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An efficient synthesis of tetrasubstituted cyclohexyl-1,2-diamines

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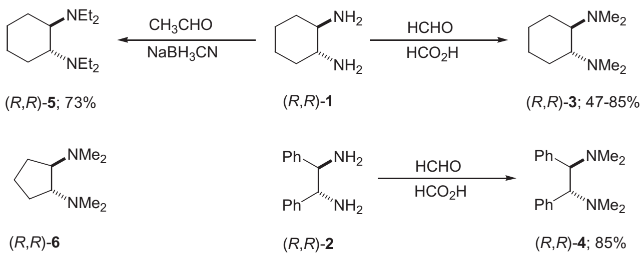
Abstract—The synthesis of symmetrically tetrasubstituted diamines derived from the (*R*,*R*)-cyclohexyl-1,2-diamine is reported. We comment on the efficiency of this sequential substitution approach as a method for the synthesis of tetrasubstituted diamines and discuss the acceptable substitution pattern for this methodology.

1. Introduction

The synthesis of enantiomerically pure tetrasubstituted diamines is well documented.[1] They have been synthesised by either direct alkylation of the parent chiral diamine with an achiral[2–18]/*meso*-based electrophile,[15,19] or by alkylation of the parent achiral diamine with a chiral electrophile.[18] Of these approaches, the more synthetically versatile appears to involve direct alkylation of a chiral diamine[6] with an achiral electrophile.[2–17] The majority of these studies have relied on stepwise[2–11,15,17] and in situ reductive amination,[8–11,16,19,20] followed by direct alkylation (using simple S_N2 displacement methodology)[11,13,19] to form the required four carbon–nitrogen (C–N) single bonds. Using this type of strategy, the synthesis of symmetrically tetrasubstituted diamines using a single-step process would appear to be relatively straightforward. However, it is surprising to find only a limited number of available methods;[8,11,12,14,16,19,21,22] the most common being the Eschweiler–Clarke methylation[23] of cyclohexyldiamine **1**[8,16,20] and diphenylethylene diamine **2**[8] using formaldehyde and formic acid to give the tetramethylcyclohexyldiamine **3** and tetramethyldiphenylethylenediamine **4** in 47–85% and 85% yields, respectively (Scheme 1). This type of reductive amination approach has also been used to synthesise the related tetraethylcyclohexyldiamine **5**[11] and tetramethylcyclopentyldiamine **6**.[11]



Scheme 1. Synthesis of diamines (*R*,*R*)-**3**, (*R*,*R*)-**4**, (*R*,*R*)-**5** and (*R*,*R*)-**6**.

From these reports, there appears to be a limited number that deal directly with the conversion of disubstituted diamines to tetrasubstituted diamines. The synthesis of disubstituted diamines such as dimethyl and dibenzyldiamines **7** and **8** appears to be relatively simple. Alexakis et al.[15] have reported both the dimethylation and dibenzylation of cyclohexyldiamine (*R*,*R*)-**1** using methyl iodide and benzyl bromide to give the dimethyl and dibenzyldiamines **7** and **8**, respectively, in low to moderate yields (Scheme 2). Alternatively, diamines **7** and **8** can be synthesised in higher yields by reduction of the corresponding bis-dicarbamate **9**[2,3,5,8,10,15] and imine **10**[4–6,10] using a nucleophilic hydride source (Scheme 2).

To overcome the poor nucleophilicity of these secondary amines, Alexakis and co-workers [16] have developed an in situ reductive amination procedure using an aldehyde

