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Chiral *N*,*N*′-Dioxide/Scandium(III)-Catalyzed Asymmetric Alkylation of *N*-Unprotected 3-Substituted Oxindoles

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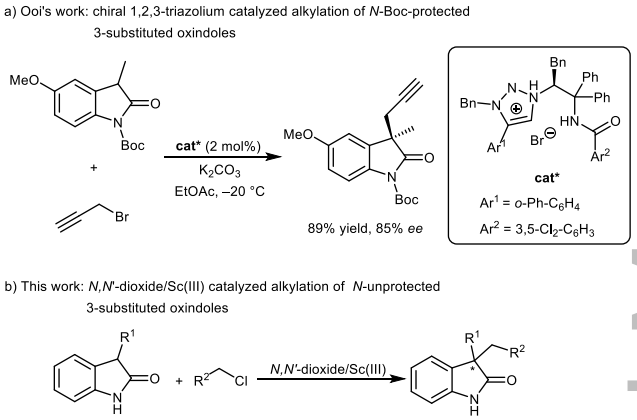
Abstract. An efficient enantioselective alkylation of *N*-unprotected 3-substituted oxindoles was realized by using a chiral *N*,*N*′-dioxide/scandium(III) complex as the catalyst. A wide range of 3,3-dialkyl substituted oxindoles with quaternary stereocenters were obtained in high yields and *ee* values (up to 98% yield and 99% *ee*).

Keywords: Asymmetric catalysis; Alkylation; Oxindole; Quaternary carbon stereocenter; Scandium



Scheme 1. The asymmetric alkylation of 3-substituted oxindoles.

The 3,3-dialkyl substituted 2-oxindole structural motifs exist in a variety of natural products, clinical pharmaceuticals and drug candidates.[1] Diverse methods are continually sought to construct these important skeletons.[2] The application of prochiral 3-substituted oxindoles as nucleophiles is a widely adopted strategy, including enantioselective aldol reaction,[3] Mannich reaction,[4] Michael reaction,[5] arylation or vinylation reaction[6] and alkylation reaction.[7,8] Most of these well-developed asymmetric reactions use *N*-protected 3-substituted oxindoles because of the high reactivity resulting when introducing a protecting group (methyl, benzyl, Boc, etc.) Unfortunately, the introduction and removal of the activating group are not atom-economic and may render the potential of breaking the molecular structure. Up to now, functionalization at the C3 position of *N*-unprotected 3-substituted oxindoles to access 3,3-dialkyl substituted oxindoles containing a chiral quaternary carbon center are still challenging,[2a] because of the poor reactivity and the side reaction of alkylation at the position of the nitrogen moiety. Shibata's, Zhou's and Chen's groups reported the direct aldol reaction, Michael addition and Mannich reaction of unprotected 3-substituted oxindoles by using cinchona alkaloid derivatives as the catalysts, respectively.[3a,4b,5g] Trost and Czabaniuk developed a method for palladium-catalyzed asymmetric benzylation of 3-aryl oxindoles.[7b] In recent years, our group also realized the functionalizations of *N*-unprotected 3-substituted oxindoles catalyzed by chiral *N*,*N*′-dioxide/metal complexes.[9,10] For instance, *N*,*N*′-dioxide/Sc(III) complexes-catalyzed asymmetric α-arylation[6b] and aldol reaction,[10b,10c] as well as *N*,*N*′-dioxide/Nd(III) complexes-catalyzed Michael addition[10e] could give efficient results.

On the other hand, the catalytic asymmetric propargylation provides productive access to optically active propargyl derivatives that are widely distributed across medicinal agents and valuable building blocks for various transformations.[11] To the best of our knowledge, most of the reported alkylation reactions of 3-substititued oxindoles focused on asymmetric allylic alkylation (AAA) reactions,[8] only one example of asymmetric alkylation of 3-substituted oxindoles including propargylation was reported by Ooi, a chiral 1,2,3-triazolium ion-based phase transfer catalyst was used, giving the corresponding propargylation product with 85% *ee*

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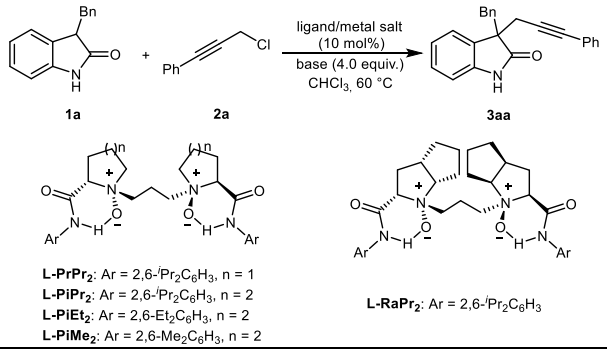
Table 1. The optimization of the reaction conditions[a]



