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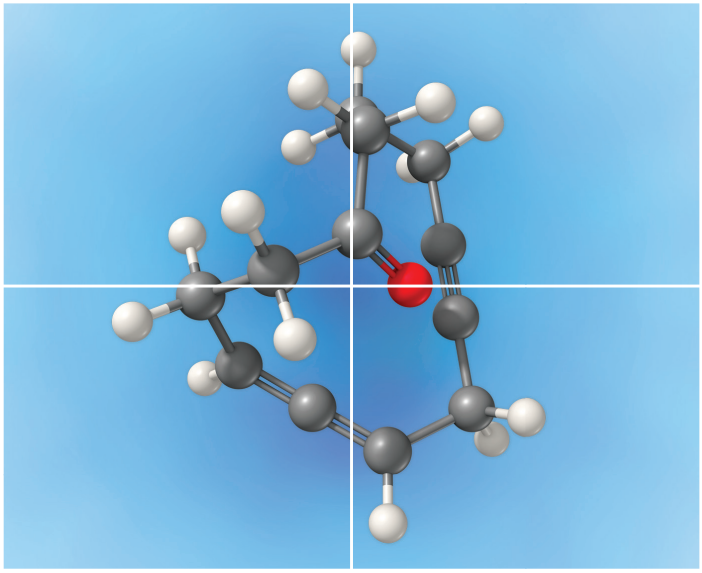

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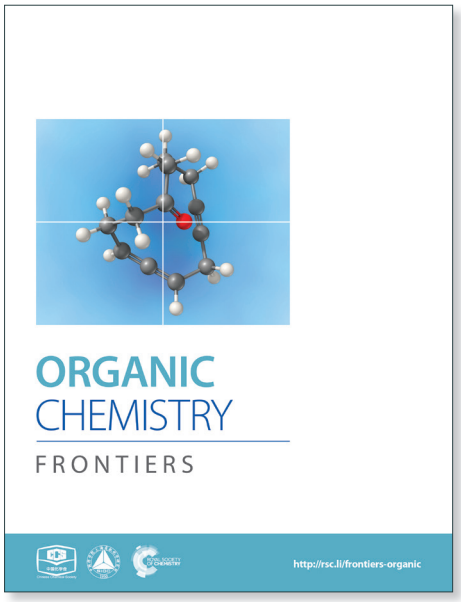

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RESEARCH ARTICLE

Catalytic Enantioselective Synthesis of Quaternary 3,3´-Indolyloxindoles by Combination of Rh(II) Complex and Chiral Phosphines

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The Rh(II)/chiral phosphine combined catalysis has been developed for a highly efficient sequential C-H functionalization/asymmetric allylation or Michael addition reaction of indoles and 3-diazooxindoles with allenoates or vinyl ketones to afford a diverse range of quaternary 3,3´-indolyloxindole derivatives. Moreover, a significantly positive effect of LiCl in the sequential C-H functionalization/allylation reaction was observed, which led to an unusual ternary activation mechanism in the allylation step.

Introduction

Optically active 3,3´-bisindole represents a unique structural element within a fascinating family of indole alkaloids exemplified in Figure 1, which have been characterized by a wide spectrum of antimicrobial, antiviral and antitumor bioactivities.[1] All-carbon quaternary stereogenic center-linking patterns (QCPs) of the bisindole unit are potential sources of structural diversity that poses great interest for chemical synthesis, especially in a catalytic enantioselective fashion. Recent reports have described a number of intra-[2] or intermolecular[3-5] methodologies, and the latter chiefly centered on asymmetric substitution reactions of racemic 3,3-disubstituted oxindoles[3] and asymmetric addition reactions of 3-indolyloxindoles to electrophiles.[4] Despite the great contributions that these existing methods made to building up the bisindole complexity and total synthesis of natural alkaloids, the QCPs are still rather limited and hence novel strategies are extremely desired to circumvent daunting challenges in the highly straightforward and stereoselective construction of all-carbon quaternary stereogenic centers of this type.[6]