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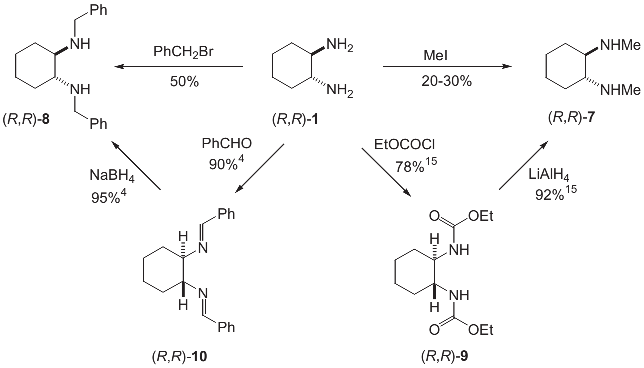
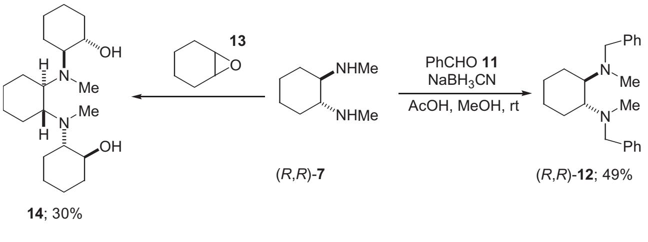
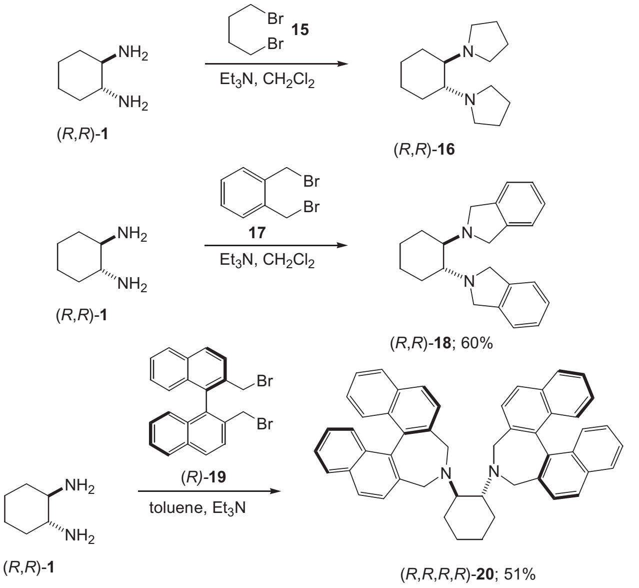


Scheme 2. Synthesis of diamines (*R*,*R*)-**7** and (*R*,*R*)-**8**.

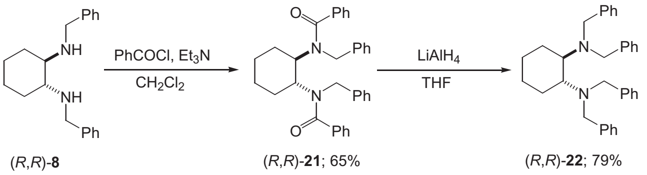
(e.g., benzaldehyde **11**) and NaBH$_3$CN to introduce the benzyl substituents in diamine **12** (Scheme 3). This procedure appears to be efficient for a wide range of substituted aldehydes. By comparison, *N*-alkylation of the parent diamine **7** has been shown to occur using an S$_N$2 activated electrophile such as an epoxide (e.g., **13**)[19] to give the bis-β-aminoalcohol **14** in moderate yield (Scheme 3). Finally, double *N*-alkylation of each amino group within the diamine (*R*,*R*)-**1** has been achieved using achiral and chiral dibromides **15**, **17** and **19** to give the tetrasubstituted diamines **16**,[12,14,24] **18**[12] and **20**[18] respectively by ensuring that the second alkylation step was intramolecular (Scheme 4).



Scheme 3. Synthesis of diamines (*R*,*R*)-**12** and **14**.

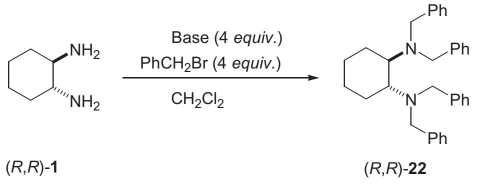


Scheme 4. Synthesis of diamines (*R*,*R*)-**16**, (*R*,*R*)-**18** and (*R*,*R*,*R*,*R*)-**20**.



Scheme 5. Synthesis of diamine (*R*,*R*)-**22**.

