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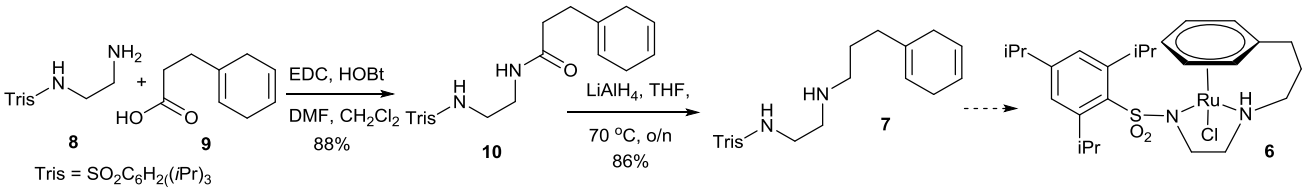

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An alternative route to tethered Ru(II) transfer hydrogenation catalysts.

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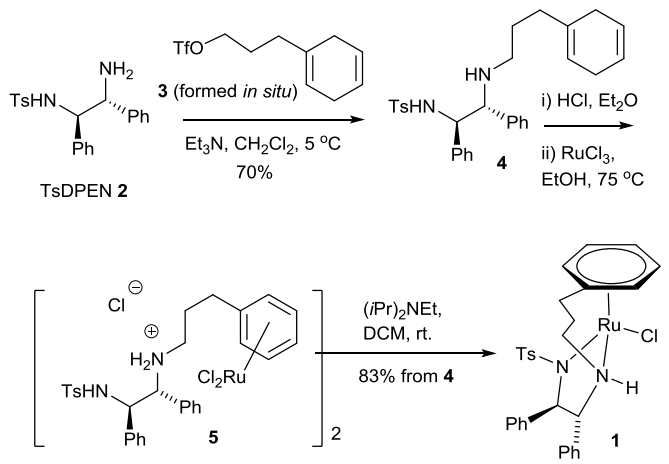
ABSTRACT

A new route towards a series of tethered η^6-arene/Ru(II) catalysts for use in the transfer and pressure hydrogenation of ketones and aldehydes to alcohols is reported. The route proceeds through the formation of an amide from the diamine precursor, followed by reduction, rather than the direct alkylation of the diamine. This has the advantage that dialkylation of the amine is avoided during the synthesis. Through this new route, both racemic and enantiomerically-pure η^6-arene/Ru(II) tethered catalysts can be prepared in high yield.

Introduction.

Enantiomerically pure tethered η^6-arene/Ru(II) complexes of type **1** have been widely applied to the asymmetric reduction of ketones and imines to alcohols and amines respectively.[1] This class of catalyst was first reported by Wills *et al*. in 2005[2] and an improved synthesis by Wills *et al*./Johnson Matthey was reported in 2012.[3] Several other groups have also reported derivatives of the original tethered complex **1** and these have also been tested in a number of synthetic applications.[1,4] Complex **1** may be prepared on a large scale through an established reaction sequence in which a diene is attached to the diamine precursor (TsDPEN) through an S_N2 substitution reaction of monotosylated diamine **2** with triflate **3** to form ligand **4** (Scheme 1).[3] In some cases, a tosylate or mesylate leaving group may be employed in this step. Complex **1** is subsequently formed *via* a dimer **4** which may isolated or converted directly into the monomer without isolation.[2,3]

