A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201804080
Angew. Chem. 10.1002/ange.201804080

Link to VoR: http://dx.doi.org/10.1002/anie.201804080
http://dx.doi.org/10.1002/ange.201804080

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10.1002/anie.201804080

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Nickel(II)-Catalyzed Asymmetric Propargyl [2,3]-Wittig Rearrangement of Oxindole Derivatives: A Remarkable Chiral Amplification Effect

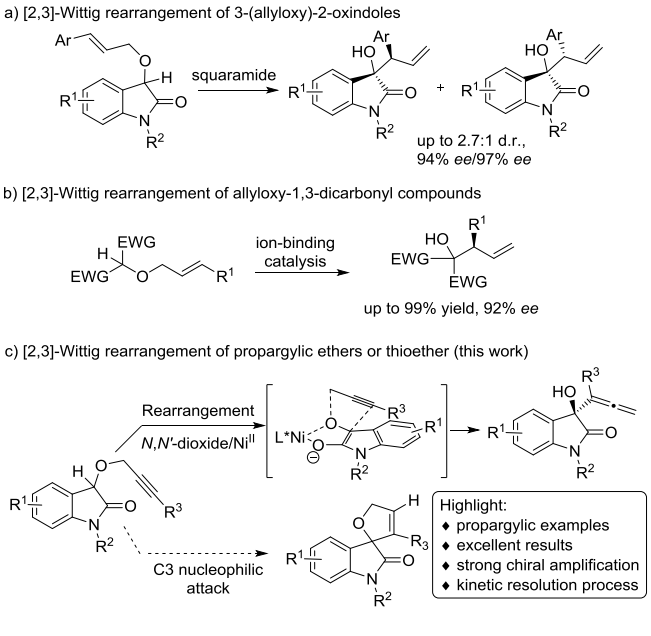
Xi Xu,[a] Jianlin Zhang,[a] Shunxi Dong,[a] Lili Lin,[a] Xiaobin Lin,[a] Xiaohua Liu[a] and Xiaoming Feng*[a,b]

Abstract: A highly enantioselective [2,3]-Wittig rearrangement of oxindole derivatives was realized by using a chiral *N*,*N*′-dioxide/Ni^{II} complex as catalyst under mild reaction conditions. A strong chiral amplification effect was observed, which allowed to access chiral 3-hydroxy 3-substituted oxindoles bearing allenyl groups in high yields and enantioselectivities (up to 92% *ee*) by using a ligand with only 15% *ee*. A reasonable explanation was given based on the experimental investigations and X-ray crystal structures of enantiomerically pure and racemic catalysts. Moreover, the first catalytic kinetic resolution of racemic oxindole derivatives via [2,3]-Wittig rearrangement was realized in high resolution efficiency and stereoselectivity.

[2,3]-Sigmatropic rearrangement has received considerable attention due to its utility in complex molecule synthesis.[1-3] Over recent years, significant advances have been made towards enantioselective catalysis of rearrangement with related ylides.[4] In comparison, anionic [2,3]-Wittig rearrangement has lagged, probably because strong bases are usually required to generate the carbanion as the promoter of the rearrangement. Methods based on chiral auxiliaries[5] or chiral substrates[6] have been developed for achieving chiral homoallyl alcohols. In addition, the enantioselective strategies involving stoichiometric amounts of chiral boron reagent[7], chiral bases or complexation of chiral ligands[8] with organolithium intermediate could afford enantioenriched rearrangement products. However, catalytic asymmetric [2,3]-Wittig rearrangements are rare. Inspired by Gaunt's work,[9] several organocatalytic examples have been reported so far. In 2015, Denmark′s group[10] presented the stereoselective rearrangements of 3-(allyloxy)-2-oxindoles and 2-(allyloxy)-1-tetralone, but moderate *ee* values (up to 54% *ee*) were obtained after investigation of various phase-transfer catalysts. In 2016, improved outcomes (up to 2.7:1 d.r., 94% *ee*/97% *ee*) were reported by Kanger′s group[11] by using squaramide (20 mol%) (Scheme 1a). Meanwhile, Jacobsen and coworkers described their unique strategy for the rearrangement of allyloxy-1,3-dicarbonyl compounds and high yields with good enantioselectivities (up to 99% yield, 92% *ee*, Scheme 1b) could be afforded under synergistic ion-binding catalysis.[12] Although great endeavors have been paid in this area as mentioned above, There is still greater room for promotion in this area in term of several limitations, such as high catalyst loading, low diastereoselectivities and limited substrates. In consequence, the discovery of other new efficient catalyst systems and new substrates for this reaction is a challenge but highly desirable.

