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Asymmetric Assisted Tandem Catalysis: Hydroamination followed by Asymmetric Friedel–Crafts Reaction from a Single Chiral *N,N,N′,N′*-Tetradentate Pyridylmethylamine-Based Ligand

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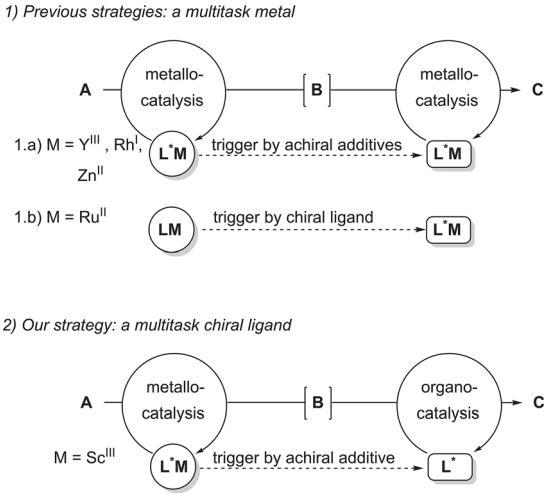
With the rising interest in asymmetric catalysis promoted by earth-abundant elements, a chiral ligand will undoubtedly be the most valuable unit of the catalyst. The first proof of concept of the use of a multitask chiral ligand in an asymmetric assisted tandem catalysis protocol that successively combines metallo- and organocatalytic processes is reported herein. In this protocol, the chiral ligand of the newly designed rare-earth catalyst of the first reaction is converted into a novel chiral organocatalyst for the second transformation by the simple addition of HCl. The observation of some enantioinduction in the tandem sequence—alkyne hydroamination followed by enantioselective Friedel–Crafts alkylation—confirms the relay of the chiral *N,N,N′,N′*-tetradentate ligand and the importance of its pyridylmethylamine scaffold.

One-pot catalysis, the incorporation of several distinct catalytic transformations into one single reaction sequence, is one of the most powerful synthetic tools in contemporary organic chemistry to rapidly introduce molecular complexity.[1] Compared with multi-stepwise catalytic transformations, this operation in a single vessel saves time and effort and reduces the cost of the synthesis by avoiding the need for intermediate workup and purification steps. Overall, this step-economical approach enhances significantly the efficiency and sustainability of the production of valuable target molecules. Among the different types of one-pot catalysis,[1] assisted tandem catalysis,[2] in which two consecutive and mechanistically distinct catalytic transformations are performed by one initial (pre)catalyst and for which the change in mechanism is triggered by the addition of a chemical reagent (or a change in the reaction conditions), offers one of the widest range of benefits to construct highly sophisticated compounds. It allows better control of the selectivity in each catalytic transformation by independent optimization of the reactions conditions. This point is central in asymmetric catalysis for which two mechanistically distinct asymmetric reactions require a different chiral environment around the catalytically active species. By avoiding detrimental interactions between two different catalytic species, this approach also allows the combination of mechanistically incompatible transformations. Moreover, it meets the demand for the greener use of a (metal) catalyst by the use of its, usually, rare and expensive noble metal component for multiple tasks. Whereas significant progress has been made in this field,[3] asymmetric applications of assisted tandem catalysis have been scarcely reported.[4] The reported systems so far rely on a multitask metal strategy in which the initial (chiral) metallocatalyst is converted into the second chiral catalyst of an identical metal source by the addition of an achiral additive[4a–d] (Scheme 1, 1 a) or a chiral ligand[4e] (Scheme 1, 1 b) to fine-tune the chiral environment in metallo–metallo-assisted tandem catalytic reactions. To our knowledge, the multiple use of chiral ligand in asymmetric assisted tandem catalysis by combining



Scheme 1. Schematic representation of the current strategies in asymmetric assisted tandem catalysis.

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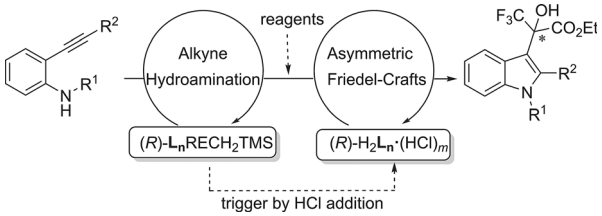
metallo- and organocatalytic processes has not been reported. With the growing interest in asymmetric catalysis promoted by earth-abundant elements,[5] a chiral ligand will undoubtedly be the most "precious" entity of the catalyst in the near future.

