Asymmetric Catalysis

DOI: 10.1002/ange.201407677

Asymmetric Triple Relay Catalysis: Enantioselective Synthesis of Spirocyclic Indolines through a One-Pot Process Featuring an Asymmetric 6π Electrocyclization**

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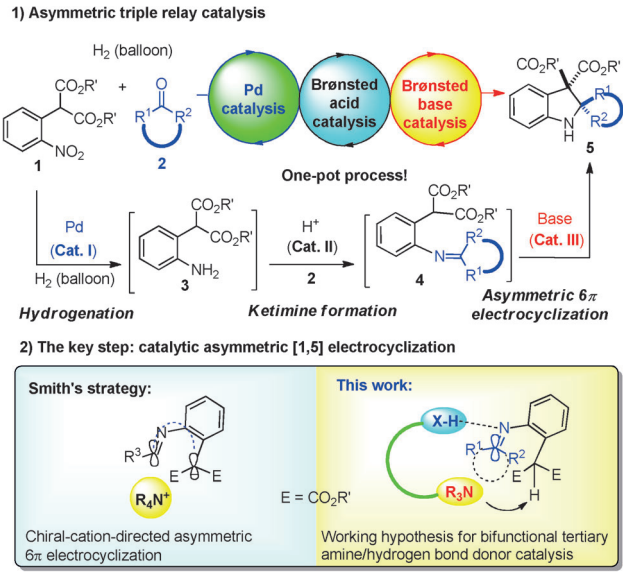
Abstract: *A rare example of a one-pot process that involves asymmetric triple relay catalysis is reported. The key step is an asymmetric [1,5] electrocyclic reaction of functionalized ketimines. The substrates for this process were obtained in situ in a two-step process that involved the hydrogenation of nitroarenes with a Pd/C catalyst to yield aryl amines and their subsequent coupling with isatin derivatives in a Brønsted acid catalyzed ketimine formation reaction. The electrocyclization was catalyzed by a bifunctional chiral Brønsted base/hydrogen bond donor catalyst. The one-pot process gave the desired products in good yields and with excellent enantioselectivity.*

Inspired by the multienzymatic tandem catalytic processes that nature uses for the efficient synthesis of complex molecules, the development of multi-catalyst-promoted asymmetric tandem reactions (MPATR) is of current interest.[1] Aside from the general advantages of tandem catalysis,[2] namely the effectiveness in minimizing waste production, the consumption of energy, labor, and time, and yield losses associated with the purification of intermediates, the use of multiple catalysts, rather than a single catalyst, offers the promise to incorporate more substrates and reaction types to design novel cascade reactions, which are very attractive for building up molecular complexity from simple materials.[1] Over the past decade, much progress has been made in this area, and asymmetric relay catalysis (or sequential catalysis) has been established as a major type of MPATR,[1,3] which refers to the sequential combination of catalytic reactions, each of which is independently operated by a distinct catalyst, into a one-pot process. Nevertheless, despite remarkable advances in the development of tandem reactions that were achieved by using two metal catalysts,[4] two organocatalysts,[5] or a metal and an organocatalyst,[6] the combination of three distinct catalysts to exploit asymmetric triple relay catalysis is still underdeveloped, although it has already exhibited its powerfulness in tackling some synthetic challenges.[7]

On the other hand, the ever-increasing demand in chemical biology and medicinal research for synthetic libraries derived from privileged scaffolds requires the development of new synthetic methods that enable the construction of libraries of optically active compounds with polycyclic structures.[8] In particular, efficient stereoselective syntheses of spirocyclic compounds are very much in demand.[9] Therefore, the exploration of asymmetric triple relay catalysis for the facile construction of spirocyclic compounds from simple materials is highly desirable. Herein, we report an unprecedented example of asymmetric triple replay catalysis, which integrates palladium, Brønsted acid, and bifunctional chiral Brønsted base/hydrogen bond donor catalysis, and we demonstrate its effectiveness in the highly enantioselective synthesis of oxindole-based spirocyclic indolines through a one-pot sequence that involves hydrogenation, ketimine formation, and an asymmetric 6π electrocyclization (Scheme 1).

