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Metal–ligand bifunctional activation and transfer of N–H bonds†

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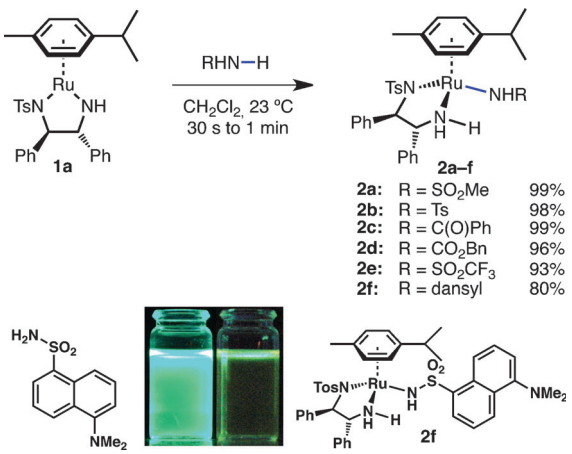
The concept of metal–ligand bifunctionality can be employed for an efficient activation of N–H bonds by well-defined ruthenium amido complexes. An enantioselective catalytic aza-Michael reaction was developed on the basis of this process, which gives rise to indoline β-amino acids.

The development and improvement of modern transition metal mediated and catalysed nitrogen transfer reactions represents an important task in the synthesis of aminated molecules.[1,2] Often, the key step requires formation of defined amide complexes *via* oxidative insertion of a transition metal into the N–H bond of an amine or amide, and these transformations have reached an impressive level of selectivity.[3,4] An alternative activation circumventing oxidation state changes could be achieved by a novel *bifunctional N–H activation mode*, which is cooperatively performed by a metal and a ligand as established for related activation of small molecules.[5] Herein, we report such a direct bifunctional N–H activation of amides and its subsequent use in a conceptually novel catalytic aza-Michael reaction.[6]

We envisioned that unsaturated transition metal amido complexes should readily activate N–H bonds. Indeed, treatment of Noyori's formally unsaturated 16e$^-$ complex **1a**[7] with various amides at room temperature instantaneously led to irreversible formation of the corresponding complexes **2a–f**, which in all cases were obtained as single stereoisomers.[8] In addition to methanesulfonamide, the corresponding complexes of tosylamide, benzamide, benzylcarbamate, and trifluoromethanesulfonamide were successfully isolated in nearly quantitative yields (Scheme 1). The course of the N–H activation could also be monitored for the reaction of **1a** with one equivalent of dansyl amide which within seconds results in the formation of ruthenium complex **2f** accompanied by quenching of the characteristic fluorescence of the free sulfonamide (Scheme 1).[9] A reaction with deuterated tosylamide TosND$_2$ led to incorporation of two deuterium atoms into the complex, however, fast deuterium scrambling resulted in a statistical distribution. This observation suggests related acidity for the N–H groups in **2b**.[9]



Scheme 1 Metal–ligand bifunctional N–H activation of amides (above) and samples of free dansyl amide and **2f** at 360 nm (below).

In order to determine the molecular basis of the N–H activation, products **2a** and **2e** were analysed by X-ray crystallography (Fig. 1).[10] The absolute configuration of the ruthenium atoms is reminiscent of related complexes from formal addition of other polarised molecules across the polar Ru–N bond in **1**.[5a–c,7] The newly formed Ru–N bonds are similar in length indicating that no anion effect is present despite the significantly different pK_a values of the free amides.[11] It is important to note that while all amide complexes **2** are stable under neutral conditions under air in solid state and solution, they readily engage in retrosynthetic loss of amide in the presence of an alkoxide base. Complex **1a** can therefore be assumed as a chiral transition metal template for the reversible storage of an amide group through metal–ligand bifunctional N–H activation.

