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FULL PAPER

Rhodium-Catalyzed Chemodivergent Regio- and Enantioselective Allylic Alkylation of Indoles

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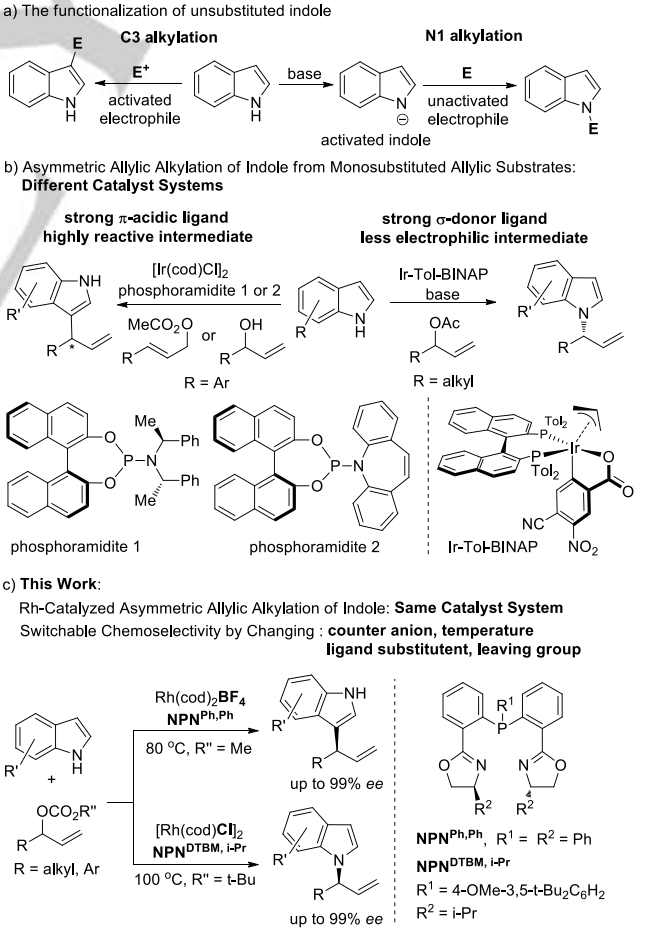
Abstract: The control of C3/N1 chemo-selectivity with the same electrophiles is still challenging in the indole alkylation. A Rh/bisoxazolinephosphine-catalyzed chemodivergent regio- and enantioselective allylic alkylation of indoles has been developed. Chiral C3- and N1-allylindoles can be selectively obtained in high branch/linear ratio and up to 99% *ee* by changing the counter anions of Rh, allylic carbonates, reaction temperatures and ligands.

Introduction

Indole skeleton is one of the privileged heterocycles and exists in many natural products and synthetic biologically active molecules.[1] The direct functionalization of indoles provides an efficient way to prepare valuable chiral indole derivatives. Because of the innate high nucleophilicity of the C3 position of unsubstituted indoles, enormous methods have been developed for the C3 alkylation, such as the asymmetric Friedel-Crafts type reactions with highly reactive electrophiles.[2] Nevertheless, the asymmetric N1-functionalization for the C3-unsubstituted indoles is much more challenging.[3] Careful selection of base, counter cation, solvent, temperature and additive is usually necessary to selectively get the N1-allylation products. Moreover, less activated electrophiles are normally used to avoid the C3 functionalization (Scheme 1, **a**). The predictable and chemo-switchable asymmetric C3/N1 alkylation of unsubstituted indoles with the same alkylation reagent is still very challenging and highly desirable.

Transition-metal-catalyzed asymmetric allylation[4] of indoles provides a powerful method to synthesize chiral C3 and N1-allyl indoles. Despite many reports on the chiral C3-allylindole synthesis,[5,6] highly branch- and enantioselective allylation of indoles from monosubstituted allylic precursors could be achieved by You and coworkers with iridium and π-acidic phosphoramidite ligands,[7a,b,c] in which highly reactive Ir(III)/π-allyl intermediates are involved (Scheme 1, **b**, left). Shen and Dong reported an asymmetric allylation of indoles with alkynes in the presence of chiral Rh complex.[7d] On the other hand, the asymmetric N1-allylation of indoles was successfully developed from either special indoles with electron-withdrawing groups[8] and C3-substitutents[9] or oxygen-substituted allylic precursors.[10] Indirect synthesis of chiral N-allylindoles from indolines, anilines and arylhydrazines is another solution.[11] Directly from unbiased indoles, the regio- and enantioselective N1[12]-allylic alkylation has only been realized recently by Krische group with less electrophilic neutral tol-BINAP-modified π-allyliridium-C, O-benzoate catalyst in the presence of base (Scheme 1, **b**, right).[13] No catalyst could realize the chemo-switchable asymmetric C3 and N1 allylation process due to the innate nature of the π-allyl-metal intermediates.[14]

Our group developed the new catalyst system based on Rh(I)/bisoxazolinephosphine to solve the regio- and enantioselective allylation from aliphatic allylic substrates with different nitrogen, carbon, oxygen and sulfur pronucleophiles.[15, 16] The easy modification of the counter anions and ligands as well as the broad reaction temperature range and the utilization of released base enables the flexible adjudgment of the electrophilicity of the π-allylrhodium intermediate. In this study,



Scheme 1. Transition-metal-catalyzed enantioselective C3- and N1-allylation of unsubstituted indoles.