As we are interested in the catalytic asymmetric synthesis of chiral spirocyclic compounds,[10] we wished to construct spirocyclic compounds through a [1,5] electrocyclic reaction of an imine as its catalytic asymmetric version is still in its infancy.[11] In 2009, the groups of List and Smith independ-



Scheme 1. One-pot reaction sequence involving hydrogenation, ketimine formation, and an asymmetric 6π electrocyclization.

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[**] We appreciate financial support from the 973 program (2015CB856600), the NSFC (21172075, 21222204), the Program of SSCS (13XD1401600), and the Ministry of Education (NCET-11-0147, PCSIRT).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201407677.

ently pioneered the catalytic asymmetric 6π electrocyclization.[12] Whereas List et al. developed a highly enantioselective cycloisomerization of α,β-unsaturated hydrazones to pyrazolines catalyzed by a chiral phosphoric acid,[12a] Smith and co-workers used functionalized aldimines as precursors to 2-aza-pentadienyl anions while employing phase transfer catalysis (PTC) to generate a tight ion pair featuring a chiral ammonium cation to achieve excellent enantioselectivity.[12b] Smith et al. further used their method to develop cascade syntheses of polycyclic compounds.[12c] Despite significant advances, the use of functionalized ketimines for such reactions is still unknown, and the identification of new catalysts for this interesting reaction is still very much in demand.

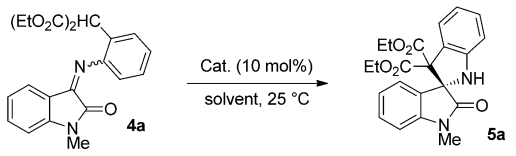
Considering the versatility of bifunctional tertiary amine/hydrogen bond donor catalysts,[13] we speculated that such a dual activation mode would be suitable for the asymmetric [1,5] electrocyclic reaction of aniline-derived ketimine **4**, which might be activated to produce 2-aza-pentadienyl anion intermediates through activation of the ketimine moiety through hydrogen bonding and simultaneous activation of the methine moiety through deprotonation. The hydrogen bonding interactions might organize a favorable transition state to control the sense of the disrotatory electrocyclization process (Scheme 1).

Importantly, with bifunctional tertiary amines as the catalyst, catalyst quenching, a major obstacle in the development of the desired tandem process, may be avoided.[1] We were also concerned that the Brønsted acid required for the synthesis of the aniline-derived ketimines might be detrimental to the electrocyclization, as it might protonate the tertiary amine moiety of the chiral catalyst. However, recent results from Wang and co-workers and our group revealed that bifunctional chiral tertiary amines could tolerate the coexistence of some acidic additives.[14] Furthermore, bifunctional tertiary amines are known to be able to tolerate some metal species,[6k–n] and might be compatible with the palladium species we wished to use for the hydrogenation of nitroarenes **1** to obtain malonate-anilines **3**. It is important to conduct the ketimine formation and the cyclization process in a one-pot fashion as the purification of such sensitive imines often incurs yield losses.[15] Based on the above analyses, it is worthwhile to combine the three distinct catalytic reactions into the one-pot process shown in Scheme 1.

With our interests in oxindole chemistry,[10,16] we first designed isatin-derived malonate-ketimine **4a** as a starting point for the study of the asymmetric 6π electrocyclization, to pave the way for the subsequent development of the tandem reaction. It should be noted that whereas the catalytic asymmetric synthesis of spirocyclic oxindoles, a prominent structural motif in natural products, drugs, and bioactive products,[17] has been extensively studied, the asymmetric synthesis of spirocyclic oxindole-indoline derivatives is unprecedented.

