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Enantioselective Desymmetrization of Bisphenol Derivatives via Ir-Catalyzed Allylic Dearomatization

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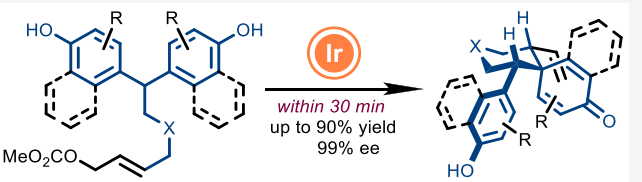
ABSTRACT: Spirocyclic hexadienones with multiple stereogenic centers are frequently found in natural products but remain challenging targets to synthesize. Herein, we report the enantioselective desymmetrization of bisphenol derivatives via Ir-catalyzed allylic dearomatization reactions, affording spirocyclic hexadienone derivatives with up to three contiguous stereogenic centers in good yields (up to 90%) and excellent enantioselectivity (up to 99% ee). The high efficiency of this reaction is exemplified by the short reaction time (30 min), low catalyst loading (down to 0.2 mol %), and ability to perform the reaction on a gram-scale. The total syntheses of (+)-tatanan B and (+)-tatanan C were also realized using this Ir-catalyzed allylic dearomatization reaction as a key step.



INTRODUCTION

Spirocyclic hexadienones bearing multiple stereogenic centers are key structural motifs found in numerous natural products (Figure 1). For example, caesalpin J[1] and futoenone[2] are

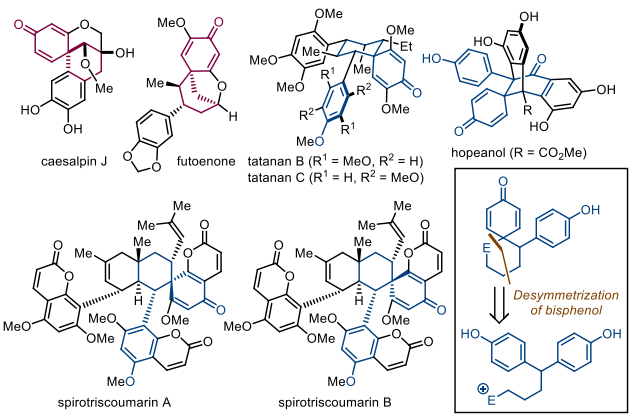


Figure 1. Selected natural products containing spirocyclic hexadienone motifs and the synthetic strategy of desymmetrization of bisphenols via dearomatization.

biologically active compounds that have been extracted from herbs used in traditional Chinese medicine. In particular, spirocyclic hexadienones bearing an adjacent phenol substituent exist in complicated natural products, including tatanans B and C, hopeanol, and spirotriscoumarins A and B. These complex natural products display a wide range of biological activities. Tatanans B and C, isolated from the rhizomes of *Acorus tatarinowii* Schott by Yu and co-workers,[3] are reported to display antidiabetic activity. Hopeanol displays potent antitumor activity and acetylcholinesterase inhibition.[4] Spirotriscoumarins A and B show antiviral activity against the influenza virus A.[5] From a retrosynthetic viewpoint, a desymmetrization reaction of bisphenol derivatives could be envisaged for the syntheses of these complex natural products.

Catalytic asymmetric dearomatization (CADA) reactions have great potential for directly converting planar aromatic starting materials into chiral spiro and fused polycyclic compounds.[6,7] Among the tremendous efforts devoted in this area, transition-metal-catalyzed asymmetric allylic substitution reactions have been applied as an efficient strategy in the construction of spirocyclic hexadienones.[8] In 2010, the Hamada group described a Pd-catalyzed spirocyclization forming the spiro[4.5]decadienone ring system.[8a] Shortly after, our group reported an Ir-catalyzed asymmetric allylic dearomatization of *para*-substituted phenols, providing cyclohexadienones containing the spiro cyclopentane, piperidine, or pyrrolidine ring structure in enantioenriched forms (Scheme 1(a)).[8b] In their elegant enantioselective synthesis of tatanans B and C in 2013, Miller, Zakarian, and co-workers implemented a Pd-catalyzed allylic dearomatization of a bisphenol derivative as a key step in forging the central cyclohexane ring, with the concurrent establishment of three stereogenic centers (Scheme 1(b)).[9] However, under their optimal conditions, a mixture of tatanans B and C and

