Asymmetric Catalysis

Deutsche Ausgabe: DOI: 10.1002/ange.201511519
Internationale Ausgabe: DOI: 10.1002/anie.201511519

Chemo-, Diastereo-, and Enantioselective Iridium-Catalyzed Allylic Intramolecular Dearomatization Reaction of Naphthol Derivatives

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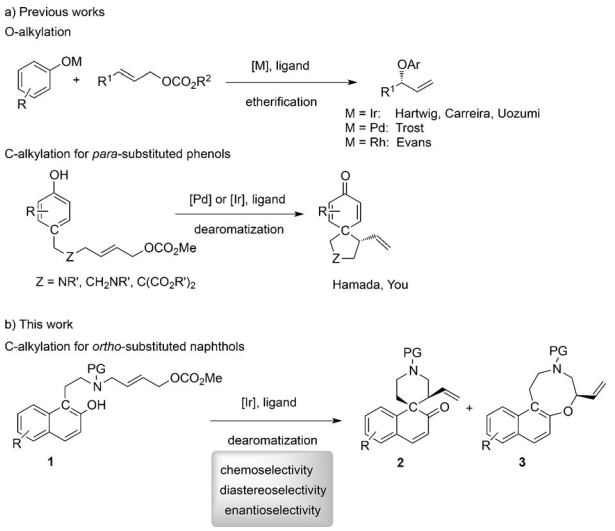
Abstract: *An iridium-catalyzed intramolecular asymmetric allylic dearomatization reaction of naphthol derivatives is described. Challenges confronted in this reaction include chemoselectivity between carbon and oxygen atoms as nucleophilic centers, diastereoselectivity when contiguous chiral centers are generated, and enantioselective control for constructing an all-carbon quaternary stereocenter. In the presence of an iridium catalyst generated from [{Ir(dbcot)Cl}$_2$] (dbcot = dibenzocyclooctatetraene) and a new THQphos (tetrahydroquinolinedinaphthophosphoramidite) ligand, various spironaphthalenones were obtained with up to greater than 95:5 C/O selectivity, greater than 95:5 d.r., and 99% ee, thus providing a general method for the dearomatization of naphthols.*

Dearomatization reactions are efficient transformations which can convert readily available aromatic compounds into a variety of non-aromatic ring systems.[1] Although a number of strategies for dearomatization have been developed, catalytic asymmetric processes are still limited.[2] Recently, catalytic asymmetric dearomatization (CADA) reactions have witnessed rapid development.[3] Notably, transition-metal-catalyzed asymmetric allylic substitution reactions were found to be compatible with the dearomatization process.[4]

Dearomatization of phenols and naphthols through transition-metal-catalyzed allylic substitution reactions remains challenging because of both the energetic barriers and the competition between C and O alkylation. Phenolates often function as oxygen nucleophiles in transition-metal-catalyzed allylic substitution reactions (Scheme 1 a).[5] An intramolecular design, reported by the group of Hamada[6] and our group,[7] wherein the nucleophilic phenolic OH group is separated from the allylic electrophile, facilitated the dearomatization reaction by minimizing the O-alkylation pathway (Scheme 1 a). In contrast, the dearomatization pathway turns into a problematic process when a nucleophilic OH group and an electrophilic allylic group are installed *ortho* to each other, because intramolecular etherification could occur. Therefore, asymmetric allylic dearomatization of 2-naphthols bearing allylic carbonates at C1 is challenging, but highly desirable given the interesting spironaphthalenone scaffold generated in a single step. Herein, we report an intramolecular allylic dearomatization reaction of naphthol derivatives under iridium catalysis to preclude the inherent chemoselectivity and deliver excellent diastereo- and enantioselectivity (Scheme 1 b). Notably, the combination of [{Ir(dbcot)Cl}$_2$] (dbcot = dibenzocyclooctatetraene) and the new ligand (S,S_a)-**L10** (for structure see Table 1) play a key role in achieving the excellent selectivity.



Scheme 1. Allylic substitution reactions of phenols and naphthols. PG = protecting group.

