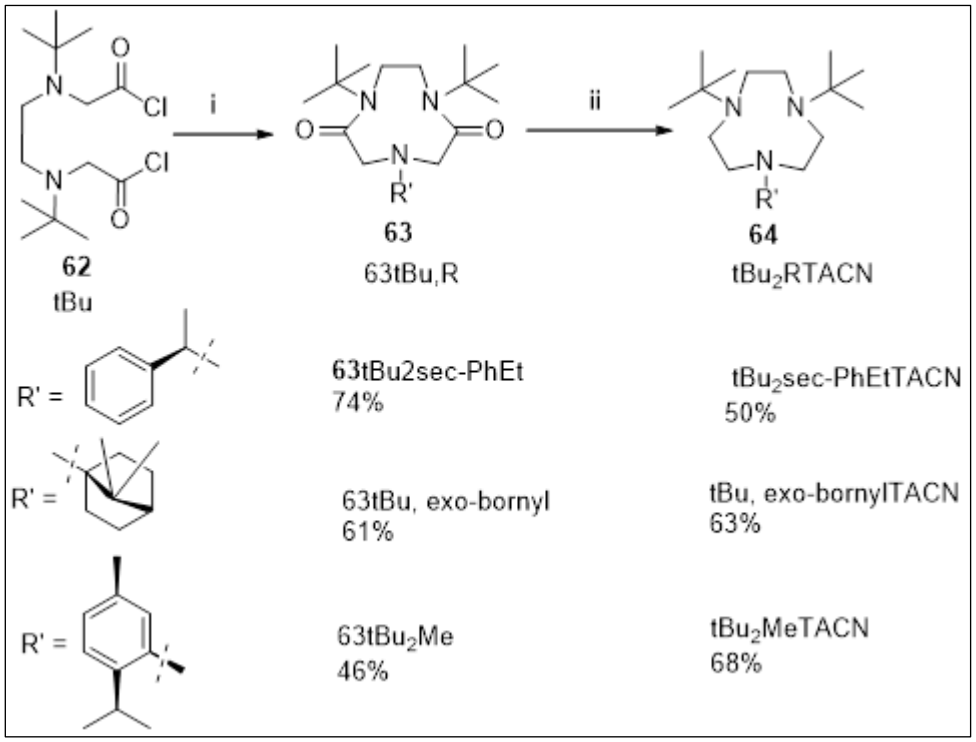


Figure 30: Synthesis of tBu_2R-TACNderivatives where R is a chiral group.[64] Reaction conditions: i) R'NH_2, DIPEA, DMF, 120°C; ii) $LiAlH_4$, Et_2O, -78 °C to rt.

2.2.6 Synthesis of a chiral TACN derivative with two chiral R groups

After having successfully utilized a "crab-like" cyclization to access TACN derivatives with one chiral R group, Pickel and co-workers sought to extend their approach to the synthesis of TACN derivatives with two chiral R groups.[64] In theory, the most straightforward route to such compounds proceeds through the synthesis of **62**R derivatives where R is a chiral functionality with an N-alpha stereocenter.[64]

However, they noted that **62**tBu was unique, allowing facile ring closure around a range of primary amines where **62**Me, **62**Bn, and **62**iPr were generally ineffective as precursors to R**62**R'TACN derivatives, with few exceptions.[64,72c,73,74] This disparity was rationalized by considering the effect amide rotamers had on the ability of **62**R derivatives to achieve the necessary conformation to undergo cyclization (vide infra).[64] Therefore, they were presented with the difficult challenge of identifying derivatives where R was an alpha-N chiral moiety useful for stereo-induction but was also sterically bulky

enough to allow for effective ring closure.[64] Hence, they began by preparing asymmetric derivatives with tertiary alpha-N stereocenters. However, in agreement with their previous observation that secondary amides were prone to oligomerization, attempted cyclization of these compounds resulted in intractable mixtures of oligomeric byproducts with no trace of the desired product.[64]

Given that the tertiary amide moiety seemed to be indispensable in the cyclization of **62**R compounds, they wondered if **62**tBu,R derivatives (where R is a secondary alkyl group), might also undergo cyclization. To probe this concept, they prepared unsymmetrical diamide tBu, exo–bornyl **68** and subjected it to cyclization conditions with exo-bornylamine **69** thus affording the corresponding exo–bornyl$_2$, tBu diamide **70**.[64] $LiAlH_4$ reduction of exo–bornyl,tBu **70** furnished exo-bornyl$_2$tBu-TACN **71**, the first TACN derivative with multiple exocyclic alpha-N stereocenters (Figure 31).[64]