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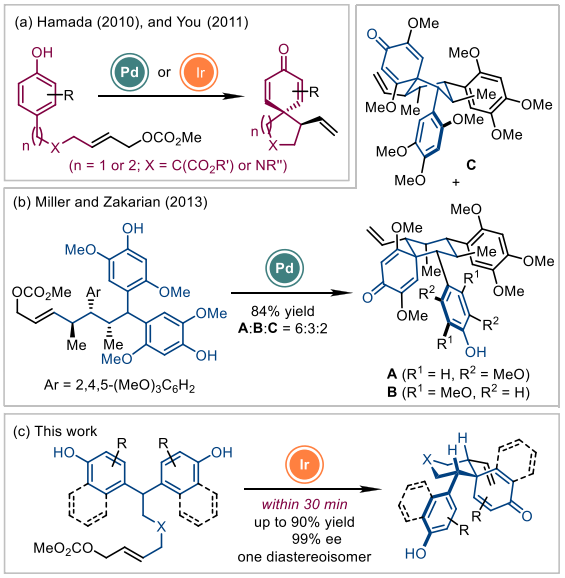
Scheme 1. Transition-Metal-Catalyzed Allylic Dearomatization of Phenols

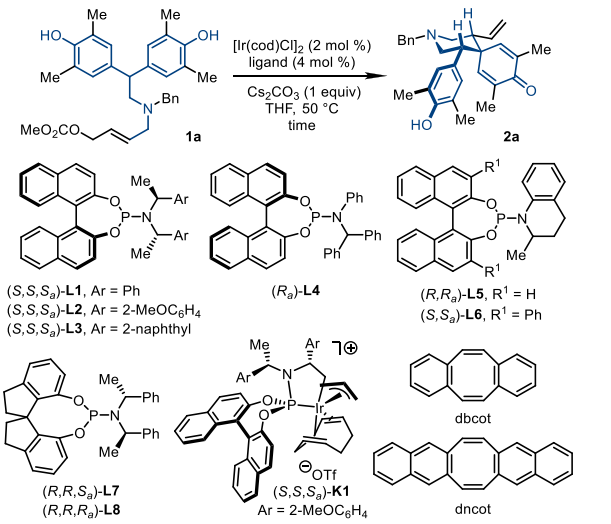


undesired isomers (6:3:2) were obtained. The authors also reported that when using an Ir-catalyst derived from $[Ir(cod)Cl]_2$ and $P(OPh)_3$, lower reactivity was observed (up to 10% yield). Recently, we found that the enantioselective desymmetrization of bisphenol-derived allylic carbonates could be achieved via an Ir-catalyzed intramolecular asymmetric allylic dearomatization reaction (Scheme 1(c)). In most cases, the desired products bearing multiple stereogenic centers could be afforded in high yields with excellent stereochemical control within 30 min. Furthermore, this method was successfully applied to the total syntheses of tatanans B and C, and the details of this study are reported herein.

