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Using ruthenium-catalysed propargylic substitutions for the efficient syntheses of rotaxanes

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Abstract—This Letter describes an efficient method—one that takes advantage of hydrogen bond-guided self-assembly and ruthenium-catalysed propargylic substitution—for the preparation of rotaxanes. The substitution reactions of a pseudorotaxane with a diverse range of heteroatom- and carbon-atom-centred nucleophiles were catalysed by the $[(Cp^*)RuCl(SMe)]_2$ complex to furnish rotaxanes in good yields.

Rotaxanes are mechanically interlocked molecules comprising a dumbbell-like component and a macrocycle.[1] To take advantage of their unique structures and properties, many methods for synthesising rotaxanes have been developed in recent years, including clipping,[2] end-capping,[3] slipping,[4] modification of [1]rotaxanes,[5] end-closing[6] and shrinking[7] strategies. Rotaxanes have potential applicability as components within molecular machines and devices.[1] Because the types of functional groups present in rotaxanes can affect their physical properties, it is desirable to devise synthetic methods so that rotaxanes possessing a variety of functionalities can be derived from a common intermediate.

The majority of rotaxane syntheses reported previously have relied upon the use of a single type of reaction. In addition, several end-capping and clipping approaches towards rotaxanes have been performed with subsequent stopper modification, but these methods have also utilised only one type of reaction. Stoddart and co-workers described the transformation of phosphonium groups as temporary stopper units of the axle into bulky alkenes through Wittig reactions.[8] Leigh developed a new strategy based on the replacement of a mechanically interlocked auxiliary through transesterification.[9] Kihara and Takata exchanged a stopper moiety through the use of a Tsuji–Trost allylation reaction.[10] We developed an efficient method for rotaxane preparation using acetylene–dicobalthexacarbonyl complexation as an initial end-capping approach towards rotaxanes with several subsequent stopper modifications,[11] such as Pauson–Khand and Nicholas reactions. Although robust, this methodology has the disadvantages that (a) not every substrate is applicable to each modification reaction and (b) it requires two steps to construct and modify a rotaxane.

Nishibayashi and co-workers have developed a range of ruthenium-catalysed substitution reactions of propargylic alcohols with various nucleophiles, including alcohols, amines and amides.[12] These reactions proceed via ruthenium–allenylidene complexes as intermediates formed from the catalyst and the propargylic alcohol; subsequently, the nucleophiles regioselectively attack the reactive C_δ atom in the intermediate. Here, we describe a novel method for end-capping pseudorotaxanes (prepared using the established[13] self-assembled secondary ammonium ion/crown ether synthon) based on ruthenium-catalysed propargylic substitution reactions with various nucleophiles and the direct introduction of various functionalities (Fig. 1).

The preparation of the key secondary ammonium salt[11] **2**·PF_6 was initiated through condensation of aldehyde **1** and 3,5-dimethylbenzylamine to afford the corresponding imine. Reduction of the imine, followed by salt formation, produced the ammonium salt **2**·PF_6, which possessed a bulky aryl group on one end and a propargyl alcohol moiety at the other. The feasibility of

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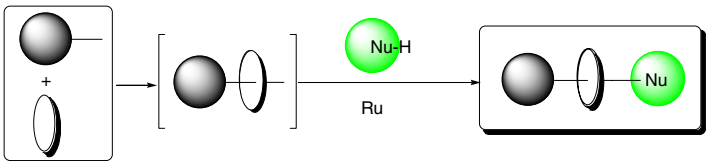
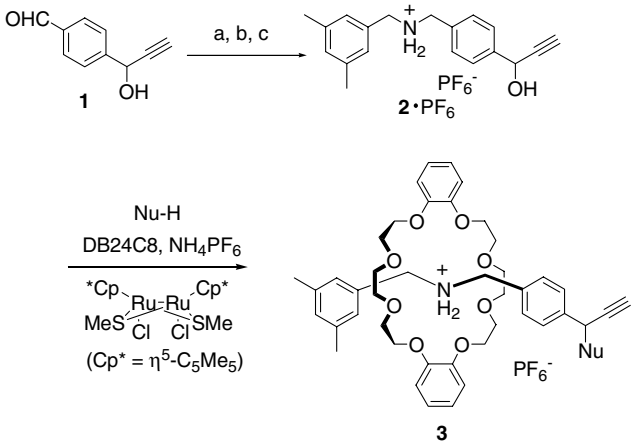
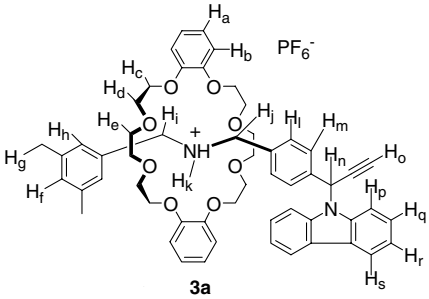