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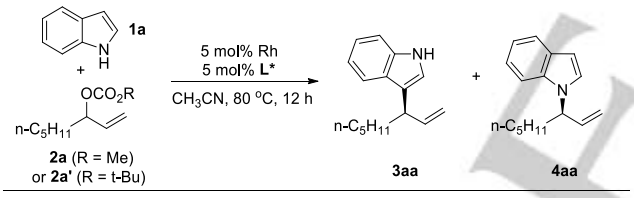
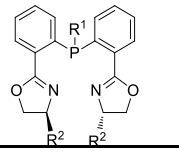
we present the chemo-switchable regio- and enantioselective allylic alkylation of unbiased indoles. C3-allylindoles could be obtained exclusively from allyl methyl carbonates in above 20 : 1 branch/linear ratio and up to 99% *ee* with $Rh(cod)_2BF_4$ and $NPN^{Ph, Ph}$ as catalyst at 80 °C. While, N1-allyl indoles were prepared from allyl t-butyl carbonates in normally the same level of regio- and enantioselectivity with $[Rh(cod)Cl]_2$ and $NPN^{DTBM, i\text{-}Pr}$ at 100 °C (Scheme 1, **c**).

Results and Discussion

The research started with allylic methyl carbonate **1a** bearing simple alkyl group and unsubstituted indole **2a** as model substrates (Table 1). Using $Rh(cod)_2BF_4$ and NPN-type ligand **L1** as the catalyst in CH_3CN at 80 °C, C3-allylation product **3aa** could be obtained in 60% yield, above 20 : 1 branch/linear ratio and 98% *ee* as the only product (entry 1). The yield could be further improved to 93% when **L2** was applied as the ligand (entry 2). To our surprise, when $[Rh(cod)Cl]_2$ was used instead of $Rh(cod)_2BF_4$, N1-allylation product **4aa** was isolated in 41% yield and 97% *ee* as the main product, along with 15% of **3aa** (entry 3). This result inspires us to explore whether the N1-allylation product can be obtained solely by adjusting the reaction conditions, which is still a big challenge in the direct functionalization of indoles. The yield of **4aa** increased to 51% by carrying out the reaction at 100 °C (entry 4). When the methyl group in the allyl carbonate **2a** was replaced by t-Bu group, **4aa** could be obtained in 88% yield and 95% *ee* (entry 5). The substituents on the ligands have a significant effect on the selectivities of the products. **3aa** was isolated as the main product when **L2** with phenyl as the R^2 groups on the oxazoline rings was used under otherwise the same condition (entry 6). **L3** with electron-withdrawing 4-$CF_3C_6H_4$ group lead to lower ratio of the N1-allylation product **4aa**, while the highest 90% yield and 99% *ee* were obtained when **L4** with 4-MeO-3,5-dit-BuC_6H_2 (DTBM) group at R^1 position was applied (entries 7 and 8).

Table 1. Optimization of reaction conditions.[a]





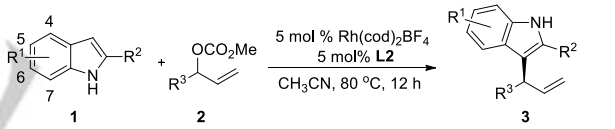
L1, R^1 = Ph, R^2 = i-Pr
L2, R^1 = Ph, R^2 = Ph
L3, R^1 = 4-$CF_3C_6H_4$, R^2 = i-Pr
L4, R^1 = 4-OMe-3,5-t-$Bu_2C_6H_2$, R^2 = i-Pr

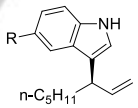
entry	R	Rh salts	L*	**3aa** (%)[b]	**4aa** (%)[b]
1	Me	$Rh(cod)_2BF_4$	**L1**	60(98)	0
2	Me	$Rh(cod)_2BF_4$	**L2**	93(98)	0
3	Me	$[Rh(cod)Cl]_2$	**L1**	15(98)	41(97)
4	Me	$[Rh(cod)Cl]_2$	**L1**	15(98)	51(95)
5[c,d]	*t*-Bu	$[Rh(cod)Cl]_2$	**L1**	8(98)	88(95)
6[c,d]	*t*-Bu	$[Rh(cod)Cl]_2$	**L2**	65(93)	24(92)
7[c,d]	*t*-Bu	$[Rh(cod)Cl]_2$	**L3**	11(99)	66(93)
8[c,d]	*t*-Bu	$[Rh(cod)Cl]_2$	**L4**	6(99)	90(99)

[a] All reactions were run with 5 mol% rhodium and 5 mol% ligand on a 0.2 mmol scale in 1 ml CH_3CN unless otherwise noted. [b] Yield of isolated product and the numbers in the parentheses were the ee values. [c] The reaction was carried out at 100 °C. [d] 36 hours.