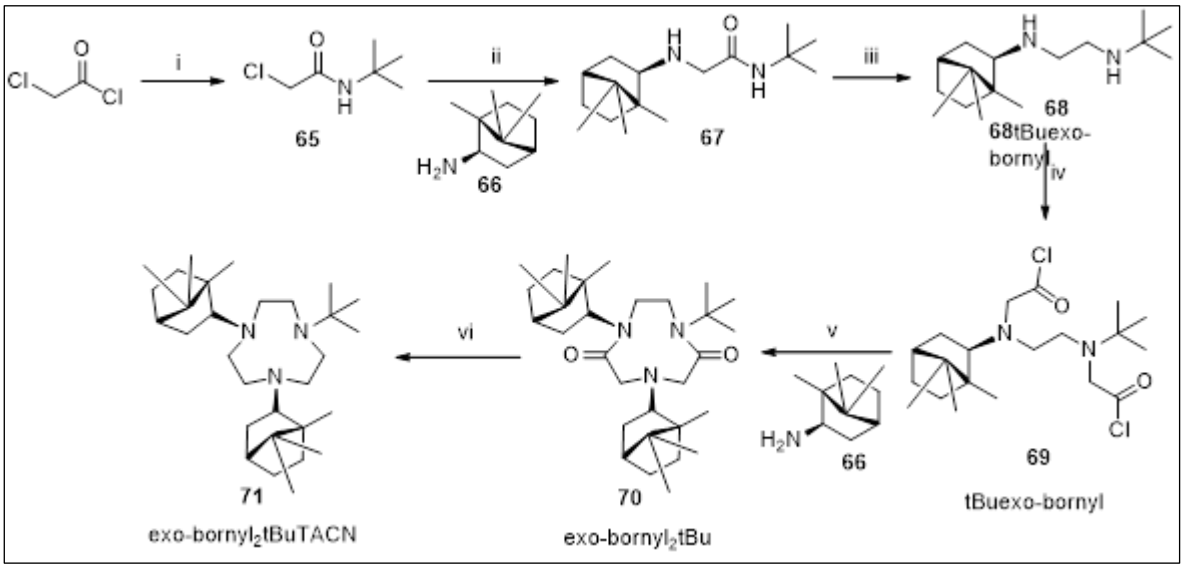


Figure 31: Synthesis of exo-bornyl$_2$tBuTACN 71.[64] Reaction conditions: i) $tBuNH_2$, NaOH, DCM, H_2O, 0 °C to rt, 4 h; ii) DPEA, DMF, 120 °C, 4 h, 72%; iii) $LiAlH_4$, toluene, reflux; iv) DCM, 0 °C, 5 h, 44%, 2 steps; v) DPEA, DMF, 120 °C, 6 h; vi) $LiAlH_4$, Et_2O, -78 °C to rt., 37%, 2 steps.

To probe the generality of tBu,R **69** (where R is a secondary alkyl group) as precursors to tBu,R **70** products, Pickel, C.T. *et al.*, prepared the simplest derivative of **69**, as tBu,iPr.[64] They established that exposure of **69** tBu,iPr to S-(–)-alpha-methylbenzylamine under the previously established cyclization conditions gave the triply unsymmetrically substituted TACN derivative tBu,iPr,sec-PhEt **72**, and reduction with $LiAlH_4$ furnished the corresponding sec-PhEtiPrtBu-TACN **73** (Figure 32).

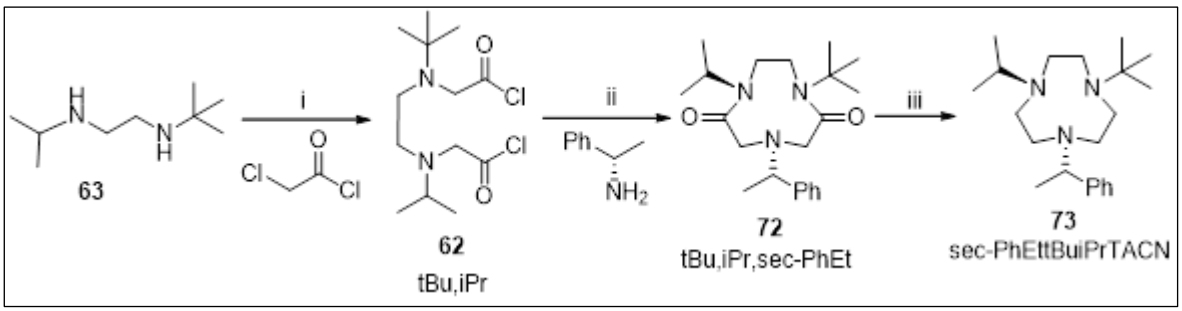


Figure 32: Synthesis of sec-PhEttBuiPrtacn 73.[64] Reaction conditions: i) DCM, 0 °C, 4 h, (78%); ii) DIPEA, DMF, 120 °C, 6 h, (58%); iii) LiAlH4, Et_2O, -78 °C - r.t., (63%).