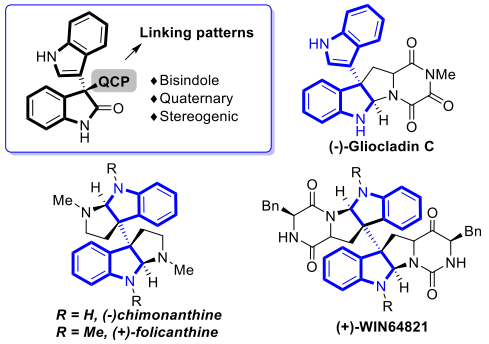
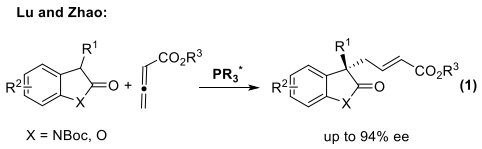
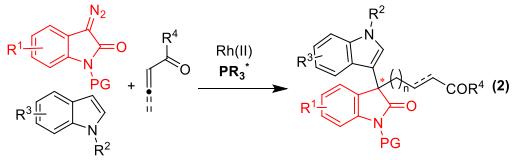


Figure 1 Natural bisindole alkaloids.



Scheme 1 Phosphine mediated asymmetric γ-additions.



Scheme 2 Rh(II)/chiral phosphine combined catalysis.

Nucleophilicity-featured chiral phosphines[7] have recently been in the center of popular asymmetric organocatalysis arose from pioneering contributions from Lu[8] and driven by important findings coming from Vedejs,[9] Zhang,[10] Fu[11], Shi[12] and others.[13-17] Simple α-amino acid- or dipeptide-based bifunctional chiral phosphines, firstly discovered by Miller[14] and Jacobsen,[15] advanced by Zhao[16] and Lu,[17] have recently proven to be extremely effective in the promotion of a number of enantioselective transformations. For example, Lu's[17g] and Zhao's[16c] groups respectively reported asymmetric γ-additions of oxindoles or benzofuran to allenoates, providing direct access to highly enantioenriched quaternary 3,3´-indolyloxindoles or benzofuran (Eq. 1). In the last decade, the

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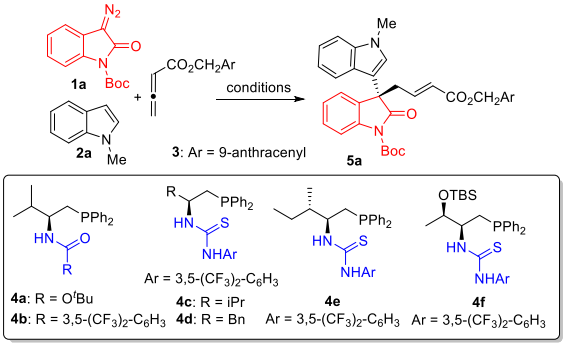
asymmetric metal/organo combined catalysis has been a valuable and versatile concept to enable the abundant creation of new tansformations.[4d,18-20] However, to the best of our knowledge, chiral phosphines have rarely been in this category with the exception of a few non-enantioselective examples described by Krische and Wu.[21] We believe that the combination of transition metals and chiral phosphines would be able to provide more opportunities to enrich the synthetic value than either type of individual catalysts. Herein, we will demonstrate our efforts directed towards developing a novel Rh(II)/chiral phosphine sequential catalysis for the efficient synthesis of enantioenriched 3,3´-indolyloxindoles with unprecedented QCPs (Scheme 2).

