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Pd-Catalyzed intermolecular asymmetric allylic dearomatization of 1-nitro-2-naphthols with MBH adducts†

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An asymmetric allylic dearomatization reaction of 1-nitro-2-naphthol derivatives with Morita–Baylis–Hillman (MBH) adducts has been developed. By utilizing Pd catalyst derived from Pd(OAc)$_2$ and Trost ligand (R,R)-L1, the reaction proceeded smoothly in 1,4-dioxane at room temperature, affording substituted β-naphthalenones in good yields (up to 92%) and enantioselectivity (up to 90% ee). A range of substituted 1-nitro-2-naphthols and MBH adducts were found to be compatible under the optimized conditions. This reaction provides a convenient method for the synthesis of enantioenriched 1-nitro-β-naphthalenone derivatives.

Dearomatization reactions can transform planar aromatic compounds into three-dimensional chiral molecules.[1] β-Naphthalenone is a core skeleton widely found in natural products and biologically active molecules.[2] Therefore, extensive efforts have been dedicated to the construction of β-naphthalenones through dearomatization of 2-naphthol derivatives. In this regard, asymmetric dearomatization of 1,3-disubstituted-2-naphthols has led to the formation of C–C,[3] C–N,[4] C–O[5] and other C–X (X = F, Cl, S) bonds with high efficiency in the past decade.[6] However, introducing a substituent at the C3 position of 2-naphthol is critical for regulating C/O selectivity and enantioselectivity of the reaction. Good chemoselectivity could be obtained only with 1,3-disubstituted 2-naphthols, wherein the steric hindrance originating from the 1,3-disubstituted groups would effectively prevent the competitive *O*-alkylation process. Correspondingly, C1-monosubstituted 2-naphthols usually suffer from poor regio- and enantio-selective control in the dearomatization reactions. Recently, dearomatization of C1-monosubstituted 2-naphthol derivatives has been accomplished through amination, halogenation, hydroxylation, azidation, and arylation reactions.[7] However, there are limited examples for their asymmetric varients.[7e,i–l,8] In 2014, our group realized an

allylic dearomatization of methyl 2-hydroxy-1-naphthoate in excellent chemo- and regio-selectivities. Unfortunately, low enantioselective control (10% ee) was observed in the presence of the (R,R)-Trost ligand after systematically screening the chiral ligands (Scheme 1a).[9] Later, Ishihara and coworkers[10] reported an elegant Cu-catalyzed asymmetric [1,3] O-to-C rearrangement reaction, giving β-naphthalenones in excellent yields and enantioselectivity (Scheme 1b). Despite of this elegant work, the development of novel intermolecular asymmetric dearomatization reaction of 1-substituted 2-naphthols for the synthesis of β-naphthalenones is still in great demand.

In our recent work, palladium-catalyzed asymmetric allylic alkylation of 1,3-disubstituted-2-naphthols with MBH adducts was relized (Scheme 1c).[11] Considering our continuous interests on asymmetric allylic dearomatization reactions, we recently investigated palladium-catalyzed allylic dearomatization reaction of 1-nitro-2-naphthol with MBH adducts. This reaction proceeded smoothly in the presence of Pd catalyst derived from the Trost ligand, resulting in 1-nitro-2-naphthalenones with moderate to excellent chemo- and enantio-selective control (≥19/1 C/O
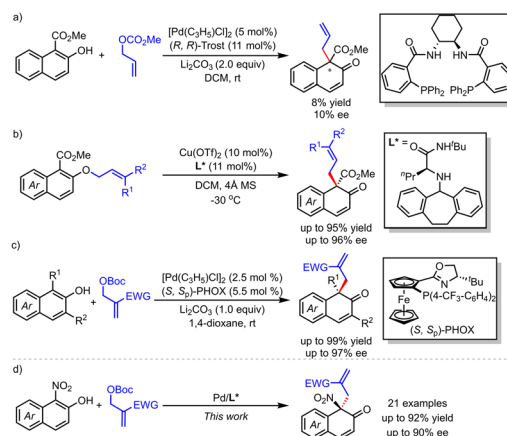
Scheme 1 Allylic dearomatization reactions of 1-monosubstituted 2-naphthols.

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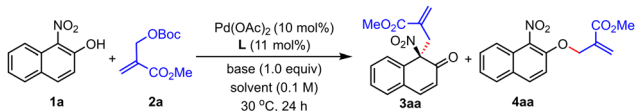
selectivity, up to 90% ee, Scheme 1d). Herein, we report the details of this study.