The Results suggested that derivatives tBu,R **62** would be used as precursors to TACN compounds. Furthermore, in addition to providing a method for accessing chiral TACN derivatives with two chiral N-substituents, this route could be used to prepare TACN derivatives with three different N-substituents in only three steps from simple ethylenediamines.[64]

2.2.7 Synthesis of tBu4dtne and H10-DTNE][Cl6]

Since [H_6-TACN][Cl]$_3$ **2** is so readily accessible through the route described above, Pickel, C.T. *et al*., questioned whether their developed approach would be competitive with the current Richman–Atkins route to Me_4-DTNE, a widely used and industrially relevant TACN derivative.[15,79] Me_4-DTNE is currently produced by selective deprotection of Ts_3-TACN to [Ts_2H_2-TACN][OTs], coupling of two Ts_2H-TACN units with $TsOCH_2CH_2OTs$ to afford Ts_4-DTNE, and tosyl deprotection to afford [H_{10}DTNE][Cl_6], which is subjected to one-pot neutralization/Eschwelier–Clark methylation to Me_4-DTNE.[77] However, given that the Eschweiler–Clark methylation proceeds in nearly quantitative yield from [H_{10}-DTNE][Cl_6], Pickel, and coworkers targeted an improved synthesis of [H_{10}-DTNE][Cl_6] by exploring routes to generate [H_{10}-DTNE][Cl_6] using the methodology described above.[64] Therefore, they attempted the cyclization of diamide **62**tBu around ethylenediamine, providing their desired tetraamide in 60 % yield; however, reduction of the product to tBu_4-DTNE using $LiAlH_4$ only occurred in 28 % yield due to isolation challenges (Figure 33).

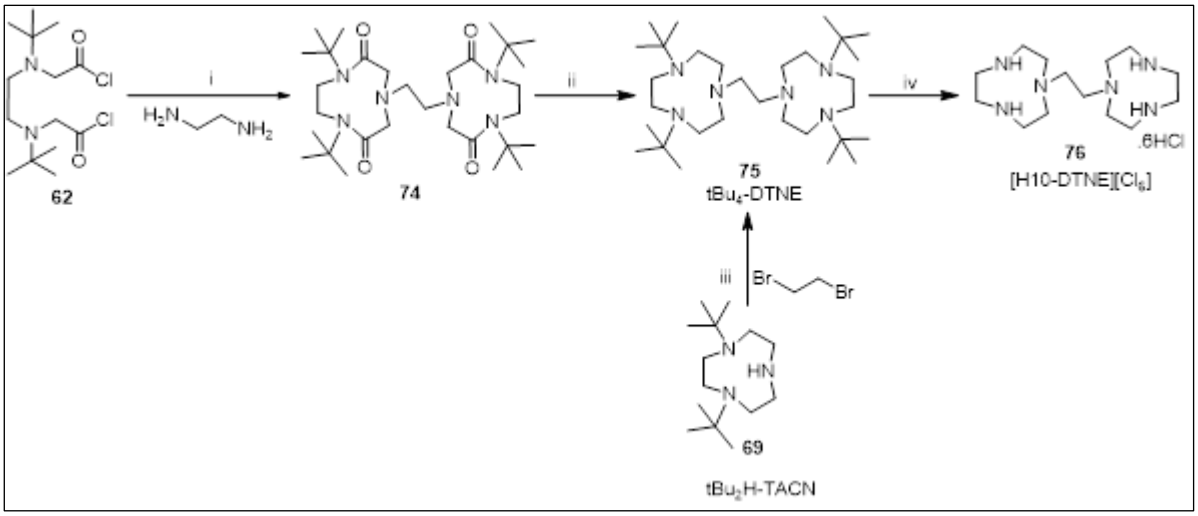


Figure 33: Synthesis of $^tBu_4$DTNE 75 and deprotection to [H_{10}DTNE][Cl]$_6$ 76.[69] Reaction conditions: i) Na_2CO_3, DMF, 120 °C; ii) $LiAlH_4$, Et_2O, (17% over, two steps); iii) sat. aq. K_2CO_3, rt.; iv) conc. HCl, 95 °C.

The removal of the tert-butyl groups in tBu_4-DTNE **75** using concentrated hydrochloric acid afforded, upon cooling, [H_{10}-DTNE][Cl_6] **76** in 86 % yield without any detectable [H_6-TACN][Cl]$_3$ **2** impurity, which is common in the industrial synthetic process.[64] However, though this four-step route seemed appealing when compared with the seven-step industrial route to this ligand, the purification of tBu_4-DTNE was found to be the major drawback.[64] Therefore, it was examined to whether two tBu_2H-TACN groups could be coupled with 1,2-dibromoethane, a preferred source of the ethylene bridge in R_4-DTNE compared to $TsOCH_2CH_2OTs$, to afford tBu_4-DTNE.[64] Thus, Pickel and coworkers successfully prepared **75** in 96% yield by reacting tBu_2H-TACN **69** with 1,2-dibromoethane in saturated aqueous K_2CO_3 and afforded a pure solid product (Figure 33). As described above, the tert-butyl groups of **75** were readily removed with hydrochloric acid to afford [H_{10}-DTNE[Cl_6] in 86 % yield.[64] Hence, they had developed a route to [H_{10}-DTNE[Cl_6] **76** that provides several advantages over the traditional route including a shorter step count (five steps vs. seven steps), superior atom economy, and fewer purification steps (one vs. four).[64]