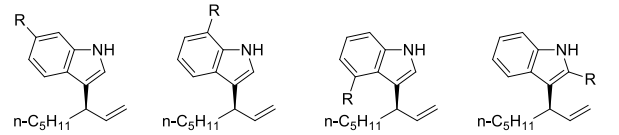
With the optimized conditions in hand, we firstly investigated the scope of indoles and allylic methyl carbonates for C3-allylation (Table 2). Indoles with a halogen substituent at the 5-position react smoothly to give the C3-allylation products **3ba** to **3ea** in high yields and *ee*s. Electron-neutral methyl, phenyl, vinyl and phenylacetylide groups have neglectable effect on the results of the reactions (**3fa** to **3ia**). Moderately electron-deficient ester and aldehyde groups can slow down the C3-allylation reactions (**3ja** and **3ka**), while only N1-allylation products could be observed when indoles **1l** and **1m** with strong electron-withdrawing CN and nitro groups were used. The absolute configuration of **3ja** was assigned to be *R* by single crystal X-ray diffraction analysis.[17] Electron-donating methoxy group at 5-position also make the reaction be sluggish, probably due to the lower acidity of the N-H proton (**3na**). In addition, electron-withdrawing chloride and electron-donating MeO groups at 4, 6, and 7 positions of the indole skeletion have little influence on the yields and enantioselectivities (**3oa** to **3ta**). Under the standard reaction conditions, indoles with methyl and phenyl groups at the

Table 2. Scope of Rh-catalyzed Regio- and Enantioselective C3-Allylation of Indoles[a]

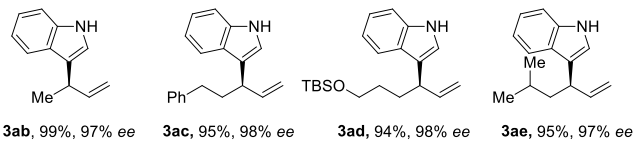




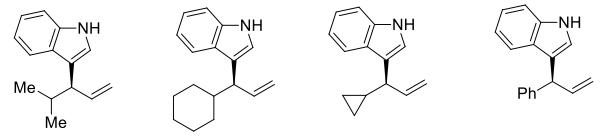
R = F, **3ba**, 95%, 98% ee
R = Cl, **3ca**, 92%, >99% ee
R = Br, **3da**, 92%, 98% ee
R = I, **3ea**, 85%, 99% ee
R = Me, **3fa**, 92%, 98% ee
R = Ph, **3ga**, 94%, 99% *ee*
R = vinyl, **3ha**, 94%, 96% *ee*
R = CCPh, **3ia**, 91%, 98% *ee*
R = COOMe, **3ja**, 85%, 97% *ee*
R = CHO, **3ka**, 70%, 98% *ee*
R = OMe, **3na**, 76%, >99% *ee*



R = Cl, **3oa** 95%, 99% *ee*
R = OMe, **3pa** 89%, 99% *ee*
R = Cl, **3qa** 80%, 96% *ee*
R = OMe, **3ra** 90%, 98% *ee*
R = Cl, **3sa** 95%, 98% *ee*
R = OMe, **3ta** 93%, 98% *ee*
R = Me, **3ua** 97%, 99% *ee*
R = Ph, **3va** 83%, 99% *ee*



3ab, 99%, 97% *ee*
3ac, 95%, 98% *ee*
3ad, 94%, 98% *ee*
3ae, 95%, 97% *ee*



3af, 80%, 98% *ee*
3ag, 87%, 99% *ee*
3ah, 92%, 94% *ee*
3ai, 90%, 88% *ee*

[a] Conditions: 0.2 mmol **1** and 0.3 mmol **2** in 1 ml CH_3CN were used as the standard condition.

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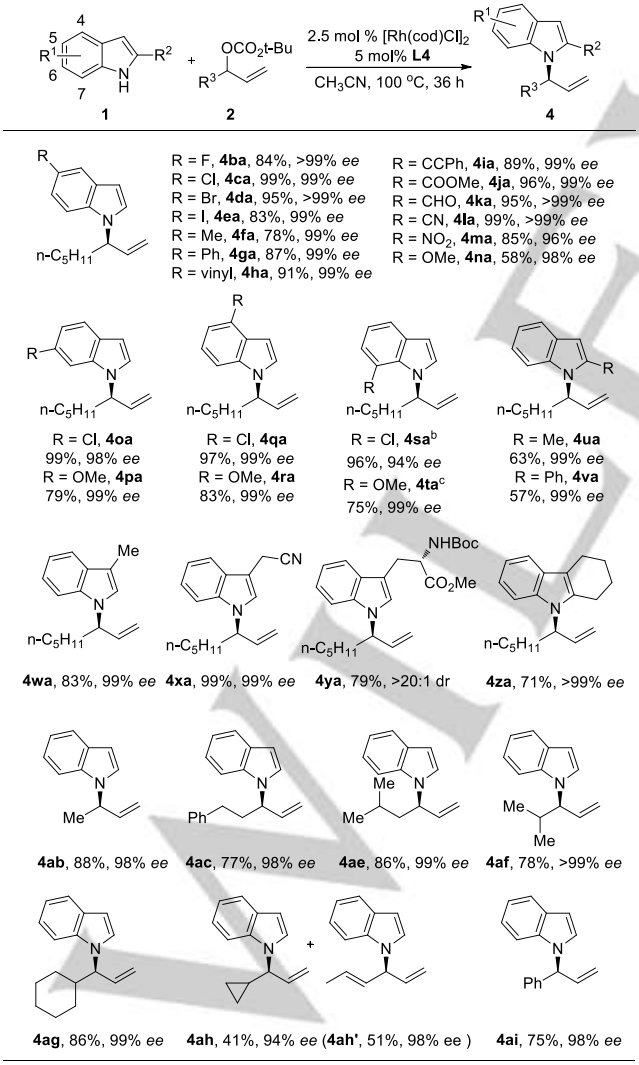
2- position can also be tolerated in the C3-allylation reaction (**3ua** and **3va**). On the other side, we also investigated the scope of allyl carbonates. Allylic methyl carbonates with simple methyl, phenylethyl and TBS-protected hydroxyl group react effciently with **1a** to give **3ab** to **3ad** in high yields and *ee*s. Sterically more hindered isobutyl, isopropyl, cyclohexyl and cyclopropyl groups could be introduced by the allylic substitution to give corresponding allylic indoles **3ae** to **3ah**. Phenyl-substituted allylic carbonate can also react to produce the target product in high yield, although a slightly reduced 88% *ee* was obtained (**3ai**). No dearomative C3-allylation products were obtained when 3-methylindole was used.