Results and discussion

We first investigated different conditions for a three-component reaction of 3-diazooxindole **1a**, N-methyl indole **2a** and allenoate **3** under the catalysis of 2 mol% of transition metal complexes and 10 mol% of organocatalysts, in CH_2Cl_2, at 25 ℃ (Table 1, entries 1-8). Since the Ru(II)/chiral squaramide binary catalyst system previously developed[4d] failed to afford the desired three-component transformation, instead, only C-H functionalization product was observed (See Figure S1 in SI for details), we turned to use more nucleophilic chiral phosphines, in combination with transition metal complexes to catalyze the reaction. In the presence of 2 mol% of $[RuCl_2(p\text{-cymene})]_2$, the L-Val derived bifunctional chiral phosphine **4a** successfully enabled a sequential C-H functionalization/allylation reaction to give **5a**, but in a low yield and with a moderate 32% ee (entry 1). The use of rhodium complexes as metal catalysts did not exert impact on the enantioselectivity while led to obviously higher yields (entries 2-3). More interestingly, the $Rh_2(esp)_2$ showed good compatibility with the chiral phosphine organocatalyst to allow the sequential reaction to give a good yield (entry 3). Then, a library of bifunctional chiral phosphines **4b**-**4f** were evaluated, and found that the original α-amino acid sources and hydrogen-bond donor moieties were both important for the stereocontrol (entries 4-8). In particular, the combination of $Rh_2(esp)_2$ and L-Phe derived thiourea phosphine **4d** enabled the reaction to give the best results of 50% yield and 77% ee (entry 6). Notably, the reaction in $CHCl_3$ displayed 87% ee (entry 9 and see Table S1 in SI for more details). Surprisingly, even better results were obtained by lowering the loading of $Rh_2(esp)_2$ to 0.02 mol% probably due to more amounts of chiral phosphine catalyst **4d** liberated from the coordination with rhodium (entry 10). The examination of additives (also see Table S1 in SI for details) identified that 1.0 equivalent of LiCl continued to improve both the yield and enantioselectivity (entry 11, 81% yield and 91% ee). However, lowering reaction temperature (0 ℃) led to significantly eroded yield, albeit with a maintained enantiomeric excess (entry 12).

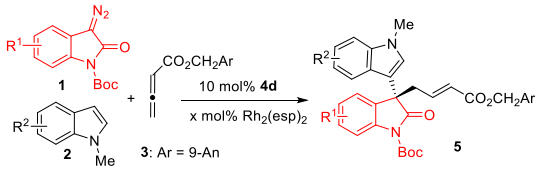
Table 1 Optimization of reaction conditions[a]



entry	[M]	4	Solvent	yield (%)[b]	ee (%)[c]
1	[Ru]	**4a**	CH_2Cl_2	10	32
2	$Rh_2(OAc)_4$	**4a**	CH_2Cl_2	21	32
3	$Rh_2(esp)_2$	**4a**	CH_2Cl_2	53	32
4	$Rh_2(esp)_2$	**4b**	CH_2Cl_2	81	16
5	$Rh_2(esp)_2$	**4c**	CH_2Cl_2	60	58
6	$Rh_2(esp)_2$	**4d**	CH_2Cl_2	50	77
7	$Rh_2(esp)_2$	**4e**	CH_2Cl_2	55	58
8	$Rh_2(esp)_2$	**4f**	CH_2Cl_2	39	46
9	$Rh_2(esp)_2$	**4d**	$CHCl_3$	52	87
10[d]	$Rh_2(esp)_2$	**4d**	$CHCl_3$	60	87
11[d,e]	**$Rh_2(esp)_2$**	**4d**	**$CHCl_3$**	**81**	**91**
12[d,e,f]	$Rh_2(esp)_2$	**4d**	$CHCl_3$	26	91

[a] Unless indicated otherwise, reactions of **1a** (0.10 mmol), **2a** (0.10 mmol), **3** (0.11 mmol), metal (0.002 mmol), **4** (0.010 mmol) were carried out in solvent (1.0 mL), at 25 ℃, for 12h. [b] Isolated yield. [c] Determined by HPLC. [d] 0.02 mol% of $Rh_2(esp)_2$ was used. [e] 1.0 equivalent of LiCl was used as an additive. [f] The reaction was conducted at 0 ℃. [Ru] = $[RuCl_2(p\text{-cymene})]_2$.