The initial exploration of the reaction was launched between 1-nitro-2-naphthol **1a** and methyl-substituted MBH carbonate **2a** (1.2 equiv.) in the presence of Pd(OAc)$_2$ (10 mol%), Trost ligand (R,R)-**L1** (11 mol%), and Li$_2$CO$_3$ (1.0 equiv.) in 1,4-dioxane under argon at 30 °C. To our delight, the reaction proceeded smoothly to deliver **3aa** in 78% NMR yield and 84% ee. Meanwhile, the etherification product **4aa** was obtained in 16% NMR yield (Table 1, entry 1). Encouraged by these preliminary results, various phosphine ligands were then investigated. The reaction did not occur when (R)-BINAP (**L2**), (R,R)-BPE (**L3**) or (S,S_p)-PHOX ligand (**L4**) was used. The Feringa ligand (S,S,S_a)-**L5** delivered the dearomatization product in racemic form, but in excellent yield and regioselectivity (entry 5, 97% yield, 19/1 C/O selectivity). Further screening of Trost-type ligands revealed that both **L6** and **L7** were sluggish in this reaction (entry 6, <5% yield; entry 7, 11% yield, 2/5 C/O selectivity, 80% ee). Thus, (R,R)-**L1** was proved to be the optimal ligand in terms of reactivity and selectivity (for complete screening of ligands, see the ESI† for details). Subsequently, the solvent effect was investigated with (R,R)-**L1**. The reaction in DCM, toluene or THF delivered **3aa** in poor yield and C/O selectivity with moderate enantioselectivity (entries 8–10, 13–43% yields, 2/1–5/11 C/O selectivity, 74–87% ee). The examination of bases indicated that Et$_3$N gave the best results (entry 13, 92% NMR yield, 84% ee). Besides, the reaction with Et$_3$N in THF was examined. It could occur smoothly with good enantioselective control, albeit with slightly reduced yield and C/O selectivity (entry 14, 60% yield, 15/1 C/O selectivity, 87% ee). Therefore, 1,4-dioxane was still chosen as the optimal solvent. Lowering the reaction temperature slightly enhanced the enantioselectivity (entry 15, 86% ee). When the reaction was conducted on a 0.2 mmol scale, **3aa** was obtained in 92% yield and 86% ee (entry 16). Notably, the reaction of methyl 2-hydroxy-1-naphthoate with **2a** can occur smoothly under the optimized conditions (83% NMR yield), but with poor C/O selectivity (1 : 1).

With the optimized conditions in hand (entry 16, Table 1), a series of 1-nitro-2-naphthols bearing different substituents were examined to test the generality of this asymmetric allylic dearomatization process (Table 2). When phenyl or methyl group was introduced at the C6 position of 2-naphthol, dearomatized products **3ac** and **3ad** could be delivered smoothly with excellent regioselectivity and reasonable enantioselectivity (**3ac** and **3ad**, 54–83% yields, 78–81% ee, >19/1 C/O selectivity). However, the enantioselectivity and yield of the reaction decreased slightly when a Br group was introduced at either the C6 or C7 position (**3ab** and **3ae**, 64–71% yields, 58–66% ee). Besides, different substituents at the C7 position of the naphthalene ring were investigated. The reactions occurred smoothly with excellent C/O selectivity and enantioselectivity for 7-phenyl and 7-methyl substituted 1-nitro-2-naphthols (**3af**, 81% yield, 80% ee; **3ag**, 87% yield, 82% ee). For 10-nitro-9-phenanthrenol, 88% yield and 68% ee were obtained for the dearomatized product **3ah**.

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

| Entry	Ligand	Base	Solvent	Yield of 3aa[b] (%)	C/O[c] (3aa/4aa)	ee[d] (%)
1	**L1**	Li$_2$CO$_3$	1,4-Dioxane	78	5/1	84
2	**L2**	Li$_2$CO$_3$	1,4-Dioxane	n.d.[e]	—	—
3	**L3**	Li$_2$CO$_3$	1,4-Dioxane	n.d.	—	—
4	**L4**	Li$_2$CO$_3$	1,4-Dioxane	n.d.	—	—
5[f]	**L5**	Li$_2$CO$_3$	1,4-Dioxane	97	19/1	0
6	**L6**	Li$_2$CO$_3$	1,4-Dioxane	<5	—	—
7	**L7**	Li$_2$CO$_3$	1,4-Dioxane	11	2/5	80
8	**L1**	Li$_2$CO$_3$	DCE	43	2/1	87
9	**L1**	Li$_2$CO$_3$	Toluene	13	1/2	74
10	**L1**	Li$_2$CO$_3$	THF	30	5/11	87
11	**L1**	K$_2$CO$_3$	1,4-Dioxane	65	33/10	84
12	**L1**	Cs$_2$CO$_3$	1,4-Dioxane	66	33/10	84
13	**L1**	Et$_3$N	1,4-Dioxane	92	>19/1	84
14	**L1**	Et$_3$N	THF	60	15/1	87
15[g]	**L1**	Et$_3$N	1,4-Dioxane	90	>19/1	86
16[gh]	**L1**	Et$_3$N	1,4-Dioxane	92[i]	>19/1	86

[a] General conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), Pd(OAc)$_2$ (10 mol%), ligand (11 mol%), base (1.0 equiv.) in solvent (1.0 mL) at 30 °C. [b] NMR yields using 1,3,5-trimethylbenzene as an internal standard. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis with a chiral stationary phase. [e] n.d. = not detected. [f] 22 mol% (S,S,S_a)-**L5** was used. [g] At 25 °C. [h] The reaction was carried out in 0.2 mmol scale. [i] Isolated yield.