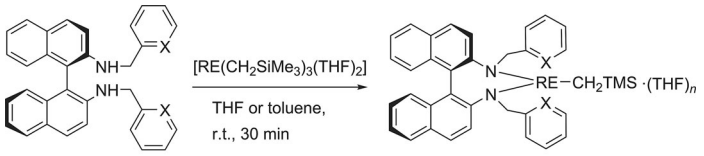
As part of a joint research program, we sought to develop such a novel strategy, in which the chiral ligand from the metallocatalyst of the first reaction would subsequently be transformed into the organocatalyst for the second reaction by the addition of an achiral additive (Scheme 1, 2). From our respective expertise,[6,7] and as proof of concept for the use of a multitask chiral ligand in asymmetric assisted-tandem catalysis, we focused our attention on a tandem sequence: metallocatalyzed alkyne hydroamination of 2-alkynylaniline derivatives followed by asymmetric organocatalyzed Friedel–Crafts (FC) alkylation, as described in Scheme 2. For



Scheme 2. Metallocatalyzed alkyne hydroamination followed by asymmetric organocatalyzed Friedel–Crafts alkylation as proof of concept for the use of a multitask ligand in asymmetric assisted tandem catalysis (L_n = chiral pyridylmethylamine-based multidentate ligand, RE = rare earth).

both targeted hydroamination and FC reactions, we planned to develop a new catalytic system derived from the same chiral pyridylmethylamine-based multidentate ligand that could form a well-defined rare-earth alkyl complex and that could act as a chiral Brønsted acid. The so-called pyridylmethylamine (pma) moiety has found valuable applications as a key (chiral) scaffold in various metallo- and organobased catalytic systems and, therefore, is a moiety of choice for the development of novel and efficient catalytic processes.[8] We hypothesize that the transformation of the initial and newly designed chiral rare-earth (RE) alkyl (pre)catalyst [(*R*)-L_nRECH_2TMS] into the organocatalyst [(*R*)-H_2L_n·$(HCl)_m$] could be triggered by the simple addition of hydrochloric acid. Herein, we report our preliminary results toward this goal.

Some of us have long been interested in the development of easily accessible, chiral, well-defined, and in situ generated binaphthylamidoalkyl rare-earth complexes for applications in catalytic, asymmetric intra- and intermolecular hydroamination reactions.[6d–h] In the context of this work, these successful results encouraged us to investigate the preparation of novel rare-earth alkyl complexes supported by an axially chiral binaphthylamine ligand featuring two pma motifs, (*R*)-H_2L_1 drawn in Scheme 3. The *N*-benzyl analogue of (*R*)-H_2L_1, that is, (*R*)-H_2L_2, was also of interest for direct comparison. Alkane elimination reactions of (*R*)-H_2L_n (n = 1, 2) ligands with the



(*R*)-H_2L_1 X = N
(*R*)-H_2L_2 X = CH

1b [(*R*)-L_1YCH_2TMS·THF]
2b [(*R*)-L_1ScCH_2TMS·THF]
2c [(*R*)-L_2ScCH_2TMS·THF]

Scheme 3. Syntheses of binaphthylamido alkyl rare-earth complexes **1b**, **2b**, and **2c** by alkane elimination route.

homoleptic neutral rare-earth alkyl source [RE$(CH_2SiMe_3)_3$$(thf)_2$] (RE = Y, Sc)[9] were used as a synthetic approach (Scheme 3).[10]

Addition of an equimolar amount of (*R*)-H_2L_1 to the appropriate [RE$(CH_2SiMe_3)_3$$(thf)_2$] [RE = Y (**1a**), Sc (**2a**)[11]] compound in THF allowed complexes **1b** and **2b** to be obtained in yields of 55 and 89%, respectively (Scheme 3). Both new complexes were isolated as brown air- and moisture-sensitive solids that were soluble in THF and toluene and poorly soluble in hexane. They could be stored in the solid state at −20 °C for a few weeks without noticeable decomposition. Complex **2c** was similarly synthesized in 85% yield in toluene, as surprisingly no alkane elimination occurred in THF as the solvent.