To realize this proposal, the naphthol derivative **1a** was utilized as a model substrate (Table 1). First, various chiral phosphoramidite ligands were examined in this iridium-catalyzed intramolecular allylic dearomatization reaction of **1a**.[8] Initial tests were conducted by employing the Feringa ligand and its variants (**L1**–**L3**), which led to poor C/O alkylation ratios and d.r. values for **2a**, but high enantiomeric excesses (entries 1–3). Deviation of the skeleton of the ligand from BINOL to SPINOL resulted in diminished reactivity (entry 4). To our surprise, the reaction with the BHPphos ligand **L5**, through a C(sp^2)–H activation mode,[4c] led to an increased C/O alkylation ratio and d.r. value of **2a** along with reduced enantioselectivity (entry 5). These results inspired us to further investigate ligands, developed by our group, having the same activation mode during the formation of the active iridacycle (entries 6–12).[9] Gratifyingly, (S,S_a)-**L10** turned out to be the most efficient ligand, thus resulting in a 75% yield of **2a** with a high *ee* value (entry 10). Further optimization of the

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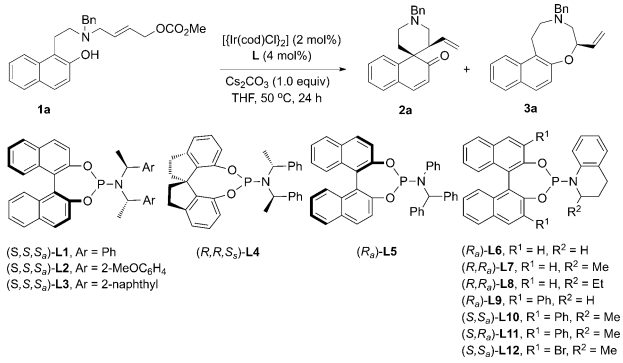
Supporting information for this article can be found under http://dx.doi.org/10.1002/anie.201511519.

Table 1: Investigation of ligands.[a]



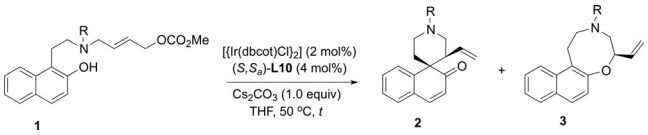
Entry	L	Conv. [%][b]	C/O[b]	d.r.[b]	Yield [%][c]	*ee* [%][d]
1	**L1**	>95	38:62	60:40	30	−87/−95
2	**L2**	>95	71:29	78:22	36	−94/−96
3	**L3**	>95	50:50	66:34	38	−90/−96
4	**L4**	67	52:48	62:38	13	82/92
5	**L5**	>95	82:18	83:17	43	−67/−91
6	**L6**	>95	53:47	73:27	41	−82/−94
7	**L7**	>95	89:11	82:18	66	−73/−92
8	**L8**	>95	86:14	78:22	52	−73/−90
9	**L9**	>95	87:13	90:10	81	−64/−63
10	**L10**	>95	89:11	86:14	75	90/86
11	**L11**	>95	89:11	86:14	72	−88/−77
12	**L12**	>95	93:7	80:20	53	60/97
13[e]	**L10**	>95	89:11	88:12	77	95/94
14[f]	**L10**	>95	89:11	86:14	70	92/96

[a] Reaction conditions: 2 mol% of $[\{Ir(cod)Cl\}_2]$, 4 mol% of **L**, 0.25 mmol of **1a**, 0.25 mmol of Cs_2CO_3 in THF (2.5 mL) at 50°C. Catalyst was prepared by nPrNH$_2$ activation.[8g] [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of the isolated major diastereoisomer. [d] Determined by HPLC analysis. The first value is for the major diastereoisomer and the second one for the minor diastereoisomer. [e] 2 mol% of $[\{Ir(dbcot)Cl\}_2]$ was used as precatalyst. [f] 2 mol% of $[\{Ir(dncot)Cl\}_2]$ was used as precatalyst. cod = 1,5-cyclooctadiene, dbcot = dibenzocyclooctatetraene, dncot = dinaphthocyclooctatetraene,[11] THF = tetrahydrofuran.

reaction conditions disclosed that Cs_2CO_3 is the best base and THF functions as the optimal solvent (see Table S1 in the Supporting Information). Notably, the diene ligand on the iridium complex affected the enantioselectivity significantly, and dbcot, introduced for iridium-catalyzed allylic substitution reactions by the Helmchen group,[10] provided the best outcome (entry 13).

With these optimized reaction conditions (2 mol% of $[\{Ir(dbcot)Cl\}_2]$, 4 mol% of (S,S_a)-**L10**, 1.0 equiv of Cs_2CO_3 in THF at 50°C) in hand, we first investigated the N-protecting groups (Table 2). Notably, substrates (**1b–d**) with electron-donating groups on N had little effect on the selectivity, thus providing good yields and excellent enantioselectivities with reasonable C/O alkylation ratios and diastereoselectivities (entries 2–4). When electron-deficient and sterically hindered protecting groups were introduced, the reaction proceeded smoothly in good yields and C/O alkylation ratios, with better diastereo- and enantioselectivities (**1e**,**f**; entries 5 and 6). Prompted by these results, we chose to use the tosyl protecting group on the nitrogen atom for further examination of the substrate scope.