Entry	Metal salt	Ligand	Base	Yield (%)[b]	*ee* (%)[c]
1	$Cu(OTf)_2$	**L-RaPr$_2$**	K_2CO_3	NR[d]	-
2	$Y(OTf)_3$	**L-RaPr$_2$**	K_2CO_3	trace	0
3	$La(OTf)_3$	**L-RaPr$_2$**	K_2CO_3	trace	0
4	$Sc(OTf)_3$	**L-RaPr$_2$**	K_2CO_3	60	24
5	$Sc(OTf)_3$	**L-PrPr$_2$**	K_2CO_3	35	15
6	$Sc(OTf)_3$	**L-PiPr$_2$**	K_2CO_3	70	53
7	$Sc(OTf)_3$	**L-PiEt$_2$**	K_2CO_3	68	34
8	$Sc(OTf)_3$	**L-PiMe$_2$**	K_2CO_3	68	0
9	$Sc(OTf)_3$	**L-PiPr$_2$**	$KHCO_3$	23	57
10	$Sc(OTf)_3$	**L-PiPr$_2$**	Na_3PO_4	70	57
11	$Sc(OTf)_3$	**L-PiPr$_2$**	K_3PO_4	76	94
12	$Sc(OTf)_3$	**L-PiPr$_2$**	$K_3PO_4{\cdot}7H_2O$	83	96
13[e]	$Sc(OTf)_3$	**L-PiPr$_2$**	$K_3PO_4{\cdot}7H_2O$	96	97
14[f]	$Sc(OTf)_3$	**L-PiPr$_2$**	$K_3PO_4{\cdot}7H_2O$	73	91

[a] Unless otherwise noted, the reaction was carried out with 3-benzylindolin-2-one **1a** (0.10 mmol), 3-phenylpropargyl chloride **2a** (0.25 mmol), metal salt/ligand (1:1, 10 mol%) and base (0.40 mmol) in $CHCl_3$ (1.0 mL) at 60 °C for 16 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] NR = no reaction
[e] $Sc(OTf)_3$/**L-PiPr$_2$** (1:1.2, 10 mol%).
[f] $Sc(OTf)_3$/**L-PiPr$_2$** (1:1.2, 5 mol%).

(Scheme 1a).[12] Based on long-term endeavor in the development of chiral *N*,*N*′-dioxide/metal complexes and our previous studies of the oxindole derivatives, we envisioned that this kind of effective catalyst system could provide a new route for the asymmetric alkylation of *N*-unprotected 3-substituted oxindoles, including propargylation, allylation and benzylation reactions (Scheme 1b).

In our preliminary investigation, *N*-unprotected 3-substituted oxindole **1a** and 3-phenylpropargyl chloride **2a** were selected as the model substrates to optimize the reaction conditions. Firstly, various metal salts were screened by coordinating with **L-RaPr$_2$** in the presence of K_2CO_3 in $CHCl_3$ at 60 °C (Table 1, entries 1-4), only the $Sc(OTf)_3$/**L-RaPr$_2$** complex could promote the reaction, giving the desired product **3aa** in 60% yield with 24% *ee* (Table 1, entry 4). The examination of the chiral ligands indicated that the L-pipecolic acid derived **L-PiPr$_2$** was superior to L-ramipril derived **L-RaPr$_2$** and L-proline derived **L-PrPr$_2$** in terms of the yield and enantioselectivity (Table 1, entry 6 vs entries 4-5). More sterically hindered *ortho*-substituents on aniline of **L-PiPr$_2$** were beneficial to achieve higher enantioselectivity (Table 1, entry 6 vs entries 7 and 8). It was worthy to note that the bases had a significant influence on both the reactivity and enantioselectivity. The product **3aa** could be obtained in 76% yield and 94% *ee* when K_3PO_4 was selected as the base (Table 1, entry 11). The trace amount of crystal water had a little effect on the yield and enantioselectivity, maybe because of the higher solubility of $K_3PO_4{\cdot}7H_2O$ in $CHCl_3$ than K_3PO_4 (Table 1, entry 12). Adjusting the ratio of $Sc(OTf)_3$/**L-PiPr$_2$** from 1:1 to 1:1.2, the yield was further improved to 96% (Table 1, entry 13). However, decreasing the catalyst loading to 5 mol%, the enantioselectivity and reactivity decreased (Table 1, entry 14). Thus, the optimized conditions were established, $Sc(OTf)_3$/**L-PiPr$_2$** (1:1.2, 10 mol%) as the catalyst with $K_3PO_4{\cdot}7H_2O$ (4 equiv.) in $CHCl_3$ at 60 °C for 16 h.