During the studies, **62**R derivatives, where at least one amide was substituted with a tertiary R group, underwent smooth cyclization to the corresponding diamide in good yield and with a broad range of sterically bulky amines.[64] This finding was in contrast with the reports by Izatt (ref) and others (ref) on the synthesis of TACN diamide derivatives from **62**Me that proceeded in modest yield and only with a narrow scope of sterically diminutive primary amines.[64] Therefore, to rationalize this disparity, they considered the effect of amide R groups on the conformation of **62**R derivatives and the ability of the various possible **62**R conformers to undergo cyclization. Results from the elementary analysis of the diamide **62**R structure suggested that since both amides could adopt either the *cis* or *trans* rotamer, there were three possible molecular conformations; a conformer A where both amides adopted the cis rotamer, conformer B where one amide was oriented cis and the other trans, and conformer C where both amides adopted the trans rotamer (Figure 34).64

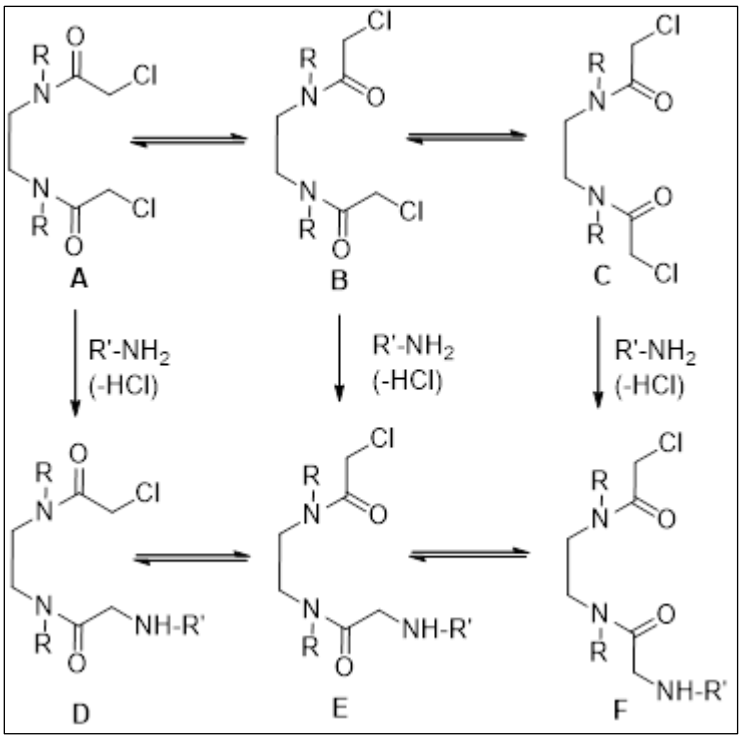


Figure 34: Conformational isomerism in 62R compounds and aminated intermediates.[64]

Following this line of reasoning, Pickel, C.T. and co-workers assessed that nucleophilic substitution of the aforementioned conformers with a primary amine gave rise to conformers **D**, **E**, and **F**. Conformer **D** was found to be situated to allow cyclization, owing to the close proximity of the amine and alkyl chloride moieties.[64] Conversely, conformers **E** and **F** were found to be unable to cyclize directly and were likely to form oligomeric byproducts.[64] From this analysis, they concluded that the cyclization would only occur directly from conformer **A**, and therefore was dependent on the ability of both amide moieties to adopt the cis rotamer.

Thus, it was speculated that **62**R compounds with tert-butyl (and other sterically bulky functionalities) were relatively more competent for cyclization than their less bulky analogues due to the increased thermodynamic stability of the cis rotamer.[64] To support this hypothesis, interest rose in the experimental identification of the conformers of a representative series of **62**R derivatives. After tedious NMR analysis, it was concluded that bulky amide R groups stabilize the cis rotamer conformation, which allows for the unusually efficient cyclization of **62**tBu and other bulky **2**R derivatives.[64]

The outcome of this work addressed the three major limitations in the accessibility of R_3-TACN derivatives viz.: i) the development of a "more efficient" and less wasteful route to R_3-TACN ligands where one or more of the R groups is unique; ii) the development of a convenient approach to access unsymmetrical R_3-TACN ligands where one or two R groups are tertiary alkyl; and iii) the development of the first chiral derivatives of R_3-TACN with chiral centers alpha to the nitrogens on the R groups.[64]

Furthermore, efficient routes to industrially important Me_3-TACN and Me_4-DTNE that produce significantly less waste compared with the conventional Richman–Atkins route were reported. The results as described above, detailed approaches to known as well as previously inaccessible R_3-TACN ligands. In particular, novel chiral examples were claimed to promote increased utilization of such R_3-TACN ligands in coordination chemistry and enabled the development of new and improved (asymmetric) catalytic methods for organic substrate transformations.[64]

Earlier, Huskens and Sherry had developed an interesting and different approach to directly functionalize the TACN.[81] A series of ligands including NOTPM **80**, NO1A-2PM **81** and NO2A-MP **82** ligand, were prepared via a novel strategy, in which no protecting groups were required (Figure 35).[81]