Subsequently, the reactions of 1-nitro-2-naphthol **1a** with various MBH carbonates **2** were examined (Table 3). With the increase of steric hindrance of the ester group of the MBH adduct, the enantiomeric excess values of the dearomatized products varied slightly and comparable yields were obtained by prolonging the reaction time (**3ai**, 86% yield, 84% ee; **3aj**, 85% yield, 89% ee; **3ak**, 82% yield, 88% ee). Good yield and enantioselectivity were well maintained for the reaction of benzyl-substituted MBH carbonate (**3al**, 80% yield, 88% ee). Meanwhile, a variety of substituents on the benzene ring of the benzyl-substituted MBH carbonates were examined. As shown in Table 3, the optimized conditions were compatible with MBH carbonates bearing an electron-donating, electron-withdrawing or halogen group at the *ortho* position of the phenyl ring, such as methyl, trifluoromethyl or chloride group (**3am–3ao**, 84–88% yields, 87–90% ee). To be noted, the absolute configuration of product **3an** (>99% ee after recrystallization) was assigned as *R* by X-ray diffraction analysis, and those of other products were assigned by analogy. Various *meta* or *para*-substituted benzyl-type MBH carbonates were tolerated
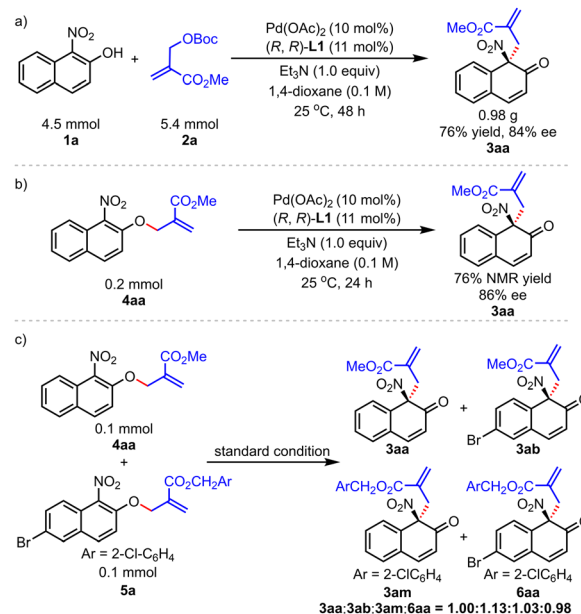
Table 2 Substrate scope of β-naphthols[abcd]
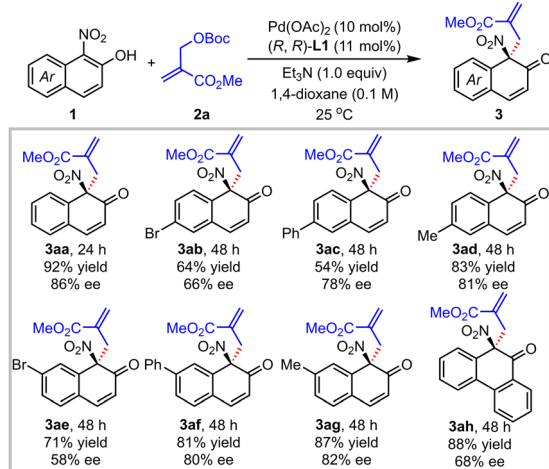
[a] General conditions: **1** (0.2 mmol), **2a** (0.24 mmol), Pd(OAc)$_2$ (10 mol%), (*R*,*R*)-**L1** (11 mol%), Et$_3$N (1.0 equiv.) in 1,4-dioxane (2.0 mL) at 25 °C. [b] Isolated yields. [c] Determined by HPLC analysis with a chiral stationary phase. [d] ≥19/1 C/O selectivity in all cases.