Table 2 Substrates scope of cascade C-H functionalization/ allylation reaction[a]

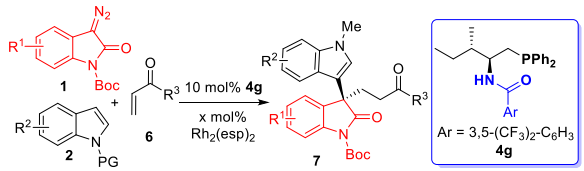


entry	R^1/R^2	x	5	Yield (%)[b]	ee (%)[c]
1	H/5-F	0.02	**5b**	69	87
2	H/5-Me	0.01	**5c**	80	90
3	H/5-OMe	0.01	**5d**	83	92
4	H/6-OMe	0.01	**5e**	81	90
5	H/6-Cl	0.02	**5f**	72	90
6	H/7-Me	0.01	**5g**	64	87
7[d]	5-Br/H	0.05	**5h**	64	92
8	5-Me/H	0.01	**5i**	80	86
9	5-OMe/H	0.01	**5j**	66	88
10	6-OMe/H	0.01	**5k**	77	86
11	6-Br/H	0.02	**5l**	66	85
12	7-Br/H	0.05	**5m**	61	72

[a] Unless indicated otherwise, reactions of 3-diazooxindoles 1 (0.10 mmol), **2** (0.10 mmol), **3** (0.11 mmol), with **4d** (0.010 mmol) and x mmol% $Rh_2(esp)_2$ and were carried out in $CHCl_3$ (1.0 mL), at 25℃ , for 12h. [b] Isolated yield. [c] Determined by HPLC. [d] 20 mol% of **4d** was used.

With the optimized reaction conditions in hand, we then examined the substrates scope. In general, this Rh(II)/**4d** combined catalytic system tolerated a wide range of substituents on either indole or 3-diazooxindole moiety, affording excellent yields and enantioselectivities in most cases (Table 2). The electron nature of substituents was crucial for the formation of final products by accelerating or slowing down the first C-H functionalization step. For example, the substrates with electron-neutral or electron-donating substituents smoothly underwent the one-pot reaction in the presence of 0.01 mol% of $Rh_2(esp)_2$ (e.g., entries 2-4, 6, 8-10), while the reaction of those with electron-withdrawing substituents

Table 3. Rh(II)/chiral phosphine sequentially catalytic C-H functionalization/Michael addition reaction[a]

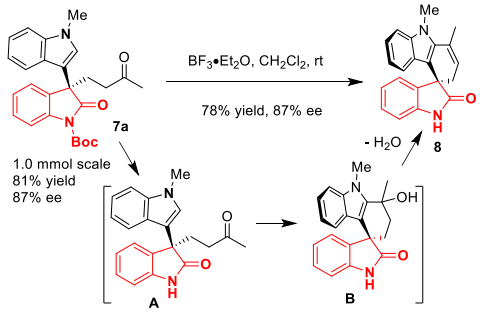


entry	$R^1/R^2/R^3$	x	7	Yield (%)[b]	ee(%)[c]
1	H/H/Me	0.02	**7a**	92	91
2[d]	H/H/Me	0.02	**7b**	82	56
3	H/5-OMe/Me	0.01	**7c**	75	92
4	H/6-OMe/Me	0.01	**7d**	88	92
5	H/6-Cl/Me	0.02	**7e**	88	87
6	H/7-Me/Me	0.01	**7f**	61	89
7	5-Br/H/Me	0.05	**7g**	87	92
8	6-OMe/H/Me	0.01	**7h**	77	90
9	H/H/Et	0.02	**7i**	86	90
10[e]	H/H/Ph	0.02	**7j**	94	77

[a] Unless indicated otherwise, reactions of 3-diazooxindoles **1** (0.10 mmol), **2** (0.10 mmol, PG = Me), **6** (0.20 mmol), with **4g** (0.010 mmol) and x mmol% $Rh_2(esp)_2$ were carried out in $CHCl_3$ (1.0 mL), at -60 ℃, for 12 h. [b] Isolated yield. [c] Determined by HPLC. [d] PG = H. [e] 10 mol% of **4c** was used instead of **4g**.

required 0.05 mol% of $Rh_2(esp)_2$ to ensure the generation of the desired products in good yields (entries 7 and 12). The subsituent on either C6- or C7-position of 3-diazooxindoles **1** had negative effect on the stereocontrol regardless of the electron feature (entries 10-12). By converting **5a** and a known compound into the same derivative, the absolute configuration of **5** were determined to be S (See Scheme S1 in SI for details).