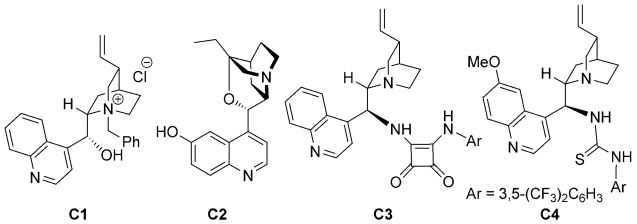
The synthesis of ketimine **4a** from malonate-aniline derivative **1a** and *N*-methylisatin (**2a**) required the use of a stronger acid catalyst,[18] namely *para*-toluenesulfonic acid (*p*-TsOH; see Supporting information). Ketimine **4a** was prepared as an inseparable mixture of the *Z* and *E* isomers in a ratio of approximately 10:1. Nevertheless, it was directly used for the optimization of the reaction conditions. First, we attempted the electrocyclization of **4a** under Smith's conditions using chiral ammonium catalyst **C1** along with K_2CO_3 as the base and toluene as the solvent at −15 °C; however, the desired product **5a** was obtained in only 6 % *ee*, albeit in 89 % yield (Table 1, entry 1). This result further suggested the importance of identifying a new catalyst motif for this valuable cyclization. In the following, various tertiary amine catalysts were evaluated at 25 °C using CH_2Cl_2 as the solvent. Not surprisingly, simple chiral tertiary amines proved to be incapable of catalyzing this transformation. For example, $(DHQD)_2PYR$ (hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether) gave only trace amounts of **5a** in 49 % *ee* even after six days (entry 2). On the other hand, it was also important for the desired reactivity and enantioselectivity that the amine catalyst featured a suitable hydrogen bond donor moiety. Cinchona alkaloid derivatives with a single hydrogen bond donor were inferior as well, and derivative **C2**, for instance, afforded product **5a** in trace amounts and 16 % *ee* (entry 3). Fortunately, cinchona alkaloid derivatives with a dual hydrogen bond donor moiety, squaramide **C3**[19] or thiourea **C4**,[20] were promising, giving **5a** in reasonable yield and ≥ 95 % *ee* (entries 4 and 5; for the full catalyst evaluation, see the Supporting Information, Table S1). Encouraged by these results, we chose the more easily available thiourea catalyst **C4** for further optimization. By replacing CH_2Cl_2

Table 1: Optimization of the reaction conditions.[a]



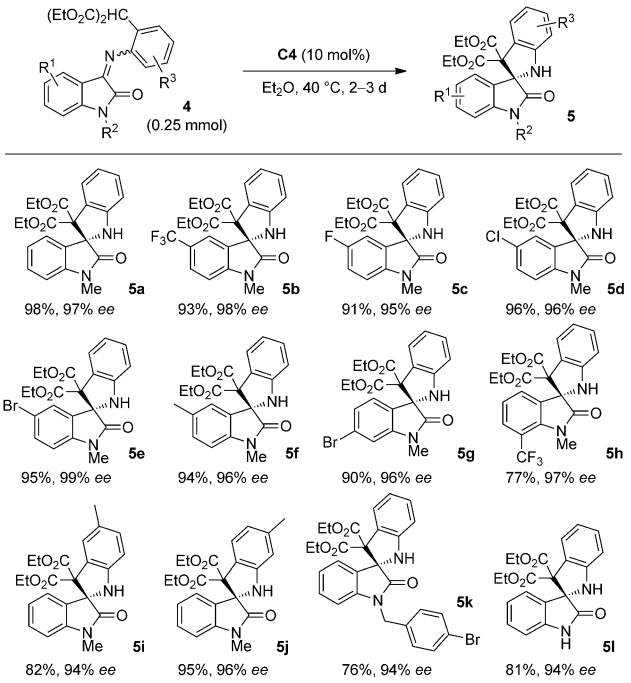
Entry	Catalyst	Solvent	*t* [d]	Yield[b] [%]	*ee*[c] [%]
1[d]	**C1**	toluene	1	89	6
2	$(DHQD)_2PYR$	CH_2Cl_2	6	trace	49
3	**C2**	CH_2Cl_2	6	trace	16
4	**C3**	CH_2Cl_2	4	78	98
5	**C4**	CH_2Cl_2	3	63	95
6	**C4**	EtOAc	3	88	97
7	**C4**	EtOH	3	94	65
8	**C4**	toluene	3	93	98
9	**C4**	THF	3	46	97
10	**C4**	Et_2O	3	90	99
11[e]	**C4**	Et_2O	2	88	98