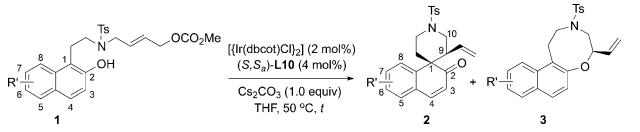
Table 2: The examination of N-protecting groups.[a]



Entry	**1**, R	t [h]	C/O[b]	d.r.[b]	**2** Yield [%][c]	*ee* [%][d]
1	**1a**, Bn	24	89:11	88:12	**2a**, 77	95
2	**1b**, 4-$(NO_2)C_6H_4CH_2$	20	84:16	84:16	**2b**, 61	91
3	**1c**, Me	24	88:12	84:16	**2c**, 55	97
4	**1d**, allyl	35	90:10	87:13	**2d**, 80	92
5	**1e**, Ts	14	89:11	94:6	**2e**, 76	99
6	**1f**, Ns	24	91:9	93:7	**2f**, 77	98

[a] Reaction conditions: 2 mol% of $[\{Ir(dbcot)Cl\}_2]$, 4 mol% of (S,S_a)-**L10**, 0.25 mmol of **1**, 0.25 mmol of Cs_2CO_3 in THF (2.5 mL) at 50°C. Catalyst was prepared by nPrNH$_2$ activation. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of the isolated major diastereoisomer. [d] Determined by HPLC analysis. Ns = 2-nitrobenzenesulfonyl, Ts = 4-toluenesulfonyl.

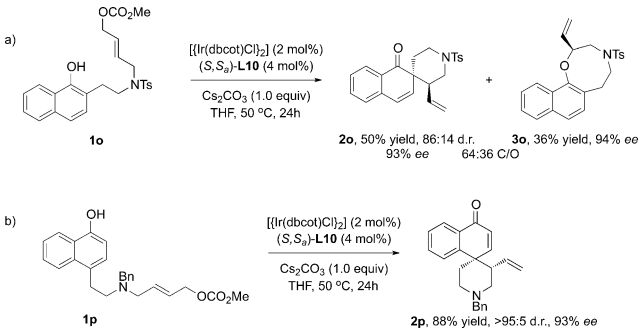
Table 3: The substrate scope with respect to the naphthols.[a]



Entry	**1**, R′	t [h]	C/O[b]	d.r.[b]	**2** Yield [%][c]	*ee* [%][d]
1	**1g**, 3-Ph	24	>95:5	87:13	**2g**, 80	99
2	**1h**, 3-(4-FC_6H_4)	24	>95:5	89:11	**2h**, 77	97
3	**1i**, 3-Me	24	91:9	93:7	**2i**, 85	97
4	**1j**, 6-Ph	10	86:14	>95:5	**2j**, 81	97
5	**1k**, 6-Br	24	84:16	94:6	**2k**, 70	99
6	**1l**, 6-MeO	20	93:7	>95:5	**2l**, 85	98
7	**1m**, 7-MeO	24	>95:5	>95:5	**2m**, 88	96
8	**1n**, 7-Br	24	88:12	>95:5	**2n**, 70	99

[a] Reaction conditions: 2 mol% of $[\{Ir(dbcot)Cl\}_2]$, 4 mol% of (S,S_a)-**L10**, 0.25 mmol of **1**, 0.25 mmol of Cs_2CO_3 in THF (2.5 mL) at 50°C. Catalyst was prepared by nPrNH$_2$ activation. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] Yield of the isolated major diastereoisomer. [d] Determined by HPLC analysis.

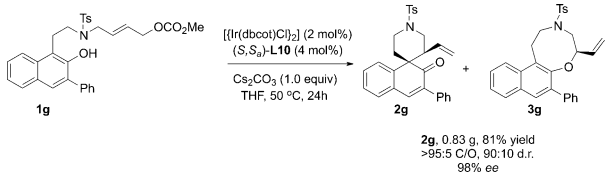
We next explored the substituents on the naphthol ring. Remarkably, 3-substituted naphthol derivatives, regardless of the electronic properties of the substituents (**1g–i**; Table 3, entries 1–3), displayed excellent C/O ratios, and it may be attributed to the steric disadvantage for nucleophilic attack by O. More intriguingly, when substituents were arrayed at either the 6- or 7-position of the naphthol ring, superior diastereoselectivity was obtained (**1j–n**; entries 4–8), and might be derived from increased spatial deviation of the two faces of the nucleophile upon the approach of the allylic electrophile. Specifically, the highest yield was observed by employing the 7-methoxy-substituted substrate **1m**, thus resulting in an 88% yield, greater than 95:5 C/O ratio, greater than 95:5 d.r., and 96% *ee*. In addition, the structure of the product was confirmed by an X-ray crystallographic analysis of the enantiopure **2k**. The absolute configuration was determined to be 1*S*,9*S*.[12]



Scheme 2. Dearomatization of α-naphthols under the same reaction conditions.