[2,3]-Wittig rearrangement of propargylic ethers provides a direct route to synthetically valuable functionalized allenes. However, to date, there is no report on such kind of [2,3]-Wittig rearrangement, probably due to challenges encountered. Firstly, the proparagylic ethers show low reactivity in that the alkyne sp centers distort the transition-state geometries. Secondly, nucleophilic attack to alkyne may compete against direct [2,3]-Wittig rearrangement. Based on Lewis acid catalyzed [2,3]-Wittig rearrangement[13] and our previous works[14], we envisioned that *N*,*N*′-dioxide/Lewis acid complex could engage the anionic proparagyloxyoxindole substrate by coordination and induce stereoselective rearrangement. Herein, we describe the first process of such type using chiral *N*,*N*′-dioxide/Ni^{II} as catalysts leading to various 3-hydroxy 3-substituted oxindoles bearing allenyl groups with excellent yields and *ee* values (up to 99% yield and 99% *ee*).

We commenced our work with the *N*-benzyl protected 3-phenylproparagyloxyoxindole **1a** as the model substrate to optimize the reaction conditions, and the representative results were summarized in Table 1. Firstly, different metal salts complexing with *N*,*N*′-dioxide **L-PiPr$_2$** were examined in the presence of Na_2CO_3 in EtOAc at 35 °C (Table 1, entries 1-4). The complexes of $Cu(OTf)_2$ or $Yb(OTf)_3$ did not show any activity towards compound **1a** (entries 1 and 2). Pleasantly, the use of



Scheme 1. Asymmetric [2,3]-sigmatropic rearrangement.

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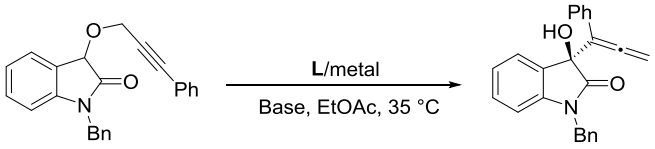
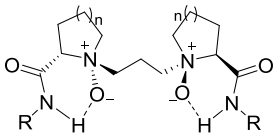
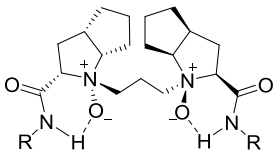
10.1002/anie.201804080

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







L-PrCHPh$_2$: R = Ph_2CH, n = 1
L-Pic*H*: R = cyclohexyl, n = 2
L-PiCHPh$_2$: R = Ph_2CH, n = 2
L-PiPr$_2$: R = 2,6-*i*$Pr_2C_6H_3$, n = 2
L-PisEPh: R = (*S*)-2-phenylethyl, n = 2

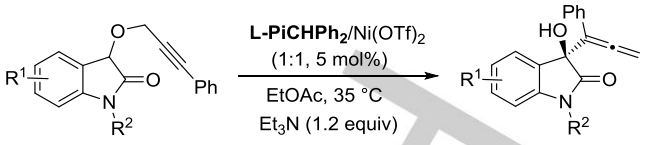
L-RaCHPh$_2$: R = Ph_2CH

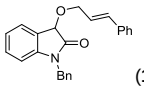
Entry	L	Metal salts	Base	Yield [%][b]	*ee* [%][c]
1	**L-PiPr$_2$**	$Yb(OTf)_3$	Na_2CO_3	trace	–
2	**L-PiPr$_2$**	$Cu(OTf)_2$	Na_2CO_3	n.r.	–
3	**L-PiPr$_2$**	$Sc(OTf)_3$	Na_2CO_3	26	56
4	**L-PiPr$_2$**	$Ni(OTf)_2$	Na_2CO_3	36	64
5	**L-PisEPh**	$Ni(OTf)_2$	Na_2CO_3	80	91
6	**L-PiCHPh$_2$**	$Ni(OTf)_2$	Na_2CO_3	99	97
7	**L-RaCHPh$_2$**	$Ni(OTf)_2$	Na_2CO_3	15	67
8	**L-PrCHPh$_2$**	$Ni(OTf)_2$	Na_2CO_3	22	93
9	**L-PiCHPh$_2$**	$Ni(OTf)_2$	Et_3N	97	99
10[d]	–	$Ni(OTf)_2$	Et_3N	18	–
11[e]	**L-PiCHPh$_2$**	$Ni(OTf)_2$	Et_3N	98	99
12[f]	**L-PiCHPh$_2$**	$Ni(OTf)_2$	Et_3N	84	96
13[g]	**L-PiCHPh$_2$**	$Ni(OTf)_2$	Et_3N	55	96