The reaction scope of N1-allylation was evaluated with the same indoles and allylic t-butyl carbonates (Table 3). Similar to the C3-allylation reactions, various indoles with halogens (**1b** to **1e**), and electron-neutral groups (**1f** to **1i**) react in the presence of $[Rh(cod)Cl]_2$/**L4** at 100 °C to give the N1-allylation products in high yields and enantioselectivities. Strong electron-withdrawing ester, aldehyde, cyano and nitro groups at 5-position can also be tolerated in **4ja** to **4ma**. Relatively lower 58% yield of **4na** was obtained when indole **1n** with electron-donating MeO group at 5-position was used. It is gratifying that the yields and

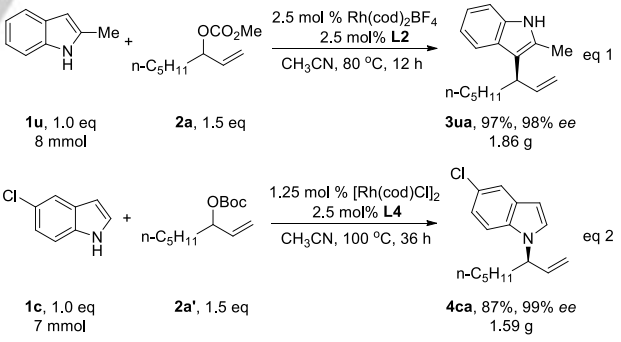
Table 3. Reaction scope of indoles and carbonates for N1-allylation[a]



[a] Conditions: 0.2 mmol **1** and 0.3 mmol **2** in 1 ml of CH_3CN were used as the standard condition. [b] B : L = 10 : 1. [c] B : L = 16 : 1.

enantioselectivities of the products with chlorides and MeO groups at 4- or 6-positions of the indole phenyl ring are also excellent (**4oa** to **4ra**). Relatively lower branch/linear ratios were observed when 7-Chloro and MeO indoles were used, probably due to the bulky environment at the nitrogen atoms. The reactions of 2-methyl or 2-phenylindoles are slower under standard reaction condition (**4ua** and **4va**). A series of 3-substituted indoles can also undergo the N1-allylation reaction (**4wa** and **4xa**). Protected tryptophan could be N1-allylated diastereoselectively, with the Boc-protected amine untouched (**4ya**). The N1-allylated indole **4za** with both 2 and 3 positions blocked can be isolated in 71% yield and >99% *ee*. Allylic carbonates with simple methyl and phenylethyl groups react under the standard condition to give **4ab** and **4ac** in high yields and *ee*s. Sterically more hindered isobutyl, isopropyl, and cyclohexyl groups could be introduced by the allylic amination to give corresponding N1-allylic indoles in high yields with excellent enantioselectivities (**4ae**, **4af** and **4ag**). It is worth noting that 51% of ring opening product **4ah'** of the cyclopropyl group by oxidative addition with Rh(I) was observed when allyl carbonate with a cyclopropyl group was used, along with 41% regular product **4ah**. In addition, phenyl substituted allyl indole **4ai** can also be obtained in 75% yield and 98% *ee* under standard condition. The absolute configuration of **4ab** to **4ag** was assigned to be *R* by comparison of their optical rotation to literature reported values.[12]

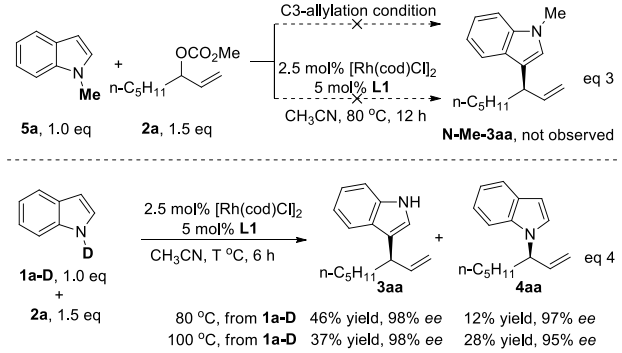
To demonstrate the practicality of the Rh-catalyzed regio- and enantioselective indole C3- and N1-allylation reactions, gram-scale synthesis was conducted (Scheme 2). 8 mmol of 2-methylindole **1u** was converted to 1.86 g of C3-allyl indole **3ua** (97% yield, 98% *ee*) with 12 mmol of allylic carbonate **1a** under 2.5 mol% catalyst (eq 1). Similarly, 1.59 g of N1-allyl indole **4ca** (87% yield, 99% *ee*) can be prepared from 7 mmol of 5-chloroindole **1c** and 10.5 mmol of allylic carbonate **2a'** under the catalysis of 1.25 mol% of $[Rh(cod)Cl]_2$/**L4**.