[a] Reactions run on a 0.1 mmol scale in 1.0 mL of solvent. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] With 0.2 mL of aqueous K_2CO_3 (33 %). [e] At 40 °C.



with Et_2O as the solvent, product **5a** could be obtained in 90% yield and 99% *ee* (entries 5–10). When the temperature was increased to 40 °C, the reaction in Et_2O could reach completion within two days, affording product **5a** in 88% yield and 98% *ee* (entry 11).

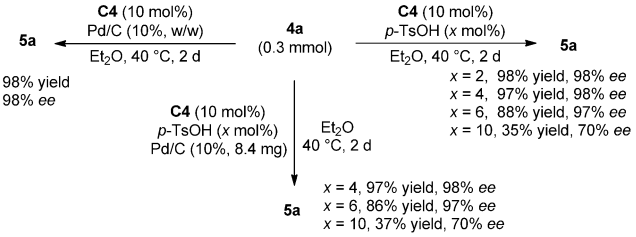
Next, the scope of the asymmetric 6π electrocyclization was examined using 10 mol% of quinine-derived bifunctional thiourea **C4** in Et_2O at 40 °C. A variety of malonate-ketimines **4** with different substituents on the isatin framework provided the desired spirocyclic oxindole derivatives **5** in good yield and with excellent *ee* values (Scheme 2), which highlights the



Scheme 2. Scope of the asymmetric 6π electrocyclization. Yields of isolated products are given. All *ee* values were determined by HPLC analysis on a chiral stationary phase.

potential of bifunctional tertiary amine/hydrogen bond donor catalysis in this type of electrocyclization. The absolute configuration of product **5e** was assigned to be *S* by X-ray analysis,[21] and those of others were tentatively assigned. Noticeably, although ketimines **4** were all prepared as mixtures of the *Z* and *E* isomers, the desired products **5** were all obtained in > 94% *ee*. We are currently investigating the origin of this high selectivity.

Having established the highly enantioselective 6π electrocyclization of ketimines **4**, we next tried to develop the triple relay sequence shown in Scheme 1. The development of this process is justified by the inconvenience in purifying **4**, which involves a flash column chromatography followed by a recrystallization, as **4** underwent partial racemic cyclization, either owing to the presence of *p*-TsOH in the reaction mixture or during the column chromatography (see the Supporting Information). Obviously, a prerequisite for the success of this sequence was to prevent the *p*-TsOH catalyzed background cyclization and the quenching of chiral catalyst **C4** by *p*-TsOH with a pK_a value of up to −2.8. Gratifyingly, it turned out that the cyclization of **4a** catalyzed by 10 mol% of **C4** could tolerate the coexistence of up to 4 mol% of *p*-TsOH, without obvious erosion in enantioselectivity and reactivity (Scheme 3). Not surprisingly, the addition of

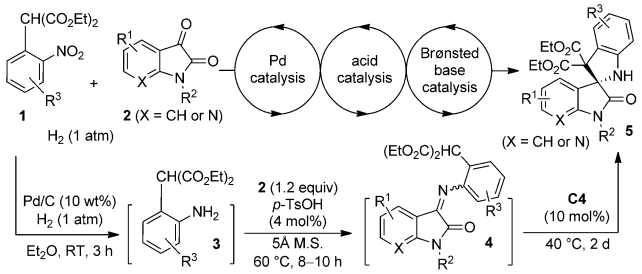


Scheme 3. Studies of the catalyst compatibility.