Figure 1. Cartoon representation of the use of nucleophilic substitution for the synthesis of various rotaxanes from the same pseudorotaxane intermediate.

performing ruthenium-catalysed nucleophilic substitution reactions with the pseudorotaxane formed from the ammonium ion **2**·PF_6 and dibenzo[24]crown8 (DB24C8) was validated through an initial experiment using carbazole as the nucleophile and dichloroethane as the solvent. We isolated the corresponding rotaxane **3a** in good yield, even though the ammonium salt **2**·PF_6 is insoluble in dichloroethane in the absence of the crown ether; that is, **2**·PF_6 is solubilised through complexation with DB24C8 and the catalyst reacts predominantly with the solvated pseudorotaxane. The preparation of **3a** suggests that (a) the interaction between DB24C8 and the secondary ammonium group is strong under the reaction conditions and (b) the carbazole group is sufficiently bulky to prevent dissociation of the components (Scheme 1). The structure of **3a** was determined from spectroscopic and analytical data. The ^{1}H NMR spectrum of **3a** (Fig. 2) suggested that it had a rotaxane structure. The most characteristic evidence for the formation of the rotaxane is the large downfield shifts of the signals for the benzylic protons (δ 4.3 and 4.6 ppm). The shifts are consistent with those reported previously for related ammonium ion/DB24C8 complexes.[3,6,8,10,11,13] Moreover, the signals of the methylene protons of the crown ether moiety were split into several sets of resonances because of the diastereotopicity induced by the loss of planar symmetry and the presence of the chiral centre at the carbazole terminus; as expected, these signals did not coalesce at temperatures below 125 °C in DMSO-d_6. The FAB mass spectrum of **3a** supported the rotaxane structure, represented by a peak for the $[M-PF_6^-]^+$ ion at m/z 877.[14]



Scheme 1. Reagents and conditions: (a) 3,5-dimethylbenzylammonium chloride, Et_3N, $MgSO_4$; (b) $NaBH_4$; (c) HPF_6 (60% for three steps).



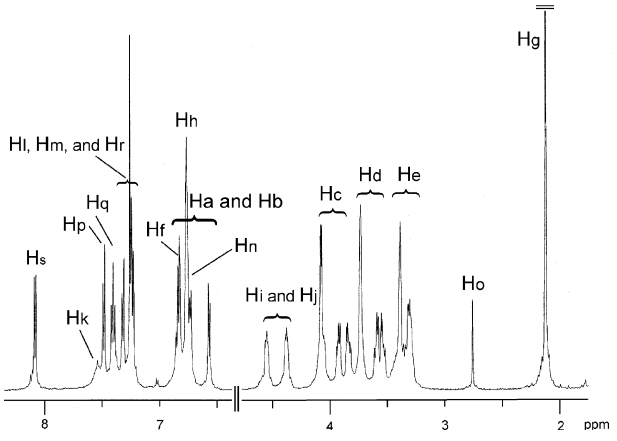


Figure 2. Partial ^{1}H NMR spectrum of rotaxane **3a**.