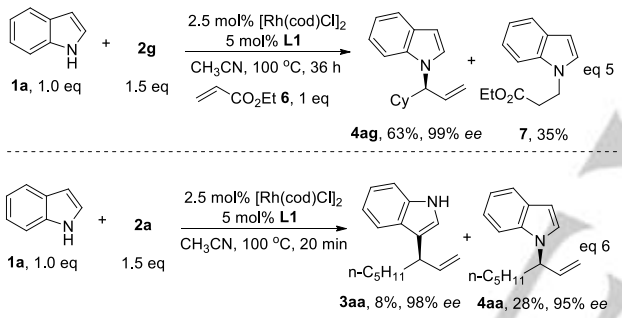
Scheme 2. Gram-Scale Synthesis.

To understand the counter-anion-switched chemo-selectivity of indole allylation, several control experiments were conducted. When N-methylindole **5a** was used as the substrate, no C3-allylation product could be isolated under either the standard C3-allylation or the N1-allylation condition (eq 3). This result suggests the π-allyl-Rh intermediate is not electrophilic enough for a Friedel-Crafts type allylation with neutral indole. A deprotonation of indole may occur in the C3-allylation process. N-deuterated indole **1a-D** was utilized to investigated the mechanism. We found the deprotonation step can switch the C3/N1 chemoselectivity (eq 4). **4aa** was the major product from normal indole **1a** (entry 3,

Table 1). However, when **1a-D** was used, the C3-allylation **3aa** became the main product, which indicates that N1-allylation is less favored when the deprotonation becomes difficult. The ratio of **4aa** increased when the reaction was conducted at 100 °C, at which the deprotonation is more effective.

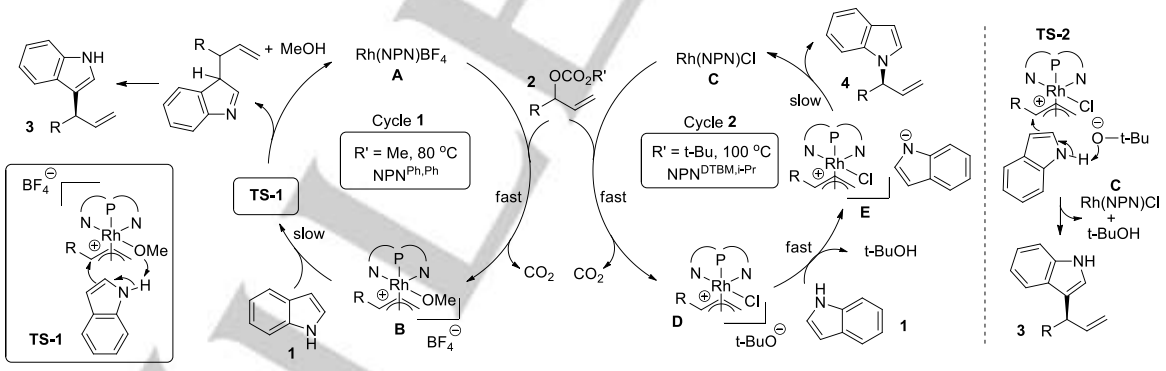


A naked N-indole anion was proposed for the formation of N1-allylation. This possible anion could be trapped as **7** when 1 equivalent of ethyl acrylate **6** was added (eq 5). The formation of 8% **3aa** under the optimized N1-allylation condition was observed when the reaction was stopped after 20 minutes. This result could be explained by the less efficient deprotonation at lower temperature during the temperature raising time (eq 6).



Kinetic study for both C3- and N1-allylations was performed (See the supporting information). The initiate reaction rate of C3-allylation is zero-order to the allylic carbonate and first order to the indole and the catalyst. The formation of π-allylic-Rh intermediate is a fast step. While, The initiate reaction rate of N1-allylation is zero-order to both the allylic carbonate and indole. The C-N bond formation process is is very likely to be the rate determining step.

Based on the experiments above and our previous study,[16a] two catalytic cycles were proposed for C3 and N1 allylation respectively in Scheme 3. When $Rh(cod)_2BF_4$/**L2** is used as the catalyst, fast oxidative addition of allyl methyl carbonate **2** with cationic Rh(I) produces the 6-coordinate π-allyl/rhodium/NPN complex intermediate **B**, in which methoxide anion is bound to rhodium (Cycle 1). A concerted deprotonation of N-H by the bounded MeO group and nucleophilic attack of C3 to the mono-cationic **B** via **TS-1** leads to the formation of C3-allylation product **3** and regenerates the $Rh(NPN)BF_4$ **A** and releases methanol.[18] Alternatively, when $[Rh(cod)Cl]_2$/**L1** or **L4** is utilized as catalyst, oxidative addition with allyl t-butyl carbonate **2'** generates the mono-cationic π-allyl/rhodium intermediate **D** with a basic t-BuO anion in the outer sphere. Fast deprotonation of indole by this t-BuO anion results in the formation of another intermediate **E** as an ionic pair, in which the N-indole anion is located out of the coordination sphere of Rh, but not bound to Rh. The mono-cationic π-allyl-Rh complex acts as the countercation. Outer-sphere nucleophilic attack of N-centered indole anion to the carbon in π-allyl/rhodium complex produces the N1-allylation product **4** and releases catalyst **C** (Cycle 2). However, when the reaction was conducted at lower temperature or with weaker base, the generation of **E** is challenging. Small amount of C3-allylation product **3** could be formed via **TS-2**.