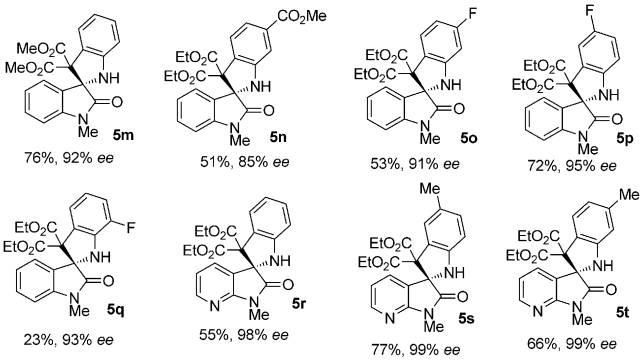
10 mol% *p*-TsOH greatly decreased the yield and *ee* value of product **5a**. However, the presence of both Pd/C and 4 mol% of *p*-TsOH had little effect on the performance of **C4** in the cyclization reaction, and product **5a** was obtained in 98% yield with 98% *ee*, which is comparable to the result obtained with **C4** alone (Table 1, entry 11). Noticeably, the use of 4 mol% of *p*-TsOH was enough to catalyze the ketimine formation at 60 °C, whilst the racemic background reaction was minimized.

The above control experiments confirmed the prerequisite catalyst compatibility; however, the merging of three distinct catalytic reactions into a one-pot process with minimal extra procedures was not as trivial as first anticipated. Attention should be paid to three issues. First, it was better to run all three steps in the same solvent to obviate the need for changing the solvent for each cycle. We chose to use the best solvent for the asymmetric step to optimize the conditions for the non-enantioselective reactions, a tactic useful for further studies of asymmetric triple relay catalysis. Fortunately, Et_2O proved to be a suitable solvent for all three steps. Second, the concentration should be adjusted to maximize the efficiency of each step. In this sequence, whereas the ketimine formation required a high substrate concentration (0.3 M), the asymmetric cyclization achieved higher enantioselectivity at a lower concentration (0.1 M). Last, the reaction time of the ketimine formation catalyzed by *p*-TsOH (4 mol%) should be limited to eight to ten hours, and no background racemic reaction was observed during this time. The full optimization of the tandem process is detailed in Table S2. Finally, a simple one-pot procedure was developed. The initial palladium-catalyzed hydrogenation of nitroarene **1** (0.3 mmol) using a H_2 balloon was run in a screw-capped pressure tube at 25 °C in Et_2O (1 mL). After **1** had been consumed (as confirmed by TLC analysis), isatin **2**, molecular sieves (M.S.; 5 Å), and *p*-TsOH (4 mol%) were added, and the reaction was heated at 60 °C for 8–10 hours. Then, the mixture was cooled down, and Et_2O (2 mL) and thiourea **C4** (10 mol%) were added for the following [1,5] electrocyclic reaction at 40 °C. According to this procedure, which only involves sequential addition steps and a single purification, all of the oxindole-indoline derivatives **5a**–**l** shown in Scheme 2 were obtained in reasonable yield with

Table 2: Scope of the cascade process.[a]



Entry	Product	Yield[b] [%]	*ee*[c] [%]
1	**5a**	85	92
2	**5b**	83	96
3	**5c**	81	92
4	**5d**	55	92
5	**5e**	66	97
6	**5f**	79	91
7	**5g**	53	93
8	**5h**	76	97
9	**5i**	78	92
10	**5j**	75	94
11	**5k**	45	86
12	**5l**	54	80



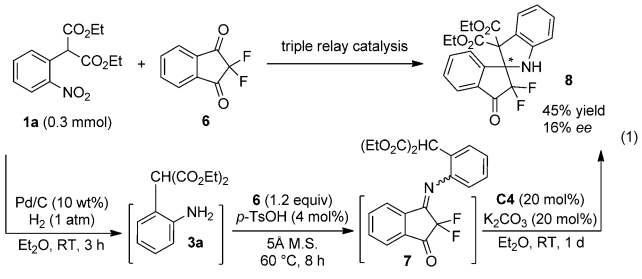
[a] Run on a 0.3 mmol scale. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. For details, see the Supporting Information.

high to excellent *ee* values from simple starting materials (Table 2, entries 1–12).