Next, we attempted to optimise the conditions for this transformation. Decreasing the amount of carbazole decreased the rotaxane yield (Table 1, entries 1–3). Interestingly, decreasing the amount of DB24C8 for 4–2 equiv relative to the ammonium salt **2**·PF_6 (cf. entries 1 and 4) had a significant impact, presumably because NH_4^+ ions, which we added to the reaction mixture as a co-catalyst (see below), competed with the $\mathbf{2}^+$ ion for complexation with DB24C8; that is, a greater excess of DB24C8 ensured complete complexation of **2**·PF_6 and

Table 1. Synthesis of rotaxane **3a** through ruthenium-catalysed propargylic substitution[a]

Entry	Carbazole (equiv)	DB24C8 (equiv)	NH_4PF_6 (equiv)	Temperature (°C)	Time (h)	Yield[b] (%)
1	5	4	0.05	60	1	97
2	3	4	0.05	60	1	90
3	2	4	0.05	60	1	76
4	5	2	0.05	60	1	86
5	5	4	0.05	40	1	90
6	5	4	0.05	60	2	84
7	5	4	0	60	1	81

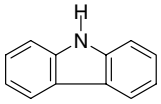
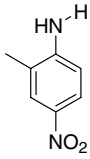
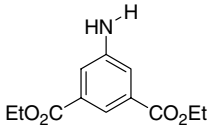
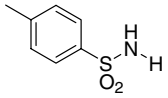
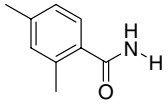
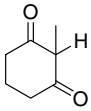
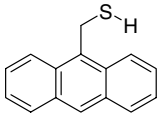
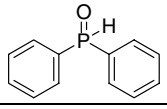
[a] 5 mol % of ruthenium catalyst was used.
[b] NMR spectroscopic yield.

improved the yield. A lower temperature (cf. entries 1 and 5) and a longer reaction time (cf. entries 1 and 6) both decreased the yield of the rotaxane slightly. The presence of NH_4PF_6 was necessary to achieve an excellent yield (cf. entries 1 and 7). Nishibayashi reported that the addition of ammonium tetrafluoroborate (NH_4BF_4) affords a cationic thiolate-bridged diruthenium complex with a vacant site after exchange of anions between the catalyst and NH_4BF_4, which improves the catalytic activity.[12e] In our case, because we already had hexafluorophosphate (PF_6^-) anion present as a counter-anion of the ammonium ion **2**, we suspected that we might obtain a cationic thiolate-bridged diruthenium complex even in the absence of added NH_4PF_6 or NH_4BF_4. In practice, however, the absence of NH_4PF_6 decreased the yield. It is likely that ion exchange of the chloride ion from the ruthenium complex to the NH_2^+ centre of the $\mathbf{2}^+$ ion[15] disrupted the complexation of the $\mathbf{2}^+$ ion with DB24C8 in the absence of NH_4PF_6.

Table 2 presents the results for the ruthenium-catalysed substitution reactions we performed using various nucleophiles in the presence of the ammonium salt $\mathbf{2}\cdot PF_6$ and DB24C8. The reaction displayed good substrate generality. A 2-substituted aniline derivative was converted to the corresponding rotaxane **3b** in excellent yield (entry 2), whereas the reaction of a 3,5-disubstituted aniline derivative afforded its corresponding rotaxane **3c** in only moderate yield (entry 3). These results agree well with previous findings that the existence of electron-donating groups on the aniline aromatic ring decreases the reaction rate for propargylic amination, whereas the presence of electron-withdrawing groups on the 2 and 4 positions of aniline improves the substitution reaction.[12e] A sulfonamide and an amide both reacted efficiently with the pseudorotaxane, with the corresponding rotaxanes **3d** and **3e**, respectively, being isolated in 60% and 64% yields, respectively (entries 4 and 5). We also investigated the propargylic substitution reactions of the pseudorotaxane with carbon-, sulfur- and phosphorus-atom-centred nucleophiles, obtaining the rotaxanes **3f**–**h**, respectively, in good to moderate yields (entries 6–8, respectively). For the phosphine oxide, we performed the reaction at low temperature to avoid the double phosphinylation reaction that proceeds at high temperature.[12] When we used 2-methylfuran and benzyl mercaptan as nucleophiles, although the corresponding carbon–carbon and sulfur–carbon bond formation reactions proceeded, the introduced stopper groups were insufficiently large to prevent dethreading of the DB24C8 moiety; that is, we did not isolate rotaxanes from these reactions.