RESULTS AND DISCUSSION

Reaction Development. Using bisphenol-derived allylic carbonate **1a** as the model substrate, various parameters were first evaluated in the Ir-catalyzed asymmetric allylic substitution reaction (Table 1).[10,11] Treatment of **1a** with an Ir-catalyst derived from $[Ir(cod)Cl]_2$ (2 mol %) and (S,S,S_a)-Feringa ligand **L1** (4 mol %), and Cs_2CO_3 (1 equiv) as the base, in THF at 50 °C gave **2a** in 82% NMR yield with 92% ee in 5 min (entry 1). Next, the effect of a variety of chiral phosphoramidites, the most frequently utilized chiral ligands in Ir-catalyzed asymmetric allylic substitution reactions, was evaluated (entries 2−8). It was found that the Alexakis ligand (S,S,S_a)-**L2** performed the best in terms of the enantioselectivity of **2a** (98% ee). Furthermore, different Ir-precursors and prepreparation methods for the chiral Ir-catalysts were screened, as these modifications have been shown to lead to marked differences in catalyst stability and often influence the overall reaction outcomes.[12−14] Using $[Ir(dbcot)Cl]_2$ or $[Ir(dncot)Cl]_2$ as the Ir-precursor led to decreased yields and enantioselectivity of **2a** (33−43% yields, 91% ee, entries 9 and 10).[12] Instead of the *in situ* preparation of the Ir-catalyst via ^{n}PrNH$_2$ activation,[13] the utilization of (S,S,S_a)-**L2**-derived cyclometalated Ir-complex (S,S,S_a)-**K1** improved the reaction efficiency (entry 11).[14] The NMR yield of **2a** was increased to 86% with an isolated yield of 81% and comparable enantioselectivity on a 0.2 mmol scale reaction. Notably, in

Table 1. Optimization of the Reaction Conditions[a]



entry	ligand	time	yield (%)[b]	ee (%)[c]
1	**L1**	5 min	82	92 (−)
2	**L2**	5 min	74	98 (−)
3	**L3**	5 min	68	93 (−)
4	**L4**	45 min	72	87 (−)
5	**L5**	45 min	63	86 (−)
6	**L6**	3 h	62	74 (+)
7	**L7**	24 h	26	87 (+)
8	**L8**	24 h	<5	N.D.[h]
9[d]	**L2**	12 h	33	91 (−)
10[e]	**L2**	12 h	43	91 (−)
11[f]	**L2**	5 min	86 (81[g])	97 (−)

[a]Reaction conditions: **1a** (0.1 mmol), $[Ir(cod)Cl]_2$ (2 mol %), ligand (4 mol %), Cs_2CO_3 (1.0 equiv) in THF (1.0 mL) at 50 °C. Catalyst was prepared via ^{n}PrNH$_2$ activation.[13] [b]Yield determined by ^{1}H NMR using mesitylene as an internal standard. [c]Determined by HPLC analysis. The sign of the optical rotation is given in parentheses. [d]$[Ir(dbcot)Cl]_2$ (2 mol %) was used. [e]$[Ir(dncot)Cl]_2$ (2 mol %) was used. [f]Independently prepared (S,S,S_a)-**K1** (4 mol %) was used. [g]Isolated yield of a 0.2 mmol scale reaction. [h]N.D.: not determined.

all cases, **2a** was obtained as a single diastereoisomer. Further screening of solvents and bases did not lead to better results (see the SI for details).

After optimal reaction conditions had been established (entry 11, Table 1), the substrate scope of this reaction was investigated (Table 2). For the reactions of symmetric 2,6-disubstituted bisphenol-derived substrates, variation of the chain linkage (**2a**−**2e**) or the alkyl groups at the C2 and C6 positions (**2f** and **2g**) were well accommodated. The corresponding products were obtained in high yields (70−88%) with excellent enantioselectivity (93−98% ee). The absolute configuration of **2c** (1*S*,3*R*) was unambiguously determined by X-ray crystallographic analysis of an enantiopure sample. However, when an O-linked substrate was employed, the target product was produced in only 7% yield (see the SI for details). Notably, when using a 2,6-unsubstituted phenol derivative, the allylic dearomatization reaction afforded the desired product **2h** in 69% yield and 95% ee. Specifically, Friedel−Crafts-type allylation at the *ortho*-position was not observed, presumably due to the strained nature of the product. Contrastingly, the incorporation of two fluorine atoms at the C2 and C6 positions led to a complex