Scheme 3. Mechanistic Proposal

Conclusion

We have developed a Rh(I)/bisoxazolinephosphine-catalyzed chemodivergent regio- and enantioselective allylic alkylation of unbiased indoles. The easy modification on the π-allylrhodium complex in this catalyst system enables the switchable reactivities of the indole nucleophiles, which provides a better understanding about the chemoselective funcationalization of indoles. By changing the catalyst precursors, allylic carbonates, reaction temperatures and ligands, C3- or N1-allylindoles can be selectively obtained in high branch/linear ratio and up to 99% *ee*. Future work will explore the sophisticated control of various challenging selectivities for other nucleophiles under the Rh/bisoxazolinephosphine catalyst system.

Acknowledgements

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Keywords: Allylic Substitutions • Rhodium • Indole • Asymmetric Catalysis • Chemo-divergent

[1] For the synthesis of indole based biologically active molecules, see: a) U. Scholz, E. Winterfeldt, *Nat. Prod. Rep.* **2000**, *17*, 349-366; b) G. R. Humphrey, J. T. Kuethe, *Chem. Rev*. **2006**, *106*, 2875-2911; c) S. E. O'Connor, J. J. Maresh, *Nat. Prod. Rep*. **2006**, *23*, 532-547; d) A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev*. **2010**, *110*, 4489-4497; e) J.-B. Chen, Y.-X. Jia, *Org. Biomol. Chem*. **2017**, *15*, 3550-3567; f) C. Zheng, S.-L. You, *Nat. Prod. Rep*. **2019**, *36*, 1589-1605.

[2] For selected reviews on asymmetric Friedel-Crafts type functionalization of indoles, see: a) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem. Int. Ed*. **2004**, *43*, 550-556; *Angew. Chem*. **2004**, *116*, 560-566; b) T. B. Poulsen, K. A. Jørgensen, *Chem. Rev*. **2008**, *108*, 2903-2915; c) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev*. **2009**, *38*, 2190-2201; d) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed*. **2009**, *48*, 9608-9644; e) M. Zeng, S.-L. You, *Synlett*. **2010**, *9*, 1289-1301; f) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev*. **2010**, *39*, 4449-4465.

[3] For selected examples on the asymmetric synthesis of N1-alkyl indoles, see: a) M. Bandini, A. Eichholzer, M. Tragni, A. Umani-Ronchi, *Angew. Chem. Int. Ed.* **2008**, *47*, 3238-3241; *Angew. Chem.* **2008**, *120*, 3282-3285; b) H.-L. Cui, X. Feng, J. Peng, J. Lei, K. Jiang, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 5737-5740; *Angew. Chem*. **2009**, *121*, 5847-5850; c) Y. Xie, Y. Zhao, B. Qian, L. Yang, C. Xia, H. Huang, *Angew. Chem. Int. Ed*. **2011**, *50*, 5682-5686; *Angew. Chem*. **2011**, *123*, 5800-5804; d) H.-G. Cheng, L.-Q. Lu, T. Wang, Q.-Q. Yang, X.-P. Liu, Y. Li, Q.-H. Deng, J.-R. Chen, W.- J. Xiao, *Angew. Chem. Int. Ed*. **2013**, *52*, 3250-3254; *Angew. Chem*. **2013**, *125*, 3332-3336; e) Q. M. Kainz, C. D. Matier, A. Bartoszewicz, S. L. Zultanski, J. C. Peters, G. C. Fu, *Science* **2016**, *351*, 681-684; f) M. Chen, J. Sun, *Angew. Chem. Int. Ed*. **2017**, *56*, 4583-4587; *Angew. Chem*. **2017**, *129*, 4654-4658; g) B. M. Trost, E. Gnanamani, C.-I. Hung, *Angew. Chem. Int. Ed*. **2017**, *56*, 10451-10456; *Angew. Chem*. **2017**, *129*, 10587-10592; h) Y. Zi, M. Lange, C. Schultz, I. Vilotijevic, *Angew. Chem. Int. Ed*. **2019**, *58*, 10727-10731; *Angew. Chem*. **2019**, *131*, 10837-10841; i) Y. Ye, S.-T. Kim, J. Jeong, M.-H. Baik, S. L. Buchwald, *J. Am. Soc. Chem*. **2019**, *141*, 3901-3909; j) J. R. Allen, A. Bahamonde, Y. Furukawa, M. S. Sigman, *J. Am. Chem. Soc*. **2019**, *141*, 8670-8674; k) Y. Wang, S. Wang, W. Shan, Z. Shao, *Nat. Commun*. **2020**, *11*, 226.