Many efficient and convenient transformations of organic compounds are mediated by transition metal catalysts; some of these reactions have been applied effectively to rotaxane syntheses and modifications.[10,16] Because it is important that the interactions between the axle and wheel be maintained under the reaction conditions, when using pseudorotaxane systems based on ammonium ions and crown ethers, only catalysts that are active under acidic and/or neutral conditions are applicable to such types of rotaxane syntheses. Furthermore, selection of the nucleophile is critical to avoid deprotonation of the secondary ammonium ion, the recognition site of the axle moiety, in these kinds of nucleophilic substitution reactions.

Table 2. Syntheses of rotaxanes **3** through ruthenium-catalysed propargylic substitutions[a]

Entry	Nu–H	Product	Yield[b]
1		**3a**	97 (83)
2		**3b**	95 (75)
3		**3c**	79 (54)
4		**3d**	87 (60)
5		**3e**	87 (64)
6		**3f**	88 (72)
7		**3g**	60 (44)
8[c]		**3h**	75 (53)

[a] Reaction conditions: A mixture of $\mathbf{2}\cdot PF_6$ (0.235 mmol), DB24C8 (4 equiv), the nucleophile (5 equiv), the catalyst (0.05 equiv) and NH_4PF_6 (0.1 equiv) in dichloroethane was heated at 60 °C for 1 h, except for entry 8.

[b] NMR spectroscopic yield; the values in parentheses are isolated yields.

[c] This reaction was performed at 40 °C.

In summary, we have constructed a number of rotaxanes featuring various functionalities through the application of ruthenium-catalysed propargylic substitution reactions. We are exploring the scope of this new technique for rotaxane synthesis in our ongoing studies.

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14. A solution of **2·PF$_6$** (100 mg, 0.235 mmol) and DB24C8 (422 mg, 0.94 mmol) in dichloroethane (5 ml) was added to a suspension of Met-DIRUX (7.5 mg, 12 μmol) and ammonium hexafluorophosphate (3.8 mg, 23.5 μmol) in dichloroethane (2 ml); after the addition of carbazole (197 mg, 1.18 mmol), the mixture was heated at 60 °C for 1 h. After cooling to room temperature, the mixture was evaporated to dryness to give a solid, which was washed with a mixture of hexane and toluene (2:1). Chloroform was added to the solid; the resulting heterogeneous mixture was filtered though celite and the filtrate was concentrated. Purification of the residue through column chromatography on silica gel ($CHCl_3$/EtOAc, 1:1) gave a solid, which was then dissolved in acetone/water (60 ml, 2:1). Ammonium hexafluorophosphate (0.156 g, 940 mmol) was added to the solution and the mixture stirred for 2 h at room temperature. After evaporation of the acetone, the precipitate was filtered off and washed with water to afford rotaxane **3a** (200 mg, 83%). IR (KBr) ν_{max} (cm^{-1}): 1057, 1106, 1252, 1325, 1453, 1596, 1624, 2128, 2923, 3161. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.13 (s, 6H), 2.77 (d, $J = 2.5$ Hz, 1H), 3.24–3.46 (m, 8H), 3.50–3.63 (m, 4H), 3.70–3.78 (m, 4H), 3.80–3.97 (m, 4H), 4.02–4.16 (m, 4H), 4.32–4.43 (m, 2H), 4.49–4.62 (m, 2H), 6.53–6.62 (m, 2H), 6.70–6.90 (m, 10H), 7.21–7.35 (m, 6H), 7.36–7.45 (m, 2H), 7.45–7.64 (m, 4H), 8.05–8.13 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.06, 48.42, 51.90, 52.52, 67.88, 68.18, 69.80, 70.05, 70.37, 70.51, 76.37, 78.13, 110.10, 112.48, 112.64, 119.73, 120.24, 121.55, 121.57, 123.41, 125.73, 126.51, 126.80, 129,78, 130.58, 131.19, 131.88, 137.54, 138.22, 139.23, 147.26. FAB-MS *m/z*: 877 $[M-PF_6^-]^+$.
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