[a] Unless otherwise noted, all reactions were carried out with **L**/metal (1:1, 10 mol%), **1a** (0.10 mmol) and base (0.12 mmol) in EtOAc (1.0 mL) at 35 °C for 36 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] without ligands. [e] 5 mol% catalyst, 0.50 mL EtOAc. [f] 2.5 mol% catalyst, 0.50 mL EtOAc. [g] 1 mol% catalyst, 0.50 mL EtOAc. Tf = trifluoromethanesulfonyl.

$Sc(OTf)_3$ and $Ni(OTf)_2$ as the central metals could promote the rearrangement, providing the desired product **2a** in moderate yields and enantioselectivities (26% yield, 56% *ee* and 36% yield, 64% *ee*, entries 3 and 4). Subsequently, various ligands were investigated. It was found that switching aromatic amide group in the ligand to aliphatic one, the outcomes increased dramatically. The use of **L-PisEPh** with (*S*)-2-phenylethyl group led to the formation of product **2a** in 80% yield and 91% *ee* (entry 5). Furtherly, 99% yield and 97% *ee* could be afforded using **L-PiCHPh$_2$** with diphenylmethyl group as the ligand (entry 6). As for the backbones of ligands, L-pipecolic acid-derived **L-PiCHPh$_2$** was superior to L-proline-derived **L-PrCHPh$_2$** and L-ramipril-derived **L-RaCHPh$_2$**, especially in activity (entey 6 vs entries 7 and 8). The screening of other bases suggested that Et_3N could furtherly improve the enantioselectivity to 99% *ee* (entry 9). When the reaction was conducted in the absence of chiral ligand, low yield (18%) was obtained, indicating that strong ligand-accelerated catalysis (LAC)[15] exists in the current system (entry 10). Notably, there is no effect on the results when reducing the loading to 5 mol% (entry 11). Further decreasing the catalyst loading to 1 mol% resulted in much lower activity (55% yield) but with maintained *ee* value (96% *ee*, entry 13). In contrast, the rearrangement reaction showed poor reactivity and stereoselective control using oxazolines as the ligands, instead of **L-PiCHPh$_2$** (see SI for details). Therefore, the optimized conditions involved the use of 5 mol% **L-PiCHPh$_2$**/$Ni(OTf)_2$ as catalyst and Et_3N as an additive in EtOAc at 35 °C for 36 h.

Table 2. Substrate scope for substituents on the oxindoles.[a]



Entry	R^1, R^2	2	Yield [%][b]	*ee* [%][c]
1	H, Bn (**1a**)	**2a**	98	99
2	5-F, Bn (**1b**)	**2b**	68	87
3	5-Cl, Bn (**1c**)	**2c**	84	92
4	6-Cl, Bn (**1d**)	**2d**	84	96
5	4-Br, Bn (**1e**)	**2e**	90	97
6	5-Br, Bn (**1f**)	**2f**	99	93
7	6-Br, Bn (**1g**)	**2g**	91	96
8[d]	7-Br, Bn (**1h**)	**2h**	96	90
9	5-I, Bn (**1i**)	**2i**	99	94
10	5-Me, Bn (**1j**)	**2j**	94	>99
11	5-MeO, Bn (**1k**)	**2k**	97	>99
12	5,7-Me_2, Bn (**1l**)	**2l**	85	99
13	5-F_3CO, Bn (**1m**)	**2m**	90	92
14	H, H (**1n**)	**2n**	51	99
15	H, Me (**1o**)	**2o**	63	99
16	H, *i*Pr (**1p**)	**2p**	83	99
17[e]	 (**1q**)	**2q**	98	99/97 (3.3/1 d.r.)

[a] Unless otherwise noted, all reactions were carried out with **L-PiCHPh$_2$**/$Ni(OTf)_2$ (1:1, 5 mol%), **1a** (0.10 mmol) and Et_3N (0.12 mmol) in EtOAc (0.50 mL) at 35 °C for 36 h. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] 10 mol% catalyst. [e] The reaction was carried out with **L-Pic*H***/$Ni(BF_4)_2$•$6H_2O$ (1:1, 10 mol%) in EtOAc (1.0 mL).