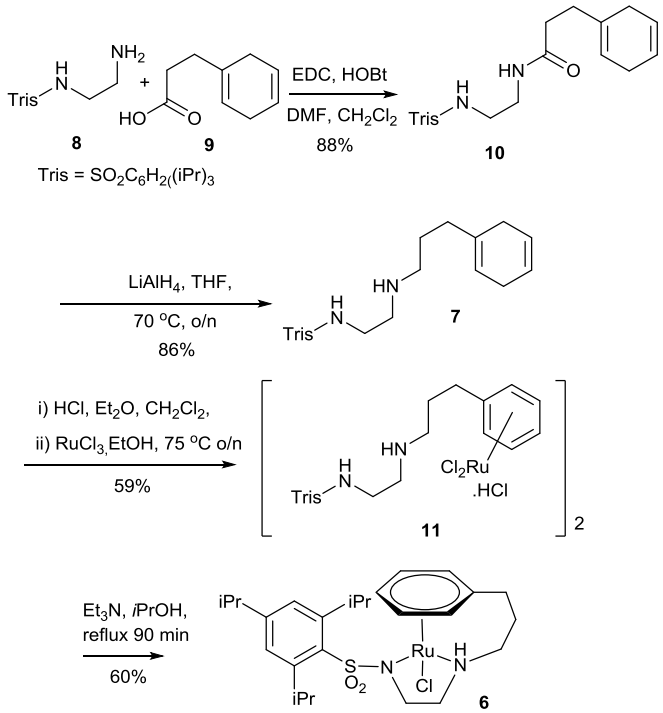


Scheme 1. Established route to tethered complexes 1.[5]

Whilst this route works well for complex **1**, the synthesis of a racemic derivative of **1** (i.e. in which the two phenyl groups were absent from the diamine unit), which is a valuable catalyst for general reduction applications,[5] has proved to be more challenging, and low yields were achieved upon cyclisation of the corresponding intermediate dimer to the required product.[3a] As it was suspected that this was due to the high polarity of the racemic complex compared with **1**, we sought to compensate for this by replacing the *p*-toluenesulfonyl group with a more lipophilic substituent. In the event, we first attempted to form ligand **7** from the reaction between **3** and TrisEN **8**[6] using the established alkylation method. Unfortunately, and in contrast to TsDPEN **2**, the reaction was complicated by a competing dialkylation reaction of TrisEN **8**. The use of tosylate and mesylate derivatives of **3** did not provide a solution as these were either unreactive or also gave competing dialkylation products. Hence, an alternative approach was required.

Results and Discussion.

Towards identifying a solution to this challenge, we considered the use of an amide intermediate, therefore avoiding issues of dialkylation. Firstly, amine **8** was coupled with acid **9**[7] to form amide **10**, which was subsequently reduced to amine **7** using lithium aluminium hydride. Subsequent complexation to the dimer **11** followed by conversion to **6** upon treatment with base, following the established protocols for this stage of the tethered catalyst synthesis, completed the development of the improved synthetic route (Scheme 2).



Scheme 2. Amide route to racemic tethered complex **6** *via* amides **10** and **13**.

Through a similar process but reversing the position of the amide, amine **7** was also formed through the combination of carboxylic acid **12** (prepared from glycine) with amine **13** to give **14**, followed by reduction, representing a further amide-based approach to the required ligands (Figure 1). The high yields obtained in each of the final steps reflects the much greater compatibility of the more lipophilic ligand **7** (compared to the NTs analogue)[3a] with the reaction conditions used.

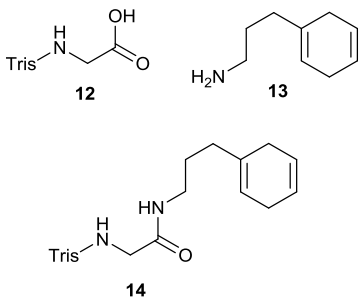
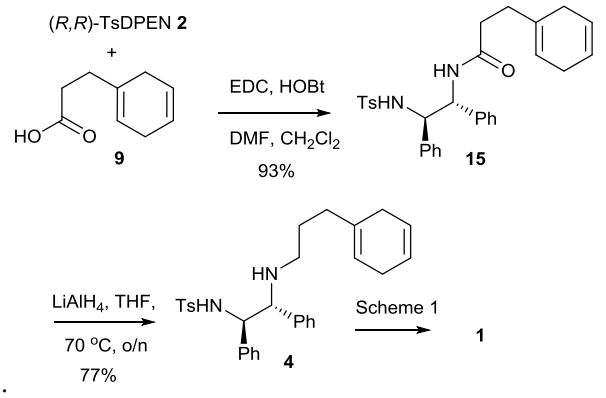