The X-ray diffraction study revealed that complex **2b** is monomeric with one scandium atom and one chiral tetradentate amido ligand (*R*)-L_1 (Figure 1).[11] The coordination sphere of the rare-earth atom is set up by the four nitrogen atoms of the chelating ligand, one carbon atom of the alkyl group, and one oxygen atom of the THF molecule in a distorted octahedral geometry, which results in a formal coordination number of 6. The tetradentate ligand adopts a C_2-*cis* coordination ge-

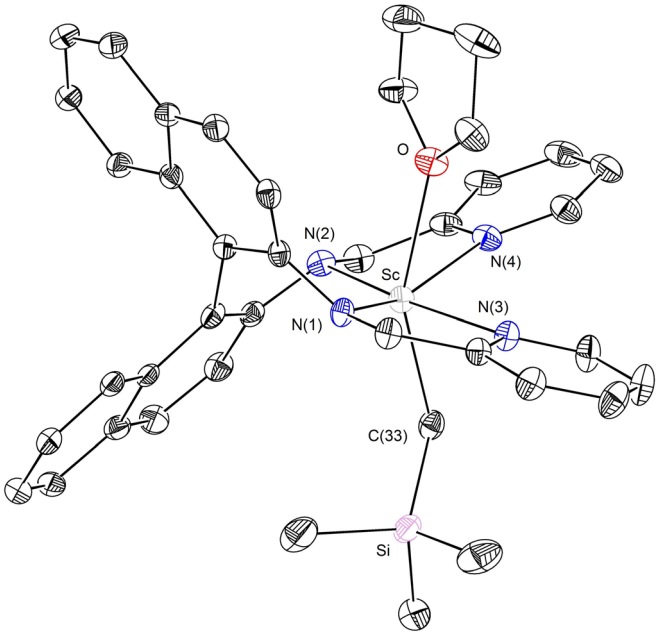


Figure 1. ORTEP drawing of complex **2b**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown at 30% probability.

ometry, and thus the carbon atom is approximatively bound *trans* to the oxygen atom [C(33)–Sc–O 154.49(11)°]. As expected, the Sc–N_{amido} [2.125(3), 2.105(3) Å] bond lengths are significantly shorter than the Sc–$N_{pyridyl}$ [2.360(3), 2.350(3) Å] bond lengths but fall in the range of those found in similar six-coordinated amido-[12] and pyridine-bound[13] scandium complexes, respectively. The Sc–C [2.279(3) Å] distance is close to the average value (2.287 Å) reported for related six-coordinated alkyl scandium complexes.[12b,14] Twisting between the naphthyl rings results in a torsion angle of 83.6(3)°. To fully characterize the metal center and its surrounding four nitrogen atoms in solution, heteronuclear ^{1}H–^{15}N NMR correlations through HMBC experiments were next undertaken. The latter technique was crucial to evaluate the coordination modes and to determine the first lines of the structure–catalytic activity relationships of the Pd complexes.[15] The effect of metal chelation was investigated by comparing the chemical shifts of the (*R*)-H_2L_1 ligand with those of complex **2b** for each nitrogen atom (Figure 2). Overlapping ^{1}H–^{15}N NMR correlations can clearly establish whether or not Sc is coordinated to the nitrogen atoms and can further confirm the coordination modes. First, the pyridine nitrogen atoms (N_{pyr}) experience deshielding, and thus the corresponding signal is shifted nearly $\Delta\delta = -30$ ppm on coordination to the metal center. However, the difference is smaller than typically observed for N–Pd complexes (ranging from $\Delta\delta = -88$ to -93 ppm).[15] Within this family of ligands, deshielding is characteristic of complexation to pyridine nitrogen atoms. In contrast, a large shielding of $\Delta\delta = +97$ ppm is observed for the amido nitrogen atoms (N_{amido}). In this case, a large positive $\Delta\delta$ value plausibly results from the contribution of the amido coordination mode to Sc, which is in sharp contrast to the small $\Delta\delta$ value observed (from $\Delta\delta = 0$ to -20 ppm) for NH–Pd bonds.