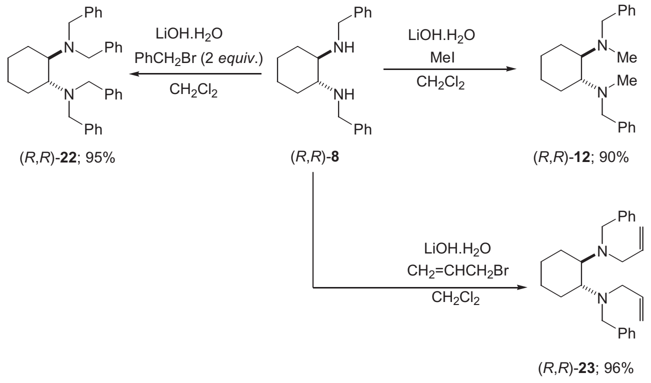
We were interested in extending this methodology towards the synthesis of novel symmetrically tetrasubstituted diamines in an attempt to gain a better understanding of these processes. We initially chose to synthesise the tetrabenzylsubstituted diamine (*R*,*R*)-**22** by reduction of the corresponding bis-amide (*R*,*R*)-**21** [25] using lithium aluminium hydride in THF (Scheme 5). The bis-amide (*R*,*R*)-**21** was synthesised in 65% yield by addition of benzoyl chloride[25] to a stirred solution of dibenzyldiamine (*R*,*R*)-**8** and triethylamine in dichloromethane (Scheme 5). Lithium aluminium hydride reduction of the bis-amide (*R*,*R*)-**21** gave the required symmetrically substituted tetrabenzyl diamine (*R*,*R*)-**22** in 79% yield. This process was moderately efficient giving access to diamine (*R*,*R*)-**22** in an overall 38% yield (over four steps)[26] starting from the parent diamine (*R*,*R*)-**1** (Schemes 2 and 5). This type of reductive amination methodology has previously been used in the synthesis of tetramethylcyclohexyldiamine (*R*,*R*)-**3**.[8,11,16] With this information at hand, we next chose to investigate the sequential benzylation of the parent diamine (*R*,*R*)-**1** using benzyl bromide as the electrophilic benzyl source. We initially probed the efficiency of *N*-benzylation by addition of benzyl bromide (4 equiv) to a solution of cyclohexyldiamine (*R*,*R*)-**1** in dichloromethane in the presence of a suitable base (e.g., Et$_3$N, K$_2$CO$_3$ and LiOH·H$_2$O) (Scheme 6). However, the use of lithium hydroxide monohydrate (LiOH·H$_2$O: Scheme 6: entry 3) was found to be more efficient leading to a higher yield of the required tetrabenzylcyclohexyldiamine (*R*,*R*)-**22** (64%). In addition, the high yield of each alkylation step (approximately 90%) enabled the efficient separation of the tetrabenzylcyclohexyldiamine (*R*,*R*)-**22** from the intermediate mono-, di- and tribenzyldiamines,



Entry	Base	Yield (%)
1	Et$_3$N	28[a]
2	K$_2$CO$_3$	41
3	LiOH.H$_2$O	64

[a] In addition 26% of the dibenzylamine (*R*,*R*)-**8** was also isolated

Scheme 6. Synthesis of diamine (*R*,*R*)-**22**.



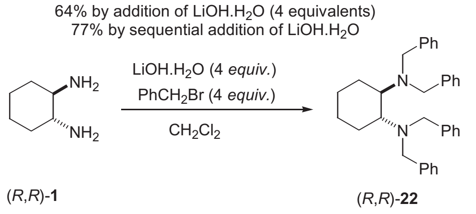
Scheme 7. Synthesis of diamines (*R*,*R*)-**12**, (*R*,*R*)-**22** and (*R*,*R*)-**23**.

which was found to be particularly problematic when using triethylamine as the base (Scheme 6: entry 1).