With the optimized reaction conditions in hand, we first investigated substituents on the oxindole ring (Table 2). It was found that the substrates with a halogen atom at different positions underwent the [2,3]-rearrangement smoothly to afford the corresponding products (**2b-i**) in good to excellent yields (68-

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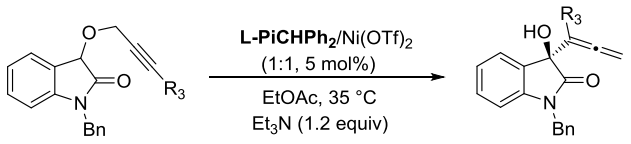
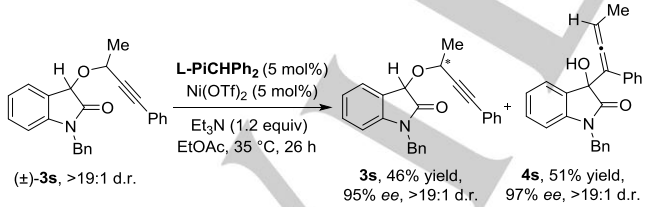
Table 3. Substrate scope for substituents at the propargyl ethers.[a]



3 **4**

Entry	R^3	4	Yield [%][b]	*ee* [%][c]
1	2-ClC_6H_4 (**3a**)	**4a**	92	99
2	3-ClC_6H_4 (**3b**)	**4b**	99	98
3	4-ClC_6H_4 (**3c**)	**4c**	99	99
4	4-FC_6H_4 (**3d**)	**4d**	99	99
5	4-BrC_6H_4 (**3e**)	**4e**	99	98
6	2-MeC_6H_4 (**3f**)	**4f**	89	99
7	3-MeC_6H_4 (**3g**)	**4g**	72	>99
8	4-MeC_6H_4 (**3h**)	**4h**	92	99
9	4-EtC_6H_4 (**3i**)	**4i**	85	98
10	4-*t*BuC_6H_4 (**3j**)	**4j**	91	>99
11	4-$MeOC_6H_4$ (**3k**)	**4k**	80	97
12	4-$F_3CC_6H_4$ (**3l**)	**4l**	96	96
13	4-$O_2NC_6H_4$ (**3m**)	**4m**	77	97
14[d]	3,4-$Cl_2C_6H_4$ (**3n**)	**4n**	95	98 (*R*)
15	1-naphthyl (**3o**)	**4o**	95	99
16	2-thienyl (**3p**)	**4p**	71	98
17	cyclohexyl (**3q**)	**4q**	43	98
18	Me (**3r**)	**4r**	50	98

[a] All reactions were the same as detailed in Table 2. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis. [d] The absolute configuration was determined to be *R* by X-ray crystallography analysis.

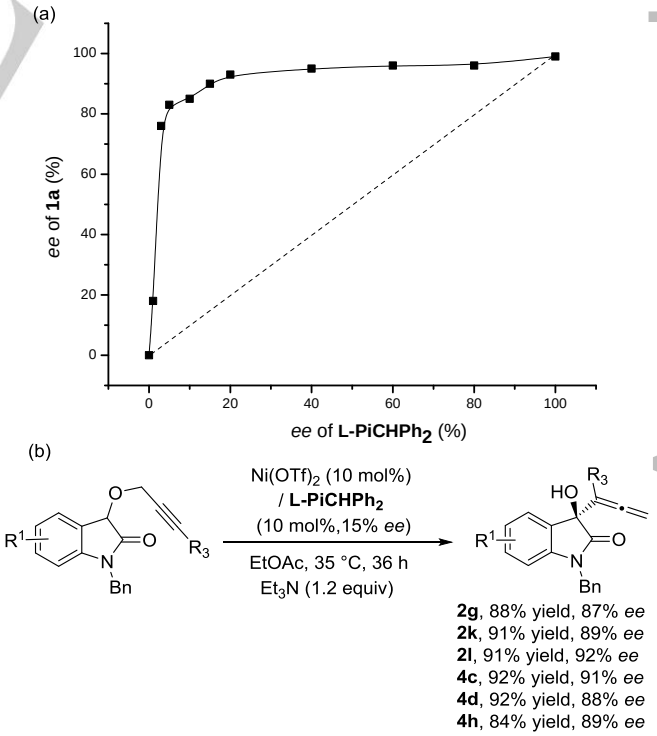


Scheme 2. Kinetic resolution/chiral transfer/asymmetric [2,3]-Wittig rearrangement.