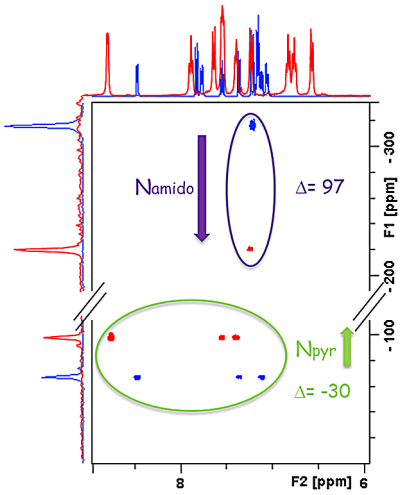


Figure 2. Overlapping heteronuclear ^{1}H–^{15}N NMR correlations for H_2L_1 in blue and complex **2b** in red. Focus in the aromatic region (chemical shifts are referred to external pure CH_3NO_2 and Δ is expressed in ppm).

Subsequently, the potential transformation of chiral scandium complex **2b** into the monoprotonated salt (*R*)-H_2L_1·HCl by an achiral additive was investigated. In regards to the high sensitivity of rare-earth alkyl complexes to protic sources,[10] it was assumed that controlled addition of a simple Brønsted acid such as hydrochloric acid would release the chiral ligand from the alkyl complex and afford the corresponding protonated salt of the ligand. To probe the viability of such an approach, the reactivity of **2b** and hydrochloric acid was evaluated. The room-temperature addition of 4 equivalents of HCl (1 M in diethyl ether) in apolar solvents led to the formation of a precipitate, which was identified as the monoprotonated amine (*R*)-H_2L_1·HCl from an independent synthesis (Scheme 4).[16,17] Overlapping of heteronuclear ^{1}H–^{15}N NMR correlations of H_2L_1 and H_2L_1·(HCl) revealed a powerful tool that gave a clear fingerprint of the evolution of H_2L_1 under acidic conditions.[17] Indeed, the chemical shifts of the pyridine nitrogen atoms were strongly impacted by the presence of H^+. A large deshielding of $\Delta\delta = -88$ ppm describes the N_{pyr}–H^+ interaction. In contrast, the binaphthylamine nitrogen atoms were barely affected by the presence of H^+ ($\Delta\delta = -2$ ppm). Complex **2b** could also be converted into the fully protonated salt (*R*)-H_2L_1·$(HCl)_4$ by the addition of 7 equivalents of HCl.[17]

$$[(R)\text{-}\mathbf{L}_1\text{ScCH}_2\text{TMS}\cdot\text{THF}]\ (\mathbf{2b}) + m\text{HCl} \xrightarrow[\text{or } C_7D_8]{C_6D_6} (R)\text{-}\mathbf{H_2L_1}\cdot(\text{HCl})_n$$

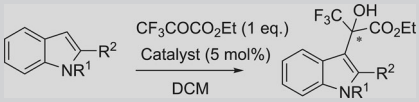
$$(m, n) = (4, 1) \text{ or } (7, 4)$$

Scheme 4. Evolution of **2b** into (*R*)-H_2L_1·(HCl)*n* ($n = 1, 4$) in the presence of HCl.

After demonstrating the viability of tuning scandium alkyl complex **2b** into the protonated salt (*R*)-H_2L_1·$(HCl)_n$ ($n = 1$ or 4), their catalytic efficiencies were independently evaluated in the targeted C–N and C–C bond-formation reactions of the tandem sequence. To our delight, 5 mol% of the monoprotonated salt (*R*)-H_2L_1·HCl promoted the alkylation of 2-methylindole (**3a**) and ethyl 3,3,3-trifluoropyruvate at 0 °C with full conversion, which afforded FC product **4a** in 86% yield with 34% enantiomeric excess (*ee*) (Table 1, entry 1). A control experiment highlighted the importance of the protonation step in the enantioinduction in the transformation (Table 1, entry 2).[18] The tetraprotonated salt (*R*)-H_2L_1·$(HCl)_4$ led to a product with a lower *ee* value, probably as a result of a racemic background reaction (Table 1, entry 3). As previously observed,[19] but in sharp contrast to our earlier findings with monoprotonated pyridylalkylamines,[7e] the presence of an *N*-methyl substituent on the indole core provided racemic products (Table 1, entries 4 and 5).