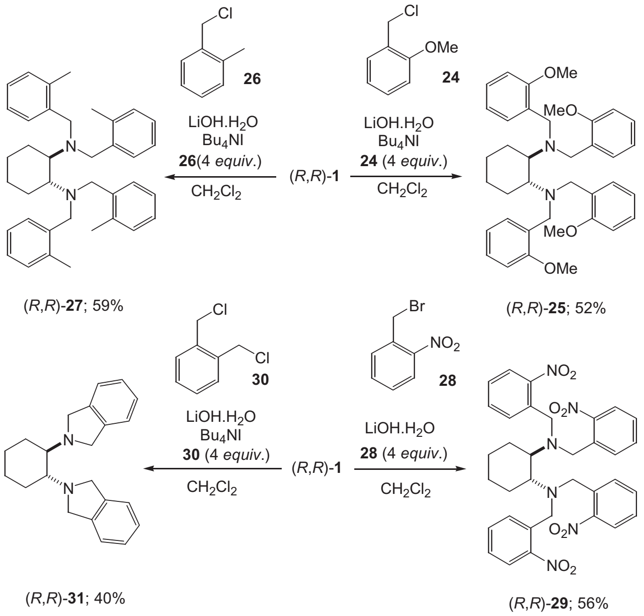
Alternatively, tetrabenzylcyclohexyldiamine (*R*,*R*)-**22** can be synthesised in near quantitative yield by direct benzylation of dibenzylcyclohexyldiamine (*R*,*R*)-**8** by addition of 2 equiv of benzyl bromide and lithium hydroxide monohydrate (Scheme 7). This *N*-alkylation process appears to be particularly efficient for a variety of S_N2 active electrophiles like methyl iodide and allyl bromide giving the corresponding dimethyldibenzyl- and diallyldibenzylcyclohexyldiamines (*R*,*R*)-**12** and (*R*,*R*)-**23** in 90% and 96% yields respectively (Scheme 7).

In an attempt to improve the overall yield by limiting the background substitution reaction between benzyl bromide and lithium hydroxide, we next investigated the sequential addition of lithium hydroxide monohydrate to a solution of the parent diamine (*R*,*R*)-**1** and benzyl bromide in dichloromethane. We chose to add 4 equiv of benzyl bromide to a stirred solution of diamine (*R*,*R*)-**1** in dichloromethane, which resulted in the formation of a precipitate after 1 h. Lithium hydroxide monohydrate (1 equiv) was added to the resulting solution and this was stirred for a further 1 h. This procedure was repeated until all 4 equiv of lithium hydroxide monohydrate had been added. The resulting solution was stirred for a further 6 h to give the required tetrabenzylcyclohexyldiamine (*R*,*R*)-**22** in an improved 77% yield (Scheme 8).

Our attention next turned towards the synthesis of other symmetrically tetrasubstituted diamines such as (*R*,*R*)-**25**, (*R*,*R*)-**27**, (*R*,*R*)-**29** and (*R*,*R*)-**31** using our sequential alkylation method by addition of the benzyl chlorides **24**, **26** and **30** and bromide **28** to a solution of cyclohexyldiamine (*R*,*R*)-**1** and tetrabutylammonium iodide (Scheme 9). These reactions proceeded smoothly giving the required symmetrically tetrasubstituted diamines (*R*,*R*)-**25**, (*R*,*R*)-**27**, (*R*,*R*)-**29** and (*R*,*R*)-**31** in moderate to good yields.

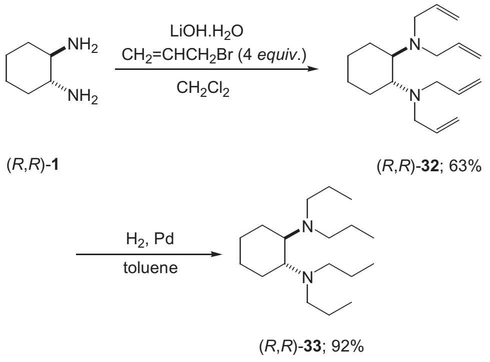


Scheme 8. Synthesis of diamine (*R*,*R*)-**22**.

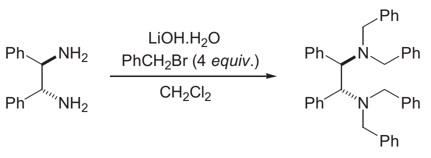


Scheme 9. Synthesis of diamines (*R*,*R*)-**25**, (*R*,*R*)-**27**, (*R*,*R*)-**29** and (*R*,*R*)-**31**.

We were next interested in the synthesis of tetraallylsubstituted diamine (*R*,*R*)-**32** as this should allow access to the tetrapropylcyclohexyldiamine (*R*,*R*)-**33** through simple hydrogenation. Sequential addition of 4 equiv of allyl bromide and lithium hydroxide monohydrate to the diamine (*R*,*R*)-**1** gave the tetraallylcyclohexyldiamine (*R*,*R*)-**32** in 63% yield. This was easily converted into the required tetrapropylcyclohexyldiamine (*R*,*R*)-**33** in good yield (92%) by hydrogenation at atmospheric pressure using palladium-on-charcoal as the mediator (Scheme 10). It is worthy of note that this particular diamine (*R*,*R*)-**33** cannot be synthesised directly by addition of propyl iodide to the diamine (*R*,*R*)-**1** as E2



Scheme 10. Synthesis of diamines (*R*,*R*)-**32** and (*R*,*R*)-**33**.