The observed reversibility of this process prompted us to investigate complex **1a** as a catalyst for N–H activation and subsequent transfer to a prochiral group. To provide the proof of principle we chose an intramolecular aza-Michael reaction[12] of **3a** to **4a** (Table 1), an indoline analogue of β-homoproline.[13] While complex **1a** was indeed found to be an efficient catalyst

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† Electronic supplementary information (ESI) available. Experimental procedures and characterisation and spectral reproduction for new compounds. CCDC 772672 (**2a**), 772673 (**2e**) and 780370. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc10999e

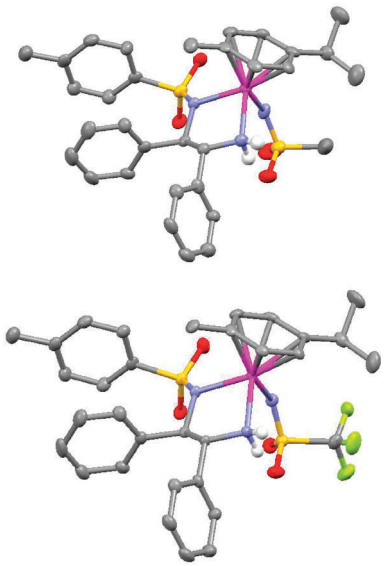
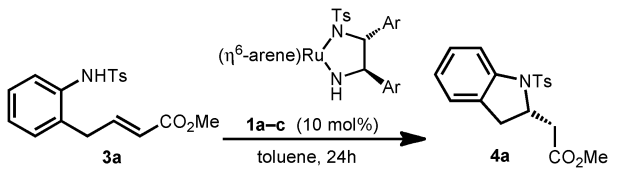


Fig. 1 Crystal structures of complexes **2a** and **2e**. Except for the NH_2 groups, hydrogen atoms are omitted for clarity.

Table 1 Catalyst optimisation for cyclisation of **3a** to **4a**



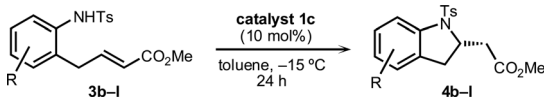
Entry	η^6-Arene	Ar	Catalyst	T^a/°C	Yield^b [%]	ee^c [%]
1	Cymene	Ph	**1a**	25	70	30
2	Cymene	Ph	**1a**	5	40	43
3	C_6Me_6	Ph	**1b**	25	99	34
4	C_6Me_6	Ph	**1b**	5	90	45
5	C_6Me_6	Ph	**1b**	−15	69	53
6	C_6Me_6	2,4,6-$C_6H_2Me_3$	**1c**	0	95	75
7	C_6Me_6	2,4,6-$C_6H_2Me_3$	**1c**	−15	84	81
8	C_6Me_6	2,4,6-$C_6H_2Me_3$	**1c**	−25	82	80

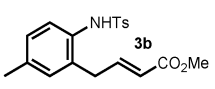
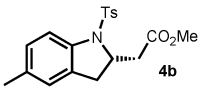
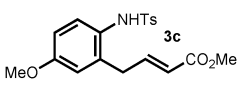
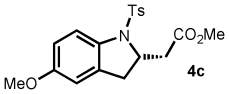
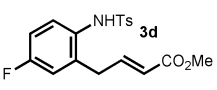
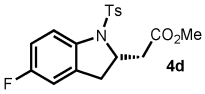
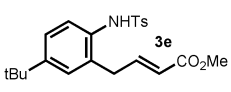
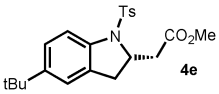
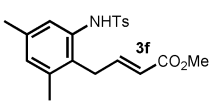
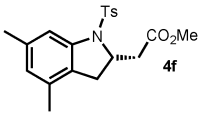
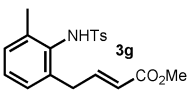
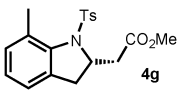
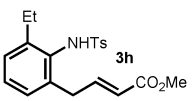
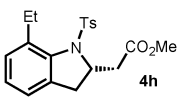
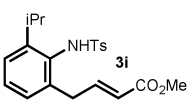
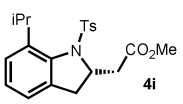
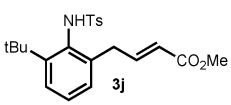
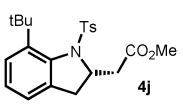
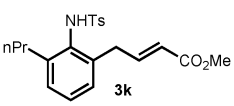
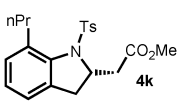
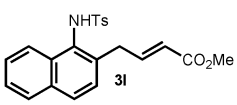
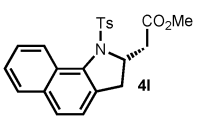
[a] Temperature of the external cooling bath. [b] Isolated yield after purification. [c] Determined by chiral analytical HPLC.