[4] For a recent book on transition-metal-catalyzed asymmetric substitutions, see: a) *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*, (Eds.: U. Kazmaier), Springer Verlag: Berlin and Heidelberg, Germany, **2012**. For selected reviews on Pd, see: b) B. M. Trost, D. L. Van Vranken, *Chem. Rev*. **1996**, *96*, 395-422; c) B. M. Trost, M. L. Crawley, *Chem. Rev*. **2003**, *103*, 2921-2943; d) Z. Lu, S. Ma, *Angew. Chem. Int. Ed*. **2008**, *47*, 258-297; *Angew. Chem*. **2008**, *120*, 264-303. For selected reviews, on Ir, see: e) J. F. Hartwig, L. M. Stanley, *Acc. Chem. Res.* **2010**, 43, 1461-1475; f) J. Qu, G. Helmchen, *Acc. Chem. Res.* **2017**, *50*, 2539-2555; g) Q. Cheng, H.-F. Tu, C. Zheng, J.-P. Qu, G. Helmchen, S.-L. You, *Chem. Rev*. **2019**, *119*, 1855-1969; h) S. L. Rössler, D. A. Petrone, E. M. Carreira, *Acc. Chem. Res*. **2019**, *52*, 2657-2672. For reviews on Rh-catalyzed asymmetric allylic substitutions,, see: i) J. S. Arnold, Q. Zhang, H. M. Nguyen, *Eur. J. Org. Chem*. **2014**, 4925−4948; j) P. Koschker, B. Breit, *Acc. Chem. Res*. **2016**, *49*, 1524-1536; k) B. W. H. Turnbull, P. A. Evans, *J. Org. Chem*. **2018**, *83*, 11463-11479; l) M. B. Thoke, Q. Kang, *Synthesis* **2019**, *51*, 2585-2631; For other metals, see: m) C. Moberg, *Top. Organomet. Chem*. **2012**, *38*, 209-234; n) V. Hornillos, J.-B. Gualtierotti, B. L. Feringa, *Top. Organomet. Chem*. **2016**, *58*, 1-40.

[5] For the asymmetric C3-allylation of indoles with symmetric substrates, see: a) H. Y. Cheung, W.-Y. Yu, F. L. Lam, T. T.-L. Au-Yeung, Z. Zhou, T. H. Chan, A. S. C. Chan, *Org. Lett*. **2007**, *9*, 4295-4298; b) T. Hoshi, K. Sasaki, S. Sato, Y. Ishii, T. Suzuki, H. Hagiwara, *Org. Lett*. **2011**, *13*, 932-935; c) Z. Cao, Y. Liu, Z. Liu, X. Feng, M. Zhuang, H. Du, *Org. Lett*. **2011**, *13*, 2164-2167; d) Z. Liu, Z. Cao, H. Du, *Org. Biomol. Chem*. **2011**, *9*, 5369-5372; e) B. Feng, X.-Y. Pu, Z.-C. Liu, W.-J. Xiao, J.-R. Chen, *Org. Chem. Front*. **2016**, *3*,1246–1249; f) S. Panda, J. M. Ready, *J. Am. Chem. Soc*. **2017**, *139*, 6038-6041; g) T. Mino, D. Yamaguchi, C. Masuda, J. Youda, T. Ebisawa, Y. Yoshida, M. Sakamoto, *Org. Biomol. Chem*. **2019**, *17*, 1455-1465. For asymmetric C3-allylation of indoles with unsymmetric disubstituted allylic substrates, see: h) L. Du, P. Cao, J. Xing, Y. Lou, L. Jiang, L. Li, J. Liao, *Angew. Chem. Int. Ed.* **2013**, *52*, 4207-4211; *Angew. Chem*. **2013**, *125*, 4301-4305.

[6] For the asymmetric dearomative C3-allylation of 3-substituted indoles, see: a) B. M. Trost, J. Quancard, *J. Am. Chem. Soc*. **2006**, *128*, 6314-6315; b) Y. Liu, H. Du, *Org. Lett.* **2013**, *15*, 740-743; c) X. Zhang, L. Han, S.-L. You, *Chem. Sci*. **2014**, *5*, 1059-1063; d) X. Zhang, W.-B. Liu, H.-F. Tu, S.-L. You, *Chem. Sci*. **2015**, *6*, 4525-4529; e) J. M. Müller, C. B. W. Stark, *Angew. Chem. Int. Ed*. **2016**, *55*, 4798-4802; *Angew. Chem*. **2016**, *128*, 4877-4881; f) R.-D. Gao, Q.-L. Xu, B. Zhang, Y. Gu, L.-X. Dai, S.-L. You, *Chem. Eur. J.* **2016**, *22*, 11601-11604; g) R.-D. Gao, L. Ding, C. Zheng, L.-X. Dai, S.-L. You, *Org. Lett*. **2018**, *20*, 748-751; h) B. M. Trost, W.-J. Bai, C. Hohn, Y. Bai, J. J. Cregg, *J. Am. Chem. Soc*. **2018**, *140*, 6710-6717.

[7] a) W.-B. Liu, H. He, L.-X. Dai, S.-L. You, *Org. Lett*. **2008**, *10*, 1815-1818; b) W.-B. Liu, H. He, L.-X. Dai, S.-L. You, *Synthesis* **2009**, 2076-2082; c) J. A. Rossi-Ashton, A. K. Clarke, J. R. Donald, C. Zheng, R. J. K. Taylor, W. P. Unsworth, S.-L. You, *Angew. Chem. Int. Ed.* **2020**, *59*, 7598-7604; *Angew. Chem*. **2020**, *132*, 7668-7674; d) F. A. Cruz, Y. Zhu, Q. D. Tercenio, Z. Shen, V. M. Dong, *J. Am. Chem. Soc*. **2017**, *139*, 10641-10644.