Under the optimized reaction conditions, the substrate scope was explored. A series of *N*-unprotected 3-substituted oxindoles could react with 3-phenylpropargyl chloride smoothly and gave the corresponding propargylated products **3aa**−**3oa** in

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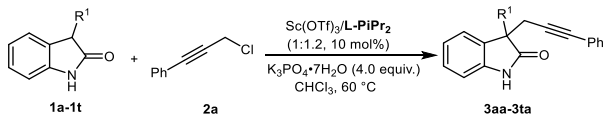
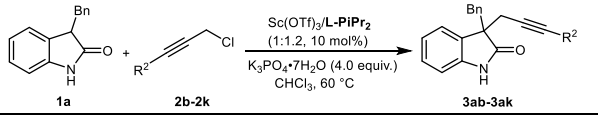
Table 2. The scope of 3-substituted 2-oxindoles[a]



Entry	R^1	Yield (%)[b]	*ee* (%)[c]
1	Bn	96 (**3aa**)	97
2	4-$FC_6H_4CH_2$	91 (**3ba**)	98
3	4-$ClC_6H_4CH_2$	94 (**3ca**)	98
4	4-$BrC_6H_4CH_2$	91 (**3da**)	98
5	3-$BrC_6H_4CH_2$	96 (**3ea**)	98
6	2-$BrC_6H_4CH_2$	96 (**3fa**)	98
7	4-$O_2NC_6H_4CH_2$	95 (**3ga**)	99
8	4-$F_3CC_6H_4CH_2$	88 (**3ha**)	99
9	4-$NCC_6H_4CH_2$	95 (**3ia**)	99
10	2,4-$Cl_2C_6H_3CH_2$	96 (**3ja**)	98
11	4-$MeOC_6H_4CH_2$	96 (**3ka**)	97
12	4-$MeC_6H_4CH_2$	92 (**3la**)	97
13	3-$MeC_6H_4CH_2$	96 (**3ma**)	96
14	2-$MeC_6H_4CH_2$	95 (**3na**)	98
15		96 (**3oa**)	97
16	1-Naphthylmethyl	98 (**3pa**)	98
17	2-Thienylmethyl	87 (**3qa**)	93 (*S*)
18	2-Furylmethyl	84 (**3ra**)	85
19	CH_3	62 (**3sa**)	81
20	$^tBuCH_2$	90 (**3ta**)	95

[a] Unless otherwise noted, the reaction was carried out with **1** (0.1 mmol), 3-phenylpropargyl chloride **2a** (0.25 mmol), $Sc(OTf)_3$/**L-PiPr2** (1:1.2, 10 mol%) and $K_3PO_4{\cdot}7H_2O$ (0.4 mmol) in $CHCl_3$ (1.0 mL) at 60 °C for 16 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.

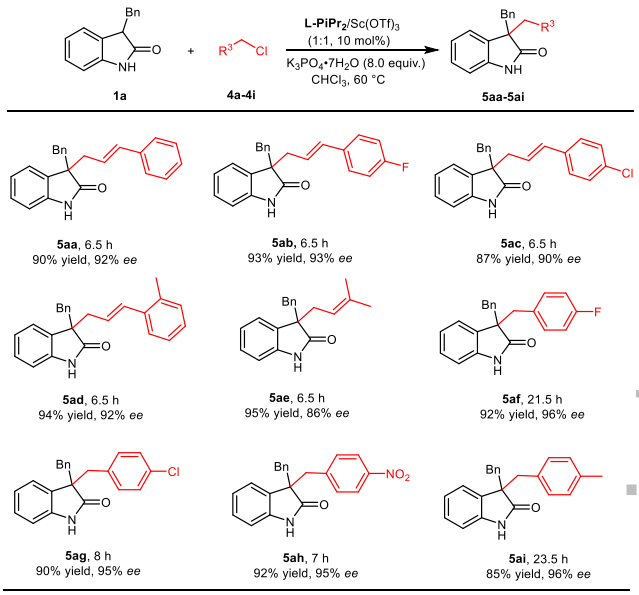
Table 3. The scope of propargyl chlorides[a]