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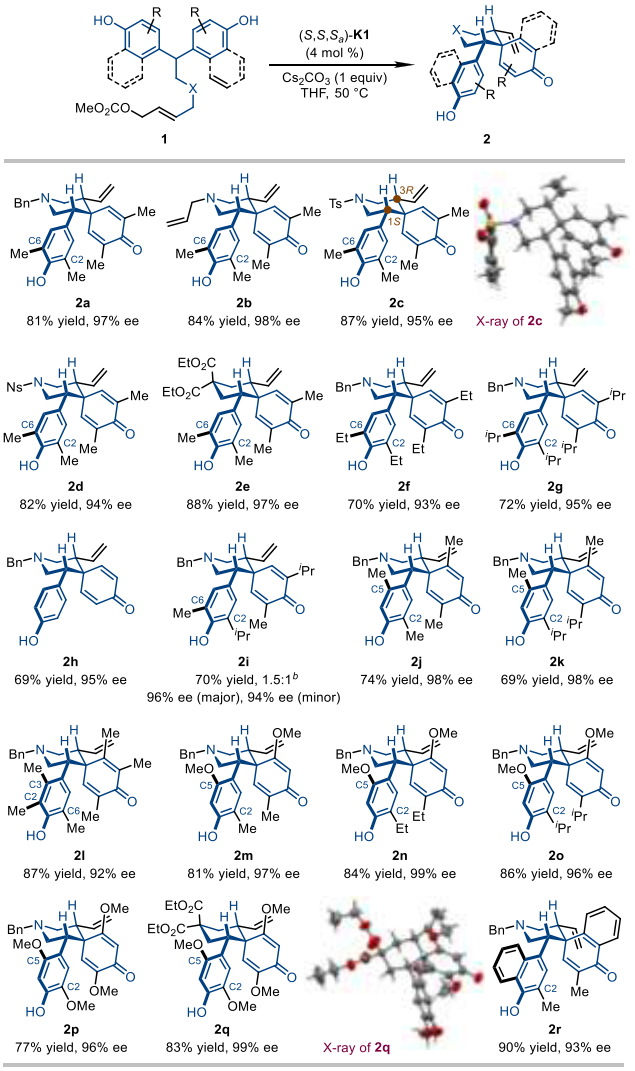
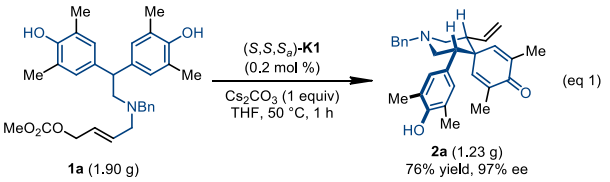
Table 2. Substrate Scope[a]



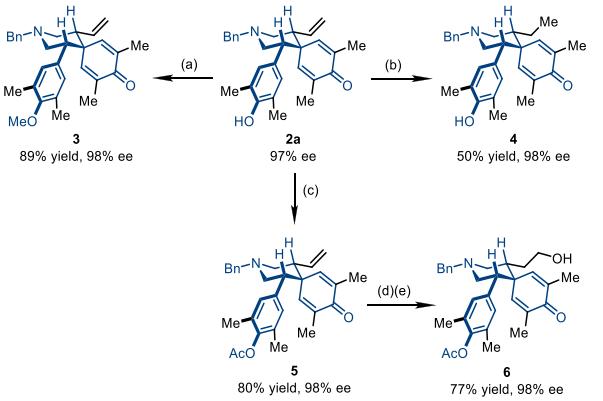
[a]Reaction conditions: **1** (0.2 mmol), (S,S,S_a)-**K1** (4 mol %), Cs_2CO_3 (1.0 equiv) in THF (2.0 mL) at 50 °C. [b]Combined yield and ratio of two diastereoisomers.