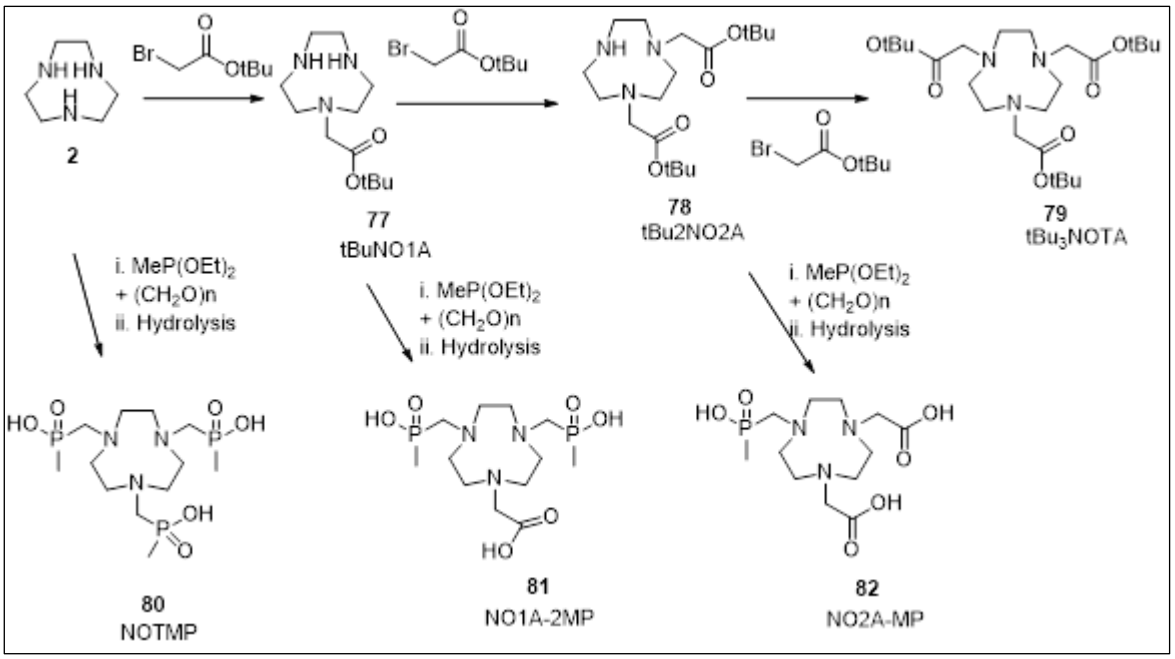


Figure 35: Proposed synthetic approach for NO2A-MP by Huskens and Sherry.[81]

Typically, starting from a commercially available H_3-TACN **2**, two acetate groups (tBu esters) were attached by reaction with 2 equiv of tert-butyl bromoacetate in ^{t}BuOH, giving ^{t}BuNO1A **77** and ^{t}Bu$_2$NO2A **78** (Figure 35). The HBr produced in the reaction was neutralized by the simultaneous addition of KO^{t}Bu. The formation of the trisubstituted product ^{t}Bu$_3$NOTA **79** was inhibited by protonating a single macrocyclic nitrogen using 1 equiv of trifluoromethanesulfonic acid (TfOH). The strategy using H^+ as the "protecting group" relied on the fact that there was a large gap between the stability constants (in water) of the first and the second protonation steps of H_3-TACN **2** and its derivatives. In this way, a selectivity of 70% toward ^{t}Bu$_2$NO2A **78**[81] was observed in contrast with earlier attempts without TfOH that showed a selectivity of only 30%. Investigating the use of TfOH as a protection agent in the synthesis of ^{t}Bu$_2$NO2A **78** was conducted by titrating ^{t}BuNO1A **77** and ^{t}Bu$_2$NO2A **78** with TfOH, while monitoring the resulting ^{1}H and ^{13}C NMR spectra.

In general, protonation of an amine would induce a large downfield shift on R-hydrogen nuclei and a large upfield one on beta-carbons.[81] To achieve the maximal selectivity, their speculation arose that this ratio had to be 1 during the course of the reaction as a larger ratio would lead to protection of tBuNO1A **77**, and therefore a competitive reaction rate between tBuNO1A and ^{t}Bu2NO2A **78**, while a smaller ratio would fail to protect ^{t}Bu$_2$NO2A **78** from the consecutive reaction toward ^{t}Bu$_3$NOTA **79**.[81] Thus, selectivity was achieved by using 1 equiv of TfOH, and by adding tert-butyl bromoacetate and KO^{t}Bu simultaneously in small equal increments.

A further observation was that the usual hydrolysis procedure of refluxing in 6 M HCl appeared unsuitable for this ligand, since more than 20% of the methylphosphinate side chain was cleaved off after 15 h at 120 °C.[81] Even lower acid concentrations and lower temperatures yielded small amounts of NO2A-MP **82** which was further purified on a cation exchange column eluted with aqueous HCl, finally yielding the free acid. Two other compounds, NO1A-2MP **81** and NOTMP **80**, were synthesized using similar methods. The preparation of NO1A-2MP **82** proceeded from ^{t}BuNO1A **77** which was isolated from a reaction of H_3-TACN with 1.5 equiv of tert-butyl bromoacetate, applying 1 equiv of TfOH. Further attempt was made to use the protective strategy described above for ^{t}Bu2-NO2A **78** in the selective synthesis of ^{t}BuNO1A **77**, by using 2 equiv of TfOH. However, the reactivity of the diprotonated H_3-TACN appeared to be too low to protect the resulting the mono-diprotonated tBuNO1A **77** from consecutive reaction toward ^{t}Bu$_2$NO$_2$A **78**.