The ability of novel binaphthylamido rare-earth complexes to catalytically promote intramolecular hydroamination reactions was first demonstrated for the cyclohydroamination of well-known benchmark alkenyl and alkynyl substrates.[17] From the outcome of this preliminary work, scandium catalysts **2b** and **2c** were chosen for the rest of the study. The aptitude of **2b** to catalyze indole-ring synthesis starting from 2-(alk-1-yn-1-yl)aniline derivatives was then assessed, and the results are gathered in Table 2. Among the various methods reported for the construction of the indole core, the metal-catalyzed cycli-

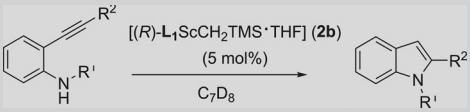
Table 1. Enantioselective Friedel–Crafts alkylation of indole derivatives and ethyl 3,3,3-trifluoropyruvate.[a]



Entry	Substrate	R^1	R^2	Product	Catalyst	Yield [%][b]	*ee* [%][c]
1	**3a**	H	Me	**4a**	(*R*)-H_2**L**$_1$·HCl	86	+34[f]
2	**3a**	H	Me	**4a**	(*R*)-H_2L_1	87	0
3	**3a**	H	Me	**4a**	(*R*)-H_2L_1·$(HCl)_4$	91	+25[f]
4	**3b**	Me	H	**4b**	(*R*)-H_2L_1·$(HCl)_4$	>95[d,e]	3
5	**3c**	Me	Me	**4c**	(*R*)-H_2L_1·$(HCl)_4$	88[d,e]	1
6[g]	**3a**	H	Me	**4a**	(*R*)-H_2L_1·HCl	>95[d,e]	+16[f]
7[g]	**3a**	H	Me	**4a**	**2b** + 4 HCl	>95[d,e]	+18[f]

[a] Reactions were run at 0 °C for 24 h with full conversion unless otherwise stated. [b] Yield of isolated product, unless otherwise stated. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Yield determined by NMR spectroscopy. [e] 72 h. [f] (*R*) configuration. [g] Reaction was run with **6d** (1 equiv.).

Table 2. Intramolecular hydroamination of 2-(alk-1-yn-1-yl)aniline derivatives catalyzed by **2b**.



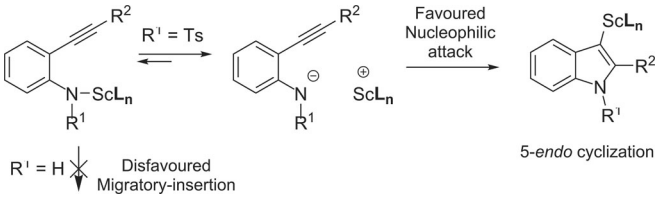
Entry	Substrate	R^1	R^2	Product	*T* [°C]	*t* [h]	Conversion [%][a]
1	**5a**	H	Ph	**6a**	150	96	0
2	**5b**	H	Pr	**6b**	150	48	16
3						168	20
4	**5c**	Ts	Ph	**6c**	150	120	79
5						169	>95
6	**5d**	Ts	Pr	**6d**	150	2	66
7						3	>95 (87[b])

[a] Determined by in situ ^{1}H NMR spectroscopy. [b] Yield of isolated product.

zation reaction of 2-alkynylanilines or derivatives thereof represents one of the most useful and straightforward methods to access this class of heterocycles. Most of the reported metal systems make use of alkali metals or Lewis acids to promote amine addition onto the triple bond.[20] To our knowledge, there is no report of such a process mediated by a rare-earth complex bearing basic alkyl groups such as in **2b**. Initial attempts to cyclize 2-(phenylethynyl)aniline (**5a**) or 2-(propylethynyl)aniline (**5b**) catalyzed by **2b** under drastic conditions were not productive, as only 20% conversion of **5b** into expected indole product **6b** was noticed after 168 h at 150 °C (Table 2, entries 1–3). However, to our surprise, introducing an electron-withdrawing tosyl (Ts) group in the amine improved the efficiency of the process significantly.[21] Indeed, the reactions of *N*-tosyl-2-(phenylethynyl)aniline (**5c**) and *N*-tosyl-2-(propylethynyl)aniline (**5d**) were almost complete (>95%) and afforded regioselectively the corresponding cyclized products after 169 and 3 h, respectively (Table 2, entries 4–7). Under these conditions, *N*-tosyl-2-propylindole (**6d**) was isolated in 87% yield (Table 2, entry 7).[22]