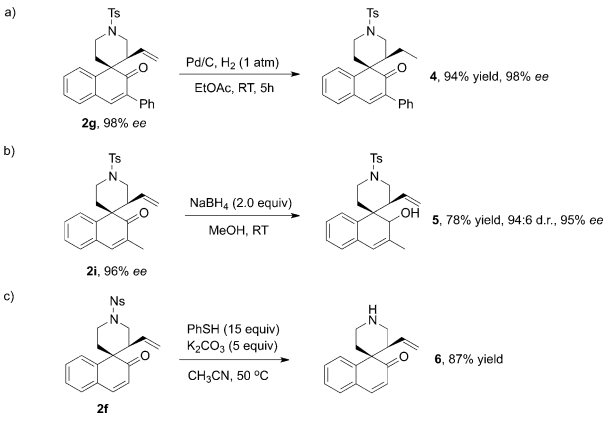
To illustrate the generality of this method, the α-naphthol substrate **1o**, known to be a more challenging substrate in asymmetric dearomatizations, was tested (Scheme 2a). To our delight, the substrate also underwent dearomatization smoothly, albeit with a moderate C/O alkylation ratio.[13] Notably, the eight-membered ring O-alkylation product **3o** was also obtained with excellent enantioselectivity (94% *ee*). More intriguingly, when **1p** was applied, dearomatization occurred smoothly to afford the spironaphthalenone **2p** in 88% yield, greater than 95:5 d.r., and 93% *ee* (Scheme 2b).[13] Encouraged by these results, we designed a phenol substrate structure similar to that of β-naphthol. However, only the O-allylated product was obtained.[14] In addition, when the substrate **1r**, designed for a seven-membered ring formation of the dearomatized product, was tested, only the nine-membered ring, O-alkylation product **3r** was observed. With the substrate **1s**, designed for a five-membered ring formation of the dearomatized product, was applied, the dearomatized product **2s** was obtained with high enantioselectivity but favored the formation of the etherification product (C/O = 26:74).[14]

Furthermore, synthesis of the 2-naphthalenone **2g** was executed on a 2.5 mmol scale to verify the practicability of this newly developed method (Scheme 3). The reaction proceeded with 81% yield and without erosion of enantioselectivity when compared with that of the small-scale reaction.



Scheme 3. A gram-scale reaction of **1g**.

To illustrate the potential synthetic application of the method, several transformations of the products were carried out. The terminal alkene group in **2g** could be readily hydrogenated with Pd/C in 94% yield and 97% *ee* (Scheme 4a). The carbonyl group in **2i** was selectively reduced to a hydroxy group by $NaBH_4$ in 78% yield and greater than 95:5 d.r., and without loss of the enantiomeric purity (Scheme 4b). For **2f**, elimination of the nosyl group was realized with 87% yield by treatment with thiophenol and K_2CO_3 in CH_3CN at 50 °C (Scheme 4c).



Scheme 4. Product transformations.

In summary, we have developed an asymmetric dearomatization process of naphthol derivatives by iridium-catalyzed asymmetric allylic substitution reactions to deliver naphthalenones bearing an all-carbon quaternary carbon center and a contiguous tertiary chiral center. The reaction by the novel catalytic system displays excellent multifold selectivity including chemo-, diastereo-, and enantioselectivity. The general substrate scope, mild reaction conditions, and versatile transformations highlight the potential utility of the current method.

Acknowledgments

We thank the National Basic Research Program of China (973 Program 2015CB856600) and National Natural Science Foundation of China (21332009, 21421091) for generous financial support.

Keywords: aromaticity · asymmetric catalysis · iridium · ligand effects · spiro compounds

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 3496–3499
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[12] CCDC 1440144 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[13] The structures and relative configurations of products **2o** and **2p** were assigned unambiguously by two-dimensional NOESY analysis.

[14] For details, see the Supporting Information.

Received: December 11, 2015
Published online: February 5, 2016