Subsequently, the intermediate ^{t}BuNO1A **77** was reacted with an excess of MeP(OEt)$_2$ and (CH$_2$O)n, followed by hydrolysis and purification with cation exchange column chromatography. Compound NOTMP **80** was synthesized in one step as the triethyl ester, starting from H_3-TACN and excess MeP(OEt)$_2$ and (CH$_2$O)n, similar to a known procedure.[82] Hydrolysis in aqueous NaOH, followed by purification on a cation exchange column, afforded the free acid compounds **81** and/or **82**, which were further complexed with Mg^{II} for further studies.[81] This novel approach seemed promising since no protecting steps were needed prior to functionalization. However, the use of an expensive commercially available H_3-TACN as starting material constituted a serious shortcoming of this approach, amongst others.

Bangal, *et al*., pioneered the introduction of unsaturation(s) into the basic skeleton of TACN.[83] With the expectation of generating some interesting chemistry, they tried to introduce two imino N atoms in the TACN skeleton by reacting benzil with diethylenetriamine (DIEN or DETA). The idea originated from the work done by Okawara *et al*. earlier,[84] who reported the reaction of benzil with DIEN in equimolar proportion in ethanol to yield 8,8a-diphenyl1,2,3,5,6,8a-hexahydroimidazo[1,2-a]pyrazine instead of its (L1) macrocyclic isomer 2,3-diphenyl-1,4,7-triazacyclonona-1,3- diene (L) (Figure 2)[84], which was later verified by X-ray crystallography.[85]

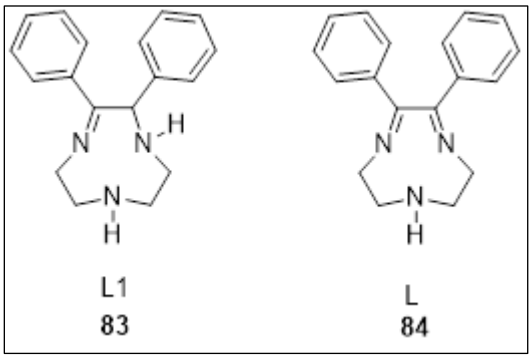


Figure 1: Chemical structures of 8,8a-diphenyl1,2,3,5,6,8a-hexahydroimidazo[1,2-a]pyrazine (L1)[84] and macrocyclic isomer 2,3-diphenyl-1,4,7-triazacyclonona-1,3- diene ligand L.[83-86]

Their Austin Model 1 (AM1) calculations[86] using standard MOPAC package indicated a small energy difference (0.81 kcal mol^{-1}) in the heats of formation of the two isomeric species L and L1 and therefore investigation into the photochemical reaction between benzil and DIEN was conducted. It was found that the irradiation with UV light in the presence of air of a moderately dilute solution of equimolar proportions of benzil and DIENin anhydrous methanol provided L (Figure 36).

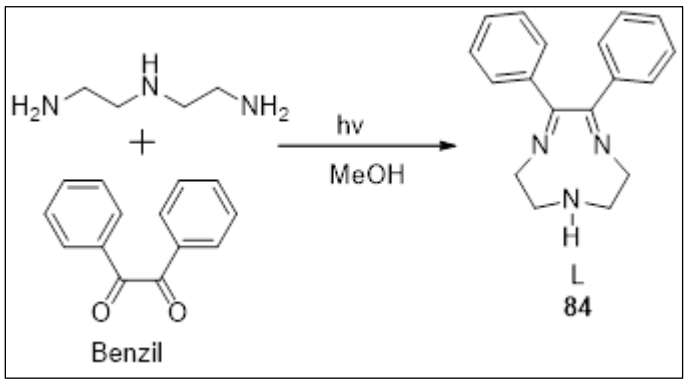


Figure 36: Proposed synthetic approach to ligand L 84 by Bangal, et *al*.[83]

The photochemical reaction temperature was crucial is and should be kept as low as possible as rising temperature resulted in more impure product the product get more and more contaminated with and above 50 °C, only could be obtained. It was further observed that in an inert atmosphere, the reaction described in Figure 36 could not proceed to L (**84**) irrespective of the temperature but rather solely L1 was solely formed.

Furthermore, the irradiation with UV light of a solution of L **84** in anhydrous methanol gave only L1, meaning that L1 was not converted to L.[83] However, the reflux of L **84** in anhydrous methanol (the reaction condition used to synthesize L1),[87] resulted in the generation L1 in moderate yield. The findings are summarized in Figure 37.[83]