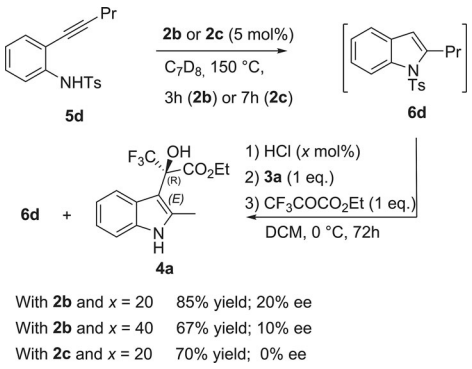
We speculate that the unexpected difference in reactivity between anilines **5a** and **5b** and tosylaniline derivatives **5c** and **5d** might arise from distinct mechanisms. Most rare-earth metal catalyzed hydroamination reactions, which are usually performed without a protecting group on the amine, tend to proceed by *syn*-migratory insertion of a RE–N bond across the carbon–carbon double or triple bond.[6a,23] However, in this case, the geometry constraint of the 5-*endo-dig* cyclization required for indole-ring formation might prevent such a pathway and implicate an alternative mechanism involving *anti*-nucleophilic attack onto the coordinated alkyne (Scheme 5). The presence of an electron-withdrawing group into the amine functionality should increase the ionic character of the RE–N bond and favor outer-sphere C–N bond formation. These findings encouraged us to investigate the influence of other alkyl and Lewis acidic triflate (OTf) complexes of scandium, free of any ligand or bearing the tetradentate (*R*)-H_2L_1 or bidentate (*R*)-H_2L_2ligand. A plot of the conversion versus the reaction time in the cyclization of **5d** catalyzed by ligand-free $[Sc(CH_2TMS)_3(thf)_2]$ (**2a**) and $[Sc(OTf)_3]$, alkyl complexes **2b** and **2c**, and the Lewis acids [(*R*)-H_2L_1·$Sc(OTf)_3$] and [(*R*)-H_2L_2·$Sc(OTf)_3$] shows clearly the beneficial effect of the use of an alkyl scandium supported by the tetradentate ligand on the rate and conversion of the reaction.[17]

Having demonstrated the catalytic efficiency of **2b** and (*R*)-H_2L_1·HCl in the alkyne hydroamination of *N*-tosyl-2-(alk-1-yn-1-yl)anilines and the enantioselective FC alkylation of 2-methylindole, respectively, as well as the HCl-triggered conversion of the former into the latter, we assessed if this could be combined into an asymmetric assisted tandem catalysis procedure. For this purpose, **5d** was first cyclized by using



Scheme 5. Proposed favored pathways to rationalize the difference in reactivities between anilines **5a** and **5b** and tosylaniline derivatives **5c** and **5d**.

5 mol% of catalyst **2b** under the optimized conditions for hydroamination (Scheme 6). After full conversion was achieved, as monitored by ^{1}H NMR spectroscopy, 20 mol% of HCl was added to the mixture to convert the organometallic species into the organocatalyst. A subsequent solvent change and the addition of 2-methylindole (**3a**) and ethyl 3,3,3-trifluoropyruvate at 0 °C allowed the enantioselective FC alkylation reaction to proceed. Gratifyingly, (*R*)-**4a** was obtained in 85% yield with 20% *ee* as the sole FC product. Indole **6d** resulting from the



Scheme 6. Proof of concept for the use of a multitask ligand in asymmetric assisted tandem catalysis: Metallocatalyzed alkyne hydroamination followed by asymmetric organocatalyzed Friedel–Crafts alkylation.