99%) with excellent *ee* values (87-97% *ee*, entries 2-9). Generally, substrates with the halogen at the C4 or C6 positions provided higher enantioselectivities compared to the ones at the C5 or C7 positions. Electron-donating groups (methyl, methoxy and dimethyl) were well tolerated and converted to the desired products (**2j-l**) in good yields with excellent enantioselectivities (99->99% *ee*).[16] Substrate **1m** bearing a trifluoromethoxy substituent at the C5 position was also suitable (90% yield, 92% *ee*, entry 13). The unprotected oxindole **1n** performed the rearrangement reaction with excellent enantioselectivity but in lower yield (51% yield, 99% *ee*, entry 14). Changing the *N*-protected group from methyl to isopropyl group, the yield increased to 83% with maintained *ee* value (99% *ee*, entries 15 and 16). For the rearrangement of *N*-benzyl protected 3-cinnamyloxyoxindole **1q**, excellent yield and *ee* value with moderate diastereoselectivity (3.3/1 d.r., 99% *ee*/97% *ee*) could be achieved by using **L-PicH**/$Ni(BF_4)_2$•$6H_2O$ complex (entry 17) and the diastereoisomers could be isolated by flash chromatography.

Next, the propargyl ether part was evaluated. As summarized in Table 3, substrates with electron-donating and withdrawing groups were well tolerated, providing the corresponding products (**3a**-**3n**) in good yields (72-99%) with excellent enantioselectivities (97->99% *ee*, entries 1-14). For naphthyl- substituted substrate, the product **4o** was isolated with 95% yield and 99% *ee* (entry 15). Heteroaromatic substrate **3p** afforded the expected product **4p** in 71% yield and 98% *ee* (entry 16). Moreover, aliphatic oxyoxindoles were tested, giving the desired product **4q** and **4r** in excellent enantioselectivities (98% *ee*, entries 17 and 18) albeit in moderate yields (43% and 50%). Additionally, the absolute configuration of the product **4n** was determined to be *R* by X-ray crystallography.[17]

During the optimization of the reaction, we recovered the unreacted starting material **1a**. It was found that the recovered **1a** was racemic, which probably caused either by non-stereoselective deprotonation or by an in-situ racemization via enolization. Based on the envelope-shaped five- membered



Scheme 3. (a) Strong chiral amplification effect. (b) All reactions were carried out with **L-PiCHPh**$_2$/$Ni(OTf)_2$ (1:1, 10 mol%, 15% *ee*), substrate (0.10 mmol) and Et_3N (0.12 mmol) in EtOAc (0.50 mL) at 35 °C for 36 h.

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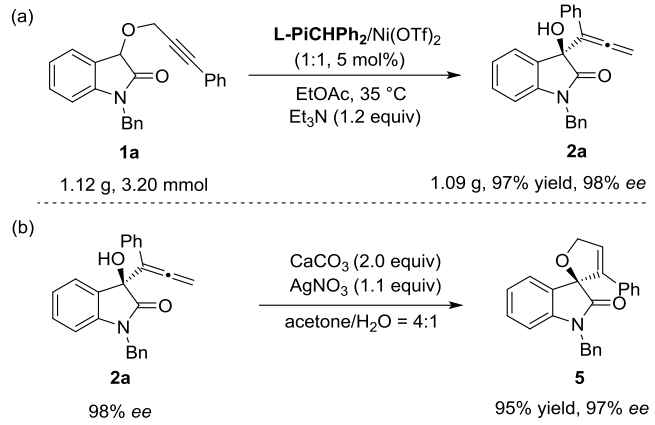

Scheme 4. (a) Gram-scaled experiment. (b) Transformation of the product **2a**.

cyclic transition state of [2,3]-Wittig rearrangement and excellent results obtained above, we envisioned that the possibility of an asymmetric [2,3]-Wittig rearrangement of 4-phenylbut-3-yn-2-ol derived **3s** taking advantage of chiral transfer by kinetic resolution (Scheme 2). To our delight, our current catalyst system could recognize one enantiomer of racemic **3s**, which then underwent a catalytic [2,3]-Wittig rearrangement to afford chiral allene **4s** (51% yield, >19:1 d.r. and 97% *ee*) by chiral transfer. The diastereoselectivity of the product was determined by both stereogenic center of the substrate and chiral catalyst (for details, see SI). Meanwhile, the unreacted **3s** was recovered in 46% yield, >19:1 d.r. and 95% *ee*.