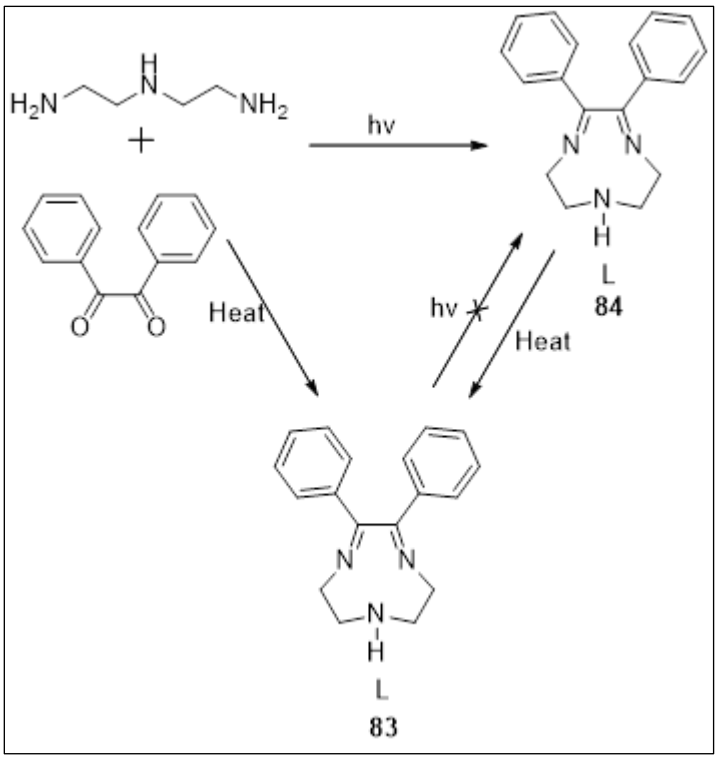


Figure 37: Finding's summary of the reaction between benzil and diethylenetriamine (DETA) under reflux and UV conditions.[83]

However, the role of oxygen in reaction Figure 36 could not be explained which resulted in speculation on one hand that some radicals might involve in the process with the generation of $^1O_2$.[83] And on the other hand, that the thermal conversion of L to L1 appeared to be a typical transannular cyclisation[88] catalyzed by a proton, which came from the protic solvent used.

In summary, it was demonstrated that by reacting DIEN with benzil in anhydrous methanol under UV radiation, two imino N atoms could be introduced into the basic skeleton of 1,4,7-triazacyclononane, resulting in a novel triaza macrocycle L. The authors described that the presence of oxygen was essential in the formation of L. However, the mechanism by which oxygen brings about the reaction remained not clear.[83] It was further?? established that the physicochemical properties of L were found to be very different from those of which is produced L1 by carrying out the reaction between benzil and DIEN thermally. Subsequently, a conclusion was drawn that ligands L and L1 should be regarded as isomers, and that the macrocycle L could be thermally converted to the non-macrocyclic L1. This finding was expected from their AM1 calculations, as L was energetically higher than L1 even though the difference was only ca. 1 kcal 1 mol^{-1}.[83]

J. Gao *et al*., speculated that integrating a π-conjugated moiety into a polyaza macrocyclic ligands would result in a new class of intercalators, which would potentially enhance the DNA-binding effect in the corresponding platinum complexes.89 Hence the first examples of a π-conjugated macrocyclic diimine 85 and a triaza 86 ligand using a slightly modified approach and reaction condition to the one described by P.R. Bangal, et al. (ref) were reported (Figure 38).

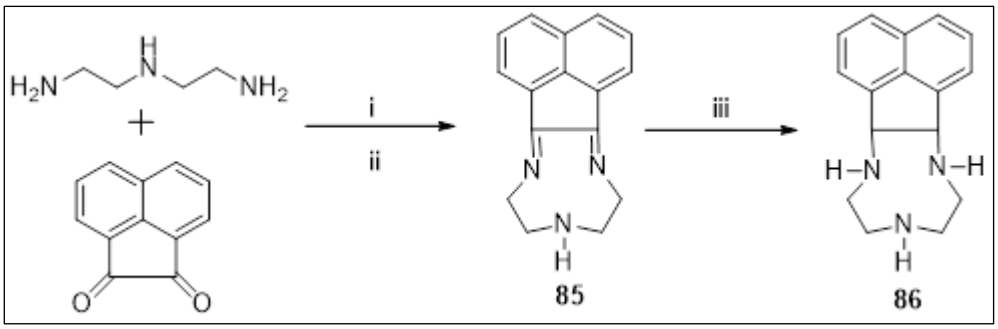


Figure 38: Proposed synthetic approach to access the new intercalative macrocycles as diamine 85 and the triaza 86.[89] Reaction condition: i) EtOH, catal. Hbr, reflux; ii) column chromatography; iii) $NaBH_4$, EtOH.

Compound **85** was prepared by an acid-catalyzed condensation between acenaphthenequinone and diethylenetriamine. The resulting reactant mixture was refluxed in EtOH under inert condition for 24 h, followed by the addition of an excess quantity of ethyl ether to the cooled mixture. This resulted in a yellow-colored precipitate that was removed by filtration. The pure ligand was obtained by recrystallization from MeOH. The reduction of **85** with $NaBH_4$ in an EtOH produced a good yield of compound **86**, which was further purified by gel column chromatography ($MeOH/CH_2Cl_2$).[89]

A Schiff-base can coordinate and stabilize various oxidation states of transition metals in organic phase.[90,91] The attraction of Schiff-base is growing because a series of changeable structures and widely diverse properties of Schiff-base ligands are easily prepared by changing the substituents of aldehyde, ketone and amine. Hence, macrocyclic Schiff-base displays a rather important role in the ligand-catalyst system[92,93] In this way, access to TACN and its derivatives by means of a condensation of DETA and aldehydes to form a Schiff base which is reduced under $NaBH_4$, has attracted much attention.[92-94] This approach is much easier and preferable than most of previously described methods??? in the literature. It allows an organized/systematic alkylation step to access symmetrically or unsymmetrically mono-, di-, or tri-substituted TACN ligands (Figure 39).