Other electrophiles such as α, β-unsaturated carbonyls could also be adopted in the sequential C-H functionalization/asymmetric Michael addition[17f] sequentially catalyzed by $Rh_2(esp)_2$ and the chiral phosphine **4g** (See Figure S2 in SI for the detailed evaluation of chiral phosphines). Under the optimal conditions (See Table S2 in SI for details), high yields and excellent enantioselectivities were generally provided (Table 3). Non-protected indole was also permitted to undergo a clean reaction, however, with a much diminished enantioselectivity of 56% ee (entry 2), presumably due to that the H-bonding interaction between the catalyst and substrate was cleaved.[17i] Again, the presence of electron-donating substituents at the indole moiety gave higher enantioelectivity than those with an electron-deficient substituent (entries 3-8). Moreover, ethyl- and phenyl vinyl ketones underwent a clean reaction to generate **7i** and **7j** in high yields and with excellent or good levels of stereocontrol. By converting **7b** and a known



Scheme 3 Synthesis of a spirocycle from **7a**.

compound into a same derivative, the absolute configuration of **7** were determined to be S (See Scheme S2 in SI for details).

Products obtained from these Rh(II)/chiral phosphine sequentially catalytic protocols could be transformed into a structurally more complicated spirocyclic 3,3′-indolyloxindole through classical procedures. For example, in the presence of excess amounts of $BF_3{\cdot}Et_2O$, the Boc group of **7a** was firstly removed to give **A**, which then underwent an intramolecular Friedel-Crafts/dehydration process, to generate a spirocycle **8** (Scheme 3).

According to previous findings,[4d] the one-pot reactions might principally encompass two catalytic cycles (Figure 2), including a insertion reaction of rhodium carbene species to C-H bond[22] to generate a nucleophilic intermediate **9**. In the sequential C-H functionalization/allylation reaction, a lithium-stabilized phosphonium enolate **10** would be generated, as suggested by previous LiCl-promoted nucleophilic catalysis,[23] and worked as a stronger base to facilitate the enolization of **9** and thereby led to the improved yield (entry 10 *vs* 11, Table 1). More importantly, the

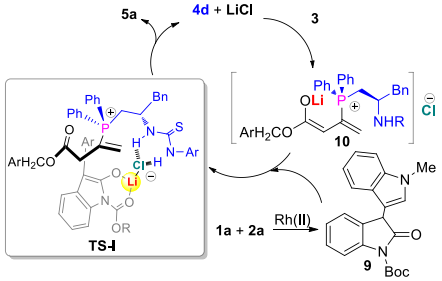


Figure 2 Proposed mechanism for the Rh(II)/chiral phosphine sequentially catalytic C-H functionalization/asymmetric allylation reaction.

LiCl, in combination with the bifunctional phosphine, constitutes a ternary synergistic activation system (that is, Lewis acid, hydrogen bonds and phosphine synergistic activation), as shown in the transition state **TS-I**, wherein the oxindole lithium enolate interacted with a chiral thiourea-chloride complex through Li-Cl coordination, as indicated by Jacobsen hypothesis,[24] to deliver

relatively higher levels of stereocontrol than the case in the absence of LiCl (entry 11 vs 12, Table 1). In contrast, the sequential process of C-H functionalization and Michael addition also involves the C-H insertion reaction to generate **9** while the formation of products **7** from **9** is considered to follow the general mechanism reported in the literature.[17f]

Conclusions

We have developed a combined catalyst system comprised of Rh(II) complexes and amino acid-derived chiral phosphines, enabling highly enantioselective sequential C-H functionalization/asymmetric addition reactions of indoles and 3-diazooxindoles with allenoates or vinyl ketones. These reactions afforded enantioenriched 3,3′-indolyloxindoles with unprecedented quaternary stereogenic center-linking patterns, which allowed further transformations into more complex molecules. Moreover, the positive effect of LiCl led to an unusual possibility that the lithium enolate might be able to form a chiral thiourea-chloride complex through Li-Cl coordination to assist the stereochemical control.

Acknowledgements

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