(*R*,*R*)-**2**

(*R*,*R*)-**34**; 62%

Scheme 11. Synthesis of diamine (*R*,*R*)-**34**.

elimination of propyl iodide appears to be the major pathway under these reaction conditions.

To ensure that this methodology was not solely dependent on the structural nature of the cyclohexyldiamine (*R*,*R*)-**1**, we additionally chose to convert the (*R*,*R*)-diphenylethylene diamine **2** into the corresponding tetrabenzyl diphenylethylene diamine (*R*,*R*)-**34** using our sequential addition procedure (Scheme 11). This reaction was efficient and gave the required diamine (*R*,*R*)-**34** in 62% yield.

In conclusion, we report an efficient and practical route to the synthesis of symmetrically substituted diamines (*R*,*R*)-**12**, (*R*,*R*)-**22**, (*R*,*R*)-**23**, (*R*,*R*)-**25**, (*R*,*R*)-**27**, (*R*,*R*)-**29**, (*R*,*R*)-**31**, (*R*,*R*)-**32**, (*R*,*R*)-**33** and (*R*,*R*)-**34** using a sequential substitution reaction mediated by lithium hydroxide monohydrate. This single-step process is particularly efficient and cost-effective since each diamine is derived from four sequential *N*-alkylations. Without the need for reductive methods (and the subsequent use of lithium aluminium hydride and/or sodium borohydride) this methodology appears to be a safer alternative to reductive amination especially when performed on a larger scale.

2. Representative experimental procedures

2.1. (+)-(*R*,*R*)-*N*,*N*,*N*′,*N*′-tetrabenzyl-1,2-diaminocyclohexane 22

(*R*,*R*)-1,2-Diaminocyclohexane (*R*,*R*)-**1** (2.00 g, 17.5 mmol) in dichloromethane (20 mL) was pre-cooled to 0 °C using an ice bath. Benzyl bromide (12.59 g, 8.74 mL, 73.5 mmol) was added to this stirred solution. After 1 h, lithium hydroxide monohydrate (0.75 g, 18.0 mmol) was added and three further additions were performed at hourly intervals until all 4 equiv of lithium hydroxide monohydrate had been added (3.00 g, 72.0 mmol). The solution was stirred for a further 6 h. Water (10 mL) was added and the resulting layers separated. The aqueous layer was washed with dichloromethane (2 × 50 mL) and the combined organic extracts were dried over chipped sodium hydroxide pellets and concentrated under reduced pressure. The residue was purified by flash column chromatography, initially eluting with light petroleum (40–60 °C)/diethyl ether (9:1), then diethyl ether/chloroform (1:1) to give (+)-(*R*,*R*)-*N*,*N*,*N*′,*N*′-tetrabenzyldiaminocyclohexane (*R*,*R*)-**22** (6.47 g, 77%) as a white crystalline solid; R_F [(diethyl ether/chloroform) 1:1] 0.49; $[\alpha]_D^{22}$ +36.0 (*c* 0.5, $CHCl_3$); υ_{max} (film)/cm^{-1} 2854 (CH), 1600 (Ph) and 1492 (Ph); mp 122 °C; δ_H (270 MHz, $CDCl_3$) 7.39 (8H, d, $J = 5.7$ Hz, 8 × CH; Ph), 7.19 (12H, m, 12 × CH; Ph), 3.76 (4H, d, $J = 13.9$ Hz, 4 × CH–Ph), 3.35 (4H, d, $J = 13.9$ Hz, 4 × CH–Ph), 2.68 (2H, br s, 2 × NCH), 2.08 (2H, m, 2 × CH), 1.72 (2H, m, 2 × CH) and 1.05 (4H, m, 4 × CH); δ_C (100 MHz, $CDCl_3$) 140.6, 128.9, 127.9, 126.5, 58.2, 53.2, 25.9 and 24.9 (Found MH^+, 474.3106. $C_{34}H_{39}N_2$ requires MH^+ 475.3108).

Acknowledgements

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