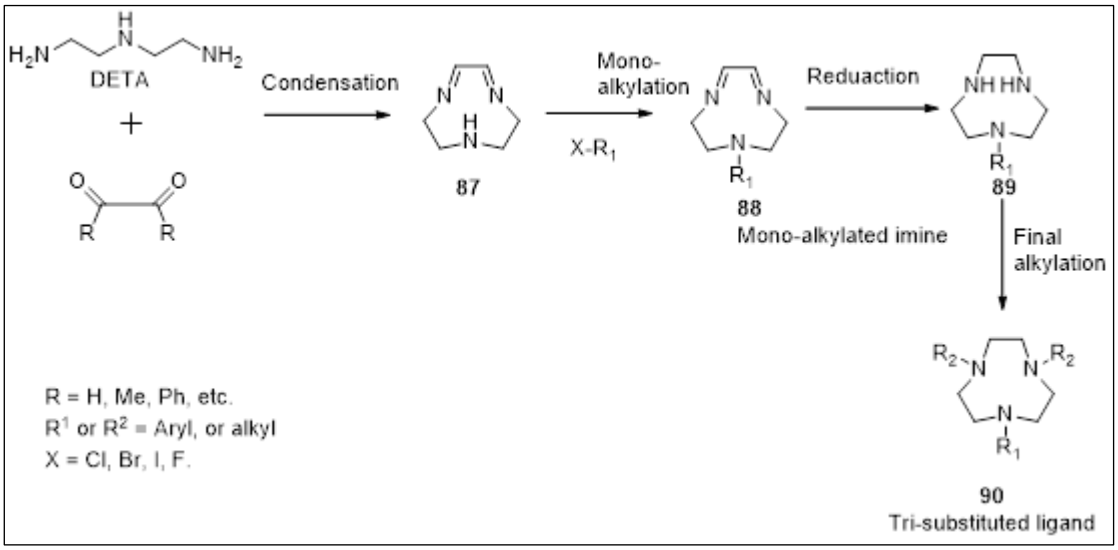


Figure 39: Possible approach to access mon-, di-, and tri-substituted symmetric or unsymmetric TACN derivatives 89 and 90.

For example, it is possible to mono-alkylate the only secondary amine of **87** derivative to afford **88** (Figure 39), whereas the two others secondary amines can follow after the reduction step to yield **89** and subsequently **90** as a trisubstituted/unsymmetric derivative and thus avoiding therefore a multiple protection/deprotection steps.

3 CONCLUSION

Research has shown that several synthetic approaches have been developed by researchers toward the synthesis and functionalization of 1,4,7-Triazacyclononanes (TACN) in the last decade. Results obtained in this qualitative study have shown that different approaches described in the literature used often protective groups that make it possible to vary

the nature of the functions grafted onto the macrocycle according to the intended application. However, the existing methods require harsh reaction conditions (acid treatment) at the final step for the deprotection step. In general, these approaches were mostly multi-steps and resulting in poor yields. Apart from a direct commercial and economic impact, the adoption of green chemistry principles would have many benefits, including minimization of waste, reduction in eco-pollution, and the potential for higher yields through the use of fewer synthetic steps. Unfortunately, results compiled in this review paper have shown that despite the increased interest in TACN and its derivatives in the last decade, only a few synthetic methodologies have been reported in the literature, of which some have been reviewed in this current work, with a special emphasis on their advantages and disadvantages as well as the N-functionalization of TACN and its derivatives therefore. It is revealed that most of researchers used the commercially available TACN as their starting material instead of developing methods to synthesize it in bulk from their labs, owing to its cost commercially. No direct cyclization of the commercially available N1-(2-aminoethyl)ethane-1,2-diamine without the need of any protection and deprotection steps has been found, to the best of our knowledge and this could be taken into account by researchers to come out with novel, shorter, simple and cost-effective synthetic approach to access TACN and/or its N-functionalized derivatives in just one-step synthesis. This study therefore, opens up new doors in this field specially, for future work, in the development and/or improvement in the search for novel synthetic approaches, which are simpler than the previously or currently used, which could be carried out without using toxic solvents and catalysts with a high environmental risk.

- To the best of our knowledge, none of the research group published this topic as a review article.
- We have covered almost all reports in this review with a detail of synthetic Figures and respective pathways with different reagents and conditions.
- We strongly believe and anticipate that the summarized literatures in this field will definitely serve as an important update on what has been done so far in the field, and permit researchers to also to develop novel, shorter, and cost-effective green synthetic approaches of this versatile chelator/ligand and its potential derivatives, owing to their useful applications.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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