Table 3 Substrate scope of MBH adducts[abcd]
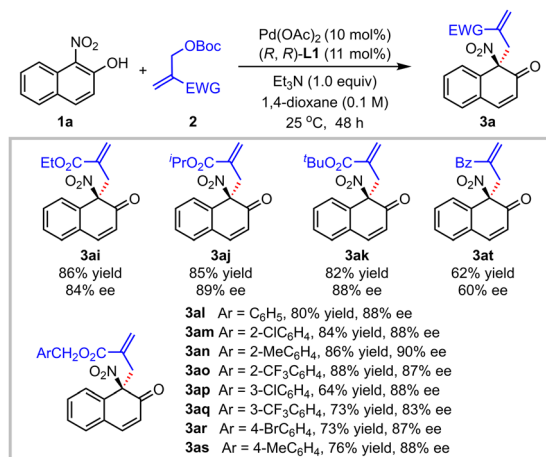
[a] General conditions: **1a** (0.2 mmol), **2** (0.24 mmol), Pd(OAc)$_2$ (10 mol%), (*R*,*R*)-**L1** (11 mol%), Et$_3$N (1.0 equiv.) in 1,4-dioxane (2.0 mL) at 25 °C. [b] Isolated yields. [c] Determined by HPLC analysis with a chiral stationary phase. [d] ≥19/1 C/O selectivity in all cases.

Scheme 2 Gram-scale reaction and mechanistic study.

notable loss of enantioselectivity (84% ee, Scheme 2a). To gain insights into the reaction mechanism, the *O*-alkylation product **4aa** was subjected to the standard conditions. Interestingly, dearomatized product **3aa** was obtained in 76% NMR yield and the same enantioselectivity (86% ee) of the standard reaction (Scheme 2b). A crossover reaction was carried out using substrates
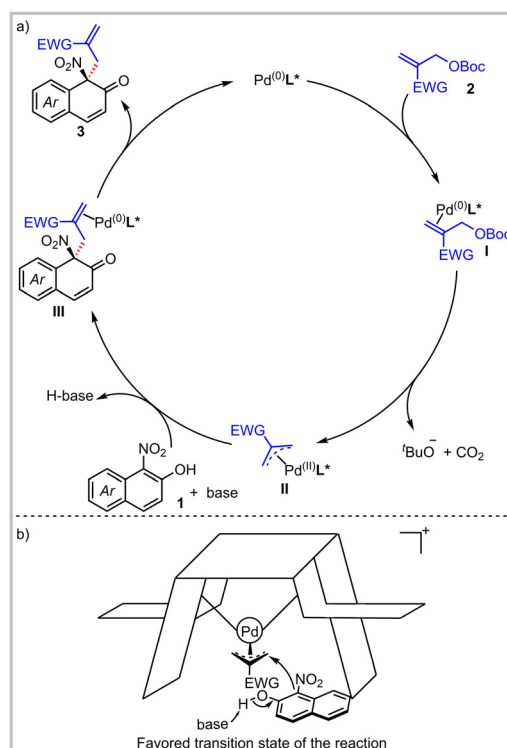
well, affording the target products **3ap–3as** in 64–76% yields and 83–88% ee. The benzoyl-substituted MBH carbonate could also be transformed to the desired product **3at** in 62% yield and 60% ee. When the reactions with either *tert*-butyl (2-cyanoallyl) carbonate or methyl 2-(((*tert*-butoxycarbonyl)oxy)(phenyl)methyl)acrylate were attempted, no corresponding dearomatized products were observed.

A gram-scale reaction was performed to examine the practicality of the current dearomatization reaction. To our delight, subjecting 1-nitro-2-naphthol **1a** on a 4.5 mmol scale under the optimal conditions led to **3aa** (0.98 g) in 76% yield without

Scheme 3 Proposed catalytic cycle.

4aa and **5a**. As shown in Scheme 2c, products **3aa**, **3ab**, **3am** and **6aa** were obtained in a ratio of 1.00 : 1.13 : 1.03 : 0.98. These results indicate that the process is an intermolecular reaction.

On the basis of the above experimental results and the reported literature,[9,12] a plausible mechanism is proposed as depicted in Scheme 3a. The direct allylic alkylation of α-C of naphthol is feasible in the reaction. First, palladium(0) is coordinated with MBH adduct **2** to form species **I**. The π-allylpalladium species **II** is generated by the oxidative addition of species **I** with the release of *tert*-butoxy anion and carbon dioxide. The α-C of 2-naphthol directly attacks species **II**, resulting in the dearomatized product **3**. Finally, the released palladium(0) complex enters into the next catalytic cycle. Meanwhile, the absolute configuration of the product is predicted to be *R* by the favored transition state model (Scheme 3b), which is consistent with the result confirmed by the single crystal structure.

In summary, we have developed an asymmetric allylic dearomatization of 1-nitro-2-naphthol derivatives with MBH adducts by using Pd catalyst derived from palladium acetate and Trost ligand. This strategy provides a direct and convenient access to a variety of β-naphthalenones bearing a nitro group in moderate to excellent yields and good enantioselectivity. Diverse functional groups were well tolerated for both 1-nitro-2-naphthols and MBH adducts.

Conflicts of interest

The authors declare no competing interests.

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