To gain insight into the mechanism, the relationship between the *ee* value of the ligand **L-PiCHPh$_2$** and that of **2a** was investigated (Scheme 3). A strong positive nonlinear effect (NLE) [18] was observed, and (*R*)-**2a** was generated in 90% *ee* even by using 15% *ee* of **L-PiCHPh$_2$** (Scheme 3a, see SI for details). To test the generality of such remarkable chiral amplification effect, various substrates were examined under 15% *ee* catalyst **L-PiCHPh$_2$**, delivering the corresponding products in good results (84-92% yield and 87-92% *ee*). Based on control experiments, X-ray crystallography data and HRMS analysis (see SI for details), it was found that the enhancement of the solution *ee* values by formation of less soluble racemic **L-PiCHPh$_2$**/Ni^{II} complexes was responsible for such remarkable chiral amplification effect.[19]

To highlight the robustness of this reaction, a gram scale synthesis of (*R*)-**2a** was performed. By treatment of 1.12 g (3.20 mmol) of **1a** in the presence of the **L-PiCHPh$_2$**-Ni(OTf)$_2$ complex for 48 h, 1.09 g (97% yield) of the isolated (*R*)-**2a** with 98% *ee* was obtained (Scheme 4a). In addition, the product **2a** could be easily transformed to dihydrofuran **5** in 95% yield and 97% *ee* by treating with $AgNO_3$ and $CaCO_3$ on 0.1 mmol scale (Scheme 4b).

In summary, we have successfully realized the highly effcient [2,3]-Wittig rearrangement of propargylic and allylic ethers by developing a nickel(II)-*N*,*N*′-dioxide catalytic system. Various 3-substituted 3-hydroxyoxindoles could be obtained in excellent yields and enantioselectivities under mild conditions. Kinetic resolution of oxindole derivatives via [2,3]-Wittig rearrangement was also realized for the first time in high resolution efficiency and stereoselectivity. This protocol presents a practical approach to synthetically valuable functionalized allenes. Meanwhile, due to the formation of less soluble racemic **L-PiCHPh$_2$**/Ni^{II} complexes, a strong positive nonlinear effect was observed, allowing to access enantioenriched products with 15% *ee* of ligand. Further studies on other 2,3-rearrangement reactions are underway.

Experimental Section

A dry reaction tube was charged with Ni(OTf)$_2$ (5 mol%), *N*,*N*′-dioxide ligand **L-PiCHPh$_2$** (5 mol%), and the substrate **1a** (0.10 mmol), and EtOAc (0.50 mL) was added and the mixture was stirred at 35 °C for 0.5 h. Then Et_3N (0.12 mmol) was added. The reaction mixture was stirred at 35 °C for 36 h, and the product was purified by flash chromatography on silica gel (petroleum ether/DCM/EtOAc = 6/2/1) to afford the desired product **2a**.

Acknowledgements

We appreciate the National Natural Science Foundation of China (Nos. 21432006, 21772127) for financial support.

Keywords: allenic compounds • asymmetric catalysis • chiral amplification • nickel • rearrangement

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[16] As suggested by one reviewer, we tried to investigate the oxindole substrates bearing a pi-acceptor, such as 5-NO_2 or 7-NO_2. However, the synthesis of corresponding substrates was failed by using the same method with other substrates, for details, see SI.

[17] CCDC 1834241 (**4n**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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10.1002/anie.201804080

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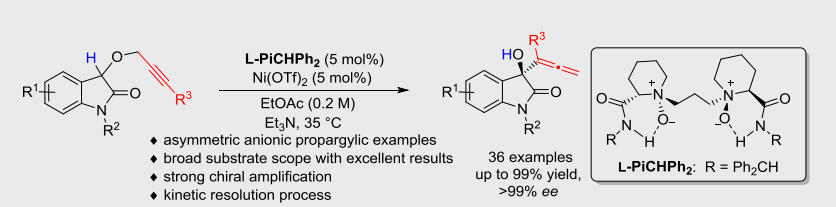

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Nickel(II)-Catalyzed Asymmetric Propargyl [2,3]-Wittig Rearrangement of Oxindole Derivatives : A Remarkable Chiral Amplification Effect

A highly enantioselective [2,3]-Wittig rearrangement of oxindole derivatives was developed by using a chiral *N*,*N*′-dioxide/Ni^{II} catalyst. This approach provides an efficient access to chiral 3-hydroxy 3-substituted oxindoles bearing allenyl groups in up to 99% yield and >99% *ee*. Catalytic kinetic resolution of racemic oxindole derivatives via [2,3]-Wittig rearrangement was realized in high resolution efficiency and stereoselectivity for the first time. Moreover, a strong chiral amplification was observed in the current system.