[8] a) L. M. Stanley, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2009**, *48*, 7841-7844; *Angew. Chem*. **2009**, *121*, 7981-7984; b) B. M. Trost, M. Osipov, G. Dong, *J. Am. Chem. Soc*. **2010**, *132*, 15800-15807; c) K.-Y. Ye, Q. Cheng, C.-X. Zhuo, L.-X. Dai, S.-L. You, *Angew. Chem. Int. Ed*. **2016**, *55*, 8113-8116; *Angew. Chem*. **2016**, *128*, 8245-8248.

[9] L.-Y. Chen, X.-Y. Yu, J.-R. Chen, B. Feng, H. Zhang, Y.-H. Qi, W.-J. Xiao, *Org. Lett*. **2015**, *17*, 1381-1384.

[10] For an example of N1 allylation from oxygen-substituted allenes, see: S. H. Jang, H. W. Kim, W. Jeong, D. Moon, Y. H. Rhee, *Org. Lett*. **2018**, *20*, 1248-1251.

[11] a) W.-B. Liu, X. Zhang, L.-X. Dai, S.-L. You, *Angew. Chem. Int. Ed*. **2012**, *51*, 5183-5187; *Angew. Chem*. **2012**, *124*, 5273-5277; b) K.-Y. Ye, L.-X. Dai, S.-L. You, *Chem. Eur. J*. **2014**, *20*, 3040-3044; c) Q.-A. Chen, Z. Chen, V. M. Dong, *J. Am. Chem. Soc.* **2015**, *137*, 8392-8395; d) K. Xu, T. Gilles, B. Breit, *Nat. Commun*. **2015**, *6*, 7616.

[12] For non-asymmetric N1-allylation, see: a) M. R. Luzung, C. A. Lewis, P. S. Baran, *Angew. Chem. Int. Ed*. **2009**, *48*, 7025−7029; *Angew. Chem*. **2009**, *121*, 7159−7163; b) C.-Y. Chang, Y.-H. Lin, Y.-K. Wu, *Chem. Commun*. **2019**, *55*, 1116-1119.

[13] a) S. W. Kim, T. T. Schempp, J. R. Zbieg, C. E. Stivala, M. J. Krische, *Angew. Chem. Int. Ed*. **2019**, *58*, 7762-7766; *Angew. Chem*. **2019**, *131*, 7844-7848. For other examples of neutral π-allyliridium-C, O-benzoate catalyst, see: b) A. T. Meza, T. Wurm, L. Smith, S. W. Kim, J. R. Zbieg, C. E. Stivala, M. J. Krische, *J. Am. Chem. Soc.* **2018**, *140*, 1275-1279; c) S. W. Kim, L. A. Schwartz, J. R. Zbieg, C. E. Stivala, M. J. Krische, *J. Am. Chem. Soc.* **2019**, *141*, 671-676.

[14] For examples of non-chiral version on the C3/N1 control of indoles, see: a) M. Bandini, A. Melloni, A. Umani-Ronchi, *Org. Lett*. **2004**, *6*, 3199-3202; b) X. Fang, Q. Li, R. Shi, H. Yao, A. Lin, *Org. Lett*. **2018**, *20*, 6084-6088.

[15] For Co/bisoxazolinephosphine-catalyzed asymmetric allylic substitutions, see: a) S. Ghorai, S. S. Chirke, W.-B. Xu, J.-F. Chen, C. Li, *J. Am. Chem. Soc.* **2019**, *141*, 11430−11434; b) S. Ghorai, S. U. Rehman, W.-B. Xu, W.-Y. Huang, C. Li, *Org. Lett*. **2020**, *22*, 3519-3523. The indoles allylation reaction cannot be catalyzed by the Co/bisoxazolinephosphine catalyst.

[16] For Rh/NPN-catalyzed asymmetric allylic substitutions, a) W.-B. Xu, S. Ghorai, W. Huang, C. Li, *ACS Catal*. **2020**, *10*, 4491-4496; b) W.-Y. Huang, C.-H. Lu, S. Ghorai, B. Li, C. Li, *J. Am. Chem. Soc.* **2020**, *142*,

10.1002/chem.202004613

15276−15281. c) M. Liu, H. Zhao, C. Li, *Chin*. *Chem*. *Lett*. doi.org/10.1016/j.cclet.2020.04.009.

[17] CCDC 2015163 (**3ja**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The For Cambridge Crystallographic Data Centre.

[18] For a proposed interaction between indole N-H and hydrogen bond acceptor in the π-allylmetal complex, see ref. 5h.

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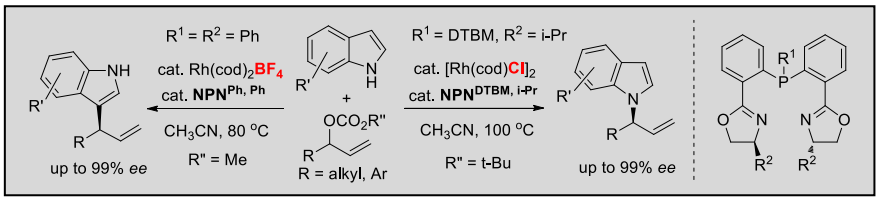

Chemodivergent regio- and enantioselective allylic alkylation of indoles has been developed with rhodium/bisoxazolinephosphine. C3- or N1 selectivity could be controlled by changing the counter anions of Rh, allylic carbonates, reaction temperatures and ligands.