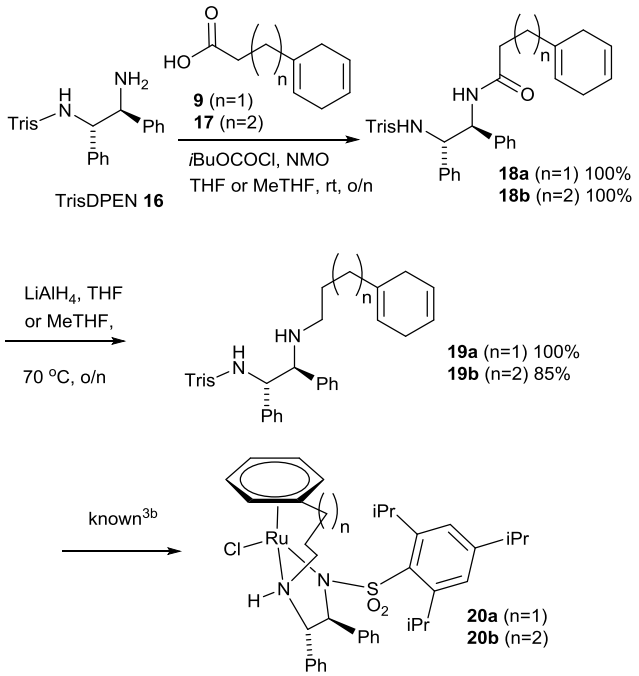
Figure 1. Amide intermediate **14** and precursors **12** and **13**.

The amide approach was also demonstrated to be effective for the synthesis of several known *asymmetric* catalysts[2,3] (Scheme 3) and was applied successfully to the ligand precursor for **1**. In this case, amide **15** was formed from TsDPEN **2** and reduced to **4** in 93% and 66% yields respectively for each step. Throughout this study, EDC/HOBt was found to be an efficient reagent combination for the amide formation step of the sequence.



Scheme 3. New route to hindered asymmetric tethered complexes *via* an amide.

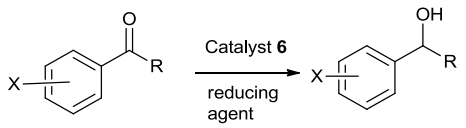
In addition, some highly hindered (also known) derivatives were also prepared by this method (Scheme 4). The extra level of steric hindrance and the variation in tether length can, in some cases, moderate the level of selectivity and activity of the complexes. In this synthesis, (*S*,*S*)-TrisDPEN **16** was first coupled with either acid **9** or **17** to give the amides **18a** and **18b** respectively in good yields. Subsequent reduction to the known amines **19a/b** proceeded cleanly; these are known precursors to the hindered tethered catalysts **20a/b** following an established method.[3b] In the synthesis of **4**, **19a** and **19b** by this method, the 1H NMR spectra indicated the formation of a single diastereoisomer of product in each case, suggesting that no epimerisation takes place at either chiral centre during the reduction reactions.



Scheme 4. New route to hindered asymmetric tethered complexes *via* an amide intermediate.