hydroamination step was fully recovered unchanged. As expected, independent experiments for the alkylation of **6d** uncatalyzed or catalyzed by (*R*)-H_2L_1·HCl confirmed the lack of reactivity of this indole under our reaction conditions. Conducting the same sequence with 40 mol% of HCl, which should have triggered the conversion of **2b** into (*R*)-H_2L_1·$(HCl)_4$, led to lower enantioinduction than that expected from our results on the FC reaction (Table 1, entries 1 and 3). The use of catalyst **2c** provided product **4a** as a racemic mixture. This result highlights once more the importance of the pma motifs of the chiral ligand. However, it is worth noting that the enantioselectivity of the alkylation step of the tandem process was notably lower than that obtained if this step was independently run with the (*R*)-H_2L_1·HCl catalyst under FC conditions (see Table 1, entry 1). Alkylation reactions of **3a** and ethyl 3,3,3-trifluoropyruvate catalyzed by (*R*)-H_2L_1·HCl and **2b** + 4 HCl performed under the same conditions but in the presence of a stoichiometric amount of **6d** revealed that the decrease in the *ee* value was only related to the presence of **6d** in the reaction medium (Table 1, entries 6 and 7). Unfortunately, as the hydroamination reaction was unpredictably low yielding with an amine free of any protecting group, the asymmetric assisted tandem catalysis sequence could not be directly conducted on **5b**.

In summary, we reported the first proof of concept of the use of a multitask chiral ligand in an asymmetric assisted tandem catalysis protocol by combining metallo- and organocatalytic processes successively. In this protocol, the chiral ligand of the newly designed rare-earth catalyst of the first reaction was converted into a novel chiral organocatalyst for the second transformation in a tandem sequence—alkyne hydroamination followed by enantioselective Friedel–Crafts (FC) alkylation. The transformation of the organometallic catalyst into the organic catalyst was simply triggered by the addition of HCl. The observation of some enantioinduction confirmed that the chiral information was relayed from the metallocatalyst to the organocatalyst. In the course of this work, we demonstrated that chiral C_2-symmetric binaphthylamine featuring the pyridylmethylamine moiety was a key scaffold for the synthesis of novel well-defined chiral rare-earth alkyl complexes and chiral protonated amine salts. Scandium complex **2b** and monoprotonated (*R*)-H_2L_1·HCl exhibited good catalytic activity in the 5-*endo-dig* cyclohydroamination of *N*-tosyl-2-(propylethynyl)-aniline and the FC alkylation of 2-methylindole, respectively, with moderate enantioselectivity for the latter. Current efforts are focused on exploring the breadth of the "multitask chiral ligand" concept demonstrating herein asymmetric assisted tandem catalysis.

Acknowledgements

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Keywords: asymmetric catalysis · hydroamination · N ligands · organocatalysis · tandem catalysis

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[2] In this manuscript, we use the term "Assisted tandem catalysis" defined by Fogg and Santos (see reference 1 m) and follow their classification.

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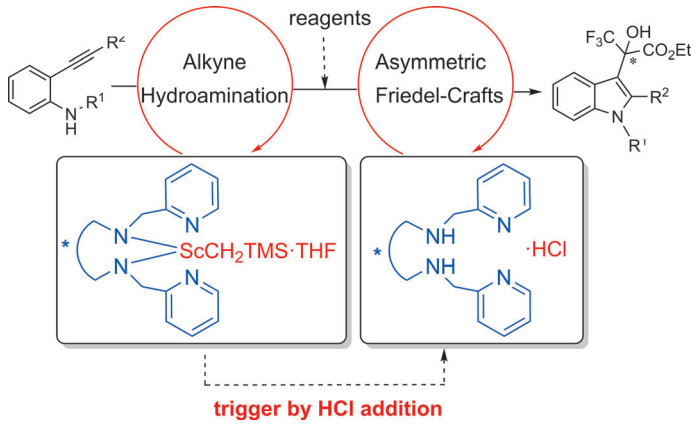

Relay race: The first example of an asymmetric assisted tandem catalysis protocol that combines a metallocatalyzed alkyne hydroamination reaction with an asymmetric organocatalyzed Friedel–Crafts reaction is reported. The chiral ligand of the metallocatalyst is converted into a chiral organocatalyst by simple HCl addition. Some enantioinduction confirms the relay of the chiral information between the two catalysts.

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Asymmetric Assisted Tandem Catalysis: Hydroamination followed by Asymmetric Friedel–Crafts Reaction from a Single Chiral *N,N,N′,N′*-Tetradentate Pyridylmethylamine-Based Ligand