for this reaction (entries 1 and 2), steric optimisation was required in order to achieve higher product ee. To this end, substituting the η^6-coordinated cymene group with hexamethyl benzene (**1b**) under concomitant lowering of the temperature to −15 °C[14] allowed for a rise to 53% ee (entries 3–5). The use of a diamine ligand with sterically more demanding mesityl substituents (**1c**) led to a maximum ee of 81% at −15 °C (entries 6 and 7). Further decrease in temperature had no effect (entry 8). Cyclization of the corresponding (*Z*)-alkene led to a product with the same absolute configuration in 78% ee suggesting identical alkene face selectivity in the enantioselection. The ethyl ester derivative of **3a** gave 80% yield and 72% ee, while the sterically more congested *tert*-butyl ester did not lead to any conversion.

Next, a series of methyl esters was investigated in the metal–ligand bifunctional catalysis of N–H activation/N–H transfer chemistry (Table 2). Here, 4-substitued substrates gave the corresponding indoline derivatives **4b–e** in very good yields

Table 2 Enantioselective amidation of acrylates *via* N–H activation



Entry	Substrate	Product	Yield^a [%]	ee^b [%]
1			80	83
2			82	85
3			89	80
4			89	76
5			99	61
6			94	94
7			97	95
8			94	93
9			99	96
10			94	97
11			94	93
12^c			95	−92

[a] Isolated yield after purification. [b] Determined by analytical HPLC at a chiral stationary phase. [c] Opposite catalyst enantiomer was employed.

with 76 to 85% ee (entries 1–4). Substrate **3f** with double meta-substitution displays high reactivity, but leads to lower enantioselection in the formation of **4f** (entry 5). Finally, 6-substituted substrates **3g–k** and the naphthalene derivative **4l** undergo cyclisation to **4g–l** in excellent yields with enantiomeric excesses of 93–97% (entries 6–11). For **3l**, use of the enantiomeric catalyst gave the other enantiomer of **4l** in 95% yield and 92% ee.

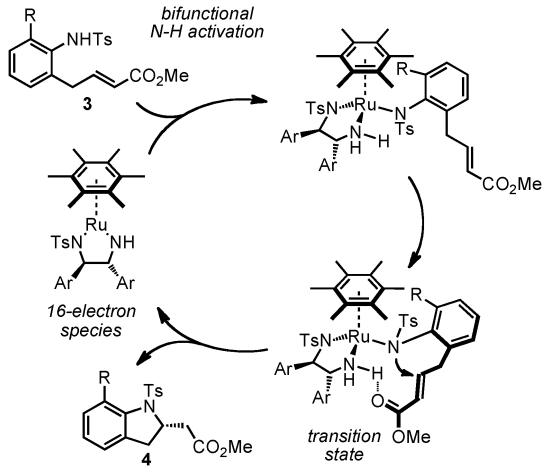


Fig. 2 Proposed catalytic cycle.

The absolute configuration for product *ent*-**4l** was determined to be *R* based on the X-ray structure analysis of a derivative.[9,10] We tentatively assign an absolute (*S*)-configuration for all other products **4a–l** assuming an identical mode of enantioselection.

A possible mechanistic scenario starts with bifunctional N–H activation of the cyclisation precursor **3**, in a manner identical to the N–H activation of tosylamides described for the stoichiometric reactions (Scheme 1). It is followed by subsequent transfer of the amidato group onto the prochiral alkene to give cyclised **4** and regeneration of the active catalyst (Fig. 2). The transition state should proceed through a cyclic arrangement including hydrogen bonding[15] and is dominated by steric repulsion between the substituent at the arene ring of the substrate and the methyl groups at the arene ring of the ruthenium catalyst. Additional interaction should occur between the aryl substituent in the diamine backbone and the ester group, while the remote tosylamido group of the diamine ligand has no major influence on enantioselection.[9]

We have developed a new process for transition metal based bifunctional N–H activation within the coordination sphere of a defined amido–ruthenium complex, and a first successful application in enantioselective catalysis was demonstrated.

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