The new racemic complex **6** worked efficiently as a catalyst for the reduction of acetophenone and several aldehydes (Table 1). In acetophenone reduction, full conversion could be achieved using as little as 0.1 mol% catalyst with either hydrogen gas or formic acid/triethylamine as the reducing agent. In all cases except entry 2, the reductions worked effectively without the requirement for the addition of a further reagent, such as a base, to activate the catalyst. In the case of the hydrogenations, ionization takes place in methanol solution.[3a,8] The reasons for the lower conversion in entry 2 are not clear however reactions in isopropanol are reversible and it may be the case that the reaction had not proceeded with full conversion even over the extended reaction time. Aldehyde reduction worked equally well and the loading could be reduced further but at the cost of a small amount of formylated side product. A series of aldehydes were reduced in full within 5h using 0.2 mol% catalyst and with high selectivity for reduction of the carbonyl group over other sensitive functions in the molecule. This preference from the selective reduction of the more reactive and polar C=O bond in the aldehyde is in common with previous observations using this class of substrate.[3a]

Table 1. Application of catalyst **6** to the racemic reduction of acetophenone and aldehydes.



entry	Substrate	Reagent, Solvent S/C	t / h S]	T/ °C	Conv /%
1	PhCOMe	FA/TEA 400:1	5h 1M	40	98%
2	PhCOMe	*i*PrOH 400:1	29h 0.1 M	40	26%,
3	PhCOMe	30 bar H_2 MeOH 500:1	24h 1 M	60	99%
4	PhCOMe	30 bar H_2 MeOH 1000:1	24h 0.5M	60	99%
5	PhCOMe	30 bar H_2 MeOH 1000:1	24h 1M	60	99%
6	PhCHO	FA/TEA 500:1	5h, 7h 1.5M	40	86, 100
7	PhCHO	FA/TEA 1000:1	5h 1.5M**	60	96%, 4%*
8	PhCHO	FA/TEA 5000:1	5h 1.5M**	60	89%, 10%*
9	PhCHO	FA/TEA 10,000:1	24h 1.5M**	60	56%, 18%*
10	PhCHO	FA/TEA 20,000:1	24h 1.5M**	60	37%, 9%*
11	*p*-Br C_6H_4CHO	FA/TEA 500:1	5h 1.5M	40	100
12	*p*-NO_2 C_6H_4CHO	FA/TEA 500:1	5h 1.5M	40	99
13	*p*-iPr C_6H_4CHO	FA/TEA 500:1	5h 1.5M	40	99
14	*p*-OMe C_6H_4CHO	FA/TEA 500:1	5h 1.5M	40	100
15	PhCH=CH CHO	FA/TEA 500:1	5h 1.5M	40	96

* Formylated alcohol. ** contains DMF (*ca* 0.25 mL).

The route was further applied to the preparation of catalyst precursor ligands **21**[9] and **22**, which contains an aromatic ring in place of the diene, i.e. *via* the amides **23** and **24** respectively in good yields (Figure 2). Intermediate **21** has been employed to form reduction catalysts such as **1** using an arene-displacement strategy recently reported by Wills *et al.*[10]

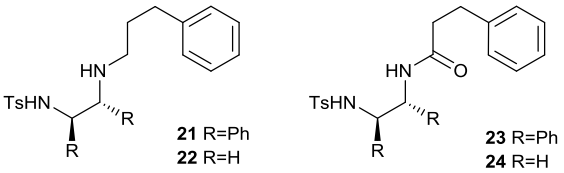


Figure 2. Precursors to the synthesis of complex **1** and its racemic analogue via an arene-exxchange route.[9]

In conclusion, we have developed an alternative route to a series of tethered Ru(II) catalysts using an amide intermediate, which avoids the problems of multiple alkylation which were encountered using the existing alkylation strategy. Through this approach, it was possible to prepare a highly effective racemic catalyst (**6**) for the reduction of ketones and aldehydes, which may also be employed with hydrogen gas or with a combination of formic acid and triethylamine. Using this method, complex **6** was prepared cleanly and in high yield without the complications of side-product formation. The clean reductions, using an economical metal source, provide an advantage over more established stoichiometric methods. The approach can also employed to form known asymmetric tethered catalysts in high yield.

Acknowledgments

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Supplementary Material

Experimental details for the synthesis of intermediates and catalysts, ketone and aldehyde reductions and characterization data are available.

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