mixture, which could be caused by the reduced nucleophilicity of the phenol ring (see the SI for details). When different alkyl groups (^{i}Pr and Me) were introduced to the C2 and C6 positions at the same time, a pair of diastereoisomers of **2i** (1.5,1) was obtained in a combined yield of 70%, with both major and minor isomers in excellent enantiopurity (94−96% ee). To our delight, the reactions of more sterically demanding substrates, containing C3 or C5 substituents at the phenol ring, all proceeded smoothly with excellent atroposelectivity (>95:5). Different alkyl (Me, Et, and ^{i}Pr) or methoxyl groups were well tolerated in these cases. All the desired products (**2j**−**2q**) were obtained in good yields (69−87%) with high enantioselectivity (92−99% ee). Notably, according to the X-ray crystallographic analysis of **2q**, the newly formed terminal olefin and the C5 substituent on the original phenol ring were located on the opposite side of the central six-membered ring, avoiding steric congestion in the C−C bond-forming transition state. Further efforts toward the synthesis of five- or seven-membered spirocyclic hexadienones were not successful (see the SI for details). Finally, the reaction could be expanded to a bis(1-naphthol) derivative, allowing facile access to **2r** in 90% yield with 93% ee. With a lower loading of the Ir-catalyst (0.2 mol %), a gram-scale synthesis of **2a** (1.23 g) also gave comparable results to the 0.2 mmol scale reaction in terms of yield (76%) and enantiopurity (97% ee) within 1 h (eq 1), which showed the robustness and practicality of this method.



Synthetic Applications. A series of synthetic transformations of spirocyclic hexadienone **2a** were carried out (Scheme 2). The O-methylation of **2a** afforded ether **3** in 89% yield. The terminal olefin group of **2a** was readily reduced under Pd/C and H_2 conditions, leading to **4** in 50% yield. Furthermore, the O-acylation of **2a** brought about **5**, which was subsequently transformed into primary alcohol **6** in 77% yield via hydroboration/oxidation of the terminal olefin moiety. Notably, no erosion of the enantiopurity of the compounds was observed.

Scheme 2. Transformations of 2a[a]



[a]Reaction conditions: (a) NaH (1.2 equiv), MeI (10 equiv), THF, 0 °C to rt, 30 min; (b) Pd/C, H_2, ethyl acetate, rt, 10 min; (c) Ac_2O (1.5 equiv), pyridine (2 equiv), DCM, 0 °C to rt; (d) 9-BBN, THF, rt, 10 min; (e) H_2O_2, NaOH, rt, 15 min.

The synthetic utility of this Ir-catalyzed allylic dearomatization of phenols was further showcased by the total synthesis of tatanans B and C (Scheme 3). Following the work of Miller, Zakarian, and their co-workers,[9] both enantiomers of functionalized bisphenol-derived allylic carbonate **7** were synthesized. Notably, a significant match/mismatch phenomenon was identified between the enantiomers of **7** and the chiral Ir-catalyst. Only (+)-**7** was found to be reactive with (S,S,S_a)-**K1**, leading to a pair of atropisomers (5:1) of dearomatized product **8** in 79% combined yield, while (−)-**7** remained mainly intact under the same reaction conditions. After subsequent O-methyl protection and hydrogenation of the terminal olefin, an inseparable mixture of atropisomers (+)-tatanan C and (+)-tatanan B (5:1) was obtained in a total yield of 55% [three steps from (+)-**7**]. Notably, the formation of other undesired isomers during the dearomatiza-