Entry	R^2	Yield (%)[b]	*ee* (%)[c]
1	4-FC_6H_4	93 (**3ab**)	97
2	4-ClC_6H_4	93 (**3ac**)	96
3	4-BrC_6H_4	94 (**3ad**)	97
4	4-$F_3CC_6H_4$	87 (**3ae**)	98
5	3,4-$Cl_2C_6H_3$	90 (**3af**)	97
6	4-MeC_6H_4	83 (**3ag**)	91
7	3-MeC_6H_4	91 (**3ah**)	96
8	2-MeC_6H_4	84 (**3ai**)	96
9	1-Naphthyl	92 (**3aj**)	97
10[d]	H	77 (**3ak**)	96

[a] Unless otherwise noted, the reaction was carried out with 3-benzylindolin-2-one **1a** (0.10 mmol), propargyl chloride derivatives **2** (0.25 mmol), $Sc(OTf)_3$/**L-PiPr2** (1:1.2, 10 mol%) and $K_3PO_4{\cdot}7H_2O$ (0.40 mmol) in $CHCl_3$ (1.0 mL) at 60 °C for 16 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] Another portion of **2k** (0.25 mmol) was added in the middle of the reaction.

Table 4. The scope of allyl and benzyl chloride derivatives[a]

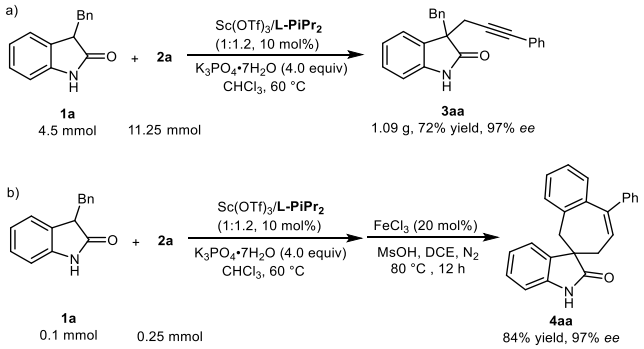


[a] Unless otherwise noted, the reaction was carried out with 3-benzylindolin-2-one **1a** (0.10 mmol), allyl and benzyl chloride derivatives **4** (0.25 mmol), $Sc(OTf)_3$/**L-PiPr2** (1:1, 10 mol%) and $K_3PO_4{\cdot}7H_2O$ (0.80 mmol) in $CHCl_3$ (1.0 mL) at 60 °C. Yield is that of isolated product. The *ee* values were determined by HPLC analysis on a chiral stationary phase.

excellent yields and *ee* values, regardless of the electronic nature and the position of substituents on the phenyl group (88-96% yield, 96-99% *ee*, Table 2, entries 1-15). 2-Oxindole with a naphthylmethyl substituent **1p** was suitable for this reaction, affording the propargylated product **3pa** in 98% yield and 98% *ee* (Table 2, entry 16). Moreover, oxindoles containing 2-thienylmethyl **1q** and 2-furylmethyl **1r** were also tolerated and the absolute configuration of **3qa** was determined to be *S* by using single-crystal X-ray diffraction analysis (Table 2, entries 17 and 18).[13] The 3-methyl-2-oxindole **1s** gave the desired product **3sa** with a decreasing yield and *ee* value (62% yield, 81% *ee*, Table 2, entry 19). Nevertheless, 3-neopentyl-2-oxindole **1t** could transform into **3ta** in 90% yield and 95% *ee* (Table 2, entry 20).

Next, we turned our attention to the scope of propargyl chloride derivatives (Table 3). The substituents on the phenyl group had little effect on this propargylation reaction. The corresponding 3,3-dialkyl substituted 2-oxindoles could be achieved in high yields with excellent ee values (83-94% yields, 91-98% *ee*, Table 3, entries 1-8). Naphthyl-substituted propargyl chloride **2j** and the terminal 3-chloroprop-1-yne **2k** were also compatible with this transformation, affording **3aj** and **3ak** with good results.