The importance of the asymmetric tandem process was further highlighted by the efficient synthesis of spirocyclic indolines **5m–t**, as the corresponding malonate-ketimine precursors were either difficult to purify or prepared from expensive substrates. For example, owing to the reduced steric hindrance of the methyl ester group, it was difficult to purify the ketimine precursor of product **5m** owing to rapid racemic cyclization during column chromatography. However, with the one-pot process, the desired product **5m** was obtained in 76% yield and 92% *ee*. The low yield of product **5q** was due to the steric hindrance imposed by the *ortho* fluorine substituent at the aryl ring. Furthermore, the one-pot method greatly improved the efficiency of the syntheses of products **5r–t** by avoiding yield losses during the purification of the ketimine precursors derived from 7-azaisatin, which are expensive and difficult to prepare.[22]

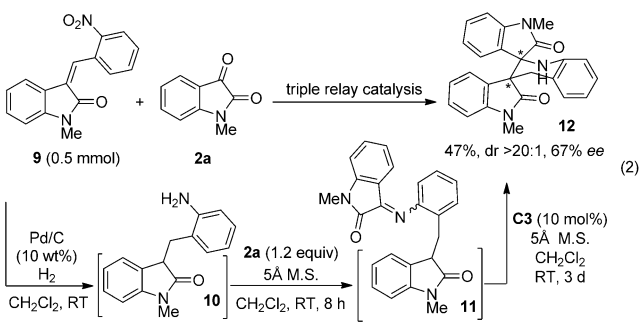
We were pleased to find that the three distinct catalytic reactions could be effectively incorporated into a one-pot process without taking special care except for adding the reagents in a sequential fashion. The finding that bifunctional tertiary amines could tolerate the presence of a stronger Brønsted acid such as *p*-TsOH and Pd species was also unprecedented and should be useful for developing new tandem sequences that feature these catalysts, in particular considering the usefulness of bifunctional chiral tertiary amines in ketimine addition reactions.[23]

Apart from (aza)isatins, α,α-difluoro-1,3-indandione (**6**) could also be integrated into this tandem sequence [Eq. (1)]. However, possibly owing to the negative influence of the difluoromethylene group on the catalyst–substrate interaction,[23a,24a] ketimine **7** failed to cyclize, both in the presence of thiourea **C4** or in the presence of PTC catalyst **C1** and K_2CO_3. Nevertheless, a combination of **C4** and K_2CO_3 (20 mol% each) could catalyze the cyclization to give the desired product **8** in 45% yield and 16% *ee* through the cascade process. Despite the moderate *ee* value, this represents a new method to prepare novel difluorinated spirocyclic indoline derivatives.[24]



The triple sequence described above could be modularly varied by using other asymmetric imine addition reactions.[25] For example, an analogous sequence involving hydrogenation, ketimine formation, and a Mannich reaction starting from 3-alkenyl-oxindole **9** and *N*-methyl isatin (**2a**) readily gave bis(spirooxindole) **12** in 47% yield, >20:1 d.r., and 67% *ee* [Eq. (2)]. The structure and relative configuration of **12** were confirmed by X-ray analysis.[21] In this case, the ketimine formation was promoted by 5 Å molecular sieves, and the use of *p*-TsOH should be avoided as it led to severe background reactions. Despite ample room for improvement, this sequence constitutes a new strategy for the synthesis of bis(spirooxindoles), which are privileged scaffolds with very limited synthetic methods known for their preparation.[26]

In conclusion, we have developed a rare example of asymmetric triple relay catalysis through the sequential use of



palladium, Brønsted acid, and Brønsted base catalysis. The key step is an asymmetric [1,5] electrocyclic reaction of functionalized ketimines,[27] which was catalyzed by a bifunctional chiral tertiary amine that also featured a hydrogen bond donor moiety for the first time. This reaction provides a facile access to oxindole-based spirocyclic indolines, which are of interest to medicinal chemists. Currently, this method is limited to active ketones such as isatins, and studies on further developments of this tandem process are currently in progress in our laboratory.

Received: July 23, 2014
Revised: September 2, 2014
Published online: October 14, 2014

Keywords: asymmetric catalysis · electrocyclic reactions · one-pot processes · tandem reaction · thioureas

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