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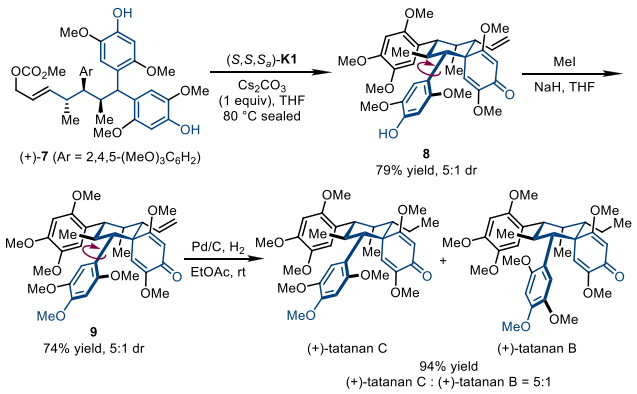
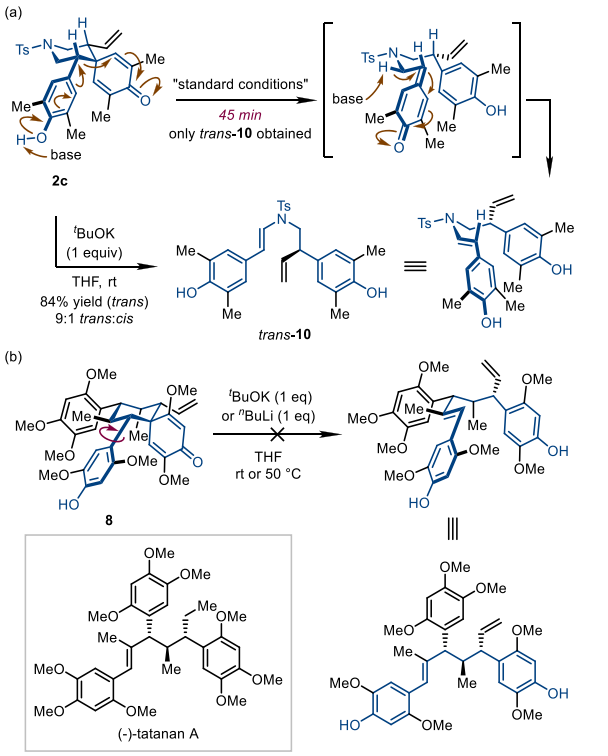
Scheme 3. Syntheses of (+)-Tatanan B and (+)-Tatanan C



tion step described in previous work[9] was avoided under our conditions.

It is noteworthy that dearomatized product **2c** can be transformed into ring-opened compound *trans*-**10** when reacting under the standard allylic dearomatization conditions for an extended period of time (45 min, Scheme 4a). We

Scheme 4. Ring-Opening/Rearomatization of 2c and Synthetic Attempts toward (−)-Tatanan A



speculated that the formation of *trans*-**10** could be attributed to a base-promoted ring-opening/rearomatization sequence. In order to verify this hypothesis, **2c** was treated with 1 equiv of ^{t}BuOK. Indeed, compound **10** was obtained smoothly in a high yield (84% for *trans*-**10**, *trans*-**10**/*cis*-**10** = 9:1). Considering the structural similarity between **10** and tatanan A,[5] we further tested the synthesis toward (−)-tatanan A from **8**. Unfortunately, the proposed transformation did not occur in the presence of ^{t}BuOK or ^{n}BuLi at room temperature or 50 °C (Scheme 4b).

CONCLUSIONS

In conclusion, we have applied our desymmetrization strategy to the Ir-catalyzed intramolecular allylic dearomatization reaction of phenols. Spirocyclic dienone derivatives with up to three stereogenic centers were synthesized with high efficiency (up to 90% yield and 99% ee within 30 min). Notably, this method could be scaled up to a gram-scale in the presence of only 0.2 mol % of the Ir-catalyst. By using this reaction as a key step, the total syntheses of (+)-tatanan B and (+)-tatanan C were accomplished with superior atroposelectivity relative to that reported in the literature.[9]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09638.

Experimental procedures and analysis data for all new compounds (PDF)

X-ray structure of **2c** (CIF)

X-ray structure of **2q** (CIF)

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Notes

The authors declare no competing financial interest.

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