Encouraged by the results of α-propargylation, we further tested the α-allylation and α-benzylation of *N*-unprotected 3-benzyl-2-oxindoles (Table 4). The corresponding oxindoles bearing chiral quaternary



Scheme 2. a) Gram-scale version of the reaction. b) Intramolecular Friedel−Crafts cyclization reaction of the product **3aa**.

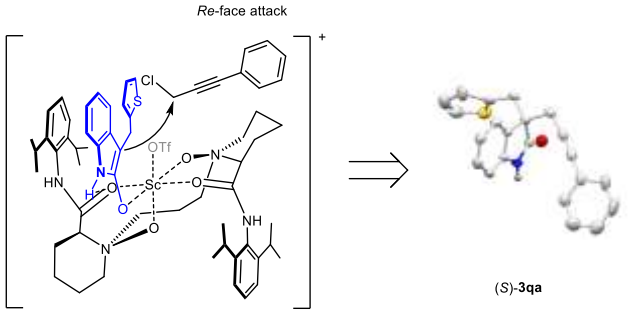


Figure 1. The proposed catalytic model.

carbon stereocenters were obtained in high yields and *ee* values (**5aa**-**5ai**, 85-95% yields, 86-96% *ee*).

To show the synthetic potential of the catalytic system, a gram-scale synthesis of **3aa** was carried out. As shown in Scheme 2a, **1a** (4.5mmol) reacted with **2a** smoothly in the presence of 10 mol% $Sc(OTf)_3$/**L-PiPr$_2$** complex, giving the desired product **3aa** in 97% *ee*. In addition, the product **3aa** underwent an intramolecular Friedel−Crafts cyclization reaction and afforded the [5.7]-spiro-oxindole **4aa** in 84% overall yield and 97% *ee* (Scheme 2b).

Based on the absolute configuration of product **3qa** and our previous works,[10] a possible transition state model was presented to explain the origin of the stereoselectivity (Figure 1). The oxygen atoms of *N*-oxides and amides in **L-PiPr$_2$** coordinated with Sc(III) in a tetradentate manner. The oxygen atom of oxindole enolate **1q** coordinated with the Sc(III) center as well. Meanwhile, a hydrogen bonding might exist between the NH moiety of **1q** and the **L-PiPr$_2$**. As a result, 3-substituted-2-oxindole **1q** preferred to attack propargyl chloride from the *Re*-face since the *Si*-face was shielded by the neighboring 2,6-diisopropylphenyl group of **L-PiPr$_2$**. Thus, the (*S*)-configured product **3qa** was obtained.

In summary, we have developed an efficient chiral *N*,*N'*-dioxide/scandium(III) complex catalytic system for the α-propargylation, allylation and benzylation of *N*-unprotected 3-substituted oxindoles. The desired 3,3-dialkyl substituted oxindoles bearing chiral quaternary carbon centers were obtained in high yields and ee values (up to 98% yield and 99% *ee*). In addition, a [5.7]-spiro-oxindole could be smoothly achieved through a simple Friedel−Crafts cyclization reaction from the α-propargyl product without loss of enantioselectivity.

Experimental Section

L-PiPr$_2$ (7.8 mg, 0.012 mmol or 6.5 mg, 0.010 mmol), $Sc(OTf)_3$ (4.9 mg, 0.010 mmol) and 3-substituted-2-oxindole **1** (0.10 mmol) were added to an oven-dried reaction tube. Then 1.0 mL anhydrous $CHCl_3$ was added and the solution was stirred at 35 °C for 30 mins. Subsequently, propargyl, allylic or alkyl chloride **2** or **4** (0.25 mmol) and $K_3PO_4 \cdot 7H_2O$ (0.40 mmol or 0.80 mmol) were added and stirred at 60 °C with indicated time. The reaction mixture was purified by silica gel column chromatographic (petroleum ether/ethyl acetate = 6:1 or 9:1) to afford the desired products.

Acknowledgements

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[13] CCDC 1590617 **(3qa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Center.

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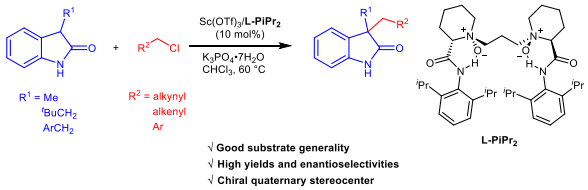
Chiral *N*,*N*′-Dioxide/Scandium(III)-Catalyzed Asymmetric Alkylation of *N*-Unprotected 3-Substituted Oxindoles



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